Everolimus-Eluting Versus Sirolimus-Eluting Stents
A Meta-Analysis of Randomized Trials

Antoinette de Waha, MD; Alban Dibra, MD; Robert A. Byrne, MB BCh; Gjin Ndrepepa, MD; Julinda Mehilli, MD; Massimiliano Fusaro, MD; Karl-Ludwig Laugwitz, MD; Steffen Massberg, MD; Albert Schömig, MD; Adnan Kastrati, MD

Background—The aim of the study was to compare the outcomes after placement of the everolimus-eluting stent (EES; Xience V) and the sirolimus-eluting stent (SES; Cypher) in patients with coronary artery disease. The second-generation EES is currently one of the most commonly used drug-eluting stents in clinical practice. Although it has clearly been shown superior to paclitaxel-eluting stents, its relative merits against SES have been less extensively assessed.

Methods and Results—We identified 5 eligible randomized trials comparing EES with SES in 7370 patients. The primary end point was major adverse cardiac events. Secondary end points were cardiac death, myocardial infarction, repeat revascularization, and the composite of definite and probable stent thrombosis. Overall hazard ratios (HR) and 95% confidence intervals (CI) were calculated for EES versus SES for each of the end points. No heterogeneity across the trials was observed regarding the primary and secondary end points. The risk of major adverse cardiac events (HR, 0.91 [95% CI, 0.77 to 1.08]; \( P = 0.28 \)), cardiac death (HR, 1.02 [95% CI, 0.73 to 1.41]; \( P = 0.92 \)), myocardial infarction (HR, 0.97 [95% CI, 0.66 to 1.35]; \( P = 0.76 \)), repeat revascularization (HR, 0.85 [95% CI, 0.68 to 1.07]; \( P = 0.16 \)), and composite of definite and probable stent thrombosis (HR, 0.79 [95% CI, 0.49 to 1.27]; \( P = 0.33 \)) were not significantly different between EES and SES.

Conclusions—This meta-analysis did not show significant differences between EES and SES in terms of clinical efficacy and safety. Future studies with longer follow-up are needed to better define the relative merits of these drug-eluting stents. (Circ Cardiovasc Interv. 2011;4:371-377.)

Key Words: everolimus-eluting stent ■ sirolimus-eluting stent ■ cardiac death ■ stent thrombosis

Drug-eluting stents (DES) represent an important achievement in the prevention of restenosis after percutaneous coronary interventions. Several randomized trials including a total of several thousands of patients have shown a considerable risk reduction in restenosis with the use of first-generation DES, namely the sirolimus-eluting stent (SES, Cypher) and the paclitaxel-eluting stent (PES, Taxus). Despite this superior performance of PES, later comparative randomized trials showed that SES is a safe and more effective alternative to PES.1,2,3 Although first-generation DES are highly effective at preventing coronary restenosis, they may lead to delayed healing of the stented arterial segment.4,5 This pathophysiological process appears to underlie the slight excess of stent thrombosis events6 late after device implantation. The rationale of the development of second-generation devices therefore has been the attainment of optimal antirestenotic efficacy at a minimum of arterial wall toxicity.7

Clinical Perspective on p 377

The everolimus-eluting stent (EES; Xience V) represents a potential step forward in DES technology.8 It releases the active drug from a thin, synthetic polymer coating deployed on a thin-strut cobalt chromium stent backbone. On the basis of a number of randomized, controlled trials that showed its superiority over the first-generation PES,9-12 EES has quickly established a position as the market-leading drug-eluting stent platform. However, direct comparison of the EES with the first-generation SES is of great importance before the true role of EES in the current treatment of patients with coronary artery disease can be defined. There are at least 2 reasons for this. First, SES has been shown to be safer and more effective than PES in head-to-head comparative randomized trials.13 Second, both everolimus and sirolimus belong to the same drug family, which makes SES an obvious control device for EES.

To fill this gap, we used meta-analytical methods to pool together reported outcomes from available randomized trials comparing EES with SES.

Methods

Inclusion Criteria

We included all reported studies comparing EES (Xience V, Abbott Vascular, Santa Clara, CA) with SES (Cypher, Cordis, Warren, NJ), if they had a randomized design, in patients with coronary artery disease.

