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FOCUS ISSUE: DRUG-ELUTING STENTS

Two-Year Clinical Follow-Up After Sirolimus-Eluting Versus Bare-Metal Stent Implantation Assisted by Systematic Glycoprotein IIb/IIIa Inhibitor Infusion in Patients With Myocardial Infarction

Results From the STRATEGY Study

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Objectives We sought to investigate whether the previously reported midterm clinical benefit of planned sirolimus-eluting stent (SES) implantation in patients with ST-segment elevation myocardial infarction (STEMI) was maintained over a 24-month time period. Moreover, the distribution of clinical events in relation to thienopyridine discontinuation was thoroughly investigated.

Background No randomized data are currently available on the safety/benefit profile of SES in this subset of patients beyond 12 months.

Methods Between March 2003 and April 2004, 175 patients with STEMI were randomly allocated to tirofiban infusion followed by SES or abciximab plus bare-metal stent (BMS). Complete follow-up information up to 720 days was available for all patients.

Results The cumulative incidence of death, myocardial infarction (MI), or target vessel revascularization (TVR) remained lower in the tirofiban-SES compared with the abciximab-BMS group at 2 years (24.2% vs. 38.6%, respectively; hazard ratio [HR] 0.56 [95% confidence interval (CI) 0.33 to 0.98]; p = 0.038). The composite of death/MI was similar in the tirofiban-SES (16.1%) and the abciximab-BMS groups (20.5%, HR 0.77 [95% CI 0.38 to 1.55]; p = 0.43) while the need for TVR was markedly reduced (9.8% vs. 25.5%, respectively; HR 0.34 [95% CI 0.16 to 0.77]; p = 0.01) in the tirofiban-SES arm. The rate of confirmed, probable, or possible stent thrombosis did not differ in the 2 groups, nor the incidence of death/MI after thienopyridine discontinuation.

Conclusions The midterm clinical benefit of planned SES implantation assisted by tirofiban infusion in STEMI patients was mainly carried over after 2 years with no overall excess of late adverse events after thienopyridine discontinuation. (J Am Coll Cardiol 2007;50:138–45) © 2007 by the American College of Cardiology Foundation

There are growing concerns as to the possibility that the safety and clinical benefit of drug-eluting stent (DES) implantation may not be sustained over time, especially when unselected patient/lesion subsets have been treated (1–3).

While the available clinical follow-up of the pivotal trials that led to the approval of the sirolimus-eluting (SES) or paclitaxel-eluting stent in Europe and the U.S. failed to show an increase in adverse events in patients treated with DES (4–8), a rising amount of reports describe the occurrence of late stent thrombosis (ST) (9–13) or even restenosis (14,15) after the conventional 8- to 12-month follow-up in a probably small but still undefined proportion of patients. Thus, long-term clinical surveillance, especially of high-risk patients after DES implantation, is particularly warranted.

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In the recently published PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recov-

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ery) registry (13), specific concerns were raised regarding the unrestricted use of DES in patients with ST-segment elevation myocardial infarction (STEMI), where compliance to long-term treatment with thienopyridines cannot be determined up front. In the first randomized trial to evaluate the benefit of DES assisted by glycoprotein IIb/IIIa infusion in STEMI patients, a clinical benefit in terms of reintervention in the previously instrumented artery has been reported at 8 months in the group assigned to SES (16). Consistent information has been more recently reported by the industry-driven TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty) study at 1 year (17). No randomized data are currently available on the safety/benefit profile of SES in this subset of patients at longer-term follow-up. We sought to investigate whether the midterm clinical benefit of planned SES implantation observed in the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus Eluting Stent Versus Abciximab and Bare Metal Stent In Acute Myocardial Infarction) trial was maintained over a 24-month time period. Moreover, the distribution of clinical events in relation to thienopyridine discontinuation was thoroughly investigated.

