The Unrestricted Use of Sirolimus- and Paclitaxel-Eluting Stents Results in Better Clinical Outcomes During 6-Year Follow-Up Than Bare-Metal Stents

An Analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus–Stent Evaluated At Rotterdam Cardiology Hospital) Registries

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Objectives The aim of this study was to assess the 6-year clinical outcome after unrestricted use of sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) as compared with bare-metal stents (BMS) in consecutive de novo patients undergoing percutaneous coronary intervention (PCI).

Background SES and PES have been shown to significantly decrease target vessel revascularization (TVR) rates compared with BMS in “real-world” registries. However, possible higher rates of very-late stent thrombosis and a restenosis “catch-up” trend might jeopardize the benefit.

Methods Three PCI cohorts, each with exclusive use of 1 stent type (BMS = 450; SES = 508; PES = 576), were systematically followed for the occurrence of major adverse cardiac events (MACE).

Results Very-late stent thrombosis was more common in SES and PES patients than BMS patients (2.4% vs. 0.9% vs. 0.4%, respectively; p = 0.02); however, there were no significant differences between the stent types for all-cause mortality and all-cause mortality/myocardial infarction at 6-year follow-up. Sixty-nine SES patients (Kaplan-Meier estimate 14%) and 72 PES patients (14%) had a TVR, as compared with 79 BMS patients (18%; log-rank p = 0.02), which maintained significance after adjustment for (potential) confounders. Multivariate analysis showed that DES implantation is associated with lower incidence of TVR and MACE than BMS implantation (hazard ratio: 0.65, 95% confidence interval: 0.49 to 0.86; p = 0.003; hazard ratio: 0.79, 95% confidence interval: 0.65 to 0.97; p = 0.02, respectively). Incidence of MACE was also lower in SES and PES patients (30% and 30%, respectively) than in BMS patients (34%); however, significance was borderline.

Conclusions The unrestricted use of both DES resulted in a sustained advantage in decreasing TVR and, to a lesser extent, MACE compared with BMS at 6 years. The SES and PES are equally safe and effective in the treatment of coronary lesions. (J Am Coll Cardiol Intv 2010;3:1051–8) © 2010 by the American College of Cardiology Foundation

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In the last decade several randomized clinical trials and registries assessed the short- and long-term clinical outcome of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) (1–6). Although drug-eluting stents (DES) lead to a decrease in angiographic restenosis and target vessel revascularization (TVR) rates compared with bare-metal stents (BMS), DES caused novel safety concerns such as possible higher very-late stent thrombosis rates (7,8). The occurrence of stent thrombosis is not merely a result of premature discontinuation of dual antiplatelet therapy but rather a multifactorial problem caused by several detrimental features, including clinical, coronary lesion, and procedural characteristics (9–14). The higher likelihood of late stent malapposition after DES implantation, which is associated with very-late stent thrombosis (≥1 year after stent implantation), could jeopardize the very long-term clinical beneficial value of DES. Also the observation of a possible clinical TVR “catch-up” phenomenon in the DES-population is of concern (15–18).

The long-term clinical results of the treatment of “all-comer” percutaneous coronary intervention (PCI) patients without using any exclusion criteria have been described by our group in the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus–Stent Evaluated At Rotterdam Cardiology Hospital) registries (19,20). Although DES have shown superior short- and long-term clinical outcome with regard to TVR rates compared with BMS, it remains unknown whether this effect is sustained. Therefore, the purpose of the present report is to investigate the safety and efficacy profile of the unrestricted use of SES and PES versus BMS in de novo patients undergoing PCI at 6-year follow-up.

**Definitions and clinical end points.** Procedural success was defined as successful stent deployment and a residual stenosis <30% by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 without the occurrence of MACE within 2 days after intervention. Definite stent thrombosis was defined as angiographically documented thrombus in or within 5 mm of the stent, accompanied by at least 1 of the following (as recommended by the Academic Research Consortium criteria): 1) acute symptoms; 2) ischemic electrocardiographic changes; and 3) typical rise and fall of cardiac markers. Stent thrombosis was categorized into early (within 30 days after stent implantation), late (within 30 days and 1 year after stent implantation), and very-late (after 1 year after stent implantation).

The primary end point was the occurrence of patient-oriented MACE (defined as a composite of all-cause mortality, any myocardial infarction [MI], and TVR). Efficacy end point included TVR, whereas safety end points consisted of stent thrombosis, all-cause mortality, and the composite of all-cause mortality/MI. Myocardial infarction was diagnosed by recurrent typical clinical symptoms, the development of ST-segment elevation or left bundle branch block on electrocardiography with a creatine kinase-myocardial band rise of 3× the upper limit of normal and/or
analyses were performed with SPSS for Windows version 15 (SPSS, Inc., Chicago, Illinois).