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<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Mean Age, y</th>
<th>Male, %</th>
<th>Key Exclusion Criteria</th>
<th>Primary End Point</th>
<th>Definition of Major Adverse Cardiac Events</th>
<th>Protocol-Mandated Follow-Up Angiography</th>
<th>Duration of Clopidogrel Therapy, mo</th>
<th>Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET-PROVE</td>
<td>1549</td>
<td>66</td>
<td>75</td>
<td>Left main or graft vessel stenosis, in-stent restenosis, vessel size &lt;3.0 mm</td>
<td>Composite of death from cardiac cause or nonfatal myocardial infarction</td>
<td>Death, myocardial infarction, target vessel revascularization</td>
<td>No</td>
<td>12</td>
<td>24</td>
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<tr>
<td>ESSENCE-DIABETES</td>
<td>300</td>
<td>63</td>
<td>59</td>
<td>No diabetes, left main or graft vessel stenosis, in-stent restenosis, bifurcation lesion, vessel size &lt;2.5 mm</td>
<td>Angiographic in-segment late loss</td>
<td>Death, myocardial infarction, target lesion revascularization</td>
<td>Yes</td>
<td>≥12</td>
<td>12</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>1443</td>
<td>63</td>
<td>64</td>
<td>Left main or graft vessel stenosis, bifurcation lesions, vessel size &lt;2.25 mm or &gt;4.25 mm</td>
<td>Angiographic in-segment late loss</td>
<td>Cardiac death, myocardial infarction, target lesion revascularization</td>
<td>Yes</td>
<td>6 or 12</td>
<td>12</td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>1304</td>
<td>67</td>
<td>77</td>
<td>Left main or graft vessel stenosis, in-stent restenosis</td>
<td>Major adverse cardiac events</td>
<td>Cardiac death, myocardial infarction, target lesion revascularization</td>
<td>Yes</td>
<td>≥6</td>
<td>36</td>
</tr>
<tr>
<td>SORT OUT IV</td>
<td>2774</td>
<td>64</td>
<td>75</td>
<td>...</td>
<td>Major adverse cardiac events</td>
<td>Cardiac death, myocardial infarction, definite stent thrombosis, target vessel revascularization</td>
<td>No</td>
<td>12</td>
<td>9</td>
</tr>
</tbody>
</table>

Trial acronyms, registration numbers, and references:
BASKET PROVE (ISR CTN 72444640): Drug-eluting vs bare-metal stents in large coronary arteries.16
ESSENCE-DIABETES (NCT 00997763): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with diabetes mellitus and coronary artery disease.17
EXCELLENT (NCT 00619860): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease.18
ISAR-TEST 4 (NCT 00598676): Two-year outcomes after everolimus- or sirolimus-eluting stents in patients with coronary artery disease.14
SORT OUT IV (NCT 00552877): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease.15
Study Identification
We performed an electronic search of the United States National Library of Medicine (PubMed, at www.pubmed.gov), the United States National Institutes of Health clinical trials registry (www.clinicaltrials.gov), and the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html). Internet-based sources of information on the results of clinical trials in cardiology (www.cardiosource.com/clinicaltrials, www.theheart.org, www.clinicaltrialresults.com, and www.tctmd.com) were also searched. Additional data sources included conference proceedings from the American College of Cardiology, the American Heart Association, Transcatheter Cardiovascular Therapeutics, the European Society of Cardiology, and EuroPCR meetings. We also identified relevant reviews and editorials from major medical journals published within the last year and assessed for possible information on trials of interest. Experts were contacted in an attempt to find unpublished trials. The last search was performed in April 2011.

A total of 5 trials were identified and included in this meta-analysis.14-18 Each trial was evaluated for the adequacy of allocation concealment, performance of the analysis according to the intention-to-treat principle, and blind assessment of the outcomes of interest. We used the criteria recommended by Altman et al19 and Jüni et al20 to assess the adequacy of allocation concealment. The main characteristics of the included trials are shown in the Table.

