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Original article

Polymer-free Sirolimus-eluting Versus Polymer-based Paclitaxel-eluting Stents: An Individual Patient Data Analysis of Randomized Trials

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ABSTRACT

Introduction and objectives: The angiographic and clinical efficacy of polymer-free sirolimus-eluting stents vs polymer-based paclitaxel-eluting stents remain a matter of debate. We sought to investigate angiographic and clinical measures of efficacy of polymer-free sirolimus-eluting stents vs polymer-based paclitaxel-eluting stents.

Methods: Patient data from the randomized intracoronary stenting and angiographic restenosis-test equivalence between the 2 drug-eluting stents (ISAR-TEST) clinical trial and the LIPSIA Yukon clinical trial (randomized comparison of a polymer-free sirolimus-eluting stent vs a polymer-based paclitaxel-eluting stent in patients with diabetes mellitus) were pooled. The angiographic (primary) endpoint was in-stent late lumen loss at 6 months to 9 months. The clinical (secondary) endpoints were death or myocardial infarction, cardiac death or myocardial infarction, target lesion revascularization, and myocardial infarction.

Results: A total of 686 patients (polymer-free sirolimus-eluting stents, n=345 vs polymer-based paclitaxel-eluting stents, n=341) and 751 lesions (polymer-free sirolimus-eluting stents, n=383 vs polymer-based paclitaxel-eluting stents, n=368) were included in the study. Control angiography (606 lesions, 80.6%) showed comparable in-stent late lumen loss for polymer-free sirolimus-eluting stents vs polymer-based paclitaxel-eluting stents (0.53 [0.59] mm vs 0.46 [0.57] mm; *P*=.15). Median follow-up was 34.8 months. Polymer-free sirolimus-eluting stents and polymer-based paclitaxel-eluting stents were associated with comparable risk of death or myocardial infarction (relative risk=1.17; 95% confidence interval, 0.49-2.80; *P*=.71), cardiac death or myocardial infarction (relative risk=1.17; 95% confidence interval, 0.72-1.89; P=.50), target lesion revascularization (relative risk=0.98; 95% confidence interval, 0.65-1.47; *P*=.93), and myocardial infarction (relative risk=1.79; 95% confidence interval, 0.85-3.76; *P*=.12).

Conclusions: In this pooled analysis, polymer-free sirolimus-eluting stents were comparable to polymer-based paclitaxel-eluting *stents* with respect to both angiographic and clinical efficacy.

Stents liberadores de rapamicina sin polímero frente a *stents* liberadores de paclitaxel con polímero: un análisis de datos de pacientes procedentes de ensayos aleatorizados

Palabras clave:
Pérdida luminal tardía
Stent liberador de paclitaxel
Polímero
Stent liberador de rapamicina

RESUMEN

Introducción y objetivos: La eficacia angiográfica y clínica de los *stents* liberadores de rapamicina sin polímero frente a los liberadores de paclitaxel con polímero sigue siendo motivo de debate. En nuestro estudio se compararon las medidas de eficacia angiográficas y clínicas de los *stents* liberadores de rapamicina sin polímero frente a los liberadores de paclitaxel con polímero.

Métodos: Se combinaron los datos de pacientes procedentes del estudio clínico aleatorizado ISAR-TEST (prueba de equivalencia entre dos *stents* farmacoactivos respecto al implante de *stent* intracoronario y reestenosis angiográfica) y el estudio clínico LIPSIA Yukon (comparación aleatorizada de *stents* farmacoactivos liberadores de rapamicina sin polímero frente a liberadores de paclitaxel con polímero en pacientes con diabetes mellitus). El criterio de valoración angiográfico (primario) fue la pérdida luminal tardía en el *stent* entre los 6 y los 9 meses. Los criterios de valoración clínicos (secundarios) fueron: infarto de miocardio o muerte, muerte cardiaca o infarto de miocardio, revascularización de la lesión tratada e infarto de miocardio.

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Resultados: El estudio incluyó a un total de 686 pacientes (*stents* liberadores de rapamicina sin polímero [n = 345] frente a *stents* liberadores de paclitaxel con polímero [n = 341]) y 751 lesiones (*stents* liberadores de rapamicina sin polímero [n = 383] frente a *stents* liberadores de paclitaxel con polímero [n = 368]). La angiografía de control (606 lesiones [80,6%]) mostró una pérdida luminal tardía en el *stent* comparable entre los dos tipos de *stents* estudiados (0,53 ± 0,59 mm en los *stents* sin polímero frente a 0,46 ± 0,57 mm en *stents* con polímero; p = 0,15). La mediana de seguimiento fue de 34,8 meses. Los *stents* liberadores de rapamicina sin polímero y los liberadores de paclitaxel con polímero se asociaron con similares riesgos de muerte o infarto de miocardio (riesgo relativo =1,17; intervalo de confianza del 95%, 0,49-2,80; p = 0,71); muerte cardiaca o infarto de miocardio (riesgo relativo = 1,17; intervalo de confianza del 95%, 0,72-1,89; p = 0,50); revascularización de la lesión que hay que tratar (riesgo relativo = 0,98; intervalo de confianza del 95%, 0,65-1,47; p = 0,93) e infarto de miocardio (riesgo relativo = 1,79; intervalo de confianza del 95%, 0,85 3,76; p = 0,12).

