Coronary Interventions

Safety and Efficacy of Resolute Zotarolimus-Eluting Stents Compared With Everolimus-Eluting Stents
A Meta-Analysis

Raffaele Piccolo, MD*; Giulio G. Stefanini, MD*; Anna Franzone, MD; Ernest Spitzer, MD; Stefan Blöchlinger, MD; Dik Heg, PhD; Peter Jüni, MD; Stephan Windecker, MD

Background—Although new-generation drug-eluting stents represent the standard of care among patients undergoing percutaneous coronary intervention, there remains debate about differences in efficacy and the risk of stent thrombosis between the Resolute zotarolimus-eluting stent (R-ZES) and the everolimus-eluting stent (EES). The aim of this study was to evaluate the safety and efficacy of the R-ZES compared with EES in patients undergoing percutaneous coronary intervention.

Methods and Results—A systematic literature search of electronic resources was performed using specific search terms until September 2014. Random-effects meta-analysis was performed comparing clinical outcomes between patients treated with R-ZES and EES up to maximum available follow-up. The primary efficacy end point was target-vessel revascularization. The primary safety end point was definite or probable stent thrombosis. Secondary safety end points were cardiac death and target-vessel myocardial infarction. Five trials were identified, including a total of 9899 patients. Compared with EES, R-ZES had similar risks of target-vessel revascularization (risk ratio [RR], 1.06; 95% confidence interval [CI], 0.90–1.24; P=0.50), definite or probable stent thrombosis (RR, 1.26; 95% CI, 0.86–1.85; P=0.24), cardiac death (RR, 1.01; 95% CI, 0.79–1.30; P=0.91), and target-vessel myocardial infarction (RR, 1.10; 95% CI, 0.89–1.36; P=0.39). Moreover, R-ZES and EES had similar risks of late definite or probable very late stent thrombosis (RR, 1.06; 95% CI, 0.53–2.11; P=0.87). No evidence of significant heterogeneity was observed across trials.

Conclusions—R-ZES and EES provide similar safety and efficacy among patients undergoing percutaneous coronary intervention. (Circ Cardiovasc Interv. 2015;8:27-34. DOI: 10.1161/CIRCINTERVENTIONS.114.002223.)

Key Words: everolimus-eluting stent ▪ meta-analysis ▪ randomized controlled trial ▪ zotarolimus-eluting stent

Drug-eluting stents (DES) have improved clinical outcomes of patients undergoing percutaneous coronary intervention (PCI) by potently suppressing neointimal hyperplasia and restenosis compared with bare-metal stents.\(^1\) However, the antirestenotic effectiveness achieved with early-generation DES came at the expense of a delay in arterial healing of the stented vessel, which was associated with a small but significant excess in late (>1 year) thrombotic events.\(^2\)\(^-\)\(^4\)

New-generation DES were developed featuring thinner stent struts, more biocompatible polymer coatings required for drug release, and different antiproliferative agents and dosages.\(^5\) These refinements resulted in considerable improvement of the safety and efficacy profile of early-generation DES. Indeed, new-generation DES have become the standard of care among patients undergoing PCI because of improved clinical outcomes in all patient and lesion subsets.\(^6\)

Thin strut, durable polymer–based, Resolute zotarolimus-eluting stent (R-ZES) and everolimus-eluting stent (EES) are the 2 only approved new-generation DES by the US Food and Drug Administration (FDA). R-ZES and EES have been directly compared in several randomized trials powered for noninferiority with respect to composite clinical end points. Notwithstanding, there remains residual uncertainty whether the 2 devices differ with respect to individual safety and efficacy outcomes, notably the risk of stent thrombosis (ST). Although several network meta-analyses compared different DES,\(^6\)\(^-\)\(^9\) there was an inconsistency between direct and indirect evidence with regard to the effectiveness of R-ZES and EES.\(^8\)

Therefore, we sought to perform a pairwise meta-analysis of randomized clinical trials with direct comparisons of FDA-approved new-generation DES to evaluate the safety and efficacy of R-ZES and EES in patients undergoing PCI.

