CLINICAL RESEARCH

Zotarolimus-eluting stent versus sirolimus-eluting and paclitaxel-eluting stents for percutaneous coronary intervention: A meta-analysis of randomized trials

Ankur Sethi a,∗, Amol Bahekar a, Rohit Bhuriya a, Anurag Bajaj b, Param Puneet Singh a, Rohit Arora a, Sandeep Khosla a

a Department of Medicine, Rosalind Franklin University of Medicine and Sciences, 3333, Green Bay Road, North Chicago, IL 60064, USA
b Department of Medicine, Wright Center of Graduate Medical Education, Scranton, PA, USA

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Summary
Background. — The zotarolimus-eluting stent (ZES) is a new drug-eluting stent that delivers zotarolimus, a synthetic analogue of sirolimus, through a biocompatible phosphorylcholine polymer coating. ZES has shown promising results compared with bare-metal stents, but its safety and efficacy against sirolimus-eluting (SES) and paclitaxel-eluting (PES) stents is yet to be established.
Aims. — We aimed to summarize current evidence from randomized trials comparing ZES with SES and PES.
Methods. — We searched the Medline, Embase and CENTRAL databases for randomized studies comparing ZES with SES and PES for percutaneous coronary intervention. Relevant clinical and

Abbreviations: CI, confidence interval; DES, drug-eluting stent(s); MACE, major adverse cardiovascular events; OR, odds ratio; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent(s); RCT, randomized controlled trial; SES, sirolimus-eluting stent(s); STEMI, ST-segment elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent.

∗ Corresponding author. Fax: +1 773 257 6726.
E-mail address: drankursethi@gmail.com (A. Sethi).

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angiographic outcomes were extracted and combined using random and fixed-effect models for heterogeneous and homogenous outcomes, respectively.

Results. — Seven randomized trials met the inclusion criteria: ZES group, n = 3787; SES group, n = 2606; PES group, n = 1966. Compared with SES, ZES was associated with significantly higher odds of clinically driven target vessel revascularization (odds ratio [OR] 2.36, 95% confidence interval [CI] 1.78–3.14) and target lesion revascularization (OR 2.46, 95% CI 1.36–4.46). Compared with SES, ZES had higher in-stent restenosis (OR 6.13, 95% CI 3.96–9.50), late lumen loss ‘in-stent’ (mean difference [MD] 0.39 mm, 95% CI 0.34–0.44) and late lumen loss ‘in-segment’ (MD 0.18 mm, 95% CI 0.15–0.21). ZES was associated with higher in-stent late lumen loss than PES (MD 0.18 mm, 95% CI 0.07–0.28). There were no differences in mortality, reinfarction or stent thrombosis with ZES compared with SES and PES.

Conclusion. — ZES is not superior to PES and is inferior to SES in terms of angiographic outcomes and clinically driven revascularization.

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Résumé

Justification. — Le stent actif au zotarolimus est un nouveau stent libérant du zotarolimus, analogue synthétique du sirolimus, au travers d’un polymère biocompatible (phosphorylcholine). Les résultats initiaux sont prometteurs en comparaison des stents métalliques mais l’efficacité et la sécurité, comparativement aux stents au sirolimus ou au paclitaxel, n’ont pas été établies. L’objectif était donc de faire la synthèse des données actuelles des études randomisées comparant ces trois types de stents (zotarolimus, sirolimus et paclitaxel).

Méthode. — Nous avons interrogé les bases Medline, Embase et CENTRAL, en nous intéressant aux études randomisées comparant ces différents types de stents pour les interventions coronaires percutanées. Les données cliniques et angiographiques, ainsi que les données évolutives ont été extraites et associées en utilisant des modèles préréétablis (randomisés et fixes) pour évaluer les données évolutives en incluant leur caractère homogène ou hétérogène.

