CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-307

OFFICE DIRECTOR MEMO

Office Director's Memo to File

Date: July 10, 2009

From: Robert Temple, MD
Director, ODE-I

To: File, NDA 22-307 – Effient (prasugrel hydrochloride) Tablets; Sponsor – Eli Lilly

Subject: Approval with REMs (Medguide)

I. Background

This review is based, in part, on the secondary review of Dr. Stockbridge, Director, HFD-110 (4/25/09), the revised CDTL review of Dr. Unger, the Deputy Director, HFD-110 (1/9/09), supplemented by his three additional reviews of chemistry, carcinogenicity, and bleeding issues (dated July 6 and 7, 2009), and the primary reviews cited by Dr. Unger, including particularly the primary medical review by Dr. Hicks, with an addendum dated July 8, 2009, and the Clinical Team Leader review by Dr. Marciniak, dated May 9, 2009.

The labeling Indications and Usage for prasugrel is:

> To reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:
>
> - Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI)
> - Patients with ST- segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.
>
> Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death.
>
> It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was

established. For the small fraction of patients that required urgent coronary CABG after treatment with Effient, the risk of significant bleeding was substantial. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

There have been few questions raised about the overall results of the clinical trial (TRITON-TIMI 38, TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) conducted to establish the effectiveness of prasugrel. TRITON-TIMI-38 was a 13,608 patient, double-blind, randomized, controlled trial comparing prasugrel and clopidogrel in patients with acute coronary syndrome (ACS, including unstable angina [UA], non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) who were to be managed with percutaneous coronary intervention (PCI). The trial showed a reduction in the combined endpoint of cardiovascular (CV) death, non-fatal MI, or non-fatal stroke in the UA/NSTEMI population (the primary endpoint), and in the entire ACS and STEMI populations, endpoints that could be analyzed after success in the UA/STEMI population. As noted in labeling, however, this represented primarily a reduction in the overall rate of non-fatal MIs, which included both clinically apparent (investigator reported) and "chemical" (CK-MB changes; seen especially in the early, in-hospital phase of the study). Much, but not all of the advantage of prasugrel was observed in the first 30 days of the study.

The TRITON-TIMI 38 trial also clearly showed a higher rate of serious bleeding on prasugrel, leading to an important concern: whether the benefit of reduced NFMI (many of them not clinically recognized) outweighed the risk of increased bleeding.

Many other concerns arose, and these were discussed at length internally and at the Cardiovascular and Renal Drugs Advisory Committee meeting on February 3, 2009 (which recommended approval by a 9 to 0 vote). They have also been raised in letters to FDA as well as in public discussion. These concerns include:

- Some instability of the prasugrel salt (conversion to base) in the lots of drug used in TRITON-TIMI 38 (and in the to-be-marketed drug). The base has poorer bioavailability (primarily C_{max}) in high pH environments (e.g., with concomitant use of proton pump inhibitors [PPIs]), and use of the salt was intended to avoid that. Correcting the instability would increase bioavailability relative to the product used in TRITON-TIMI-38, in patients receiving PPIs, so that there might be greater platelet inhibition.
- A finding of an increased rate of newly diagnosed malignancies in the prasugrel group after several months, raising the question whether the duration of recommended use should be limited, especially given that much of the advantage of prasugrel was early.
- Whether the delay in giving both drugs compared to recommended (although not uniform) practice disadvantaged clopidogrel compared to prasugrel (see third paragraph of Indications, above).
- Whether, in seeking a superior effect on platelet inhibition, and thus a greater reduction in CV events, Lilly chose too high a dose of prasugrel, thereby causing excess bleeding that might have been avoided. This question is not easily separated from the question of the underlying reason for prasugrel's greater effect in TRITON. There are two candidate explanations: 1) greater inhibition of platelet function by the chosen dose (60 mg loading, 10 mg

maintenance), or 2) the presence in the population (about 1/3) of CYP 2C19 poor metabolizers, who do not form any, or as much, of the active metabolite of clopidogrel that is wholly responsible for its platelet-inhibiting effect, leading to a significant fraction of clopidogrel "non-responders." This potential non-responder subset may be enlarged by concomitant use of proton pump inhibitors (PPIs), at least some of which are strong inhibitors of CYP 2C19 and cause reduced active metabolite formation. There is evidence, mainly from observational data, that there is, in fact, a clopidogrel non-responder subset. Whether this group, or part of it, could gain improved benefit from a higher clopidogrel dose is under study, but the question is not yet settled, and there are suggestions of decreased clopidogrel CV endpoint response in the presence of PPIs, as would be predicted.

II. Effectiveness

A. Overall Results

The principal evidence of effectiveness of prasugrel comes from a study called TAAL or TRITON-TIMI-38 that is described at length by Dr. Unger and Dr. Hicks (Clinical Review dated April 28, 2008). As noted earlier, it was a randomized double-blind (double dummy) trial comparing prasugrel (loading dose 60 mg plus 10 mg daily maintenance) with clopidogrel (300 mg loading dose plus 75 mg daily), in patients with ACS scheduled to undergo PCI. The objective was to show a reduction in a composite endpoint of CV death, NFMI, and NF stroke, over a median follow up of ≥ 12 months. It was an international study (30 countries) conducted at 725 study sites.

ACS included 1) UA: patients with a history of chest discomfort for ≥ 10 minutes at rest within 72 hours of randomization with persistent or transient ST segment deviation ≥ 1mm in ≥ 1 ECG leads but without CK-MB or troponin T elevation 2) NSTEMI: all of the above but without persistent ST elevation, and with elevated CK-MB or troponin T, or 3) STEMI: ≥ 20 minutes chest discomfort within 14 days and one of a) ST elevation ≥ 1min in ≥ 2 ECG leads, b) new LBBB, or c) ST depression ≥ 1min in 2 anterior precordial leads with history suggesting true posterior infarction. Patients were not to have had a thrombolytic within 24 hours, or streptokinase within 48 hours, active bleeding, a history of hemorrhagic or ischemic stroke within 3 months, INR > 1.5, platelets < 100,000/mm, or anemia (Hgb < 10 gm/dL), recent thienopyridine, need for anticoagulants or daily NSAID.

Randomization was stratified by presentation (UA/NSTEMI vs STEMI) and subjects could be randomized only after coronary arteriography with anatomy confirmed suitable for PCI, except that STEMI-patients within 12 hours of symptoms could be randomized at time of diagnosis if PCI was planned. Dosing could occur at any time between randomization and PCI.

All patients were given ASA, and anti-thrombin treatment was given as part of care. Essentially all other treatments (statins, anti-HTs, CCBs, BBs) could be given as needed.

Evaluations took place at 24 hours post PCI or discharge and at days 30, 90, 180, 270, 360, and 450.

The primary endpoint was based on a time to event analysis for a composite of CV death, NFMI and NF stroke in the UA/NSTEMI population, with further primary endpoints being the same composite in the total ACS and in the STEMI populations using a hierarchical approach. Secondary endpoints included effects at other times (day 30, day 90). In addition, and appropriately, analyses of total events (i.e., that were not the first event) were performed. This would include, e.g., deaths that occurred after an earlier acute MI. Results were generally similar for all of these analyses and for UA/NSTEMI and STEMI. All reported endpoints were adjudicated by a blinded clinical events committee.

