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Circulation. 1998;98:1597-1603

doi: 10.1161/01.CIR.98.16.1597

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Randomized Multicenter Comparison of Conventional Anticoagulation Versus Antiplatelet Therapy in Unplanned and Elective Coronary Stenting

The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study

Michel E. Bertrand, MD; Victor Legrand, MD; Jean Boland, MD; Eckart Fleck, MD; Johannes Bonnier, MD; Hakan Emmanuelson, MD; Matty Vrolix, MD; Luc Missault, MD; Sergio Chierchia, MD; Michele Casaccia, MD; Luigi Niccoli, MD; Ali Oto, MD; Christopher White, MD; Michael Webb-Peploe, MD; Eric Van Belle, MD; Eugène P. McFadden, MRCP

Background—Dual therapy with ticlopidine and aspirin has been shown to be as effective as or more effective than conventional anticoagulation in patients with an optimal result after implantation of intracoronary metallic stents. However, the safety and efficacy of antiplatelet therapy alone in an unselected population has not been evaluated.

Methods—Patients were randomized to conventional anticoagulation or to treatment with antiplatelet therapy alone. Indications for stenting were classified as elective (decided before the procedure) or unplanned (to salvage failed angioplasty or to optimize the results of balloon angioplasty). After stenting, patients received aspirin and either ticlopidine or conventional anticoagulation (heparin or oral anticoagulant). The primary end point was the occurrence of bleeding or peripheral vascular complications; secondary end points were cardiac events (death, infarction, or stent occlusion) and duration of hospitalization.

Results—In 13 centers, 236 patients were randomized to anticoagulation and 249 to antiplatelet therapy. Stenting was elective in 58% of patients and unplanned in 42%. Stent implantation was successfully achieved in 99% of patients. A primary end point occurred in 33 patients (13.5%) in the antiplatelet group and 48 patients (21%) in the anticoagulation group (odds ratio=0.6 [95% CI 0.36 to 0.98], $P=0.03$). Major cardiac-related events in electively stented patients were less common (odds ratio=0.23 [95% CI 0.05 to 0.91], $P=0.01$) in the antiplatelet group (3 of 123, 2.4%) than the anticoagulation group (11 of 111, 9.9%). Hospital stay was significantly shorter in the antiplatelet group (4.3 ± 3.6 versus 6.4 ± 3.7 days, $P=0.0001$).

Conclusions—Antiplatelet therapy after coronary stenting significantly reduced rates of bleeding and subacute stent occlusion compared with conventional anticoagulation. (*Circulation*. 1998;98:1597-1603.)

Key Words: stents ■ antiplatelet agents ■ anticoagulants

Intracoronary implantation of permanent metallic stents, introduced more than a decade ago, failed to achieve widespread acceptance because of high rates of stent occlusion and peripheral vascular complications. Two recent major randomized trials^{1,2} showed that elective stent implantation reduced clinical and angiographic restenosis in selected patients. Despite the intensive anticoagulation regimen used (heparin followed by oral anticoagulation), stent occlusion still occurred in 3% to 5% of stented segments, and major bleeding was frequently observed (15% to 18%). Finally, the extended hospital stay required for therapeutic anticoagulation or for treating complications negated the potential economic advantage of the lower restenosis rate.

Two major advances have contributed to the increased use of coronary stenting in recent years. First, there is evidence that stent occlusion frequently results from inadequate stent impaction and that high-pressure (12 to 15 atm) stent deployment significantly reduces the rate of stent occlusion.³ Second, it has been demonstrated that antiplatelet therapy alone was at least as effective as full anticoagulation in patients with an optimal angiographic result after stent implantation.^{4,5} We undertook a randomized multicenter trial to compare aggressive antiplatelet treatment to anticoagulation after implantation of a Wiktor stent (Medtronic). The trial was intentionally designed to compare the 2 treatments in a patient population representative of that encountered in cur-

Received March 16, 1998; revision received May 27, 1998; accepted June 6, 1998.

Author affiliations are listed in the Appendix.

