INTERVENTIONAL CARDIOLOGY

Maintenance of Long-Term Clinical Benefit With Sirolimus-Eluting Stents in Patients With ST-Segment Elevation Myocardial Infarction

3-Year Results of the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute Myocardial Infarction) Trial

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Objectives   The aim of this study was to investigate whether the reported favorable 1-year outcome of the sirolimus-eluting stent (SES) versus the bare-metal stent (BMS) in the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute Myocardial Infarction) trial, in the setting of ST-segment elevation myocardial infarction (STEMI), is maintained at 3-year follow-up.

Background   At present, only long-term registry data, but not randomized trials, on the safety and effectiveness of SES in STEMI patients are available.

Methods   Overall, 320 STEMI patients were randomized to receive SES or BMS. The primary end point was the incidence of major adverse cardiovascular events (MACE), at 3-year follow-up. The secondary end points were the rate of target lesion revascularization (TLR) and target vessel revascularization (TVR) and target vessel failure (TVF). The incidence of late events, starting from clopidogrel withdrawal, was also investigated.

Results   The 3-year incidence of MACE was lower in the SES group compared with the BMS group (12.7% vs. 21%, $p = 0.034$), as were TLR (7% vs. 13.5%, $p = 0.048$), TVR (8% vs. 16%, $p = 0.027$), and TVF (11.5% vs. 20.5%, $p = 0.028$) rates. The 3-year survival rate free from MACE, TLR, and TVF was significantly higher in the SES group than in the BMS group (87%, 93%, and 89.5% vs. 79%, 86.5%, and 79.5%, respectively, $p < 0.05$). The lower incidence of adverse events in the SES group was driven by TLR reduction and achieved in the first year of follow-up. The cumulative incidence of death and recurrent myocardial infarction, starting from clopidogrel discontinuation, was comparable in the 2 groups.

Conclusions   The clinical benefits of SES have been shown to be greater than those of BMS at 3-year follow-up.   (J Am Coll Cardiol 2010;55:810–4) © 2010 by the American College of Cardiology Foundation

Primary percutaneous coronary intervention (PCI) has become the treatment of choice in patients presenting with ST-segment elevation myocardial infarction (STEMI) (1). Drug-eluting stents (DES) effectively reduce neointimal proliferation with better short- and long-term clinical and angiographic results, and these are as safe as bare-metal stents (BMS) (2–4). However, concerns have been raised regarding the long-term safety and effectiveness of DES implantation in the setting of STEMI (5). Long-term

randomized data in this subgroup of patients have usually been limited to ≤2 years (6–8). The aim of the present analysis was to define whether the favorable effect on clinical outcome, observed in the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute Myocardial Infarction) trial (7), persisted at 3 years' follow-up.

Methods

Patient selection.   The design and detailed methods of the SESAMI trial have been published elsewhere (7).

Study end points and definitions.   The primary end point of this trial was the incidence of major adverse cardiovascular events (MACE) at 3-year follow-up, defined as a composite of cardiac and noncardiac death, Q-wave and

non–Q-wave myocardial infarction (MI), coronary artery bypass grafting (CABG), or target lesion revascularization (TLR). The secondary end points were: 1) 3-year TLR, defined as repeated PCI or CABG of the target lesion driven by clinical symptoms of myocardial ischemia, a positive stress test due to the target vessel, or in-stent restenosis >70% of the reference luminal diameter; 2) 3-year target vessel revascularization (TVR), defined as repeated revascularization within the treated vessel; and 3) 3-year target vessel failure (TVF), defined as a combination of TVR, recurrent MI, and target vessel-related death.

Stent thrombosis (ST) was classified according to the definitions of the Academic Research Consortium (9).

The cumulative incidence of death from all causes and recurrent MI, starting from dual antiplatelet therapy discontinuation, was also recorded.

Follow-up protocol. Patients were scheduled to undergo clinical follow-up at 30 days and thereafter at 6, 12, 24, and 36 months. An independent clinical-event committee, the members of which were unaware of the patient's treatment, reviewed all clinical end points during follow-up.