As will be seen below, there is considerable interest in a variety of population subsets and their impact on both benefit (reduced NFMI) and risk (bleeding). These must be considered with care. Nonetheless, although we recognize the uncertainties inherent in unplanned subset analyses and treat subset results with caution, we also believe that efforts to optimize the benefit/ risk relationship for prasugrel, as is true for many drugs, demands attention to such subgroups.

Study results are shown in the following table from the approved labeling.

Table 5: Patients with Outcome Events (CV Death, MI, Stroke) in TRITON-TIMI 38

	Patients with events		From Kaplan-Meier analysis	
	Effient (%)	Clopidogrel (%)	Relative Risk Reduction (%)[a] (95% CI)	p-value
UA/NSTEMI	**N=5044**	**N=5030**		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	18.0 (7.3, 27.4)	0.002
CV death	1.8	1.8	2.1 (-30.9, 26.8)	0.885
Nonfatal MI	7.1	9.2	23.9 (12.7, 33.7)	<0.001
Nonfatal Stroke	0.8	0.8	2.1 (-51.3, 36.7)	0.922
STEMI	**N=1769**	**N=1765**		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	20.7 (3.2, 35.1)	0.019
CV death	2.4	3.3	26.2 (-9.4, 50.3)	0.129
Nonfatal MI	6.7	8.8	25.4 (5.2, 41.2)	0.016
Nonfatal Stroke	1.2	1.1	-9.7 (-104.0, 41.0)	0.77

[a] RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

The composite endpoint results are based on an analysis of time to first event (of CV death, NFMI, and NF stroke) and show statistically significant results in UA/NSTEMI (n=10,074) and in the smaller STEMI population (n=3534), with results clearly driven by NFMI. The individual endpoints reflect both primary and second events. There is a favorable trend on survival in the STEMI population but no evidence of an effect on survival in UA/NSTEMI. Labeling does not show results for the whole ACS population, as we felt the effect in the combined group was less informative, but this was a prospective primary endpoint (sequentially), and this larger population (n=13,608) there was a 19% risk reduction in the prasugrel group (9.4% vs 11.5%, p< 0.001).

The timing of benefit is of interest and shows an effect that is predominantly early in both UA/NSTEMI and STEMI, as shown in 2 figures from labeling:

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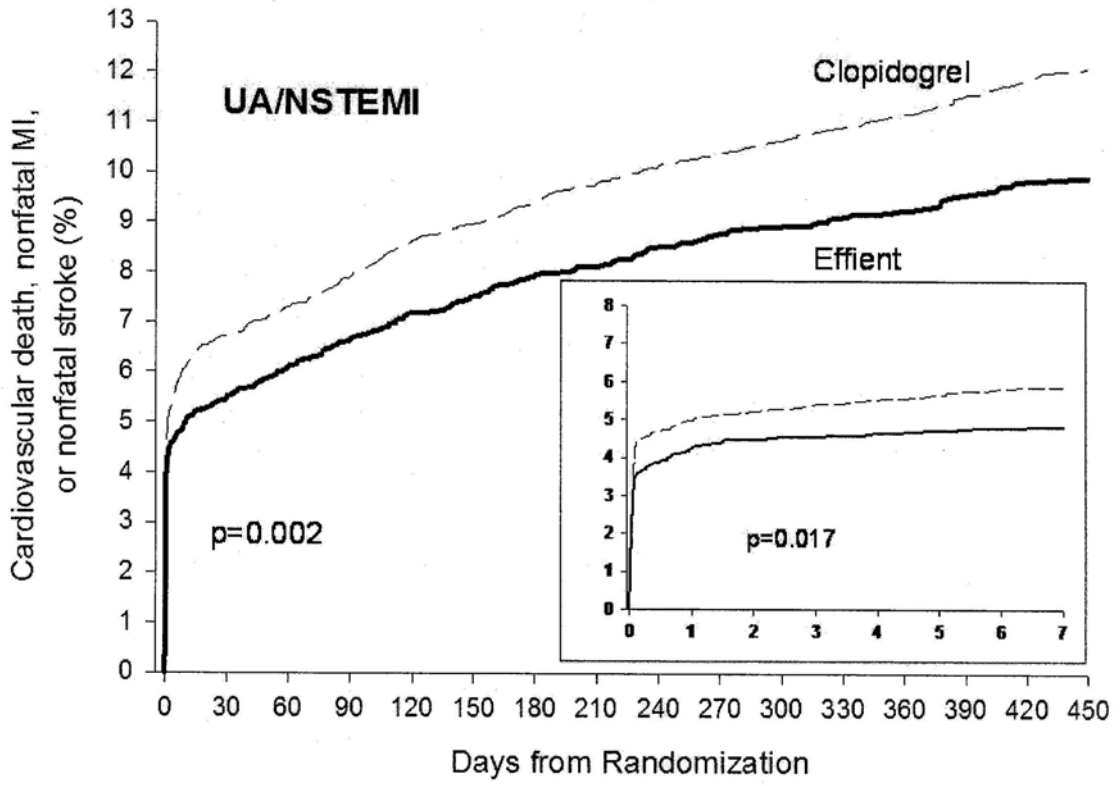
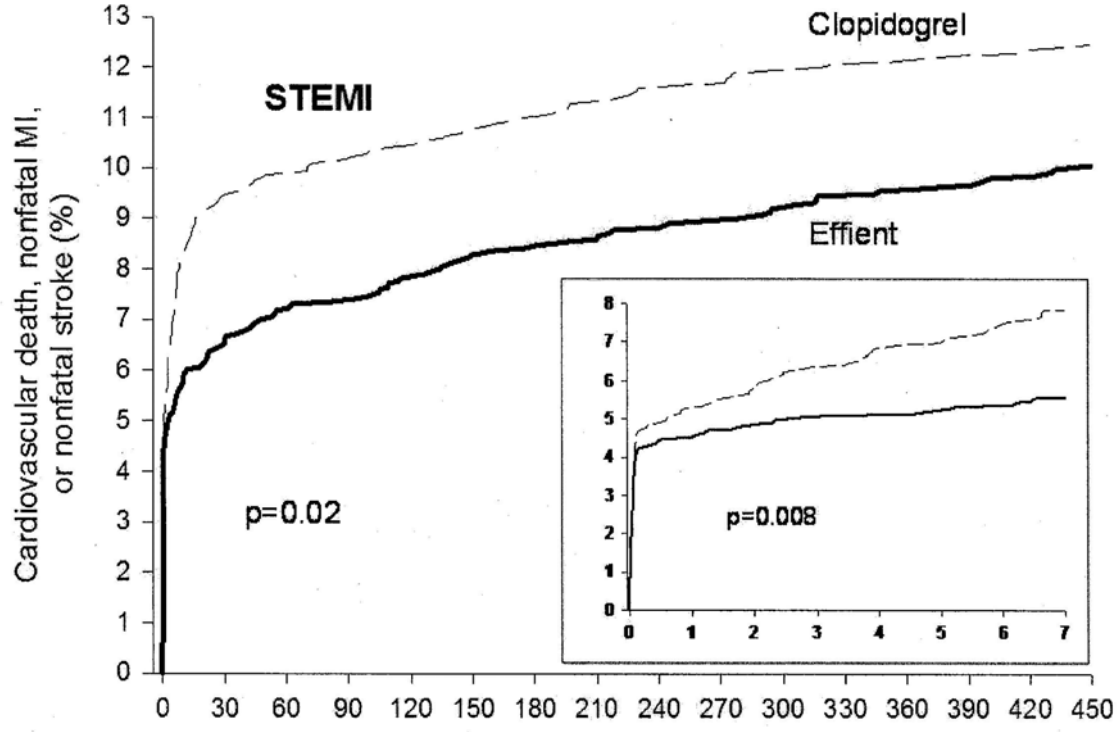

