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Medical Review(s)

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MEMORANDUM

DATE: 10.11.00

FROM: Douglas C. Throckmorton, M.D., Deputy Division Director DCT 10.11.00
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TO: Raymond Lipicky, M.D., Division Director
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SUBJECT: Ticlopidine efficacy supplement for coronary stenting

PURPOSE OF MEMO

This memorandum reviews the materials submitted by Hoffman-La Roche Inc. in support of a proposed labeling change for Ticlid® (ticlopidine hydrochloride).

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0.0 OVERALL SUMMARY

The sponsor has submitted data in support of an indication for ticlopidine use following coronary stent placement. The data consist of one large, open-label trial (STAR) and 32 other trials comparing ticlopidine with other therapies in patients after stent placement. The STAR trial is the only trial with available primary data; the other trial data come almost exclusively from publications.

The first major issue is whether the use of ticlopidine +aspirin (ASA) was effective at reducing relevant cardiac events after coronary stenting, when compared with standard therapies (ASA-alone and anticoagulation +ASA). In the STAR trial, patients who received successful stent placement were randomized to receive one of three therapies: ticlopidine +ASA, coumadin +ASA, and ASA-alone. For the primary endpoint (death, Q-wave MI, and recurrent stent thromboses), significantly fewer events were seen in the ticlopidine +ASA group, when compared with the combination of the ASA-alone group and the coumadin +ASA group (relative risk 0.17, p=0.004). A critical feature of this endpoint is the inclusion of Q-wave MIs only. When the endpoint death/Q-wave MI is examined from STAR there was a significant advantage for ticlopidine +ASA compared with the pooled group (relative risk 0.10, p=0.025). When all MIs are included in the endpoint, however, the difference is substantially less and is no longer nominally significant (relative risk 0.78, p=0.18).

The analysis from the STAR study above compares the use of ticlopidine +ASA with the patients who received either ASA-alone or coumadin +ASA. It starts with the assumption that the addition of coumadin to ASA adds no additional risk to the benefits of ASA-alone (otherwise a more appropriate comparator would be the ASA-alone group). Evidence from the STAR trial suggested that the use of coumadin +ASA was not associated with more adverse events than ASA-alone This issue was also addressed in two smaller trials looking at the effects of adding coumadin to existing therapy. In the study by Park et al, there was a numerical excess of cardiac events in the group who received ticlopidine +coumadin +ASA, compared with the ticlopidine +ASA arm. This result was driven by an excess of non-Q-wave MIs in the coumadin arm.

Lack of access to the primary data limits the contribution of the remainder of the trials comparing ticlopidine plus aspirin with other therapies following coronary artery stenting. The FDA pooled the available data from the four other randomized trials (MATTIS, ISAR, FANTASTIC, Hall et al) to compare the occurrence of clinical cardiac events. This analysis appears to support the conclusions reached by the STAR trial: the use of ticlopidine +ASA is associated with fewer adverse cardiac events following stent placement, when compared with other anti-thrombotic and anti-coagulant therapies. The data are not sufficient from these trials to allow an examination of ticlopidine's effects on the incidence of Q-wave and non-Q-wave MIs separately. The conclusion that ticlopidine +ASA reduces the incidence of cardiac events relative to the comparator therapies was not undermined by the results reported for the remainder of the trials, which were non-randomized and/or retrospective.

The second major issue is the safety of ticlopidine in the post-stent population, compared with the use of either ASA-alone or ASA combined with coumadin. In general, the use of ticlopidine +ASA was associated with a higher risk of bleeding than ASA-alone, and with a comparable level of bleeding seen with anticoagulation +ASA. There is no evidence that ASA + ticlopidine use was associated with more bleeding than the combination of ASA and anticoagulation. Other adverse events previously associated with ticlopidine use (neutropenia, rash, GI disturbances) occurred at a higher frequency in the ticlopidine +ASA group compared with the other treatments. There were no cases of TTP reported in the 31 studies reported in the NDA in the post-stent population (n=12,977 patients exposed to ticlopidine).

In addition, ticlopidine safety after coronary stenting must be compared with the safety reported in patients who received ticlopidine for stroke prevention (its current indication), to determine if there are additional safety concerns evident in the post-stent population. Comparison between these two populations is problematic, as the available trials in the stroke prevention population treated patients with ticlopidine for a much longer period of time than the stent trials in the current submission. In addition, ticlopidine was administered with other anti-thrombotic and anti-coagulant drugs in the stent population (*e.g.*, heparin, ASA). As a result, while there were increased rates of bleeding reported in the stent trials relative to the trials post-stroke, the increased rates of bleeding in the stent population can't solely be attributed to ticlopidine. Within the limits of the data, there was no evidence that any of the non-bleeding adverse events associated with ticlopidine occurred at a higher rate in the coronary stent population.

0.0 Overall Summary (cont)

Approval of ticlopidine to reduce the risk of adverse cardiac events after coronary stent placement relies on the use of two imperfect datasets comparing the use of ticlopidine +ASA and other therapies: the STAR trial data and the pooled data from the other four randomized trials (ISAR, FANTASTIC, ISAR, Hall et al). There are 28 other trials identified by the sponsor: all were either retrospective reviews or registries and contribute little to the decision beyond that none of them undermine the beneficial effect of ticlopidine reported in the randomized trials. Both the STAR and pooled trial datasets included >1500 subjects and followed clinically-relevant endpoints for at least 30 days. All five trials reported reductions in the rates of cardiac events in the ticlopidine +ASA arm relative to the comparators (odds ratios from 0.17 around 0.50) for death/MI/stent thrombosis. Unfortunately, all of the trials were open-label, and significant differences exist in some of the details of patient enrollment and treatment. Additionally, the STAR study results hinge prominently on a difference in the rate of Q-wave and non-Q-wave MIs (NQWMIs): fewer Q-wave MIs, but increased numbers of peri-procedural NQWMIs, were seen in the ticlopidine arm compared with the other therapies. As a result, the odds ratio comparing ticlopidine +ASA with the other therapies for Death/MI was not significant: odds ratio 0.78 (0.51, 1.13), p=0.18. By contrast, the pooled analysis of the four randomized trials, ticlopidine +ASA reported a reduced rate of Death/MI: odds ratio 0.55 (0.36, 0.91), p=0.0019.

The approval of ticlopidine for stenting does not hinge on the available safety data: there are no data to suggest that the use of ticlopidine in the stent population is associated with new or increased rates of adverse events. There was increased bleeding in the stent group relative to the bleeding reported in the stroke-prophylaxis group currently approved for ticlopidine use. The use of concomitant heparin and ASA in the stent population makes this difficult to interpret.

The recommendation of this reviewer is that the current database is sufficient to support the approval of ticlopidine as therapy after coronary stenting.

1.0 Materials Utilized in Review

1.1 Materials from NDA/IND

1. NDA 19-979 (Ticlopidine hydrochloride), supplement dated 1.24.00.

1.2 Related Reviews, Consults for the NDA

1. Review of aspirin effects in prevention of vascular events, by Charles Ganley, M.D., dated 9.22.97.
2. Statistical review and evaluation of the STAR trial by James Hung, Ph.D., dated 10.6.98.
3. Memorandum on STAR trial and stent labeling for CDRH by Stephen Fredd, M.D., dated 10.15.98.
4. Statistical review of present ticlopidine supplement by James Hung, Ph.D., dated 9.13.00.
5. Approved label for the Palmaz-Schatz stent, revised 5.12.98 to include description of the STAR trial.

1.3 Other Resources

1. Published references on use of ticlopidine in coronary stenting (bibliography appears at the end of current document).

2.0 Background

2.1 Administrative History

Ticlopidine was approved in 10.91, and is indicated 'to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because ticlopidine is associated with a risk of neutropenia/ agranulocytosis, which may be life-threatening, ticlopidine 'should be reserved for patients who are intolerant to aspirin therapy where indicated to prevent stroke.'

2.2 Proposed Indication

The sponsor has submitted data in support of the following indication for ticlopidine: 'as adjunctive therapy with aspirin for the subacute stent thrombosis in patients undergoing successful coronary stent implantation.'

2.3 Information from Related INDs and NDAs

No other product is indicated for therapy following coronary stent implantation.

The approved label for the Palmaz-Schatz stent includes a description of the STAR trial as follows:

"Three anti-thrombotic drug regiments were compared in a randomized clinical trial after optimal angiographic results were obtained with the Palmaz-Schatz balloon expandable stent (STARS trial). Patients enrolled in the STARS trial had 1 or 2 significant *de novo* or restenotic lesions in 1 or 2 native arteries able to be treated with 1 or 2 stents. Of 1,965 patients enrolled, 1,653 were judged to have optimal results and were entered into the randomized cohort. For the primary endpoint (30-day stent thrombosis) there was a statistically significantly lower rate for the group treated with aspirin + ticlopidine (see Tables 7 & 8). The lower thrombosis rate for aspirin + ticlopidine was associated with a slightly higher rate of hemorrhagic and vascular surgical complications compared to aspirin alone (and comparable to aspirin + Coumadin), but was not associated with a higher rate of hematological dyscrasias."

Data from the STAR trial were also included in tables included in the label of the Palmaz-Schatz stent.

3.0 Issues Related to Approval Decision

3.1 Adequacy of Clinical Data Sources

The first issue is whether the clinical database is sufficient to address the proposed supplemental indication. It's also relevant to ask whether the available trials are sufficiently 'similar' to allow for analysis using meta-analytic tools. The database consists of one trial with available primary data (STAR) and many other trials with data available from publications.

STAR Study

Primary data are available for the STAR study (Stent Anti-Thrombotic Regimen study). These data consist of SAS transport tapes of the individual patient data, including outcomes.

Other Trials Using Ticlopidine after PCI

There were 33 trials comparing the use of ticlopidine +ASA to other comparator therapies following Percutaneous Coronary Intervention (PCI) with coronary stent placement. Aside from the STAR trial, data from all of the other trials come from published sources. Concerted attempts to get the primary data from the ISAR study (Intracoronary Stenting and Antithrombotic Regimen study) were unsuccessful.

The table below summarizes the patient enrollment in trials comparing the combination of ticlopidine +Aspirin (ASA) to either ASA-alone or anticoagulation +ASA.

Patient Enrollment in Trials With Ticlopidine Following PCI[a].

Study Type	Patients Receiving Ticlopidine +ASA	Patients Receiving Comparator Therapies[b]	Patient Totals
Prospective, Randomized, Controlled Trials (5 trials)	1346	1873[c]	3219
Prospective, Nonrandomized Trials (5 trials)	2274	2463[d]	4737
Prospective Observational Cohort Studies (19 trials)	9085	291	9376
Retrospective Reviews (4 reports)	272	205[e]	477
Total (33 trials)	12,977	4832	17,809

a. Percutaneous Coronary Intervention. Summarized from NDA supplement vol. M67.1, tables 18, 15, and 13.
b. Either Anticoagulation +ASA (C +ASA) or ASA-alone.
c. Of these, 1213 received C +ASA, 660 received ASA-alone
d. Of these, 201 received C +ASA, 354 received ASA-alone, and 1908 got Ticlopidine +ASA +LMWH (or Coumadin).
e. All received C +ASA.

3.1.1a Demographics of the Prospective Randomized Trials Database

The five prospective, randomized, controlled trials used an open-label design and randomly allocated patients to a particular treatment group. The next table lists the patient enrollment in the prospective, randomized, controlled trials.

Patient Enrollment in Randomized Controlled Trials of Ticlopidine after Stenting[a].

Study	Ticlopidine +ASA	Coumadin[b] +ASA	ASA
FANTASTIC	243	230	--
Hall	123	--	103
ISAR	257	260	--
MATTIS	177	173	--
STAR	546	550	557
Total	1346	1213	660

a. From NDA 19-979, vol. 67.1.
b. Or other anticoagulant.

The relevant patient demographics of these same prospective randomized trials are summarized below.

Demographics from Randomized Controlled Trials with Ticlopidine[a].

