

A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

MARTIN B. LEON, M.D., DONALD S. BAIM, M.D., JEFFREY J. POPMA, M.D., PAUL C. GORDON, M.D., DONALD E. CUTLIP, M.D., KALON K.L. HO, M.D., ALEX GIAMBARTOLOMEI, M.D., DANIEL J. DIVER, M.D., DAVID M. LASORDA, D.O., DAVID O. WILLIAMS, M.D., STUART J. POCOCK, PH.D., AND RICHARD E. KUNTZ, M.D., FOR THE STENT ANTICOAGULATION RESTENOSIS STUDY INVESTIGATORS*

ABSTRACT

Background Antithrombotic drugs are used after coronary-artery stenting to prevent stent thrombosis. We compared the efficacy and safety of three antithrombotic-drug regimens — aspirin alone, aspirin and warfarin, and aspirin and ticlopidine — after coronary stenting.

Methods Of 1965 patients who underwent coronary stenting at 50 centers, 1653 (84.1 percent) met angiographic criteria for successful placement of the stent and were randomly assigned to one of three regimens: aspirin alone (557 patients), aspirin and warfarin (550 patients), or aspirin and ticlopidine (546 patients). All clinical events reflecting stent thrombosis were included in the prespecified primary end point: death, revascularization of the target lesion, angiographically evident thrombosis, or myocardial infarction within 30 days.

Results The primary end point was observed in 38 patients: 20 (3.6 percent) assigned to receive aspirin alone, 15 (2.7 percent) assigned to receive aspirin and warfarin, and 3 (0.5 percent) assigned to receive aspirin and ticlopidine ($P=0.001$ for the comparison of all three groups). Hemorrhagic complications occurred in 10 patients (1.8 percent) who received aspirin alone, 34 (6.2 percent) who received aspirin and warfarin, and 30 (5.5 percent) who received aspirin and ticlopidine ($P<0.001$ for the comparison of all three groups); the incidence of vascular surgical complications was 0.4 percent (2 patients), 2.0 percent (11 patients), and 2.0 percent (11 patients), respectively ($P=0.02$). There were no significant differences in the incidence of neutropenia or thrombocytopenia (overall incidence, 0.3 percent) among the three treatment groups.

Conclusions As compared with aspirin alone and a combination of aspirin and warfarin, treatment with aspirin and ticlopidine resulted in a lower rate of stent thrombosis, although there were more hemorrhagic complications than with aspirin alone. After coronary stenting, aspirin and ticlopidine should be considered for the prevention of the serious complication of stent thrombosis. (N Engl J Med 1998;339:1665-71.)

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THE implantation of coronary stents has become a major form of revascularization therapy for coronary artery disease. In early clinical trials,¹ there were high rates of stent thrombosis (approaching 20 percent), leading to the adoption of an antiplatelet and anticoagulant regimen that included intravenous low-molecular-weight dextran, oral aspirin and dipyridamol, and intravenous

heparin followed by oral warfarin. The incorporation of this aggressive antithrombotic treatment strategy in subsequent randomized clinical trials²⁻⁴ reduced the risk of acute and subacute stent thrombosis to approximately 3.5 percent. However, as compared with conventional balloon angioplasty, stenting with aggressive antithrombotic-drug therapy doubled the length of hospitalization (from three to six days) and increased the rate of hemorrhagic and vascular complications from 3 to 4 percent to 7 to 13 percent.^{2,3,5}

More recently, registry data have demonstrated that the risk of stent thrombosis can be further reduced by the use of a combination of high-pressure, balloon-expandable stents and antithrombotic therapy with aspirin and ticlopidine.⁶⁻⁸ A single-center, randomized trial also demonstrated the superiority of aspirin and ticlopidine over aspirin and warfarin for the prevention of stent thrombosis in high-risk patients.⁹ Moreover, a single-center registry and one small, randomized trial suggested that aspirin alone might be adequate for the prevention of stent thrombosis.^{10,11} There has also been concern about the possibility of neutropenia and thrombocytopenia in association with ticlopidine therapy.¹² We compared the 30-day clinical outcomes for three antithrombotic-drug regimens — aspirin alone, aspirin and warfarin, and aspirin and ticlopidine — after elective coronary-artery stenting.

