

## A RANDOMIZED COMPARISON OF ANTIPLATELET AND ANTICOAGULANT THERAPY AFTER THE PLACEMENT OF CORONARY-ARTERY STENTS

ALBERT SCHÖMIG, M.D., FRANZ-JOSEF NEUMANN, M.D., ADNAN KASTRATI, M.D., HELMUT SCHÜHLEN, M.D.,  
RUDOLF BLASINI, M.D., MARTIN HADAMITZKY, M.D., HANNA WALTER, M.D.,  
EVA-MARIA ZITZMANN-ROTH, M.D., GERT RICHARDT, M.D., ECKHARD ALT, M.D.,  
CLAUS SCHMITT, M.D., AND KURT ULM, PH.D.

**Abstract Background.** The clinical benefit of coronary-artery stenting performed in conjunction with coronary angioplasty is limited by the risk of thrombotic occlusion of the stent as well as hemorrhagic and vascular complications of intensive anticoagulation. We compared antiplatelet therapy with conventional anticoagulant therapy with respect to clinical outcomes 30 days after coronary-artery stenting.

**Methods.** After successful placement of Palmaz-Schatz coronary-artery stents, 257 patients were randomly assigned to receive antiplatelet therapy (ticlopidine plus aspirin) and 260 to receive anticoagulant therapy (intravenous heparin, phenprocoumon, and aspirin). The primary cardiac end point was a composite measure reflecting death from cardiac causes or the occurrence of myocardial infarction, aortocoronary bypass surgery, or repeated angioplasty. The primary noncardiac end point comprised death from noncardiac causes, cerebrovascular accident, severe hemorrhage, and peripheral vascular events.

**Results.** Of the patients assigned to antiplatelet therapy, 1.6 percent reached a primary cardiac end point, as did 6.2 percent of those assigned to anticoagulant therapy

(relative risk, 0.25; 95 percent confidence interval, 0.06 to 0.77). With antiplatelet therapy, there was an 82 percent lower risk of myocardial infarction than in the anticoagulant-therapy group, and a 78 percent lower need for repeated interventions. Occlusion of the stented vessel occurred in 0.8 percent of the antiplatelet-therapy group and in 5.4 percent of the anticoagulant-therapy group (relative risk, 0.14; 95 percent confidence interval, 0.02 to 0.62). A primary noncardiac end point was reached by 1.2 percent of the antiplatelet-therapy group and 12.3 percent of the anticoagulant-therapy group (relative risk, 0.09; 95 percent confidence interval, 0.02 to 0.31). Hemorrhagic complications occurred only in the anticoagulant-therapy group (in 6.5 percent). An 87 percent reduction in the risk of peripheral vascular events was observed with antiplatelet therapy.

**Conclusions.** As compared with conventional anticoagulant therapy, combined antiplatelet therapy after the placement of coronary-artery stents reduces the incidence of both cardiac events and hemorrhagic and vascular complications. (N Engl J Med 1996;334:1084-9.)

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**I**NTRACORONARY stenting is an accepted treatment for vessel closure after percutaneous transluminal coronary angioplasty (PTCA).<sup>1-3</sup> Moreover, as compared with balloon angioplasty, elective stent placement reduces the rate of restenosis.<sup>4,5</sup> However, thrombotic occlusion of the stent, as well as hemorrhagic and peripheral vascular complications due to the intensive anticoagulation recommended for the first few weeks after the procedure, seriously limits the benefits of intracoronary stenting.<sup>6,7</sup> Recent studies with intravascular ultrasonography or coated stents suggest that anticoagulant therapy may be dispensable.<sup>8,9</sup> We recently identified a high level of surface expression of the inducible fibrinogen receptor on platelets as a strong independent predictor of thrombosis in the stented vessel, whereas monitoring of anticoagulation was not predictive.<sup>10</sup> These findings suggest that effective inhibition of platelet function may be superior to anticoagulant therapy in preventing occlusion of the stent.

We therefore conducted the Intracoronary Stenting and Antithrombotic Regimen trial, a prospective, randomized study designed to compare the early outcome

of patients treated with two different antithrombotic regimens after the placement of coronary-artery stents: combined antiplatelet therapy with ticlopidine plus aspirin, and conventional anticoagulant therapy with intravenous heparin, phenprocoumon (a coumarin derivative), and aspirin.

