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Long-term results of the randomized comparison of everolimus-eluting stents and sirolimus-eluting stent in patients with ST elevation myocardial infarction (RACES-MI trial)

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ABSTRACT

Background: Several concerns have emerged about the higher risk of very late stent thrombosis (ST) with first generation drug-eluting stent (DES), especially in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI). New generation DES have demonstrated reduction in ST at mid-term follow-up, however no data are available on long-term follow-up. Therefore, the aim of this study was to report long-term results of the RACES-MI trial conducted to compare Everolimus-Eluting Stent (EES) vs Sirolimus-Eluting Stent (SES) in patients undergoing primary PCI.

Methods: The RACES-MI trial enrolled consecutive STEMI patients admitted within 12 h of symptom onset, undergoing primary PCI with stent implantation at a tertiary center with 24-hour primary PCI capability, who were randomly assigned to SES or EES. Primary endpoint of this analysis is major adverse cardiac events (MACE) at long-term follow-up. Secondary endpoints are 1) death; 2) reinfarction; 3) definite or probable ST; 4) target-vessel revascularization (TVR) at long-term follow-up.

Results: From April 2007 to May 2009 500 patients with STEMI were randomized to EES (n = 250) or SES (n = 250). No difference was observed between the groups either in baseline clinical characteristics, in the number of implanted stent or total stent length per patient. However, a larger reference diameter was observed with SES (3.35 ± 0.51 mm vs 3.25 ± 0.51 mm, p = 0.001), whereas patients randomized to EES received Gp IIb–IIIa inhibitors more often (54.4% vs 42.4%, p = 0.006). At long-term follow-up (2132 ± 528 days), EES was associated with a significant reduction in MACE (23.8 vs 34.1%, adjusted p = 0.028), ST (2.5% vs 7.7%, adjusted p = 0.009), without any difference in death (8.7% vs 11.4%, adjusted p = 0.47), reMI (9.3% vs 13.1%; adjusted p = 0.18) and TVR (8.6% vs 12.3%, adjusted p = 0.31).

Conclusions: This study shows that among STEMI patients undergoing primary PCI EES, as compared to SES, is associated with significant reduction in MACE and ST at long-term follow-up.

1. Trial registration clinicaltrials.gov identifier: NCT01684982

Primary percutaneous coronary intervention (PCI) currently represents the best reperfusion therapy for ST-segment elevation myocardial infarction (STEMI) when applied without significant adjunctive delays as compared to thrombolysis [1,2]. Despite the beneficial effects of stenting as compared to balloon angioplasty [3,4], restenosis still remains high in high-risk unselected patients, with target-vessel revascularization (TVR) rates up to 20% [5,6]. Several randomized trials have shown that drug-eluting stents (DES) are associated with a significant reduction in restenosis and TVR as compared to bare-metal stents (BMS) in STEMI patients [7–17]. However, concerns have emerged on the higher risk of stent thrombosis (ST) with first generation DES [18]. New generation DES with more biocompatible polymers have been shown to provide benefits in ST at mid-term follow-up in the setting of STEMI [19–21], but no data have been so far available on long-term follow-up. In this study we report long-term results of the randomized comparison of everolimus eluting stents and sirolimus eluting stent in

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patients with ST elevation myocardial infarction (RACES-MI) trial, comparing everolimus-eluting stent (EES) vs sirolimus-eluting stent (SES) in patients undergoing primary PCI for STEMI [20].

2. Methods

The randomized comparison of everolimus-eluting stents and sirolimus-eluting stent in patients with ST Elevation myocardial infarction (RACES-MI) trial is a prospective, single-center, randomized trial evaluating the benefits of EES as compared to SES implantation in patients undergoing primary PCI for STEMI. Detailed data have already been described [20]. Briefly, individuals eligible for enrolment were consecutive patients presenting with STEMI who fulfilled all the following inclusion criteria: 1) chest pain for more than 30 min; 2) ST-segment elevation of 1 mm or more in 2 or more contiguous electrocardiograph leads or with presumably new left bundle-branch block. Exclusion criteria included: 1) Active internal bleeding or a history of bleeding diathesis within the previous 30 days; 2) contraindication to dual antiplatelet therapy for 12 months; 3) known allergy to sirolimus or everolimus; 4) a history of stroke within 30 days or any history of hemorrhagic stroke; 5) history, symptoms, or findings suggestive of aortic dissection; 6) pregnancy; and 7) participation in other trials. No angiographic exclusion criteria were used.

All patients gave written informed consent. Open-label randomization was performed in the catheterization laboratory after initial angiography by the treating physician when eligibility criteria were met. A 1:1 computer-generated random sequence, without blocking or stratification, was used. Sealed envelopes indicated the treatment group to which the patients were assigned: SES or EES.

2.1. Medications

All patients received 70 U/kg i.v. bolus of unfractionated heparin (UFH), aspirin intravenously (500 mg) and clopidogrel (600 mg loading dose). GP IIb–IIIa inhibitors administration was left to the operator's discretion. Postinterventional antiplatelet therapy for all patients consisted of aspirin (100 mg/day) indefinitely and clopidogrel (75 mg daily recommended for 12 months).

2.2. Angioplasty procedure

Stenting procedures were performed according to standard techniques. The number and length of stents to be implanted were left to the operator's discretion. The operator was allowed to implant DES to cover the entire length of the lesion with coverage of the entire stented segment and of 5 mm proximal and distal segments. The use of IVUS, adjunctive thrombectomy devices, distal protection devices and IABP were left to the operator's discretion.