METHODS**Objectives and Design of the Study and Selection of Patients**

The primary objective was to compare the incidence of stent thrombosis in patients with single-vessel or multivessel disease of native coronary arteries who were successfully treated with a high-pressure, balloon-expandable stent at 1 of 50 centers in the United States and who were then randomly assigned to receive one of three antithrombotic-drug regimens. The implantation of a Palmaz-Schatz stent (Cordis, Warren, N.J.) was considered to

From Washington Hospital Center, Washington, D.C. (M.B.L., J.J.P.); Beth Israel Deaconess Medical Center, Boston (D.S.B., D.E.C., K.K.L.H., R.E.K.); Miriam Hospital, Providence, R.I. (P.C.G.); St. Joseph's Hospital, Syracuse, N.Y. (A.G.); Georgetown Medical Center, Washington, D.C. (D.J.D.); Allegheny General Hospital, Pittsburgh (D.M.L.); Rhode Island Hospital, Providence (D.O.W.); and London School of Hygiene and Tropical Medicine, London (S.J.P.). Address reprint requests to Dr. Leon at Cardiovascular Research and Education, Cardiology Research Foundation at the Washington Hospital Center, 110 Irving St. NW, Suite 4B-1, Washington, DC 20010.

*Other members of the Stent Anticoagulation Restenosis Study are listed in the Appendix.

be successful if the final degree of stenosis within the stent was less than 10 percent (by visual estimate), there was no evidence of thrombus or of dissections (more than grade B according to the National Heart, Lung, and Blood Institute criteria), there was grade 3 flow according to the criteria of the Thrombolysis in Myocardial Infarction study, and no more than two stents were needed to treat one long (≤ 25 mm) lesion or two focal (≤ 12 mm) lesions in one or two native coronary arteries. Patients who did not meet the criteria for successful stenting were enrolled in a prospective trial that was identical to the randomized trial in terms of data collection and follow-up except that patients were not assigned to a specific drug-treatment strategy.

Randomization was not blinded, but all end points were adjudicated by a clinical events committee whose members were unaware of the patients' treatment assignments. The study complied with the Declaration of Helsinki regarding investigations in humans and was approved for an investigational-device exemption by the Food and Drug Administration (FDA), and all investigational sites received approval from their local hospital investigational review boards. All patients gave written informed consent.

Patients were eligible for enrollment if they had one or two target lesions with more than 60 percent stenosis in a 3-to-4-mm native coronary artery, not involving the left main coronary artery or a major coronary bifurcation. Other exclusion criteria were the presence of additional stenoses within the target vessel; recent (within 7 days before enrollment) acute myocardial infarction; known contraindications to the use of aspirin, ticlopidine, or warfarin; a history of bleeding diathesis; current treatment with abiximab; and planned angioplasty of another lesion within 30 days after enrollment.

Eligible patients were randomly assigned in equal proportions with use of a prespecified randomization sequence to one of the three antithrombotic-drug regimens, according to clinical site and history of diabetes mellitus.

Coronary-Stent Procedure

All patients received nongeneric, non-enteric-coated aspirin (325 mg) and intravenous heparin (10,000 to 15,000 U) to maintain an activated clotting time of 250 to 300 seconds during the implantation of the stents. Before the stents were implanted, lesions were treated with balloon angioplasty, directional atherectomy, or rotational atherectomy. The stent was implanted with a stent delivery system (Johnson and Johnson, Warren, N.J.) approved by the FDA that consisted of a specially designed balloon catheter onto which a standard 15-mm Palmaz-Schatz coronary stent had been crimped within a protective nylon sheath. The sizing of the stents followed standard FDA guidelines: the ratio of the diameter of the balloon to the diameter of the artery was 1.1 to 1.0, with a deployment pressure of 6 to 8 atmospheres. The technique used in this study was designed to achieve a residual stenosis of less than 10 percent by visual estimate, which usually required further dilation of the balloon at high pressure (≥ 16 atmospheres) with a separate high-pressure balloon measuring 15 to 20 mm. To reduce the number of variables that might influence stent thrombosis, all procedures were performed with use of the same low osmolar ionic angiographic contrast medium (ioxaglate meglumine, Mallinckrodt, St. Louis).

Antithrombotic-Drug Regimens

The three regimens were as follows: 325 mg of non-enteric-coated aspirin (Bayer, West Haven, Conn.) orally per day; 325 mg of non-enteric-coated aspirin per day and intravenous heparin (initial dose, 10,000 to 15,000 U per day), with the dose titrated to achieve an activated partial-thromboplastin time of 40 to 60 seconds and discontinued once an international normalized ratio of 2.0 to 2.5 was reached with the use of oral warfarin; and 325 mg of non-enteric-coated aspirin per day and 250 mg of ticlopidine (Ticlid, Sanofi, New York) orally twice a day. No further heparin was given after the procedure except among patients assigned to receive warfarin. The duration of ticlopidine and war-

farin treatment was four weeks. Treatment assignments were not masked, and the first dose of ticlopidine or warfarin was administered at the conclusion of the stenting procedure.