Characteristic	FANTASTIC	Hall et al	STAR	ISAR	MATTIS
Age, mean ±SD	60±11	57±9	61±12	62±11	60±0
Gender (Male, %)	82%	88%	71%	77%	85%
Cardiac Risks					
Smokers	77%	70%	29%	52%	32%
Diabetes	15%	16%	18%	16%	25%
HTN	33%	40%	50%	62%	35%
PMH					
MI	49%	50%	36%	42%	50%
CABG	14%	11%	8%	8%	7%
PTCA	35%	10%	15%	18%	23%
Severe Lesion (B2 or C)	Unknown	59%	65%	87%	Unknown

a. Data from NDA vol. 67.1, table 14.

3.1.1b Methodology Used in the Prospective Randomized Trials Database

The methodologies used in the randomized trials varied slightly, as summarized below. While all of the trials examined the effects of ticlopidine after successful coronary stent placement, the definition of success and the ways that success were determined varied between the trials. In addition, the types of stents and the patient populations enrolled differed between the trials.

Methodologies Used in Randomized Coronary Stent Trials with Ticlopidine[a].

Study	Patient Selection Criteria	Stent Types(s)	IVUS[b]	High Pressure Placement
STAR	Elective planned stent placement	Palmaz-Schatz	Not used	Yes
FANTASTIC	Planned and unplanned stent placement	Wiktor	Not used	Yes
Hall et al	Planned and unplanned stent placement	Various	Used	No
ISAR	Planned and unplanned stent placement	Palmaz-Schatz	Not used	Yes
MATTIS	Stent placement with a high risk of re-occlusion	Various	Some	No

a. Data from NDA vol. 67.1, table 9.
b. Intravascular Ultrasound (IVUS) used to assess successful stent placement.

While the use of heparin and coumadin specified in the protocols were fairly similar across the randomized studies, the dose of ASA used in the various trials ranged between 100 and 325 mg per day. The dose of ticlopidine is also summarized.

Study Drugs in Randomized Coronary Stent Trials with Ticlopidine[a].

Study	ASA Dose	Ticlopidine Dose
STAR	325 mg/day	500 mg/day for 30 days
FANTASTIC	100 to 325 mg/day	500 mg/day for 6 weeks
Hall et al	325 mg/day	500 mg/day for 30 days
ISAR	100 mg/day	500 mg/day for 30 days
MATTIS	250 mg/day	500 mg/day for 30 days

a. Data from individual study publications.

3.1.2 Demographics and Methodology Used in the Supportive Studies

Information on the non-randomized trials using ticlopidine after PCI can be found in the sponsor's Integrated Summary Of Safety and Efficacy, NDA volume 67.1.

3.1.3 Extent of Exposure (Dose/Duration)

Dosage Administered

The majority of the patients (74%) in the 31 studies received 500 mg per day of ticlopidine. A smaller percentage of subjects in the overall trials (17%) received a dose of between 250 and 500 mg per day. Very few patients (2%) received >500 mg per day.

All of the subjects in the randomized controlled trials received ticlopidine 500 mg/day.

Duration of Exposure

The majority (approximately 75%) of the patients received 30 days of therapy. All of the prospective randomized and nonrandomized controlled trials treated patients with ticlopidine for at least 30 days. The period of exposure to ticlopidine varied between 14 and 180 days in the observational trials.

3.1.4 Secondary Source Data

Publications related to the 33 trials of ticlopidine after PCI were submitted in the NDA. References cited in this review can be found at the end of this document.

3.1.5 Comment on Adequacy of Clinical Experience and Data Quality

While the database submitted by the sponsor is sizable (17,000+ patients), derived from 33 separate studies, the majority of these patients were enrolled in non-randomized trials. There were 5 randomized trials that enrolled 3219 patients (1346 received ticlopidine). Primary data are available for only one of these trials (STAR). The STAR trial data are sufficient in quality to allow standard statistical review and comment (see Dr. Hung's Statistical Review). For the other trials in the database, use of secondary sources (publications) prevents any comment being made related to the adequacy and quality of the data.

3.2 Review of Efficacy Data

What follows is a summary of the results from the trials submitted in support of the indication for ticlopidine use after percutaneous coronary intervention (PCI) with coronary stent placement. The reader is referred to the Statistical Review by James Hung, Ph.D. for details of the analyses for each of the trials. The reader is also referred to the previous review of the STAR study by Steve Fredd, M.D.

The five randomized controlled trials will be reviewed individually, followed by general comments about the results from the other 28 supportive trials. Following this, an analysis of the combined data from the five randomized trials, performed by James Hung, will be summarized. The overarching theme, to be discussed after the review, is to determine the persuasiveness of a single trial with primary data (STAR) combined with a large database of trials with only secondary data available.

3.2.1 Review of Results from the Five Randomized Trials

3.2.1a STAR Study Results

The STAR study was a randomized, open-label study comparing three regimens of anti-thrombotics/anti-coagulants following coronary stenting. Treatment assignments were unblinded at the site by the investigator or coordinator.

Primary Endpoint from the STAR study

The primary endpoint of the trial was the incidence of 'stent thrombosis' defined as the occurrence of one of the following: death, Q-wave MI, and sub-acute stent closure requiring revascularization, as assessed by a Clinical Events Committee (CEC). The results for the Intent to Treat population are shown below. Starred results were significantly different from ticlopidine +ASA at $p \leq 0.05$. The difference between the ASA and the coumadin +ASA group for the primary endpoint was not significant ($p > 0.10$).

3.2.1a STAR Study Results (cont)

Incidence of Stent Thrombosis in STAR[c].

Endpoint[a]	ASA + Ticlopidine N=546	Coumadin +ASA N=550	ASA N=557	Rate Difference and Odds Ratio (95% C.I.) for Ticlopidine +ASA vs. ASA +Warfarin
Primary Endpoint by CEC[a]	3 (0.5%)	14 (2.5%)*	21 (3.8%)*	0.21 (0.06, 0.74) -2.0% (-3.5%, -0.5%)
Primary Endpoint by CRF review[b]	5 (0.9%)	14 (2.5%)*	23 (4.1%)*	0.35 (0.13, 0.99) -1.6% (-3.2%, -0.09%)

a. Death, Q-wave MI, and sub-acute stent closure requiring revascularization.

b. CRF review performed by James Hung and Steve Fredd as part of earlier review of STAR.

c. See publication, NEJM (1998) 339: 1665-1671 for additional details.

Post-Hoc Analyses from STAR

The results from the ticlopidine +ASA group were compared with the results from the combined ASA-alone and coumadin +ASA groups by James Hung. The results for the primary endpoint and other relevant endpoints are summarized below. Significant differences were seen for the primary endpoint and for the incidence of Death/ Q-Wave MI between the two groups. Note, however, when the non-Q-wave MIs (NQWMIs) are included there is no nominally significant difference between the two treatment groups. This outcome is driven by an increase in the number of NQWMIs in the ticlopidine +ASA group, when compared with the combined group. These increased NQWMIs in the ticlopidine +ASA arm, in turn, were driven an excess of 'peri-procedural' NQWMIs (defined as an elevation of CK to ≤2X above normal without Q-wave or detectable CK-MB occurring in the setting of stenting or atherectomy). It should be remembered that ticlopidine was started after completion of the stenting in the STAR trial, such that there is little expectation that the first dose of ticlopidine would influence any 'peri-procedural' MIs in the period just after the initial PCI and stent placement. In the coumadin +ASA arm, by contrast, heparin was continued after PCI until the INR was >2.5. It could be argued that this heparin would reduce the rate of early 'peri-procedural MIs' in the coumadin +ASA arm, relative to the ticlopidine +ASA arm. While information on the timing of the peri-procedural MIs is not available, approximately 50% of the primary endpoint events occurred in the first 2 days after the initial PCI in the STAR trial (while the patients in the coumadin +ASA arm were still likely to be on heparin).

Cardiac Endpoint Post-Hoc Analyses from STAR[a].

Endpoint	Ticlopidine +ASA N=546	ASA and Coumadin +ASA N=1107	Odds Ratio and Rate Difference (95% C.I.) for Ticlopidine +ASA vs. Coumadin +ASA and ASA-alone
Primary Endpoint by CEC[a]	3 (0.5%)	35 (3.2%)	0.17 (0.05, 0.055), p=0.003 -2.6% (-3.8%, -1.4%), p=0.004
Death	0 (0%)	1 (0.1%)	–
Death/ Q-Wave MI	1 (0.2%)	20 (1.8%)	0.10 (0.01, 0.75) p=0.025 -1.6% (-2.5%, -0.7%), p=0.004
Death/ MI[b]	36 (6.6%)	94 (8.5%)	0.78 (0.51, 1.13), p=0.18 -1.9% (-4.6%, +0.8%), p=0.21
All Q-Wave MIs[b]	1 (0.2%)	19 (1.7%)	NA
All NQWMIs	25 (4.6%)	45 (4.1%)	NA
'Peri-procedural' NQWMIs[c]	23 (4.2%)	35 (3.2%)	NA
'Endpoint' NQWMIs	2 (0.4%)	10 (0.9%)	NA

a. Clinical Events Committee. Primary endpoint is combination of death, Q-wave MI, and sub-acute stent closure requiring revascularization. Data from review by Jim Hung and from publication.

b. Q-wave and Non-Q-wave MIs.

c. From consultation by Steve Fredd dated 10.15.98. Also shown are rates of events for 'procedure-related' and 'Primary' endpoints.

3.2.1b FANTASTIC Study Results

This study randomized patients who had successful coronary stent placement to either coumadin +ASA or to ticlopidine +ASA, and examined the incidence of cardiac events after 45 days (longer initial follow-up than other studies). Primary endpoint of the study was the rate of bleeding complications (data not shown). The only nominally significant difference detected was in the incidence of stent thrombosis. Blinding was not specified in the paper and the trial is assumed to be open-label.

3.2.1b FANTASTIC Study Results (cont)

FANTASTIC Study Results[a].

30-Day Event Rates[a]	Ticlopidine +ASA N=243	Coumadin +ASA N=230	p-Value
Death	2 (0.8%)	4 (1.7%)	0.37
Q-Wave MI	3 (1.2%)	6 (2.6%)	0.27
Non-Q-Wave MI	9 (3.7%)	9 (3.9%)	0.9
Death/MI	14 (5.8%)	19 (8.3%)	0.29
Stent Thrombosis, Subacute	1 (0.4%)	8 (3.5%)	0.01

a. From publication, Circulation (1998) 98: 1597-1603.

3.2.1c Hall et al Study Results

This study randomized patients who had successful coronary stent placement to either ASA-alone or to Ticlopidine +ASA, and examined the incidence of cardiac events after 30 days. The trial was open-label. At the end of one month, very few cardiac events had occurred, and no significant differences between the treatment groups were claimed by the investigators.

Hall et al Study Results[a].

30-Day Event Rates	Ticlopidine +ASA N=123	ASA N=103	p-Value
Any 'major' event	1 (0.8%)	4 (3.9%)	0.10
Death	0 (0%)	3 (2.9%)	0.10
MI	1 (0.8%)	4 (3.9%)	0.10
Death/MI[b]	1 (0.8%)	4 (3.9%)	0.18
Stent Thrombosis	1 (0.8%)	3 (2.9%)	0.20

a. Derived by James Hung from information provided by the sponsor.
b. Data from publication, Circulation (1996) 93:215-222.

3.2.1d ISAR Study Results

This study randomized patients who had successful coronary stent placement to either Phenprocouman (a coumadin derivative) +ASA or to ticlopidine +ASA, and examined the incidence of cardiac events after 30 days. The trial was open-label. Significant differences were reported between treatment groups for the primary endpoint (death, MI, CABG, repeat PTCA), for MI and for stent thrombosis.

ISAR Study Results[a].

30-Day Event Rates[a]	Ticlopidine +ASA N=257	Phenprocouman +ASA N=260	p-Value
Death, MI, CABG, repeat PTCA	4 (1.6%)	16 (6.2%)	0.01
Death	1 (0.4%)	2 (0.8%)	1.0
MI	2 (0.8%)	11 (4.2%)	0.02
Death/MI	3 (1.2%)	11 (4.2%)	0.032
Stent Thrombosis	2 (0.8%)	14 (5.4%)	0.004

a. From publication, NEJM (1996) 334:1084.

