

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-979/S-018

Statistical Review(s)

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STATISTICAL REVIEW AND EVALUATION

SEP 13 2000

NDA #: 19-979 SE1-018

Applicant: Hoffman-La Roche Inc.

Drug Name: Ticlid (ticlodipine hydrochloride)

Indication: Reduce thrombotic stroke and prevention of subacute stent thrombosis

Document Reviewed: Volumes S67.1, S67.2, S67.3, S67.4

The sponsor submitted this supplemental new drug application to provide data derived from a review of the medical literature to support the use of Ticlid as adjunctive therapy with aspirin for the prevention of subacute stent thrombosis in patients undergoing successful coronary stent implantation. The sponsor's review of the published literature identified 44 published articles pertaining to 5 controlled randomized studies, 7 nonrandomized comparative studies, 23 observational/retrospective studies, 7 pharmacodynamic studies, and 4 case studies for safety only. One of the randomized controlled trials, STARS, had been reviewed by the Agency before; see statistical review of October 6, 1998, which demonstrated that the ASA+Ticlid group seemed to have a significantly smaller 30 day stent thrombosis rate than the ASA+Warfarin group and the ASA group.

This review will give a brief overview of the remaining four randomized controlled trials. Several integrated analyses will be performed on these trials. There is no raw data available; thus, checking validity of statistical data is not possible. The reviewer's analysis will be performed using the numbers published in the articles and/or supplied by the sponsor.

Nonrandomized and observation/retrospective studies are known to have significant amount of biases, which are not assessable and make valid statistical inference impossible. Therefore, these studies are not evaluated in this review. The readers are referred to medical review for descriptive statistics.

1. BRIEF SUMMARY OF STARS RESULTS

STARS was a randomized, open study of three antithrombotic regimens in optimal stenting. A total of 1,653 patients who had undergone stenting considered optimal were randomized to one of three drug regimens briefly labeled as ASA (aspirin alone), ASA+Ticlid (aspirin plus ticlodipine), ASA+Warfarin (aspirin plus coumadin). The physician or coordinator on site opened the sealed envelope to make the treatment assignment if the patient qualified for randomization.

The primary objective of the trial was to demonstrate that optimal stent deployment with ASA alone or ASA plus ticlopidine is as safe as optimal stent deployment with ASA plus coumadin. The primary endpoint was 30 day stent thrombosis, a composite endpoint of death, Q-wave MI,

and subabrupt closure requiring revascularization using a hierarchical classification scheme approved by the Data and Safety Monitoring Board (DSMB).

According to the protocol, two interim analyses would be performed after the first 300 patients had analyzable 30-day stent thrombosis data and at the halfway point of the study, respectively. The planned stopping rules appeared to be that any of the treatment strategies determined unsafe (a primary endpoint of abrupt closure at 30 days post treatment greater than 8% in any arm) would be dropped. The exact rules were to be determined by DSMB but not provided in the report. According to the DSMB's meeting minutes, it appeared that the analyses were performed only on the components of stent thrombosis; all nominal p-values of the components were large (> 0.14). The trial was not terminated early.

The primary endpoint was 30 day stent thrombosis. The incidences were given in Table 1.1. The nominal p-values (uncorrected for multiple comparisons) for the results of Table 1.1 are provided in Table 1.2. Overall speaking, the three treatment strategies appeared to differ on the incidence of stent thrombosis ($p = 0.001$). Based on the Bonferroni method selected post hoc by the sponsor to adjust the nominal p-values for the two primary comparisons (ASA vs. ASA+Warfarin, ASA+Ticlid vs. ASA+Warfarin), the ASA+Ticlid group appeared to have a significantly smaller stent thrombosis rate than the ASA+Warfarin group (adjusted p-value = 0.016 based on CEC data and 0.078 based on CRF data). The difference between ASA and ASA+Warfarin was not conclusive. The stent thrombosis rate with ASA+Ticlid seemed to be smaller than that with ASA alone.

Table 1.1. Incidence of 30 day stent thrombosis (ST) for ITT population

RX	ASA	ASA + Ticlid	ASA + Warfarin
N	557	546	550
ST (CEC)	21 (3.8%)	3 (0.5%)	14 (2.5%)
ST (CRF)#	23 (4.1%)	5 (0.9%)	14 (2.5%)

2 additional patients (04/001, 50/009) in the ASA+Ticlid group appeared to qualify as Q-wave MI according to the hospital discharge form; 2 additional patients (10/067, 19/038) in the ASA group appeared to be subabrupt closure requiring revascularization according to hospital discharge form or one month contact form

Table 1.2. Nominal P-value for 30 day stent thrombosis (ST) for ITT population

	ASA vs. ASA+Warfarin	ASA+Ticlid vs. ASA+Warfarin	ASA+Ticlid vs. ASA
ST (CEC)	0.24	0.008	0.001
ST (CRF)	0.14	0.039	0.001

* All P-values are based on chi-square test

Table 1.3. Confidence interval (CI)

	ASA+Ticlid vs. ASA+Warfarin	ASA vs. ASA+Warfarin
95% CI:		
ST (CEC)	(-3.5%, -0.5%)	(-0.8%, 3.3%)
ST (INV)	(-3.2%, -0.09%)	(-0.5%, 3.7%)

In summary, the ASA+Ticlid group seemed to have a significantly smaller 30 day stent thrombosis rate than the ASA+Warfarin group (adjusted p-value = 0.016 based on CEC data). The difference between ASA and ASA+Warfarin was not conclusive. The 30 day stent thrombosis rate with ASA+Ticlid seemed to be smaller than that with ASA alone ($p < 0.002$). This trend was seen in almost all subgroups (see Appendix A). However, as a result of the investigators knowing the medical treatment assignments when assessing the patient's event status, the potential biases, which are not assessable, need be of concern. Because of this concern plus the potential impact of the informal interim analyses explained above, statistical significance for these treatment contrasts should be interpreted with great caution.

2. OVERVIEW OF REMAINING FOUR RANDOMIZED CONTROLLED TRIALS

2.1. Hall et al. Study (Circulation, 1996, 93: 215-222)

This is an open label study. It appeared to be a European study.

Between 1/94 and 3/95, 226 patients were randomized to receive either short-term aspirin 325 mg and ticlopidine 250 mg BID (N=123) or aspirin 325 mg/day alone (N=103) after successful intravascular ultrasound-guided stent implantation. The number of centers is unknown.

The primary efficacy endpoints appeared to be the major clinical events [death, emergency bypass surgery, elective bypass surgery, Q-wave or non-Q-wave MI, emergency repeated intervention (bailout stenting or repeated angioplasty), and vascular complications] in the 30 days after stenting.

There was no information on interim analysis, DSMB, or whether an event adjudication committee was called to adjudicate the events. The study was terminated prematurely before the expected target of 450 patients after the three deaths in the aspirin group.

There appeared to be some imbalance at baseline (see Table 2.1.1). Numerically, the ASA group seemed to have a greater rate of cardiac-related events at 30 days than the ASA+Ticlid group (Table 2.1.2). None of the treatment differences are statistically significant.

Table 2.1.1. Baseline characteristics

	Ticlopidine + aspirin (N=123)	Aspirin alone (N=103)
Age	57±9	58±10
Men	108 (88%)	92 (89%)
Current smoking	36 (29%)	40 (39%)
Ever smoked	70 (56%)	70 (68%)
Diabetes mellitus ²	20 (16%)	6 (6%)
Hypertension	50 (40%)	41 (40%)
Hypercholesterolemia	70 (57%)	49 (48%)
Previous MI	62 (50%)	49 (48%)
Previous CABG ¹	14 (11%)	3 (3%)
Previous PTCA	13 (10%)	10 (10%)
Unstable angina	27 (33%)	18 (28%)
Total occlusions ³	13 (8%)	20 (15%)

¹p = 0.02 ²p=0.01 ³p<0.05

Table 2.1.2. Cardiac-related endpoints

	Ticlopidine + aspirin (N=123)	Aspirin alone (N=103)	p-value
30 days			
Any major event	1 (0.8%)	4 (3.9%)	0.10
Death	0	3 (2.9%)	0.10
MI	1 (0.8%)	4 (3.9%)	0.10
Death, MI*	1 (0.8%)	4 (3.9%)	0.18*
Stent thrombosis	1 (0.8%)	3 (2.9%)	0.20
Emergency bypass	0	0	
Elective bypass	0	0	
Repeated PTCA	1 (0.8%)	2 (1.9%)	0.40
Vascular complications	0	1 (1.0%)	0.50

* derived by the reviewer and Fisher Exact test used in analysis

2.2. ISAR Study (New England Journal of Medicine, 1996, 334: 1084-1089)

Between 10/94 and 9/95, a total of 517 patients in whom intracoronary stents were successfully placed after PTCA were randomized to receive either antiplatelet therapy (N=257) or anticoagulation therapy (N=260). The number of centers is unknown. All patients were included in the analysis.

In patients assigned to antiplatelet therapy, heparin was discontinued 12 hours after stent replacement. Ticlodipine (250 mg BID) was started immediately after the procedure and continued for four weeks. In patients assigned to anticoagulant therapy, phenprocoumon (a coumarin derivative) therapy was initiated immediately after placement of the stent and continued for four weeks. The heparin infusion was continued for 5 to 10 days until a stable degree of oral anticoagulation was achieved. All patients in both groups received aspirin 100 mg twice a day throughout the study.

Two primary clinical endpoints were studied, cardiac and noncardiac. The primary cardiac endpoint was defined as death due to cardiac causes or the occurrence of MI, aortocoronary bypass surgery, or repeated PTCA of the stented vessel, whichever occurred first. All deaths were considered due to cardiac causes unless an autopsy established a noncardiac cause, in the 30 days after stenting. The primary noncardiac endpoint was a composite endpoint of death from noncardiac causes, cerebrovascular accident, severe hemorrhage, and peripheral vascular events in the 30 days after stenting.

There was a scheduled interim analysis to confirm the prospectively determined sample size. The trial did not stop early. The article provides no information on DSMB, or on event adjudication process.

There was no death from noncardiac causes.

According to the article, patients and physicians were not blinded to the treatment assignment and this fact represents a limitation of the study. Bias on the part of investigators or patients cannot be fully excluded as a factor influencing management after stenting. However, to minimize investigator bias, definitions of events were specified in the protocol and based on objective criteria.

There was no evidence indicating any baseline imbalance (Table 2.2.1). The antiplatelet group seemed to have a significantly smaller rate of composite endpoint of death, MI, CABG, or repeated PTCA at 30 days than the anticoagulant group (Table 2.2.2), $p=0.01$. From the tables provided in the article, the reviewer was able to get the incidence of death or MI. The antiplatelet group seemed to have a significantly smaller rate of this composite endpoint (death or MI), $p=0.032$. The relative risk of antiplatelet versus anticoagulant for reintervention component was slightly smaller than that for death or MI composite endpoint (22% versus 28%). It is not clear how much of these treatment differences might be affected by any factor influencing after-stenting management because of unblinding patients and physicians.

Table 2.2.1. Baseline characteristics

	Antiplatelet (N=257)	Anticoagulant (N=260)
Age	62±12	62±11
Men	197 (77%)	199 (77%)
Cigarette smoking	133 (52%)	140 (54%)
Diabetes mellitus	40 (16%)	51 (20%)
Arterial hypertension	158 (62%)	166 (64%)
Hypercholesterolemia	82 (32%)	92 (35%)
Previous MI	108 (42%)	117 (45%)
Acute MI	61 (24%)	62 (24%)
Unstable angina	119 (46%)	112 (43%)
Previous CABG	20 (8%)	33 (13%)
Previous PTCA	47 (18%)	54 (21%)
Multivessel disease	199 (77%)	183 (70%)

Table 2.2.2. Cardiac-related endpoints

	Antiplatelet (N=257)	Anticoagulant (N=260)	p-value
30 days			
Death, MI, CABG, repeated 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
Fatal	0	2 (0.8%)	0.5
Nonfatal	2 (0.8%)	9 (3.5%)	0.06
Reintervention	3 (1.2%)	14 (5.4%)	0.01
CABG	0	1 (0.4%)	1.0
Repeated PTCA	3 (1.2%)	13 (5.0%)	0.02
Death, MI, CABG*	3 (1.2%)	11 (4.2%)	0.032
Death, MI*	3 (1.2%)	11 (4.2%)	0.032
Occlusion of stented vessel	2 (0.8%)	14 (5.4%)	0.004
Thrombosis	0	13 (5.0%)	<0.001
Dissection	2 (0.8%)	1 (0.4%)	1.0

* derived by reviewer from Tables 3 and 4 in NEJM (1996, 1084-1089)

2.3. FANTASTIC Study (Circulation, 1998, 98: 1597-1603)

Between 5/95 and 5/96, 485 patients in whom planned or unplanned stent implantation was attempted from 13 European centers were randomized to receive either conventional anticoagulation (N=236) and antiplatelet therapy (N=249). Stent implantation was not possible in 4 patients, 3 were referred for emergency coronary artery bypass, and 5 withdrew informed consent. The final analysis cohort comprised 473 patients. Stenting was elective in 58% patients and unplanned in 42%. Stent implantation was successfully achieved in 99% of the patients.

In the anticoagulation therapy group, patients were started on oral anticoagulant immediately after stent implantation and then bolus of heparin (2500 IU) followed by continuous infusion of 1000 IU/h. At discharge, patients were placed on oral anticoagulants for 6 weeks and aspirin (100 to 325 mg) for life. In the antiplatelet therapy group, patients received first dose of ticlopidine (500 mg) and were discharged on ticlopidine (250 mg bid) for 6 weeks and aspirin (100 to 325 mg) for life.

The primary study endpoint was rate of bleeding complications in the 6 weeks after stent implantation. Secondary endpoints were rate of acute (occurring \leq 24 hours) or subacute (occurring $>$ 24 hours) stent occlusion, clinical cardiac-related events (death, Q-wave or non-Q-wave MI) and duration of hospitalization in the 6 weeks after stent implantation.

There was no evidence for baseline imbalance between the two treatment groups. The antiplatelet group appeared to have a smaller rate of subacute stent occlusion and a smaller duration of hospital stays (Table 2.3.2) in the 6 weeks after stent implantation.

Table 2.3.1. Baseline characteristics

	Antiplatelet (N=243)	Anticoagulant (N=230)
Age	60 \pm 11	60 \pm 10
Men	197 (82%)	185 (80%)
Current smokers	78 (33%)	63 (27%)
Former smokers	109 (45%)	98 (43%)
Insulin-dependent diabetes	8 (3%)	6 (3%)
Non-insulin-dependent diabetes	29 (12%)	28 (12%)
Hypertension ($>$ 160/90 mmHg)	79 (33%)	74 (32%)
Hypercholesterolemia ($>$ 240 mg)	115 (48%)	101 (44%)
Family history of coronary disease	116 (48%)	103 (45%)
Previous MI	118 (51%)	108 (47%)
Previous coronary bypass surgery	33 (14%)	31 (14%)
Previous angioplasty	84 (35%)	72 (31%)
Unstable angina	105 (43%)	94 (41%)
Stable angina	119 (49%)	115 (50%)
Atypical chest pain	19 (8%)	20 (9%)

Elective Stenting	127 (52%)	109 (47%)
Stenting for bailout for failed angioplasty/suboptimal	116 (48%)	121 (53%)

Table 2.3.2. Cardiac-related endpoints

	Antiplatelet (N=243)	Anticoagulant (N=230)	p-value
6 weeks			
Acute Stent occlusion	6 (2.4%)	1 (0.4%)	0.08
Subacute stent occlusion	1 (0.4%)	8 (3.5%)	0.01
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 and MI*	14 (5.8%)	19 (8.3%)	0.29
Hospital stays, d±sd	4.3±3.6	6.4±3.4	0.0001
6 months follow-up			
Death	2 (0.8%)	5 (2.2%)	0.21
Acute MI	13 (5.4%)	16 (7.1%)	0.44
Q wave	3 (1.2%)	7 (3.1%)	0.16
Non-Q wave	10 (4.1%)	9 (4.0%)	0.93
Coronary artery bypass	3 (1.2%)	3 (1.3%)	0.93
Repeat target lesion angioplasty	13 (5.4%)	11 (4.9%)	0.80
Total (6 months)	31 (12.8%)	35 (15.5%)	0.40

* derived

2.4. MATTIS Study (Circulation, 1998, 98: 2126-2132)

This is an open label study.

Between 2/96 and 1/97, 350 high-risk patients from 31 European centers were randomized to receive either aspirin 250 mg/d and ticlopidine 500 mg/d (N=177) or aspirin 250 mg/d and oral anticoagulation (N=173) within 6 hours after stent implantation.

The primary efficacy endpoint was the occurrence of cardiovascular death, any MI in the territory of the stented vessel, repeated PTCA or CABG involving the previously stented segment because of recurrent ischemia, arrhythmia, or hemodynamic failure, whichever occurred first in the 30 days after stenting.

There was no information on interim analysis, DSMB, or whether an event adjudication committee was called to adjudicate the events.

There was no evidence for baseline imbalance between the two treatment groups (Table 2.4.1). The antiplatelet group seemed to have a smaller rate of the composite endpoint of death, MI, CABG, or repeated PTCA at 30 days (Table 2.4.2).

Table 2.4.1. Baseline characteristics

	Antiplatelet (N=177)	Anticoagulant (N=173)
Age	60±10	60±10
Men	150 (85%)	131 (76%)
Current smoker	32 (18%)	38 (22%)
Diabetes mellitus	25 (14%)	26 (15%)
Hypertension	81 (35%)	67 (39%)
Hypercholesterolemia	87 (49%)	80 (46%)
Previous MI	88 (50%)	84 (49%)
Previous CABG	13 (7%)	18 (10%)
Previous PTCA	41 (23%)	40 (23%)
Previous vascular disease	14 (8%)	23 (13%)
Previous stroke	4 (2%)	5 (3%)
Previous cerebral TIA	5 (3%)	2 (1%)

Table 2.4.2. Cardiac-related endpoints

	Antiplatelet (N=177)	Anticoagulant (N=173)	p-value
30 days			
Death, MI, CABG, repeated 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
Q wave	1 (0.6%)	2 (1.2%)	0.62
Non-Q wave	5 (2.8%)	10 (5.8%)	0.17
Reintervention	6 (3.4%)	14 (8.1%)	0.06
CABG	2 (1.1%)	2 (1.2%)	1.0
Repeated PTCA	4 (2.3%)	12 (6.9%)	0.04
Death, MI, CABG*	ND	ND	
Death, MI [†]	9 (5.1%)	13 (7.5%)	0.35
Between 30 days and 6 months			
Death, MI, CABG, repeated PTCA	28 (16.8%)	25 (16.2%)	NA
Death	2 (1.1%)	3 (1.7%)	NA
MI	4 (2.3%)	3 (1.7%)	NA
Q wave	1 (0.6%)	2 (1.2%)	

Non-Q wave	3 (1.7%)	1 (0.6%)	
Reintervention	27 (15.3%)	22 (12.7%)	NA
CABG	5 (2.8%)	5 (2.9%)	
Repeated PTCA	22 (12.4%)	17 (9.8%)	

* ND: not derivable from the article @ provided by the sponsor

NA: not applicable

3. REVIEWER'S EVALUATION

Several statistical analyses were requested by the Division of Cardio-Renal Drug Products. First, in STARS, ASA+Warfarin and ASA alone will be pooled and compared with ASA+Ticlid, and also a composite endpoint of death and MI will be analyzed. Secondly, the remaining four randomized controlled studies will be integrated for analysis. The composite endpoint of death, MI and re-intervention and the composite endpoint of death and MI at 30 days will be analyzed.

STARS

Table 3.1 summarizes the results of comparison of ASA+Ticlid with the combined group of ASA and ASA+Warfarin using CEC adjudication results. The ASA+Ticlid group seemed to have a significantly smaller rate of 30 days stent thrombosis (death, Q-wave MI, subacute closure requiring revascularization) than the pooled group of ASA alone and ASA+Warfarin. As for death and MI, the relative effect of ASA+Ticlid versus the pooled comparator can change from a risk reduction of 88% to 23% with p-value changing from 0.004 to 0.21 when non-Q-wave MI is counted as MI. The classification of MI into Q-wave or non-Q wave is critically important to interpretation of the trial results.

Table 3.1. Incidence of 30 day events (based on CEC adjudication) for ITT population

	ASA and ASA+Warfarin (N=1107)	ASA + Ticlid (N=546)	Effect parameter	ASA+Ticlid minus ASA & ASA+Warfarin (95% CI)	Nominal p-value
Stent thrombosis	35 (3.2%)	3 (0.5%)	Rate difference Relative risk Odds ratio	-2.6% (-3.8%, -1.4%) 0.17 (0.05, 0.56) 0.17 (0.05, 0.55)	0.004* 0.004@ 0.003@
Death, MI ^{\$}	94 (8.5%)	36 (6.6%)	Rate difference Relative risk Odds ratio	-1.9% (-4.6%, 0.8%) 0.78 (0.54, 1.12) 0.76 (0.51, 1.13)	0.21* 0.18@ 0.18@
Death, Q-wave MI	20 (1.8%)	1 (0.2%)	Rate difference Relative risk Odds ratio	-1.6% (-2.5%, -0.7%) 0.10 (0.01, 0.75) 0.10 (0.01, 0.75)	0.004* 0.025@ 0.025@

* Fisher's exact test (2-tailed) @ normal approximation \$ MI: Q-wave and Non-Q-wave

Integrated analysis of HALL, ISAR, FANTASTIC and MATTIS Studies

For the four studies, there was no sufficient statistical evidence to indicate inter-study heterogeneity in the effect of antiplatelet therapy versus the pooled group of anticoagulation therapy and ASA alone ($p > 0.35$ for testing heterogeneity). Table 3.2 summarizes the results of the reviewer's integrated analyses on major events occurring at 30 days or 6 weeks (definition of major events depends on study by study). The integrated analysis seems to suggest that the rate of the composite endpoint of death, MI, CABG, and PTCA is smaller with antiplatelet therapy than the pooled comparator.

