Comparison of Two Antiplatelet Regimens (*Aspirin* Alone Versus *Aspirin* + *Ticlopidine* or *Clopidogrel*) After Intracoronary Implantation of a *Carbofilm*-Coated Stent

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Stent thrombosis (ST) is an infrequent (0.5% to 1.5%) complication of intracoronary stenting, with severe clinical consequences. This multicenter, randomized study evaluated the clinical outcome in 479 patients (598 lesions treated) who underwent elective coronary stenting with a Carbofilm-coated stent (CarboStent) who met prespecified eligibility criteria and were randomly assigned to receive aspirin alone (n = 235) or aspirin plus a thienopyridine antiplatelet regimen (n = 244). Clinical, angiographic, and procedural characteristics were similar between groups. The primary end point was the incidence of 30-day ST; secondary end points included major vascular or bleeding complications within 30 days and death, acute myocardial infarction, and target vessel revascularization at 6 months. ST occurred in 4 patients (1.4%) in the aspirin-only group and in 1 patient (0.3%) in the aspirin-plus-thienopyridine group (relative risk 0.23, 95% confidence interval 0.03 to 2.08, p = NS). After careful review of cases, 89 patients (19%) with protocol deviations were identified. When they were excluded from the analysis, no ST was observed in either group. Secondary end points were reached by 4% of the aspirin-alone group and 8% of the aspirin-plus-thienopyridine group (relative risk 2.35, 95% confidence interval 0.94 to 5.85, p = NS). In conclusion, after optimal intracoronary implantation of the CarboStent, antiplatelet therapy with aspirin alone was safe and provided efficacy comparable to aspirin plus a thienopyridine in the prevention of ST. **(Am J Cardiol 2007;99:1062–1066)**

The present trial evaluated the protection provided by a stent with Carbofilm coating (Sorin Group, Saluggia, Italy)[1,2] by comparing the clinical outcome for 2 antithrombotic regimens, aspirin alone versus aspirin and a thienopyridine (ticlopidine or clopidogrel), after elective coronary stenting with Carbofilm-coated stents.[3]

Methods

Study design and end points: The Sorin and Aspirin Following Elective Stenting (SAFE) study was designed as a multicenter, prospective, randomized trial. Thirteen Italian centers enrolled patients between January 2001 and July 2003. The protocol was performed according to the Declaration of Helsinki and was approved by each site's local institutional ethics review committee. The primary end point was the incidence of acute or subacute stent thrombosis (ST) at 30 days after the procedure. Secondary end points included major vascular or bleeding complications within the first 30 days and death, acute myocardial infarction, and target vessel revascularization at 6 months. The clinical events committee, composed of independent experts, monitored and adjudicated these end points. The data safety monitoring board, whose members were not affiliated with the sponsor of the study and were unaware of the patient treatment assignments, was responsible for reviewing the data and identifying potential safety issues related to the conduct of the study.

Patient selection: Consecutive patients who met prespecified clinical and angiographic inclusion criteria and criteria of optimal stent implantation (see the following) were randomly assigned to receive aspirin alone or aspirin and a thienopyridine (ticlopidine or clopidogrel). Randomization was performed according to a computer-generated random sequence. Sealed envelopes contained the treatment regimen to which the patients were assigned. Patients were eligible for enrollment if they satisfied the following inclusion criteria: stable angina, unstable angina, or documented

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Table 1
Preprocedural antiplatelet therapy*

Variable	Aspirin Alone (n = 235)	Aspirin + Ticlopidine/ Clopidogrel (n = 244)	p Value
None	12 (5%)	13 (5%)	0.9132
Aspirin	167 (71%)	175 (72%)	0.8735
Aspirin + ticlopidine	20 (8%)	17 (7%)	0.5271
Aspirin + clopidogrel	2 (1%)	6 (2%)	0.2856
Ticlopidine	1 (0.4%)	5 (2%)	0.2163
Clopidogrel	3 (1%)	0	0.1173

* By protocol, ticlopidine or clopidogrel had to be withdrawn 5 days before the index procedure.

