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Five-Year Follow-up of Polymer-free Sirolimus- and Probucol-eluting Stents Versus New Generation Zotarolimus-eluting Stents in Patients Presenting With ST-elevation Myocardial Infarction

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Background: Patients with ST-segment elevation myocardial infarction (STEMI) undergoing drug-eluting stent (DES) implantation are at increased risk of late adverse events, partly explained by an exaggerated inflammatory reaction to durable-polymer stent coatings. Objectives: We sought to investigate whether implantation of polymer-free DES would reduce this risk. Methods: In the ISAR-TEST 5 (the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus-Eluting Stents) trial, patients were randomly allocated to receive a polymer-free sirolimus- and probucol-eluting stent or a new generation durable-polymer zotarolimus-eluting stent. We analyzed late clinical outcomes in the subgroup of patients presenting with STEMI. The primary endpoint was the combined incidence of cardiac death, target vessel-related myocardial infarction or target lesion revascularization at 5 years. Results: 311 patients with STEMI were randomized to receive sirolimus- and probucol-eluting stents ($n = 215$) or zotarolimus-eluting stents ($n = 96$). At 5 years, there was no difference in the incidence of the primary endpoint in patients treated with sirolimus- and probucol-eluting stents versus zotarolimus-eluting stents (18.3% versus 20.1% respectively, hazard ratio = 0.87, 95% CI, 0.50–1.51; $P = 0.62$). Rates of the individual components of the primary endpoint were also comparable in both groups. The incidence of definite/probable stent thrombosis was 1.4% versus 1.0% respectively (hazard ratio = 1.35, 95% CI, 0.14–12.94, $P = 0.80$). Conclusions: Long-term outcomes of patients with STEMI treated with polymer-free sirolimus- and probucol-eluting stents versus durable-polymer zotarolimus-eluting stents were similar. Stent thrombosis rates were low and

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comparable in both treatment groups, with no events beyond 12 months. Clinical Trial Registration: Registered at ClinicalTrials.gov (Identifier NCT 00598533)

Key words: drug-eluting stent; STEMI; long-term follow-up; probucol; randomized controlled trial; sirolimus; zotarolimus

INTRODUCTION

It is well recognized that at a pathophysiological level, an inflammatory reaction to durable polymer coatings plays an important etiological role in the process of delayed arterial healing after drug-eluting stent (DES) implantation [1,2]. Delayed vessel healing is the principal substrate underlying a spectrum of late adverse events including late stent thrombosis, delayed late luminal loss and de novo in-stent atherosclerosis [3]. In the setting of STEMI, although the efficacy of DES has been shown to be superior to that of bare metal stents [4], the long-term safety of DES use for this indication is less clear. This is attributable to higher rates of very late stent thrombosis for DES compared with bare metal stents implanted for STEMI [5,6]. This has been explained, in part, by an exaggerated inflammatory response to durable polymer coatings in STEMI patients, at least with first generation DES. Autopsy studies of stented arterial segments in patients with DES implantation demonstrate more inflammation and less healing at acute myocardial infarction (AMI) culprit sites compared with culprit sites in stable angina patients [7].

Newer generation stents attempt to overcome the limitation of polymer-induced inflammation seen with earlier devices by using more biocompatible polymer coatings or polymer-free antirestenotic drug elution [8]. We previously showed that a polymer-free sirolimus- and probucol-eluting stent was noninferior to a new generation durable polymer-based zotarolimus-eluting stent with respect to clinical outcomes at 12 months [9]. We also reported similar longterm clinical efficacy and safety profiles for these two devices at 5-year follow-up [10]. However, in STEMI patients, the long-term performance of polymer-free DES technology has not yet been investigated. Against this background, we performed 5-year follow-up of the subgroup of STEMI patients enrolled in the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus- Eluting Stents (ISAR-TEST 5) randomized trial.

METHODS

Study Population, Device Description, and Study Protocol

Full details of the study population, methods, endpoints and primary analysis have been previously reported [9]. In brief, patients older than 18 years of age, with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of $\geq$50% *de novo* stenosis located in native coronary arteries were considered eligible, provided that written, informed consent by the patient or his/her legally authorized representative was obtained for participation in the study. Patients with a target lesion located in the left main stem, cardiogenic shock, a malignancy or other comorbid condition with life expectancy $<$12 months or that may result in protocol noncompliance were considered ineligible for the study. Patients were assigned in a 2:1 allocation to receive polymer-free sirolimus- and probucol-eluting stents or permanent polymer zotarolimus-eluting stents.