UA/NSTEMI
Clopidogrel
Effient
p=0.002
p=0.017
Cardiovascular death, nonfatal MI, or nonfatal stroke (%)
Days from Randomization

12


STEMI
Clopidogrel
Effient
p=0.02
p=0.008
Cardiovascular death, nonfatal MI, or nonfatal stroke (%)

These figures show clearly that many events occurred within hours of PCI (most of these were NFMIs detected by CK-MB blood tests), and that the advantage of prasugrel was also seen early, especially for UA/NSTEMI; in this group, however, there was a continued increase in between-group difference after 30 days. In the STEMI population, the advantage of prasugrel was seen over the first 7 and 30 days, with little further increase in that advantage after 30 days. This will be considered further when duration of treatment with prasugrel is discussed.

Labeling also notes a 50% reduction in stent thrombosis in the prasugrel-treated patients.

In any outcome trial, there is interest in effects in a variety of subsets of the population and forest plots, also taken from the label, are shown in the following two figures, one for UA/NSTEMI, the second for STEMI.

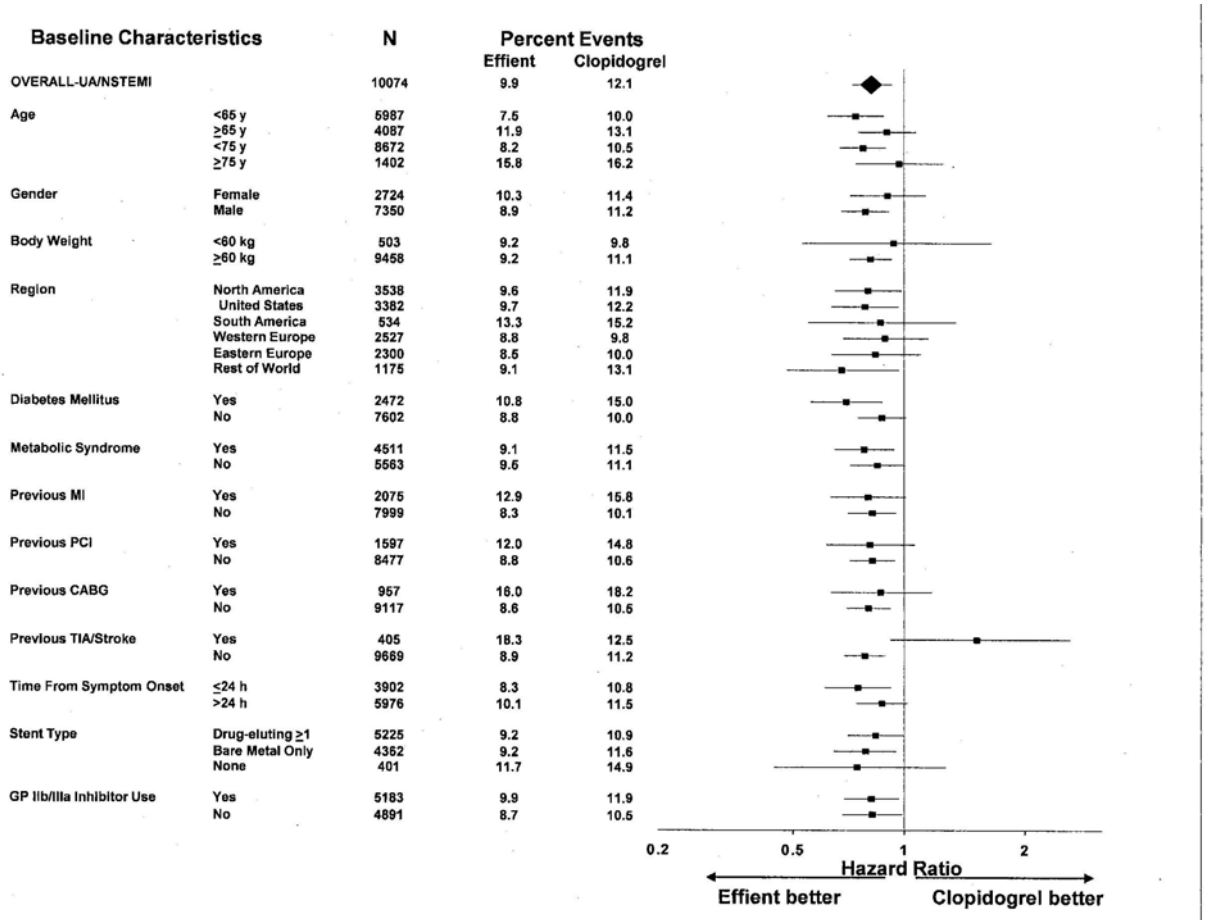


Figure 4: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – UA/NSTEMI Patients.

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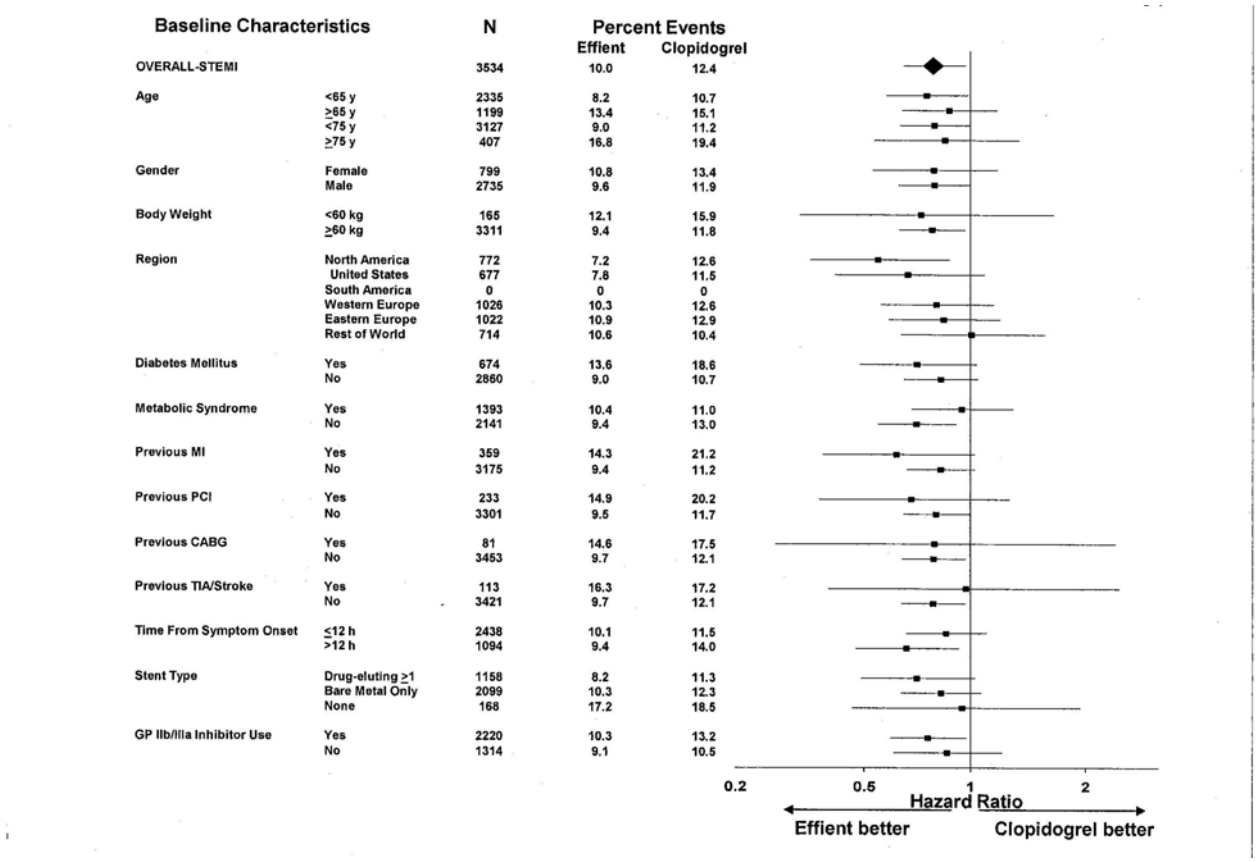