Correspondence to Michel E. Bertrand, Dept de Cardiologie B, Hôpital Cardiologique, 59037 Lille, France. E-mail bertrandme@aol.com

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rent clinical practice. Thus, treatment allocation was performed before attempted stent implantation; all patients in whom stent implantation was deemed necessary (whether elective or unplanned) were eligible for inclusion; and finally, all patients continued in the trial even if the final result after stent implantation was suboptimal.

The primary objective of the study was to determine whether aggressive treatment with antiplatelet drugs significantly reduced the rate of bleeding complications compared with that observed with full anticoagulation. The secondary objective was to establish that the antiplatelet regimen did not compromise stent patency by increasing the rate of acute or subacute occlusion.

Methods

Inclusion and Exclusion Criteria and Randomization

All patients in whom planned or unplanned stent implantation was attempted were eligible for inclusion. Thus, patients scheduled for elective stent implantation, those in whom stent implantation was performed for a suboptimal result after balloon angioplasty, or those for whom it was required as a bailout procedure after failed balloon angioplasty were potential candidates for inclusion.

The exclusion criteria were similar to those for conventional anticoagulation after stent implantation. Patients excluded were those with known bleeding disorders, thrombocytopenia ($<150\,000/\text{mm}^3$), recent (<6 months) gastrointestinal bleeding, recent cerebrovascular accident, recent intracranial or eye surgery, severe hepatic or renal dysfunction, malignant hypertension, angiographic evidence of thrombus at the proposed stent site, history of allergy to aspirin or ticlopidine, history of heparin-related thrombocytopenia, or systemic disease that significantly limited life expectancy.

Randomization was performed before angioplasty for elective procedures and before stent implantation for unplanned stent implantation by telephoning a central randomization center. The randomization sequence was established before the study began. The Ethical Committee of each participating center approved the protocol and all patients gave written informed consent.

Stent Implantation Procedure

Before intervention, patients were pretreated with aspirin (100 to 300 mg) at the discretion of the investigator. In addition, a bolus of heparin (10 000 IU) was administered just before angioplasty, with supplemental boluses (5000 IU) for each additional hour of procedural time. Stent implantation was performed after balloon predilatation. Subsequently, a premounted Wiktor stent with a diameter equivalent to or slightly ($<10\%$) greater than the mean reference diameter of the adjacent vessel was deployed at the nominal balloon inflation pressure. Subsequently, a final inflation with a noncompliant or semicompliant balloon at high pressure (>10 atm) was performed. When required, 2 or more stents were implanted to achieve an optimal angiographic result.

Stent placement was classified as elective when the decision to implant a stent was made before the procedure. Randomization was performed in these patients before the angioplasty procedure. Unplanned stent implants were those performed for a suboptimal result (residual stenosis $>40\%$, visual estimate) with or without dissection grade B or C or for failed angioplasty (dissection grade D1, D2, E, or F).⁶ Randomization was performed as soon as the decision to implant a stent had been taken. After the procedure, no further heparin was given to patients who left the catheterization laboratory before 2 PM, and their femoral artery sheaths were removed 4 hours later. In the remaining patients, the sheaths were removed the following day. These patients received an intravenous infusion of heparin (1000 IU/h) 6 AM the next day. The sheaths were removed 4 hours after discontinuation of heparin.

TABLE 1. Population Characteristics

	Antiplatelet Therapy, n (%) (n=243)	Conventional Anticoagulation, n (%) (n=230)	P
Age, \pm SD	60.0 \pm 10.8	60.3 \pm 10.4	
Men	197 (81.5)	185 (80.4)	0.77
Current smokers	78 (32.5)	63 (27.4)	0.22
Former smokers	109 (44.9)	98 (42.6)	0.62
Insulin-dependent diabetes	8 (3.3)	6 (2.6)	0.66
Non-insulin-dependent diabetes	29 (12.3)	28 (12.2)	0.95
Hypertension ($>160/90$ mm Hg)	79 (32.5)	74 (32.2)	0.93
Hypercholesterolemia (>240 mg)	115 (47.7)	101 (43.9)	0.40
Family history of coronary disease	116 (48.1)	103 (44.8)	0.46