The polymer-free stent platform consists of a premounted, sand-blasted, 316-L stainless steel microporous stent coated with a mixture of sirolimus and probucol (commercially-available as the Coroflex ISAR, B. Braun Melsungen, Berlin, Germany). The permanent polymer zotarolimus-eluting stent (Resolute™, Medtronic Cardiovascular, Santa Clara, CA) consists of a thin strut stainless steel stent platform with a polymer coating system consisting of three different polymers: a hydrophobic C10 polymer, a hydrophilic C19 polymer and polyvinylpyrrolidinone. Further detailed descriptions of stent platforms and elution characteristics of both stents have been reported previously [11,12]. The aim of the current study was to compare outcomes of patients presenting with STEMI treated with polymer-free sirolimus- and probucol-eluting stents versus permanent polymer zotarolimus-eluting stents after 5 years of clinical follow up.

End Points and Definitions

The primary endpoint of this study was the device-oriented composite of cardiac death, myocardial infarction related to the target vessel, or target lesion revascularization at 5 years post index intervention. Secondary endpoints were: cardiac death, myocardial infarction related to the target vessel, target lesion revascularization, all-cause mortality, any myocardial infarction, any revascularization, target vessel revascularization and the incidence of definite/probable stent thrombosis (by Academic Research Consortium definition) at 5 years. Detailed definitions of endpoints have been previously reported [9].

Follow-up and Analysis

Patients were systematically evaluated at 1, 12, 24, and 60 months by telephone call or office visit. Repeat coronary angiography was scheduled for 6–8 months, according to the trial protocol. Additional analyses at long-term follow-up (beyond 12 months) may be regarded as post hoc. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.

Statistical Analysis

Continuous data are presented as mean (standard deviation) or median [25th-75th percentiles]. Categorical data are presented as counts or proportions (%). Data distribution was tested for normality using the Kolmogorov–Smirnov test for goodness of fit. Patient-level data differences between groups were checked for significance using Student's *t* test or Wilcoxon rank sum test (continuous data) or the chi-squared or Fisher's exact test where the expected cell value was < 5 (categorical variables). For lesion-level data, differences between groups were checked for significance using generalized estimating equations for non-normally distributed data in order to address intra-patient correlation in patients who underwent multilesion intervention [13].

Event-free survival was assessed using the methods of Kaplan–Meier. Hazard ratios, confidence intervals and *P* values were calculated from univariate Cox proportional hazards models. The proportional hazards assumption was checked by the method of Grambsch and Therneau [14] and was fulfilled in all cases in which we used Cox proportional hazards models. The analysis of primary and secondary endpoints was performed on an intention-to-treat basis [15]. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, WA) was used for analysis.

RESULTS

Patients

A total of 311 patients presenting with STEMI were randomized to receive either polymer-free sirolimus- and probucol-eluting ($n = 215$) or durable polymer zotarolimus-eluting ($n = 96$) stents. As shown in Table I, the groups were well matched in terms of baseline patient and lesion characteristics. Incidence of previous coronary artery bypass grafting was higher in the zotarolimus-eluting stent group ($P = 0.03$). Ejection fraction was $46.3\% \pm 9.6\%$ and $47.6\% \pm 9.6\%$ in both groups, respectively ($P = 0.28$).

The total number of treated lesions was 422 (sirolimus- and probucol-eluting stent, $n = 297$; zotarolimus-eluting stent, $n = 125$). More than one lesion was treated in 30.2% of patients in the sirolimus- and probucol-eluting stent group versus 28.1% in the zotarolimus-eluting group ($P = 0.71$). Five-year follow-up was complete on all but 19 patients (6.1%), without any significant difference between the two study groups, with 11 patients (5.1%) missing in the sirolimus- and probucol-eluting stent group and 8 patients (8.3%) in the zotarolimus-eluting stent group ($P = 0.11$).

Device-Oriented Outcomes at 5 Years

The results of 5-year follow-up are shown in Table II. Regarding the primary endpoint, the composite of cardiac death, myocardial infarction related to target vessel and target lesion revascularization, there was no difference between the sirolimus- and probucol-eluting stent and zotarolimus-eluting stent (18.3% versus 20.1% respectively, hazard ratio = 0.87, 95% CI, 0.50–1.51; $P = 0.62$). Figure 1A shows survival analysis curves for the occurrence of the primary endpoint.