Abbreviations and Acronyms

BMS = bare-metal stent
CI = confidence interval
DES = drug-eluting stent
HR = hazard ratio
MACE = major adverse cardiovascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PHM = proportional hazards model
SES = sirolimus-eluting stent
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization

Methods

Study design and medications. The design of the study has been previously reported (16,18). Briefly, patients with STEMI were randomly assigned before obtaining initial angiogram to single high-dose bolus tirofiban infusion (25 μg/kg/3 min and 0.15 μg/kg/min for 18 to 24 h) followed by SES implantation or abciximab (bolus of 0.25 μg/kg/3 min with 0.125 μg/kg/min for 12 h) and bare-metal stent (BMS) implantation. All patients received aspirin (250 mg intravenous followed by 100 mg/day), clopidogrel (300 mg followed by 75 mg/day), and heparin (50 to 70 U/kg with additional bolus if necessary) according to current guidelines.

Study population and end points definition. Between March 6, 2003 and April 23, 2004, 175 patients with STEMI were included. Three patients in the tirofiban-SES group and 5 in the abciximab-BMS group did not undergo percutaneous coronary intervention (PCI). Overall, 74 (85%) patients in the tirofiban-SES and 77 (88%) in the abciximab-BMS arm received the protocol-mandated treatment combination. Patients were considered for 6-month angiographic follow-up if protocol-mandated PCI had been attempted. The primary end point was freedom, at 8 months after randomization, from death, nonfatal myocardial infarction (MI), stroke, and binary restenosis. Patients were scheduled to undergo clinical follow-up at 30 days and then every 6 months from enrollment. The 2-year analysis was prespecified per the protocol; follow-up information was planned to be collected every year until 5 after randomization. All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. A definite diagnosis of MI after normalization of cardiac markers was made if there was documentation of new abnormal Q waves (according to the Minnesota code) or a confirmed elevation above upper limit of normal of creatine kinase/creatine kinase-MB or troponin I or T in at least 1 blood sample.

A *definite* ST was considered to have occurred based on: 1) an angiographic documentation of target vessel occlusion or both reduced Thrombolysis in Myocardial Infarction flow and the presence of thrombus in the stented region coupled with at least one of the following: a) new acute onset of ischemic symptoms at rest; b) new ischemic electrocardiogram changes suggestive of acute ischemia; or c) typical rise and fall in cardiac biomarkers; or 2) evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved after thrombectomy.

Probable ST was defined as any unexplained death within the first 30 days or any MI with evidence of acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

Possible ST was considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Unlike previous definitions (8), freedom from interim target vessel revascularization (TVR) was not a prerequisite for satisfying the diagnosis of confirmed or possible ST. This employed broad definition of ST is post hoc and in keeping with recently proposed Academic Research Consortium classification (19).

Statistical analysis. All analyses were conducted according to the intention-to-treat principle when not otherwise stated. Discrete data were summarized as frequencies, whereas continuous data were expressed as mean ± SD. Fisher exact test (categorical variables) and Student *t* test (continuous variables) were employed to analyze differences between the 2 study arms. Event-free survival curves were generated by the Kaplan-Meier method, and survival between groups was compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a proportional hazards model (PHM).

The proportionality assumptions for PHM were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after index procedure and by applying a test for nonproportional hazards using the Schoenfeld residuals as previously described (20). Moreover,

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to formally investigate the relation of thienopyridine discontinuation to events, we performed a multivariable PHM including treatment with ticlopidine or clopidogrel as a time-dependent variable. A 2-sided p value <0.05 was considered significant for all tests. All analyses were performed using STATISTICA version 6.1 (Statsoft Inc., Tulsa, Oklahoma) or R-language (R Foundation, Vienna, Austria).

Results

As previously reported, both groups had similar baseline clinical and angiographic characteristics, procedural factors, with the only exception of a smaller nominal stent diameter in the SES group, and 30-day results. Complete follow-up information up to 720 days was available for all patients.