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WHAT IS KNOWN

• New-generation drug-eluting stents are the standard of care in patients undergoing percutaneous coronary intervention.
• There remains residual uncertainty whether the 2 approved new-generation drug-eluting stents—the Resolute zotarolimus-eluting stent and everolimus-eluting stent—differ with respect to safety and efficacy outcomes.

WHAT THE STUDY ADDS

• In this meta-analysis of 5 randomized trials, including 9899 percutaneous coronary intervention patients, there was no significant difference in risk of target-vessel revascularization and stent thrombosis between Resolute zotarolimus-eluting stent and everolimus-eluting stent.
• Both Resolute zotarolimus-eluting stent and everolimus-eluting stent were associated with low event rates, indicating a favorable safety and efficacy of these devices in patients with a wide range of clinical and lesion characteristics.

Methods

The study protocol has been registered in PROSPERO International prospective register of systematic reviews (Identifier: CRD42014015020).

Search Strategy and Selection Criteria

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific session abstracts in Circulation, European Heart Journal, Journal of the American College of Cardiology, and The American Journal of Cardiology, and relevant websites (http://www.acc.org, http://www.americanheart.org, http://www.escardio.org, http://www.europcr.com, http://www.clinicaltrial-results.org, http://www.tctmd.com, and http://www.theheart.org) for randomized trials directly comparing R-ZES and EES without language restriction, from inception of each database until September 2014. The reference list of relevant studies was additionally screened. The key words used for the search were zotarolimus-eluting stent, everolimus-eluting stent, and drug-eluting stent. The full search strategy is reported in Table 1 in the Data Supplement. To be included, the citation had to meet the following criteria: (1) comparison of R-ZES versus EES, (2) random treatment allocation, and (3) availability of relevant clinical data. Trials investigating the Endeavor ZES or other non-FDA approved EES were excluded.

Data Collection and Quality Assessment

Two investigators (R.P. and G.G.S.) independently assessed the reports for eligibility at title or at abstract level, with divergences resolved by consensus or consultation with a third investigator (A.F.). Studies that met inclusion criteria were selected for further analysis. Included studies were evaluated with respect to the following methodological items: randomization, adequacy of allocation concealment, blinding of participants, personnel and outcome assessors, handling of incomplete (or missing) outcome data, performance of the analysis according to the intention-to-treat principle, selective reporting, sample size calculation, and specification of loss of patients to follow-up.

Outcome Variables

The prespecified primary efficacy end point was target-vessel revascularization (TVR). The prespecified primary safety end point was definite or probable ST according to the Academic Research Consortium criteria. In case of data unavailability, definite ST was used as a proxy measure. Secondary safety end points were cardiac death and target-vessel myocardial infarction (TV-MI). All end points were evaluated at the longest available follow-up.

Statistical Analysis

The \( \kappa \) statistic was used to assess agreement between reviewers for study selection. Risk ratio (RR) and 95% confidence intervals (CI) were used as summary statistics and were derived from the number of patients with an event and the number of patients randomized in each arm. The summary RR was calculated by using the random effects, DerSimonian and Laird model. The Breslow–Day \( \chi^2 \) test was calculated to test the statistical evidence of heterogeneity across the studies. In addition, we used the \( I^2 \) statistic, which describes the percentage variation across studies that is because of heterogeneity rather than chance. As a guide, \( I^2 \) values \(<25\%\) indicated low, 25% to 50% indicated moderate, and >50% indicated high heterogeneity. We performed a sensitivity analysis, in which the meta-analysis estimates are computed omitting one study at time. A funnel plot was used to assess publication bias with respect to primary end points. However, because graphical evaluation can be subjective, we performed both Harbord and Peters tests, as formal statistical tests for publication bias. Statistical analyses were performed using STATA 12.0 statistical software (STATA Corp, College Station, TX).

Sample Size

Trial sequential analysis was performed according to the monitoring boundaries approach, by using TSA version 0.9 beta (http://www.ctu.dk/taa). This is a methodology that combines an a priori information size calculation for a meta-analysis with the adaptation of monitoring boundaries to evaluate the accumulating evidence and sample size. Our assumptions included 2-sided testing, type 1 error of 5%, and a power of 80%. We tested the hypothesis of an increased 25% and 50% relative risk of TVR and ST with R-ZES. The expected absolute event rates in the EES arms at the longest time of follow-up were 5% for TVR and 1.2% for ST. The main results were shown through a graph of the cumulative \( Z \) curve, and the O’Brien–Fleming spending function was used to determine the boundaries in this graph for concluding superiority or inferiority or futility.