Antiplatelet and Anticoagulation Regimens

After stent implantation, patients randomized to antiplatelet therapy (group A) received their first dose of ticlopidine (500 mg) in the catheterization laboratory. Patients were discharged on ticlopidine (250 mg BID) for 6 weeks, and aspirin (100 to 325 mg daily) for life. Patients randomized to conventional anticoagulation (group B) were started on oral anticoagulant immediately after stent implantation. After removal of the sheaths and after hemostasis, they received a bolus of heparin (2500 IU) followed by a continuous infusion of 1000 IU/h that was adjusted to achieve a target activated partial thromboplastin time value of 2.0 times to 2.5 times control. The daily dose of oral anticoagulant was adjusted to achieve stable oral anticoagulation. The target international normalized ratio (INR) was between 2.5 and 3.0. When the target INR had been documented on 2 consecutive days, heparin was discontinued. At discharge, patients were placed on oral anticoagulants for 6 weeks and aspirin (100 to 325 mg) for life.

Follow-Up

An ECG was recorded before the procedure, immediately after the procedure, and before discharge. The day after the procedure and before discharge, blood samples were obtained for measurement of

TABLE 2. Cardiac History, Symptomatic Status at Baseline, and Extent of Coronary Disease

	Antiplatelet Therapy, n (%) (n=243)	Conventional Anticoagulation, n (%) (n=230)	P
Previous myocardial infarction	118 (51.3)	109 (47.4)	0.79
Previous coronary bypass surgery	33 (14.3)	31 (13.5)	0.97
Previous angioplasty	84 (36.5)	72 (31.3)	0.45
Unstable angina	105 (43)	94 (41)	0.60
Stable angina	119 (49)	116 (50)	0.75
Canadian class			
1	5 (2)	4 (2)	0.79
2	47 (19)	47 (20)	0.76
3	58 (24)	52 (23)	0.74
4	9 (4)	13 (6)	0.29
Atypical chest pain	19 (8)	20 (9)	0.72
No. of diseased vessels			
1	109 (47.4)	108 (47)	0.64
2	86 (37.7)	85 (37)	0.73
3	48 (20.9)	37 (16.1)	0.30

TABLE 3. Indication for Stent Implantation and Procedural Details

	Antiplatelet Therapy, n (%) (n=243)	Conventional Anticoagulation, n (%) (n=230)	P
Elective	127 (52.3)	109 (47.4)	0.28
Bailout for failed angioplasty/suboptimal results	116 (47.7)	121 (52.6)	0.28
De novo lesion	198 (81.5)	197 (85.7)	0.22
Restenotic lesion	45 (18.5)	33 (14.3)	0.22
RCA	102 (42)	86 (37)	0.30
LAD	35 (14.5)	32 (14)	0.87
LCx	84 (34.5)	96 (42)	0.11
SVG	22 (9)	16 (7)	0.40
Vessel diameter (mm)			
<3.0	39 (16)	40 (17)	0.69
>3.0	204 (84)	190 (83)	0.34
No. of stents implanted			
1	211 (86.4)	188 (81.7)	0.16
2	29 (12.3)	32 (13.9)	0.61
>2	3 (1.3)	7 (3)	0.17
Maximal balloon inflation pressure, atm±SD	13.5±2.9	13.7±3.4	

RCA indicates right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; and SVG, saphenous vein graft.

creatinine phosphokinase and its MB isoenzyme fraction. After discharge, full blood counts (including platelet count) were performed at 2 weeks, 1 month, and 6 weeks after stent implantation. Patients assigned to oral anticoagulation had close monitoring of their prothrombin time at the hospital outpatient clinic or by their general practitioner. An outpatient visit was scheduled at 1 month, at which time a physical examination was performed and an ECG obtained. A final outpatient visit was scheduled 6 months after the procedure. Coronary angiography, although optional, was recommended at 6-month follow-up.

Because ticlopidine therapy is associated, albeit rarely, with leukopenia, thrombocytopenia, or agranulocytosis, and in view of the limited experience with the use of ticlopidine in combination with aspirin after coronary stenting, the following guidelines were proposed if hematological abnormalities occurred during follow-up. If the white cell count was between 1200 and 1700/mm³ or the platelet count between 80 000 and 150 000/mm³, it was recommended that a blood count be obtained every 2 days and the treatment continued. If

the white cell count fell to <1200/mm³ and/or the platelet count to <80 000/mm³, it was recommended that the treatment be stopped and a blood count obtained 1 and 2 weeks later (or more frequently if judged necessary).

