JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 8, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.01.009

Randomized Trial of Polymer-Free Sirolimus- and Probucol-Eluting Stents Versus Durable Polymer Zotarolimus-Eluting Stents

5-Year Results of the ISAR-TEST-5 Trial

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the late clinical performance of a polymer-free sirolimus- and probucol-eluting stent compared with a new-generation durable polymer-based zotarolimus-eluting stent.

BACKGROUND It was previously shown that polymer-free sirolimus- and probucol-eluting stents were noninferior to zotarolimus-eluting stents at 12 months. However, long-term follow-up of these devices is critical to evaluate late comparative efficacy.

METHODS In a clinical trial with minimal exclusion criteria, 3,002 patients were randomly assigned to treatment with polymer-free sirolimus- and probucol-eluting stents versus zotarolimus-eluting stents. The primary endpoint was the combined incidence of cardiac death, target vessel–related myocardial infarction, or target lesion revascularization.

RESULTS At 5 years, there was no difference in the incidence of the primary endpoint between sirolimus- and probucol-eluting stents and zotarolimus-eluting stents (23.8% vs. 24.2%, respectively; hazard ratio: 0.98; 95% confidence interval: 0.84 to 1.15; $p = 0.80$). The rates of the individual components of the primary endpoint were also comparable in both groups. The incidence of definite or probable stent thrombosis was low in both groups (1.3% vs. 1.6%, respectively; hazard ratio: 0.86; 95% confidence interval: 0.46 to 1.62; $p = 0.64$). The rates of any death, myocardial infarction, and revascularization were similar in both groups. Results were consistent across pre-specified subgroups of age, sex, diabetes, and vessel size.

CONCLUSIONS Long-term outcomes of patients treated with polymer-free sirolimus- and probucol-eluting stents compared with a new-generation durable polymer-based zotarolimus-eluting stent were similar. Rates of stent thrombosis were low and comparable in both treatment groups, with few events beyond 12 months. (Efficacy Study of Rapamycin- vs. Zotarolimus-Eluting Stents to Reduce Coronary Restenosis [ISAR-TEST-5]; NCT00598533)
(J Am Coll Cardiol Intv 2016;9:784–92) © 2016 by the American College of Cardiology Foundation.

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Manuscript received September 28, 2015; revised manuscript received December 14, 2015, accepted January 1, 2016.

Polymer coatings are important components of drug-eluting stent (DES) technology, controlling the release kinetics of the active drug, the critical determinant of antirestenotic efficacy (1). Furthermore, there is ongoing debate over potential beneficial antithrombogenic effects of polymer coatings (2,3). At the same time, it is well recognized that inflammatory reaction to durable polymer coatings plays an important causative role in the process of delayed arterial healing after DES implantation (4,5). This pathophysiological condition likely underlies a spectrum of late adverse events, including late stent thrombosis, delayed late luminal loss, and de novo in-stent atherosclerosis (6). Therefore, great efforts have been made to create polymer coatings with higher biocompatibility in new-generation permanent polymer DES (7). The new-generation zotarolimus-eluting stent represents a potential forward step in DES therapy. A 3-component durable polymer combines hydrophilic surface elements with a hydrophobic core and offers potentially improved biocompatibility, with enhanced drug-release kinetics.

Probucol is an antioxidant with efficacy as a systemic agent in preventing restenosis after coronary intervention (8–10). In addition, when used as a component of a stent coating matrix, its high lipophilicity means that it can retard the release of sirolimus, enhancing its antirestenotic efficacy (11). 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 (12). However, despite encouraging clinical data at short- to medium-term follow-up, the late performance of these stents remains poorly delineated. Against this background, we performed 5-year follow-up of patients enrolled in the ISAR-TEST-5 (Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus-Eluting Stents) randomized trial.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CK = creatine kinase
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
ULN = upper limit of normal

METHODS

STUDY POPULATION, DEVICE DESCRIPTION, AND STUDY PROTOCOL. Full details of the study population, methods, endpoints, and primary analysis have been previously reported (12). In brief, between February 2008 and August 2009, patients older than 18 years of age with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥50% de novo stenosis located in native coronary vessels were considered eligible, provided that written informed consent from patients or their legally authorized representatives for participation in the study was obtained. Patients with target lesions located in the left main stem, cardiogenic shock, malignancies or other comorbid conditions with life expectancy less than 12 months or that may result in protocol noncompliance, known allergy to the study medications (probucol, sirolimus, and zotarolimus), or pregnancy (present, suspected, or planned) were considered ineligible for the study. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocol was approved by the institutional ethics committee of the 2 participating centers: Deutsches Herzzentrum München and I. Medizinische Klinik, Klinikum Rechts der Isar, both in Munich, Germany.

Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order in which they qualified. Patients were assigned to receive polymer-free sirolimus- and probucol-eluting stents or permanent polymer zotarolimus-eluting stents in a 2:1 allocation. The polymer-free stent platform consists of a premounted, sand-blasted, 316L stainless steel microporous stent coated with a mixture of sirolimus, probucol, and shellac resin (a biocompatible resin widely used in the coating of medical tablets). The permanent polymer zotarolimus-eluting stent (Resolute; Medtronic Cardiovascular, Santa Clara, California) consists of a thin-strut stainless steel stent platform (Driver). The polymer coating system (BioLinx) consists of 3 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 (7,11,13,14). The aim of the present study was to compare outcomes of patients treated with polymer-free sirolimus- and probucol-eluting stents versus permanent polymer zotarolimus-eluting stents after 5-year clinical follow-up.

ENDPOINTS AND DEFINITIONS. The primary endpoint of this study was the device-oriented composite of cardiac death, myocardial infarction (MI) related to the target vessel, or target lesion revascularization at 60 months post-index intervention. Secondary endpoints were cardiac death, MI related to the target vessel, target lesion revascularization, all-cause mortality, any MI, any revascularization, target vessel revascularization, and the incidence of definite or probable stent thrombosis (by