Results

Population characteristics. Survival status was available for 98% of the patients. The baseline and procedural characteristics of the BMS, SES, and PES groups are shown in Table 1. In summary, the population consisted mostly of men (71%), and the mean age was 61 years (±11.1 years). There were no significant differences in baseline characteristics among the 3 groups, except for BMS patients who had more prior PCIs (p < 0.01) compared with SES and PES patients. Significantly more patients presented with an acute coronary syndrome in the PES group. Type C and bifurcation lesions were more often treated in the SES and PES groups (p < 0.01). There were more stents with smaller diameters implanted in the SES and PES patients with a longer total stented length compared with BMS patients (p < 0.01).

The usage of glycoprotein IIb/IIa inhibitors was more common in the BMS population compared with the SES and PES population (p < 0.01). The duration of clopidogrel usage after stent implantation increased over time, being shortest for the BMS group (mean of 1 month) and longest in the PES population (mean of 6 months).

6-year outcome: safety end points. The cumulative incidence and the associated adjusted multivariate hazard ratios (HRs) (BMS vs. SES, BMS vs. PES, SES vs. PES) of the 6-year follow-up of the BMS, SES, and PES cohorts are shown in Table 2 for each of the safety end points (i.e., stent thrombosis, all-cause mortality, and all-cause mortality/MI). Although very-late stent thrombosis was more common in SES patients than BMS patients (SES = 2.4% vs. PES = 0.9% vs. BMS = 0.4%; [analysis of variance] p value = 0.02; [Bonferroni-test] BMS vs. SES = 0.02, BMS vs. PES = NS, SES vs. PES = NS), it did not influence the incidence of the end points all-cause mortality and the composite end point of all-cause mortality or MI at 6-year follow-up on multivariate analysis (Tables 2 and 3).

6-year outcome: efficacy end points. Univariate analysis showed that there were no significant differences in MACE and TVR rates between SES and PES at 6 years (HR: 0.95, 95% CI: 0.85 to 1.06; HR: 1.02, 95% CI: 0.87 to 1.21, respectively) and therefore we could analyze both SES and PES together as a broader DES group (n = 1,084). The TVR rates of PES patients were significantly lower compared with BMS patients (HR: 0.84, 95% CI: 0.71 to 0.98) and borderline significant for SES patients (HR: 0.86, 95% CI: 0.73 to 1.01). DES significantly reduced TVR rates (HR: 0.72, 95% CI: 0.55 to 0.95); however, MACE rates were similar (HR: 0.91, 95% CI: 0.75 to 1.10).
The multivariate Cox regression analysis showed that MACE rates were lower in the DES group compared with the BMS group (HR: 0.79, 95% CI: 0.65 to 0.97). This was primarily because significantly fewer TVR procedures were performed in the DES group (HR: 0.65, 95% CI: 0.49 to 0.86). The same findings were present for TVR when SES and PES were independently compared with BMS (HR: 0.81, 95% CI: 0.68 to 0.96; and HR: 0.81, 95% CI: 0.68 to 0.96, respectively) with lower Kaplan-Meier estimates (14% and 18%; log-rank \( p = 0.02 \), respectively) (Figs. 2 and 3).
although significance was borderline for MACE (HR: 0.90, 95% CI: 0.80 to 1.01; and HR: 0.89, 95% CI: 0.79 to 1.00, respectively). No significant differences were observed for MACE and TVR rates between SES and PES.

**Discussion**

The 2-year follow-up of the T-SEARCH registry and the 4-year follow-up of the RESEARCH registry have already been published (3,22). Briefly, there were no significant differences in MACE between PES and SES (18.9% vs. 15.4%, p = 0.12) in the T-SEARCH registry at 2-year follow-up, but the incidence of MACE was higher in the BMS group compared with the SES group (28.7% vs. 23.0%, p = 0.05) in the RESEARCH registry at 4-year follow-up. The main finding of the 6-year follow-up of the RESEARCH and T-SEARCH registries is that DES reduced TVR by 35% and MACE by nearly 20% compared with BMS at 6-year follow-up in an unselected population. Although several clinical trials found contradictory results for SES outperforming PES in terms of TVR rates, no significant differences were found between SES and PES for all investigated end points at 6 years in our study (23–28). The Kaplan-Meier curve illustrates that the TVR- and MACE-graphic lines for both DES remain nearly parallel to the BMS-graphic line after 1 year of follow-up, proving

