# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:
## 22-512

## MEDICAL REVIEW(S)

# Addendum to Clinical Review for NDA 22-512

Drug: dabigatran (Pradaxa)
Sponsor: Boehringer Ingelheim
Indication: Prevention of stroke and systemic embolism in atrial fibrillation

Division: Division of Cardiovascular and Renal Products
Reviewers: Nhi Beasley

Subject: Risk of myocardial infarction
Date: September 2, 2010

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## Reviewer's conclusions/recommendations

The rate of myocardial infarction (MI) was higher on dabigatran compared to warfarin in RE-LY. The reason for the higher rate of MI with dabigatran is unclear. Baseline subject characteristics and medication use were similar between treatment arms and do not in part explain the higher rate of MI with dabigatran. The imbalance in MIs was seen on drug as well as off drug. Whether or not the higher rate of MI with dabigatran represents the play of chance, an adverse effect of dabigatran or beneficial effects of warfarin on infarction risk remains unclear. If this is truly a drug-related adverse event, then treating 1000 subjects for one year will cause 2 excess MIs compared to treating with warfarin. This risk should be weighed with the other benefits and risks of dabigatran. At this time, the reviewer recommends describing the higher rate of MI with dabigatran in the label. The sponsor's phase 3 development program in subjects with Acute Coronary Syndromes (ACS) will likely provide a more definitive answer to this question.

## Background

*Experience with other drugs in its class*

The risks of cardiovascular events with ximelagatran, another oral direct thrombin inhibitor, were unclear. There were more coronary artery disease (CAD) adverse events in ximelagatran compared to warfarin treated subjects in the short term studies for prevention of venous thromboembolism (VTE).[1] However, the long-term studies for stroke prevention in atrial fibrillation were inconsistent. SPORTIF III had a greater number of adjudicated acute MIs in ximelagatran compared to warfarin treated subjects, (24 (1.1%) and 3 (0.6%) respectively), as well as more serious cardiac events.[2] In contrast, SPORTIF V had a smaller number of adjudicated MIs in ximelagatran compared to warfarin treated subjects (26 (1.0%) and 37 (1.4%), respectively); serious cardiac events were less in the ximelagatran arm.[2] Lastly, the secondary prevention

[1] See appendix for table of CAD adverse events in EXULT trials.
[2] Taken from SPORTIF trial publications. For SPORTIF V, number given is reported as "on-treatment"; number for SPORTIF III described as ITT. See appendix for table of serious coronary adverse events in SPORTIF trials.

following MI phase 2 study suggested favorable effects of ximelagatran on secondary prevention.[3]

*Warfarin*

To interpret the findings, it is important to understand the effect of warfarin. As noted in the appendix of the primary review, few MIs were reported in the historical trials that established warfarin's efficacy for the prevention of stroke in subjects with atrial fibrillation. This makes it difficult to ascertain what, if any effect, warfarin has on this outcome. In the Warfarin, Aspirin, Re-Infarction study (WARIS II), an open-label, randomized study of patients hospitalized for acute myocardial infarction and treated with warfarin (target INR 2.8 to 4.2), aspirin (160 mg) or a combination of warfarin (target INR 2.0 to 2.5) plus aspirin (81 mg) post-infarction, a statistically significant reduction in the risk of re-infarction was seen in the warfarin compared to aspirin arm (rate ratio 0.74, 95% CI: 0.55-0.98, p-value <0.03). Relative to the aspirin arm, a statistically significant reduction in re-infarction was also seen in the group treated with warfarin plus aspirin (rate ratio 0.56, 95% CI: 0.41-0.78, p-value <0.001). Whether or not similar warfarin effects would be expected in current practice (i.e., given other advances in anti-platelet therapies) is not clear.

*Experience with dabigatran in other treatment programs*

Data with dabigatran for the treatment of VTE and following ACS do not suggest an increased risk of MI or ACS. RE-COVER was a phase 3, non-inferiority trial comparing 6 months of dabigatran 150 mg BID to warfarin (adjusted to an INR 2-3) for the treatment of acute VTE. Very few ACS events were observed in the 1273 subjects treated with dabigatran and in the 1266 subjects treated with warfarin.[4] In RE-DEEM, a phase 2, placebo-controlled study of dabigatran dosed twice daily for 6 months in patients on dual antiplatelet therapy after ACS (n~1860), the number of coronary events in the 110 mg and 150 mg dabigatran treatment arms were not greater than in the placebo arm or in subjects on lower doses of dabigatran (see table below). The events were small, however, and the sponsor's categorization of events for the purpose of analyses (non-fatal MI versus CV death) prevents a comparison of total MI event rates (fatal and non-fatal) across treatment arms.

**Table 1. CV death, non fatal MI and non-hemorrhagic stroke in RE-DEEM**

| | Placebo | | DE 50 | | DE 75 | | DE 110 | | DE 150 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Treated patients | 371 | (100) | 369 | (100) | 368 | (100) | 406 | (100) | 347 | (100) |
| Patients with event | 14 | (3.8) | 17 | (4.6) | 18 | (4.9) | 12 | (3.0) | 12 | (3.5) |
| Cardiovascular death | 9 | (2.4) | 8 | (2.2) | 9 | (2.5) | 5 | (1.2) | 4 | (1.2) |
| Non-fatal MI | 4 | (1.1) | 9 | (2.4) | 8 | (2.2) | 7 | (1.7) | 8 | (2.3) |
| Non-haemorrhagic stroke | 3 | (0.8) | 0 | | 1 | (0.3) | 0 | | 0 | |

Each patient with an event was counted once for the composite endpoint and once for each individual component

[Source: REDEEM Clinical Trial Report dated February 25, 2010, Table 11.4.1.2.2:1]

[3] See appendix for discussion of ESTEEM.

[4] Schulman S et al for the RE-COVER Study Group. NEJM 2009; 361:2342-52.

## Review

*Reviewer's comment: This addendum to the clinical review for NDA 22-512, (dabigatran for prevention of stroke and systemic embolic events) addresses the risk of MI in the RE-LY trial. Throughout this document, the term MI refers to a clinical MI. All references that include silent MI are clearly stated.*

In RE-LY, myocardial infarction was an adjudicated outcome event[5] and was a component of a composite secondary endpoint that included stroke, systemic embolism, pulmonary embolism, and vascular deaths. Though analysis suggested favorable effects of dabigatran (relative to warfarin) on the composite endpoint, the original NDA submission (December 15, 2009) indicated an increased risk of MI with dabigatran as compared to warfarin (Table 2).

**Table 2. Relative and absolute risk of MI in RE-LY (original submission)**

| | D110 v. W HR (95%CI) p-value | D150 v. W HR (95%CI) p-value | D110 v. D150 HR (95%CI) p-value | D110 N (%/yr) | D150 N (%/yr) | W N (%/yr) |
|---|---|---|---|---|---|---|
| **Randomized**[6] | 1.35 (0.98, 1.87) 0.070 | 1.38 (1.00, 1.91) 0.049 | 0.98 (0.73, 1.31) 0.88 | 86 (0.72) | 89 (0.74) | 63 (0.53) |
| **Safety population**[7] | 1.40 (0.98, 2.01) 0.066 | 1.42 (0.99, 2.03) 0.055 | 0.99 (0.71, 1.37) 0.94 | 70 (0.68) | 71 (0.69) | 52 (0.49) |

[source: Sponsor's tables 15.2.5:2, 15.2.2.3:1, 15.2.5:1, 15.2.5:3]
In case of recurrent event, the first adjudicated event was considered. The yearly event rate (%/yr) was calculated as the # of subjects with event/subject years *100.

Following the refuse to file letter, the sponsor took measures to confirm the accuracy and integrity of the outcome events, including MI and silent MI (see Appendix). Silent MIs were a predefined outcome event, but because new Q-waves were not reported on the MI case report form, silent MIs were not considered in the sponsor's original analysis. The results of the quality roadmap check are shown in Table 3.

**Table 3. Additional adjudicated MI's identified by quality roadmap check**

| | D110 | D150 | W |
|---|---|---|---|
| **MI** | 1 | 0 | 3 |
| **Silent MI** | 11 | 8 | 9 |

[5] MI definition located in Appendix.
[6] These analyses included all events that occurred between the date of randomization and the date of study termination. Subject-years =sum (date of study termination-date of randomization +1) of all randomized subjects/365.25. Subject-years were 11,900, 12,039, and 11,797 for D110, D150, and W, respectively.
[7] These analyses included all events that occurred from the date of first study medication to the date of last study medication plus 6 days. Subject-years =sum (date of last study drug intake-date of first study drug intake +1) of all treated subjects/365.25. Subject-years were 10,229, 10,253, and 10,661 for D110, D150, and W, respectively.

The new clinical MI findings slightly reduced the risk of MI on dabigatran relative to warfarin and slightly shifted the p-value (Table 4). The absolute risk of MI, however, remained ~0.2% higher with dabigatran (and was not dose dependent).

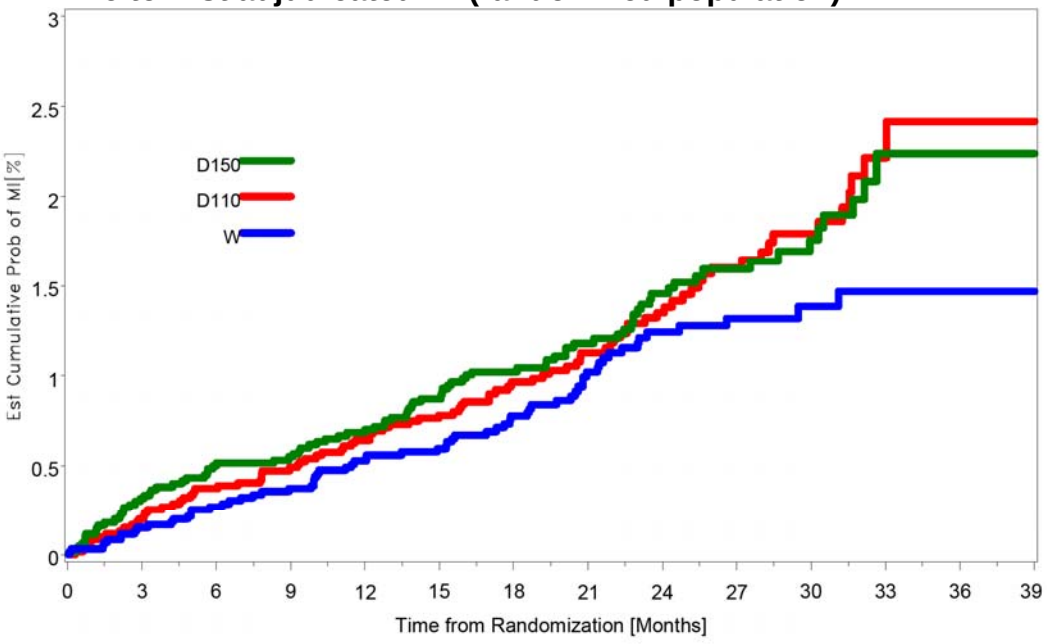
**Table 4. Relative and absolute risk of MI in RE-LY (resubmission)**

| | D110 v. W HR (95%CI) p-value | D150 v. W HR (95%CI) p-value | D110 N (%/yr) | D150 N (%/yr) | W N (%/yr) |
|---|---|---|---|---|---|
| **MI + silent MI, randomized**[8] | 1.29 (0.96,1.75) 0.09 | 1.27 (0.94,1.71) 0.12 | 98 (0.82) | 97 (0.81) | 75 (0.64) |
| **MI, randomized** | 1.30 (0.95, 1.80) 0.10 | 1.32 (0.96, 1.81) 0.09 | 87 (0.73) | 89 (0.74) | 66 (0.56) |
| **MI + silent MI, safety population**[9] | 1.32 (0.95, 1.84) 0.20 | 1.30 (0.94, 1.81) 0.12 | 80 (0.78 | 79 (0.77) | 63 (0.59) |

[source: Sponsor's tables 15.2.6.1: 1, 15.2.2.2:1_new, 15.2.5:2_new, 15.2.6.2:1_new, 15.2.6.1: 2, 15.2.6.2:7, resubmission]

The time to first adjudicated MI in the randomized population is shown in Figure 1. The curves are constant over time with the risk in the dabigatran arms greater than warfarin.

**Figure 1. Time to first adjudicated MI (randomized population)**




| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5940 | 5884 | 5821 | 5747 | 5515 | 4657 | 3806 | 3170 | 2415 | 1466 | 496 | 85 |
| D150 | 6076 | 6006 | 5941 | 5872 | 5802 | 5564 | 4718 | 3851 | 3237 | 2441 | 1489 | 487 | 88 |
| W | 6022 | 5952 | 5896 | 5821 | 5760 | 5469 | 4651 | 3728 | 3108 | 2369 | 1376 | 381 | 74 |

[Source: Reviewer's analysis: mi\time mi km (Kaplan Meier analysis of randomized population), sponsor's data set: adjrand]

[8] Subject-years were 11,899, 12,033, and 11,794 for D110, D150, and W, respectively.
[9] Subject-years were 10,242, 10,261, and 10,659 for D110, D150, and W, respectively.

*MI occurrence with respect to medication discontinuation*
There were numerically more MIs on dabigatran compared to warfarin during treatment, (table below). This numerical imbalance persisted off drug.

**Table 5. Number of subjects with MI by time of occurrence from study drug discontinuation**

| | D110 | | D150 | | W | |
|---|---|---|---|---|---|---|
| | n | % | n | % | N | % |
| Total randomized | 6015 | (100) | 6076 | (100) | 6022 | (100) |
| Total number of first MIs | 87[1] | (1.4) | 89 | (1.5) | 66 | (1.1) |
| MI on drug | 56 | (0.9) | 59 | (1.0) | 46 | (0.8) |
| MI within 6 days off | 13 | (0.2) | 10 | (0.2) | 8 | (0.1) |
| MI within 30 days off | 15 | (0.2) | 13 | (0.2) | 12 | (0.2) |
| MI > 30 days off | 15 | (0.2) | 17 | (0.3) | 8 | (0.1) |

[source: adapted from sponsor's table 15.2.5:15, resubmission] 1. The mutually exclusive categories total 86 because 1 MI occurred in a subject randomized but not treated.

*Reviewer's comment: There are a few points to consider for the table above. 1. The protocol specified that for dabigatran treatment groups with suspected ACS, dabigatran was to be temporarily discontinued. 2. The determination of the MI event date was not prespecified. Some source documents indicated that the MI date was the hospitalization date; some indicated the MI date was the date of clinically significant cardiac enzymes.*

*Baseline characteristics*
There were no clear baseline differences between treatment groups that might in part explain the imbalance in MIs with dabigatran. Treatment groups were reasonably similar at baseline with respect to the following cardiovascular risk factors: hypertension, diabetes, coronary artery disease (CAD), prior MI, smoking status, age, and total cholesterol.[10,11] Baseline concomitant medications across treatment groups were also reasonably similar (notably, beta blockers, ACE inhibitors, statins, aspirin, clopidogrel, proton pump inhibitors).[10]

*MI severity*
Information on MI severity with respect to location (anterior or inferior) and post MI heart failure data were not routinely collected, but of the information available (see next table), the numbers suggest that the MIs on dabigatran were worse than the MIs on warfarin (more hospitalizations, more very high enzyme elevations). ECG changes were only captured as new Q-wave or ST-T changes. Characterization of severity by ST elevation or non-ST elevation was not captured. There were very few invasive procedures performed prior to the MI. The incidence of cardiovascular death following recent MI

[10] FDA clinical review
[11] Mean total cholesterol was 180 mg/dL across all treatment arms. LDL cholesterol was not available.[reviewer's analysis]

was low, with 15, 7, and 8 fatal MIs in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively [source: sponsor's listing 7.29, submission 132].

**Table 6. Summary of MI report**

| | DE 110mg bid N (%) | DE 150mg bid N (%) | Warfarin N (%) |
|---|---|---|---|
| Total number of adjudicated MIs | 90 (100.0) | 102 (100.0) | 74 (100.0) |
| Hospitalized for the event | 85 ( 94.4) | 93 ( 91.2) | 68 ( 91.9) |
| Symptom compatible with acute MI | 74 ( 82.2) | 92 ( 90.2) | 61 ( 82.4) |
| ECG changes | 56 ( 62.2) | 59 ( 57.8) | 49 ( 66.2) |
| New Q-wave | 10 ( 11.1) | 7 ( 6.9) | 12 ( 16.2) |
| ST-T changes | 52 ( 57.8) | 56 ( 54.9) | 47 ( 63.5) |
| Cardiac enzymes/markers of myocardial necrosis completed | 83 ( 92.2) | 95 ( 93.1) | 70 ( 94.6) |
| Peak CK | 55 ( 61.1) | 63 ( 61.8) | 41 ( 55.4) |
| Within normal range | 17 ( 18.9) | 17 ( 16.7) | 8 ( 10.8) |
| >ULN and <=2xULN | 12 ( 13.3) | 18 ( 17.6) | 14 ( 18.9) |
| >2xULN and <=3xULN | 7 ( 7.8) | 5 ( 4.9) | 4 ( 5.4) |
| >3xULN and <=5xULN | 6 ( 6.7) | 5 ( 4.9) | 4 ( 5.4) |
| >5xULN | 13 ( 14.4) | 18 ( 17.6) | 11 ( 14.9) |
| Peak CK-MB | 52 ( 57.8) | 54 ( 52.9) | 44 ( 59.5) |
| Within normal range | 9 ( 10.0) | 5 ( 4.9) | 7 ( 9.5) |
| >ULN and <=2xULN | 11 ( 12.2) | 11 ( 10.8) | 6 ( 8.1) |
| >2xULN and <=3xULN | 4 ( 4.4) | 6 ( 5.9) | 5 ( 6.8) |
| >3xULN and <=5xULN | 9 ( 10.0) | 6 ( 5.9) | 7 ( 9.5) |
| >5xULN | 19 ( 21.1) | 26 ( 25.5) | 19 ( 25.7) |
| Troponin | 80 ( 88.9) | 91 ( 89.2) | 68 ( 91.9) |
| Within normal range | 0 | 2 ( 2.0) | 2 ( 2.7) |
| >ULN and <=2xULN | 15 ( 16.7) | 13 ( 12.7) | 10 ( 13.5) |
| >2xULN and <=3xULN | 4 ( 4.4) | 3 ( 2.9) | 6 ( 8.1) |
| >3xULN and <=5xULN | 7 ( 7.8) | 8 ( 7.8) | 5 ( 6.8) |
| >5xULN | 54 ( 60.0) | 65 ( 63.7) | 45 ( 60.8) |
| Invasive procedure performed prior to the event | | | |
| Angio | 7 ( 7.8) | 11 ( 10.8) | 7 ( 9.5) |
| PCI | 5 ( 5.6) | 10 ( 9.8) | 3 ( 4.1) |
| CABG | 0 | 0 | 0 |
| Other | 2 ( 2.2) | 4 ( 3.9) | 2 ( 2.7) |

[source: sponsor's table 7.25, appendix 3, submission 132]

The serious adverse event (SAE) data do not indicate more heart failure in the dabigatran arms compared to warfarin, however the reviewer did not link these SAEs to the MI event.

**Table 7. Heart failure serious adverse event terms**

| | D110 | D150 | W |
|---|---|---|---|
| cardiac failure congestive | 83 | 58 | 73 |
| cardiac failure | 51 | 62 | 65 |
| cardiac failure acute | 5 | 1 | 7 |
| acute LV failure | 1 | 0 | 1 |
| cardiac failure chronic | 0 | 1 | 0 |
| cardiomyopathy | 2 | 0 | 1 |
| congestive cardiomyopathy | 2 | 0 | 0 |
| ischemic cardiomyopathy | 0 | 1 | 2 |
| LV dysfunction | 2 | 0 | 2 |
| LV failure | 1 | 1 | 0 |
| RV failure | 0 | 1 | 2 |
| **total** | **147** | **125** | **153** |

[source: adapted from sponsor's table 15.3.2.6:2, resubmission]

*Serious adverse events across treatment arms*

If dabigatran is likely to cause MI, then one would expect a trend for more unstable angina cases. There were 7, 13, and 5 serious unstable angina reports. Although numerically higher, these numbers are too small to definitively conclude that dabigatran increases the risk of MI.

# Appendix

## Background

*Ximelagatran*

The table below shows the greater number of CAD adverse events (MI, "other CAD") in ximelagatran compared to warfarin-treated subjects in the VTE prevention studies. In the EXULT trials, treatment with ximelagatran/warfarin started after total knee replacement and continued for 7 to 12 days.

**Table 8. Summary of CAD adverse events in trials of ximelagatran for VTE prevention following total knee replacement**

| | Exult A | | Exult B## | | Exult A and B | |
|---|---|---|---|---|---|---|
| Event: N (%) | Exanta N=1526 | Warfarin N=759 | Exanta N=1151 | Warfarin N=1148 | Exanta N=2677 | Warfarin N=1907 |
| MI | 11 (0.72) | 1 (0.13) | 5 (0.43) | 3 (0.26) | 16* (0.60) | 4* (0.21) |
| Other CAD (Angina/ischemia) | 3 (0.2) | 0 | 1 (0.17) | 1 (0.09) | 4 (0.15) | 1 (0.05) |
| Total | 14 (0.92) | 1 (0.13) | 6 (0.7) | 4 (0.35) | 20** (0.75) | 5** (0.26) |

*p=0.04951; ** p=0.02800

#Excluded 4 patients who did not take study medications, 3 in ximelagatran group (ID: #3206, #7086 and #10944) and 1 in warfarin group (ID: #9089) whose death was also adjudicated by the central adjudication committee as PE.

##one case of sudden death (#15016) in the warfarin group was included as MI and two cases of sudden deaths in the Exanta group (ID: #14366 and 12122) were excluded from the analysis.

Summarized from Module 5, vol. 1 Table 54 and vol. 2 Table 11.3.5.1; vol. 3 Table 55 and vol. 4 Table 11.3.5.1

[Source: Ximelagatran Clinical Review, Table 12]

In the SPORTIF trials, a relationship between ximelagatran and cardiac events was not clearly seen. In contrast, to the VTE trials, the mean duration of use of ximelagatran was upwards of a year in the SPORTIF trials (phase 3 studies of ximelagatran for the prevention of stroke and systemic embolism events in patients with atrial fibrillation). The discrepancies in MI findings were discussed on page 1. The table below also shows a numerically greater number of serious cardiac adverse events in the ximelagatran compared to warfarin arm in SPORTIF III; a finding not seen in SPORTIF V.

**Table 9. Cardiac adverse events in SPORTIF trials**

| | SPORTIF III | | SPORTIF V | |
|---|---|---|---|---|
| | Ximelagatran N=1698 | Warfarin N=1699 | Ximelagatran N=1953 | Warfarin N=1953 |
| MI as AE leading to death | 10 | 3 | 26 | 31 |
| MI as SAE not leading to death | 25 | 14 | 39 | 48 |
| Angina Pectoris as SAE not leading to death | 26 | 36 | 34 | 44 |
| Coronary artery disorder as SAE not leading to death | 6 | 6 | 20 | 15 |

[Source: FDA Clinical Review Ximelagatran for atrial fibrillation]

Numbers represent number of events; AE terms as reported in Review

The findings in ESTEEM, a phase 2 study comparing 6 months of treatment with ximelagatran (4 doses) against placebo in the long-term treatment of patients who had recently been admitted for ST-segment elevation or non-ST-segment myocardial infarction (MI), did not suggest adverse cardiac effects of ximelagatran in this population. In ESTEEM, no increased incidence of MI's was seen in ximelagatran compared to placebo-treated subjects; in fact the numerical imbalance in MI events suggested possible favorable effects of ximelagatran on secondary prevention.

**RE-LY trial**

*Definition of myocardial infarction*

**Table 10. Definition of myocardial infarction in RE-LY**

| **Efficacy outcome** | **Definition** |
|---|---|
| Myocardial infarction | Depending on whether or not PCI or CABG has been performed, a myocardial infarction (MI) was defined as**:**<br>a. In subjects not undergoing PCI or CABG, at least 2 of the following 3 criteria had to be present:<br>i. Typical prolonged severe chest pain or related symptoms or signs (e.g., ST-changes of T-wave inversion in the ECG) suggestive of MI.<br>ii. Elevation of troponin or CK-MB to more than the upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level.<br>iii. New significant Q-waves in at least 2 adjacent ECG leads.<br>b. After PCI (within 24 h): Elevation of troponin or CK-MB to more than 3xULN or, if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.<br>c. After CABG (within 72 h): Elevation of CK-MB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.<br>d. Silent MI: retrospectively diagnosed by the appearance of significant new Q-waves between study visits. (In such cases, the date of the event was to be recorded as the midpoint between the 2 study visits)<br>e. Demonstrated by autopsy |

Additional notes: Total CK could be used if CK-MB unavailable; significant Q-waves were defined as a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads.

**Quality Control Roadmap checks for MI**

This process has been described in the clinical review (Section 3.1, Submission quality and integrity). Checks specific to MI included comparison of the MI Case Report Form (CRF) to the adjudication page, a keyword search on various CRFs (i.e., serious adverse events, hospitalization, etc.), and a check for new pathological Q-waves on the study termination CRF.

The silent MI cases were reviewed by “qualified and specially trained clinical monitors”. Cases with obvious symptoms or other indicators of an MI were forwarded from the data center to the clinical site for confirmation/rejection of an event. All re-assessed cases received from the sites as confirmed events were sent to adjudication. Cases with no site response were also sent for adjudication. For silent MIs, the ECG traces were sent straight to adjudication.

Adjudication was done as previously described in the clinical review. All available ECGs were blindly adjudicated by at least two independent cardiologists. The diagnosis of silent MI was based on the study definition.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22512 | ORIG-1 | BOEHRINGER INGELHEIM PHARMACEUTICALS INC | PRADAXA (DABIGATRAN ETEXILATE MESYLATE) |

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BACH N BEASLEY
09/02/2010

# CLINICAL REVIEW

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|---|---|
| Application Type | NDA |
| Application Number(s) | 022-512 |
| Priority or Standard | Priority |
| Submit Date(s) | December 15, 2009 (Initial)<br>April 19, 2010 (Resubmission) |
| Received Date(s) | As above |
| PDUFA Goal Date | October 19, 2010 |
| Division / Office | Cardiovascular and Renal Products/ODE1 |
| Reviewer Name(s) | Nhi Beasley (Safety)<br>Aliza Thompson (Efficacy) |
| Review Completion Date | August 25, 2010 |
| Established Name | Dabigatran |
| (Proposed) Trade Name | Pradaxa |
| Therapeutic Class | Anticoagulant |
| Applicant | Boehringer-Ingelheim |
| Formulation(s) | Oral |
| Dosing Regimen | 110 and 150 mg BID |
| Indication(s) | Prevention of stroke and systemic embolism in atrial fibrillation |
| Intended Population(s) | Adults |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Dabigatran should be approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The 150 mg dose of dabigatran should be approved but not the 110 mg dose. A superiority claim over warfarin should not be granted.

## 1.2 Risk Benefit Assessment

*Reviewer's comment: This section focuses on key analyses related to net benefit. A more thorough discussion of RE-LY's efficacy and safety findings, the adequacy of anticoagulation in the warfarin arm, the PROBE design and effects on mortality can be found in the Reviews of Efficacy and Safety (Sections 6 and 7, respectively).*

Dabigatran etexilate is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), randomized, non-inferiority study of unblinded warfarin administration and blinded administration of two doses of dabigatran (110 mg and 150 mg). RE-LY's primary endpoint was a composite of adjudicated stroke and systemic embolism. The sponsor's primary analysis, conducted on the ITT population, established efficacy. Compared to warfarin treated subjects, the HR was 0.66 (95% CI 0.53 to 0.82, p<0.003 for superiority) in the dabigatran 150 arm and 0.91 (95% CI 0.74 to 1.11, p<0.0001 for non-inferiority) in the 110 arm.

Bleeding was the only important safety concern that we identified in RE-LY. Relative to warfarin, dabigatran 150 mg was not associated with an increased risk of adjudicated major bleeds (HR of 0.93, 95% CI 0.81, 1.07) whereas dabigatran 110 mg was associated with fewer major bleeding events (HR of 0.80, 95% CI 0.68, 0.90, p<0.003).[1] How a major bleed, as defined in RE-LY (see table below), compares in clinical significance to a stroke is questionable. To assess the net benefit of dabigatran (relative to warfarin, and the two doses relative to one another), a finer classification of both types of events is perhaps needed.

The sponsor defined subtypes of adjudicated bleeding and stroke events (e.g., life threatening bleeds, GUSTO-severe, intracranial hemorrhage [ICH], disabling and fatal strokes) using information submitted by investigators. There are limitations to this approach. Investigators may not have uniformly applied or reported the necessary

1 The RE-LY definition of major bleed is the same as ISTH (International Society on Thrombosis and Haemostasis).

information to create the classification. For example, Rankin scores[2], used to define the severity of a stroke, were not consistently reported by site investigators. It is also not clear how investigators defined a symptomatic bleed or whether or not investigators used similar criteria. Such limitations impose a level of imprecision on the analyses of net benefit that follow and future development programs should perhaps strive to implement a more uniform and formal process for identifying those events of greatest clinical importance.

**Table 1. Definitions of terms**

| Term | Definition |
|---|---|
| Adjudicated major bleed | Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding) |
| Adjudicated life-threatening bleed (sub classification of major bleed) | An adjudicated major bleed meeting at least one of the following criteria: fatal; symptomatic intracranial bleed; reduction in hemoglobin of at least 5 grams per deciliter; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; required surgical intervention |
| GUSTO severe | An adjudicated ICH event; An adjudicated major bleed with at least one of the following criteria: associated with hypotension requiring use of intravenous inotropic agents; required surgical intervention to stop bleeding |
| ICH | Includes adjudicated hemorrhagic stroke or adjudicated major bleed that was symptomatic intracranial |
| Adjudicated fatal or disabling stroke | Adjudicated stroke with initial Rankin* score of 3 or greater |

*The Rankin scale runs from no symptoms (0) to death (6). A Rankin score of 3 represents moderate disability (requires some help, but able to walk unassisted); a copy of the scale is provided in the appendix.

In the analyses of "net benefit" shown below, dabigatran's effects on various composite endpoints (composites of different types of bleeding, stroke and non-CNS systemic embolism events) were explored. These composite endpoint analyses suggest a favorable profile for dabigatran relative to warfarin. With respect to the two doses of dabigatran, no clear and consistent differences are seen between the 150 mg and 110

2 The reported Rankin scores in this review are based on the Modified Rankin Scale; an overview of this scale can be found in the appendix.

mg dose using these definitions of "net benefit". As shown below, net benefit does not strongly or consistently favor one or the other dabigatran arm; the confidence intervals for the 150 mg to 110 mg comparisons are also, for the most part, broad and cross one, raising questions about which dabigatran dose better balances safety against efficacy.

**Table 2. Analyses of net benefit**

| **Net Benefit** | | **D110 vs. warfarin** | **D150 vs. warfarin** | **D150 vs. D110** |
|---|---|---|---|---|
| Adjudicated life threatening bleed or stroke/SEE | HR | 0.82 | 0.77 | 0.94 |
| | 95% CI | 0.71, 0.96 | 0.66, 0.90 | 0.80, 1.11 |
| | p-value | 0.01 | 0.001 | 0.47 |
| Adjudicated life threatening bleed or disabling or fatal stroke | HR | 0.81 | 0.80 | 0.99 |
| | 95% CI | 0.68, 0.96 | 0.68, 0.96 | 0.83, 1.19 |
| | p-value | 0.02 | 0.01 | 0.94 |
| ICH or stroke/SEE | HR | 0.79 | 0.63 | 0.79 |
| | 95% CI | 0.66,0.96 | 0.52,0.77 | 0.64, 0.98 |
| | p-value | 0.02 | <0.0001 | 0.03 |
| ICH or disabling or fatal stroke | HR | 0.71 | 0.61 | 0.85 |
| | 95% CI | 0.56, 0.91 | 0.48, 0.78 | 0.65, 1.11 |
| | p-value | 0.006 | <0.0001 | 0.24 |
| GUSTO-severe or disabling or fatal stroke | HR | 0.74 | 0.74 | 1.00 |
| | 95% CI | 0.60,0.91 | 0.60,0.91 | 0.81,1.24 |
| | p-value | 0.0034 | 0.0035 | 0.99 |
| Major bleed or stroke/SEE | HR | 0.87 | 0.88 | 1.01 |
| | 95% CI | 0.77, 0.99 | 0.78, 1.00 | 0.89,1.15 |
| | p-value | 0.03 | 0.04 | 0.87 |

Analyses excluding SEE produced similar/near identical point estimates, 95% confidence intervals and p-values and hence are not shown.

**Table 3. Net benefit: event rate per subject-year follow-up**

| Event | D110 (n=6015) | | D150 (n=6076) | | W (n=6022) | |
|---|---|---|---|---|---|---|
| | # events | %/yr | # events | %/yr | # events | %/yr |
| Adjudicated life threatening bleed or stroke/SEE | 302 | 2.5 | 288 | 2.4 | 364 | 3.1 |
| Adjudicated life threatening bleed or disabling or fatal stroke | 233 | 2.0 | 234 | 1.9 | 285 | 2.4 |
| ICH or stroke/SEE | 195 | 1.6 | 157 | 1.3 | 243 | 2.1 |
| ICH or disabling or fatal stroke | 117 | 1.0 | 101 | 0.8 | 162 | 1.4 |
| GUSTO-severe or disabling or fatal stroke | 163 | 1.4 | 165 | 1.4 | 218 | 1.9 |
| Major bleed or stroke/SEE | 485 | 4.1 | 494 | 4.1 | 550 | 4.7 |

Annual event rate calculated using sponsor's study termination date and randomization date for all randomized subjects.

**Dose:** While the composite endpoint analyses show very similar findings for the two doses of dabigatran, these findings are reached via different pathways/effects on the bleeding vs. stroke components of the composite. The yearly event rate for all of the events shown is low and the likely imprecision in the estimate of these event rates limits conclusions about the absolute risk of one event versus another. Nonetheless, we believe these analyses suggest that the 150 mg dose provides greater net benefit than the 110 mg dose. At the 110 mg dose, the rate of important stroke events (fatal/disabling strokes) perhaps still exceeds the rates of some of the worst bleeding events (e.g., GUSTO severe bleeds and ICH). At the 150 mg dose, the point estimate for the rate of life threatening and GUSTO severe bleeds begins to meet or exceed the point estimate for the stroke rate (overall and subset adjudicated to be ischemic or of uncertain classification). At this dose, the rates of disabling and hemorrhagic strokes and ICH also move closer, suggesting that a dose greater than 150 mg might result in an increase in clinically important bleeding events that could outweigh any benefit gained from stroke reduction.

**Figure 1. Event rate per subject-year follow up**

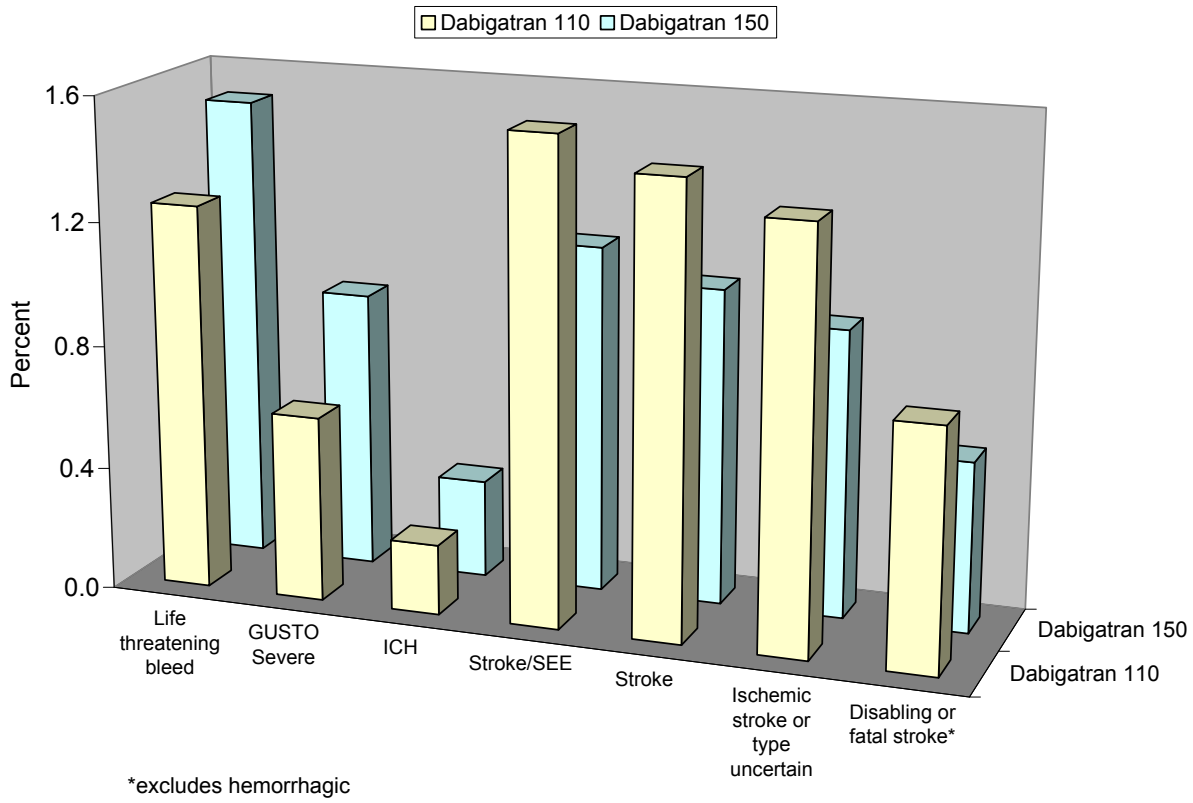


**Table 4. Event rate per subject-year follow up in dabigatran treatment arms**

| | D110 (n=6015) | | D150 (n=6076) | |
|---|---|---|---|---|
| **Event** | # events | %/yr | # events | %/yr |
| Life threatening bleed | 147 | 1.2 | 179 | 1.5 |
| GUSTO severe | 74 | 0.6 | 106 | 0.9 |
| ICH | 27 | 0.2 | 38 | 0.3 |
| Stroke/SEE | 183 | 1.5 | 134 | 1.1 |
| Stroke | 171 | 1.4 | 122 | 1.0 |
| Ischemic stroke | 152 | 1.3 | 103 | 0.9 |
| Ischemic stroke or type uncertain | 159 | 1.4 | 111 | 0.9 |
| Disabling/fatal strokes | 103 | 0.9 | 76 | 0.6 |
| Disabling /fatal strokes excluding hemorrhagic | 92 | 0.8 | 66 | 0.6 |

Annual event rate calculated using sponsor's study termination date and randomization date for all randomized subjects.

In the proposed dabigatran label, the sponsor has approached the issue of dose by recommending the 150 mg dose, adding that "For patients with a potentially higher risk

of bleeding" a dose of 110 mg "may be considered". While this approach seems reasonable, it may be problematic.

- Though subjects with moderate renal impairment (CrCl 30 -50) had high rates of major bleeds in all treatment arms of RE-LY (high relative to the rates seen in the RE-LY population as a whole), there did not appear to be a difference in the risk of major bleeds in the 150 mg treatment arm compared to the 110 mg treatment arm. In contrast, there appeared to be a greater reduction in ischemic strokes at a dose of 150 mg than 110 mg, suggesting greater net benefit from the higher dose in this population.
- Subjects 75 years of age and older are another group perceived to be at increased risk of hemorrhage; yet, in analyses of net benefit (composites of various stroke and bleeding events), no clear advantage of the 110 mg dose over the 150 mg dose was seen.[3]

In light of these findings, the merits of adjusting dabigatran dose based on perceived bleeding risk is not immediately clear to us. While one could attempt to explore this issue by performing subgroup analyses of "net-benefit" in various RE-LY subpopulations, any findings generated by such analyses may be more reflective of chance than true dose-dependent drug effects. For this reason, we are wary of including recommendations on dose adjustment based on perceived bleeding risk in the dabigatran label and recommend that only the 150 mg dose be approved.

**Efficacy vs. "Superiority":** The efficacy and safety findings of dabigatran relative to warfarin are bolstered by a dose-response relationship for both bleeding and stroke events in the blinded portion of the trial (though why such a relationship should exist given the substantial overlap in exposure at the two doses is not entirely clear). The finding of a highly statistically significant reduction in the risk of stroke/SEE (p=0.0002) in the dabigatran 150 mg arm relative to warfarin is also notable but should be considered in light of RE-LY's open label design, as well as the lack of replication. In the ximelagatran experience, the stroke and systemic thromboembolism rate was numerically lower with ximelagatran in an open-label study and numerically higher in the blinded trial; according to an analysis based on risk reduction, the open label study supported the noninferiority of ximelagatran, but the blinded study did not. Whether the discrepant study findings in the ximelagatran program should serve as an example of the limitations of open-label studies, the importance of replication, or some other issue is debatable. It does raise questions, however, about granting a superiority claim based on the results of a single, open-label study. Moreover, consideration should be given to the late date at which the statistical analysis plan was finalized (essentially after all of the study data had been amassed), as well as the factors driving the highly statistically significant p-value/finding. As shown in the table below, much of the relative risk

3 This experience is perhaps not so dissimilar to the experience in BAFTA (Mant et al., 2007), a study comparing warfarin with aspirin in patients over the age of 75. In BAFTA, warfarin was superior to aspirin in the prevention of stroke (HR of 0.52, 95% CI of 0.33 to 0.80 warfarin vs. aspirin) and yet was not clearly associated with a greater incidence of major hemorrhage (HR of 0.96, 95% CI of 0.53 to 1.75 warfarin vs. aspirin).

reduction in stroke/SEE in the 150 mg arm vs. warfarin arm (and the associated p-value) is driven by subjects at sites with poorer INR control (as defined by a center-level INR below the median). Although the findings in subjects at centers achieving levels of INR control above the median are still supportive of efficacy, they are not supportive of superiority over warfarin.[4]

**Table 4. Relative risk for stroke/SEE by center-level INR control**

| | **Center-level INR control < Median** | | **Center-level INR control ≥ Median** | |
|---|---|---|---|---|
| | D110 vs. warfarin | D150 vs. warfarin | D110 vs. warfarin | D150 vs. warfarin |
| HR | 0.86 | 0.57 | 0.96 | 0.77 |
| 95% CI | 0.66, 1.12 | 0.42, 0.76 | 0.71, 1.30 | 0.56, 1.06 |
| p-value | 0.26 | 0.0002 | 0.78 | 0.10 |

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor has proposed a REMS to mitigate the bleeding risk of dabigatran. The proposed REMS elements include a Medication Guide, Dear Health Care Professional Letter and Prescriber Brochure; these elements seem appropriate. In addition to a general discussion on the risk of bleeding, more specific topics that should be addressed in the REMS (Medication Guide, Dear Health Care Professional Letter and/or Prescriber Brochure) include:

- important issues impacted by dabigatran's short half life (relative to warfarin): the importance of patient compliance, what to do if a dose is missed, transitioning to and from dabigatran to warfarin/other anticoagulants, and the use/holding of medication in the peri-procedural/operative period;
- the effect of renal function on drug elimination (and how this impacts the use/holding of medication in the peri-procedural/operative period);
- the risk of gastrointestinal bleeding;
- use with antiplatelet agents;
- the performance of available assays in measuring the anticoagulant activity of dabigatran

The pharmacology-toxicology review has not yet been finalized. At this time, a concern has been raised for potential embryo toxicant effects in the clinical setting (based on findings in a rat study). This issue may also need to be addressed within the proposed REMS elements.

4 For further explanation of center-level based INR analyses as well as a discussion of the impact of center-level INR control on the treatment benefit of oral anticoagulant therapy, see the appendix.

### 1.4 Recommendations for Postmarket Requirements and Commitments

1. The mechanism behind the increased risk of gastrointestinal bleeding as well as measures that can mitigate this risk need further study.

2. In contrast to warfarin, effective interventions to stop dabigatran-related hemorrhage have not been established. Further studies should be done to determine the measures that physicians should take to stop bleeding in dabigatran treated subjects.

Postmarketing clinical studies may or may not be necessary to address the aforementioned concerns; if informative data can be obtained via *in vitro or* preclinical studies and/or post-hoc analyses of available clinical data, then this route should be pursued.

Finally, subjects with marked renal impairment (CrCl <30) were excluded from RE-LY. Whether or not further studies should be required in this populations (and if so, what types of studies) merits further discussion.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Dabigatran etexilate mesylate (proposed trade name Pradaxa) is an orally available, reversible, direct thrombin inhibitor and NME with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The chemical structure of dabigatran etexilate mesylate and an overview of key product attributes are provided below.

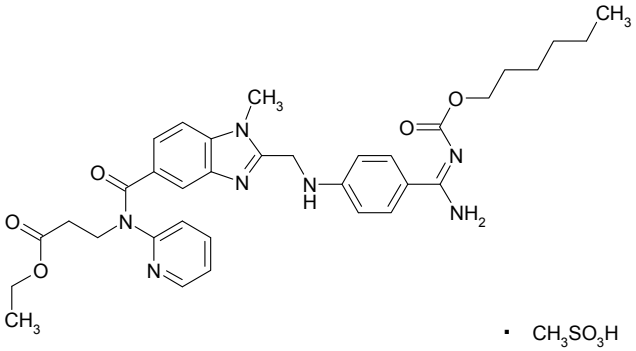


**Figure 1. Chemical structure dabigatran etexilate mesylate**

**Table 5. Dabigatran etexilate mesylate product information**

| Attribute | Description |
|---|---|
| Chemical Name | β-Alanine, N-[[2-[[[(hexyloxy)carbonyl]4-amino] iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methane-sulfonate |
| Appearance | Dabigatran etexilate mesylate is a yellow-white to yellow powder |
| Molecular Formula | $C_{35}H_{45}N_7O_8S$ [molecular weight: 723.86 (mesylate salt), 627.75 (free base)] |
| Dosing Regimen | 150 mg taken orally, twice daily; for patients "with a potentially higher risk of bleeding," a dose of 110 mg taken orally, twice daily "may be considered" |
| Proposed Age Group | Adults |

## 2.2 Tables of Currently Available Treatments for Proposed Indication

Atrial fibrillation is thought to affect approximately 2.3 million patients in North America and embolic events, primarily strokes, are an important complication of this condition. Warfarin, a vitamin K antagonist and antithrombotic agent, is approved in the United States for the prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation. Six trials, five primary prevention and one secondary prevention, are widely referenced as establishing the efficacy of warfarin in preventing ischemic strokes in patients with atrial fibrillation (see appendix). A meta-analysis of these trials suggests that warfarin reduces the relative risk of ischemic stroke by 67% (95% CI, 54% to 77%). Though these trials clearly establish warfarin's efficacy, the safe and effective use of warfarin is limited by dietary and drug interactions and intersubject variability in exposure. Frequent blood test (INR) monitoring is needed and bleeding remains an important complication of therapy.

## 2.3 Availability of Proposed Active Ingredient in the United States

Dabigatran is not currently approved in the United States. Dabigatran was approved by the EMEA (EMA) in 2008 for the primary prevention of venous thromboembolic events in adults after elective total hip or knee replacement surgery.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Dabigatran is a direct thrombin inhibitor. Approved direct thrombin inhibitors (all parenteral) include hirudin, argatroban, bivalirudin and desirudin. These agents are approved as anticoagulants for a variety of different conditions (e.g., bivalirudin for use in patients with unstable angina undergoing percutaneous intervention; desirudin as prophylaxis against deep venous thrombosis in hip replacement). Like other anticoagulants, an important safety concern with the use of these drugs is bleeding.

Ximelagatran, an oral member of this class, was also associated with hepatotoxicity, and a possible increased risk of serious coronary events, and was not approved in the United States. Bleeding and hepatotoxicity are discussed further in the review of safety.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

**Table 6. Regulatory advice**

| Source (date of meeting or submission) | Advice from Agency |
|---|---|
| Meeting Minutes Type C Guidance Meeting (March 24, 2005) | • non-inferiority must be attained with optimal warfarin control<br>• large safety database needed to address liver toxicity<br>• single-dose strategy questioned (as opposed to having a parameter measurement and adjusting dose)<br>• concern raised for ascertainment bias in identification of potential endpoint events given open-label nature of study |
| SPA response (July 11, 2005) | • double-blind trial preferred; more detail regarding why blinding was not feasible should be provided<br>• warfarin control achieved in the proposed trial would need to be as good as that achieved in the historical warfarin trials; instructed to perform sensitivity analyses (for both efficacy and safety) including only warfarin patients for whom the monitoring and dosage adjustment matched “minimal specifications”<br>• doses studied should be more widely spaced, and dose adjustment should be made based on renal function |
| Type C Guidance Meeting (August 18, 2008) | • late change to the SAP proposed by sponsor: testing for superiority in anticoagulant naïve patients and analysis pooling doses to test for superiority<br>• Agency expressed significant concerns about the changes given the amount of information that was available to influence the decision to alter the statistical analysis plan<br>• Agency reiterated that 1.38 was the recommended margin for non-inferiority |
| Type C Guidance Meeting (August 17, 2009) | • NDA should be submitted for rolling review; priority review was likely |

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

*Refuse to File*
On December 15, 2009, the NDA for dabigatran was filed; on February 12, 2010, following several discussions with the sponsor regarding data integrity issues, the Agency issued a refuse to file letter. While the sponsor claimed an overall data error rate of 0.1% or less for primary outcome data and 0.25% or less for all other data, during the clinical review, a number of obvious and easily identified errors were found in data sets felt by the review team to be important for establishing dabigatran's efficacy and safety. The frequency and relative ease with which these errors were identified raised questions about the true error rate in the submitted data and undermined reviewer confidence in the data. These errors were found in two data sets examined early in the review: a data set containing information on INR and warfarin dosing and one containing information on blood transfusions (felt to be critical by the review team as the sponsor's definition of a "major bleed" was based in part on the number of units of blood transfused). With regard to the INR data, transcription, transposition and auditing errors were found in reported INR values and/or warfarin dose. The blood transfusion data set contained inaccurate data on the number of transfusions received. For example, the data set incorrectly reported that three subjects received 92 U, 82 U and 62 U, respectively, of a blood product in one day when these subjects had in fact received 2 U each. The errors were thought to stem in part from the use of optical character recognition (OCR) without a subsequent check of the scanned data (such errors occurred in both data sets). The second type of error (found in the INR data set) was a type of error that could have been detected by auditing/performing additional checks of the data. A transposition error had been made by the clinical site whereby the warfarin doses had clearly been transposed with the INR values.

As a result of the refuse to file letter and following agreement with the review team on a plan, the sponsor engaged in additional data quality checks to establish the integrity of the submitted data. These cross-checks focused on data critical for the establishment of efficacy and safety and included: cross-checks of different case report forms for possible inconsistencies in reporting outcome events; plausibility and range checks of particular CRFs; and sampling checks to evaluate the accuracy of the optical character recognition (OCR) process originally used to capture the data, including double-data entry of particular CRF pages. According to the sponsor, all SAE narratives were also reviewed for potential endpoint events.

According to the sponsor, these checks identified 3848 findings in 3054 subjects requiring further review. These events were reviewed by unblinded "Tier 1" reviewers who were instructed to look for evidence of an unreported outcome event in the materials provided (CRFs, narrative, adjudication documents of other events). If there was additional evidence of an outcome event, or if the reviewer suspected an event

based on the clinical course of the subject or some other evidence, the case was escalated as a possible outcome event. Unblinded Tier 2 reviewers, individuals involved with RE-LY or familiar with the trial, reviewed the escalated cases and decided whether or not the event should be pursued as a potential outcome event (i.e., sent to the data center for distribution to the site). Additional events were identified via unblinded Tier 2 reviewer over-reads of a subset of events not escalated by Tier 1 reviewers.

*Reviewer's comment: How the subset of events were selected for over-read is not clear. According to the April 19, 2010 resubmission (page 33), "This over-read looked at a minimum of 10% of negative cases from each Tier 1 reviewer, trying to select representative cases. In addition, the Tier 2 reviewers examined additional negative cases from Tier 1 reviewers who, in their judgment, may not have been consistent in their application of the review guidelines."*

Events of interest identified by Tier 2 reviewers were sent to the data center for verification that the event had not been previously reported. Cases that had not been previously reported were sent to the study site for review. Sites were to indicate if an event had occurred. Events confirmed by the study site (and also events at sites that did not respond to the inquiry) were sent for adjudication. The adjudication process was similar to that used in the original protocol- adjudication was to be conducted by two reviewers blinded to treatment assignment with a third reviewer used when the initial reviewers disagreed. An overview of the process implemented by the sponsor as well as the number of potential events identified/escalated at each stage of the review is shown in the figure and table below. Across the treatment arms, a similar proportion of events were escalated at each stage of the review.

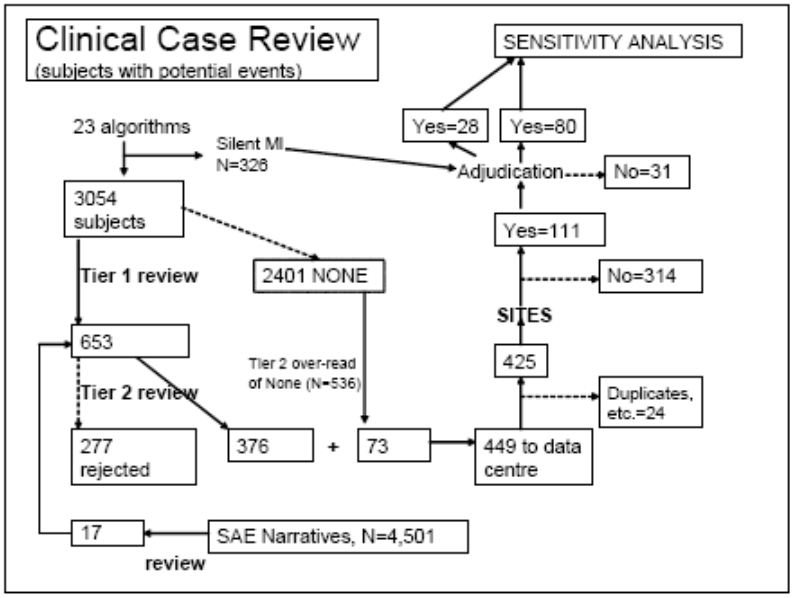


**Figure 2. Overview of dataflow for subjects with potential events**

[Source: Sponsor Information Amendment dated April 19, 2010, Figure 4.1.1]

**Table 7. Numbers of subjects identified by quality checks**

| | DE 110mg bid N (%) | DE 150 mg bid N(%) | Warfarin N(%) | Total N(%) |
|---|---|---|---|---|
| Reviewed by Tier 1 | 986 (100.0) | 1039 (100.0) | 1029 (100.0) | 3054 (100.0) |
| Reviewed by Tier 2 | 377 (38.2) | 406 (39.1) | 406 (39.5) | 1189 (38.9) |
| Submitted to Data Center | 147 (14.9) | 158 (15.2) | 144 (14.0) | 449 (14.7) |
| Submitted to Site | 135 (13.7) | 153 (14.7) | 137 (13.3) | 425 (13.9) |
| Submitted to Adjudication | 31 (3.1) | 39 (3.8) | 41 (4.0) | 111 (3.6) |
| Adjudicated Subjects with Outcome Events | 22 (2.2) | 29 (2.8) | 29 (2.8) | 80(2.6) |

[Source: Sponsor Information Amendment dated April 19, 2010, Table 4.1.7]

An overview of the adjudicated events by treatment arm is shown in the sponsor's table below. Few additional efficacy endpoint events were reported. Of the 68 newly identified adjudicated major bleeds, 32 were identified by programmed checks of hemoglobin drops of > 2 g/dL, 19 were identified by programmed checks of the blood transfusion data, 11 were identified by programmed checks comparing AE terms to potential outcome event terms, three were identified by a free text search of reported admission reasons, and three were identified by other checks.

**Table 8. Additional outcome events identified by quality checks**

| | **DE 110 N** | **DE 150 N(%)** | **Warfarin N(%)** | **Total N(%)** |
|---|---|---|---|---|
| Stroke | 0 | 0 | 1 | 1 |
| SEE | 0 | 0 | 1 | 1 |
| Death | 0 | 0 | 0 | 0 |
| TIA | 3 | 1 | 1 | 5 |
| MI | 1 | 0 | 3 | 4 |
| PE | 0 | 0 | 1 | 1 |
| Major Bleed | 18 | 28 | 22 | 68 |
| **Subtotal Subjects** | **22** | **29** | **29** | **80** |
| Silent MI | 11 | 8 | 9 | 28 |
| **Total Subjects** | **33** | **37** | **38** | **108** |

[Source: Sponsor Information Amendment dated April 19, 2010, Table 1.1]

With regard to the INR and warfarin dose data, these dose were manually reentered; the error rate in the originally submitted data was found to be ~2%. As a result of the manual re-entry process, a total of 3,743 of 174,773 dose values changed and 3,856 of 175,190 INR values changed. Forty-seven records were added and 59 records were removed.

*Reviewer's comment: Tier 1 and 2 reviewers were unblinded to treatment assignment and some Tier 2 reviewers were "involved with RE-LY" and hence ascertainment bias is possible. Throughout the subsequent FDA Clinical Review, numerous checks were done, comparing the information reported in key resubmitted data sets to the CRF documents themselves. With the exception of errors in the disposition data (see Section*

*6.1.3), the data contained in the resubmitted data sets appear to match the data contained in the CRFs. Hence, at this time, we think the data are of sufficient quality to allow substantive review. Whether or not there were additional events that were not reported by investigators is an issue that the DSI audits will address.*

## 3.2 Compliance with Good Clinical Practices

*See also discussion under section 3.1.*

*Sites closed for cause by the sponsor*
According to the sponsor, eight RE-LY study sites were closed for cause; these sites randomized a total of 166 subjects. At this time, DSI has inspected seven of these sites and recommended that data from a total of 43 subjects not be used to support the application. The inspection did not support the sponsor's allegation at one site (251). According to the TSAP events, events occurring at these sites prior to study site closure (defined as the date the site was notified of closure) are included in efficacy analyses (page 22 of TSAP). Subjects at sites closed for cause were not followed up for vital status.

**Table 9. Sites closed for cause by sponsor**

| Site | Subjects (screened/ randomized) | DSI findings |
|---|---|---|
| 108 | 41/31 | OAI (letter/inspection findings pending) |
| 128 | 8/6 | Inspection confirmed sponsor's allegations; DSI recommended exclusion of subject 002 (no evidence AF on ECG) |
| 146 | 10/4 | NAI; Though site closed for lack of clinical investigator involvement in study, protocol violations and consent irregularities (IRB had withdrawn approval prior to sponsor site closure), inspection found that there had been substantial efforts to reconcile deficiencies and respond to queries |
| 354 | 7/7 | VAI: Investigator failed to maintain adequate case histories; data may be used to support application |
| 251 | 68/52 | VAI: Inspection did not support sponsor's allegations; data may be used to support application |
| 265 | 60/37 | OAI: Warning letter; data should not be used to support application |
| 276 | 7/5 | OAI: Warning letter; data should not be used to support application |
| 6 | 27/24 | Confirmed sponsor allegations for GCP violations, and resulting site closure |

With regard to site 251, the sponsor alleged that their audit revealed missing or inconsistent study data and source documentation, protocol violations

(inclusion/exclusion criteria) and patient safety related issues including failure to report SAE and non-serious events to the sponsor, INR monitoring, patients bleeds and drug accountability issues (several subjects took drug beyond the expiration date). According to what was written in the EIR by the field investigators, the inspection found "no evidence to support the sponsor's allegations," despite inspection of documents for all 52 randomized subjects.

The table below shows the number of discontinuations, primary endpoint events, deaths and SAEs reported at site 251. The TTR reported at site 251 was 64.9%.

**Table 10. Events at site 251**

| | Number (%) with event | | |
|---|---|---|---|
| | **Dabigatran 110 (N=17)** | **Dabigatran 150 (N=17)** | **Warfarin (N=18)** |
| Discontinuations | 4 | 6 | 7 |
| Stroke or SEE | 0 | 1 | 0 |
| Death | 1 | 0 | 0 |
| SAE | 14 | 0 | 4 |

Regarding "test article accountability," the DSI inspector at site 251 also commented that documentation left on site by the sponsor monitors was "inadequate, inaccurate and much of it was illegible." DSI plans to investigate the issue further with an audit of the sponsor/monitor and will also obtain additional data during their clinical investigator site audits.

*Other sites for which DSI received complaints*
In addition to the sites closed for cause by the sponsor, DSI received complaints for an additional three sites; information regarding two of these sites is provided in the table below. The third complaint was a notification from the sponsor: a Clinical Investigator had informed the sponsor that a study coordinator at his site had used a professional license and CV that belonged to somebody else.

**Table 11. Sites for which DSI received complaints**

| **Principle Investigator** | **Site** | **Subjects (screened/ randomized)** | **DSI findings** |
|---|---|---|---|
| (b) (6) | | 10/9 | (b) (6) |
| Pilcher, George | 232 | 44/43 | VAI (data can be used in support of application) |

*Sites selected for audit following NDA submission*
Six investigator sites were selected for audit; four foreign and three in the United States. A for-cause inspection was conducted at an additional site (Tonkin, site 351). No deficiencies were noted by the field investigator at the Ezekowitz site (site 32). A VAI was issued at the Tonkin site which had enrolled 5 subjects; it was concluded that the data could be used to support the application. At this time, no other inspection reports have been finalized. In addition to these sites, audits of the sponsor and academic research organization are also planned.

*Reviewer's comment: The inspections have not yet been completed; however at this time, results of DSI audits suggest that there was compliance with good clinical practices and the trials were conducted in accordance with accepted ethical standards.*

### 3.3 Financial Disclosures

Fourteen investigators enrolling subjects from 13 clinical sites were listed as holding financial interests requiring disclosure; all reported significant payments with a cumulative monetary value of $25,000 or more made by the sponsor to the investigator or investigator's institution exclusive of the costs of conducting the clinical study. Collectively, these sites enrolled 418 subjects (2.3% of subjects) and accounted for 2.5% of adjudicated primary endpoint events (stroke or SEE) and 3.5% of deaths. One of 13 sites at which investigators were reported to hold financial interests requiring disclosure was selected for audit.

*Reviewer's comment: The applicant has adequately disclosed financial arrangements. These arrangements do not raise questions about the integrity of the data.*

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Minor CMC issues have been communicated to the sponsor, however no significant efficacy or safety issues have been identified at this time. See section 2.1 for an overview of the drug substance/product.

### 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

Dr. Harlow's draft review dated August 12, 2010, judged dabigatran approvable from a nonclinical perspective. Most of the observed toxicities were attributable to the pharmacodynamic effect of dabigatran or its active metabolite (e.g., decreases in hemoglobin, hematocrit and red blood cells). Other notable findings:

- In rat studies, dabigatran acted as an embryo toxicant. Dabigatran decreased the number of implantations, decreased the number of viable fetuses, increased the resorption rate, increased the post-implantation loss, and increased the number of dead offspring when given at doses of 70 mg/kg (about 2.3 times the MRHD of 300 mg/day on a mg/$m^2$ basis) to female rats prior to mating to implantation, from implantation to the end of organogenesis, and from implantation to weaning. Dr. Harlow has recommended specific language for describing these effects in the label.

- Dabigatran was not carcinogenic in mice and rats (doses were 3.2, and 6.5 times the MRHD) for up to two years, however an increased incidence of liver necrosis in all treated groups was observed in the rat carcinogenicity study. This was seen after a lifetime of treatment and without an accompanying increase in liver tests (AST/ALT). In contrast, no liver necrosis was observed in the 26- or 52-week monkey studies.

*Reviewer's comment: The clinical significance of the liver findings in the rat carcinogenicity studies is unclear.*

## 4.4 Clinical Pharmacology

No significant efficacy or safety issues have been identified at this time. Key pharmacodynamic and pharmacokinetic characteristics are described below. For a more comprehensive overview, see the Clinical Pharmacology Review.

### 4.4.1 Mechanism of Action

Dabigatran etexilate, a prodrug, is converted to dabigatran, the active metabolite. Dabigatran is a direct thrombin inhibitor that reversibly inhibits fibrin-bound thrombin, free circulating thrombin and thrombin-induced platelet aggregation.

### 4.4.2 Pharmacodynamics

The relationship between dabigatran plasma concentration and various pharmacodynamic markers in healthy subjects is shown in the sponsor's figure below. Of these tests, ecarin clotting time (ECT) values appear to correlate best with plasma concentrations; ECT appears to be linearly related to dabigatran concentration and

does not appear to reach a maximum/plateau at higher concentrations

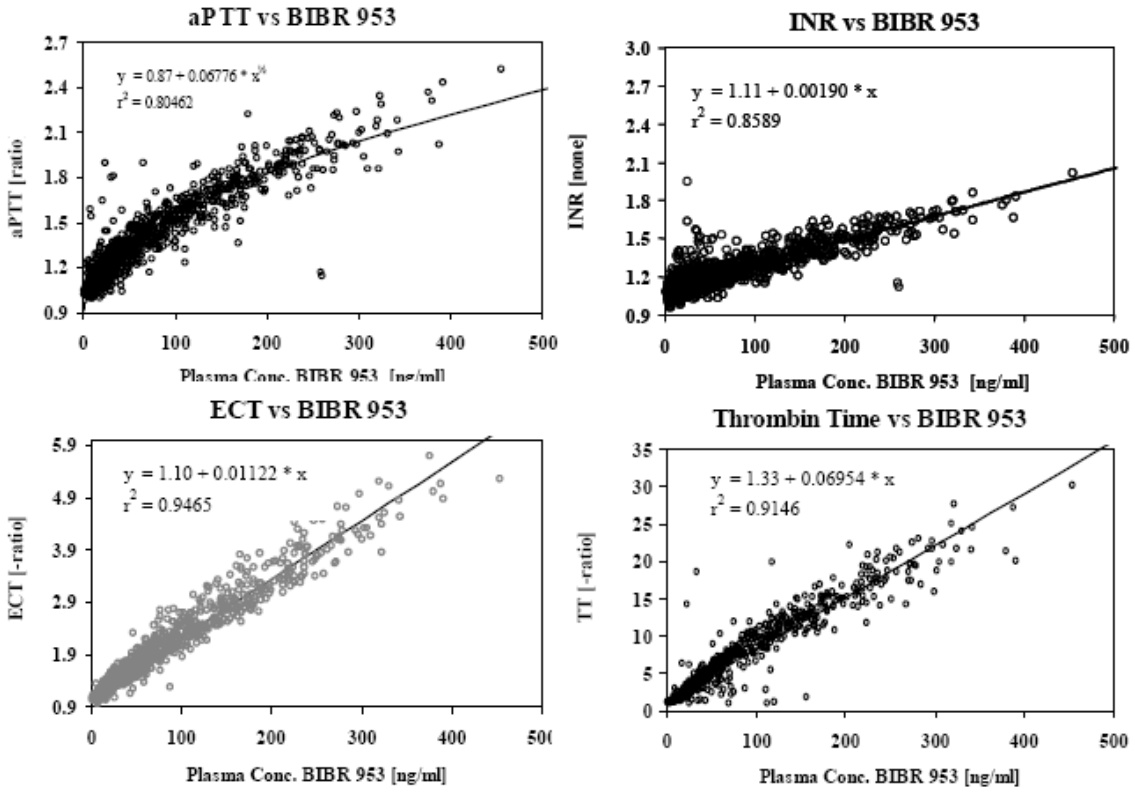


**Figure 3. Relationship between dabigatran (BIBR 953) concentration and aPTT, ECT, Thrombin time, and INR**

[Source: Sponsor's Clinical Overview (module 2): Figure 2.5.3.2:1]

APTT and ECT were measured in RE-LY at one month post randomization in dabigatran subjects. While both APTT and ECT were significant predictors of life-threatening bleeds (see next figure), ECT performed better overall.

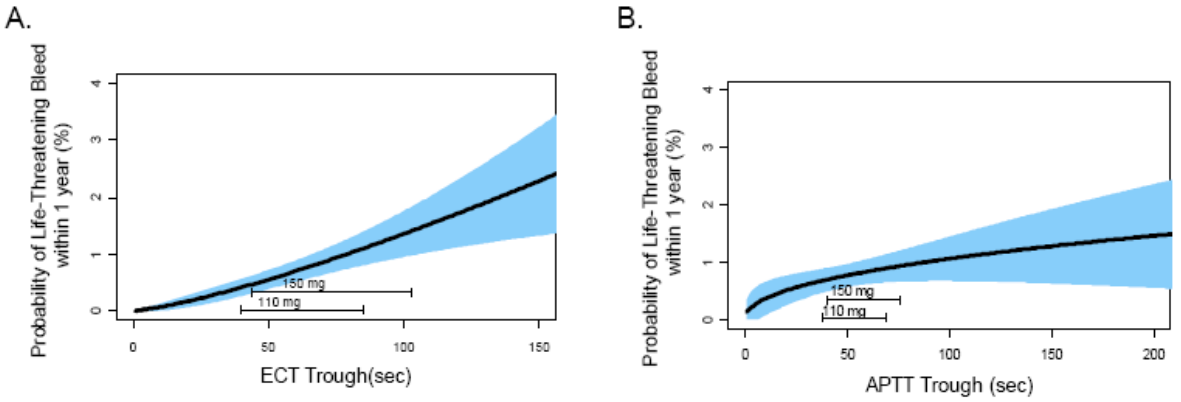


**Figure 4. ECT and APTT and the probability of a life-threatening bleed within 1 year in RE-LY**

[Source: Email correspondence from Dr. Krudys FDA Pharmacometrics Reviewer]
The shaded region represents the 95% CI; the bars on the bottom of the plot region represent the 10th to 90th percentiles of observed dabigatran predose concentrations in the RE-LY trial.

*Reviewer's comment: Of the assays studied, ECT appears to be the best marker of bleeding risk and ECT should be recommended for monitoring the anticoagulant activity of dabigatran. Ecarin chromogenic assays (ECA) have also been developed and, based on a preliminary review of the literature, may also be suitable[5].*

### 4.4.3 Pharmacokinetics

Renal function appears to be the most important parameter influencing the pharmacokinetics of dabigatran. In a Phase I study, exposure levels were ~3-fold higher in moderate renal impairment (CrCl 30 - < 50 mol/min) compared to normal renal function (> 80 mol/min). The difference between these two classes was ~2.3-fold in RE-LY. In subjects with severe renal impairment (CrCl <30 mol/min), the mean AUC of dabigatran was increased ~6.3 compared to normal renal function.

Key pharmacokinetic attributes are summarized in the next table.

5 An ecarin chromogenic assay, in which ecarin is added to a plasma sample and meizothrombin generation is measured using a chromagenic substrate, has been used to measure the anticoagulant activity of direct thrombin inhibitors and, according to some literature, may offer advantages over ECT (Lange et al., 2004).

**Table 12. Key pharmacokinetic attributes**

| Parameter | Comments |
|---|---|
| Bioavailability | 3 to 7%, pH dependent |
| Cmax and AUC | Cmax obtained 0.5 to 2.0 hours post administration; dose proportional increase in Cmax and AUC (after single oral doses from 10 to 400 mg); average ratio of accumulation of 150 mg dose with repeated dosing 1.4 and 1.3-fold for AUC and Cmax, respectively; after repeated dosing, steady state reached by Day 3 of treatment |
| High Fat Meal | No effect on bioavailability, delayed time to peak plasma concentration (~2 hrs) |
| Distribution | 34-35% plasma protein binding; volume of distribution 60-70 L |
| Elimination | Primarily renal (85% urine), eliminated primarily unchanged at a rate of ~100 mol/min; ½ life ~10-11 hrs; ~15 and ~18 hours in mild and moderate renal impairment respectively; ½ life is independent of dose; 61 to 68% of systemic dabigatran removed by dialysis |
| Metabolism | Dabigatran etexilate rapidly converted to dabigatran (active form) by esterase catalyzed hydrolysis; neither dabigatran etexilate nor dabigatran are metabolized by the cytochrome P450 system. Dabigatran etexilate (but not dabigatran) is a substrate for the efflux transporter protein p-glycoprotein. |

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

According to the sponsor, dabigatran has been studied in 40 phase I studies, six completed phase 2 studies and four completed phase 3 trials. These studies were conducted either as part of the atrial fibrillation development program or for other indications. An overview of phase 2 studies conducted in patients with atrial fibrillation is provided in section 6.1.8. RE-LY, a phase 3 trial conducted in support of the proposed indication, is discussed in section 5.3. RE-LY-ABLE, a long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial, is currently underway and is not described further in this review.

## 5.2 Review Strategy

The Clinical Review focused on the design and conduct of RE-LY and the resulting data. Efficacy was reviewed by Dr. Thompson; Safety was addressed by Dr. Beasley.

## 5.3 Discussion of Individual Studies/Clinical Trials

In support of the proposed indication, the sponsor conducted a single phase 3 trial titled "Randomized Evaluation of Long term anticoagulant therapy comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY)." An overview of the study protocol, as laid out in the sponsor's finalized protocol dated September 12, 2005 is provided below. Important revisions enacted by protocol amendments accompany the relevant sections of text; these amendments are also summarized at the end of this section.

*RE-LY Overview*

### 5.3.1 Study Design and Objectives

RE-LY was a randomized, active controlled, multi-center, non-inferiority study of open-label warfarin administration and blinded dabigatran administration at two doses (110 and 150 mg). RE-LY was an event-driven trial and the stated primary objective was to demonstrate the efficacy and safety of dabigatran in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism.

### 5.3.2 Study Duration/Dates

December 22, 2005 to March 15, 2009 (Final close out visit period- December 16, 2008 to March 15, 2009, visits 1-3 months earlier also accepted as normal study closeout)

### 5.3.3 Study Sample Size and Power Considerations

The study sample size was initially set at 15,000 subjects. Based on an assumed event rate of 1.6%/year (equal across treatment arms), with 5000 subjects per treatment group and a total of 450 events, each comparison would have ~90% power to conclude the non-inferiority of dabigatran to warfarin at a one-sided alpha=0.025 (without adjusting for multiple comparisons). The trial was expected to have ~84% power to declare non-inferiority for both dabigatran doses to warfarin. Protocol Amendment 2 dated 2007 increased the sample size to 18,000.
*Reviewer's comment: The amendment noted faster than anticipated enrollment and cited the need to "maintain the statistical power in case of event rate < 1.6% within the original study time line." Correspondence between those conducting the trial and BI cite an opportunity to increase the power to determine whether both dabigatran doses are noninferior to warfarin.* [6.]

[6] Letter to M. Haehl (BI) from S. Connolly, M. Ezekowitz, L. Wallentin and S. Yusef, dated April 19, 2007

### 5.3.4 Study Population

Key enrollment criteria included non-valvular atrial fibrillation and one of the following additional risk factors: previous ischemic stroke, TIA, or systemic embolism, left ventricular ejection fraction < 40, symptomatic heart failure (NYHA class II or greater), age ≥75 years, or age ≥65 with either diabetes mellitus, history of coronary artery disease, or hypertension.

A diagnosis of atrial fibrillation was established based on:

- ECG documented AF on the day of screening or randomization (protocol Amendment 1 expanded this criterion to include ECG documented AF within one week of screening);
- A symptomatic episode of paroxysmal or persistent AF documented by 12 lead ECG within six months prior to randomization;
- Documentation of symptomatic or asymptomatic paroxysmal or persistent AF (at least 30 seconds) on two separate occasions, at least one day apart, one of which within six months prior to randomization. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators could be used to document only one episode of paroxysmal or persistent AF.

Patients with active liver disease, anemia (defined as a hemoglobin <10 mg/dL), severe renal impairment (eGFR < 30 mol/min), contraindication to warfarin or conditions associated with an increased risk of bleeding were excluded. For a full listing of inclusion and exclusion criteria, see Appendix 9.5.1.

To better ensure enrollment of Vitamin K naïve patients, the protocol was amended (see Amendment 1) to specify that the proportion of Vitamin K naïve subjects would be monitored at randomization by IVRS; the Operations Committee could impose additional measures (e.g. a quota system) to ensure balanced enrollment.

### 5.3.5 Procedures

Patients were randomized by IVRS (1:1:1) without stratification for any baseline variables. Following randomization, telephone contact was made at 2 weeks and subjects were seen at 1, 3, 6, 9 and 12 months and then every 4 months thereafter. According to the original protocol, a final follow up visit was to be performed whenever a patient terminated the study, either prematurely or according to the protocol. Protocol Amendment 2 (May 24, 2007) clarified that the final follow-up visit would be performed in subjects who terminated prematurely via withdrawal of consent or according to the protocol. At this follow-up visit, adverse events, bleeding events, efficacy events and changes in concomitant medications since the last visit were to be assessed, in addition to other assessments (physical exam, laboratory, ECG, vital signs).

### *5.3.5.1 Liver monitoring*

Liver tests (ALT, AST, Alk. phos, bilirubin) were evaluated monthly for the first 12 months of treatment and every 4 months thereafter. After liver test data were accrued on 6000 patients exposed for at least 6 months, the frequency of abnormalities was examined and a decision was made to reduce monitoring to every 3 months in subjects randomized after September 25, 2006 (see Protocol Amendment 3). See Appendix for details of specified follow-up for elevated liver tests.

### *5.3.5.2 Anticoagulation initiation, maintenance and monitoring*

Anticoagulation was to be stopped on the day of randomization[7]. Subjects assigned to dabigatran therapy had their study medication started (if INR<2) or held (if INR ≥ 2) until their INR was < 2 (checked every 1-3 days). Subjects assigned to warfarin therapy started warfarin if their INR was less then 3.0, continued warfarin with dose adjustment based on their current INR or switched from other anticoagulant to warfarin therapy. Protocol Amendment 1 clarified that for subjects previously taking phenprocoumon, warfarin would be started when their INR was < 2.0.

During the course of the study, INR was to be monitored at least every 4 weeks in subjects assigned to warfarin or more frequently if needed, based on the clinical judgment of the investigator. Failure to measure the INR level was to be reported as a protocol violation[8]. All dose adjustments were to be done according to usual clinical practice; a nomogram containing recommended dose changes and INR re-testing times for different INR values was also provided to investigators to assist in dose adjustment. Copies of the initiation and maintenance nomograms are provided below.

7 Protocol amendment 1 added that the exact timing for stopping anticoagulation might be adjusted based on the subject's next possible clinic visit and last INR.
8 According to the sponsor, this practice (reporting the failure to measure INR as a protocol violation) was never implemented and this requirement was removed by protocol amendment 5.

**Table 13. Nomogram for initiating warfarin**

| DAY | INR | WARFARIN DOSE (MG PER DAY) |
|---|---|---|
| 1 | - | 5 |
| 2 | - | 5 |
| 3 | <1.5<br>1.5-1.9<br>2.0-3.0<br>>3.0 | 10<br>5<br>2-3*<br>0 |
| 4 | <1.5<br>1.5-1.9<br>2.0-3.0<br>>3.0 | 10<br>7-8*<br>5<br>0 |
| 5 | <2.0<br>2.0-3.0<br>>3.0 | 10<br>5<br>0 |
| 6 | <1.5<br>1.5-1.9<br>2.0-3.0<br>>3.0 | 12-13*<br>10<br>7-8*<br>0 |
| *at discretion of physician | | |

**Lower doses**: age > 75 yrs, weight < 60 kg, interacting medications known to potentiate warfarin, hepatic dysfunction, hypoproteinemia, hyperthyroid, impaired nutritional intake, increased baseline INR.

**Higher doses**: hypothyroid, interacting medications known to inhibit warfarin, diet rich in vitamin K.

**Table 14. Nomogram for warfarin maintenance**

| INR | ACTION |
|---|---|
| ≤ 1.5 | Increase weekly dose by 15%; repeat INR in 7 – 10 days. |
| 1.51 – 1.99 | If unexplained, increase weekly dose by 10%; repeat INR in 7 – 10 days. |
| 2.00 – 3.00** | No change |
| 3.01 – 4.99 | If INR 3.01 – 3.99 do not hold warfarin. If high on two consecutive occasions, decrease weekly dose by 10%;<br>If INR 4.00 – 4.99 hold for 1 day; repeat INR in 7 – 10 days. |
| 5.00 – 8.99 | Hold warfarin. Consider Vitamin K 2-4 mg PO if at increased risk of bleeding. If INR still high 24 hours later, consider giving 1-2mg additional Vitamin K PO and restart at lower dose (decrease weekly dose by 15%) when INR therapeutic. Check INR weekly until stable. |
| ≥ 9.0 | Hold warfarin and give Vitamin K 5.0-10 mg PO. Monitor more frequently and repeat Vitamin K if necessary. |
| Serious bleeding regardless of INR | Hold dose and give Vitamin K 10 mg IV and fresh frozen plasma, recombinant Factor VIIa, or prothrombin complex concentrates depending on urgency of situation. |
| **If INR between 1.80 – 2.00 or 3.00 – 3.20, consider no change in with repeat INR in 7 – 10 days, for first occurrence ONLY. | |

### *5.3.5.3 Treatment of bleeds*

*Major bleeds:* The protocol specified that study medication should be stopped and the treatment of major bleeds left to local practice. Bleeding in subjects on warfarin was to be reversed with Vitamin K and/or fresh frozen plasma (FFP) and consideration was to be given to prothrombin concentrates or recombinant factor VIIa (if used, guidance from a coagulation expert was recommended). For bleeding in the setting of dabigatran administration, the protocol originally noted that packed cells or FFP may be administered with consideration given to the use of prothrombin complex concentrates and recombinant factor VIIa, though their role in reversing the anticoagulant effect of dabigatran was unproven. If thrombocytopenia was present, consideration was also to be given to platelet concentrates. Protocol Amendment 5 (dated August 7, 2008, over 2.5 years after study initiation) indicated that it may be possible to remove dabigatran by hemodialysis and also added that though consideration may be given to the use of FFP

in subjects who are still anticoagulated at the time of surgery, there was no evidence that this would reverse dabigatran's anticoagulant effect. For subjects on warfarin or dabigatran, re-initiation of study medication after bleeding had resolved was left to the discretion of the local investigator.

*Minor bleeds:* Treatment of minor bleeds was left to the discretion of the investigator. Stopping medication was not required.

### *5.3.5.4 Emergency and elective surgery*

For emergency and elective surgery, the following was specified:

- Warfarin Treatment Group, Preoperative Phase: Patients could be managed with or without bridging anticoagulant therapy. Warfarin should be stopped 5 days before the procedure and, if the physician considers the patient to be higher risk, replaced by either low molecular weight heparin or unfractionated heparin. If INR the day before surgery is >1.4, 1 mg of oral vitamin K can be prescribed. If the INR measurement repeated the day of surgery is >1.4, postponement of surgery should be considered.
- Warfarin Treatment Group, Post Procedural Period: Anticoagulation could be started as soon as clinically feasible with IV (unfractionated) or subcutaneous low molecular weight heparin and simultaneously with oral warfarin, if possible.
- Dabigatran Treatment Groups, Preoperative Phase: Dabigatran treatment could be continued until 24 hours before surgery.
- Dabigatran Treatment Groups, Post Procedural Period: Dabigatran could be initiated as soon as clinically indicated. If oral medication is not feasible, heparinization intravenously or subcutaneously should be considered.

In a protocol amendment dated August 7, 2008, a more detailed algorithm for holding dabigatran prior to surgery was added, with the discontinuation algorithm based in part on a subject's renal function, as indicated in the table below.

**Table 15. Sponsor's algorithm for stopping dabigatran before surgery**

| Renal function (CrCl, mL/min) | Estimated half-life in hours | Stop dabigatran before surgery | |
|---|---|---|---|
| | | High risk of bleeding* | Standard risk |
| ≥50-80 | ~15 (12-18) | 2-3 days before | 24 h prior (2 doses) |
| ≥30 to <50 | ~18 (18-24) | 4 days | at least 2 days (48 h) |
| <30 | ~27 (>24 ) | > 5 days | 2-5 days |

### *5.3.5.5 Discontinuation of study medication and follow-up of subjects*

Study medication could be temporarily discontinued for procedures, diseases or diagnoses that did not permit continued treatment with study medication, the need for a

concomitant medication excluded by the study protocol or intolerable adverse events. In subjects who temporarily discontinued therapy, attempts were to be made to re-start study medication if the investigator thought it was appropriate.

Subjects who experienced a "clear, persistent contraindication" to study medication (such as a major bleeding event or non-compliance with the dosing regimen or visit schedule) or who requested withdrawal of study drug were to have their study medication permanently discontinued and followed for the duration of the study. For subjects randomized to dabigatran, dabigatran was to be held if CrCl fell to <30 mol/min and was to be re-started if CrCl rose above 30 mol/min. If the CrCl fell below 30 mol/min for a second time, dabigatran was to be permanently discontinued and the subject was to be followed until trial completion. Of note, Amendment 2 to the RE-LY study protocol (dated May 24, 2007) changed how subjects who either permanently discontinued study drug or requested to be withdrawn from study drug treatment were followed. Amendment 2 allowed clinical investigator to "negotiate a revised visit schedule should the patient be unwilling to adhere to the regular schedule." Amendment 2 also specified that these follow-up visits could occur either be by telephone or in clinic.

*Reviewer's comment: In addition to these protocol-specified measures, other steps were also taken to obtain vital status information. According to the sponsor, if "it became apparent" that a normal study completion visit could not be obtained within the closeout time window, information on vital status was sought in these subjects. Vital status was to be obtained in all study subjects with the exception of those subjects enrolled from sites that were closed for cause and subjects who had withdrawn consent and, as part of the consent withdrawal, had documented in writing that they would not attend study visits and were not to be contacted (based on local regulations concerning the meaning of withdrawal of consent). Sites were directed to contact the patient or primary care provider by phone and by letter; two contacts were required before a patient was considered lost to follow up. If a patient could come in for a final follow up visit within the close out window, a normal study completion visit was conducted and the patient was not categorized as vital status only (the patient was categorized as normal study termination). In some countries, where permitted by laws, an agency was hired to establish whether a subject was alive or dead.*

### 5.3.6 Endpoints

The primary efficacy endpoint was the incidence of stroke (including hemorrhagic) and systemic embolism.

Secondary efficacy endpoints included the incidence of:

- stroke (including hemorrhagic), systemic embolism, or all-cause mortality
- stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding)

Efficacy outcome events were defined as shown in the table below.