3.2.1e MATTIS Study Results

This study randomized patients who had successful coronary stent placement to either oral anti-coagulation (type not specified) +ASA or to ticlopidine +ASA, and examined the incidence of cardiac events after 30 days. The trial was open-label. The primary endpoint was the occurrence of cardiovascular death, MI in the territory of the stent, repeat PCI or CABG. No significant differences were claimed by the investigators for the endpoints listed below.

MATTIS Study Results[a].

30-Day Event Rates[a]	Ticlopidine +ASA N=177	Oral Anti-Coag +ASA N=173	p-Value
Death, MI, CABG, repeat PTCA	10 (5.6%)	19 (11.0%)	0.07
Death	3 (1.7%)	2 (1.2%)	0.67
MI	6 (3.4%)	12 (6.9%)	0.14
Death/MI	9 (5.1%)	13 (7.5%)	0.35

a. From publication, Circulation (1998) 98:215-222.

3.2.2 Review of the Results from the Twenty-Eight Non-Randomized Trials

The majority of the other trials were open-label registries, comparing sequential patients treated with either ticlopidine or anticoagulation. There were five prospective, non-randomized, controlled studies using ticlopidine after coronary stenting, of which 4 compared ticlopidine +ASA to either ASA-alone or anticoagulation +ASA. Of these four trials, three reported fewer cardiac events in the comparator arm than in the ticlopidine +ASA arm (see table below). One trial (Albiero et al) reported similar rates of cardiac events in the two treatment groups. None of the reported differences achieved nominal statistical significance. The overall mortality rate in the combined dataset was small (0.6%).

Results from Non-Randomized Stent Trials[a].

Trial	Endpoint	Ticlopidine +ASA	Oral AC +ASA	ASA
Albiero et al	Death, MI, CABG, repeat PTCA or stenting	11 (2.0%)	ND[b]	5 (1.9%)
Goods et al	Death, MI, Stent Thrombosis	18 (5.3%)	ND	8 (17.4%)
Mann et al	Subacute Closure	0 (0%)	ND	3 (1.5%)
Park	Death, MI, CABG	0 (0%)	11 (6.7%)	5 (11.4%)
Combined 4 Trials	Death	55/9170 (0.6%)	ND	ND

a. From NDA vol. 67.1, table 27. Not independently confirmed by FDA.
b. ND = Not measured or not reported in the publication.

No pooled comparison of the results from the other trials (registries or the retrospective reviews) was submitted by the sponsor or performed by the FDA.

3.2.3 Integrated Analysis of the Results from the ISAR, FANTASTIC, MATTIS and Hall et al Trials

There were four randomized, controlled trials comparing the use of ticlopidine with other therapies post-stent placement. While there are some relevant differences in trial design (summarized in section 3.1.1 above) among the four trials, it is attractive to examine their combined database as a source of additional information about the efficacy of ticlopidine in this setting. James Hung performed such an analysis, based on the published material as well as some additional data obtained by the sponsor.

After concluding that there was not statistical evidence of inter-study heterogeneity between treatment groups in the four trials, Dr. Hung performed and integrated analysis based on the data from the four trials. The first endpoint examined (and least open to investigator bias) was the incidence of death and MI. Exact definitions of MI varied among the trials, but included both Q-wave and non-Q-wave MI.

The other two analyses look at the incidence of death/MI/CABG and repeat PTCA from the trials. As the FANTASTIC trial used a 45 day endpoint, the final analysis looks only at the three trials with data at 30 days. The incidence rates for the death/MI endpoint and for the composite of death, MI, CABG and PTCA were reduced in the ticlopidine +ASA arm, relative to the pooled comparator therapies. Note that odds ratio and rate difference were calculated using a weighted-pooling method, so that the incidence rates shown cannot be used to derive the odds ratios or rate differences.

Integrated Results from Randomized Controlled Stent Trials[a].

30-Day Event Rates[a]	Ticlopidine +ASA # of Events /Total N (%)	AC[d] +ASA or ASA-alone # of Events /Total N (%)	Odds Ratio and Rate Difference (95% C.I.) and p-Value
Death/MI[b]	27/800 (3.4%)	47/766 (6.1%)	0.55 (0.36, 0.91), p=0.019 -2.9% (-4.8%, -1.0%), p=0.003
Death/ MI/ CABG/ PCI[b]	29/800 (3.6%)	58/766 (7.6%)	0.48 (0.30, 0.76) p=0.0019 -3.9% (-5.9%, -1.8%), p=0.0003
Death/ MI/ CABG/ PCI[c]	15/557 (2.7%)	39/536 (7.3%)	0.36 (0.20, 0.68), p=0.0014 -4.2% (-6.5%, -1.9%) p=0.0004

a. From Statistical Review by James Hung, Ph.D.
b. From Hall, ISAR, MATTIS and FANTASTIC trials.
c. From Hall, ISAR and MATTIS trials.
d. AC: Anti-coagulation.

3.2.4 Comparison of ASA and Anti-coagulation +ASA

The integrated analysis discussed above combines the ASA-alone and anticoagulation +ASA arms of the various trials in order to create a single 'active control' category for comparison. A circumstance where this could be problematic is if the use of anti-coagulation and ASA was in fact adverse compared with ASA-alone. In such a case, a more appropriate comparator might be ASA-alone. As summarized below, in the STAR trial there was a trend favoring coumadin +ASA versus ASA-alone for prevention of stent thrombosis. In two smaller published trials that also looked at the consequences of adding anti-coagulation to existing therapy, the results were mixed (see below).

STAR Trial

As discussed above the STAR trial randomized patients after successful coronary stenting to one of three regimens, including one group who received ASA-alone and one who received coumadin +ASA. Their results are summarized below. Dr. Hung performed additional analyses (see his review) and concluded the following:

1) the difference in the incidence rates between ASA and coumadin +ASA 'was not conclusive.'

2) 'one cannot conclude that ASA and coumadin +ASA are equivalent with respect to the 30 day stent thrombosis rate.'

STAR Trial Results for ASA Versus Coumadin +ASA[a].

Endpoint	Coumadin +ASA N=550	ASA N=557	Odds Ratio (95% C.I.) and Rate Difference for Coumadin +ASA vs. ASA
Primary Endpoint by CEC[a]	14 (2.5%)	21 (3.8%)	0.67 (0.34, 1.32), p=NS -1.3% (-1.1%, +3.6%), p=0.24
Primary Endpoint by CRF review[b]	14 (2.5%)	23 (4.1%)	0.61 (0.31, 1.19), p=NS -1.6% (-0.5%, +3.7%), p=0.14
Components of Primary Endpoint			
Death[c]	0 (0%)	1 (0.2%)	--
MI[c]	3 (0.5%)	12 (2.2%)	--
Revascularization (PTCA/ CABG)[c]	14 (2.5%)	19 (3.4%)	--
Safety Endpoints[c]			
Major Bleeding	4 (0.7%)	1 (0.2%)	--
Major Vascular	31 (5.6%)	10 (1.8%)	--
CVA	1 (0.2%)	2 (0.4%)	--

a. Death, Q-wave MI, and sub-acute stent closure requiring revascularization.
b. CRF review performed by James Hung and Steve Fredd as part of earlier review of STAR.
c. Data from publication, NEJM (1998) 339: 1665-1671, not independently confirmed by FDA.

Park et al

In this trial, 275 consecutive patients undergoing PCI with stent placement were 'divided' into three groups: ASA-alone, ticlopidine +ASA, and ticlopidine +coumadin +ASA. 'In-hospital' complications were collected, and are summarized below. The two groups of interest in this regard are those with and without coumadin on a background of ticlopidine +ASA. In these two groups there was a numerical excess of cardiac events in the group who received ticlopidine +coumadin +ASA, driven by an excess of non-Q-wave MIs.

Results from Park Et Al[a].

30-Day Event Rates[a]	Ticlopidine +ASA +Coumadin N=165	Ticlopidine +ASA N=66	ASA N=44	p-Value
Death, MI, Sub-Acute Stent Thrombosis[b]	0 (0%)	11 (6.7%)	5 (11.4%)	N/A
Death	0 (0%)	0 (0%)	0 (0%)	N/A
Q-Wave MI	2 (1.2%)	0 (0%)	0 (0%)	N/A
Non-Q-Wave MI	5 (3.0%)	0 (0%)	1 (2.3%)	N/A
Sub-Acute Stent Thrombosis	2 (1.2%)	0 (0%)	3 (6.8%)	N/A

a. From publication, Amer Jnl of Cardiol (1997) 79: 901-904.
b. From sponsor, not independently confirmed by FDA.

3.2.4 Comparison of ASA and Anti-coagulation +ASA (cont)

Galli et al

In this trial, reported in abstract form, results from patients who underwent PCI with stent placement were assigned to one of three groups: acenocoumarol +ASA, ticlopidine +ASA, and ASA-alone. The results after 30 days are summarized below. Patients who received acecoumarol +ASA had more deaths and stent thromboses than those who received ASA-alone, but fewer MIs.

Results from Galli et al[a].

30-Day Event Rates[a]	Acenocoumarol +ASA N=95	Ticlopidine +ASA N=50	ASA N=88	p-Value
Death	2 (2.1%)	0	1 (1.0%)	>0.05
MI	3 (3.1%)	1 (1%)	5 (5.7%)	>0.05
Stent Thrombosis	2 (2.1%)	0	1 (1.1%)	

a. From abstract, Circulation (1996) 94: I-684 (A).

3.3 Review of Safety Data

We also need to ask if the use of ticlopidine after coronary stenting is associated with increased risk relative to its use as stroke prophylaxis (current indication). The most common and/or significant adverse events (AEs) associated with ticlopidine use are: diarrhea, skin rash/urticaria, increased bleeding, and changes in the risks for rare, serious hematological adverse events (neutropenia, TTP). The sections below will address the available data on these points, beginning with bleeding.

3.3.1a Bleeding in Patients Following Coronary Stenting

In terms of incidence, the two major classes of adverse event associated with anti-thrombotic and anti-coagulant therapies are bleeding and vascular complications (including CVAs and the need for surgical vascular repair). The interpretation of these adverse events is complicated, as the investigators in all of the trials had access to the individual patient treatment assignments. The arms containing ticlopidine and coumadin had a higher rate of bleeding AEs than the ASA-alone arm.

The first table summarizes the incidence of these AEs from the STAR trial.

Bleeding in STAR Trial[a].

30-Day Event Rates[a]	Ticlopidine +ASA N=546	Coumadin +ASA N=550	ASA N=557	p-Value[b]
Major Bleeding	5 (0.9%)	4 (0.7%)	1 (0.2%)	0.197
Major Vascular AE[c]	27 (4.9%)	31 (5.6%)	10 (1.8%)	0.001
CVA	3 (0.5%)	1 (0.2%)	2 (0.4%)	0.777

a. From memo by Steve Fredd, M.D.

b. p-Value per sponsor, not confirmed by FDA.

c. Pseudoaneurysms, vascular access bleeding with drop in Hgb of >5 g/dl, and vascular events requiring surgery.

The next table summarizes the incidence of these same adverse events from the other four randomized, controlled trials. While the reported rates vary, in general the rates for the various 'bleeding' AEs were higher in the anticoagulation +ASA group when compared with the ticlopidine +ASA group.

Bleeding in Other Randomized Stent Trials[a].