Statistical analysis. The comparison between variables representing counts was assessed with the chi-square test or Fisher exact test. Normally distributed variables were assessed with Student t test. The TLR and the composite of MACE and TVF were analyzed by the Kaplan-Meier method, and survival between groups was compared with the log-rank test. A 2-sided probability value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics. Baseline characteristics and procedural results of patients are shown in Table 1.

Long-term clinical follow-up. Complete datasets were available in 157 of 160 (98%) patients in the SES group and in 156 of 160 (97.5%) patients in the BMS group.

The 3-year outcome is outlined in Table 2. The SES implantation showed a reduction of 40.5% in MACE risk compared with BMS (12.7% vs. 21%, p = 0.034). The cumulative 3-year survival rates free from MACE were 87% and 79% for the SES group and the BMS group, respectively (p < 0.05) (Fig. 1A). Results of the SES were, with regard to concerns overall secondary end points, better than those of BMS: TLR 7% versus 13.5% (p = 0.048) with 48% of risk reduction; TVR 8% versus 16% (p = 0.027) with 50% of risk reduction; and TVF 11.5% versus 20.5% (p = 0.028) with 44% of risk reduction. The lower incidence of adverse events in the SES group was due primarily to fewer TLRs. The greatest benefit was achieved in the first year of follow-up with no significant differences between 12 and 36 months. The cumulative 3-year survival rates free from TLR (Fig. 1B) and TVF (Fig. 1C) were 93% and 89.5% for the SES group and 86.5% and 79.5% for the BMS group, respectively (p < 0.05). There was no

statistical difference in terms of death, recurrent MI, or ST between the 2 groups.

We revealed, compared with the previous assessment of clinical outcome at 1-year, 12 new MACE, 7 in the SES group (Table 3). In this group 2 more patients died—1 from gastric cancer, and 1 from pulmonary embolism. One patient presented with nonfatal recurrent MI, and 4 patients underwent TLR—3 underwent re-PCI for a focal in-stent restenosis in 2 cases and ST in 1 case. The fourth patient underwent CABG for in-stent restenosis and progression of the left main coronary artery disease. In the BMS group, another patient died from lung cancer, and another had nonfatal MI. Another 3 patients underwent percutaneous TLR—1 for focal in-stent restenosis, 1 for diffuse in-stent restenosis, and 1 for ST.

The mean duration of dual antiplatelet therapy was 375 ± 12 days and 369 ± 35 days for the SES and BMS groups, respectively (p = NS). The cumulative incidence of death for all causes and nonfatal MI was comparable in the 2 groups starting from the time of clopidogrel discontinuation at 3-year follow-up.

Table 1	Baseline and Procedural Characteristics of the SES and BMS Group		
	SES Group	**BMS Group**	**p Value**
Baseline characteristics			
n	160	160	
Age, yrs	63 (54–70)	62 (52–72)	0.81
Male sex	128 (80)	128 (80)	
Diabetes mellitus	28 (17.5)	37 (23.7)	0.13
Hypertension	87 (54.3)	98 (58.7)	0.20
Hyperlipidemia	123 (62.5)	105 (65%)	0.12
Smoker	91 (56.8)	83 (51.7)	0.1
Prior myocardial infarction	9 (5.6)	20 (12.5)	0.047
Prior PCI	15 (9.4)	17 (10.6%)	0.38
Time from symptom onset to PCI	4 (3–7)	4 (3–6)	0.64
DAT, days	375 ± 12	369 ± 35	NS
Procedural characteristics			
PCI rescue	28 (17.5)	29 (18.2)	0.54
Abciximab therapy	124 (77.5)	118 (74%)	NS
Stent length, mm	19.4 ± 4.8	16.9 ± 4.1	0.001
Stent diameter, mm	3.02 ± 0.28	3.14 ± 0.034	0.001

Values are n, mean (range), n (%), or mean ± SD.
  BMS = bare-metal stent(s); DAT = dual antiplatelet treatment; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

Table 2	Clinical Outcome at 3 Years		
	SES Group	**BMS Group**	**p Value**
n	157	156	
Death	5 (3.2) (1–7.2)	8 (5) (2.2–10)	0.38
Reinfarction	4 (2.5) (0.7–6.3)	4 (2.5) (0.7–6.4)	NS
Stent thrombosis			
Definite	3 (1.9) (0.4–5.4)	2 (1.3) (0.1–4.5)	NS
Probable/possible	5 (3.2) (1–7.2)	6 (3.8) (1.4–8.1)	NS
MACE	20 (12.7) (8–18)	33 (21) (15–28)	0.034
TLR	11 (7) (3.5–12)	21 (13.5) (8.5–19)	0.048
TVR	13 (8.3) (4–13)	25 (16) (10–22)	0.027
TVF	18 (11.5) (7–17)	32 (20.5) (14–27)	0.028

Values are n (%) (95% confidence interval).