Résultats. — Sept études randomisées répondaient aux critères d’inclusion incluant 3787 patients dans le groupe zotarolimus, 2606 patients dans le groupe sirolimus et 1966 patients dans le groupe paclitaxel. Le groupe zotarolimus est associé à un taux accru d’efficacité sur la revascularisation du vaisseau site (OR 2,36, IC 95% 1,78–3,14) et de traitement de la lésion cible (OR 2,46, IC 95% 1,36–4,46), comparativement aux stents au sirolimus. Le stent au sirolimus était associé à un taux de resténose intra-stent plus élevé (OR 6,13, IC 95% 3,87–9,50), une réduction de calibre intra-stent (différence moyenne 0,39 mm, IC 95% 0,34–0,44) ainsi qu’à la réduction de calibre du segment considéré (différence moyenne 0,18 mm, IC 95% 0,15–0,21) comparativement aux stents au sirolimus. Enfin, le stent au zotarolimus est associé avec une réduction de calibre intra-stent plus élevé (différence 0,18 mm, IC 95% 0,07–0,28) comparativement au paclitaxel. Il n’y avait pas de différence du taux de réinfarctus ou de thrombose de stent avec le stent au zotarolimus, comparativement aux stents au sirolimus ou au paclitaxel.

Conclusion. — Le stent au zotarolimus n’est pas supérieur au stent au paclitaxel et est inférieur en termes d’efficacité sur les critères angiographiques et l’indication à une revascularisation sur les critères cliniques, comparativement au stent au sirolimus.

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Introduction

The first commercially available drug-eluting stents (DES) — the sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES) — significantly reduced rates of restenosis and repeat revascularization after percutaneous coronary intervention (PCI) compared with bare-metal stents, in a wide variety of patients [1]. However, the long-term safety of these stents has been questioned by the reports of increased incidence of stent thrombosis, especially with PES [2,3]. Arterial wall inflammation, delayed healing and poor endothelialization are some of the factors thought to be responsible for late stent thrombosis events after DES implantation [4,5].

Zotarolimus is a novel agent with structural homology to sirolimus, developed exclusively for its use in DES. The zotarolimus-eluting stent (ZES) has a low profile, a thin strut design and a biocompatible phosphorylcholine polymer coating (which mimics the red blood cell outer membrane), and it elutes more than 90% of the drug in the first few weeks after implantation [6]. These advances in stent design, polymer and drug elution kinetics are thought to reduce platelet adhesion and improve arterial healing, and may therefore decrease the incidence of stent thrombosis
compared with SES and PES. ZES has been found to have better neointimal strut coverage compared with SES, as measured by optical coherence tomography at 9 months [7]. Also, a randomized controlled trial (RCT) comparing ZES with a bare-metal stent showed a reduction in the rates of angiographic and clinical restenosis, with no difference in stent thrombosis [8]. Despite early success, the role of ZES compared with SES and PES is unclear. RCTs comparing ZES with SES and PES have shown mixed results. Therefore, we decided to perform a meta-analysis of RCTs comparing ZES with SES and PES for PCI.

Methods

Objective

Our goal was to compare ZES with two established stents used for PCI—SES and PES—in terms of angiographic and clinical endpoints.

Search strategy

We performed a systematic search of the Medline, Cochrane Central Register of Controlled Trials (CENTRAL) and Embase databases for RCTs comparing ZES with SES and/or PES, published before 30 September 2010. The keywords ‘zotarolimus’ and ‘zotarolimus eluting stent’ were used. All retrieved abstracts and/or articles were reviewed for possible inclusion. The references of review articles and included studies were hand-searched for any relevant studies. In addition, the manufacturer’s website (http://www.medtronic.com/for-healthcare-professionals/products-therapies/cardiovascular/coronary-stents/index.htm) was screened for any potentially relevant studies on 30 September 2010. No language restriction was imposed. RCTs comparing ZES with SES and/or PES and reporting angiographic and clinical endpoints were eligible for inclusion. Non-randomized studies or registries; comparisons with stents other than SES or PES and studies reporting no clinical or angiographic endpoints were excluded.