Complication[a]	FANTASTIC		ISAR		MATTIS		Hall et al	
	Tic/ASA N=243	AC[b]/ASA N=230	Tic/ASA N=257	AC/ASA N=260	Tic/ASA N=177	AC/ASA N=173	Tic/ASA N=123	ASA N=103
Ecchymoses	16 (6.6%)	38 (16.5%)	ND	ND	ND	ND	ND	ND
Access Bleeding	25 (10.3%)	34 (10.8%)	2 (0.8%)	15 (5.8%)	0 (0%)	0 (0%)	ND	ND
Aneurysm	2 (0.6%)	6 (2.6%)	ND	ND	(1 0.6%)	2 (1.2%)	NR	NR
Transfusion	4 (1.6%)	6 (2.5%)	0 (0%)	12 (4.6%)	NR	NR	0 (0%)	0 (0%)
Other Bleeding	2 (0.8%)	7 (3.0%)	NR	NR	1 (0.6%)	2 1.2%)	ND	ND

a. Data from sponsor table 10, NDA vol. 67.1, section 6.2.1.

b. AC = Anticoagulation.

The sponsor also combined the data on the incidence of bleeding and vascular complications from the FANTASTIC, ISAR, MATTIS, Hall and STAR trials. These data are summarized below.

3.3.1a Bleeding in Patients Following Coronary Stenting

Incidence of Bleeding Adverse Events in Randomized Trials[a].

Study	Tic/ASA	ASA	AC/ASA
STAR	30 (5.5%)	10 (1.8%)	34 (6.2%)
FANTASTIC	6 (2.5%)	--	13 (5.7%)
ISAR	0 (0%)	--	17 (6.5%)
MATTIS	1 (0.6%)	--	12 (6.9%)
Hall et al	0 (0%)	0 (0%)	--
Total	37 (2.7%)	10 (1.5%)	76 (6.3%)

a. Data from NDA vol. 67.1, section 6.2.1, table 11.

Incidence of Vascular Complications in Randomized Trials[a,b].

Study	Tic/ASA	ASA	AC/ASA
STAR	11 (2.0%)	2 (0.4%)	11 (2.0%)
FANTASTIC	44 (18.1%)	--	80 (34.8%)
ISAR	0 (0%)	--	16 (6.2%)
MATTIS	2 (1.1%)	--	2 (1.2%)
Hall et al	0 (0%)	1 (1%)	--
Total	57 (4.2%)	3 (0.2%)	109 (9.0%)

a. Data from NDA vol. 67.1, section 6.2.1, table 12.

b. Definitions of vascular complication varied, but included pseudoaneurysms, vascular access bleeding with significant drop in Hgb, and vascular events requiring surgery

3.3.1b Bleeding in Patients Taking Ticlopidine for Stroke Prevention

The only data on risk of bleeding when ticlopidine is used for stroke prevention is on long-term bleeding (24-36 months). Based on the available literature, use of ticlopidine in this population does increase the long-term risk of bleeding when compared with placebo (CATS study) but not when compared with ASA (TASS study).

The table below summarizes the risk of bleeding from the Canadian American Ticlopidine Study in Thromboembolic Stroke (CATS), which compared ticlopidine and placebo in patients with thromboembolic strokes within 4 months of trial entry. The patients were given drug for an average of 24 months. The incidence of 'Bleeding disorder' in the two populations is summarized below along with the rates of intracranial hemorrhage. Ticlopidine alone had a higher incidence of bleeding complications than placebo in this population.

Incidence of Bleeding Complications in the CATS study[a].

Adverse Event	Ticlopidine N=525	Placebo N=528
'Bleeding Disorder'	34 (6.5%)	16 (3.0%)
Severe 'Bleeding Disorder'	2 (0.4%)	1 (0.2%)
Subarachnoid hemorrhage	0 (0%)	2 (0.4%)
Intracerebral hemorrhage	2 (0.4%)	0 (0%)

a. From publication, Lancet (1989) June 3 edition. 1215-1220.

The next table summarizes data from the Ticlopidine Aspirin Stroke Study (TASS) for the bleeding AEs. Follow-up in TASS (judged by duration of drug therapy) was 24 to 36 months.

Incidence of Bleeding Complications in the TASS study[a]

Adverse Event	Ticlopidine N=1518	ASA N=1527
All Hemorrhagic AEs	137 (9.0%)	152 (10.0%)
GI hemorrhage	7 (0.5%)	21 (1.4%)
Intracranial hemorrhage	3 (0.4%)	4 (0.4%)

a. From publication, NEJM (1989) 321: 501-507.

3.3.2a Rare, Serious Adverse Events in Patients Following Coronary Stenting

Neutropenia

In the five randomized trials (STAR, ISAR, FANTASTIC, Hall et al, MATTIS) there were 11 cases of neutropenia (0.8%) of 1346 patients treated with ticlopidine. Four of these had an absolute neutrophil count (ANC) ≤500. By comparison, in the group exposed to anticoagulation +ASA or ASA-alone, there was only one case out of 1873 patients (0.05%).

3.3.2a Rare, Serious Adverse Events in Patients Following Coronary Stenting (cont)

TTP

There were no cases of TTP reported among the 31 studies of ticlopidine after coronary stenting.

3.3.2b Rare, Serious Adverse Events in Patients Taking Ticlopidine for Stroke Prevention

Neutropenia

In the CATS trial, there were six cases of neutropenia (5 with ANC ≤500) out of 525 patients given ticlopidine (0.9%). In the TASS trial, 35 patients out of 1346 patients on ticlopidine developed neutropenia (ANC <1200) (2.6%), of which 13 (0.9%) developed severe neutropenia (ANC <450).

TTP

There one case of TTP reported in the TASS study out of 1518 patients treated with ticlopidine (0.06%), and no cases reported in the CATS study.

3.3.3a GI Complaints and Rash in Patients Following Coronary Stenting

Rash

The most frequent side-effect of therapy with ticlopidine in the past has been rash, which is severe enough to require discontinuation in some cases. In the five randomized trials of ticlopidine after stent use, rashes were reported in 17/1346 (1.3%) in the ticlopidine +ASA group, compared with 10/1213 (0.8%) in the anticoagulation +ASA arm and 0/660 (0%) of the ASA-alone patients.

Gastrointestinal Complaints

In the five randomized controlled clinical trials, GI complaints (diarrhea, nausea, dyspepsia, and anorexia) were reported in 22 patients taking ticlopidine +ASA (1.6%) compared with 7/1213 (0.5%) of the anticoagulation +ASA group and no patients in the ASA-alone group.

3.3.3b GI Complaints and Rash in Patients Taking Ticlopidine for Stroke Prevention

GI complaints were much more common in the patients treated with ticlopidine for longer periods of time in the stroke prevention trials.

Rash

In the TASS trial, rash was reported as an AE in 180/1518 patient taking ticlopidine (11.9%) compared with 80/1527 taking ASA (5.2%). In the CATS study, only the incidence of diarrhea was reported, and it occurred in 113/525 (21.5%) of the ticlopidine group and 53/528 of the ASA group (10.0%). In the CATS study, rash was reported in 78/525 of the ticlopidine group (14.8%) compared with 43/525 of the placebo group (8.2%).

Gastrointestinal Complaints

In the TASS trial, GI complaints (diarrhea, nausea, dyspepsia, and anorexia) were reported as an AE in 670/1518 patient taking ticlopidine (44.1%) compared with 516/1527 taking ASA (33.8%). In the CATS study, only the incidence of diarrhea was reported, and it occurred in 113/525 (21.5%) of the ticlopidine group and 53/528 of the placebo group. (10.0%).

4.0 COMMENTS OF REVIEWER

4.1 Efficacy of Ticlopidine +ASA compared with other therapies in patients undergoing stent placement after PCI

The sponsor has submitted data in support of an indication for ticlopidine use following coronary stent placement. The data consist of one large, open-label trial (STAR) and 32 other trials comparing ticlopidine with other therapies in patients after stent placement. The STAR trial is the only trial with available primary data; the other trial data come almost exclusively from publications.

1. In the STAR trial, patients who received successful stent placement were randomized to receive one of three therapies: ticlopidine +ASA, coumadin +ASA, and ASA-alone (section 3.2.1a above). For the primary endpoint (death, Q-wave MI, and recurrent stent thromboses), significantly fewer events were seen in the ticlopidine +ASA group, when compared with the combination of the ASA-alone group and the coumadin +ASA group (relative risk 0.17, p=0.004). A critical feature of this endpoint is the inclusion of Q-wave MIs only. When the endpoint death/Q-wave MI is examined from STAR there was a significant advantage for ticlopidine +ASA compared with the pooled group (relative risk 0.10, p=0.025). When all MIs are included in the endpoint, however, the difference is substantially less and is no longer nominally significant (relative risk 0.78, p=0.18).

2. The remaining four randomized trials compared ticlopidine +ASA to various other anti-coagulant and anti-thrombotic regimens, and the results all favored ticlopidine +ASA (sections 3.2.1b to 3.2.1e above). Two of the trials (FANTASTIC and ISAR) reported nominally significant reductions in stent thrombosis in the ticlopidine group.

3. In a pooled analysis of the available data (section 3.2.3 above) from the four other randomized trials (MATTIS, ISAR, FANTASTIC, Hall et al) the use of ticlopidine +ASA is associated with fewer adverse cardiac events following stent placement, when compared with other anti-thrombotic and anti-coagulant therapies. For the endpoint death/MI/CABG/PCI, the odds ratio favoring ticlopidine was 0.48 (0.30, 0.76, p=0.0019). In the pooled analysis, ticlopidine +ASA reduced the rate of Death/MI: odds ratio 0.55 (0.36, 0.91), p=0.0019.

4. The findings from the five randomized trials were not undermined by any of the data available from the 28 retrospective and/or registry trials of ticlopidine in stented populations.

4.1 Safety of Ticlopidine +ASA compared with other therapies in patients undergoing stent placement after PCI

Differences in the methods of safety data collection limit the conclusions that can be made about the comparative safety of ticlopidine +ASA versus the other therapies following PCI and stent placement as follows:

1. For the available trials, the incidence of clinically-significant bleeding for patients receiving ticlopidine +ASA was greater than the bleeding seen when ASA-alone was used, but somewhat less than the bleeding seen when anti-coagulation +ASA was used (sections 3.3.1a and 3.3.1b above).

2. The use of ticlopidine +ASA in the PCI/stent population was associated with a higher risk of bleeding than the risk of bleeding reported for the use of ticlopidine alone or ASA-alone in the stroke/ TIA population (sections 3.3.1a and 3.3.1b above).

3. For rarer adverse events (GI, Hematological, Dermatological) the data suggest a lower incidence of these events in the anticoagulation +ASA arm compared with ticlopidine + ASA.

4. The data from the available trials are in conflict as to whether the use of anticoagulation confers an additional risk of cardiac adverse events, when compared with patients taking ASA-alone. In the largest trial (STAR) coumadin +ASA had a lower rate of cardiac events than ASA-alone, although the difference was not significant per Dr. Hung. In contrast, in a smaller trial (Park et al), addition of coumadin to patients taking anti-thrombotic therapy increased the risk of adverse cardiac events (section 3.2.4 above), including MI and stent thrombosis. A third trial (Galli et al) reported that the addition of coumadin to ASA increased the incidence of stent thrombosis numerically but lowered the incidence of MIs.

5.0 CONCLUSIONS AND RECOMMENDATIONS

Approval of ticlopidine to reduce the risk of adverse cardiac events after coronary stent placement relies on the use of two imperfect datasets comparing the use of ticlopidine +ASA and other therapies: the STAR trial data and the pooled data from the other four randomized trials (ISAR, FANTASTIC, ISAR, Hall et al). Both the STAR and pooled trial datasets included >1500 subjects and followed clinically-relevant endpoints for at least 30 days. All five trials reported reductions in the rates of cardiac events in the ticlopidine +ASA arm relative to the comparators (odds ratios from 0.17 around 0.50) for death/MI/stent thrombosis. The pooled analysis also reported a nominally significant reductions in the rate of Death/MI in the ticlopidine +ASA group. Unfortunately, all of the trials were open-label, and significant differences exist in some of the details of patient enrollment and treatment. Additionally, the STAR study results hinge prominently on a difference in the rate of Q-wave and non-Q-wave MIs (NQWMIs): fewer Q-wave MIs, but increased numbers of peri-procedural NQWMIs, were seen in the ticlopidine arm compared with the other therapies.