Table 3.2. Incidence of major events occurring at 30 days (or 6 weeks)

Studies	Endpoints	Effect parameter	Antiplatelet (N=800) vs. Anticoagulant [§] (N=766) point estimate (95% CI)	Nominal p-value
F,I,M,H	D+MI+C+P*	Rate difference	-3.9% (-5.9% , -1.8%)	0.0003
		Relative risk	0.50 (0.32 , 0.79)	0.0026
		Odds ratio	0.48 (0.30 , 0.76)	0.0019
I,M,H	D+MI+C+P*	Rate difference	-4.2% (-6.5% , -1.9%)	0.0004
		Relative risk	0.39 (0.22 , 0.70)	0.0017
		Odds ratio	0.36 (0.20 , 0.68)	0.0014

§ Aspirin only in HALL et al trial

F: FANTASTIC I: ISAR M: MATTIS H: HALL ET AL.

D: death MI: MI C: CABG P: PTCA

* FANTASTIC: death and MI (42 days)

ISAR: death, MI, CABG, PTCA (30 days)

MATTIS: death, MI, CABG, PTCA (30 days)

HALL et al: death, MI, CABG, repeat stent, PTCA (30 days)

Table 3.3. Incidence of death and MI at 30 days (or 6 weeks)

Studies	Endpoints	Effect Parameter	Antiplatelet (N=800) vs. Anticoagulant [§] (N=766) Point estimate (95% CI)	Nominal p-value
F,I,M,H	D+MI*	Rate difference	-2.9% (-4.8% , -1.0%)	0.003
		Relative risk	0.58 (0.36 , 0.92)	0.021
		Odds ratio	0.55 (0.36 , 0.91)	0.019

§ Aspirin only in HALL et al trial

F: FANTASTIC I: ISAR M: MATTIS H: HALL ET AL.

D: death MI: MI C: CABG P: PTCA

* FANTASTIC: death and MI (42 days)

The same analysis was performed on the composite endpoint of death and MI (see Table 3.3). The integrated analysis also seems to suggest that the rate of the composite endpoint of death and

MI is smaller with antiplatelet therapy than with the pooled group of anticoagulation therapy and ASA alone. The effect on this endpoint seems to be a bit smaller than that on the composite endpoint that includes CABG and PTCA.

CONCLUSION

Five randomized comparative studies are included in this NDA submission and evaluated in this review. Of these studies, STARS with case report form data supplied by the company had been reviewed (see statistical review of October 6, 1998). For the remaining four studies there is no raw data available; thus, checking validity of statistical data is not possible. The reviewer's analyses on these studies are based on the numbers published in the articles or supplied by the sponsor.

The STARS results show that the ASA+Ticlid group seemed to have a significantly smaller rate of 30 days stent thrombosis (death, Q-wave MI, subabrupt closure-requiring revascularization) than the pooled group of ASA alone and ASA+Warfarin. As for death and MI, the relative effect of ASA+Ticlid versus the pooled comparator can change from a risk reduction of 0.88 to 0.22 with p-value changing from 0.004 to 0.21 when non-Q-wave MI is counted as MI (see Table 3.1). The classification of MI into Q-wave or non-Q wave is critically important to interpretation of the trial results in this study. In addition, this is an open study in which the investigators knew the medical treatment assignments to the patients. To what extent such knowledge may affect measurement of data necessary for adjudication of event and after-stenting management that ultimately induce unassessable bias needs consideration. Statistical significance for these treatment contrasts need to be interpreted with great caution.

The reviewer's integrated analyses of the remaining four studies using meta-analytic methods suggest that the antiplatelet therapy group seemed to have a smaller rate of composite endpoint of death, MI, CABG and PTCA than the combined group of anticoagulation therapy and ASA alone group (see Table 3.2). The incidence rate of death and MI also seemed to be smaller in the antiplatelet therapy group (see Table 3.3). As often is the case in meta analysis, there are differences in these four studies, such as, aspirin dose, dosing regimens in the study treatments, trial conduct (some had interim analyses, Hall et al trial was terminated prematurely, etc), apparent between-group baseline imbalance in Hall et al trial. All the four trials are open studies. Patients and investigators in ISAR trial were not blinded to treatment assignments.

For the death and MI endpoint, the relative effect of the antiplatelet therapy versus the anticoagulation therapy and/or ASA alone was almost double in the four studies combined as compared to STARS (0.42 versus 0.22, comparing Tables 3.3 and Table 3.1). The estimated effect sizes in terms of relative risk or odds ratio are not consistent between STARS and the four studies. In addition, the nominal p-values of these integrated analyses are not impressive. It is not clear how these p-values will be affected by the between-study differences described above and most importantly by the fact that all the trials are not blinded to investigators and/or patients. Thus, in this reviewer's view, considering the inconsistency described and unimpressive p-

values, it remains inconclusive that the results of the four trials integrated meet the usual standard in terms of strength of statistical evidence we normally require for a well-controlled trial.