As compared with the previously reported clinical events at 8 months, we observed 13 new major adverse cardiovascular event (MACE) episodes, 6 of which occurred in patients assigned to receive tirofiban + SES. In this group, 3 additional patients died, 2 of them from cancer and 1 from fatal reinfarction, 1 patient had a nonfatal reinfarction, and 2 patients underwent coronary artery bypass grafting for angiographically confirmed disease progression at coronary sites distant from the previously stented segments. In the group allocated to abciximab and bare-metal stenting, 4 additional patients died, 2 from cancer, 1 from fatal pulmonary infection, and 1 due to sudden death, and 3 patients underwent TVR for angiographically confirmed disease progression in 1 case and for stent reocclusion in 2 patients who had previously refused to undergo 6-month angiographic follow-up.

The cumulative incidence of MACE (death, MI, or TVR) remained lower in the tirofiban-SES compared with the abciximab-BMS group at 2 years (24.2% vs. 38.6%, respectively; HR 0.56 [95% CI 0.33 to 0.98]; p = 0.038) (Fig. 1A, Table 1). Overall, the composite of death/MI was similar in the tirofiban-SES (16.1%) and the abciximab-BMS group (20.5%, HR 0.77 [95% CI 0.38 to 1.55]; p = 0.43) (Fig. 1B, Table 1), while the need for TVR remained markedly reduced (9.8% vs. 25.5%, respectively; HR 0.34 [95% CI 0.16 to 0.77]; p = 0.01) in the tirofiban-SES group (Fig. 1C, Table 1).

Within 30 days, 2 definite, angiographically confirmed ST occurred, both in the abciximab + BMS group. In one of the patients, who suffered from diabetes, a SES had been implanted as a protocol violation. Between 30 and 720 days, there were no cases of definite ST, while probable ST occurred in 1 patient in the tirofiban + SES (1.1%) and in 2 cases in the abciximab + BMS (2.2%) group. There were 2 additional episodes of possible ST in each group (Table 2). Thus, the cumulative incidence of definite, probable, or possible ST were 0%, 1.1%, and 2.2% in the tirofiban + SES arm versus 2.2% (p = 0.49), 2.2% (p > 0.99), and 2.2% (p > 0.99) in the abciximab + BMS group, respectively (Tables 1 and 2).