Table 2
Baseline characteristics of study patients

Clinical Characteristics	Aspirin Alone (n = 235)	Aspirin + Ticlopidine/ Clopidogrel (n = 244)	p Value
Age (yrs)	63 ± 10	62 ± 10	0.54
Men	195 (83%)	201 (82%)	0.86
Diabetes mellitus	45 (19%)	40 (16%)	0.43
Insulin dependent	10 (4%)	8 (3%)	0.57
Noninsulin dependent	35 (15%)	32 (13%)	0.57
Hypercholesterolemia (cholesterol >200 mg/dl)	132 (56%)	140 (57%)	0.79
Hypertension	151 (64%)	153 (63%)	0.72
Current smoker	139 (59%)	134 (55%)	0.35
Previous myocardial infarction	126 (54%)	110 (45%)	0.062
Previous coronary bypass	20 (8%)	11 (4%)	0.075
Previous coronary angioplasty	36 (15%)	24 (10%)	0.069
Left ventricular ejection fraction (%)	56 ± 9	57 ± 9	0.28
Stable angina pectoris	102 (43%)	102 (42%)	0.72
Unstable angina pectoris	86 (37%)	86 (35%)	0.75
Positive functional test result	30 (13%)	42 (17%)	0.17
Silent ischemia	41 (17%)	50 (20%)	0.39

Values are means ± SDs or numbers of patients (percentages).

myocardial ischemia due to de novo or restenotic coronary lesions; left ventricular ejection fraction >40%; 1 to 3 significant (≥50%) lesions with a length ≤25 mm in 1 to 3 native coronary arteries (≤1 lesion in the same vessel) with a reference vessel diameter ≥2.5 mm and no significant (≥50%) lesion proximal or distal to the target site. Clinical exclusion criteria included bleeding diathesis or coagulopathy, stroke or transient ischemic attack within 1 month, Q-wave or non–Q-wave myocardial infarction within the previous 48 hours, previous stenting within 6 months, known allergy or contraindications to study medications (i.e., aspirin, ticlopidine, or clopidogrel), leucopenia (leukocyte count $<10^9/mm^3$), neutropenia (<1,000 neutrophils/mm^3), thrombocytopenia (<100,000 platelets/mm^3), severe hepatic or renal dysfunction, peptic ulcer or gastric/intestinal bleeding in the previous 6 months, and systemic diseases that significantly limited life expectancy. Unprotected left main coronary artery disease with ≥50% stenosis, and long-term total occlusion, severe calcification, massive thrombus, and bifurcation lesions within the proposed stent site were angiographic exclusion criteria.

Definitions: Procedural success was defined as the achievement of a residual stenosis <10% by visual estimate, associated with Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow, in the absence of dissection within the treated vessel and without the occurrence of death, myocardial infarction, or repeated target lesion revascularization during hospitalization. ST was defined as closure of the stented vessel (TIMI grade 0/1 flow) with or without angiographic evidence of thrombus at the time of repeat coronary angiography driven by chest pain and electrocardiographic changes suggesting myocardial ischemia or infarction in the territory of the index vessel. Acute ST was defined as stent occlusion occurring within 24 hours of coronary stenting, and subacute ST was defined as stent occlusion occurring >24 hours and within 1 month after stent implantation. In the absence of angiographic confirmation, the appearance of new pathologic Q waves on the surface electrocardiogram or an increase in creatine kinase and creatine kinase-MB isoenzyme were considered evidence of stent occlusion. Any death occurring within the first 30 days and attributable to a cardiac cause was considered a substitute for ST, unless stent patency was demonstrated by angiography or autopsy. Q-wave myocardial infarction was defined as the occurrence of prolonged chest pain followed by new Q waves that lasted ≥0.04 second in ≥2 contiguous leads on standard electrocardiography, accompanied by an increase in creatine kinase-MB isoenzyme above the upper limit of normal. A non–Q-wave myocardial infarction was defined as an increase in creatine kinase-MB isoenzyme in the absence of new pathologic Q waves on standard electrocardiography. Major vascular complications included retroperitoneal hematoma, vascular access hematoma >4 cm, and pseudoaneurysms or arteriovenous fistula requiring surgery or ultrasonographically guided compression. A major bleeding complication was defined as any procedure-related bleeding episode requiring transfusion. Target lesion revascularization was defined as repeated emergency or elective percutaneous coronary intervention or emergency or elective coronary artery bypass grafting performed because of ST or restenosis of the target lesion in association with angina and/or objective evidence of myocardial ischemia.