**Table 16. Definitions of key efficacy outcome events**

| Efficacy outcome | Definition |
|---|---|
| Stroke | Acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. The stroke is categorized as ischemic or hemorrhagic or cause unknown (based on CT or MR scanning or autopsy). Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin score at discharge from hospital and at 3-6 months later. |
| Systemic embolism | Acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts), and must be documented by angiography, surgery, scintigraphy, or autopsy. |
| Myocardial infarction | Depending on whether or not PCI or CABG has been performed, a myocardial infarction (MI) was defined as**:**<br>a. In subjects not undergoing PCI or CABG, at least 2 of the following 3 criteria had to be present:<br>i. Typical prolonged severe chest pain or related symptoms or signs (e.g., ST-changes of T-wave inversion in the ECG) suggestive of MI.<br>ii. Elevation of troponin or CK-MB to more than the upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level.<br>iii. New significant Q-waves in at least 2 adjacent ECG leads.<br>b. After PCI (within 24 h): Elevation of troponin or CK-MB to more than 3xULN or, if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.<br>c. After CABG (within 72 h): Elevation of CK-MB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.<br>d. Silent MI: retrospectively diagnosed by the appearance of significant new Q-waves between study visits. (In such cases, the date of the event was to be recorded as the midpoint between the 2 study visits)<br>e. Demonstrated by autopsy |
| Deaths | Classified as vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy)], or of unknown etiology. [The definition of vascular death was expanded by the adjudication committee charter; see “Adjudication of Events” below] |

Additional notes: Total CK could be used if CK-MB unavailable; significant Q-waves were defined as a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads.

Prespecified safety endpoints included major and minor bleeds; life threatening bleeds were a subclassification of major bleeds (major bleed definitions presented in Table 1).

Additional safety endpoints included intracerebral hemorrhage, other ICH, elevations in liver transaminases, bilirubin and hepatic dysfunction, and other adverse events.

### 5.3.7 Statistical Analysis Plan

The protocol finalized on September 12, 2005 pre-specified one primary and two secondary endpoints (see "Endpoints" above) as well as an approach to their statistical analysis. On May 8, 2009, approximately two months after the study end date, a document entitled Trial Statistical Analysis Plan (TSAP) was finalized. The stated purpose of the TSAP was to specify the details of the statistical analyses described in the September 2005 protocol. The TSAP is described by the sponsor as a working document that could be amended as the trial progressed and was to be signed off at least 4 weeks prior to unblinding. The TSAP largely preserved the primary non-inferiority analysis specified in the 2005 protocol; the TSAP approach to the analysis of the secondary endpoints specified in the 2009 protocol also appears to mirror that specified in the 2005 protocol. In addition, the TSAP addresses analytic/endpoint changes made subsequent to the 2005 finalization of the protocol.

#### *5.3.7.1 Primary endpoint analysis as specified in the 2005 protocol (and TSAP)*

The primary efficacy variable was the time to first occurrence of stroke or systemic embolism and the study was designed to test the hypothesis that the hazard ratio of dabigatran vs. warfarin was larger than or equal to a non-inferiority margin of 1.46. The primary efficacy analysis was to be performed on all randomized subjects (full analysis set or FAS) using a Cox proportional hazard model that included treatment as a factor. All adjudicated and/or "un-refuted" [9] events were to be used. The protocol specified the Hochberg procedure to test each dose against warfarin separately. If the upper bound of the 95% CI for the less effective dose was < 1.46, then non-inferiority for both doses would be claimed. Otherwise, the upper bound of the 97.5% CI for the more effective dose had to be < 1.46 to claim non-inferiority for the more effective dose.

The non-inferiority margin was calculated using data from the historical placebo-controlled trials of warfarin (see appendix and sponsor's table below). To calculate the non-inferiority margin, the sponsor used 0.52 as the upper limit of the 95% CI of the hazard ratio of warfarin vs. placebo. There was a clinical decision to ensure that more than 50% of the effect was preserved giving a non-inferiority margin of 1.46.

9 Though no definition of this term could be found in the protocol, according to the sponsor (submission dated January 6, 2010), an un-refuted event is one that meets at least one of the following criteria: the adjudicator agrees with the investigator, the event has not been adjudicated (no events fell into this category in RE-LY) or no additional information can be checked (absent additional information, investigator judgment was acceptable).

**Table 17. Meta-analyses of historical placebo-controlled trials**

| Meta-analysis | Hazard (Risk) ratio of warfarin vs. placebo (95% CI) |
|---|---|
| Hart et al of six-trial meta-analysis for strokes using summary statistics from each trial | 0.38 (0.28, 0.52) |
| Meta-analysis for strokes/systemic embolisms of the five primary prevention trials, using pooled individual patient data | 0.35 (0.23, 0.52) |
| Six-trial meta-analysis for strokes using constant hazard assumption | 0.37(0.27, 0.50) |
| Meta-analysis for strokes of the five primary prevention trials for strokes, using constant hazard assumption | 0.38(0.25, 0.57) |

[Source: RE-LY protocol, Table 7.6.1:2]

### *5.3.7.2 Secondary endpoint analysis as specified in the 2005 protocol (and TSAP)*

Secondary efficacy endpoints specified in the 2005 protocol included the incidence of:

- stroke (including hemorrhagic), systemic embolism, or all-cause mortality
- stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding).

For these secondary efficacy endpoints, the same statistical model as that for the primary endpoint was to be applied. A FAS population was to be used and all "adjudicated and/or un-refuted" events were to be utilized. No approach to controlling the type 1 error rate was specified in the 2005 protocol for the analyses of secondary endpoints. The plan for analyzing these endpoints in the TSAP appeared to mirror that contained in the 2005 protocol.

## 5.3.8 Identification of potential endpoint events

(see appendix for relevant CRF pages):
According to the 2005 protocol, a patient's stroke status and bleeding events were to be evaluated at each visit by asking the patient a series of questions regarding the period of time since their last clinic visit.

*Reviewer's comment: The CRF for scheduled study visits asked if the patient had experienced any of the study outcome events since the last visit (these individual events were listed with a check box next to each event for indicating yes/no).*

In addition, the following measures were to be taken:

- Screening for signs and symptoms of stroke and bleeding: A questionnaire querying patients for signs and symptoms of stroke and bleeding was to be administered at each visit. All symptoms were to be evaluated and, if potentially consistent with a study event, were to be referred to the Adjudication Committee.

*Reviewer's comment: According to the RE-LY Central Adjudication Core-Committee meeting February 2, 2009, PHRI created a CRF "to be completed by sites (applicable sites only) to document an 'Investigator verification' that the symptoms were not related to an event."*

- Screening of hospitalizations: All hospitalizations were to be recorded with the reason for admission and all inter-current diagnoses. Any hospital diagnosis that included loss of neurological function, loss of organ function or need for surgical intervention, or reduction in hemoglobin was to trigger a request for more information from the centre and if potentially consistent with a study event was to be referred to the Adjudication Committee

*Reviewer's comment: The measures implemented during the study appear to be more limited than those originally specified in the protocol. The CRF for hospitalizations captured data on the reason for admission (not all inter-current diagnoses) with possible answers including "outcome event" and other events falling into the following categories specified on the CRF: other cardiovascular, surgery, and other non-cardiovascular. Under some of these headings, there was an option for free text to specify the particular event that was the reason for hospitalization. According to the sponsor (Response to information request dated February 12, 20101), checks were performed on the hospitalization CRF page to confirm that events reported on this page as outcome events/ potential outcome events (those reported as "outcome event" or identified via a free text term match to a list of terms for outcome events) were captured as outcome events; if no event was reported by the site, the site was queried (for events indicated by free text search) or told to submit the appropriate outcome event CRF page (for events reported as "outcome event").*

- Review of adverse events: Any adverse event indicating potential loss of neurological function, such as unilateral weakness, loss of vision or sensory disturbance was to trigger a request for more information from the centre for event adjudication if potentially consistent with a study event. Any decrease in hemoglobin of > 2 gm/dL was to be similarly investigated.

*Reviewer's comment: According to the sponsor (response to information request dated February 12, 2010), adverse events were searched using a list of terms for the outcomes of stroke, MI, non-CNS systemic embolism, major bleed, death and TIA; minor bleeds were not cross checked. Hemoglobin drops of > 2, >4, or >5 g/dL between visits were identified and the results were also compared with the major or minor bleeding reports.*

- Review of TIAs: All reported TIA events were to be referred to the Adjudication Committee for full adjudication of any possible strokes that may have been improperly reported.

- All reported major bleeding events, bleeds requiring discontinuation of study medication, hospitalizations or physician intervention, were to be forwarded for adjudication.

*Reviewer's comment: In addition to these measures, additional steps were taken by PHRI/the sponsor. According to the sponsor, following database lock on June 17, 2009, additional outcome events were identified through two separate processes. In one process, the data coordinating center, PHRI, continued to query sites on outcome events for subjects lost to follow-up; this process continued until the finalization of the publication manuscript and was reported to be "part of PHRI's normal procedure." A separate process conducted by the sponsor after trial completion and database lock was routine site closeout visits. A total of 27 potential outcome events were identified via these processes of which 22 were adjudicated as meeting the criteria of an outcome event.*

### 5.3.9 Protocol Amendments:

Global as well as region-specific protocol amendments were enacted over the course of the trial. Major revisions enacted by global protocol amendments are described in the table below.

**Table 18. RE-LY protocol amendments**

| Amendment (date) | Key changes enacted |
|---|---|
| Amendment 1 (August 31, 2006) | To ensure balanced enrollment of Vitamin K antagonist (VKA) naïve and VKA-experienced subjects, the proportion of subjects falling into these categories was to be monitored at randomization by IVRS; if the proportion of subjects in these groups became "consistently disproportional," the Operations Committee could impose additional measures (e.g. a quota system) to ensure balanced enrollment.<br><br>The definition of VKA naïve was also revised to include subjects treated with VK antagonist for two months or less (original definition= not previously treated with a VKA for 30 days or more). |
| Amendment 2 (May 24, 2007) | Increased subject number from 15,000 to 18,000. The stated rationale for the increase was that because of the faster enrollment, 15,000 patients will be randomized prior to the planned date. In order to maintain the statistical power in case of an event rate < 1.6% (the |

| | |
|---|---|
| | originally projected event rate), the enrollment should continue.<br><br>Required that all subjects, including those that discontinued treatment, be followed until the end of the study. Patients who prematurely discontinue treatment were to be contacted at regular intervals (according to the regular visit schedule, an alternative reduced schedule negotiated with the subject either by clinic visits or phone in order to record endpoints (survival, stroke or embolic events or MI) and "other clinical status when feasible"<br><br>Clarified that subjects terminating prematurely by withdrawal of consent would undergo a final follow-up visit. |
| Amendment 3 (September 11, 2007) | Decreased frequency of liver function test (LFT) monitoring (from monthly to ~every 3 months in the first year of the study) in subjects randomized after September 25, 2006. Change was based on a Data Safety Monitoring Board (DSMB) recommendation following a protocol specified review of LFT data accrued on 6000 subjects exposed for at least 6 months. |
| Amendment 4 (February 15, 2008) | Revised protocol to address new information regarding effect of p-gp inhibitors on dabigatran exposure: Contraindicated concomitant use of dabigatran and quinidine. Caution advised regarding use of dabigatran and moderate to strong p-glycoprotein (P-gp) inhibitors (e.g. verapamil and clarithromycin); physician to consider the use of a suitable alternative. |
| Amendment 5 (August 7, 2008) | Established a more detailed algorithm for holding dabigatran prior to surgery, with the discontinuation algorithm based in part on subject's renal function.<br><br>Provided additional instruction on the treatment of major bleeds.<br><br>Revised how the quality of INR control would be assessed (adopted Rosendale method and specified that the mean percentage of time of INR in range was to be calculated for each center and each country); also removed the failure to measure INR values per protocol as a protocol violation. |

## 5.3.10 Adjudication process

[The submission contains a copy of the RE-LY Central Adjudication Manual Version 3 dated April 24, 2007 which serves as the source of the following information unless otherwise noted].

An Adjudication Committee adjudicated reported primary and secondary events including potential strokes, systemic embolism, pulmonary embolism, acute myocardial infarction (AMI), TIAs (to rule out strokes), major bleeding, life threatening bleeding and cause of death. The committee was comprised of experts in the field of neurology and cardiology; neurologists were to adjudicate potential strokes and other endpoints were to be "usually" adjudicated by cardiologists. A stroke subcommittee was also formed to review stroke, TIA and systemic embolism cases when the individual adjudicators could not reach consensus. Events were to be adjudicated using the definitions provided in the protocol with the exception of pulmonary embolism (no definition was provided in the protocol) and vascular death. In the charter, pulmonary embolism was defined as "clinical symptoms compatible" and at least one of the following:

a. High probability V/Q scan (one or more segmental or larger perfusion defects with normal ventilation
b. Positive CT angiogram showing an intraluminal filling defect
c. Positive pulmonary angiogram
d. Autopsy showing pulmonary embolism
e. Other objective imaging for DVT if investigations for pulmonary embolism not done, or non-diagnostic.

According to the adjudication committee charter, death was to be classified as vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy)], or of unknown etiology. Vascular death was considered to occur when no obvious nonvascular event to explain death was noted; sudden or unwitnessed deaths were considered vascular.

*Reviewer's comment: While the adjudication form asked adjudicators to sub classify the major bleed, the second version of the adjudication charter (dated September 14, 2007) stated that the adjudication coordinator would identify the sub classification of major bleeds as life-threatening. Hence, it is unclear who did the adjudication.*

All reported events were to be adjudicated independently and in a blinded manner by two members of the committee; if consensus was not achieved, the event was reviewed and the final decision was determined by a third adjudicator (in the case of potential endpoint events for stroke, TIA and systemic embolism events, a stroke subcommittee made the final decision if consensus was not achieved). Event information to be provided to members included event case report forms and supporting documentation. References to treatment arm, INRs and "other relevant clinical information" were to be removed from these documents. As a verification of blinding, the adjudication form asked adjudicators if they remained blinded to study treatment during the review of a

given event; if the adjudicator reported unblinding, the event was to be adjudicated by another member of the committee.

*Reviewer's comments: Review of the meeting minutes of the Central Adjudication Core Committee revealed difficulty with blinding non-English documents and concern for inconsistencies in the adjudication of non-CNS embolic events. The latter concern resulted in a second review of these events: non-CNS embolic events were to be reviewed by one of two reviewers and the outcome of this second review was to be considered final and supersede previous documented decisions in the main clinical data base. Relevant excerpts from the February 2, 2009 Central Adjudication Core Committee Meeting Minutes are provided below:*

- ***Verification of Blinding***

M. Robinson reported that an internal quality assurance review of Adjudicated Non-English events had been performed to verify the report by the Adjudicator of maintaining blinding during their review. A total of 30 adjudicated Non-English events that had been subsequently translated after adjudication, were randomly selected and reviewed by Marlene. The purpose of the review was to verify whether any evidence of potential unblinding was present and evaluate the declaration of the Adjudicator as to whether he/she was unblinded (note: a required question on each adjudication form).

M. Robinson reported that 6 (20%) of the 30 events reviewed potentially showed evidence of unblinding in the source documentation review by the adjudicator. In these instances, the report by the Adjudicator was that he/she was NOT unblinded.

M. Robinson reported samples of the phrases that had been identified as potential sources of unblinding;; *patient warfarinized; INR values visible, may need to speak with cardiologist regarding starting patient on an alternate anticoagulant such as Marveran at discharge*.

The group discussed the findings in detail and agreed upon the following points:

- The adjudicators generally review the documentation at a high level and apply the necessary criteria. Text embedded in documents may have been missed or overlooked the areas where unblinding may have occurred. (ie. for a stroke only reviewing the CT and discharge summary, and not reading the consults or progress notes).
- There are different levels of unblinding and revealing an INR of 5.0 may not necessarily unblind the Adjudicator to Coumadin (Warfarin), as it could also indicate Dabigatran effect.
- It is important to know the context within which the unblinding may have occurred, as it may not have been the case at all.
- It is important to take the word of the adjudicators.

**Action:**

- The committee agreed that another 30 events be reviewed and graded accordingly; true unblinding, and potentially unblinded. These events will be reviewed to determine blinding status with further discussion based on findings.

*Reviewer's comment: While the minutes documented plans to review additional events with "further discussion based on findings," according to the sponsor (submission dated March 30, 2010), "The last meeting of the Adjudication Committee occurred on Feb 2, 2009 before data base lock in June. This item of reviewing 30 other events, was not pursued."*

- ***Non-CNS Embolic Event Agreement Rate and Response***

M. Robinson noted the consistent low agreement rate of Non-CNS Embolic Event. The committee reviewed various considerations related to the interpretation, definitions and processing of this event and concluded the following:

- Nurses are completing the CRF for this event and may not be as familiar with the protocol definition and continue to capture venous events as opposed to 'systemic' arterial events
- The definitions are clearly outlined in the protocol.

M. Robinson reported that an internal quality assurance review of Adjudicated random selection of Non-CNS Embolic Events has been performed. A total of 30 events were randomly selected and reviewed by Marlene to review the supporting documents included and apply and verify the definitions and criteria for Non-CNS Embolic Events. The purpose of the review was to evaluate the Adjudicator application of the criteria of Non-CNS Embolic Event.

M. Robinson reported that 5 of the 30 (17%) Non-CNS Embolic selected were DVTs or Apical Thrombus.

The committee supported the initiatives and concluded that there is some evidence to suggest that there are inconsistencies in the adjudication of Non-CNS Embolic Events that need to be addressed. The committee unanimously agreed that all of the current

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adjudicated Non-CNS Embolic Events will require a second review. C. Joyner and H-C. Diener will each review 50% of the cases.

**Action:**

- M. Robinson will prepare and issue 50% of the Non-CNS Embolic Events to both C. Joyner and H-C. Diener. The additional review will be independent of the previous Adjudicator decision and without knowledge of this previous decision. The outcome of this second review will be considered final and supersede previous documented decisions in the main clinical data base.
- In the event that C. Joyner or H-C. Diener are uncertain about an event, they will forward the event to each other for comment and consensus.

*Reviewer's comment: Though a description of this process was not otherwise noted in the submission, when asked about the readjudication, the sponsor confirmed that all but 3 of the 98 events were re-read as described above (sponsor submission dated February 11, 2010).*

# 6 Review of Efficacy

*Reviewer's comment: This section focuses on key analyses related to efficacy and addresses topics including the adequacy of anticoagulation in the warfarin arm, the PROBE design, and dabigatran's effect on mortality. For analyses addressing net benefit, as well as further discussion regarding a superiority claim, see Section 1 titled "Recommendations/Risk-Benefit Assessment".*

Dabigatran etexilate is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism and reduction of vascular mortality in patients with atrial fibrillation. In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), randomized, non-inferiority study of open-label warfarin administration and blinded administration of two doses of dabigatran (110 and 150 mg). RE-LY's primary endpoint was a composite of stroke and systemic embolism. The sponsor's primary analysis, conducted on the ITT population, established efficacy. Compared to warfarin treated subjects, the HR in the dabigatran 150 arm was 0.66 (95% CI 0.53 to 0.82, $p<0.003$ for superiority) and in the 110 arm was 0.91 (95% CI 0.74 to 1.11, $p<0.0001$ for non-inferiority). Sensitivity analyses performed on "as treated" populations, as well as an analysis addressing a change in the protocol design (increase in sample size) were supportive of the ITT analysis. Importantly, efficacy findings for the 150 mg dose also appeared to be preserved across important subgroups of patients, including subjects previously treated with warfarin, those with a history of TIA/stroke and the subset of subjects enrolled from US sites. The efficacy of the 150 dose also appeared to be maintained in comparisons against the sub-population of warfarin-treated subjects who had achieved more optimal levels of INR control. The primary endpoint findings were further supported by a numerical imbalance in the number of disabling and fatal strokes in the dabigatran 150 compared to warfarin treatment arm, favoring subjects randomized to the 150 dose.

**Adequacy of anticoagulation in the warfarin treatment arm:** Dabigatran was studied against warfarin in RE-LY and hence to interpret the efficacy findings, one must understand the expected benefit of warfarin as it was given in this trial. Six randomized, placebo-controlled trials (five primary and one secondary prevention) are widely referenced as establishing the efficacy of warfarin for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (see appendix). According to a 2007 meta-analysis by Hart et al, in these studies warfarin reduced the risk of ischemic stroke by 67% (95% CI, 54% to 77%) and the risk of stroke (ischemic and hemorrhagic) by 64% (95% CI, 49% to 74%). There are certainly differences between these historical trials and RE-LY that affect the constancy assumption. Though the mean INR achieved in the historical studies was between 2 and 3, for the most part these studies targeted different INR values /prothrombin time ratios and a wider range of values than the 2-3 range currently recommended and used in RE-LY. The percentage of subjects with important risk markers for thromboembolic complications/strokes (e.g., heart failure, diabetes, and hypertension) was greater in RE-LY than in these historical trials (see table below). At

the same time, there have also been therapeutic advances in the treatment of at least some of these concomitant conditions that would be expected to lower the risk of stroke. For these reasons, it seems likely that the risk reduction associated with warfarin in RE-LY would be different than that seen in historical trials. Whether these differences, in balance, would translate into greater or lesser benefit from warfarin is not clear; either way, substantial benefit would still be expected.

**Table 19. Demographics historical warfarin trials vs. RE-LY**

| | Historical trials of primary prevention | RE-LY |
|---|---|---|
| Year(s) published | 1989-1992 | 2009 |
| Mean Age (>75 years) | 69 (20) | 71 (40*) |
| Sex (%) Male | 71 | 64 |
| Prior stroke (%) | 5 | 13 |
| Hypertension (%) | 45 | 79 |
| CHF (%) | 26 | 32 |
| Diabetes (%) | 13 | 23 |

[Sources: Historical trials- Jackson et al, 2008; RE-LY- Reviewer's analysis (Sponsor's dataset=basco; reviewer's filename=demographics]
*≥ 75 years

Several metrics can be used to assess the adequacy of anticoagulation in warfarin treated subjects in RE-LY a comparison with rates in other warfarin trials, the exposure to warfarin, time in therapeutic range, as well as the appropriateness of INR monitoring. Each measure has its limitations but as a whole, these measures suggested reasonable anticoagulation in subjects randomized to warfarin.

- In the warfarin arm of historical and more recently completed clinical trials, the absolute incidence of strokes was low (see table below). The incidence reported in RE-LY, as an absolute number, seems comparable. In comparison with the incidence of strokes in the placebo arm in the historical trials, the incidence of strokes in the warfarin treatment arm of RE-LY (both the absolute and relative incidence) is much lower.

**Table 20. Stroke incidence per 100 subject-years in historical trials**

| | Year | Placebo | Warfarin/Vitamin K antagonist |
|---|---|---|---|
| Primary prevention | | | |
| AFASAK I | 1989 | 4.8 | 2.2 |
| SPAF I | 1991 | 7.8 | 3.0 |
| BAATAF | 1990 | 3.0 | 0.6 |
| CAFA | 1991 | 3.7 | 2.5 |
| SPINAF | 1992 | 4.8 | 1.4 |

| | | | |
|---|---|---|---|
| Overall | 1989-1992 | 4.6 | 1.7 |
| Secondary prevention | | | |
| EAFT | 1993 | 12.3 | 3.9 |

[Calculations based on rates reported by Aguilar et al.]

**Table 21. Demographics and stroke incidence in RE-LY, ACTIVE W and SPORTIF trials**

| | SPORTIF III | SPORTIF V | ACTIVE W | RE-LY |
|---|---|---|---|---|
| Year(s) published | 2003 | 2005 | 2006 | 2009 |
| Mean Age (% ≥75 years) | 70 (34) | 70 (42) | 70 (NA) | 71 (40) |
| Sex (%) Male | 69 | 72 | 67 | 64 |
| Prior stroke/TIA % | 24 | 18 | 15 | 20 |
| Hypertension % | 72 | 81 | 83 | 79 |
| CHF % | 34** | 39* | 30 | 32 |
| Diabetes % | 22 | NA | 21 | 23 |
| Strokes/100 subject-years (warfarin arm) | 2.2 | 1.1 | 1.4 | 1.6 |
| Hemorrhagic stroke/100 subject-years (warfarin arm) | 0.4 | 0.1 | 0.4 | 0.4 |

*CHF/LV dysfunction; **LV dysfunction

- With regard to exposure to warfarin in RE-LY, 80.8% (4849) of subjects randomized to warfarin completed the study on study medication. Over 50% of subjects had at least one interruption of study medication over the course of the trial; overall, subjects in the warfarin arm were on study medication for ~91% of study days of follow up.

- The mean time in therapeutic range (2-3) was 64.4% (analyses excluding values obtained during treatment interruptions) and 63.4% (analyses including values obtained during treatment interruptions). The overall mean percent of reported INR measurements greater than 4 was ~2%; the overall mean percent of INR measurements <2.0 was ~22 to 23% and < 1.5 was ~5%.Compared to later months, during the first month of therapy, a greater percentage of INR measurements were greater than 4 (~5 vs. ~2%), less than 2 (32% vs. 23-24%) or less than 1.5 (~11% vs. ~5%). The results are not so dissimilar to those reported in recently reported controlled trials such as ACTIVE-W and SPORTIF III and V: 64-68% for an INR of 2 to 3 and ~20% for an INR<2; again suggesting reasonable control using these trials as benchmarks.

**The PROBE design:** RE-LY was open-label with respect to warfarin administration and to mitigate potential bias, several measures were implemented. Other means were used to identify potential events such as screening of adverse events, a questionnaire

querying patients for signs/symptoms of stroke, and a review of investigator-reported hospitalizations. The protocol specified that TIAs were to be adjudicated and events were to undergo blinded adjudication. Finally, the endpoints chosen were, for the most part, more objective endpoints.

Though warfarin administration was open-label, two doses of dabigatran, 110 and 150, were also studied and were administered in a blinded fashion. The inclusion of these two doses was perhaps one of the most important design aspects of RE-LY; while it cannot mitigate potential bias in comparisons of dabigatran against warfarin, it can allow establishment of efficacy via a dose-response relationship. In subjects treated with dabigatran 110 mg BID, 171 strokes were reported compared to 122 in subjects randomized to dabigatran 150 mg BID. Compared to the lower dose, the hazard ratio for the higher dose was 0.71 (95% CI 0.56 to 0.90, p-value=0.003). The finding of a dose response relationship changes the nature of the question surrounding dabigatran's efficacy. The question is no longer whether or not dabigatran at some dose is effective. The question is whether, in the setting of open-label warfarin administration, one can draw any conclusions about superiority over warfarin.

Bias can be introduced because of how events were ascertained or because of differential management or follow up of study subjects. As described above, several measures were implemented to minimize ascertainment bias and it is perhaps worthwhile to explore these measures and the results of these measures as implemented in RE-LY. Of investigator reported strokes, similar percentages were adjudicated as strokes in the three treatment arms of RE-LY. Similar percentages of investigator-reported TIAs were also upgraded to strokes by the adjudication committee across the treatment arms. Moreover, a sampling of investigator-reported events conducted by this reviewer suggested that the adjudications were, as a whole, reasonable. Such findings provide some reassurance; however, there were problematic aspects of the adjudication process, as well as limitations to the methods used to identify potential endpoint events in RE-LY:

- The adjudication documents often contained text that could potentially unblind reviewers. This was the case in 17% of documents reviewed by this reviewer, a figure not so dissimilar to the 20% noted by the Adjudication Core Committee in their review of non-English source documents reviewed by adjudicators. That said, on some occasions, adjudication documents with text indicating warfarin use were actually from subjects randomized to dabigatran who had discontinued study therapy.
- The screening of hospitalizations was a screening not of the hospitalization record itself, but of a CRF page completed by the investigator indicating that the patient had been hospitalized and containing the investigator reported reason for hospitalization. Hence, the screening of investigator-reported adverse events, investigator-reported reasons for hospitalization and questionnaire querying patients for signs/symptoms of stroke required that the investigator first report a suggestive event in order to capture additional events via this method; whether or not there were additional

events that were not reported by investigators is an issue that the DSI audits, some still pending, will address.

Even in the absence of any clear evidence of bias in the ascertainment of strokes/SEE, analysis of study findings suggests that knowledge of treatment arm may have led to important differences in the treatment of subjects. For example, if a subject experienced an ischemic stroke, TIA (a non-endpoint event) or minor bleed, she was more likely to have her study medication permanently discontinued in the dabigatran than the warfarin treatment arms (see Section 6.1.10). There were other treatment specific differences in management. According to the protocol, subjects whose CrCl fell and stayed below 30 mol/min (a sicker population) were to have their medication permanently discontinued in the dabigatran but not the warfarin-treatment arm. Because these subjects were to be followed until trial completion (assuming they were), these differences may not be so critical. Nonetheless, whether or not the management of subjects in the dabigatran and warfarin treatment arms differed in other important ways is uncertain. In light of the open-label design and these differences, one should perhaps be wary of attributing differences in patient outcomes solely to the study drug and also wary of granting dabigatran a superiority claim over warfarin.

**Effects on mortality:** Analyses conducted according to the finalized statistical analysis plan suggested favorable effects of the higher dose of dabigatran on all cause mortality (HR of 0.88, p-value 0.052 relative to warfarin) and vascular specific mortality (HR of 0.84, p-value of 0.04 relative to warfarin). While all-cause mortality and vascular mortality were specified as components of composite secondary endpoints, the RE-LY protocol did not pre-specify a plan for controlling the type-1 error rate in the analysis of secondary endpoints and neither endpoint was specified as an individual secondary endpoint. Moreover, RE-LY was an open label trial and the sponsor's statistical analysis plan was finalized late (essentially after all of the study data had been amassed). An analysis including deaths censored by the sponsor's statistical analysis plan, as well as an analysis excluding deaths identified by vital status queries in subjects who had prematurely discontinued from the trial shift the p-value for all-cause mortality higher (to 0.06 and 0.09, respectively). In addition, an analysis based on center-level INR control suggests that the imbalance in deaths (dabigatran relative to warfarin) is driven by subjects with poorly controlled INRs. Based on these findings, a mortality claim should not be given.

## 6.1 Indication

As previously stated, the proposed indication is for the prevention of stroke and systemic embolism. Though the sponsor requested an indication for the reduction of vascular mortality in the original NDA submission, in an amendment to the NDA dated July 27, 2010, the sponsor requested that the claim be removed from the proposed US indication statement; the letter cited "an effort to harmonize the indication statement for PRADAXA globally."

### 6.1.1 Methods

In the sponsor's efficacy analyses and in the efficacy analyses that follow, subjects without a reported endpoint event are censored at the last time vital status information was available. Subject-years of follow up are also calculated based on the last date vital status information was available.[10] For the primary efficacy endpoint, analyses were also conducted:

(1) censoring subjects without a reported endpoint event at the last time follow up information was available for the particular endpoint of interest, and
(2) censoring subjects without a reported endpoint event at the last clinic follow up visit at which a pulse was recorded.

These analyses produced similar findings as the analysis in which subjects were censored based on vital status information.

### 6.1.2 Demographics

Baseline demographics, including type of atrial fibrillation, history of stroke/TIA, risk factors for stroke and baseline use of warfarin and other anticoagulant medications, were similar across treatment arms. Baseline blood pressure and heart rate was 131/77 and 74, respectively, and was also similar across the treatment arms. Thirty-six percent of study subjects were enrolled from U.S. and Canadian sites. According to the sponsor, 70% of subjects were White, 16% Asian, 7% Hispanic or Latino and 1% were Black.

**Table 22. Baseline demographics**

| Characteristic* | Dabigatran110 N=6015 | Dabigatran150 N=6076 | Warfarin N=6022 |
|---|---|---|---|
| Male | 3865(64.3) | 3840(63.2) | 3809(63.3) |
| Age | | | |
| Mean | 71 | 71 | 72 |
| 65<= and <75 | 2668(44.4) | 2580(42.5) | 2646(43.9) |
| <65 | 998(16.6) | 1030(17) | 953(15.8) |
| >=75 | 2349(39.1) | 2466(40.6) | 2423(40.2) |
| AF type | | | |
| Paroxysmal | 1929(32.1) | 1978(32.6) | 2036(33.8) |
| Permanent | 2132(35.4) | 2188(36) | 2055(34.1) |
| Persistent | 1950(32.4) | 1909(31.4) | 1930(32) |
| AF diagnosis | | | |
| <3 months | 1844(30.7) | 1854(30.5) | 1929(32) |

[10] Subject-years = sum(date of study termination – date of randomization +1) of all randomized subjects / 365.25

| | | | |
|---|---|---|---|
| 3 months to 2 years | 1324(22) | 1344(22.1) | 1315(21.8) |
| >2 years | 2843(47.3) | 2876(47.3) | 2776(46.1) |
| **Characteristic*** | **Dabigatran110 N=6015** | **Dabigatran150 N=6076** | **Warfarin N=6022** |
| VKA use | | | |
| VKA Naive | 3005(50) | 3028(49.8) | 3093(51.4) |
| On VKA at randomization | 3751(62.4) | 3760(61.9) | 3678(61.1) |
| Risk Factors | | | |
| History of stroke | 761(12.7) | 756(12.4) | 756(12.6) |
| History of TIA | 548(9.1) | 587(9.7) | 528(8.8) |
| History of stroke/TIA/SEE | 1308(21.7) | 1358(22.4) | 1287(21.4) |
| History of hypertension | 4738(78.8) | 4795(78.9) | 4750(78.9) |
| History of diabetes | 1409(23.4) | 1402(23.1) | 1410(23.4) |
| History of HF | 1937(32.2) | 1934(31.8) | 1922(31.9) |
| History of MI | 1008(16.8) | 1029(16.9) | 968(16.1) |
| History of CAD | 1661(27.6) | 1710(28.1) | 1663(27.6) |
| Smoker | 440(7.3) | 447(7.4) | 448(7.4) |
| NYHA class | | | |
| NYHA I | 295(4.9) | 292(4.8) | 297(4.9) |
| NYHA II | 1225(20.4) | 1198(19.7) | 1222(20.3) |
| NYHA III | 386(6.4) | 401(6.6) | 353(5.9) |
| NYHA IV | 30(0.5) | 41(0.7) | 48(0.8) |
| CHADS2 score | | | |
| 0 | 151(2.5) | 146(2.4) | 155(2.6) |
| 1 | 1809(30.1) | 1815(29.9) | 1707(28.3) |
| 2 | 2088(34.7) | 2136(35.2) | 2229(37) |
| 3+ | 1966(32.7) | 1979(32.6) | 1931(32.1) |
| Creatinine clearance | | | |
| 30<= and <50 | 1136(18.9) | 1156(19) | 1051(17.5) |
| 50<= and <80 | 2714(45.1) | 2777(45.7) | 2806(46.6) |
| >=80 | 1899(31.6) | 1882(31) | 1877(31.2) |

[Source: Reviewer's analysis (Sponsor's dataset=basco; reviewer filename=baseline_dm]
*Percentages may not add up to 100% because of missing data; a small number of subjects with a CrCl<30 were randomized (<0.05%).

Concomitant medications were also similar across the three treatment arms at baseline, as shown in the table below.

**Table 23. Baseline medication use**

| Baseline medication | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Beta blocker | 3789(63) | 3887(64) | 3722(61.8) |
| Digoxin | 1781(29.6) | 1742(28.7) | 1767(29.3) |
| Amiodarone | 647(10.8) | 672(11.1) | 657(10.9) |
| Verapamil | 352(5.9) | 350(5.8) | 369(6.1) |
| Diltiazem | 564(9.4) | 541(8.9) | 581(9.6) |
| ACEI | 2699(44.9) | 2754(45.3) | 2670(44.3) |
| ARB | 1448(24.1) | 1470(24.2) | 1418(23.5) |
| Aspirin | 2384(39.6) | 2338(38.5) | 2431(40.4) |
| Clopidogrel | 338(5.6) | 337(5.5) | 345(5.7) |
| Aggrenox | 16(0.3) | 9(0.1) | 16(0.3) |
| Statin | 2702(44.9) | 2682(44.1) | 2673(44.4) |
| Proton Pump Inhibitor | 847(14.1) | 878(14.5) | 842(14) |
| H2 receptor blocker | 239(4) | 257(4.2) | 262(4.4) |
| NSAID | 311(5.2) | 294(4.8) | 319(5.3) |

[Source: Reviewer's analysis (Sponsor's dataset=basco; reviewer filename=subgroups]

### 6.1.3 Subject Disposition

Of 20,377 subjects screened, a total of 18,113 were randomized in RE-LY. Of the subjects that were screened but not randomized, approximately 70% did not meet study inclusion/exclusion criteria and another 18% withdrew consent. Over 99% of randomized subjects received at least one dose of study medication.

The disposition of subjects, as reported by the sponsor in an amendment dated August 4, 2010, is shown in the table below. The treatment groups do not appear to differ significantly in the number of subjects lost to follow up. Slightly more warfarin treated subjects were reported to have completed the study on study medication than dabigatran-treated subjects. The reasons for discontinuation of study medication are discussed further in section 6.1.10

**Table 24. Disposition of subjects**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Randomized | 6015 | 6076 | 6022 |
| Treated | 5983 | 6059 | 5998 |
| Completed study | 5765 ( 96.4) | 5808 ( 95.9) | 5748 (95.8) |
| Completed on study medication | 4610 (77.1) | 4625 (76.3) | 4848 (80.8) |
| Completed follow up but stopped study medication prematurely | 1155 (19.3) | 1183 ( 19.5) | 900 ( 15.0) |
| Premature discontinuation* | 218 (3.6) | 251 (4.1) | 250 (4.2) |

[Source: Sponsor submission dated August 4, 2010, Table 2.18.5.1]
*Included in this category: lost to follow up, withdrew consent, "Other", centers closed early for cause, and subjects with "no CRF pages 196, 126, 194 entered"

*Reviewer's comment: Late in the review cycle, errors were found in the sponsor's disposition data. A few subjects who were initially counted by the sponsor as having a "normal study completion" were found to have prematurely discontinued from follow up. As a result, the sponsor performed additional checks of the data and identified 39 subjects in the database listed as having a "normal study termination status" who should have been counted as "early study termination". The disposition data shown above reflects the amended data.*

The protocol allowed clinical investigators to "negotiate a revised visit schedule" for subjects who permanently discontinued study medication and follow up visits could occur by telephone. To further assess the adequacy of follow up, an analysis was conducted in which a subject's last day of follow up was defined as the last clinic visit at which a pulse was recorded. The number of days of follow up based on pulse data (shown below) appears similar across the treatment arms. Using the pulse data, subject years of follow up was ~8% less than that calculated using vital status information; the mean duration of follow up was ~ 1.5 months shorter.

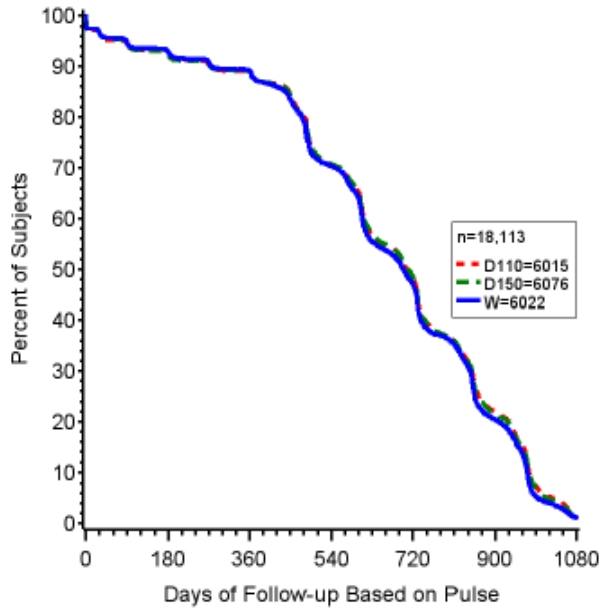



**Figure 5. Days of follow- up based on pulse data**

The mode of follow up (telephone vs. clinic visit) could impact the ascertainment of endpoint events, and in particular the ascertainment of non-disabling strokes. A total of 489, 499, and 469 subjects in the dabigatran 110, dabigatran 150 and warfarin treatment arms did not have a pulse reported within 6 months of the close out period.[11] These analyses, based on pulse data, suggest a greater loss of information (~8% across treatment arms) than the sponsor's analysis of "premature discontinuations" (~4% as shown in the table above).

*Reviewer's comment: The missing data should be viewed in light of the efficacy findings. The number of additional events needed in the dabigatran treatment arms to reverse the efficacy findings is discussed in Section 6.1.4 below. It seems unlikely that this amount of missing information would reverse the efficacy findings, at least for non-inferiority.*

### 6.1.4 Analysis of Primary Endpoint(s)

In the original NDA submission, it was reported that 182 subjects randomized to dabigatran 110 mg (1.5%), 133 subjects randomized to dabigatran 150 mg (1.1%) and 198 subjects randomized to warfarin (1.7%) experienced a stroke/SEE. A few additional events were identified following database lock as a result of queries to sites on outcome

11 For the purposes of this analysis, a subject was counted if no pulse was reported after 6/15/2008 (~6 months prior to study close out); subjects that died at any time prior to 12/15/2008 were excluded. The 6 month cut-off date was arbitrary.

events in subjects lost to follow up, routine site close out visits, and the data quality checks implemented in response to the Agency's refuse to file letter.

**Table 25. Number of subjects with strokes/SEE**

| | Dabigatran 110 N | Dabigatran 150 N | Warfarin N |
|---|---|---|---|
| Original submission | 182 | 133 | 198 |
| Including events identified post Database lock | 183 | 134 | 200 |
| NDA resubmission | 183 | 134 | 202 |

In addition to these events, two other strokes, one in the dabigatran 110 arm and one in the dabigatran 150 arm, were reported by investigators and adjudicated as stroke events but were not included in the sponsor's analysis of the primary endpoint. Both of these events occurred after the subject was reported to have had a "normal study termination" as indicated by the site investigator on the study termination CRF (CRF 196); according to the rules specified in the statistical analysis plan (finalized after the study was completed), events occurring after a "normal study termination" were not to be included in the primary endpoint analysis. Inclusion of these subjects did not alter the results of the primary endpoint analysis and in the analyses that follow, these subjects are excluded.

**Table 26. Strokes excluded by the statistical analysis plan**

| Subject | Arm | Comments |
|---|---|---|
| 1160-0026-00195011 | Dabigatran 110 | CRF 196 completed with visit date given as 12/17/2008, stroke on (b) (6) |
| 1160-0026-01752009 | Dabigatran 150 | CRF 196 completed with visit date given as 2/11/2009, contact for this visit made by phone, stroke on (b) (6) stroke, death on (b) (6) |

The primary endpoint, non-inferiority to warfarin for the time to the first occurrence of stroke/SEE, was established for both doses of dabigatran based on the margin recommended by the Agency, 1.38 ($p<0.0001$ for both comparisons) and the protocol-specified non-inferiority margin of 1.46 ($p<0.0001$ for both comparisons). The HR and 95% CI for the primary endpoint are shown below for both doses of dabigatran using the resubmitted data sets. The 150 mg dose was superior ($p<0.0001$) to warfarin for the primary endpoint. Analyses censoring subjects at the last clinic follow up visit at which a pulse was reported do not alter the findings. According to the FDA statistical reviewer, an additional 46 events (110 arm) and 97 events (150 arm) would be needed to reverse the non-inferiority findings (margin of 1.38) while an additional 33 events (150 arm) would be needed to reverse the superiority results. Hence, even in light of the missing disposition data, it seems unlikely that the efficacy findings (at least for noninferiority for the 150 dose) would be lost.

**Table 27. Hazard ratios for stroke/SEE**

| | Dabigatran 110 vs. warfarin | Dabigatran 150 vs. warfarin |
|---|---|---|
| Hazard Ratio (95% CI) | 0.90 (0.74, 1.10) | 0.65 (0.52, 0.81) |
| P-value non-inferiority using 1.38 | <0.0001 | <0.0001 |
| P-value non-inferiority using 1.46 | <0.0001 | <0.0001 |
| P-value superiority | 0.29 | 0.0001 |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename= primary_endpoint)]
P-values for non-inferiority confirmed by Dr. Bai, FDA statistical reviewer.

The Kaplan-Meier estimate of time to first stroke/SEE by treatment arm is shown below.

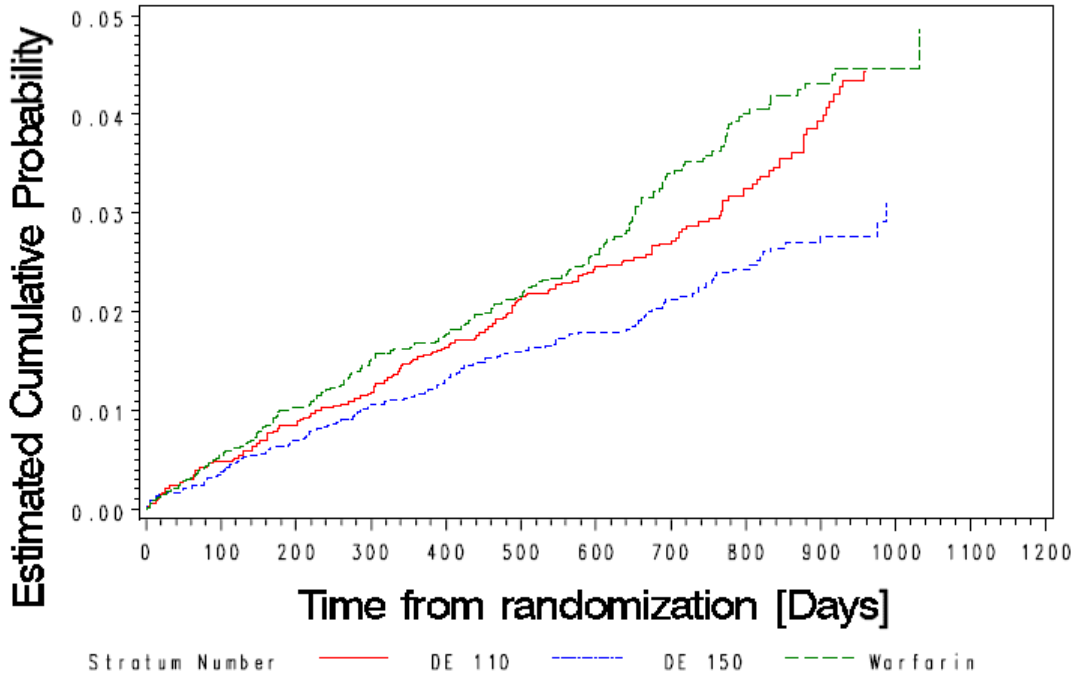



**Figure 6. Kaplan Meier estimate of time to first stroke/SEE**

[Source: FDA Statistical Reviewer]

Exclusion of sites/subjects recommended by DSI thus far (site 265 and 276 and subject 128002) do not alter the results of the primary endpoint analysis. A sensitivity analysis using the first 450$^{th}$ adjudicated events for data cut-off gives a HR of 0.94 (0.75, 1.16) for dabigatran 110 vs. warfarin, and a HR of 0.70 (0.56, 0.89) for dabigatran 150 vs. warfarin. "As treated" analyses censoring subjects 30 days after the time of first discontinuation of study medication (temporary or permanent), and 30 days after the last study medication date are also supportive of the ITT analysis (see table below). Analyses addressing effects in various subpopulations (baseline aspirin use, baseline

warfarin use, history of stroke/SEE/TIA) are presented in section 6.1.7. Analyses by center-level INR control are presented in section 6.10.

**Table 28. "As treated" analysis of the primary endpoint**

| Time of censor | Dabigatran 110 vs. Warfarin | | Dabigatran 150 vs. Warfarin | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Within 30 days of first discontinuation of study medication (temporary or permanent) | 0.91 (0.70, 1.19) | 0.50 | 0.67 (0.50, 0.89) | 0.006 |
| Within 30 days of last date of study medication usage | 0.81 (0.65, 1.01.) | 0.06 | 0.57 (0.45, 0.73) | <0.0001 |

[Source: Reviewer's analysis (Sponsor's datasets= lastmed, timev, timecens, adjrand; reviewer's filename= astreatedanalysis)]
P-values are for superiority; analyses are limited to subjects who were randomized and treated.

The yearly event rates (# of subjects with event/subject-years), HRs and 95% CIs for the individual components of the composite endpoint of stroke/SEE are shown in the tables below. The difference in the total number of stroke events in the dabigatran 150 mg versus warfarin treatment arms (65 events) is driven by a smaller number of both ischemic and hemorrhagic strokes. This contrasts with the findings in the dabigatran 110 mg arm where a smaller number of hemorrhagic strokes and numerically greater number of ischemic strokes are seen relative to warfarin.

**Table 29. Yearly event rate for strokes and SEE**

| | Dabigatran 110 N (%) | Dabigatran 150 N (%) | Warfarin N (%) |
|---|---|---|---|
| Subject years of follow up | 11899 | 12033 | 11794 |
| Subjects with stroke/SEE | 183 (1.5) | 134 (1.1) | 202 (1.7) |
| Subjects with stroke* | 171 (1.4) | 122 (1.0) | 186 (1.6) |
| Ischemic | 152 (1.3) | 103 (0.9) | 134 (1.1) |
| Hemorrhagic | 14 (0.1) | 12 (0.1) | 45 (0.4) |
| SEE | 15 (0.1) | 13 (0.1) | 21 (0.2) |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename=primary_ endpoint)] The numbers of ischemic and hemorrhagic strokes do not add up to the total strokes as some strokes were classified as "uncertain classification".

**Table 30. Hazard ratios for components of primary endpoint**

| | Dabigatran 110 vs. warfarin | | Dabigatran 150 vs. warfarin | |
|---|---|---|---|---|
| | HR (95% CI) | p-value superiority | HR (95% CI) | p-value superiority |
| Stroke | 0.91 (0.74, 1.12) | 0.38 | 0.64 (0.51,0.81) | .0001 |
| Ischemic | 1.13 (0.89,1.42) | 0.31 | 0.75 (0.58,0.97) | 0.030 |
| Hemorrhagic | 0.31 (0.17,0.56) | 0.0001 | 0.26 (0.14,0.49) | <0.0001 |
| SEE | 0.71 (0.37,1.38) | 0.31 | 0.61 (0.30,1.21) | 0.16 |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename=primary_ endpoint)]

Compared to warfarin treatment, treatment with Dabigatran 150 mg was associated with a smaller absolute number of strokes at each Rankin score, including fatal and disabling strokes.

**Table 31. Investigator-reported Rankin scores at 3-6 months**

| Rankin Score 3-6 months | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Missing | 10 | 4 | 11 |
| 0 | 21 | 21 | 21 |
| 1 | 31 | 24 | 35 |
| 2 | 20 | 12 | 22 |
| 3 | 18 | 6 | 17 |
| 4 | 16 | 9 | 14 |
| 5 | 8 | 4 | 8 |
| 6 | 47 | 42 | 58 |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand plt110n; reviewer's filename=primary_ endpoint)]
The Rankin scale runs from no symptoms (0) to death (6); a copy of the scale is provided in the appendix.

### 6.1.5 Analysis of Secondary Endpoints(s)

The results of secondary endpoint analyses as well as the yearly event rate of the individual components of these composites are shown below. The statistical analysis plan described in the 2005 protocol did not specify a strategy for controlling the type 1 error rate in testing these secondary endpoints and interpretation of their findings is limited. Mortality (all cause and vascular) appears to favor the dabigatran arms and is discussed further in section 6.1.6. The yearly event rate of PEs appears to be similar

across the three treatment arms. Finally, there is a numerical imbalance in the number of MI's that favors subjects randomized to warfarin.

**Table 32. Hazard ratios for secondary endpoints**

| | **Dabigatran 110 vs. warfarin** | | **Dabigatran 150 vs. warfarin** | |
|---|---|---|---|---|
| Secondary endpoints | HR (95% CI) | p-value for superiority | HR (95% CI) | p-value for superiority |
| Stroke (including hemorrhagic), systemic embolism, and all-cause mortality | 0.93 (0.83,1.04) | 0.22 | 0.83 (0.74,0.93) | 0.0015 |
| Stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, and vascular deaths (including deaths from bleeding) | 0.98 (0.87, 1.11) | 0.75 | 0.84 (0.74, 0.96) | 0.009 |

[Source: Sponsor's April 19, 2010 submission; Tables 15.2.2.1:2 and 15.2.6.2:2]

**Table 33. Yearly event rate (%) for stroke, SEE, PE, MI and vascular death**

| | **Dabigatran 110 N (%)** | **Dabigatran 150 N (%)** | **Warfarin N (%)** |
|---|---|---|---|
| Subject years of follow up | 11899 | 12033 | 11794 |
| Stroke | 171 (1.4) | 122 (1.0) | 186 (1.6) |
| SEE | 15 (0.1) | 13 (0.1) | 21 (0.2) |
| PE | 14 (0.1) | 18 (0.2) | 12 (0.1) |
| MI | 87 (0.7) | 89 (0.7) | 66 (0.6) |
| Silent MI | 11 (0.1) | 8 (0.1) | 9 (0.1) |
| Vascular mortality | 289 (2.4) | 274 (2.3) | 317 (2.7) |
| All cause morality | 446 (3.7) | 438 (3.6) | 487 (4.1) |

6.1.6 Mortality

The number of deaths in RE-LY, by treatment arm, is shown in the table below. Following database lock, two additional deaths were identified; one in the dabigatran 110 arm and one in the dabigatran 150 arm. In addition to these deaths, ten other deaths (six in the dabigatran 150 mg arm and four in the warfarin arm) were reported by investigators but were excluded from key analyses based on rules specified by the sponsor's statistical analysis plan.

**Table 34. Number of deaths by treatment arm**

| Deaths | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Original submission | 445 | 437 | 486 |
| Inclusive of events identified post database lock | 446 | 438 | 487* |
| NDA resubmission | 446 | 438 | 487 |
| Inclusive of events excluded by sponsor's statistical analysis plan | 446 | 444 | 491 |

*According to the sponsor (email correspondence dated 8.9.2010), one warfarin treated subject who died while in the study did not sign the Health Insurance Portability and Accountability Act form and was censored at the date of randomization in the original submission.

The events excluded by the sponsor's statistical analysis plan occurred after March 15, 2009, after the site was closed for cause, or after a patient was reported as having a "normal study termination" as indicated on the sponsor's study termination report ,CRF 196 (see table below). According to the statistical analysis plan (finalized on May 8 2009, after study completion), such events were not to be included "in the specified formal analysis."

**Table 35. Deaths excluded by the sponsor's statistical analysis plan**

| Subject | Arm | Comments |
|---|---|---|
| 1160-0026-00270004 | Dabigatran 150 | Death occurring after censor (b) (6) |
| 1160-0026-00715033 | Dabigatran 150 | Death occurring after censor date/ (b) (6) |
| 1160-0026-00682034 | Warfarin | Death occurring after censor (b) (6) |
| 1160-0026-00052015 | Warfarin | Death occurring after censor date/ (b) (6) |
| 1160-0026-00354003 | Dabigatran 150 | site closed for cause prior to death |
| 1160-0026-00933035 | Warfarin | CRF 196 completed with visit date given as 1/14/2009 (however investigator notes on form that patient didn't return for this visit given bad state of health), dies (b) (6) |
| 1160-0026-01635006 | Dabigatran 150 | CRF 196 completed with visit date (b) (6) |
| 1160-0026-01677007 | Dabigatran 150 | CRF 196 completed with visit date given as (b) (6) |

| | | |
|---|---|---|
| 1160-0026-01752003 | Warfarin | CRF 196 completed with visit date given as (b) (6), contact for this visit made by phone, admitted with fall on (b) (6) |
| 1160-0026-01752009* | Dabigatran 150 | CRF 196 completed with visit date given as (b) (6), contact for this visit made by phone, (b) (6) |

*This subject is also presented in section 6.1.4

The yearly event rate for all cause mortality was 3.8, 3.6 and 4.1% in the dabigatran 110, dabigatran 150 and warfarin arms, respectively. The hazard ratios (relative to warfarin) are shown in the tables below. Conducting the analysis according to the finalized statistical analysis plan gives a p-value of 0.052 for the 150 dose; inclusion of the ten deaths described above shifts the p-value to 0.060. An analysis stratifying subjects by center-level INR control (subjects at centers with mean TTRs above the median and below the median) shows that the imbalance between treatment arms is driven by subjects at centers with less optimal levels of INR control (see the appendix for further explanation of center-level based analyses as well as a discussion of the impact of center-level INR control on the treatment benefit of warfarin).

**Table 36. Hazard ratios for all cause mortality**

| | **Dabigatran 110 vs. warfarin** | | **Dabigatran 150 vs. warfarin** | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| According to SAP | 0.91 (0.80,1.03) | 0.13 | 0.88 (0.77, 1.00) | 0.052 |
| Inclusive of deaths excluded by SAP | 0.90 (0.88, 1.02) | 0.10 | 0.88 (0.78,1.00) | 0.060 |
| According to center-level INR control | | | | |
| Subjects at centers with mean TTR<67% | 0.77 (0.65, 0.92) | 0.005 | 0.78 (0.66, 0.93) | 0.007 |
| Subjects at center with mean TTR≥67% | 1.08 (0.89, 1.30) | 0.43 | 1.01 (0.84,1.23) | 0.89 |

[Reviewer's analysis (sponsor's datasets=inrvis, adjrand timev, timecens; reviewer sas file=other_efficicacy_endpoints and inr)]; TTR=time in therapeutic range.

| | Dabigatran 110 vs. warfarin | | Dabigatran 150 vs. warfarin | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| According to SAP | 0.91 (0.80,1.03) | 0.13 | 0.88 (0.77, 1.00) | 0.052 |
| Inclusive of deaths excluded by SAP | 0.90 (0.88, 1.02) | 0.10 | 0.88 (0.78,1.00) | 0.060 |
| According to center-level INR control | | | | |
| Subjects at centers with mean TTR<67% | 0.77 (0.65, 0.92) | 0.005 | 0.78 (0.66, 0.93) | 0.007 |
| Subjects at center with mean TTR≥67% | 1.08 (0.89, 1.30) | 0.43 | 1.01 (0.84,1.23) | 0.89 |

[Reviewer's analysis (sponsor's datasets=inrvis, adjrand timev, timecens; reviewer sas file=other_efficicacy_endpoints and inr)]; TTR=time in therapeutic range.

The imbalance in all-cause mortality (relative to warfarin) was driven by an effect on adjudicated vascular specific mortality in the dabigatran 150 arm and by a numerically smaller number of adjudicated vascular and non vascular deaths in the dabigatran 110 arm[12]. The yearly event rate for adjudicated vascular mortality was 2.5, 2.3 and 2.7% in the dabigatran 110, dabigatran 150 and warfarin arms, respectively; the HR of dabigatran 150 relative to warfarin was 0.84 (p-value of 0.04).

In the CRF used to report deaths, investigators were to specify the cause of death. Relative to warfarin, a numerically smaller number of investigator reported fatal strokes were reported in the dabigatran arms (both doses); a slightly smaller number of deaths attributed to hemorrhage were also reported at the 110 dose. Other causes of death also contributed to the imbalance in all cause mortality in one or the other treatment arms (e.g. investigator-reported sudden/arrhythmic death, investigator reported non-vascular mortality "other").

**Table 37. Adjudicated and investigator-reported cause of death**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| | **N=446** | **N=438** | **N=487** |
| **Adjudicated vascular mortality** | 289 (2.4) | 274 (2.3) | 317 (2.7) |
| **Adjudicated non-vascular mortality** | 157 (1.3) | 164 (1.4) | 170 (1.5) |
| **Inv-reported vascular mortality** | 266 | 244 | 284 |
| Sudden/arrhythmic death | 89 | 75 | 87 |
| Pump failure death | 71 | 76 | 69 |
| Stroke | 30 | 23 | 44 |

12 Deaths were adjudicated as vascular (including bleeding) or non-vascular. Vascular deaths were considered to occur when no obvious nonvascular event to explain death was noted; sudden or unwitnessed deaths were also considered vascular.

| | | | |
|---|---|---|---|
| Pulmonary Embolism | 2 | 1 | 4 |
| Peripheral Embolus | 2 | 1 | 2 |
| Aortic dissection/rupture | 4 | 1 | 3 |
| Hemorrhage | 11 | 14 | 18 |
| Unknown Cause | 46 | 41 | 46 |
| Other | 12 | 14 | 11 |
| **Inv-reported non-vascular mortality** | 163 | 173 | 177 |
| Cancer | 64 | 68 | 61 |
| Respiratory Failure | 33 | 29 | 31 |
| Trauma | 3 | 6 | 6 |
| Infection | 22 | 24 | 21 |
| Other | 41 | 47 | 59 |
| **Missing/Unknown** | 17 | 21 | 26 |

[Reviewer's analysis (sponsor's datasets=plt126n, adjrand; reviewer sas file=other_efficacy_endpoints)]

*Reviewer's comments: The number of investigator reported stroke-related deaths differs from the number obtained using Investigator Rankin scores.*

Vital status queries were made for subjects who prematurely discontinued from the study. A greater number of deaths were reported as part of these queries in the warfarin compared to dabigatran arms; when viewed as a proportion of the number of deaths reported in each treatment arm in the trial, the proportion was greatest in the warfarin arm. Analyses excluding this subpopulation give a HR for all cause mortality of 0.89 (95% CI 0.78 to 1.02, p= 0.09) for dabigatran 150 and 0.92 (95% CI 0.81 to 1.05, p= 0.20) for dabigatran 110.

**Table 38. Results of vital status queries***

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| All subjects reported by sponsor as prematurely discontinuing from study | 203 | 235 | 242 |
| Subjects who prematurely discontinued from study and vital status information sought | 119 (58.6) | 147 (62.6) | 156 (63.7) |
| Alive | 100 (84.0) | 120 (81.0)* | 126 (80.8) |
| Died | 7 (5.9) | 8 (5.4)* | 17 (10.9) |
| Unknown | 12 (10.1) | 19 (12.9) | 13 (8.3) |
| As a proportion of deaths reported for given treatment arm in the ITT population | 1.6% | 1.8% | 3.5% |

Because deaths occurring after 3.15.2009 were not included in efficacy analyses, one subject who died after 3.15.2009 is counted as being alive for the purposes of this table.
*These analyses were conducted prior to the submission of the corrected disposition data and hence the numbers of subjects prematurely discontinuing from the study differ from those shown in section 6.1.3.

*Reviewer's comment: The results suggest possible bias in the ascertainment of vital status in subjects who prematurely discontinued from the study.*

### 6.1.7 Subpopulations and concomitant medications

Effects on the primary endpoint, stroke and systemic embolic events were also explored across important subpopulations as shown in the sponsor's figure below. The efficacy of the 150 dose appeared to be preserved across these subpopulations (as defined by the sponsor) with no clear interaction seen; this was not consistently the case in subgroup analyses of the 110 dose (e.g., .subjects < 65, atrial fibrillation type, CHADS2 score). Few blacks were studied (167), limiting the ability to draw conclusions about efficacy/safety in this population; the point estimates were favorable, but the confidence intervals were wide (see FDA Statistical Reviewer's analysis). Analyses based on center-level INR control are discussed further in section 6.1.10.

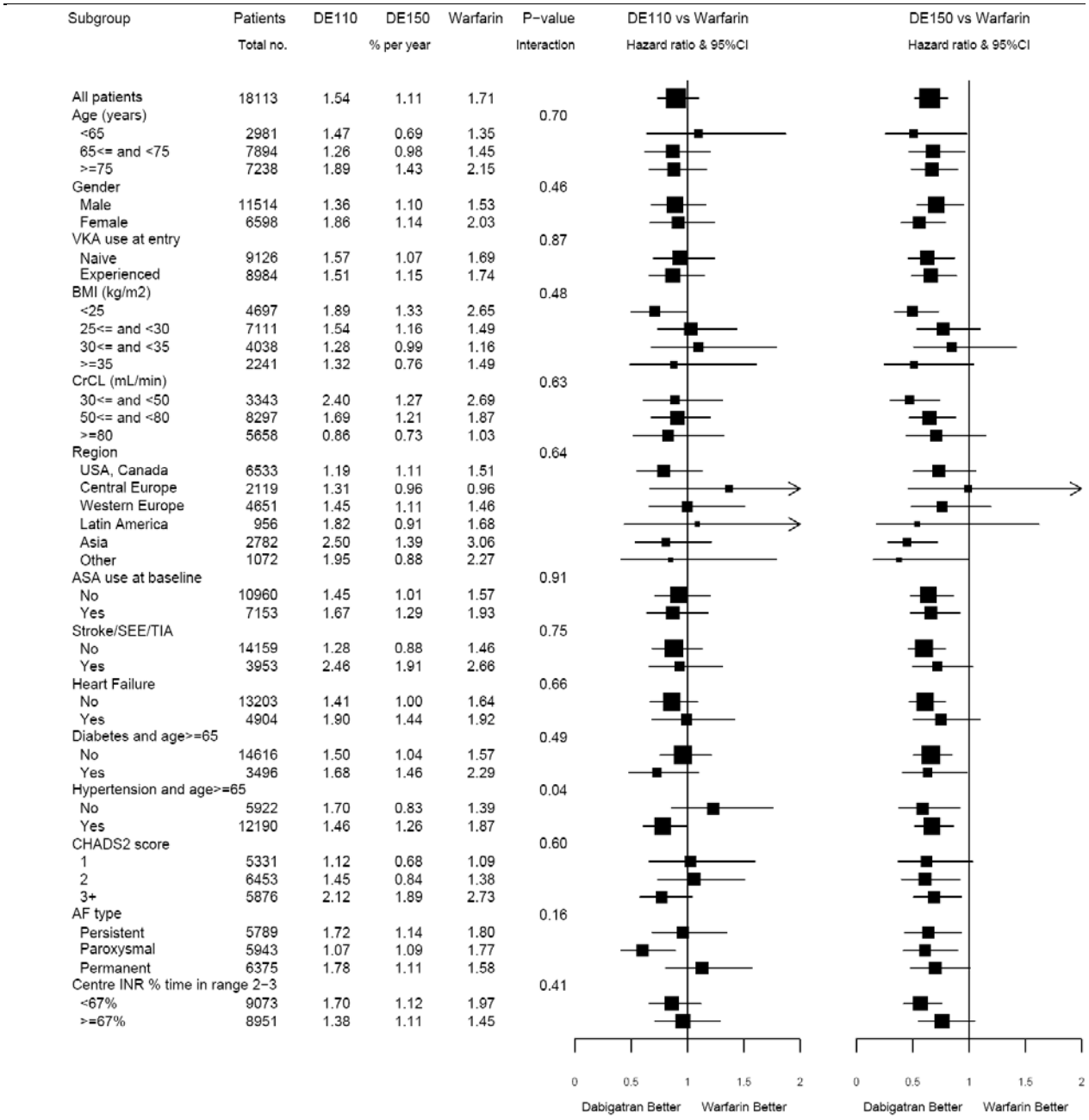



**Figure 7. Stroke/SEE hazard ratios by baseline characteristics**

[Source: Sponsor's proposed label dated May 27, 2010, Figure 3]

The FDA statistical reviewer also conducted sub-group analyses by history of stroke/SEE/TIA, age, gender, prior VKA use, country and aspirin use; these analyses were supportive of the findings shown above.

In light of the drug's pH dependent solubility and pharmacodynamic effects, additional sub-group analyses were also performed exploring the affect of concomitant

medications including aspirin, clopidogrel, proton pump inhibitors and H2 blockers on efficacy outcomes. As shown in Section 6.1.2, reported use of these medications was similar across treatment arms at baseline; whereas ~40% of subjects were on aspirin at baseline, use of clopidogrel and H2 blockers was uncommon (~5-6% and ~4%, respectively). Of subjects reported to be taking aspirin between randomization and study termination, the mean and median percent of time on aspirin was ~62-65% and 100%, respectively (incidence similar across treatment arms).

With the exception of the proton pump inhibitors, use of the aforementioned concomitant medications appeared to be comparable across treatment arms over time without any marked increase over the course of the study. In contrast, proton pump inhibitor use appeared to increase over the course of the trial and, over time, an imbalance was seen across the treatment arms, with greater use in dabigatran compared to warfarin-treated subjects (possibly secondary to the greater incidence of GI adverse events in the dabigatran arms). This change in use over time further complicates analyses addressing the effect of concomitant PPI usage on the incidence of efficacy outcome events.

**Table 39. Changes in the use of proton pump inhibitor therapy during RE-LY**

| Proton Pump Inhibitor Use | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Baseline | 847(14.1) | 878(14.5) | 842(14) |
| anytime during year one | 1279(21.3) | 1315(21.6) | 1108(18.4) |
| anytime during year two | 1247(20.7) | 1275(21) | 1087(18.1) |
| anytime during year three | 610(10.1) | 614(10.1) | 510(8.5) |
| anytime during study | 1474(24.5) | 1500(24.7) | 1268(21.1) |

As shown in the table below, the data from RE-LY do not suggest decreased efficacy in the setting of PPI use. The relationship between proton pump inhibitor use and the risk of ischemic stroke (relative to warfarin) was not consistent at the 110 and 150 dose and the confidence intervals encompassed the point estimates seen in the larger study population (HR of 1.12 and 0.75 for the 110 dose vs. warfarin and 150 dose vs. warfarin, respectively). There were few ischemic strokes reported in subjects on clopidogrel at baseline (29) or H2 blockers at baseline (19); point estimates were associated with very broad confidence intervals and hence interpretation was limited (results of analyses are not shown).

**Table 40. Proton Pump Inhibitor use and the risk of ischemic stroke**

| | HR (95% CI) | | |
|---|---|---|---|
| Proton Pump Inhibitor | D110 vs. warfarin | D150 vs. warfarin | D150 vs. D110 |
| Never Used* | 1.37 (1.04, 1.80) | 0.75 (0.54, 1.03) | 0.55 (0.41, 0.74) |
| Use at baseline | 0.83 (0.45, 1.54) | 1.12 (0.63, 1.97) | 1.3 (0.74, 2.4) |
| 100% Use | 0.69 (0.35, 1.37) | 1.10 (0.61, 2.01) | 1.59 (0.82, 3.09) |

[Reviewer's analysis (sponsor's datasets=bascocm, timecens and timev; reviewer sas file=ASA_PPI_analyses)]
*If subject had been on proton pump inhibitor, stop date was prior to date of first intake of study drug.

The HRs and 95% CIs for ischemic strokes by concomitant usage of aspirin is shown below. Though the confidence intervals of the hazard ratios are wide and cross one, the point estimates suggest that even in the setting of concomitant aspirin use, the 150 dose may provide greater benefit (ischemic stroke reduction) than the 110 dose.

**Table 41. Aspirin use and the risk of ischemic stroke**

| | **HR (95% CI)** | | |
|---|---|---|---|
| Aspirin | D110 vs. warfarin | D150 vs. warfarin | D150 vs. D110 |
| Never Used* | 1.0 (0.72, 1.39) | 0.44 (0.29, 0.67) | 0.44 (0.29, 0.67) |
| Use at baseline | 1.30 (0.91, 1.85) | 0.93 (0.63, 1.36) | 0.72 (0.50, 1.03) |
| 100% Use | 1.38 (0.82, 2.32) | 0.95 (0.53, 1.70) | 0.69 (0.41, 1.18) |

[Reviewer's analysis (sponsor's datasets=bascocm, timecens and timev; reviewer sas file=ASA_PPI_analyses)]
*If a subject had been on aspirin, stop date was prior to date of first intake of study drug.

### 6.1.8 Analysis of clinical information relevant to dosing recommendations

Three phase 2 dose-ranging studies were conducted in patients with atrial fibrillation. These studies, along with studies conducted as part of other indications, are cited by the sponsor as supporting the choice of dose selection in RE-LY. The phase 2 trials conducted in patients with atrial fibrillation studied doses ranging from 50 mg bid to 300 mg bid and are shown in the table below.

**Table 42. Phase 2 studies in patients with atrial fibrillation**

| Study | Design | Doses (N) |
|---|---|---|
| 1160.20 (PETRO) | Randomized, controlled, double-blind (dabigatran doses), open label (ASA and warfarin) 12-week study in patients with non-rheumatic atrial fibrillation and one stroke risk factor | *Dabigatran:*<br>50 mg bid (58)<br>50 mg bid + ASA 81 mg (20)<br>50 mg bid + ASA 325 mg (27)<br>150 mg bid (99)<br>150 mg bid + ASA 81 mg (34)<br>150 mg bid + ASA 325 mg (33)<br>300 mg bid (98)<br>300 mg bid + ASA 81 mg (33)<br>300 mg bid + ASA 325 mg (30)<br>*Warfarin* to target INR 2-3 (70) |
| 1160.42 (PETRO-EX) | Long-term (5 years), open-label, uncontrolled, non-randomized study of dabigatran (with ASA added at the investigator's discretion) in patients previously treated with dabigatran in Study 1160.2013 | *Dabigatran*:<br>150 mg qd<br>150 mg bid<br>300 mg qd<br>300 mg bid |
| 1160.49 | Randomized, open label 12-week study in Japanese patients with moderate to high risk atrial fibrillation | *Dabigatran*:<br>110 mg bid (53)<br>150 mg bid (59)<br><br>*Warfarin* to target INR 2-3, INR 1.6-2.6 in patients age ≥ 70 (62) |

As a whole, the phase 2 studies suggest that over the dose range studied, increasing doses/exposures result in greater prolongation of aPTT and ECT. These studies also suggest that (at least at some dose levels of dabigatran) there may be a relationship between concomitant aspirin use and increased risk of bleeding; this issue is addressed further under safety. These studies do not, however, provide significant insight into the optimal dosing regimen for the prevention of thromboembolic events. Studies 1160.20 and 1160.49 were limited in size and study duration and few thromboembolic events were observed. In trial 1160.49, no thromboembolic events were seen during dabigatran treatment and in trial 1160.20, two thromboembolic events were reported (both in the 50 mg bid treatment arm). In study 1160.42, a long-term, open-label, non-randomized

13 Although treatment group assignment in study 1160.42 was based on treatment group assignment in study 1160.20, patients did not necessarily remain in the same treatment arm as in 1160.42. The doses administered in some treatment arms were also changed during the course of the study (with amendment 4, patients previously treated with dabigatran 150 mg QD or 300 mg BID were administered 150 mg BID). Down titration in dose also occurred in patients with both a low GFR and high corrected aPTT (but not below 150 mg QD).

study, a small number of strokes were reported (see table below). However, interpretation of the data from this trial is not straightforward. Patient-years of exposure is limited for doses other than 150 mg BID doses, some subjects were crossed-over to other treatment arms, the study was not randomized, nor was it blinded.

With respect to the lower end of the effective dose range, RE-LY itself provides the most informative data regarding thromboembolic prevention. In subjects randomized to dabigatran 110, 171 strokes were reported compared to 122 in subjects randomized to dabigatran 150. Compared to the lower dose, the hazard ratio for the higher dose was 0.71 (95% CI 0.56 to 0.90, p-value=0.003), suggesting a clinically important reduction in the risk of such events with the higher dose. RE-LY also provides important data that can speak to the upper end of the dose range likely to provide "net benefit;" an issue that is addressed in Section 1.2 on Risk-Benefit .

**Table 43. Incidence of secondary efficacy endpoints in PETRO-EX (1160.42)**

| Event | 50 mg QD | 50 mg BID | 150 mg QD | 150 mg BID | 300 mg QD | 300 mg BID | Total Dabig. |
|---|---|---|---|---|---|---|---|
| Cumulative exposure (patient years) | 0.05 | 24 | 60 | 842 | 242 | 82 | 1250 |
| **Any stroke** | | | | | | | |
| N | 0 | 1 | 3 | 9 | 4 | 0 | 17 |
| Per 100 patient-years [1] | 0.0 | 4.3 | 5.0 | 1.1 | 1.7 | 0.0 | 1.4 |
| **Ischaemic stroke** | | | | | | | |
| N | 0 | 1 | 3 | 4 | 4 | 0 | 12 |
| Per 100 patient-years | 0.0 | 4.3 | 5.0 | 0.5 | 1.7 | 0.0 | 1.0 |
| **Haemorrhagic stroke** | | | | | | | |
| N | 0 | 0 | 0 | 5 | 0 | 0 | 5 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 0.6 | 0.0 | 0.0 | 0.4 |
| **Any TIA** | | | | | | | |
| N | 0 | 0 | 0 | 2 | 1 | 0 | 3 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 0.2 | 0.4 | 0.0 | 0.2 |
| **Non-CNS systemic thromboembolism** | | | | | | | |
| N | 0 | 2 | 0 | 2 | 1 | 1 | 6 |
| Per 100 patient-years | 0.0 | 8.5 | 0.0 | 0.2 | 0.4 | 1.2 | 0.5 |
| **Myocardial infarction** | | | | | | | |
| N | 0 | 0 | 0 | 9 | 1 | 0 | 10 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 1.1 | 0.4 | 0.0 | 0.8 |
| **Other MACE** | | | | | | | |
| N | 0 | 2 [2] | 0 | 9 | 2 | 1 | 14 |
| Per 100 patient-years | 0.0 | 8.5 | 0.0 | 1.1 | 0.8 | 1.2 | 1.1 |
| **All cause death** | | | | | | | |
| N | 0 | 0 | 0 | 23 | 5 | 0 | 28 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 2.7 | 2.1 | 0.0 | 2.2 |
| **Ischaemic stroke, TIA, non-CNS TE, MI, MACE, death** | | | | | | | |
| N | 0 | 4 [3] | 3 | 46 | 11 | 2 | 66 |
| Per 100 patient-years | 0.0 | 17.0 | 5.0 | 5.5 | 4.5 | 2.4 | 5.3 |
| **Stroke, non-CNS TE** | | | | | | | |
| N | 0 | 2 | 3 | 11 | 5 | 1 | 22 |
| Per 100 patient-years | 0.0 | 8.5 | 5.0 | 1.3 | 2.1 | 1.2 | 1.8 |

[Source: Table 11.4.1.2:1]

In addition to the studies conducted in patients with atrial fibrillation, studies have also been conducted in other patient populations and indications, including primary and secondary prevention of venous thrombosis and as a treatment for acute coronary syndrome. From the standpoint of safety, these studies generally support the concept that higher doses are associated with increased risk of bleeding. With regard to efficacy, according to the sponsor, a dose dependent decrease in the frequency of venous thromboembolism events was seen with increasing dabigatran dose: 28.5%, 17.4%, 16.6%, 13.1%, of subjects assigned to dabigatran 50 BID, 150 BID, 300 QD, and 225 BID, respectively in a phase 2 study of primary venous thromboembolism prevention (study 1160.19). The sponsor noted that this effect was "more prominent" between the 50 and 150 BID dose and "less striking" at the higher doses. A relationship between increasing dabigatran dose and decreasing incidence of a composite endpoint of venous thromboembolism events and all-cause mortality is also cited by the sponsor (study 1160.50, another study of primary venous thromboembolism prevention). Differences in populations, concomitant medications, and indications limit the ability to extrapolate from the experience in these studies to the proposed indication and these studies were not reviewed further.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan-Meier curves of time to first stroke/SEE (see section 6.1.4) suggest no loss of efficacy over time.

### 6.1.10 Additional Efficacy Issues/Analyses

#### *6.1.10.1 Warfarin administration and INR control*

The following analyses address exposure to warfarin and the quality of INR control in subjects randomized to warfarin.

Exposure to warfarin
Of the 6,022 subjects randomized to warfarin in RE-LY, 80.8% (4849) completed the study on study medication. Over 50% of subjects had at least one interruption of study medication over the course of the trial; a similar percentage of subjects had interruptions in the dabigatran treatment arm (see section 7.2.1) As shown in the table below, most interruptions were for less than 30 days. Approximately 35% of temporary interruptions of study medication in the warfarin treatment arm were in the setting of a surgery or procedure; around 20% occurred in the context of an adverse event and 16% in the context of a hospitalization (source: sponsor's table 15.1.1:4; subjects were counted in multiple categories when multiple reasons were given). Subjects in the warfarin arm were on study medication for 91.0% of study days of follow up (source; reviewer's analysis using FDA censoring rules).

**Table 44. Interruptions of study medication**

| | Subjects (%) |
|---|---|
| Randomized to warfarin | 6022 |
| Randomized and treated | 5998 |
| Number with interruptions | 3120 (52.0) |
| Total temporary interruptions (days*) | |
| 1 ≤ and < 8 | 1112 (18.5) |
| 8 ≤ and <30 | 877 (14.6) |
| 30 ≤ and <60 | 222 (3.7) |
| ≥ 60 | 194 (3.2) |
| Permanently discontinued study medication | 1073 (17.9) |

[Source: adapted from sponsor's table 15.1.5:1, April 19, 2010 resubmission]
For subjects with more than one interruption, the cumulative days of interruptions were calculated. Subjects who had both temporary and permanent discontinuations were counted in both categories, hence these categories do not add up.

INR control
Of the 5998 subjects randomized and treated with warfarin, 134 subjects lacked follow up INR data (as reported in the CRF INR log). Of these, approximately 45% permanently discontinued study medication within one week of starting therapy; approximately 72% were on therapy for 30 days or less. Of those subjects with measurements that were taken and reported, approximately 32% of subjects had at least one INR measurement taken >60 days from the prior INR measurement and approximately 16% had at least one INR measurement taken > 90 days from the prior measurement.

To assess the adequacy of INR control, the percent of time reported INR values were within and outside the therapeutic range (2-3) were calculated using available data. Analyses of the percent of time values were in the therapeutic range (2-3) were initially performed by the sponsor excluding days in the first week after randomization and days while study warfarin was temporarily or permanently stopped. Because one reason given by investigators for holding warfarin was an elevated INR and because embolic strokes are likely to occur while anticoagulation is on hold, even if the reason for holding therapy is appropriate (e.g., bleed or procedure), an analysis was also performed in which available data during periods of medication interruption were included. The results of analyses excluding days while warfarin was temporarily or permanently stopped and including periods of medication interruption are shown in the tables below. The mean time in therapeutic range (2-3) was 64.4% (analyses excluding interruptions) and 63.4% (analyses including interruptions). The mean percent of time U.S. subjects were in an INR range of 2-3 was 66% (64.7% including available data during periods of medication interruption).

**Table 45. Mean percent of time INR 2 to 3**

| | Percent of time INR 2 to 3 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR 2 to 3 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 49.2 | 38.5 | 4956 | 48.7 | 38.2 |
| 3 | 5668 | 56.3 | 30.4 | 5711 | 55.6 | 30.2 |
| 6 | 5565 | 60.3 | 25.3 | 5624 | 59.4 | 25.4 |
| 12 | 5236 | 64.0 | 20.4 | 5301 | 63.0 | 20.7 |
| Overall | 5791 | 64.4 | 19.8 | 5812 | 63.4 | 19.9 |

[Reviewer's analysis (sponsor's dataset=inrvis); reviewer sas file=inr)]

The percent of INR measurements greater than 4, less than 2, and less than 1.5 (as determined using the Rosendale method) is shown in the tables below. The overall mean percent of reported INR measurements greater than 4 was ~2%; the overall mean percent of INR measurements < 2 and <1.5 was ~22-23% and ~5%, respectively. Compared to later months, during the first month of therapy, a greater percentage of INR measurements were greater than 4 or less than 1.5.

**Table 46. Mean percent of time INR>4**

| | Percent of time INR >4 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR> 4 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 5.2 | 16.4 | 4956 | 5.4 | 16.6 |
| 3 | 5668 | 3.1 | 9.7 | 5711 | 3.1 | 9.3 |
| 6 | 5565 | 2.3 | 6.3 | 5624 | 2.3 | 6.2 |
| 12 | 5236 | 1.9 | 4.2 | 5301 | 1.9 | 4.2 |
| Overall | 5791 | 2.2 | 6.0 | 5812 | 2.1 | 5.5 |

**Table 47. Mean percent of time INR<2**

| | Percent of time INR <2.0 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR< 2.0 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 31.6 | 38.7 | 4956 | 31.9 | 38.6 |
| 3 | 5668 | 29.0 | 30.7 | 5711 | 30.0 | 30.9 |
| 6 | 5565 | 26.2 | 25.5 | 5624 | 27.3 | 25.8 |
| 12 | 5236 | 22.8 | 19.9 | 5301 | 23.9 | 20.5 |
| Overall | 5791 | 22.2 | 19.1 | 5812 | 23.4 | 19.5 |

**Table 48. Mean percent of time INR <1.5**

| | Percent of time INR <1.5 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR< 1.5 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 10.6 | 26.2 | 4956 | 10.9 | 26.3 |
| 3 | 5668 | 8.4 | 20.2 | 5711 | 9.0 | 20.7 |
| 6 | 5565 | 6.6 | 15.7 | 5624 | 7.3 | 16.4 |
| 12 | 5236 | 4.7 | 10.8 | 5301 | 5.5 | 11.9 |
| Overall | 5791 | 4.8 | 11.3 | 5812 | 5.5 | 12.2 |

[Reviewer's analysis (sponsor's dataset=inrvis); reviewer sas file=inr)]

*Reviewer's comment: These analyses suggest that, as a whole, reasonable INR control was achieved in warfarin-treated subjects in RE-LY. For further discussion, see the Efficacy Summary.*

It has been shown that the time in therapeutic range measured at the center-level and country-level (determined by averaging the individual times in therapeutic range for all subjects randomized to oral anticoagulant therapy within a center or country to yield a value for that center or country), has an important impact on the treatment benefit of warfarin in intervention trials. The benefit of oral anticoagulants over antiplatelet agents has been shown to be dependent upon the quality of INR control as measured by the time in therapeutic range at the center and country level (Connolly et al. 2008; see also Appendix).

Analyses stratifying subjects by center-level INR control (stratifying centers into quartiles) are shown in the table below. These analyses do not show a clear graded

relationship between the center-level of INR control and the benefit of dabigatran relative to warfarin. For the primary efficacy endpoint, the point estimate of the HR for the 150 dose moves closer to one with broad confidence intervals that exceed one in the subset of subjects enrolled at sites achieving the highest quartile of INR control, suggesting that the benefit of the 150 dose of dabigatran (relative to warfarin) is somewhat dependent upon the level of INR control achieved in warfarin-treated subjects. With regard to bleeding, there appears to be a graded relationship between quartile of center-level INR control and the relative risk of adjudicated major bleeds, with much of the relative risk reduction in bleeding in the 110 arm driven by subjects at centers achieving lower levels of INR control. These results suggest that in patients with well controlled INRs, the 110 dose may not provide a significant reduction in the risk of bleeding relative to warfarin.