Study Outcomes and Definitions
Major adverse cardiac events at the longest available follow-up were the primary end point of this meta-analysis. The events included in this composite end point are displayed in the Table. The secondary end points were cardiac death, myocardial infarction, repeat target lesion/vessel revascularization, and the composite of definite or probable stent thrombosis defined according to the Academic Research Consortium.23

The results of one of the trials have been presented at a meeting but not published in full form.15 However, the definitions of events reported in detail in a full publication of the study design for this trial.22

Statistical Methods
Overall median follow-up was calculated according to a previously reported method.23 Reported risk estimates for each event of interest from individual trials were used for this meta-analysis. No risk estimates were reported from 1 trial.17 For the calculation of risk estimates for this trial, we used the reported absolute numbers of patients with events.17 Trials in which the event of interest was not observed in either study group were omitted from the analysis of that event. If only 1 of the groups had no event of interest, the estimate observed in either study group were omitted from the analysis of that event. If only 1 of the groups had no event of interest, the estimate of treatment effect and its standard error were calculated after adding 0.5 to each cell of the 2×2 table for the trial.24 Risk estimates from individual trials were pooled using the DerSimonian and Laird method for random effects.25

We used the Cochran test to assess heterogeneity across trials. Also, we calculated the F statistic to measure the consistency between trials, with values <25% indicating low, 25% to 50% indicating moderate, and >50% indicating high heterogeneity.26

Results were considered statistically significant at 2-sided P<0.05. Statistical analysis was performed with the use of Stata software, version 9.2 (Stata Corp, College Station, TX).

Results
Five trials with 7370 patients were included in this meta-analysis.14-18 Of these, 4044 patients were assigned to EES and 3326 patients to SES. Overall median follow-up was 13.3 months. The main characteristics and definitions of individual trials are summarized in the Table. The mean age of participants in individual trials varied from 63 to 67 years; the length of follow-up ranged from 9 to 36 months. Recommended duration of clopidogrel therapy was at least 6
months; in 1 of the trials, patients were also randomly assigned to either 6- or 12-month duration.

Figure 1 shows the overall hazard ratio (HR) as well as the HRs of individual trials regarding the primary end point of this meta-analysis, major adverse cardiac events. There was no heterogeneity across the trials. The analysis indicated no significant difference in the risk of major adverse cardiac events between EES and SES (HR, 0.91 [95% confidence interval (CI), 0.77 to 1.08]; \( P = 0.28 \)).

Figure 2 shows the overall HR as well as the HRs of individual trials regarding cardiac death. No heterogeneity across the trials was observed regarding this event. There was no significant difference in the risk of cardiac death between EES and SES (HR, 1.02 [95% CI, 0.73 to 1.41]; \( P = 0.92 \)).

Figure 3 shows the overall HR as well as the HRs of individual trials regarding myocardial infarction. The treatment effect was homogenous across the trials. There was no significant difference in the risk of myocardial infarction between EES and SES (HR, 0.97 [95% CI, 0.66 to 1.35]; \( P = 0.76 \)).

Regarding repeat revascularization, 4 trials evaluated target lesion revascularization and 1 trial evaluated target vessel revascularization. The pooled analysis of this adverse event did not show heterogeneity across the trials (Figure 4). There was no significant difference in the risk of repeat revascularization between the EES and the SES groups (HR, 0.85 [95% CI, 0.68 to 1.07]; \( P = 0.16 \)). Because of the specific inclusion criteria of the BASKET-PROVE trial (exclusion of lesions in vessels <3 mm in size), which may blunt differences in antirestenotic efficacy between 2 DES, we also performed an analysis of target lesion revascularization, based on the other 4 trials alone. The obtained HR (0.84 [95% CI, 0.65 to 1.09]; \( P = 0.19 \)) was in essence similar to that yielded by the analysis of all 5 trials together. In addition, the 2 trials without scheduled follow-up angiography showed similar treatment effects, not significantly different between EES and SES.

Finally, there was also no significant difference between the 2 DES regarding the composite of definite and probable stent thrombosis with an HR of 0.79 [95% CI, 0.49 to 1.27], \( P = 0.33 \) without any evidence of heterogeneity across the trials.