The study was realized in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results

The process of study selection is outlined in the Figure 1 in the Data Supplement. We screened the title or the abstract of 3677 potentially eligible publications. Of these, 3585 citations were excluded as they were not relevant to this study or were duplicate publications. Ninety-two studies were assessed for eligibility, and 87 records were discarded due to unmet inclusion criteria. Finally, 5 trials were entered into this meta-analysis, including a total of 9899 patients (4319 patients randomly allocated to treatment with R-ZES and 5580 patients randomly allocated to treatment with EES). The interobserver agreement for study selection was excellent (\( \kappa=0.95 \)). The main characteristics of included studies are summarized in Table 1. The principal characteristics of patients enrolled in each study are reported in Table 2. In general, trials were considered to be of high methodological quality (Table II in the Data Supplement). All the included studies had a noninferiority design, and 4 trials were multicentre investigations.

Figure 1 summarizes principal characteristics of both study devices. R-ZES (Resolute or Resolute Integrity; Medtronic Cardiovascular, Santa Rosa, CA) was compared with cobalt...
chromium–based EES (Xience or Xience V; Abbott Vascular, Santa Clara, CA) in 3 studies,15-17 whereas in the remaining 2 studies,18,19 R-ZES was compared with platinum chromium–based EES (Promus Element; Boston Scientific, Natick, MA). Four trials included all-comers populations,15,16,18,19 whereas one trial17 specifically enrolled patients with unprotected left main coronary artery lesions. The rate of patients lost to follow-up ranged from 0 to 2%. Recommended antplatelet therapy (data available for 3 trials11,12,15).

Clinical Outcomes
Pooled estimates of random-effects meta-analyses for clinical outcomes are shown in Figure 2. TVR occurred in 556 patients (5.61%). The risk of TVR was similar in patients randomly allocated to treatment with R-ZES compared with patients randomly allocated to treatment with EES (6.34% versus 5.05%; RR [95% CI], 1.06 [0.90–1.24]; P=0.50; Figure 3A). These results are consistent for target-lesion revascularization (RR [95%], 1.17 [0.97–1.42]) and angiographic in-stent restenosis (RR [95%], 1.26 [0.88–1.79]; Figure II in the Data Supplement).

Definite or probable ST occurred in 104 patients (1.05%). The risk of ST did not differ in patients randomly allocated to treatment with R-ZES or EES (1.27% versus 0.88%, respectively; RR [95% CI], 1.26 [0.86–1.85]; P=0.24; Figure 3B).

Table 1. Main Characteristics of Trials Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design (No. of Patients)</th>
<th>Primary End Point</th>
<th>Multicentre</th>
<th>Follow-Up</th>
<th>R-ZES Type</th>
<th>EES Type</th>
<th>Patients Lost to Follow-Up, %*</th>
<th>Publication Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOLUTE All Comers (12)</td>
<td>R-ZES (n=1140) vs EES (n=1152)</td>
<td>12-month cardiac death, target-vessel MI, and clinically driven TLR</td>
<td>Yes</td>
<td>5-year</td>
<td>Resolute</td>
<td>Xience V</td>
<td>2</td>
<td>2010</td>
</tr>
<tr>
<td>TWENTE (13)</td>
<td>R-ZES (n=697) vs EES (n=694)</td>
<td>12-month cardiac death, target-vessel MI, and clinically driven TLR</td>
<td>No</td>
<td>3-year</td>
<td>Resolute</td>
<td>Xience V</td>
<td>0.7</td>
<td>2013</td>
</tr>
<tr>
<td>ISAR-LEFT-MAIN 2 (14)</td>
<td>R-ZES (n=324) vs EES (n=326)</td>
<td>12-month death, MI, and TLR</td>
<td>Yes</td>
<td>1-year</td>
<td>Resolute Integrity</td>
<td>Xience V</td>
<td>0</td>
<td>2013</td>
</tr>
<tr>
<td>DUTCH PEERS (15)</td>
<td>R-ZES (n=906) vs EES (n=905)</td>
<td>12-month cardiac death, target-vessel MI, and clinically driven TLR</td>
<td>Yes</td>
<td>2-year</td>
<td>Resolute Integrity</td>
<td>Promus Element</td>
<td>0.1</td>
<td>2014</td>
</tr>
<tr>
<td>HOST-ASSURE (16)</td>
<td>R-ZES (n=1252) vs EES (n=2503)</td>
<td>12-month cardiac death, target-vessel MI, and clinically driven TLR</td>
<td>Yes</td>
<td>1-year</td>
<td>Resolute Integrity</td>
<td>Promus Element</td>
<td>1.3</td>
<td>2014</td>
</tr>
</tbody>
</table>