**Table 49. Analyses by quartile of center-level INR control**

| **Quartile of center-level INR control*** | | **1 <58.5** | **2 ≥58.5 and <66.8** | **3 ≥66.8 and <74.2** | **4 ≥74.2** |
|---|---|---|---|---|---|
| Number of subjects | | N=4162 | N=4662 | N=4772 | N=4428 |
| **Stroke/SEE** | | | | | |
| Dabigatran 110 vs. warfarin | HR | 0.95 | 0.79 | 0.97 | 0.92 |
| | 95% CI | 0.64,1.40 | 0.54, 1.16 | 0.65,1.44 | 0.59,1.44 |
| | p-value | 0.79 | 0.23 | 0.87 | 0.72 |
| Dabigatran 150 vs. warfarin | HR | 0.60 | 0.53 | 0.65 | 0.90 |
| | 95% CI | 0.39, 0.94 | 0.35,0.81 | 0.42,1.02 | 0.57,1.41 |
| | p-value | 0.02 | 0.003 | 0.06 | 0.63 |
| **Major Bleeds** | | | | | |
| Dabigatran 110 vs. warfarin | HR | 0.64 | 0.74 | 0.90 | 0.93 |
| | 95% CI | 0.46, 0.88 | 0.57, .097 | 0.69, 1.17 | 0.68, 1.26 |
| | p-value | 0.005 | 0.03 | 0.43 | 0.62 |
| Dabigatran 150 vs. warfarin | HR | 0.68 | 0.90 | 1.00 | 1.20 |
| | 95% CI | 0.50, 0.93 | 0.70, 1.16 | 0.77, 1.30 | 0.90, 1.60 |
| | p-value | 0.016 | 0.41 | 1.00 | 0.21 |

[Reviewer's analysis (sponsor's datasets= inrvis, adjrand); reviewer sas file=inr]
*Center-level INR control was determined by averaging the individual times in therapeutic range for all subjects randomized to warfarin within a center to yield a value for that center. Centers were than stratified into quartiles by center-level INR control.

The level of INR monitoring (as determined by the days on warfarin/the number of reported INR measurements) in subjects included in the sponsor's calculations of time in therapeutic range is shown in the figure below. As shown in the figure, the majority of subjects had at least one INR measurement for every 30 days of treatment, though some subjects had infrequent monitoring despite poor control. Some subjects with

reported optimal control (higher percent time in therapeutic range) also had infrequent monitoring.

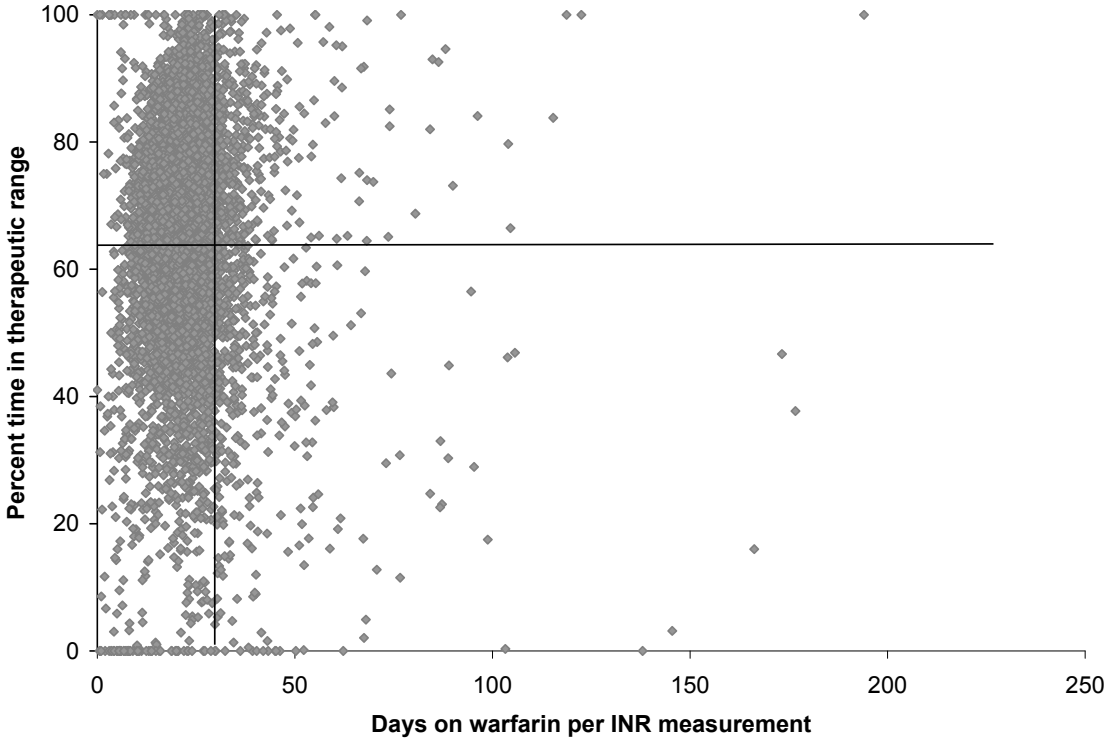
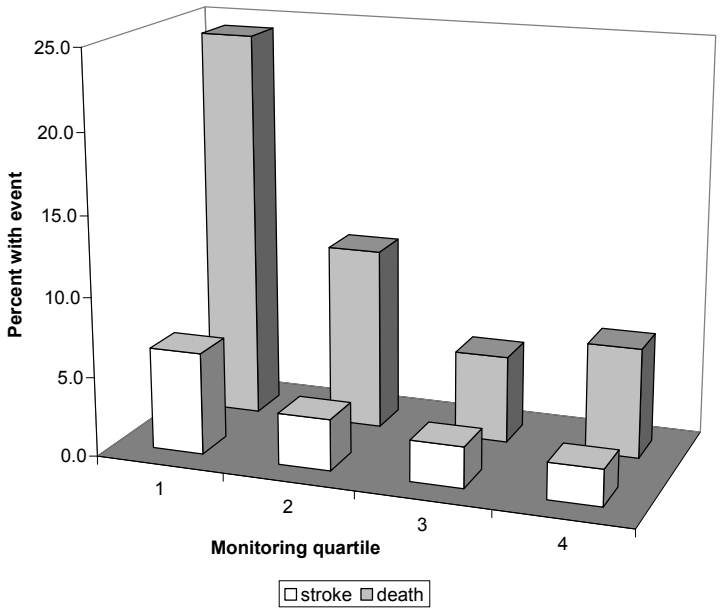



**Figure 8. Percent time in therapeutic range vs. frequency of monitoring**

[Reviewer's analysis (sponsor's datasets=offmed, inr2, inrvis); reviewer sas file=inr]
*Days on warfarin are cumulative and not necessarily consecutive. Vertical line drawn at 30 days; horizontal line drawn at 64% time in therapeutic range.

Analyses looking at adjudicated strokes and deaths in subjects by frequency of INR monitoring (broken into quartiles) and further stratified by the percentage of time a subject was in the therapeutic range (above and below the median value) did not suggest worse outcomes in those with less frequent INR monitoring. There did appear to be a numerical increase in the number of events (deaths and strokes) in subjects undergoing the most frequent monitoring, possibly representing the subset of subjects with more difficult to control or variable INRs.

A.




B.

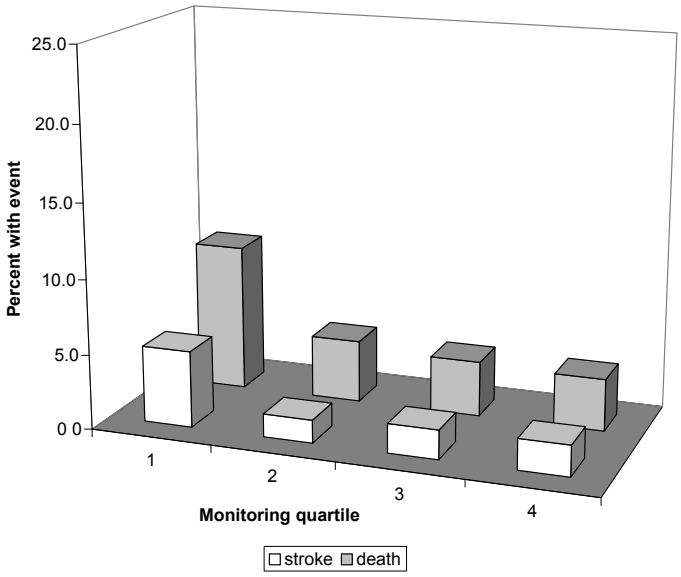



**Figure 9. Events by frequency of monitoring and level of INR control**

[Reviewer's analysis (sponsor's datasets=offmed, inr2, inrvis); reviewer sas file=inr]
A. Subjects with TTR >67%; B. Subjects with TTR≤67%
The frequency of monitoring decreases with increasing quartile.

### *6.1.10.2 Analyses pertaining to RE-LY's open-label design*

RE-LY was an open-label study with respect to warfarin. The following analyses focus on the adjudication process. The differential treatment of subjects in the dabigatran vs. warfarin treatment arms is also addressed.

*Investigator-reported vs. Adjudicated strokes, SEE and major bleeds*
Of subjects with investigator reported strokes, similar percentages were adjudicated as having a stroke in the three treatment arms. Of subjects with investigator-reported TIAs, similar percentages were adjudicated as having a stroke. In contrast, a smaller percentage of subjects with investigator-reported systemic embolic events were adjudicated as having had systemic embolic events in the dabigatran compared to warfarin-treatment arms (discussed further below).

**Table 50. Investigator-reported vs. adjudicated strokes, TIAs and SEE**

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| Subjects with investigator-reported strokes | 183 | 143 | 205 |
| Number (%) of subjects with adjudicated stroke | 163 (89.1) | 120 (83.9) | 181 (88.3) |
| Subjects with investigator-reported TIAs | 85 | 90 | 107 |
| Number (%) of subjects with adjudicated stroke | 16 (18.8) | 12 (13.3) | 17 (15.9) |
| Subjects with investigator-reported SEE | 32 | 29 | 29 |
| Number (%) of subjects with adjudicated SEE | 15 (46.9) | 13 (44.8) | 21 (72) |

[Reviewer's analysis (sponsor's datasets=timev; reviewer sas file=primary_endpoint)]

As a percentage of investigator reported major bleeds, the percentage of major bleeds adjudicated as "no event" was also similar across the treatment arms.

**Table 51 Investigator-reported vs. adjudicated major bleeds**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Investigator reported major bleed | 427 | 528 | 515 |
| Total subjects (n) | 355 | 427 | 449 |
| Adjudicated bleeds | | | |
| Total Major bleed | 404 | 492 | 478 |
| Major bleed | 248 | 296 | 250 |
| Life threatening bleed | 156 | 196 | 228 |
| No Event | 34 | 45 | 44 |

[Reviewer's analysis: (sponsor's datasets= adjud, adjud3, timev and plt122n; reviewer sas file= mj\adjud\original\adj and major) .Total major bleed + no event does not equal investigator reported because some major bleeds were not identified by the investigator

*Identification of endpoint events and adjudication process*

As previously noted in the review, the central adjudication committee had concluded that there were inconsistencies in the adjudication of Non-CNS embolic events and, as a result, non-CNS embolic events were re-adjudicated. The outcome of this second review was to be final and supersede previous documented decisions in the main clinical data base. A random sample of five events adjudicated as SEE in the warfarin arm and five investigator-reported events not adjudicated as SEE in the dabigatran arm were reviewed. In all of the warfarin cases, the re-adjudication was consistent with the original adjudication. In two of five dabigatran cases, the original adjudication was that an event had occurred. In both these cases, the re-adjudication appeared appropriate.

**Table 52. Review of adjudicated SEE**

| Subject | Adjudication | | FDA Reviewer | Comments |
|---|---|---|---|---|
| | Second | Original | | |
| **Warfarin** | | | | |
| 00035039 | yes | yes | yes | |
| 00474008 | yes | yes | yes | |
| 01095010 | yes | yes | yes | |
| 01396006 | yes | yes | yes | |
| 01589031 | NA | yes | yes | identified post database lock, not re-adjudicated |
| **Dabigatran** | | | | |
| 00226020 | no | yes | no | DVT |
| 00432016 | no | no | no | DVT |
| 00432019 | no | no | no | DVT |
| 00452014 | no | no | no | DVT |
| 01425011 | no | yes | no | not documented via imaging, though history suggestive |

To evaluate the adjudication process for stroke events, a random sample was taken of subjects with investigator reported strokes (59 events in 54 subjects). As suggested by the endpoint committee meeting minutes (see section 5.3), blinding, particularly of non-English documents, was not adequate. In 10 of 59 events reviewed (17%), the adjudication package contained information that could have unblinded adjudicators to treatment assignment (see table below). Unblinding was possible in 2 of 20 subjects (10%) from North American sites and in 8 of 34 subjects (24%) from non-North American sites; phrases found in these documents included the following:

- "recruited in RE-LY study…on Dabigatran"
- “atrial fibrillation being treated with warfarin”
- “on warfarin”
- "he is using an experimental blood thinner"
- “Sunday to check INR levels..consult with physician regarding the coumadin dose. Target INR 2.0”
- reference to antivitamin K being suspended
- "elevated INR blood test"
- "despite therapeutic anticoagulation"
- "Regular checks of INR"

Despite this text, many adjudicators reported that they remained blinded during their adjudication. With regard to the adjudication decisions themselves, although some cases were less clear cut than others, as a whole, the decisions reached by adjudicators seemed reasonable.

*Reviewer's comment: The subject reported to be "on warfarin" was in the dabigatran treatment arm. A significant number of subjects who were randomized to dabigatran permanently discontinued study medication and some number of subjects with references to warfarin/INR in their adjudication documents may have been in the dabigatran treatment arms.*

*Discontinuation of study medication*

Permanent discontinuations of study medication were more common in dabigatran compared to warfarin treated subjects. As a way to further explore the reason for permanent interruption of study medication, the sponsor performed an analysis of events occurring around the time of permanent interruptions of study medication. For the purposes of this analysis, when an outcome event was given as the reason for interruption, the exact event was identified using a 30 day window around the event. The results of this analysis are shown below (see appendix for timing of events). The numerically greater incidence of permanent study medication discontinuations for ischemic stroke, TIA (a non-endpoint event) or minor bleed in the dabigatran compared to warfarin treatment arms suggests that knowledge of treatment assignment in this open-label study may have led to differences in how subjects were treated. Though the sponsor reports reason for discontinuation of medication as "Death" for some subjects, such a categorization is nonsensical.

**Table 52. Reasons for permanent discontinuation of study medication**

| | **Dabigatran 110 N=1318** | **Dabigatran 150 N=1382** | **Warfarin N=1073** |
|---|---|---|---|
| Serious AE not related to outcome event | 162 ( 2.7) | 170 ( 2.8) | 119 ( 2.0) |
| Subject didn't want to take study drug | 424 ( 7.1) | 459 ( 7.6) | 405 ( 6.8) |
| Outcome event | 261 ( 4.4) | 246 ( 4.1) | 177 ( 3.0) |
| Stroke | 53 ( 0.9) | 42 ( 0.7) | 26 ( 0.4) |
| Ischemic stroke | 43 ( 0.7) | 34 ( 0.6) | 13 ( 0.2) |
| Hemorrhagic stroke | 4 ( 0.1) | 5 ( 0.1) | 13 ( 0.2) |
| Stroke of uncertain classifications | 6 ( 0.1) | 4 ( 0.1) | 0 |
| SEE | 10 ( 0.2) | 1 ( 0.0) | 2 ( 0.0) |
| PE | 5 ( 0.1) | 5 ( 0.1) | 1 ( 0.0) |
| MI | 9 ( 0.2) | 8 ( 0.1) | 8 ( 0.1) |
| Major Bleed | 53 ( 0.9) | 61 ( 1.0) | 66 ( 1.1) |
| Life threatening major bleeds | 20 ( 0.3) | 37 ( 0.6) | 47 ( 0.8) |
| Other major bleeds | 33 ( 0.6) | 24 ( 0.4) | 19 ( 0.3) |
| Minor bleed | 67 ( 1.1) | 76 ( 1.3) | 37 ( 0.6) |
| TIA | 20 ( 0.3) | 15 ( 0.2) | 0 |
| Death | 18 ( 0.3) | 17 ( 0.3) | 18 ( 0.3) |
| Not matched with the algorithm | 42 ( 0.7) | 37 ( 0.6) | 33 ( 0.6) |
| Other | 471 ( 7.9) | 507 ( 8.4) | 372 ( 6.2) |

| | | | |
|---|---|---|---|
| Adverse Event | 157 ( 2.6) | 164 ( 2.7) | 72 ( 1.2) |
| Lab changes | 44 ( 0.7) | 57 ( 0.9) | 17 ( 0.3) |
| Procedure/hospitalization/surgery | 30 ( 0.5) | 35 ( 0.6) | 46 ( 0.8) |
| Other | 240 ( 4.0) | 251 ( 4.1) | 237 ( 4.0) |

[Source: Sponsor; Modified from Table 15.1.1:3]
For the purposes of this analysis subjects who discontinued the study early without reason for discontinuation CRF were not included. A subject was counted in multiple categories when multiple reasons were given.

# 7 Review of Safety

## 7.1 Methods

In the sponsor's safety analyses and in the safety analyses that follow, subjects without a reported major bleed were censored at the last time vital status information was available. There were a few exceptions (noted in footnotes) where the reviewer's analyses did not use these censoring rule. As noted earlier, errors were found in the disposition data. These errors impact the censoring dates used for analyses, and in particular for those analyses in which subjects were to be censored based on the last date follow up information was available for the outcome of interest.[14] These errors, occurring in a small percentage of subjects, do not alter the results of key analyses and hence many analyses were not re-run using the corrected data sets submitted in August.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review focuses on the findings in RE-LY, and in particular, on the subset of subjects in RE-LY who received at least one dose of study medication (18,040 out of 18,113 randomized subjects). Though dabigatran has also been studied for VTE prevention (and has been approved outside the U.S. for the prevention of VTE post total hip/knee replacement), safety data from the VTE program were not, for the most part, analyzed. RE-LY provides more than 20,000 subject years of exposure and differences in populations, concomitant medications and the use of dabigatran (dose and duration) limit the ability to extrapolate from the safety experience in the VTE program to the proposed indication. However for rare events, such as drug induced liver injury (DILI) , the Periodic Safety Update Report (last dated March 2010) was used.

*Reviewer's comment: A 4 month safety update was submitted on August 17, 2010; an addendum will be filed if the data contained in this submission significantly alter the safety findings/conclusions given in this review.*

14 Datasets named adjrand2 and timecen2

### 7.1.2 Categorization of Adverse Events

The sponsor's coding of adverse events seemed, as a whole, appropriate. Adverse events (AE) were coded to MeDRA version 12.0.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from different studies were not pooled.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure is adequate to describe safety in the intended population. There were over 20,000 subject years of dabigatran exposure in the RE-LY trial. Because more than 50% of subjects on dabigatran temporarily discontinued medication, exposure was calculated including and excluding periods of temporary discontinuation of study medication. In analyses excluding these periods, exposure was on average 9 days less than in analyses in which these periods were included. Subjects on dabigatran took study drug for approximately 1 month less than subjects on warfarin.

**Table 53. Subject years of medication exposure**

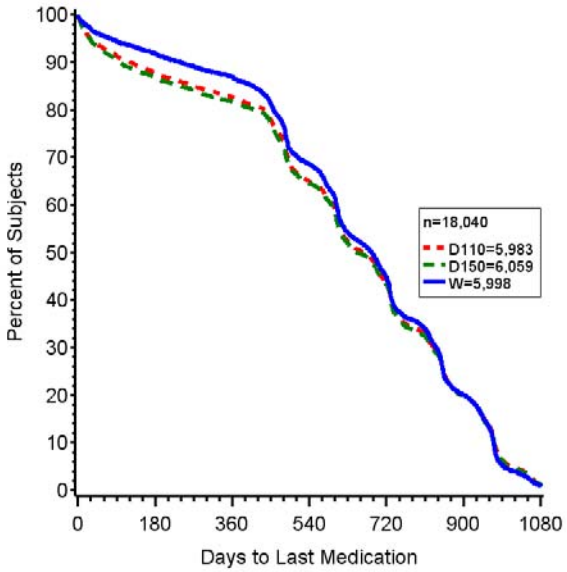
| | **D110 N=5983** | **D150 N=6059** | **W N=5998** |
|---|---|---|---|
| Including periods of temporary medication discontinuation | | | |
| Subject years[1] | 10242 | 10261 | 10659 |
| Mean exposure (mo) | 20.8 | 20.6 | 21.6 |
| Excluding periods of temporary medication discontinuation | | | |
| Subject years | 10089 | 10115 | 10508 |
| Mean exposure (mo) | 20.5 | 20.3 | 21.3 |

1. Subject years calculated as sum [(last med date – first med date) +1]; these calculations were used for the sponsor's safety analyses
[Source: reviewer's analysis file: ds\exposure; sponsor's data set: basco]

More subjects (4-5%) on dabigatran prematurely discontinued medication than on warfarin. The reasons for premature medication discontinuation have been presented in Section 6.1.10.2. The figure below shows the days to last medication in all subjects

treated in RE-LY. More subjects on dabigatran discontinue medication early as compared to warfarin, and the percent of subjects on treatment starts to coincide around 15 months.

**Figure 10. Days to last medication**




[Source: reviewer's analysis: Med dc perm days to; sponsor dataset:lastmed, popu, disco ]

The demographics of the safety population mirror the demographics of the randomized population (see Section 6.1.2 for information). Exposure appears to be adequate in important patient subsets (e.g., age ≥ 75, CHADS2 score 3+, history of stroke/TIA/SEE), Mean exposure in subjects with and without prior VKA use was also explored. As shown in the table below, in VKA experienced subjects, mean exposure appeared to be greater in warfarin than dabigatran treated subjects, suggesting a greater tendency for VKA experienced subjects to discontinue from the dabigatran arms than the warfarin arms.

**Table 54. Study drug exposure in VKA naïve and VKA experienced subjects**

| | VKA naïve | | | | VKA Experienced | | | |
|---|---|---|---|---|---|---|---|---|
| | **D110** | **D150** | **W** | **Total** | **D110** | **D150** | **W** | **Total** |
| Total n | 2990 | 3019 | 3082 | 9091 | 2991 | 3039 | 2916 | 8946 |
| Mean (months) | 19.4 | 19.2 | 19.7 | 19.4 | 21.7 | 21.5 | 23.0 | 22.1 |
| Subject years | 10242 | 10261 | 10659 | 14721 | 5411 | 5432 | 5595 | 16438 |

[Source: Sponsor's table 15.3.1:2 of QC report]

### 7.2.2 Explorations for Dose Response

There is a dose-response relationship for bleeding (see safety sections on bleeding and section 6.1.8).

### 7.2.3 Special Animal and/or In Vitro Testing

The nonclinical testing was adequate to explore potential adverse reactions of particular interest, including bleeding and liver toxicity.

### 7.2.4 Routine Clinical Testing

Routine clinical testing of clinical trial subjects, including the methods and tests used and the frequency of testing, was adequate. Information on outcome events (including stroke and bleeding questionnaires), adverse events, cardioversion, emergency/elective surgery, hospitalization, concomitant medications, INR evaluations, study medication, laboratory evaluation were assessed at each follow-up visit (every 3 months for the first year, then every 4 months until study end). ECGs were assessed at baseline, month 12, 24, 36 and at final follow-up.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Based on the draft Clinical Pharmacology Review dated August 4, 2010, the workup was sufficient to characterize the metabolism and excretion of dabigatran and important drug-drug interactions (see section 4.4)

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor's evaluation for potential adverse events associated with other drugs in this class (thrombin inhibitors/anticoagulants) was adequate. Major adverse events of interest include bleeding and the potential for drug induced liver injury (DILI); these are discussed in detail. A discussion of serious cardiovascular events, including myocardial infarction, will be provided in an addendum to this review.

## 7.3 Major Safety Results

### 7.3.1 Deaths

An imbalance in deaths was seen across the three treatment arms, with a numerically smaller number of deaths reported in dabigatran treated subjects (relative to warfarin). The mortality findings are not a safety concern and are discussed under Efficacy (Section 6.1.6).

## 7.3.2 Nonfatal Serious Adverse Events

### *7.3.2.1. Major Bleeding*

**Overview of findings and conclusions**

Bleeding was the most common and important safety concern identified in RE-LY. Major bleeds and life threatening bleeds (defined in the table below) were pre-specified, adjudicated safety endpoints in RE-LY. Relative to warfarin, there was no difference in major bleeds with dabigatran 150 mg (HR 0.93, 95% CI: 0.81, 1.07) whereas dabigatran 110 mg was associated with fewer major bleeds (HR 0.80, 95% CI: 0.68, 0.90, p<0.003). The risk reduction in major bleeds and life threatening bleeds (relative to warfarin) was influenced by the level of INR control. Subgroup analyses based on the level of INR control (center-level and subject- level) suggest that the risk reduction in major bleeds seen with dabigatran 110 mg is driven to some extent by the subset of warfarin treated subjects achieving lower levels of INR control.

Assessments of bleeding should take into consideration the severity/reversibility of the bleeding event. Important major bleeding has been defined in different ways in clinical trials; the definitions/categories used in RE-LY are shown in the table below. Of note, the ISTH, ESTEEM, and ISCOAT definitions[15] of major bleed are very similar to that used in RE-LY. The ISTH and ISCOAT criteria have also been used in patients receiving long-term anticoagulation.

**Table 55. Various bleeding definitions used in RE-LY**

| Term | Definition |
|---|---|
| Adjudicated major bleed | Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding) |
| Adjudicated life-threatening bleed (sub classification of major bleed) | An adjudicated major bleed meeting at least one of the following criteria: fatal; symptomatic intracranial bleed; reduction in hemoglobin of at least 5 grams per deciliter; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; required surgical intervention |
| RE-LY's GUSTO | An adjudicated ICH event or an adjudicated major bleed with at |

15 ISTH =International Society on Thrombosis & Haemostasis; ESTEEM =Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage; ISCOAT =Italian Study of Complications of Anticoagulant Therapy

| | |
|---|---|
| severe | least one of the following criteria: associated with hypotension requiring use of intravenous inotropic agents; required surgical intervention to stop bleeding |
| Intracranial hemorrhage (ICH) | Includes adjudicated hemorrhagic stroke or adjudicated major bleed that was symptomatic intracranial |

Compared to TIMI major or GUSTO severe, bleed categorizations used in well known intravenous thrombolytic trials, major bleeds, as defined in RE-LY, are not as severe. TIMI major bleeding includes ICH, overt bleeding with a 5 g/dL decrease in hemoglobin and GUSTO severe includes ICH or bleeding that causes hemodynamic compromise and requires intervention. In contrast, major bleeds in RE-LY included relatively small reductions in hemoglobin/transfusion requirements and hence more readily reversible bleeding events. In terms of the severity of the event, RE-LY's life-threatening bleeds and "GUSTO severe" bleeds[16] are perhaps more similar to the definitions of major bleeds used in past thrombolytic trials.

With regard to GUSTO-severe bleeding, dabigatran 110 mg was associated with a 52% reduction (HR 0.48, 95% CI: 0.37, 0.64, p-value <0.0001) relative to warfarin and dabigatran 150 mg was associated with a 31% reduction (HR 0.69, 95% CI: 0.54, 0.88, p-value 0.003) relative to warfarin. Compared to dabigatran 110 mg, dabigatran 150 mg was associated with a 42% greater risk of GUSTO-severe bleed (p=0.02). The reduction in ICH in comparison to warfarin was even greater. Dabigatran 110 mg was associated with a 70% reduction (HR 0.30, 95% CI: 0.19, 0.46, p-value <0.0001) in ICH relative to warfarin, and dabigatran 150 mg was associated with a 59% reduction (HR 0.41, 95% CI: 0.28, 0.60, p-value <0.0001) relative to warfarin. Thus, the findings in RE-LY support a relationship between dabigatran dose and major bleeding risk and suggest a favorable profile relative to warfarin.

**Overview of major bleeds in RE-LY**

The total number of adjudicated major bleeds is shown in the table below. While there were more adjudicated major bleeds in the warfarin arm, there were more subjects with multiple occurrences of major bleeds in the dabigatran arms.

**Table 56. Total adjudicated major bleeds**

| | D110 | % | D150 | % | W | % | Total |
|---|---|---|---|---|---|---|---|
| **Randomized** | **6015** | | **6076** | | **6022** | | |
| Subjects with major bleed | 342 | (5.7) | 399 | (6.6) | 421 | (7.0) | 1162 |

16 RE-LY's "GUSTO severe" definition differs slightly from that used in the GUSTO trials. In the GUSTO trials, GUSTO severe was defined as ICH or bleeding that caused hemodynamic compromise **AND** required intervention.

| | D110 | % | D150 | % | W | % | Total |
|---|---|---|---|---|---|---|---|
| **Randomized** | **6015** | | **6076** | | **6022** | | |
| Number of major bleeds | 406 | (6.7) | 489 | (8.0) | 483 | (8.0) | 1378 |
| Number of subjects with occurrences | | | | | | | |
| 1 | 291 | (4.8) | 335 | (5.5) | 367 | (6.1) | |
| 2 | 38 | (0.6) | 44 | (0.7) | 49 | (0.8) | |
| ≥ 3 | 13 | (0.2) | 20 | (0.3) | 5 | (0.1) | |
| Total life threatening bleeds | 159 | (2.6) | 193 | (3.2) | 233 | (3.9) | |

[source: Adapted from sponsor's table 15.3.5.4:11_New and reviewer's analysis: filename major, sponsor dataset timev]

The table below describes characteristics of the adjudicated major bleed that are not described elsewhere in the review. Deaths associated with major bleeds appeared to be more common in the warfarin arm than in the dabigatran arms.

**Table 57. Characteristics of adjudicated major bleed not described elsewhere**

| Category | D110 | % | D150 | % | W | % |
|---|---|---|---|---|---|---|
| Total adjudicated major bleed* | 397 | (100) | 486 | (100) | 476 | (100) |
| Hg Drop of 2 gm/dL | 266 | (67.0) | 330 | (67.9) | 282 | (59.2) |
| Died | 25 | (6.3) | 28 | (5.8) | 40 | (8.4) |
| Hospitalization | 286 | (72.0) | 368 | (75.7) | 364 | (76.5) |

[source: Reviewer's analysis: mj\tx\adj_plt122n, sponsor dataset plt122n,adjrand,popu]
*These descriptions were available for 1359 adjudicated bleeds.

**Overall risk of bleeding**

Compared to warfarin, the overall relative risk of major bleeding was 20% less for dabigatran 110 mg, and no different for dabigatran 150 mg. Compared to dabigatran 110 mg, dabigatran 150 mg was associated with a 16% greater risk of major bleeding. The relative risk of more severe bleeds (e.g., GUSTO severe, ICH) also appeared to be greater in the warfarin arm than in the dabigatran arms.

**Table 58. Overall relative risk of serious bleeding**

| Type | D110 v. W<br>HR (95%CI)<br>p-value | D150 v. W<br>HR (95%CI)<br>p-value | D150 v. D110<br>HR (95%CI)<br>p-value |
|---|---|---|---|
| Adjudicated major bleeding | 0.80 (0.70, 0.93)<br>0.002 | 0.93 (0.81, 1.07)<br>0.31 | 1.16 (1.00, 1.34)<br>0.04 |
| Life threatening bleed | 0.67 (0.54, 0.81) | 0.80 (0.66, 0.98) | 1.21 (0.97, 1.50) |
| GUSTO severe | 0.48 (0.37, 0.64) | 0.69 (0.54, 0.88) | 1.42 (1.05, 1.91) |
| ICH | 0.30 (0.19, 0.46) | 0.41 (0.28, 0.60) | 1.39 (0.85, 2.28) |
| Adjudicated hemorrhagic strokes | 0.31 (0.17, 0.56) | 0.26 (0.14, 0.49) | 0.85 (0.39, 1.83) |
| Reported symptomatic intracranial bleeds | 0.29 (0.19, 0.44) | 0.47 (0.33, 0.67) | 1.61 (1.00, 2.61) |

[Source: Reviewer's analysis, filename: timev\HR, sponsor's data;adjrand] Cox proportional regression, data shown are Hazard ratio (95% confidence interval)

The absolute event rates using various definitions of major bleeding are shown in the table below. As a whole, these data support a relationship between dabigatran dose and bleeding risk.

**Table 59. Overall absolute risk of major bleeding**

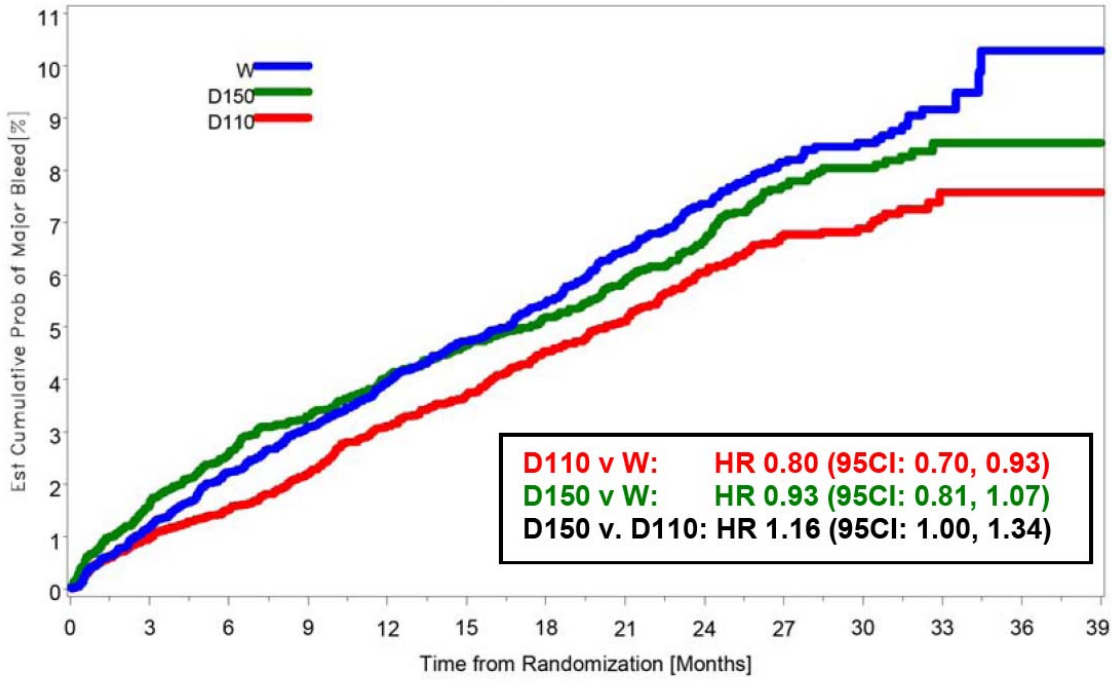
| | D110<br>(n=6015) | | D150<br>(n=6076) | | W<br>(n=6022) | |
|---|---|---|---|---|---|---|
| **Type** | **# events** | **%/yr** | **# events** | **%/yr** | **# events** | **%/yr** |
| Major bleed | 342 | 2.87 | 399 | 3.32 | 421 | 3.57 |
| Life threatening bleed | 147 | 1.24 | 179 | 1.49 | 218 | 1.85 |
| GUSTO severe | 74 | 0.62 | 106 | 0.88 | 151 | 1.28 |
| ICH | 27 | 0.23 | 38 | 0.32 | 90 | 0.76[17] |

[Source: reviewer's analysis, file: eventrate, sponsor's data: timev, adjrand]
Study duration=date of study termination-date of randomization +1
Subject years=sum (study duration for all subjects)/365.25
Yearly event rate (%/yr)=# subjects with event/subject years*100

The time to first major bleed is shown in the next figure. Throughout the period of follow up, the rates of major bleeding in the dabigatran 110 mg arm appear to be lower than the rates seen in the other treatment arms.[18]

17. It is noted that the rate of ICH in the warfarin arm seems high when compared to ACTIVE-W (annual rate 0.4% from Dr. U clinical review), despite the use of, what appears to be, similar definitions of ICH in the two trials. It is unclear what to make of this.

**Figure 11. Time to first major bleed**



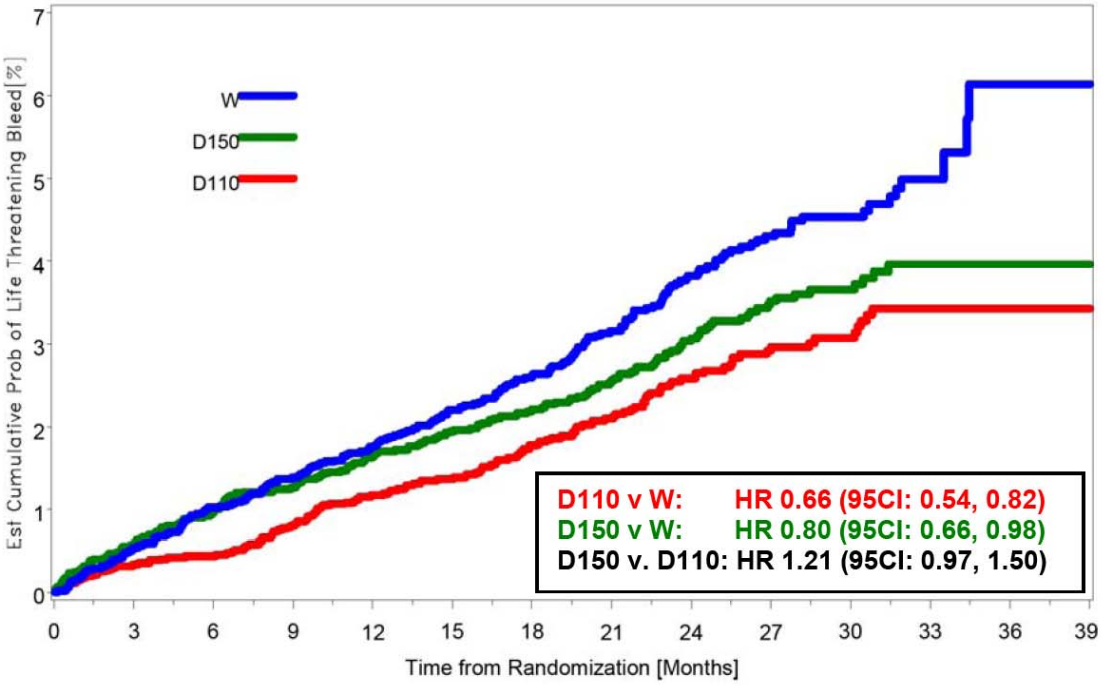

| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5830 | 5738 | 5637 | 5527 | 5274 | 4409 | 3564 | 2972 | 2236 | 1365 | 447 | 75 |
| D150 | 6076 | 5858 | 5731 | 5613 | 5519 | 5264 | 4450 | 3596 | 3022 | 2243 | 1367 | 450 | 82 |
| W | 6022 | 5822 | 5693 | 5567 | 5462 | 5138 | 4347 | 3444 | 2869 | 2160 | 1250 | 343 | 71 |

[Source: Reviewer's analysis, filename: time mjbleed, HR mjbleed; Kaplan Meier analysis, sponsor data: adjrand]

18. While there was no difference in major bleeding between dabigatran 150 mg and warfarin, it is noted that in the beginning of the trial the risk of bleeding appears higher with dabigatran 150 mg as compared to warfarin. After approximately 12-16 months, the slope of the curve decreases and runs below warfarin. Although completely speculative, the timing of the change in slope may be related to the permanent discontinuation of dabigatran (see Figure 9).

For life threatening bleeds, the curve for dabigatran 110 mg starts to separate from the curve for warfarin after about 3 months; the curve for dabigatran 150 mg starts to separate from warfarin after about 1 year.

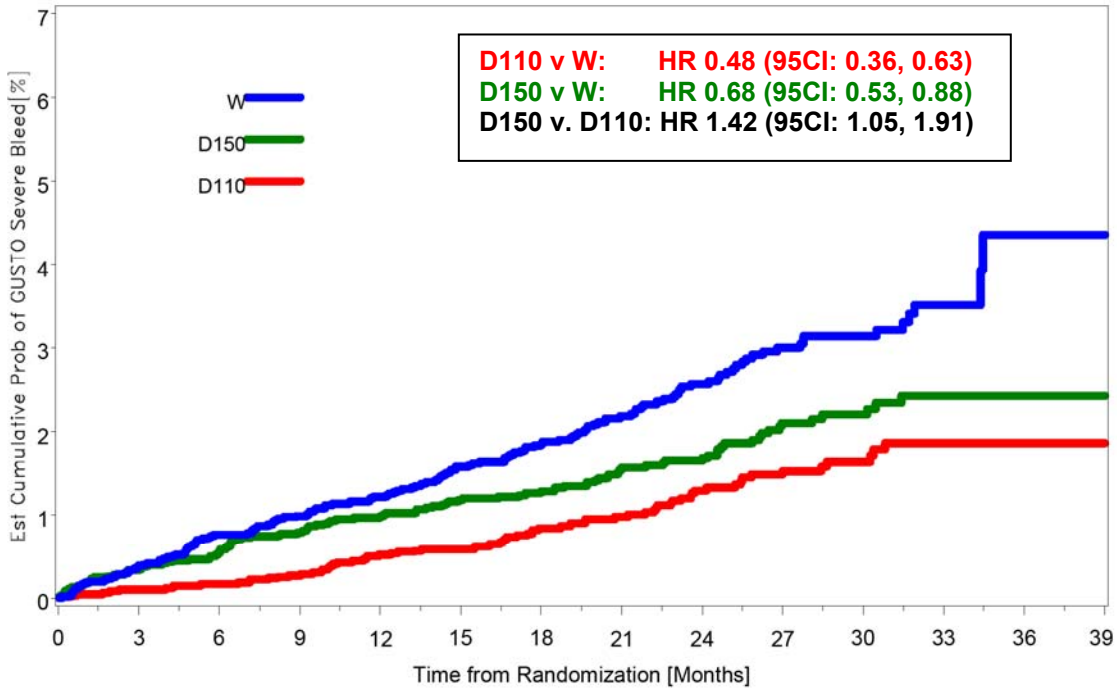
**Figure 12. Time to first life threatening bleed**




| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5861 | 5791 | 5705 | 5622 | 5383 | 4519 | 3663 | 3064 | 2315 | 1409 | 461 | 79 |
| D150 | 6076 | 5912 | 5816 | 5720 | 5642 | 5396 | 4570 | 3711 | 3128 | 2336 | 1427 | 471 | 86 |
| W | 6022 | 5857 | 5757 | 5657 | 5571 | 5253 | 4452 | 3541 | 2956 | 2235 | 1296 | 353 | 72 |

The next figure shows the time to first GUSTO severe bleed. The curves appear to separate earlier than for the other bleeding categories.

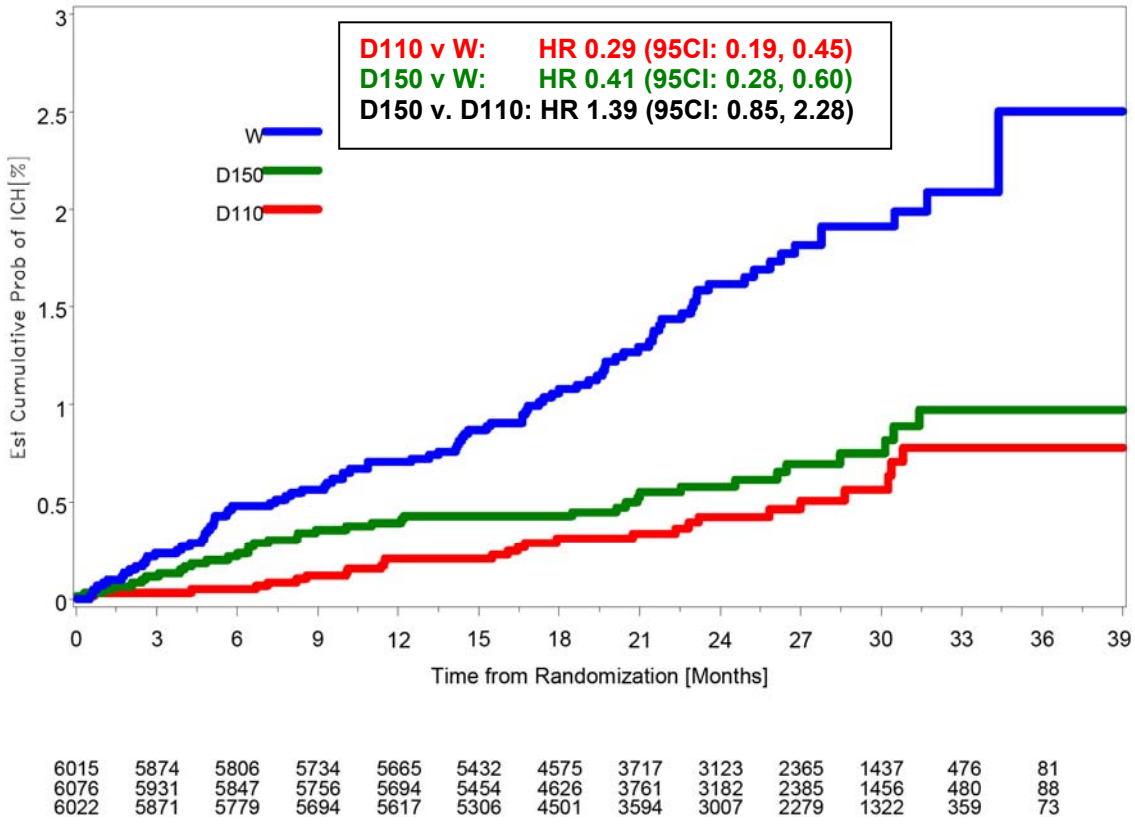
**Figure 13. Time to first GUSTO severe bleed**




| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5872 | 5802 | 5729 | 5653 | 5418 | 4557 | 3697 | 3102 | 2344 | 1422 | 467 | 81 |
| D150 | 6076 | 5923 | 5836 | 5741 | 5672 | 5427 | 4603 | 3737 | 3162 | 2362 | 1442 | 477 | 88 |
| W | 6022 | 5864 | 5767 | 5674 | 5595 | 5278 | 4478 | 3571 | 2987 | 2255 | 1306 | 355 | 72 |

The next figure shows the time to first ICH.

**Figure 14. Time to first ICH**

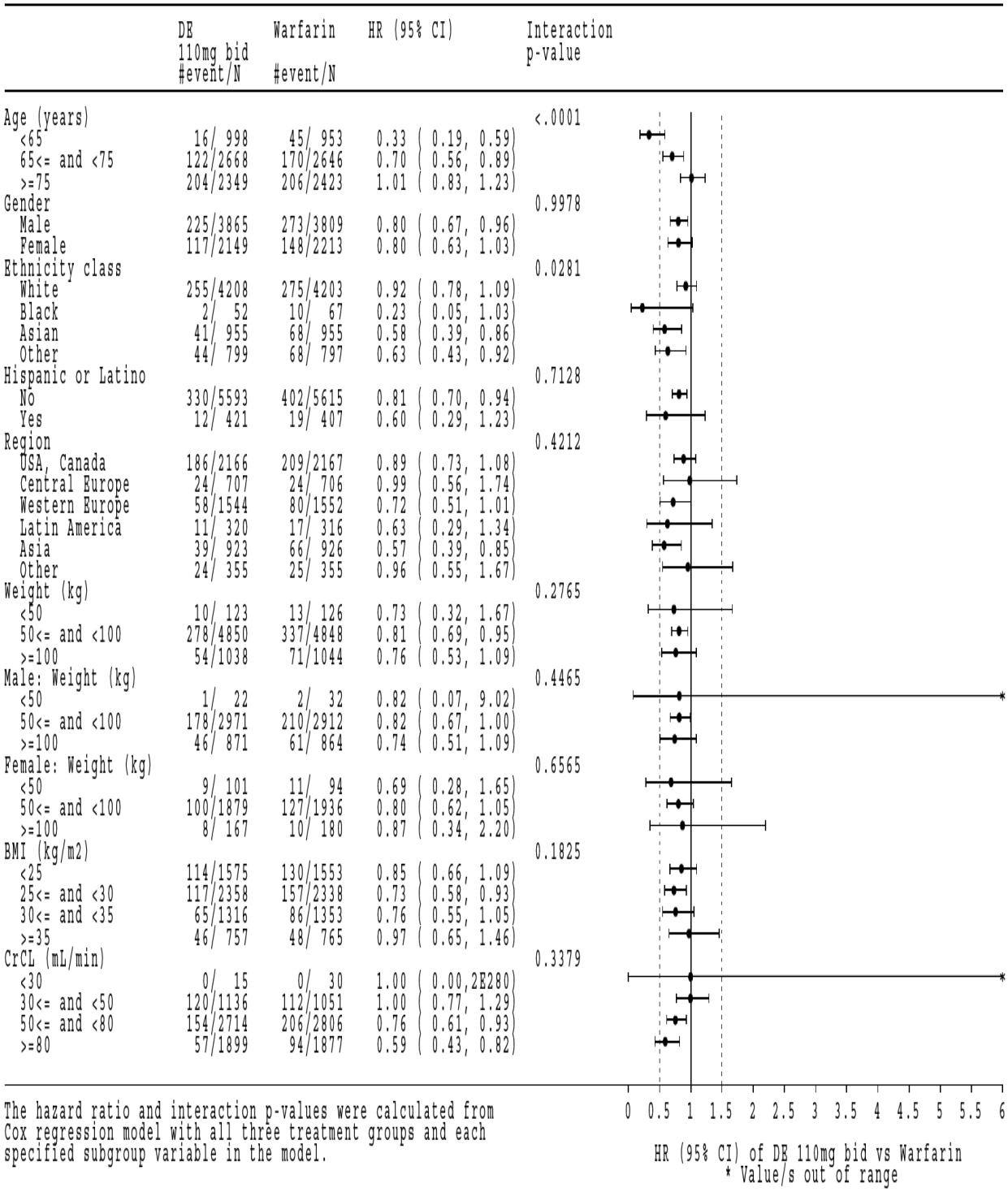



| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5874 | 5806 | 5734 | 5665 | 5432 | 4575 | 3717 | 3123 | 2365 | 1437 | 476 | 81 |
| D150 | 6076 | 5931 | 5847 | 5756 | 5694 | 5454 | 4626 | 3761 | 3182 | 2385 | 1456 | 480 | 88 |
| W | 6022 | 5871 | 5779 | 5694 | 5617 | 5306 | 4501 | 3594 | 3007 | 2279 | 1322 | 359 | 73 |

**Subgroup analysis – baseline demographics**

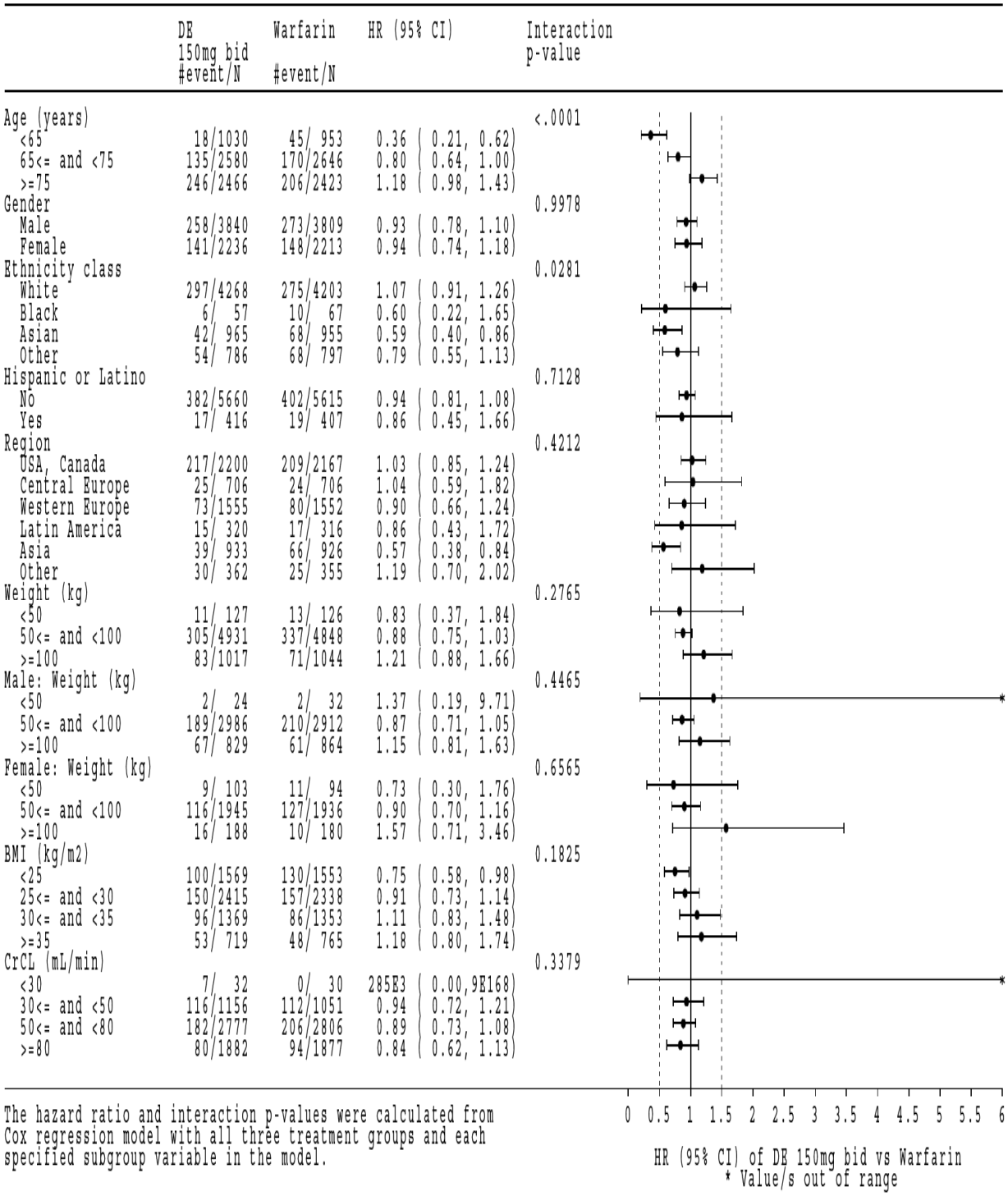
As a whole, subgroup analyses suggested no difference in major bleeding by gender, race, region, or weight compared to warfarin. In the Chinese, both the 110 and 150 mg doses of dabigatran were associated with a lower risk of major bleeding (relative to warfarin. Very few blacks were studied, limiting conclusions in this population. The effects of age and impaired renal function are discussed in sections 7.5.3 and 7.5.4, respectively.

**Figure 15. Dabigatran 110 mg v. warfarin subgroup analysis**




[Source: Sponsor Figure 15.3.2.2.2:1, 4.19.10 resubmission]

**Figure 16. Dabigatran 150 v. warfarin subgroup analysis (baseline demographics)**




[Source: Sponsor Figure 15.3.2.2.2:2, 4.19.10 resubmission]

**VKA use and INR control**

Prior VKA use (as defined by the sponsor) did not clearly affect the relationship between risk of bleeding on dabigatran relative to warfarin.

**Table 53. Relative and absolute risk by vitamin K antagonist use**

| Type | D110 v. W HR (95%CI) | D150 v. W HR (95%CI) | D110 %/yr | D150 %/yr | W %/yr |
|---|---|---|---|---|---|
| Adjudicated major bleeding | 0.80 (0.70, 0.93) | 0.93 (0.81, 1.07) | 2.87 | 3.32 | 3.57 |
| Naïve | 0.87 (0.71, 1.07) | 0.94 (0.77, 1.14) | 3.11 | 3.33 | 3.57 |
| Experienced | 0.74 (0.60, 0.91) | 0.93 (0.76,1.12) | 2.66 | 3.30 | 3.57 |
| Life threatening bleed | 0.67 (0.54, 0.81) | 0.80 (0.66, 0.98) | 1.24 | 1.49 | 1.85 |
| Naïve | 0.75 (0.55, 1.01) | 0.84 (0.62, 1.12) | 1.27 | 1.42 | 1.71 |
| Experienced | 0.60 (0.45, 0.80) | 0.78 (0.60, 1.02) | 1.20 | 1.55 | 1.98 |
| GUSTO severe | 0.48 (0.37, 0.64) | 0.69 (0.54, 0.88) | 0.62 | 0.88 | 1.28 |
| Naïve | 0.47 (0.31, 0.72) | 0.77 (0.53, 1.11) | 0.55 | 0.89 | 1.17 |
| Experienced | 0.49 (0.34, 0.71) | 0.62 (0.44, 0.88) | 0.69 | 0.87 | 1.39 |
| ICH | 0.30 (0.19, 0.46) | 0.41 (0.28, 0.60) | 0.23 | 0.32 | 0.76 |
| Naïve | 0.27 (0.14, 0.51) | 0.43 (0.25, 0.75) | 0.19 | 0.32 | 0.73 |
| Experienced | 0.32 (0.18, 0.57) | 0.40 (0.24, 0.67) | 0.26 | 0.32 | 0.79 |

[source:reviewer's analysis: sub\vka, sponsor's file: adjrand, basco]

*Relative risk: An analysis focusing on the subset of subjects known to be well controlled on warfarin at baseline is perhaps of greater interest. To this reviewer's knowledge, such information was not collected in the trial.*

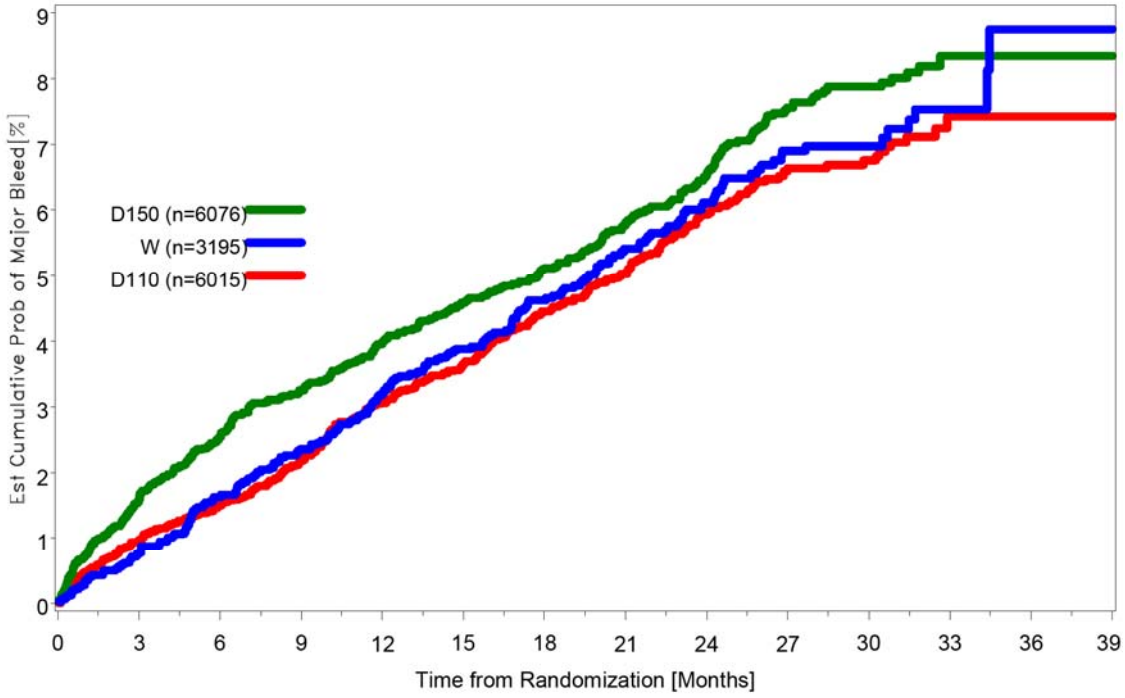
The risk reduction in major bleeds and life threatening bleeds (relative to warfarin) was influenced by the level of INR control; however such a relationship was not seen for GUSTO severe or ICH bleeding. Subgroup analyses based on the level of INR control (center-level and subject- level) suggest that the risk reduction in major bleeds seen with dabigatran 110 mg is driven to some extent by the subset of warfarin treated subjects achieving lower levels of INR control (see table below and section 6.1.10.1 ).

**Table 54. Risk of bleeding compared to warfarin subjects with INR in range (2-3) ≥ 65% of the time**

| Type | D110 v. W<br>HR (95%CI)<br>p-value | D150 v. W<br>HR (95%CI)<br>p-value |
|---|---|---|
| Adjudicated major bleeding | 0.95 (0.80, 1.13) | 1.10 (0.93, 1.31) |
| Life threatening bleed | 0.78 (0.61, 1.004) | 0.94 (0.74, 1.20) |
| GUSTO severe | 0.46 (0.34, 0.62) | 0.65 (0.49, 0.86) |
| ICH | 0.32 (0.21, 0.52) | 0.45 (0.29, 0.70) |

N=15,286 (3,195 on warfarin)[source: reviewer's analysis: inr\inr65, sponsor's data: adjrand, basco]

**Figure 17. Time to first major bleed, warfarin subjects with INR 2-3 ≥ 65% of the time**




| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5904 | 5826 | 5739 | 5624 | 5379 | 4510 | 3674 | 3039 | 2304 | 1401 | 469 | 79 |
| D150 | 6076 | 5936 | 5832 | 5731 | 5633 | 5387 | 4558 | 3701 | 3101 | 2309 | 1407 | 464 | 82 |
| W | 3195 | 3165 | 3126 | 3091 | 3050 | 2891 | 2477 | 1997 | 1682 | 1280 | 777 | 223 | 50 |

[source: reviewer's analysis: time mjb INR, sponsor data: adjrand, basco]

**Concomitant medications**

The yearly event rate of major bleeds based on baseline concomitant medication use and use during the study was higher for subjects on aspirin, clopidogrel or aspirin plus

clopidogrel across all treatment arms. This relationship didn't appear to be affected by whether or not a subject was treated with dabigatran or warfarin. Subjects that experienced significant bleeding were likely taken off of concomitant medications that also cause bleeding, which may explain the lower rates of bleeding in subjects reporting 100% use of these medications (relative to the other groupings of use).

**Table 55. Yearly event rate of major bleeds by medication use during the study**

| | DE 110mg bid | | | | DE 150mg bid | | | | Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % of time taking concomitant medication | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) |
| Antithrombotic therapy | | | | | | | | | | | | |
| ASA | | | | | | | | | | | | |
| 0% (never) | 3615 | 7219 | 153 | 2.12 | 3687 | 7357 | 178 | 2.42 | 3616 | 7162 | 187 | 2.61 |
| Used at least one time | 2400 | 4681 | 189 | 4.04 | 2389 | 4676 | 221 | 4.73 | 2406 | 4632 | 234 | 5.05 |
| 0%< and <=50% | 854 | 1680 | 76 | 4.52 | 907 | 1788 | 105 | 5.87 | 918 | 1762 | 92 | 5.22 |
| 50% <and < 100% | 272 | 541 | 41 | 7.58 | 292 | 588 | 45 | 7.66 | 241 | 494 | 52 | 10.53 |
| 100% (always) | 1274 | 2460 | 72 | 2.93 | 1190 | 2300 | 71 | 3.09 | 1247 | 2376 | 90 | 3.79 |
| Clopidogrel | | | | | | | | | | | | |
| 0% (never) | 5572 | 11044 | 295 | 2.67 | 5624 | 11109 | 344 | 3.10 | 5581 | 10930 | 363 | 3.32 |
| Used at least one time | 443 | 855 | 47 | 5.50 | 452 | 924 | 55 | 5.95 | 441 | 864 | 58 | 6.71 |
| 0%< and <=50% | 218 | 428 | 26 | 6.08 | 248 | 509 | 35 | 6.88 | 225 | 462 | 29 | 6.28 |
| 50% <and < 100% | 82 | 167 | 14 | 8.37 | 71 | 160 | 13 | 8.14 | 64 | 129 | 15 | 11.59 |
| 100% (always) | 143 | 260 | 7 | 2.69 | 133 | 256 | 7 | 2.74 | 152 | 273 | 14 | 5.13 |
| Dipyridamole | | | | | | | | | | | | |
| 0% (never) | 5987 | 11841 | 339 | 2.86 | 6049 | 11981 | 397 | 3.31 | 5998 | 11743 | 420 | 3.58 |
| Used at least one time | 28 | 58 | 3 | 5.18 | 27 | 53 | 2 | 3.81 | 24 | 51 | 1 | 1.96 |
| 0%< and <=50% | 12 | 25 | 2 | 8.03 | 7 | 14 | 0 | 0.00 | 11 | 23 | 0 | 0.00 |
| 50% <and < 100% | 5 | 11 | 1 | 8.93 | 5 | 9 | 1 | 10.70 | 0 | 0 | 0 | 0.00 |
| 100% (always) | 11 | 22 | 0 | 0.00 | 15 | 30 | 1 | 3.37 | 13 | 28 | 1 | 3.63 |

[sponsor table 15.3.2.2.3:3]

Dabigatran etexilate (but not dabigatran) is a substrate of p-gp, so a relationship between p-gp inhibitors and bleeding risk was also explored. No consistent pattern is seen with regard to the effect of these medications on the relative risk of bleeding on dabigatran (compared to warfarin). While the risk of bleeding was sometimes higher with concomitant p-gp inhibitors amiodarone, diltiazem, and verapamil, it also seemed higher in the warfarin arms. Since warfarin does not have an interaction with p-gp, it is difficult to draw conclusions from these analyses. There were too few subjects taking ketoconazole and p-gp inducers to make any definitive conclusions.

**Table 56. Yearly event rate of major bleeds by concomitant p-gp inhibitor during treatment period safety set**

| | DE 110mg bid | | | | DE 150mg bid | | | | Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % of time taking concomitant medication | # of subj | Subject-years | Subjects with event | Yearly event rate (%) | # of subj | Subject-years | Subjects with event | Yearly event rate (%) | # of subj | Subject-years | Subjects with event | Yearly event rate (%) |
| P-gp inhibitor | | | | | | | | | | | | |
| Amiodarone | | | | | | | | | | | | |
| 0% (never) | 5139 | 8855 | 241 | 2.72 | 5191 | 8792 | 295 | 3.36 | 5097 | 9118 | 321 | 3.52 |
| Used at least once | 844 | 1387 | 54 | 3.89 | 868 | 1469 | 55 | 3.74 | 901 | 1542 | 57 | 3.70 |
| 0%< and <=50% | 209 | 379 | 19 | 5.01 | 200 | 360 | 21 | 5.84 | 209 | 387 | 19 | 4.91 |
| 50% <and < 100% | 311 | 546 | 26 | 4.76 | 328 | 606 | 24 | 3.96 | 377 | 680 | 28 | 4.12 |
| 100% (always) | 324 | 462 | 9 | 1.95 | 340 | 503 | 10 | 1.99 | 315 | 475 | 10 | 2.11 |
| Diltiazem | | | | | | | | | | | | |
| 0% (never) | 5310 | 9028 | 240 | 2.66 | 5384 | 9032 | 302 | 3.34 | 5298 | 9350 | 323 | 3.45 |
| Used at least once | 673 | 1214 | 55 | 4.53 | 675 | 1229 | 48 | 3.91 | 700 | 1309 | 55 | 4.20 |
| 0%< and <=50% | 147 | 273 | 12 | 4.40 | 168 | 329 | 9 | 2.74 | 168 | 326 | 18 | 5.52 |
| 50% <and < 100% | 260 | 513 | 31 | 6.04 | 268 | 526 | 27 | 5.14 | 287 | 571 | 29 | 5.08 |
| 100% (always) | 266 | 428 | 12 | 2.80 | 239 | 374 | 12 | 3.20 | 245 | 412 | 8 | 1.94 |
| Verapamil | | | | | | | | | | | | |
| 0% (never) | 5574 | 9530 | 273 | 2.86 | 5650 | 9521 | 321 | 3.37 | 5553 | 9818 | 350 | 3.56 |
| Used at least once | 409 | 712 | 22 | 3.09 | 409 | 740 | 29 | 3.92 | 445 | 841 | 28 | 3.33 |
| 0%< and <=50% | 83 | 158 | 7 | 4.44 | 95 | 178 | 6 | 3.38 | 103 | 200 | 7 | 3.50 |
| 50% <and < 100% | 138 | 264 | 9 | 3.41 | 142 | 276 | 14 | 5.08 | 164 | 330 | 13 | 3.94 |
| 100% (always) | 188 | 291 | 6 | 2.07 | 172 | 286 | 9 | 3.14 | 178 | 311 | 8 | 2.57 |

[sponsor's table 15.3.2.2.3:6]

**Location of symptomatic major bleeds**

The location of symptomatic adjudicated major bleeds is shown in the table below. Most of the symptomatic bleeding was gastrointestinal, followed by intracranial, and then intraocular bleeding. The risk of GI bleeding appears to be greater in the dabigatran arms compared to warfarin (discussed further below).

**Table 57. Location of adjudicated major bleeds[19]**

| Location | D110 | % | D150 | % | W | % |
|---|---|---|---|---|---|---|
| Total adjudicated major bleeding | 397 | (100) | 486 | (100) | 476 | (100) |
| Symptomatic bleeding | 225 | (56.7) | 285 | (58.6) | 237 | (49.8) |
| Gastrointestinal | 155 | (39.0) | 219 | (45.1) | 141 | (29.6) |
| Symptomatic intracranial | 27 | (6.8) | 33 | (6.8) | 82 | (17.2) |
| Intraocular | 16 | (4.0) | 11 | (2.3) | 16 | (3.4) |
| Retroperitoneal | 2 | (0.5) | 9 | (1.9) | 12 | (2.5) |
| Intramuscular | 8 | (2.0) | 8 | (1.6) | 19 | (4.0) |
| Genito-urinary | 16 | (4.0) | 7 | (1.4) | 10 | (2.1) |
| ENT | 4 | (1.0) | 7 | (1.4) | 7 | (1.5) |
| Surgical | 8 | (2.0) | 6 | (1.2) | 13 | (2.7) |
| Intra-abdominal | 3 | (0.8) | 5 | (1.0) | 2 | (0.4) |
| Intra-thoracic | 8 | (2.0) | 4 | (0.8) | 7 | (1.5) |
| Intra-articular | 5 | (1.3) | 4 | (0.8) | 7 | (1.5) |
| Pericardial | 2 | (0.5) | 3 | (0.6) | 3 | (0.6) |
| Other area | 1 | (0.3) | 2 | (0.4) | 7 | (1.5) |
| Source unidentified | 1 | (0.3) | 1 | (0.2) | . | . |
| Intraspinal | . | . | . | . | 1 | (0.2) |

[source: Reviewer's analysis: mj\tx\adj_plt122n, sponsor dataset plt122n,adjrand,popu] This description was available for 1359 adjudicated bleeds. Includes those subjects with an adjudicated major bleed for which CRF 122 or CRF 97 was completed.

**GI Bleeds**

There was a greater risk of a GI bleed with dabigatran 150 mg compared to warfarin (see table below). This effect persisted over time and was dose related (see figure). Relative to warfarin, the risk of a major GI bleed on dabigatran increased with age, with the greatest relative risk seen in subjects≥ 75 years treated with dabigatran 150 mg: HR 1.79 (95%CI: 1.32, 2.42). Across all treatment arms, subjects on aspirin, clopidogrel, or aspirin+clopidogrel at baseline had a greater absolute risk of a major GI bleed compared to subjects not on these medications at baseline (sponsor table 15.3.2.2.8:13).

19 *Under the category, "Symptomatic bleeding in a critical area or organ", there was box left for "Other". PHRI recoded the "other" to an organ, if it could be, except for 15 of the major bleeds. These 15 were identified during the QC roadmap or during the close out period. For the purposes of this table, the reviewer categorized the 15 "Other"(if the event could be categorized), using a similar algorithm as that used by PHRI. The following "Other" were not categorized: Cancer of prostate, penile trauma, SAE anemia cancer treated with chemotherapy.*

**Table 58. Risk of serious and any GI bleed**

| Type | D110 v. W HR (95%CI) | D150 v. W HR (95%CI) | D150 v. D110 HR (95%CI) | D110 %/yr | D150 %/yr | W %/yr |
|---|---|---|---|---|---|---|
| Adjudicated major bleeding, GI | 1.07 (0.84, 1.36) | 1.47 (1.17, 1.85) | 1.38 (1.10, 1.72) | 1.14 | 1.57 | 1.07 |
| Life threatening, GI | 1.17 (0.82, 1.67) | 1.62 (1.17, 2.26) | 1.39 (1.02, 1.90) | 0.57 | 0.79 | 0.49 |
| Any GI bleed | 1.35 (1.19, 1.53) | 1.52 (1.35, 1.72) | 1.13 (1.01, 1.26) | 5.41 | 6.13 | 4.02 |

[source: reviewer's analysis: hr\phreg_GI, sponsor dataset: timev]

**Figure 18. Time to first major GI bleed**

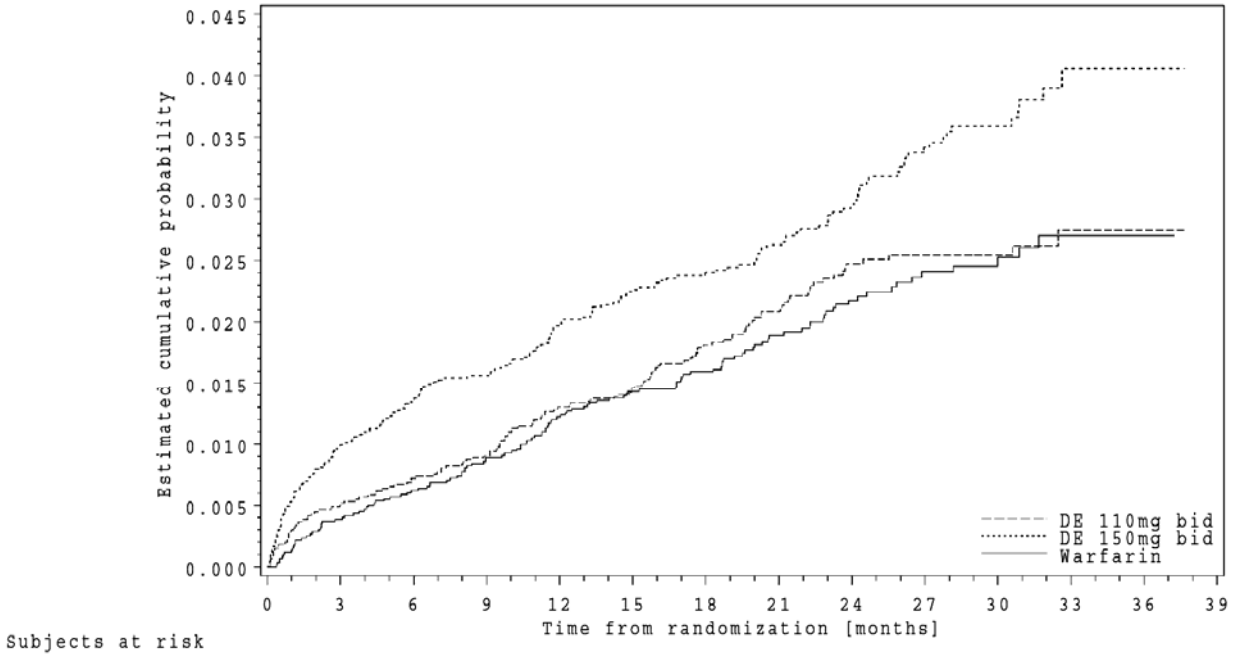
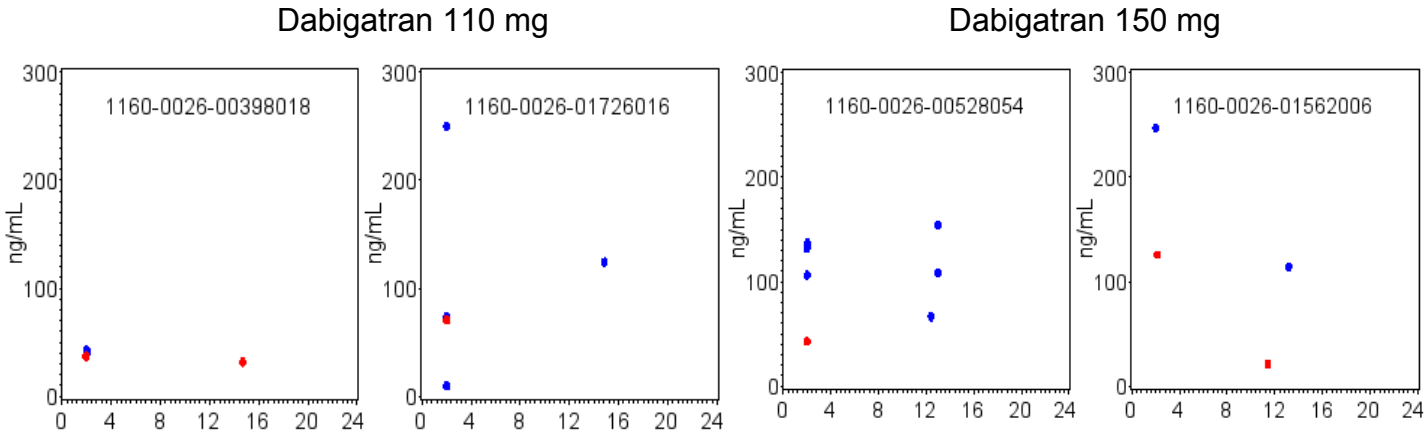



Figure 15.3.2.2.8: 1 Kaplan-Meier estimates of time to first gastrointestinal major bleeds randomized set

**Dabigatran plasma concentrations**

Four subjects were identified who had dabigatran concentration data at the time of an adjudicated major bleed who also had concentration data while not bleeding. Although the number of subjects is very small, it raises questions about the utility of using plasma concentrations to monitor individual subjects/adjust dose based on dabigatran concentrations.

**Figure 19. Dabigatran concentrations in four subjects during a major bleed (red) and not during a major bleed (blue)**




The x-axis is time in hours from last dose and the y-axis is the dabigatran plasma concentration in ng/mL. [Source: Reviewer's analysis: mj\conc\conc_2; sponsor datasets: timev, pk4p (5.3.10)]

### *7.3.2.2. Summary of non-bleeding SAEs*

The total number of reported SAEs are shown by treatment arm in the table below, along with the reason given for reporting the event as "serious". The number of events reported as well as the reason given appears similar across the treatment arms.

**Table 59. Reason given for reporting event as SAE**

| Category | D110 N=5983 | % | D150 n=6059 | % | W n=5998 | % |
|---|---|---|---|---|---|---|
| SAE | 1263 | (21.2) | 1290 | (21.3) | 1357 | (22.6) |
| Fatal | 107 | (1.8) | 100 | (1.7) | 122 | (2.0) |
| Immediately life threatening | 50 | (0.8) | 46 | (0.8) | 64 | (1.1) |
| Disability/incapacitated | 575 | (9.6) | 532 | (8.8) | 592 | (9.9) |
| Required hospitalization | 1073 | (17.9) | 1090 | (18.0) | 1178 | (19.6) |
| Prolonged hospitalization | 95 | (1.6) | 71 | (1.2) | 89 | (1.5) |
| Congenital anomaly | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Other | 1138 | (19.0) | 1243 | (20.5) | 939 | (15.7) |

[Source: Adapted from sponsor's table 15.3.2.6:1, sponsor resubmission 4.19.10. Subjects may be counted in more than one seriousness category]

There were no notable differences between treatment arms for any of the system organ classes (SOCs). The following table shows SAEs for selected SOC and associated SAEs of particular interest (i.e., cardiac, gastrointestinal). The SAE data do not markedly alter our understanding of the safety profile.

**Table 16. SAE by system organ class (SOC)**

| SAE | D110 N=5983 | % | D150 n=6059 | % | W n=5998 | % |
|---|---|---|---|---|---|---|
| SAE | 1263 | (21.2) | 1290 | (21.3) | 1357 | (22.6) |
| Cardiac disorders | 310 | (5.2) | 291 | (4.8) | 321 | (5.4) |
| Angina pectoris | 29 | (0.5) | 30 | (0.5) | 22 | (0.4) |
| Unstable angina | 7 | (0.1) | 13 | (0.2) | 5 | (0.1) |
| Gastrointestinal disorders | 212 | (3.5) | 241 | (4.0) | 214 | (3.6) |
| Abdominal pain | 11 | (0.2) | 8 | (0.1) | 17 | (0.3) |
| Dyspepsia | 6 | (0.1) | 1 | (0.0) | 0 | (0.0) |
| Pancreatitis (includes chronic) | 1 | (0.0) | 5 | (0.1) | 8 | (0.1) |
| Pancreatitis acute | 3 | (0.1) | 1 | (0.0) | 0 | (0.0) |
| Blood and lymphatic system disorders | 68 | (1.1) | 69 | (1.1) | 71 | (1.2) |
| Anemia | 34 | (0.6) | 47 | (0.8) | 33 | (0.6) |
| Renal and urinary disorders | 104 | (1.7) | 94 | (1.6) | 113 | (1.9) |
| Renal failure acute* | 62 | (1.0) | 58 | (1.0) | 64 | (1.1) |
| Renal impairment | 3 | (0.1) | 5 | (0.1) | 2 | (0.0) |

[Source: Adapted from sponsor's table 15.3.2.6:2, sponsor resubmission 4.19.10. Subjects may be counted in more than one category] *includes acute, failure, renal tubular necrosis, azotemia, prerenal failure

### 7.3.3 Dropouts and/or Discontinuations

Adverse events leading to treatment discontinuation are shown in the table below. GI disorders were the most common adverse events leading to drug discontinuation in the dabigatran treatment arm. Other reasons for discontinuation of study medication are described in section 6.1.10.

**Table 16. AE leading to treatment discontinuations**

| | D110 N=5983 | % | D150 n=6059 | % | W n=5998 | % |
|---|---|---|---|---|---|---|
| Total subjects with AE leading to med d/c | 1138 | (19.0) | 1243 | (20.5) | 939 | (15.7) |
| Gastrointestinal disorders | 387 | (6.5) | 422 | (7.0) | 232 | (3.9) |
| Dyspepsia | 57 | (1.0) | 57 | (0.9) | 2 | (0.0) |
| GI hemorrhage | 39 | (0.7) | 55 | (0.9) | 37 | (0.6) |
| Cardiac disorders | 144 | (2.4) | 140 | (2.3) | 120 | (2.0) |
| Nervous system disorders | 138 | (2.3) | 129 | (2.1) | 96 | (1.6) |
| Renal and urinary disorders | 129 | (2.2) | 119 | (2.0) | 85 | (1.4) |
| Renal failure acute* | 63 | (1.1) | 58 | (1.0) | 45 | (0.8) |

[source: Adapted from sponsor table 15.3.2.6:4, resubmission] *includes acute, failure, renal tubular necrosis, azotemia, prerenal failure

### 7.3.4 Significant Adverse Events

As noted under efficacy, there was a numerical imbalance in the number of MI's that favored subjects randomized to warfarin. This finding will be addressed further in a safety addendum.

### 7.3.5 Drug induced liver injury

**Overview of findings and conclusions**

Ximelagatran, an oral direct thrombin inhibitor, was associated with hepatotoxicity[20], raising concern for drug induced liver injury with dabigatran. To address this issue, the reviewer's comprehensive review included analyses of liver-related laboratory data and adverse event data, a review of cases of interest from the RE-LY trial, as well as an assessment of potential cases of DILI in the postmarketing setting. Drs. Senior and Seefe, from the Office of Surveillance and Epidemiology (OSE), reviewed the cases of interest and applied a scoring scale that assesses the severity (SEV) of liver injury and likelihood (LIK) of DILI,.[21]

Review of the laboratory data revealed 55 cases of interest in RE-LY: 16 occurring in subjects randomized to dabigatran 110, 16 in subjects randomized to dabigatran 150, and 23 in subjects randomized to warfarin. Among these cases, there were no definite

20. There were 14 cases of concern on ximelagatran (n=1960) in SPORTIF V; 1 very likely and 5 probable

21. This scoring system has been used in the past at FDA. It differs slightly from the Drug Induced Liver Injury Network (DILIN) scoring system and considerably from the NIH/NCI/CTEP/CTC (common toxicity criteria) manual.

or very likely DILI cases. One probable cause subject (51-75% likelihood, more likely than all other causes combined, only one other cause possible) was identified in the dabigatran 110 mg arm. There was not a greater frequency of more serious liver injury from dabigatran as compared to warfarin. While the review of postmarketing cases is not yet completed, to date, no definite DILI case has been identified in the postmarketing setting. Finally, no greater incidence of liver-related laboratory abnormalities or adverse events was seen in dabigatran treated subjects (compared to warfarin) in RE-LY.

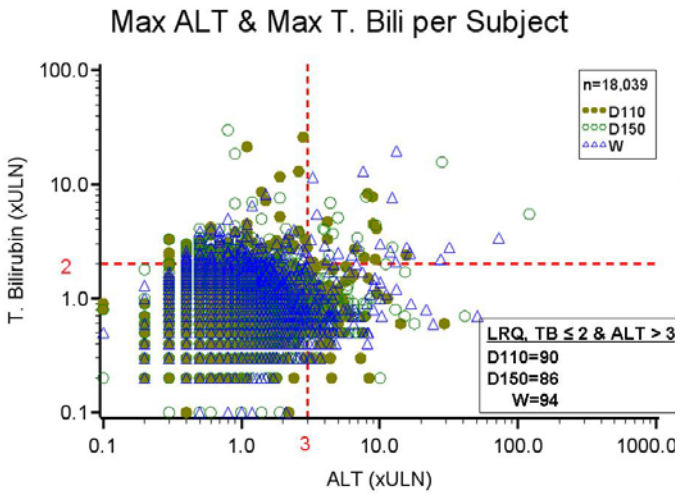
Based on these data, the risk of severe drug induced liver injury from dabigatran appears to be low. Because the perceived risk is low and frequent liver monitoring may not prevent serious cases from occurring (even if an association did exist), regular monitoring of liver tests is not recommended. A baseline assessment should perhaps be done for comparative purposes.

**Assessments for DILI**

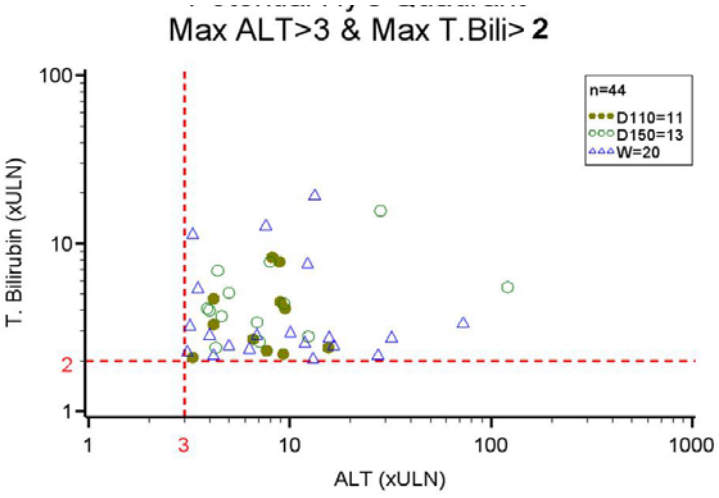
A total of 44 cases of interest were identified via a screen of peak ALT and peak total bilirubin(Tbili) values. The distribution of these values (taken as a ratio of the maximum ALT and maximum Tbili reported for a given subject) is shown below. Of the 44 subjects identified via this method, 11, 13, and 20 subjects were randomized to dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively (Figure B).

**Figure 20. Maximum ALT vs. maximum total bilirubin per subject**

A. All subjects in safety database




B. Potential Hy's Quadrant




[Source: Reviewer's analysis: hep\figs\create ALT_TB.sas, sponsor's dataset: labdata]. Note that A. reflects only 18,039 subjects because one subject in the safety dataset did not have these labs done. This analysis was done without regard to the timing of the ALT and Tbili.

Eleven additional cases of interest (five dabigatran 110, three dabigatran 150, and three warfarin) were identified after including AST >3xULN, the results (line Cat 1) of which are shown in the table below.

For the analyses shown in the table below several bins of liver test abnormalities were created. For analyses not requiring a temporal relationship between the elevated aminotransferase (AT) and Tbili, the maximum liver test value was determined (Cat 1, 5, and 6-13 in table below). For analyses requiring a temporal relationship between the liver test findings (Cat 2, 3, and 4), the maximum AT value was determined and the maximum Tbili within 30 days after the maximum AT value was selected. For the potential Hy's Law cases (Cat 3), subjects with an ALKP ≥ 2 xULN within 30 days after the maximum AT were excluded.

**Table 60. Liver test abnormalities in randomized population**

| Cat | | D 110 | % | D 150 | % | W | % | Total |
|---|---|---|---|---|---|---|---|---|
| | Randomized (n) | 6015 | | 6076 | | 6022 | | 18113 |
| 1 | ALT>3xULN &/or AST>3xULN and Tbili>2xULN | 16 | (0.3) | 16 | (0.3) | 23 | (0.4) | 55 |
| 2 | ALT>3xULN &/or AST>3xULN w/concurrent Tbili>2xULN* | 12 | (0.2) | 14 | (0.2) | 18 | (0.3) | 44 |
| 3 | ALT>3xULN &/or AST>3xULN w/concurrent Tbili>2xULN & ALKP<2xULN* | 10 | (0.2) | 8 | (0.1) | 8 | (0.1) | 26 |
| 4 | ALT>3xULN with concurrent Tbili>2xULN* | 7 | (0.1) | 12 | (0.2) | 16 | (0.3) | 35 |
| 5 | ALT>3xULN & Tbili>2xULN | 11 | (0.2) | 13 | (0.2) | 20 | (0.3) | 44 |
| 6 | ALT>3xULN | 101 | (1.7) | 99 | (1.6) | 115 | (1.9) | 315 |
| 7 | ALT>5xULN | 29 | (0.5) | 37 | (0.6) | 45 | (0.7) | 111 |
| 8 | ALT>10xULN | 4 | (0.1) | 10 | (0.2) | 19 | (0.3) | 33 |
| 9 | ALT>20xULN | 1 | (0.0) | 3 | (0.) | 6 | (0.1) | 10 |
| 10 | ALT>20xULN not in Cat 1 | 1 | | 1 | | 3 | | 5 |
| | Acute myocardial infarction | | | | | 1 | | |
| | Elevation prior to randomized treatment | | | 1 | | 1 | | |
| | Normalized despite continued treatment | | | | | 1 | | |
| | Likely due to amiodarone | 1 | | | | | | |
| 11 | Tbili>2 xULN | 114 | (1.9) | 114 | (1.9) | 121 | (2.0) | 349 |
| 12 | ALT or AST > 3 xULN | 125 | (2.1) | 118 | (1.9) | 136 | (2.3) | 379 |
| 13 | ALKP>1.5xULN | 773 | (12.9) | 393 | (6.5) | 869 | (14.4) | 2035 |

3 = Potential Hy's Cases
* = Concurrent defined as 30 days after max ALT or AST
Cat=category, Cat 4 is also a subset of Cat 5

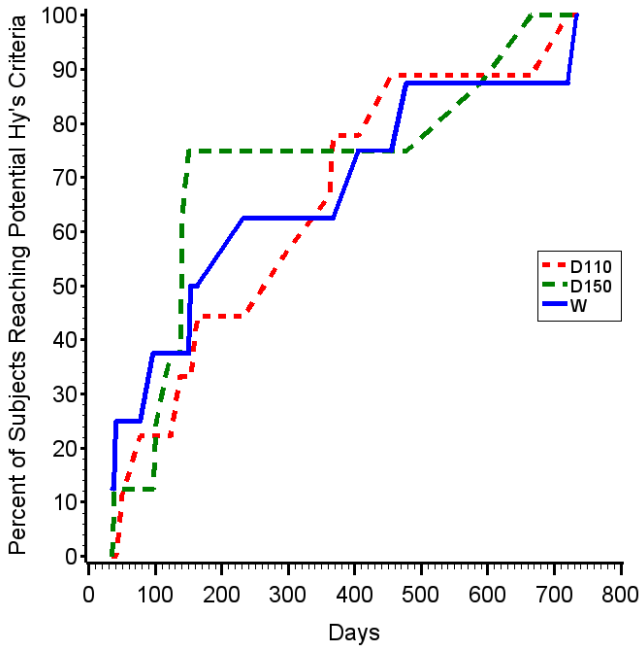
[Source: Reviewer's analysis: liver analysis time30.sas, liver analysis reviewer.sas, TA cats.xls, sponsor's dataset: labdata]

Regardless of how liver test elevations were defined (see table above), there did not appear to be a greater number of liver test abnormalities/Hy's Law cases in the dabigatran treatment arms relative to warfarin; if anything, there appeared to be more potential cases in the warfarin arm. No clear differences were seen in comparisons between the two dabigatran doses. Since hepatotoxic drugs with high rates of DILI have all caused an increased rate of AT elevations compared to control, categories 6-9 in the table shows results of various levels of ALT elevation since it might be a better indicator of the potential for severe DILI. Again, the data consistently show more subjects in the comparator arm. Lowering the degree of AT elevation to 2.5xULN and Tbili to 1.5xULN for categories 1-3 results in findings similar to above with more cases in the warfarin arm.

The time from the start of study medication to the development of liver abnormalities meeting Hy's Law criteria (Cat 3 in the table above) is shown in the figure below. The

time ranged from 35 to 734 days. With regard to onset, no clear differences were seen among the treatment arms.

**Figure 21. Days to reach potential Hy's criteria (n=25)**




[Source: Reviewer's analysis: hep2\time freq, sponsor's dataset, timeL]
Figure shows 25 subjects with potential Hy's criteria
Days are from the start of study medication. One subject (on dabigatran 110 mg) was removed because he met Hy's Law criteria at baseline.

**Scoring results for 55 cases reviewed by OSE**

Dr. Senior's review has not yet been finalized, but Drs. Senior and Seefe have evaluated and scored the 55 cases of interest. These cases were evaluated using a scoring scale that assesses both the severity (SEV) of liver injury and likelihood (LIK) of DILI.[22] The cases were also scored for completeness of information (CMP) and informative use of the data (INF).[23]

In terms of the clinical severity of the liver injury in RE-LY, one subject on dabigatran 150 mg received a score of 5 (death results from liver failure or liver transplant required because of liver failure) and 3 subjects on warfarin received a score of 4 (acute liver failure with secondary failure of brain or kidney function due to liver injury). The one death on dabigatran that was scored a 5 was a 57 year-old obese woman in the US with other valvular heart disease, hypertension, and heart failure who after approximately 4

22. This scoring system has been used in the past at FDA. It differs slightly from the Drug Induced Liver Injury Network (DILIN) scoring system and considerably from the NIH/NCI/CTEP/CTC (common toxicity criteria) manual.
23. For further discussion of CMP and INF, see the Appendix, section 9.7.

months on treatment developed significant AT elevations, endocarditis, septicemia, anemia, renal failure, and respiratory distress. Dabigatran was stopped and six days later she acutely decompensated and had an embolic stroke. She died nine days after drug was stopped. Though she was given a severity score of 5, the event was scored as being very unlikely to be DILI (LIK 0). Her CMP score was 2 (several items) and her INF score was 4 (very good basis for causal decision).

**Table 61. Summary of severity (SEV) of DILI injury scores**

| SEV | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 1 | ALT or AST >3xULN, usually transient and reversible by adaptation = mild | 5 | 1 | 1 |
| 2 | Also TBL >2xULN, after or concurrent, indicating early functional loss = Hy's Law case | 2 | 4 | 8 |
| 3 | Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction | 9 | 10 | 11 |
| 4 | Acute liver failure, with secondary failure of brain or kidney function due to liver injury | 0 | 0 | 3 |
| 5 | Fatal, or requiring liver transplantation due to liver failure | 0 | 1 | 0 |

Of the 55 cases reviewed[24], no definite or very likely DILI case was seen. One probable case (51-75% likelihood, more likely than all other causes combined, only one other cause possible) was identified in the dabigatran 110 mg arm (see table below).

**Table 62. Summary of likelihood (LIK) of DILI injury scores**

| LIK | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 0 | Very unlikely, >5%, relatively rare cause for DILI | 5 | 9 | 7 |
| 1 | Unlikely, 5-25%, no other cause very likely or definite | 9 | 7 | 13 |
| 2 | Possible, 26-50% likely, up to three possible alternative causes | 1 | 0 | 3 |
| 3 | Probable, 51-75%, more likely than all other causes combined, only one other possible | 1 | 0 | 0 |
| 4 | Very likely, 76-95% likely, no other cause even rated as possible | 0 | 0 | 0 |
| 5 | Definite, >95% likely, no other cause even unlikely | 0 | 0 | 0 |

The probable cause subject was a 67 year-old South Korean male with a history of hypertension, diabetes, heart failure, and benign prostatic hypertrophy. He did not have a known history of pancreatitis, cholecystitis or viral hepatitis. His symptoms began after 77 days of drug exposure and lasted until he was hospitalized for persistent pain. Dabigatran was stopped at the time of hospitalization (~3 days after the onset of

24 Of the 55 cases reviewed, the most probable cause of liver injury was heart failure with or without hypotension or shock.

symptoms). His liver tests were normal prior to his symptoms and were elevated upon hospital admission (see table below).

**Table 63. Liver test ratios in probable DILI subject**

| Date | ALTx | ASTx | TBilix | ALKPx | Central lab |
|---|---|---|---|---|---|
| 07-JUL-2006 | 0.6 | 0.8 | 1.1 | 0.6 | 0 |
| 26-JUL-2006* | 9.0 | 10.0 | 4.5 | 1.0 | 1 |

Central lab indicated by a 1, local lab=0
*This lab was the one taken upon hospital admission

During his hospitalizations, the following laboratory abnormalities were also noted: lipase 128 (0-6 U/L), indirect bilirubin 55 (17-21 umol/L), and ceruloplasmin 350 (20-50 mg/L). Notably, the following laboratory tests were unremarkable/negative: AMA, ANA, ASMA, LKM-1, alpha-1 antitrypsin, Anti-HCV, and HBsAG screen w/ confirmation. An abdominal (liver, gall bladder, pancreas) ultrasound showed peripheral ductal dilatations without an abnormal mass in the liver and a mildly enlarged spleen. Coarse and prominent echogenicity of the liver was seen and was read as being suggestive of a diffuse hepatocellular process, but not cholecystitis. A CT scan reported no liver lesion.

It was reported that the patient drank "some amount" of concentrates of red ginseng (2 pack, about 80 mol/pack) for 1 year. Concomitant medications are as shown below.

| Medication: provide generic name | Start Date Year/month/day | Stop Date Year/month/day |
|---|---|---|
| Antibiotics : Unknown | | 2006/07/25 |
| NSAIDs | | 2006/07/25 |
| KERLONE(selective b-blocker) | | Ongoing |
| COZAAR(Angiotensin 2 recepterAntagonist | | Ongoing |
| CADIL(alpha blocker) | | Ongoing |
| LASIX(Loop diuretics) | | Ongoing |

The site investigator diagnosed him with DILI. He was switched to warfarin and discharged after 8 days in the hospital. His liver abnormalities normalized 13 days after hospital admission and remained normal while on warfarin for 30 months.

While his likelihood score was a 3, heart failure was also considered a possible cause (though he was not treated for heart failure during the hospitalization). His other scores were SEV 3 (serious, disabling, requiring or prolonging hospitalization), CMP 3 (most of the key items provided) and INF 3 (very well supported conclusion).

For summary of CMP and INF scores see the Appendix.

**Adverse event data**

As another way to identify potential cases of DILI, the adverse event data set (aeads18.xpt) was searched for terms suggestive of drug induced liver injury. Because of the high incidence of abdominal pain and the poor specificity of this term, "jaundice" was used as a High Level Term to identify subjects with potential liver-related adverse events. The subjects identified had the following lower level terms: cholestasis, cholestatic jaundice, hyperbilirubinaemia/hyperbilirubinemia, icterus, jaundice, liver cholestasis, and obstructive jaundice. Subjects who were rechallenged with drug and had normal liver function tests following rechallenge were removed. This search identified an additional 36 subjects (beyond the 55 initially identified). These subjects were randomized as follows: 9, 8, and 19 on dabigatran 110, dabigatran 150, and warfarin, respectively. The adverse event data do not raise concerns of potential DILI.

**Discontinuations**

The table below shows subjects whose reason for discontinuation of study medication was given by the investigator as "elevated LFT". As shown in the table below, a greater number of subjects on dabigatran (relative to warfarin) were discontinued from study medication for reason of elevated LFT.

The table also looks at the last AT prior to discontinuation in subjects who either permanently discontinued study or prematurely discontinued from the trial. This analysis was done to evaluate subjects who might have been developing liver injury. The AT cut-off ratios (1.5x and 2x) were arbitrarily chosen. There was no clear indication based on last AT value that more subjects on dabigatran compared to warfarin might have been at risk for potential liver injury. Additionally, there were more subjects on warfarin who discontinued medication and had a last AT >3xULN, an elevation more clinically meaningful than the arbitrarily chosen cut-offs.

**Table 64. Premature discontinuations with elevated aminotransaminases**

| | D1101 | D150 | W |
|---|---|---|---|
| Treated | N=5983 | N=6059 | N=5998 |
| Completed follow-up but stopped med prematurely[1] | 1170 | 1197 | 907 |
| Elevated LFT result given by investigator as reason for discontinuation[1] | 25 | 16 | 11 |
| Last AT > 1.5 xULN (not in Cat 1)[2] | 49 | 32 | 34 |
| Last AT > 1.5 xULN (subjects that are not included in sponsor's elevated LFT result)[2] | 48 | 33 | 37 |
| Last AT > 3xULN | 9 | 6 | 14 |
| Premature d/c from trial[1] | 203 | 235 | 242 |
| Premature d/c with last AT > 1.5xULN[3] | 4 | 7 | 6 |
| Premature d/c w/ last AT > 2.0 xULN*,[3] | 1 | 3 | 2 |

AT=ALT or AST, d/c=discontinue, LFT=liver function test
Cat 1 = 55 identified subjects of interest to evaluate for potential drug induced liver injury
1. Adapted from sponsor's table 15.1.1:1.

2. Reveiwer's analysis: last lft dcmed, sponsor's data: disco, labdata
3. Reviewer's analysis: last lft dcmed dcstud

**Postmarketing data**

Three cases of interest have been reported in the postmarketing experience: one death (2009-RA-00265RA), one hospitalization (2010-CN-00363CN), and a case of elevated liver enzymes associated with jaundice, skin rash and pruritis (2010-AP-00222AP). These cases are currently being review by OSE at FDA. An addendum will be filed for these cases if their review affects the conclusions of the hepatic safety analysis presented in this review.

**Table 65. Three postmarketing cases under review**

| |
|---|
| **2009-RA-00265RA**: This is a death in a 72 year old Hispanic man taking dabigatran 220 mg for superficial venous thrombosis (also on paracetamol). One day after starting dabigatran, he experienced non-serious diarrhea and abdominal pain. Dabigatran was stopped 2 days later. His symptoms subsided and warfarin was started. Two days after dabigatran was stopped he developed severe liver failure and died two weeks later. The investigator's causation was "not reasonably possible". |
| **2010-CN-00363CN**: This was a male from Canada taking dabigatran 150 mg BID for atrial fibrillation who experienced "Hy's elevation" 12 weeks after starting drug and requiring hospitalization. Dabigatran was stopped and the investigator's assessment was likely DILI; alcohol and autoimmune etiologies were considered unlikely. According to the sponsor, because of privacy laws in Canada, further information could not be obtained. |
| **2010-AP-00222AP**: This is a 79 year old female with diabetes, hypertension, hyperlipidemia, hyperuricemia and prior cholecystectomy who was taking dabigatran 150 mg following elective knee replacement. She presented with generalized pruritis and significant elevations in AT, GGT, ALKP and TBili 1-2 weeks after completing a 49 day course of dabigatran. Liver biopsy showed severe hepatic steatosis and the investigator could not exclude dabigatran. She subsequently recovered and liver tests returned to normal. |

**Incidence of liver test abnormalities on warfarin**

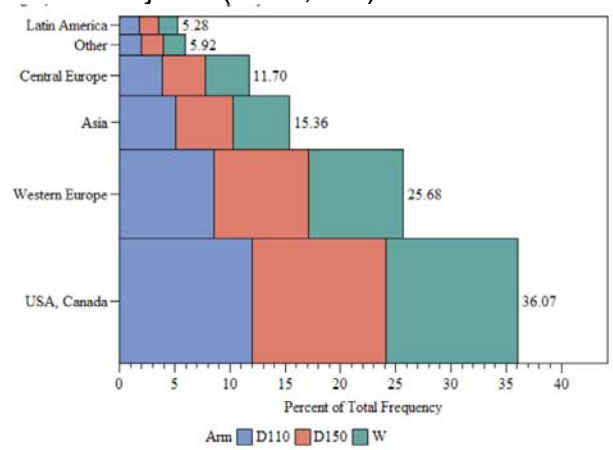
The incidence of cases of interest in the warfarin treatment arm of RE-LY was ~6.5-fold greater than that seen in SPORTIF V, a randomized controlled trial comparing ximelagatran against warfarin for stroke prevention in atrial fibrillation (20 cases in 6021 subjects in RE-LY vs. 1 case in 1922 subjects in SPORTIF V). The reason for this difference is not clear. Monitoring of liver tests did not appear to be markedly different between the two studies[25]; nor did there appear to be clear differences between the studies in the incidence of background diseases[26] that might provide some explanation. It is possible that the difference in incidence may be attributable in part to the longer

25 SPORTIF V liver tests were drawn monthly for 6 months, then bimonthly for the first year, and then quarterly
26 SPORTIF V population had 40% with heart failure versus 32% in RE-LY

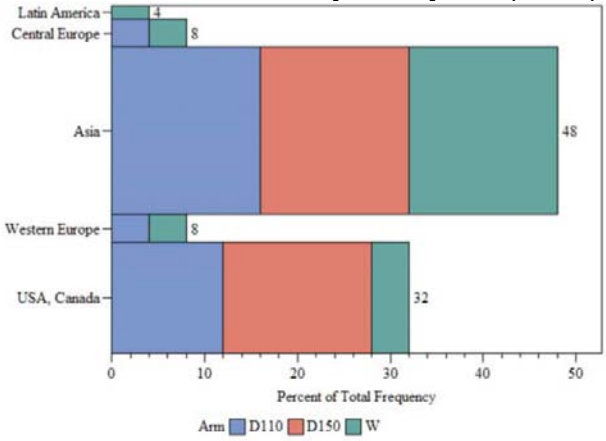
duration and larger size of RE-LY and the geographic locations where these studies were conducted. Whereas SPORTIF V was conducted in the US and Canada, RE-LY was an international study. As shown in the figure below, approximately ½ of the 25 potential Hy's cases were from sites in Asia and Latin America.

**Figure 22. Regional population in RE-LY**

A. All subjects (n=18,113)




B. Potential Hy's subjects (n=25)




[source: reviewer's analysis:hep\region, sponsor datast: basco]

If laboratory measurements were drawn more frequently in the warfarin arm, it may help explain the greater number of cases of interest compared to dabigatran. However, laboratory monitoring of each liver test was equally distributed (33%) between the treatment arms (ALT monitoring shown in next table).

**Table 66. Frequency of ALT monitoring in treated subjects, n (%)**

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| Entire study duration | 78,362 (33) | 78,735 (33) | 78,709 (33) |
| Central lab | 66,902 (85) | 67,357 (86) | 66,951 (85) |
| | | | |
| Prior to September 25, 2006[1] | 27,576 (34) | 26,801(33) | 26,652 (33) |
| Central lab | 22,983 (83) | 22,401 (84) | 22,218 (83) |
| | | | |

1 This is based on treatment starting (not randomization) prior to September 25, 2006
[Source: Reviewer's analysis: liver lab freq, sponsor dataset=labdata]

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Bleeding and GI adverse events were among the most common adverse events reported in RE-LY. Dyspepsia/gastritis was reported at a greater frequency in dabigatran compared to warfarin-treated subjects, as shown in the table below. Study medication discontinuation because of dyspepsia/gastritis was also more common in dabigatran treated subjects. Approximately 2% of dabigatran treated subjects discontinued study medication because of dyspepsia. In contrast, 0.6% of warfarin treated subjects discontinued study medication for this reason. Study medication discontinuation as a result of gastritis was 0.6% and 0.3% in the dabigatran and warfarin treatment arms, respectively.

**Table 67. Frequency of dyspepsia and gastritis**

Table 15.3.2.8: 1 Frequency (%) of subjects with dyspepsia/gastritis ++ by treatment

| User-defined AE category/ Preferred term | DE 110mg bid N (%) | DE 150mg bid N (%) | Warfarin N (%) |
|---|---|---|---|
| Number of patients | 5983 (100.0) | 6059 (100.0) | 5998 (100.0) |
| Total with dyspepsia/gastritis++ | 983 ( 16.4) | 940 ( 15.5) | 470 ( 7.8) |
| Dyspepsia+ | 761 ( 12.7) | 738 ( 12.2) | 354 ( 5.9) |
| Dyspepsia | 368 ( 6.2) | 345 ( 5.7) | 83 ( 1.4) |
| Abdominal pain upper | 177 ( 3.0) | 170 ( 2.8) | 80 ( 1.3) |
| Abdominal pain | 130 ( 2.2) | 137 ( 2.3) | 141 ( 2.4) |
| Abdominal discomfort | 119 ( 2.0) | 112 ( 1.8) | 64 ( 1.1) |
| Epigastric discomfort | 40 ( 0.7) | 40 ( 0.7) | 9 ( 0.2) |
| Gastritis+ | 297 ( 5.0) | 257 ( 4.2) | 142 ( 2.4) |
| Gastritis | 147 ( 2.5) | 127 ( 2.1) | 87 ( 1.5) |
| Gastrooesophageal reflux disease | 117 ( 2.0) | 99 ( 1.6) | 46 ( 0.8) |
| Oesophagitis | 32 ( 0.5) | 27 ( 0.4) | 8 ( 0.1) |
| Gastritis erosive | 21 ( 0.4) | 19 ( 0.3) | 3 ( 0.1) |
| Gastric haemorrhage | 0 ( 0.0) | 4 ( 0.1) | 3 ( 0.1) |
| Gastritis haemorrhagic | 5 ( 0.1) | 4 ( 0.1) | 3 ( 0.1) |
| Haemorrhagic erosive gastritis | 2 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |

In the dabigatran and warfarin treatment groups, the yearly event rate for dyspepsia and gastritis was slightly higher in subjects taking aspirin (no aspirin use vs. use at least once).

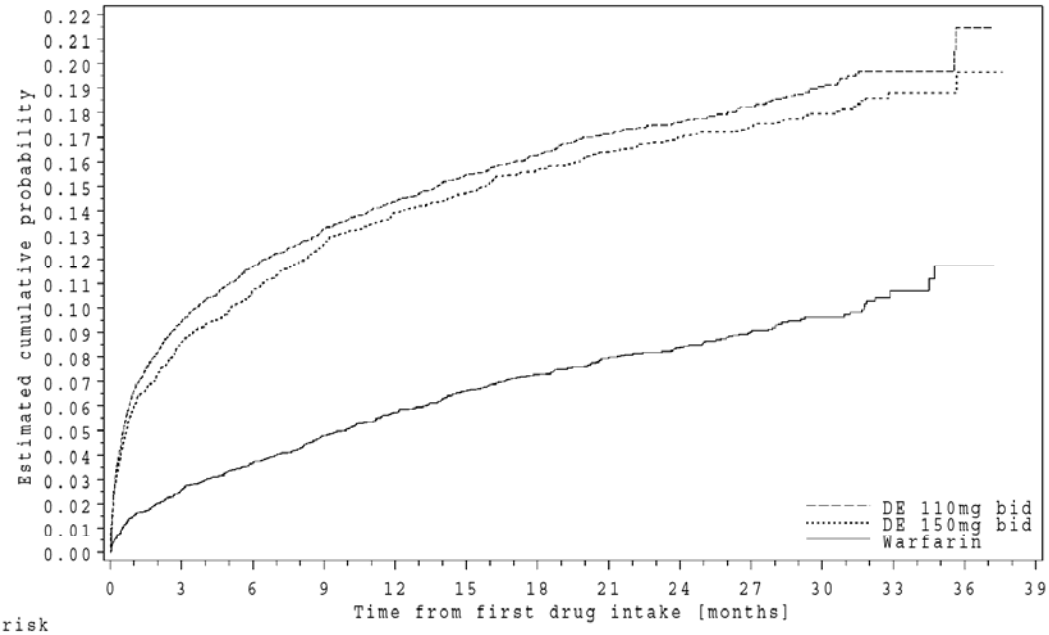
## Table 68. Frequency of dyspepsia and gastritis by aspirin use

Table 15.3.2.8: 4 Yearly event rate of dyspepsia/gastritis ++ by ASA use during treatment period safety set

| | DE 110mg bid | | | | DE 150mg bid | | | | Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) |
| Dyspepsia+ | 5983 | 10242 | 761 | 7.43 | 6059 | 10261 | 738 | 7.19 | 5998 | 10659 | 354 | 3.32 |
| No ASA | 3779 | 6551 | 452 | 6.90 | 3880 | 6615 | 446 | 6.74 | 3780 | 6814 | 198 | 2.91 |
| Use ASA at least once | 2204 | 3691 | 309 | 8.37 | 2179 | 3646 | 292 | 8.01 | 2218 | 3846 | 156 | 4.06 |
| Gastritis+ | 5983 | 10242 | 297 | 2.90 | 6059 | 10261 | 257 | 2.50 | 5998 | 10659 | 142 | 1.33 |
| No ASA | 3779 | 6551 | 181 | 2.76 | 3880 | 6615 | 136 | 2.06 | 3780 | 6814 | 74 | 1.09 |
| Use ASA at least once | 2204 | 3691 | 116 | 3.14 | 2179 | 3646 | 121 | 3.32 | 2218 | 3846 | 68 | 1.77 |
| Dyspepsia/gastritis ++ | 5983 | 10242 | 983 | 9.60 | 6059 | 10261 | 940 | 9.16 | 5998 | 10659 | 470 | 4.41 |
| No ASA | 3779 | 6551 | 592 | 9.04 | 3880 | 6615 | 553 | 8.36 | 3780 | 6814 | 262 | 3.85 |
| Use ASA at least once | 2204 | 3691 | 391 | 10.59 | 2179 | 3646 | 387 | 10.61 | 2218 | 3846 | 208 | 5.41 |

A Kaplan-Meier estimate of the time to first dyspepsia/gastritis event suggests that this adverse event manifests soon after the start of therapy with dabigatran.

## Figure 23. Time to first dyspepsia/gastritis




Subjects at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DE 110mg bid | 5983 | 5034 | 4736 | 4511 | 4342 | 4054 | 3348 | 2688 | 2217 | 1664 | 996 | 335 | 54 |
| DE 150mg bid | 6059 | 5107 | 4800 | 4565 | 4383 | 4097 | 3399 | 2702 | 2237 | 1662 | 997 | 313 | 71 |
| Warfarin | 5998 | 5546 | 5336 | 5121 | 4954 | 4608 | 3857 | 3019 | 2498 | 1882 | 1100 | 291 | 57 |

Figure 15.3.2.8: 2 Kaplan-Meier estimates of time to first dyspepsia/gastritis ++ safety set

Source data: Appendix 16.1.9.2, Statdoc 7.3.5.2 scs26\sf_kaplan_ad.sas 03APR2010

### 7.4.2 Laboratory Findings

The significant laboratory findings related to liver tests are discussed in section 7.3.5.1.

### 7.4.3 Vital Signs

No clear differences were seen across treatment arms in terms of changes in blood pressure over the course of the study. Approximately 66-67% of subjects were in atrial fibrillation at study end; the incidence was similar in the dabigatran and warfarin treatment arms.

### 7.4.4 Electrocardiograms (ECGs)

The Interdisciplinary QT Team reviewed the thorough QT study (placebo and moxifloxacin controlled) and found no significant QT prolonging effect with a single dabigatran dose of 150 mg and 600 mg. Assay sensitivity was established via the moxifloxacin control. The largest upper bounds of the 2-sided 90% CI for the mean difference between dabigatran and placebo were below 10 ms, the threshold for regulatory concern. However, there was concern that the QT study did not explore a high enough dose to cover a potential worse case scenario. In RE-LY, no cases of torsade de pointe on dabigatran were noted and there was not an increased incidence of sudden/arrhythmic deaths in dabigatran compared to warfarin treated subjects (1.5% on dabigatran 110 mg, 1.2% on dabigatran 150 mg and 1.4 % on warfarin).

### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted other than a thorough QT study.

### 7.4.6 Immunogenicity

Not applicable. Dabigatran is not a therapeutic protein.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

A dose dependent relationship was seen for major bleeding events.

### 7.5.2 Time Dependency for Adverse Events

This is discussed within each SAE.

## 7.5.3 Drug-Demographic Interactions: Eldery

Subjects 75 years of age and older are perceived to be at increased risk of hemorrhage and also have impaired renal function which would result in increased exposure to dabigatran. Relative to warfarin, rates of major bleeds appeared similar if not greater in dabigatran treated subjects ≥ 75 years of age. In contrast, rates appeared lower (relative to warfarin) in those less than 75.

**Table 69. Frequency and yearly event rate of major bleed in elderly (age ≥ 75 years)**

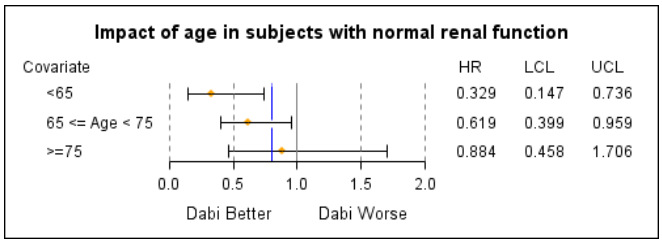
| | DE 110 | | DE 150 | | Warfarin | |
|---|---|---|---|---|---|---|
| | #of subjects | Yearly event rate (%) | # of subjects | Yearly event rate (%) | # of subjects | Yearly event rate (%) |
| Age (years) | | | | | | |
| <65 | 998 | 0.71 | 1030 | 0.79 | 953 | 2.26 |
| 65<= and <75 | 2668 | 2.10 | 2580 | 2.45 | 2646 | 3.07 |
| >=75 | 2349 | 4.18 | 2466 | 4.82 | 2423 | 4.11 |

[Source: Sponsor, Original submission, Table 12.2.2.5:1]

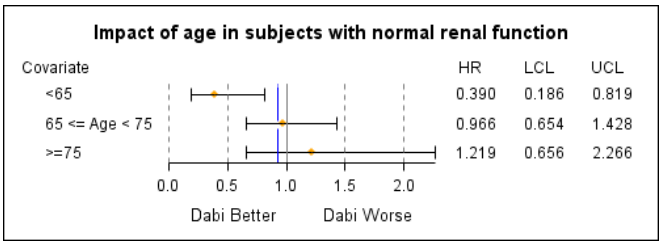
*Reviewer's comment: Though renal function plays an important role in this relationship, analyses suggest that increasing age, independent of renal function, may be associated with a greater risk (relative to warfarin) of a major bleed on dabigatran. (see figure)*

**Figure 24. Impact of age on major bleeding in subjects with normal renal function**

A. D110 v. W




B. D150 v. W




[source: reviewer's analysis, sponsor's data: adjrand2]

While subjects ≥ 75 years of age may be at greater risk for bleeding, analyses of net benefit (composites of bleeding and stroke/SEE), do not suggest a clear benefit of the 110 mg dose over the 150 mg dose in this population. These data as a whole indicate that there is no reason to dose adjust in the elderly.

**Table 70. Net benefit comparison of dabigatran doses in elderly**

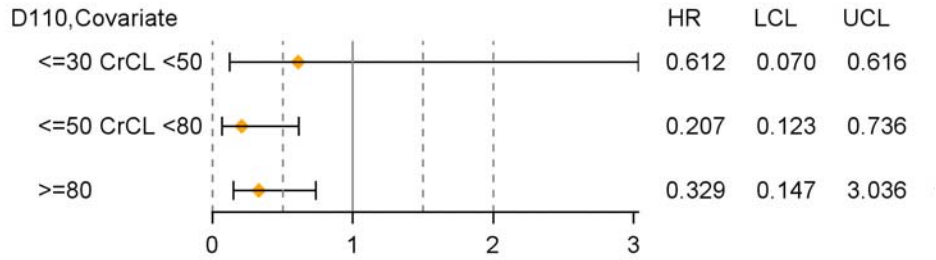
| Net benefit | D150vD110 HR | 95% LL | 95% UL | p-value |
|---|---|---|---|---|
| Adjudicated life threatening bleed or stroke/SEE | 0.98 | 0.79 | 1.22 | 0.87 |
| Adjudicated life threatening bleed or disabling or fatal stroke | 0.96 | 0.76 | 1.21 | 0.72 |
| ICH or stroke/SEE | 0.82 | 0.61 | 1.11 | 0.20 |
| ICH or disabling or fatal stroke | 0.77 | 0.54 | 1.09 | 0.13 |
| GUSTO-severe or disabling or fatal stroke | 0.98 | 0.74 | 1.30 | 0.88 |
| Major bleed or stroke/SEE | 1.07 | 0.91 | 1.26 | 0.42 |

[source: reviewer's analysis: net\age, sponsor's data adjrand, timev, timecens]

### 7.5.4 Drug-Disease Interactions: Renal impairment

Dabigatran is primarily renally cleared with an ~2-3-fold increase in exposure seen in subjects with moderate renal impairment (creatinine clearance of 30 to 50 mol/min). Despite an expected increase in exposure, no greater risk of bleeding was seen in dabigatran compared to warfarin treated subjects with baseline renal clearance between 30 and 50 mol/min (see figure).

**Figure 25. Impact of renal function on major bleeding in subjects less than 65 years old**




[source: reviewer's analysis, sponsor dataset adjrand2]. Since there is a relationship with bleeding and age, this analysis looks at an age subpopulation.

Relative to the dabigatran 110 mg dose, the incidence of bleeding was not greater at the 150 mg dose, though a dose-response relationship still existed for stroke/SEE. Why bleeding rates were not greater in subjects receiving dabigatran 150 mg is not clear. The results suggest that a dose of 150 mg should be used in patients with moderate renal impairment.

**Table 71. Frequency and yearly event rate for major bleeds by baseline renal function**

| | DE 110 | | DE 150 | | Warfarin | |
|---|---|---|---|---|---|---|
| | #of subjects | Yearly event rate (%) | # of subjects | Yearly event rate (%) | # of subjects | Yearly event rate (%) |
| CrCL (ml/min) | | | | | | |
| <30 | 15 | 0.00 | 32 | 13.31 | 30 | 0.00 |
| 30<= and <50 | 1136 | 5.42 | 1157 | 5.08 | 1050 | 5.28 |
| 50<= and <80 | 2714 | 2.59 | 2777 | 3.17 | 2807 | 3.63 |
| >=80 | 1899 | 1.40 | 1882 | 1.86 | 1877 | 2.27 |

[Source: Sponsor, Original submission, Table 12.2.2.5:1]

**Table 72. Frequency and yearly event rate for stroke/SEE by baseline renal function**

| | DE 110 | | DE 150 | | Warfarin | |
|---|---|---|---|---|---|---|
| | # of subject | Event rate | # of subject | Event rate | # of subject | Event rate |
| CrCL (ml/Min) | | | | | | |
| 30<= and <50 | 1136 | 2.36 | 1157 | 1.23 | 1050 | 2.64 |
| 50<= and <80 | 2714 | 1.69 | 2777 | 1.21 | 2807 | 1.82 |
| >=80 | 1899 | 0.86 | 1882 | 0.73 | 1877 | 1.03 |

[Source: Sponsor, Original submission, Table 11.4.1.4.1:1]

### 7.5.5 Drug-Drug Interactions

Drug-Drug interactions are discussed under concomitant medications (Section 7.3.2.1).

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Preclinical data were not suggestive of carcinogenicity and no imbalance was seen across treatment arms in the incidence of neoplasms.

### 7.6.2 Human Reproduction and Pregnancy Data

There is no information on drug exposure in pregnant or lactating women.

## 7.6.3 Pediatrics and Assessment of Effects on Growth

Studies were not conducted in children.

## 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose would be expected to result in hemorrhagic complications. There is no established antidote to dabigatran-induced hemorrhage and in RE-LY, investigator were told to give consideration to the following therapies in subjects with major bleeding on dabigatran: packed cells, FFP, prothrombin complex concentrates, and recombinant factor VIIa. Hemodialysis could also be considered. The measures taken by investigators are shown in the tables below for all subjects with adjudicated major bleeds and by whether or not the subject lived or died. Subjects were not randomized to the intervention that they received and interpretation of the data is limited.

**Table 73. Corrective therapies used in subjects with adjudicated major bleed**

| | D110 | % | D150 | % | W | % |
|---|---|---|---|---|---|---|
| Total subjects | 397 | (100) | 486 | (100) | 476 | (100) |
| Required Transfusion | 234 | (58.9) | 315 | (64.8) | 246 | (51.7) |
| Associated with Hypotension requiring pressors | 18 | (4.5) | 34 | (7.0) | 22 | (4.6) |
| Required surgical intervention | 36 | (9.1) | 57 | (11.7) | 65 | (13.7) |
| Other corrective treatment for bleed | 132 | (33.2) | 170 | (35.0) | 244 | (51.3) |
| FFP | 73 | (18.4) | 107 | (22.0) | 144 | (30.3) |
| VitaminK | 37 | (9.3) | 53 | (10.9) | 124 | (26.1) |
| Other | 56 | (14.1) | 50 | (10.3) | 56 | (11.8) |
| Platelets | 13 | (3.3) | 18 | (3.7) | 24 | (5.0) |
| Cryoprecipitate | 3 | (0.8) | 5 | (1.0) | 7 | (1.5) |
| Recombinant Factor VIIa | 1 | (0.3) | 7 | (1.4) | 3 | (0.6) |
| Coagulation Factor | 1 | (0.3) | 3 | (0.6) | 5 | (1.1) |
| Prothrombin Complex Conc | 3 | (0.8) | 2 | (0.4) | 5 | (1.1) |

[Source: reviewer's analysis: adj_plt122n, sponsor's data plt122n, timev,adjrand].

**Table 74. Corrective therapies used for adjudicated major bleeds in subjects that died**

| Corrective therapy | D110 | D150 | W |
|---|---|---|---|
| Subject died | 25 | 28 | 40 |
| Required Transfusion | 8 | 11 | 10 |
| Associated with Hypotension requiring pressors | 6 | 11 | 8 |
| Required surgical intervention | 1 | 8 | 8 |
| Other corrective treatment for bleed | 10 | 14 | 18 |
| FFP | 7 | 9 | 11 |
| VitaminK | 5 | 4 | 10 |
| Other | 2 | 3 | 4 |
| Platelets | 2 | 3 | 2 |
| Cryoprecipitate | 1 | 3 | . |
| Recombinant Factor VIIa | 1 | 4 | 1 |
| Coagulation Factor | 1 | 2 | 1 |
| Prothrombin Complex Conc | 2 | . | . |

[source: reviewer's analysis, filename: Tx\Dead v alive corrective, sponsor data plt122n, timev]

**Table 75. Corrective therapies used for adjudicated major bleeds in subjects that did not die**

| Corrective therapy | D110 | D150 | W |
|---|---|---|---|
| Subject alive | 369 | 456 | 435 |
| Required Transfusion | 225 | 304 | 236 |
| Associated with Hypotension requiring pressors | 12 | 23 | 14 |
| Required surgical intervention | 35 | 49 | 57 |
| Other corrective treatment for bleed | 120 | 156 | 226 |
| FFP | 65 | 98 | 133 |
| VitaminK | 32 | 49 | 114 |
| Other | 53 | 47 | 52 |
| Platelets | 11 | 15 | 22 |
| Cryoprecipitate | 2 | 2 | 7 |
| Recombinant Factor VIIa | . | 3 | 2 |
| Coagulation Factor | . | 1 | 4 |
| Prothrombin Complex Conc | 1 | 2 | 5 |

[source: reviewer's analysis, filename: Tx\Dead v alive corrective, sponsor data plt122n, timev]

## 7.7 Interruptions for elective surgeries/procedures

The RE-LY protocol provided guidance on the use of warfarin and dabigatran around the time of emergency and elective surgeries/procedures (see section 5.3.5.4). Overall, 4623 subjects (25.6%) had interruptions of anticoagulant therapy for a surgery/procedure; the numbers/percents were similar across the three treatment arms. A minority of subjects (525) had interruptions for an emergency surgery/procedure.

In upwards of 70% of subjects on dabigatran who had interruptions for a procedure/surgery, bridging therapy was not used, as shown in the table below.

**Table 76. Summary of bridging therapy for subjects with interruptions of anticoagulant for surgery/procedure**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Subject with interruptions for procedure/surgery | 1501 | 1554 | 1568 |
| Subjects with no bridging therapy | 1190 ( 79.3) | 1203 ( 77.4) | 1030 ( 65.7) |

| | | | |
|---|---|---|---|
| Subjects with bridging therapy* | 311 ( 20.7) | 351 ( 22.6) | 538 ( 34.3) |
| Pre-procedural bridging | 203 ( 13.5) | 210 ( 13.5) | 394 ( 25.1) |
| Post-procedural bridging | 262 ( 17.5) | 293 ( 18.9) | 447 ( 28.5) |
| Pre- and Post procedural bridging | 154 ( 10.3) | 152 ( 9.8) | 303 ( 19.3) |

*subjects counted in more than one category if multiple interruptions for surgery/procedure occurred. [Source: taken from sponsor's table 17.2, appendix-3, 7.30.10 submission]

The nature of the procedures, medication used for bridging and timing of procedures since previous dose of anticoagulation therapy is shown below for subjects undergoing pre-procedural bridging therapy. The majority of dabigatran subjects receiving a bridge had been off of therapy for more than 2 days.

**Table 77. Summary of surgery/procedures for subjects used pre-procedural bridging therapy**

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| Day procedure or hospital admission | | | |
| Day procedure | 104 | 122 | 246 |
| Hospital admission | 273 | 265 | 452 |
| Type of procedure | | | |
| Pacemaker/ICD | 36 | 37 | 56 |
| Surgery | 215 | 215 | 356 |
| Dental procedure | 11 | 21 | 59 |
| Diagnostic procedure | 72 | 73 | 140 |
| Other | 43 | 41 | 87 |
| Emergency or elective | | | |
| Emergency | 51 | 36 | 58 |
| Elective | 326 | 351 | 639 |
| Time of procedure since previous dose (days) | | | |
| <= 2 | 99 | 89 | 50 |
| 2< and <= 5 | 98 | 91 | 169 |
| > 5 | 53 | 58 | 204 |
| Medication used for bridging | | | |
| Subcutaneous LMWH | 175 | 172 | 421 |
| Unfractionated heparin | 74 | 70 | 107 |
| Study medication restarted after procedure | | | |
| No | 51 | 42 | 68 |
| Yes | 326 | 344 | 630 |
| Blood transfusion required | | | |

| | | | |
|---|---|---|---|
| No | 344 | 369 | 653 |
| Yes | 31 | 18 | 44 |

[Source: taken from sponsor's table 17.3, appendix-3, 7.30.10 submission]

Of the subjects who did not use a bridge, the number/percent experiencing an important outcome event (stroke/SEE, major bleed) around the time of surgery appeared similar in the dabigatran compared to warfarin treatment arms. This also appeared to be the case in subjects who used a bridge.

**Table 78. Summary of outcome events for subjects without bridging therapy for surgery/procedure**

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| Subjects with interruptions for procedure/surgery and no bridging therapy | 1190 | 1203 | 1030 |
| Subjects with outcome events occurred within 7 days prior to surgery/procedure | 43 ( 3.6) | 51 ( 4.2) | 38 ( 3.7) |
| Stroke/SEE | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.2) |
| Major bleed | 23 ( 1.9) | 17 ( 1.4) | 13 ( 1.3) |
| Minor bleed | 23 ( 1.9) | 34 ( 2.8) | 25 ( 2.4) |
| Death | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Subjects with outcome events occurring within 30 days post surgery/procedure | 135 ( 11.3) | 155 ( 12.9) | 115 ( 11.2) |
| Stroke/SEE | 2 ( 0.2) | 3 ( 0.2) | 6 ( 0.6) |
| Major bleed | 29 ( 2.4) | 45 ( 3.7) | 25 ( 2.4) |
| Minor bleed | 106 ( 8.9) | 114 ( 9.5) | 92 ( 8.9) |
| Death | 5 ( 0.4) | 2 ( 0.2) | 2 ( 0.2) |

[Source: taken from sponsor's table 17.8, appendix-3, 7.30.10 submission]

In subjects undergoing interruptions for emergency surgery/procedure, outcomes were not worse in dabigatran compared to warfarin treated subjects.

**Table 79. Summary of outcome events for subjects using emergency procedure for surgery/procedure**

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| Subjects with interruptions for emergency surgery/procedure | 167 | 196 | 162 |
| Subjects with outcome events occurring within 7 days prior to surgery/procedure | 26 ( 15.6) | 26 ( 13.3) | 24 ( 14.8) |

| | | | |
|---|---|---|---|
| Stroke/SEE | 2 ( 1.2) | 1 ( 0.5) | 3 ( 1.9) |
| Major bleed | 17 ( 10.2) | 13 ( 6.6) | 15 ( 9.3) |
| Minor bleed | 10 ( 6.0) | 12 ( 6.1) | 11 ( 6.8) |
| Death | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Subjects with outcome events occurring within 30 days post surgery/procedure | 40 ( 24.0) | 42 ( 21.4) | 44 ( 27.2) |
| Stroke/SEE | 5 ( 3.0) | 1 ( 0.5) | 5 ( 3.1) |
| Major bleed | 17 ( 10.2) | 26 ( 13.3) | 24 ( 14.8) |
| Minor bleed | 20 ( 12.0) | 20 ( 10.2) | 23 ( 14.2) |
| Death | 4 ( 2.4) | 3 ( 1.5) | 1 ( 0.6) |

[Source: taken from sponsor's table 17.10, appendix-3, 7.30.10 submission]

# 9 Appendices

## 9.1 Literature Review/References

Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001927. DOI: 10.1002/14651858.CD001927.pub2.

Connolly et al. Benefit of Oral Anticoagulants over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range. Circulation. 1008; 118: 2029-2037.

Fuster et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. Circulation. 2006; 114:700-752.

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Hart et al. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. Ann Intern Med. 2007; 146: 857-867.

Hirsh et al. American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy. Circulation. 2003; 107: 1692-1711.

Jackson et al. Antithrombotic drug development for atrial fibrillation: Proceedings, Washington, DC, July 25-27, 2005. Am Heart J. 2008; 155: 829-840.

Jones M et al. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvular atrial fibrillation: a record linkage study in a large British population. Heart 2005; 91:472–477.

Lange U, Nowak G, Bucha E. Ecarin Chromogenic Assay- A New Method for Quantitative Determination of Direct Thrombin Inhibitors Like Hirudin. Pahtophysiol Haemost Thromb. 2003/04; 33:184-191.

Mant J et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. Lancet 2007; 370: 493-503.

Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993; 342(8882):1255-62.

White HD et al. Comparison of Outcomes among Patients Randomized to Warfarin Therapy according to Anticoagulant Control. Arch Intern Med. 2007; 167: 239-245.

## 9.2 Labeling Recommendations

The labeling review will be provided as an addendum.

## 9.3 Advisory Committee Meeting

An advisory committee meeting has been scheduled for September 20, 2010. We believe that the advisory committee meeting should focus on dose selection for anticoagulant therapies and how to weigh the benefits of these therapies against their risks (specifically when the risk of bleeding events balances the risk of stroke). We think that the advisory committee should be asked to opine on the dose(s) of dabigatran that should be approved and the particular population(s) in which the dose(s) should be used. In particular, we think that there needs to be discussion about whether or not it makes sense to recommend a lower dose of dabigatran in patients at increased risk of bleeding, and, if so, how one defines this population.

## 9.4 Efficacy of Warfarin

The clinical trial experience supporting the efficacy of warfarin in the treatment of atrial fibrillation is discussed below. Topics addressed include the nature of the benefit of warfarin (effect on stroke and magnitude of effect) and how warfarin was used and in whom it was used in the referenced clinical trials. This section also reviews the data

supporting time in therapeutic range (TTR) as a measure of the quality/adequacy of anticoagulation in warfarin treated subjects in clinical trials.

*The nature of the benefit of warfarin:* Five randomized, placebo-controlled primary prevention trials are widely referenced as establishing the efficacy of warfarin for the primary prevention of ischemic stroke in patients with non-valvular atrial fibrillation: Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK I), Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), Canadian Atrial Fibrillation Anticoagulation (CAFA), Stroke Prevention in Atrial Fibrillation (SPAF I), Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF). A sixth study, European Atrial Fibrillation Trial (EAFT), addressed the efficacy of warfarin for the prevention of stroke in patients with atrial fibrillation and a history of nondisabling stroke or TIA within 3 months (trial of secondary prevention). As shown in the table below, the primary endpoint varied somewhat across the studies. Four of the five primary prevention trials were terminated early for reasons of efficacy; a fifth (CAFA) was terminated in light of the efficacy findings in the other studies.

| Study | Participants (follow up) | Target INR | Mean INR | Primary Endpoint |
|---|---|---|---|---|
| *Open Label* | | | | |
| AFASAK I | Denmark, chronic AF, median age 74.2, 54% male (~1.2 years/subject) | 2.8-4.2 | ~ 2.5 | TIA, stroke, systemic embolism |
| SPAF I | U.S., constant or intermittent chronic AF, mean age 67, 71% male (~2.2 years/subject) | 2-4.5 | ~2.6 | Ischemic stroke, systemic embolism |
| BAATAF† | U.S., chronic or intermittent AF, mean age 68, 75% male | 1.5-2.7 | ~2.1 | Ischemic stroke |
| EAFT (group I) | 12 European countries and Israel, nonrheumatic AF and a recent (< 3 months) TIA or minor ischemic stroke, mean age ~71, ~56% male; (2.3 years mean) | 2.5-4.0 | ~2.9 | Composite: vascular death, nonfatal stroke, nonfatal myocardial infarction, systemic embolism |
| *Blinded* | | | | |
| CAFA | Canada, chronic or paroxysmal AF, mean age 67, 75% male (~1.3 years/subject) | 2.0-3.0 | ~2.4 | Ischemic stroke, systemic embolism, intracranial or fatal hemorrhage |
| SPINAF | U.S., chronic AF, mean age 67, 100% male | 1.4-2.8 | ~2.0 | Ischemic stroke |

[Sources: Aguilar et al. 2005; EAFT. 1993]

†ASA permitted in control group

These six trials were included in two published meta-analyses by Hart et al. which addressed the efficacy of anticoagulant therapy for the prevention of stroke (ischemic and hemorrhagic). The table below shows the number of strokes per patients/patient-years in the warfarin and control treatment arms as well as the relative and absolute risk reduction in stroke for subjects without a baseline history of stroke or transient ischemic attack. According to the 2007 meta-analysis of these studies, warfarin reduced the risk of stroke (ischemic and hemorrhagic) by 64% (95% CI, 49% to 74%) and the risk of ischemic stroke by 67% (95% CI, 54% to 77%).

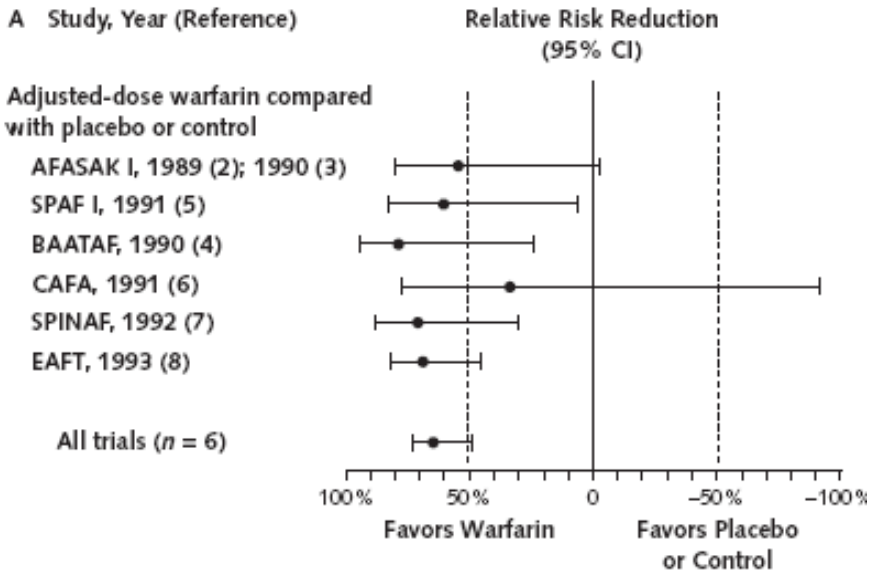
*Table 2.* **Adjusted-Dose Warfarin Compared with Placebo or No Treatment***

| Study, Year (Reference) | Secondary Prevention, %† | Participants, *n* | Target INR | Strokes/Patients/Patient-Years; Warfarin vs. Placebo or Control, *n/n/n* | Relative Risk Reduction (95% CI), %‡ | Absolute Risk Re %/y‡ |
|---|---|---|---|---|---|---|
| AFASAK I, 1989 (2); 1990 (3) | 6 | 671 | 2.8–4.2 | 9/335/413 vs. 19/336/398 | 54 | 2.6 |
| SPAF I, 1991 (5) | 8 | 421 | 2.0–4.5§ | 8/210/263 vs. 19/211/245 | 60‖ | 4.7 |
| BAATAF, 1990 (4)¶ | 3 | 420 | 1.5–2.7§ | 3/212/487 vs. 13/208/435 | 78‖ | 2.4 |
| CAFA, 1991 (6) | 4 | 378 | 2.0–3.0 | 6/187/237 vs. 9/191/241 | 33 | 1.2 |
| SPINAF, 1992 (7) | 8 | 571 | 1.4–2.8§ | 7/281/489 vs. 23/290/483 | 70‖ | 3.3 |
| EAFT, 1993 (8)** | 100 | 439 | 2.5–4.0 | 20/225/507 vs. 50/214/405 | 68‖ | 8.4 |
| 6 trials†† | 20 | 2900 | – | 53/1450/2396 vs. 133/1450/2207 | 64 (49 to 74) | Primary preventio secondary prev |

* Please see footnote in Table 1 for definitions of study acronyms. INR = international normalized ratio.
† Proportion of patients who had previous stroke or transient ischemic attack.
‡ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis.
§ Prothrombin time ratios were used with INR equivalents estimated by the investigators.
¶ A total of 46% of exposure in the control group was during self-selected use of various dosages of aspirin.
‖ $P < 0.05$, 2-sided.
** Several oral vitamin K antagonists were used (warfarin was not exclusively used).
†† Meta-analysis estimates of relative risk reductions ($P > 0.2$ for homogeneity) and absolute risk reductions ($P > 0.2$ for homogeneity) for trials of primary preve with ≤20% of participants with previous stroke) vs. secondary prevention; see Methods.

[Source: Hart RG et al. 2007]

A forest plot of warfarin's effect on stroke (ischemic and hemorrhagic), taken from the 2007 meta-analysis, is shown below.




[Source: Hart RG et al. 2007]

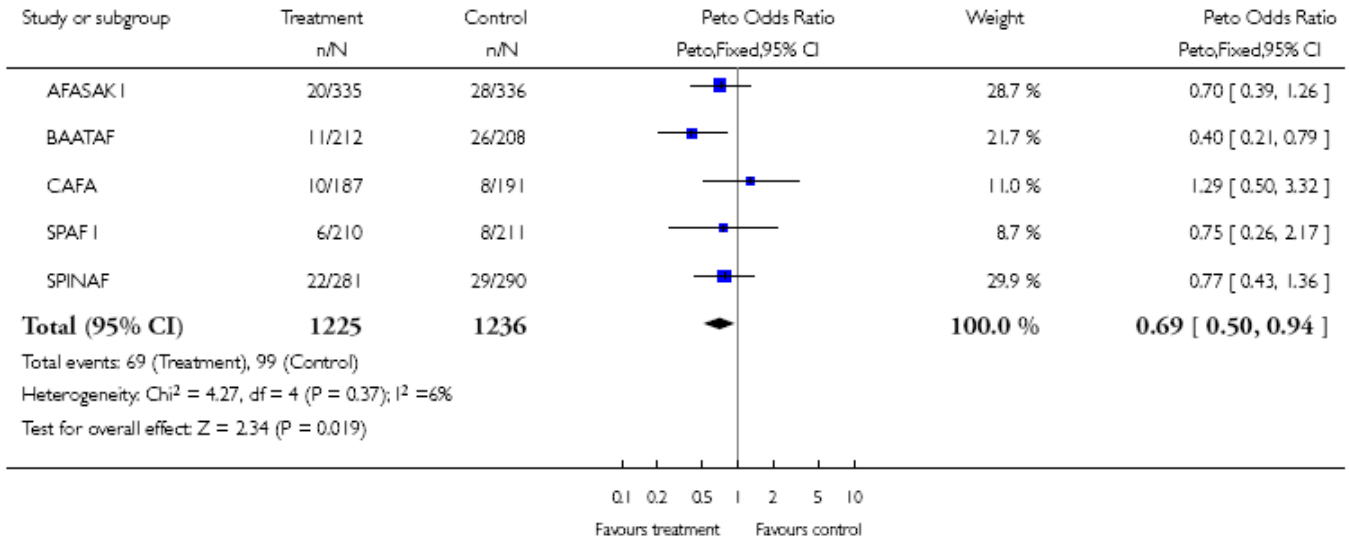
A Cochrane review published in 2005 also addressed the efficacy of warfarin for the prevention of all-cause mortality and myocardial infarction using available data from the five primary prevention trials for subjects with no previous history of stroke or transient ischemic attack. The effect of warfarin on these outcomes, as reported in this review, is shown in the figures below. The meta-analysis suggests favorable effects on all-cause mortality in these historical trials. As noted in the Cochrane review, few MIs occurred in these trials, making it difficult to ascertain what, if any effect, warfarin therapy has on this outcome.

**Analysis 1.10. Comparison 1 Anticoagulants versus control, Outcome 10 All cause mortality.**

Review: Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks

Comparison: 1 Anticoagulants versus control

Outcome: 10 All cause mortality

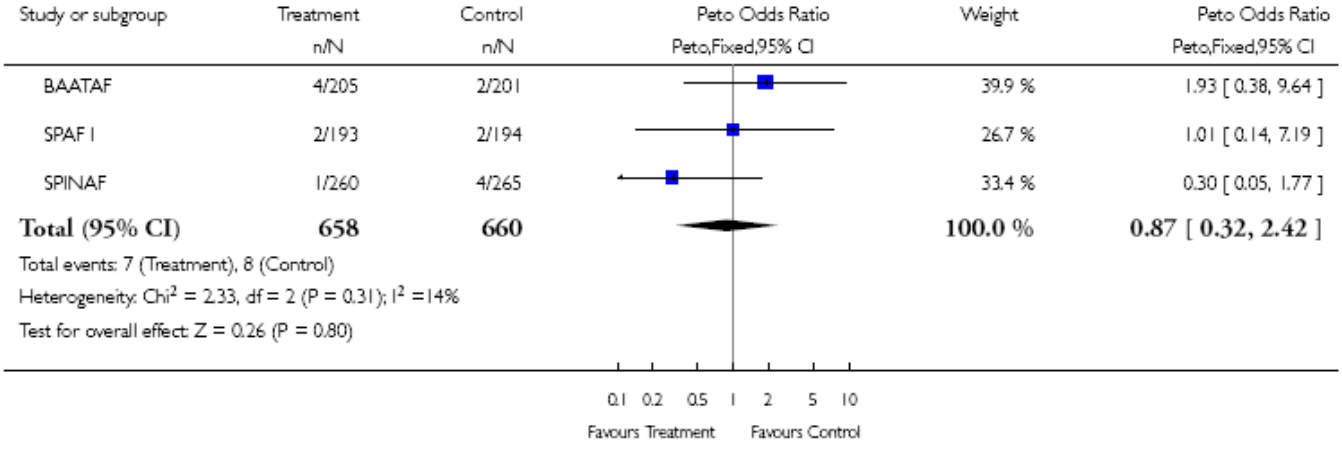



**Analysis 1.4. Comparison 1 Anticoagulants versus control, Outcome 4 Myocardial infarction.**

Review: Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks

Comparison: 1 Anticoagulants versus control

Outcome: 4 Myocardial infarction




[Source for all figures: Aguilar et al. 2005.]

*The quality of INR control:* An INR range of 2-3 is thought to maximize protection against ischemic stroke in patients with atrial fibrillation without incurring a marked increase in the risk of intracranial bleeding. In observational studies, the percent of time spent out of this range by patients has been associated with the risk of death, ischemic stroke and other thromboembolic events (Jones et al. 2005). Among patients randomized to warfarin therapy in randomized-controlled trials, the risk of death, MI, major bleeding and stroke or SEE have also been shown to be related to INR control as assessed by the percentage of time in the therapeutic range (White et al. 2007).

It has also been shown that the time in therapeutic range measured at the center-level and country-level (determined by averaging the individual times in therapeutic range for all of the subjects randomized to oral anticoagulant therapy within a center or country to yield a value for that center or country), has an important impact on the treatment benefit of warfarin in intervention trials. The benefit of oral anticoagulants over antiplatelet agents has been shown to be dependent upon the quality of INR control achieved as measured by the time in therapeutic range at the center and country level. In ACTIVE W, for patients at centers below the median time in therapeutic range (65%), no treatment benefit was demonstrated as measured by the relative risk for vascular events of clopidogrel plus aspirin versus oral anticoagulation; however, for patients at centers with a time in therapeutic range above the study median, oral anticoagulation was associated with a statistically significant ~ 2-fold reduction in the relative risk of vascular events (Connolly et al. 2008).

*Reviewer's comment: Though these studies all support the concept that a greater percentage of time in the therapeutic range is associated with a better outcome on warfarin, different approaches to censoring INR values from the calculation of a subject's time in therapeutic range have been used in studies, making it difficult to compare the quality of INR control across studies using the reported time in therapeutic range. Further, the reported time in therapeutic range reflects the percentage of measured and reported values falling within a given range; depending upon the adequacy of INR monitoring, it may or may not be indicative of the percentage of time trial participants were actually in the reported ranges. These factors limit the ability to use the time in therapeutic range as the sole metric for assessing the relative quality of INR control in RE-LY and emphasize the need for additional metrics to help ascertain the adequacy of anticoagulation in warfarin-treated subjects in clinical trials of new anticoagulants.*

## 9.5 Rankin Scale

For the purposes of this review, the term "Rankin Scale" refers to the Modified Rankin Scale.

**Table 80. Rankin Scale**

| Score | Symptoms | Description |
|---|---|---|

| | | |
|---|---|---|
| 0 | No symptoms | |
| 1 | No significant disabling symptoms | No significant disability despite symptoms; able to carry out all usual duties and activities. |
| 2 | Slight disability | Unable to carry out all previous activities but able to look after their own affairs without assistance. |
| 3 | Moderate disability | Requiring some help but able to walk without assistance. |
| 4 | Moderate / Severe disability | Unable to walk without assistance and unable to attend to own bodily needs without assistance. |
| 5 | Severe disability | Bedridden, incontinent and requiring constant nursing care and attention. |
| 6 | Dead | |

## 9.6 RE-LY protocol additional information

### 9.6.1. Full Inclusion/Exclusion Criteria

Inclusion criteria

1.) AF documented as follows (Amendment 1 changed this to 'documented by one of the' ):

a. There is ECG documented AF on the day of screening or randomization (Amendment 1 changed this to within 1 week of)

b. The patient has had a symptomatic episode of paroxysmal or persistent AF documented by 12 lead ECG within six months prior to randomization

c. There is documentation of symptomatic or asymptomatic paroxysmal or persistent AF on two separate occasions, at least one day apart, one of which is within six months prior to randomization. In this case, AF may be documented by 12 lead ECG, rhythm strip, pacemaker/ICD electrogram, or Holter ECG. The duration of AF should be at least 30 seconds. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators can be used to document only one episode of paroxysmal or persistent AF

2.) In addition to documented AF, patients must have one of the following additional risk factors for stroke:

a. History of previous stroke, transient ischemic attack, or systemic embolism

b. Left ventricular ejection fraction <40% documented by echocardiogram, radionuclide or contrast angiogram (Amendment 1 changed this to in the last 6 months)

c. Symptomatic heart failure, documented to be NYHA Class 2 or greater (Amendment 1 changed this to in the last 6 months)

d. Age ≥ 75 years

e. Age ≥ 65 years and one of the following additional risk factors:

i) diabetes mellitus on treatment (Amendment 1 specified treatment to include diet)

ii) documented coronary artery disease (any of: prior MI, positive stress exercise test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing ≥75% stenosis in a major coronary artery
iii) hypertension requiring medical treatment

3.) Age ≥18 years at entry
4.) Written, informed consent.

Exclusion criteria
• History of heart valve disorders (i.e., prosthetic valve or hemodynamically relevant valve disease) Amendment 1 specified

Patients with prosthetic heart valves requiring anticoagulation per se, or with haemodynamically relevant valve disease that is expected to require surgical intervention during the course of the study

• Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days
• Conditions associated with an increased risk of bleeding:
a. Major surgery in the previous month
b. Planned surgery or intervention in the next 3 months
c. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding (Amendment 1 added, "unless the causative factor has been permanently eliminated or repaired (e.g. by surgery))
d. Gastrointestinal hemorrhage within the past year (Amendment 1 added, "unless the cause has been permanently eliminated (e.g. by surgery))
e. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
f. Hemorrhagic disorder or bleeding diathesis
g. Need for anticoagulant treatment for disorders other than atrial fibrillation
h. Fibrinolytic agents within 48 hours of study entry
i. Uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg)
j. Recent malignancy or radiation therapy (=6 months) and not expected to survive 3 years

5.) Contraindication to warfarin treatment
6.) Reversible causes of atrial fibrillation (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism).
7.) Plan to perform a pulmonary vein ablation or surgery for cure of the AF
8.) Severe renal impairment (estimated creatinine clearance ≤30 mol/min)
9.) Active infective endocarditis
10.) Active liver disease, including but not limited to
a. Persistent ALT, AST, Alk. Phos. >2 x ULN
b. Known active hepatitis C* (as evidenced by positive HCV RNA by sensitive PCR-based assay, such as Roche Monitor or Bayer TMA assay)
c. Active hepatitis B* (HBs antigen +, anti HBc IgM+) (Amendment 1 clarified (HBs antigen +or anti HBc IgM+)
d. Active hepatitis A

11.) Women who are pregnant or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study (NOTE: A negative pregnancy test must be obtained for any woman of childbearing potential prior to entry into the study) (Amendment 2 added "lactating")

12.) Anemia (hemoglobin <10g/dL) or thrombocytopenia (platelet count <100 x 109/L)
13.) Patients who have developed transaminase elevations upon exposure to ximelagatran.
14.) Patients who have received an investigational drug in the past 30 days
15.) Patients considered unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than the expected duration of the trial due to concomitant disease, or has any condition which in the opinion of the Investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse).
*Patients with a known history of hepatitis B or C must undergo hepatitis serology for hepatitis B and C prior to inclusion in the study.

### 9.6.2. Liver abnormality follow-up

*Alert Status 1:* ALT or AST > 2x ULN and ≤ 3x ULN or Alk Phos > 2x ULN

- Weekly LFTs until ALT, AST and Alk Phos < 2x ULN

*Alert Status 2:* ALT or AST > 3x ULN and ≤ 5x ULN or Tbili > 2x ULN*

- Weekly LFTS until ALT, AST and Tbili < 2x ULN
- Evaluate for liver disease by reviewing alcohol intake, medications, concomitant disease, and further lab analyses. Additional evaluations including abdominal ultrasound with special attention to the liver, biliary tree, and pancreas should be considered.[3]

Note that a bulletin sent to investigators dated Oct 16, 2006 clarified that the "enhanced hepatic function kit"[1] be used for the first occurrence of an Alert 2. All subsequent LFT testing should be done using the LFT visit kit.[2] The abdominal ultrasound with special attention to liver, biliary tree and pancreas are clinically indicated and **must** be performed. Results of any tests or investigations must be sent to PHRI. (This bulletin note was also applicable for Alert Status 3).

*Alert Status 3:* ALT or AST > 5x ULN or ALT or AST > 3x ULN with a Tbili > 2x ULN*
Or development of hepatic disease related symptoms

- Discontinue medication. If first abnormal LFT, the test should be repeated for verification. Alert sponsor.
- Evaluate for liver disease (as specified for Alert Status 2)
- If jaundice or other symptoms (in the investigator's judgement) likely attributable to hepatic disease (e.g., fatigue, nausea, vomiting, loss of appetitie, new onset itching, upper abdominal pain, especially right upper quadrant abdominal pain), then withhold study medication and perform hepatic lab screening.

The sponsor and investigator had to agree that there was no evidence of liver disease to restart medication.

*If patient has Gilbert's Syndrome, the total bilirubin must be > 4 xULN to be classified as Alert Status 2/3.
1. Enhanced Hepatic Function Kit includes ALT, AST, AlkPhos, TBili, indirect bilirubin if TBili elevated, glucose, transferring saturation, amylase, lipase, cholesterol,

trigylcerides, TSH, Hepatitis B Surface Antigen (HBsAg) screen w/ confirmation, Hepatitis C Antibody (Anti-HCV), HBV PCR, HVC PCR, Anti-Liver-Kidney-Microsome (Anti-LKM-1), Anti-Mitochondrial Antibody (AMA), Anti-Nuclear Antibody (ANA), Anti-Smooth Muscle Antibody (ASMA), Ceruloplasmin, and alpha 1-anti-trypsin. Use instituted with Protocol Amendment 2 (dated May 24 2007).

The bulletin noted that if the LFTs normalize and then rise, then the enhanced hepatic function kit should be repeated because of the possibility of acute viral hepatitis.
2. Liver Function Test kit includes AST, ALT, AlkPhos and TBili (and indirect bilirubin if TBili elevated).

Subjects discontinuing medication should receive appropriate anticoagulation per the investigator.

For any subject being followed with weekly monitoring, if after 4 weeks of monitoring, these values are either stable or improving, but remain > 2 xULN, or if the cause of the LFT abnormality is deemed by the investigator and the sponsor not to be drug related, the monitoring may be decreased.

## 9.7 Additional information on FDA liver review

Drug induced liver injury is a diagnosis of exclusion; hence, to make a diagnosis, the results of tests excluding other etiologies of injury (pertinent positive as well as negative findings) are needed. The cases of interest reviewed by Drs. Senior and Seefe were scored for completeness of information (CMP) and informative use of the data (INF). These scores were based primarily on information provided to the Agency at the time of NDA filing, including brief sponsor narratives, case report forms and any available source documents. In some cases, additional information submitted in response to an Agency request was also considered.

The CMP score was based on the extent to which alternative causes for liver findings were investigated. The INF score was based on whether the information obtained from testing supported the likelihood decision. For example, whether or not the result of hepatitis A IgM testing was positive (and if so, just once or serially), when the test was done relative to the course of acute liver injury, and whether the result was confirmed by PCR and later, by the development of IgG.

The CMP and INF scores are shown below for the 55 liver cases reviewed. Very few cases had all key elements/enough for a definite conclusion of cause (CMP scale). Very few cases were scored as having a good basis for the causal decision/an incontrovertible causality assessment. This should be viewed as a limitation of the data.

## Table 81. Completeness and Information scores for 55 liver cases

| CMP | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 0 | No information provided | 0 | 2 | 0 |
| 1 | A couple of items | 4 | 1 | 5 |
| 2 | Several items | 6 | 6 | 11 |
| 3 | Most of the key items | 6 | 5 | 7 |
| 4 | All key items | 0 | 2 | 0 |
| 5 | Enough for definite conclusion of cause | 0 | 0 | 0 |

| INF | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 0 | Completely unsupported attribution | 0 | 1 | 0 |
| 1 | Very poor or weak attribution | 4 | 1 | 3 |
| 2 | Somewhat supported attribution | 5 | 6 | 8 |
| 3 | Very well supported conclusion | 5 | 6 | 9 |
| 4 | Very good basis for causal decision | 2 | 2 | 3 |
| 5 | Incontrovertible causality assessment | 0 | 0 | 0 |

## 9.9 Timing of events following medication discontinuation

### Table 82. Strokes or SEEs occurring off of therapy

| | DE 110mg bid | DE 150mg bid | Warfarin N |
|---|---|---|---|
| After permanent stop of study medication | 72 | 62 | 44 |
| 1<= and <2 days | 6 | 2 | 0 |
| 2<= and <3 days | 1 | 3 | 2 |
| 3<= and <4 days | 2 | 0 | 0 |
| 4<= and <=6 days | 5 | 3 | 2 |
| 6< and <=14 days | 9 | 8 | 9 |
| 14< and <= 30 days | 5 | 6 | 1 |
| 30< and <=60 days | 7 | 8 | 2 |
| 60< and <=90 days | 4 | 4 | 2 |
| > 90 days | 33 | 28 | 26 |
| Randomized but not treated | 0 | 0 | 0 |
| After temporary stop of study medication | 10 | 6 | 10 |
| 1<= and <2 days | 0 | 2 | 2 |
| 2<= and <3 days | 0 | 0 | 1 |
| 3<= and <4 days | 0 | 0 | 0 |
| 4<= and <=6 days | 1 | 1 | 1 |
| 6< and <=14 days | 3 | 1 | 1 |
| 14< and <= 30 days | 3 | 1 | 2 |
| 30< and <=60 days | 2 | 0 | 0 |
| 60< and <=90 days | 0 | 1 | 0 |
| > 90 days | 1 | 0 | 3 |
| Before start of study medication | 0 | 2 | 0 |

[Source: Sponsor, Table 15.3.5.4:1]

**Table 83. Major bleeds occurring off of study medication**

| | DE 110mg bid | DE 150mg bid | Warfarin N |
|---|---|---|---|
| After permanent stop of study medication | 102 | 107 | 84 |
| 1<= and <2 days | 16 | 10 | 8 |
| 2<= and <3 days | 5 | 6 | 5 |
| 3<= and <4 days | 4 | 2 | 1 |
| 4<= and <=6 days | 11 | 6 | 7 |
| 6< and <=14 days | 9 | 5 | 15 |
| 14< and <= 30 days | 8 | 6 | 9 |
| 30< and <=60 days | 4 | 10 | 6 |
| 60< and <=90 days | 6 | 5 | 4 |
| > 90 days | 39 | 57 | 29 |
| Randomized but not treated | 0 | 0 | 1 |
| After temporary stop of study medication | 50 | 53 | 66 |
| 1<= and <2 days | 8 | 9 | 7 |
| 2<= and <3 days | 8 | 5 | 5 |
| 3<= and <4 days | 4 | 10 | 5 |
| 4<= and <=6 days | 13 | 10 | 19 |
| 6< and <=14 days | 9 | 10 | 19 |
| 14< and <= 30 days | 3 | 3 | 3 |
| 30< and <=60 days | 1 | 3 | 3 |
| 60< and <=90 days | 2 | 1 | 0 |
| > 90 days | 2 | 2 | 5 |
| Before start of study medication | 0 | 2 | 0 |

[Source: sponsor, Table 15.3.5.4:2]

## 9.10 RE-LY Follow-up visit CRF

RE-LY 1 MONTH FOLLOW-UP VISIT FORM CRF 14

DataFax #177 Plate #014 Visit #004

PATIENT ID: Centre No. Patient No. PATIENT INITIALS: F M L

1. Date of Visit: year month day

2. Type of Visit ☐ Clinic Visit ☐ Home Visit ☐ Telephone Visit ☐ Other _____

**PART A. STUDY OUTCOME EVENTS**

*Since the last follow-up visit, up to and including this visit, has the patient experienced any of the following study outcomes:*

| | No | Yes | | Report Number(s) Submitted |
|---|---|---|---|---|
| 1. Stroke | ☐ | ☐ | → Stroke Report CRF 110 | # ☐☐ TO ☐☐ |
| 2. Myocardial Infarction | ☐ | ☐ | → MI Report CRF 114 | # ☐☐ TO ☐☐ |
| 3. Non-CNS systemic embolism | ☐ | ☐ | → Non-CNS Systemic Embolus Report CRF 116 | # ☐☐ TO ☐☐ |
| 4. Transient ischemic attack | ☐ | ☐ | → TIA Report CRF 118 | # ☐☐ TO ☐☐ |
| 5. Major bleeding | ☐ | ☐ | → Major Bleeding Report CRF 122 | # ☐☐ TO ☐☐ |
| 6. Minor Bleeding | ☐ | ☐ | → Minor Bleeding Report CRF 124 | # ☐☐ TO ☐☐ |
| 7. Pulmonary Embolism | ☐ | ☐ | → Pulmonary Embolism Report CRF 128 | # ☐☐ TO ☐☐ |
| 8. Death | ☐ | ☐ | → Death Report CRF 126 and 127 | |

**PART B. OTHER INFORMATION**

*Since the last follow-up visit, up to and including this visit, has any of the following occurred:*

| | | | | |
|---|---|---|---|---|
| 1. Cardioversion | ☐ | ☐ | → Cardioversion Report CRF 132 | # ☐☐ TO ☐☐ |
| 2. Emergency/Elective Surgery | ☐ | ☐ | → Interruption of Anticoagulant Report CRF 140 | # ☐☐ TO ☐☐ |
| 3. Admission to hospital | ☐ | ☐ | → Hospitalization Report CRF 120 | # ☐☐ TO ☐☐ |
| 4. Serious Adverse Event | ☐ | ☐ | → Serious Adverse Event (SAE) Report, Page 1 and 3 (Page 2 is optional) | # ☐☐☐ TO ☐☐☐ |
| 5. Experienced any other untoward medical occurrence | ☐ | ☐ | → Adverse Event CRF 155 | # ☐☐☐ TO ☐☐☐ |
| 6. Change in concomitant medications | ☐ | ☐ | → Concomitant Medications Report CRF 09 | # ☐☐ TO ☐☐ |
| 7. INR Evaluations done | ☐ | ☐ | → INR Log CRF 60 | # ☐☐ TO ☐☐ |



*Please fax this form to the PHRI Project Office within 48 hours of the patient follow-up visit*

PART C. CLINICAL ASSESSMENT AT THIS VISIT:

1. Sitting Heart Rate: ☐☐☐ beats/min (Patient sits for 3 min. before measuring)

2. Sitting Arm BP: Systolic ☐☐☐ / Diastolic ☐☐☐ mmHg (Patient sits for 3 min. before measuring)

PART D. STUDY MEDICATION

1. Was study medication discontinued (temporary or permanent) or re-started ☐ No ☐ Yes → Complete Study Medication Discontinuation/Restart CRF 151 # ☐☐ TO ☐☐

2. Was study medication dispensed since last visit? ☐ No ☐ Yes → Complete Study Medication Dispensation CRF 04 Report # ☐☐

3. Was study medication returned at this visit? ☐ No ☐ Yes

4. Study medication compliance: (dabigatran patients only) ☐☐☐ %

PART E. LABORATORY EVALUATIONS

1. Was blood collected since the last follow-up visit, up to and including this visit?

☐ No → Explain: _____

☐ Yes → Specify where sample sent:

a. Central Lab: ☐ No ☐ Yes → Blood Collection and Shipment Report CRF 66 Report# ☐☐

→ PK/PD/aPTT Blood Collection and Shipment Report CRF 68 ☐☐ OR ☐ Indicate if Not Done

b. For Hepatic Function lab tests:
Complete the Hepatic Function Laboratory Report CRF 62 → Report # ☐☐

PA

1. Has the patient reported a stroke since the last visit: ☐ Yes → *Ensure you have completed CRF 110 and recorded the report # on CRF 14*

☐ No → *Complete questions below*

***NOTE: Please ask these questions exactly as they are written and record patient's response.***

a. Since the last visit, have you been told by a physician that you had a stroke?

☐ No ☐ Yes

b. Since the last visit, have you had a sudden numbness or painless weakness on one side of your body that lasted for more than one day?

☐ No ☐ Yes

c. Since the last visit, have you had a sudden painless loss of vision on one side or in one or both eyes that lasted for more than one day?

☐ No ☐ Yes

d. Since the last visit, have you suddenly lost the ability to understand what people are saying or lost the ability to express yourself verbally or in writing for more than one day?

☐ No ☐ Yes

PART G. BLEEDING EVALUATION

1. Has the patient reported a bleed since the last visit:

☐ Yes → *Ensure you have completed CRF 122 or CRF 124 and recorded the report # on CRF 14*

☐ No → *Complete questions below*

***NOTE: Please ask these questions exactly as they are written and record patient's response.***

a. Since the last visit, have you had any unusual bleeding?

☐ No ☐ Yes → Specify: _____

b. Since the last visit, have you had any unusual black tarry bowel movements?

☐ No ☐ Yes → Specify: _____

c. Since the last visit, have you been told about any reduced blood count/haemoglobin?

☐ No ☐ Yes → Specify: _____

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22512 | ORIG-1 | BOEHRINGER INGELHEIM PHARMACEUTICALS INC | PRADAXA (DABIGATRAN ETEXILATE MESYLATE) |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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BACH N BEASLEY
08/25/2010

ALIZA M THOMPSON
08/25/2010

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 022-512 |
| Priority or Standard | Priority |
| Submit Date(s) | December 15, 2009 (Initial)<br>April 19, 2010 (Resubmission) |
| Received Date(s) | As above |
| PDUFA Goal Date | October 19, 2010 |
| Division / Office | Cardiovascular and Renal Products/ODE1 |
| Reviewer Name(s) | Nhi Beasley (Safety)<br>Aliza Thompson (Efficacy) |
| Review Completion Date | August 24, 2010 |
| Amended | October 17, 2010 |
| Established Name | Dabigatran |
| (Proposed) Trade Name | Pradaxa |
| Therapeutic Class | Anticoagulant |
| Applicant | Boehringer-Ingelheim |
| Formulation(s) | Oral |
| Dosing Regimen | 110 and 150 mg BID |
| Indication(s) | Prevention of stroke and systemic embolism in atrial fibrillation |
| Intended Population(s) | Adults |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Dabigatran should be approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The 150 mg dose of dabigatran should be approved but not the 110 mg dose. A superiority claim over warfarin should not be granted.

## 1.2 Risk Benefit Assessment

*Reviewer's comment: This section focuses on key analyses related to net benefit. A more thorough discussion of efficacy and safety findings, the adequacy of anticoagulation in the warfarin arm and the PROBE design of the phase 3 trial, as well as effects on mortality can be found in the Reviews of Efficacy and Safety (Sections 6 and 7, respectively).*

Dabigatran etexilate is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), randomized, non-inferiority study of unblinded warfarin administration and blinded administration of two doses of dabigatran (110 mg and 150 mg). RE-LY's primary endpoint was a composite of adjudicated stroke and systemic embolism (SEE). The sponsor's primary analysis, conducted on the intention to treat (ITT) population, established efficacy. Compared to warfarin treated subjects, the hazard ratio (HR) was 0.66 (95% CI 0.53 to 0.82, $p<0.003$ for superiority) in the dabigatran 150 arm and 0.91 (95% CI 0.74 to 1.11, $p<0.0001$ for non-inferiority) in the 110 mg arm.

Bleeding was the only important safety concern that we identified in RE-LY. Relative to warfarin, dabigatran 150 mg was not associated with an increased risk of adjudicated major bleeds (HR of 0.93, 95% CI 0.81, 1.07) whereas dabigatran 110 mg was associated with fewer major bleeding events (HR of 0.80, 95% CI 0.68, 0.90, $p<0.003$).[1] How a major bleed, as defined in RE-LY (see Table 1), compares in clinical significance to a stroke is questionable. To assess the net benefit of dabigatran (relative to warfarin, and the two doses relative to one another), a finer classification of both types of events is perhaps needed.

The sponsor defined subtypes of adjudicated bleeding and stroke events (e.g., life threatening bleeds, GUSTO-severe, intracranial hemorrhage [ICH], disabling and fatal

1 The RE-LY definition of major bleed is the same as the ISTH (International Society on Thrombosis and Haemostasis).

strokes) using information submitted by investigators. There are limitations to this approach. Investigators may not have uniformly applied or reported the necessary information to create the classification. For example, Rankin scores[2], used to define the severity of a stroke, were not consistently reported by site investigators. It is also not clear how investigators defined a symptomatic bleed or whether or not investigators used similar criteria. Such limitations impose a level of imprecision on the analyses of net benefit that follow and future development programs should perhaps strive to implement a more uniform and formal process for identifying those events of greatest clinical importance.

**Table 1. Definitions of terms**

| Term | Definition |
|---|---|
| Adjudicated major bleed | Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding) |
| Adjudicated life-threatening bleed (sub classification of major bleed) | An adjudicated major bleed meeting at least one of the following criteria: fatal; symptomatic intracranial bleed; reduction in hemoglobin of at least 5 grams per deciliter; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; required surgical intervention |
| GUSTO severe | An adjudicated ICH event; an adjudicated major bleed with at least one of the following criteria: associated with hypotension requiring use of intravenous inotropic agents; required surgical intervention to stop bleeding |
| Intracranial hemorrhage (ICH) | Includes adjudicated hemorrhagic stroke or adjudicated major bleed that was symptomatic intracranial |
| Adjudicated fatal or disabling stroke | Adjudicated stroke with initial Rankin* score of 3 or greater |

*The Rankin scale runs from no symptoms (0) to death (6). A Rankin score of 3 represents moderate disability (requires some help, but able to walk unassisted); a copy of the scale is provided in the appendix.

In the analyses of "net benefit" shown in Table 2, dabigatran's effects on various composite endpoints (composites of different types of bleeding, stroke and non-CNS systemic embolism events) were explored. These composite endpoint analyses suggest a favorable profile for dabigatran relative to warfarin. With respect to the two doses of

2 The reported Rankin scores in this review are based on the Modified Rankin Scale; an overview of this scale can be found in the appendix.

dabigatran, no clear and consistent differences are seen between the 150 mg and 110 mg dose using these definitions of "net benefit". As shown below, net benefit does not strongly or consistently favor one or the other dabigatran arm; the confidence intervals for the 150 mg to 110 mg comparisons are also, for the most part, broad and cross one, raising questions about which dabigatran dose better balances safety against efficacy.

**Table 2. Analyses of net benefit**

| **Net Benefit** | | **D110 vs. warfarin** | **D150 vs. warfarin** | **D150 vs. D110** |
|---|---|---|---|---|
| Adjudicated life threatening bleed or stroke/SEE | HR | 0.82 | 0.77 | 0.94 |
| | 95% CI | 0.71, 0.96 | 0.66, 0.90 | 0.80, 1.11 |
| | p-value | 0.01 | 0.001 | 0.47 |
| Adjudicated life threatening bleed or disabling or fatal stroke | HR | 0.81 | 0.80 | 0.99 |
| | 95% CI | 0.68, 0.96 | 0.68, 0.96 | 0.83, 1.19 |
| | p-value | 0.02 | 0.01 | 0.94 |
| ICH or stroke/SEE | HR | 0.79 | 0.63 | 0.79 |
| | 95% CI | 0.66,0.96 | 0.52,0.77 | 0.64, 0.98 |
| | p-value | 0.02 | <0.0001 | 0.03 |
| ICH or disabling or fatal stroke | HR | 0.71 | 0.61 | 0.85 |
| | 95% CI | 0.56, 0.91 | 0.48, 0.78 | 0.65, 1.11 |
| | p-value | 0.006 | <0.0001 | 0.24 |
| GUSTO-severe or disabling or fatal stroke | HR | 0.74 | 0.74 | 1.00 |
| | 95% CI | 0.60,0.91 | 0.60,0.91 | 0.81,1.24 |
| | p-value | 0.0034 | 0.0035 | 0.99 |
| Major bleed or stroke/SEE | HR | 0.87 | 0.88 | 1.01 |
| | 95% CI | 0.77, 0.99 | 0.78, 1.00 | 0.89,1.15 |
| | p-value | 0.03 | 0.04 | 0.87 |

Analyses excluding SEE produced similar/near identical point estimates, 95% confidence intervals and p-values and hence are not shown.

**Table 3. Net benefit: event rate per subject-year follow-up**

| Event | D110 (n=6015) | | D150 (n=6076) | | W (n=6022) | |
|---|---|---|---|---|---|---|
| | # events | %/yr | # events | %/yr | # events | %/yr |
| Adjudicated life threatening bleed or stroke/SEE | 302 | 2.5 | 288 | 2.4 | 364 | 3.1 |
| Adjudicated life threatening bleed or disabling or fatal stroke | 233 | 2.0 | 234 | 1.9 | 285 | 2.4 |
| ICH or stroke/SEE | 195 | 1.6 | 157 | 1.3 | 243 | 2.1 |
| ICH or disabling or fatal stroke | 117 | 1.0 | 101 | 0.8 | 162 | 1.4 |
| GUSTO-severe or disabling or fatal stroke | 163 | 1.4 | 165 | 1.4 | 218 | 1.9 |
| Major bleed or stroke/SEE | 485 | 4.1 | 494 | 4.1 | 550 | 4.7 |

Annual event rate calculated using sponsor's study termination date and randomization date for all randomized subjects.

**Dose:** While the composite endpoint analyses show very similar findings for the two doses of dabigatran, these findings are reached via different pathways/effects on the bleeding vs. stroke components of the composite. The yearly event rate for all of the events shown is low and the likely imprecision in the estimate of these event rates limits conclusions about the absolute risk of one event versus another. Nonetheless, we believe these analyses suggest that the 150 mg dose provides greater net benefit than the 110 mg dose. At the 110 mg dose, the rate of important stroke events (fatal/disabling strokes) perhaps still exceeds the rates of some of the worst bleeding events (e.g., GUSTO severe bleeds and ICH). At the 150 mg dose, the point estimate for the rate of life threatening and GUSTO severe bleeds begins to meet or exceed the point estimate for the stroke rate (overall and subset adjudicated to be ischemic or of uncertain classification). At this dose, the rates of disabling and hemorrhagic strokes and ICH also move closer, suggesting that a dose greater than 150 mg might result in an increase in clinically important bleeding events that could outweigh any benefit gained from stroke reduction.

**Figure 1. Event rate per subject-year follow-up**

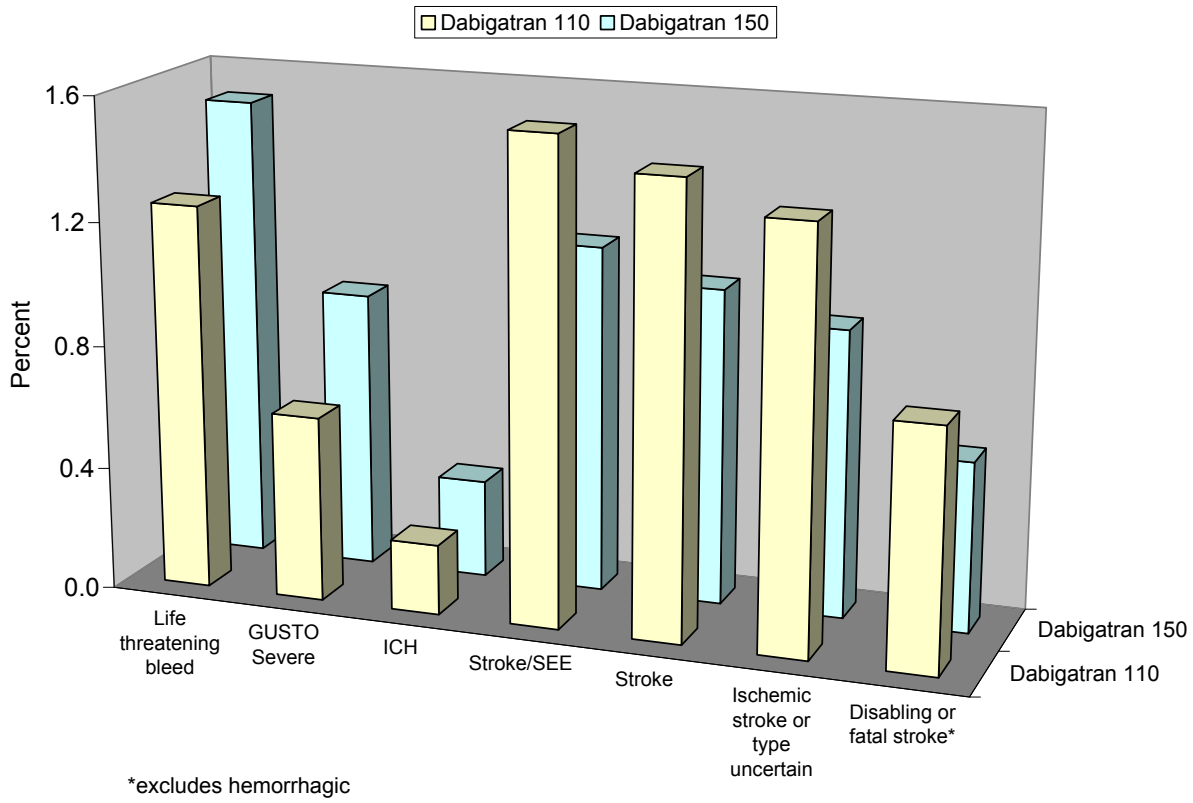



**Table 4. Event rate per subject-year follow-up in dabigatran treatment arms**

| | D110 (n=6015) | | D150 (n=6076) | |
|---|---|---|---|---|
| **Event** | # events | %/yr | # events | %/yr |
| Life threatening bleed | 147 | 1.2 | 179 | 1.5 |
| GUSTO severe | 74 | 0.6 | 106 | 0.9 |
| ICH | 27 | 0.2 | 38 | 0.3 |
| Stroke/SEE | 183 | 1.5 | 134 | 1.1 |
| Stroke | 171 | 1.4 | 122 | 1.0 |
| Ischemic stroke | 152 | 1.3 | 103 | 0.9 |
| Ischemic stroke or type uncertain | 159 | 1.4 | 111 | 0.9 |
| Disabling/fatal strokes | 103 | 0.9 | 76 | 0.6 |
| Disabling /fatal strokes excluding hemorrhagic | 92 | 0.8 | 66 | 0.6 |

Annual event rate calculated using sponsor's study termination date and randomization date for all randomized subjects.

In the proposed dabigatran label, the sponsor has approached the issue of dose by recommending the 150 mg dose, adding that "For patients with a potentially higher risk of bleeding" a dose of 110 mg "may be considered". While this approach seems reasonable, it may be problematic.

- Though subjects with moderate renal impairment (CrCl 30 -50) had high rates of major bleeds in all treatment arms of RE-LY (high relative to the rates seen in the RE-LY population as a whole), there did not appear to be a difference in the risk of major bleeds in the 150 mg compared to 110 mg treatment arms. In contrast, there appeared to be a greater reduction in ischemic strokes at a dose of 150 mg than 110 mg, suggesting greater net benefit from the higher dose in this population.
- Subjects 75 years of age and older are another group perceived to be at increased risk of hemorrhage; yet, this population also has an increased risk of stroke and in analyses of net benefit (composites of various stroke and bleeding events) no clear advantage of the 110 mg dose over the 150 mg dose was seen.[3]

In light of these findings, the merits of adjusting dabigatran dose based on perceived bleeding risk is not immediately clear to us. While one could attempt to explore this issue by performing subgroup analyses of "net-benefit" in various RE-LY subpopulations, any findings generated by such analyses may be more reflective of chance than true dose-dependent drug effects. For this reason, we are wary of including recommendations on dose adjustment based on perceived bleeding risk in the dabigatran label and recommend that only the 150 mg dose be approved.

**Efficacy vs. "Superiority":** The efficacy and safety findings of dabigatran relative to warfarin are bolstered by a dose-response relationship for both bleeding and stroke events in the blinded portion of the trial (though why such a relationship should exist given the substantial overlap in exposure at the two doses is not entirely clear). The finding of a highly statistically significant reduction in the risk of stroke/SEE (p=0.0002) in the dabigatran 150 mg arm relative to warfarin is also notable but should be considered in light of the open-label use of warfarin in RE-LY, as well as the lack of replication of the study's findings. In the ximelagatran experience, the stroke and systemic thromboembolism rate was numerically lower with ximelagatran in an open-label study and numerically higher in the blinded trial; according to an analysis based on risk reduction, the open label study supported the non-inferiority of ximelagatran, but the blinded study did not. Whether the discrepant study findings in the ximelagatran program should serve as an example of the limitations of open-label studies, the importance of replication, or some other issue is debatable. It does raise questions, however, about granting a superiority claim based on the results of a single, open-label study. Moreover, consideration should be given to the late date at which the statistical analysis plan was finalized (essentially after all of the study data had been amassed), as well as the factors driving the highly statistically significant p-value/finding. As shown in the Table 5, much of the relative risk reduction in stroke/SEE in the 150 mg arm vs. warfarin arm (and the associated p-value) is driven by subjects at sites with poorer INR control (as defined by a center-level INR below the median). Although the findings in

3 This experience is perhaps not so dissimilar to the experience in BAFTA (Mant et al., 2007), a study comparing warfarin with aspirin in patients over the age of 75. In BAFTA, warfarin was superior to aspirin in the prevention of stroke (HR of 0.52, 95% CI of 0.33 to 0.80 warfarin vs. aspirin) and yet was not clearly associated with a greater incidence of major hemorrhage (HR of 0.96, 95% CI of 0.53 to 1.75 warfarin vs. aspirin).

subjects at centers achieving levels of INR control above the median are still supportive of efficacy, they are not supportive of superiority over warfarin.[4]

**Table 5. Relative risk of stroke/SEE by center-level INR control**

| | Centers with INR control < median of 67% | | Centers with INR control ≥ median of 67% | |
|---|---|---|---|---|
| | D110 vs. warfarin | D150 vs. warfarin | D110 vs. warfarin | D150 vs. warfarin |
| HR | 0.86 | 0.57 | 0.96 | 0.77 |
| 95% CI | 0.66, 1.12 | 0.42, 0.76 | 0.71, 1.30 | 0.56, 1.06 |
| p-value | 0.26 | 0.0002 | 0.78 | 0.10 |

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor has proposed a REMS to mitigate the bleeding risk of dabigatran. The proposed REMS elements include a Medication Guide, Dear Health Care Professional Letter and Prescriber Brochure; these elements seem appropriate. In addition to a general discussion on the risk of bleeding, more specific topics that should be addressed in the REMS (Medication Guide, Dear Health Care Professional Letter and/or Prescriber Brochure) include:

- important issues impacted by dabigatran's short half life (relative to warfarin): the importance of patient compliance, what to do if a dose is missed, transitioning to and from dabigatran to warfarin/other anticoagulants, and the use/holding of medication in the peri-procedural/operative period;
- the effect of renal function on drug elimination (and how this impacts the use/holding of medication in the peri-procedural/operative period);
- the risk of gastrointestinal bleeding;
- use with antiplatelet agents;
- the performance of available assays in measuring the anticoagulant activity of dabigatran

The pharmacology-toxicology review has not yet been finalized. At this time, a concern has been raised for potential embryo toxicant effects in the clinical setting (based on findings in a rat study). This issue may also need to be addressed within the proposed REMS elements.

## 1.4 Recommendations for Postmarket Requirements and Commitments

1. The mechanism behind the increased risk of gastrointestinal bleeding as well as measures that can mitigate this risk need further study.

4 For further explanation of center-level based INR analyses as well as a discussion of the impact of center-level INR control on the treatment benefit of oral anticoagulant therapy, see the appendix.

2. In contrast to warfarin, effective interventions to stop dabigatran-related hemorrhage have not been established. Further studies should be done to determine the measures that physicians should take to stop bleeding in dabigatran treated subjects.

Postmarketing clinical studies may or may not be necessary to address the aforementioned concerns; if informative data can be obtained via *in vitro or* preclinical studies and/or post-hoc analyses of available clinical data, then this route should be pursued.

Finally, subjects with marked renal impairment (CrCl <30) were excluded from RE-LY. Whether or not further studies should be required in this populations (and if so, what types of studies) merits further discussion.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Dabigatran etexilate mesylate (proposed trade name Pradaxa) is an orally available, reversible, direct thrombin inhibitor and NME with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The chemical structure of dabigatran etexilate mesylate and an overview of key product attributes are provided below.

**Figure 2. Chemical structure dabigatran etexilate mesylate**

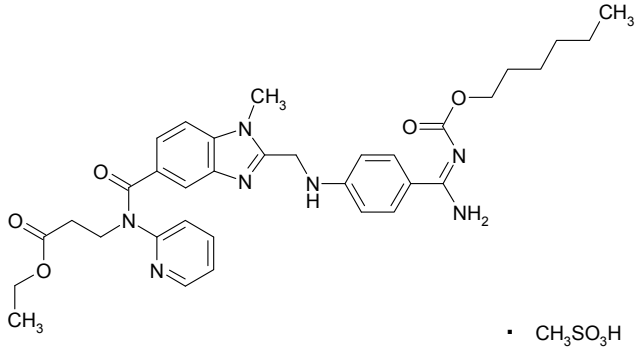


**Table 6. Dabigatran etexilate mesylate product information**

| Attribute | Description |
|---|---|
| Chemical Name | β-Alanine, N-[[2-[[[(hexyloxy)carbonyl]4-amino] iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methane-sulfonate |
| Appearance | Dabigatran etexilate mesylate is a yellow-white to yellow powder |
| Molecular Formula | $C_{35}H_{45}N_7O_8S$ [molecular weight: 723.86 (mesylate salt), 627.75 (free base)] |
| Dosing Regimen | 150 mg taken orally, twice daily; for patients "with a potentially higher risk of bleeding," a dose of 110 mg taken orally, twice daily "may be considered" |
| Proposed Age Group | Adults |

## 2.2 Tables of Currently Available Treatments for Proposed Indication

Atrial fibrillation is thought to affect approximately 2.3 million patients in North America and embolic events, primarily strokes, are an important complication of this condition. Warfarin, a vitamin K antagonist and antithrombotic agent, is approved in the United States for the prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation. Six trials, five primary prevention and one secondary prevention, are widely referenced as establishing the efficacy of warfarin in preventing ischemic strokes in patients with atrial fibrillation (see appendix). A meta-analysis of these trials suggests that warfarin reduces the relative risk of ischemic stroke by 67% (95% CI, 54% to 77%). Though these trials clearly establish warfarin's efficacy, the safe and effective use of warfarin is limited by dietary and drug interactions and intersubject variability in exposure. Frequent blood test (INR) monitoring is needed and bleeding remains an important complication of therapy.

## 2.3 Availability of Proposed Active Ingredient in the United States

Dabigatran is not currently approved in the United States. Dabigatran was approved by the EMEA (EMA) in 2008 for the primary prevention of venous thromboembolic events in adults after elective total hip or knee replacement surgery.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Dabigatran is a direct thrombin inhibitor. Approved direct thrombin inhibitors (all parenteral) include hirudin, argatroban, bivalirudin and desirudin. These agents are approved as anticoagulants for a variety of different conditions (e.g., bivalirudin for use in patients with unstable angina undergoing percutaneous intervention; desirudin as prophylaxis against deep venous thrombosis in hip replacement). Like other anticoagulants, an important safety concern with the use of these drugs is bleeding.

Ximelagatran, an oral member of this class, was also associated with hepatotoxicity, and a possible increased risk of serious coronary events, and was not approved in the United States. Bleeding and hepatotoxicity are discussed further in the review of safety.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

**Table 7. Regulatory advice**

| Source (date of meeting or submission) | Advice from Agency |
|---|---|
| Meeting Minutes Type C Guidance Meeting (March 24, 2005) | • non-inferiority must be attained with optimal warfarin control<br>• large safety database needed to address liver toxicity<br>• single-dose strategy questioned (as opposed to having a parameter measurement and adjusting dose)<br>• concern raised for ascertainment bias in identification of potential endpoint events given open-label nature of study |
| SPA response (July 11, 2005) | • double-blind trial preferred; more detail regarding why blinding was not feasible should be provided<br>• warfarin control achieved in the proposed trial would need to be as good as that achieved in the historical warfarin trials; instructed to perform sensitivity analyses (for both efficacy and safety) including only warfarin patients for whom the monitoring and dosage adjustment matched “minimal specifications”<br>• doses studied should be more widely spaced, and dose adjustment should be made based on renal function |
| Type C Guidance Meeting (August 18, 2008) | • late change to the SAP proposed by sponsor: testing for superiority in anticoagulant naïve patients and analysis pooling doses to test for superiority<br>• Agency expressed significant concerns about the changes given the amount of information that was available to influence the decision to alter the statistical analysis plan<br>• Agency reiterated that 1.38 was the recommended margin for non-inferiority |
| Type C Guidance Meeting (August 17, 2009) | • NDA should be submitted for rolling review; priority review was likely |

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

*Refuse to File*
On December 15, 2009, the NDA for dabigatran was filed; on February 12, 2010, following several discussions with the sponsor regarding data integrity issues, the Agency issued a refuse to file letter. While the sponsor claimed an overall data error rate of 0.1% or less for primary outcome data and 0.25% or less for all other data, during the clinical review, a number of obvious and easily identified errors were found in data sets felt by the review team to be important for establishing dabigatran's efficacy and safety. The frequency and relative ease with which these errors were identified raised questions about the true error rate in the submitted data and undermined reviewer confidence in the data. These errors were found in two data sets examined early in the review: a data set containing information on INR and warfarin dosing and one containing information on blood transfusions (felt to be critical by the review team as the sponsor's definition of a "major bleed" was based in part on the number of units of blood transfused). With regard to the INR data, transcription, transposition and auditing errors were found in reported INR values and/or warfarin dose. The blood transfusion data set contained inaccurate data on the number of transfusions received. For example, the data set incorrectly reported that three subjects received 92 U, 82 U and 62 U, respectively, of a blood product in one day when these subjects had in fact received 2 U each. The errors were thought to stem in part from the use of optical character recognition (OCR) without a subsequent check of the scanned data (such errors occurred in both data sets). The second type of error (found in the INR data set) was a type of error that could have been detected by auditing/performing additional checks of the data. A transposition error had been made by the clinical site whereby the warfarin doses had clearly been transposed with the INR values.

As a result of the refuse to file letter and following agreement with the review team on a plan, the sponsor engaged in additional data quality checks to establish the integrity of the submitted data. These cross-checks focused on data critical for the establishment of efficacy and safety and included: cross-checks of different case report forms for possible inconsistencies in reporting outcome events; plausibility and range checks of particular CRFs; and sampling checks to evaluate the accuracy of the optical character recognition (OCR) process originally used to capture the data, including double-data entry of particular CRF pages. According to the sponsor, all SAE narratives were also reviewed for potential endpoint events.

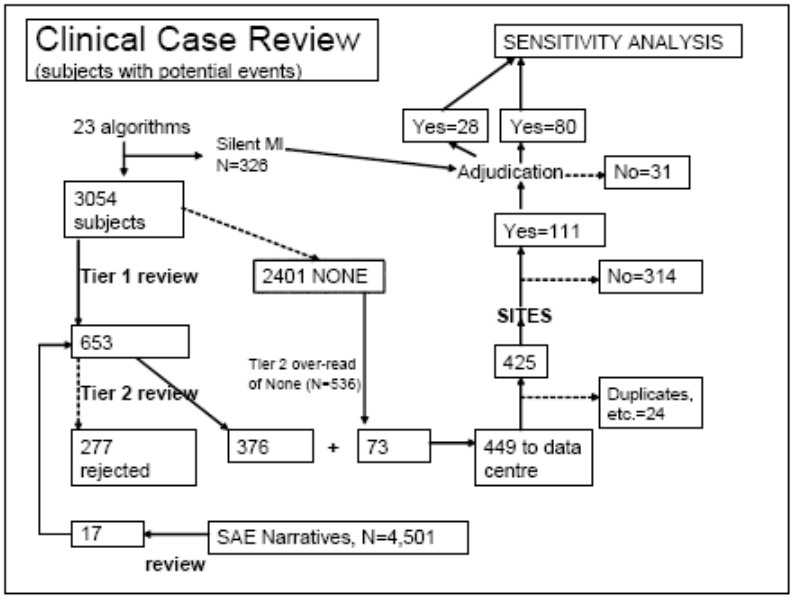
According to the sponsor, these checks identified 3848 findings in 3054 subjects requiring further review. These events were reviewed by unblinded "Tier 1" reviewers who were instructed to look for evidence of an unreported outcome event in the materials provided (CRFs, narrative, adjudication documents of other events). If there was additional evidence of an outcome event, or if the reviewer suspected an event

based on the clinical course of the subject or some other evidence, the case was escalated as a possible outcome event. Unblinded Tier 2 reviewers, individuals involved with RE-LY or familiar with the trial, reviewed the escalated cases and decided whether or not the event should be pursued as a potential outcome event (i.e., sent to the data center for distribution to the site). Additional events were identified via unblinded Tier 2 reviewer over-reads of a subset of events not escalated by Tier 1 reviewers.

*Reviewer's comment: How the subset of events were selected for over-read is not clear. According to the April 19, 2010 resubmission (page 33), "This over-read looked at a minimum of 10% of negative cases from each Tier 1 reviewer, trying to select representative cases. In addition, the Tier 2 reviewers examined additional negative cases from Tier 1 reviewers who, in their judgment, may not have been consistent in their application of the review guidelines."*

Events of interest identified by Tier 2 reviewers were sent to the data center for verification that the event had not been previously reported. Cases that had not been previously reported were sent to the study site for review. Sites were to indicate if an event had occurred. Events confirmed by the study site (and also events at sites that did not respond to the inquiry) were sent for adjudication. The adjudication process was similar to that used in the original protocol- adjudication was to be conducted by two reviewers blinded to treatment assignment with a third reviewer used when the initial reviewers disagreed. An overview of the process implemented by the sponsor as well as the number of potential events identified/escalated at each stage of the review is shown in the figure and table below. Across the treatment arms, a similar proportion of events were escalated at each stage of the review.

**Figure 3. Overview of dataflow for subjects with potential events**




[Source: Sponsor Information Amendment dated April 19, 2010, Figure 4.1.1]

**Table 8. Numbers of subjects identified by quality checks**

| | DE 110mg bid N (%) | DE 150 mg bid N(%) | Warfarin N(%) | Total N(%) |
|---|---|---|---|---|
| Reviewed by Tier 1 | 986 (100.0) | 1039 (100.0) | 1029 (100.0) | 3054 (100.0) |
| Reviewed by Tier 2 | 377 (38.2) | 406 (39.1) | 406 (39.5) | 1189 (38.9) |
| Submitted to Data Center | 147 (14.9) | 158 (15.2) | 144 (14.0) | 449 (14.7) |
| Submitted to Site | 135 (13.7) | 153 (14.7) | 137 (13.3) | 425 (13.9) |
| Submitted to Adjudication | 31 (3.1) | 39 (3.8) | 41 (4.0) | 111 (3.6) |
| Adjudicated Subjects with Outcome Events | 22 (2.2) | 29 (2.8) | 29 (2.8) | 80(2.6) |

[Source: Sponsor Information Amendment dated April 19, 2010, Table 4.1.7]

An overview of the adjudicated events by treatment arm is shown in the sponsor's table below. Few additional efficacy endpoint events were reported. Of the 68 newly identified adjudicated major bleeds, 32 were identified by programmed checks of hemoglobin drops of > 2 g/dL, 19 were identified by programmed checks of the blood transfusion data, 11 were identified by programmed checks comparing AE terms to potential outcome event terms, three were identified by a free text search of reported admission reasons, and three were identified by other checks.

**Table 9. Additional outcome events identified by quality checks**

| | **DE 110 N** | **DE 150 N(%)** | **Warfarin N(%)** | **Total N(%)** |
|---|---|---|---|---|
| Stroke | 0 | 0 | 1 | 1 |
| SEE | 0 | 0 | 1 | 1 |
| Death | 0 | 0 | 0 | 0 |
| TIA | 3 | 1 | 1 | 5 |
| MI | 1 | 0 | 3 | 4 |
| PE | 0 | 0 | 1 | 1 |
| Major Bleed | 18 | 28 | 22 | 68 |
| **Subtotal Subjects** | **22** | **29** | **29** | **80** |
| Silent MI | 11 | 8 | 9 | 28 |
| **Total Subjects** | **33** | **37** | **38** | **108** |

[Source: Sponsor Information Amendment dated April 19, 2010, Table 1.1]

With regard to the INR and warfarin dose data, these dose were manually reentered; the error rate in the originally submitted data was found to be ~2%. As a result of the manual re-entry process, a total of 3,743 of 174,773 dose values changed and 3,856 of 175,190 INR values changed. Forty-seven records were added and 59 records were removed.

*Reviewer's comment: Tier 1 and 2 reviewers were unblinded to treatment assignment and some Tier 2 reviewers were "involved with RE-LY" and hence ascertainment bias is possible. Throughout the subsequent FDA Clinical Review, numerous checks were done, comparing the information reported in key resubmitted data sets to the CRF documents themselves. With the exception of errors in the disposition data (see Section*

*6.1.3), the data contained in the resubmitted data sets appear to match the data contained in the CRFs. Hence, at this time, we think the data are of sufficient quality to allow substantive review. Whether or not there were additional events that were not reported by investigators is an issue that the DSI audits will address.*

## 3.2 Compliance with Good Clinical Practices

*See also discussion under section 3.1.*

*Sites closed for cause by the sponsor*
According to the sponsor, eight RE-LY study sites were closed for cause; these sites randomized a total of 166 subjects. At this time, DSI has inspected seven of these sites and recommended that data from a total of 43 subjects not be used to support the application. The inspection did not support the sponsor's allegation at one site (251). According to the TSAP events, events occurring at these sites prior to study site closure (defined as the date the site was notified of closure) are included in efficacy analyses (page 22 of TSAP). Subjects at sites closed for cause were not followed up for vital status.

**Table 10. Sites closed for cause by sponsor**

| Site | Subjects (screened/ randomized) | DSI findings |
|---|---|---|
| 108 | 41/31 | OAI (letter/inspection findings pending) |
| 128 | 8/6 | Inspection confirmed sponsor's allegations; DSI recommended exclusion of subject 002 (no evidence AF on ECG) |
| 146 | 10/4 | NAI; Though site closed for lack of clinical investigator involvement in study, protocol violations and consent irregularities (IRB had withdrawn approval prior to sponsor site closure), inspection found that there had been substantial efforts to reconcile deficiencies and respond to queries |
| 354 | 7/7 | VAI: Investigator failed to maintain adequate case histories; data may be used to support application |
| 251 | 68/52 | VAI: Inspection did not support sponsor's allegations; data may be used to support application |
| 265 | 60/37 | OAI: Warning letter; data should not be used to support application |
| 276 | 7/5 | OAI: Warning letter; data should not be used to support application |
| 6 | 27/24 | Confirmed sponsor allegations for GCP violations, and resulting site closure |

With regard to site 251, the sponsor alleged that their audit revealed missing or inconsistent study data and source documentation, protocol violations

(inclusion/exclusion criteria) and patient safety related issues including failure to report SAE and non-serious events to the sponsor, INR monitoring, patients bleeds and drug accountability issues (several subjects took drug beyond the expiration date). According to what was written in the EIR by the field investigators, the inspection found “no evidence to support the sponsor’s allegations,” despite inspection of documents for all 52 randomized subjects.

The table below shows the number of discontinuations, primary endpoint events, deaths and SAEs reported at site 251. The TTR reported at site 251 was 64.9%.

**Table 11. Events at site 251**

| | Number (%) with event | | |
|---|---|---|---|
| | **Dabigatran 110 (N=17)** | **Dabigatran 150 (N=17)** | **Warfarin (N=18)** |
| Discontinuations | 4 | 6 | 7 |
| Stroke or SEE | 0 | 1 | 0 |
| Death | 1 | 0 | 0 |
| SAE | 14 | 0 | 4 |

Regarding "test article accountability," the DSI inspector at site 251 also commented that documentation left on site by the sponsor monitors was "inadequate, inaccurate and much of it was illegible." DSI plans to investigate the issue further with an audit of the sponsor/monitor and will also obtain additional data during their clinical investigator site audits.

*Other sites for which DSI received complaints*
In addition to the sites closed for cause by the sponsor, DSI received complaints for an additional three sites; information regarding two of these sites is provided in the table below. The third complaint was a notification from the sponsor: a Clinical Investigator had informed the sponsor that a study coordinator at his site had used a professional license and CV that belonged to somebody else.

**Table 12. Sites for which DSI received complaints**

| **Principal Investigator** | **Site** | **Subjects (screened/ randomized)** | **DSI findings** |
|---|---|---|---|
| (b) (6) | | 10/9 | (b) (6) |
| Pilcher, George | 232 | 44/43 | VAI (data can be used in support of application) |

*Sites selected for audit following NDA submission*
Six investigator sites were selected for audit; four foreign and three in the United States. A for-cause inspection was conducted at an additional site (Tonkin, site 351). No deficiencies were noted by the field investigator at the Ezekowitz site (site 32). A VAI was issued at the Tonkin site which had enrolled 5 subjects; it was concluded that the data could be used to support the application. At this time, no other inspection reports have been finalized. In addition to these sites, audits of the sponsor and academic research organization are also planned.

*Reviewer's comment: The inspections have not yet been completed; however at this time, results of DSI audits suggest that there was compliance with good clinical practices and the trials were conducted in accordance with accepted ethical standards.*

### 3.3 Financial Disclosures

Fourteen investigators enrolling subjects from 13 clinical sites were listed as holding financial interests requiring disclosure; all reported significant payments with a cumulative monetary value of $25,000 or more made by the sponsor to the investigator or investigator's institution exclusive of the costs of conducting the clinical study. Collectively, these sites enrolled 418 subjects (2.3% of subjects) and accounted for 2.5% of adjudicated primary endpoint events (stroke or SEE) and 3.5% of deaths. One of 13 sites at which investigators were reported to hold financial interests requiring disclosure was selected for audit.

*Reviewer's comment: The applicant has adequately disclosed financial arrangements. These arrangements do not raise concerns about the integrity of the study's findings; a small percentage of key efficacy endpoint events were reported in subjects at these sites and exclusion of subjects/events at these sites would not alter the overall study findings.*

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Minor CMC issues have been communicated to the sponsor, however no significant efficacy or safety issues have been identified at this time. See section 2.1 for an overview of the drug substance/product.

### 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

Dr. Harlow's draft review dated August 12, 2010, judged dabigatran approvable from a nonclinical perspective. Most of the observed toxicities were attributable to the pharmacodynamic effect of dabigatran or its active metabolite (e.g., decreases in hemoglobin, hematocrit and red blood cells). Other notable findings:

- In rat studies, dabigatran acted as an embryo toxicant. Dabigatran decreased the number of implantations, decreased the number of viable fetuses, increased the resorption rate, increased the post-implantation loss, and increased the number of dead offspring when given at doses of 70 mg/kg (about 2.3 times the MRHD of 300 mg/day on a $mg/m^2$ basis) to female rats prior to mating to implantation, from implantation to the end of organogenesis, and from implantation to weaning. Dr. Harlow has recommended specific language for describing these effects in the label.

- Dabigatran was not carcinogenic in mice or rats (doses were 3.2, and 6.5 times the MRHD) for up to two years, however an increased incidence of liver necrosis in all treated groups was observed in the rat carcinogenicity study. This was seen after a lifetime of treatment and without an accompanying increase in liver tests (AST/ALT). In contrast, no liver necrosis was observed in the 26- or 52-week monkey studies.

*Reviewer's comment: The clinical significance of the liver findings in the rat carcinogenicity studies is unclear.*

## 4.4 Clinical Pharmacology

No significant efficacy or safety issues have been identified at this time. Key pharmacodynamic and pharmacokinetic characteristics are described below. For a more comprehensive overview, see the Clinical Pharmacology Review.

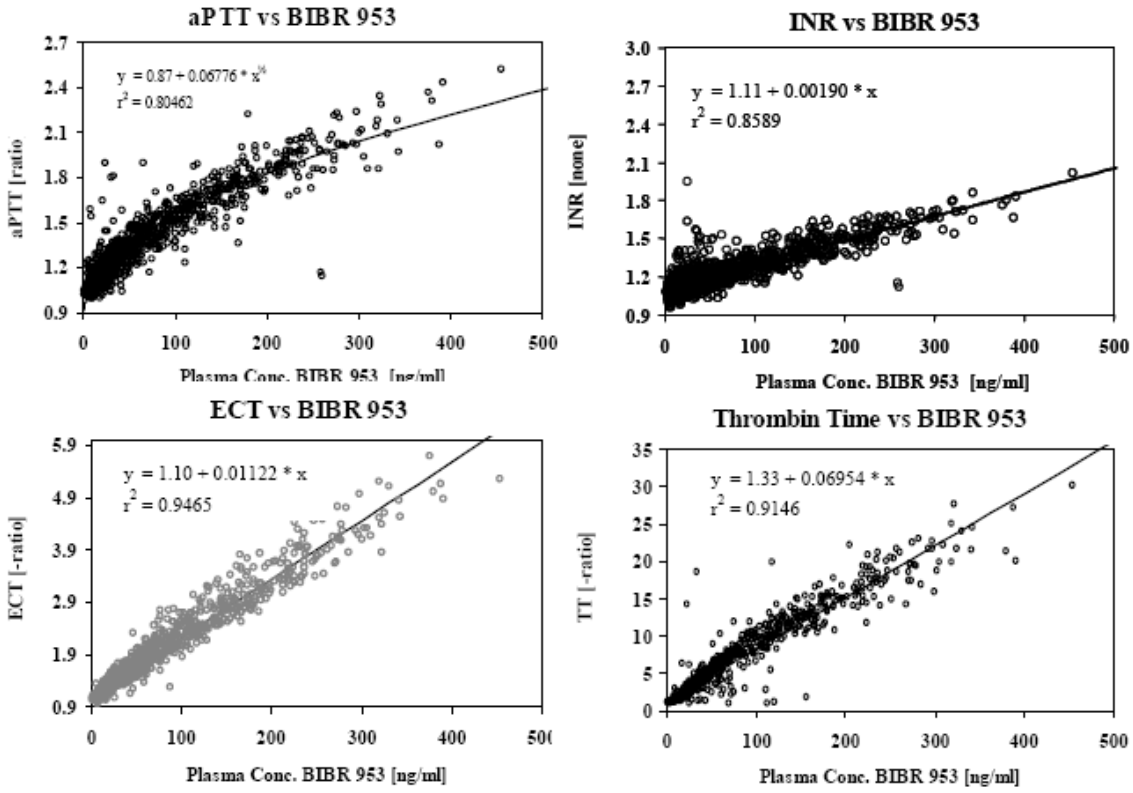
### 4.4.1 Mechanism of Action

Dabigatran etexilate, a prodrug, is converted to dabigatran, the active metabolite. Dabigatran is a direct thrombin inhibitor that reversibly inhibits fibrin-bound thrombin, free circulating thrombin and thrombin-induced platelet aggregation.

## 4.4.2 Pharmacodynamics

The relationship between dabigatran plasma concentration and various pharmacodynamic markers in healthy subjects is shown in the sponsor's figure below. Of these tests, ecarin clotting time (ECT) values appear to correlate best with plasma concentrations; ECT appears to be linearly related to dabigatran concentration and does not appear to reach a maximum/plateau at higher concentrations

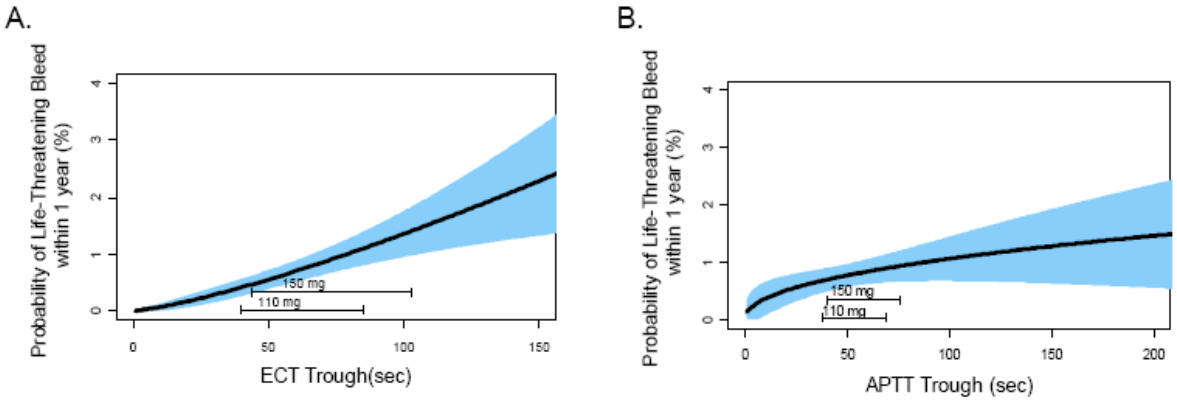
**Figure 4. Relationship between dabigatran (BIBR 953) concentration and aPTT, ECT, Thrombin time, and INR**




[Source: Sponsor's Clinical Overview (module 2): Figure 2.5.3.2:1]

APTT and ECT were measured in RE-LY at one month post randomization in dabigatran subjects. While both APTT and ECT were significant predictors of life-threatening bleeds (see next figure), ECT performed better overall.

**Figure 5. ECT and APTT and the probability of a life-threatening bleed in RE-LY**




[Source: Email correspondence from Dr. Krudys FDA Pharmacometrics Reviewer]
The shaded region represents the 95% CI; the bars on the bottom of the plot region represent the 10th to 90th percentiles of observed dabigatran predose concentrations in the RE-LY trial.

*Reviewer's comment: Of the assays studied, ECT appears to be the best marker of bleeding risk and ECT should be recommended for monitoring the anticoagulant activity of dabigatran. Ecarin chromogenic assays (ECA) have also been developed and, based on a preliminary review of the literature, may also be suitable*[5]*.*

### 4.4.3 Pharmacokinetics

Renal function appears to be the most important parameter influencing the pharmacokinetics of dabigatran. In a Phase I study, exposure levels were ~3-fold higher in moderate renal impairment (CrCL 30 - < 50 mL/min) compared to normal renal function (> 80 mL/min). The difference between these two classes was ~2.3-fold in RE-LY. In subjects with severe renal impairment (CrCL <30 mL/min), the mean AUC of dabigatran was increased ~6.3 compared to normal renal function.

Key pharmacokinetic attributes are summarized in the next table.

5 An ecarin chromogenic assay, in which ecarin is added to a plasma sample and meizothrombin generation is measured using a chromagenic substrate, has been used to measure the anticoagulant activity of direct thrombin inhibitors and, according to some literature, may offer advantages over ECT (Lange et al., 2004).

**Table 13. Key pharmacokinetic attributes**

| Parameter | Comments |
|---|---|
| Bioavailability | 3 to 7%, pH dependent |
| Cmax and AUC | Cmax obtained 0.5 to 2.0 hours post administration; dose proportional increase in Cmax and AUC (after single oral doses from 10 to 400 mg); average ratio of accumulation of 150 mg dose with repeated dosing 1.4 and 1.3-fold for AUC and Cmax, respectively; after repeated dosing, steady state reached by Day 3 of treatment |
| High Fat Meal | No effect on bioavailability, delayed time to peak plasma concentration (~2 hrs) |
| Distribution | 34-35% plasma protein binding; volume of distribution 60-70 L |
| Elimination | Primarily renal (85% urine), eliminated primarily unchanged at a rate of ~100 mL/min; T½ life ~10-11 hrs; ~15 and ~18 hours in mild and moderate renal impairment respectively; T½ life is independent of dose; 61 to 68% of systemic dabigatran removed by dialysis |
| Metabolism | Dabigatran etexilate rapidly converted to dabigatran (active form) by esterase catalyzed hydrolysis; neither dabigatran etexilate nor dabigatran are metabolized by the cytochrome P450 system. Dabigatran etexilate (but not dabigatran) is a substrate for the efflux transporter protein p-glycoprotein. |

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

According to the sponsor, dabigatran has been studied in 40 phase I studies, six completed phase 2 studies and four completed phase 3 trials. These studies were conducted either as part of the atrial fibrillation development program or for other indications. An overview of phase 2 studies conducted in patients with atrial fibrillation is provided in section 6.1.8. RE-LY, a phase 3 trial conducted in support of the proposed indication, is discussed in section 5.3. RE-LY-ABLE, a long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial, is currently underway and is not described further in this review.

## 5.2 Review Strategy

The Clinical Review focused on the design and conduct of RE-LY and the resulting data. Efficacy was reviewed by Dr. Thompson; Safety was addressed by Dr. Beasley.

## 5.3 Discussion of Individual Studies/Clinical Trials

In support of the proposed indication, the sponsor conducted a single phase 3 trial titled "Randomized Evaluation of Long term anticoagulant therapY comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY)." An overview of the study protocol, as laid out in the sponsor's finalized protocol dated September 12, 2005 is provided below. Important revisions enacted by protocol amendments accompany the relevant sections of text; these amendments are also summarized at the end of this section.

*RE-LY Overview*

### 5.3.1 Study Design and Objectives

RE-LY was a randomized, active controlled, multi-center, non-inferiority study of open-label warfarin administration and blinded dabigatran administration at two doses (110 and 150 mg). RE-LY was an event-driven trial and the stated primary objective was to demonstrate the efficacy and safety of dabigatran in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism.

### 5.3.2 Study Duration/Dates

December 22, 2005 to March 15, 2009 (Final close out visit period- December 16, 2008 to March 15, 2009, visits 1-3 months earlier also accepted as normal study closeout)

### 5.3.3 Study Sample Size and Power Considerations

The study sample size was initially set at 15,000 subjects. Based on an assumed event rate of 1.6%/year (equal across treatment arms), with 5000 subjects per treatment group and a total of 450 events, each comparison would have ~90% power to conclude the non-inferiority of dabigatran to warfarin at a one-sided alpha=0.025 (without adjusting for multiple comparisons). The trial was expected to have ~84% power to declare non-inferiority for both dabigatran doses to warfarin. Protocol Amendment 2 dated 2007 increased the sample size to 18,000.
*Reviewer's comment: The amendment noted faster than anticipated enrollment and cited the need to "maintain the statistical power in case of event rate < 1.6% within the original study time line." Correspondence between those conducting the trial and BI cite an opportunity to increase the power to determine whether both dabigatran doses are noninferior to warfarin.* [6.]

[6] Letter to M. Haehl (BI) from S. Connolly, M. Ezekowitz, L. Wallentin and S. Yusef, dated April 19, 2007

### 5.3.4 Study Population

Key enrollment criteria included non-valvular atrial fibrillation and one of the following additional risk factors: previous ischemic stroke, TIA, or systemic embolism, left ventricular ejection fraction < 40, symptomatic heart failure (NYHA class II or greater), age ≥75 years, or age ≥65 with either diabetes mellitus, history of coronary artery disease, or hypertension.

A diagnosis of atrial fibrillation was established based on:

- ECG documented AF on the day of screening or randomization (protocol Amendment 1 expanded this criterion to include ECG documented AF within one week of screening);
- A symptomatic episode of paroxysmal or persistent AF documented by 12 lead ECG within six months prior to randomization;
- Documentation of symptomatic or asymptomatic paroxysmal or persistent AF (at least 30 seconds) on two separate occasions, at least one day apart, one of which within six months prior to randomization. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators could be used to document only one episode of paroxysmal or persistent AF.

Patients with active liver disease, anemia (defined as a hemoglobin <10 mg/dL), severe renal impairment (eGFR < 30 mL/min), contraindication to warfarin or conditions associated with an increased risk of bleeding were excluded. For a full listing of inclusion and exclusion criteria, see Appendix 9.5.1.

To better ensure enrollment of Vitamin K naïve patients, the protocol was amended (see Amendment 1) to specify that the proportion of Vitamin K naïve subjects would be monitored at randomization by IVRS; the Operations Committee could impose additional measures (e.g. a quota system) to ensure balanced enrollment.

### 5.3.5 Procedures

Patients were randomized by IVRS (1:1:1) without stratification for any baseline variables. Following randomization, telephone contact was made at 2 weeks and subjects were seen at 1, 3, 6, 9 and 12 months and then every 4 months thereafter. According to the original protocol, a final follow up visit was to be performed whenever a patient terminated the study, either prematurely or according to the protocol. Protocol Amendment 2 (May 24, 2007) clarified that the final follow-up visit would be performed in subjects who terminated prematurely via withdrawal of consent or according to the protocol. At this follow-up visit, adverse events, bleeding events, efficacy events and changes in concomitant medications since the last visit were to be assessed, in addition to other assessments (physical exam, laboratory, ECG, vital signs).

### *5.3.5.1 Liver monitoring*

Liver tests (ALT, AST, Alk. phos, bilirubin) were evaluated monthly for the first 12 months of treatment and every 4 months thereafter. After liver test data were accrued on 6000 patients exposed for at least 6 months, the frequency of abnormalities was examined and a decision was made to reduce monitoring to every 3 months in subjects randomized after September 25, 2006 (see Protocol Amendment 3). See Appendix for details of specified follow-up for elevated liver tests.

### *5.3.5.2 Anticoagulation initiation, maintenance, and monitoring*

Anticoagulation was to be stopped on the day of randomization[7]. Subjects assigned to dabigatran therapy had their study medication started (if INR<2) or held (if INR ≥ 2) until their INR was < 2 (checked every 1-3 days). Subjects assigned to warfarin therapy started warfarin if their INR was less then 3.0, continued warfarin with dose adjustment based on their current INR or switched from other anticoagulant to warfarin therapy. Protocol Amendment 1 clarified that for subjects previously taking phenprocoumon, warfarin would be started when their INR was < 2.0.

During the course of the study, INR was to be monitored at least every 4 weeks in subjects assigned to warfarin or more frequently if needed, based on the clinical judgment of the investigator. Failure to measure the INR level was to be reported as a protocol violation[8]. All dose adjustments were to be done according to usual clinical practice; a nomogram containing recommended dose changes and INR re-testing times for different INR values was also provided to investigators to assist in dose adjustment. Copies of the initiation and maintenance nomograms are provided below.

7 Protocol amendment 1 added that the exact timing for stopping anticoagulation might be adjusted based on the subject's next possible clinic visit and last INR.
8 According to the sponsor, this practice (reporting the failure to measure INR as a protocol violation) was never implemented and this requirement was removed by protocol amendment 5.

**Table 14. Nomogram for initiating warfarin**

| DAY | INR | WARFARIN DOSE (MG PER DAY) |
|---|---|---|
| 1 | - | 5 |
| 2 | - | 5 |
| 3 | <1.5<br>1.5-1.9<br>2.0-3.0<br>>3.0 | 10<br>5<br>2-3*<br>0 |
| 4 | <1.5<br>1.5-1.9<br>2.0-3.0<br>>3.0 | 10<br>7-8*<br>5<br>0 |
| 5 | <2.0<br>2.0-3.0<br>>3.0 | 10<br>5<br>0 |
| 6 | <1.5<br>1.5-1.9<br>2.0-3.0<br>>3.0 | 12-13*<br>10<br>7-8*<br>0 |
| *at discretion of physician | | |

**Lower doses**: age > 75 yrs, weight < 60 kg, interacting medications known to potentiate warfarin, hepatic dysfunction, hypoproteinemia, hyperthyroid, impaired nutritional intake, increased baseline INR.

**Higher doses**: hypothyroid, interacting medications known to inhibit warfarin, diet rich in vitamin K.

**Table 15. Nomogram for warfarin maintenance**

| INR | ACTION |
|---|---|
| ≤ 1.5 | Increase weekly dose by 15%; repeat INR in 7 – 10 days. |
| 1.51 – 1.99 | If unexplained, increase weekly dose by 10%; repeat INR in 7 – 10 days. |
| 2.00 – 3.00** | No change |
| 3.01 – 4.99 | If INR 3.01 – 3.99 do not hold warfarin. If high on two consecutive occasions, decrease weekly dose by 10%;<br>If INR 4.00 – 4.99 hold for 1 day; repeat INR in 7 – 10 days. |
| 5.00 – 8.99 | Hold warfarin. Consider Vitamin K 2-4 mg PO if at increased risk of bleeding. If INR still high 24 hours later, consider giving 1-2mg additional Vitamin K PO and restart at lower dose (decrease weekly dose by 15%) when INR therapeutic. Check INR weekly until stable. |
| ≥ 9.0 | Hold warfarin and give Vitamin K 5.0-10 mg PO. Monitor more frequently and repeat Vitamin K if necessary. |
| Serious bleeding regardless of INR | Hold dose and give Vitamin K 10 mg IV and fresh frozen plasma, recombinant Factor VIIa, or prothrombin complex concentrates depending on urgency of situation. |
| **If INR between 1.80 – 2.00 or 3.00 – 3.20, consider no change in with repeat INR in 7 – 10 days, for first occurrence ONLY. | |

### *5.3.5.3 Treatment of bleeds*

*Major bleeds:* The protocol specified that study medication should be stopped and the treatment of major bleeds left to local practice. Bleeding in subjects on warfarin was to be reversed with Vitamin K and/or fresh frozen plasma (FFP) and consideration was to be given to prothrombin concentrates or recombinant factor VIIa (if used, guidance from a coagulation expert was recommended). For bleeding in the setting of dabigatran administration, the protocol originally noted that packed cells or FFP may be administered with consideration given to the use of prothrombin complex concentrates and recombinant factor VIIa, though their role in reversing the anticoagulant effect of dabigatran was unproven. If thrombocytopenia was present, consideration was also to be given to platelet concentrates. Protocol Amendment 5 (dated August 7, 2008, over 2.5 years after study initiation) indicated that it may be possible to remove dabigatran by hemodialysis and also added that though consideration may be given to the use of FFP

in subjects who are still anticoagulated at the time of surgery, there was no evidence that this would reverse dabigatran's anticoagulant effect. For subjects on warfarin or dabigatran, re-initiation of study medication after bleeding had resolved was left to the discretion of the local investigator.

*Minor bleeds:* Treatment of minor bleeds was left to the discretion of the investigator. Stopping medication was not required.

### *5.3.5.4 Emergency and elective surgery*

For emergency and elective surgery, the following was specified:

- Warfarin Treatment Group, Preoperative Phase: Patients could be managed with or without bridging anticoagulant therapy. Warfarin should be stopped 5 days before the procedure and, if the physician considers the patient to be higher risk, replaced by either low molecular weight heparin or unfractionated heparin. If INR the day before surgery is >1.4, 1 mg of oral vitamin K can be prescribed. If the INR measurement repeated the day of surgery is >1.4, postponement of surgery should be considered.
- Warfarin Treatment Group, Post Procedural Period: Anticoagulation could be started as soon as clinically feasible with IV (unfractionated) or subcutaneous low molecular weight heparin and simultaneously with oral warfarin, if possible.
- Dabigatran Treatment Groups, Preoperative Phase: Dabigatran treatment could be continued until 24 hours before surgery.
- Dabigatran Treatment Groups, Post Procedural Period: Dabigatran could be initiated as soon as clinically indicated. If oral medication is not feasible, heparinization intravenously or subcutaneously should be considered.

In a protocol amendment dated August 7, 2008, a more detailed algorithm for holding dabigatran prior to surgery was added, with the discontinuation algorithm based in part on a subject's renal function, as indicated in the table below.

**Table 16. Sponsor's algorithm for stopping dabigatran before surgery**

| Renal function (CrCl, mL/min) | Estimated half-life in hours | Stop dabigatran before surgery | |
|---|---|---|---|
| | | High risk of bleeding* | Standard risk |
| ≥50-80 | ~15 (12-18) | 2-3 days before | 24 h prior (2 doses) |
| ≥30 to <50 | ~18 (18-24) | 4 days | at least 2 days (48 h) |
| <30 | ~27 (>24 ) | > 5 days | 2-5 days |

### *5.3.5.5 Discontinuation of study medication and follow-up of subjects*

Study medication could be temporarily discontinued for procedures, diseases or diagnoses that did not permit continued treatment with study medication, the need for a

concomitant medication excluded by the study protocol or intolerable adverse events. In subjects who temporarily discontinued therapy, attempts were to be made to re-start study medication if the investigator thought it was appropriate.

Subjects who experienced a "clear, persistent contraindication" to study medication (such as a major bleeding event or non-compliance with the dosing regimen or visit schedule) or who requested withdrawal of study drug were to have their study medication permanently discontinued and followed for the duration of the study. For subjects randomized to dabigatran, dabigatran was to be held if CrCl fell to <30 mL/min and was to be re-started if CrCl rose above 30 mL/min. If the CrCl fell below 30 mL/min for a second time, dabigatran was to be permanently discontinued and the subject was to be followed until trial completion. Of note, Amendment 2 to the RE-LY study protocol (dated May 24, 2007) changed how subjects who either permanently discontinued study drug or requested to be withdrawn from study drug treatment were followed. Amendment 2 allowed clinical investigator to "negotiate a revised visit schedule should the patient be unwilling to adhere to the regular schedule." Amendment 2 also specified that these follow-up visits could occur either be by telephone or in clinic.

*Reviewer's comment: In addition to these protocol-specified measures, other steps were also taken to obtain vital status information. According to the sponsor, if "it became apparent" that a normal study completion visit could not be obtained within the closeout time window, information on vital status was sought in these subjects. Vital status was to be obtained in all study subjects with the exception of those subjects enrolled from sites that were closed for cause and subjects who had withdrawn consent and, as part of the consent withdrawal, had documented in writing that they would not attend study visits and were not to be contacted (based on local regulations concerning the meaning of withdrawal of consent). Sites were directed to contact the patient or primary care provider by phone and by letter; two contacts were required before a patient was considered lost to follow up. If a patient could come in for a final follow up visit within the close out window, a normal study completion visit was conducted and the patient was not categorized as vital status only (the patient was categorized as normal study termination). In some countries, where permitted by laws, an agency was hired to establish whether a subject was alive or dead.*

### 5.3.6 Endpoints

The primary efficacy endpoint was the incidence of stroke (including hemorrhagic) and systemic embolism.

Secondary efficacy endpoints included the incidence of:

- stroke (including hemorrhagic), systemic embolism, or all-cause mortality
- stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding)

Efficacy outcome events were defined as shown in the table below.

**Table 17. Definitions of key efficacy outcome events**

| Efficacy outcome | Definition |
|---|---|
| Stroke | Acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. The stroke is categorized as ischemic or hemorrhagic or cause unknown (based on CT or MR scanning or autopsy). Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin score at discharge from hospital and at 3-6 months later. |
| Systemic embolism | Acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts), and must be documented by angiography, surgery, scintigraphy, or autopsy. |
| Myocardial infarction | Depending on whether or not PCI or CABG has been performed, a myocardial infarction (MI) was defined as**:**<br>a. In subjects not undergoing PCI or CABG, at least 2 of the following 3 criteria had to be present:<br>i. Typical prolonged severe chest pain or related symptoms or signs (e.g., ST-changes of T-wave inversion in the ECG) suggestive of MI.<br>ii. Elevation of troponin or CK-MB to more than the upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level.<br>iii. New significant Q-waves in at least 2 adjacent ECG leads.<br>b. After PCI (within 24 h): Elevation of troponin or CK-MB to more than 3xULN or, if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.<br>c. After CABG (within 72 h): Elevation of CK-MB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.<br>d. Silent MI: retrospectively diagnosed by the appearance of significant new Q-waves between study visits. (In such cases, the date of the event was to be recorded as the midpoint between the 2 study visits)<br>e. Demonstrated by autopsy |
| Deaths | Classified as vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy)], or of unknown etiology. [The definition of vascular death was expanded by the adjudication committee charter; see “Adjudication of Events” below] |

Additional notes: Total CK could be used if CK-MB unavailable; significant Q-waves were defined as a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads.

Prespecified safety endpoints included major and minor bleeds; life threatening bleeds were a subclassification of major bleeds (major bleed definitions presented in Table 1).

Additional safety endpoints included intracerebral hemorrhage, other ICH, elevations in liver transaminases, bilirubin and hepatic dysfunction, and other adverse events.

## 5.3.7 Statistical Analysis Plan

The protocol finalized on September 12, 2005 pre-specified one primary and two secondary endpoints (see "Endpoints" above) as well as an approach to their statistical analysis. On May 8, 2009, approximately two months after the study end date, a document entitled Trial Statistical Analysis Plan (TSAP) was finalized. The stated purpose of the TSAP was to specify the details of the statistical analyses described in the September 2005 protocol. The TSAP is described by the sponsor as a working document that could be amended as the trial progressed and was to be signed off at least 4 weeks prior to unblinding. The TSAP largely preserved the primary non-inferiority analysis specified in the 2005 protocol; the TSAP approach to the analysis of the secondary endpoints specified in the 2009 protocol also appears to mirror that specified in the 2005 protocol. In addition, the TSAP addresses analytic/endpoint changes made subsequent to the 2005 finalization of the protocol.

### *5.3.7.1 Primary endpoint analysis as specified in the 2005 protocol (and TSAP)*

The primary efficacy variable was the time to first occurrence of stroke or systemic embolism and the study was designed to test the hypothesis that the hazard ratio of dabigatran vs. warfarin was larger than or equal to a non-inferiority margin of 1.46. The primary efficacy analysis was to be performed on all randomized subjects (full analysis set or FAS) using a Cox proportional hazard model that included treatment as a factor. All adjudicated and/or "un-refuted" [9] events were to be used. The protocol specified the Hochberg procedure to test each dose against warfarin separately. If the upper bound of the 95% CI for the less effective dose was < 1.46, then non-inferiority for both doses would be claimed. Otherwise, the upper bound of the 97.5% CI for the more effective dose had to be < 1.46 to claim non-inferiority for the more effective dose.

The non-inferiority margin was calculated using data from the historical placebo-controlled trials of warfarin (see appendix and sponsor's table below). To calculate the non-inferiority margin, the sponsor used 0.52 as the upper limit of the 95% CI of the hazard ratio of warfarin vs. placebo. There was a clinical decision to ensure that more than 50% of the effect was preserved giving a non-inferiority margin of 1.46.

9 Though no definition of this term could be found in the protocol, according to the sponsor (submission dated January 6, 2010), an un-refuted event is one that meets at least one of the following criteria: the adjudicator agrees with the investigator, the event has not been adjudicated (no events fell into this category in RE-LY) or no additional information can be checked (absent additional information, investigator judgment was acceptable).

**Table 18. Meta-analyses of historical placebo-controlled trials**

| Meta-analysis | Hazard (Risk) ratio of warfarin vs. placebo (95% CI) |
|---|---|
| Hart et al of six-trial meta-analysis for strokes using summary statistics from each trial | 0.38 (0.28, 0.52) |
| Meta-analysis for strokes/systemic embolisms of the five primary prevention trials, using pooled individual patient data | 0.35 (0.23, 0.52) |
| Six-trial meta-analysis for strokes using constant hazard assumption | 0.37(0.27, 0.50) |
| Meta-analysis for strokes of the five primary prevention trials for strokes, using constant hazard assumption | 0.38(0.25, 0.57) |

[Source: RE-LY protocol, Table 7.6.1:2]

### *5.3.7.2 Secondary endpoint analysis as specified in the 2005 protocol (and TSAP)*

Secondary efficacy endpoints specified in the 2005 protocol included the incidence of:

- stroke (including hemorrhagic), systemic embolism, or all-cause mortality
- stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (including deaths from bleeding).

For these secondary efficacy endpoints, the same statistical model as that for the primary endpoint was to be applied. A FAS population was to be used and all "adjudicated and/or un-refuted" events were to be utilized. No approach to controlling the type 1 error rate was specified in the 2005 protocol for the analyses of secondary endpoints. The plan for analyzing these endpoints in the TSAP appeared to mirror that contained in the 2005 protocol.

## 5.3.8 Identification of Potential Endpoint Events

(see appendix for relevant CRF pages):
According to the 2005 protocol, a patient's stroke status and bleeding events were to be evaluated at each visit by asking the patient a series of questions regarding the period of time since their last clinic visit.

*Reviewer's comment: The CRF for scheduled study visits asked if the patient had experienced any of the study outcome events since the last visit (these individual events were listed with a check box next to each event for indicating yes/no).*

In addition, the following measures were to be taken:

- Screening for signs and symptoms of stroke and bleeding: A questionnaire querying patients for signs and symptoms of stroke and bleeding was to be administered at each visit. All symptoms were to be evaluated and, if potentially consistent with a study event, were to be referred to the Adjudication Committee.

*Reviewer's comment: According to the RE-LY Central Adjudication Core-Committee meeting February 2, 2009, PHRI created a CRF "to be completed by sites (applicable sites only) to document an 'Investigator verification' that the symptoms were not related to an event."*

- Screening of hospitalizations: All hospitalizations were to be recorded with the reason for admission and all inter-current diagnoses. Any hospital diagnosis that included loss of neurological function, loss of organ function or need for surgical intervention, or reduction in hemoglobin was to trigger a request for more information from the centre and if potentially consistent with a study event was to be referred to the Adjudication Committee.

*Reviewer's comment: The measures implemented during the study appear to be more limited than those originally specified in the protocol. The CRF for hospitalizations captured data on the reason for admission (not all inter-current diagnoses) with possible answers including "outcome event" and other events falling into the following categories specified on the CRF: other cardiovascular, surgery, and other non-cardiovascular. Under some of these headings, there was an option for free text to specify the particular event that was the reason for hospitalization. According to the sponsor (Response to information request dated February 12, 20101), checks were performed on the hospitalization CRF page to confirm that events reported on this page as outcome events/ potential outcome events (those reported as "outcome event" or identified via a free text term match to a list of terms for outcome events) were captured as outcome events; if no event was reported by the site, the site was queried (for events indicated by free text search) or told to submit the appropriate outcome event CRF page (for events reported as "outcome event").*

- Review of adverse events: Any adverse event indicating potential loss of neurological function, such as unilateral weakness, loss of vision or sensory disturbance was to trigger a request for more information from the centre for event adjudication if potentially consistent with a study event. Any decrease in hemoglobin of > 2 gm/dL was to be similarly investigated.

*Reviewer's comment: According to the sponsor (response to information request dated February 12, 2010), adverse events were searched using a list of terms for the outcomes of stroke, MI, non-CNS systemic embolism, major bleed, death and TIA; minor bleeds were not cross checked. Hemoglobin drops of > 2, >4, or >5 g/dL between visits were identified and the results were also compared with the major or minor bleeding reports.*

- Review of TIAs: All reported TIA events were to be referred to the Adjudication Committee for full adjudication of any possible strokes that may have been improperly reported.

- All reported major bleeding events, bleeds requiring discontinuation of study medication, hospitalizations or physician intervention, were to be forwarded for adjudication.

*Reviewer's comment: In addition to these measures, additional steps were taken by PHRI/the sponsor. According to the sponsor, following database lock on June 17, 2009, additional outcome events were identified through two separate processes. In one process, the data coordinating center, PHRI, continued to query sites on outcome events for subjects lost to follow-up; this process continued until the finalization of the publication manuscript and was reported to be "part of PHRI's normal procedure." A separate process conducted by the sponsor after trial completion and database lock was routine site closeout visits. A total of 27 potential outcome events were identified via these processes of which 22 were adjudicated as meeting the criteria of an outcome event.*

### 5.3.9 Protocol Amendments

Global as well as region-specific protocol amendments were enacted over the course of the trial. Major revisions enacted by global protocol amendments are described in the table below.

**Table 19. RE-LY protocol amendments**

| Amendment (date) | Key changes enacted |
|---|---|
| Amendment 1 (August 31, 2006) | To ensure balanced enrollment of Vitamin K antagonist (VKA) naïve and VKA-experienced subjects, the proportion of subjects falling into these categories was to be monitored at randomization by IVRS; if the proportion of subjects in these groups became "consistently disproportional," the Operations Committee could impose additional measures (e.g. a quota system) to ensure balanced enrollment.<br><br>The definition of VKA naïve was also revised to include subjects treated with VK antagonist for two months or less (original definition= not previously treated with a VKA for 30 days or more). |
| Amendment 2 (May 24, 2007) | Increased subject number from 15,000 to 18,000. The stated rationale for the increase was that because of the faster enrollment, 15,000 patients will be randomized prior to the planned date. In order to maintain the statistical power in case of an event rate < 1.6% (the |

| | |
|---|---|
| | originally projected event rate), the enrollment should continue.<br><br>Required that all subjects, including those that discontinued treatment, be followed until the end of the study. Patients who prematurely discontinue treatment were to be contacted at regular intervals (according to the regular visit schedule, an alternative reduced schedule negotiated with the subject either by clinic visits or phone in order to record endpoints (survival, stroke or embolic events or MI) and "other clinical status when feasible"<br><br>Clarified that subjects terminating prematurely by withdrawal of consent would undergo a final follow-up visit. |
| Amendment 3 (September 11, 2007) | Decreased frequency of liver function test (LFT) monitoring (from monthly to ~every 3 months in the first year of the study) in subjects randomized after September 25, 2006. Change was based on a Data Safety Monitoring Board (DSMB) recommendation following a protocol specified review of LFT data accrued on 6000 subjects exposed for at least 6 months. |
| Amendment 4 (February 15, 2008) | Revised protocol to address new information regarding effect of P-gp inhibitors on dabigatran exposure: Contraindicated concomitant use of dabigatran and quinidine. Caution advised regarding use of dabigatran and moderate to strong p-glycoprotein (P-gp) inhibitors (e.g. verapamil and clarithromycin); physician to consider the use of a suitable alternative. |
| Amendment 5 (August 7, 2008) | Established a more detailed algorithm for holding dabigatran prior to surgery, with the discontinuation algorithm based in part on subject's renal function.<br><br>Provided additional instruction on the treatment of major bleeds.<br><br>Revised how the quality of INR control would be assessed (adopted Rosendale method and specified that the mean percentage of time of INR in range was to be calculated for each center and each country); also removed the failure to measure INR values per protocol as a protocol violation. |

## 5.3.10 Adjudication Process

[The submission contains a copy of the RE-LY Central Adjudication Manual Version 3 dated April 24, 2007 which serves as the source of the following information unless otherwise noted].

An Adjudication Committee adjudicated reported primary and secondary events including potential strokes, systemic embolism, pulmonary embolism, acute myocardial infarction (AMI), TIAs (to rule out strokes), major bleeding, life threatening bleeding and cause of death. The committee was comprised of experts in the field of neurology and cardiology; neurologists were to adjudicate potential strokes and other endpoints were to be "usually" adjudicated by cardiologists. A stroke subcommittee was also formed to review stroke, TIA and systemic embolism cases when the individual adjudicators could not reach consensus. Events were to be adjudicated using the definitions provided in the protocol with the exception of pulmonary embolism (no definition was provided in the protocol) and vascular death. In the charter, pulmonary embolism was defined as "clinical symptoms compatible" and at least one of the following:

a. High probability V/Q scan (one or more segmental or larger perfusion defects with normal ventilation
b. Positive CT angiogram showing an intraluminal filling defect
c. Positive pulmonary angiogram
d. Autopsy showing pulmonary embolism
e. Other objective imaging for DVT if investigations for pulmonary embolism not done, or non-diagnostic.

According to the adjudication committee charter, death was to be classified as vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy)], or of unknown etiology. Vascular death was considered to occur when no obvious nonvascular event to explain death was noted; sudden or unwitnessed deaths were considered vascular.

*Reviewer's comment: While the adjudication form asked adjudicators to sub classify the major bleed, the second version of the adjudication charter (dated September 14, 2007) stated that the adjudication coordinator would identify the sub classification of major bleeds as life-threatening. Hence, it is unclear who did the adjudication.*

All reported events were to be adjudicated independently and in a blinded manner by two members of the committee; if consensus was not achieved, the event was reviewed and the final decision was determined by a third adjudicator (in the case of potential endpoint events for stroke, TIA and systemic embolism events, a stroke subcommittee made the final decision if consensus was not achieved). Event information to be provided to members included event case report forms and supporting documentation. References to treatment arm, INRs and "other relevant clinical information" were to be removed from these documents. As a verification of blinding, the adjudication form asked adjudicators if they remained blinded to study treatment during the review of a

given event; if the adjudicator reported unblinding, the event was to be adjudicated by another member of the committee.

*Reviewer's comments: Review of the meeting minutes of the Central Adjudication Core Committee revealed difficulty with blinding non-English documents and concern for inconsistencies in the adjudication of non-CNS embolic events. The latter concern resulted in a second review of these events: non-CNS embolic events were to be reviewed by one of two reviewers and the outcome of this second review was to be considered final and supersede previous documented decisions in the main clinical data base. Relevant excerpts from the February 2, 2009 Central Adjudication Core Committee Meeting Minutes are provided below:*

- ***Verification of Blinding***

M. Robinson reported that an internal quality assurance review of Adjudicated Non-English events had been performed to verify the report by the Adjudicator of maintaining blinding during their review. A total of 30 adjudicated Non-English events that had been subsequently translated after adjudication, were randomly selected and reviewed by Marlene. The purpose of the review was to verify whether any evidence of potential unblinding was present and evaluate the declaration of the Adjudicator as to whether he/she was unblinded (note: a required question on each adjudication form).

M. Robinson reported that 6 (20%) of the 30 events reviewed potentially showed evidence of unblinding in the source documentation review by the adjudicator. In these instances, the report by the Adjudicator was that he/she was NOT unblinded.

M. Robinson reported samples of the phrases that had been identified as potential sources of unblinding;; *patient warfarinized; INR values visible, may need to speak with cardiologist regarding starting patient on an alternate anticoagulant such as Marveran at discharge*.

The group discussed the findings in detail and agreed upon the following points:

- The adjudicators generally review the documentation at a high level and apply the necessary criteria. Text embedded in documents may have been missed or overlooked the areas where unblinding may have occurred. (ie. for a stroke only reviewing the CT and discharge summary, and not reading the consults or progress notes).
- There are different levels of unblinding and revealing an INR of 5.0 may not necessarily unblind the Adjudicator to Coumadin (Warfarin), as it could also indicate Dabigatran effect.
- It is important to know the context within which the unblinding may have occurred, as it may not have been the case at all.
- It is important to take the word of the adjudicators.

**Action:**

- The committee agreed that another 30 events be reviewed and graded accordingly; true unblinding, and potentially unblinded. These events will be reviewed to determine blinding status with further discussion based on findings.

*Reviewer's comment: While the minutes documented plans to review additional events with "further discussion based on findings," according to the sponsor (submission dated March 30, 2010), "The last meeting of the Adjudication Committee occurred on Feb 2, 2009 before data base lock in June. This item of reviewing 30 other events, was not pursued."*

- ***Non-CNS Embolic Event Agreement Rate and Response***

M. Robinson noted the consistent low agreement rate of Non-CNS Embolic Event. The committee reviewed various considerations related to the interpretation, definitions and processing of this event and concluded the following:

- Nurses are completing the CRF for this event and may not be as familiar with the protocol definition and continue to capture venous events as opposed to 'systemic' arterial events
- The definitions are clearly outlined in the protocol.

M. Robinson reported that an internal quality assurance review of Adjudicated random selection of Non-CNS Embolic Events has been performed. A total of 30 events were randomly selected and reviewed by Marlene to review the supporting documents included and apply and verify the definitions and criteria for Non-CNS Embolic Events. The purpose of the review was to evaluate the Adjudicator application of the criteria of Non-CNS Embolic Event.

M. Robinson reported that 5 of the 30 (17%) Non-CNS Embolic selected were DVTs or Apical Thrombus.

The committee supported the initiatives and concluded that there is some evidence to suggest that there are inconsistencies in the adjudication of Non-CNS Embolic Events that need to be addressed. The committee unanimously agreed that all of the current

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adjudicated Non-CNS Embolic Events will require a second review. C. Joyner and H-C. Diener will each review 50% of the cases.

**Action:**

- M. Robinson will prepare and issue 50% of the Non-CNS Embolic Events to both C. Joyner and H-C. Diener. The additional review will be independent of the previous Adjudicator decision and without knowledge of this previous decision. The outcome of this second review will be considered final and supersede previous documented decisions in the main clinical data base.
- In the event that C. Joyner or H-C. Diener are uncertain about an event, they will forward the event to each other for comment and consensus.

*Reviewer's comment: Though a description of this process was not otherwise noted in the submission, when asked about the readjudication, the sponsor confirmed that all but 3 of the 98 events were re-read as described above (sponsor submission dated February 11, 2010).*

# 6 Review of Efficacy

*Reviewer's comment: This section focuses on key analyses related to efficacy and addresses topics including the adequacy of anticoagulation in the warfarin arm, the PROBE design, and dabigatran's effect on mortality. For analyses addressing net benefit, as well as further discussion regarding a superiority claim, see Section 1 titled "Recommendations/Risk-Benefit Assessment".*

Dabigatran etexilate is an orally available, reversible, direct thrombin inhibitor with a proposed indication for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In support of this indication, the sponsor conducted the RE-LY trial, a large (~18,000 subjects), randomized, non-inferiority study of open-label warfarin administration and blinded administration of two doses of dabigatran (110 and 150 mg). RE-LY's primary endpoint was a composite of stroke and systemic embolism. The sponsor's primary analysis, conducted on the ITT population, established efficacy. Compared to warfarin treated subjects, the HR in the dabigatran 150 arm was 0.66 (95% CI 0.53 to 0.82, p<0.003 for superiority) and in the 110 arm was 0.91 (95% CI 0.74 to 1.11, p<0.0001 for non-inferiority). Sensitivity analyses performed on "as treated" populations, as well as an analysis addressing a change in the protocol design (increase in sample size) were supportive of the ITT analysis. Importantly, efficacy findings for the 150 mg dose also appeared to be preserved across important subgroups of patients, including subjects previously treated with warfarin, those with a history of TIA/stroke and the subset of subjects enrolled from US sites. The efficacy of the 150 dose also appeared to be maintained in comparisons against the sub-population of warfarin-treated subjects who had achieved more optimal levels of INR control. The primary endpoint findings were further supported by a numerical imbalance in the number of disabling and fatal strokes in the dabigatran 150 compared to warfarin treatment arm, favoring subjects randomized to the 150 dose.

**Adequacy of anticoagulation in the warfarin treatment arm:** Dabigatran was studied against warfarin in RE-LY and hence to interpret the efficacy findings, one must understand the expected benefit of warfarin as it was given in this trial. Six randomized, placebo-controlled trials (five primary and one secondary prevention) are widely referenced as establishing the efficacy of warfarin for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation (see appendix). According to a 2007 meta-analysis by Hart et al, in these studies warfarin reduced the risk of ischemic stroke by 67% (95% CI, 54% to 77%) and the risk of stroke (ischemic and hemorrhagic) by 64% (95% CI, 49% to 74%). There are certainly differences between these historical trials and RE-LY that affect the constancy assumption. Though the mean INR achieved in the historical studies was between 2 and 3, for the most part these studies targeted different INR values /prothrombin time ratios and a wider range of values than the 2-3 range currently recommended and used in RE-LY. The percentage of subjects with important risk markers for thromboembolic complications/strokes (e.g., heart failure, diabetes, and hypertension) was greater in RE-LY than in these historical trials (see table below). At the same time, there have also been therapeutic advances in the treatment of at least some of these concomitant conditions that would be expected to lower the risk of stroke. For these reasons, it seems likely that the risk reduction associated with warfarin in RE-LY would be different than that seen in historical trials. Whether these differences, in balance, would translate into greater or lesser benefit from warfarin is not clear; either way, substantial benefit would still be expected.

**Table 20. Demographics historical warfarin trials vs. RE-LY**

| | Historical trials of primary prevention | RE-LY |
|---|---|---|
| Year(s) published | 1989-1992 | 2009 |
| Mean Age (>75 years) | 69 (20) | 71 (40*) |
| Sex (%) Male | 71 | 64 |
| Prior stroke (%) | 5 | 13 |
| Hypertension (%) | 45 | 79 |
| CHF (%) | 26 | 32 |
| Diabetes (%) | 13 | 23 |

[Sources: Historical trials- Jackson et al, 2008; RE-LY- Reviewer's analysis (Sponsor's dataset=basco; reviewer's filename=demographics]
*≥ 75 years

Several metrics can be used to assess the adequacy of anticoagulation in warfarin-treated subjects in RE-LY: a comparison with rates in other warfarin trials, the exposure to warfarin, time in therapeutic range, as well as the appropriateness of INR monitoring. Each measure has its limitations but as a whole, these measures suggested reasonable anticoagulation in subjects randomized to warfarin.

- In the warfarin arm of historical and more recently completed clinical trials, the absolute incidence of strokes was low (see tables below). The incidence reported in RE-LY, as an absolute number, seems comparable. In comparison with the incidence of strokes in the placebo arm in the historical trials, the incidence of strokes in the warfarin treatment arm of RE-LY (both the absolute and relative incidence) is much lower.

**Table 21. Stroke incidence per 100 subject-years in historical trials**

| | Year | Placebo | Warfarin/Vitamin K antagonist |
|---|---|---|---|
| Primary prevention | | | |
| AFASAK I | 1989 | 4.8 | 2.2 |
| SPAF I | 1991 | 7.8 | 3.0 |
| BAATAF | 1990 | 3.0 | 0.6 |
| CAFA | 1991 | 3.7 | 2.5 |
| SPINAF | 1992 | 4.8 | 1.4 |
| Overall | 1989-1992 | 4.6 | 1.7 |
| Secondary prevention | | | |
| EAFT | 1993 | 12.3 | 3.9 |

[Calculations based on rates reported by Aguilar et al.]

**Table 22. Demographics and stroke incidence RE-LY, ACTIVE W and SPORTIF**

| | SPORTIF III | SPORTIF V | ACTIVE W | RE-LY |
|---|---|---|---|---|
| Year(s) published | 2003 | 2005 | 2006 | 2009 |
| Mean Age (% ≥75 years) | 70 (34) | 70 (42) | 70 (NA) | 71 (40) |
| Sex (%) Male | 69 | 72 | 67 | 64 |
| Prior stroke/TIA % | 24 | 18 | 15 | 20 |
| Hypertension % | 72 | 81 | 83 | 79 |
| CHF % | 34** | 39* | 30 | 32 |
| Diabetes % | 22 | NA | 21 | 23 |
| Strokes/100 subject-years (warfarin arm) | 2.2 | 1.1 | 1.4 | 1.6 |
| Hemorrhagic stroke/100 subject-years (warfarin arm) | 0.4 | 0.1 | 0.4 | 0.4 |

*CHF/LV dysfunction; **LV dysfunction

- With regard to exposure to warfarin in RE-LY, 80.8% (4849) of subjects randomized to warfarin completed the study on study medication. Over 50% of subjects had at least one interruption of study medication over the course of the trial; overall, subjects in the warfarin arm were on study medication for ~91% of study days of follow up.

- The mean time in therapeutic range (2-3) was 64.4% (analyses excluding values obtained during treatment interruptions) and 63.4% (analyses including values obtained during treatment interruptions). The overall mean percent of reported INR measurements greater than 4 was ~2%; the overall mean percent of INR measurements <2.0 was ~22 to 23% and < 1.5 was ~5%.Compared to later months, during the first month of therapy, a greater percentage of INR measurements were greater than 4 (~5 vs. ~2%), less than 2 (32% vs. 23-24%) or less than 1.5 (~11% vs. ~5%). The results are not so dissimilar to those reported in recently reported controlled trials such as ACTIVE W and SPORTIF III and V: 64-68% for an INR of 2 to 3 and ~20% for an INR<2; again suggesting reasonable control using these trials as benchmarks.

**The PROBE design:** RE-LY was open-label with respect to warfarin administration and to mitigate potential bias, several measures were implemented. Other means were used to identify potential endpoint events such as screening of adverse events, a questionnaire querying patients for signs/symptoms of stroke, and a review of investigator-reported hospitalizations. The protocol specified that TIAs were to be adjudicated and events were to undergo blinded adjudication. Finally, the endpoints chosen were, for the most part, more objective endpoints.

Though warfarin administration was open-label, two doses of dabigatran, 110 and 150, were also studied and were administered in a blinded fashion. The inclusion of these two doses was perhaps one of the most important design aspects of RE-LY; while it cannot mitigate potential bias in comparisons of dabigatran against warfarin, it can allow establishment of efficacy via a dose-response relationship. In subjects treated with dabigatran 110 mg BID, 171 strokes were reported compared to 122 in subjects randomized to dabigatran 150 mg BID. Compared to the lower dose, the hazard ratio for the higher dose was 0.72 (95% CI 0.58 to 0.90, p-value=0.004). The finding of a dose response relationship changes the nature of the question surrounding dabigatran's efficacy. The question is no longer whether or not dabigatran at some dose is effective. The question is whether, in the setting of open-label warfarin administration, one can draw any conclusions about superiority over warfarin.

Bias can be introduced because of how events were ascertained or because of differential management or follow up of study subjects. As described above, several measures were implemented to minimize ascertainment bias and it is perhaps worthwhile to explore these measures and the results of these measures as implemented in RE-LY. Of investigator reported strokes, similar percentages were adjudicated as strokes in the three treatment arms of RE-LY. Similar percentages of investigator-reported TIAs were also upgraded to strokes by the adjudication committee across the treatment arms. Moreover, a sampling of investigator-reported events conducted by this reviewer suggested that the adjudications were, as a whole, reasonable. Such findings provide some reassurance; however, there were problematic aspects of the adjudication process, as well as limitations to the methods used to identify potential endpoint events in RE-LY:

- The adjudication documents often contained text that could potentially unblind reviewers. This was the case in 17% of documents reviewed by this reviewer, a figure not so dissimilar to the 20% noted by the Adjudication Core Committee in their review of non-English source documents reviewed by adjudicators. That said, on some occasions, adjudication documents with text indicating warfarin use were actually from subjects randomized to dabigatran who had discontinued study therapy.
- The screening of hospitalizations was a screening not of the hospitalization record itself, but of a CRF page completed by the investigator indicating that the patient had been hospitalized and containing the investigator reported reason for hospitalization. Hence, the screening of investigator-reported adverse events, investigator-reported reasons for hospitalization and questionnaire querying patients for signs/symptoms of stroke required that the investigator first report a suggestive event in order to capture additional events via this method; whether or not there were additional events that were not reported by investigators is an issue that the DSI audits, some still pending, will address.