MACE = major adverse cardiovascular event; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization; other abbreviations as in Table 1.

Discussion

The present study demonstrates that SES implantation is better, in terms of MACE, TLR, TVR, and TVF, compared with BMS in patients with STEMI at 3-year follow-up. The greatest benefit was achieved in the first year and maintained at 3 years.

The main proven benefit of DES versus BMS is the reduction of restenosis in various clinical and angiographic settings (10), especially in high-risk patients such as those presenting with STEMI (6–8,11). Restenosis is not a benign clinical occurrence, because it has been associated with increased risk of death and MI (12). However, randomized data on long-term safety and efficacy of DES in the STEMI setting are still lacking. In the STRATEGY (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction) trial (7) it has been demonstrated that the cumulative incidence of MACE was constantly lower in the tirofiban + SES group compared with Abciximab + BMS group due primarily to the different rate of TVR without any significant increase in the death rate, recurrent MI, or ST at 2-year clinical follow-up. Our study confirms these findings and extends the clinical follow-up to 3 years. The SES treatment was associated with a 40.5% risk reduction of MACE with a cumulative incidence of MACE-free survival of 87% compared with 79% in the BMS group, even if the SES group had longer and smaller implanted stents. In agreement with our results, a recent meta-analysis of randomized trials comparing the short- and the long-term clinical benefit of SES versus BMS showed a significant reduction in TVR with no significant difference in ST incidence in SES patients at 1-, 2-, and 3-year follow-up (13). In contrast to our results, a recent nonrandomized study, comparing 3-year clinical outcome of SES, paclitaxel-eluting stent, and BMS in patients with STEMI, showed that SES was more efficacious in triggering a decrease in TVR compared with paclitaxel-eluting stent or BMS only at 1-year follow-up. This advantage was lost at 3-year follow-up, partly explained by the occurrence of late

ST in the SES group (14). In a recent multinational registry of patients with STEMI, who had undergone PCI with DES or BMS, a similar mortality was reported for the first 6 months after discharge but was significantly higher from 6 months to 2 years for DES patients, compared with BMS patients (15). Indeed, primary stenting has been recognized as an independent predictor of late stent malapposition in BMS (16) as well as in DES patients (17), with an incidence 2- to 3-fold higher compared with elective stenting. Potential mechanisms of late adverse events are still controversial. Thrombus displacement by the stent struts with abluminal thrombus resolution in the long-term might lead to a major incidence of stent malapposition and might account for the
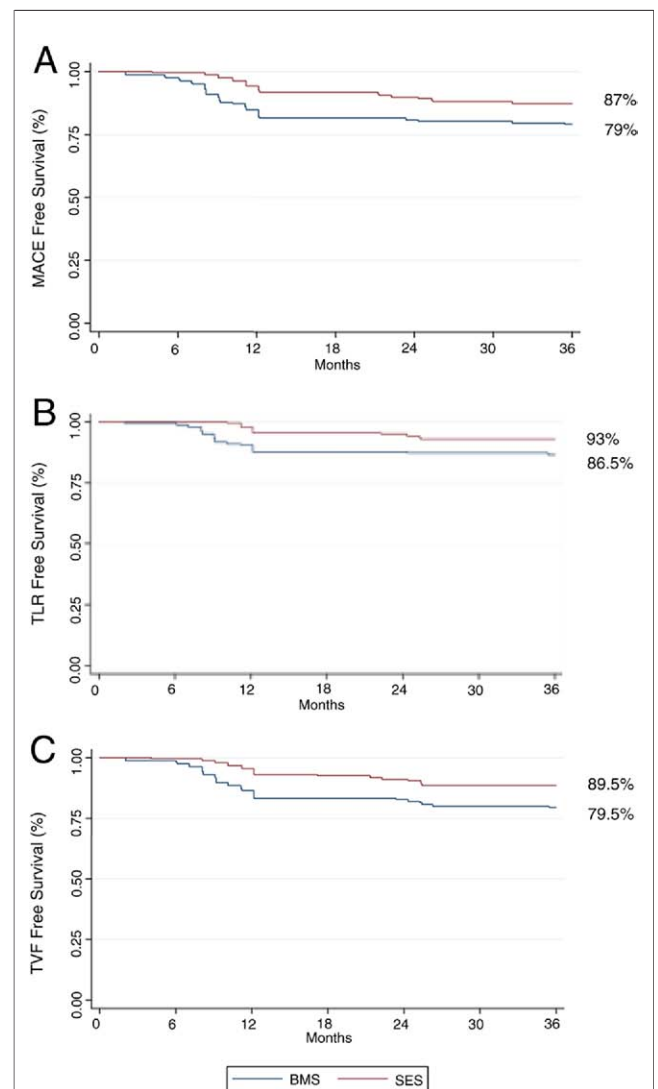

Figure 1	Actuarial Rates of Survival Free From MACE, TLR, and TVR

Kaplan-Meier estimates of survival free from major adverse cardiovascular events (MACE) **(A)**, target lesion revascularization (TLR) **(B)**, and target vessel failure (TVF) **(C)** among patients treated with a sirolimus-eluting stent (SES) or bare-metal stent (BMS). The MACE, TLR and TVF free survival was significantly higher in the SES group than the BMS group (p < 0.05).

Table 3	Clinical Events During 12- to 36-Month Follow-Up		
	SES Group	**BMS Group**	**p Value**
n	144	127	
Death	2 (1.4) (0.1–4)	1 (0.8) (0.01–4.3)	NS
Reinfarction	1 (0.7) (0.01–3)	1 (0.8) (0.01–4.3)	NS
Stent thrombosis			
Definite	1 (0.7) (0.01–3)	1 (0.8) (0.01–4.3)	NS
Probable/possible	0	0	NS
MACE	7 (4.8) (1.9–9)	5 (3.9) (1.2–8.9)	NS
TLR	4 (2.7) (0.7–6.9)	3 (2.3) (0.4–6.7)	NS
TVR	6 (4.1) (1.5–8.8)	7 (5.5) (2.2–11)	NS
TVF	7 (4.8) (1.9–9.7)	8 (6.3) (2.7–12)	NS
Death/re-MI	3 (2) (0.4–5.9)	2 (1.5) (0.1–5.5)	NS

Values are n (%) (95% confidence interval).
MI = myocardial infarction; other abbreviations as in Tables 1 and 2.

higher rates of early and late ST (18). Moreover, a large thrombus burden can affect stent-based drug-elution and significantly alter vessel wall drug levels and potentially the efficacy, thus explaining the higher rate of in-stent restenosis in patients with STEMI compared with that in those with other clinical settings (19). By contrast, recent data suggest that late adverse events are caused mainly by a ruptured plaque in the adjacent vessel outside the stent and are not strictly stent-related (20,21). Another risk factor for late adverse events seems to be premature discontinuation of dual antiplatelet therapy (22). In a large observational study, DES ST was observed in approximately 30% of patients who prematurely discontinued antiplatelet therapy (23). Much controversy still exists concerning the duration of dual antiplatelet therapy in STEMI patients. Some authors concluded that, because the cardiovascular outcomes improved with more robust or prolonged antiplatelet therapy in patients with acute coronary syndromes or prior history of ischemic events or PCI, it should be recommended for >1 year—perhaps indefinitely—in all patients receiving DES (24).

In contrast with these findings, in our study, the rate of definite ST was 1.9% in the SES group and 1.3% in the BMS group (p = NS), whereas the cumulative incidence of death and nonfatal recurrent MI was comparable in the 2 groups starting from the time of clopidogrel discontinuation. In agreement with our data it has been reported that, although withdrawal of clopidogrel was associated with an increased mortality risk, it does not depend upon the type of stent implanted (25). Moreover, a recent collaborative network meta-analysis (26) focused on safety and effectiveness of DES and BMS in high-risk patients such as those with diabetes mellitus. Results suggested that the previously reported increased risk of death, associated with SES, was probably due to the short duration of dual antiplatelet therapy in early studies but was no longer found in trials in which dual antiplatelet therapy was given for >6 months.
Study limitations. First, this 3-year follow-up study is limited to clinical end points. Second, although no differ-

ences were found in terms of incidence of death, recurrent MI, and ST at 3-year follow-up or in MACE during 12- to 36-month follow-up, the study does not have sufficient power to demonstrate significant differences in these adverse clinical events.

Conclusions

The present study demonstrates that SES are associated with a significant reduction of MACE, TLR, TVR, and TVF compared with BMS at 3-year follow-up after stenting for STEMI. The SES seems to be as safe as BMS, without evidence of any increased risk of death, recurrent MI, or ST, including no incremental risks after withdrawal of dual antiplatelet therapy.

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REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
2. Kelbaek H, Thuesen L, Helqvist S, et al. The Stenting Coronary Arteries in Non-Stress/Benestent Disease (SCANDSTENT) trial. J Am Coll Cardiol 2006;47:449–55.
3. Marroquin OC, Selzer F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indication. N Engl J Med 2008;358:342–52.
4. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
5. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
6. Spaulding C, Henry P, Teiger E, et al., for the TYPHOON Investigators. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;55:1093–104.
7. Valgimigli M, Campo G, Arcozzi C, et al. 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. J Am Coll Cardiol 2007;50:138–45.
8. Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). J Am Coll Cardiol 2007;49:1924–30.
9. Vranckx P, Kint PP, Morel MA, et al. Identifying stent thrombosis, a critical appraisal of academic research consortium (ARC) consensus definitions: a lighthouse and as a toe in the water. EuroIntervention 2008;4 Suppl C:C39–44.
10. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stent with bare-metal stents. N Engl J Med 2007; 356:1030–39.
11. van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome. J Am Coll Cardiol 2008;51:618–26.

12. Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcome of stent thrombosis and restenosis during extended follow-up of patients treated with bare metal coronary stent. Circulation 2007;116:2391–8.

13. De Luca G, Valgimigli M, Spaulding C, et al. Short and long-term benefits of sirolimus-eluting stent in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. J Thromb Thrombolysis 2009;2:200–10.

14. Daemen J, Tanimoto S, Garcia-Garcia HM, et al. Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stent versus bare metal stent in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2007;99:1027–32.

15. Steg PG, Keith AAF, Eagle KA, et al. Mortality following placement of drug-eluting and bare-metal stents for ST-segment elevation acute myocardial infarction in the Global Registry of Acute Coronary Events. Eur Heart J 2009;30:321–9.

16. Hong MK, Mintz GS, Lee CW, et al. Incidence, mechanism, predictors and long-term prognosis of late malapposition after bare-metal stent implantation. Circulation 2004;109:881–6.

17. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. Circulation 2006;113:414–9.

18. Sianos G, Papafaklis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction. J Am Coll Cardiol 2007;50:573–83.

19. Hwang CW, Levin AD, Jonas M, et al. Thrombosis modulates arterial drug distribution for drug-eluting stents. Circulation 2005; 111:1619–26.

20. Leon MB, Allocco DJ, Dawkins KD, et al. Late clinical events after drug-eluting stents. J Am Coll Cardiol Intv 2009;2:504–12.

21. Fischell TA, Holmes DR Jr. Late DES thrombosis: a lot of smoke, very little fire? Cath Cardiovas Interv 2007;69:609:15.

22. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–54.

23. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.

24. Colombo A, Gerber RT. Should dual antiplatelet therapy after drug-eluting stents be continued for more than 1 year? Circ Cardiovasc Intervent 2008;1;226–32.

25. Le Feuvre C, Helft, G, Cohen S, et al. Characteristics and prognosis of patients with angiographic stent thrombosis: comparison between drug-eluting and bare-metal stents. Arch Cardiovasc Dis 2008;101: 220–5.

26. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008;337:1331–41.