/S/

H.M. James Hung, Ph.D.
Acting Team 1 Leader

This review consists of 14 pages of text, followed by an appendix.

Concur: Dr. Chi 

cc: NDA 19-979 SE1-018
HFD-110/Dr. Lipicky
HFD-110/Dr. Throckmorton
HFD-110/Ms. Locicero
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/chron

Appendix A

The following tables, Tables A and B, replace Tables B and C, respectively, in the Appendices of the statistical review dated 10/06/98. This replacement does not affect the conclusion drawn in that review.

Table A. Incidence of 30 days stent thrombosis by site

Center	ASA		ASA+Warfarin		ASA+Ticlid	
	N	%	N	%	N	%
1	8	0	8	12.5	8	0
2	10	10	10	10	10	0
4	10	0	10	20	10	0
5	15	0	15	0	15	0
6	12	0	12	8.33	12	0
7	8	0	8	0	8	12.5
8	14	28.57	14	7.14	14	0
9	21	4.76	21	0	21	0
10	25	0	25	4	25	0
11	0	0	1	0	0	0
12	7	0	7	0	7	0
13	9	0	9	11.11	9	0
14	1	0	0	0	1	0
15	27	3.7	27	3.7	27	3.7
17	47	8.51	47	0	47	0
18	10	0	10	0	10	0
19	14	0	14	0	14	0
20	3	0	3	0	3	0
21	3	0	3	0	3	0
23	7	0	7	0	7	0
24	33	3.03	33	0	33	0
25	18	0	18	0	18	0
26	3	0	3	0	3	0
27	15	6.67	15	0	15	0
28	5	0	5	0	5	0
29	0	0	2	0	0	0
30	8	0	8	0	8	0
31	15	20	15	0	15	0
32	7	14.29	7	0	7	14.29
33	14	7.14	14	0	14	0
34	7	0	7	0	7	0
35	7	14.29	7	0	7	0
36	14	0	14	0	14	0
37	8	12.5	8	25	8	0
38	13	0	13	0	13	0
39	13	0	13	7.69	13	0
40	0	0	1	0	0	0
41	12	0	12	0	12	0
42	3	0	3	0	3	0
43	21	4.76	21	0	21	0

44	21	0	21	0	21	0
45	3	0	3	0	3	0
46	13	7.69	13	7.69	13	0
47	16	6.25	16	0	16	0
48	22	4.55	22	0	22	0
49	3	0	0	0	3	0
50	12	0	12	8.33	12	0
52	12	0	12	0	12	0
54	4	0	4	0	4	0
55	6	0	6	0	6	0

N: sample size %: event rate

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Table B. Incidence of 30 day stent thrombosis by subgroup

Subgroup	ASA		ASA+Warfarin		ASA+Ticlid	
	N	%	N	%	N	%
Male	403	4	387	2.6	390	0.3
Female	154	3.2	163	2.5	156	1.3
White	507	4.1	493	2.4	478	0.6
Others	50	0	57	3.5	68	0
<65 yrs	330	3.9	315	3.5	325	0.3
>=65=+ yrs	227	3.5	235	1.3	221	0.9
Current Cigarette Use						
Yes	140	2.9	149	4	150	0
No	417	4.1	401	2	396	0.8
History of CABG						
Yes	44	2.3	40	7.5	41	0
No	513	3.9	510	2.2	505	0.6
History of dyslipidemia						
Yes	186	3.2	194	3.1	169	1.2
No	371	4	356	2.2	377	0.3
History of diabetes Mellitus						
Yes	99	1	111	4.5	99	1
No	458	4.4	439	2.1	447	0.4
History of hypertension						
Yes	289	2.4	301	2.3	274	0.7
No	268	5.2	249	2.8	272	0.4
History of MI						
Yes	176	3.4	214	2.8	192	1
No	381	3.9	336	2.4	354	0.3
CCS/CHC Angina Class						
I	53	0	47	2.1	53	0
II	120	3.3	115	2.6	116	0.9
III	145	5.5	127	2.4	132	0.8
IV	190	3.7	212	3.3	191	0.5

N: sample size %: event rate

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STATISTICAL REVIEW AND EVALUATION

OCT 6 1998

PMA #: 900043 (Supplement)

Applicant:

Subject: STARS Trial

Statistical evaluation of STARS (STENT ANTITHROMBOTIC REGIMEN STUDY) trial data was requested by the Division of Cardio-Renal Drug Products for Dr. Fredd's consultation to CDRH on adding the results of STARS to the labeling for Palmaz-Schatz stent. This reviewer's statistical evaluation was based on the sponsor's submitted raw CRF data, analysis data, protocol, Volume 1 of the four volumes dated May 6, 1998, and Dr. Fredd's draft review.

The STARS trial was a randomized, open study of three antithrombotic regimens in optimal stenting. A total of 1,653 patients who had undergone stenting considered optimal were randomized to one of three drug regimens briefly labeled as ASA (aspirin alone), ASA+Ticlid (aspirin plus ticlodipine), ASA+Warfarin (aspirin plus coumadin).