### METHODS

#### Selection of Patients

The study population consisted of patients in whom intracoronary stents were successfully placed after PTCA at our institution. The indications for stenting were extensive coronary-artery dissection after PTCA, complete vessel closure, residual stenosis of 30 percent or more of the vessel diameter, and lesions in venous bypass grafts. All patients in whom stenting was successful (i.e., in whom the stent was placed at the desired position and there was less than 30 percent residual stenosis) who gave their written, informed consent to participate in the study were eligible for randomization, if they had no contraindications to the use of aspirin, ticlopidine, or phenprocoumon and no absolute indication for anticoagulant therapy. We excluded patients in whom stenting was intended primarily as a bridge to aortocoronary bypass grafting, who had cardiogenic shock, or who had needed mechanical ventilation before undergoing PTCA. All eligible patients were randomly assigned to a treatment group, by means of sealed envelopes, immediately after the intervention. The randomization sequence was specified before the study began. The study was carried out according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.

#### Placement of Coronary Stents

Stents were implanted as previously described.<sup>3</sup> Before undergoing PTCA, patients received heparin (15,000 units) and aspirin (500 mg) intravenously. Conventional rapid-exchange balloon catheters were

From the 1. Medizinische Klinik (A.S., F.-J.N., A.K., H.S., R.B., M.H., H.W., E.-M.Z.-R., G.R., E.A., C.S.), and the Institut für Medizinische Statistik und Epidemiologie (K.U.), Klinikum rechts der Isar, Technische Universität München, Munich, Germany. Address reprint requests to Dr. Schömig at the 1. Medizinische Klinik der Technischen Universität München, Klinikum rechts der Isar, Ismaninger Strasse 22, 81675 Munich, Germany.

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used for angioplasty (Express, Scimed, Verviers, Belgium). The 7-mm or the articulated 15-mm standard Palmaz-Schatz stent (Johnson and Johnson, Warren, N.J.) was folded by hand onto the angioplasty balloon. Balloon catheters for the deployment of stents were chosen with the intention of using a slightly oversized balloon. In addition, relatively noncompliant balloon catheters (High Energy, Boston Scientific, Hilden, Germany) were used in most of the patients for high-pressure dilation. If necessary, multiple stents were used for complete coverage of the area of dissection. Intravascular ultrasonography was not used routinely.

The arterial sheath was removed when the partial-thromboplastin time fell below 60 seconds, typically within three hours after the procedure. After manual compression of the groin, carried out as long as necessary for local hemostasis (at least 30 minutes), a pressure bandage was applied. No other specific devices to promote hemostasis were used.

### Antiplatelet and Anticoagulant Regimens

Immediately after the application of the pressure bandage, a continuous heparin infusion, adjusted to achieve a partial-thromboplastin time of 80 to 100 seconds, was started in all patients. In patients assigned to antiplatelet therapy, heparin was discontinued 12 hours after stent placement. Ticlopidine therapy (250 mg twice a day; Tiklyd, Sanofi-Winthrop, Munich, Germany) was started immediately after the procedure and continued for four weeks. In patients assigned to anticoagulant therapy, phenprocoumon therapy (Marcumar, Hoffmann-LaRoche, Granzach-Wyhlen, Germany) 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. The target international normalized ratio (INR) was between 3.5 and 4.5, a range selected on the basis of our previous experience.<sup>3</sup> The partial-thromboplastin time and INR were monitored twice daily. All patients in both groups received aspirin (100 mg twice a day) throughout the study.

### Angiographic Analysis

Coronary angiography was performed with a digital angiographic system (Hicor, Siemens, Erlangen, Germany). Qualitative and quantitative analysis was performed at a digital angiographic work station (AWOS, Siemens) by operators who were unaware of the study groups to which the patients were assigned.

### Follow-up

All patients remained in the hospital for at least 10 days to ensure identical observation after the stenting procedure. Complete blood counts and enzyme measurements were performed three times each week. Electrocardiograms were recorded daily. Duplex ultrasonography of the groin was performed routinely by operators unaware of the patients' antithrombotic regimens. Coronary angiography was repeated in patients with suspected myocardial ischemia. All patients were seen as outpatients one month after discharge.

### Events and End Points

This study was designed to assess the incidence of two types of clinical events — cardiac events, and vascular and bleeding events — in the 30 days after placement of the stent. We defined two summary variables for the primary clinical end points, cardiac and noncardiac, since these two types of events may reflect different responses to the two antithrombotic regimens.