Data Collection and Analysis of End Points

Detailed case-report forms were completed by the clinical coordinator at each site, monitored by independent study monitors, and submitted to the data-coordinating center (Department of Medicine, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston). Angiograms obtained during the stenting procedure were submitted to the angiographic core laboratory (Washington Hospital Center, Washington, D.C.), where they were analyzed with a computer-based system (Medis, Leiden, the Netherlands). The patients were assessed at discharge and four weeks after the stenting procedure for the occurrence of adverse clinical events. All events were classified by an independent clinical events committee whose members were unaware of the patients' treatment assignments.

The prespecified 30-day primary end point, which reflected the occurrence of stent thrombosis, was a hierarchical composite of death from any cause, revascularization of the target lesion without death, evidence of thrombosis of the target vessel on repeated angiography without revascularization, or nonfatal myocardial infarction in patients who did not undergo repeated angiography. Secondary end points included the achievement of less than 50 percent residual stenosis without death or emergency bypass surgery (defined as procedure success), procedure-related myocardial infarction, hematologic dyscrasias (neutropenia or thrombocytopenia), hemorrhagic complications, and vascular surgical complications. Myocardial infarctions (procedure-related and within 30 days after the procedure) were defined by a new Q wave that lasted at least 0.04 second in two or more contiguous leads or a creatine kinase concentration that was more than two times the upper limit of normal in the presence of an elevated concentration of MB isoenzyme. A major bleeding complication was defined as any procedure-related bleeding episode that required transfusion. Vascular surgical complications included any retroperitoneal hematoma, a vascular-access hematoma of more than 4 cm, and a pseudoaneurysm or arteriovenous fistula requiring surgery or ultrasonographic compression. Hematologic status was evaluated on the basis of a minimum of two complete blood counts performed two and four weeks after the stenting procedure; neutropenia was defined as a reduction in the absolute white-cell count to less than 1200 per cubic millimeter, and thrombocytopenia as a reduction in the platelet count to below 80,000 per cubic millimeter.

Statistical Analysis

The trial was designed to determine whether the regimen of aspirin and ticlopidine was as effective as the regimen of aspirin and warfarin in preventing stent thrombosis (the null hypothesis) and whether there were any significant differences in the primary end point between the regimen of aspirin and ticlopidine and the regimen of either aspirin and warfarin or aspirin alone. The prespecified plan therefore called for a sequential-analysis strategy. The null hypothesis was established with use of Blackwelder's formula,¹³ and two comparisons of difference in the primary end point were then made. Adjustments for multiple comparisons were made to maintain an overall type I error rate of 0.05 and are reflected in the reported P values. There was no prespecified interim analysis for early termination of the study, but the data and safety monitoring committee reviewed early safety data after the enrollment of each 250 patients.

For the null hypothesis, we assumed that the rate of stent thrombosis was 4 percent in the group assigned to aspirin and warfarin, with an increase of 3 percent or more in this value taken as an indication of the inferiority of this treatment. A total of 528 patients were required in each group for the study to have the power to detect such a difference, with a type I error of 0.05 and a type II error of 0.2. For the two conditional tests of difference,

the same 4 percent rate of stent thrombosis was assumed for the group assigned to aspirin and warfarin and the aspirin-only group. For the study to have the ability to detect a 30-day stent-thrombosis rate of 1.1 percent or less in the group assigned to ticlopidine and aspirin with a statistical power of 80 percent and a one-sided alpha error of 0.025, 527 patients were required for each group. The trial was therefore designed to enroll 550 patients per group, for a total of 1650 patients.

All comparisons were based on the intention-to-treat principle. Continuous variables were compared with the use of analysis of variance for comparisons among all three groups, and binary variables were compared with the use of the chi-square test (or Fisher's exact test in the case of any variable that included fewer than five events) and were presented with nominal two-tailed P values. Relative risks of selected primary and secondary end points were also calculated (with confidence intervals) for the prespecified pairwise comparison. Differences in the median time to a primary event were analyzed with the Kruskal-Wallis nonparametric rank-sum test for multiple groups. A stepwise multivariable logistic model of the primary end point was used to evaluate base-line predictors and the treatment effect simultaneously. All statistical analyses were performed with SAS computer software (version 6.12, SAS Institute, Cary, N.C.).¹⁴