In any such display, there will be subgroups that appear to have greater or lesser effects. Such displays must be interpreted carefully, but several subgroups should be noted:

1. Age > 75

In the larger UA/NSTEMI group, the effect seems smaller in the subset of patients > 75 years, a group that probably also has only a small benefit from clopidogrel (CURE study). This minimal effect in the > 75 patients was notable because these patients also had more bleeding. Labeling therefore does not recommend use in most patients > 75. It was also noted, however, that high risk patients (patients with diabetes or prior MI) over 75, considering the entire ACS (UA/NSTEMI and STEMI) population, did appear to benefit, as shown in the following table from labeling

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Table 6: Subgroup Analyses for Time to First Event of CV Death, MI, or Stroke: Patients < or ≥75 Years of Age, ± Diabetes, ± Prior History of MI, All ACS Patient Population

	Effient		Clopidogrel			
	N	% with events	N	% with events	Hazard Ratio (95% CI)	p-value
Age ≥75						
Diabetes - yes	249	14.9	234	21.8	0.64 (0.42, 0.97)	0.034
Diabetes - no	652	16.4	674	15.3	1.1 (0.83, 1.43)	NS
Age <75						
Diabetes - yes	1327	10.8	1336	14.8	0.72 (0.58, 0.89)	0.002
Diabetes - no	4585	7.8	4551	9.5	0.82 (0.71, 0.94)	0.004
Age ≥75						
Prior MI - yes	220	17.3	212	22.6	0.72 (0.47, 1.09)	0.12
Prior MI - no	681	15.6	696	15.2	1.05 (0.80, 1.37)	NS
Age <75						
Prior MI - yes	1006	12.2	996	15.4	0.78 (0.62, 0.99)	0.04
Prior MI - no	4906	7.7	4891	9.7	0.78 (0.68, 0.90)	<0.001

The labeling notes that such subgroup analyses must be interpreted with caution, but the data fairly strongly suggest that it would be reasonable to consider use in patients over 75 who are at high risk because of, for example, diabetes or a remote history of MI, but not in other patients over 75.

2. Previous Transient Ischemic Attack/Stroke

In both UA/ NSTEMI and STEMI, patients with a prior transient ischemic attack (TIA) or stroke did badly on prasugrel (UA/NSTEMI) or show no advantage over clopidogrel (STEMI) on the composite endpoint. Indeed, they had a strikingly higher rate of stroke, both thrombotic and hemorrhagic.

	Prasurgel	Clopidogrel
Total Stroke	6.5%	1.2%
Thrombotic	4.2%	1.2%
Hemorrhagic	2.3%	0

In patients without a history of prior TIA or stroke, total strokes occurred at a rate of about 1% in both groups.

Use of prasugrel in patients with a prior history of stroke (even long ago; patients with a stroke or TIA within 3 months were excluded from TRITON) is contraindicated.

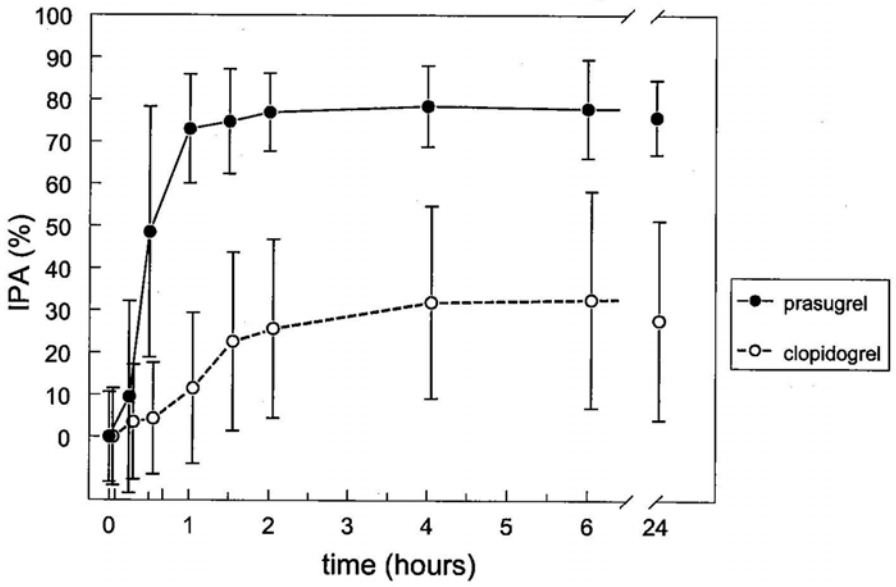
B. Reasons for effectiveness advantage and bleeding disadvantage of prasugrel.

1. Greater inhibition of platelet aggregation

As described in Dr. Unger's CDTL review of 1/1/09, the prasugrel dose was chosen based on two relatively small studies (TAAD and TAAH) comparing effects of clopidogrel and prasugrel on inhibition of platelet aggregation (IPA) and bleeding. TAAD showed that a loading dose of 60 mg

prasugrel gave more rapid and higher IPA than clopidogrel 300 mg and that maintenance doses above 10 mg caused excess bleeding. A small phase 2 study in patients undergoing PCI showed that a dose of 60 mg loading/ 10 mg daily did not seem to cause excess bleeding. The greater platelet inhibition by the 60 mg loading dose is shown in the following figure from Dr. Unger's review.

Figure 3: Inhibition of Platelet Aggregation (IPA) to 20 μM ADP, Following Loading Doses of Prasugrel 60 mg or Clopidogrel 300 mg (from Study TAAJ, mean ± SD)



Note that prasugrel rapidly (within an hour) gives 75-80% IPA inhibition, compared to about 30% after 1½-2 hours with 75 mg clopidogrel. There have been suggestions that the clopidogrel loading dose should be increased, but this has not been fully tested and, of course, the bleeding consequences have not been fully examined.