Data extraction and validity assessment

Two investigators (A.S. and A.B.) independently searched the databases for eligible studies. The original manuscripts of potentially relevant studies were reviewed. The study characteristics and endpoints were entered on a prespecified data form. The following study characteristics were extracted: sample size; method of randomization; inclusion and exclusion criteria; mean age; use of angiographic follow-up; primary endpoint; duration of dual antiplatelet therapy; follow-up duration; method of evaluation of angiographic outcomes; and criteria for target vessel or lesion revascularization. Any inconsistencies were reviewed with the help of a third author.

Endpoints

The following clinical endpoints were evaluated: major adverse cardiac events (MACE); mortality; myocardial infarction; target vessel revascularization (TVR); target lesion revascularization (TLR); and stent thromboses. The following angiographic outcomes were evaluated: in-stent and in-segment restenosis; and in-stent and in-segment late lumen loss.

Statistical analysis

A study-level analysis was done. Data were analysed using Review Manager 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Odds ratios (ORs) and 95% confidence intervals (CIs) were used as summary statistics for all outcomes except the continuous variables in-stent and in-segment late lumen loss, for which mean differences were calculated. Studies were evaluated for heterogeneity by visual inspection of the CIs and by means of $I^2$ ($I^2 = (Q−df)/Q$), where $Q$ is the $\chi^2$ statistic and df is degree of freedom. A value of $I^2 > 30\%$ was considered as an indicator of significant heterogeneity. A Mantel–Haenszel fixed-effect model was used to calculate the pooled ORs for non-heterogeneous endpoints. Random effect (DerSimonian) analysis was performed in the presence of significant heterogeneity across the studies. A $P$ value < 0.05 was considered significant.