**Table 2. Crude Event Rates and Multivariate Analysis Stratified According to Different Stent Types at 6 Years**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>2-yr</th>
<th>6-yr</th>
<th>Δ2–6 yrs</th>
<th>BMS vs. SES</th>
<th>BMS vs. PES</th>
<th>PES vs. SES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
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<tr>
<td>2-yr</td>
<td>28 (6.2%)</td>
<td>29 (5.7%)</td>
<td>43 (7.5%)</td>
<td>0.90 (0.69–1.18)</td>
<td>0.97 (0.75–1.26)</td>
<td>0.96 (0.75–1.23)</td>
</tr>
<tr>
<td>6-yr</td>
<td>77 (17.1%)</td>
<td>83 (16.3%)</td>
<td>92 (16.0%)</td>
<td>1.00 (0.85–1.18)</td>
<td>0.97 (0.82–1.15)</td>
<td>1.00 (0.86–1.17)</td>
</tr>
<tr>
<td>Δ2–6 yrs</td>
<td>49 (10.9%)</td>
<td>54 (10.6%)</td>
<td>49 (8.5%)</td>
<td>0.95 (0.84–1.09)</td>
<td>0.86 (0.56–1.33)</td>
<td>0.98 (0.80–1.12)</td>
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<tr>
<td><strong>Mortality/MI</strong></td>
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<td></td>
</tr>
<tr>
<td>2-yr</td>
<td>53 (11.8%)</td>
<td>49 (9.6%)</td>
<td>67 (11.6%)</td>
<td>0.88 (0.72–1.08)</td>
<td>0.97 (0.79–1.18)</td>
<td>0.98 (0.81–1.18)</td>
</tr>
<tr>
<td>6-yr</td>
<td>105 (23.3%)</td>
<td>111 (21.9%)</td>
<td>122 (21.2%)</td>
<td>0.97 (0.84–1.11)</td>
<td>0.94 (0.81–1.08)</td>
<td>1.02 (0.89–1.17)</td>
</tr>
<tr>
<td>Δ2–6 yrs</td>
<td>52 (11.5%)</td>
<td>62 (12.3%)</td>
<td>55 (9.6%)</td>
<td>0.94 (0.83–1.06)</td>
<td>0.92 (0.60–1.40)</td>
<td>0.92 (0.76–1.12)</td>
</tr>
<tr>
<td><strong>TVR</strong></td>
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<tr>
<td>2-yr</td>
<td>63 (14.0%)</td>
<td>39 (7.7%)</td>
<td>52 (9.0%)</td>
<td>0.66 (0.54–0.82)</td>
<td>0.77 (0.63–0.93)</td>
<td>0.95 (0.77–1.18)</td>
</tr>
<tr>
<td>6-yr</td>
<td>79 (17.6%)</td>
<td>69 (13.6%)</td>
<td>72 (12.5%)</td>
<td>0.81 (0.68–0.96)</td>
<td>0.81 (0.68–0.96)</td>
<td>1.06 (0.89–1.26)</td>
</tr>
<tr>
<td>Δ2–6 yrs</td>
<td>16 (3.6%)</td>
<td>30 (5.9%)</td>
<td>20 (3.5%)</td>
<td>0.87 (0.71–1.07)</td>
<td>0.83 (0.42–1.64)</td>
<td>0.86 (0.64–1.15)</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
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<tr>
<td>2-yr</td>
<td>99 (22.0%)</td>
<td>77 (15.2%)</td>
<td>106 (18.4%)</td>
<td>0.75 (0.64–0.88)</td>
<td>0.85 (0.74–0.99)</td>
<td>0.96 (0.82–1.11)</td>
</tr>
<tr>
<td>6-yr</td>
<td>153 (34.0%)</td>
<td>151 (29.7%)</td>
<td>172 (29.9%)</td>
<td>0.90 (0.80–1.01)</td>
<td>0.89 (0.79–1.00)</td>
<td>1.01 (0.90–1.14)</td>
</tr>
<tr>
<td>Δ2–6 yrs</td>
<td>54 (12.0%)</td>
<td>74 (14.5%)</td>
<td>66 (11.5%)</td>
<td>0.92 (0.82–1.04)</td>
<td>0.80 (0.54–1.18)</td>
<td>0.96 (0.80–1.14)</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; other abbreviations as in Table 1.

**Table 3. Incidence of ST in the 3 PCI Cohorts**

<table>
<thead>
<tr>
<th>ST Type</th>
<th>BMS (n = 450)</th>
<th>SES (n = 508)</th>
<th>PES (n = 576)</th>
<th>ANOVA p Value</th>
<th>Bonferroni Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early ST</td>
<td>8 (1.8%)</td>
<td>2 (0.4%)</td>
<td>7 (1.2%)</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Acute ST</td>
<td>4 (0.9%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Subacute ST</td>
<td>4 (0.9%)</td>
<td>1 (0.2%)</td>
<td>6 (1%)</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Late ST</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>4 (0.7%)</td>
<td>0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Very-late ST</td>
<td>2 (0.4%)</td>
<td>12 (2.4%)</td>
<td>5 (0.9%)</td>
<td>0.02</td>
<td>BMS vs. SES = 0.02</td>
</tr>
<tr>
<td>Total ST</td>
<td>12 (2.7%)</td>
<td>16 (3.1%)</td>
<td>16 (2.8%)</td>
<td>0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Stent thrombosis (ST) occurring within 30 days after stent implantation is defined as early ST, categorized into acute ST (within 24 h) and subacute ST (1 to 30 days); Late ST is defined as ST occurring between 30 days and 1 year; Stent thrombosis occurring >1 year after the index procedure is defined as very-late ST.