If ticlopidine was discontinued, recommendations for subsequent treatment were given depending on the duration of ticlopidine treatment. If ticlopidine was stopped within 4 weeks of stent implantation, it was recommended that oral anticoagulation be instituted and continued until 6 weeks after stent implantation. If ticlopidine was stopped >4 weeks after stent implantation it was recommended that it be replaced by dipyridamole (450 mg daily) until 6 weeks after stent implantation.

Primary Study End Points and Definitions

The primary end point of the study was the rate of bleeding complications in the 6 weeks after stent implantation. Bleeding complications were subdivided depending on whether they were local complications (at the vascular access site) or occurred at another site. Local complications were divided into ecchymoses, hematomas, and false aneurysms. An ecchymosis was defined as subcutaneous bleeding with discoloration of the skin around the puncture site. Ecchymoses were subdivided depending on their size, >5 or <5 cm. A hematoma was defined as subcutaneous bleeding around the puncture site that was accompanied by swelling. False aneurysms, diagnosed by ultrasound, were subdivided in 2 groups depending on whether surgical repair was undertaken. Other bleeding events were intracranial bleeding, gastrointestinal bleeding, intraocular bleeding, macroscopic hematuria (not related to urinary catheterization), or any bleeding that required blood transfusion.

Secondary Study End Points and Definitions

The secondary end points were the rates of acute or subacute stent occlusion, clinical cardiac-related events (death, Q-wave or non-Q wave myocardial infarction) and the duration of hospitalization. Acute stent occlusion was defined as stent occlusion occurring within 24 hours of stent implantation. In the absence of angiographic confirmation, the appearance of new Q waves, or an increase in the creatine kinase concentration to 2 times the upper limit of normal with a concomitant rise in the creatine kinase MB isoenzyme (>10%) were considered as evidence of stent occlusion. Subacute stent occlusion was defined as stent occlusion occurring >24 hours after stent implantation. In the absence of angiographic confirmation, the ECG and cardiac enzyme criteria (outlined above) were used. All deaths were considered to be related to cardiac causes unless an autopsy established a noncardiac cause. The diagnosis of acute myocardial infarction (MI) was based on the occurrence of typical chest pain, lasting >30 minutes, the appearance of new Q waves, or an increase in the creatine kinase concentration to 2 times the upper limit of normal with a concomitant rise in the creatine kinase MB isoenzyme. The duration of hospitalization was counted from the day of the procedure to the day of discharge (discharge after noon was counted as a full day).

TABLE 4. Primary Study End Points: Bleeding Complications

	Antiplatelet Therapy, n (%)	Conventional Anticoagulation, n (%)	P	Odds Ratio (95% CI)
Local bleeding complications				
Ecchymosis (>5 cm)	16 (6.6)	38 (16.5)	0.006	0.36 (0.18–0.68)
Hematoma	25 (10.3)	34 (14.8)	0.13	0.66 (0.37–1.18)
False aneurysm	2 (0.8)	6 (2.6)	0.13	0.31 (0.04–1.74)
Surgical repair	1 (0.4)	2 (0.9)	0.52	0.47 (0.01–9.04)
Other bleeding	2 (0.8)	7 (3.0)	0.07	0.26 (0.04–1.40)
Transfusion	4 (1.6)	6 (2.6)	0.45	0.62 (0.14–2.51)
Any bleeding complication	33 (13.5)	48 (21)	0.03	0.59 (0.36–0.98)

TABLE 5. Secondary End Points

	Antiplatelet Therapy, n (%)	Conventional Anticoagulation, n (%)	P	Odds Ratio (95% CI)
Acute stent occlusion	6 (2.4)	1 (0.4)	0.06	0.17 (0.01–1.45)
Subacute stent occlusion	1 (0.4)	8 (3.5)	0.01	0.12 (0.01–0.91)
Death	2 (0.8)	4 (1.7)	0.37	0.47 (0.06–3.00)
Q-wave myocardial infarction	3 (1.2)	6 (2.6)	0.27	0.47 (0.09–2.13)
Non-Q wave myocardial infarction	9 (3.7)	9 (3.9)	0.9	0.94 (0.34–2.65)
Hospital stay, d±SD	4.3±3.6	6.4±3.7	0.0001	