*DUTCH PEERS indicates Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity; EES, everolimus-eluting stent; HOST-ASSURE, Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis—Safety & Effectiveness of Drug-Eluting Stents & Antiplatelet Regimen; ISAR-LEFT-MAIN, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions; MI, myocardial infarction; R-ZES, Resolute zotarolimus-eluting stent; RESOLUTE All Comers, Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; TLR, target-lesion revascularization; TVR, target-vessel revascularization; and TWENTE, The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente.

Visual inspection of the funnel plot did not reveal a skewed distribution for the study end points, suggesting the absence of small-study effects. Furthermore, neither the Harbord

Sensitivity Analyses
No single study significantly altered the summary RRs because one-at-a-time study omission did not result in a shift of the point estimate out of the 95% CI (Figure III in the Data Supplement). Study results were consistent when fixed effect model or risk differences were applied. In addition, the different follow-up lengths across included trials was not associated with estimated RRs (Table III in the Data Supplement).

Moreover, there was no significant interaction between the comparisons of R-ZES with cobalt chromium or platinum chromium EES, respectively (Table IV in the Data Supplement).
Table 2. Main Characteristics of Patients Enrolled in Trials Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Age, mean, y</th>
<th>Diabetes Mellitus, %</th>
<th>Acute Coronary Syndrome, %</th>
<th>Reference Vessel Diameter, mm</th>
<th>Total Stent Length, mm</th>
<th>Type B2/C Lesion, %</th>
<th>Angiographic Follow-Up, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOLUTE All Comers</td>
<td>All-comers design (at least 1 coronary lesion ≥50% with a reference vessel diameter of 2.25–4.0 mm)</td>
<td>Intolerance to study drug or stent; planned surgery within 6 months</td>
<td>64</td>
<td>77</td>
<td>23</td>
<td>48</td>
<td>2.63</td>
<td>35.7</td>
<td>N/A</td>
</tr>
<tr>
<td>TWENTE</td>
<td>All-comers design (patients scheduled for PCI using DES)</td>
<td>Recent ST-segment–elevation MI</td>
<td>64</td>
<td>73</td>
<td>22</td>
<td>51</td>
<td>N/A</td>
<td>26.9</td>
<td>70</td>
</tr>
<tr>
<td>ISAR-LEFT-MAIN</td>
<td>Ischemic symptoms or evidence of myocardial ischemia in the presence of ≥50% de novo left main stem stenosis</td>
<td>Recent ST-segment–elevation MI; previous CABG; in-stent restenosis; cardiogenic shock; intolerance to study drug or stent; planned surgery within 6 months</td>
<td>70</td>
<td>75</td>
<td>28</td>
<td>35</td>
<td>3.65</td>
<td>N/A</td>
<td>100</td>
</tr>
<tr>
<td>DUTCH PEERS</td>
<td>All-comers design</td>
<td>Intolerance to study drug or stent; planned surgery within 6 months</td>
<td>64</td>
<td>73</td>
<td>17</td>
<td>59</td>
<td>2.65</td>
<td>29</td>
<td>65</td>
</tr>
<tr>
<td>HOST-ASSURE</td>
<td>All-comers design</td>
<td>LVEF&lt;25%; increased bleeding risk; planned surgery within 6 months</td>
<td>63</td>
<td>68</td>
<td>32</td>
<td>65</td>
<td>3.00</td>
<td>37.9</td>
<td>49</td>
</tr>
</tbody>
</table>

CBG indicates coronary artery bypass graft; DES, drug-eluting stent; DUTCH PEERS, Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity; HOST-ASSURE, Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis—Safety & Effectiveness of Drug-Eluting Stents & Antiplatelet Regimen; ISAR-LEFT-MAIN, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RESOLUTE All Comers, Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent For Percutaneous Coronary Intervention; and TWENTE, The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente.