Even in the absence of any clear evidence of bias in the ascertainment of strokes/SEE, analysis of study findings suggests that knowledge of treatment arm may have led to

important differences in the treatment of subjects. For example, if a subject experienced an ischemic stroke, TIA (a non-endpoint event) or minor bleed, she was more likely to have her study medication permanently discontinued in the dabigatran than the warfarin treatment arms (see Section 6.1.10). There were other treatment specific differences in management. According to the protocol, subjects whose CrCl fell and stayed below 30 mL/min (a sicker population) were to have their medication permanently discontinued in the dabigatran but not the warfarin-treatment arm. Because these subjects were to be followed until trial completion (assuming they were), these differences may not be so critical. Nonetheless, whether or not the management of subjects in the dabigatran and warfarin treatment arms differed in other important ways is uncertain. In light of the open-label design and these differences, one should perhaps be wary of attributing differences in patient outcomes solely to the study drug and also wary of granting dabigatran a superiority claim over warfarin.

**Effects on mortality:** Analyses conducted according to the finalized statistical analysis plan suggested favorable effects of the higher dose of dabigatran on all cause mortality (HR of 0.88, p-value 0.052 relative to warfarin) and vascular specific mortality (HR of 0.84, p-value of 0.04 relative to warfarin). While all-cause mortality and vascular mortality were specified as components of composite secondary endpoints, the RE-LY protocol did not pre-specify a plan for controlling the type-1 error rate in the analysis of secondary endpoints and neither endpoint was specified as an individual secondary endpoint. Moreover, RE-LY was an open label trial and the sponsor's statistical analysis plan was finalized late (essentially after all of the study data had been amassed). An analysis including deaths censored by the sponsor's statistical analysis plan, as well as an analysis excluding deaths identified by vital status queries in subjects who had prematurely discontinued from the trial shift the p-value for all-cause mortality higher (to 0.06 and 0.09, respectively). In addition, an analysis based on center-level INR control suggests that the imbalance in deaths (dabigatran relative to warfarin) is driven by subjects with poorly controlled INRs. Based on these findings, a mortality claim should not be given.

## 6.1 Indication

As previously stated, the proposed indication is for the prevention of stroke and systemic embolism. Though the sponsor requested an indication for the reduction of vascular mortality in the original NDA submission, in an amendment to the NDA dated July 27, 2010, the sponsor requested that the claim be removed from the proposed U.S. indication statement; the letter cited "an effort to harmonize the indication statement for PRADAXA globally."

### 6.1.1 Methods

In the sponsor's efficacy analyses and in the efficacy analyses that follow, subjects without a reported endpoint event are censored at the last time vital status information was available. Subject-years of follow up are also calculated based on the last date vital status information was available.[10] For the primary efficacy endpoint, analyses were also conducted:

(1) censoring subjects without a reported endpoint event at the last time follow up information was available for the particular endpoint of interest, and
(2) censoring subjects without a reported endpoint event at the last clinic follow up visit at which a pulse was recorded.

These analyses produced similar findings as the analysis in which subjects were censored based on vital status information.

### 6.1.2 Demographics

Baseline demographics, including type of atrial fibrillation, history of stroke/TIA, risk factors for stroke and baseline use of warfarin and other anticoagulant medications, were similar across treatment arms. Baseline blood pressure and heart rate was 131/77 and 74, respectively, and was also similar across the treatment arms. Thirty-six percent of study subjects were enrolled from U.S. and Canadian sites. According to the sponsor, 70% of subjects were White, 16% Asian, 7% Hispanic or Latino and 1% were Black.

**Table 23. Baseline demographics**

| Characteristic* | Dabigatran110 N=6015 | Dabigatran150 N=6076 | Warfarin N=6022 |
|---|---|---|---|
| Male | 3865(64.3) | 3840(63.2) | 3809(63.3) |
| Age | | | |
| Mean | 71 | 71 | 72 |
| 65<= and <75 | 2668(44.4) | 2580(42.5) | 2646(43.9) |
| <65 | 998(16.6) | 1030(17) | 953(15.8) |
| >=75 | 2349(39.1) | 2466(40.6) | 2423(40.2) |
| AF type | | | |
| Paroxysmal | 1929(32.1) | 1978(32.6) | 2036(33.8) |
| Permanent | 2132(35.4) | 2188(36) | 2055(34.1) |
| Persistent | 1950(32.4) | 1909(31.4) | 1930(32) |
| AF diagnosis | | | |
| <3 months | 1844(30.7) | 1854(30.5) | 1929(32) |
| 3 months to 2 years | 1324(22) | 1344(22.1) | 1315(21.8) |
| >2 years | 2843(47.3) | 2876(47.3) | 2776(46.1) |

[10] Subject-years = sum(date of study termination – date of randomization +1) of all randomized subjects / 365.25

| Characteristic* | Dabigatran110 N=6015 | Dabigatran150 N=6076 | Warfarin N=6022 |
|---|---|---|---|
| VKA use | | | |
| VKA Naive§ | 3005(50) | 3028(49.8) | 3093(51.4) |
| On VKA at randomization | 3751(62.4) | 3760(61.9) | 3678(61.1) |
| Risk Factors | | | |
| History of stroke | 761(12.7) | 756(12.4) | 756(12.6) |
| History of TIA | 548(9.1) | 587(9.7) | 528(8.8) |
| History of stroke/TIA/SEE | 1308(21.7) | 1358(22.4) | 1287(21.4) |
| History of hypertension | 4738(78.8) | 4795(78.9) | 4750(78.9) |
| History of diabetes | 1409(23.4) | 1402(23.1) | 1410(23.4) |
| History of HF | 1937(32.2) | 1934(31.8) | 1922(31.9) |
| History of MI | 1008(16.8) | 1029(16.9) | 968(16.1) |
| History of CAD | 1661(27.6) | 1710(28.1) | 1663(27.6) |
| Smoker | 440(7.3) | 447(7.4) | 448(7.4) |
| NYHA class | | | |
| NYHA I | 295(4.9) | 292(4.8) | 297(4.9) |
| NYHA II | 1225(20.4) | 1198(19.7) | 1222(20.3) |
| NYHA III | 386(6.4) | 401(6.6) | 353(5.9) |
| NYHA IV | 30(0.5) | 41(0.7) | 48(0.8) |
| CHADS2 score | | | |
| 0 | 151(2.5) | 146(2.4) | 155(2.6) |
| 1 | 1809(30.1) | 1815(29.9) | 1707(28.3) |
| 2 | 2088(34.7) | 2136(35.2) | 2229(37) |
| 3+ | 1966(32.7) | 1979(32.6) | 1931(32.1) |
| Creatinine clearance | | | |
| 30<= and <50 | 1136(18.9) | 1156(19) | 1051(17.5) |
| 50<= and <80 | 2714(45.1) | 2777(45.7) | 2806(46.6) |
| >=80 | 1899(31.6) | 1882(31) | 1877(31.2) |

[Source: Reviewer's analysis (Sponsor's dataset=basco; reviewer filename=baseline_dm]
*Percentages may not add up to 100% because of missing data; a small number of subjects with a CrCl<30 were randomized (<0.05%). § The sponsor classified subjects as VKA naïve if they had received ≤ 2 months of any VKA during their lifetime.

Concomitant medications were also similar across the three treatment arms at baseline, as shown in the table below.

**Table 24. Baseline medication use**

| Baseline medication | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Beta blocker | 3789(63) | 3887(64) | 3722(61.8) |
| Digoxin | 1781(29.6) | 1742(28.7) | 1767(29.3) |
| Amiodarone | 647(10.8) | 672(11.1) | 657(10.9) |
| Verapamil | 352(5.9) | 350(5.8) | 369(6.1) |
| Diltiazem | 564(9.4) | 541(8.9) | 581(9.6) |
| ACEI | 2699(44.9) | 2754(45.3) | 2670(44.3) |
| ARB | 1448(24.1) | 1470(24.2) | 1418(23.5) |
| Aspirin | 2384(39.6) | 2338(38.5) | 2431(40.4) |
| Clopidogrel | 338(5.6) | 337(5.5) | 345(5.7) |
| Aggrenox | 16(0.3) | 9(0.1) | 16(0.3) |
| Statin | 2702(44.9) | 2682(44.1) | 2673(44.4) |
| Proton Pump Inhibitor | 847(14.1) | 878(14.5) | 842(14) |
| H2 receptor blocker | 239(4) | 257(4.2) | 262(4.4) |
| NSAID | 311(5.2) | 294(4.8) | 319(5.3) |

[Source: Reviewer's analysis (Sponsor's dataset=basco; reviewer filename=subgroups]

### 6.1.3 Subject Disposition

Of 20,377 subjects screened, a total of 18,113 were randomized in RE-LY. Of the subjects that were screened but not randomized, approximately 70% did not meet study inclusion/exclusion criteria and another 18% withdrew consent. Over 99% of randomized subjects received at least one dose of study medication.

The disposition of subjects, as reported by the sponsor in an amendment dated August 4, 2010, is shown in the table below. The treatment groups do not appear to differ significantly in the number of subjects lost to follow up. Slightly more warfarin treated subjects were reported to have completed the study on study medication than dabigatran-treated subjects. The reasons for discontinuation of study medication are discussed further in section 6.1.10

**Table 25. Disposition of subjects**

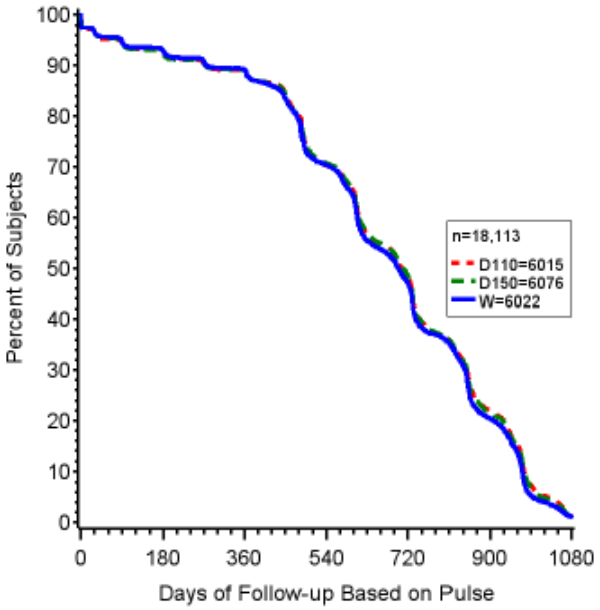
| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Randomized | 6015 | 6076 | 6022 |
| Treated | 5983 | 6059 | 5998 |
| Completed study | 5765 ( 96.4) | 5808 ( 95.9) | 5748 (95.8) |
| Completed on study medication | 4610 (77.1) | 4625 (76.3) | 4848 (80.8) |
| Completed follow up but stopped study medication prematurely | 1155 (19.3) | 1183 ( 19.5) | 900 ( 15.0) |
| Premature discontinuation* | 218 (3.6) | 251 (4.1) | 250 (4.2) |

[Source: Sponsor submission dated August 4, 2010, Table 2.18.5.1]
*Included in this category: lost to follow up, withdrew consent, "Other", centers closed early for cause, and subjects with "no CRF pages 196, 126, 194 entered"

*Reviewer's comment: Late in the review cycle, errors were found in the sponsor's disposition data. A few subjects who were initially counted by the sponsor as having a "normal study completion" were found to have prematurely discontinued from follow up. As a result, the sponsor performed additional checks of the data and identified 39 subjects in the database listed as having a "normal study termination status" who should have been counted as "early study termination". The disposition data shown above reflects the amended data.*

The protocol allowed clinical investigators to "negotiate a revised visit schedule" for subjects who permanently discontinued study medication and follow up visits could occur by telephone. To further assess the adequacy of follow up, an analysis was conducted in which a subject's last day of follow up was defined as the last clinic visit at which a pulse was recorded. The number of days of follow up based on pulse data (shown below) appears similar across the treatment arms. Using the pulse data, subject years of follow up was ~8% less than that calculated using vital status information; the mean duration of follow up was ~ 1.5 months shorter.

**Figure 6. Days of follow up based on pulse data**




The mode of follow up (telephone vs. clinic visit) could impact the ascertainment of endpoint events, and in particular the ascertainment of non-disabling strokes. A total of 489, 499, and 469 in the dabigatran 110, dabigatran 150 and warfarin treatment arms did not have a pulse reported within 6 months of the close out period.[11] These analyses, based on pulse data, suggest a greater loss of information (~8% across treatment arms) than the sponsor's analysis of "premature discontinuations" (~4% as shown in the table above).

Reviewer's comment: The missing data should be viewed in light of the efficacy findings. The number of additional events needed in the dabigatran treatment arms to reverse the efficacy findings is discussed in Section 6.1.4 below. It seems unlikely, that this amount of missing information would reverse the efficacy findings, at least for non-inferiority.

### 6.1.4 Analysis of Primary Endpoint(s)

In the original NDA submission, it was reported that 182 subjects randomized to dabigatran 110 mg (1.5%), 133 subjects randomized to dabigatran 150 mg (1.1%) and 198 subjects randomized to warfarin (1.7%) experienced a stroke/SEE. A few additional events were identified following database lock as a result of queries to sites on outcome events in subjects lost to follow up, routine site close out visits, and the data quality checks implemented in response to the Agency's refuse to file letter.

11 For the purposes of this analysis, a subject was counted if no pulse was reported after 6/15/2008 (~6 months prior to study close out); subjects that died at any time prior to 12/15/2008 were excluded. The 6 month cut-off date was arbitrary.

**Table 26. Number of subjects with stroke/SEE**

| | Dabigatran 110 N | Dabigatran 150 N | Warfarin N |
|---|---|---|---|
| Original submission | 182 | 133 | 198 |
| Including events identified post Database lock | 183 | 134 | 200 |
| NDA resubmission | 183 | 134 | 202 |

In addition to these events, two other strokes, one in the dabigatran 110 arm and one in the dabigatran 150 arm, were reported by investigators and adjudicated as stroke events but were not included in the sponsor's analysis of the primary endpoint. Both of these events occurred after the subject was reported to have had a "normal study termination" as indicated by the site investigator on the study termination CRF (CRF 196); according to the rules specified in the statistical analysis plan (finalized after the study was completed), events occurring after a "normal study termination" were not to be included in the primary endpoint analysis. Inclusion of these subjects did not alter the results of the primary endpoint analysis and in the analyses that follow, these subjects are excluded.

**Table 27. Strokes excluded by the statistical analysis plan**

| Subject | Arm | Comments |
|---|---|---|
| 1160-0026-00195011 | Dabigatran 110 | CRF 196 completed with visit date given as 12/17/2008, stroke on (b) (6) |
| 1160-0026-01752009 | Dabigatran 150 | CRF 196 completed with visit date given as 2/11/2009, contact for this visit made by phone, stroke on (b) (6) stroke, death on (b) (6) |

The primary endpoint, non-inferiority to warfarin for the time to the first occurrence of stroke/SEE, was established for both doses of dabigatran based on the margin recommended by the Agency, 1.38 ($p<0.0001$ for both comparisons) and the protocol-specified non-inferiority margin of 1.46 ($p<0.0001$ for both comparisons). The HR and 95% CI for the primary endpoint are shown below for both doses of dabigatran using the resubmitted data sets. The 150 mg dose was superior ($p<0.0001$) to warfarin for the primary endpoint. Analyses censoring subjects at the last clinic follow up visit at which a pulse was reported do not alter the findings. According to the FDA statistical reviewer, an additional 46 events (110 arm) and 97 events (150 arm) would be needed to reverse the non-inferiority findings (margin of 1.38) while an additional 33 events (150 arm) would be needed to reverse the superiority results. Hence, even in light of the missing disposition data, it seems unlikely that the efficacy findings (at least for noninferiority for the 150 dose) would be lost.

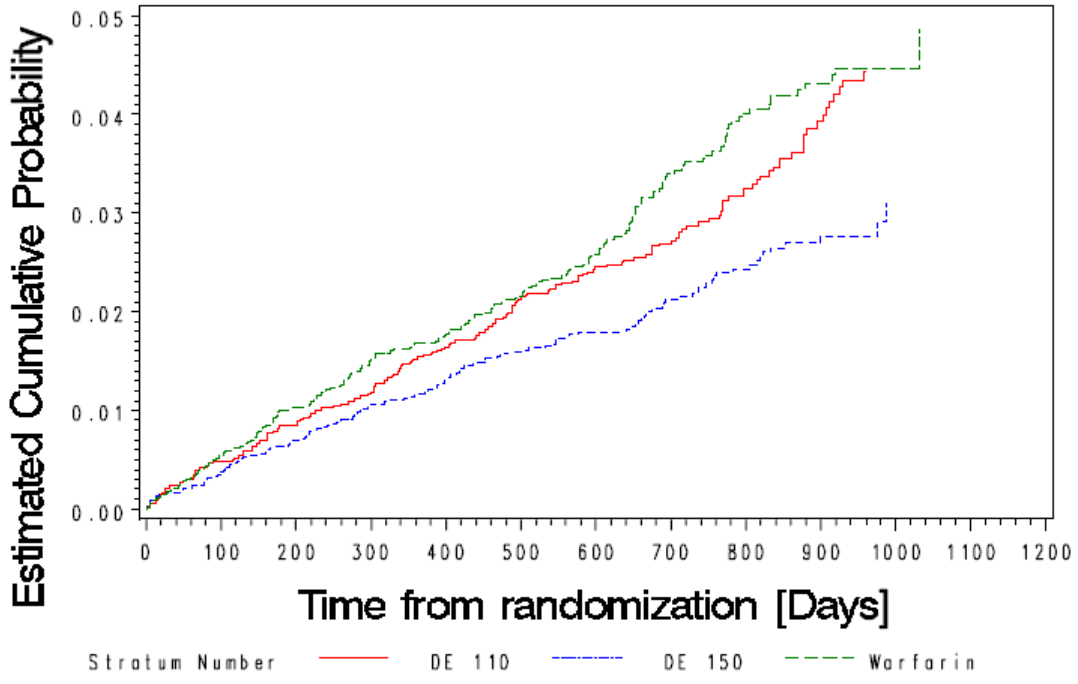
**Table 28. Hazard ratios for stroke/SEE**

| | Dabigatran 110 vs. warfarin | Dabigatran 150 vs. warfarin |
|---|---|---|
| Hazard Ratio (95% CI) | 0.90 (0.74, 1.10) | 0.65 (0.52, 0.81) |
| P-value non-inferiority using 1.38 | <0.0001 | <0.0001 |
| P-value non-inferiority using 1.46 | <0.0001 | <0.0001 |
| P-value superiority | 0.29 | 0.0001 |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename= primary_endpoint)]
P-values for non-inferiority confirmed by Dr. Bai, FDA statistical reviewer.

The Kaplan-Meier estimate of time to first stroke/SEE by treatment arm is shown below.

**Figure 7. Kaplan Meier estimate of time to first stroke/SEE**




[Source: FDA Statistical Reviewer]

Exclusion of sites/subjects recommended by DSI thus far (site 265 and 276 and subject 128002) do not alter the results of the primary endpoint analysis. A sensitivity analysis using the first 450$^{th}$ adjudicated events for data cut-off gives a HR of 0.94 (0.75, 1.16) for dabigatran 110 vs. warfarin, and a HR of 0.70 (0.56, 0.89) for dabigatran 150 vs. warfarin. "As treated" analyses censoring subjects 30 days after the time of first discontinuation of study medication (temporary or permanent), and 30 days after the last study medication date are also supportive of the ITT analysis (see table below). Analyses addressing effects in various subpopulations (baseline aspirin use, baseline

warfarin use, history of stroke/SEE/TIA) are presented in section 6.1.7. Analyses by center-level INR control are presented in section 6.10.

**Table 29. "As treated" analysis of the primary endpoint**

| Time of censor | Dabigatran 110 vs. Warfarin | | Dabigatran 150 vs. Warfarin | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Within 30 days of first discontinuation of study medication (temporary or permanent) | 0.91 (0.70, 1.19) | 0.50 | 0.67 (0.50, 0.89) | 0.006 |
| Within 30 days of last date of study medication usage | 0.81 (0.65, 1.01.) | 0.06 | 0.57 (0.45, 0.73) | <0.0001 |

[Source: Reviewer's analysis (Sponsor's datasets= lastmed, timev, timecens, adjrand; reviewer's filename= astreatedanalysis)]
P-values are for superiority; analyses are limited to subjects who were randomized and treated.

The yearly event rates (# of subjects with event/subject-years), HRs and 95% CIs for the individual components of the composite endpoint of stroke/SEE are shown in the tables below. The difference in the total number of stroke events in the dabigatran 150 mg versus warfarin treatment arms (65 events) is driven by a smaller number of both ischemic and hemorrhagic strokes. This contrasts with the findings in the dabigatran 110 mg arm where a smaller number of hemorrhagic strokes and numerically greater number of ischemic strokes are seen relative to warfarin.

**Table 30. Yearly event rate for strokes and SEE**

| | Dabigatran 110 N (%) | Dabigatran 150 N (%) | Warfarin N (%) |
|---|---|---|---|
| Subject years of follow up | 11899 | 12033 | 11794 |
| Subjects with stroke/SEE | 183 (1.5) | 134 (1.1) | 202 (1.7) |
| Subjects with stroke* | 171 (1.4) | 122 (1.0) | 186 (1.6) |
| Ischemic | 152 (1.3) | 103 (0.9) | 134 (1.1) |
| Hemorrhagic | 14 (0.1) | 12 (0.1) | 45 (0.4) |
| SEE | 15 (0.1) | 13 (0.1) | 21 (0.2) |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename=primary_ endpoint)] The numbers of ischemic and hemorrhagic strokes do not add up to the total strokes as some strokes were classified as "uncertain classification".

**Table 31. Hazard ratios for components of primary endpoint**

| | Dabigatran 110 vs. warfarin | | Dabigatran 150 vs. warfarin | |
|---|---|---|---|---|
| | HR (95% CI) | p-value superiority | HR (95% CI) | p-value superiority |
| Stroke | 0.91 (0.74, 1.12) | 0.38 | 0.64 (0.51,0.81) | .0001 |
| Ischemic | 1.13 (0.89,1.42) | 0.31 | 0.75 (0.58,0.97) | 0.030 |
| Hemorrhagic | 0.31 (0.17,0.56) | 0.0001 | 0.26 (0.14,0.49) | <0.0001 |
| SEE | 0.71 (0.37,1.38) | 0.31 | 0.61 (0.30,1.21) | 0.16 |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand; reviewer's filename=primary_ endpoint)]

Compared to warfarin treatment, treatment with Dabigatran 150 mg was associated with a smaller absolute number of strokes at each Rankin score, including fatal and disabling strokes.

**Table 32. Investigator-reported Rankin scores at 3-6 months**

| Rankin Score 3-6 months | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Missing | 10 | 4 | 11 |
| 0 | 21 | 21 | 21 |
| 1 | 31 | 24 | 35 |
| 2 | 20 | 12 | 22 |
| 3 | 18 | 6 | 17 |
| 4 | 16 | 9 | 14 |
| 5 | 8 | 4 | 8 |
| 6 | 47 | 42 | 58 |

[Source: Reviewer's analysis (Sponsor's datasets=adjrand plt110n; reviewer's filename=primary_ endpoint)]
The Rankin scale runs from no symptoms (0) to death (6); a copy of the scale is provided in the appendix.

### 6.1.5 Analysis of Secondary Endpoints(s)

The results of secondary endpoint analyses as well as the yearly event rate of the individual components of these composites are shown below. The statistical analysis plan described in the 2005 protocol did not specify a strategy for controlling the type 1 error rate in testing these secondary endpoints and interpretation of their findings is limited. Mortality (all cause and vascular) appears to favor the dabigatran arms and is discussed further in section 6.1.6. The yearly event rate of PEs appears to be similar

across the three treatment arms. Finally, there is a numerical imbalance in the number of myocardial infarctions that favors subjects randomized to warfarin.

**Table 33. Hazard ratios for secondary endpoints**

| | **Dabigatran 110 vs. warfarin** | | **Dabigatran 150 vs. warfarin** | |
|---|---|---|---|---|
| Secondary endpoints | HR (95% CI) | p-value for superiority | HR (95% CI) | p-value for superiority |
| Stroke (including hemorrhagic), systemic embolism, and all-cause mortality | 0.93 (0.83,1.04) | 0.22 | 0.83 (0.74,0.93) | 0.0015 |
| Stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, and vascular deaths (including deaths from bleeding) | 0.98 (0.87, 1.11) | 0.75 | 0.84 (0.74, 0.96) | 0.009 |

[Source: Sponsor's April 19, 2010 submission; Tables 15.2.2.1:2 and 15.2.6.2:2]

**Table 34. Yearly event rate (%) for stroke, SEE, PE, MI and vascular death**

| | **Dabigatran 110 N (%)** | **Dabigatran 150 N (%)** | **Warfarin N (%)** |
|---|---|---|---|
| Subject years of follow up | 11899 | 12033 | 11794 |
| Stroke | 171 (1.4) | 122 (1.0) | 186 (1.6) |
| SEE | 15 (0.1) | 13 (0.1) | 21 (0.2) |
| PE | 14 (0.1) | 18 (0.2) | 12 (0.1) |
| MI | 87 (0.7) | 89 (0.7) | 66 (0.6) |
| Silent MI | 11 (0.1) | 8 (0.1) | 9 (0.1) |
| Vascular mortality | 289 (2.4) | 274 (2.3) | 317 (2.7) |
| All cause morality | 446 (3.7) | 438 (3.6) | 487 (4.1) |

### 6.1.6 Mortality

The number of deaths in RE-LY, by treatment arm, is shown in the table below. Following database lock, two additional deaths were identified; one in the dabigatran 110 arm and one in the dabigatran 150 arm. In addition to these deaths, ten other deaths (six in the dabigatran 150 mg arm and four in the warfarin arm) were reported by investigators but were excluded from key analyses based on rules specified by the sponsor's statistical analysis plan.

**Table 35. Number of deaths by treatment arm**

| Deaths | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Original submission | 445 | 437 | 486 |
| Inclusive of events identified post database lock | 446 | 438 | 487* |
| NDA resubmission | 446 | 438 | 487 |
| Inclusive of events excluded by sponsor's statistical analysis plan | 446 | 444 | 491 |

*According to the sponsor (email correspondence dated 8.9.2010), one warfarin treated subject who died while in the study did not sign the Health Insurance Portability and Accountability Act form and was censored at the date of randomization in the original submission.

The events excluded by the sponsor's statistical analysis plan occurred after March 15, 2009, after the site was closed for cause, or after a patient was reported as having a "normal study termination" as indicated on the sponsor's study termination report ,CRF 196 (see table below). According to the statistical analysis plan (finalized on May 8 2009, after study completion), such events were not to be included "in the specified formal analysis."

**Table 36. Deaths excluded by the sponsor's statistical analysis plan**

| Subject | Arm | Comments |
|---|---|---|
| 1160-0026-00270004 | Dabigatran 150 | Death occurring after censor date/ (b) (6) |
| 1160-0026-00715033 | Dabigatran 150 | Death occurring after censor date (b) (6) |
| 1160-0026-00682034 | Warfarin | Death occurring after censor date/ (b) (6) |
| 1160-0026-00052015 | Warfarin | Death occurring after censor date/ (b) (6) |
| 1160-0026-00354003 | Dabigatran 150 | site closed for cause prior to death |
| 1160-0026-00933035 | Warfarin | CRF 196 completed with visit date given as 1/14/2009 (however investigator notes on form that patient didn't return for this visit given bad state of health), dies (b) (6) |
| 1160-0026-01635006 | Dabigatran 150 | CRF 196 completed with visit date of (b) (6) |
| 1160-0026-01677007 | Dabigatran 150 | CRF 196 completed with visit date given as (b) (6) |

| | | |
|---|---|---|
| 1160-0026-01752003 | Warfarin | CRF 196 completed with visit date given as (b) (6) contact for this visit made by phone, admitted with fall on (b) (6) |
| 1160-0026-01752009* | Dabigatran 150 | CRF 196 completed with visit date given as (b) (6), contact for this visit made by phone, |

*This subject is also presented in section 6.1.4

The yearly event rate for all cause mortality was 3.8, 3.6 and 4.1% in the dabigatran 110, dabigatran 150 and warfarin arms, respectively. The hazard ratios (relative to warfarin) are shown in the tables below. Conducting the analysis according to the finalized statistical analysis plan gives a p-value of 0.052 for the 150 dose; inclusion of the ten deaths described above shifts the p-value to 0.060. An analysis stratifying subjects by center-level INR control (subjects at centers with mean TTRs above the median and below the median) shows that the imbalance between treatment arms is driven by subjects at centers with less optimal levels of INR control (see the appendix for further explanation of center-level based analyses as well as a discussion of the impact of center-level INR control on the treatment benefit of warfarin).

**Table 37. Hazard ratios for all cause mortality**

| | **Dabigatran 110 vs. warfarin** | | **Dabigatran 150 vs. warfarin** | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| According to SAP | 0.91 (0.80,1.03) | 0.13 | 0.88 (0.77, 1.00) | 0.052 |
| Inclusive of deaths excluded by SAP | 0.90 (0.88, 1.02) | 0.10 | 0.88 (0.78,1.00) | 0.060 |
| According to center-level INR control | | | | |
| Subjects at centers with mean TTR<67% | 0.77 (0.65, 0.92) | 0.005 | 0.78 (0.66, 0.93) | 0.007 |
| Subjects at center with mean TTR≥67% | 1.08 (0.89, 1.30) | 0.43 | 1.01 (0.84,1.23) | 0.89 |

[Reviewer's analysis (sponsor's datasets=inrvis, adjrand timev, timecens; reviewer sas file=other_efficacy_endpoints and inr)]; TTR=time in therapeutic range.

| | Dabigatran 110 vs. warfarin | | Dabigatran 150 vs. warfarin | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| According to SAP | 0.91 (0.80,1.03) | 0.13 | 0.88 (0.77, 1.00) | 0.052 |
| Inclusive of deaths excluded by SAP | 0.90 (0.88, 1.02) | 0.10 | 0.88 (0.78,1.00) | 0.060 |
| According to center-level INR control | | | | |
| Subjects at centers with mean TTR<67% | 0.77 (0.65, 0.92) | 0.005 | 0.78 (0.66, 0.93) | 0.007 |
| Subjects at center with mean TTR≥67% | 1.08 (0.89, 1.30) | 0.43 | 1.01 (0.84,1.23) | 0.89 |

[Reviewer's analysis (sponsor's datasets=inrvis, adjrand timev, timecens; reviewer sas file=other_efficacy_endpoints and inr)]; TTR=time in therapeutic range.

The imbalance in all-cause mortality (relative to warfarin) was driven by an effect on adjudicated vascular specific mortality in the dabigatran 150 arm and by a numerically smaller number of adjudicated vascular and non vascular deaths in the dabigatran 110 arm[12]. The yearly event rate for adjudicated vascular mortality was 2.5, 2.3 and 2.7% in the dabigatran 110, dabigatran 150 and warfarin arms, respectively; the HR of dabigatran 150 relative to warfarin was 0.84 (p-value of 0.04).

In the CRF used to report deaths, investigators were to specify the cause of death. Relative to warfarin, a numerically smaller number of investigator reported fatal strokes were reported in the dabigatran arms (both doses); a slightly smaller number of deaths attributed to hemorrhage were also reported at the 110 dose. Other causes of death also contributed to the imbalance in all cause mortality in one or the other treatment arms (e.g. investigator-reported sudden/arrhythmic death, investigator reported non-vascular mortality "other").

**Table 38. Adjudicated and investigator-reported cause of death**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| | **N=446** | **N=438** | **N=487** |
| **Adjudicated vascular mortality** | 289 (2.4) | 274 (2.3) | 317 (2.7) |
| **Adjudicated non-vascular mortality** | 157 (1.3) | 164 (1.4) | 170 (1.5) |
| **Inv-reported vascular mortality** | 266 | 244 | 284 |
| Sudden/arrhythmic death | 89 | 75 | 87 |
| Pump failure death | 71 | 76 | 69 |
| Stroke | 30 | 23 | 44 |

12 Deaths were adjudicated as vascular (including bleeding) or non-vascular. Vascular deaths were considered to occur when no obvious nonvascular event to explain death was noted; sudden or unwitnessed deaths were also considered vascular.

| | | | |
|---|---|---|---|
| Pulmonary Embolism | 2 | 1 | 4 |
| Peripheral Embolus | 2 | 1 | 2 |
| Aortic dissection/rupture | 4 | 1 | 3 |
| Hemorrhage | 11 | 14 | 18 |
| Unknown Cause | 46 | 41 | 46 |
| Other | 12 | 14 | 11 |
| **Inv-reported non-vascular mortality** | 163 | 173 | 177 |
| Cancer | 64 | 68 | 61 |
| Respiratory Failure | 33 | 29 | 31 |
| Trauma | 3 | 6 | 6 |
| Infection | 22 | 24 | 21 |
| Other | 41 | 47 | 59 |
| **Missing/Unknown** | 17 | 21 | 26 |

[Reviewer's analysis (sponsor's datasets=plt126n, adjrand; reviewer sas file=other_efficacy_endpoints)]

*Reviewer's comments: The number of investigator reported stroke-related deaths differs from the number obtained using Investigator Rankin scores.*

With the exception of some subjects (those enrolled from sites that were closed for cause and subjects who had withdrawn consent and, as part of the consent withdrawal, had documented in writing that they would not attend study visits and were not to be contacted), vital status queries were to be made for subjects who prematurely discontinued from the study (see section 5.3.5.5). A greater number of deaths were reported as part of these queries in the warfarin compared to dabigatran arms; when viewed as a proportion of the number of deaths reported in each treatment arm in the trial, the proportion was greatest in the warfarin arm. Analyses excluding this subpopulation give a HR for all cause mortality of 0.89 (95% CI 0.78 to 1.02, p= 0.09) for dabigatran 150 and 0.92 (95% CI 0.81 to 1.05, p= 0.20) for dabigatran 110.

**Table 39. Results of vital status queries**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| All subjects reported by sponsor as prematurely discontinuing from study | 203 | 235 | 242 |
| Subjects who prematurely discontinued from study and vital status information sought | 119 (58.6) | 147 (62.6) | 156 (63.7) |
| Alive | 100 (84.0) | 120 (81.0)* | 126 (80.8) |
| Died | 7 (5.9) | 8 (5.4)* | 17 (10.9) |
| Unknown | 12 (10.1) | 19 (12.9) | 13 (8.3) |
| As a proportion of deaths reported for given treatment arm in the ITT population | 1.6% | 1.8% | 3.5% |

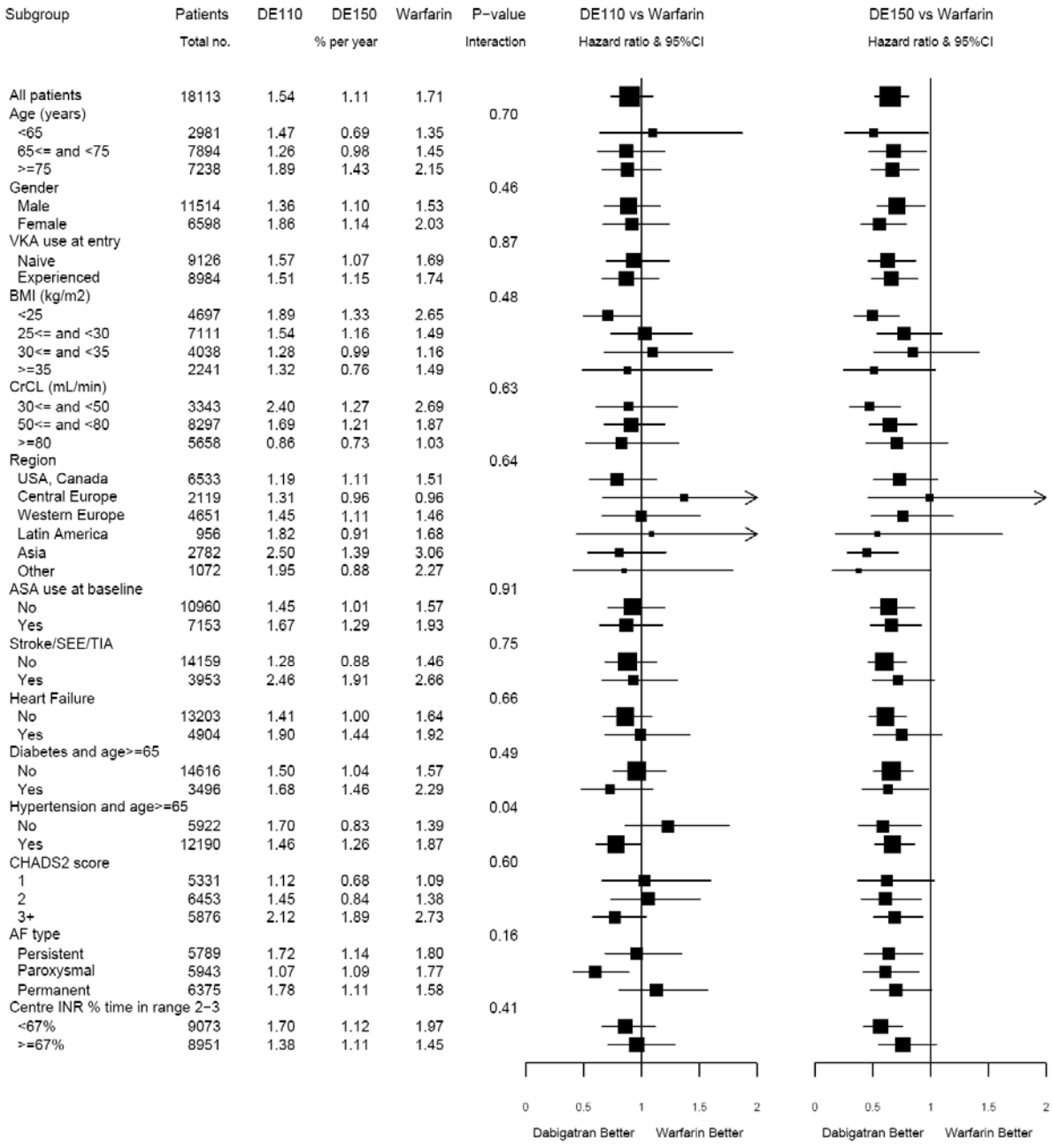
*Because deaths occurring after 3.15.2009 were not included in efficacy analyses, one subject who died after 3.15.2009 is counted as being alive for the purposes of this table.
These analyses were conducted prior to the submission of the corrected disposition data and hence the numbers of subjects prematurely discontinuing from the study differ from those shown in section 6.1.3.

*Reviewer's comment: The reason for this finding is not clear and the finding raises the question of possible bias in the ascertainment of vital status in subjects who prematurely discontinued from the study.*

### 6.1.7 Subpopulations and Concomitant Medications

Effects on the primary endpoint, stroke and systemic embolic events were also explored across important subpopulations as shown in the sponsor's figure below. The efficacy of the 150 dose appeared to be preserved across these subpopulations (as defined by the sponsor) with no clear interaction seen; this was not consistently the case in subgroup analyses of the 110 dose (e.g., .subjects < 65, atrial fibrillation type, CHADS2 score). Few blacks were studied (167), limiting the ability to draw conclusions about efficacy/safety in this population; the point estimates were favorable, but the confidence intervals were wide (see FDA Statistical Reviewer's analysis). Analyses based on center-level INR control are discussed further in section 6.1.10.

**Figure 8. Stroke/SEE hazard ratios by baseline characteristics**




[Source: Sponsor's proposed label dated May 27, 2010, Figure 3]

The FDA statistical reviewer also conducted sub-group analyses by history of stroke/SEE/TIA, age, gender, prior VKA use, country and aspirin use; these analyses were supportive of the findings shown above.

In light of the drug's pH dependent solubility and pharmacodynamic effects, additional sub-group analyses were also performed exploring the effect of concomitant

medications including aspirin, clopidogrel, proton pump inhibitors and H2 blockers on efficacy outcomes. As shown in Section 6.1.2, reported use of these medications was similar across treatment arms at baseline; whereas ~40% of subjects were on aspirin at baseline, use of clopidogrel and H2 blockers was uncommon (~5-6% and ~4%, respectively). Of subjects reported to be taking aspirin between randomization and study termination, the mean and median percent of time on aspirin was ~62-65% and 100%, respectively (incidence similar across treatment arms).

With the exception of the proton pump inhibitors, use of the aforementioned concomitant medications appeared to be comparable across treatment arms over time without any marked increase over the course of the study. In contrast, proton pump inhibitor use appeared to increase over the course of the trial and, over time, an imbalance was seen across the treatment arms, with greater use in dabigatran compared to warfarin-treated subjects (possibly secondary to the greater incidence of GI adverse events in the dabigatran arms). This change in use over time further complicates analyses addressing the effect of concomitant PPI usage on the incidence of efficacy outcome events.

**Table 40. Changes in the use of proton pump inhibitor therapy during RE-LY**

| Proton Pump Inhibitor Use | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Baseline | 847(14.1) | 878(14.5) | 842(14) |
| anytime during year one | 1279(21.3) | 1315(21.6) | 1108(18.4) |
| anytime during year two | 1247(20.7) | 1275(21) | 1087(18.1) |
| anytime during year three | 610(10.1) | 614(10.1) | 510(8.5) |
| anytime during study | 1474(24.5) | 1500(24.7) | 1268(21.1) |

As shown in the table below, the data from RE-LY do not suggest decreased efficacy in the setting of PPI use. The relationship between proton pump inhibitor use and the risk of ischemic stroke (relative to warfarin) was not consistent at the 110 and 150 dose and the confidence intervals encompassed the point estimates seen in the larger study population (HR of 1.12 and 0.75 for the 110 dose vs. warfarin and 150 dose vs. warfarin, respectively). There were few ischemic strokes reported in subjects on clopidogrel at baseline (29) or H2 blockers at baseline (19); point estimates were associated with very broad confidence intervals and hence interpretation was limited (results of analyses are not shown).

**Table 41. Proton pump Inhibitor use and the risk of ischemic stroke**

| | HR (95% CI) | | |
|---|---|---|---|
| Proton Pump Inhibitor | D110 vs. warfarin | D150 vs. warfarin | D150 vs. D110 |
| Never Used* | 1.37 (1.04, 1.80) | 0.75 (0.54, 1.03) | 0.55 (0.41, 0.74) |
| Use at baseline | 0.83 (0.45, 1.54) | 1.12 (0.63, 1.97) | 1.3 (0.74, 2.4) |
| 100% Use | 0.69 (0.35, 1.37) | 1.10 (0.61, 2.01) | 1.59 (0.82, 3.09) |

[Reviewer's analysis (sponsor's datasets=bascocm, timecens and timev; reviewer sas file=ASA_PPI_analyses)]
*If subject had been on proton pump inhibitor, stop date was prior to date of first intake of study drug.

The HRs and 95% CIs for ischemic strokes by concomitant usage of aspirin is shown below. Though the confidence intervals of the hazard ratios are wide and cross one, the point estimates suggest that even in the setting of concomitant aspirin use, the 150 dose may provide greater benefit (ischemic stroke reduction) than the 110 dose.

**Table 42. Aspirin use and the risk of ischemic stroke**

| | HR (95% CI) | | |
|---|---|---|---|
| Aspirin | D110 vs. warfarin | D150 vs. warfarin | D150 vs. D110 |
| Never Used* | 1.0 (0.72, 1.39) | 0.44 (0.29, 0.67) | 0.44 (0.29, 0.67) |
| Use at baseline | 1.30 (0.91, 1.85) | 0.93 (0.63, 1.36) | 0.72 (0.50, 1.03) |
| 100% Use | 1.38 (0.82, 2.32) | 0.95 (0.53, 1.70) | 0.69 (0.41, 1.18) |

[Reviewer's analysis (sponsor's datasets=bascocm, timecens and timev; reviewer sas file=ASA_PPI_analyses)]
*If a subject had been on aspirin, stop date was prior to date of first intake of study drug.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Three phase 2 dose-ranging studies were conducted in patients with atrial fibrillation. These studies, along with studies conducted as part of other indications, are cited by the sponsor as supporting the choice of dose selection in RE-LY. The phase 2 trials conducted in patients with atrial fibrillation studied doses ranging from 50 mg bid to 300 mg bid and are shown in the table below.

**Table 43. Phase 2 studies in patients with atrial fibrillation**

| Study | Design | Doses (N) |
|---|---|---|
| 1160.20 (PETRO) | Randomized, controlled, double-blind (dabigatran doses), open label (ASA and warfarin) 12-week study in patients with non-rheumatic atrial fibrillation and one stroke risk factor | *Dabigatran:*<br>50 mg bid (58)<br>50 mg bid + ASA 81 mg (20)<br>50 mg bid + ASA 325 mg (27)<br>150 mg bid (99)<br>150 mg bid + ASA 81 mg (34)<br>150 mg bid + ASA 325 mg (33)<br>300 mg bid (98)<br>300 mg bid + ASA 81 mg (33)<br>300 mg bid + ASA 325 mg (30)<br>*Warfarin* to target INR 2-3 (70) |
| 1160.42 (PETRO-EX) | Long-term (5 years), open-label, uncontrolled, non-randomized study of dabigatran (with ASA added at the investigator's discretion) in patients previously treated with dabigatran in Study 1160.2013 | *Dabigatran*:<br>150 mg qd<br>150 mg bid<br>300 mg qd<br>300 mg bid |
| 1160.49 | Randomized, open label 12-week study in Japanese patients with moderate to high risk atrial fibrillation | *Dabigatran*:<br>110 mg bid (53)<br>150 mg bid (59)<br><br>*Warfarin* to target INR 2-3, INR 1.6-2.6 in patients age ≥ 70 (62) |

As a whole, the phase 2 studies suggest that over the dose range studied, increasing doses/exposures result in greater prolongation of aPTT and ECT. These studies also suggest that (at least at some dose levels of dabigatran) there may be a relationship between concomitant aspirin use and increased risk of bleeding; this issue is addressed further under safety. These studies do not, however, provide significant insight into the optimal dosing regimen for the prevention of thromboembolic events. Studies 1160.20 and 1160.49 were limited in size and study duration and few thromboembolic events were observed. In trial 1160.49, no thromboembolic events were seen during dabigatran treatment and in trial 1160.20, two thromboembolic events were reported (both in the 50 mg bid treatment arm). In study 1160.42, a long-term, open-label, non-randomized

13 Although treatment group assignment in study 1160.42 was based on treatment group assignment in study 1160.20, patients did not necessarily remain in the same treatment arm as in 1160.42. The doses administered in some treatment arms were also changed during the course of the study (with amendment 4, patients previously treated with dabigatran 150 mg QD or 300 mg BID were administered 150 mg BID). Down titration in dose also occurred in patients with both a low GFR and high corrected aPTT (but not below 150 mg QD).

study, a small number of strokes were reported (see table below). However, interpretation of the data from this trial is not straightforward. Patient-years of exposure is limited for doses other than 150 mg BID doses, some subjects were crossed-over to other treatment arms, the study was not randomized, nor was it blinded.

With respect to the lower end of the effective dose range, RE-LY itself provides the most informative data regarding thromboembolic prevention. In subjects randomized to dabigatran 110, 171 strokes were reported compared to 122 in subjects randomized to dabigatran 150. Compared to the lower dose, the hazard ratio for the higher dose was 0.71 (95% CI 0.56 to 0.90, p-value=0.003), suggesting a clinically important reduction in the risk of such events with the higher dose. RE-LY also provides important data that can speak to the upper end of the dose range likely to provide "net benefit;" an issue that is addressed in Section 1.2 on Risk-Benefit .

**Table 44. Incidence of secondary efficacy endpoints in PETRO-EX (1160.42)**

| Event | 50 mg QD | 50 mg BID | 150 mg QD | 150 mg BID | 300 mg QD | 300 mg BID | Total Dabig. |
|---|---|---|---|---|---|---|---|
| Cumulative exposure (patient years) | 0.05 | 24 | 60 | 842 | 242 | 82 | 1250 |
| **Any stroke** | | | | | | | |
| N | 0 | 1 | 3 | 9 | 4 | 0 | 17 |
| Per 100 patient-years [1] | 0.0 | 4.3 | 5.0 | 1.1 | 1.7 | 0.0 | 1.4 |
| **Ischaemic stroke** | | | | | | | |
| N | 0 | 1 | 3 | 4 | 4 | 0 | 12 |
| Per 100 patient-years | 0.0 | 4.3 | 5.0 | 0.5 | 1.7 | 0.0 | 1.0 |
| **Haemorrhagic stroke** | | | | | | | |
| N | 0 | 0 | 0 | 5 | 0 | 0 | 5 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 0.6 | 0.0 | 0.0 | 0.4 |
| **Any TIA** | | | | | | | |
| N | 0 | 0 | 0 | 2 | 1 | 0 | 3 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 0.2 | 0.4 | 0.0 | 0.2 |
| **Non-CNS systemic thromboembolism** | | | | | | | |
| N | 0 | 2 | 0 | 2 | 1 | 1 | 6 |
| Per 100 patient-years | 0.0 | 8.5 | 0.0 | 0.2 | 0.4 | 1.2 | 0.5 |
| **Myocardial infarction** | | | | | | | |
| N | 0 | 0 | 0 | 9 | 1 | 0 | 10 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 1.1 | 0.4 | 0.0 | 0.8 |
| **Other MACE** | | | | | | | |
| N | 0 | 2 [2] | 0 | 9 | 2 | 1 | 14 |
| Per 100 patient-years | 0.0 | 8.5 | 0.0 | 1.1 | 0.8 | 1.2 | 1.1 |
| **All cause death** | | | | | | | |
| N | 0 | 0 | 0 | 23 | 5 | 0 | 28 |
| Per 100 patient-years | 0.0 | 0.0 | 0.0 | 2.7 | 2.1 | 0.0 | 2.2 |
| **Ischaemic stroke, TIA, non-CNS TE, MI, MACE, death** | | | | | | | |
| N | 0 | 4 [3] | 3 | 46 | 11 | 2 | 66 |
| Per 100 patient-years | 0.0 | 17.0 | 5.0 | 5.5 | 4.5 | 2.4 | 5.3 |
| **Stroke, non-CNS TE** | | | | | | | |
| N | 0 | 2 | 3 | 11 | 5 | 1 | 22 |
| Per 100 patient-years | 0.0 | 8.5 | 5.0 | 1.3 | 2.1 | 1.2 | 1.8 |

[Source: Table 11.4.1.2:1]

In addition to the studies conducted in patients with atrial fibrillation, studies have also been conducted in other patient populations and indications, including primary and secondary prevention of venous thrombosis and as a treatment for acute coronary syndrome. From the standpoint of safety, these studies generally support the concept that higher doses are associated with increased risk of bleeding. With regard to efficacy, according to the sponsor, a dose dependent decrease in the frequency of venous thromboembolism events was seen with increasing dabigatran dose: 28.5%, 17.4%, 16.6%, 13.1%, of subjects assigned to dabigatran 50 BID, 150 BID, 300 QD, and 225 BID, respectively in a phase 2 study of primary venous thromboembolism prevention (study 1160.19). The sponsor noted that this effect was "more prominent" between the 50 and 150 BID dose and "less striking" at the higher doses. A relationship between increasing dabigatran dose and decreasing incidence of a composite endpoint of venous thromboembolism events and all-cause mortality is also cited by the sponsor (study 1160.50, another study of primary venous thromboembolism prevention). Differences in populations, concomitant medications, and indications limit the ability to extrapolate from the experience in these studies to the proposed indication and these studies were not reviewed further.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan-Meier curves of time to first stroke/SEE (see section 6.1.4) suggest no loss of efficacy over time.

### 6.1.10 Additional Efficacy Issues/Analyses

#### *6.1.10.1 Warfarin administration and INR control*

The following analyses address exposure to warfarin and the quality of INR control in subjects randomized to warfarin.

Exposure to warfarin
Of the 6,022 subjects randomized to warfarin in RE-LY, 80.8% (4849) completed the study on study medication. Over 50% of subjects had at least one interruption of study medication over the course of the trial; a similar percentage of subjects had interruptions in the dabigatran treatment arm (see section 7.2.1) As shown in the table below, most interruptions were for less than 30 days. Approximately 35% of temporary interruptions of study medication in the warfarin treatment arm were in the setting of a surgery or procedure; around 20% occurred in the context of an adverse event and 16% in the context of a hospitalization (source: sponsor's table 15.1.1:4; subjects were counted in multiple categories when multiple reasons were given). Subjects in the warfarin arm were on study medication for 91.0% of study days of follow up (source; reviewer's analysis using FDA censoring rules).

**Table 45. Interruptions of study medication**

| | Subjects (%) |
|---|---|
| Randomized to warfarin | 6022 |
| Randomized and treated | 5998 |
| Number with interruptions | 3120 (52.0) |
| Total temporary interruptions (days*) | |
| 1 ≤ and < 8 | 1112 (18.5) |
| 8 ≤ and <30 | 877 (14.6) |
| 30 ≤ and <60 | 222 (3.7) |
| ≥ 60 | 194 (3.2) |
| Permanently discontinued study medication | 1073 (17.9) |

[Source: adapted from sponsor's table 15.1.5:1, April 19, 2010 resubmission]
For subjects with more than one interruption, the cumulative days of interruptions were calculated. Subjects who had both temporary and permanent discontinuations were counted in both categories, hence these categories do not add up.

INR control
Of the 5998 subjects randomized and treated with warfarin, 134 subjects lacked follow up INR data (as reported in the CRF INR log). Of these, approximately 45% permanently discontinued study medication within one week of starting therapy; approximately 72% were on therapy for 30 days or less. Of those subjects with measurements that were taken and reported, approximately 32% of subjects had at least one INR measurement taken >60 days from the prior INR measurement and approximately 16% had at least one INR measurement taken > 90 days from the prior measurement.

To assess the adequacy of INR control, the percent of time reported INR values were within and outside the therapeutic range (2-3) were calculated using available data. Analyses of the percent of time values were in the therapeutic range (2-3) were initially performed by the sponsor excluding days in the first week after randomization and days while study warfarin was temporarily or permanently stopped. Because one reason given by investigators for holding warfarin was an elevated INR and because embolic strokes are likely to occur while anticoagulation is on hold, even if the reason for holding therapy is appropriate (e.g., bleed or procedure), an analysis was also performed in which available data during periods of medication interruption were included. The results of analyses excluding days while warfarin was temporarily or permanently stopped and including periods of medication interruption are shown in the tables below. The mean time in therapeutic range (2-3) was 64.4% (analyses excluding interruptions) and 63.4% (analyses including interruptions). The mean percent of time U.S. subjects were in an INR range of 2-3 was 66% (64.7% including available data during periods of medication interruption).

**Table 46. Mean percent of time INR 2 to 3**

| | Percent of time INR 2 to 3 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR 2 to 3 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 49.2 | 38.5 | 4956 | 48.7 | 38.2 |
| 3 | 5668 | 56.3 | 30.4 | 5711 | 55.6 | 30.2 |
| 6 | 5565 | 60.3 | 25.3 | 5624 | 59.4 | 25.4 |
| 12 | 5236 | 64.0 | 20.4 | 5301 | 63.0 | 20.7 |
| Overall | 5791 | 64.4 | 19.8 | 5812 | 63.4 | 19.9 |

[Reviewer's analysis (sponsor's dataset=inrvis); reviewer sas file=inr)]

The percent of INR measurements greater than 4, less than 2, and less than 1.5 (as determined using the Rosendale method) is shown in the tables below. The overall mean percent of reported INR measurements greater than 4 was ~2%; the overall mean percent of INR measurements < 2 and <1.5 was ~22-23% and ~5%, respectively. Compared to later months, during the first month of therapy, a greater percentage of INR measurements were greater than 4 or less than 1.5.

**Table 47. Mean percent of time INR>4**

| | Percent of time INR >4 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR> 4 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 5.2 | 16.4 | 4956 | 5.4 | 16.6 |
| 3 | 5668 | 3.1 | 9.7 | 5711 | 3.1 | 9.3 |
| 6 | 5565 | 2.3 | 6.3 | 5624 | 2.3 | 6.2 |
| 12 | 5236 | 1.9 | 4.2 | 5301 | 1.9 | 4.2 |
| Overall | 5791 | 2.2 | 6.0 | 5812 | 2.1 | 5.5 |

**Table 48. Mean percent of time INR<2**

| | Percent of time INR <2.0 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR< 2.0 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 31.6 | 38.7 | 4956 | 31.9 | 38.6 |
| 3 | 5668 | 29.0 | 30.7 | 5711 | 30.0 | 30.9 |
| 6 | 5565 | 26.2 | 25.5 | 5624 | 27.3 | 25.8 |
| 12 | 5236 | 22.8 | 19.9 | 5301 | 23.9 | 20.5 |
| Overall | 5791 | 22.2 | 19.1 | 5812 | 23.4 | 19.5 |

**Table 49. Mean percent of time INR <1.5**

| | Percent of time INR <1.5 excluding data while study warfarin temporarily or permanently stopped | | | Percent of time INR< 1.5 including available data during periods of medication interruption | | |
|---|---|---|---|---|---|---|
| Months (cumulative) | N | MEAN | STD | N | MEAN | STD |
| 1 | 4899 | 10.6 | 26.2 | 4956 | 10.9 | 26.3 |
| 3 | 5668 | 8.4 | 20.2 | 5711 | 9.0 | 20.7 |
| 6 | 5565 | 6.6 | 15.7 | 5624 | 7.3 | 16.4 |
| 12 | 5236 | 4.7 | 10.8 | 5301 | 5.5 | 11.9 |
| Overall | 5791 | 4.8 | 11.3 | 5812 | 5.5 | 12.2 |

[Reviewer's analysis (sponsor's dataset=inrvis); reviewer sas file=inr)]

*Reviewer's comment: These analyses suggest that, as a whole, reasonable INR control was achieved in warfarin-treated subjects in RE-LY. For further discussion, see the Efficacy Summary.*

It has been shown that the time in therapeutic range measured at the center-level and country-level (determined by averaging the individual times in therapeutic range for all subjects randomized to oral anticoagulant therapy within a center or country to yield a value for that center or country), has an important impact on the treatment benefit of warfarin in intervention trials. The benefit of oral anticoagulants over antiplatelet agents has been shown to be dependent upon the quality of INR control as measured by the time in therapeutic range at the center and country level (Connolly et al. 2008; see also Appendix).

Analyses stratifying subjects by center-level INR control (stratifying centers into quartiles) are shown in the table below. These analyses do not show a clear graded

relationship between the center-level of INR control and the benefit of dabigatran relative to warfarin. For the primary efficacy endpoint, the point estimate of the HR for the 150 dose moves closer to one with broad confidence intervals that exceed one in the subset of subjects enrolled at sites achieving the highest quartile of INR control, suggesting that the benefit of the 150 dose of dabigatran (relative to warfarin) is somewhat dependent upon the level of INR control achieved in warfarin-treated subjects. With regard to bleeding, there appears to be a graded relationship between quartile of center-level INR control and the relative risk of adjudicated major bleeds, with much of the relative risk reduction in bleeding in the 110 arm driven by subjects at centers achieving lower levels of INR control. These results suggest that in patients with well controlled INRs, the 110 dose may not provide a significant reduction in the risk of bleeding relative to warfarin.

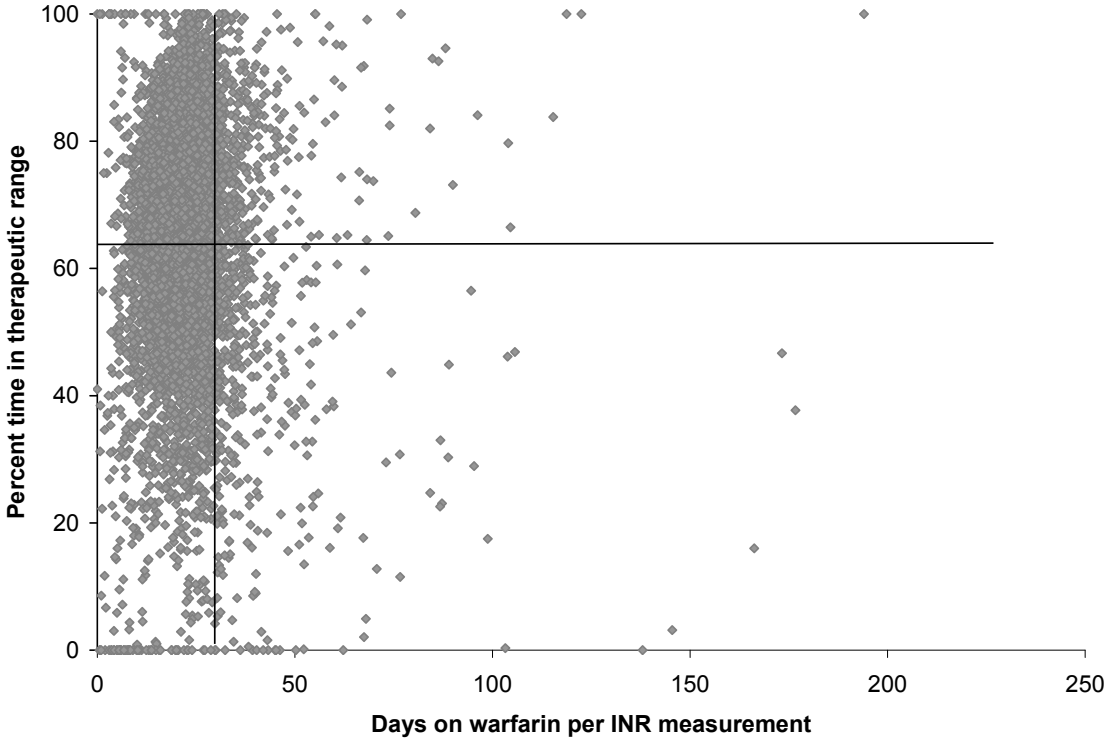
**Table 50. Analyses by quartile of center-level INR control**

| **Quartile of center-level INR control*** | | **1 <58.5** | **2 ≥58.5 and <66.8** | **3 ≥66.8 and <74.2** | **4 ≥74.2** |
|---|---|---|---|---|---|
| Number of subjects | | N=4162 | N=4662 | N=4772 | N=4428 |
| **Stroke/SEE** | | | | | |
| Dabigatran 110 vs. warfarin | HR | 0.95 | 0.79 | 0.97 | 0.92 |
| | 95% CI | 0.64,1.40 | 0.54, 1.16 | 0.65,1.44 | 0.59,1.44 |
| | p-value | 0.79 | 0.23 | 0.87 | 0.72 |
| Dabigatran 150 vs. warfarin | HR | 0.60 | 0.53 | 0.65 | 0.90 |
| | 95% CI | 0.39, 0.94 | 0.35,0.81 | 0.42,1.02 | 0.57,1.41 |
| | p-value | 0.02 | 0.003 | 0.06 | 0.63 |
| **Major Bleeds** | | | | | |
| Dabigatran 110 vs. warfarin | HR | 0.64 | 0.74 | 0.90 | 0.93 |
| | 95% CI | 0.46, 0.88 | 0.57, .097 | 0.69, 1.17 | 0.68, 1.26 |
| | p-value | 0.005 | 0.03 | 0.43 | 0.62 |
| Dabigatran 150 vs. warfarin | HR | 0.68 | 0.90 | 1.00 | 1.20 |
| | 95% CI | 0.50, 0.93 | 0.70, 1.16 | 0.77, 1.30 | 0.90, 1.60 |
| | p-value | 0.016 | 0.41 | 1.00 | 0.21 |

[Reviewer's analysis (sponsor's datasets= inrvis, adjrand); reviewer sas file=inr]
*Center-level INR control was determined by averaging the individual times in therapeutic range for all subjects randomized to warfarin within a center to yield a value for that center. Centers were than stratified into quartiles by center-level INR control.

The level of INR monitoring (as determined by the days on warfarin/the number of reported INR measurements) in subjects included in the sponsor's calculations of time in therapeutic range is shown in the figure below. As shown in the figure, the majority of subjects had at least one INR measurement for every 30 days of treatment, though some subjects had infrequent monitoring despite poor control. Some subjects with reported optimal control (higher percent time in therapeutic range) also had infrequent monitoring.

**Figure 9. Percent time in therapeutic range vs. frequency of monitoring**

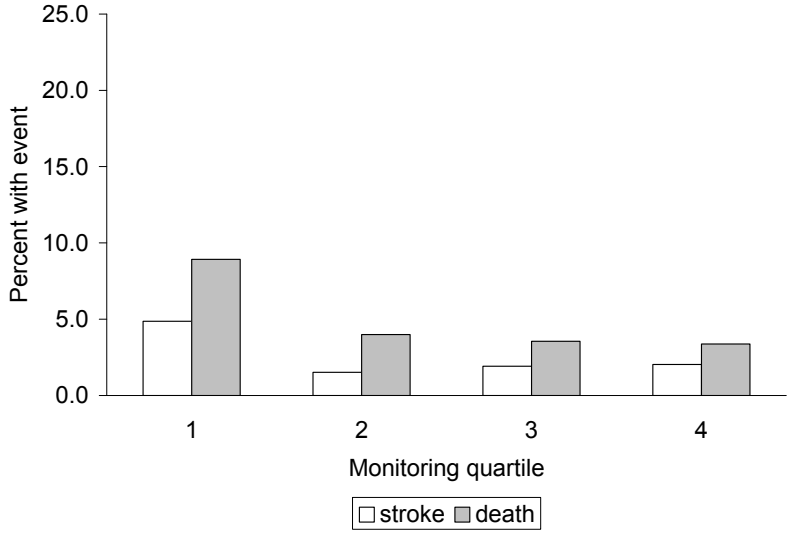



[Reviewer's analysis (sponsor's datasets=offmed, inr2, inrvis); reviewer sas file=inr]
*Days on warfarin are cumulative and not necessarily consecutive. Vertical line drawn at 30 days; horizontal line drawn at 64% time in therapeutic range.

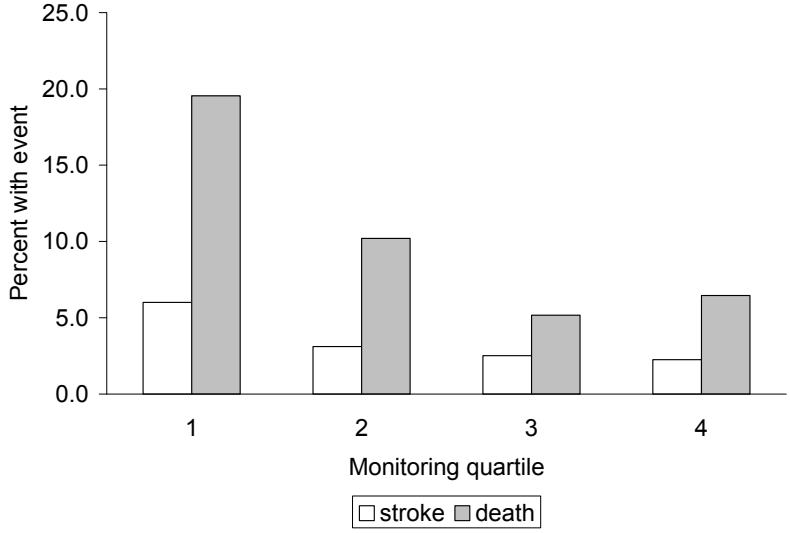
Analyses looking at adjudicated strokes and deaths in subjects by frequency of INR monitoring (broken into quartiles) and further stratified by the percentage of time a subject was in the therapeutic range (above and below the median value) did not suggest worse outcomes in those with less frequent INR monitoring. There did appear to be a numerical increase in the number of events (deaths and strokes) in subjects undergoing the most frequent monitoring, possibly representing the subset of subjects with more difficult to control or variable INRs.

**Figure 10. Events by frequency of monitoring and level of INR control**

A. Subjects with time in therapeutic range >67%




B. Subjects with time in therapeutic range ≤67%




[Reviewer's analysis (sponsor's datasets=offmed, inr2, inrvis); reviewer sas file=inr]
Monitoring quartiles: 1=most frequent INR monitoring and 4=least frequent

### *6.1.10.2 Analyses pertaining to RE-LY's open-label design*

RE-LY was an open-label study with respect to warfarin. The following analyses focus on the adjudication process. The differential treatment of subjects in the dabigatran vs. warfarin treatment arms is also addressed.

*Investigator-reported vs. Adjudicated strokes,SEE and major bleeds*
Of subjects with investigator reported strokes, similar percentages were adjudicated as having a stroke in the three treatment arms. Of subjects with investigator-reported TIAs, similar percentages were adjudicated as having a stroke. In contrast, a smaller percentage of subjects with investigator-reported systemic embolic events were adjudicated as having had systemic embolic events in the dabigatran compared to warfarin-treatment arms (discussed further below).

**Table 51. Investigator-reported vs. adjudicated stroke, TIA and SEE**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Subjects with investigator-reported strokes | 183 | 143 | 205 |
| Number (%) of subjects with adjudicated stroke | 163 (89.1) | 120 (83.9) | 181 (88.3) |
| Subjects with investigator-reported TIAs | 85 | 90 | 107 |
| Number (%) of subjects with adjudicated stroke | 16 (18.8) | 12 (13.3) | 17 (15.9) |
| Subjects with investigator-reported SEE | 32 | 29 | 29 |
| Number (%) of subjects with adjudicated SEE | 15 (46.9) | 13 (44.8) | 21 (72) |

[Reviewer's analysis (sponsor's datasets=timev; reviewer sas file=primary_endpoint)]

As a percentage of investigator reported major bleeds, the percentage of major bleeds adjudicated as "no event" was also similar across the treatment arms.

**Table 52. Investigator-reported vs. adjudicated major bleeds**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Investigator reported major bleed | 427 | 528 | 515 |
| Total subjects (n) | 355 | 427 | 449 |
| Adjudicated bleeds | | | |
| Total Major bleed | 404 | 492 | 478 |
| Major bleed | 248 | 296 | 250 |
| Life threatening bleed | 156 | 196 | 228 |
| No Event | 34 | 45 | 44 |

[Reviewer's analysis: (sponsor's datasets= adjud, adjud3, timev and plt122n; reviewer sas file= mj\adjud\original\adj and major) .Total major bleed + no event does not equal investigator reported because some major bleeds were not identified by the investigator]

*Identification of endpoint events and adjudication process*

As previously noted in the review, the central adjudication committee had concluded that there were inconsistencies in the adjudication of Non-CNS embolic events and, as a result, non-CNS embolic events were re-adjudicated. The outcome of this second review was to be final and supersede previous documented decisions in the main clinical data base. A random sample of five events adjudicated as SEE in the warfarin arm and five investigator-reported events not adjudicated as SEE in the dabigatran arm were reviewed. In all of the warfarin cases, the re-adjudication was consistent with the original adjudication. In two of five dabigatran cases, the original adjudication was that an event had occurred. In both these cases, the re-adjudication appeared appropriate.

**Table 53. Review of adjudicated SEE**

| Subject | Adjudication | | FDA Reviewer | Comments |
|---|---|---|---|---|
| | Second | Original | | |
| **Warfarin** | | | | |
| 00035039 | yes | yes | yes | |
| 00474008 | yes | yes | yes | |
| 01095010 | yes | yes | yes | |
| 01396006 | yes | yes | yes | |
| 01589031 | NA | yes | yes | identified post database lock, not re-adjudicated |
| **Dabigatran** | | | | |
| 00226020 | no | yes | no | DVT |
| 00432016 | no | no | no | DVT |
| 00432019 | no | no | no | DVT |
| 00452014 | no | no | no | DVT |
| 01425011 | no | yes | no | not documented via imaging, though history suggestive |

To evaluate the adjudication process for stroke events, a random sample was taken of subjects with investigator reported strokes (59 events in 54 subjects). As suggested by the endpoint committee meeting minutes (see section 5.3), blinding, particularly of non-English documents, was not adequate. In 10 of 59 events reviewed (17%), the adjudication package contained information that could have unblinded adjudicators to treatment assignment (see table below). Unblinding was possible in 2 of 20 subjects (10%) from North American sites and in 8 of 34 subjects (24%) from non-North American sites; phrases found in these documents included the following:

- "recruited in RE-LY study…on Dabigatran"
- “atrial fibrillation being treated with warfarin”
- “on warfarin”
- "he is using an experimental blood thinner"
- “Sunday to check INR levels…consult with physician regarding the coumadin dose. Target INR 2.0”
- reference to antivitamin K being suspended

- "elevated INR blood test"
- "despite therapeutic anticoagulation"
- "Regular checks of INR"

Despite this text, many adjudicators reported that they remained blinded during their adjudication. With regard to the adjudication decisions themselves, although some cases were less clear cut than others, as a whole, the decisions reached by adjudicators seemed reasonable.

*Reviewer's comment: The subject reported to be "on warfarin" was in the dabigatran treatment arm. A significant number of subjects who were randomized to dabigatran permanently discontinued study medication and some number of subjects with references to warfarin/INR in their adjudication documents may have been in the dabigatran treatment arms.*

*Discontinuation of study medication*

Permanent discontinuations of study medication were more common in dabigatran compared to warfarin treated subjects. As a way to further explore the reason for permanent interruption of study medication, the sponsor performed an analysis of events occurring around the time of permanent interruptions of study medication. For the purposes of this analysis, when an outcome event was given as the reason for interruption, the exact event was identified using a 30 day window around the event. The results of this analysis are shown below (see appendix for timing of events). The numerically greater incidence of permanent study medication discontinuations for ischemic stroke, TIA (a non-endpoint event) or minor bleed in the dabigatran compared to warfarin treatment arms suggests that knowledge of treatment assignment in this open-label study may have led to differences in how subjects were treated. Though the sponsor reports reason for discontinuation of medication as "Death" for some subjects, such a categorization is nonsensical.

**Table 54. Reasons for permanent discontinuation of study medication**

| | **Dabigatran 110 N=1318** | **Dabigatran 150 N=1382** | **Warfarin N=1073** |
|---|---|---|---|
| Serious AE not related to outcome event | 162 ( 2.7) | 170 ( 2.8) | 119 ( 2.0) |
| Subject didn't want to take study drug | 424 ( 7.1) | 459 ( 7.6) | 405 ( 6.8) |
| Outcome event | 261 ( 4.4) | 246 ( 4.1) | 177 ( 3.0) |
| Stroke | 53 ( 0.9) | 42 ( 0.7) | 26 ( 0.4) |
| Ischemic stroke | 43 ( 0.7) | 34 ( 0.6) | 13 ( 0.2) |
| Hemorrhagic stroke | 4 ( 0.1) | 5 ( 0.1) | 13 ( 0.2) |
| Stroke of uncertain classifications | 6 ( 0.1) | 4 ( 0.1) | 0 |
| SEE | 10 ( 0.2) | 1 ( 0.0) | 2 ( 0.0) |
| PE | 5 ( 0.1) | 5 ( 0.1) | 1 ( 0.0) |

| | | | |
|---|---|---|---|
| MI | 9 ( 0.2) | 8 ( 0.1) | 8 ( 0.1) |
| Major Bleed | 53 ( 0.9) | 61 ( 1.0) | 66 ( 1.1) |
| Life threatening major bleeds | 20 ( 0.3) | 37 ( 0.6) | 47 ( 0.8) |
| Other major bleeds | 33 ( 0.6) | 24 ( 0.4) | 19 ( 0.3) |
| Minor bleed | 67 ( 1.1) | 76 ( 1.3) | 37 ( 0.6) |
| TIA | 20 ( 0.3) | 15 ( 0.2) | 0 |
| Death | 18 ( 0.3) | 17 ( 0.3) | 18 ( 0.3) |
| Not matched with the algorithm | 42 ( 0.7) | 37 ( 0.6) | 33 ( 0.6) |
| Other | 471 ( 7.9) | 507 ( 8.4) | 372 ( 6.2) |
| Adverse Event | 157 ( 2.6) | 164 ( 2.7) | 72 ( 1.2) |
| Lab changes | 44 ( 0.7) | 57 ( 0.9) | 17 ( 0.3) |
| Procedure/hospitalization/surgery | 30 ( 0.5) | 35 ( 0.6) | 46 ( 0.8) |
| Other | 240 ( 4.0) | 251 ( 4.1) | 237 ( 4.0) |

[Source: Sponsor; Modified from Table 15.1.1:3]
For the purposes of this analysis subjects who discontinued the study early without reason for discontinuation CRF were not included. A subject was counted in multiple categories when multiple reasons were given.

# 7 Review of Safety

## 7.1 Methods

In the sponsor's safety analyses and in the safety analyses that follow, subjects without a reported major bleed were censored at the last time vital status information was available. There were a few exceptions (noted in footnotes) where the reviewer's analyses did not use this censoring rule; instead the analyses used data sets submitted in April that censored subjects without a major bleed at the time information was last known about major bleeds. [14] As noted earlier, errors were found in the disposition data. These errors impact the censoring dates used for analyses, and in particular for those analyses in which subjects were to be censored based on the last date follow up information was available for the outcome of interest. These errors, occurring in a small percentage of subjects, do not alter the results of key analyses and hence many analyses were not re-run using the corrected data sets submitted in August.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review focuses on the findings in RE-LY, and in particular, on the subset of subjects in RE-LY who received at least one dose of study medication (18,040 out of 18,113 randomized subjects). Though dabigatran has also been studied for VTE prevention (and has been approved outside the U.S. for the prevention of VTE post total

14 Datasets named adjrand2 and timecen2

hip/knee replacement), safety data from the VTE program were not, for the most part, analyzed. RE-LY provides more than 20,000 subject years of exposure and differences in populations, concomitant medications and the use of dabigatran (dose and duration) limit the ability to extrapolate from the safety experience in the VTE program to the proposed indication. However for rare events, such as drug induced liver injury (DILI), the Periodic Safety Update Report (last dated March 2010) was used.

*Reviewer's comment: A 4 month safety update was submitted on August 17, 2010; an addendum will be filed if the data contained in this submission significantly alter the safety findings/conclusions given in this review.*

### 7.1.2 Categorization of Adverse Events

The sponsor's coding of adverse events seemed, as a whole, appropriate. Adverse events (AE) were coded to MeDRA version 12.0.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from different studies were not pooled.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure is adequate to describe safety in the intended population. There were over 20,000 subject years of dabigatran exposure in the RE-LY trial. Because more than 50% of subjects on dabigatran temporarily discontinued medication, exposure was calculated including and excluding periods of temporary discontinuation of study medication. In analyses excluding these periods, exposure was on average 9 days less than in analyses in which these periods were included. Subjects on dabigatran took study drug for approximately 1 month less than subjects on warfarin.

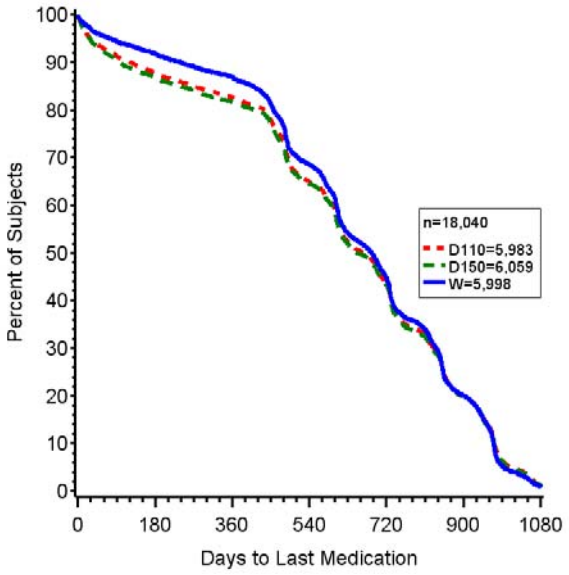
**Table 55. Subject years of medication exposure**

| | D110 N=5983 | D150 N=6059 | W N=5998 |
|---|---|---|---|
| Including periods of temporary medication discontinuation | | | |
| Subject years[1] | 10242 | 10261 | 10659 |
| Mean exposure (mo) | 20.8 | 20.6 | 21.6 |
| Excluding periods of temporary medication discontinuation | | | |
| Subject years | 10089 | 10115 | 10508 |
| Mean exposure (mo) | 20.5 | 20.3 | 21.3 |

1. Subject years calculated as sum [(last med date – first med date) +1]; these calculations were used for the sponsor's safety analyses
[Source: reviewer's analysis file: ds\exposure; sponsor's data set: basco]

More subjects (4-5%) on dabigatran prematurely discontinued medication than on warfarin. The reasons for premature medication discontinuation were shown in Table 54. The figure below shows the days to last medication in all subjects treated in RE-LY. More subjects on dabigatran discontinued medication early as compared to warfarin, and the percent of subjects on treatment starts to coincide around 15 months.

**Figure 11. Days to last medication**




[Source: reviewer's analysis: Med dc perm days to; sponsor dataset:lastmed, popu, disco ]

The demographics of the safety population mirror the demographics of the randomized population (see Section 6.1.2 for information). Exposure appears to be adequate in

important patient subsets (e.g., age ≥ 75, CHADS2 score 3+, history of stroke/TIA/SEE), Mean exposure in subjects with and without prior VKA use was also explored. As shown in the table below, in VKA experienced subjects, mean exposure appeared to be greater in warfarin than dabigatran-treated subjects, suggesting a greater tendency for VKA experienced subjects to discontinue from the dabigatran arms than the warfarin arms.

**Table 56. Study drug exposure in VKA naïve and VKA experienced subjects**

| | VKA naïve | | | | VKA Experienced | | | |
|---|---|---|---|---|---|---|---|---|
| | **D110** | **D150** | **W** | **Total** | **D110** | **D150** | **W** | **Total** |
| Total n | 2990 | 3019 | 3082 | 9091 | 2991 | 3039 | 2916 | 8946 |
| Mean (months) | 19.4 | 19.2 | 19.7 | 19.4 | 21.7 | 21.5 | 23.0 | 22.1 |
| Subject years | 10242 | 10261 | 10659 | 14721 | 5411 | 5432 | 5595 | 16438 |

[Source: Sponsor's table 15.3.1:2 of QC report]

### 7.2.2 Explorations for Dose Response

There is a dose-response relationship for bleeding (see safety sections on bleeding and section 6.1.8).

### 7.2.3 Special Animal and/or In Vitro Testing

The nonclinical testing was adequate to explore potential adverse reactions of particular interest, including bleeding and liver toxicity.

### 7.2.4 Routine Clinical Testing

Routine clinical testing of clinical trial subjects, including the methods and tests used and the frequency of testing, was adequate. Information on outcome events (including stroke and bleeding questionnaires), adverse events, cardioversion, emergency/elective surgery, hospitalization, concomitant medications, INR evaluations, study medication, laboratory evaluation were assessed at each follow-up visit (every 3 months for the first year, then every 4 months until study end). ECGs were assessed at baseline, month 12, 24, 36 and at final follow-up.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Based on the draft Clinical Pharmacology Review dated August 4, 2010, the workup was sufficient to characterize the metabolism and excretion of dabigatran and important drug-drug interactions (see section 4.4)

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor's evaluation for potential adverse events associated with other drugs in this class (thrombin inhibitors/anticoagulants) was adequate. Major adverse events of interest include bleeding and the potential for drug induced liver injury (DILI); these are discussed in detail. A discussion of serious cardiovascular events, including myocardial infarction, is provided in the appendix as an addendum to this review.

## 7.3 Major Safety Results

### 7.3.1 Deaths

An imbalance in deaths was seen across the three treatment arms, with a numerically smaller number of deaths reported in dabigatran-treated subjects (relative to warfarin). The mortality findings are not a safety concern and are discussed under Efficacy (Section 6.1.6).

### 7.3.2 Nonfatal Serious Adverse Events

#### *7.3.2.1. Major bleeding*

**Overview of findings and conclusions**

Bleeding was the most common and important safety concern identified in RE-LY. Major bleeds and life threatening bleeds (defined in the table below) were pre-specified, adjudicated safety endpoints in RE-LY. Relative to warfarin, there was no difference in major bleeds with dabigatran 150 mg (HR 0.93, 95% CI: 0.81, 1.07) whereas dabigatran 110 mg was associated with fewer major bleeds (HR 0.80, 95% CI: 0.68, 0.90, $p<0.003$). The risk reduction in major bleeds and life threatening bleeds (relative to warfarin) was influenced by the level of INR control. Subgroup analyses based on the level of INR control (center-level and subject- level) suggest that the risk reduction in major bleeds seen with dabigatran 110 mg is driven to some extent by the subset of warfarin treated subjects achieving lower levels of INR control.

Assessments of bleeding should take into consideration the severity/reversibility of the bleeding event. Important major bleeding has been defined in different ways in clinical trials; the definitions/categories used in RE-LY are shown in the table below. Of note, the ISTH, ESTEEM, and ISCOAT definitions[15] of major bleed are very similar to that

15 ISTH =International Society on Thrombosis & Haemostasis; ESTEEM =Efficacy and Safety of the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Recent Myocardial Damage; ISCOAT =Italian Study of Complications of Anticoagulant Therapy

used in RE-LY. The ISTH and ISCOAT criteria have also been used in patients receiving long-term anticoagulation.

**Table 57. Various bleeding definitions used in RE-LY**

| Term | Definition |
|---|---|
| Adjudicated major bleed | Satisfying at least one: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood or packed cells; symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding) |
| Adjudicated life-threatening bleed (sub classification of major bleed) | An adjudicated major bleed meeting at least one of the following criteria: fatal; symptomatic intracranial bleed; reduction in hemoglobin of at least 5 grams per deciliter; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; required surgical intervention |
| RE-LY's GUSTO severe | An adjudicated ICH event; An adjudicated major bleed with at least one of the following criteria: associated with hypotension requiring use of intravenous inotropic agents; required surgical intervention to stop bleeding |
| Intracranial hemorrhage (ICH) | Includes adjudicated hemorrhagic stroke or adjudicated major bleed that was symptomatic intracranial |

Compared to TIMI major or GUSTO severe, bleed categorizations used in well known intravenous thrombolytic trials, major bleeds, as defined in RE-LY, are not as severe. TIMI major bleeding includes ICH, overt bleeding with a 5 g/dL decrease in hemoglobin and GUSTO severe includes ICH or bleeding that causes hemodynamic compromise and requires intervention. In contrast, major bleeds in RE-LY included relatively small reductions in hemoglobin/transfusion requirements and hence more readily reversible bleeding events. In terms of the severity of the event, RE-LY's life-threatening bleeds and "GUSTO severe" bleeds[16] are perhaps more similar to the definitions of major bleeds used in past thrombolytic trials. Notably, GUSTO severe bleeding in RE-LY did not necessarily include a fatal bleed.