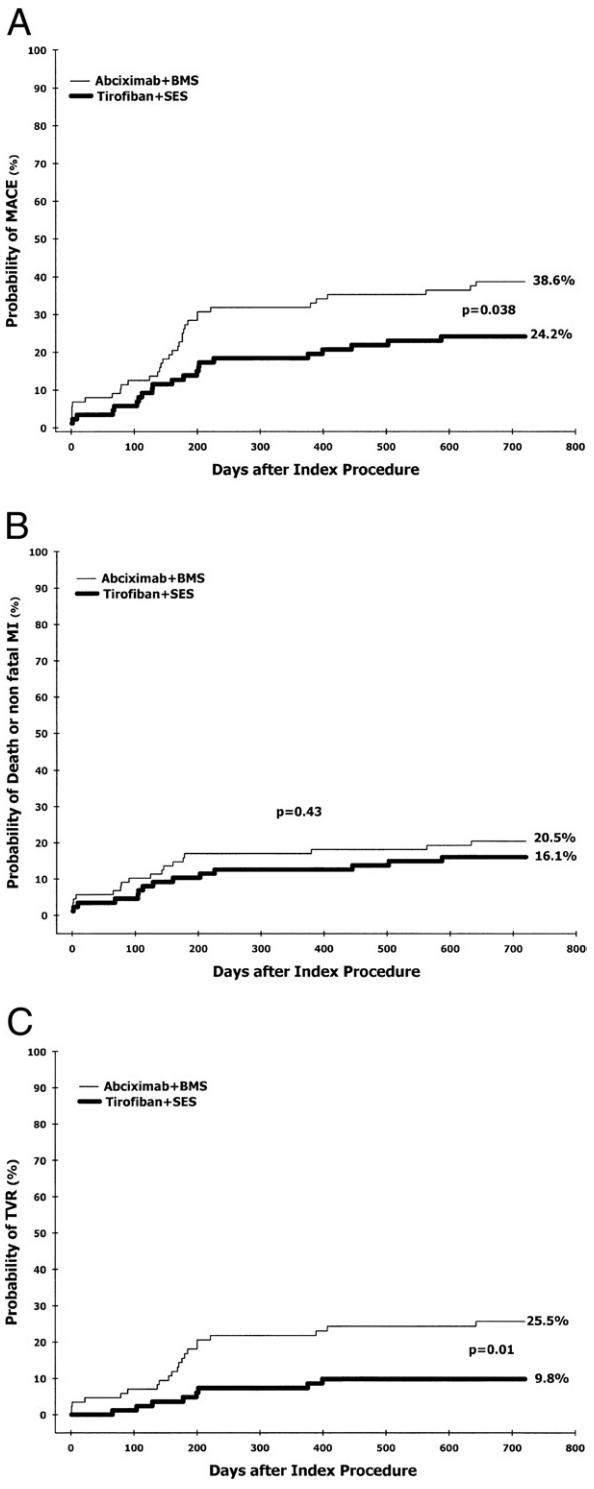

Figure 1 Event-Free Survival After Randomization

Two-year adverse events in patients allocated to tirofiban + sirolimus-eluting stent (tirofiban + sirolimus-eluting stent [SES] group) and in patients randomized to abciximab infusion plus bare-metal stenting (abciximab + bare-metal stent [BMS] group). Cumulative risk of major adverse events **(A)**, death or myocardial infarction **(B)**, and target vessel revascularization **(C)**.

Table 1 30-Day, 12- and 24-Month Outcome

Variables	Abciximab BMS (n = 88)	SHDB Tirofiban SES (n = 87)	HR (95% CI)	p Value*
30-day outcome, n (%)				
Death	3 (3)	2 (2)	—	>0.99
Re-AMI	3 (3)	1 (1)	—	0.62
Urgent TVR	3 (3)	1 (1)	—	0.62
CVA	0 (0)	0 (0)	—	>0.99
Stent thrombosis†	2 (2)	0 (0)	—	0.24
Death/re-AMI	6 (7)	3 (3)	—	0.49
Death/re-AMI/urgent TVR	7 (8)	3 (3)	—	0.33
12-month outcome, n (%)				
Death	8 (9)	7 (8)	HR 0.77 [95% CI: 0.29–2.1]	0.59
Re-AMI	8 (9)	6 (7)	HR 0.75 [95% CI: 0.26–2.22]	0.60
TVR	18 (20)	6 (7)	HR 0.30 [95% CI: 0.12–0.77]	0.01
Definite stent thrombosis†	2 (2)	0 (0)	—	0.24
Probable stent thrombosis	2 (2)	1 (1)	—	>0.99
Possible stent thrombosis	1 (1)	2 (2)	—	>0.99
Any stent thrombosis	5 (6)	3 (3)	0.63 [95% CI: 0.15–2.5]	0.50
Death/re-AMI	15 (17)	11 (13)	0.71 [95% CI: 0.34–1.5]	0.39
Death/re-AMI/TVR	28 (32)	16 (18)	HR 0.53 [95% CI: 0.28–0.92]	0.04
24-month outcome, n (%)				
Death	12 (14)	10 (11)	HR 0.84 [95% CI: 0.36–1.96]	0.66
Re-AMI	8 (9)	7 (8)	HR 0.82 [95% CI: 0.31–2.4]	0.77
TVR	21 (24)	8 (9)	HR 0.34 [95% CI: 0.16–0.77]	0.01
Stroke	0 (0)	0 (0)	—	>0.99
Definite stent thrombosis†	2 (2)	0 (0)	—	0.49
Probable stent thrombosis	2 (2)	1 (1)	—	>0.99
Possible stent thrombosis	2 (2)	2 (2)	—	>0.99
Any stent thrombosis	6 (7)	3 (3)	0.51 [95% CI: 0.13–2.1]	0.34
Death/re-AMI	18 (20)	14 (16)	HR 0.77 [95% CI: 0.38–1.55]	0.56
Death/re-AMI/TVR	34 (39)	21 (24)	HR 0.56 [95% CI: 0.33–0.98]	0.038
Death/re-AMI/CVA/restenosis	41 (46)	21 (24)	—	0.002

*By Fisher exact test for 30-day outcomes and for stent thrombosis or composite end points including binary restenosis and by Cox regression analysis for remaining 12- and 24-month events; †both episodes were angiographically confirmed.