Discussion

The main findings of this meta-analysis are that the 2 FDA-approved new-generation DES—R-ZES and EES—have a comparable safety and efficacy profile, without significant differences in the risks of TVR, definite or probable ST, cardiac death, and TV-MI. Moreover, both R-ZES and EES were associated with low event rates, indicating a favorable safety and efficacy of these devices in patients with a wide range of patient and lesion characteristics reflecting routine clinical practice.

DES represent the standard of care in contemporary clinical practice and are used in >80% of patients undergoing PCI.20 In recent years, new-generation DES replaced early-generation DES because of improved stent design, similar or superior antirestenotic efficacy, and consistently lower rates of late ST.21,22 Both zotarolimus and everolimus are sirolimus analogues, in which the hydroxyl group at position 40 of the sirolimus has been replaced by a lipophilic tetrazole and hydroxyethyl group, respectively. Antiproliferative agents are released from biocompatible durable polymers in both devices: the BioLink polymer in R-ZES, which consists of 3 polymers (a hydrophobic C10 polymer, a hydrophilic C19 polymer, and water-soluble polyvinyl pyrrolidinone) and a 2-layer polymer system in EES, with an acrylate primer and a fluorinated copolymer. The stent platforms are cobalt chromium in R-ZES and EES (Xience or Xience V) or platinum chromium (Promus Element; Figure 1).1,5

The first, large-scale, randomized clinical trial23 comparing these 2 devices demonstrated noninferiority for the composite end point target-lesion failure at 12 months. However, ST had occurred more frequently in patients treated with R-ZES when compared with patients treated with EES at 12 months.23 Although this early difference in the risk of definite ST diminished during long-term follow-up,24 there remains uncertainty whether R-ZES and EES feature a different propensity for ST during the periprocedural period.2,26 Although many randomized trials directly comparing R-ZES and EES were conducted, all of these studies had an inadequate sample size to assess the individual components of the primary composite end points. We therefore undertook this meta-analysis to investigate the clinical performance of R-ZES compared with EES, with a particular focus on device safety (ST) and efficacy (TVR).
Our findings confirm the similar safety and efficacy profile of R-ZES and EES, with no evidence of heterogeneity for any of the analyzed end points. It is noteworthy that all but one\textsuperscript{15} studies had attenuated statistical power because of the lower than expected event rates of the primary composite end point events. To evaluate the robustness of the available evidence, we conducted a trial sequential analysis that allows the estimation of sample size for a meta-analysis. With $\approx 10000$
patients, this study provides additional evidence to support the lack of significant difference between R-ZES and EES with respect to TVR and ST. Although several network meta-analyses compared different DES,6–9 Navarese et al8 found a significant inconsistency between direct and indirect evidence about the clinical efficacy of R-ZES versus EES. This observation reinforces the necessity of a pairwise meta-analysis with appropriate power to evaluate TVR with >90% of the required sample size accrued.

The patients included in the analyzed trials represented patient populations with a wide range of patient and lesion characteristics, including high-risk population as 4 studies15,16,18,19—accounting for >90% of the sample size—featuring an all-comer design. Furthermore, 2 trials reported similar outcomes for R-ZES and EES in patients with complex coronary lesions.26,27 These aspects along with low rates of adverse events observed in both R-ZES and EES cohorts are reassuring in view of the widespread use of new-generation DES in current clinical practice.