With regard to GUSTO-severe bleeding, dabigatran 110 mg was associated with a 52% reduction (HR 0.48, 95% CI: 0.37, 0.64, p-value <0.0001) relative to warfarin and dabigatran 150 mg was associated with a 31% reduction (HR 0.69, 95% CI: 0.54, 0.88,

16 RE-LY's "GUSTO severe" definition differs slightly from that used in the GUSTO trials. In the GUSTO trials, GUSTO severe was defined as ICH or bleeding that caused hemodynamic compromise **AND** required intervention.

p-value 0.003) relative to warfarin. Compared to dabigatran 110 mg, dabigatran 150 mg was associated with a 42% greater risk of GUSTO-severe bleed (p=0.02). The reduction in ICH in comparison to warfarin was even greater. Dabigatran 110 mg was associated with a 70% reduction (HR 0.30, 95% CI: 0.19, 0.46, p-value <0.0001) in ICH relative to warfarin, and dabigatran 150 mg was associated with a 59% reduction (HR 0.41, 95% CI: 0.28, 0.60, p-value <0.0001) relative to warfarin. Thus, the findings in RE-LY support a relationship between dabigatran dose and major bleeding risk and suggest a favorable profile relative to warfarin.

**Overview of major bleeds in RE-LY**

The total number of adjudicated major bleeds is shown in the table below. While there were more adjudicated major bleeds in the warfarin arm, there were more subjects with multiple occurrences of major bleeds in the dabigatran arms.

**Table 58. Total adjudicated major bleeds**

| | D110 | % | D150 | % | W | % | Total |
|---|---|---|---|---|---|---|---|
| **Randomized** | **6015** | | **6076** | | **6022** | | |
| Subjects with major bleed | 342 | (5.7) | 399 | (6.6) | 421 | (7.0) | 1162 |
| Total major bleeds[1] | 406 | (6.7) | 489 | (8.0) | 483 | (8.0) | 1378 |
| Total subjects with occurrences | | | | | | | |
| 1 | 291 | (4.8) | 335 | (5.5) | 367 | (6.1) | |
| 2 | 38 | (0.6) | 44 | (0.7) | 49 | (0.8) | |
| ≥ 3 | 13 | (0.2) | 20 | (0.3) | 5 | (0.1) | |
| Total life threatening bleeds | 159 | (2.6) | 193 | (3.2) | 233 | (3.9) | |

[source: Adapted from sponsor's table 15.3.5.4:10_New and reviewer's analysis: filename major, sponsor dataset timev]

1. These numbers are more than those in Table 59 because this table includes adjudicated major bleeds identified from other sources: 6 from minor bleed CRF, 8 hemorrhagic strokes not reported on the major bleed CRF, and 5 post RTF not reported on major bleed CRF.

The table below describes characteristics of the adjudicated major bleed that are not described elsewhere in the review. Deaths associated with major bleeds appeared to be more common in the warfarin arm than in the dabigatran arms. Approximately 25% of major bleeds did not require hospitalization, suggesting that not all major bleeds were serious.

**Table 59. Characteristics of adjudicated major bleed not described elsewhere**

| Category | D110 | % | D150 | % | W | % |
|---|---|---|---|---|---|---|
| Total major bleed[1] | 397 | (100) | 486 | (100) | 476 | (100) |
| Hg Drop of 2 gm/dL | 266 | (67.0) | 330 | (67.9) | 282 | (59.2) |
| Died | 25 | (6.3) | 28 | (5.8) | 40 | (8.4) |
| Hospitalization | 286 | (72.0) | 368 | (75.7) | 364 | (76.5) |

[source: Reviewer's analysis: mj\tx\adj_plt122n, sponsor dataset plt122n,adjrand,popu]
1.These descriptions were available for 1359 adjudicated bleeds identified by major bleed CRF.

**Overall risk of bleeding**

Compared to warfarin, the overall relative risk of major bleeding was 20% less for dabigatran 110 mg, and no different for dabigatran 150 mg. Compared to dabigatran 110 mg, dabigatran 150 mg was associated with a 16% greater risk of major bleeding. The relative risk of more severe bleeds (e.g., GUSTO severe, ICH) also appeared to be greater in the warfarin arm than in the dabigatran arms.

**Table 60. Overall relative risk of serious bleeding**

| Type | D110 v. W HR (95%CI) | D150 v. W HR (95%CI) | D150 v. D110 HR (95%CI) |
|---|---|---|---|
| Adjudicated major bleeding | 0.80 (0.70, 0.93) p-value= 0.002 | 0.93 (0.81, 1.07) p-value= 0.31 | 1.16 (1.00, 1.34) p-value= 0.04 |
| Life threatening bleed | 0.67 (0.54, 0.82) | 0.80 (0.66, 0.98) | 1.21 (0.97, 1.50) |
| GUSTO severe | 0.48 (0.37, 0.64) | 0.69 (0.54, 0.88) | 1.42 (1.05, 1.91) |
| ICH | 0.30 (0.19, 0.46) | 0.41 (0.28, 0.60) | 1.39 (0.85, 2.28) |
| Adjudicated hemorrhagic strokes | 0.31 (0.17, 0.56) | 0.26 (0.14, 0.49) | 0.85 (0.39, 1.83) |
| Reported symptomatic intracranial bleeds | 0.29 (0.19, 0.44) | 0.47 (0.33, 0.67) | 1.61 (1.00, 2.61) |

[Source: Reviewer's analysis, filename: timev\HR, sponsor's data;adjrand] Cox proportional regression, data shown are Hazard ratio (95% confidence interval)

The absolute event rates using various definitions of major bleeding are shown in the table below. As a whole, these data support a relationship between dabigatran dose and bleeding risk.

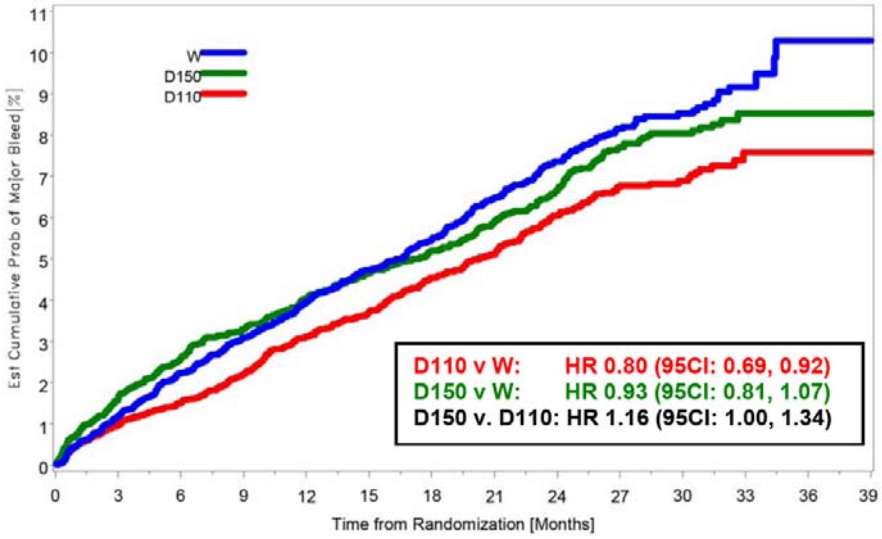
**Table 61. Overall absolute risk of major bleeding**

| | D110 (n=6015) | | D150 (n=6076) | | W (n=6022) | |
|---|---|---|---|---|---|---|
| **Type** | **# events** | **%/yr** | **# events** | **%/yr** | **# events** | **%/yr** |
| Major bleed | 342 | 2.87 | 399 | 3.32 | 421 | 3.57 |
| Life threatening bleed | 147 | 1.24 | 179 | 1.49 | 218 | 1.85 |
| GUSTO severe | 74 | 0.62 | 106 | 0.88 | 151 | 1.28 |
| ICH | 27 | 0.23 | 38 | 0.32 | 90 | 0.76[17] |

[Source: reviewer's analysis, file: eventrate, sponsor's data: timev, adjrand]
Study duration=date of study termination-date of randomization +1
Subject years=sum (study duration for all subjects)/365.25
Yearly event rate (%/yr)=# subjects with event/subject years*100; only first event counted

The time to first major bleed is shown below. Throughout the period of follow up, the rates of major bleeding in the dabigatran 110 mg arm appear to be lower than the rates seen in the other treatment arms.[18]

**Figure 12. Time to first major bleed**

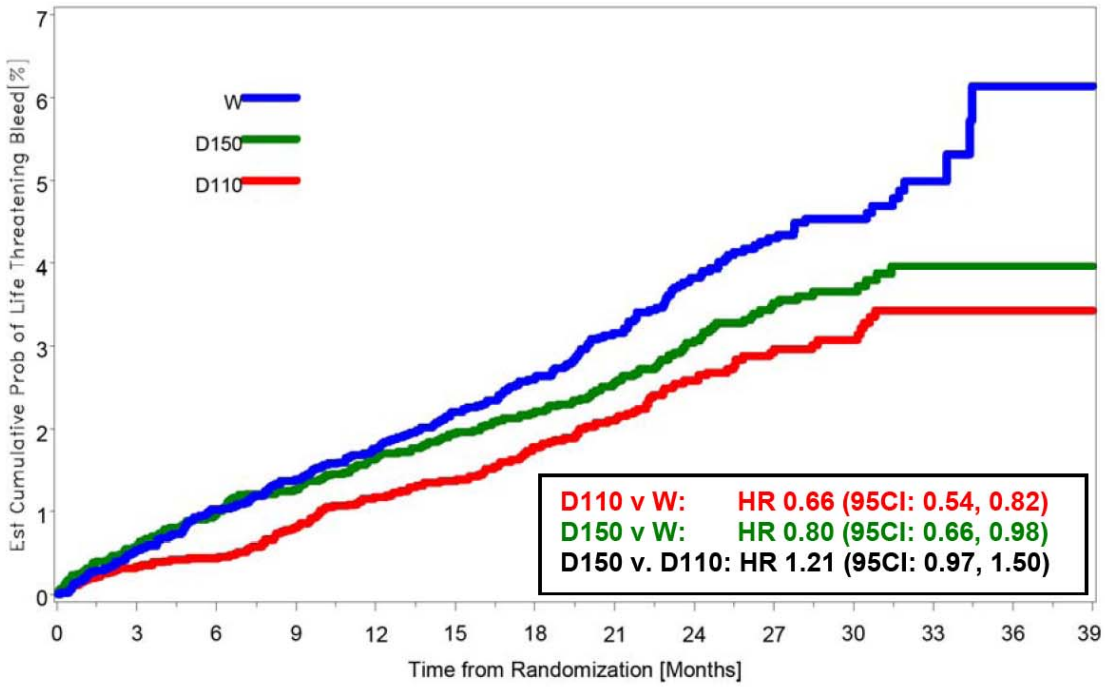



[Source: Reviewer's analysis: time mjbleed, HR mjbleed; KM analysis, sponsor data: adjrand2]

17. It is noted that the rate of ICH in the warfarin arm seems high when compared to ACTIVE-W (annual rate 0.4% from Dr. U clinical review), despite the use of, what appears to be, similar definitions of ICH in the two trials. It is unclear what to make of this.
18. While there was no difference in major bleeding between dabigatran 150 mg and warfarin, it is noted that in the beginning of the trial the risk of bleeding appears higher with dabigatran 150 mg as compared to warfarin. After approximately 12-16 months, the slope of the curve decreases and runs below warfarin. Although completely speculative, the timing of the change in slope may be related to the permanent discontinuation of dabigatran (see Figure 11).

For life threatening bleeds, the curve for dabigatran 110 mg starts to separate from the curve for warfarin after about 3 months; the curve for dabigatran 150 mg starts to separate from warfarin after about 1 year.

**Figure 13. Time to first life threatening bleed**

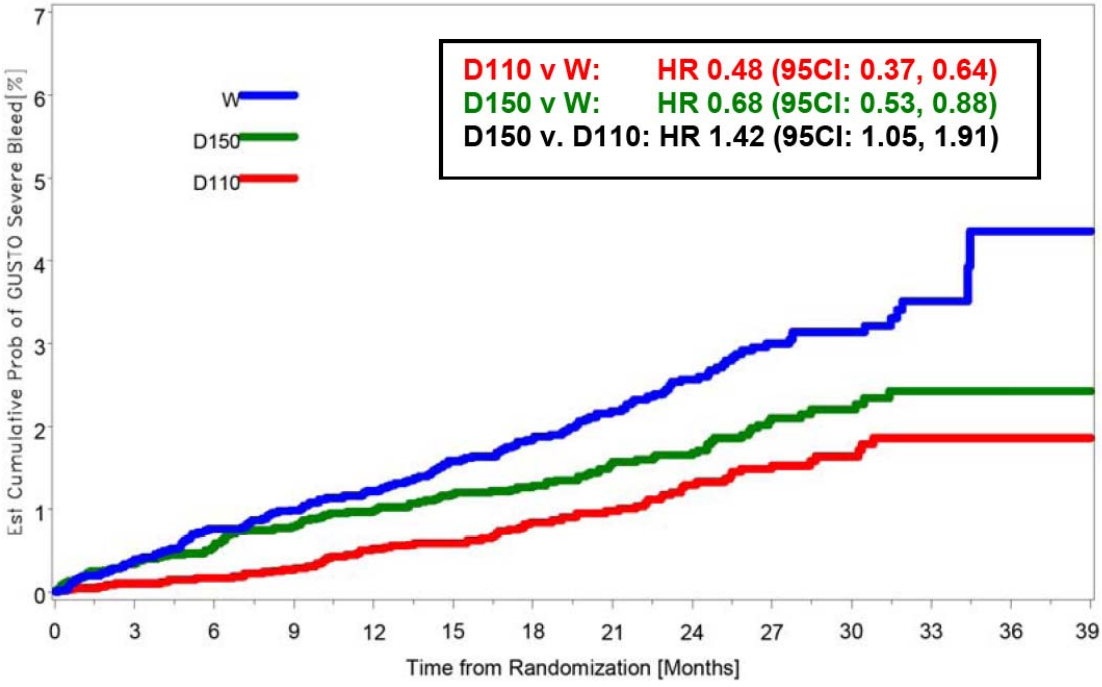



| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5861 | 5791 | 5705 | 5622 | 5383 | 4519 | 3663 | 3064 | 2315 | 1409 | 461 | 79 |
| D150 | 6076 | 5912 | 5816 | 5720 | 5642 | 5396 | 4570 | 3711 | 3128 | 2336 | 1427 | 471 | 86 |
| W | 6022 | 5857 | 5757 | 5657 | 5571 | 5253 | 4452 | 3541 | 2956 | 2235 | 1296 | 353 | 72 |

[Source: Reviewer's analysis, filename: time LT, HR mjbleed; Kaplan Meier analysis, sponsor data: adjrand2]

The next figure shows the time to first GUSTO severe bleed. The curves appear to separate earlier than for the other bleeding categories.

**Figure 14. Time to first GUSTO severe bleed**

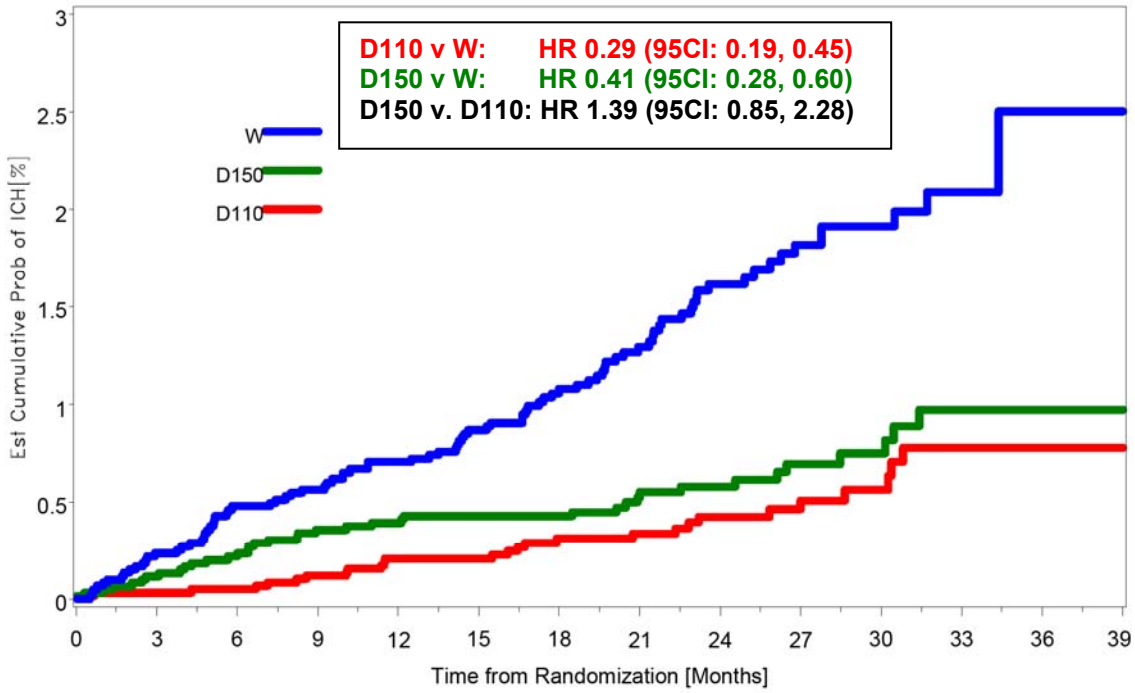



| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5872 | 5802 | 5729 | 5653 | 5418 | 4557 | 3697 | 3102 | 2344 | 1422 | 467 | 81 |
| D150 | 6076 | 5923 | 5836 | 5741 | 5672 | 5427 | 4603 | 3737 | 3162 | 2362 | 1442 | 477 | 88 |
| W | 6022 | 5864 | 5767 | 5674 | 5595 | 5278 | 4478 | 3571 | 2987 | 2255 | 1306 | 355 | 72 |

[Source: Reviewer's analysis, filename: time gustosev, HR mjbleed; Kaplan Meier analysis, sponsor data: adjrand2]

The next figure shows the time to first ICH.

**Figure 15. Time to first ICH**




| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5874 | 5806 | 5734 | 5665 | 5432 | 4575 | 3717 | 3123 | 2365 | 1437 | 476 | 81 |
| D150 | 6076 | 5931 | 5847 | 5756 | 5694 | 5454 | 4626 | 3761 | 3182 | 2385 | 1456 | 480 | 88 |
| W | 6022 | 5871 | 5779 | 5694 | 5617 | 5306 | 4501 | 3594 | 3007 | 2279 | 1322 | 359 | 73 |

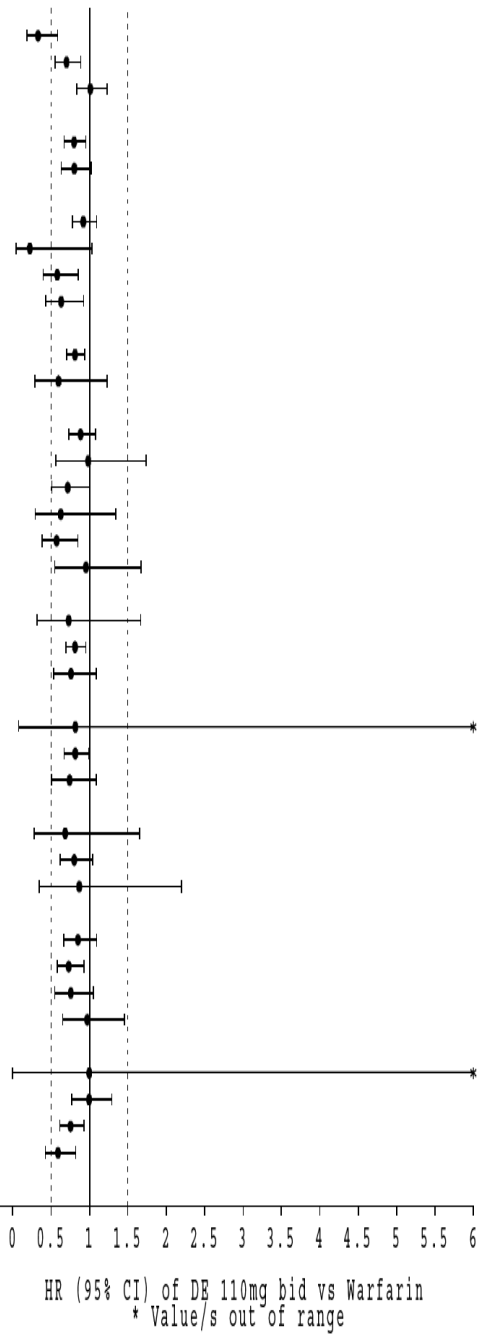
[Source: Reviewer's analysis, filename: time ICH, HR mjbleed; Kaplan Meier analysis, sponsor data: adjrand2]

**Subgroup analysis – baseline demographics**

As a whole, subgroup analyses suggested no difference in major bleeding by gender, race, region, or weight compared to warfarin. In the Chinese, both the 110 and 150 mg doses of dabigatran were associated with a lower risk of major bleeding (relative to warfarin. Very few blacks were studied, limiting conclusions in this population. The effects of age and impaired renal function are discussed in sections 7.5.3 and 7.5.4, respectively.

**Figure 16. Dabigatran 110 mg vs. warfarin subgroup analysis**

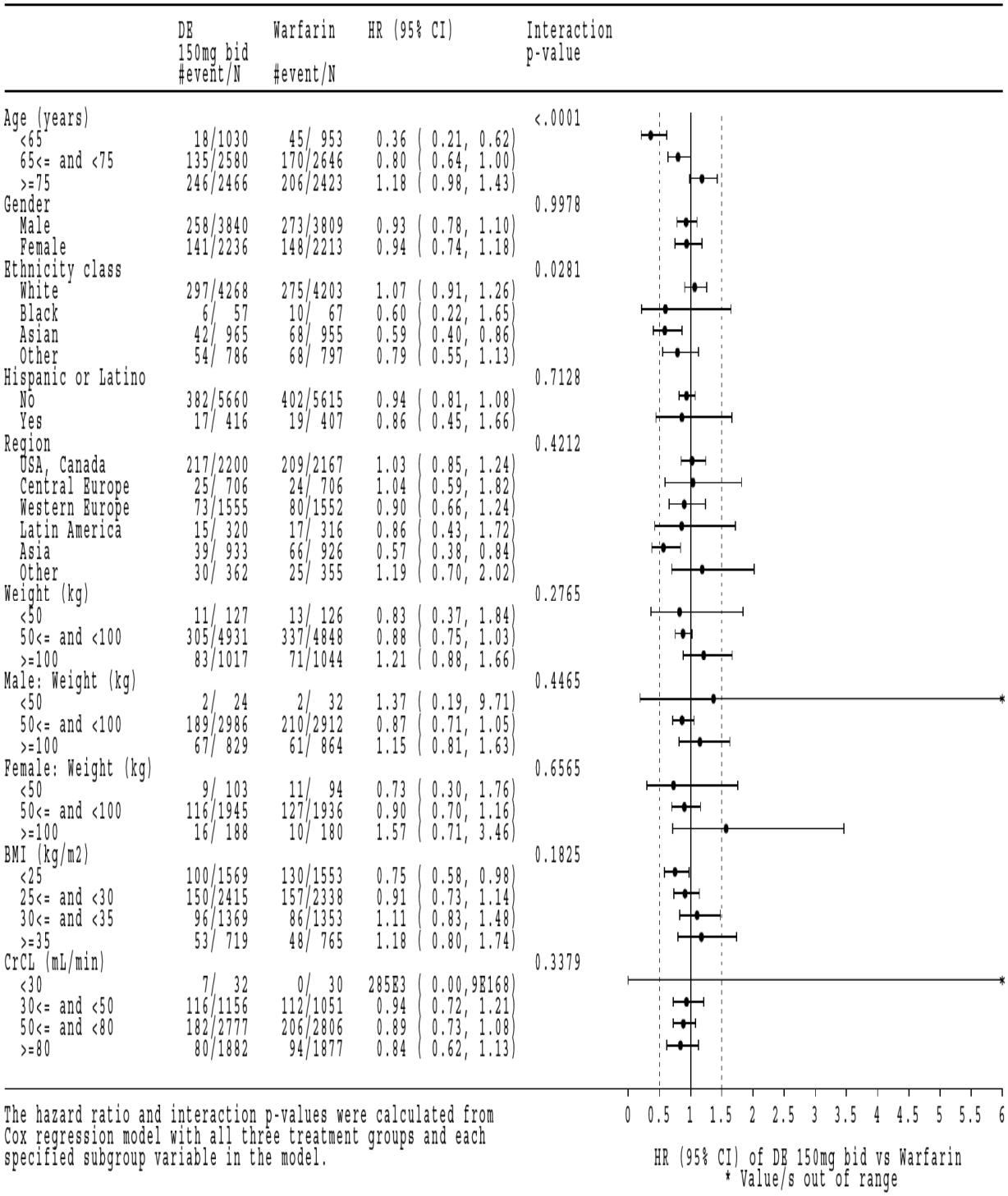
| | DE 110mg bid #event/N | Warfarin #event/N | HR (95% CI) | Interaction p-value |
|---|---|---|---|---|
| Age (years) | | | | <.0001 |
| <65 | 16/ 998 | 45/ 953 | 0.33 ( 0.19, 0.59) | |
| 65<= and <75 | 122/2668 | 170/2646 | 0.70 ( 0.56, 0.89) | |
| >=75 | 204/2349 | 206/2423 | 1.01 ( 0.83, 1.23) | |
| Gender | | | | 0.9978 |
| Male | 225/3865 | 273/3809 | 0.80 ( 0.67, 0.96) | |
| Female | 117/2149 | 148/2213 | 0.80 ( 0.63, 1.03) | |
| Ethnicity class | | | | 0.0281 |
| White | 255/4208 | 275/4203 | 0.92 ( 0.78, 1.09) | |
| Black | 2/ 52 | 10/ 67 | 0.23 ( 0.05, 1.03) | |
| Asian | 41/ 955 | 68/ 955 | 0.58 ( 0.39, 0.86) | |
| Other | 44/ 799 | 68/ 797 | 0.63 ( 0.43, 0.92) | |
| Hispanic or Latino | | | | 0.7128 |
| No | 330/5593 | 402/5615 | 0.81 ( 0.70, 0.94) | |
| Yes | 12/ 421 | 19/ 407 | 0.60 ( 0.29, 1.23) | |
| Region | | | | 0.4212 |
| USA, Canada | 186/2166 | 209/2167 | 0.89 ( 0.73, 1.08) | |
| Central Europe | 24/ 707 | 24/ 706 | 0.99 ( 0.56, 1.74) | |
| Western Europe | 58/1544 | 80/1552 | 0.72 ( 0.51, 1.01) | |
| Latin America | 11/ 320 | 17/ 316 | 0.63 ( 0.29, 1.34) | |
| Asia | 39/ 923 | 66/ 926 | 0.57 ( 0.39, 0.85) | |
| Other | 24/ 355 | 25/ 355 | 0.96 ( 0.55, 1.67) | |
| Weight (kg) | | | | 0.2765 |
| <50 | 10/ 123 | 13/ 126 | 0.73 ( 0.32, 1.67) | |
| 50<= and <100 | 278/4850 | 337/4848 | 0.81 ( 0.69, 0.95) | |
| >=100 | 54/1038 | 71/1044 | 0.76 ( 0.53, 1.09) | |
| Male: Weight (kg) | | | | 0.4465 |
| <50 | 1/ 22 | 2/ 32 | 0.82 ( 0.07, 9.02) | |
| 50<= and <100 | 178/2971 | 210/2912 | 0.82 ( 0.67, 1.00) | |
| >=100 | 46/ 871 | 61/ 864 | 0.74 ( 0.51, 1.09) | |
| Female: Weight (kg) | | | | 0.6565 |
| <50 | 9/ 101 | 11/ 94 | 0.69 ( 0.28, 1.65) | |
| 50<= and <100 | 100/1879 | 127/1936 | 0.80 ( 0.62, 1.05) | |
| >=100 | 8/ 167 | 10/ 180 | 0.87 ( 0.34, 2.20) | |
| BMI (kg/m2) | | | | 0.1825 |
| <25 | 114/1575 | 130/1553 | 0.85 ( 0.66, 1.09) | |
| 25<= and <30 | 117/2358 | 157/2338 | 0.73 ( 0.58, 0.93) | |
| 30<= and <35 | 65/1316 | 86/1353 | 0.76 ( 0.55, 1.05) | |
| >=35 | 46/ 757 | 48/ 765 | 0.97 ( 0.65, 1.46) | |
| CrCL (mL/min) | | | | 0.3379 |
| <30 | 0/ 15 | 0/ 30 | 1.00 ( 0.00,2E280) | |
| 30<= and <50 | 120/1136 | 112/1051 | 1.00 ( 0.77, 1.29) | |
| 50<= and <80 | 154/2714 | 206/2806 | 0.76 ( 0.61, 0.93) | |
| >=80 | 57/1899 | 94/1877 | 0.59 ( 0.43, 0.82) | |




The hazard ratio and interaction p-values were calculated from Cox regression model with all three treatment groups and each specified subgroup variable in the model.

[Source: Sponsor Figure 15.3.2.2.2:1, 4.19.10 resubmission]

**Figure 17. Dabgiatran 150 mg vs. warfarin subgroup analysis**




[Source: Sponsor Figure 15.3.2.2.2:2, 4.19.10 resubmission]

**VKA use and INR control**

Prior VKA use (as defined by the sponsor) did not clearly affect the relationship between risk of bleeding on dabigatran relative to warfarin.

**Table 62. Relative and absolute risk by vitamin K antagonist use**

| Type | D110 v. W HR (95%CI) | D150 v. W HR (95%CI) | D110 %/yr | D150 %/yr | W %/yr |
|---|---|---|---|---|---|
| Adjudicated major bleeding | 0.80 (0.70, 0.93) | 0.93 (0.81, 1.07) | 2.87 | 3.32 | 3.57 |
| Naïve | 0.87 (0.71, 1.07) | 0.94 (0.77, 1.14) | 3.11 | 3.33 | 3.57 |
| Experienced | 0.74 (0.60, 0.91) | 0.93 (0.76,1.12) | 2.66 | 3.30 | 3.57 |
| Life threatening bleed | 0.67 (0.54, 0.81) | 0.80 (0.66, 0.98) | 1.24 | 1.49 | 1.85 |
| Naïve | 0.75 (0.55, 1.01) | 0.84 (0.62, 1.12) | 1.27 | 1.42 | 1.71 |
| Experienced | 0.60 (0.45, 0.80) | 0.78 (0.60, 1.02) | 1.20 | 1.55 | 1.98 |
| GUSTO severe | 0.48 (0.37, 0.64) | 0.69 (0.54, 0.88) | 0.62 | 0.88 | 1.28 |
| Naïve | 0.47 (0.31, 0.72) | 0.77 (0.53, 1.11) | 0.55 | 0.89 | 1.17 |
| Experienced | 0.49 (0.34, 0.71) | 0.62 (0.44, 0.88) | 0.69 | 0.87 | 1.39 |
| ICH | 0.30 (0.19, 0.46) | 0.41 (0.28, 0.60) | 0.23 | 0.32 | 0.76 |
| Naïve | 0.27 (0.14, 0.51) | 0.43 (0.25, 0.75) | 0.19 | 0.32 | 0.73 |
| Experienced | 0.32 (0.18, 0.57) | 0.40 (0.24, 0.67) | 0.26 | 0.32 | 0.79 |

[source:reviewer's analysis: sub\vka, sponsor's file: adjrand, basco]

*Relative risk: An analysis focusing on the subset of subjects known to be well controlled on warfarin at baseline is perhaps of greater interest. To this reviewer's knowledge, such information was not collected in the trial.*

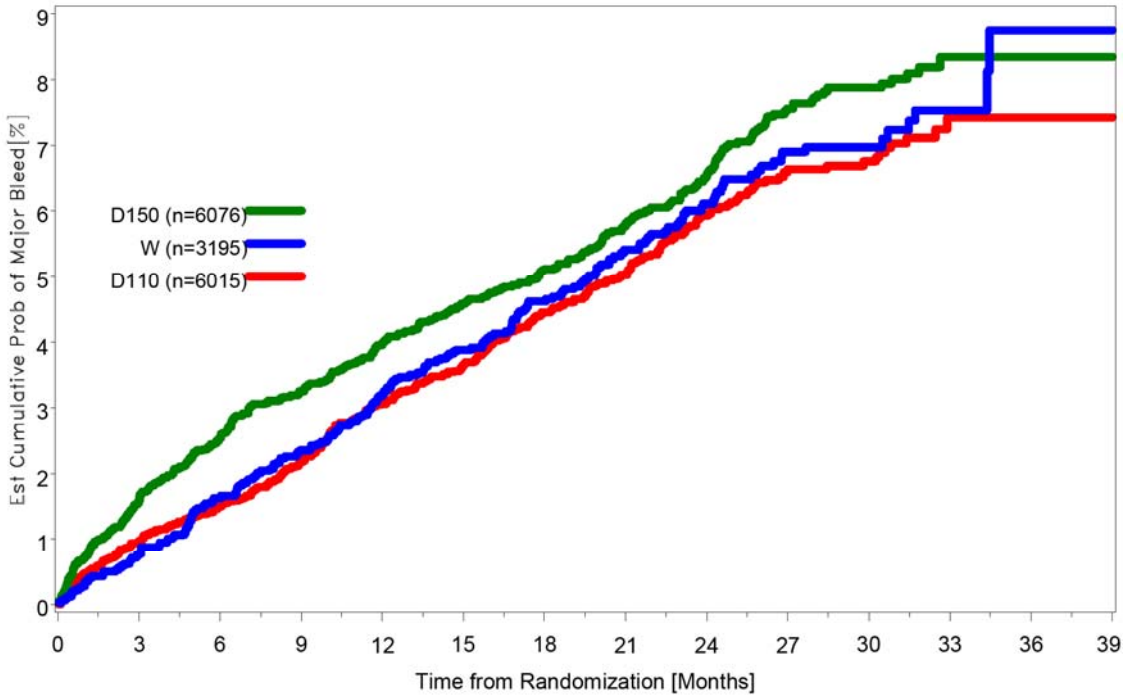
The risk reduction in major bleeds and life threatening bleeds (relative to warfarin) was influenced by the level of INR control; however such a relationship was not seen for GUSTO severe or ICH bleeding. Subgroup analyses based on the level of INR control (center-level and subject- level) suggest that the risk reduction in major bleeds seen with dabigatran 110 mg is driven to some extent by the subset of warfarin treated subjects achieving lower levels of INR control (see table below and section 6.1.10.1 ).

**Table 63. Risk of bleeding compared to warfarin subjects with INR in range (2-3) ≥ 65% of the time**

| Type | D110 v. W HR (95%CI) | D150 v. W HR (95%CI) |
|---|---|---|
| Adjudicated major bleeding | 0.95 (0.80, 1.13) | 1.10 (0.93, 1.31) |
| Life threatening bleed | 0.78 (0.61, 1.00) | 0.94 (0.74, 1.20) |
| GUSTO severe | 0.46 (0.34, 0.62) | 0.65 (0.49, 0.86) |
| ICH | 0.32 (0.21, 0.52) | 0.45 (0.29, 0.70) |

N=15,286 (3,195 on warfarin)[source: reviewer's analysis: inr\inr65, sponsor's data: adjrand, basco]

**Figure 18. Time to first major bleed, warfarin subjects with INR 2-3 ≥ 65% of the time**




| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D110 | 6015 | 5904 | 5826 | 5739 | 5624 | 5379 | 4510 | 3674 | 3039 | 2304 | 1401 | 469 | 79 |
| D150 | 6076 | 5936 | 5832 | 5731 | 5633 | 5387 | 4558 | 3701 | 3101 | 2309 | 1407 | 464 | 82 |
| W | 3195 | 3165 | 3126 | 3091 | 3050 | 2891 | 2477 | 1997 | 1682 | 1280 | 777 | 223 | 50 |

[source: reviewer's analysis: time mjb INR, sponsor data: adjrand, basco]

**Concomitant medications**

The yearly event rate of major bleeds based on baseline concomitant medication use and use during the study was higher for subjects on aspirin, clopidogrel or aspirin plus clopidogrel across all treatment arms. This relationship didn't appear to be affected by

whether or not a subject was treated with dabigatran or warfarin. Subjects that experienced significant bleeding were likely taken off of concomitant medications that also cause bleeding, which may explain the lower rates of bleeding in subjects reporting 100% use of these medications (relative to the other groupings of use).

**Table 64. Yearly event rate of major bleeds by medication use during the study**

| | DE 110mg bid | | | | DE 150mg bid | | | | Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % of time taking concomitant medication | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) |
| Antithrombotic therapy | | | | | | | | | | | | |
| ASA | | | | | | | | | | | | |
| 0% (never) | 3615 | 7219 | 153 | 2.12 | 3687 | 7357 | 178 | 2.42 | 3616 | 7162 | 187 | 2.61 |
| Used at least one time | 2400 | 4681 | 189 | 4.04 | 2389 | 4676 | 221 | 4.73 | 2406 | 4632 | 234 | 5.05 |
| 0%< and <=50% | 854 | 1680 | 76 | 4.52 | 907 | 1788 | 105 | 5.87 | 918 | 1762 | 92 | 5.22 |
| 50% <and < 100% | 272 | 541 | 41 | 7.58 | 292 | 588 | 45 | 7.66 | 241 | 494 | 52 | 10.53 |
| 100% (always) | 1274 | 2460 | 72 | 2.93 | 1190 | 2300 | 71 | 3.09 | 1247 | 2376 | 90 | 3.79 |
| Clopidogrel | | | | | | | | | | | | |
| 0% (never) | 5572 | 11044 | 295 | 2.67 | 5624 | 11109 | 344 | 3.10 | 5581 | 10930 | 363 | 3.32 |
| Used at least one time | 443 | 855 | 47 | 5.50 | 452 | 924 | 55 | 5.95 | 441 | 864 | 58 | 6.71 |
| 0%< and <=50% | 218 | 428 | 26 | 6.08 | 248 | 509 | 35 | 6.88 | 225 | 462 | 29 | 6.28 |
| 50% <and < 100% | 82 | 167 | 14 | 8.37 | 71 | 160 | 13 | 8.14 | 64 | 129 | 15 | 11.59 |
| 100% (always) | 143 | 260 | 7 | 2.69 | 133 | 256 | 7 | 2.74 | 152 | 273 | 14 | 5.13 |
| Dipyridamole | | | | | | | | | | | | |
| 0% (never) | 5987 | 11841 | 339 | 2.86 | 6049 | 11981 | 397 | 3.31 | 5998 | 11743 | 420 | 3.58 |
| Used at least one time | 28 | 58 | 3 | 5.18 | 27 | 53 | 2 | 3.81 | 24 | 51 | 1 | 1.96 |
| 0%< and <=50% | 12 | 25 | 2 | 8.03 | 7 | 14 | 0 | 0.00 | 11 | 23 | 0 | 0.00 |
| 50% <and < 100% | 5 | 11 | 1 | 8.93 | 5 | 9 | 1 | 10.70 | 0 | 0 | 0 | 0.00 |
| 100% (always) | 11 | 22 | 0 | 0.00 | 15 | 30 | 1 | 3.37 | 13 | 28 | 1 | 3.63 |

[sponsor table 15.3.2.2.3:3]

Dabigatran etexilate (but not dabigatran) is a substrate of p-gp, so a relationship between p-gp inhibitors and bleeding risk was also explored. No consistent pattern is seen with regard to the effect of these medications on the relative risk of bleeding on dabigatran (compared to warfarin). While the risk of bleeding was sometimes higher with concomitant p-gp inhibitors amiodarone, diltiazem, and verapamil, it also seemed higher in the warfarin arm. Since warfarin does not have an interaction with p-gp, it is difficult to draw conclusions from these analyses. There were too few subjects taking ketoconazole and p-gp inducers to make any definitive conclusions.

**Table 65. Yearly event rate of major bleeds by concomitant p-gp inhibitor during treatment period safety set**

| | DE 110mg bid | | | | DE 150mg bid | | | | Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % of time taking concomitant medication | # of subj | Subject-years | Subjects with event | Yearly event rate (%) | # of subj | Subject-years | Subjects with event | Yearly event rate (%) | # of subj | Subject-years | Subjects with event | Yearly event rate (%) |
| P-gp inhibitor | | | | | | | | | | | | |
| Amiodarone | | | | | | | | | | | | |
| 0% (never) | 5139 | 8855 | 241 | 2.72 | 5191 | 8792 | 295 | 3.36 | 5097 | 9118 | 321 | 3.52 |
| Used at least once | 844 | 1387 | 54 | 3.89 | 868 | 1469 | 55 | 3.74 | 901 | 1542 | 57 | 3.70 |
| 0%< and <=50% | 209 | 379 | 19 | 5.01 | 200 | 360 | 21 | 5.84 | 209 | 387 | 19 | 4.91 |
| 50% <and < 100% | 311 | 546 | 26 | 4.76 | 328 | 606 | 24 | 3.96 | 377 | 680 | 28 | 4.12 |
| 100% (always) | 324 | 462 | 9 | 1.95 | 340 | 503 | 10 | 1.99 | 315 | 475 | 10 | 2.11 |
| Diltiazem | | | | | | | | | | | | |
| 0% (never) | 5310 | 9028 | 240 | 2.66 | 5384 | 9032 | 302 | 3.34 | 5298 | 9350 | 323 | 3.45 |
| Used at least once | 673 | 1214 | 55 | 4.53 | 675 | 1229 | 48 | 3.91 | 700 | 1309 | 55 | 4.20 |
| 0%< and <=50% | 147 | 273 | 12 | 4.40 | 168 | 329 | 9 | 2.74 | 168 | 326 | 18 | 5.52 |
| 50% <and < 100% | 260 | 513 | 31 | 6.04 | 268 | 526 | 27 | 5.14 | 287 | 571 | 29 | 5.08 |
| 100% (always) | 266 | 428 | 12 | 2.80 | 239 | 374 | 12 | 3.20 | 245 | 412 | 8 | 1.94 |
| Verapamil | | | | | | | | | | | | |
| 0% (never) | 5574 | 9530 | 273 | 2.86 | 5650 | 9521 | 321 | 3.37 | 5553 | 9818 | 350 | 3.56 |
| Used at least once | 409 | 712 | 22 | 3.09 | 409 | 740 | 29 | 3.92 | 445 | 841 | 28 | 3.33 |
| 0%< and <=50% | 83 | 158 | 7 | 4.44 | 95 | 178 | 6 | 3.38 | 103 | 200 | 7 | 3.50 |
| 50% <and < 100% | 138 | 264 | 9 | 3.41 | 142 | 276 | 14 | 5.08 | 164 | 330 | 13 | 3.94 |
| 100% (always) | 188 | 291 | 6 | 2.07 | 172 | 286 | 9 | 3.14 | 178 | 311 | 8 | 2.57 |

[sponsor's table 15.3.2.2.3:6]

**Location of symptomatic major bleeds**

The location of symptomatic adjudicated major bleeds is shown in the table below. Most of the symptomatic bleeding was gastrointestinal, followed by intracranial, and then intraocular bleeding. The risk of GI bleeding appears to be greater in the dabigatran arms compared to warfarin (discussed further below).

**Table 66. Location of adjudicated major bleeds[19]**

| Location | D110 | % | D150 | % | W | % |
|---|---|---|---|---|---|---|
| Total adjudicated major bleeding | 397 | (100) | 486 | (100) | 476 | (100) |
| Symptomatic bleeding | 225 | (56.7) | 285 | (58.6) | 237 | (49.8) |
| Gastrointestinal | 155 | (39.0) | 219 | (45.1) | 141 | (29.6) |
| Symptomatic intracranial | 27 | (6.8) | 33 | (6.8) | 82 | (17.2) |
| Intraocular | 16 | (4.0) | 11 | (2.3) | 16 | (3.4) |
| Retroperitoneal | 2 | (0.5) | 9 | (1.9) | 12 | (2.5) |
| Intramuscular | 8 | (2.0) | 8 | (1.6) | 19 | (4.0) |
| Genito-urinary | 16 | (4.0) | 7 | (1.4) | 10 | (2.1) |
| ENT | 4 | (1.0) | 7 | (1.4) | 7 | (1.5) |
| Surgical | 8 | (2.0) | 6 | (1.2) | 13 | (2.7) |
| Intra-abdominal | 3 | (0.8) | 5 | (1.0) | 2 | (0.4) |
| Intra-thoracic | 8 | (2.0) | 4 | (0.8) | 7 | (1.5) |
| Intra-articular | 5 | (1.3) | 4 | (0.8) | 7 | (1.5) |
| Pericardial | 2 | (0.5) | 3 | (0.6) | 3 | (0.6) |
| Other area | 1 | (0.3) | 2 | (0.4) | 7 | (1.5) |
| Source unidentified | 1 | (0.3) | 1 | (0.2) | . | . |
| Intraspinal | . | . | . | . | 1 | (0.2) |

[source: Reviewer's analysis: mj\tx\adj_plt122n, sponsor dataset plt122n,adjrand,popu] This description was available for 1359 adjudicated bleeds. Includes those subjects with an adjudicated major bleed for which CRF 122 or CRF 97 was completed.

**GI Bleeds**

There was a greater risk of a GI bleed with dabigatran 150 mg compared to warfarin (see table below). This effect persisted over time and was dose related (see figure). Relative to warfarin, the risk of a major GI bleed on dabigatran increased with age, with the greatest relative risk seen in subjects≥ 75 years treated with dabigatran 150 mg: HR 1.79 (95%CI: 1.32, 2.42). Across all treatment arms, subjects on aspirin, clopidogrel, or aspirin+clopidogrel at baseline had a greater absolute risk of a major GI bleed compared to subjects not on these medications at baseline (sponsor table 15.3.2.2.8:13).

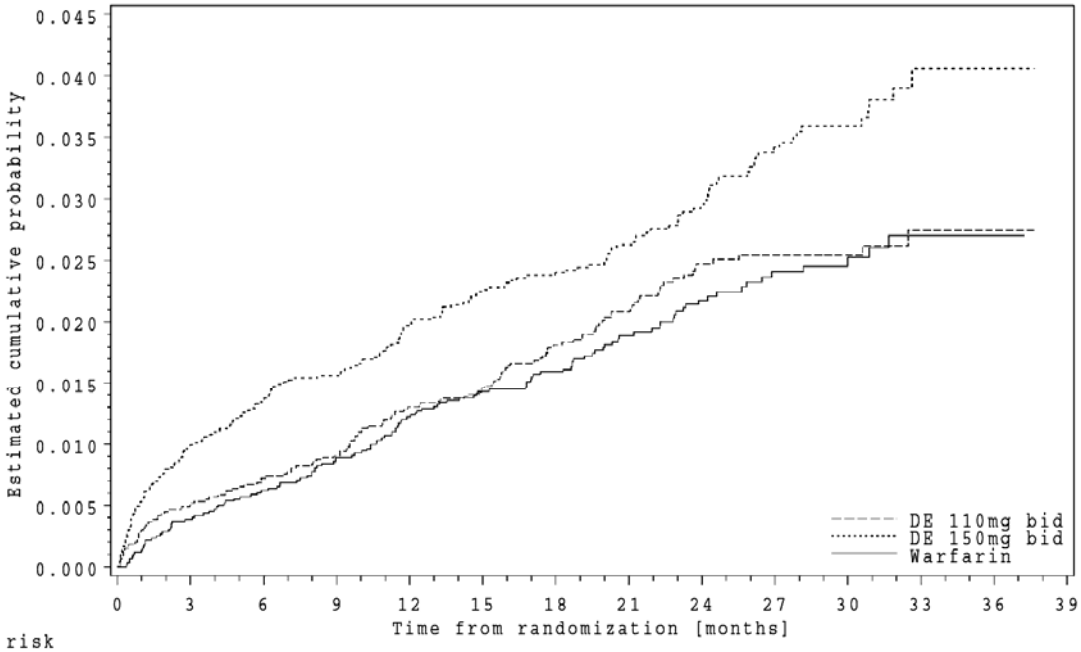
19 *Under the category, "Symptomatic bleeding in a critical area or organ", there was box left for "Other". PHRI recoded the "other" to an organ, if it could be, except for 15 of the major bleeds. These 15 were identified during the QC roadmap or during the close out period. For the purposes of this table, the reviewer categorized the 15 "Other"(if the event could be categorized), using a similar algorithm as that used by PHRI. The following "Other" were not categorized: Cancer of prostate, penile trauma, SAE anemia cancer treated with chemotherapy.*

**Table 67. Risk of serious and any GI bleed**

| Type | D110 v. W HR (95%CI) | D150 v. W HR (95%CI) | D150 v. D110 HR (95%CI) | D110 %/yr | D150 %/yr | W %/yr |
|---|---|---|---|---|---|---|
| Adjudicated major bleeding, GI | 1.07 (0.84, 1.36) | 1.47 (1.17, 1.85) | 1.38 (1.10, 1.72) | 1.14 | 1.57 | 1.07 |
| Life threatening, GI | 1.17 (0.82, 1.67) | 1.62 (1.17, 2.26) | 1.39 (1.02, 1.90) | 0.57 | 0.79 | 0.49 |
| Any GI bleed | 1.35 (1.19, 1.53) | 1.52 (1.35, 1.72) | 1.13 (1.01, 1.26) | 5.41 | 6.13 | 4.02 |

[source: reviewer's analysis: hr\phreg_GI, sponsor dataset: timev]

**Figure 19. Time to first major GI bleed**




Subjects at risk

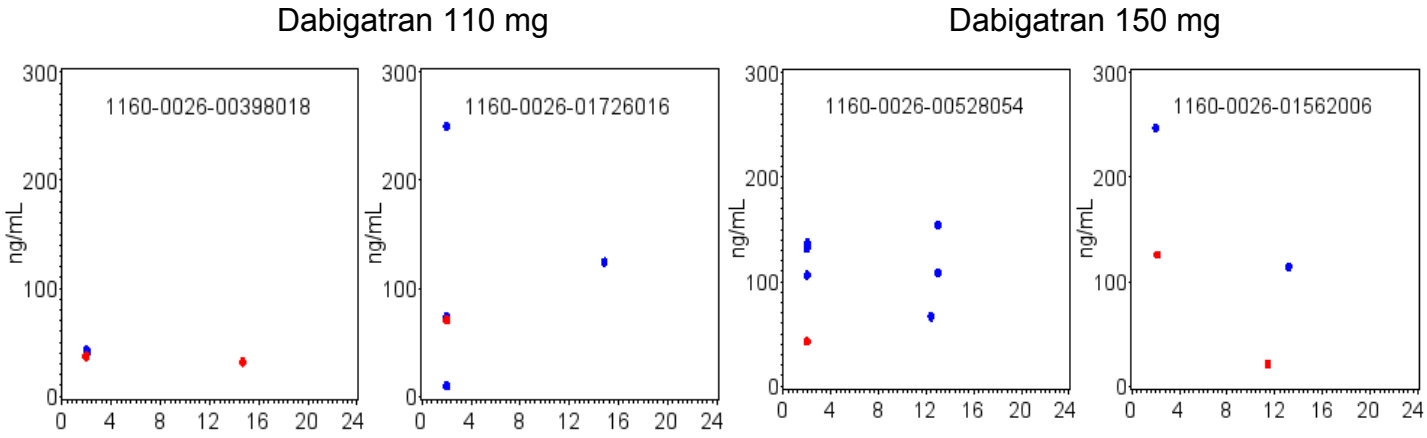
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DE 110mg bid | 6015 | 5925 | 5863 | 5799 | 5710 | 5485 | 4615 | 3778 | 3133 | 2393 | 1457 | 496 | 86 |
| DE 150mg bid | 6076 | 5971 | 5894 | 5816 | 5732 | 5505 | 4663 | 3813 | 3204 | 2400 | 1461 | 487 | 89 |
| Warfarin | 6022 | 5938 | 5876 | 5790 | 5718 | 5443 | 4624 | 3709 | 3109 | 2353 | 1372 | 391 | 78 |

Figure 15.3.2.2.8: 1 Kaplan-Meier estimates of time to first gastrointestinal major bleeds randomized set

**Dabigatran plasma concentrations**

Four subjects were identified who had dabigatran concentration data at the time of an adjudicated major bleed who also had concentration data while not bleeding. Although the number of subjects is very small, it raises questions about the utility of using plasma concentrations to monitor individual subjects/adjust dose based on dabigatran concentrations.

**Figure 20. Dabigatran concentrations in four subjects during a major bleed (red) and not during a major bleed (blue)**




The x-axis is time in hours from last dose and the y-axis is the dabigatran plasma concentration in ng/mL. [Source: Reviewer's analysis: mj\conc\conc_2; sponsor datasets: timev, pk4p (5.3.10)]

### *7.3.2.2. Summary of non-bleeding SAEs*

The total number of reported SAEs are shown by treatment arm in the table below, along with the reason given for reporting the event as "serious". The number of events reported as well as the reason given appears similar across the treatment arms.

**Table 68. Reason given for reporting event as SAE**

| Category | D110 N=5983 | % | D150 n=6059 | % | W n=5998 | % |
|---|---|---|---|---|---|---|
| SAE | 1263 | (21.2) | 1290 | (21.3) | 1357 | (22.6) |
| Fatal | 107 | (1.8) | 100 | (1.7) | 122 | (2.0) |
| Immediately life threatening | 50 | (0.8) | 46 | (0.8) | 64 | (1.1) |
| Disability/incapacitated | 575 | (9.6) | 532 | (8.8) | 592 | (9.9) |
| Required hospitalization | 1073 | (17.9) | 1090 | (18.0) | 1178 | (19.6) |
| Prolonged hospitalization | 95 | (1.6) | 71 | (1.2) | 89 | (1.5) |
| Congenital anomaly | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Other | 1138 | (19.0) | 1243 | (20.5) | 939 | (15.7) |

[Source: Adapted from sponsor's table 15.3.2.6:1, sponsor resubmission 4.19.10. Subjects may be counted in more than one seriousness category]

There were no notable differences between treatment arms for any of the system organ classes (SOCs). The following table shows SAEs for selected SOC and associated SAEs of particular interest (i.e., cardiac, gastrointestinal). The SAE data do not markedly alter our understanding of the safety profile.

**Table 69. SAE by system organ class (SOC)**

| SAE | D110 N=5983 | % | D150 n=6059 | % | W n=5998 | % |
|---|---|---|---|---|---|---|
| SAE | 1263 | (21.2) | 1290 | (21.3) | 1357 | (22.6) |
| Cardiac disorders | 310 | (5.2) | 291 | (4.8) | 321 | (5.4) |
| Angina pectoris | 29 | (0.5) | 30 | (0.5) | 22 | (0.4) |
| Unstable angina | 7 | (0.1) | 13 | (0.2) | 5 | (0.1) |
| Gastrointestinal disorders | 212 | (3.5) | 241 | (4.0) | 214 | (3.6) |
| Abdominal pain | 11 | (0.2) | 8 | (0.1) | 17 | (0.3) |
| Dyspepsia | 6 | (0.1) | 1 | (0.0) | 0 | (0.0) |
| Pancreatitis (includes chronic) | 1 | (0.0) | 5 | (0.1) | 8 | (0.1) |
| Pancreatitis acute | 3 | (0.1) | 1 | (0.0) | 0 | (0.0) |
| Blood and lymphatic system disorders | 68 | (1.1) | 69 | (1.1) | 71 | (1.2) |
| Anemia | 34 | (0.6) | 47 | (0.8) | 33 | (0.6) |
| Renal and urinary disorders | 104 | (1.7) | 94 | (1.6) | 113 | (1.9) |
| Renal failure acute* | 62 | (1.0) | 58 | (1.0) | 64 | (1.1) |
| Renal impairment | 3 | (0.1) | 5 | (0.1) | 2 | (0.0) |

[Source: Adapted from sponsor's table 15.3.2.6:2, sponsor resubmission 4.19.10. Subjects may be counted in more than one category] *includes acute, failure, renal tubular necrosis, azotemia, prerenal failure

### 7.3.3 Dropouts and/or Discontinuations

Adverse events leading to treatment discontinuation are shown in the table below. GI disorders were the most common adverse events leading to drug discontinuation in the dabigatran treatment arm. Other reasons for discontinuation of study medication are described in section 6.1.10.

**Table 70. AE leading to treatment discontinuations**

| | D110 N=5983 | % | D150 n=6059 | % | W n=5998 | % |
|---|---|---|---|---|---|---|
| Total subjects with AE leading to med d/c | 1138 | (19.0) | 1243 | (20.5) | 939 | (15.7) |
| Gastrointestinal disorders | 387 | (6.5) | 422 | (7.0) | 232 | (3.9) |
| Dyspepsia | 57 | (1.0) | 57 | (0.9) | 2 | (0.0) |
| GI hemorrhage | 39 | (0.7) | 55 | (0.9) | 37 | (0.6) |
| Cardiac disorders | 144 | (2.4) | 140 | (2.3) | 120 | (2.0) |
| Nervous system disorders | 138 | (2.3) | 129 | (2.1) | 96 | (1.6) |
| Renal and urinary disorders | 129 | (2.2) | 119 | (2.0) | 85 | (1.4) |
| Renal failure acute* | 63 | (1.1) | 58 | (1.0) | 45 | (0.8) |

[source: Adapted from sponsor table 15.3.2.6:4, resubmission] *includes acute, failure, renal tubular necrosis, azotemia, prerenal failure

### 7.3.4 Significant Adverse Events

As noted under efficacy, there was a numerical imbalance in the number of myocardial infarctions that favored subjects randomized to warfarin. This finding was addressed in an addendum dated September 2, 2010 (appended to this review).

### 7.3.5 Drug Induced Liver Injury

**Overview of findings and conclusions**

Ximelagatran, an oral direct thrombin inhibitor, was associated with hepatotoxicity[20], raising concern for drug induced liver injury with dabigatran. To address this issue, the reviewer's comprehensive review included analyses of liver-related laboratory data and adverse event data, a review of cases of interest from the RE-LY trial, as well as an assessment of potential cases of DILI in the postmarketing setting. Drs. Senior and Seeff, in the Office of Surveillance and Epidemiology (OSE), reviewed the cases of interest and applied a scoring scale that assesses the severity (SEV) of liver injury and likelihood (LIK) of DILI,.[21]

Review of the laboratory data revealed 55 cases of interest in RE-LY: 16 occurring in subjects randomized to dabigatran 110 mg, 16 in subjects randomized to dabigatran 150 mg, and 23 in subjects randomized to warfarin. Among these cases, there were no

20. There were 14 cases of concern on ximelagatran (n=1960) in SPORTIF V; 1 very likely and 5 probable

21. This scoring system has been used in the past at FDA. It differs slightly from the Drug Induced Liver Injury Network (DILIN) scoring system and considerably from the NIH/NCI/CTEP/CTC (common toxicity criteria) manual.

definite or very likely DILI cases. One probable cause subject (51-75% likelihood, more likely than all other causes combined, only one other cause possible) was identified in the dabigatran 110 mg arm. There was not a greater frequency of more serious liver injury from dabigatran as compared to warfarin. While the review of postmarketing cases is not yet complete, to date, no definite DILI case has been identified in the postmarketing setting. Finally, no greater incidence of liver-related laboratory abnormalities or adverse events was seen in dabigatran-treated subjects (compared to warfarin) in RE-LY.

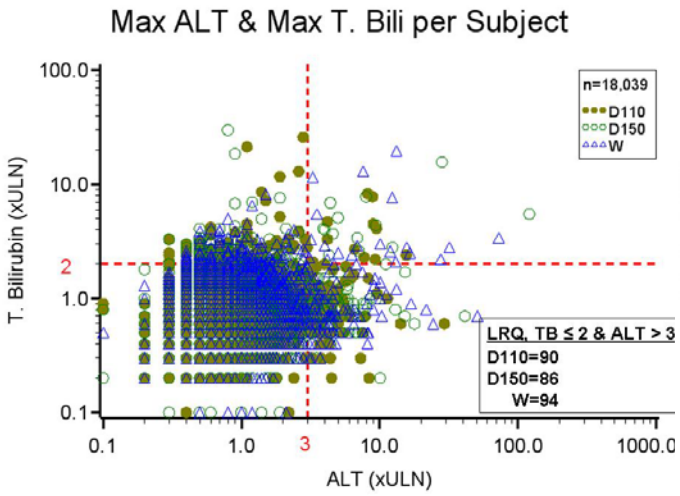
Based on these data, the risk of severe drug induced liver injury from dabigatran appears to be low. Because the perceived risk is low and frequent liver monitoring may not prevent serious cases from occurring (even if an association did exist), regular monitoring of liver tests is not recommended. A baseline assessment should perhaps be done for comparative purposes.

**Assessments for DILI**

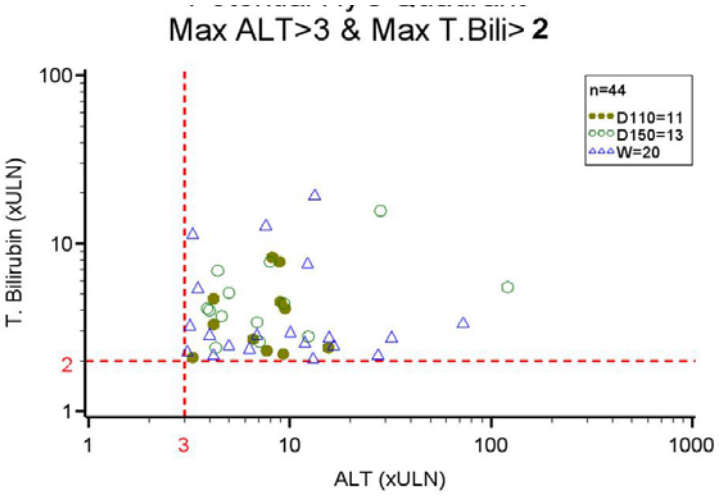
A total of 44 cases of interest were identified via a screen of peak ALT and peak total bilirubin(Tbili) values. The distribution of these values (taken as a ratio of the maximum ALT and maximum Tbili reported for a given subject) is shown below. Of the 44 subjects identified via this method, 11, 13, and 20 subjects were randomized to dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively (Figure B).

**Figure 21. Maximum ALT vs. maximum total bilirubin per subject**

A. All subjects in safety database




B. Potential Hy's Quadrant




[Source: Reviewer's analysis: hep\figs\create ALT_TB.sas, sponsor's dataset: labdata]. Note that A. reflects only 18,039 subjects because one subject in the safety dataset did not have these labs done. This analysis was done without regard to the timing of the ALT and Tbili.

Eleven additional cases of interest (five dabigatran 110, three dabigatran 150, and three warfarin) were identified after including AST >3xULN; the results (line Cat 1) are shown in Table 72.

For the analyses shown in the table below several bins of liver test abnormalities were created. For analyses not requiring a temporal relationship between the elevated aminotransferase (AT) and Tbili, the maximum liver test value was determined (Cat 1 and 5 table below). For analyses requiring a temporal relationship between AT and Tbili (Cat 2, 3, and 4), the maximum AT value was determined and the maximum Tbili within 30 days after the maximum AT value was selected. For the potential Hy's Law cases (Cat 3), subjects with an ALKP ≥ 2 xULN within 30 days after the maximum AT were excluded.

**Table 71. Liver test abnormalities in randomized population**

| Cat | | D 110 | % | D 150 | % | W | % | Total |
|---|---|---|---|---|---|---|---|---|
| | Randomized (n) | 6015 | | 6076 | | 6022 | | 18113 |
| 1 | ALT>3xULN &/or AST>3xULN and Tbili>2xULN | 16 | (0.3) | 16 | (0.3) | 23 | (0.4) | 55 |
| 2 | ALT>3xULN &/or AST>3xULN w/concurrent Tbili>2xULN* | 13 | (0.2) | 14 | (0.2) | 20 | (0.3) | 47 |
| 3 | ALT>3xULN &/or AST>3xULN w/concurrent Tbili>2xULN & ALKP<2xULN* | 11 | (0.2) | 8 | (0.1) | 10 | (0.2) | 29 |
| 4 | ALT>3xULN with concurrent Tbili>2xULN* | 8 | (0.1) | 12 | (0.2) | 16 | (0.3) | 36 |
| 5 | ALT>3xULN & Tbili>2xULN | 11 | (0.2) | 13 | (0.2) | 20 | (0.3) | 44 |
| | | | | | | | | 0 |
| 6 | ALT>3xULN | 101 | (1.7) | 99 | (1.6) | 115 | (1.9) | 315 |
| 7 | ALT>5xULN | 29 | (0.5) | 37 | (0.6) | 45 | (0.7) | 111 |
| 8 | ALT>10xULN | 4 | (0.1) | 10 | (0.2) | 19 | (0.3) | 33 |
| 9 | ALT>20xULN | 1 | (0.0) | 3 | (0.) | 6 | (0.1) | 10 |
| 10 | ALT>20xULN not in Cat 1 | 1 | | 1 | | 3 | | 5 |
| | Acute myocardial infarction | | | | | 1 | | |
| | Elevation prior to randomized treatment | | | 1 | | 1 | | |
| | Normalized despite continued treatment | | | | | 1 | | |
| | Likely due to amiodarone | 1 | | | | | | |
| 11 | Tbili>2 xULN | 114 | (1.9) | 114 | (1.9) | 121 | (2.0) | 349 |
| 12 | ALT or AST > 3 xULN | 125 | (2.1) | 118 | (1.9) | 137 | (2.3) | 380 |
| 13 | ALKP>1.5xULN | 773 | (12.9) | 393 | (6.5) | 869 | (14.4) | 2035 |

3 = Potential Hy's Cases
* = Concurrent defined as 30 days after max ALT or AST
Cat=category
Cat 4 is also a subset of Cat 5

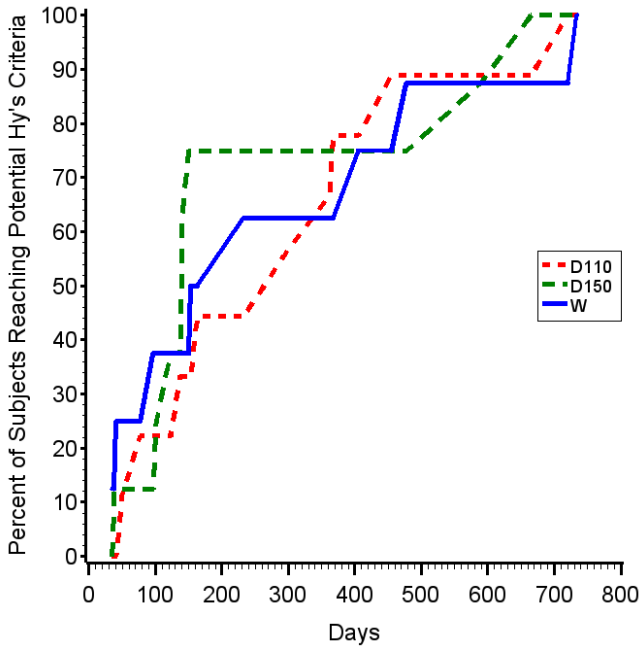
[Source: Reviewer's analysis: liver analysis time30.sas, liver analysis reviewer.sas, TA cats.xls, sponsor's dataset: labdata]

Regardless of how liver test elevations were defined (see table above), there did not appear to be a greater number of liver test abnormalities/Hy's Law cases in the dabigatran treatment arms relative to warfarin; if anything, there appeared to be more potential cases in the warfarin arm. No clear differences were seen in comparisons between the two dabigatran doses. Since hepatotoxic drugs with high rates of DILI have all caused an increased rate of AT elevations compared to control, categories 6-9 in the table shows results of various levels of ALT elevation since it might be a better indicator of the potential for severe DILI. Again, the data consistently show more subjects in the comparator arm. Lowering the degree of AT elevation to 2.5xULN and Tbili to 1.5xULN for categories 1-3 results in findings similar to above with more cases in the warfarin arm.

The time from the start of study medication to the development of liver abnormalities meeting Hy's Law criteria (Cat 3 in the table above) is shown in the figure below. The

time ranged from 35 to 734 days. With regard to onset, no clear differences were seen among the treatment arms.

**Figure 22. Days to reach potential Hy's criteria (n=28)**




[Source: Reviewer's analysis: hep2\time freq, sponsor's dataset, timeL]
Figure shows 28 subjects with potential Hy's criteria
Days are from the start of study medication. One subject (on dabigatran 110 mg) was removed because he met Hy's Law criteria at baseline.

**Scoring results for 55 cases reviewed by OSE**

Dr. Senior's review has not yet been finalized, but Drs. Senior and Seeff have evaluated and scored the 55 cases of interest. These cases were evaluated using a scoring scale that assesses both the severity (SEV) of liver injury and likelihood (LIK) of DILI.[22] The cases were also scored for completeness of information (CMP) and informative use of the data (INF).[23]

In terms of the clinical severity of the liver injury in RE-LY, one subject on dabigatran 150 mg received a score of 5 (death results from liver failure or liver transplant required because of liver failure) and 3 subjects on warfarin received a score of 4 (acute liver failure with secondary failure of brain or kidney function due to liver injury). The one death on dabigatran that was scored a 5 was a 57 year-old obese woman in the US with other valvular heart disease, hypertension, and heart failure who after approximately 4

22. This scoring system has been used in the past at FDA. It differs slightly from the Drug Induced Liver Injury Network (DILIN) scoring system and considerably from the NIH/NCI/CTEP/CTC (common toxicity criteria) manual.
23. For further discussion of CMP and INF, see the Appendix, section 9.7.

months on treatment developed significant AT elevations, endocarditis, septicemia, anemia, renal failure, and respiratory distress. Dabigatran was stopped and six days later she acutely decompensated and had an embolic stroke. She died nine days after drug was stopped. Though she was given a severity score of 5, the event was scored as being very unlikely to be DILI (LIK 0). Her CMP score was 2 (several items) and her INF score was 4 (very good basis for causal decision).

**Table 72. Summary of severity (SEV) of DILI injury scores**

| SEV | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 1 | ALT or AST >3xULN, usually transient and reversible by adaptation = mild | 5 | 1 | 1 |
| 2 | Also TBL >2xULN, after or concurrent, indicating early functional loss = Hy's Law case | 2 | 4 | 8 |
| 3 | Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction | 9 | 10 | 11 |
| 4 | Acute liver failure, with secondary failure of brain or kidney function due to liver injury | 0 | 0 | 3 |
| 5 | Fatal, or requiring liver transplantation due to liver failure | 0 | 1 | 0 |

Of the 55 cases reviewed[24], no definite or very likely DILI case was seen. One probable case (51-75% likelihood, more likely than all other causes combined, only one other cause possible) was identified in the dabigatran 110 mg arm (see table below).

**Table 73. Summary of likelihood (LIK) of DILI injury scores**

| LIK | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 0 | Very unlikely, >5%, relatively rare cause for DILI | 5 | 9 | 7 |
| 1 | Unlikely, 5-25%, no other cause very likely or definite | 9 | 7 | 13 |
| 2 | Possible, 26-50% likely, up to three possible alternative causes | 1 | 0 | 3 |
| 3 | Probable, 51-75%, more likely than all other causes combined, only one other possible | 1 | 0 | 0 |
| 4 | Very likely, 76-95% likely, no other cause even rated as possible | 0 | 0 | 0 |
| 5 | Definite, >95% likely, no other cause even unlikely | 0 | 0 | 0 |

The probable cause subject was a 67 year-old South Korean male with a history of hypertension, diabetes, heart failure, and benign prostatic hypertrophy. He did not have a known history of pancreatitis, cholecystitis or viral hepatitis. His symptoms began after 77 days of drug exposure and lasted until he was hospitalized for persistent pain. Dabigatran was stopped at the time of hospitalization (~3 days after the onset of

24 Of the 55 cases reviewed, the most probable cause of liver injury was heart failure with or without hypotension or shock.

symptoms). His liver tests were normal prior to his symptoms and were elevated upon hospital admission (see table below).

**Table 74. Liver test ratios in probable DILI subject**

| Date | ALTx | ASTx | TBilix | ALKPx | Central lab |
|---|---|---|---|---|---|
| 07-JUL-2006 | 0.6 | 0.8 | 1.1 | 0.6 | 0 |
| 26-JUL-2006* | 9.0 | 10.0 | 4.5 | 1.0 | 1 |

Central lab indicated by a 1, local lab=0
*This lab was the one taken upon hospital admission

During his hospitalizations, the following laboratory abnormalities were also noted: lipase 128 (0-6 U/L), indirect bilirubin 55 (17-21 umol/L), and ceruloplasmin 350 (20-50 mg/L). Notably, the following laboratory tests were unremarkable/negative: AMA, ANA, ASMA, LKM-1, alpha-1 antitrypsin, Anti-HCV, and HBsAG screen w/ confirmation. An abdominal (liver, gall bladder, pancreas) ultrasound showed peripheral ductal dilatations without an abnormal mass in the liver and a mildly enlarged spleen. Coarse and prominent echogenicity of the liver was seen and was read as being suggestive of a diffuse hepatocellular process, but not cholecystitis. A CT scan reported no liver lesion.

It was reported that the patient drank “some amount” of concentrates of red ginseng (2 pack, about 80 mL/pack) for 1 year. Concomitant medications are as shown below.

| Medication: provide generic name | Start Date Year/month/day | Stop Date Year/month/day |
|---|---|---|
| Antibiotics : Unknown | (b) (6) | 2006/07/25 |
| NSAIDs | | 2006/07/25 |
| KERLONE(selective b-blocker) | | Ongoing |
| COZAAR(Angiotensin 2 recepterAntagonist | | Ongoing |
| CADIL(alpha blocker) | | Ongoing |
| LASIX(Loop diuretics) | | Ongoing |

The site investigator diagnosed him with DILI. He was switched to warfarin and discharged after 8 days in the hospital. His liver abnormalities normalized 13 days after hospital admission and remained normal while on warfarin for 30 months.

While his likelihood score was a 3, heart failure was also considered a possible cause (though he was not treated for heart failure during the hospitalization). His other scores were SEV 3 (serious, disabling, requiring or prolonging hospitalization), CMP 3 (most of the key items provided) and INF 3 (very well supported conclusion).

For summary of CMP and INF scores see the Appendix.

**Adverse event data**

As another way to identify potential cases of DILI, the adverse event data set (aeads18.xpt) was searched for terms suggestive of drug induced liver injury. Because of the high incidence of abdominal pain and the poor specificity of this term, "jaundice" was used as a High Level Term to identify subjects with potential liver-related adverse events. The subjects identified had the following lower level terms: cholestasis, cholestatic jaundice, hyperbilirubinaemia/hyperbilirubinemia, icterus, jaundice, liver cholestasis, and obstructive jaundice. Subjects who were rechallenged with drug and had normal liver function tests following rechallenge were removed. This search identified an additional 36 subjects (beyond the 55 initially identified). These subjects were randomized as follows: 9, 8, and 19 on dabigatran 110, dabigatran 150, and warfarin, respectively. The adverse event data do not raise concerns of potential DILI.

**Discontinuations**

The table below shows subjects whose reason for discontinuation of study medication was given by the investigator as "elevated LFT". As shown in the table below, a greater number of subjects on dabigatran (relative to warfarin) were discontinued from study medication for reason of elevated LFT.

The table also looks at the last AT prior to discontinuation in subjects who either permanently discontinued study or prematurely discontinued from the trial. This analysis was done to evaluate subjects who might have been developing liver injury. The AT cut-off ratios (1.5x and 2x) were arbitrarily chosen. There was no clear indication based on last AT value that more subjects on dabigatran compared to warfarin might have been at risk for potential liver injury. Additionally, there were more subjects on warfarin who discontinued medication and had a last AT >3xULN, an elevation more clinically meaningful than the arbitrarily chosen cut-offs.

**Table 75. Premature discontinuations with elevated aminotransaminases**

| | D110 | D150 | W |
|---|---|---|---|
| Treated | N=5983 | N=6059 | N=5998 |
| Completed follow-up but stopped med prematurely[1] | 1170 | 1197 | 907 |
| Elevated LFT result given by investigator as reason for discontinuation[1] | 25 | 16 | 11 |
| Last AT > 1.5 xULN (not in Cat 1)[2] | 49 | 32 | 34 |
| Last AT > 1.5 xULN (subjects that are not included in sponsor's elevated LFT result)[2] | 48 | 33 | 37 |
| Last AT > 3xULN | 9 | 6 | 14 |
| Premature d/c from trial[1] | 203 | 235 | 242 |
| Premature d/c with last AT > 1.5xULN[3] | 4 | 7 | 6 |
| Premature d/c w/ last AT > 2.0 xULN[3] | 1 | 3 | 2 |

AT=ALT or AST, d/c=discontinue, LFT=liver function test
Cat 1 = 55 identified subjects of interest to evaluate for potential drug induced liver injury

1. Adapted from sponsor's table 15.1.1:1.
2. Reviewer's analysis: last lft dcmed, sponsor's data: disco, labdata
3. Reviewer's analysis: last lft dcmed dcstud

**Postmarketing data**

Three cases of interest have been reported in the postmarketing experience: one death (2009-RA-00265RA), one hospitalization (2010-CN-00363CN), and a case of elevated liver enzymes associated with jaundice, skin rash and pruritis (2010-AP-00222AP). These cases are currently being review by OSE at FDA. An addendum will be filed for these cases if their review affects the conclusions of the hepatic safety analysis presented in this review.

**Table 76. Three postmarketing cases under review**

| |
|---|
| **2009-RA-00265RA**: This is a death in a 72 year old Hispanic man taking dabigatran 220 mg for superficial venous thrombosis (also on paracetamol). One day after starting dabigatran, he experienced non-serious diarrhea and abdominal pain. Dabigatran was stopped 2 days later. His symptoms subsided and warfarin was started. Two days after dabigatran was stopped he developed severe liver failure and died two weeks later. The investigator's causation was "not reasonably possible". |
| **2010-CN-00363CN**: This was a male from Canada taking dabigatran 150 mg BID for atrial fibrillation who experienced "Hy's elevation" 12 weeks after starting drug and requiring hospitalization. Dabigatran was stopped and the investigator's assessment was likely DILI; alcohol and autoimmune etiologies were considered unlikely. According to the sponsor, because of privacy laws in Canada, further information could not be obtained. |
| **2010-AP-00222AP**: This is a 79 year old female with diabetes, hypertension, hyperlipidemia, hyperuricemia and prior cholecystectomy who was taking dabigatran 150 mg following elective knee replacement. She presented with generalized pruritis and significant elevations in AT, GGT, ALKP and TBili 1-2 weeks after completing a 49 day course of dabigatran. Liver biopsy showed severe hepatic steatosis and the investigator could not exclude dabigatran. She subsequently recovered and liver tests returned to normal. |

**Incidence of liver test abnormalities on warfarin**

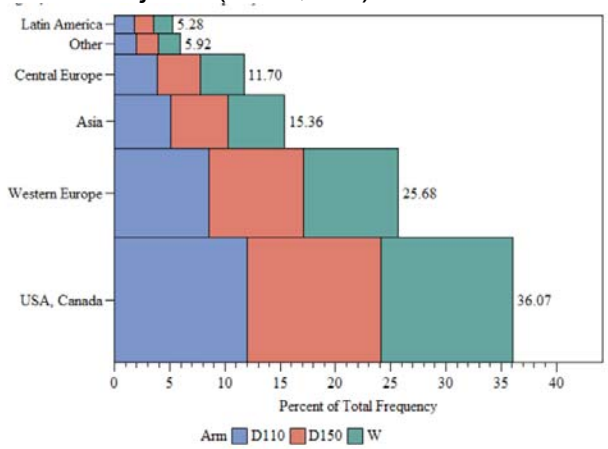
The incidence of cases of interest in the warfarin treatment arm of RE-LY was ~6.5-fold greater than that seen in SPORTIF V, a randomized controlled trial comparing ximelagatran against warfarin for stroke prevention in atrial fibrillation (23 cases in 6022 subjects in RE-LY vs. 1 case in 1922 subjects in SPORTIF V). The reason for this difference is not clear. Monitoring of liver tests did not appear to be markedly different between the two studies[25]; nor did there appear to be clear differences between the studies in the incidence of background diseases[26] that might provide some explanation.

25 SPORTIF V liver tests were drawn monthly for 6 months, then bimonthly for the first year, and then quarterly
26 SPORTIF V population had 40% with heart failure versus 32% in RE-LY

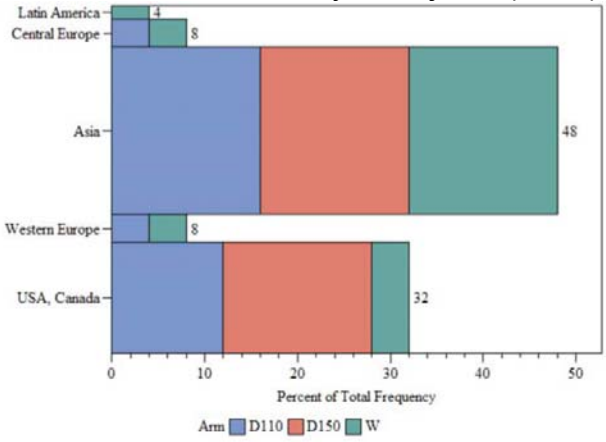
It is possible that the difference in incidence may be attributable in part to the longer duration and larger size of RE-LY and the geographic locations where these studies were conducted. Whereas SPORTIF V was conducted in the US and Canada, RE-LY was an international study. As shown in the figure below, approximately ½ of the 25 potential Hy's cases were from sites in Asia and Latin America.

**Figure 23. Regional population in RE-LY**

A. All subjects (n=18,113)




B. Potential Hy's subjects (n=25)




[source: reviewer's analysis:hep\region, sponsor datast: basco]

If laboratory measurements were drawn more frequently in the warfarin arm, it may help explain the greater number of cases of interest compared to dabigatran. However, laboratory monitoring of each liver test was equally distributed (33%) between the treatment arms (ALT monitoring shown in next table).

**Table 77. Frequency of ALT monitoring in treated subjects, n (%)**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Entire study duration | 78,362 (33) | 78,735 (33) | 78,709 (33) |
| Central lab | 66,902 (85) | 67,357 (86) | 66,951 (85) |
| | | | |
| Prior to September 25, 2006[1] | 27,576 (34) | 26,801(33) | 26,652 (33) |
| Central lab | 22,983 (83) | 22,401 (84) | 22,218 (83) |

1 This is based on treatment starting (not randomization) prior to September 25, 2006
[Source: Reviewer's analysis: liver lab freq, sponsor dataset=labdata]

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Bleeding and GI adverse events were among the most common adverse events reported in RE-LY. Dyspepsia/gastritis was reported at a greater frequency in dabigatran compared to warfarin-treated subjects, as shown in the table below. Study medication discontinuation because of dyspepsia/gastritis was also more common in dabigatran treated subjects. Approximately 2% of dabigatran treated subjects discontinued study medication because of dyspepsia. In contrast, 0.6% of warfarin treated subjects discontinued study medication for this reason. Study medication discontinuation as a result of gastritis was 0.6% and 0.3% in the dabigatran and warfarin treatment arms, respectively.

**Table 78. Frequency of dyspepsia and gastritis**

Table 15.3.2.8: 1 Frequency (%) of subjects with dyspepsia/gastritis ++ by treatment

| User-defined AE category/ Preferred term | DE 110mg bid N (%) | DE 150mg bid N (%) | Warfarin N (%) |
|---|---|---|---|
| Number of patients | 5983 (100.0) | 6059 (100.0) | 5998 (100.0) |
| Total with dyspepsia/gastritis++ | 983 ( 16.4) | 940 ( 15.5) | 470 ( 7.8) |
| Dyspepsia+ | 761 ( 12.7) | 738 ( 12.2) | 354 ( 5.9) |
| Dyspepsia | 368 ( 6.2) | 345 ( 5.7) | 83 ( 1.4) |
| Abdominal pain upper | 177 ( 3.0) | 170 ( 2.8) | 80 ( 1.3) |
| Abdominal pain | 130 ( 2.2) | 137 ( 2.3) | 141 ( 2.4) |
| Abdominal discomfort | 119 ( 2.0) | 112 ( 1.8) | 64 ( 1.1) |
| Epigastric discomfort | 40 ( 0.7) | 40 ( 0.7) | 9 ( 0.2) |
| Gastritis+ | 297 ( 5.0) | 257 ( 4.2) | 142 ( 2.4) |
| Gastritis | 147 ( 2.5) | 127 ( 2.1) | 87 ( 1.5) |
| Gastrooesophageal reflux disease | 117 ( 2.0) | 99 ( 1.6) | 46 ( 0.8) |
| Oesophagitis | 32 ( 0.5) | 27 ( 0.4) | 8 ( 0.1) |
| Gastritis erosive | 21 ( 0.4) | 19 ( 0.3) | 3 ( 0.1) |
| Gastric haemorrhage | 0 ( 0.0) | 4 ( 0.1) | 3 ( 0.1) |
| Gastritis haemorrhagic | 5 ( 0.1) | 4 ( 0.1) | 3 ( 0.1) |
| Haemorrhagic erosive gastritis | 2 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |

In the dabigatran and warfarin treatment groups, the yearly event rate for dyspepsia and gastritis was slightly higher in subjects taking aspirin (no aspirin use vs. use at least once) (see next table).