The approval of ticlopidine for stenting is not undermined by the available safety data: there are no data to suggest that the use of ticlopidine in the stent population is associated with new or increased rates of adverse events relative to stroke prophylaxis population. There was increased bleeding in the stent group relative to the bleeding reported in the stroke-prophylaxis group currently approved for ticlopidine use. The use of concomitant heparin and ASA in the stent population makes this difficult to interpret.

The recommendation of this reviewer is that the current database is sufficient to support the approval of ticlopidine as therapy after coronary stenting.

6.0 REFERENCES

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7. Comparison of anticoagulation, combined with ticlopidine and aspirin, and aspirin alone therapy following coroanry stenting. Galli, S., Trabattoni, D. et al., Circulation (1996) 94: I-684 (A).

cc:

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION — **Public Health Service**

Division of Cardio-Renal Drug Products

Memorandum

DATE : NOV - 2 2000

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Ticlopidine, NDA 19-979/SE1-018, Hoffman-La Roche

TO : Office of Drug Evaluation I, HFD-100

Just a very few words, to add to Dr. Hung's statistical review and to Dr. Throckmorton's Memorandum. Also attached is a consult review performed by Dr. Fredd for Devices.

This Supplement does not contain a powerful argument that Ticlopidine should be approved for use as an adjunct to coronary stent placement. It was, however, good enough for Dr. Throckmorton to conclude that it should be approved and for Dr. Fredd to recommend including it in stent labeling.

Among the 33 trials that are referenced, none were placebo-controlled (all were open label), one (STAR) came with data and a protocol. Four (Hall et al., ISAR, MATTIS, FANTASTIC) were subject to a meta-analysis from published reports. These 5 trials are the totality of randomized trials that were submitted. The other 27 submitted reports were nonrandomized, observational, or reviews.

The 5 randomized trials involved 3,219 total patients, STAR accounting for 1,653 patients alone (51% of the total). There were, overall, a total of 17,809 patients in all of the trial reports submitted. Of interest is that no case (0 observations)of TTP was observed in the 17,809 reported patients (not all on Ticlopidine, but many were). Clearly, this was not a formal development program. Cardiologists thought ticlopicine was mandated(in every patient that received a stent. Aspirin (ASA) is considered a background, all patients always receiving ASA.

STAR received most review attention, since that was the largest single trails and it was the only trial that we had raw data for. The primary endpoint was 30 day stent thrombosis. It was defined as a composite of death, Q-wave MI, and subabrupt closure requiring revascularization. There was a Central Evaluation Committee (CEC) and the raw data (Case Report Forms, CRF). Both the CEC results and the CRF results were the subject of Dr. Hung's analyses. There were 3 arms (ASA, ASA + ticlopidine, ASA + warfarin). Adding warfarin to ASA was a wash. Adding ticlid to ASA appeared to have been advantageous, by ITT analysis of the primary endpoint.

Had the primary endpoint been death and myocardial infraction at up to 30 days after stent placement(Q-wave and non-Q-wave: table 3.1, page 10 of Dr. Hung's review) STAR would not have achieved conventional statistical significance. In my view, the driving force in this open-label trial was "subacute closure, requiring a revascularization procedure". Details (differences in analysis based on the raw data [the CRF analyses

conducted by Dr. Hung] and CEC adjudicated results) are complicated, and are well presented and discussed in the 3 reviews. Certainly, one would want confirmation of what looked good but not dispositive.

The Hall et al. study adds nothing, it was terminated prematurely (3 deaths ASA vs 0 ticlopidine + ASA), not achieving any statistical significance.

ISAR did reach a claimed statistical significance ($p = 0.01$) for the published endpoint equivalent to the STAR 30 day thrombosis endpoint. The combination of death and myocardial infarction did not fare as well ($p = 0.32$), just as in STAR. Again, in my view, this open label trial was largely driven by subabprupt closure.

FANTASTIC had a primary endpoint of bleeding for the 6 weeks post-stent placement. There was no statistically significant difference between the two arms for this primary endpoint. Nor was there any statistically significant effect on any irreversible endpoint. There was an effect ($p = 0.01$) on subacute thrombosis.

MATTIS found no statistically significant effect on anything.

So individually the additional 4 randomized, open-label trials don't confirm STAR in a convincing manner. But there is an integrated (meta-) analysis.

The integrated analysis involved 800 patients who received ticlopidine and 766 who received ASA and or a coumadin anticoagulant. The analysis for endpoints that are like the 30 day thrombosis endpoint yielded p values with 3 zeroes before the first significant figure. For the endpoint of death and myocardial infarction only one zero before the first significant digit. Not very impressive. Once again, need for revascularization seems to be carrying the day.

Summary

It seems to me that subabprupt closure (i.e., the need for revascularization, be it urgent or not-urgent) is the major signal detected by these randomized, open-label trials. I guess it is true, but I would like to have one blinded trial to lean on. Absent that, I think it is close but would recommend not approving this supplement. This is not a data base I would like to have setting a precedent.

We are including both an approvable letter and a non-approval letter for your signature. It will be a difficult choice.

I have included, on a separate page my labeling suggestions, should you think the supplement approvable.

Labeling suggestions

Stent Patients: Data from 5 randomized, open-label trials support the use of ticlopidine after successful placement of coronary stents. These trials which randomized a total of 3,219 patients are: STARS (Stent Anticoagulation Restenoses Study), ISAR (Intracoronary Stenting and Antithrombotic Regimen trial), MATTIS (Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting tial),FANTASTIC (??????) and a trial published by Hall, et al. In each of these trials, a group that received aspirin and ticlopidine were able to be compare to a variety of other anticoagulation or antiplatlet therapies (including aspirin) and or coumadin. Only the raw data data from STARS was available to construct the following tables, the remainder of the data used was gleaned from publications.

One endpoint of interest is the occurrence of stent thrombosis after randomization at 30 and 42 days after randomization. This was defined as a combination of death, myocardial infarction (Q-wave and non-Q-wave) and the occurrence of revascularation (CABG or PTCA).

30 to 42 day stent thrombosis

	Effect Parameter	Estimate (95% Confidence Limits)	Nominal p Value
	rate difference	-2.6% (-3.8%, -1.4%)	0.004
STARS	relative risk	0.17 (0.05, 0.56)	0.004
	Odds ratio	0.17 (0.05, 0.55)	0.003
	Rate difference	-3.9% (-5.9%, -1.8%)	0.003
4 Others	relative risk	0.50 (0.32, 0.79)	0.0026
	odds ratio	0.48 (0.30, 0.76)	0.0019

Another endpoint of interest is the occurrence of death and myocardial infarction (Q-wave and non-Q-wave) at 30 and 42 days after randomization.

30 to 42 day death and myocardial infarction

	Effect Parameter	Estimate (95% Confidence Limits)	Nominal p Value
	rate difference	-1.9% (-4.6%, -0.8%)	0.21
STARS	relative risk	0.78 (0.54, 1.12)	0.18
	Odds ratio	0.76 (0.51, 1.13)	0.18
	Rate difference	-2.9% -4.8%, -1.0%)	0.003
4 Others	relative risk	0.58 (0.36, 0.92)	0.021
	odds ratio	0..55 (0.36, 0.91)	0.019

In appears reasonably clear that the investigators conducting these trials performed fewer post-stent revascularization procedures in patients receiving ticlopidine. The 30 to 42 day outcomes with respect to death and myocardial infarction are ambiguous.

Indications and dosage and administration seem O.K.

There were no reported cases of TTP in these trials, but pos-marketing surveilence estimates a rate of as great as one in every 2000 to 4000 patients (see Black Box). Neutropenia was observed at about the expected rate of 0.8%.

APPEARS THIS WAY
ON ORIGINAL

P900043

To:Dr. Dan Spyker, CDRH 10/15/1998
From:Dr. Stephen Fredd,HFD-110 SF 1/19/98
Through:Dr. Raymond Lipicky,HFD-110 /S/ 1/16/98
Subject: Consultation On STARS Trial And Stent Labeling

You requested our consultation on adding the results of STARS(STENT ANTI-THROMBOTIC REGIMEN STUDY) to the labeling for the Palmaz-Schatz stent. Our comments follow.

BACKGROUND

The Palmaz-Schatz stent was approved on November 7, 1994 for use in selected patients eligible for balloon angioplasty. The approval was based primarily on two clinical studies, STRESS and BENESTENT.
These were randomized trials comparing the stent to balloon angioplasty alone. In that labeling, noted as safety measures, were results for in and out of hospital clinical events which was the composite of death, non-fatal MI, coronary bypass surgery, or stent bailout. In STRESS there appeared to be nominal significance for in-hospital clinical events, and in BENESTENT for out of hospital clinical events. Numerically each result favored the stent.

In these studies an anti-coagulant-anti-thrombotic regimen including aspirin, dipyridamole, low molecular weight dextran, heparin, and coumadin were used for the stent procedure(but not all drugs for the balloon procedure), and the initial labeling included a recommended drug regimen with these drugs as well as dose and timing for administration.

Following approval there apparently was more bleeding than acceptable, and along with improved ways of stenting, reduced anti-thrombotic regimens were tested. Columbo in Italy, Morice in France among others evaluated antiplatelet therapy alone(with periprocedural heparin) where stenting was optimal. Aspirin alone was used by Columbo.
Others used aspirin and ticlopidine. Concern that coumadin might be harmful in stenting led to a randomized comparison of antiplatelet therapy(aspirin plus ticlopidine) and anticoagulant therapy(aspirin, iv heparin and phenprocoumon reported by Schomig et al, New England Journal of Medicine 1996:334:1084-9. 257 patients were randomized to antiplatelet therapy and 260 to anticoagulant therapy. For the primary cardiac end point of death, MI, and reintervention up to 30 days, 4 events were reported for the antiplatelet group, and 16 for the anticoagulant group with a p-value of 0.01. Both q and non-q wave infarcts were included in this endpoint.

Given the adverse reaction profiles of ticlopidine and coumadin, the STARS study was developed to determine whether these regimens gave similar results to prevent major clinical events post optimal stenting.

Prior to considering what labeling might be appropriate for the P-S stent, STARS will be considered as well as additional available data, particularly a study by Shomig et al and information related to the safety of the drugs used in STARS.

STARS

Materials provided for review initially were the Clinical Summary section of PMA 900043-Supplement, one volume, the 6/8/95 protocol for STARS, and a draft report of STARS by Leon et al. Subsequently raw data were submitted for statistical review. Additionally the safety database for ticlopidine at CDER, reports from Dr. Charles Bennett and other investigators, as well as Roche's reports of adverse experience with Ticlid were consulted.

The Stent Antithrombotic Regimen Study was a randomized, open study of three antithrombotic regimens in optimal stenting. It was conducted at 47 sites in the US from February 1996 through November 1996. The sponsor was . Principal investigators were Martin B. Leon, MD, Washington Hospital Center, Washington, D.C.,and Donald S. Baim, MD, Beth Israel Hospital, Boston, Massachusetts.

1965 patients with de novo or restenotic native coronary lesions were enrolled, of whom 1653 patients who had undergone stenting which was considered optimal were randomized to one of three drug regimens as follows:

	Pre and Intra-Procedural Medications		
	Prior to Randomization		
Pre-Procedural			
Bayer Aspirin	325 mg p.o. daily		
Intra-Procedural			
Heparin	10,000-15,000 IV; maintain ACT >250-300 seconds		
	Randomization after Stents Placed		
Post-Procedural	Aspirin Alone	Aspirin and Ticlopidine	Aspirin and Coumadin
Heparin	None	None	Discontinue heparin. Sheath removal when ACT <150 seconds. 6 hours after sheath removal, administer 2000 U heparin bolus followed by 1000 U/hr infusion to maintain aPTT 50-70 seconds. Begin Coumadin and continue heparin until INR between 2.0-2.5.
Bayer Aspirin	325 mg p.o. daily	325 mg p.o. daily	325 mg p.o. daily
Ticlopidine	None	250 mg p.o. bid x 1 month	None
Coumadin	None	None	Adequate Coumadin to maintain INR between 2.0-2.5 x 4 weeks

Although no placebo was added to the aspirin alone arm, this is an add-on study of Ticlid or Warfarin to aspirin and heparin. By design the study cannot prove that aspirin and heparin are necessary in addition to Ticlid or Warfarin, but the use of asprin and heparin can be justified on other bases. The duration of Ticlid use is arbitrary, perhaps modeled on the suggested duration of use for some components of the originally recommended five drug regimen. In the results section of this review, a display of events will be provided that suggests that most stent thromboses occur early after stenting, and a shorter duration of Ticlid than used in STARS may be justified on that and pharmacological grounds.

Randomization

As noted randomization was done after stent placement and only those patients who had optimal stent placement as specified by criteria in the protocol were randomized. The random sequences used were not specified in the protocol or report, but it was noted that the randomization was blocked by "unplanned" or "planned" stenting. The physician or coordinator on site opened the appropriate envelope to make the treatment assignment if the patient qualified for randomization. The prespecified randomization sequence, actual treatment sequence and discussion of any discrepancies was not provided. In this open trial, evaluation of how randomization was carried out would be helpful in establishing that efforts to minimize bias were made.

OBJECTIVES AND ENDPOINTS

The primary objective of the trial was:
"to demonstrate that optimal(<10% residual diameter stenosis)stent deployment using high pressure balloon inflations followed by treatment consisting of either: 1)aspirin alone or 2) aspirin and ticlopidine, is as safe as optimal stent deployment with aspirin and coumadin."
The primary endpoint was stent thrombosis: a composite "using a hierarchical classification scheme approved by the Data and Safety Monitoring Board" of stent thrombosis(angiographic thrombus within the stented vessel demonstrated at the time of documented ischemia—chest pain and ECG changes) requiring emergent revascularization, death, and Q-wave MI.
Secondary objectives with prespecified endpoints were:
Other Procedural complications defined as non Q-wave myocardial infarction(clinically significant as defined by the Clinical Events Committee(all categorizations to be subject to approval of the Data and Safety Monitoring Board), transient abrupt closure defined as Timi grade flow 0-1 which is reversed without the use of additional device intervention although medications might be used, recurrent ischemia without repeat revascularization, adverse vascular events such as hematoma, a-v fistula, pseudoaneuysm, peripheral ischemia and transfusion requirements, and adverse bleeding events.

For both primary and secondary endpoints the primary timepoint was 30 days.

Nine month clinical events for the primary endpoint with the addition of ischemic revascularization events not due to thrombosis were also to be reported, as were late cardiovascular complications overall and for cardiovascular death, Q-wave and large non Q-wave MIs, and clinically driven target site and target vessel revascularization.

Other variables such as acute procedural success,economic and quality of life evaluations were to be done, but will not be commented on in this review.

STATISTICAL PLAN AND ANALYSES

The statistical plan as presented in the protocol was:

Sample size calculations. Sample size calculations will be based upon equivalency of the primary endpoint (stent thrombosis) rate among the 3 randomized arms. The prevalence of stent thrombosis in either treatment is hypothesized to be low (<4%), and a trial powered on showing significant reduction in this already low rate would require well over 10,000 patients. instead, a trial of equivalency sets the standard of this low rate as being the goal for each arm, so that a higher rate seen in any arm will be considered unequivalent to the other arms. Practically, the coumadin-aspirin arm will have an expected 30-day thrombosis rate <4%, and the other two less aggressive arms be at least as low, or equivalent. An estimated sample size of 1650 patients (550 patients per arm) in this 3-arm randomized trial was based on calculations with the following parameters.

1) The abrupt closure rate for the control anticoagulation arm (coumadin and aspirin) is <4%.
2) Equivalency is considered to be within 3% of any comparable arm.
3) The acute success rate for both groups will be 96%.
4) The desired power is 80%.
5) The 1-sided level of significance is 5%.

Interim analyses and stopping rules. An interim analysis will be performed after the first 300 patients have analyzable 30-day stent thrombosis data (approximately 100 in each arm), and a second interim analysis at the halfway point of the study, with planned stopping rules if any of the treatment strategies are determined to be unsafe (a primary endpoint of abrupt closure at 30 days post treatment greater than 8% in any arm). The exact rules and reasons for stopping will be determined by the DSM committee alone. Therefore, the interim analysis will focus on the primary endpoint and other acute complication endpoints, including a combined acute endpoint of death, Q-wave myocardial infarction, emergent CABG, repeat PTCA or subacute thrombosis.

Analyses of the endpoints were to be for the intention-to-treat population, but the protocol goes on to state: "Those patients who meet eligibility requirements for primary endpoint ascertainment include all patients randomized who are not deregistered, do not sustain emergency surgery or death within two weeks of treatment, and who are available for angiographic or clinical follow-up." Chi-square or Fisher's exact test were to be used for endpoint analyses.

COMMITTEES

1.Clinical Events Committee:

"Charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints..." Criteria were to be established for stent thrombosis, vascular complications, myocardial infarction, target site/vessel revascularization, and cardiac death.
Those criteria and information as to when, how, why promulgated and applied to the results are not provided.
This committee was to meet regularly to review and adjudicate in a blinded fashion all major clinical events where the required minimum data were not available. The Cardiovascular Data Analysis center was responsible for categorizing all clinical events, and the Clinical Events Committee was to audit a 10% sample of clinical events categorized by the Analysis Center. It is assumed that the Data Center categorized events blindly, but the criteria on which they did so are not provided, nor are the results of the Clinical Events Committee audit given.

2. Data and Safety Monitoring Board:

Responsible for review and approval of the final version of the protocol, interim analysis plans and stopping rules, and to make recommendations to the Operations Committee regarding endpoint analysis and problems, if any. Information as to what the committee recommended and approved is not available.

3. Operations Committee:

Responsible for the day to day management of the study, monitoring patient enrollment and
clinical site progress, approving the final protocol and clinical sites, and reviewing the final results. Two members of this committee were from

4. Steering Committee:

Reviewed progress of the trial and provided feedback to the Operations Committee and the study chairmen. This committee was composed of members of the Operations Committee and the site Principal Investigators.

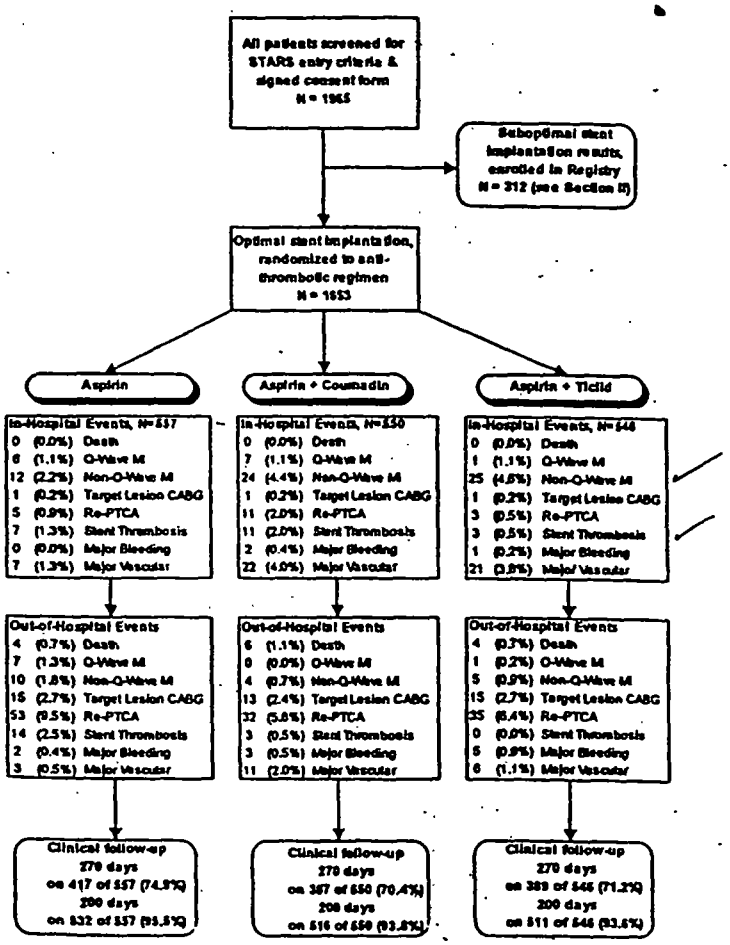
RESULTS

EFFICACY

557 patients were randomized to ASA, 546 to ASA+Ticlid and 550 to ASA+Warfarin. In the randomized study the baseline characteristics of the patients randomized were balanced between the three groups but for prior MI(32% ASA, 39% ASA + Warfarin, 36% ASA + Ticlid), angulation>45°(8%,8%,11% respectively) and mean pressure in atmospheres to deploy stent(17.6± 2.9, 17.7±3.1, 17.3± 3.0). Many other baseline characterics were considered, and were not different between treatments.
The mean age of the patients was 61±11. 71% were male, 90% Caucasian. 52% had hypertension. 19% had diabetes. 28% were current smokers. 34% had dyslipidemia requiring treatment. 8% had had a prior CABG.
The in-lesion % diameter stenosis was not similar for the ASA and ASA + Ticlid groups, though there was a slight non-significant difference between the ASA+Ticlid group and the ASA + Warfarin group with a somewhat greater residual stenosis in the latter group.

47 clinical sites participated. Those enrolling over 100 patients were:
Miriam Hospital, Providence,RI; Washington Hospital Center, Wash.D.C.; St. Joseph Hospital, Syracuse,N.Y.; Georgetown University, Wash.D.C.; Allegheny General Hospital, Pittsburgh,PA.; Rhode Island Hospital,Providence,RI; and Temple University,Philadelphia,PA. Indidual center results were not provided, but the cases which contributed events to the primary endpoint do not appear to be clustered at any particular center. Only 4 centers did not enroll sufficient patients to have at least one patient in each treatment group.

Patient flow and major clinical events were displayed in the PMA supplement as follows:



The out-of hospital events noted above are 9 month results. Since the primary timepoint for analysis is 30 days, out-of-hospital results to 30 days, alone and combined, with in-hospital results follows.

Major Clinical Events – In-Hospital vs. Out-of-Hospital (30 days)
All Patients Randomized (n=1653)