In terms of individual components of the primary endpoint, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates of cardiac death or myocardial infarction related to target vessel (7.7% versus 8.6% respectively, hazard ratio = 0.89, 95% CI, 0.38–2.08; $P = 0.79$, Fig. 1B), cardiac death (6.8% versus 8.6% respectively, hazard ratio = 0.78, 95% CI, 0.33–1.85; $P = 0.57$), and myocardial infarction related to target vessel (1.9% versus 1.0% respectively, hazard ratio = 1.79, 95% CI, 0.20–16.00; $P = 0.60$); rates of target lesion revascularization were also similar in both groups (12.3% vs. 14.0%, respectively; hazard ratio = 0.83 [95% CI, 0.43–1.63], $P = 0.59$, Fig. 1C).

In terms of safety endpoints, the sirolimus- and probucol-eluting stent, in comparison with the zotarolimus-eluting stent, showed similar rates of definite/probable stent thrombosis (1.4% vs. 1.0% respectively; hazard ratio = 1.35 [95% CI, 0.14–12.94], $P = 0.80$; Fig. 2). Detailed outcomes for definite, probable and possible stent thrombosis are displayed in Table III.

Patient-oriented Outcomes at Five Years

Regarding the composite endpoint of death, any myocardial infarction or any revascularization, there was no difference between the sirolimus- and probucol-eluting stent and zotarolimus-eluting stent (46.6% versus 49.1% respectively, hazard ratio = 0.94, 95% CI, 0.66–1.33; $P = 0.71$). The sirolimus- and probucol-eluting stent, in comparison with the zotarolimus-eluting stent, showed similar rates of all-cause death (11.8% versus 16.8%, respectively, hazard ratio = 0.69, 95% CI, 0.37–1.30; $P = 0.25$), any myocardial

TABLE I. Selected Baseline Patient and Procedural Characteristics

	Sirolimus- and probucol-eluting stent	Zotarolimus-eluting stent	*P* value
Patient characteristics	***n* = 215**	***n* = 96**	
Age (years)	64.3 ± 13.8	64.2 ± 12.4	0.98
Female	49 (23.0)	25 (26.0)	0.53
Diabetes mellitus	44 (20.5)	20 (20.8)	0.94
insulin-dependent	12 (5.6)	7 (7.3)	0.56
Hypertension	159 (74.0)	73 (76.0)	0.70
Hyperlipidemia	89 (41.0)	45 (47.0)	0.37
Current smoker	76 (35.0)	33 (34.0)	0.87
Prior myocardial infarction	35 (16.3)	13 (13.5)	0.54
Prior bypass surgery	6 (2.8)	8 (8.3)	0.03
Multi-vessel disease	150 (69.8)	67 (69.8)	0.99
Ejection fraction (%)[a]	46.3 ± 9.6	47.6 ± 9.6	0.28
Lesions characteristics	***n* = 297**	***n* = 125**	
Target vessel			0.47
left anterior descending	131 (44.1)	58 (46.4)	
left circumflex	68 (22.9)	22 (17.6)	
right coronary artery	98 (33.0)	45 (36.0)	
Chronic total occlusion	3 (1.0)	3 (2.4)	0.27
Bifurcation	60 (20.2)	25 (20.0)	0.96
Ostial	51 (17.2)	30 (24.0)	0.10
Complex morphology (B2/C)	264 (88.9)	105 (84.0)	0.17
Lesion length (mm)	17.2 ± 9.9	17.0 ± 9.7	0.58
Vessel size (mm)	2.89 ± 0.48	2.88 ± 0.54	0.74
Minimal lumen diameter, pre (mm)	0.59 ± 0.57	0.56 ± 0.56	0.48
Stented length (mm)	27.0 ± 13.0	28.9 ± 12.9	0.42
% Diameter stenosis, post	12.8 ± 9.7	12.2 ± 10.4	0.20

Data shown as means ± SD or number (percentage).
Data available for 283 patients (91.0%).