Results

Seven RCTs were included in the meta-analysis (Fig. 1) [9–15], resulting in a total of 8359 patients: 3787 patients in the ZES group; 2606 in the SES group; and 1966 in the PES group. The characteristics of included studies are shown in Table 1. Three studies compared ZES with SES, two compared ZES with PES and two compared all three stents. Three studies included patients with elective PCI only, one study included stable angina or acute coronary syndrome but excluded ST-segment elevation myocardial infarction (STEMI), one study included patients with STEMI only and two included all-comers (Table 1). In addition,
### Table 1  Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Inclusion criteria</th>
<th>Major exclusion criteriaa</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR III</td>
<td>323 113 NA</td>
<td>Elective PCI for symptomatic CAD due to native vessel lesion diameter 2.5–3.5 mm &amp; length 14–27 mm</td>
<td>Recent MI or PCI; LVEF &lt; 30%; &gt; 40% lesion other than target lesion; unprotected left main; chronic total occlusion; TIMI flow grade &lt; 2</td>
<td>61.4 61.7 NA</td>
</tr>
<tr>
<td>ENDEAVOR IV</td>
<td>773 NA 775</td>
<td>Clinical CAD or positive functional study with single de novo lesion diameter 2.5–3.5 mm &amp; length &lt; 27 mm</td>
<td>Recent AMI; LVEF &lt; 30%; left main or ostial lesion</td>
<td>63.5 NA 63.6</td>
</tr>
<tr>
<td>ISAR-TEST-2</td>
<td>339 335 NA</td>
<td>Ischaemic symptoms or evidence of myocardial ischaemia with &gt; 50% de novo stenosis in native vessels</td>
<td>Left main disease; in-stent stenosis; cardiogenic shock</td>
<td>67.2 66.6 NA</td>
</tr>
<tr>
<td>SORT OUT III</td>
<td>1162 1170 NA</td>
<td>Chronic stable angina or ACS</td>
<td>None</td>
<td>64.3 64.3 NA</td>
</tr>
<tr>
<td>ZEST</td>
<td>883 878 884</td>
<td>Stable angina or ACS with ≥ 1 lesion</td>
<td>STEMI; LVEF &lt; 25%; shock; left main disease</td>
<td>61.7 61.9 62</td>
</tr>
<tr>
<td>ZEST-AMI</td>
<td>108 110 110</td>
<td>STEMI</td>
<td>LVEF &lt; 30%; left main disease; previous MI; shock</td>
<td>61.9 57.8 59.3</td>
</tr>
<tr>
<td>ZoMaxx I</td>
<td>199 NA 197</td>
<td>Stable or unstable angina or objective evidence of ischaemia with lesion diameter 2.5–3.5 mm &amp; length 10–30 mm</td>
<td>Recent MI; LVEF &lt; 30%; left main disease or ostial lesion within 2 mm</td>
<td>63 NA 63</td>
</tr>
</tbody>
</table>
Table 1  (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Routine angiographic follow-up</th>
<th>Primary endpoint</th>
<th>Longest available follow-up (months)</th>
<th>Stent type</th>
<th>ZES</th>
<th>SES</th>
<th>PES</th>
<th>Duration of dual antiplatelet therapy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR III [11]</td>
<td>8 months</td>
<td>In-segment late lumen loss at 8 months</td>
<td>36</td>
<td>Endeavor (Medtronic)</td>
<td>Cypher (Cordis)</td>
<td>NA</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ENDEAVOR IV  [13]</td>
<td>8 months</td>
<td>TVF&lt;sup&gt;b&lt;/sup&gt; at 9 months</td>
<td>24</td>
<td>Endeavor (Medtronic)</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>ISAR-TEST-2  [9]</td>
<td>6–8 months and 2 years</td>
<td>Binary restenosis</td>
<td>24</td>
<td>Endeavor (Medtronic)</td>
<td>Cypher (Cordis)</td>
<td>NA</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>SORT OUT III [15]</td>
<td>Not done</td>
<td>MACE at 9 months</td>
<td>18</td>
<td>Endeavor (Medtronic)</td>
<td>Cypher Select/Plus (Cordis)</td>
<td>NA</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>ZEST        [14]</td>
<td>9 months</td>
<td>MACE&lt;sup&gt;c&lt;/sup&gt; at 12 months</td>
<td>12</td>
<td>Endeavor (Medtronic)</td>
<td>Cypher Select (Cordis)</td>
<td>Taxus Liberte (Boston Scientific)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>ZEST-AMI    [12]</td>
<td>8 months</td>
<td>MACE at 12 months</td>
<td>12</td>
<td>Endeavor (Medtronic)</td>
<td>Cypher (Cordis)</td>
<td>Taxus Liberte (Boston Scientific)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>ZoMaxx I    [10]</td>
<td>9 months</td>
<td>In-segment late lumen loss at 9 months</td>
<td>9</td>
<td>ZoMaxx (Abbott)</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; AMI: acute myocardial infarction; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular events; MI: myocardial infarction; NA: not applicable; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; STEMI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction; TVF: target vessel failure; TVR: target vessel revascularization; ZES: zotarolimus-eluting stent.

<sup>a</sup> Only major exclusion criteria are presented here.

<sup>b</sup> Cardiac death, MI or TVR.