BMS = bare-metal stent; CI = confidence interval; CVA = cerebrovascular accident; HR = hazard ratio; re-AMI = reinfarction; SES = sirolimus-eluting stent; SHBD = single high bolus dose; TVR = target vessel revascularisation.

At per-protocol analysis, after exclusion of those patients where protocol violations took place, the overall incidence of definite, probable, or possible ST was 4% in the tirofiban + SES versus 5.2% in the abciximab + BMS group ($p > 0.99$).

At per-stent analysis, the cumulative incidence of definite, probable, or possible ST was 6.6% versus 4.8% ($p = 0.44$) in the SES and BMS groups, respectively.

The mean duration of dual antiplatelet treatment (either clopidogrel or ticlopidine and aspirin) was 182 ± 92 days in the tirofiban + SES versus 155 ± 105 days in the abciximab + BMS group ($p = 0.073$). The multivariable proportional hazard model including dual antiplatelet treatment as time-dependent variable showed only a trend for the use of thienopyridines to be protective with respect to major cardiac adverse events at follow-up (HR 0.74 [95% CI 0.36 to 1.53]; $p = 0.42$).

When the cumulative incidence of death or nonfatal MI was compared between the 2 groups starting from the time of thienopyridine discontinuation, the event rate was again similar in the tirofiban + SES (7.7%) versus the abciximab + BMS group at 2 years (7%, HR 1.07 [95% CI 0.33 to 3.57]; $p = 0.90$) (Fig. 2). It is noteworthy that 4 events per group clustered within 30 days of therapy discontinuation.

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Table 2 Clinical and Procedural Characteristics of Patients With Confirmed or Possible Stent Thrombosis Up to 2 Year Follow-Up

	Confirmed or Suspected Stent Thrombosis								
	(Sub)acute		Late						
Patient No.	#22	#174	#115	#15	#105	#78	#54	#35	#57
Age, yrs	64	57	82	65	81	68	80	32	72
Gender	M	M	M	M	F	M	F	M	M
Diabetes	Yes	No	No	No	Yes	No	No	No	No
Previous MI	No	No	No	No	Yes	No	No	Yes	No
Creatinine clearance (ml/min)	64.2	91.3	37.2	82.3	53	57.6	33.3	61.7	48.7
IRA	LAD	RCA	RCA	CFX	RCA	LAD	CFX	LAD	LAD
Killip	I	I	III	I	I	III	I	I	I
Randomization arm	Ab-BMS	Ab-BMS	Tir-SES	Tir-SES	Tir-SES	Ab-BMS	Ab-BMS	Ab-BMS	Ab-BMS
GP IIb/IIIa inhibitor received	Abciximab	Abciximab	Tirofiban	Tirofiban	Tirofiban	Abciximab	Abciximab	Abciximab	Abciximab
Implanted stent type/n	SES/1	BMS/1	SES/1	SES/1	SES/2	BMS/2	BMS/1	SES/1	BMS/1
Stent diameter	2.25	2.5	2.5	3.0	3.0	3.0	3.0	3.0	2.5
Total stent length, mm	23	23	16	18	40	23	13	28	23
Days after index procedure	1	1	68	112	128	142	145	176	512
Clinical presentation	Re-AMI	ACS	SD	SD	Re-AMI/D	SD	Re-AMI	Re-AMI/D	SD
ARC stent thrombosis classification	Definite	Definite	Possible	Possible	Probable	Possible	Probable	Probable	Possible
On thienopiridine*/type	Yes/Clo	Yes/Clo	No	No	No	No	No	Yes/Clo	No
Previous TLR	No	No	No	No	No	No	No	No	Yes†
LVEF at discharge (%)	43	46	40	40	30	32	45	40	40
QCA post-PCI									
RVD (mm)	2.20	2.23	2.50	2.18	2.44	2.69	2.50	3.08	2.6
MLD (mm)	1.9	2.18	2.50	1.90	1.99	2.50	2.23	2.34	1.93
Vessel stenosis (%)	26	3	0	13	18	6	11	24	26
QCA at follow-up									
RVD (mm)	2.22	2.23	—	—	—	—	—	—	2.32
MLD (mm)	0	0.02	—	—	—	—	—	—	0.02
Vessel stenosis (%)	100	98	—	—	—	—	—	—	99
Late loss (mm)	1.9	2.16	—	—	—	—	—	—	1.91