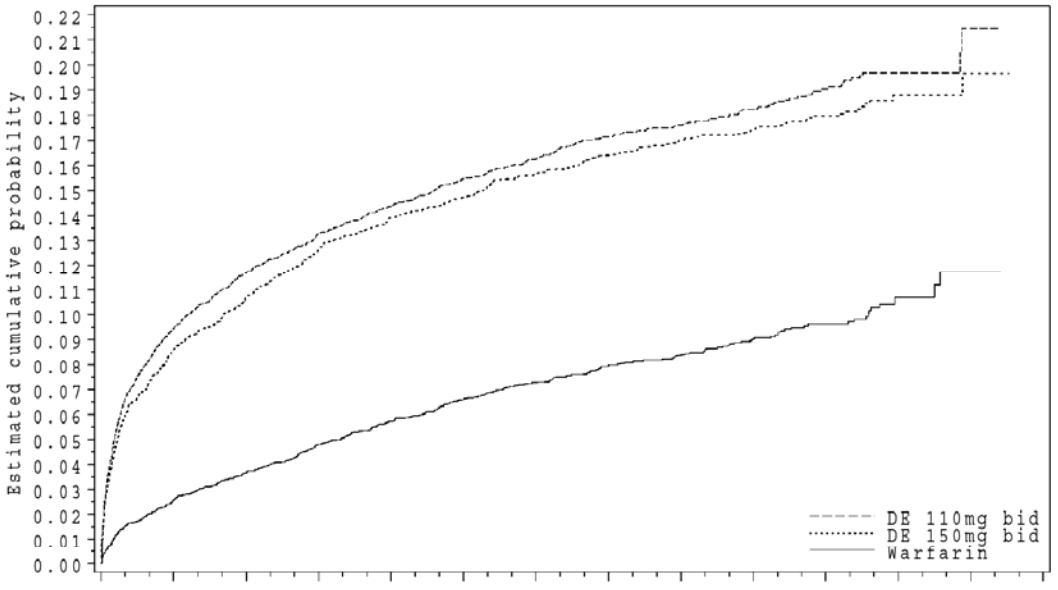
## Table 79. Frequency of dyspepsia and gastritis by aspirin use

Table 15.3.2.8: 4 Yearly event rate of dyspepsia/gastritis ++ by ASA use during treatment period safety set

| | DE 110mg bid | | | | DE 150mg bid | | | | Warfarin | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) | # of subjects | Subject-years | Subjects with event | Yearly event rate (%) |
| Dyspepsia+ | 5983 | 10242 | 761 | 7.43 | 6059 | 10261 | 738 | 7.19 | 5998 | 10659 | 354 | 3.32 |
| No ASA | 3779 | 6551 | 452 | 6.90 | 3880 | 6615 | 446 | 6.74 | 3780 | 6814 | 198 | 2.91 |
| Use ASA at least once | 2204 | 3691 | 309 | 8.37 | 2179 | 3646 | 292 | 8.01 | 2218 | 3846 | 156 | 4.06 |
| Gastritis+ | 5983 | 10242 | 297 | 2.90 | 6059 | 10261 | 257 | 2.50 | 5998 | 10659 | 142 | 1.33 |
| No ASA | 3779 | 6551 | 181 | 2.76 | 3880 | 6615 | 136 | 2.06 | 3780 | 6814 | 74 | 1.09 |
| Use ASA at least once | 2204 | 3691 | 116 | 3.14 | 2179 | 3646 | 121 | 3.32 | 2218 | 3846 | 68 | 1.77 |
| Dyspepsia/gastritis ++ | 5983 | 10242 | 983 | 9.60 | 6059 | 10261 | 940 | 9.16 | 5998 | 10659 | 470 | 4.41 |
| No ASA | 3779 | 6551 | 592 | 9.04 | 3880 | 6615 | 553 | 8.36 | 3780 | 6814 | 262 | 3.85 |
| Use ASA at least once | 2204 | 3691 | 391 | 10.59 | 2179 | 3646 | 387 | 10.61 | 2218 | 3846 | 208 | 5.41 |

A Kaplan-Meier estimate of the time to first dyspepsia/gastritis event suggests that this adverse event manifests ~1 month after the start of therapy with dabigatran.

## Figure 24. Time to first dyspepsia/gastritis




Subjects at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DE 110mg bid | 5983 | 5034 | 4736 | 4511 | 4342 | 4054 | 3348 | 2688 | 2217 | 1664 | 996 | 335 | 54 |
| DE 150mg bid | 6059 | 5107 | 4800 | 4565 | 4383 | 4097 | 3399 | 2702 | 2237 | 1662 | 997 | 313 | 71 |
| Warfarin | 5998 | 5546 | 5336 | 5121 | 4954 | 4608 | 3857 | 3019 | 2498 | 1882 | 1100 | 291 | 57 |

Figure 15.3.2.8: 2 Kaplan-Meier estimates of time to first dyspepsia/gastritis ++ safety set

Source data: Appendix 16.1.9.2, Statdoc 7.3.5.2 scs26\sf_kaplan_ad.sas 03APR2010

### 7.4.2 Laboratory Findings

The significant laboratory findings related to liver tests are discussed in section 7.3.5.1.

### 7.4.3 Vital Signs

No clear differences were seen across treatment arms in terms of changes in blood pressure over the course of the study. Approximately 66-67% of subjects were in atrial fibrillation at study end; the incidence was similar in the dabigatran and warfarin treatment arms.

### 7.4.4 Electrocardiograms (ECGs)

The Interdisciplinary QT Team reviewed the thorough QT study (placebo and moxifloxacin controlled) and found no significant QT prolonging effect with a single dabigatran dose of 150 mg and 600 mg. Assay sensitivity was established via the moxifloxacin control. The largest upper bounds of the 2-sided 90% CI for the mean difference between dabigatran and placebo were below 10 ms, the threshold for regulatory concern. However, there was concern that the QT study did not explore a high enough dose to cover a potential worse case scenario. However, in RE-LY, there were no cases of torsades de pointes on dabigatran and there was not an increased incidence of sudden/arrhythmic deaths in dabigatran compared to warfarin treated subjects (1.5% on dabigatran 110 mg, 1.2% on dabigatran 150 mg and 1.4 % on warfarin). So while the plasma concentrations in the QT study were not as high as they might be from other variables (i.e., drugs and age), the large clinical trial (which included many variables) did not raise concerns of proarrhythmia.

### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted other than a thorough QT study.

### 7.4.6 Immunogenicity

Not applicable. Dabigatran is not a therapeutic protein.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

A dose dependent relationship was seen for major bleeding events.

### 7.5.2 Time Dependency for Adverse Events

This is discussed within each SAE.

## 7.5.3 Drug-Demographic Interactions: Elderly

Subjects 75 years of age and older are perceived to be at increased risk of hemorrhage and also have impaired renal function which would result in increased exposure to dabigatran. Relative to warfarin, rates of major bleeds appeared similar (110 mg dose) or greater (150 mg dose) in dabigatran-treated subjects ≥ 75 years of age. In contrast, rates appeared lower at both doses (relative to warfarin) in those less than 75.

**Table 80. Frequency and yearly event rate of major bleed by age**

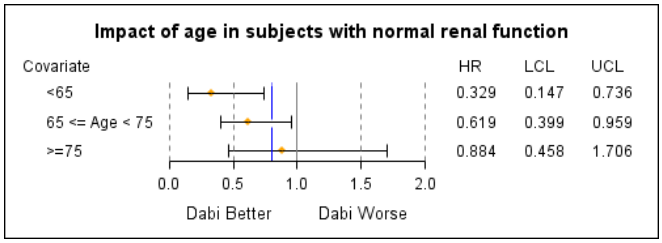
| Age group | D110 | | | D150 | | | W | | |
|---|---|---|---|---|---|---|---|---|---|
| | Subjects with event | Total subjects | Yearly rate (%) | Subjects with event | Total subjects | Yearly rate (%) | Subjects with event | Total subjects | Yearly rate (%) |
| < 65 | 16 | 998 | 0.8 | 18 | 1030 | 0.9 | 45 | 953 | 2.4 |
| 65 ≤ age < 75 | 122 | 2668 | 2.3 | 135 | 2580 | 2.6 | 170 | 2646 | 3.2 |
| ≥ 75 | 204 | 2349 | 4.4 | 246 | 2466 | 5.1 | 206 | 2423 | 4.4 |

[Source: reviewer's analysis: \net\age]

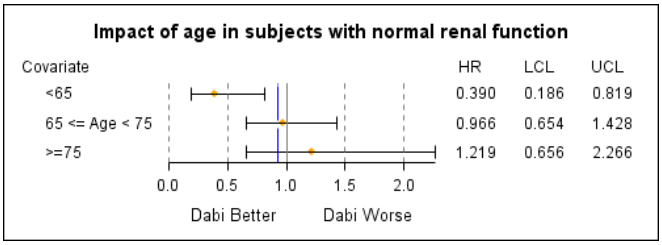
*Reviewer's comment: Though renal function plays an important role in this relationship, analyses suggest that increasing age, independent of renal function, may be associated with a greater risk (relative to warfarin) of a major bleed on dabigatran. (see figure)*

**Figure 25. Impact of age on major bleeding in subjects with normal renal function**

A. D110 vs. W




B. D150 vs. W




[source: reviewer's analysis, sponsor's data: adjrand2]

While subjects ≥ 75 years of age have higher rates of bleeding, they also have higher rates of stroke (see Forest plot in section 6.1.7). Analyses of net benefit (composites of bleeding and stroke/SEE) do not suggest a clear advantage of the 110 mg dose over the 150 mg dose in this population. These data as a whole suggest that there is no reason to dose adjust for age.

**Table 81. Net benefit comparison of dabigatran doses in elderly**

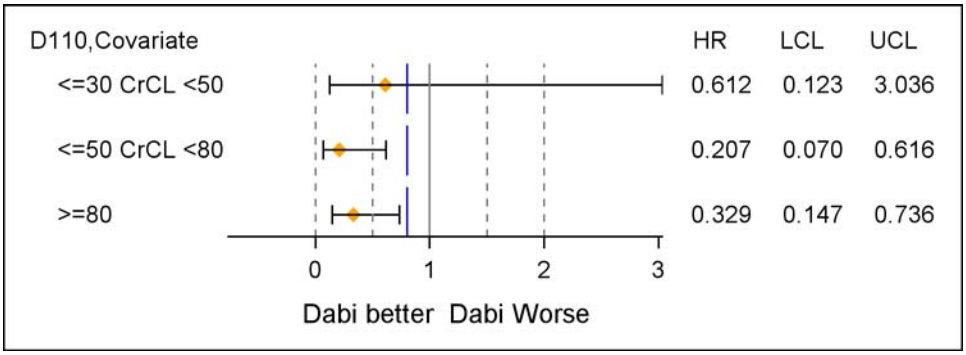
| Net benefit | HR D150 vs. D110 | 95% LL | 95% UL | p-value |
|---|---|---|---|---|
| Adjudicated life threatening bleed or stroke/SEE | 0.98 | 0.79 | 1.22 | 0.87 |
| Adjudicated life threatening bleed or disabling or fatal stroke | 0.96 | 0.76 | 1.21 | 0.72 |
| ICH or stroke/SEE | 0.82 | 0.61 | 1.11 | 0.20 |
| ICH or disabling or fatal stroke | 0.77 | 0.54 | 1.09 | 0.13 |
| GUSTO-severe or disabling or fatal stroke | 0.98 | 0.74 | 1.30 | 0.88 |
| Major bleed or stroke/SEE | 1.07 | 0.91 | 1.26 | 0.42 |

[source: reviewer's analysis: net\age, sponsor's data adjrand, timev, timecens]

### 7.5.4 Drug-Disease Interactions: Renal Impairment

Dabigatran is primarily renally cleared with an ~2-3-fold increase in exposure seen in subjects with moderate renal impairment (creatinine clearance of 30 to 50 mL/min). Despite an expected increase in exposure, no greater risk of bleeding was seen in dabigatran compared to warfarin treated subjects with baseline renal clearance between 30 and 50 mL/min (see figure).

**Figure 26. Impact of renal function on major bleeding in subjects less than 65 years old**




[source: reviewer's analysis, sponsor dataset adjrand2]. Since there is a relationship with bleeding and age, this analysis looks at an age subpopulation.

Relative to the dabigatran 110 mg dose, the incidence of bleeding was not higher at the 150 mg dose, though a dose-response relationship still existed for stroke/SEE (see tables below). Why bleeding rates were not higher in subjects receiving dabigatran 150 mg than 110 mg is not clear. The results suggest that a dose of 150 mg should be used in patients with moderate renal impairment.

**Table 82. Frequency and yearly event rate for major bleeds by baseline renal function**

| | DE 110 | | DE 150 | | Warfarin | |
|---|---|---|---|---|---|---|
| | #of subjects | Yearly event rate (%) | # of subjects | Yearly event rate (%) | # of subjects | Yearly event rate (%) |
| CrCL (ml/min) | | | | | | |
| <30 | 15 | 0.00 | 32 | 13.31 | 30 | 0.00 |
| 30<= and <50 | 1136 | 5.42 | 1157 | 5.08 | 1050 | 5.28 |
| 50<= and <80 | 2714 | 2.59 | 2777 | 3.17 | 2807 | 3.63 |
| >=80 | 1899 | 1.40 | 1882 | 1.86 | 1877 | 2.27 |

[Source: Sponsor, Original submission, Table 12.2.2.5:1]

**Table 83. Frequency and yearly event rate for stroke/SEE by baseline renal function**

| | DE 110 | | DE 150 | | Warfarin | |
|---|---|---|---|---|---|---|
| | # of subject | Event rate | # of subject | Event rate | # of subject | Event rate |
| CrCL (ml/Min) | | | | | | |
| 30<= and <50 | 1136 | 2.36 | 1157 | 1.23 | 1050 | 2.64 |
| 50<= and <80 | 2714 | 1.69 | 2777 | 1.21 | 2807 | 1.82 |
| >=80 | 1899 | 0.86 | 1882 | 0.73 | 1877 | 1.03 |

[Source: Sponsor, Original submission, Table 11.4.1.4.1:1]

### 7.5.5 Drug-Drug Interactions

Drug-Drug interactions are discussed under concomitant medications (Section 7.3.2.1).

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Preclinical data were not suggestive of carcinogenicity and no imbalance was seen across treatment arms in the incidence of neoplasms.

### 7.6.2 Human Reproduction and Pregnancy Data

There is no information on drug exposure in pregnant or lactating women.

## 7.6.3 Pediatrics and Assessment of Effects on Growth

Studies were not conducted in children.

## 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose would be expected to result in hemorrhagic complications. There is no established antidote to dabigatran-induced hemorrhage and in RE-LY, investigator were told to give consideration to the following therapies in subjects with major bleeding on dabigatran: packed cells, FFP, prothrombin complex concentrates, and recombinant factor VIIa. Hemodialysis could also be considered. The measures taken by investigators are shown in the tables below for all subjects with adjudicated major bleeds and by whether or not the subject lived or died. Subjects were not randomized to the intervention that they received and interpretation of the data is limited.

**Table 84. Corrective therapies used in subjects with adjudicated major bleed**

| | D110 | % | D150 | % | W | % |
|---|---|---|---|---|---|---|
| Total subjects | 397 | (100) | 486 | (100) | 476 | (100) |
| Received Transfusion | 234 | (58.9) | 315 | (64.8) | 246 | (51.7) |
| Associated with Hypotension requiring pressors | 18 | (4.5) | 34 | (7.0) | 22 | (4.6) |
| Required surgical intervention | 36 | (9.1) | 57 | (11.7) | 65 | (13.7) |
| Other corrective treatment for bleed | 132 | (33.2) | 170 | (35.0) | 244 | (51.3) |
| FFP | 73 | (18.4) | 107 | (22.0) | 144 | (30.3) |
| Vitamin K | 37 | (9.3) | 53 | (10.9) | 124 | (26.1) |
| Other | 56 | (14.1) | 50 | (10.3) | 56 | (11.8) |
| Platelets | 13 | (3.3) | 18 | (3.7) | 24 | (5.0) |
| Cryoprecipitate | 3 | (0.8) | 5 | (1.0) | 7 | (1.5) |
| Recombinant Factor VIIa | 1 | (0.3) | 7 | (1.4) | 3 | (0.6) |
| Coagulation Factor | 1 | (0.3) | 3 | (0.6) | 5 | (1.1) |
| Prothrombin Complex Conc | 3 | (0.8) | 2 | (0.4) | 5 | (1.1) |

[Source: reviewer's analysis: adj_plt122n, sponsor's data plt122n, timev,adjrand].

**Table 85. Corrective therapies for adjudicated major bleeds in subjects that died**

| Corrective therapy | D110 | D150 | W |
|---|---|---|---|
| Subject died | 25 | 28 | 40 |
| Required Transfusion | 8 | 11 | 10 |
| Associated with Hypotension requiring pressors | 6 | 11 | 8 |
| Required surgical intervention | 1 | 8 | 8 |
| Other corrective tx for bleed | 10 | 14 | 18 |
| FFP | 7 | 9 | 11 |
| Vitamin K | 5 | 4 | 10 |
| Other | 2 | 3 | 4 |
| Platelets | 2 | 3 | 2 |
| Cryoprecipitate | 1 | 3 | . |
| Recombinant Factor VIIa | 1 | 4 | 1 |
| Coagulation Factor | 1 | 2 | 1 |
| Prothrombin Complex Conc | 2 | . | . |

[source: reviewer's analysis, filename: Tx\Dead v alive corrective, sponsor data plt122n, timev]

**Table 86. Corrective therapies for adjudicated major bleeds in subjects that did not die**

| Corrective therapy | D110 | D150 | W |
|---|---|---|---|
| Subject alive | 369 | 456 | 435 |
| Required Transfusion | 225 | 304 | 236 |
| Associated with Hypotension requiring pressors | 12 | 23 | 14 |
| Required surgical intervention | 35 | 49 | 57 |
| Other corrective tx for bleed | 120 | 156 | 226 |
| FFP | 65 | 98 | 133 |
| Vitamin K | 32 | 49 | 114 |
| Other | 53 | 47 | 52 |
| Platelets | 11 | 15 | 22 |
| Cryoprecipitate | 2 | 2 | 7 |
| Recombinant Factor VIIa | . | 3 | 2 |
| Coagulation Factor | . | 1 | 4 |
| Prothrombin Complex Conc | 1 | 2 | 5 |

[source: reviewer's analysis, filename: Tx\Dead v alive corrective, sponsor data plt122n, timev]

## 7.7 Interruptions for Elective Surgeries/Procedures

The RE-LY protocol provided guidance on the use of warfarin and dabigatran around the time of emergency and elective surgeries/procedures (see section 5.3.5.4). Overall, 4623 subjects (25.6%) had interruptions of anticoagulant therapy for a surgery/procedure; the numbers/percents were similar across the three treatment arms. A minority of subjects (525) had interruptions for an emergency surgery/procedure.

Approximately 70% of subjects on dabigatran who had interruptions for a procedure/surgery, bridging therapy was not used, as shown in the table below.

**Table 87. Summary of bridging therapy for subjects with interruptions of anticoagulant for surgery/procedure**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Subject with interruptions for procedure/surgery | 1501 | 1554 | 1568 |
| Subjects with no bridging therapy | 1190 (79.3) | 1203 (77.4) | 1030 (65.7) |
| Subjects with bridging therapy* | 311 (20.7) | 351 (22.6) | 538 (34.3) |
| Pre-procedural bridging | 203 (13.5) | 210 (13.5) | 394 (25.1) |
| Post-procedural bridging | 262 (17.5) | 293 (18.9) | 447 (28.5) |
| Pre- and Post procedural bridging | 154 (10.3) | 152 (9.8) | 303 (19.3) |

*subjects counted in more than one category if multiple interruptions for surgery/procedure occurred. [Source: taken from sponsor's table 17.2, appendix-3, 7.30.10 submission]

The nature of the procedures, medication used for bridging and timing of procedures since previous dose of anticoagulation therapy is shown below for subjects undergoing pre-procedural bridging therapy. The majority of dabigatran subjects receiving a bridge had been off of therapy for more than 2 days.

**Table 88. Summary of surgery/procedures for subjects who used pre-procedural bridging therapy**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Day procedure or hospital admission | | | |
| Day procedure | 104 | 122 | 246 |
| Hospital admission | 273 | 265 | 452 |
| Type of procedure | | | |
| Pacemaker/ICD | 36 | 37 | 56 |
| Surgery | 215 | 215 | 356 |
| Dental procedure | 11 | 21 | 59 |
| Diagnostic procedure | 72 | 73 | 140 |
| Other | 43 | 41 | 87 |
| Emergency or elective | | | |
| Emergency | 51 | 36 | 58 |
| Elective | 326 | 351 | 639 |
| Time of procedure since previous dose (days) | | | |
| <= 2 | 99 | 89 | 50 |
| 2< and <= 5 | 98 | 91 | 169 |
| > 5 | 53 | 58 | 204 |
| Medication used for bridging | | | |

| | | | |
|---|---|---|---|
| Subcutaneous LMWH | 175 | 172 | 421 |
| Unfractionated heparin | 74 | 70 | 107 |
| Study medication restarted after procedure | | | |
| No | 51 | 42 | 68 |
| Yes | 326 | 344 | 630 |
| Blood transfusion required | | | |
| No | 344 | 369 | 653 |
| Yes | 31 | 18 | 44 |

[Source: taken from sponsor's table 17.3, appendix-3, 7.30.10 submission]

Of the subjects who did not use a bridge, the number/percent experiencing an important outcome event (stroke/SEE, major bleed) around the time of surgery appeared similar in the dabigatran compared to warfarin treatment arms. This also appeared to be the case in subjects who used a bridge.

**Table 89. Summary of outcome events for subjects without bridging therapy for surgery/procedure**

| | **Dabigatran 110** | **Dabigatran 150** | **Warfarin** |
|---|---|---|---|
| Subjects with interruptions for procedure/surgery and no bridging therapy | 1190 | 1203 | 1030 |
| Subjects with outcome events occurred within 7 days prior to surgery/procedure | 43 ( 3.6) | 51 ( 4.2) | 38 ( 3.7) |
| Stroke/SEE | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.2) |
| Major bleed | 23 ( 1.9) | 17 ( 1.4) | 13 ( 1.3) |
| Minor bleed | 23 ( 1.9) | 34 ( 2.8) | 25 ( 2.4) |
| Death | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Subjects with outcome events occurring within 30 days post surgery/procedure | 135 (11.3) | 155 ( 2.9) | 115 (11.2) |
| Stroke/SEE | 2 ( 0.2) | 3 ( 0.2) | 6 ( 0.6) |
| Major bleed | 29 ( 2.4) | 45 ( 3.7) | 25 ( 2.4) |
| Minor bleed | 106 ( 8.9) | 114 ( 9.5) | 92 ( 8.9) |
| Death | 5 ( 0.4) | 2 ( 0.2) | 2 ( 0.2) |

[Source: taken from sponsor's table 17.8, appendix-3, 7.30.10 submission]

In subjects undergoing interruptions for emergency surgery/procedure, outcomes were similar in dabigatran compared to warfarin treated subjects.

**Table 90. Summary of outcome events for subjects using emergency procedure for surgery/procedure**

| | Dabigatran 110 | Dabigatran 150 | Warfarin |
|---|---|---|---|
| Subjects with interruptions for emergency surgery/procedure | 167 | 196 | 162 |
| Subjects with outcome events occurring within 7 days prior to surgery/procedure | 26 ( 15.6) | 26 ( 13.3) | 24 ( 14.8) |
| Stroke/SEE | 2 ( 1.2) | 1 ( 0.5) | 3 ( 1.9) |
| Major bleed | 17 ( 10.2) | 13 ( 6.6) | 15 ( 9.3) |
| Minor bleed | 10 ( 6.0) | 12 ( 6.1) | 11 ( 6.8) |
| Death | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Subjects with outcome events occurring within 30 days post surgery/procedure | 40 ( 24.0) | 42 ( 21.4) | 44 ( 27.2) |
| Stroke/SEE | 5 ( 3.0) | 1 ( 0.5) | 5 ( 3.1) |
| Major bleed | 17 ( 10.2) | 26 ( 13.3) | 24 ( 14.8) |
| Minor bleed | 20 ( 12.0) | 20 ( 10.2) | 23 ( 14.2) |
| Death | 4 ( 2.4) | 3 ( 1.5) | 1 ( 0.6) |

[Source: taken from sponsor's table 17.10, appendix-3, 7.30.10 submission]

# 9 Appendices

## 9.1 Literature Review/References

Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001927. DOI: 10.1002/14651858.CD001927.pub2.

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Fuster et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. Circulation. 2006; 114:700-752.

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Hirsh et al. American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy. Circulation. 2003; 107: 1692-1711.

Jackson et al. Antithrombotic drug development for atrial fibrillation: Proceedings, Washington, DC, July 25-27, 2005. Am Heart J. 2008; 155: 829-840.

Jones M et al. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvular atrial fibrillation: a record linkage study in a large British population. Heart 2005; 91:472–477.

Lange U, Nowak G, Bucha E. Ecarin Chromogenic Assay- A New Method for Quantitative Determination of Direct Thrombin Inhibitors Like Hirudin. Pathophysiol Haemost Thromb. 2003/04; 33:184-191.

Mant J et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomized controlled trial. Lancet 2007; 370: 493-503.

Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993; 342(8882):1255-62.

White HD et al. Comparison of Outcomes among Patients Randomized to Warfarin Therapy according to Anticoagulant Control. Arch Intern Med. 2007; 167: 239-245.

## 9.2 Labeling Recommendations

- Dabigatran 150 mg should be labeled for the reduction of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- No superiority claim over warfarin should be given.
- The Warnings and Precautions section should address the general risk of bleeding as well as the risk of stroke during temporary discontinuations/lapses in therapy.
- In RE-LY the advantage of dabigatran relative to warfarin was in part driven by subjects enrolled at centers achieving lower levels of INR control (as defined by a center-level INR below the median). The Clinical Studies section should, among other things, show findings (stroke/SEE, mortality and major bleeds) by center-level INR control.

## 9.3 Advisory Committee Meeting

An advisory committee meeting has been scheduled for September 20, 2010. We believe that the advisory committee meeting should focus on dose selection for anticoagulant therapies and how to weigh the benefits of these therapies against their risks (specifically when the risk of bleeding events balances the risk of stroke). We think that the advisory committee should be asked to opine on the dose(s) of dabigatran that should be approved and the particular population(s) in which the dose(s) should be used. In particular, we think that there needs to be discussion about whether or not it makes sense to recommend a lower dose of dabigatran in patients at increased risk of bleeding, and, if so, how one defines this population.

*Reviewer's comment: Following the Advisory Committee Meeting, additional analyses were performed to determine if there was a population in which there was compelling evidence of greater net benefit from the 110 mg dose. One analysis (see table) looked at the percentage of subjects in the dabigatran treatment arms of RE-LY who had no interruption of study medication or resumed study medication after their first major bleed and the incidence of another major bleed. Of subjects who experienced a major bleed in the 110 and 150 mg arms, a similar percentage (over 50%) had no interruption of study medication or resumed study medication following their first major bleed. In the subset of subjects who continued/resumed study medication following their first major bleed, the proportion that experienced another major bleed was similar at the two doses. In sum, while there may be a population at high risk of bleeding that would receive greater net benefit from the 110 mg dose, we are unable to clearly identify such a population at this time.*

**Table 91. Medication interruptions and recurrent major bleeds following the first major bleed**

| | **Dabigatran 110** | **Dabigatran 150** |
|---|---|---|
| Subjects with a major bleed | 295 | 350 |
| Number (%) who had no interruption or resumed study medication after the first major bleed* | 161 (55%) | 210 (60%) |
| Of subjects who had no interruption or resumed study medication, number (%) who did not have another major bleed** | 136 (84%) | 181 (86%) |

[Source: data submitted by sponsor via email on October 4, 2010]
*Denominator is number of subjects with major bleed in that treatment arm
**Denominator is number of subjects with major bleed who resumed study medication/had no interruption

## 9.4 Efficacy of Warfarin

The clinical trial experience supporting the efficacy of warfarin in the treatment of atrial fibrillation is discussed below. Topics addressed include the nature of the benefit of warfarin (effect on stroke and magnitude of effect) and how warfarin was used and in whom it was used in the referenced clinical trials. This section also reviews the data supporting time in therapeutic range (TTR) as a measure of the quality/adequacy of anticoagulation in warfarin treated subjects in clinical trials.

*The nature of the benefit of warfarin:* Five randomized, placebo-controlled primary prevention trials are widely referenced as establishing the efficacy of warfarin for the primary prevention of ischemic stroke in patients with non-valvular atrial fibrillation: Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK I), Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), Canadian Atrial Fibrillation Anticoagulation (CAFA), Stroke Prevention in Atrial Fibrillation (SPAF I), Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF). A sixth study, European Atrial Fibrillation Trial (EAFT), addressed the efficacy of warfarin for the prevention of stroke in patients with atrial fibrillation and a history of nondisabling stroke or TIA within 3 months (trial of secondary prevention). As shown in the table below, the primary endpoint varied somewhat across the studies. Four of the five primary prevention trials were terminated early for reasons of efficacy; a fifth (CAFA) was terminated in light of the efficacy findings in the other studies.

| Study | Participants (follow up) | Target INR | Mean INR | Primary Endpoint |
|---|---|---|---|---|
| *Open Label* | | | | |
| AFASAK I | Denmark, chronic AF, median age 74.2, 54% male (~1.2 years/subject) | 2.8-4.2 | ~ 2.5 | TIA, stroke, systemic embolism |
| SPAF I | U.S., constant or intermittent chronic AF, mean age 67, 71% male (~2.2 years/subject) | 2-4.5 | ~2.6 | Ischemic stroke, systemic embolism |
| BAATAF† | U.S., chronic or intermittent AF, mean age 68, 75% male | 1.5-2.7 | ~2.1 | Ischemic stroke |
| EAFT (group I) | 12 European countries and Israel, nonrheumatic AF and a recent (< 3 months) TIA or minor ischemic stroke, mean age ~71, ~56% male; (2.3 years mean) | 2.5-4.0 | ~2.9 | Composite: vascular death, nonfatal stroke, nonfatal myocardial infarction, systemic embolism |

| | | | | |
|---|---|---|---|---|
| *Blinded* | | | | |
| CAFA | Canada, chronic or paroxysmal AF, mean age 67, 75% male (~1.3 years/subject) | 2.0-3.0 | ~2.4 | Ischemic stroke, systemic embolism, intracranial or fatal hemorrhage |
| SPINAF | U.S., chronic AF, mean age 67, 100% male | 1.4-2.8 | ~2.0 | Ischemic stroke |

[Sources: Aguilar et al. 2005; EAFT. 1993]
†ASA permitted in control group

These six trials were included in two published meta-analyses by Hart et al. which addressed the efficacy of anticoagulant therapy for the prevention of stroke (ischemic and hemorrhagic). The table below shows the number of strokes per patients/patient-years in the warfarin and control treatment arms as well as the relative and absolute risk reduction in stroke for subjects without a baseline history of stroke or transient ischemic attack. According to the 2007 meta-analysis of these studies, warfarin reduced the risk of stroke (ischemic and hemorrhagic) by 64% (95% CI, 49% to 74%) and the risk of ischemic stroke by 67% (95% CI, 54% to 77%).

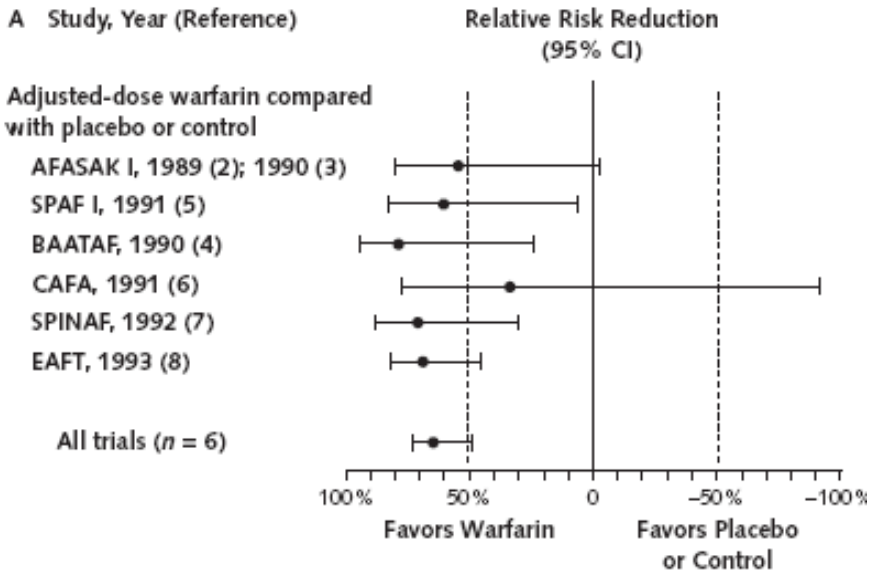
*Table 2.* **Adjusted-Dose Warfarin Compared with Placebo or No Treatment***

| Study, Year (Reference) | Secondary Prevention, %† | Participants, *n* | Target INR | Strokes/Patients/Patient-Years; Warfarin vs. Placebo or Control, *n/n/n* | Relative Risk Reduction (95% CI), %‡ | Absolute Risk Reduction, %/y‡ |
|---|---|---|---|---|---|---|
| AFASAK I, 1989 (2); 1990 (3) | 6 | 671 | 2.8–4.2 | 9/335/413 vs. 19/336/398 | 54 | 2.6 |
| SPAF I, 1991 (5) | 8 | 421 | 2.0–4.5§ | 8/210/263 vs. 19/211/245 | 60‖ | 4.7 |
| BAATAF, 1990 (4)¶ | 3 | 420 | 1.5–2.7§ | 3/212/487 vs. 13/208/435 | 78‖ | 2.4 |
| CAFA, 1991 (6) | 4 | 378 | 2.0–3.0 | 6/187/237 vs. 9/191/241 | 33 | 1.2 |
| SPINAF, 1992 (7) | 8 | 571 | 1.4–2.8§ | 7/281/489 vs. 23/290/483 | 70‖ | 3.3 |
| EAFT, 1993 (8)** | 100 | 439 | 2.5–4.0 | 20/225/507 vs. 50/214/405 | 68‖ | 8.4 |
| 6 trials†† | 20 | 2900 | – | 53/1450/2396 vs. 133/1450/2207 | 64 (49 to 74) | Primary prevention, 2.7; secondary prevention, 8.4 |

* Please see footnote in Table 1 for definitions of study acronyms. INR = international normalized ratio.
† Proportion of patients who had previous stroke or transient ischemic attack.
‡ Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis.
§ Prothrombin time ratios were used with INR equivalents estimated by the investigators.
¶ A total of 46% of exposure in the control group was during self-selected use of various dosages of aspirin.
‖ $P < 0.05$, 2-sided.
** Several oral vitamin K antagonists were used (warfarin was not exclusively used).
†† Meta-analysis estimates of relative risk reductions ($P > 0.2$ for homogeneity) and absolute risk reductions ($P > 0.2$ for homogeneity) for trials of primary prevention (trials with ≤20% of participants with previous stroke) vs. secondary prevention; see Methods.

[Source: Hart RG et al. 2007]

A forest plot of warfarin's effect on stroke (ischemic and hemorrhagic), taken from the 2007 meta-analysis, is shown below.




[Source: Hart RG et al. 2007]

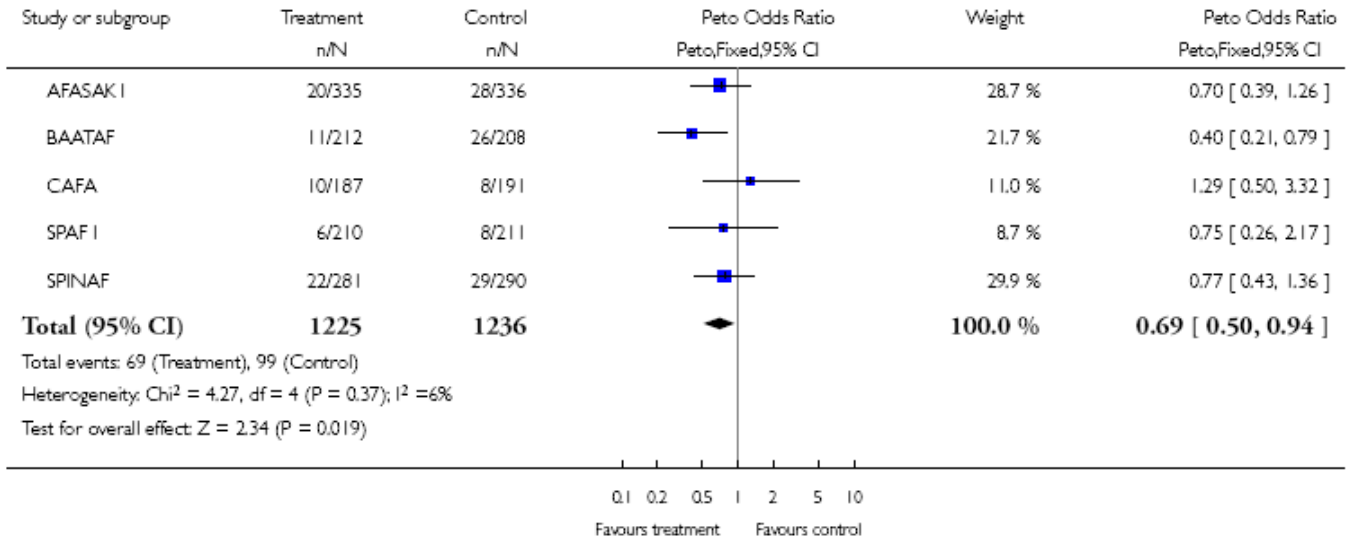
A Cochrane review published in 2005 also addressed the efficacy of warfarin for the prevention of all-cause mortality and myocardial infarction using available data from the five primary prevention trials for subjects with no previous history of stroke or transient ischemic attack. The effect of warfarin on these outcomes, as reported in this review, is shown in the figures below. The meta-analysis suggests favorable effects on all-cause mortality in these historical trials. As noted in the Cochrane review, few MIs occurred in these trials, making it difficult to ascertain what, if any effect, warfarin therapy has on this outcome.

**Analysis 1.10. Comparison 1 Anticoagulants versus control, Outcome 10 All cause mortality.**

Review: Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks

Comparison: 1 Anticoagulants versus control

Outcome: 10 All cause mortality

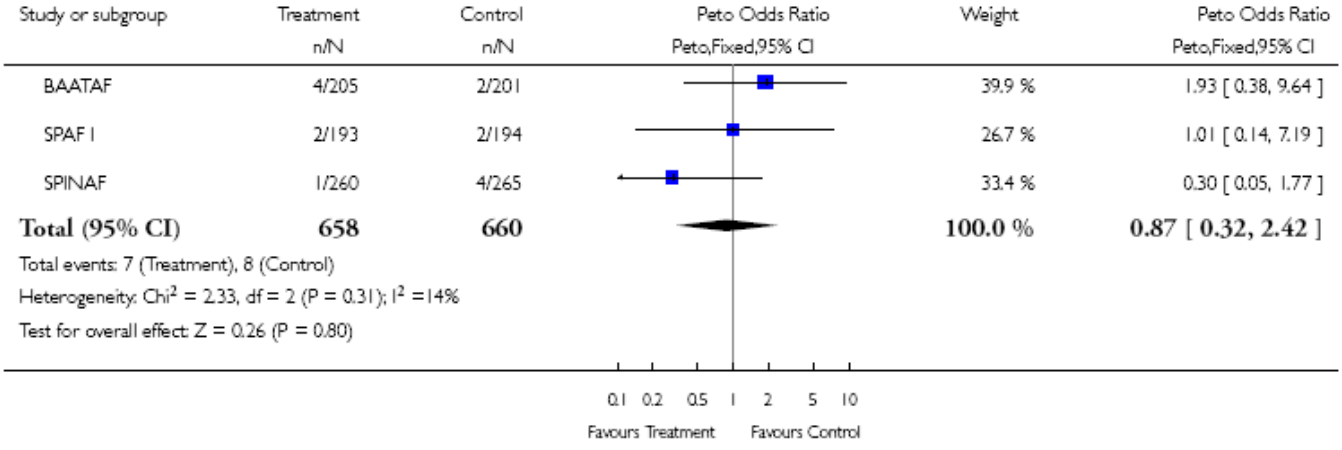



**Analysis 1.4. Comparison 1 Anticoagulants versus control, Outcome 4 Myocardial infarction.**

Review: Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks

Comparison: 1 Anticoagulants versus control

Outcome: 4 Myocardial infarction




[Source for all figures: Aguilar et al. 2005.]

*The quality of INR control:* An INR range of 2-3 is thought to maximize protection against ischemic stroke in patients with atrial fibrillation without incurring a marked increase in the risk of intracranial bleeding. In observational studies, the percent of time spent out of this range by patients has been associated with the risk of death, ischemic stroke and other thromboembolic events (Jones et al. 2005). Among patients randomized to warfarin therapy in randomized-controlled trials, the risk of death, MI, major bleeding and stroke or SEE have also been shown to be related to INR control as assessed by the percentage of time in the therapeutic range (White et al. 2007).

It has also been shown that the time in therapeutic range measured at the center-level and country-level (determined by averaging the individual times in therapeutic range for all of the subjects randomized to oral anticoagulant therapy within a center or country to yield a value for that center or country), has an important impact on the treatment benefit of warfarin in intervention trials. The benefit of oral anticoagulants over antiplatelet agents has been shown to be dependent upon the quality of INR control achieved as measured by the time in therapeutic range at the center and country level. In ACTIVE W, for patients at centers below the median time in therapeutic range (65%), no treatment benefit was demonstrated as measured by the relative risk for vascular events of clopidogrel plus aspirin versus oral anticoagulation; however, for patients at centers with a time in therapeutic range above the study median, oral anticoagulation was associated with a statistically significant ~ 2-fold reduction in the relative risk of vascular events (Connolly et al. 2008).

*Reviewer's comment: Though these studies all support the concept that a greater percentage of time in the therapeutic range is associated with a better outcome on warfarin, different approaches to censoring INR values from the calculation of a subject's time in therapeutic range have been used in studies, making it difficult to compare the quality of INR control across studies using the reported time in therapeutic range. Further, the reported time in therapeutic range reflects the percentage of measured and reported values falling within a given range; depending upon the adequacy of INR monitoring, it may or may not be indicative of the percentage of time trial participants were actually in the reported ranges. These factors limit the ability to use the time in therapeutic range as the sole metric for assessing the relative quality of INR control in RE-LY and emphasize the need for additional metrics to help ascertain the adequacy of anticoagulation in warfarin-treated subjects in clinical trials of new anticoagulants.*

## 9.5 Rankin Scale

For the purposes of this review, the term "Rankin Scale" refers to the Modified Rankin Scale.

**Table 92. Rankin Scale**

| Score | Symptoms | Description |
|---|---|---|
| 0 | No symptoms | |
| 1 | No significant disabling symptoms | No significant disability despite symptoms; able to carry out all usual duties and activities. |
| 2 | Slight disability | Unable to carry out all previous activities but able to look after their own affairs without assistance. |
| 3 | Moderate disability | Requiring some help but able to walk without assistance. |
| 4 | Moderate / Severe disability | Unable to walk without assistance and unable to attend to own bodily needs without assistance. |
| 5 | Severe disability | Bedridden, incontinent and requiring constant nursing care and attention. |
| 6 | Dead | |

## 9.6 RE-LY Protocol Additional Information

### 9.6.1. Full Inclusion/Exclusion Criteria

Inclusion criteria

1.) AF documented as follows (Amendment 1 changed this to 'documented by one of the' ):

a. There is ECG documented AF on the day of screening or randomization (Amendment 1 changed this to within 1 week of)

b. The patient has had a symptomatic episode of paroxysmal or persistent AF documented by 12 lead ECG within six months prior to randomization

c. There is documentation of symptomatic or asymptomatic paroxysmal or persistent AF on two separate occasions, at least one day apart, one of which is within six months prior to randomization. In this case, AF may be documented by 12 lead ECG, rhythm strip, pacemaker/ICD electrogram, or Holter ECG. The duration of AF should be at least 30 seconds. Electrograms (not marker channels or mode switch episodes) from pacemakers and defibrillators can be used to document only one episode of paroxysmal or persistent AF

2.) In addition to documented AF, patients must have one of the following additional risk factors for stroke:

a. History of previous stroke, transient ischemic attack, or systemic embolism

b. Left ventricular ejection fraction <40% documented by echocardiogram, radionuclide or contrast angiogram (Amendment 1 changed this to in the last 6 months)

c. Symptomatic heart failure, documented to be NYHA Class 2 or greater (Amendment 1 changed this to in the last 6 months)

d. Age ≥ 75 years

e. Age ≥ 65 years and one of the following additional risk factors:

i) diabetes mellitus on treatment (Amendment 1 specified treatment to include diet)

ii) documented coronary artery disease (any of: prior MI, positive stress exercise test, positive nuclear perfusion study, prior CABG surgery or PCI, angiogram showing ≥75% stenosis in a major coronary artery

iii) hypertension requiring medical treatment
3.) Age ≥18 years at entry
4.) Written, informed consent.

Exclusion criteria
• History of heart valve disorders (i.e., prosthetic valve or hemodynamically relevant valve disease) Amendment 1 specified
Patients with prosthetic heart valves requiring anticoagulation per se, or with haemodynamically relevant valve disease that is expected to require surgical intervention during the course of the study

• Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days
• Conditions associated with an increased risk of bleeding:
a. Major surgery in the previous month
b. Planned surgery or intervention in the next 3 months
c. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding (Amendment 1 added, "unless the causative factor has been permanently eliminated or repaired (e.g. by surgery))
d. Gastrointestinal hemorrhage within the past year (Amendment 1 added, "unless the cause has been permanently eliminated (e.g. by surgery))
e. Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
f. Hemorrhagic disorder or bleeding diathesis
g. Need for anticoagulant treatment for disorders other than atrial fibrillation
h. Fibrinolytic agents within 48 hours of study entry
i. Uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg)
j. Recent malignancy or radiation therapy (=6 months) and not expected to survive 3 years
5.) Contraindication to warfarin treatment
6.) Reversible causes of atrial fibrillation (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism).
7.) Plan to perform a pulmonary vein ablation or surgery for cure of the AF
8.) Severe renal impairment (estimated creatinine clearance ≤30 mL/min)
9.) Active infective endocarditis
10.) Active liver disease, including but not limited to
a. Persistent ALT, AST, Alk. Phos. >2 x ULN
b. Known active hepatitis C* (as evidenced by positive HCV RNA by sensitive PCR-based assay, such as Roche Monitor or Bayer TMA assay)
c. Active hepatitis B* (HBs antigen +, anti HBc IgM+) (Amendment 1 clarified (HBs antigen +or anti HBc IgM+)
d. Active hepatitis A
11.) Women who are pregnant or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study (NOTE: A negative pregnancy test must be obtained for any woman of childbearing potential prior to entry into the study) (Amendment 2 added "lactating")
12.) Anemia (hemoglobin <10g/dL) or thrombocytopenia (platelet count <100 x 109/L)
13.) Patients who have developed transaminase elevations upon exposure to ximelagatran.
14.) Patients who have received an investigational drug in the past 30 days

15.) Patients considered unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, has a life expectancy less than the expected duration of the trial due to concomitant disease, or has any condition which in the opinion of the Investigator, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse).
*Patients with a known history of hepatitis B or C must undergo hepatitis serology for hepatitis B and C prior to inclusion in the study.

### 9.6.2. Liver Abnormality Follow-up

*Alert Status 1:* ALT or AST > 2x ULN and ≤ 3x ULN or Alk Phos > 2x ULN

- Weekly LFTs until ALT, AST and Alk Phos < 2x ULN

*Alert Status 2:* ALT or AST > 3x ULN and ≤ 5x ULN or Tbili > 2x ULN*

- Weekly LFTS until ALT, AST and Tbili < 2x ULN
- Evaluate for liver disease by reviewing alcohol intake, medications, concomitant disease, and further lab analyses. Additional evaluations including abdominal ultrasound with special attention to the liver, biliary tree, and pancreas should be considered.[3]

Note that a bulletin sent to investigators dated Oct 16, 2006 clarified that the "enhanced hepatic function kit"[1] be used for the first occurrence of an Alert 2. All subsequent LFT testing should be done using the LFT visit kit.[2] The abdominal ultrasound with special attention to liver, biliary tree and pancreas are clinically indicated and **must** be performed. Results of any tests or investigations must be sent to PHRI. (This bulletin note was also applicable for Alert Status 3).

*Alert Status 3:* ALT or AST > 5x ULN or ALT or AST > 3x ULN with a Tbili > 2x ULN*
Or development of hepatic disease related symptoms

- Discontinue medication. If first abnormal LFT, the test should be repeated for verification. Alert sponsor.
- Evaluate for liver disease (as specified for Alert Status 2)
- If jaundice or other symptoms (in the investigator's judgment) likely attributable to hepatic disease (e.g., fatigue, nausea, vomiting, loss of appetite, new onset itching, upper abdominal pain, especially right upper quadrant abdominal pain), then withhold study medication and perform hepatic lab screening.

The sponsor and investigator had to agree that there was no evidence of liver disease to restart medication.

*If patient has Gilbert's Syndrome, the total bilirubin must be > 4 xULN to be classified as Alert Status 2/3.
1. Enhanced Hepatic Function Kit includes ALT, AST, AlkPhos, TBili, indirect bilirubin if TBili elevated, glucose, transferring saturation, amylase, lipase, cholesterol, triglycerides, TSH, Hepatitis B Surface Antigen (HBsAg) screen w/ confirmation, Hepatitis C Antibody (Anti-HCV), HBV PCR, HVC PCR, Anti-Liver-Kidney-Microsome (Anti-LKM-1), Anti-Mitochondrial Antibody (AMA), Anti-Nuclear Antibody (ANA), Anti-

Smooth Muscle Antibody (ASMA), Ceruloplasmin, and alpha 1-anti-trypsin. Use instituted with Protocol Amendment 2 (dated May 24 2007).

The bulletin noted that if the LFTs normalize and then rise, then the enhanced hepatic function kit should be repeated because of the possibility of acute viral hepatitis. 2. Liver Function Test kit includes AST, ALT, AlkPhos and TBili (and indirect bilirubin if TBili elevated).

Subjects discontinuing medication should receive appropriate anticoagulation per the investigator.

For any subject being followed with weekly monitoring, if after 4 weeks of monitoring, these values are either stable or improving, but remain > 2 xULN, or if the cause of the LFT abnormality is deemed by the investigator and the sponsor not to be drug related, the monitoring may be decreased.

## 9.7 Additional Information on FDA Liver Review

Drug induced liver injury is a diagnosis of exclusion; hence, to make a diagnosis, the results of tests excluding other etiologies of injury (pertinent positive as well as negative findings) are needed. Drs. Senior and Seeff reviewed and scored the cases of interest for completeness of information (CMP) and informative use of the data (INF). These scores were based primarily on information provided to the Agency at the time of NDA filing, including brief sponsor narratives, case report forms and any available source documents. In some cases, additional information submitted in response to an Agency request was also considered.

The CMP score was based on the extent to which alternative causes for liver findings were investigated. The INF score was based on whether the information obtained from testing supported the likelihood decision. For example, whether or not the result of hepatitis A IgM testing was positive (and if so, just once or serially), when the test was done relative to the course of acute liver injury, and whether the result was confirmed by PCR and later, by the development of IgG.

The CMP and INF scores are shown below for the 55 liver cases reviewed. Very few cases had all key elements/enough for a definite conclusion of cause (CMP scale). Very few cases were scored as having a good basis for the causal decision/an incontrovertible causality assessment. This should be viewed as a limitation of the data.

**Table 93. Completeness and information scores for 55 liver cases**

| CMP | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 0 | No information provided | 0 | 2 | 0 |
| 1 | A couple of items | 4 | 1 | 5 |
| 2 | Several items | 6 | 6 | 11 |
| 3 | Most of the key items | 6 | 5 | 7 |
| 4 | All key items | 0 | 2 | 0 |
| 5 | Enough for definite conclusion of cause | 0 | 0 | 0 |

| INF | Definition | D110 | D150 | W |
|---|---|---|---|---|
| 0 | Completely unsupported attribution | 0 | 1 | 0 |
| 1 | Very poor or weak attribution | 4 | 1 | 3 |
| 2 | Somewhat supported attribution | 5 | 6 | 8 |
| 3 | Very well supported conclusion | 5 | 6 | 9 |
| 4 | Very good basis for causal decision | 2 | 2 | 3 |
| 5 | Incontrovertible causality assessment | 0 | 0 | 0 |

## 9.8 Timing of Events Following Medication Discontinuation

### Table 94. Stroke or SEE occurring off of therapy

| | DE 110mg bid | DE 150mg bid | Warfarin N |
|---|---|---|---|
| After permanent stop of study medication | 72 | 62 | 44 |
| 1<= and <2 days | 6 | 2 | 0 |
| 2<= and <3 days | 1 | 3 | 2 |
| 3<= and <4 days | 2 | 0 | 0 |
| 4<= and <=6 days | 5 | 3 | 2 |
| 6< and <=14 days | 9 | 8 | 9 |
| 14< and <= 30 days | 5 | 6 | 1 |
| 30< and <=60 days | 7 | 8 | 2 |
| 60< and <=90 days | 4 | 4 | 2 |
| > 90 days | 33 | 28 | 26 |
| Randomized but not treated | 0 | 0 | 0 |
| After temporary stop of study medication | 10 | 6 | 10 |
| 1<= and <2 days | 0 | 2 | 2 |
| 2<= and <3 days | 0 | 0 | 1 |
| 3<= and <4 days | 0 | 0 | 0 |
| 4<= and <=6 days | 1 | 1 | 1 |
| 6< and <=14 days | 3 | 1 | 1 |
| 14< and <= 30 days | 3 | 1 | 2 |
| 30< and <=60 days | 2 | 0 | 0 |
| 60< and <=90 days | 0 | 1 | 0 |
| > 90 days | 1 | 0 | 3 |
| Before start of study medication | 0 | 2 | 0 |

[Source: Sponsor, Table 15.3.5.4:1]

**Table 95. Major bleeds occurring off of study medication**

| | DE 110mg bid | DE 150mg bid | Warfarin N |
|---|---|---|---|
| After permanent stop of study medication | 102 | 107 | 84 |
| 1<= and <2 days | 16 | 10 | 8 |
| 2<= and <3 days | 5 | 6 | 5 |
| 3<= and <4 days | 4 | 2 | 1 |
| 4<= and <=6 days | 11 | 6 | 7 |
| 6< and <=14 days | 9 | 5 | 15 |
| 14< and <= 30 days | 8 | 6 | 9 |
| 30< and <=60 days | 4 | 10 | 6 |
| 60< and <=90 days | 6 | 5 | 4 |
| > 90 days | 39 | 57 | 29 |
| Randomized but not treated | 0 | 0 | 1 |
| After temporary stop of study medication | 50 | 53 | 66 |
| 1<= and <2 days | 8 | 9 | 7 |
| 2<= and <3 days | 8 | 5 | 5 |
| 3<= and <4 days | 4 | 10 | 5 |
| 4<= and <=6 days | 13 | 10 | 19 |
| 6< and <=14 days | 9 | 10 | 19 |
| 14< and <= 30 days | 3 | 3 | 3 |
| 30< and <=60 days | 1 | 3 | 3 |
| 60< and <=90 days | 2 | 1 | 0 |
| > 90 days | 2 | 2 | 5 |
| Before start of study medication | 0 | 2 | 0 |

[Source: sponsor, Table 15.3.5.4:2]

## 9.9 RE-LY Follow-up Visit CRF

RE-LY 1 MONTH FOLLOW-UP VISIT FORM CRF 14

DataFax #177 Plate #014 Visit #004

PATIENT ID: Centre No. Patient No. PATIENT INITIALS: F M L

1. Date of Visit: year month day

2. Type of Visit
- ☐ Clinic Visit
- ☐ Home Visit
- ☐ Telephone Visit
- ☐ Other _____

**PART A. STUDY OUTCOME EVENTS**

*Since the last follow-up visit, up to and including this visit, has the patient experienced any of the following study outcomes:*

| | No | Yes | | Report Number(s) Submitted |
|---|---|---|---|---|
| 1. Stroke | ☐ | ☐ | → Stroke Report CRF 110 | # ☐☐ TO ☐☐ |
| 2. Myocardial Infarction | ☐ | ☐ | → MI Report CRF 114 | # ☐☐ TO ☐☐ |
| 3. Non-CNS systemic embolism | ☐ | ☐ | → Non-CNS Systemic Embolus Report CRF 116 | # ☐☐ TO ☐☐ |
| 4. Transient ischemic attack | ☐ | ☐ | → TIA Report CRF 118 | # ☐☐ TO ☐☐ |
| 5. Major bleeding | ☐ | ☐ | → Major Bleeding Report CRF 122 | # ☐☐ TO ☐☐ |
| 6. Minor Bleeding | ☐ | ☐ | → Minor Bleeding Report CRF 124 | # ☐☐ TO ☐☐ |
| 7. Pulmonary Embolism | ☐ | ☐ | → Pulmonary Embolism Report CRF 128 | # ☐☐ TO ☐☐ |
| 8. Death | ☐ | ☐ | → Death Report CRF 126 and 127 | |

**PART B. OTHER INFORMATION**

*Since the last follow-up visit, up to and including this visit, has any of the following occurred:*

| | | | | |
|---|---|---|---|---|
| 1. Cardioversion | ☐ | ☐ | → Cardioversion Report CRF 132 | # ☐☐ TO ☐☐ |
| 2. Emergency/Elective Surgery | ☐ | ☐ | → Interruption of Anticoagulant Report CRF 140 | # ☐☐ TO ☐☐ |
| 3. Admission to hospital | ☐ | ☐ | → Hospitalization Report CRF 120 | # ☐☐ TO ☐☐ |
| 4. Serious Adverse Event | ☐ | ☐ | → Serious Adverse Event (SAE) Report, Page 1 and 3 (Page 2 is optional) | # ☐☐☐ TO ☐☐☐ |
| 5. Experienced any other untoward medical occurrence | ☐ | ☐ | → Adverse Event CRF 155 | # ☐☐☐ TO ☐☐☐ |
| 6. Change in concomitant medications | ☐ | ☐ | → Concomitant Medications Report CRF 09 | # ☐☐ TO ☐☐ |
| 7. INR Evaluations done | ☐ | ☐ | → INR Log CRF 60 | # ☐☐ TO ☐☐ |



*Please fax this form to the PHRI Project Office within 48 hours of the patient follow-up visit*

PART C. CLINICAL ASSESSMENT AT THIS VISIT:

1. Sitting Heart Rate: ☐☐☐ beats/min (Patient sits for 3 min. before measuring)

2. Sitting Arm BP: Systolic ☐☐☐ / Diastolic ☐☐☐ mmHg (Patient sits for 3 min. before measuring)

PART D. STUDY MEDICATION

1. Was study medication discontinued (temporary or permanent) or re-started ☐ No ☐ Yes → Complete Study Medication Discontinuation/Restart CRF 151 # ☐☐ TO ☐☐

2. Was study medication dispensed since last visit? ☐ No ☐ Yes → Complete Study Medication Dispensation CRF 04 Report # ☐☐

3. Was study medication returned at this visit? ☐ No ☐ Yes

4. Study medication compliance: (dabigatran patients only) ☐☐☐ %

PART E. LABORATORY EVALUATIONS

1. Was blood collected since the last follow-up visit, up to and including this visit?

☐ No → Explain: _____

☐ Yes → Specify where sample sent:

a. Central Lab: ☐ No ☐ Yes → Blood Collection and Shipment Report CRF 66 Report# ☐☐

→ PK/PD/aPTT Blood Collection and Shipment Report CRF 68 ☐☐ OR ☐ Indicate if Not Done

b. For Hepatic Function lab tests:
Complete the Hepatic Function Laboratory Report CRF 62 → Report # ☐☐

PART F. STROKE EVALUATION

1. Has the patient reported a stroke since the last visit:

☐ Yes → *Ensure you have completed CRF 110 and recorded the report # on CRF 14*

☐ No → *Complete questions below*

*NOTE: Please ask these questions exactly as they are written and record patient's response.*

a. Since the last visit, have you been told by a physician that you had a stroke?

☐ No ☐ Yes

b. Since the last visit, have you had a sudden numbness or painless weakness on one side of your body that lasted for more than one day?

☐ No ☐ Yes

c. Since the last visit, have you had a sudden painless loss of vision on one side or in one or both eyes that lasted for more than one day?

☐ No ☐ Yes

d. Since the last visit, have you suddenly lost the ability to understand what people are saying or lost the ability to express yourself verbally or in writing for more than one day?

☐ No ☐ Yes

PART G. BLEEDING EVALUATION

1. Has the patient reported a bleed since the last visit:

☐ Yes → *Ensure you have completed CRF 122 or CRF 124 and recorded the report # on CRF 14*

☐ No → *Complete questions below*

*NOTE: Please ask these questions exactly as they are written and record patient's response.*

a. Since the last visit, have you had any unusual bleeding?

☐ No ☐ Yes → Specify: _____

b. Since the last visit, have you had any unusual black tarry bowel movements?

☐ No ☐ Yes → Specify: _____

c. Since the last visit, have you been told about any reduced blood count/haemoglobin?

☐ No ☐ Yes → Specify: _____

# 10 Overview of Changes Made to August 24, 2010 Review

The initial Clinical review of NDA 22-512, dabigatran for the prevention of stroke and systemic embolism in patients with atrial fibrillation, was finalized on August 24, 2010 and was included in the FDA Briefing Document for the September 20, 2010 Cardiovascular and Renal Drugs Advisory Committee meeting for NDA 22-512. This amended review contains Dr. Beasley's addendum on the risk of myocardial infarction (finalized on September 2, 2010), comments on labeling and an additional analysis performed after the Advisory Committee Meeting (see section 9.3). This amended review also corrects:

1. Figure 10 (Figure 9 in initial review) showing events (death and stroke) by the frequency of INR monitoring and level of INR control in subjects;
2. Table 71 (Table 60 in initial review) showing liver test abnormalities in the randomized population;
3. the numbering of tables and figures[27];
4. typographical and formatting errors; it also further clarifies some text contained in the review.

## 10.1 Myocardial Infarction Addendum Dated September 2, 2010

**Background**

*Experience with other drugs in its class*

The risks of cardiovascular events with ximelagatran, another oral direct thrombin inhibitor, were unclear. There were more coronary artery disease (CAD) adverse events in ximelagatran compared to warfarin treated subjects in the short term studies for prevention of venous thromboembolism (VTE).28 However, the long-term studies for stroke prevention in atrial fibrillation were inconsistent. SPORTIF III had a greater number of adjudicated acute MIs in ximelagatran compared to warfarin treated subjects, (24 (1.1%) and 3 (0.6%) respectively), as well as more serious cardiac events.29 In contrast, SPORTIF V had a smaller number of adjudicated MIs in ximelagatran compared to warfarin treated subjects (26 (1.0%) and 37 (1.4%), respectively); serious cardiac events were less in the ximelagatran arm.[2] Lastly, the secondary prevention

27 Some of the tables and figures in the August 24, 2010 FDA Briefing Document lacked numbers and were not included in the Table of Contents. This error has been correctly in the amended review and, as a result, table and figure numbers in the amended document may or may not correspond with the numbers in the August 24, 2010 Briefing Document.

28 See appendix for table of CAD adverse events in EXULT trials.

29 Taken from SPORTIF trial publications. For SPORTIF V, number given is reported as "on-treatment"; number for SPORTIF III described as ITT. See appendix for table of serious coronary adverse events in SPORTIF trials.

following MI phase 2 study suggested favorable effects of ximelagatran on secondary prevention.30

*Warfarin*

To interpret the findings, it is important to understand the effect of warfarin. As noted in the appendix of the primary review, few MIs were reported in the historical trials that established warfarin's efficacy for the prevention of stroke in subjects with atrial fibrillation. This makes it difficult to ascertain what, if any effect, warfarin has on this outcome. In the Warfarin, Aspirin, Re-Infarction study (WARIS II), an open-label, randomized study of patients hospitalized for acute myocardial infarction and treated with warfarin (target INR 2.8 to 4.2), aspirin (160 mg) or a combination of warfarin (target INR 2.0 to 2.5) plus aspirin (81 mg) post-infarction, a statistically significant reduction in the risk of re-infarction was seen in the warfarin compared to aspirin arm (rate ratio 0.74, 95% CI: 0.55-0.98, p-value <0.03). Relative to the aspirin arm, a statistically significant reduction in re-infarction was also seen in the group treated with warfarin plus aspirin (rate ratio 0.56, 95% CI: 0.41-0.78, p-value <0.001). Whether or not similar warfarin effects would be expected in current practice (i.e., given other advances in anti-platelet therapies) is not clear.

*Experience with dabigatran in other treatment programs*

Data with dabigatran for the treatment of VTE and following ACS do not suggest an increased risk of MI or ACS. RE-COVER was a phase 3, non-inferiority trial comparing 6 months of dabigatran 150 mg BID to warfarin (adjusted to an INR 2-3) for the treatment of acute VTE. Very few ACS events were observed in the 1273 subjects treated with dabigatran and in the 1266 subjects treated with warfarin.31 In RE-DEEM, a phase 2, placebo-controlled study of dabigatran dosed twice daily for 6 months in patients on dual antiplatelet therapy after ACS (n~1860), the number of coronary events in the 110 mg and 150 mg dabigatran treatment arms were not greater than in the placebo arm or in subjects on lower doses of dabigatran (see table below). The events were small, however, and the sponsor's categorization of events for the purpose of analyses (non-fatal MI versus CV death) prevents a comparison of total MI event rates (fatal and non-fatal) across treatment arms.

30 See appendix for discussion of ESTEEM.
31 Schulman S et al for the RE-COVER Study Group. NEJM 2009; 361:2342-52.

**Table 96. CV death, non fatal MI and non-hemorrhagic stroke in RE-DEEM**

| | Placebo | | DE 50 | | DE 75 | | DE 110 | | DE 150 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Treated patients | 371 | (100) | 369 | (100) | 368 | (100) | 406 | (100) | 347 | (100) |
| Patients with event | 14 | (3.8) | 17 | (4.6) | 18 | (4.9) | 12 | (3.0) | 12 | (3.5) |
| Cardiovascular death | 9 | (2.4) | 8 | (2.2) | 9 | (2.5) | 5 | (1.2) | 4 | (1.2) |
| Non-fatal MI | 4 | (1.1) | 9 | (2.4) | 8 | (2.2) | 7 | (1.7) | 8 | (2.3) |
| Non-haemorrhagic stroke | 3 | (0.8) | 0 | | 1 | (0.3) | 0 | | 0 | |

Each patient with an event was counted once for the composite endpoint and once for each individual component

[Source: REDEEM Clinical Trial Report dated February 25, 2010, Table 11.4.1.2.2:1]

**Review**

*Reviewer's comment: This addendum to the clinical review for NDA 22-512, (dabigatran for prevention of stroke and systemic embolic events) addresses the risk of MI in the RE-LY trial. Throughout this document, the term MI refers to a clinical MI. All references that include silent MI are clearly stated.*

In RE-LY, myocardial infarction was an adjudicated outcome event32 and was a component of a composite secondary endpoint that included stroke, systemic embolism, pulmonary embolism, and vascular deaths. Though analysis suggested favorable effects of dabigatran (relative to warfarin) on the composite endpoint, the original NDA submission (December 15, 2009) indicated an increased risk of MI with dabigatran as compared to warfarin (Table 2).

**Table 97. Relative and absolute risk of MI in RE-LY (original submission)**

| | **D110 v. W HR (95%CI) p-value** | **D150 v. W HR (95%CI) p-value** | **D110 v. D150 HR (95%CI) p-value** | **D110 N (%/yr)** | **D150 N (%/yr)** | **W N (%/yr)** |
|---|---|---|---|---|---|---|
| **Randomized**33 | 1.35 (0.98, 1.87) 0.070 | 1.38 (1.00, 1.91) 0.049 | 0.98 (0.73, 1.31) 0.88 | 86 (0.72) | 89 (0.74) | 63 (0.53) |
| **Safety population34** | 1.40 (0.98, 2.01) 0.066 | 1.42 (0.99, 2.03) 0.055 | 0.99 (0.71, 1.37) 0.94 | 70 (0.68) | 71 (0.69) | 52 (0.49) |

[source: Sponsor's tables 15.2.5:2, 15.2.2.3:1, 15.2.5:1, 15.2.5:3]
In case of recurrent event, the first adjudicated event was considered. The yearly event rate (%/yr) was calculated as the # of subjects with event/subject years *100.

32 MI definition located in Appendix.
33 These analyses included all events that occurred between the date of randomization and the date of study termination. Subject-years =sum (date of study termination-date of randomization +1) of all randomized subjects/365.25. Subject-years were 11,900, 12,039, and 11,797 for D110, D150, and W, respectively.
34 These analyses included all events that occurred from the date of first study medication to the date of last study medication plus 6 days. Subject-years =sum (date of last study drug intake-date of first study drug intake +1) of all treated subjects/365.25. Subject-years were 10,229, 10,253, and 10,661 for D110, D150, and W, respectively.

Following the refuse to file letter, the sponsor took measures to confirm the accuracy and integrity of the outcome events, including MI and silent MI (see Appendix). Silent MIs were a predefined outcome event, but because new Q-waves were not reported on the MI case report form, silent MIs were not considered in the sponsor's original analysis. The results of the quality roadmap check are shown in Table 3.

**Table 98. Additional adjudicated MIs identified by quality roadmap check**

| | D110 | D150 | W |
|---|---|---|---|
| **MI** | 1 | 0 | 3 |
| **Silent MI** | 11 | 8 | 9 |

The new clinical MI findings slightly reduced the risk of MI on dabigatran relative to warfarin and slightly shifted the p-value (Table 4). The absolute risk of MI, however, remained ~0.2% higher with dabigatran (and was not dose dependent).

**Table 99. Relative and absolute risk of MI in RE-LY (resubmission)**

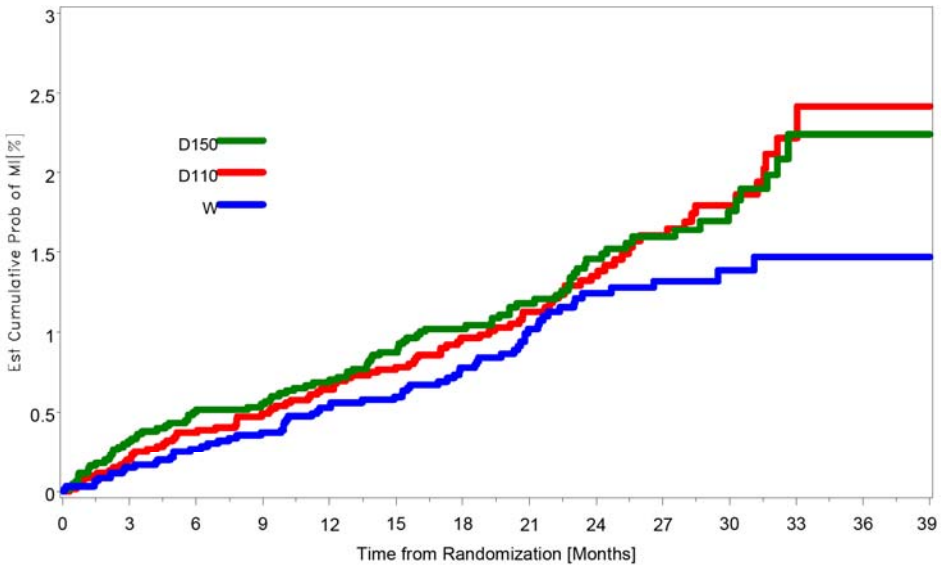
| | D110 v. W HR (95%CI) p-value | D150 v. W HR (95%CI) p-value | D110 N (%/yr) | D150 N (%/yr) | W N (%/yr) |
|---|---|---|---|---|---|
| **MI + silent MI, randomized35** | 1.29 (0.96,1.75) 0.09 | 1.27 (0.94,1.71) 0.12 | 98 (0.82) | 97 (0.81) | 75 (0.64) |
| **MI, randomized** | 1.30 (0.95, 1.80) 0.10 | 1.32 (0.96, 1.81) 0.09 | 87 (0.73) | 89 (0.74) | 66 (0.56) |
| **MI + silent MI, safety population36** | 1.32 (0.95, 1.84) 0.20 | 1.30 (0.94, 1.81) 0.12 | 80 (0.78 | 79 (0.77) | 63 (0.59) |

[source: Sponsor's tables 15.2.6.1: 1, 15.2.2.2:1_new, 15.2.5:2_new, 15.2.6.2:1_new, 15.2.6.1: 2, 15.2.6.2:7, resubmission]

The time to first adjudicated MI in the randomized population is shown in Figure 1. The curves are constant over time with the risk in the dabigatran arms greater than warfarin.

35 Subject-years were 11,899, 12,033, and 11,794 for D110, D150, and W, respectively.
36 Subject-years were 10,242, 10,261, and 10,659 for D110, D150, and W, respectively.

**Figure 27.Time to first adjudicated MI (randomized population)**




[Source: Reviewer's analysis: mi\time mi km (Kaplan Meier analysis of randomized population), sponsor's data set: adjrand]

*MI occurrence with respect to medication discontinuation*
There were numerically more MIs on dabigatran compared to warfarin during treatment, (table below). This numerical imbalance persisted off drug.

**Table 100. Number of subjects with MI by time of occurrence from study drug discontinuation**

| | D110 | | D150 | | W | |
|---|---|---|---|---|---|---|
| | n | % | n | % | N | % |
| Total randomized | 6015 | (100) | 6076 | (100) | 6022 | (100) |
| Total number of first MIs | 87[1] | (1.4) | 89 | (1.5) | 66 | (1.1) |
| MI on drug | 56 | (0.9) | 59 | (1.0) | 46 | (0.8) |
| MI within 6 days off | 13 | (0.2) | 10 | (0.2) | 8 | (0.1) |
| MI within 30 days off | 15 | (0.2) | 13 | (0.2) | 12 | (0.2) |
| MI > 30 days off | 15 | (0.2) | 17 | (0.3) | 8 | (0.1) |

[source: adapted from sponsor's table 15.2.5:15, resubmission] 1. The mutually exclusive categories total 86 because 1 MI occurred in a subject randomized but not treated.

*Reviewer's comment: There are a few points to consider for the table above. 1. The protocol specified that for dabigatran treatment groups with suspected ACS, dabigatran was to be temporarily discontinued. 2. The determination of the MI event date was not prespecified. Some source documents indicated that the MI date was the*

*hospitalization date; some indicated the MI date was the date of clinically significant cardiac enzymes.*

*Baseline characteristics*

There were no clear baseline differences between treatment groups that might in part explain the imbalance in MIs with dabigatran. Treatment groups were reasonably similar at baseline with respect to the following cardiovascular risk factors: hypertension, diabetes, coronary artery disease (CAD), prior MI, smoking status, age, and total cholesterol (see Table 23).[37] Baseline concomitant medications across treatment groups were also reasonably similar (notably, beta blockers, ACE inhibitors, statins, aspirin, clopidogrel, proton pump inhibitors).[10]

*MI severity*

Information on MI severity with respect to location (anterior or inferior) and post MI heart failure data were not routinely collected, but of the information available (see next table), the numbers suggest that the MIs on dabigatran were worse than the MIs on warfarin (more hospitalizations, more very high enzyme elevations). ECG changes were only captured as new Q-wave or ST-T changes. Characterization of severity by ST elevation or non-ST elevation was not captured. There were very few invasive procedures performed prior to the MI. The incidence of cardiovascular death following recent MI was low, with 15, 7, and 8 fatal MIs in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively [source: sponsor's listing 7.29, submission 132].

37 Mean total cholesterol was 180 mg/dL across all treatment arms. LDL cholesterol was not available.[reviewer's analysis]

**Table 101. Summary of MI report**

| | DE 110mg bid N (%) | DE 150mg bid N (%) | Warfarin N (%) |
|---|---|---|---|
| Total number of adjudicated MIs | 90 (100.0) | 102 (100.0) | 74 (100.0) |
| Hospitalized for the event | 85 ( 94.4) | 93 ( 91.2) | 68 ( 91.9) |
| Symptom compatible with acute MI | 74 ( 82.2) | 92 ( 90.2) | 61 ( 82.4) |
| ECG changes | 56 ( 62.2) | 59 ( 57.8) | 49 ( 66.2) |
| New Q-wave | 10 ( 11.1) | 7 ( 6.9) | 12 ( 16.2) |
| ST-T changes | 52 ( 57.8) | 56 ( 54.9) | 47 ( 63.5) |
| Cardiac enzymes/markers of myocardial necrosis completed | 83 ( 92.2) | 95 ( 93.1) | 70 ( 94.6) |
| Peak CK | 55 ( 61.1) | 63 ( 61.8) | 41 ( 55.4) |
| Within normal range | 17 ( 18.9) | 17 ( 16.7) | 8 ( 10.8) |
| >ULN and <=2xULN | 12 ( 13.3) | 18 ( 17.6) | 14 ( 18.9) |
| >2xULN and <=3xULN | 7 ( 7.8) | 5 ( 4.9) | 4 ( 5.4) |
| >3xULN and <=5xULN | 6 ( 6.7) | 5 ( 4.9) | 4 ( 5.4) |
| >5xULN | 13 ( 14.4) | 18 ( 17.6) | 11 ( 14.9) |
| Peak CK-MB | 52 ( 57.8) | 54 ( 52.9) | 44 ( 59.5) |
| Within normal range | 9 ( 10.0) | 5 ( 4.9) | 7 ( 9.5) |
| >ULN and <=2xULN | 11 ( 12.2) | 11 ( 10.8) | 6 ( 8.1) |
| >2xULN and <=3xULN | 4 ( 4.4) | 6 ( 5.9) | 5 ( 6.8) |
| >3xULN and <=5xULN | 9 ( 10.0) | 6 ( 5.9) | 7 ( 9.5) |
| >5xULN | 19 ( 21.1) | 26 ( 25.5) | 19 ( 25.7) |
| Troponin | 80 ( 88.9) | 91 ( 89.2) | 68 ( 91.9) |
| Within normal range | 0 | 2 ( 2.0) | 2 ( 2.7) |
| >ULN and <=2xULN | 15 ( 16.7) | 13 ( 12.7) | 10 ( 13.5) |
| >2xULN and <=3xULN | 4 ( 4.4) | 3 ( 2.9) | 6 ( 8.1) |
| >3xULN and <=5xULN | 7 ( 7.8) | 8 ( 7.8) | 5 ( 6.8) |
| >5xULN | 54 ( 60.0) | 65 ( 63.7) | 45 ( 60.8) |
| Invasive procedure performed prior to the event | | | |
| Angio | 7 ( 7.8) | 11 ( 10.8) | 7 ( 9.5) |
| PCI | 5 ( 5.6) | 10 ( 9.8) | 3 ( 4.1) |
| CABG | 0 | 0 | 0 |
| Other | 2 ( 2.2) | 4 ( 3.9) | 2 ( 2.7) |

[source: sponsor's table 7.25, appendix 3, submission 132]

The serious adverse event (SAE) data do not indicate more heart failure in the dabigatran arms compared to warfarin, however the reviewer did not link these SAEs to the MI event.

**Table 102. Heart failure serious adverse event terms**

| | D110 | D150 | W |
|---|---|---|---|
| cardiac failure congestive | 83 | 58 | 73 |
| cardiac failure | 51 | 62 | 65 |
| cardiac failure acute | 5 | 1 | 7 |
| acute LV failure | 1 | 0 | 1 |
| cardiac failure chronic | 0 | 1 | 0 |
| cardiomyopathy | 2 | 0 | 1 |
| congestive cardiomyopathy | 2 | 0 | 0 |
| ischemic cardiomyopathy | 0 | 1 | 2 |
| LV dysfunction | 2 | 0 | 2 |
| LV failure | 1 | 1 | 0 |
| RV failure | 0 | 1 | 2 |
| **total** | **147** | **125** | **153** |

[source: adapted from sponsor's table 15.3.2.6:2, resubmission]

*Serious adverse events across treatment arms*
If dabigatran is likely to cause MI, then one would expect a trend for more unstable angina cases. There were 7, 13, and 5 serious unstable angina reports. Although numerically higher, these numbers are too small to definitively conclude that dabigatran increases the risk of MI.

## Reviewer's conclusions/recommendations

The rate of myocardial infarction (MI) was higher on dabigatran compared to warfarin in RE-LY. The reason for the higher rate of MI with dabigatran is unclear. Baseline subject characteristics and medication use were similar between treatment arms and do not in part explain the higher rate of MI with dabigatran. The imbalance in MIs was seen on drug as well as off drug. Whether or not the higher rate of MI with dabigatran represents the play of chance, an adverse effect of dabigatran or beneficial effects of warfarin on infarction risk remains unclear. If this is truly a drug-related adverse event, then treating 1000 subjects for one year will cause 2 excess MIs compared to treating with warfarin. This risk should be weighed with the other benefits and risks of dabigatran. At this time, the reviewer recommends describing the higher rate of MI with dabigatran in the label. The sponsor's phase 3 development program in subjects with Acute Coronary Syndromes (ACS) will likely provide a more definitive answer to this question.

## Appendix

### Background

*Ximelagatran*

The table below shows the greater number of CAD adverse events (MI, "other CAD") in ximelagatran compared to warfarin-treated subjects in the VTE prevention studies. In the EXULT trials, treatment with ximelagatran/warfarin started after total knee replacement and continued for 7 to 12 days.

**Table 103. Summary of CAD adverse events in trials of ximelagatran for VTE prevention following total knee replacement**

| | Exult A | | Exult B## | | Exult A and B | |
|---|---|---|---|---|---|---|
| Event: N (%) | Exanta N=1526 | Warfarin N=759 | Exanta N=1151 | Warfarin N=1148 | Exanta N=2677 | Warfarin N=1907 |
| MI | 11 (0.72) | 1 (0.13) | 5 (0.43) | 3 (0.26) | 16* (0.60) | 4* (0.21) |
| Other CAD (Angina/ischemia) | 3 (0.2) | 0 | 1 (0.17) | 1 (0.09) | 4 (0.15) | 1 (0.05) |
| Total | 14 (0.92) | 1 (0.13) | 6 (0.7) | 4 (0.35) | 20** (0.75) | 5** (0.26) |

*p=0.04951; ** p=0.02800

#Excluded 4 patients who did not take study medications, 3 in ximelagatran group (ID: #3206, #7086 and #10944) and 1 in warfarin group (ID: #9089) whose death was also adjudicated by the central adjudication committee as PE.

##one case of sudden death (#15016) in the warfarin group was included as MI and two cases of sudden deaths in the Exanta group (ID: #14366 and 12122) were excluded from the analysis.

Summarized from Module 5, vol. 1 Table 54 and vol. 2 Table 11.3.5.1; vol. 3 Table 55 and vol. 4 Table 11.3.5.1

[Source: Ximelagatran Clinical Review, Table 12]

In the SPORTIF trials, a relationship between ximelagatran and cardiac events was not clearly seen. In contrast, to the VTE trials, the mean duration of use of ximelagatran was upwards of a year in the SPORTIF trials (phase 3 studies of ximelagatran for the prevention of stroke and systemic embolism events in patients with atrial fibrillation). The discrepancies in MI findings were discussed on page 1. The table below also shows a numerically greater number of serious cardiac adverse events in the ximelagatran compared to warfarin arm in SPORTIF III; a finding not seen in SPORTIF V.

**Table 103. Cardiac adverse events in SPORTIF trials**

| | SPORTIF III | | SPORTIF V | |
|---|---|---|---|---|
| | Ximelagatran N=1698 | Warfarin N=1699 | Ximelagatran N=1953 | Warfarin N=1953 |
| MI as AE leading to death | 10 | 3 | 26 | 31 |
| MI as SAE not leading to death | 25 | 14 | 39 | 48 |
| Angina Pectoris as SAE not leading to death | 26 | 36 | 34 | 44 |
| Coronary artery disorder as SAE not leading to death | 6 | 6 | 20 | 15 |

[Source: FDA Clinical Review Ximelagatran for atrial fibrillation]

Numbers represent number of events; AE terms as reported in review

The findings in ESTEEM, a phase 2 study comparing 6 months of treatment with ximelagatran (4 doses) against placebo in the long-term treatment of patients who had recently been admitted for ST-segment elevation or non-ST-segment myocardial infarction (MI), did not suggest adverse cardiac effects of ximelagatran in this population. In ESTEEM, no increased incidence of MIs was seen in ximelagatran compared to placebo-treated subjects; in fact the numerical imbalance in MI events suggested possible favorable effects of ximelagatran on secondary prevention.

**RE-LY trial**

**Quality Control Roadmap checks for MI**

This process has been described in the clinical review (Section 3.1, Submission quality and integrity). Checks specific to MI included comparison of the MI Case Report Form (CRF) to the adjudication page, a keyword search on various CRFs (i.e., serious adverse events, hospitalization, etc.), and a check for new pathological Q-waves on the study termination CRF.

The silent MI cases were reviewed by "qualified and specially trained clinical monitors". Cases with obvious symptoms or other indicators of an MI were forwarded from the data center to the clinical site for confirmation/rejection of an event. All re-assessed cases received from the sites as confirmed events were sent to adjudication. Cases with no site response were also sent for adjudication. For silent MIs, the ECG traces were sent straight to adjudication.

Adjudication was done as previously described in the clinical review. All available ECGs were blindly adjudicated by at least two independent cardiologists. The diagnosis of silent MI was based on the study definition.

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/s/

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BACH N BEASLEY
10/18/2010

ALIZA M THOMPSON
10/18/2010
Amended Clinical Review NDA 22-512

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 22-512** **Applicant: Boehringer Ingelheim** **Stamp Date: Resubmitted April 19, 2010**

**Drug Name: Dabigatran** **NDA/BLA Type: P**

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | X | | | eCTD |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | X | | | |
| **LABELING** | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | X | | | |
| **SUMMARIES** | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | x | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | | | x | The vast majority of subjects in the clinical development program were enrolled in a single phase 3 clinical trial. There is a summary of clinical efficacy in module 2 that describes results in other trials. |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | x | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | | | | 505(b)(1) |
| **DOSE** | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title:<br>Sample Size: Arms: | X | | | Three phase 2 dose ranging studies were conducted in patients with atrial fibrillation. The extent to which these provide |

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | Location in submission: | | | | informative data on dosing will be a review issue. |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application?<br><br>Pivotal Study #1<br>Indication:<br><br>Pivotal Study #2<br>Indication: | X | | | A single, large phase 3 trial was conducted. |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | X | | | |
| **SAFETY** | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | X | | | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | X | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | x | |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| 23. | Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| **OTHER STUDIES** | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X | | | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | x | |
| **PEDIATRIC USE** | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | waiver |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | x | |
| **FOREIGN STUDIES** | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | X | | | |
| **DATASETS** | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |
| **CASE REPORT FORMS** | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | X | | | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **GOOD CLINICAL PRACTICE** | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

NONE AT THIS TIME.

| | |
|---|---|
| Nhi Beasley | June 3, 2010 |
| Reviewing Medical Officer | Date |
| Aliza Thompson | June 3, 2010 |
| Reviewing Medical Officer | Date |
| Avi Karkowsky | June 3, 2010 |
| Clinical Team Leader | Date |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22512 | ORIG-1 | BOEHRINGER INGELHEIM PHARMACEUTICALS INC | PRADAXA (DABIGATRAN ETEXILATE MESYLATE) |

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/s/

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BACH N BEASLEY
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06/03/2010

ABRAHAM M KARKOWSKY
06/03/2010