Statistical Analysis

The primary end point was the occurrence of bleeding complications (defined in Methods). Given an estimated rate of 15% in the population treated with conventional anticoagulation² and assuming that aggressive antiplatelet treatment is able to reduce bleeding complications from 15% to <5%, a sample size of 160 patients per group would be required for this end point (allowing for an α error of 0.05 and a β error of 0.20). It was decided to enroll 400 patients. The statistical analysis was performed with use of the StatView software program (StatView Inc). Baseline characteristics were compared in the 2 groups by use of the *t* test, χ^2 test, or Fisher's exact test as appropriate. Clinical events related to the procedure and those occurring during follow-up were compared with the χ^2 test or the Mantel-Haenszel test on ordered categories, as appropriate. When >1 clinical event occurred per patient, the most severe event was used for the analysis.

Results

Baseline Characteristics, Indications for Stenting, and Procedural Variables

Thirteen European centers (listed in the Appendix) participated in this trial. Between May 1995 and May 1996, they enrolled 485 patients: 249 were randomized to antiplatelet therapy and 236 were randomized to conventional anticoagulation. Stent implantation was not possible in 4 patients (3 randomized to treatment with ticlopidine and aspirin and 1 randomized to conventional anticoagulation) and 3 were referred for emergency coronary artery bypass surgery (1 randomized to antiplatelet therapy and 2 randomized to conventional anticoagulation). Five patients withdrew informed consent. Thus, the final cohort for the per protocol analysis comprised 473 patients (243 in the antiplatelet therapy group and 230 in the conventional anticoagulation group). Baseline characteristics of the population, including the distribution of risk factors for coronary disease, are presented in Table 1. Cardiac history, baseline symptoms, and the extent of coronary disease are presented in Table 2. Stent placement (Table 3) was performed electively in 52.3% of patients randomized to antiplatelet therapy and in 47.4% of patients randomized to conventional anticoagulation ($P=0.25$), and was unplanned in 48% of patients randomized to antiplatelet therapy and in 53% of patients randomized to conventional anticoagulation ($P=0.55$). The proportion of patients in whom stents were implanted for restenosis was similar in patients randomized to conventional anticoagulation or to antiplatelet therapy ($P=0.22$). There were no significant differences between groups with respect to mean vessel diameter adjacent to the stented site, the number of

stents implanted, or the maximum inflation pressure used to impact the stent (Table 3).

Primary End Points

The bleeding complications are presented in Table 4. There was a significant decrease in the occurrence of significant ecchymoses (>5 cm diameter) in patients randomized to antiplatelet therapy ($P=0.006$). Major bleeding ($P=0.07$) and false aneurysm formation ($P=0.13$) were less frequently

TABLE 6. Major Cardiac Clinical Events: Effects of Indication for Stenting and Immediate Angiographic Results

	Antiplatelet Therapy, n (%)	Conventional Anticoagulation, n (%)	P
Elective stenting (n=123)	(n=123)	(n=110)	
Death	1 (0.8)	1 (0.9)	
Acute myocardial infarction	2 (1.6)	10 (9)	
Q wave	0 (0)	4 (3.6)	
Non-Q wave	2 (1.6)	6 (5.4)	
Total cardiac-related events	3 (2.4)	11 (9.9)	0.01
Unplanned stenting (n=120)	(n=120)	(n=120)	
Death	1 (0.8)	4 (3.3)	
Acute myocardial infarction	10 (6.9)	5 (4.1)	
Q wave	3 (2.5)	2 (1.7)	
Non-Q wave	7 (5.8)	3 (2.7)	
Total cardiac-related events	11 (8.9)	9 (8.1)	0.6
Optimal result after stenting (n=225)	(n=225)	(n=209)	
Death	2 (0.9)	4 (1.9)	
Acute myocardial infarction	10 (4.5)	13 (6.2)	
Q wave	3 (1.3)	6 (2.9)	
Non-Q wave	7 (3.1)	7 (3.3)	
Total cardiac-related events	12 (5.3)	17 (8.1)	0.24
Suboptimal result after stenting (n=18)	(n=18)	(n=21)	
Death	0 (0)	0 (0)	
Acute myocardial infarction	2 (11.1)	2 (9.5)	
Q wave	0 (0)	0 (0)	
Non-Q wave	2 (11.1)	2 (9.5)	
Total cardiac-related events	2 (11.1)	2 (9.5)	0.87