*Whether the patient was taking thienopyridines at the time of the event; †2 additional BMS were deployed during TLR.

Ab-BMS = abciximab bare-metal stent; ACS = acute coronary syndrome; ARC = Academic Research Consortium; Clo = clopidogrel; D = death; GP = glycoprotein; IRA = infarct-related artery; LAD = left anterior descending; LVEF = left ventricular ejection fraction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; QCA = quantitative coronary analysis; RVD = reference vessel diameter; SA = stable angina; SD = sudden death; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; Ticlo = ticlopidine; Tir = tirofiban; TLR = target lesion revascularisation; UA = unstable angina followed by Braunwald classification; other abbreviations as in Table 1.

Discussion

While the risk of ST after BMS decreases rapidly after 2 to 4 weeks, delayed endothelial coverage, endothelial dysfunction, and positive vessel remodeling are thought to prolong the window of vulnerability to acute, subacute, or late thrombotic stent closure after DES implantation. Consequently, recommendations for currently approved DES include a minimum of 3 to 6 months of thienopyridine therapy, in addition to long-term aspirin use.

After the pivotal reports describing the occurrence of late ST after DES implantation, especially in the setting of cessation of antiplatelet therapy (9,12), consistent findings have been echoed by several different groups (1,3), raising a note of caution regarding the safety/efficacy profile of this new coronary technology when employed in unselected patient/lesion subsets. More recently, the BASKET-LATE (Basel Stent Cost-Effectiveness Trial—Late Thrombotic Events) trial reported a trend towards an increase of death or nonfatal MI in patients treated with DES after thienopyridine discontinuation as compared with the BMS group (11), and 2 meta-analyses suggested a time-dependent increase either in noncardiac mortality (21) or the composite of total mortality and Q-wave MI in patients treated with SES compared with BMS (22).

While subject to an ongoing intense debate, current data emphasize, however, the need to scrutinize long-term outcome of all randomized controlled trials of DES versus BMS, especially for those complex lesion/patient subsets that were originally excluded from pivotal studies. This may help avoid negatively selecting those studies where no excess of late events is observed (23). Several registries have reported that DES deployment for ongoing MI or acute coronary syndrome at presentation is associated with an increased risk of overall ST, especially if complex coronary lesions such as bifurcations are being treated (24,25). This evidence should be interpreted bearing in mind that the risk for early (acute and subacute) ST is also known to be increased when BMS are implanted in such conditions (26). Accordingly, results from randomized controlled trials comparing DES (either SES or paclitaxel-eluting stents) versus