**Discussion**

Meta-analyses of head-to-head comparative, randomized trials have considerably contributed to the definition of the role of first- and second-generation DES in terms of efficacy and safety. In a pooled analysis of 14 randomized trials including 4958 patients, Kastrati et al found that the first-generation SES (Cypher) was more effective than and as safe as bare-metal stents in patients with coronary artery disease. Similar results were also reported for PES (Taxus) by Stone et al after they performed a meta-analysis of 5 randomized trials comparing PES with bare-metal stents in 3513 patients. Furthermore, another meta-analysis clearly showed that SES (Cypher) was more effective and safer than PES (Taxus). It included 16 randomized trials of SES versus PES, with a total number of 8695 patients. Four randomized trials with 6792 patients have recently been dedicated to the comparison between the second-generation EES (Xience V) and the first-generation PES (Taxus).
With 7370 patients enrolled in 5 randomized trials of EES versus SES, the present study represents one of the largest meta-analyses to date on the value of DES in patients with coronary artery disease. Notably, the trials included in this meta-analysis adopted very few exclusion criteria and may well be considered as “all-comers” trials. Another strength is the focus on the comparison of EES with SES. SES is the most obvious control comparator for EES for at least 2

<table>
<thead>
<tr>
<th>Randomized Trial</th>
<th>Total No of Patients</th>
<th>EES</th>
<th>SES</th>
<th>Hazard Ratio (95% CI) for MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET-PROVE</td>
<td>13/774</td>
<td>7775</td>
<td>1.85(0.74, 4.55)</td>
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<td>ESSENCE-DIABETES</td>
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<td>2/151</td>
<td>0.20(0.01, 4.19)</td>
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<td>EXCELLENT</td>
<td>15/1079</td>
<td>5/364</td>
<td>1.01(0.37, 2.77)</td>
<td></td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>26/652</td>
<td>30/652</td>
<td>0.87(0.51, 1.47)</td>
<td></td>
</tr>
<tr>
<td>SORT OUT IV</td>
<td>15/1390</td>
<td>19/1384</td>
<td>0.79(0.40, 1.55)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>69/4044</td>
<td>63/3326</td>
<td>0.97(0.66, 1.35)</td>
<td></td>
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</tbody>
</table>

Figure 3. Forest plot with hazard ratios for myocardial infarction associated with everolimus-eluting stents versus sirolimus-eluting stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. CI indicates confidence interval; EES, everolimus-eluting stent; MI, myocardial infarction; and SES, sirolimus-eluting stent. Trial acronyms, registration numbers, and references: BASKET PROVE (ISR CTN 72444640): Drug-eluting vs bare-metal stents in large coronary arteries.16 ESSENCE-DIABETES (NCT 00997763): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with diabetes mellitus and coronary artery disease.17 EXCELLENT (NCT 00698607): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease.16 ISAR-TEST 4 (NCT 00598676): Two-year outcomes after everolimus- or sirolimus-eluting stents in patients with coronary artery disease.14 SORT OUT 4 (NCT 00552877): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease.15

<table>
<thead>
<tr>
<th>Randomized Trial</th>
<th>Total No of Patients</th>
<th>EES</th>
<th>SES</th>
<th>Hazard Ratio (95% CI) for Reintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET-PROVE</td>
<td>29/774</td>
<td>33/775</td>
<td>0.88(0.53, 1.47)</td>
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<tr>
<td>ESSENCE-DIABETES</td>
<td>1/149</td>
<td>4/151</td>
<td>0.26(0.03, 2.25)</td>
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<tr>
<td>EXCELLENT</td>
<td>26/1079</td>
<td>6/364</td>
<td>1.47(0.61, 3.53)</td>
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<td>ISAR-TEST 4</td>
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<td>96/652</td>
<td>0.80(0.59, 1.08)</td>
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<tr>
<td>SORT OUT IV</td>
<td>20/1390</td>
<td>23/1394</td>
<td>0.87(0.48, 1.58)</td>
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<tr>
<td>Overall</td>
<td>153/4044</td>
<td>161/3326</td>
<td>0.85(0.68, 1.07)</td>
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</tr>
</tbody>
</table>