A primary cardiac end point was defined as death due to cardiac causes or the occurrence of myocardial infarction, 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. The diagnosis of acute myocardial infarction was based on typical chest pain lasting more than 30 minutes, abnormal Q waves not present on the base-line electrocardiogram, or an increase in the creatine kinase concentration to twice the upper limit of normal, with a concomitant rise in the crea-

tine kinase MB isoenzyme. The diagnosis of recurrent myocardial infarction was also based on an increase of more than 30 percent in the creatine kinase concentration.

A primary noncardiac end point was defined as death from any noncardiac cause or the occurrence of cerebrovascular accident or a severe peripheral vascular or hemorrhagic event. A diagnosis of cerebrovascular accident was made only when prolonged neurologic deficit was present. Severe peripheral vascular events were pseudoaneurysms or arteriovenous fistulas at the access site requiring surgery or prolonged, ultrasound-guided compression.<sup>11</sup> The diagnosis was always based on color-coded duplex ultrasonography performed by physicians blinded to the patient's study-group assignment. Severe hemorrhagic events were defined as bleeding complications requiring surgery or transfusion, or bleeding associated with objective signs of organ dysfunction. Blood transfusion was considered indicated at hemoglobin concentrations below 8 g per deciliter.

We also defined two secondary end points: a combined clinical end point comprising all cardiac and noncardiac events, and the angiographic end point of occlusion in the stented vessel.

### Statistical Analysis

All data were analyzed on an intention-to-treat basis. The prospectively determined sample size was confirmed in a scheduled interim analysis at six months. Discrete variables, expressed as counts, were compared by means of Fisher's exact test.<sup>12</sup> Continuous data, expressed as means  $\pm$ SD, were analyzed with unpaired, two-tailed *t*-tests. The main analysis focused on comparisons of the two groups with respect to the primary cardiac and noncardiac end points. In a second step, the two groups were compared with respect to secondary end points. Finally, data were analyzed with Fisher's exact test, and relative risks with 95 percent confidence intervals were computed for antiplatelet therapy as compared with conventional anticoagulant therapy.<sup>12,13</sup> Cumulative-event-rate curves were used for graphic presentation of the differences between the groups and of the time course of events. Differences were considered to be statistically significant when the *P* values were less than 0.05.

## RESULTS

### Characteristics of the Patients

Among 626 consecutive patients who underwent stent implantation at our institution from October 1994 through September 1995, 517 patients were eligible for enrollment and consented to be randomly assigned to treatment; 257 patients were assigned to antiplatelet therapy and 260 to anticoagulant therapy. No patient was excluded after randomization. As Table 1 shows, there were no significant differences between the groups in base-line characteristics.

The angiographic and procedural data are summarized in Table 2. There was no significant difference between the groups with respect to the distribution of target vessels, characteristics of the target lesions, or luminal and balloon diameters.

### Cardiac Events

The clinical outcomes during the first 30 days after implantation of the stents are summarized in Table 3. Table 4 lists the cardiac events individually. A primary cardiac end point was reached by 16 patients in the anticoagulant-therapy group (6.2 percent), as compared with 4 in the antiplatelet therapy group (1.6 percent). This difference resulted from a decrease of 82 percent in the incidence of myocardial infarction and a 78 per-

cent lower rate of reintervention (coronary-artery by-pass grafting or repeated PTCA) among patients assigned to antiplatelet therapy.

As shown in Figure 1, all cardiac events among patients assigned to antiplatelet therapy occurred within the first week. Among those who received anticoagulant therapy, cardiac events occurred up to day 26; most of them occurred after day 3. During the first three days after stenting, the rate of cardiac events was similar in the two groups.

### Noncardiac Events

As Table 3 shows, there were significantly fewer noncardiac events in the antiplatelet-therapy group than in the group that received anticoagulant therapy ( $P<0.001$ ); there were no severe hemorrhagic events in the antiplatelet-therapy group ( $P<0.001$ ) and fewer peripheral vascular events ( $P=0.001$ ). One patient receiving antiplatelet therapy had an ischemic stroke confirmed by computed tomography. Severe hemorrhagic events occurred during all phases of anticoagulant therapy: four during heparin treatment before oral anticoagulation became effective, five during the period of overlap between intravenous and oral therapy, and eight after the withdrawal of heparin. The bleeding was gastrointestinal in three patients, urogenital in three, in the respiratory tract in two, retroperitoneal in three, in the groin in five, and in both the gastrointestinal tract and the groin in one. As to reversible organ dysfunction associated with bleeding, three patients had renal dysfunction, three had neurologic symptoms due to compression of a nerve by a retroperitoneal or groin hematoma, and one had pulmonary bleeding with respiratory insufficiency. Twelve patients receiving anticoagulant therapy required blood transfusion, and two required surgery (one for gastric bleeding and one for groin complications). All