Conclusiones: En este análisis combinado, los valores de eficacia angiográfica y clínica fueron similares para los *stents* liberadores de rapamicina sin polímero y los liberadores de paclitaxel con polímero.

Abbreviations

DES: drug-eluting stents
LLL: late lumen loss
MI: myocardial infarction
PB-PES: polymer-based paclitaxel-eluting stents
PF-SES: polymer-free sirolimus-eluting stents
ST: stent thrombosis

INTRODUCTION

Drug-eluting stents (DES) reduce the need for repeat revascularization as compared to bare-metal stents.[1] However, subsequent reinterventions to the target vessel may still be required and the initial enthusiasm for DES has been somewhat attenuated by results from extended follow-up studies.[2] The main components of DES are drugs, supportive metallic or inorganic scaffolds, and polymers.[3] Permanent (nondegradable) polymers are used to bind eluted drugs (both limus and nonlimus) to the scaffold and allow progressive release, thereby prolonging the duration of the antirestenotic effect. However, permanent polymers remain after drug elution and are involved in the chronic inflammatory response at the site of stent implantation and in late adverse clinical events.[4,5]

Strategies to avoid these consequences of permanent polymers include the use of biodegradable polymers, bioabsorbable DES, and polymer-free DES. Unlike polymer-based DES, polymer-free DES uses a mechanically modified strut surface to bind drugs directly without recourse to a polymer.[6] Several studies have investigated polymer-free stents which elute the immunosuppressive drug sirolimus.[7] However, recent publications have questioned their angiographic and clinical efficacy as compared to polymer-based paclitaxel-eluting stents (PB-PES), especially in high-risk subgroups.[8]

We performed an updated, individual patient level, pooled analysis of the intracoronary stenting and angiographic restenosis-test equivalence between the 2 DES (ISAR-TEST) clinical trial and the LIPSIA Yukon clinical trial[9,10] (randomized comparison of a polymer-free sirolimus-eluting stent [PF-SES] vs a PB-PES in patients with diabetes mellitus). The main objective of the present study was to investigate the performance of PF-SES vs PB-PES in relation to angiographic and clinical outcomes. In addition, the performance of PF-SES vs PB-PES was assessed in subgroups of certain interest.

METHODS

Patient Population and Study Protocol

The design of the ISAR-TEST and LIPSIA Yukon clinical trials as well as the characteristics of the patients enrolled in these trials have been described previously[9,10] and are listed in detail in, Table 1, supplementary material. In brief, both trials were prospective, multicenter, controlled clinical trials in which patients were randomized to receive PF-SES (Yukon or Yukon Choice, Translumina GmbH; Hechingen, Germany) or PB-PES (Taxus Express 2 or Taxus Liberté, Boston Scientific; Natick, Massachusetts, United States). Enrollment was completed in 2006 for ISAR-TEST and in 2008 for LIPSIA Yukon. Patients were eligible if they were ≥18 years old, had stable or unstable angina or a positive stress test, and if percutaneous coronary intervention for de novo lesions (≥50%) in a native coronary artery was indicated. In the LIPSIA Yukon trial, only patients with diabetes mellitus were enrolled. Both trials mandated the exclusive use of randomized stents in cases where multiple lesions were treated or multiple stents were required. The main exclusion criteria were recent myocardial infarction (MI) (≤48 h after symptom onset), a target lesion or significant (≥50%) stenosis located in the left main trunk, and contraindications or known allergies to contrast medium, acetylsalicylic acid, heparin, thienopyridines, sirolimus, paclitaxel, or stainless steel. Severe disorders of hemostasis or platelet aggregation, pregnancy, other trial participation, and severe comorbidities (ie, malignancy) were also considered as exclusion criteria.

Randomization Process and Intervention

Both studies were approved by the ethics committee at each participating institution, and eligible patients gave their written informed consent. After confirmation of the enrollment criteria and wiring of the target lesion, patients were randomly assigned to the treatment groups. A computer-generated random sequence list and sealed opaque envelopes were used in the ISAR-TEST trial; an internet-based randomization system was used in the LIPSIA Yukon trial. Randomization was not stratified in either of the trials. Patients were assigned to receive either the PF-SES or PB-PES; detailed description and in-depth background of the PF-SES have been published elsewhere.[6,11] The ISAR-TEST trial used a first-generation Yukon stent scaffold, while the LIPSIA Yukon trial used the second generation platform (Yukon Choice). Although there were trivial differences in terms of strut thickness (115 μm for first generation vs 87 μm for second generation), the total amount of drug used for the coating process remained the same (2% sirolimus solution). This concentration of sirolimus had the highest antirestenotic efficacy in a previous report.[6] The 2 PB-PES