	Aspirin (N=557)		Aspirin + Coumadin (N=550)		Aspirin + Ticlid (N=546)		Among Treatment P-value
Description of Event	Number	%	Number	%	Number	%	
In-Hospital Complications							
Death	0	0.0%	0	0.0%	0	0.0%	NA
Myocardial Infarction (Q or Non-Q)	18	3.2%	31	5.6%	26	4.8%	0.147
Q-Wave MI	6	1.1%	7	1.3%	1	0.2%	0.104
Non-Q-Wave MI	12	2.2%	24	4.4%	25	4.6%	0.049
Emergent CABG	1	0.2%	1	0.2%	1	0.2%	>0.999
Target Lesion Revascularization	6	1.1%	11	2.0%	3	0.5%	0.091
CABG	1	0.2%	1	0.2%	1	0.2%	>0.999
PTCA	5	0.9%	11	2.0%	3	0.5%	0.083
Stent Thrombosis (30 days)	7	1.3%	11	2.0%	3	0.5%	0.100
Major Bleeding	0	0.0%	2	0.4%	1	0.2%	0.329
Major Vascular	7	1.3%	22	4.0%	21	3.8%	0.006
Cerebrovascular Accident	1	0.2%	1	0.2%	0	0.0%	>0.999
Hematological Dyscrasia	1	0.2%	0	0.0%	0	0.0%	>0.999
Subacute Closure with Revascularization (30 days)	3	0.5%	11	2.0%	3	0.5%	0.043
Out-of-Hospital Complications (30 days)							
Death	1	0.2%	0	0.0%	0	0.0%	>0.999
Myocardial Infarction (Q or Non-Q)	12	2.2%	3	0.5%	0	0.0%	<0.001
Q-Wave MI	6	1.1%	0	0.0%	0	0.0%	0.004
Non-Q-Wave MI	6	1.1%	3	0.5%	0	0.0%	0.050
Emergent CABG	2	0.4%	0	0.0%	0	0.0%	0.333
Target Lesion Revascularization	13	2.3%	4	0.7%	0	0.0%	<0.001
CABG	2	0.4%	0	0.0%	0	0.0%	0.333
PTCA	12	2.2%	4	0.7%	0	0.0%	0.001
Stent Thrombosis (30 days)	14	2.5%	3	0.5%	0	0.0%	<0.001
Major Bleeding	1	0.2%	2	0.4%	4	0.7%	0.277
Major Vascular	3	0.5%	9	1.6%	6	1.1%	0.196
Cerebrovascular Accident	1	0.2%	0	0.0%	0	0.0%	>0.999
Hematological Dyscrasia	1	0.2%	1	0.2%	3	0.5%	0.463
Subacute Closure with Revascularization (30 days)	13	2.3%	3	0.5%	0	0.0%	<0.001
Combined (In- and Out-of-Hospital) Complications (30 days)							
Death	1	0.2%	0	0.0%	0	0.0%	>0.999
Myocardial Infarction (Q or Non-Q)	30	5.4%	34	6.2%	26	4.8%	0.582
Q-Wave MI	12	2.2%	7	1.3%	1	0.2%	0.006
Non-Q-Wave MI	18	3.2%	27	4.9%	25	4.6%	0.327
Emergent CABG	3	0.5%	1	0.2%	1	0.2%	0.629
Target Lesion Revascularization	19	3.4%	14	2.5%	3	0.5%	0.002
CABG	3	0.5%	1	0.2%	1	0.2%	0.629
PTCA	17	3.1%	14	2.5%	3	0.5%	0.004
Stent Thrombosis (30 days)	21	3.8%	14	2.5%	3	0.5%	0.001
Major Bleeding	1	0.2%	4	0.7%	5	0.9%	0.197
Major Vascular	10	1.8%	31	5.6%	27	4.9%	0.001
Cerebrovascular Accident	2	0.4%	1	0.2%	0	0.0%	0.777
Hematological Dyscrasia	2	0.4%	1	0.2%	3	0.5%	0.625
Subacute Closure with Revascularization (30 days)	16	2.9%	14	2.5%	3	0.5%	0.006

NQWMI ~ + ε Ticlid and Coumadin?

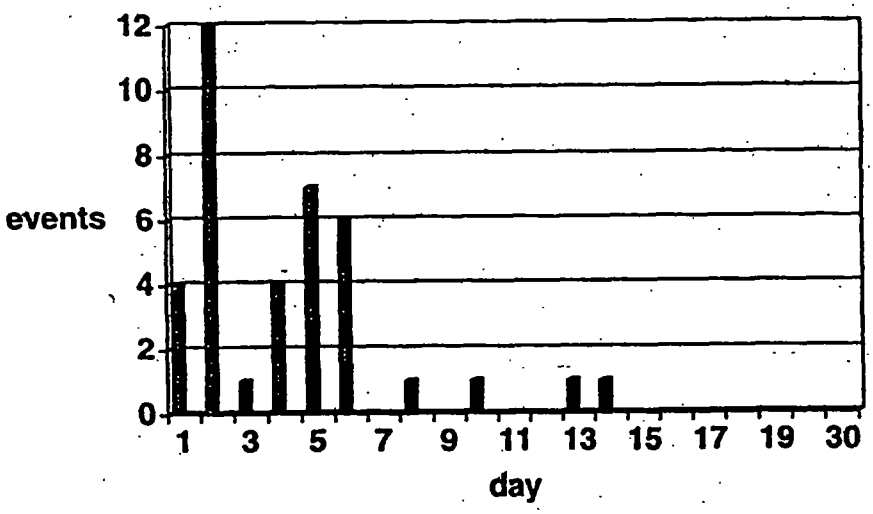
For the primary endpoint of stent thrombosis, the results to 30 days for the ITT population were:

RX	ASA	ASA+Ticlid	ASA+ Warfarin
N	557	546	550
ST	21(3.8%)	3(0.5%)	14(2.5%)

The P-values provided by the sponsor corrected by the Bonferroni method, were:

ASA+Ticlid compared to ASA+warfarin 0.024
ASA+Ticlid compared to ASA 0.008
The point estimate for ASA+Warfarin is not inferior to ASA alone, but the results are not significantly different.

The following chart depicts the day events used in the primary endpoint analysis occurred.



The results as determined by this reviewer from the case synopses for the components of the primary endpoint with each patient being counted once with the hierarchical order of death, q-wave MI, and urgent revascularization were:

	ASA	ASA+WARFARIN	ASA+TICLID
Death	1	0	0
Q-wave MI	12	7	1
Urgent Revasc.	8	7	2

Three additional cases appear to qualify as events:06/026,38/022,09/005. Since if accepted as events these would add one event to each group, the results as reported would be essentially unaffected, but a more thorough review from original case report forms might be useful to validate the sponsor's result.

The results for non-fatal Q-wave MI as a single endpoint are provided as follows:

Pairwise Comparisons

	Relative Risk (95% CI) Aspirin + Ticlid relative to Aspirin	P-Value	Difference (95% CI) Aspirin + Ticlid relative to Aspirin
Non-fatal Q-Wave MI	0.09 [0.02,0.42]	0.007	-2.0% [-3.2%,-0.7%]

	Relative Risk (95% CI) Aspirin + Ticlid relative to Aspirin + Coumadin	P-Value	Difference (95% CI) Aspirin + Ticlid relative to Aspirin + Coumadin
Non-fatal Q-Wave MI	0.14 [0.02,0.87]	0.139	-1.1% [-2.1%,-0.1%]

P-values in the pairwise comparisons are corrected for the comparison-wise error rate by the Bonferroni method; the P-value displayed represents the original P-value multiplied by 2. (i.e., p=0.01 becomes p=0.02).

The primary comparison of ASA+Ticlid to ASA+Warfarin was NS, but even with corrections for the secondary comparison the difference for ASA+Ticlid to ASA appears to be significant .

Whether non-Q wave MIs should be considered in a more usual, but not predefined endpoint of death, non-fatal MIs and need for urgent revascularization is controversial, although analysis of non-fatal non-q-wave MIs was prespecified as a secondary endpoint. in STRESS and BENESTENT both q-wave and non-q-wave MIs were considered as has been customary in antiplatelet drug trials. Procedures such as stenting, atherectomy are very frequently associated with small elevations of CK. However, in this protocol not all

elevations of CK were to be considered non-Q wave MIs, only those with post-procedure CK>2xnormal with detectable CK-MB and no pathological Q waves. Where CK-MB was not done, CK elevations 2xnormal were sufficient for the diagnosis of non-Q wave MI to be made.

The results for the non-Q wave MIs up to 30 days as reported by the sponsor were:

	ASA	ASA+Ticlid	ASA+Warfarin
N	557	546	550
	18(3.2%)	25(4.6%)	27(4.9%)

When all non-fatal MIs are considered, there are no significant differences for this parameter between treatment groups.

For the endpoint of death, non-fatal MIs(Q and non-Q wave), and urgent revascularization up to 30 days, the results using the sponsor's data were:

ASA(n=557)	ASA+Ticlid(n=546)	ASA+Warfarin(n=550)
39(7.0%)	28(5.1%)	41(7.5%)

P-values,2-sided,unadjusted,by Fisher's exact test (provided by Dr. Kooros Mahjoob)were:

ASA+Ticlid versus ASA+Warfarin 0.14

ASA+Ticlid versus ASA 0.21

For the unplanned analysis of death, q and non-q-wave MIs, and urgent interventions, the overall result is NS. The interpretation of the clinical significance of the statistically significant primary endpoint depends to some extent on whether one believes that non-q-wave infarctions as defined by the protocol have prognostic significance. A recent meta-analysis by Cutlip et al(Circulation, supplement,vol.96,#8, October 21,1997, #162) found no association between non-q-wave MIs and long-term prognosis, but follow-up was only for 1 year, and many patients were lost to follow up(see 9 month results below). Califf et. al(JACC,vol.31,#2,Feb.1998,241-251) find an association between elevated CK or CK-MB levels and higher mortality and subsequent cardiac events.

Other cuts of the non-q-wave data by clinical symptoms and level of CK or CK-MB by treatment group have been requested, but it is doubtful that the interpretation of the trial will be much changed by these additional analyses.

MAJOR VASCULAR COMPLICATIONS

These are defined in the protocol as all pseudoaneurysms, vascular access site bleeding associated with a decreased in hemoglobin of>5 g/dl and vascular events requiring repair. The results were in favor of the asa alone arm as noted below:

	ASA	ASA+Warfarin	ASA+Ticlid
Major Vascular	10(1.8%)	31(5.6%)	27(4.9%)

P-value ASA vs. ASA+Ticlid 0.008

The overall clinical benefit of ASA+Ticld versus Aspirin alone would take into account not only the result for the primary stent thrombosis endpoint, but also non-q-wave infarctions, major vascular complications and drug toxicity to be addressed later.

THE NINE MONTH RESULTS

As noted in the patient flow chart on page 7, 1193 patients out of the 1653 randomized had follow-up to 270 days. While the lost-to-follow-up cases were similar among the treatment groups, the 9 month results must be viewed cautiously. The combined in-and-out of hospital major clinical events captured to 9 months are provided in the following chart.

	Aspirin		ASA+Warfarin		ASA+Ticlid		
Combined (In- and Out-of-Hospital) Complication							
Death	4	0.7%	6	1.1%	4	0.7%	0.795
Myocardial Infarction (Q or Non-Q)	35	6.3%	35	6.4%	32	5.9%	0.934
Q-Wave MI	13	2.3%	7	1.3%	2	0.4%	0.015
Non-Q-Wave MI	22	3.9%	28	5.1%	30	5.5%	0.449
Emergent CABG	3	0.5%	1	0.2%	1	0.2%	0.629
Target Lesion Revascularization	69	12.4%	53	9.6%	48	8.8%	0.125
CABG	16	2.9%	14	2.5%	16	2.9%	0.930
PTCA	57	10.2%	42	7.6%	38	7.0%	0.120
Stent Thrombosis (30 days)	21	3.8%	14	2.5%	3	0.5%	0.001
Major Bleeding	2	0.4%	5	0.9%	6	1.1%	0.330
Major Vascular	10	1.8%	33	6.0%	27	4.9%	0.001 ←
Cerebrovascular Accident	4	0.7%	2	0.4%	2	0.4%	0.743
Hematological Dyscrasia	2	0.4%	2	0.4%	3	0.5%	0.806
Subacute Closure with Revascularization (30 days)	16	2.9%	14	2.5%	3	0.5%	0.006

The results are less impressive than the 30 day results, though numerically the ASA+Ticlid arm appears best. As has been said, the number of dropouts makes these data of little value.

STATISTICAL REVIEW

Raw Data from STARS have been received and reviewed by Dr. James Hung, mathematical statistician ,who verified some of the components of the primary endpoint. His review and conclusions are attached.

SAFETY

BLEEDING

Major bleeding was defined as any intracranial bleeding, cardiac tamponade, bleeding events associated with a decrease in hemoglobin of >or=5 g/dl, transfusion or surgical repair. the results up to 30 days were not significantly different between treatments: ASA-1(0.2%), ASA+Warfarin-4(0.7%), ASA+TICLID-5(0.9%).

CVA

Defined as cerebral hemorrhage, thrombosis, or embolism leading to a neurological deficit, there were no significant differences at 30 or 270 days.

	ASA	ASA+WARFARIN	ASA+TICLID
30days	2(0.4%)	1(0.2%)	0
270days	4(0.7%)	2(0.4%)	2(0.4%)

HEMATOLOGIC DYSCRASIAS

This category included neutropenia (severe-ANC <450 neutrophils/mm3, mild to moderate-ANC 451-1200 neutrophils/mm3), thrombocytopenia(<80,000 cells/mm3), and pancytopenia. 7 cases were reported from the randomized study; 1 from the suboptimal stent registry.