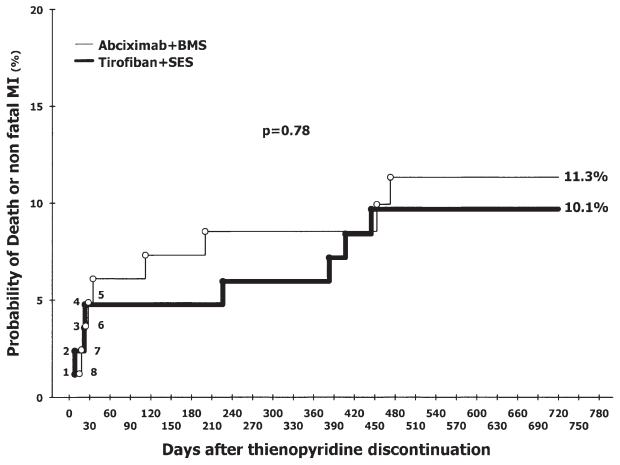

Figure 2 **Event-Free Survival After Thienopyridine Discontinuation**

Cumulative risk of death or nonfatal myocardial infarction after thienopyridine discontinuation in patients either allocated to receive tirofiban + SES or abciximab + BMS. **(1)** Patient #115 experienced a sudden death at home 8 days after ticlopidine discontinuation. **(2)** Patient #105 presented 8 days after clopidogrel discontinuation at emergency department with typical chest pain, cardiogenic shock, and new-onset left bundle branch block. The patient died immediately after admission, before a diagnostic coronary angiogram could be obtained. **(3)** Patient #15 died suddenly at home 22 days after clopidogrel discontinuation. **(4)** Patient #165 died 23 days after ticlopidine discontinuation from gastric cancer. **(5)** Patient #42 had a reinfarction 28 days after clopidogrel discontinuation due to an angiographically confirmed disease progression in the first obtuse marginal branch (the patient underwent intervention in the left anterior descending artery at the time of index event). **(6)** Patient #45 was a 78-year-old male with a history of anterior infarction who was treated at the time of the index procedure for a proximal occlusion of a dominant circumflex artery who died due to end-stage heart failure 24 days after ticlopidine discontinuation. **(7)** Patient #94 died 18 days after clopidogrel discontinuation due to chronic obstructive pulmonary disease. **(8)** Patient #54 experienced non–Q-wave lateral myocardial infarction 15 days after clopidogrel discontinuation. The patient received treatment at the circumflex artery at the time of the index procedure and refused recatheterization. Abbreviations as in Figure 1.

BMS during primary PCI unanimously failed to show an excess of ST in the DES arm within 1 year (16,17,27,28). Whether the use of DES during acute MI puts the patient at increased risk for the occurrence of late ST is unclear. Stent malapposition occurs more frequently during intervention for acute MI. Similarly, thrombus apposed on stents creates large variations in drug uptake and can act to either increase or decrease wall deposition according to the clot and stent geometry (29).

Thus, current data strongly suggest that long-term follow-up is needed particularly in this patient/lesion subset to rule out the possibility of late increase in adverse events in patients treated with DES.

In the first study to evaluate the benefit of SES assisted by glycoprotein IIb/IIIa infusion in STEMI patients, a clinical benefit in terms of reintervention in the previously instrumented artery has been reported at 8 months with no excess of subacute or late ST compared with BMS (16). In this study thienopyridine therapy was recommended for at least 3 months, yet the median treatment duration was around 6 months in both groups. This likely reflects uncertainties in the medical community regarding optimal duration of long-term dual antiplatelet treatment after an episode of myocardial ischemia requiring coronary stenting (30). Thus, an extended clinical follow-up appears mandatory to collect information on the long-term DES safety profile in STEMI patients, especially after thienopyridine therapy discontinuation.

At 2-year follow-up, the cumulative incidence of MACE remained lower in the tirofiban + SES group, which was largely driven by the different rate of TVR. The rate of death or nonfatal MI was similar in the 2 study groups, and even when applying a broad clinical definition of probable or possible ST we failed to observe a significant excess of events in those patients assigned to receive SES implantation.

On an intention-to-treat basis, the cumulative incidence of any ST (the sum of definite, probable, or possible) trended lower in the tirofiban + SES group (from 6.8% to 3.4%). This finding was counterbalanced by an opposite trend at per-stent analysis, with a cumulative rate of ST of 6.6% in patients who received SES irrespective of the original randomization scheme as compared with 4.8% in the BMS group. No episode of ST occurred in the SES group beyond 1 year. While not prespecified, the results of the per-stent analysis may have been biased by the fact that a shift towards SES may have occurred in particularly complex lesions in the abciximab + BMS arm. Thus, this analysis should be regarded as purely explorative. Indeed, at per-protocol analysis, there was again no signal towards an excess of ST events in the tirofiban + SES arm, which seems consistent with the protocol-mandated intention-to-treat analysis. Thus, our data, while not being conclusive, fail to show a late hazard in the group of patients allocated to receive SES.