A previous meta-analysis by Zhang et al28 reported a greater safety and efficacy with EES when compared with ZES. However, the report included observational studies and pooled both Endeavor and Resolute ZES, without a detailed analysis to elucidate differences between these stent types and how they may have affected outcomes. In contrast, our results derived from randomized trials are in line with more recent

Figure 3. Forest plots for clinical outcomes. All weights are from random-effects analysis. The squares and the horizontal lines indicate the risk ratio (RR) and the 95% confidence interval (CI) for each trial included; the size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis, with the center indicating the point estimate and the left and the right ends the 95% CI. DUTCH PEERS indicates Durable Polymer-Based Stent Challenge of Promus Element Versus Resolute Integrity; EES, everolimus-eluting stent; HOST-ASSURE, Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis—Safety & Effectiveness of Drug-Eluting Stents & Antiplatelet Regimen; ISAR-LEFT-MAIN, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions; R-ZES, Resolute zotarolimus-eluting stent; RESOLUTE All Comers, Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; and TWENTE, The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente.
observational evidence. In a large, multicentre, Korean registry, there was no significant difference in clinical outcomes among 5054 patients treated with R-ZES or EES at 1-year follow-up. Event rates were lower than observed in this meta-analysis, providing evidence of external validity and applicability to broader clinical practice.

Noteworthy, the similar clinical performance of R-ZES and EES may be the result of similar arterial healing properties related to lower arterial drug concentrations observed in preclinical models, which may exert a favourable effect on endothelial maturation above stent struts. Along this line, optical coherence tomographic studies found no significant differences between R-ZES and EES in terms of tissue coverage, malapposition, and neointimal thickness throughout different follow-up periods. In fact, favorable outcomes related to premature discontinuation of dual-antiplatelet therapy have been reported with both R-ZES and EES. The consistency between findings from preclinical investigations, intracoronary imaging studies, and clinical trials further supports the equivalent safety and efficacy profile of R-ZES and EES.

**Study Limitations**

First, although 4 trials had an all-comer design, there were several differences with respect to inclusion criteria. However, the lack of significant heterogeneity for all the analyzed study end points underlies the consistency of effects across studies. Second, long-term data are still limited. This is an important aspect because target-lesion revascularization continues to represent nearly one-half of all repeat revascularization procedures at late follow-up. Third, our meta-analysis was limited to FDA-approved new-generation DES and we did not include the equivalent biodegradable, polymer-based DES.

**Conclusions**

The present meta-analysis shows that R-ZES and EES have a similar safety and efficacy profile in patients with a wide range of clinical and angiographic risk characteristics.

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**Disclosures**

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**References**

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Safety and Efficacy of R-ZES vs EES


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http://circinterventions.ahajournals.org/content/suppl/2015/04/15/CIRCINTERVENTIONS.114.002223.DC1

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SUPPLEMENTAL MATERIAL

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Table I. Search strategy: MEDLINE (PubMed).

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<th>Search Line</th>
<th>Search Term</th>
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<td>everolimus-eluting stent*[Title/Abstract]</td>
<td>418</td>
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<tr>
<td>3</td>
<td>1 or 2</td>
<td>635</td>
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<td>everolimus* random*[Title/Abstract]</td>
<td>584</td>
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<td>5</td>
<td>zotarolimus* random*[Title/Abstract]</td>
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<tr>
<td>6</td>
<td>5 or 6</td>
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<td>7</td>
<td>drug-eluting stent* random*[Title/Abstract]</td>
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<td>3,356</td>
</tr>
</tbody>
</table>
Table II. Risk of bias assessment.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment used</th>
<th>Blinding</th>
<th>Incomplete data outcome addressed</th>
<th>Free of selective reporting</th>
<th>Free of other sources of bias</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOLUTE All Comers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Outcome assessors)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>TWENTE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Patients, Outcome assessors)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ISAR-LEFT-MAIN 2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Outcome assessors)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DUTCH PEERS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Patients, Outcome assessors)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HOST-ASSURE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Outcome assessors)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table III. Results with fixed effects, risk differences and impact of follow-up length.

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Fixed effect Meta-analysis</th>
<th>Random effects Meta-analysis with risk differences</th>
<th>Change in RR per 1 year increase in follow-up time*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RD (95% CI)</td>
<td>Ratio of RR  95% CI  SE  Change in Tau  p</td>
</tr>
<tr>
<td>Target-vessel revascularization</td>
<td>1.06 (0.90-1.24)</td>
<td>0.002 (-0.005;0.009)</td>
<td>0.98  0.84-1.15  0.05 -0.26  0.81</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.26 (0.86-1.84)</td>
<td>0.002 (-0.002;0.006)</td>
<td>1.01  0.69-1.49  0.12  0.12  0.91</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>1.02 (0.81-1.27)</td>
<td>0.000 (-0.007;0.007)</td>
<td>1.01  0.76-1.36  0.09  0.16  0.881</td>
</tr>
<tr>
<td>Target-vessel myocardial infarction</td>
<td>1.10 (0.89-1.37)</td>
<td>0.003 (-0.003-0.008)</td>
<td>0.95  0.75-1.20  0.07 -0.71  0.53</td>
</tr>
</tbody>
</table>