Percutaneous coronary intervention: Standard techniques were used. Lesion predilation with conventional undersized balloon catheters was recommended but not requested. Coronary stenting using a CarboStent (Sorin Group, Saluggia, Italy) 9, 15, or 25 mm in length was mandatory for all patients enrolled in the trial. This stent has 2 main features: an innovative closed-cell design, conceived to decrease stress concentration and elastic distortion of the stent and underlying vessel wall, and an integral and permanent coating (0.3 to 0.5 μm) of pure carbon (Carbofilm) characterized by a polycrystalline structure virtually identical to that of pyrolytic carbon used in heart valve compo-

Table 3
Baseline angiographic characteristics

	Aspirin Alone (n = 235)	Aspirin + Ticlopidine/ Clopidogrel (n = 244)	p Value
Coronary artery disease extension			
Single vessel	146 (62%)	155 (64%)	0.66
Multivessel	89 (38%)	87 (36%)	0.66
Target vessel			
No. of lesions	289	309	
Left anterior descending coronary artery	119 (42%)	128 (43%)	0.85
Left circumflex coronary artery	72 (25%)	78 (26%)	0.85
Right coronary artery	93 (33%)	94 (31%)	0.71
Target lesion			
De novo	282 (99%)	302 (99%)	0.68
Restenotic	3 (1%)	2 (1%)	0.68
Ostial	7 (2%)	13 (4%)	0.21
Bifurcation	24 (8%)	26 (9%)	0.89
Concentric	145 (51%)	163 (53%)	0.53
Eccentric	141 (49%)	142 (47%)	0.53
Calcification	36 (12%)	37 (12%)	0.91
Tortuosity	41 (14%)	35 (12%)	0.34
ACC/AHA lesion type			
A	43 (16)	60 (21)	0.14
B1	142 (55)	143 (51)	0.43
B2	57 (22)	62 (22)	0.93
C	18 (7)	14 (5)	0.35

ACC/AHA = American College of Cardiology/American Heart Association.

Table 4
Procedural characteristics

Variable	Aspirin Alone (n = 235)	Aspirin + Ticlopidine/ Clopidogrel (n = 244)	p Value
No. of vessels treated			
1	207 (88%)	205 (84%)	0.20
2	26 (11%)	37 (15%)	0.18
3	2 (1%)	2 (1%)	0.10
No. of lesions treated			
1	191 (81%)	192 (78%)	0.41
2	34 (14%)	41 (17%)	0.48
3	10 (4%)	12 (5%)	0.73
Direct stenting	136 (48%)	133 (45%)	0.50
No. of stents/patient	1.26	1.26	
No. of stents/lesion	1.02	0.99	
Total stent length/patient (mm)	18.8	18.4	
Total stent length/lesion (mm)	15.3	14.5	
Postdilation	53 (18%)	61 (21%)	0.43
Final balloon size (mm)			
Mean ± SD	3.5 ± 0.6	3.38 ± 0.67	0.48
Range	2.0–4.5	1.0–5.0	
Maximum inflation pressure (atm)			
Mean ± SD	14.7 ± 3.2	13.7 ± 3.2	0.08
Range	8–24	6–20	
Dissection after stenting	3.9% (11/281)	4.2% (12/284)	0.85
Glycoprotein IIb/IIIa receptor antagonists			
Abciximab	3.4% (8/235)	5.3% (13/244)	0.3040
Eptifibatide	4.3% (10/235)	2.5% (6/244)	0.2741
Tirofiban	3.4% (8/235)	3.7% (9/244)	0.8665

nents.[1,3] After stent deployment, further dilatation was performed with short and low-compliance balloons at >12 atm. To meet the criteria of optimal stent implantation required for patient randomization, a residual stenosis <10% with a TIMI grade 3 flow had to be achieved by visual estimate, without evidence of dissection or thrombus proximal, distal, or within the stented segment on the final angiogram.

Antithrombotic and antiplatelet regimens: Aspirin 325 mg was begun 12 hours before percutaneous coronary intervention in all patients and continued indefinitely. Heparin was administered in the catheterization laboratory only, in intravenous boluses to maintain an activated clotting time >250 seconds for the duration of the procedure. Use of platelet glycoprotein IIb/IIIa receptor antagonists was allowed at the discretion of the operators. In patients assigned to combined antiplatelet therapy, ticlopidine 250 mg 2 times/day was begun immediately after the procedure and continued for 1 month. Alternatively, a loading dose of clopidogrel 300 mg was administered immediately after the procedure followed by 75 mg/day for 1 month. By protocol, ticlopidine or clopidogrel had to be withdrawn 5 days before the index procedure in those patients pretreated with these drugs (Table 1).

Data collection and analysis: At each site, the clinical coordinator, monitored by independent study monitors, completed a detailed case-report form for each enrolled patient and submitted it to the data coordinating center. A 12-lead electrocardiogram was obtained before the procedure, 24 hours later, or at discharge within 24 hours and in case of clinical symptoms suggesting myocardial ischemia. Cardiac enzymes (creatine kinase and creatine kinase-MB isoenzyme) were evaluated before the procedure and 2 times at 6 and 12 hours after the procedure. Study patients were clinically assessed for the occurrence of adverse events at discharge and 1 and 6 months later by an outpatient visit, at which time a physical examination was performed and electrocardiogram obtained. Repeat coronary angiograms were obtained on clinical indication, e.g., recurrence of angina or positive cardiac scintigraphic finding. The independent clinical events committee classified all events.