In the PREMIER registry reporting on consecutive patients treated for acute MI, premature discontinuation of thienopyridine therapy was frequent and strongly associated with subsequent mortality (13).

In the present study, overall there were 8 events, 4 in each group, in terms of the composite of death or MI, in the first 30 days after thienopyridine therapy discontinuation. Among those, 4 events (Patients #115, #105, #15, and #54) were highly suspected for ST, 3 of which occurred in the tirofiban + SES group whereas the remaining 1 took place in a patient allocated to abciximab + BMS. The remaining 3 deaths (Patients #165, #45, and #94) were related to the expected progression of pre-existing morbidity. After interviewing patients' families, we came to know that therapy discontinuation was due to the impossibility to swallow pills (Patient #165) or spontaneous treatment cessation due to the incoming fatal event (Patients #45 and #94). Thus, in such circumstances, thienopyridine withdrawal should be likely regarded as an effect more than the cause of the pathological disorder that finally led to fatality. Finally, in Patient #42, it remains possible that clopidogrel withdrawal contributed to trigger a nonculprit vessel-related reinfarction.

Our finding that after thienopyridine discontinuation a cluster of events occurred in both groups was unexpected and deserves special attention.

Angiolillo et al. (31) have recently reported a proinflammatory and prothrombotic effect after clopidogrel withdrawal in patients with diabetes after long-term (12 months) dual antiplatelet therapy. Whether this phenomenon occurs also in patients without diabetes is currently unknown. Similarly, whether long-term treatment with thienopyridines makes patients particularly exposed to platelet hyperactivity and, as such, to cardiovascular events after discontinuation is unclear. This may help explain why such a *rebound* phenomenon has never been described in the BMS era where thienopyridines were recommended for much shorter time. At the same time, our analysis also suggests that thienopyridine withdrawal may partly be the consequence more than the cause of conditions in which death is expected. This carries relevant implications for a correct interpretation of all-comer registries, where a detailed analysis of the cause/effect relationship between thienopyridine discontinuation and fatal events cannot be frequently carried out. Finally, while unlikely because our results were highly consistent with previous findings, we cannot exclude that due to the limited sample size of the present study, our findings that a cluster of cardiovascular events occurred soon after dual therapy cessation in both groups may simply reflect a chance finding. Similarly, it remains theoretically possible that our overall findings may be confounded by a type II error. Bigger datasets contrasting long-term outcome after implantation of both Food and Drug Administration-approved DES versus BMS during acute MI are in demand to expand and corroborate our preliminary observations.

Based on available data, it seems reasonable to speculate that taking into consideration whether a dual antiplatelet treatment is still on board or it has been recently discontinued—this may similarly apply to aspirin alone when evaluating very late episodes of possible ST (32)—may help increase the signal-to-noise ratio when a broad clinically driven definition of confirmed or possible ST is employed, as has been recently widely suggested.

Conclusions

At 2-year follow-up, the cumulative incidence of MACE remained lower in the tirofiban + SES group, which was largely driven by the different rate of TVR. The rate of death or nonfatal MI was similar in the 2 study groups, and even applying a broad clinical definition of possible or probable ST, we failed to observe an excess of events in those patients assigned to receive SES implantation. A clear cluster of events among death or nonfatal MI was, however, noted in both groups after thienopyridine discontinuation. In some of the cases (3 in the tirofiban + SES vs. 2 in abciximab + BMS), a causal link between treatment discontinuation and the MACE may be suspected whereas in some others this was reasonably ruled out by interviewing patients' families. Our findings support the need to design randomized controlled studies to evaluate the optimal duration of dual antiplatelet treatment in post-MI patients receiving DES. Markers of early vulnerability to coronary events together with dedicated strategies to avoid the *rebound* phenomenon, if any, after thienopyridine discontinuation should be similarly investigated.

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