Optimal result after stenting: residual stenosis <30%, no residual dissection, and no evidence of thrombus. Suboptimal result after stenting (any of the following): residual stenosis >30%, presence of residual dissection, or presence of thrombus.

TABLE 7. Major Cardiac Clinical Events Within 6-Month Follow-Up

	Antiplatelet Therapy, n (%)	Conventional Anticoagulation, n (%)	P
Death	2 (0.8)	5 (2.2)	0.21
Acute myocardial infarction	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 surgery	3 (1.2)	3 (1.3)	0.93
Repeat target lesion angioplasty	13 (5.4)	11 (4.9)	0.80
Total	31 (12.9)	35 (15.5)	0.40

observed in patients randomized to antiplatelet therapy. The rate of surgical repair was similar in both groups. Overall, bleeding complications were significantly less frequent in the antiplatelet therapy group with a risk reduction of 41% (95% CI, 0.35 to 0.98).

Secondary End Points

The overall rate of stent occlusion (Table 5) did not differ significantly ($P=0.53$) between the group randomized to antiplatelet therapy (2.8%) and the group randomized to conventional anticoagulation (3.9%). However, acute (<24 hours) stent occlusion was more frequent ($P=0.06$) in the group randomized to antiplatelet therapy (2.4% versus 0.4%) whereas subacute (>24 hours) stent occlusion was more frequent ($P=0.01$) in the group randomized to conventional anticoagulation (3.5% versus 0.4%). All the subacute occlusions occurred within 1 week of the procedure.

The cardiac events occurring in the 2 groups during the procedure and the subsequent 6 weeks are presented in Table 5. Six patients died: 3 of acute MI after stent occlusion, 1 suddenly, 1 of a cerebrovascular accident, and 1 of renal failure. There were 2 deaths (0.8%) in the group randomized to antiplatelet therapy and 4 (1.7%) in the group randomized to conventional anticoagulation ($P=0.37$). Q-wave MI occurred in 3 patients (1.2%) randomized to antiplatelet therapy and 6 patients (2.6%) randomized to conventional anticoagulation. There was a lower overall cardiac event rate in the group randomized to antiplatelet therapy (5.7%) than in the group randomized to full anticoagulation (8.3%), but the difference was not statistically significant ($P=0.37$).

Duration of Hospitalization

Patients randomized to antiplatelet therapy had a significantly ($P<0.00001$) shorter hospital stay (4.3 ± 3.6 days; median, 3 days; range, 1 to 29 days) than those randomized to conventional anticoagulation (6.4 ± 3.4 days; median, 6 days; range, 1 to 29 days).

Indication for Stenting and Immediate Angiographic Result: Effects on Outcome

In patients who underwent elective stenting, the overall rate of cardiac-related events was significantly ($P<0.01$) less in the group randomized to antiplatelet therapy than in the group randomized to full anticoagulation (Table 6). No such differ-

ence was observed in patients for whom stenting was unplanned.

Side Effects

In the group treated with antiplatelet therapy, rashes occurred in 3.3% of patients and gastrointestinal side effects in 2.4% of patients. Leukopenia, with a total white cell count <3000, occurred in 4 patients (1.6%) treated with antiplatelet therapy, but none of these cases were severe (white cell count <1200). Ticlopidine treatment was stopped because of side effects in 13 patients (5.2%) treated with antiplatelet therapy.

Six-Month Follow-up

The cumulative totals of clinical events in both groups at 6-month follow-up is presented in Table 7. There was no significant difference between the groups. Four hundred patients were free of events (death, MI, or revascularization) at 6 months. The rate of target vessel revascularization was low and similar in both groups.

Discussion

The implantation of metallic coronary stents has increased dramatically in recent years. This reflects not only the perceived benefit of stent implantation in the prevention of restenosis, which has only been conclusively demonstrated in patients with new lesions in native vessels >3.00 mm in diameter,^{1,2} but also the increasing complexity of lesions for which angioplasty is attempted. The high rate of stent occlusion documented in the early experience with coronary stenting has decreased in recent years. However, the rate of subacute stent occlusion in patients treated with conventional anticoagulation, $\approx 4\%$ of patients, represents a major clinical concern as subacute occlusion almost invariably results in death or acute MI.⁷

Recent clinical studies have had a major impact on the management of patients after stent implantation. Using intravascular ultrasound, Colombo and colleagues³ showed that stents were often inadequately impacted in the vessel wall and that further balloon inflation at pressures as high as 20 atm (with appropriately sized balloons) was required to ensure optimal stent expansion. They further demonstrated that high pressure-assisted stent implantation accomplished without intravascular ultrasound guidance and subsequent anticoagulation was safe and associated with a low risk of subacute stent occlusion.⁴ In a recent pooled analysis,⁸ stent-related thrombosis occurred in only 33 of 2630 patients who did not receive anticoagulant therapy. The majority of the patients in this report did not have ultrasound-guided stent implantation whereas high-pressure inflation was commonly used.

Only 2 major randomized studies (Schömig et al⁹ and STARS¹⁰) have compared antiplatelet therapy alone with conventional anticoagulation in the management of patients after stent implantation. The anticoagulation strategy and the antiplatelet therapy used were similar to those in the present trial. However, although a different stent was used in the 2 studies, there were important differences in the study design. First, randomization was performed in these trials after successful stent implantation and only patients with an

optimal angiographic result after stent implantation were enrolled. In the present study, randomization was performed before stent implantation was attempted. Patients were continued in the trial regardless of whether the result (after stent implantation, as assessed by angiography) was optimal. Second, although the ISAR study⁹ was a single-center study, the STARS¹⁰ and the present study were multicentric. STARS is the most complete study, because 3 different strategies were compared: aspirin alone, aspirin in conjunction with oral anticoagulation, and aspirin in conjunction with ticlopidine. The results are unequivocal: the rate of stent occlusion was significantly lower with aspirin and ticlopidine (0.6%) than with conventional anticoagulation (2.5%) and aspirin alone (3.6%).

The results of the present study, in agreement with the results of the Schömig et al⁹ and the STARS¹⁰ trials and of numerous observational studies, demonstrate that the use of antiplatelet therapy alone after stent implantation is associated with a reduction in the overall rate of bleeding complications and in the rate of subacute stent occlusion. However, the overall mortality and nonfatal MI rates did not differ significantly between patients treated with antiplatelet therapy alone and those treated with conventional anticoagulant therapy. The use of antiplatelet therapy to manage stent implantation and the simplicity of the treatment regimen has led cardiologists to treat more complex lesions, secure in the knowledge that elective or bailout stent implantation can be safely achieved. Bleeding complications, the primary study end point, were less frequent with antiplatelet therapy. Although the only significantly different bleeding complication was large ecchymosis, a trend toward a lower rate of more serious bleeding was also observed (0.8% versus 3.0%, $P=0.07$). The avoidance of anticoagulation therapy may be the major contributor to the lack of bleeding in the group treated with antiplatelet therapy.

The results of the present study show that, even with antiplatelet therapy, there is still a significant morbidity associated with coronary stent implantation. In the era of conventional anticoagulation, the major source of coronary morbidity was subacute occlusion in the week after stent implantation. With antiplatelet therapy, coronary morbidity is almost exclusively related to acute occlusion in the 24 hours after the procedure. In the present study, acute stent occlusion occurred in 1.7% of the entire population and was more common ($P=0.06$) in the antiplatelet therapy group (2.4%) than in the conventionally treated group (0.4%).

The mechanisms of acute stent occlusion are incompletely understood. However, observational studies^{4,10} have demonstrated that a suboptimal result after stent implantation (significant residual stenosis, residual dissection, or angiographic evidence of thrombus) is associated with acute stent occlusion that may be a consequence of distal extension of residual dissection, superimposed thrombosis, or a combination of both these mechanisms. In the present study, the overall rate of cardiac events in patients in whom stent implantation was electively performed was significantly less in the group treated with antiplatelet therapy. No such difference was observed for patients in whom stent implantation was performed for a suboptimal result after balloon

angioplasty or to salvage failed angioplasty. Finally, the rate of cardiac events was higher in patients with a suboptimal result after stenting (10.3%, 4 of 39 patients) than in patients with optimal stent implantation (6.7%, 29 of 234 patients), although the number of patients with a suboptimal result was small. Obviously, these observations result from a post hoc analysis with the limitations inherent to such an analysis. However, this information is of potential interest because the appropriate management (in particular, the role of antiplatelet therapy) of patients with suboptimal results is unclear. Indeed, the vast majority of studies of antiplatelet therapy after stent implantation, including the only other randomized study to date, have specifically excluded this patient population.^{4,9,11,12}

The present study shows that acute stent occlusion may also occur in the absence of mechanical predisposing factors such as residual dissection. Indeed, in 2 of the 6 cases of acute occlusion in the antiplatelet group, the procedure was uncomplicated and the angiographic result optimal. Such occlusions are likely related to thrombus formation at the stented site, a hypothesis that is supported by the observation that only 1 occlusion occurred in the conventionally anticoagulated group and by the observation that the peak antiplatelet effect of ticlopidine therapy is observed only after 72 hours of treatment.^{13,14} In the present study, as in common clinical practice, ticlopidine was given only after the procedure. It is also possible that acute thrombosis in the antiplatelet treatment group could have been related to the lack of continued anticoagulation.

In summary, the present study demonstrates that antiplatelet therapy reduces the rate of subacute stent occlusion compared with conventional anticoagulation therapy. However, stent occlusion in the 24 hours after the procedure remains a problem. Pretreatments with both ticlopidine and aspirin or the use of other potent antiplatelet agents, such as inhibitors of glycoprotein IIb/IIIa, represent potential approaches that may help to further reduce stent-related morbidity and mortality. Such approaches could be applied indiscriminately or only in high-risk groups; furthermore, such treatments expose patients to an increased risk of bleeding, and the cost of the newer antiplatelet agents presents potential economic difficulties. The answers to these questions will require further randomized trials.

Appendix

Principal Investigators and Participating Centers

Number of patients is listed in parentheses.

Belgium

Dr V. Legrand, CHU Sart Tilman, B-4000 Liège (90); Dr J. Boland, Hôpital de la Citadelle, Boulevard du 12^{ième} de Ligne, B-4000 Liège (65); Dr M. Vrolix, OCMW St Jans Hospital, Schiepsebos 2, B-3600 Genk (50); and Dr L. Missault, Academisch Ziekenhaus St Jan, Ruddershove 10, B-8000 Brugge (39).

Germany

Dr E. Fleck, Deutsches Herzzentrum Berlin, Augustenburger Platz 1, 13353 Berlin (60).

Italy

Dr S. Chierchia, Ospedale San Raffaele, Via Olgettina 60, 20090 Segrate, Milan (30); Dr Cassaccia, Azienda Ospedaliera F. Giovan, Corsa Bramente 88, I-10100 Torino (19); and Dr Niccoli, Azienda

Ospedaliere Speciale Civili, Piazzale Speciali Civili 1, I-25123 Brescia (9).

The Netherlands

Dr H. Bonnier, Catharina Ziekenhuis, Michelangelolaan 2, 5623 EJ Eindhoven (56).

Sweden

Dr H. Emmanuelson, Sahlgrenska Hospital, S-41345 Goteborg (54).

Turkey

Dr Ali Oto, Hacettepe University Hospital, 0610 Ankara, Turkey (6).

United Kingdom

Dr C. White, HCI Medical, Beardmore St, Clydebank G81 4HX, Scotland (4); Dr M. Webb Pelpoe, St Thomas Hospital, Lambeth Palace Rd, London SE1 7EH (3).

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