The primary objective of the trial was to demonstrate that optimal stent deployment with ASA alone or ASA plus ticlopidine is as safe as optimal stent deployment with ASA plus coumadin. The primary endpoint was 30 day stent thrombosis, a composite endpoint of death, Q-wave MI, and subabrupt closure requiring revascularization using a hierarchical classification scheme approved by the Data and Safety Monitoring Board (DSMB). This was an equivalence trial and the equivalence margin was specified as 3% given the assumption that the stent thrombosis rate with ASA+Warfarin is <4%. It was planned to test the equivalence hypothesis at 1-sided 5% level, equivalently, with 90% two-sided confidence interval. The sample size was calculated to demonstrate equivalence with 80% power. This reviewer confirmed the sponsor's sample size calculation.

It should be noted that although the trial is designed to test for equivalence, superiority can still be tested at the same alpha level as that for equivalence, that is, there is no need to adjust the alpha level because of testing both equivalence and superiority hypotheses. However, based on the convention, both equivalence and superiority should be tested at two-sided 0.05 level.

From the study objective, there were basically two primary treatment comparisons: ASA versus ASA+Warfarin and ASA+Ticlid versus ASA+Warfarin. The adjustment of multiple comparisons was not proposed in the protocol. In the analysis, the sponsor used

Bonferroni method for adjustment and this selection seemed post hoc.

Randomization and Blinding

The physician or coordinator on site opened the sealed envelope to make the treatment assignment if the patient qualified for randomization. Some sites did not follow the pre-established randomization sequence. In response to Dr. Fredd's request, the sponsor provided pre-established randomization sequence, actual treatment assignments and explanations for any discrepancies (date May 6, 1998; see #1 of Appendix A). This reviewer's tallies from the table of the sponsor's Appendix B show that slightly less than 10% of the randomized patients had actual treatment assignment differing from the pre-established assignment and it appeared to be even among the three treatment groups.

Sites reported all deaths, Q wave myocardial infarctions, elevations of CK or CKMB, abrupt closures, and repeat revascularization procedures, but did not report stent thrombosis, per se. Following the criteria established by Clinical Event Committee (CEC), the project team of nurses and physicians at Cardiovascular Data Analysis Center adjudicated the occurrence of composite endpoint of stent thrombosis after review of CRF's for all patients with any suggestion of the component complications, using the reports that were blinded through use of arbitrary treatment group identifiers. These cases were then presented to the CEC.

Interim analysis

According to the protocol, two interim analyses would be performed after the first 300 patients had analyzable 30-day stent thrombosis data and at the halfway point of the study, respectively. The planned stopping rules appeared to be that any of the treatment strategies determined unsafe (a primary endpoint of abrupt closure at 30 days post treatment greater than 8% in any arm) would be dropped. The exact rules were to be determined by DSMB but not provided in the report.

The DSMB's meeting minutes indicated that five interim analyses were performed (on 01/13/96, 02/08/96, 03/22/96, 05/06/96, 07/01/96). It appeared that the analyses were performed only on the components of stent thrombosis; all nominal p-values of the components were large (> 0.14). The composite endpoint of stent thrombosis in its entirety did not appear to be discussed in any of these meetings, thus, it was examined by analyzing its

components. Such informal analysis may inflate the overall type I error rate, particularly, if some components seemed to show a substantial treatment difference leading to a formal testing for the composite endpoint. To what degree the inflation will be is an open question.

Primary endpoint - 30 day stent thrombosis

On page 3 of Volume 1 of the submission dated May 6, 1998, the sponsor itemized the discrepancies between the site reported and CEC (Clinical Event Committee) adjudicated endpoint events. From the raw CRF database provided by the sponsor, this reviewer has confirmed most of discrepancies. From the reviewer's analysis, there appeared to be some additional discrepancies, see Table 1.

Table 1. Incidence of 30 day stent thrombosis (ST) for ITT population

RX	ASA	ASA + Ticlid	ASA + Warfarin
N	557	546	550
ST (CEC)	21 (3.8%)	3 (0.5%)	14 (2.5%)
ST (CRF) #	23 (4.1%)	5 (0.9%)	14 (2.5%)

2 additional patients (04/001, 50/009) in the ASA+Ticlid group appeared to qualify as Q-wave MI according to the hospital discharge form; 2 additional patients (10/067, 19/038) in the ASA group appeared to be subabrupt closure requiring revascularization according to hospital discharge form or one month contact form

The nominal p-values (uncorrected for multiple comparisons) for the results of Table 1 are provided in Table 1P; note that the p-values were for the purpose of testing whether the comparative treatment groups differ. Overall speaking, the three treatment strategies appeared to differ in some fashion on the incidence of stent thrombosis ($p = 0.001$). Based on the Bonferroni method selected post hoc by the sponsor to adjust the nominal p-values for the two primary comparisons (ASA vs. ASA+Warfarin, ASA+Ticlid vs. ASA+Warfarin), the ASA+Ticlid group appeared to have a significantly smaller stent thrombosis rate than the ASA+Warfarin group (adjusted p-value = 0.016 based on CEC data and 0.078 based on CRF data). The difference between ASA and ASA+Warfarin was not conclusive. The stent thrombosis rate with ASA+Ticlid seemed to be smaller than that with ASA alone.