2.3. Angiographic analysis

Thrombolysis in Myocardial Infarction (TIMI) grade 3 coronary flow in the treated vessel and a residual stenosis less than 30% were the criteria used to define a successful PCI. Quantitative angiographic analyses (Integris Allura, Philiphs, The Netherlands) were performed on line and off line by two experienced technicians who were unaware of treatment assignment with the averaging scores if they were not in agreement.

2.4. Data collection and follow-up

Patients were examined at our outpatient clinic or interviewed by telephone at 6, 12, 24, 36 and later than 60 months. For patients who died during follow up, hospital records and necropsy data were reviewed, when possible.

2.5. Study end points and definitions

The primary end point was major adverse cardiac events (MACE) at 5–7 years follow-up, defined as combined death, recurrent myocardial infarction (ReMI), definite or probable ST and TVR. Secondary endpoints were cumulative occurrence of 1) death; 2) ReMI; 3) definite or probable ST and 4) TVR at long-term follow-up. ReMI was defined as recurrence on angina symptoms with typical ECG changes and increase above upper limit of normal of CKMB or troponin. The indication for a second intervention had to be substantiated by symptoms or by ECG or scintigraphic evidence of ischemia at rest or during exercise. Subsequent revascularisation of other coronary arteries did not constitute an end point. All events were reviewed by two cardiologists blinded to treatment assignment.

2.6. Statistical analysis

Continuous data were expressed as mean (SD) and categorical data as percentages. The analysis of variance was appropriately used for continuous variables. The χ^2 test or the Fisher's exact test was used for categorical variables. The difference in events between groups during the follow up period was assessed by the Kaplan–Meier method with the log rank test, and data were presented as Kaplan–Meier time-to-event estimates. Furthermore, Cox-regression analysis was performed to adjust the results for any difference in baseline demographic, clinical, angiographic or procedural characteristics between the two groups. A probability value of $p < 0.05$ was considered significant. Data were analyzed according to intention to treat analysis. Statistical analysis was performed using SPSS 17.0.

3. Results

3.1. Patient characteristics and procedural results

Our final population is represented by 500 STEMI patients who were randomized from April 2007 to May 2009 to EES (n = 250) or SES (n = 250). As reported on Table 1, no difference was observed in terms of baseline demographic, clinical and angiographic characteristics between the groups. As shown in Table 1, no difference was observed in terms of procedural characteristics. No difference was observed between the groups in the number of implanted stents per patient (1.12 ± 0.35 vs 1.11 ± 0.35, $p = 0.8$). Almost 50% of patients underwent PCI of left anterior descending artery. Glycoprotein IIb–IIIa inhibitors were more often administrated among patients randomized to EES. Procedural success was obtained in 83–86% of patients. No difference was observed in medical therapy at discharge (Table 2).

Table 1
Demographic, clinical and procedural characteristics of the two groups of patients.

Variable	SES (n = 250)	EES (N = 250)	p value
Age (years)	59 ± 12	59 ± 11	0.53
Male gender (%)	62	67.6	0.19
Hypertension (%)	41.2	42	0.86
Diabetes (%)	27.2	25.6	0.69
IDDM (%)	9.6	10	
NIDDM (%)	17.6	15.6	
Smoking (%)	34.4	33.6	0.85
Previous MI (%)	12	14.4	0.43
Previous CABG (%)	8	6.8	0.61
Previous PCI (%)	12.4	9.6	0.32
Previous CVA (%)	3.2	4	0.63
Family history of CAD (%)	32.4	36	0.4
PAD (%)	2.4	3.2	0.59
Chronic renal failure (%)	8.4	10.4	0.45
Anemia (%)	10.4	8.8	0.54
Heart rate at presentation (bpm)	65 ± 24	69 ± 24	0.25
Killip class > 1 (%)	14.4	15.2	0.80
Anterior MI (%)	45.2	42.4	0.53
Ejection fraction (%)	47.4 ± 8.4	47.5 ± 8	0.9
Ischemia time (min)	177 ± 148	182 ± 152	0.67
Door-to-balloon time (min)	44 ± 17	46 ± 16	0.16
IRA			
LM	3.2	2.4	0.69
LAD (%)	42.4	45.2	
LCX (%)	20	16.8	
RCA (%)	32	34.8	
SVG (%)	1.6	0.8	
Preprocedural TIMI Flow			
0–1 (%)	62	69.6	0.063
2 (%)	26.8	18	
3 (%)	11.2	12.4	
Postprocedural TIMI flow			
0–1 (%)	6.6	8.8	0.48
2 (%)	8	7.6	
3 (%)	86	83.6	
Vessel disease			
1 (%)	50.4	53.8	0.48
2 (%)	39.2	34.1	
3 (%)	10.4	12	
RD (mm)	3.35 + 0.51	3.25 + 0.51	0.001
Stent diameter (mm)	3.16 + 0.39	3.09 + 0.45	0.071
Total Stent length (mm)	22 + 7.7	22.3 + 8	0.72
N. stents	1.12 + 0.35	1.11 + 0.35	0.8
Gp IIb–IIIa inhibitors (%)	42.4	54.4	0.006
Thrombectomy devices (%)	23.2	21.2	0.59

IDDM = insulin-dependent diabetes mellitus; NIDDM = non insulin-dependent diabetes mellitus; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; BMS = bare-metal stent; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; IRA = infarct-related artery; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction.