Nobori Biolimus-Eluting Stent vs. Permanent Polymer Drug-Eluting Stents in Patients Undergoing Percutaneous Coronary Intervention – Meta-Analysis of Randomized Clinical Trials –
Gian Battista Danzi, MD; Raffaele Piccolo, MD; Gennaro Galasso, MD, PhD; Federico Piscione, MD

Background: Permanent polymer coatings on drug-eluting stents (DES) surface have been identified as triggers of adverse events following percutaneous coronary intervention (PCI). However, efficacy and safety data for the Nobori biolimus-eluting stent (BES), a biodegradable polymer DES, are limited, so the aim of this study was to evaluate clinical outcomes associated with the Nobori BES compared with permanent polymer DES in patients undergoing PCI.

Methods and Results: Randomized trials comparing Nobori BES vs. other DES were included in the meta-analysis. The 12-month clinical endpoints were: target lesion revascularization (TLR), all-cause mortality, myocardial infarction (MI) and stent thrombosis (ST). Seven trials totaling 12,090 PCI patients met the inclusion criteria. Nobori BES vs. other DES had a comparable risk of TLR (odds ratio [OR] 0.94; 95% confidence interval [CI], 0.66–1.34; P=0.74), mortality (OR 1.00; 95% CI, 0.78–1.28; P=0.98), MI (OR 1.10; 95% CI, 0.87–1.40; P=0.42) and definite/probable ST (OR 1.01; 95% CI, 0.45–2.25; P=0.99). Despite Nobori BES showing similar clinical results to sirolimus-, everolimus- and zotarolimus-eluting stents, it was superior to paclitaxel-eluting stents in reducing the risk of TLR (OR 0.31; 95% CI, 0.10–0.90; P=0.03).

Conclusions: Nobori BES use is associated with a similar safety and efficacy as permanent polymer DES at 1-year follow-up, albeit it is superior to paclitaxel-eluting stents in terms of TLR. Long-term follow-up data are needed in order to establish whether polymer degradation related to Nobori BES implantation improves clinical outcomes. (Circ J 2014; 78: 1858–1866)

Key Words: Biodegradable polymers; Drug-eluting stents; Meta-analyses; Nobori biolimus-eluting stent; Percutaneous coronary intervention

Drug-eluting stents (DES) represented a breakthrough technology in the treatment of patients by percutaneous coronary intervention (PCI), because of the potent inhibition of neointima hyperplasia and restenosis as compared with bare-metal stents. After initial enthusiasm, however, there has been controversy about the long-term safety and efficacy of DES, focusing on their potential for an increased risk of late stent thrombosis (ST), as well as delayed neointimal proliferation and subsequent late restenosis.1–6

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Currently approved DES consist of a metallic stent platform, an antiproliferative agent resulting in local suppression of neointimal hyperplasia, and a polymer coating that is applied to the stent’s surface and serves as carrier vehicle, permitting controlled drug release.7 First-generation DES use permanent polymer coatings that have been identified as possible triggers for the induction of a chronic inflammatory response, delayed hypersensitivity reactions, and chronic fibrin deposition at the site of stent implantation, resulting in impaired endothelialization of the stent struts, delayed vessel healing, and increased risk of very late ST.8

Biodegradable polymer DES aimed to overcome this problem by providing drug release in a similar controlled fashion, but using biodegradable polymers that convert to water and carbon dioxide, by means of Krebs cycle enzymes, after their carrier vehicle function has been accomplished.9

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The Nobori biolimus-eluting stent (BES; Terumo, Tokyo, Japan) is a newly developed DES that uses the biodegradable polylactic acid (PLA) polymer, coated only on the abluminal side of stent platform from which biolimus A9, a highly lipophilic analog of sirolimus, is eluted. Several recent trials compared the Nobori BES with permanent polymer DES, but opposing results were reported. Therefore, we performed a meta-analysis of randomized trials in order to evaluate the efficacy and safety of the Nobori BES vs. permanent polymer DES.

**Methods**

**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 (www.acc.org, www.americanheart.org, www.escardio.org, www.europcr.com, www.clinicaltrialresults.org, www.tctmd.com and www.theheart.org) for studies in any language (from inception of each database until November 2013). The reference list of relevant studies was additionally scanned. The key words were: “biolimus-eluting stent”, “biolimus A9”, “Nobori”, and “biodegradable polymer”. To be included, the citation had to meet the following criteria: (a) comparison of the Nobori BES vs. permanent polymer DES, (b) random treatment allocation and (c) availability of complete clinical data. We excluded trials using biodegradable polymer DES other than the Nobori BES. No language restrictions were enforced.

**Data Collection and Quality Assessment**

Two investigators independently assessed reports for eligibility at the title and/or abstract level, with divergences resolved by consensus; studies that met inclusion criteria were selected for further analysis. Studies were evaluated with respect to the following methodological items: randomization, adequacy of allocation concealment, blinding of participants, personnel and outcome assessors, handling 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 at follow-up. We did not use a quality score, because this practice has been previously discouraged.
Table 1. Main Characteristics of RCTs Included in the Meta-Analysis of the Nobori BES vs. Permanent Polymer DES in Patients Undergoing PCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study design (no. of patients)</th>
<th>Primary endpoint</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPARE II&lt;sup&gt;19&lt;/sup&gt;</td>
<td>BES (n=1,795) vs. EES (n=912)</td>
<td>12-month cardiac death, MI, and clinically-driven TVR</td>
<td>Life expectancy ≥5-year; reference vessel diameter between 2 and 4 mm</td>
</tr>
<tr>
<td>NEXT&lt;sup&gt;20&lt;/sup&gt;</td>
<td>BES (n=1,617) vs. EES (n=1,618)</td>
<td>12-month any TLR, and 3-year death or MI</td>
<td>Patients scheduled for PCI using DES</td>
</tr>
<tr>
<td>NOBORI I Phase 1&lt;sup&gt;21&lt;/sup&gt;</td>
<td>BES (n=85) vs. PES (n=35)</td>
<td>9-month in-stent late loss</td>
<td>De novo coronary lesions in ≤2 coronary arteries; reference vessel diameter between 2.5 and 3.5mm and lesion length between 5 and 25mm</td>
</tr>
<tr>
<td>NOBORI I Phase 2&lt;sup&gt;22&lt;/sup&gt;</td>
<td>BES (n=153) vs. PES (n=90)</td>
<td>9-month in-stent late loss</td>
<td>De novo coronary lesions in ≤2 coronary arteries; reference vessel diameter between 2.5 and 3.5mm and lesion length between 5 and 25mm</td>
</tr>
<tr>
<td>NOBORI JAPAN&lt;sup&gt;23&lt;/sup&gt;</td>
<td>BES (n=198) vs. SES (n=137)</td>
<td>9-month cardiac death, MI, TVR</td>
<td>Stable or unstable angina or provicable ischemia in ≤2 coronary lesions in different epicardial vessels; reference vessel diameter between 2.5 and 3.5mm and lesion length ≤30mm</td>
</tr>
<tr>
<td>SORT OUT V&lt;sup&gt;24&lt;/sup&gt;</td>
<td>BES (n=1,229) vs. SES (n=1,239)</td>
<td>9-month cardiac death, MI, definite ST, and clinically-driven TVR</td>
<td>Stable CAD or ACS with at least 1 coronary lesion ≥50% requiring DES implantation</td>
</tr>
<tr>
<td>SORT OUT VI&lt;sup&gt;25&lt;/sup&gt;</td>
<td>BES (n=1,497) vs. ZES (n=1,502)</td>
<td>12-month cardiac death, MI, TLR</td>
<td>Stable CAD or ACS with at least 1 coronary lesion ≥50% requiring DES implantation</td>
</tr>
</tbody>
</table>

(Table 1 continued the next page.)

**Outcome Variables**
Clinical endpoints were target lesion revascularization (TLR), all-cause mortality, myocardial infarction (MI) and ST. All endpoints were evaluated up to 12-month follow-up, according to per protocol definitions (Table S1). ST was considered as definite/probable according to ARC (Academic Research Consortium) criteria.<sup>13</sup>

**Statistical Analysis**
The $\kappa$ statistic was used to assess agreement between reviewers for study selection. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. The summary OR was calculated by using the random effects DerSimonian and Laird model. The Breslow-Day chi-squared test was calculated to test the statistical evidence of heterogeneity across the studies ($P<0.1$). In addition, we used the $I^2$ statistic, which describes the percentage variation across studies that is related to heterogeneity rather than chance, and we considered an $I^2$ index >30% as a high heterogeneity value. We performed a sensitivity analysis, in which the meta-analysis estimates are computed by omitting 1 study at time. A funnel plot was used to assess publication bias with respect to each endpoint. How-
<table>
<thead>
<tr>
<th>Trial</th>
<th>Exclusion criteria</th>
<th>Multicenter</th>
<th>Follow-up</th>
<th>Routine angiographic follow-up (%)</th>
<th>DAT</th>
<th>Publication year</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPARE II 19</td>
<td>Contraindication/nonadherence to 12-month DAT; planned major surgery within 30-day; cardiac shock; previous PCI with DES within 1 year</td>
<td>Yes</td>
<td>12-month</td>
<td>0</td>
<td>Aspirin indefinitely; 300 or 600 mg LD clopidogrel, than 75 mg/die prasugrel for 12 months</td>
<td>2013</td>
</tr>
<tr>
<td>NEXT 20</td>
<td>None</td>
<td>Yes</td>
<td>12-month</td>
<td>16.3</td>
<td>Aspirin indefinitely; 75 mg clopidogrel or 200 mg ticlopidine for at least 3 months</td>
<td>2013</td>
</tr>
<tr>
<td>NOBORI I Phase 1 21</td>
<td>LVEF &lt;30%; MI within 48h; intolerance to study drug or stent; serum creatinine &gt;2mg/dl; stroke or TIA within 3 months; GI bleeding; planned surgery within 6 months; previous stenting of the target vessel; left main disease; ostial lesions; total occlusion; thrombus-containing lesion; severe tortuosity</td>
<td>Yes</td>
<td>12-month</td>
<td>100</td>
<td>Aspirin indefinitely; 300 or 600 mg LD clopidogrel, than 75 mg/die clopidogrel for at least 6 months</td>
<td>2007</td>
</tr>
<tr>
<td>NOBORI I Phase 2 22</td>
<td>LVEF &lt;30%; MI within 48h; intolerance to study drug or stent; serum creatinine &gt;2mg/dl; stroke or TIA within 3 months; GI bleeding; planned surgery within 6 months; previous stenting of the target vessel; left main disease; ostial lesions; total occlusion; thrombus-containing lesion; severe tortuosity</td>
<td>Yes</td>
<td>9-month</td>
<td>100</td>
<td>Aspirin indefinitely; clopidogrel for at least 3 months aspirin indefinitely; 300 or 600 mg LD clopidogrel, than 75 mg/die clopidogrel for at least 6 months</td>
<td>2009</td>
</tr>
<tr>
<td>NOBORI JAPAN 23</td>
<td>LVEF &lt;30%; MI within 72h; intolerance to study drug or stent; serum creatinine &gt;2mg/dl; stroke or TIA within 3 months; GI bleeding; planned surgery within 6 months; any coronary procedure within 30-day; DES implanted within 1-year; left main disease;</td>
<td>Yes</td>
<td>9-month</td>
<td>94</td>
<td>Aspirin indefinitely; 75 mg clopidogrel or 200 mg ticlopidine for at least 3 months</td>
<td>2011</td>
</tr>
<tr>
<td>SORT OUT V 24</td>
<td>Life expectancy &lt;1-year; allergy to antiplatelet drugs, sirolimus or biolimus; inability to tolerate 12-month DAT</td>
<td>Yes</td>
<td>12-month</td>
<td>0</td>
<td>Aspirin indefinitely; 600 mg clopidogrel LD or 60 mg prasugrel LD, than 75 mg/ die clopidogrel or 10mg/die prasugrel for 12 months</td>
<td>2013</td>
</tr>
<tr>
<td>SORT OUT VI 25</td>
<td>Life expectancy &lt;1-year; allergy to antiplatelet drugs, zotarolimus or biolimus; inability to tolerate 12-month DAT</td>
<td>Yes</td>
<td>12-month</td>
<td>0</td>
<td>NA</td>
<td>2013*</td>
</tr>
</tbody>
</table>

*Presented at the TCT Congress 2013, San Francisco, CA, USA.