RESULTS

Enrollment of Patients and Base-Line Characteristics

A total of 1965 patients with 2147 lesions were enrolled between February 1996 and November 1996. Of these, 1653 patients (84.1 percent) with 1772 lesions met the criteria for successful stent placement and were enrolled in the randomized trial. The remaining 312 patients with 375 lesions were enrolled in a parallel registry. Overall, 99.3 percent met the secondary end point of procedure success (less than 50 percent residual stenosis without death or emergency bypass surgery), including all 1653 patients who underwent randomization and 298 of the 312 patients (95.5 percent) entered in the parallel registry. This report focuses on the results of the randomized patients, of whom 1534 had a single lesion treated and 119 had two lesions treated. A total of 557 patients were assigned to receive aspirin alone, 550 patients were assigned to receive aspirin and warfarin, and 546 patients were assigned to receive aspirin and ticlopidine. The base-line characteristics of the patients were similar in the three groups (Tables 1 and 2). Before placement of the stent, balloon angioplasty alone was performed in 88.1 percent, rotational atherectomy in 6.2 percent, and directional atherectomy in 0.6 percent, with no pretreatment in 5.1 percent.

Primary End Point

The overall incidence of the combined primary end point was 2.3 percent, and the overall incidence of death within 30 days was 0.06 percent. The primary and secondary end points in the individual groups are summarized in Table 3, and the relative risks of selected end points are given in Table 4. The primary end point occurred in a total of 38 patients, 20 (3.6 percent) assigned to aspirin only, 15 (2.7 percent) assigned to aspirin and warfarin, and 3 (0.5 percent)

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ASPIRIN ALONE (N=557)	ASPIRIN AND WARFARIN (N=550)	ASPIRIN AND TICLOPIDINE (N=546)
Age — yr	61±11	62±11	61±12
Ejection fraction — %	56±11	56±11	57±11
Female sex — no. (%)	154 (28)	163 (30)	156 (29)
Diabetes mellitus — no. (%)	99 (18)	111 (20)	99 (18)
Dyslipidemia requiring treatment — no. (%)	189 (34)	198 (36)	169 (31)
Hypertension requiring treatment — no. (%)	289 (52)	301 (55)	274 (50)
Cigarette smoking in preceding year — no. (%)	150 (27)	160 (29)	158 (29)
Single-vessel disease — no. (%)	373 (67)	369 (67)	371 (68)
Previous myocardial infarction — no. (%)	176 (32)	214 (39)	196 (36)
Angina of grade III or IV — no. (%)†	335 (60)	339 (62)	323 (59)
Previous PTCA — no. (%)	83 (15)	94 (17)	82 (15)
Previous CABG — no. (%)	44 (8)	40 (7)	41 (8)
Previous restenosis — no. (%)‡	92 (17)	98 (17)	90 (15)
Lesion grade B2 or C — no. (%)‡§	392 (66)	353 (60)	382 (65)
Angiographically evident thrombus — no. (%)‡	20 (3)	18 (3)	25 (4)
Moderate or severe calcification — no. (%)‡	133 (22)	107 (18)	122 (21)
Ostial location of lesion — no. (%)‡	42 (7)	34 (6)	37 (6)
Bifurcation — no. (%)‡	38 (6)	36 (6)	33 (6)
TIMI grade 0 flow (total occlusion) — no. (%)	11 (2)	11 (2)	10 (2)
Length of lesion — mm	10.8±5.6	10.5±5.5	10.8±5.4
Target vessel LAD — no. (%)‡	255 (43)	245 (41)	254 (44)

*Plus-minus values are means ±SD. PTCA denotes percutaneous transluminal coronary angioplasty, CABG coronary-artery bypass grafting, TIMI Thrombolysis in Myocardial Infarction, and LAD left anterior descending artery.

†The Canadian Heart Cardiovascular classification was used.

‡Not all the data were available for all the patients.

§The American College of Cardiology classification was used.

assigned to aspirin and ticlopidine (P=0.001 for the comparison of all three groups). The relative risk of the primary end point in the group assigned to aspirin and ticlopidine was 0.15, as compared with the risk in the group assigned to aspirin alone (P<0.001), and 0.20, as compared with the risk in the group assigned to aspirin and warfarin (P=0.01) (Table 4).