Figure 4. Forest plot with hazard ratios for repeat revascularization associated with everolimus-eluting stents versus sirolimus-eluting stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. CI indicates confidence interval; EES, everolimus-eluting stent; and SES, sirolimus-eluting stent. Trial acronyms, registration numbers, and references: BASKET PROVE (ISR CTN 72444640): Drug-eluting vs bare-metal stents in large coronary arteries.16 ESSENCE-DIABETES (NCT 00997763): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with diabetes mellitus and coronary artery disease.17 EXCELLENT (NCT 00698607): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease.16 ISAR-TEST 4 (NCT 00598676): Two-year outcomes after everolimus- or sirolimus-eluting stents in patients with coronary artery disease.14 SORT OUT 4 (NCT 00552877): A prospective randomized trial of everolimus-eluting stents and sirolimus-eluting stents in patients with coronary artery disease.15
reasons: First, SES (Cypher) is the most effective first-generation DES and provides the best benchmark against which second-generation DES should be evaluated. Second, everolimus is a sirolimus analog, and comparison against SES constitutes a more intuitive target for interdevice efficacy trials. The present meta-analysis shows that there are no significant differences between EES and SES regarding restenosis and thrombosis-induced adverse events. In fact, there was a tendency for EES to lead to fewer reinterventions than SES. However, the fact that even an analysis with the strength of a total number of 7370 patients and 585 primary events was not able to detect a significant advantage of EES may be interpreted as a signal that any true difference is likely to be of limited relevance and highlights the great challenge in the design of future trials targeting this comparison.

The second-generation EES (Xience V) consists of a thin-strut CoCr platform with a 6- to 8-µm-thick, nonerodable biocompatible polymer and 100 µg/cm² everolimus, a synthetic derivative of sirolimus. About 80% of the drug is released within 30 days, with nearly all the drug released within 4 months. The studies focusing on the comparison of EES with SES came after a series of randomized trials showing a clear superiority of EES over PES regarding the risk of both in-stent restenosis and thrombosis. The results of the present meta-analysis confirm that EES are a very effective and safe second-generation DES. On the other hand, the results of our meta-analysis show that good first-generation DES such as SES (Cypher) may still represent a valid treatment option for patients with coronary artery disease.

Three limitations of the present study deserve special consideration. First, the lack of full sets of individual data prevents analysis of important subgroups such as patients with diabetes and those with acute myocardial infarction. These subgroups are still at the center of ongoing debate about relative value of available DES. Second, the definition of major adverse cardiac events—the primary end point of this meta-analysis—was not consistent across the trials. Notably, in one of the trials—the SORT OUT IV trial—the investigators included definite stent thrombosis as part of major adverse cardiac events. Because these cases of definite stent thrombosis represent only a small fraction of those with major adverse cardiac events in the SORT OUT IV trial (11 patients) and a much smaller fraction of those with major adverse cardiac events in all 5 trials (585 patients), it is unlikely for this definition characteristic to have had a relevant impact on the overall result of the present meta-analysis. Third, although the follow-up in 2 of the included trials was 24 and 36 months, respectively, overall median follow-up was 13.3 months. We cannot exclude that significant differences in outcomes may emerge after a longer follow-up.

In conclusion, this meta-analysis did not show significant differences between EES and SES in terms of clinical efficacy and safety. Future studies with longer follow-up are needed to better define the relative merits of these drug-eluting stents.

Disclosures
Dr Kastrati received lecture fees from Abbott and Cordis.
References


CLINICAL PERSPECTIVE
A large number of randomized, controlled trials showed the superiority of sirolimus-eluting stents (SES; Cypher) over first-generation paclitaxel-eluting stents (PES). The second-generation everolimus-eluting stent (EES; Xience V) has clearly been shown superior to PES, but its relative merits against SES have been less extensively assessed. To fill this gap, we performed a meta-analysis of randomized, controlled trials comparing EES and SES in patients with coronary artery disease. We identified 5 eligible randomized trials comparing EES with SES in 7370 patients. The primary end point was major adverse cardiac events. The risk of major adverse cardiac events (P=0.28), cardiac death (P=0.92), myocardial infarction (P=0.76), repeat revascularization (P=0.16), and composite of definite and probable stent thrombosis (P=0.33) were not significantly different between EES and SES. Thus, this meta-analysis does not show significant differences between EES and SES in terms of clinical efficacy and safety. This confirms that EES are very effective and safe second-generation drug-eluting stents. On the other hand, the results show that good first-generation drug-eluting stents such as SES may still represent a valid treatment option for patients with coronary artery disease.
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