<sup>c</sup> Death, MI, ischaemia-driven TVR.
Table 2 Definitions of clinical endpoints in included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>MACE</th>
<th>Stent thrombosis reported per Academic Research Consortium [27]</th>
<th>Clinically or ischaemia-driven TVR/TLR</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENDEAVOR III [11]</td>
<td>Death, MI and clinically driven TLR at 9 months; and death, MI and TVR at 3 years</td>
<td>No, per protocol only</td>
<td>Ischaemic symptoms or abnormal functional study with &gt; 50% stenosis or &gt; 70% stenosis</td>
<td>Q wave MI: q wave in two or more contiguous leads with elevated CKMB or CK Non Q wave: CK &gt; 2 times normal with elevated CKMB</td>
</tr>
<tr>
<td>ENDEAVOR IV [13]</td>
<td>Death, MI and clinically driven TLR</td>
<td>Yes (definite, probable and possible)</td>
<td>Reported but not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>ISAR-TEST-2 [9]</td>
<td>Death, MI and TLR</td>
<td>Yes (definite, probable and possible)</td>
<td>Clinical symptoms or objective signs of ischaemia</td>
<td>New Q waves and/or CK or CKMB &gt; 3 times ULN in two or more blood samples</td>
</tr>
<tr>
<td>SORT OUT III [15]</td>
<td>Cardiac death, MI and clinically driven TVR</td>
<td>Yes (definite)</td>
<td>No routine follow-up angiography, revascularization only if indicated clinically</td>
<td>Universal definition of MI per Thygesen et al. [28]</td>
</tr>
<tr>
<td>ZEST [14]</td>
<td>Death, MI and ischaemia-driven TVR</td>
<td>Yes (definite, probable and possible)</td>
<td>Documented ischaemia (symptoms, ECG changes or functional study) with &gt; 50% stenosis or &gt; 70% stenosis</td>
<td>New Q waves or CKMB &gt; 3 times ULN</td>
</tr>
<tr>
<td>ZEST-AMI [12]</td>
<td>Death, MI and ischaemia-driven TVR</td>
<td>Yes (definite and probable)</td>
<td>Ischaemic symptoms or functional study and &gt; 50% stenosis or &gt; 70% stenosis</td>
<td>Symptoms or ECG changes with CKMB &gt; 3 times ULN</td>
</tr>
<tr>
<td>ZoMaxx [10]</td>
<td>Cardiac death, MI and ischaemia-driven TVR</td>
<td>Yes (definite, probable and possible)</td>
<td>Reported but not defined</td>
<td>Q wave MI: q wave in two or more contiguous leads with elevated CKMB or CK Non Q wave: CK &gt; 2 times normal with elevated CKMB</td>
</tr>
</tbody>
</table>

CK: creatine kinase; CKMB: creatine kinase-MB; ECG: electrocardiogram; MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR: target lesion revascularization; TVR: target vessel revascularization; ULN: upper limit of normal.
three studies [10,11,13] had specific angiographic criteria for inclusion, as shown in Table 1. The mean age of the study population varied from 57 to 67 years. Patients groups were well balanced with regard to the most relevant characteristics within individual studies. All studies except SORT OUT III [15] had routine angiographic follow-up. All studies used the Endeavor stent (Medtronic, Santa Rosa, CA, USA) in the ZES group, except for one study [10], which used the ZoMaxx stent (Abbott Laboratories, Chicago, IL, USA). The definitions of the relevant clinical endpoints used in the included studies are shown in Table 2. Clinical endpoints were adjudicated by an independent committee blinded to stent assignment in all seven studies. Angiographic analysis was done at independent core laboratories blinded to stent assignment in all studies. A 3-year follow-up for the ENDEAVOR III study [16] and 2-year follow-up for the ENDEAVOR IV [17] and ISART-TEST-2 [9] studies were reported subsequently, in addition to the respective 9-month, 12-month and 12-month follow-up periods published initially. Also, the SORT OUT III trial reported clinical endpoints at 9 months and 18 months. The other three studies had a follow-up duration of 1 year or less (Table 1). To accommodate the variable follow-up periods, we decided to combine the clinical endpoints at follow-up of up to 1 year and at longest available follow-up. No significant disagreement was found between the data retrieved by two investigators.

Clinical endpoints

MACE

The definition of MACE used in each study is shown in Table 2. MACE were experienced by 12%, 8.6% and 11.8% of patients randomized to the ZES, SES and PES groups, respectively. There was moderate heterogeneity among the studies for the endpoint of MACE, as evidenced by the I² in excess of 40% for all four comparisons. Therefore, a random-effect meta-analysis was performed. Compared with SES, ZES was associated with significantly higher MACE up to 1 year (OR 1.50, 95% CI 1.06—2.13) and at longest available follow-up (OR 1.39, 95% CI 1.01—1.91). There was no difference in MACE between PES and ZES up to 1 year (OR 0.94, 95% CI 0.67—1.32) and at longest available follow-up (OR 0.94, 95% CI 0.68—1.30).