Three components of the primary end point were mainly responsible for the differences among the three groups and were highly correlated: revascularization of the target lesion (P=0.002), angiographically evident thrombosis (P=0.005), and recurrent myocardial infarction (P=0.01). There were also significant differences in the incidence of revascularization of the target lesion and angiographically evident thrombosis between the group assigned to aspirin

TABLE 2. ANGIOGRAPHIC AND PROCEDURAL CHARACTERISTICS.*

CHARACTERISTIC	ASPIRIN ALONE	ASPIRIN AND WARFARIN	ASPIRIN AND TICLOPIDINE
Target vessel — no. (%)	595 (34)	592 (33)	585 (33)
Dimensions of lesion before procedure			
Reference artery — mm	3.00±0.50	3.03±0.54	3.02±0.46
Minimal luminal diameter — mm	1.02±0.51	1.02±0.43	0.99±0.42
Stenosis — %†	65.8±13.1	66.1±13.5	66.9±13.0
Dimensions of lesion before stenting			
Reference artery — mm	2.98±0.51	2.99±0.52	3.00±0.48
Minimal luminal diameter — mm	1.72±0.49	1.71±0.50	1.70±0.47
Stenosis — %†	41.6±15.8	42.1±15.9	42.8±15.5
Final luminal dimensions			
Reference artery — mm	3.06±0.49	3.10±0.52	3.07±0.6
Minimal luminal diameter — mm	2.80±0.40	2.79±0.46	2.80±0.43
Stenosis — %†	7.8±12.1	9.4±11.7	8.2±11.5
Final balloon dimensions			
Mean diameter — mm	3.40±0.60	3.48±0.51	3.44±0.49
Balloon:artery ratio	1.15±0.17	1.13±0.16	1.13±0.17
Final stent dimensions — mm			
Minimal diameter	2.80±0.49	2.79±0.53	2.80±0.51
Mean diameter	3.26±0.42	3.25±0.48	3.26±0.42
Increase in diameter	1.8±0.5	1.8±0.5	1.8±0.5

*Plus-minus values are means ±SD.

†Stenosis was calculated as the average reference luminal diameter minus the minimal luminal diameter divided by the average reference luminal diameter times 100 (for the worse of two orthogonal views).

and ticlopidine and either the group assigned to aspirin only or the group assigned to aspirin and warfarin (Table 4). Among the entire randomized cohort, there was only one death, in the aspirin-alone group.

The cumulative incidence of primary events is shown in Figure 1, with a mean time to a primary event of 0.7 day for the group assigned to aspirin and ticlopidine, 2.9 days for the group assigned to aspirin and warfarin, and 3.7 days for the group assigned to aspirin alone (P=0.17 for the difference among the three groups). A stepwise logistic model of the primary end point was evaluated for the following potential predictors: age, sex, presence of diabetes mellitus, number of lesions treated (two vs. one), length of the lesion, dissection grade, appearance of angiographically evident thrombus, and post-treatment minimal diameter of the lumen after adjustment for the type of antithrombotic-drug regimen. The primary end point was positively associated with a dissection grade of B or greater (odds ratio, 3.82; P=0.002) and a smaller post-treatment minimal luminal diameter (odds ratio, 5.00 for each additional 1-mm decrease; P<0.001).

Among the 312 patients who did not undergo randomization, the incidence of the combined primary end point was 3.5 percent. Multivariable analysis indicated that the number of stents implanted was positively associated with stent thrombosis (P=0.01) and the use of aspirin and ticlopidine was negatively associated with stent thrombosis (P=0.08).

TABLE 3. PRIMARY AND SECONDARY EVENTS IN THE FIRST 30 DAYS AFTER STENTING.*

EVENT	ASPIRIN ALONE (N=557)	ASPIRIN AND WARFARIN (N=550)	ASPIRIN AND TICLOPIDINE (N=546)	P VALUE†
	number (percent)			
Primary end point	20 (3.6)	15 (2.7)	3 (0.5)	0.001
Death	1 (0.2)	0	0	
Revascularization of target lesion	19 (3.4)	14 (2.5)	3 (0.5)	0.002
CABG	3 (0.5)	1 (0.2)	1 (0.2)	0.63
PTCA	17 (3.1)	14 (2.5)	3 (0.5)	0.003
Angiographically evident thrombosis	16 (2.9)	15 (2.7)	3 (0.5)	0.005
Recurrent myocardial infarction	15 (2.7)	11 (2.0)	3 (0.5)	0.01
Q-wave	8 (1.4)	8 (1.5)	1 (0.2)	0.04
Non-Q-wave	7 (1.3)	3 (0.5)	2 (0.4)	0.27
Other clinical events				
Procedure-related myocardial infarction	16 (2.9)	23 (4.2)	23 (4.2)	0.41
Q-wave	4 (0.7)	0	0	0.04
Non-Q-wave	12 (2.2)	23 (4.2)	23 (4.2)	0.10
Hemorrhagic complications	10 (1.8)	34 (6.2)	30 (5.5)	<0.001
Vascular surgical complications	2 (0.4)	11 (2.0)	11 (2.0)	0.02
Neutropenia or thrombocytopenia	1 (0.2)	1 (0.2)	3 (0.5)	0.46
Cerebrovascular accident	2 (0.4)	1 (0.2)	0	0.78

*CABG denotes coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†The P values are for the comparison of the three groups by the chi-square test.

TABLE 4. RELATIVE RISK OF PRIMARY AND SECONDARY EVENTS IN THE GROUP ASSIGNED TO ASPIRIN AND TICLOPIDINE AS COMPARED WITH THE GROUP ASSIGNED TO ASPIRIN ALONE AND THE GROUP ASSIGNED TO ASPIRIN AND WARFARIN.*

EVENT	RELATIVE RISK (95% CI) AS COMPARED WITH ASPIRIN ALONE	P VALUE	RELATIVE RISK (95% CI) AS COMPARED WITH ASPIRIN AND WARFARIN	P VALUE
Primary end point	0.15 (0.05–0.43)	<0.001	0.20 (0.07–0.61)	0.01
Death				
Revascularization of target lesion	0.16 (0.06–0.46)	0.001	0.22 (0.07–0.66)	0.02
Angiographically evident thrombosis	0.19 (0.06–0.57)	0.001	0.20 (0.07–0.61)	0.01
Recurrent myocardial infarction	0.20 (0.07–0.62)	0.014	0.27 (0.08–0.90)	0.11
Neutropenia or thrombocytopenia	3.06 (0.36–26.2)	0.74	3.02 (0.35–25.91)	0.75
Hemorrhagic complications	3.06 (1.57–5.97)	0.002	0.88 (0.55–1.43)	0.99
Vascular surgical complications	5.61 (1.49–21.16)	0.02	1.01 (0.44–2.30)	0.99

*CI denotes confidence interval.

Secondary End Points

There were no significant differences in the incidence of procedure-related myocardial infarctions among the three groups (overall incidence, 3.8 percent) (Table 3). There were three cerebrovascular accidents (overall incidence, 0.2 percent) and five cases of severe neutropenia or thrombocytopenia (overall incidence, 0.3 percent). The incidence of hemorrhagic complications and vascular surgical complications was significantly different among the three groups (P<0.001 and P=0.02, respectively) (Table 3). The group assigned to aspirin and ticlopidine had a relative risk of hemorrhagic complications of 3.06 (P=0.002) and a relative risk of vascular surgical complications

of 5.61 (P=0.02) as compared with the group assigned to aspirin alone. The risk of these events in the group assigned to aspirin and ticlopidine was similar to that in the group assigned to aspirin and warfarin.

DISCUSSION

This randomized trial compared the ability of three antithrombotic-drug regimens to prevent stent thrombosis. The chief finding was that a combination of aspirin and ticlopidine was superior to either a combination of warfarin and aspirin or aspirin alone in the prevention of stent thrombosis after successful stenting. The risk of stent thrombosis with aspirin and warfarin was slightly lower than with aspirin alone.

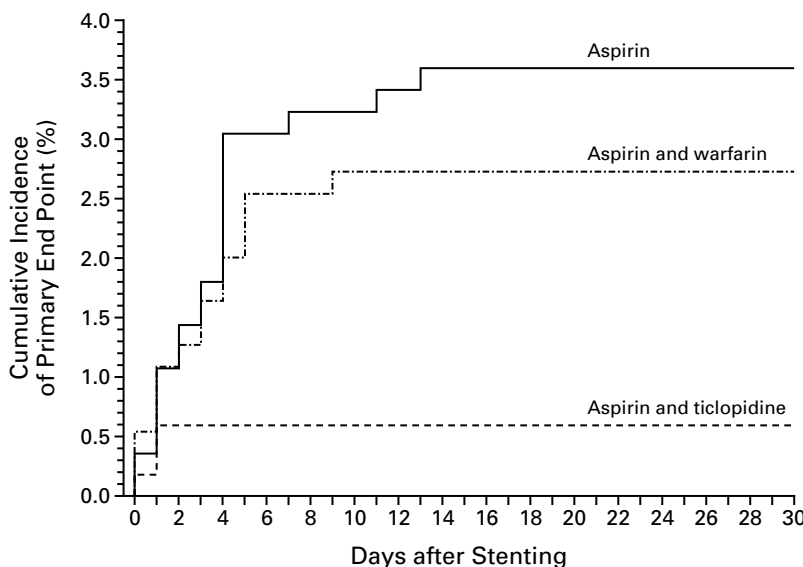


Figure 1. Cumulative Incidence of the Primary End Point in the Three Treatment Groups.

Our study differs from earlier trials in that randomization required high stent-implantation pressures and the achievement of a predefined optimal result. Our finding of an intermediate (2.7 percent) risk of stent thrombosis among patients assigned to receive aspirin and warfarin, between that of the patients assigned to receive aspirin and ticlopidine (0.5 percent) and that of the patients assigned to receive aspirin alone (3.6 percent), is in contradistinction to earlier data from a single-center randomized trial conducted in Germany, which suggested that warfarin may promote stent thrombosis.⁹ Several factors may explain this difference: the intensity of anticoagulation was lower in our study (target international normalized ratio, 2.0 to 2.5), the sample population in the German study included many patients with acute myocardial infarction (24 percent), and our patients had to have a successful angiographic result before they underwent randomization. The modified regimen of aspirin and warfarin that was used in our study was at least as effective as aspirin alone in preventing stent thrombosis, with no added risk of stent thrombosis. The high rate of stent thrombosis in the group assigned to aspirin alone is an important finding and contradicts the results of a recent registry study and of a small, randomized trial, which reported that the rate of stent thrombosis was similar in the group assigned to aspirin and ticlopidine and the group treated with aspirin alone.^{11,12}

Our study has several important secondary findings. The overall death rate was 0.06 percent, and only 1 of 38 patients (2.6 percent) who reached the primary end point died. This rate is markedly lower than the rate of death from stent thrombosis in previous trials (range, 11 to 24 percent^{1-3,9,15,16}) and may reflect differences in selection factors used or improved diagnosis and treatment strategies for stent thrombosis. The fact that Q-wave myocardial infarction occurred in 45 percent of those who reached the primary end point in our study is evidence that the clinical consequences of stent thrombosis remain severe.

The significantly lower incidence of stent thrombosis during treatment with aspirin and ticlopidine as compared with treatment with aspirin alone was offset by a slight but significantly increased risk of hemorrhagic and vascular surgical complications. Despite the widespread belief that combination therapy with aspirin and ticlopidine is associated with a lower rate of vascular surgical complications than therapy with aspirin and warfarin, there was no significant difference in these end points between the two groups. Interestingly, the incidence of hemorrhagic complications in the group assigned to aspirin and warfarin was lower in our study than in previous trials,^{2,3} suggesting that femoral-artery puncture and sheath-removal techniques have improved over the years.

There was also no significant difference in the risk of neutropenia or thrombocytopenia between the

group assigned to aspirin and ticlopidine (0.5 percent) and either the group assigned to aspirin alone (0.2 percent) or the group assigned to aspirin and warfarin (0.2 percent). These values are similar to the 0.8 percent incidence of severe neutropenia more than two months after the start of treatment reported for patients who receive long-term ticlopidine therapy to prevent strokes.¹⁰ An incidence of reversible ticlopidine-induced neutropenia of 0.8 percent was also reported in the French Multicenter Registry of 2900 patients.¹⁶ Although these data may be taken as evidence that it is safe to use ticlopidine for up to 4 weeks, stent thrombosis generally occurs within the first 14 days after the stenting procedure and may occur even earlier (a mean of 0.7 day in our study) in patients who are given aspirin and ticlopidine. Although not directly evaluated in this study, the early time to thrombosis indirectly suggests that the course of ticlopidine may be shortened to two weeks, which may further reduce the risk of neutropenia and thrombocytopenia. Importantly, despite the absence of severe hematologic dyscrasias in our study, there are continued reports of thrombotic thrombocytopenic purpura in association with ticlopidine therapy (incidence, approximately 1 in 1600 patients), including short-term treatment after coronary stenting.^{17,18} The vast majority of these hematologic disturbances occur after two weeks of ticlopidine treatment,¹⁸ thereby lending further support to the suggestion to shorten the duration of ticlopidine therapy after stenting to two weeks.

In summary, we demonstrated the efficacy and safety of a combination of ticlopidine and aspirin as a means of preventing stent thrombosis in patients with ischemic coronary syndromes. The superiority of this antithrombotic regimen over aspirin alone and a combination of aspirin and warfarin supports its use as the primary therapy after coronary stenting.