Statistical analysis: This trial tested the equivalence between "aspirin alone" treatment and an "aspirin plus ticlopidine or clopidogrel" antiplatelet regimen in the incidence of the primary end point. In previous studies with bare metal stents, the incidence of ST using aspirin and ticlopidine or clopidogrel was 0% to 1.5%. Based on these estimates, the sample size was obtained by assuming a ST incidence in the standard treatment (i.e., aspirin plus ticlopidine or clopidogrel) group equal to 0.3% and a clinical equivalence tolerability range equal to 1.2 percentage points. From the clinical viewpoint, it meant that the "true" difference in ST incidence between the 2 groups would be <1.2%. Aiming

Table 5
Primary and secondary end points

	Aspirin Alone	Aspirin + Ticlopidine/Clopidogrel	p Value	RR (95% CI)
ST				
No. of patients	235	244		
Excluding protocol deviations				
Acute	0	0	—	—
Subacute	0	0	—	—
Including protocol deviations				
Acute	2† (0.7%)	1* (0.32%)	0.61	0.47 (0.04–5.17)
Subacute	2‡ (0.7%)	0	0.23	—
Total	4 (1.4%)	1 (0.3%)	0.20	0.23 (0.03–2.08)
MACEs				
No. of patients	191	195		
Cardiac death	0	0	—	—
Myocardial infarction	0	1 (0.5%)	1.00	1.00 (0.99–1.02)
Target lesion revascularization	7 (4%)	15 (8%)	0.09	2.19 (0.87–5.50)
Coronary bypass	0	1 (0.5%)	1.00	1.00 (0.99–1.02)
Repeat angioplasty	4 (2%)	13 (7)	0.04	3.32 (1.07–10.43)
Repeat angioplasty + stent	3 (2%)	1 (0.5%)	0.37	0.32 (0.03–3.13)
Total	7 (4%)	16 (8%)	0.06	2.35 (0.94–5.85)

* Suboptimal result.
† Reference vessel diameter <2.5 mm and reprocedural thrombus.
‡ Reference vessel diameter <2.5 mm and severe calcification in addition to suboptimal result and edge dissection.
CI = confidence interval; MACEs = major adverse cardiac events; RR = relative risk.

for 80% power and 5% 1-sided α level, a total of 480 patients was required. Categorical variables are presented as percentages (number of cases/number of total cases per group) and compared by chi-square test or Fisher's exact test; continuous variables are expressed as mean ± SD and compared with Student's *t* test or Wilcoxon 2-sample test. Analysis included all baseline clinical and angiographic features, treatment assignment, and procedural variables. Differences were considered statistically significant when the p value was <0.05. All p values were 2-sided. Data were analyzed with SAS 8.2 (SAS Institute, Cary, North Carolina).

Results

A total of 479 patients (83% men, mean age 62 ± 10 years) with 598 coronary lesions were enrolled in this trial. No patient was excluded after randomization. In total, 235 patients were assigned to receive aspirin alone and 244 patients were assigned to receive aspirin and a thienopyridine (ticlopidine or clopidogrel). Baseline clinical, angiographic, and procedural characteristics were similar in the 2 groups and are presented in Tables 2 to 4. Single-vessel disease was present in 301 patients (63%), and 176 patients (37%) had multivessel disease. After careful review, 89 patients (19%) with protocol deviations were identified. Of these, 44 were randomized to the aspirin regimen and 45 to the aspirin-plus-ticlopidine or clopidogrel treatment. Five patients (2.1%) in the aspirin-alone group had >1 protocol deviation, whereas 4 (1.6%) in the aspirin-plus-ticlopidine or clopidogrel group had >1 protocol deviation. All patients with protocol deviations were included in the primary analysis.

The overall incidence of acute and subacute ST was 1% (5 of 479 patients), including protocol deviations. When protocol deviations were excluded from analysis, no ST was observed in either group. Coronary angiography confirmed ST in all these patients. Primary and secondary end points and relative risk in the 2 groups are presented in Table 5. ST occurred in 4 (1.4%) coronary vessels of the aspirin-only group and in 1 (0.3%) coronary vessel of the aspirin-plus-ticlopidine or clopidogrel group (p = NS). The relative risk of ST in the group assigned to aspirin alone was 0.23 (95% confidence interval 0.03 to 2.08, p = NS) compared with the risk in the group assigned to aspirin plus ticlopidine or clopidogrel. At 30 days, no significant difference in the incidence of major vascular or bleeding complications was observed with either antiplatelet treatment. At 6 months, major adverse cardiac events were 4% and 8% in the aspirin-alone group and aspirin-plus-ticlopidine or clopidogrel group, respectively (RR 2.35, 95% confidence interval 0.94 to 5.85, p = NS), and were due to target lesion revascularization only (Table 5).