TABLE II. Clinical Results at 5 Years

	Sirolimus- and probucol-eluting stent (*n* = 215)	Zotarolimus-eluting stent (*n* = 96)	Hazard ratio (95% CI)	*P* value
Device-oriented outcomes				
Cardiac death, MI related to target vessel or target lesion revascularization	38 (18.3)	19 (20.1)	0.87 (0.50–1.51)	0.62
Cardiac death or MI related to target vessel	16 (7.7)	8 (8.6)	0.89 (0.38–2.08)	0.79
Cardiac death	14 (6.8)	8 (8.6)	0.78 (0.33–1.85)	0.57
MI related to target vessel	4 (1.9)	1 (1.0)	1.79 (0.20–16.00)	0.60
Target lesion revascularization	25 (12.3)	13 (14.0)	0.83 (0.43–1.63)	0.59
Patient-oriented outcomes				
All-cause death, any MI or any revascularization	99 (46.6)	47 (49.1)	0.94 (0.66–1.33)	0.71
All-cause death or any MI	27 (12.7)	16 (16.8)	0.75 (0.41–1.40)	0.37
All-cause death	25 (11.8)	16 (16.8)	0.69 (0.37–1.30)	0.25
Any MI	4 (1.9)	1 (1.0)	1.79 (0.20–16.00)	0.60
Any revascularization	77 (37.8)	34 (36.7)	1.00 (0.67–1.50)	0.99
Target vessel revascularization	48 (23.6)	21 (22.7)	0.98 (0.59–1.64)	0.94

Data shown as number (percentage) by Kaplan–Meier analysis; hazard ratios and *P*-values were calculated from Cox proportional hazard methods.
MI = myocardial infarction.

infarction (1.9% versus 1.0%, respectively, hazard ratio = 1.79 95% CI, 0.20–16.00; $P = 0.60$) and any revascularization (37.8% vs. 36.7%, respectively; hazard ratio = 1.00, 95% CI, 0.67–1.50, $P = 0.99$).

DISCUSSION

The main findings of our report were that in patients presenting with STEMI enrolled in a large-scale clinical trial, the primary composite outcome measure of

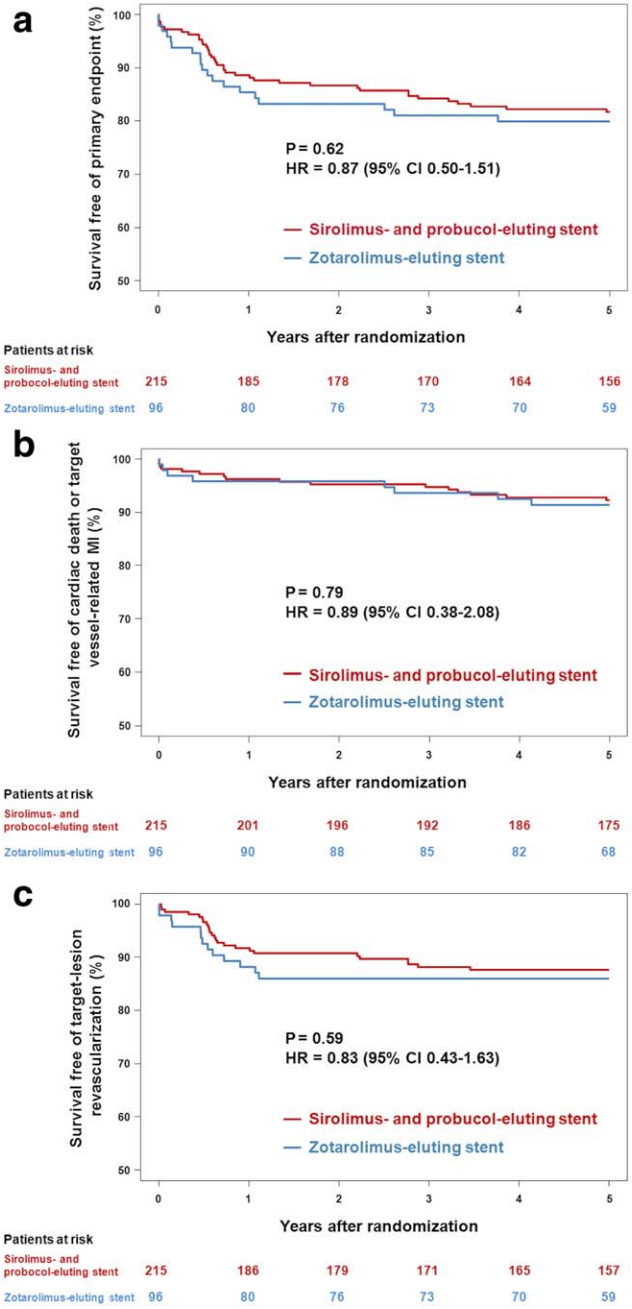

Fig. 1. Time to event curve for survival free of (A) the primary composite endpoint of cardiac death, myocardial infarction related to the target vessel or target lesion revascularization; (B) the composite of cardiac death or myocardial infarction related to the target vessel and (C) target lesion revascularization. Hazard ratios and *P* values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio. [Color figure can be viewed at wileyonlinelibrary.com]

cardiac death, target vessel-related myocardial infarction or target lesion revascularization occurred with equal frequency at 5 years in patients randomized to treatment with a polymer-free probucol- and sirolimus-

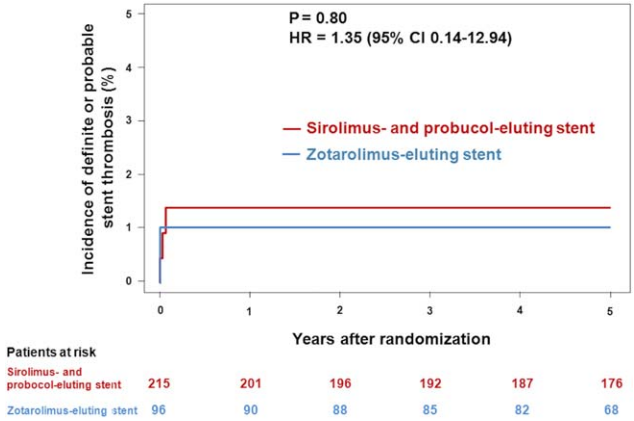

Fig. 2. Time to event curve for incidence of definite or probable stent thrombosis. Hazard ratios and *P* values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio. [Color figure can be viewed at wileyonlinelibrary.com]

eluting stent in comparison with a durable polymer zotarolimus-eluting stent. Moreover, late safety events—including stent thrombosis—were low and comparable in both groups beyond 1 year.

The long-term safety of DES implantation in the setting of STEMI remains somewhat uncertain [16]. Randomized trials comparing outcomes with first-generation DES versus bare metal stents implanted in the setting of AMI demonstrated superior efficacy at 1 year [17–19]. In addition, a meta-analysis of 8 randomized trials comparing first-generation DES with bare metal stents in STEMI patients showed no difference in stent thrombosis at 1–2 years [4]. Four-year follow-up of the randomized TYPHOON study demonstrated sustained efficacy superiority of the sirolimus-eluting stent over bare metal stents, with no difference in safety outcomes, including stent thrombosis [20]. However, complete follow-up data was available for only 501 (70%) patients. Five-year follow-up of the PASSION trial also showed comparable efficacy and safety outcomes for the paclitaxel-eluting stent versus bare metal stents [21]. However, definite very late stent thrombosis was seen almost exclusively after DES implantation, with nine cases (3.3%) in the DES arm versus two (0.7%) in the bare metal stent arm at 5 years ($P = 0.04$). Observational studies have raised similar concerns regarding the long-term safety of DES use in this setting, also reporting increased rates of very late stent thrombosis in patients with DES compared with bare metal stents [5,6]. In addition, observational studies have shown that acute coronary syndrome at the time of the index stenting is an independent risk factor for late stent thrombosis [22].

A potential explanation for the higher rate of stent thrombosis after primary angioplasty with DES is the

TABLE III. Stent Thrombosis at 5 Years

	Sirolimus- and probucol-eluting stent ($n = 215$)	Zotarolimus-eluting stent ($n = 96$)	Hazard ratio (95% CI)	P value
Stent thrombosis				
Definite	2 (0.9)	1 (1.0)	0.90 (0.08–9.90)	0.93
Probable	1 (0.5)	0 (0.0)	NA	0.91
Possible	2 (0.9)	1 (1.0)	0.89 (0.08–9.84)	0.93
Definite or probable	3 (1.4)	1 (1.0)	1.35 (0.14–12.94)	0.80

Data shown as number (percentage) by Kaplan–Meier analysis; hazard ratios and P values were calculated from Cox proportional hazard methods; NA = not applicable.

effect of underlying plaque morphology on local healing characteristics [7]. Delayed arterial healing is the principal substrate for late DES stent thrombosis [23]. In STEMI patients, there may be a more pronounced inflammatory reaction to durable polymer DES coatings. Autopsy studies of stented arterial segments in patients treated with DES for AMI versus stable angina have demonstrated increased inflammation with delayed healing and increased rates of stent thrombosis at AMI culprit sites compared with both non-culprit sites within the same stent and culprit sites in stable angina patients [7]. An additional factor that may contribute to delayed healing in this setting is strut penetration of necrotic core underlying a ruptured fibrous cap [7]. As plaque rupture is the most frequent cause of AMI, penetration of necrotic core is frequently found at the site of culprit lesions.

In terms of clinical data, an OCT substudy of HORIZONS-AMI reported decreased neointimal growth but higher rates of uncovered struts and strut malapposition at 13-month follow-up in patients who received DES compared with bare metal stents in the setting of STEMI [24]. Another OCT study also demonstrated a higher incidence of incomplete stent apposition and delayed tissue coverage in patients who underwent DES implantation in the setting of primary percutaneous intervention versus in the setting of stable or unstable angina [25]. This supports the theory that late dissolution of thrombus underlying stent struts may also contribute to late acquired malapposition and adverse clinical events. For DES implanted in the setting of AMI, rates of definite stent thrombosis in first-generation DES have been reported at 3.7% at 2 years [26].

Newer generation stents have attempted to overcome the limitation of polymer-induced inflammation and delayed healing using polymers with improved biocompatibility—either durable or biodegradable—or polymer-free DES platforms. In the setting of AMI, two randomized trials have demonstrated superior efficacy of second-generation DES over bare metal stents. The COMFORTABLE-AMI trial compared biodegradable polymer biolimus A9-eluting stents to bare metal stents implanted for AMI and showed superior efficacy of the DES, with no significant difference in stent thrombosis rates at 1 year [27]. The EXAMINATION trial compared a durable polymer everolimus-eluting stent with a bare metal stent implanted in the setting of STEMI and demonstrated superior efficacy and significantly lower rates of stent thrombosis in the DES arm at 1 year [28]. A pooled analysis of these trials demonstrated improved efficacy with a significantly reduced risk of late stent thrombosis for newer generation DES versus bare metal stents at 1 year but it remains to be seen if these results are sustained at long-term follow-up [29].

The results of the current study are important as they represent the first long-term report of patients with STEMI implanted with a polymer-free DES. The data show long-term clinical efficacy which is comparable to leading durable polymer stents. Although no difference in late clinical outcomes in favor of the polymer-free DES was seen, the study was significantly underpowered to detect such a difference. Importantly, rates of stent thrombosis were low and numerically similar with both stent platforms. The low rates in the control group are consistent with findings from long-term follow-up of patients enrolled in the EXAMINATION trial who received durable polymer DES in the setting of STEMI, with rates of definite stent thrombosis of 2.0% (versus 1.0% in the current report) at 5 years [30]. Dedicated randomized trials of polymer-free versus durable-polymer DES in STEMI patients are ultimately needed to determine the comparative efficacy and safety of these devices.

Limitations

Our report has a number of important limitations. First, the trial was powered to show noninferiority of the probucol- and sirolimus-eluting stent compared with the zotarolimus-eluting stent at 12 months. Additional analysis at long-term follow-up and post hoc analysis of subgroups of enrolled patients should be interpreted with caution. Second, the trial was not powered to detect differences in rarely occurring late adverse clinical events, so failure to detect significant differences does not reliably rule out a difference [31]. Third, protocol-mandated surveillance angiography

increases rates of target lesion revascularization to a level that is higher than would otherwise be seen in routine clinical practice [31]. Fourth, although both treatment groups received the same recommendation for duration of dual antiplatelet therapy after stenting, complete data relating to compliance or actual duration of same was not available. In addition, the use of more potent ADP receptor antagonists nowadays in patients undergoing coronary stenting for acute myocardial infarction is likely to reduce the risk of stent thrombosis in both treatment groups [32].

CONCLUSION

In patients undergoing percutaneous coronary intervention in the setting of STEMI, long-term outcomes of patients randomized to revascularization with a polymer-free sirolimus- and probucol-eluting stent versus a new generation durable polymer-based zotarolimus-eluting stent were similar at 5 years. Rates of late adverse events such as stent thrombosis were low and comparable in both treatment groups with few events beyond 12 months.

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