Table 2. Angiographic and Procedural Characteristics, According to Study Group.\*

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.<sup>14</sup>

pseudoaneurysms and the arteriovenous fistula were successfully treated with ultrasound-guided compression. The cumulative rate of noncardiac events is shown in Figure 1. All noncardiac events in the patients receiving antiplatelet therapy occurred within the first four days after stenting. Such events occurred up to 28 days after stenting in those assigned to anticoagulant therapy.

### Secondary End Points

The cumulative rate of any cardiac or noncardiac event (the combined clinical end point) was significantly lower among the patients assigned to antiplatelet therapy than among those in the anticoagulant-therapy group; the reduction in risk was 84 percent (Table 3). The cumulative rate of clinical events is shown in Figure 2. Among the patients given antiplatelet therapy, the last event occurred on day 7, whereas among those given anticoagulant therapy, complications continued to occur throughout the 30-day follow-up period.

The angiographic end point of occlusion of the stented vessel occurred in 14 patients assigned to anticoagulant therapy and 2 patients assigned to antiplatelet therapy. Progressive dissection with subsequent vessel closure outside the stented segment occurred in three patients within the first three days. Thrombotic occlusion of the stent occurred in 13 patients assigned to anticoagulant therapy and in none of the patients assigned to antiplatelet therapy. The association of occlusion of the stented vessel with other cardiac events is

Table 1. Base-Line Clinical Characteristics of the Patients, According to Study Group.\*

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.

Table 3. Relative Risk of End Points and Events.\*

EVENT	ANTIPLATELET THERAPY (N = 257)	ANTICOAGULANT THERAPY (N = 260)	P VALUE	RELATIVE RISK (95% CI)
	no. (%)			
<b>Primary cardiac end point</b>	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)
<b>Primary noncardiac end point</b>	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)
<b>Combined clinical end point</b>	7 (2.7)	43 (16.5)	<0.001	0.16 (0.06–0.36)
<b>Occlusion of stented vessel</b>	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.

shown in Table 4. The median interval between implantation and thrombosis in the stented vessel was seven days. In 3 of the 13 patients who had thrombosis, anticoagulation was inadequate within 12 hours before the event; anticoagulant agents had been purposely withheld in 1 patient because of pulmonary bleeding; in 1 patient the target partial-thromboplastin time had not been reached 3 hours after removal of the sheath. In the third patient, the partial-thromboplastin time had dropped to 48 seconds during the period of overlapping heparin and phenprocoumon therapy while the INR was still below the therapeutic range.

#### Discontinuation of the Assigned Therapy

In the anticoagulant-therapy group, bleeding and peripheral vascular complications necessitated the discontinuation of anticoagulants in 24 patients an average of 8.5 days after the intervention. The subsequent clinical course was uneventful in all but one patient, who had subacute thrombosis in the stented vessel. In four patients assigned to antiplatelet therapy, ticlopidine was discontinued without subsequent complications; one of these patients had an allergic skin reaction, and three had evidence of substantial left ventricular thrombus on the echocardiogram and subsequently required full anticoagulation.

### DISCUSSION

Our prospective, randomized trial compared antiplatelet and anticoagulant therapy after the placement of intracoronary stents in a large cohort of patients. The

study population encompassed the entire spectrum of symptomatic coronary artery disease, including patients with stable angina and acute ischemic syndromes, as well as a substantial number of patients with complex coronary-artery lesions. Our data show that, as compared with anticoagulant therapy, antiplatelet therapy was associated with a lower rate of noncardiac events (including hemorrhagic and peripheral vascular complications), a lower rate of cardiac events (such as death, myocardial infarction, and the need for repeated interventions), and in particular, a lower incidence of thrombotic occlusion of the stented vessel. The incidence of severe hemorrhagic and peripheral vascular events was significantly lower with antiplatelet therapy, for a risk reduction of 91 percent. Our most notable finding was the significantly lower rate of cardiac events in the group that received antiplatelet therapy, which translated into a reduction of 75 percent in the risk of such events.

This reduction was due to the significantly lower rates of myocardial infarction and reintervention. Rates of cardiac events in both groups were similar to those of previously studied patients given antiplatelet therapy (0 to 1.1 percent)<sup>8,15</sup> and anticoagulant therapy (5.9 to 6.9 percent).<sup>3-5</sup>

Our data show that the reduction in the incidence of cardiac events with antiplatelet therapy can be attributed largely to a reduction in the frequency of thrombotic occlusion of the stented vessel. Several mechanisms may account for this outcome, including possible thrombogenic effects of phenprocoumon or heparin and antithrombotic effects of ticlopidine (since the patients in both groups received aspirin). Phenprocoumon, like warfarin, induces a decrease in the natural anticoagulants protein C and protein S before the reduction in prothrombin occurs.<sup>16</sup> This factor is unlikely to have played a major part in our results, however, since most thrombotic occlusions of stents occurred either during intravenous heparin treatment or in a later phase of phenprocoumon therapy. The differences between the two regimens appear to be more readily explained by their differential effect on platelet function. Synergistically with aspirin, ticlopidine interferes with platelet activation by strong agonists; it does so by limiting exposure of fibrinogen receptors and platelet aggregation.<sup>17,18</sup> In contrast, heparin stimulates fibrinogen-receptor activation and  $\alpha$ -degranulation in platelets,<sup>19</sup> and it may induce IgG antibodies that cause platelet activation and thrombocytopenia.<sup>20</sup> Evidence for this hypothesis comes from a recent study showing pro-

gressive activation of platelets after coronary-artery stenting in patients who received anticoagulant agents; in patients given combined antiplatelet therapy, on the contrary, the surface expression of activated fibrinogen receptors decreased during the first few days after stenting.<sup>21</sup> The latter finding is in accord with the known delay in the onset of action of ticlopidine<sup>17</sup> and may explain the different rates of thrombotic occlusion of the stented vessels after day 3 in our study. Within the first two days, however, the rates of cardiac events did not differ significantly between the groups. In this early post-intervention period, subacute occlusion of the stented vessel is caused primarily by residual dissection.

Severe neutropenia has been noted in 0.8 percent of patients receiving long-term ticlopidine therapy; in all cases it has occurred in the second and third months of therapy and is fully reversible after the discontinuation of ticlopidine.<sup>22</sup> Although neutropenia developed in none of our patients, this complication may have been missed after discharge from the hospital when blood-cell counts were not monitored in most patients. However, published data suggest that neutropenia would be of little clinical importance because of the short duration of therapy.<sup>22,23</sup>

Antiplatelet therapy after stenting has been advocated along with the use of intravascular ultrasonography

Table 4. Individual Cardiac Events and Occlusions of Stented Vessels.\*

PATIENT NO.	DEATH	MI	CABG	PTCA	VESSEL OCCLUSION	DAYS AFTER STENTING
<b>Antiplatelet-therapy group</b>						
1		X		X	O†	3
2		X		X	O†	1
3	X‡				P	3
4				X§	P	7
<b>Anticoagulant-therapy group</b>						
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.

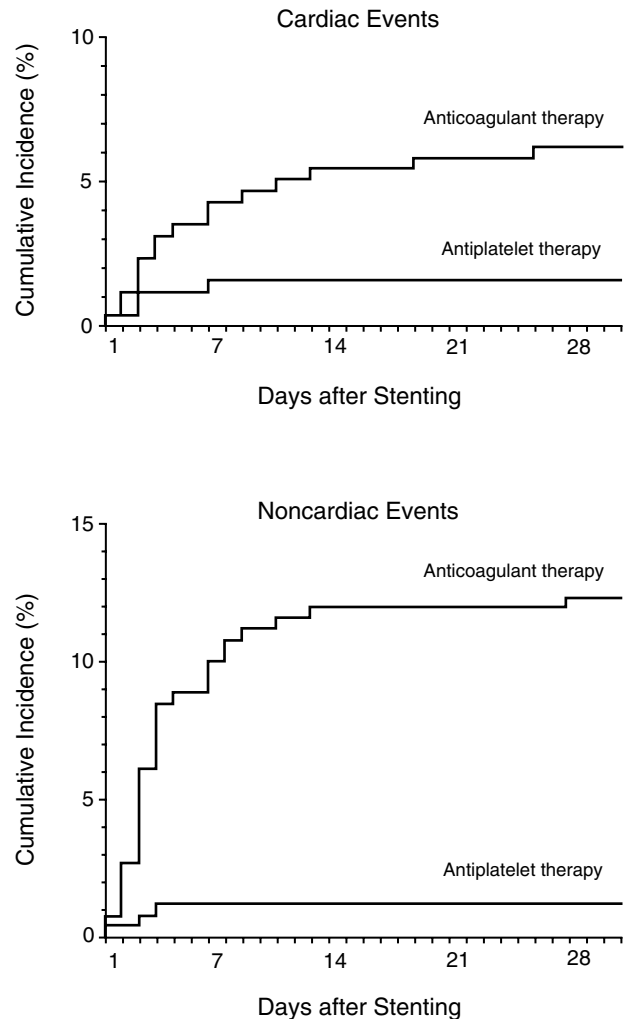


Figure 1. Cumulative Incidence of Cardiac and Noncardiac Events in the Study Groups.

A cardiac event was defined as death due to cardiac causes or the occurrence of myocardial infarction, bypass surgery, or repeated balloon angioplasty, whichever occurred first. A noncardiac event was defined as death due to noncardiac causes or the occurrence of cerebrovascular accident or severe hemorrhagic and peripheral vascular complications, whichever occurred first.

and high balloon pressures.<sup>8</sup> Our study was not intended to assess the specific role of these procedural elements. Although high balloon pressures were not required by the protocol, the mean values of 15.8 and 16.0 atmospheres for the procedures in patients assigned to anticoagulant and antiplatelet therapy, respectively, compare well with the recently reported value of 14.9 atmospheres.<sup>8</sup> We rarely performed ultrasound studies during the procedures. Although the outcome of patients in our study who received aspirin plus ticlopidine is similar to results reported previously with ultrasound-guided stenting and antiplatelet therapy,<sup>8</sup> this similarity does not rule out the possibility of further benefit with the addition of ultrasound guidance.

The study protocol included a hospital stay of at least

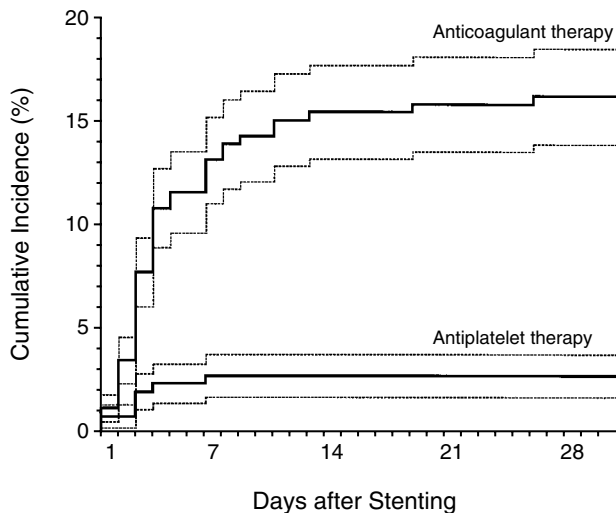


Figure 2. Cumulative Incidence of Any Cardiac or Noncardiac Event, Whichever Occurred First.

The dotted lines represent 95 percent confidence intervals.

10 days after the procedure. Such in-hospital surveillance of all patients guaranteed a comprehensive assessment and detailed analysis of the time course of complications. In the anticoagulant-therapy group, two additional complications occurred more than three weeks after the procedure, whereas with antiplatelet therapy, only one additional event occurred later than day 4 after the procedure. On the basis of these data, a shorter hospital stay may be safe for patients receiving antiplatelet therapy.

The fact that patients and physicians were not blinded to the treatment assignment represents a further limitation of our study. Consequently, bias on the part of investigators or patients cannot be fully excluded as a factor influencing management after stenting. However, bias in the angiographic analyses and in surveillance of the access site was precluded by blinding of the personnel who performed these assessments. As an added measure to minimize investigator bias, definitions of events were specified in the protocol and based on objective criteria.

Although previous studies have established that the outcome is more favorable after elective coronary-stent placement than after conventional balloon angioplasty,<sup>4,5</sup> widespread clinical use of the technique has been limited by the risk of thrombotic occlusion of the stented vessel and of complications of the anticoagulant regimen. Our results indicate that the risk-benefit ratio for stenting may be substantially improved by the use of combined antiplatelet therapy. The marked decrease in thrombotic stent occlusions with antiplatelet therapy

implies that platelets have a crucial role in the pathogenesis of this complication.

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