ANOVA = analysis of variance; other abbreviations as in Tables 1 and 2.
that the beneficial effect in reducing neointimal hyperplasia occurs in the first year, but most importantly the effect is sustained at 6 years.

The 5-year results of the RAVEL (RAAndomized study with the sirolimus-eluting VELocty balloon-expandable stent4) clinical trial, which compared the SES with the BMS in patients with single de novo coronary lesions, showed that target-lesion revascularization and MACE rates were lower in SES patients compared with BMS patients (10.3% vs. 26%, p < 0.001; 25.8% vs. 35.2%, p = 0.03, respectively) (3). These results were reproduced in the 5-year clinical outcome results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial (SES = 9.4% vs. BMS = 24.4%, p < 0.001; SES = 20.3% vs. BMS = 33.5%, p < 0.001, respectively) and the TAXUS (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent) trial (PES = 16.9% vs. BMS = 27.4%, p < 0.001; PES = 24.0% vs. BMS = 32.8%, p < 0.001) (5,29). The findings of these clinical trials are mostly in line with the results found in our registries, in which we have used patient-orientated MACE (death, any MI, any revascularization) instead of device-orientated MACE (cardiac death, target-vessel related MI, and target-lesion revascularization).

Although there were more patients with very-late stent thrombosis in the SES and PES groups, it did not influence the safety outcome of either stent. In spite of controversial findings of several large (multicenter) registries and clinical trials concerning the possibility of an increased risk of definite very-late stent thrombosis with SES and PES implantation compared with BMS implantation, DES implantation has never been associated with higher mortality rates (30–32). Even though some factors causing very-late stent thrombosis are patient (behavior)-related, the higher
occurrence of late stent malapposition in SES and PES patients compared with BMS is a stent type-related factor contributing to higher stent thrombosis rates (33). Previously published larger studies showed higher late stent thrombosis rates in the PES population than in the SES population (34,35). However, the main factor causing this difference in stent thrombosis rates between the different stents remains undetermined, because of considerable differences in stent design (closed-cell design of the SES, and the different strut thicknesses of the first- [132 μm] and second-generation [97 μm] PES), dissimilar stent rigidity, and inability to compare anti-restenotic mechanisms of the drug and drug-release patterns of the stent platforms used (36,37).

Although “real-world” registries are the best way to mimic the complex clinical situation of most patients, several shortcomings need to be addressed and acknowledged. Because the described cohorts are single-center, nonrandomized, and purely observational, they have different complexity levels. During the inclusion years, increasingly more diseased patients and more complex lesions were being treated with PCI. Although this has been corrected for in statistical analysis, it is debatable whether this was sufficient. Because the BMS population consisted of the least complex patients and it had higher TVR rates and MACE rates than SES and PES, the BMS has proven to be inferior. It is noteworthy that nearly 20% of the SES patients and 40% of the PES patients had a planned angiographic follow-up at 6 months. This is a possible explanation for the sudden rise of TVR rates at 6-month follow-up in the DES groups, in which occlusostenotic-driven TVR might have occurred that had a negative influence on the end point, which actually strengthens our current findings showing that DES have a better clinical safety and efficacy compared with BMS. Third, some cardiac events could have been missed, because of data collection relied on the ability of the patient to remember events of the past year. However, we have no reason to believe that this was not identically distributed between the stent cohorts. Finally, the sample size of this study led to inadequate statistical power for detecting differences for stent thrombosis in the 3 cohorts.

The 6-year follow-up of the RESEARCH and T-SEARCH registries shows that SES and PES have a beneficial effect on safety and efficacy outcome compared with BMS, in terms of decreased TVR procedures and, to a lesser extent, MACE when used in unselected de novo patients. Although the occurrence of more very late stent thrombosis in SES and PES patients remains a safety concern, this did not influence the safety end points all-cause mortality and the composite end point all-cause mortality/MI, which were equally distributed. The safety and efficacy outcomes for SES and PES were similar for all end points.

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**REFERENCES**


Key Words: bare-metal stent(s) • paclitaxel-eluting stent(s) • sirolimus-eluting stent(s) • target vessel revascularization.