Table 1P. Nominal P-value for 30 day stent thrombosis (ST) for ITT population

	ASA vs. ASA+Warfarin	ASA+Ticlid vs. ASA+Warfarin	ASA+Ticlid vs. ASA
ST (CEC)	0.24	0.008	0.001
ST (CRF)	0.14	0.039	0.001

* All P-values are based on chi-square test

To test equivalence which was the objective of the trial, Table 2 provides 97.5% confidence intervals and 95% confidence intervals. According to the usual standard, the overall type I error rate needs to be controlled at 5%, that is, 2.5% for each primary comparison, which amounts to use of 97.5% confidence interval for each primary comparison. The 95% confidence intervals correspond to the sponsor's plan of testing equivalence at 1-sided 5% level. The 97.5% confidence interval should be used according to the convention. If the confidence interval is fully contained in the equivalence range (-3%, 3%), then equivalence can be established, assuming that the margin of 3% for equivalence is acceptable (whether this equivalence margin is acceptable is left to the medical division). From Table 2, one can not conclude that ASA and ASA+Warfarin are equivalent with respect to the 30 day stent thrombosis rate.

Table 2. Confidence interval (CI) for testing equivalence.

	ASA+Ticlid vs. ASA+Warfarin	ASA vs. ASA+Warfarin
97.5% CI:		
ST (CEC)	(-3.7%, -0.3%)	(-1.1%, 3.6%)
ST (INV)	(-3.4%, 0.1%)	(-0.8%, 4.0%)
95% CI:		
ST (CEC)	(-3.5%, -0.5%)	(-0.8%, 3.3%)
ST (INV)	(-3.2%, -0.09%)	(-0.5%, 3.7%)

Center Results

Sample sizes did not differ greatly among the sites, except Sites 15 and 17. The trend shown in the overall study results was seen in most of the centers (see Appendix B).

Subgroup Results

The incidence rate of 30 day stent thrombosis by gender, race, cigarette use, history of CABG, dyslipidemia, diabetes mellitus, hypertension, MI, and CCS/CHC angina class is summarized in Appendix C. Numerically, ASA+Ticlid had the smallest incidence rate in all subgroups and ASA+Warfarin had a smaller incidence in most subgroups, except those with a small sample size.

Non-Q-wave MI

The submitted database does not contain sufficient information for verifying the frequency of Non-Q-wave MIs adjudicated by the Clinical Event Committee.

Major Vascular Events

Verification of major vascular events is also very difficult based on the CRF database because the definition of major vascular events is not quite clear in the protocol. Based on the CRF database, all the 30 day major vascular events adjudicated by CEC (ASA: 10, ASA+Warfarin: 31, ASA+Ticlid: 27) were also reported by site on Hospital Discharge or One Month Contact Form; of them, 9 patients (ASA: 1, ASA+Warfarin: 5, ASA+Ticlid: 3) did not have Hemorrhagic/Vascular Event Form for verification.

There were additional 27 cases in which the hospital discharge or one month form seemed to indicate a major vascular event but these were not adjudicated by CEC. For nineteen of these cases, no Hemorrhagic/Vascular Event Form is available for verification. Thus, there were only 8 additional cases (ASA: 2, ASA+Warfarin: 4, ASA+Ticlid: 2) that might be major vascular events.

Regardless of the minor deviations described above, the nominal p-value for comparing treatment groups with this endpoint does not change much.

The Nine Month Results

This reviewer confirmed the sponsor's nine month figures (displayed on page 11 of Dr. Fredd's review) using the submitted analysis database, since as described above the deviations between the CEC results and the site results appear to be minor. However, there were 460 patients lost to follow up to 270 days; in my view, the nine month results are of little value. *

SUMMARY

The ASA+Ticlid group seemed to have a significantly smaller 30 day stent thrombosis rate than the ASA+Warfarin group (adjusted p-value = 0.016 based on CEC data). The difference between ASA and ASA+Warfarin was not conclusive, nor was equivalence. The 30 day stent thrombosis rate with ASA+Ticlid seemed to be smaller than that with ASA alone (p < 0.002). This trend was seen in almost all subgroups. However, as a result of the investigators knowing the medical treatment assignments when

<Continuation of Table A>						
Center	ASA		ASA+Warfarin		ASA+Ticlid	
	N	%	N	%	N	%
48	6	0.17	6	0	6	0
49	3	0	0	0	0	0
50	5	0	5	0.2	5	0
52	6	0	6	0	6	0
54	2	0	2	0	2	0
55	0	0	3	0	3	0

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Appendix C

Table C. Incidence of 30 day stent thrombosis by subgroup

Subgroup	ASA		ASA+Warfarin		ASA+Ticlid	
	n	%	n	%	n	%
Male	94	17	96	10.4	96	1
Female	43	11.6	67	6	52	3.8
White	123	17.1	146	8.2	130	2.3
Others	14	0	17	11.8	18	0
< 65 yrs	83	15.7	76	14.5	74	1.4
>= 65 yrs	54	14.8	87	3.4	74	2.7
Current Cigarette Use						
Yes	43	9.3	47	12.8	38	0
No	94	18.1	116	6.9	110	2.7
History of CABG						
Yes	11	9.1	12	25	14	0
No	126	15.9	151	7.3	134	2.2
History of Dyslipidemia						
Yes	38	15.8	58	10.3	36	5.6
No	99	15.2	105	7.6	112	0.9
History of Diabetes Mellitus						
Yes	23	4.3	40	12.5	34	2.9
No	114	17.5	123	7.3	114	1.8
History of Hypertension						
Yes	65	10.8	88	8	78	2.6
No	72	19.4	75	9.3	70	1.4
History of MI						
Yes	46	13	78	7.7	52	3.8
No	91	16.5	85	9.4	96	1
CCS/CHC Angina Class						
I	13	0	14	7.1	18	0
II	18	22.2	29	10.3	25	4
III	39	20.5	42	7.1	38	2.6
IV	55	12.7	66	10.6	49	2