RX	Neutropenia	Thrombocytopenia	time to event
ASA	1		7 days
		1	1 month
ASA+WARFARIN		1	13 days
ASA+TICLID	4		1 month
			20 days
			28 days
			1 month

5 cases reversed. In 3 cases no lab follow-up was given, but "no clinical sequelae" was noted. No case of pancytopenia or TTP was reported. What was provided for review was otherwise silent on adverse events.

To further address the safety of the proposed regimens, specifically the ASA+Ticlid regimen which appears to be most effective in this study, other safety information about Ticlid needs to be considered, particularly hematologic dyscrasias. Not only is Ticlid associated with severe neutropenia/agranulocytosis, TTP, thrombocytopenia and aplastic anemia, but the possibility of a higher than expected incidence of TTP in patients stented on Ticlid has been raised by Dr. Charles Bennett of Northwestern University in Chicago. Briefly, by surveying plasmapharesis centers for TTP cases in stented patients in a fixed locale(Pittsburgh, Chicago) for a period of time, and estimating the number of patients who received stents in that period, he has postulated a incidence of 1 case in 1000 patients. Initially this was thought to be much higher than the "rare" TTP occurrence on Ticlid to prevent stroke. That latter belief has been drastically revised by review of recent data on postmarketing AE reports and postulated patient use. An incidence as high as 1 in 2000 has recently been suggested from these data, and incorporated into revised labeling for Ticlid. For whatever use, Ticlid carries a risk of TTP and other blood dyscrasias which has to be balanced against benefit for any indication.
Labeling the Palmaz-Schatz stent with the safety data from STARS alone would be insufficient in presenting the risks of adding Ticlid to Aspirin. While it may not be reasonable to provide full drug labeling in the device labeling, critical information as provided in the WARNINGS section of the Ticlid label might be given with a reference to the full Ticlid prescribing information.

To mitigate the risk of using Ticlid for stenting, consideration should be given to limiting the duration of Ticlid administration to 3 weeks. This would be justified based on the period of greatest risk of thrombosis post-stenting(see chart page 9) and the pharmacodynamic information available that shows some continued anti-platelet effect up to 2 weeks post-dosing with Ticlid. Given the delay in onset of Ticlid's antiplatelet action, it would be reasonable to begin treatment 24-48 hours before stenting, and continue for no more than 3 weeks.

ADDITIONAL STUDIES

Schomig et al have published A Randomized Comparison of Antiplatelet and Anticoagulant Therapy After the Placement of Coronary-Artery Stents(NEJM,1996;334:1084-9). We have information from that publication only, but it appears to support the findings of STARS.

This study done at a single center in Munich, Germany randomized 517 patients after successful stenting(defined as stent placed at the desired position with <30% residual stenosis) to an antiplatelet or anticoagulant regimen.

All patients received heparin and aspirin before PTCA. A 7-mm or articulated 15-mm standard Palmaz-Schatz stent was placed under high pressure, but not always with intravascular ultrasound, for coronary artery dissections, vessel closure, >30% residual stenosis or lesions in venous bypass grafts post PTCA.

The antiplatelet regimen consisted of ticlopidine 250 mg BID for 4 weeks. Heparin was discontinued 12 hours after stent placement.

Both groups continued on ASA 100mg BID.

The anticoagulant group received Phenprocoumon, started immediately after stent placement, to a target INR of 3,5-4.5. The heparin infusion was continued for 5-7 days until a therapeutic INR was reached.

The study was open.

The primary cardiac endpoint was defined as cardiac death(all deaths considered cardiac unless an autopsy proved otherwise), q- and non-q wave MI, and CABG or repeat PTCA, whichever came first. A primary noncardiac endpoint was defined as death from noncardiac cause, cva , bleeding or severe peripheral vascular event.

257 patients were randomized to ticlopidine;260 to Phenprocoumon. Baseline characteristics were:

Characteristic	Antiplatelet Therapy (N = 257)	Anticoagulant Therapy (N = 260)
Age (yr)	61.6±11.5	61.5±10.7
	no. (%)	
Female sex	60 (23.3)	61 (23.5)
Cigarette smoking	133 (51.8)	140 (53.8)
Hypercholesterolemia	82 (31.9)	92 (35.4)
Arterial hypertension	158 (61.5)	166 (63.8)
Diabetes mellitus	40 (15.6)	51 (19.6)
Multivessel disease	199 (77.4)	183 (70.4)
Previous myocardial infarction	108 (42.0)	117 (45.0)
Acute myocardial infarction	61 (23.7)	62 (23.8)
Unstable angina	119 (46.3)	112 (43.1)
Previous CABG	20 (7.8)	33 (12.7)
Previous PTCA	47 (18.3)	54 (20.8)

*Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

Variable	Antiplatelet Therapy	Anticoagulant Therapy
Target vessels — no. (%)		
Total	273	281
Left main	5 (1.8)	4 (1.4)
LAD	116 (42.5)	115 (40.9)
LCx	42 (15.4)	54 (19.2)
RCA	99 (36.3)	92 (32.7)
Venous bypass graft	11 (4.0)	16 (5.7)
ACC–AHA lesion type — no. of vessels (%)		
A	12 (4.4)	10 (3.6)
B1	27 (9.9)	19 (6.8)
B2	87 (31.9)	93 (33.1)
C	147 (53.8)	159 (56.6)
Restenotic lesion — no. of vessels (%)	38 (13.9)	32 (11.4)
Occluded vessel — no. of vessels (%)	41 (15.0)	42 (14.9)
Thrombus in the stented area — no. of vessels (%)	53 (19.4)	59 (21.0)
Dissection before stenting — no. of vessels (%)	161 (59.0)	161 (57.3)
Dimensions before stenting		
Reference diameter — mm	3.04±0.55	3.03±0.55
Minimal lumen diameter — mm	0.65±0.50	0.63±0.47
Percent stenosis	78.4±15.4	79.0±14.5
Maximal balloon pressure — atmospheres	16.0±2.6	15.8±2.6
Measured balloon size — mm	3.38±0.48	3.36±0.48
Balloon-to-vessel ratio	1.13±0.17	1.13±0.17
Intravascular ultrasound performed — no. of vessels (%)	34 (12.5)	28 (10.0)
No. of 7-mm stent segments/vessel	2.9±1.7	2.9±1.8
Dimensions after stenting		
Reference diameter — mm	3.12±0.50	3.14±0.52
Minimal lumen diameter — mm	3.03±0.49	3.03±0.53
Percent stenosis	2.4±11.5	2.9±12.4

*Plus–minus values are means ±SD. LAD denotes left anterior descending artery, LCx left circumflex artery, RCA right coronary artery, and ACC–AHA American College of Cardiology and American Heart Association.[44]

APPEARS THIS WAY
ON ORIGINAL

The results were:

Event	Antiplatelet Therapy (N = 257)	Anticoagulant Therapy (N = 260)	P Value	Relative Risk (95% CI)
	no. (%)			
Primary cardiac end point	4 (1.6)	16 (6.2)	0.01	0.25 (0.06–0.77)
Death	1 (0.4)	2 (0.8)	1.0	0.50 (0.01–9.66)
Myocardial infarction	2 (0.8)	11 (4.2)	0.02	0.18 (0.02–0.83)
Fatal	0	2 (0.8)	0.50	0.00 (0.00–3.51)
Nonfatal	2 (0.8)	9 (3.5)	0.06	0.22 (0.02–1.07)
Reintervention	3 (1.2)	14 (5.4)	0.01	0.22 (0.04–0.77)
CABG	0	1 (0.4)	1.0	
Repeated PTCA	3 (1.2)	13 (5.0)	0.02	0.23 (0.04–0.84)
Primary noncardiac end point	3 (1.2)	32 (12.3)	<0.001	0.09 (0.02–0.31)
Death	0	0		
Cerebrovascular accident	1 (0.4)	0	1.0	
Hemorrhagic event	0	17 (6.5)	<0.001	0.00 (0.00–0.19)
Surgical correction	0	1 (0.4)	1.0	
Transfusion	0	12 (4.6)	0.001	0.00 (0.00–0.29)
Organ dysfunction	0	7 (2.7)	0.02	0.00 (0.00–0.53)
Peripheral vascular event	2 (0.8)	16 (6.2)	0.001	0.13 (0.01–0.53)
Surgical correction	0	1 (0.4)	1.0	
Ultrasound-guided compression	2 (0.8)	15 (5.8)	0.002	0.14 (0.02–0.57)
Combined clinical end point	7 (2.7)	43 (16.5)	<0.001	0.16 (0.06–0.36)
Occlusion of stented vessel	2 (0.8)	14 (5.4)	0.004	0.14 (0.02–0.62)
Thrombosis	0	13 (5.0)	<0.001	0.00 (0.00–0.26)
Dissection	2 (0.8)	1 (0.4)	1.0	2.03 (0.11–120)

*Relative risks are for the patients in the antiplatelet-therapy group as compared with those in the anticoagulant-therapy group. CI denotes confidence interval, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty. Patients with more than one event are counted only once for each type of end point, though the events are listed separately in the relevant categories.

APPEARS THIS WAY
ON ORIGINAL

Individual cardiac events are depicted below.

Patient No.	Death	MI	CABG	PTCA	Vessel Occlusion	Days after Stenting
Antiplatelet-therapy group						
1		X		X	O†	3
2		X		X	O†	1
3	X‡				P	3
4				X§	P	7
Anticoagulant-therapy group						
1	X¶	X				7
2		X		X	O	4
3					O	18
4				X§	P	3
5		X		X	O†	2
6		X	X		O	26
7		X		X	O	7
8		X		X	O	2
9				X	O	13
10		X		X	O	3
11				X	O	11
12				X	O	19
13	X	X			O	5
14		X		X	O	9
15		X		X	O	4
16				X§	P	1
17		X		X	O	3

*MI denotes myocardial infarction, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty. X indicates that the patient had the event in question. For vessel occlusion, O denotes occlusion demonstrated by angiography, and P patent vessel demonstrated by angiography or autopsy.

†Vessel occlusion due to progressive dissection outside the stented segment.

‡Death without evidence of myocardial ischemia. Autopsy and postmortem angiography revealed a patent stent; the precise cause of death could not be established at autopsy.

§PTCA outside the stented segment, necessitated by recurrent angina.

¶Death during acute myocardial infarction related to stented vessel. No angiogram was obtained after the event.

In the ticlopidine group, the last event occurred on day 7, but events continued to occur to day 26 in the Phenprocoumon group. For the first 2 days post-stenting, no difference in events were found between groups, and the authors note that fibrinogen receptor surface expression decreased over a 3 day period after ticlopidine administration.

No neutropenia or other hematological dyscrasias were noted in the article.

THE PROPOSED RELABELING

With approval of the Palmaz-Schatz stent on November 7,1994, an anticoagulation regimen was recommended for placement of the stent and follow-up care. This regimen was used in the STRESS and BENESTENT studies that formed the basis for approval of the stent, and results of these trials were part of the labeling.

The draft CDRH labeling provided to us removes all mention of that regimen, makes no recommendation for any antithrombotic regimen, but proposes to give a synopsis of the results from STARS in the clinical trials and the adverse reaction sections. There are adequate data to support the use of aspirin and ticlopidine for stenting.

The risk of adding ticlopidine to aspirin and heparin is a significant concern, and therefore a relabeling of either component of this device-drug combination should be based on full information. The ticlopidine labeling has been revised recently to emphasize the higher than previously thought risk of thrombotic thrombocytopenic purpura(TTP). Cases of TTP are occurring post-stenting, and therefore it is important that device labeling carry the ticlopidine warnings for agranulocytosis and TTP.

RECOMMENDATIONS

1. The STARS data, supported by the Schomig study, provides evidence to support the efficacy of ticlopidine to prevent stent thrombosis. Aspirin and heparin are adjunctive regimens in this context.

2. Analysis of the period of risk for stent thrombosis post-stenting, the adverse reaction data and the pharmacology of ticlopidine might support limiting use to no more than 2 weeks.

3. Comprehensive adverse reaction experience with ticlopidine should be included in the stent labeling with efficacy information from the STARS study. The boxed warning should be included in the device labeling with further reference to the drug's label for safety.