Myocardial infarction

There was no difference in myocardial infarction between ZES versus SES (OR 1.0, 95% CI 0.41—2.45) and ZES versus PES (OR 0.55, 95% CI 0.55—1.04) up to 1 year and at longest available follow-up (ZES versus SES: OR 0.83, 95% CI 0.40—1.72; ZES versus PES: OR 0.71, 95% CI 0.48—1.07).

Mortality

There was no difference in mortality between ZES versus SES (OR 1.23, 95% CI 0.80—1.89) and ZES versus PES (OR 1.11, 95% CI 0.59—2.06) up to 1 year and at longest available follow-up (ZES versus SES: OR 1.01, 95% CI 0.62—1.65; ZES versus PES: OR 1.20, 95% CI 0.74—1.96).

Clinically driven target vessel and lesion revascularization

All seven studies reported an incidence of clinically or ischaemia-driven TVR and/or TLR, as defined in Table 2. ZES was associated with significantly higher odds of clinically driven TVR compared with SES up to 1 year (OR 2.31, 95% CI 1.65—3.22) and at longest available follow-up (OR 2.36, 95% CI 1.78—3.14), as shown in Fig. 2A. Similarly, ZES use was associated with significantly higher odds of clinically driven TLR compared with SES up to 1 year (OR 2.87, 95% CI 1.89—4.35) and at longest available follow-up (OR 2.46, 95% CI 1.36—4.46), as shown in Fig. 2B. There was no difference in clinically driven TVR and TLR between ZES and PES up to 1 year (TVR: OR 0.85, 95% CI 0.61—1.18; TLR: OR 0.94, 95% CI 0.71—1.26) and at longest available follow-up (TVR: OR 0.88, 95% CI 0.63—1.23; TLR: OR 1.11, 95% CI 0.58—2.13), as shown in Fig. 3A and B.

Stent thromboses

There was no significant difference in stent thromboses between ZES and SES up to 1 year (OR 1.53, 95% CI 0.39—5.96) and at longest available follow-up (OR 1.12, 95% CI 0.41—3.08), as shown in Fig. 2C. Similarly, there was no difference in stent thromboses between ZES and PES up to 1 year (OR 1.05, 95% CI 0.56—2) and at longest available follow-up (OR 0.88, 95% CI 0.51—1.55), as shown in Fig. 3C.

Angiographic outcomes

Compared with SES, ZES was associated with a significantly higher rate of in-stent restenosis (OR 6.13, 95% CI 3.96—9.50) and in-segment restenosis (OR 3.46, 95% CI 1.59—7.50), as shown in Fig. 4A and B, respectively. There was no difference between ZES and PES in in-stent restenosis (OR 1.56, 95% CI 0.84—2.90) and in-segment restenosis (OR 1.44, 95% CI 0.88—2.35) (Fig. 5A and B). Also, compared with SES, ZES was associated with higher in-stent late lumen loss (mean difference 0.39 mm, 95% CI 0.34—0.44; Fig. 4C) and in-segment late lumen loss (mean difference 0.18 mm, 95% CI 0.15—0.21). However, in-segment late lumen loss was similar (mean difference 0.06 mm, 95% CI —0.04—0.16) but in-segment lumen loss was higher (mean difference 0.18 mm, 95% CI 0.07—0.28) in the ZES group compared with the PES group (Fig. 5C).

Discussion

The present meta-analysis found that ZES use was associated with significantly higher revascularization rates compared with SES use. Also, ZES was inferior to SES in terms of the angiographic endpoints of restenosis and late lumen loss. ZES was similar to PES for all clinical and most angiographic endpoints, except in-stent late lumen loss. In addition, no difference in stent thromboses was apparent during follow-up when ZES was compared with SES and PES. To the best of our knowledge, this is the first meta-analysis comparing ZES directly with SES and PES separately. The included studies varied in terms of patient population, ranging from stable coronary artery disease to acute coronary syndrome, STEMI and all-comers, a pattern that represents the state of DES.
Figure 2. Forest plots comparing the zotarolimus-eluting stent (ZES) with the sirolimus-eluting stent (SES) for the following endpoints: (A) target vessel revascularization; (B) target lesion revascularization; (C) stent thrombosis. CI: confidence interval; M-H: Mantel–Haenszel.