The 60/10 regimen thus represented a dose with greater IPA than clopidogrel and it was hoped and expected that this would yield a greater effect on CV events. And, indeed, a greater effect was seen. The same reasoning of course, leads to an expectation of more bleeding. But the relationship between the effect on IPA (a biomarker surrogate) to the effect on actual CV events is not established (we don't know, for example if, beyond some IPA inhibition, say 50%, no further reduction in CV events occurs) and thus can only be determined in outcome trials (like TRITON). Unfortunately, the size of these outcome trials makes good dose finding (say, randomization to low, medium, and high doses of prasugrel and to a standard dose of clopidogrel) difficult and, at least in most cases, such studies are not carried out. The early studies are not large enough to predict accurately the event rates and bleeding rates in a large study. We therefore do not have a good dose-response outcome study for CV events or for bleeding. It should be appreciated that there have also been suggestions that the loading dose of clopidogrel should be increased, both for the whole population and in patients who do not form as much of the active metabolite (see below).

The results of TRITON could be interpreted as confirming the sponsor's hypothesis that greater platelet inhibition would indeed yield greater reduction of CV events and, perhaps not surprisingly, greater numbers of bleeding events (see below), a known consequence of treatment with any thienopyridine platelet inhibitor. Although this may indeed be true, there is, however, an alternative explanation for at least some of that advantage.

2. Prasugrel is potentially effective in 100% of patients.

Both prasugrel and clopidogrel must be converted to an active metabolite to inhibit platelet aggregation. This is done by a number of CYP P450 enzymes for prasugrel but primarily by CYP 2C19 for clopidogrel; 2C19 is subject to genetic variations such that as much as a third of the population may form limited amounts of the active metabolite. In addition, some proton pump inhibitors, commonly used in older populations receiving anti-clotting drugs, can inhibit formation of the active metabolite. If, say, 25-30% of patients given clopidogrel have a diminished response, that might account for some of the TRITON results, both the greater effectiveness of prasugrel and the greater bleeding rate, depending on what the effect size of clopidogrel was in this study. In CURE (ACS study of clopidogrel) the overall effect vs placebo was about 2%. If 1/3 of patients could not respond, the effect in responders might be 3% vs placebo, or a 1% difference. If TRITON and CURE had the same clopidogrel effect, then if prasugrel differed from clopidogrel only in being effective in all patients, it should be about 1% better. In TRITON, however, the difference was 2%, suggesting that the advantage of prasugrel could have more than one basis.

Genomic data (specifically 2C19 deficiency) were collected from a 2534-patient subset of the TRITON study (about 20%); unfortunately, not all the samples were collected at baseline and many patients had had events by the time of sampling. The subset is thus a "convenience sample" that may not have been a random subset.

Of particular concern is the fact that the whole sampled population did not show the effect seen in the overall ACS population, i.e., a 19% reduction by prasugrel in event rate (11.5% vs 9.4%) but instead showed essentially no effect (both 8.8-8.9%). The results in the subset are nonetheless of interest. The following data come from the analysis (5/2/2007) of Dr. Ququan Liu.

In the extensive metabolizer group there was little difference between prasugrel and clopidogrel; in fact, clopidogrel was somewhat favored.

	Prasugrel		Clopidogrel	
	N	events	N	events
UA/NSTEMI	596	58 (9.7%)	623	47 (7.5%)
STEMI	243	18 (7.4%)	253	22 (8.7%)
All ACS	839	76 (9.1%)	876	69 (7.9%)

In the clopidogrel poor metabolizer group, in contrast, there was a suggestion of a substantial prasugrel advantage, but it was not consistent.

		Prasugrel		Clopidogrel
	N	events	N	events

UA/NSTEMI	284	18 (6.39%)	291	36 (12.4%)
STEMI	131	17 (12.9%)	113	10 (8.9%)
All ACS	415	35 (8.4%)	404	46 (11.4%)

In the UA/NSTEMI and all ACS populations prasugrel was superior in the poor metabolizers. In the small STEMI group, however, results went the other way, favoring clopidogrel, an inconsistency that is troublesome and precludes a firm conclusion. These data were therefore not included in labeling, although the last paragraph of section 14 (clinical studies) notes the possibility that the greater effect of prasugrel is the result of the presence of clopidogrel poor responders. Further genetic analyses are clearly needed [and are being conducted as a post-marketing commitment in Lilly's ongoing TRILOGY (medically managed ACS) study]. Nonetheless, although the data are not complete, there remains the possibility that the greater platelet inhibition of prasugrel is not the reason for all or most of prasugrel's advantage on CV events, or for its increased rate of bleeding, but that both prasugrel's advantage and bleeding disadvantage comes from the presence of a 2C19 deficient subset in the population, about 1/3 of patients in the TRITON sample. There were more bleeding events in the 2C19 poor metabolizers (5.6% to 1.5%) than in the normal metabolizers (6.8% vs 3.9%), again an observation that needs expansion and replication.

III. Safety

A. Bleeding

The clearest "downside" of prasugrel in the TRITON study is the excess of important bleeding, both TIMI major (clinically overt bleeding with a fall in hemoglobin of ≥ 3g/dL but < 5g/dL or intracranial hemorrhage), and TIMI minor (overt bleeding with a fall in hemoglobin of ≥ 3 g/dL but < 5 g/dL) with an overall rate of TIMI major or minor of 4.5% for prasugrel and 3.4% for clopidogrel (p =0.002). The following tables taken from labeling show these outcomes overall, in the weight < 60 kg and age > 75 subgroups, and in people who underwent CABG, who show a strikingly greater risk of bleeding on prasugrel.

Table 1: Non-CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)	p-value
TIMI Major or Minor bleeding	4.5	3.4	p=0.002
TIMI Major bleeding[b]	2.2	1.7	p=0.029
Life-threatening	1.3	0.8	p=0.015
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage (ICH)	0.3	0.3	
Requiring inotropes	0.3	0.1	
Requiring surgical intervention	0.3	0.3	
Requiring transfusion (≥4 units)	0.7	0.5	
TIMI Minor bleeding[b]	2.4	1.9	p=0.022

[a] Patients may be counted in more than one row.

Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient (%)	Clopidogrel (%)	Effient (%)	Clopidogrel (%)
Weight <60kg (N=308 Effient, N=356 clop)	10.1	6.5	0.0	0.3
Weight ≥60kg (N=6373 Effient, N=6299 clop)	4.2	3.3	0.3	0.1
Age <75 years (N=5850 Effient, N=5822 clop)	3.8	2.9	0.2	0.1
Age ≥75 years (N=891 Effient, N=894 clop)	9.0	6.9	1.0	0.1

Table 3: CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

[a] Patients may be counted in more than one row.

Note that there was no difference in intracranial hemorrhage and that fatal bleeds occurred at a low rate. Bleeding after CABG was a significant problem.

The risk of bleeding is greatest shortly after PCI, but persists over time, as shown in a figure from labeling.

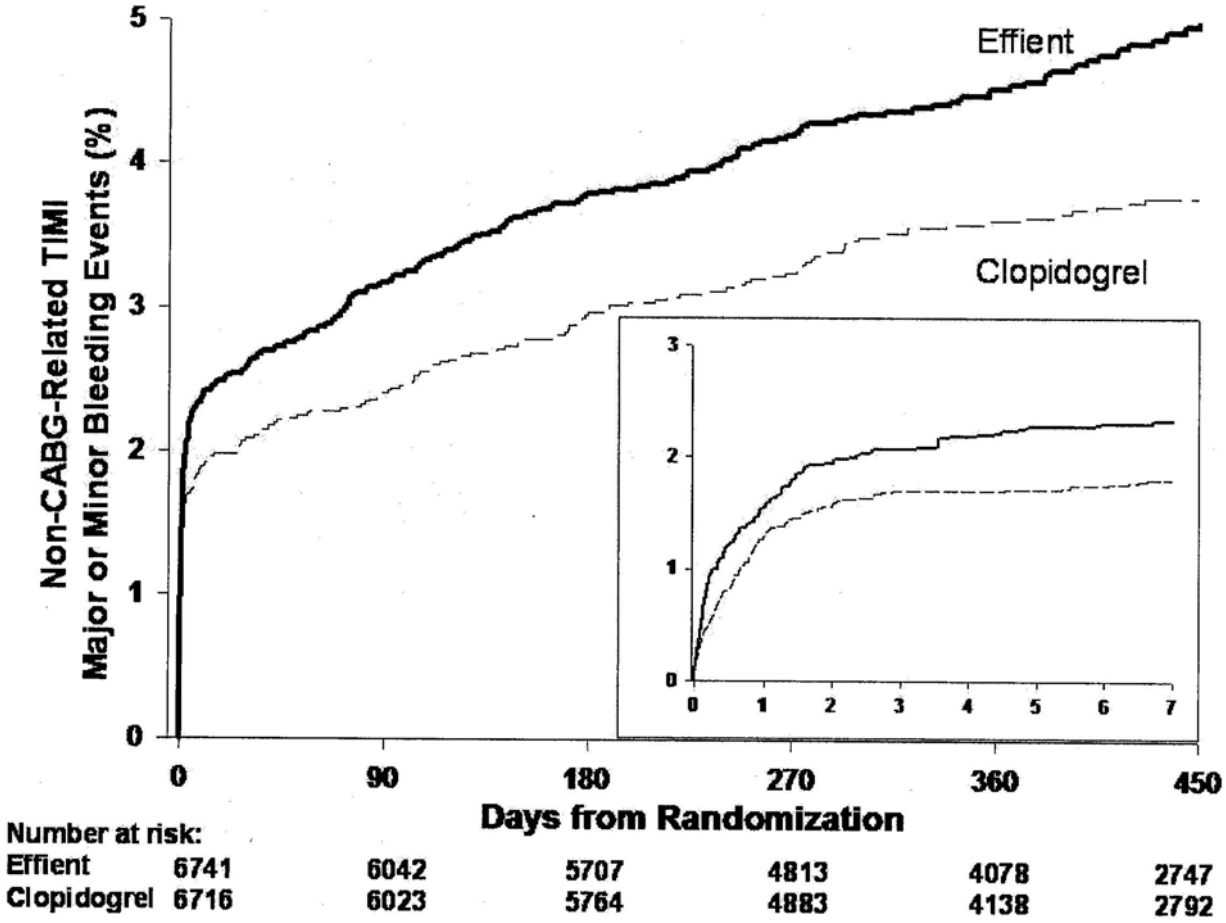


Figure 1: Non-CABG-Related TIMI Major or Minor Bleeding Events

The bleeding risk has led to

1. A boxed warning and warnings about bleeding risk and the particular risk in patients > 75 or who undergo CABG.

2. A statement in Clinical Studies that choice of therapy requires balancing the reduction of total endpoint events against the greater risk of significant bleeding.

3. A REMS consisting primarily of a Medguide warning about bleeding.

4. A post-marketing requirement to study reversal of prasugrel-induced platelet inhibition by exogenous platelets. This study will examine a potential treatment for CABG-related bleeding.

B. Malignancies

It was recognized by the sponsor and the review team that the prasugrel group in TRITON had experienced more malignancies than the clopidogrel group. There have been countless internal discussions, blinded analyses by staff of new (or possibly new) tumors, consideration of whether

our primary interest was in “new” or “new and worse” tumors, and statistical analyses. An early view by the sponsor that the excess of newly diagnosed malignancies, particularly of the GI tract, could be explained by bleeding has, on the whole, not been accepted. Dr. Unger’s July 7, 2009 review of this issue covers the discussion and the history and conclusions of our analyses, and Dr. Marciniak (updated review of May 6, 2009) discusses this issue in detail.

There is clearly an excess of newly identified tumors (or new and worse tumors) in the prasugrel group, beginning at about 4 months. This is too soon to represent de novo tumor induction but could suggest tumor growth promotion. The exact risk depends on whether one counts non-melanomatous skin cancer (clinically not important but arguably a pertinent tumor); labeling gives rates as 1.6% and 1.2% for prasugrel and clopidogrel, respectively, a risk increase of about 33% with colon and lung contributing most of the difference. The risk increase and nominal statistical significance depend on which tumors are included. There was also an increase in cancer-related deaths, but overall mortality was somewhat decreased in the prasugrel group for the whole study.

The pre-clinical evaluation (Carcinogenicity Assessment Committee) concluded that there was no evidence that prasugrel promoted malignancies and there is no history of such promotion in a human setting (erythropoietin perhaps representing an exception). They were aware of increased hepatocellular adenomas at high doses and some tendency toward increased hepatocellular carcinoma at the highest dose but did not find these observations critical. The rat showed no suggestion of increased neoplasia. The sponsor, at FDA’s request, carried out tumor promotion studies using explants of lung, colon and prostate cell lines in immunodeficient nude mice and in vitro studies of proliferation of cell lines derived from lung, colon, and prostate tumors. Prasugrel did not stimulate cell proliferation or growth of xenografts.

No one believes a definitive answer is possible without further data. Dr. Unger is skeptical about the reality of the increased rate of new tumors, given the benign animal data, including the recent tumor progression studies, the absence of examples of such tumor promotion or any mechanistic explanation, the similarity of its structure to clopidogrel, which shows no suggestion of tumor stimulation, and the inherent multiplicity of our safety analyses. I concur in this and would add to those reservations the marginal statistical support for the increase.

The February 2009 Advisory Committee noted the finding but was skeptical, urging its placement in the Adverse Reactions section, rather than in Warnings/Precautions, which is where it has been placed. There is a post-marketing requirement to collect baseline and subsequent cancer data in the ongoing TRILOGY trial.

Although no one in the Division of Cardiovascular and Renal Products believes the cancer findings should block approval, Dr. Marciniak believes the finding merits restriction of use to one month. This was at least partly because the mouse hepatic adenoma and carcinoma data convinced him that prasugrel may have the ability to stimulate tumor growth, the cardiovascular event rate diminishes with time, and the advantage of prasugrel relative to clopidogrel wanes over time. For the reasons given by Dr Unger, and additional considerations described below, I do not believe that would be appropriate.

IV. Risk-Benefit Considerations, Duration of Use, Time of Administration, Product Quality

A. Risk-Benefit

It is clear that prasugrel reduces the rate of NFMIs by about 20% and increases the rate of serious bleeds by about 30%. Although it might be tempting to add all the events (composite CV and bleeding) that does not appear reasonable, as the specific events must be weighed and judged. Thus, the excess of bleeding is troubling but there was no increase in fatal intracranial hemorrhage, a particular concern, and fatal bleeds were relatively few. Dr. Unger has summarized bleeding events in a review dated 7/6/09 and all cause mortality in a review dated 1/9/2009.