Discussion

In the present study, the observed rate of 30-day ST was 0% in the 2 groups when protocol deviations were excluded. Although a trend in favor of the combined antiplatelet therapy was observed when patients with protocol deviations, which were mainly angiographic, were included in the analysis, the rate of the primary end point was low and without significant difference between the 2 regimens. These results indicate the feasibility and safety of the aspirin-alone regimen in patients treated with the CarboStent, particularly in those in whom the angiographic criteria for optimal stent implantation used in this trial are applied. These findings have important clinical implications in certain patient subgroups. After coronary stenting, bleeding risk in thienopyridine-treated patients who undergo cardiac or noncardiac surgery is substantial. In contrast, antiplatelet

therapy decrease or withdrawal in the first weeks after coronary stenting greatly increases the likelihood of ST and associated catastrophic outcome.[4,5] Although elective surgery can be delayed after stenting, a clinical dilemma is present when surgery is semi-elective or an emergency and preoperative treatment of coronary artery disease is indicated to decrease perioperative morbidity and mortality, particularly in patients with acute coronary syndromes. Moreover, patients who require coronary stent implantation and are under long-term oral anticoagulation, such as those with mechanical heart valves, long-term atrial fibrillation, venous thromboembolism, or post-myocardial infarction left ventricular thrombus, pose another serious problem to clinicians.[6] They represent 2% to 3% of those undergoing percutaneous coronary intervention, and this percentage will likely increase due to patient aging and increased stent use.[7] This is a clinical condition in which an aspirin-alone regimen after coronary implantation of a less thrombogenic stent may decrease the threat of bleeding imposed by the addition of a dual antiplatelet therapy to systemic anticoagulation. Marked individual variability in response to clopidogrel and resistance to this drug have been observed.[8] Although a direct correlation between ST and clopidogrel resistance is not conclusive evidence, nonresponders may be at increased risk.[9] They may therefore benefit from a less thrombogenic stent. It is interesting to note that the aforementioned clinical conditions may pose a more serious threat to patients treated with drug-eluting stents and may be contraindications to their use. Due to the inherent delayed endothelization,[10] drug-eluting stents require prolongation of combined antiplatelet therapy and have significantly expanded the thrombotic hazard "window" compared with bare metal stents in case of antiplatelet discontinuation.

Exclusion of patients who did not meet the prespecified clinical and angiographic inclusion criteria and criteria of optimal stent implantation does not allow easy transfer of the results of this trial to a real-world stenting and everyday practice. However, it should be noted that the overall ST rate was low and did not differ significantly between the 2 antiplatelet regimens, although a sizeable proportion (19%) of patients enrolled in the trial and included in the primary analysis had protocol deviations. Moreover, because ST has a very low incidence, the number of patients enrolled in this trial may be not enough to fully establish equivalence between aspirin alone and a combination of aspirin and a thienopyridine after intracoronary implantation of the CarboStent.

Appendix

The following institutions and investigators participated in the SAFE study: Azienda Ospedaliera Ferrarotto, Catania: C. Tamburino, A. Galassi (82 patients); Centro Cardiologico Monzino, Institute of Cardiology, University of Milan, Milan: A.L. Bartorelli, D. Trabattoni, P. Montorsi, F. Fabbiocchi, P. Ravagnani, S. Galli (70 patients); Ospedale S. Pietro FBF, Rome: R. Serdoz (62 patients); Ospedale Sant'Annunziata, Chieti: M. Zimarino, A Maggi (54 patients); Ospedale San Raffaele, Milan: C. Di Mario (54 patients); Ospedale San Giovanni Battista—Cardiologia Universitaria, Torino: I. Sheiban (33 patients); Ospedale degli Infermi, Rimini: G. Piovaccari (26 patients); Ospedale Maggiore, Bologna: P. Sangiorgio (26 patients); Ospedale San Martino, Genova: S. Chierchia (25 patients); Centro Cuore Columbus, Milan: A. Colombo (23 patients); Hesperia Hospital, Modena: A. Benassi (20 patients); Ospedale di Mirano, Mirano: B. Reimers, S. Saccà (4 patients).

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