ZES compared with SES and PES in PCI

use in contemporary practice (Table 1). We combined these studies to achieve a higher power to evaluate ZES (a relatively new DES), against established DESs (SES and PES), in terms of both clinical and angiographic endpoints.

Zotarolimus is an analogue of sirolimus, which binds to the immunophilin protein FKBP 12 to inhibit a growth-regulating enzyme known as mammalian target of rapamycin (mTOR) [18]. Zotarolimus has a shorter half-life and less affinity for FKBP 12 than sirolimus. In addition, the two ZES evaluated in our analysis — Endeavor (Medtronic, Santa Rosa, CA, USA) and ZoMaxx (Abbott Laboratories, Chicago, IL, USA) — have rapid drug elution kinetics, a clear distinction from currently available SES, which have a slower drug release [18]. These pharmacological differences may explain the relatively weak antiproliferative effect of ZES and consequently higher restenosis compared with SES. On the other hand, ZES was similar to PES with regard to most angiographic endpoints, which is consistent with previous studies [19,20] that showed a higher incidence of clinical and angiographic stenosis with PES compared with SES. The
Figure 3. Forest plots comparing the zotarolimus-eluting stent (ZES) with the paclitaxel-eluting stent (PES) for the following endpoints: (A) target vessel revascularization; (B) target lesion revascularization; (C) stent thrombosis. CI: confidence interval; M-H: Mantel–Haenszel.

difference in late lumen loss between SES and ZES was higher than reported previously between SES and PES [20]. As some authors have suggested a curvilinear relationship between late lumen loss and probability of TLR [21], this accentuated late lumen loss may place patients treated with ZES closer to the steeper slope of the curve. Although the ZoMaxx and Endeavor stents have a similar thin strut design, biocompatible phosphorylcholine polymer and zotarolimus concentration (10 μg/mm), there are some differences in the stent platforms and drug elution kinetics [18]. Exclusion of the ZoMaxx I study from the meta-analysis did not change the results for any endpoint significantly.

All studies except the SORT OUT III study had a routine angiographic follow-up (Table 1), which raises concern about increased revascularization rates secondary to occlusive stenotic reflex. All included studies reported clinically or ischaemia-driven revascularization rates. In addition, studies comparing ZES with SES reported explicit indications used for clinically or ischaemia-driven revascularization (Table 2). Although more than 70% stenosis on follow-up angiogram was considered as one of the indication for TLR, but TLR in the ZES group in the SORT OUT III study (6.1%), which had no angiographic follow-up, and in the ENDEAVOR III (6.3%) and ZEST (4.8%) studies, which had planned
ZES compared with SES and PES in PCI

Figure 4. Forest plots comparing the zotarolimus-eluting stent (ZES) with the sirolimus-eluting stent (SES) for: (A) in-stent restenosis; (B) in-segment restenosis; (C) in-segment late lumen loss. CI: confidence interval; M-H: Mantel–Haenszel.

angiographic follow-up, were not significantly different. On the other hand, TLR in the ISAR-TEST-2 study was higher in both the ZES (14%) and SES (10.7%) groups. All statistical heterogeneity in the analysis for TLR was explained by the ISAR-TEST-2 study; its exclusion reduced I² from 74% to 0% without loss of statistical significance (OR 3.43, 95% CI 2.36–4.98). Therefore, the impact of routine angiographic follow-up of revascularization rates cannot be clearly determined from our analysis. However, the results of TLR for ZES versus SES were robust, and remain significant on exclusion of one study at a time from the meta-analysis. Also, the odds of in-stent restenosis were lower in the ENDEAVOUR III study (4.67), which systematically excluded patients with complex lesions or acute coronary syndrome, than in the SORT OUT III (6.38), ZEST (5.86) and ZEST-AMI (13.66) studies, which included patients with acute coronary syndrome and had no angiographic exclusion criteria (Fig. 4). Moreover, both the ZEST and SORT OUT III trials
independently found a significant increase in TVR and TLR with ZES use. Therefore, it is possible that clinical and angiographic differences between ZES and SES will become apparent in high-risk patients in the real-world clinical setting.