Table 3: CEC Adjudicated Bleeding

Non-CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58,11.1)	0.002
TIMI Life-Threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08,2.13)	0.015
TIMI Major	6741	146	2.2	6716	111	1.7	1.32 (1.03,1.68)	0.029
TIMI Minor	6741	164	2.4	6716	125	1.9	1.31 (1.04,1.66)	0.022
TIMI Minimal	6741	460	6.8	6716	314	4.7	1.47 (1.28,1.70)	0.022

CABG-Related

bleeding endpoint	Prasugrel			Clopidogrel			HR (95% C.I.)	p
	N	n	%	N	n	%		
TIMI Fatal	213	2	0.9	224	0	0.0		
TIMI Major	213	24	11.3	224	8	3.6	3.50 (1.53,7.99)	0.002

Table 10: Summary of Deaths in TAAL (adapter from sponsor's Table TAAL.11.10)

	Prasugrel n=6813		Clopidogrel n=6795		delta events per 1000 patients treated (positive = favorable for prasugrel)
	n	%	n	%	
All Cause Death	**188**	**2.76**	**197**	**2.9**	**1.4**
Cardiovascular (conponent of 1° efficacy endpoint)	**133**	**1.95**	**150**	**2.21**	**2.6**
atherosclerotic vascular disease (excluding coronary)	0	0	3	0.04	0.4
CHF/cardiogenic shock	31	0.46	30	0.44	-0.1
related to CABG or PCI	15	0.22	16	0.24	0.2
dysrhythmia	4	0.06	7	0.1	0.4
pulmonary embolism	3	0.04	0	0	-0.4
acute MI	24	0.35	36	0.53	1.8
sudden or unwitnessed	36	0.53	42	0.62	0.9
ICH	9	0.13	5	0.07	-0.6
non-hemorrhagic stroke	5	0.07	6	0.09	0.1
other cardiovascular	6	0.09	5	0.07	-0.1
Non-Cardiovascular	**55**	**0.81**	**47**	**0.69**	**-1.2**
accident/trauma	4	0.06	4	0.06	0.0
hemorrhage, non-ICH	9	0.13	1	0.01	-1.2
infection	11	0.16	10	0.15	-0.1
malignancy	21	0.31	17	0.25	-0.6
suicide	3	0.04	2	0.03	-0.1
other	7	0.1	13	0.19	0.9

The numbers in these tables differ slightly because of different adjudication times. There were 23 hemorrhagic deaths on prasugrel (about 0.3%) vs 5 (about 0.07%) on clopidogrel. Overall CV deaths were decreased on prasugrel by 17, and overall deaths were reduced by about 9. The time course of CV and overall deaths are shown in two figures.

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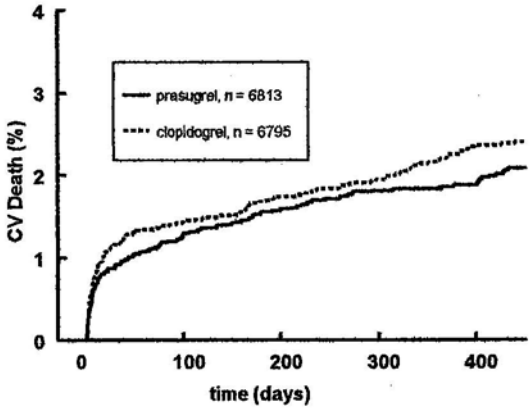

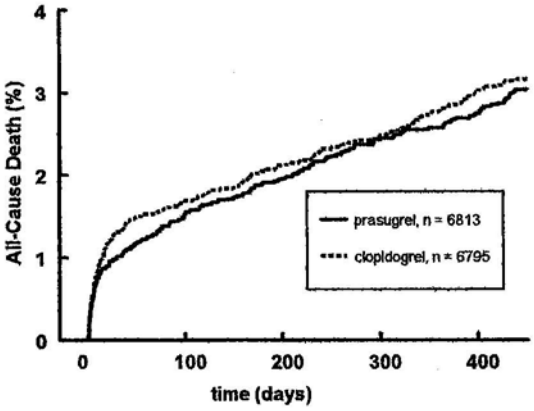

TRITON thus shows no real difference in survival between the two treatment groups. The effort to identify high risk groups in labeling and contraindicate or discourage prasugrel use in them (prior stroke, TIA, age > 75, CABG), should at least somewhat reduce the risk of hemorrhagic deaths. As Dr. Unger shows, in the < 75 group there were 12 bleeding deaths vs 4 (rather than 22/5). With no net adverse effect on deaths, prasugrel showed a decrease of some 145 NFMIs, about 25%. As expressed by Dr. Stockbridge, and as the Advisory Committee agreed, non-fatal MI's, even asymptomatic and peri-procedural ones, about 40% of the events in TRITON, are a concern and are widely thought to have long-term consequences (heart failure, arrhythmias, etc.) Certainly we have treated non-fatal MIs as a major concern with VIOXX, Zelnorm, etc. It must be noted also that much of the effect of clopidogrel in ACS is also on the same, often asymptomatic, MIs. Plainly, there is a judgment involved, but many will value the reduction in NFMIs that prasugrel can provide. Patients and physicians, of course, need to be fully informed, and patient- and physician-directed labeling will do so. What TRITON shows, even before use in high bleeding risk people was discouraged, is that prasugrel does not cause an increase in overall mortality, despite an excess or serious bleeds, but provides a substantial reduction in NFMI.

B. Duration of Use

As shown above, the advantage of prasugrel did not increase in the STEMI population after 30 days, although it does increase over time in UA/NSTEMI. The excess of bleeding does continue to grow slowly after 30 days. The absence of major increasing benefit over time, together with the malignancy finding, has convinced Dr. Marciniak that a switch to clopidogrel after 30 days is warranted. Dr. Hicks, in early reviews, also thought duration of use should be limited, but her most recent review, dated 7/8/09, reached the opposite conclusion, and strongly urges long-term treatment, largely because her detailed analyses showed that prasugrel gives a substantial (as much as 50%, from 1.8% to 0.9%) reduction in stent thrombosis, a potentially fatal event that is often a late event. She also notes, and I concur, that the stable (albeit not increasing) difference favoring prasugrel in the STEMI group after 1 month could represent continued prevention of events in a vulnerable population and that a switch to clopidogrel (something not studied) might lead to loss of the advantage and an increase in events.

C. Timing of Administration

TRITON initiated treatment, particularly in the UA/NSTEMI group, only after coronary anatomy was established, leading to some delay, after symptoms were recognized, in initiation of anti-platelet therapy. This delay to allow assessment of coronary anatomy allows avoidance of prasugrel or clopidogrel in patients who will need CABG, a group with a high rate of bleeding, especially after prasugrel.

As many of the CV events occur early after PCI, however, delay might be expected to increase the risk of CV events, especially in the hour or so after initiation when platelet inhibition was incomplete.

Dr. Marciniak (review of 5/6/2009) has been concerned that the delay might have substantially disadvantaged clopidogrel because of its slower onset of platelet inhibition (about an hour slower, as shown above), allowing events to occur, and that this use did not represent the early use of these agents generally recommended. He analyzed rates of primary endpoint events (first 10 days) for patients with varying times of initiation of treatment compared to the start of PCI, from 2 hours before to 3 hours after, finding a suggestion of greater benefit of prasugrel compared to clopidogrel when initiation was delayed.