*Results are from a weighted random-effect meta-regression analysis in which the length of follow-up expressed in years was used as covariate. RR: risk ratio. RD: risk difference. SE: standard error.
Table IV. Sensitivity analysis for the comparison of R-ZES vs. CoCr or PlCr EES.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>RR (95% CI)</th>
<th>p</th>
<th>p-interaction</th>
<th>I²</th>
<th>p-het</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target-vessel revascularization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ZES vs. CoCr EES</td>
<td>1.07 (0.89-1.30)</td>
<td>0.45</td>
<td>0.73</td>
<td>0.0%</td>
<td>0.78</td>
</tr>
<tr>
<td>R-ZES vs. PlCr EES</td>
<td>1.01 (0.73-1.24)</td>
<td>0.96</td>
<td></td>
<td>0.0%</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Stent thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ZES vs. CoCr EES</td>
<td>1.26 (0.79-2.00)</td>
<td>0.33</td>
<td>0.85</td>
<td>0.0%</td>
<td>0.66</td>
</tr>
<tr>
<td>R-ZES vs. PlCr EES</td>
<td>1.27 (0.64-2.55)</td>
<td>0.49</td>
<td></td>
<td>0.7%</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Cardiac Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ZES vs. CoCr EES</td>
<td>0.91 (0.60-1.39)</td>
<td>0.67</td>
<td>0.42</td>
<td>48.4%</td>
<td>0.14</td>
</tr>
<tr>
<td>R-ZES vs. PlCr EES</td>
<td>1.12 (0.74-1.30)</td>
<td>0.54</td>
<td></td>
<td>0.0%</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Target-vessel myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ZES vs. CoCr EES</td>
<td>1.07 (0.84-1.36)</td>
<td>0.52</td>
<td>0.60</td>
<td>0.0%</td>
<td>0.43</td>
</tr>
<tr>
<td>R-ZES vs. PlCr EES</td>
<td>1.23 (0.77-1.95)</td>
<td>0.38</td>
<td></td>
<td>0.0%</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Figure 1. Identification of eligible trials.

**Literature search** (n=3,677):
- Databases: Medline, the Cochrane Library and Embase
- Scientific Abstracts: Circulation, JACC, EHJ, AIC

**Records after duplicates removed** (n=3,072)

**Records excluded based on titles or abstracts using general criteria:** (n=2,978)
- Study design non-eligible (n=51)
- Intervention non-eligible (n=10)
- Only protocol available (n=1)
- Other reasons (n=25)

**Full-text articles assessed for eligibility** (n=92)

**Full-text articles excluded** (n=87)

**Studies included** (n=5)
Figure II. Meta-analysis of additional outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nr of Trials/Patients Contributing Outcome</th>
<th>Events/Nr of patients</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
<th>1.25</th>
<th>2</th>
<th>Pooled RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>4/8088</td>
<td>202/3413</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.17 (0.97-1.42)</td>
<td>0.105</td>
</tr>
<tr>
<td>In-stent restenosis*</td>
<td>2/840</td>
<td>59/428</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.26 (0.88-1.79)</td>
<td>0.237</td>
</tr>
<tr>
<td>Definite ST</td>
<td>5/9899</td>
<td>37/4319</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.53 (0.91-2.57)</td>
<td>0.109</td>
</tr>
<tr>
<td>Probable ST</td>
<td>3/6697</td>
<td>16/2716</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.39 (0.68-2.82)</td>
<td>0.364</td>
</tr>
</tbody>
</table>

Figure III. Influence analysis of included studies on target-vessel revascularization (A) and stent thrombosis (B).
Figure IV. Funnel plots for target-vessel revascularization (A) and stent thrombosis (B).

A)

B)
Figure V. Trial sequential analysis for target-vessel revascularization (A) and stent thrombosis (B).

A)

B)