ZES was designed with the intention of reducing stent thrombosis compared with SES and PES. The cumulative incidence of stent thrombosis in the ENDEAVOR I–IV and PK studies at 5 years was about 0.8% (95% CI 0.66–1.54), which is lower than the cumulative incidence of 1% in our meta-analysis, considering the difference in duration of follow-up [21]. This could be due to the inclusion of acute myocardial infarction and complex lesions in the studies [9,14,15], which contributed the majority of patients to our analysis, compared with elective PCI for a single angiographically defined lesion in the ENDEAVOR I–IV studies. The incidence of stent thromboses in the SES (0.8%) and PES (1.3%) cohorts in our analysis were similar to those in previous studies [22,23]. It is important to note that only the

Figure 5. Forest plots comparing the zotarolimus-eluting stent (ZES) with the paclitaxel-eluting stent (PES) for: (A) in-stent restenosis; (B) in-segment restenosis; (C) in-segment late lumen loss. CI: confidence interval; M-H: Mantel–Haenszel.
ENDEAVOR III [16], ENDEAVOR IV [17] and ISAR-TEST-2 [9] trials reported the incidence of stent thromboses later than 6 months after completion of the recommended duration of dual antiplatelet therapy, at follow-up periods of 3 years, 2 years and 2 years, respectively (Table 1). Although there was no difference in very late stent thromboses between ZES and SES in the ENDEAVOR III and ISAR-TEST-2 studies, a trend (P = 0.069) towards higher very late stent thromboses with PES compared with SES was seen in the ENDEAVOR IV trial.

The results of the PROTECT trial — a large randomized-design trial comparing ZES with SES for the primary endpoint of stent thromboses at 3 years — recently became available [24]. Considering the magnitude and relevance of this study, we performed an updated analysis. The addition of the PROTECT trial further strengthened our conclusions, as there was no difference in mortality (OR, 1.03, 95% CI 0.75—1.41), myocardial infarction (OR 0.93, 95% CI 0.63—1.38) or stent thrombosis (OR 1.06, 95% CI 0.57—1.97) between ZES and SES. However, ZES was associated with a higher incidence of TVR (OR 1.87, 95% CI 1.13—3.08) and TLR (OR 2.18, 95% CI 1.44—3.31). The forest plots are shown in Figs. S1 and S2, respectively, in the supplementary appendix.

To decrease the incidence of stent thrombosis while maintaining the benefit of low repeat revascularization is one of the key objectives of current research into stent design and development [25]. As opposed to TLR, the incidence of stent thrombosis is very low in contemporary clinical studies examining the newer stents. Therefore, a very large sample size with a long follow-up period is needed to detect any statistically significant difference compared with established stents. Also, the SES (Cypher; Cordis/Johnson and Johnson, FL, USA), which remains unsurpassed in terms of TLR and restenosis, will be no longer manufactured by the end of 2011. These limitations pose a challenge to the design and conduct of clinical trials evaluating the newer coronary stents.

Study limitations

This was a study-level analysis; patient-level data may improve the accuracy of the results. Owing to the small number of studies in our analysis, no formal test to detect publication bias was done. As long-term follow-up was not available for most studies, no robust conclusion can be drawn about the difference in very late stent thrombosis, particularly after the completion of dual antiplatelet therapy. Also of note, these results are not applicable to the newer generation ZES (Endeavor Resolute), which has a different polymer and drug elution kinetics [17]. A recent observational study with the Resolute ZES found a very low rate of clinical restenosis compared with historical Endeavor ZES data [26].

Conclusion

ZES appears inferior to SES and similar to PES in terms of angiographic outcomes and revascularization rates. Mortality and reinfarction were similar when ZES was compared with SES and PES. Also, no difference in stent thromboses was apparent in studies with follow-up periods ranging from 1 to 3 years.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acvd.2012.01.014.

References