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APPENDIX

The following principal investigators and study coordinators also participated in the Stent Anticoagulation Restenosis Study: *University of Texas Health Science Center—Brooke Army Medical Center, San Antonio:* S. Bailey, G. Cooper-Read; *Beth Israel Deaconess Medical Center, Boston:* P. Rooney; *Scripps Memorial Hospital, La Jolla, Calif.:* M. Buchbinder, D. Koester; *Lancaster Heart Foundation, Lancaster, Pa.:* P. Casale, J. Tuzi; *Yale University Hospital, New Haven, Conn.:* M. Cleman, J. Davey; *Northwestern University Medical School, Chicago:* C. Davidson, J. Espisito; *Baylor University Medical Center, Dallas:* S. DeMaio, I. Joukova; *Temple University, Philadelphia:* E. Deusch, B. Flynn; *Georgetown University, Washington, D.C.:* J. Gannuscio; *Cleveland Clinic Foundation, Cleveland:* S. Ellis, L. Korcuska; *Texas Heart Institute, Houston:* D. Fish, M. Harlan; *Aurora Denver Cardiology, Aurora, Colo.:* S. Friedrich, K. Bickett; *Mid-West Cardiology Research Foundation, Columbus, Ohio:* B. George, D. Smith; *St. Joseph's Hospital, Syracuse, N.Y.:* S. Wagner; *Miriam Hospital, Providence, R.I.:* N. Wright; *Arizona Heart Institute, Phoenix:* R. Heuser, S. Spooner; *University of Pennsylvania, Philadelphia:* J. Hirshfeld, L. Felderstein; *Mayo Clinic, Rochester, Minn.:* D. Holmes, L. Pierre; *Christ Hospital, Cincinnati:* D. Kereiakes, B. Gervers, L. Martin; *Atlanta Cardiology, Atlanta:* W. Knopf, N. Yarbrough; *Washington Hospital Center, Washington, D.C.:* K. Donovan; *Hartford Hospital,*

Hartford, Conn.: R. McKay, D. Hall; *University of Chicago, Chicago*: T. Feldman, C. Kienlen; *Lenox Hill Hospital, New York*: J. Moses, N. Cohen; *Stanford University Hospital, Stanford, Calif.*: S. Oesterle, N. Jenkins; *Cardiology Associates of Lubbock, Lubbock, Tex.*: P. Overlie, D. Stone; *Massachusetts General Hospital, Boston*: I. Palacios, K. Martin; *Mount Sinai Hospital, New York*: S. Sharma, D. Ratner; *University of Florida, Gainesville*: C. Pepine, E. Franco; *Ochsner Clinic, New Orleans*: S. Ramee, N. McCarthy; *Scottsdale Cardiovascular Center, Scottsdale, Ariz.*: D. Rizik, C. Wojciechowski; *Monroe Regional Medical Center, Ocala, Fla.*: R. Feldman, B. Merchant; *William Beaumont Hospital, Royal Oaks, Mich.*: R. Safian, M. Safian, D. Davey; *Oklahoma Foundation for Cardiovascular Research, Oklahoma City*: D. Schmidt, M. Johnson; *Maimonides Medical Center, Brooklyn, N.Y.*: J. Shani, N. Schulhoff; *Washington Adventist Hospital, Takoma Park, Md.*: F. Shawl, S. Cornell; *St. Luke's Medical Center, Kansas City, Mo.*: T. Shimshack, P. Rosson; *Sanger Clinic, Charlotte, N.C.*: C. Simonton, G. Schwarz; *University of Texas Medical School, Houston*: R. Smalling, C. Underwood; *Allegheny General Hospital, Pittsburgh*: R. Saputski; *Chattanooga Heart Institute, Chattanooga, Tenn.*: A. Stratienko, V. Marion; *Scripps Clinic and Research Foundation, La Jolla, Calif.*: P. Teirstein, K. Stevens; *Medical College of Virginia, Richmond*: G. Vetrovec, R. O'Brien; *Sharp Memorial Hospital, San Diego, Calif.*: M. Buchbinder, J. Fenner; *Rhode Island Hospital, Providence*: J. Muratori, E. Donaghey; *Duke University Medical Center, Durham, N.C.*: J. Zidar, S. Sawchak; *Washington University School of Medicine, St. Louis*: J. Lasala, K. Meyers. *Coordinating Center and Biostatistical Core Laboratory*: M. Fitzpatrick, C. Senerchia, A. Dejardin (Boston); *Quantitative Angiographic Core Laboratory*: A. Merrit, A. Lansky (Washington, D.C.); *Data Safety and Monitoring Committee*: T. Ryan (chair), J. Orav (statistician), B. Gersh, S. Smith, D. Faxon; *Clinical Events Committee*: J. Marcus, J. Carrozza, W. Manning, D. Cohen, J. Kannam, L. Epstein (Boston); *Electrocardiographic Core Laboratory*: A. Goldberger (Boston).

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