The problems with this analysis are several. As Dr. Marciniak notes, the timing of drug administration is not random but could reflect patient conditions. More critical, probably, is that only a tiny fraction of patients received drug prior to PCI. The results of the event vs time of loading dose are shown in the following 2 figures from Dr. Marciniak's review.

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Figure 29: Rates of UA/NSTEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TAAL

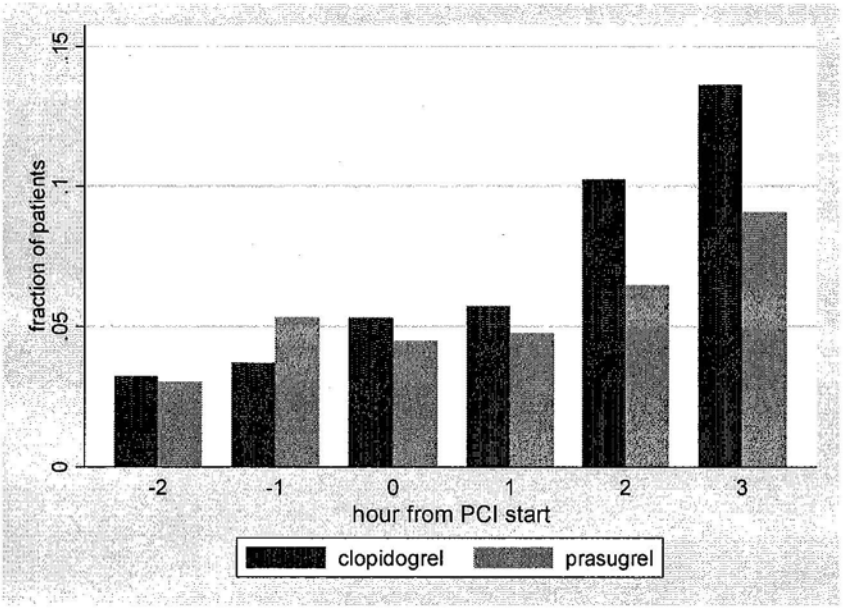
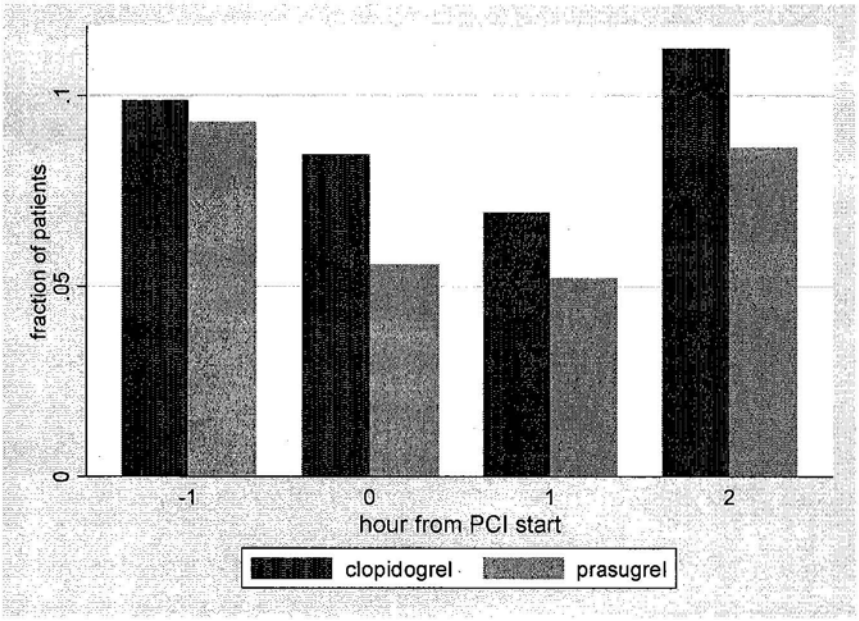


Figure 30: Rates of STEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TAAL



For the UA/NSTEMI group, there is a suggestion that delay might disadvantage both drugs, but especially clopidogrel, but the fraction of patients getting drug at -2 or -1 hours is very small, barely 200 total (vs 4500 with later treatment). For all treatment times with more patients,

prasugrel shows the advantage seen in the overall data. In STEMI (still smaller numbers, it is hard to see any relation of effect to timing.

Labeling for prasugrel will note that many events occur early and that use before coronary anatomy is established can be considered if need for CABG, with its increased risk of bleeding, is considered unlikely.

D) Product Quality

Prasugrel was prepared as a hydrochloride salt after it was recognized that the free base was less well absorbed in a high pH environment, an environment that would occur in patients using proton pump inhibitors (PPIs), a widely used class of drugs in older people. It was found, however, that conversion of salt to base occurred at many stages of manufacturing, so that the product used in TRITON was not entirely the salt but 60-70% base. Dr. Unger, in a memo drafted 7/6/2009 discusses this at length.

It cannot be known exactly what base proportion patients in TRITON received, but it was around 60-70%. Bioavailability studies showed that low (5%) conversion product and medium and high conversion product (58%, 70%) were bioequivalent (C_{max} and AUC) in low pH settings, but were not when given with lansoprazole (i.e., a high pH setting), where the highest conversion product had lower C_{max}.

The main effect of such a difference would be on the speed of inhibiting platelet aggregation (IPA) after the loading dose and indeed, a study of IPA after dosing with low, medium and high conversion lots showed a small delay in reaching 40-50% inhibition (but still well above clopidogrel's effect). Given the prolonged inhibitory effect on platelets of prasugrel or clopidogrel, the main concern would be delayed effect. All dosages reached similar levels of IPA inhibitor by 2 hours and were close at 1 hour. No decreased effect on effectiveness other than in the first 20 minutes seems conceivable even with the highest conversion product. A possible concern would be the greater inhibition in the PPI setting provided by a low conversion product, like the one being developed by the sponsor, but 60% of patients in the trial did not take PPIs and would have been experiencing that level of inhibition already. An examination of the effective of prasugrel vs clopidogrel in people taking vs not taking a PPI showed essentially no difference in effect.

V. Conclusion

It is relatively unusual for a drug within a class to have a greater effect than other members of the class and when this is shown, there is inevitably the question of the cost in adverse effects. In the present case, the advantage shown by prasugrel in TRITON could represent primarily a greater willingness to "push" the dose and inhibit platelets more than the control drug, clopidogrel had, with a resulting greater reduction in NFMIs and a greater likelihood of significant bleeds. It may also represent a drug that does not require metabolic activation by an enzyme missing in many people, so that there are fewer non-responders, i.e., people who both do not receive beneficial effects on CV events and do not face a bleeding risk. Further study will help determine which of these mechanisms is more important.

An ACS population has a risk of CV events that decreases over time, so that how long to treat becomes a difficult question, one not settled in many other situations too. Practitioners will need to weigh benefits and risks over time. It should also be noted that the TRITON study compared prasugrel, not with placebo, but with an active agent, so that the number of CV events was already decreased. In this setting, a further time-related decline in events makes a showing of continued benefit challenging.

Prasugrel represents a useful therapeutic option that will be the subject of further study that will continue to refine its role in cardiovascular therapy.

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Robert Temple
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