ACS, acute coronary syndrome; BES, biolimus-eluting stent; CAD, coronary artery disease; COMPARE II, Comparison of the Everolimus Eluting (XIENCE-V®, XIENCE-Prime® or PROMUSPR Stent) With the Biolimus A9 Eluting NOBORIR Stent in All-comers: a Randomized Open Label Study; DAT, dual antiplatelet therapy; DES, drug-eluting stent; EES, everolimus-eluting stent; GI, gastrointestinal; LD, loading dose; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; NEXT, NOBORI Biolimus-Eluting Versus XIENCE/ PROMUS Everolimus-eluting Stent Trial; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; TCT, Transcatheter Cardiovascular Therapeutics; TIA, transient ischemic attack; TLR, target lesion revascularization; TVR, target vessel revascularization; SORT OUT V, Randomized Clinical Comparative Study of the Nobori and the Cypher Stents in Unselected Subjects With Ischemic Heart Disease; SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity Coronary Stents in Non-selected Patients With Ischemic Heart Disease.

ever, because graphical evaluation can be subjective, we performed both Harbord and Peters tests as formal statistical tests for publication bias. Statistical analyses were performed with Review Manager 5.2 (RevMan, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), and STATA 10.0 statistical software (STATA Corp, College Station, TX, USA).

Sample Size
Trial sequential analysis was performed according to the monitoring boundaries approach, by using TSA version 0.9 β (www.ctu.dk/tsa). 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% relative risk of TLR with the Nobori BES, with an expected absolute event rate in the other DES arms of 5%. The main results were shown in a graph of the cumulative Z curve and the O’Brien-Fleming α-spending function was used to determine the boundaries in this graph for concluding superiority or inferiority or noninferiority/futility.

The study was realized in compliance with the Preferred
Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.18

Results

As reported in Figure 1, we screened the title and/or abstract of 331 potentially eligible publications. Of these, 272 citations were excluded because they were not relevant or were duplicated publications. Thus, 59 studies were assessed for eligibility and 52 records were discarded because the inclusion criteria were not met. Finally, 7 trials19–25 were included in this meta-analysis, enrolling a total of 12,090 participants (6,566 or 54.3% randomly assigned to the Nobori BES and 5,524 or 45.7% randomly assigned to other DES). The interobserver agreement for study selection was very good, with k=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. Two trials19,21 compared the Nobori BES with a sirolimus-eluting stents (SES: Cypher Select Plus or Cypher, Cordis, Johnson & Johnson, Warren, NJ, USA), 2 trials20,24 compared the Nobori BES with everolimus-eluting stents (EES: Xience V or Prime, Abbott Vascular, Santa Clara, CA, USA; Promus, Boston Scientific, Natick, MA, USA) and 1 study25 compared the Nobori BES with the Resolute zotarolimus-eluting stent (R-ZES, Medtronic, Santa Rosa, CA, USA). The remaining 2 studies evaluated the Nobori BES against paclitaxel-eluting stents (PES), the Taxus Express (Boston Scientific) in the NOBORI I Phase 1 trial,21 and the Taxus Liberté (Boston Scientific) in the NOBORI I Phase 2 trial.22

All trials had a multicenter, noninferiority design. The risk of bias among studies is reported in Table S2. The primary endpoint was a composite clinical endpoint in 5 trials19,20,23–25 Two trials provided an angiographic endpoint (late lumen loss at 9 months).21,22 All trials had clinical follow-up available at 12 months, with the exception of NOBORI I Phase 1 and 2 trials21,22 that presented clinical data at 9 month. Routine angiographic follow-up was performed in 4 trials,20–23 although in the NEXT (NOBORI Biolimus-Eluting Versus XIENCE/ PROMUS Everolimus-eluting Stent Trial) trial only 16.3% of participants was enrolled in the angiographic substudy.26 Dual antiplatelet therapy was prescribed for a period ranging from 3 to 12 months and consisted of aspirin and clopidogrel in the majority of patients. However, ticlopidine and/or prasugrel were permitted in 4 trials.19,20,23,24 Diabetes prevalence among the included trials ranged from 15% to 46%. PCI patients with acute coronary syndrome were enrolled in all trials, albeit in 3 studies21–23 only unstable angina patients could be considered for study inclusion.

Clinical Endpoints

As reported in Figure 2A, a total of 388 patients (3.2%) underwent repeat revascularization of the target lesion. No significant difference in the risk of TLR was observed in patients treated with the Nobori BES as compared with other DES (3.2% vs. 3.3% respectively, OR [95% CI] 0.94 [0.66–1.34], P=0.74). A high heterogeneity was found across the included trials (I²=52%; p het =0.05). However, there was a significant reduction in the risk of TLR with the Nobori BES vs. PES (2.5% vs. 7.2% respectively, OR [95% CI] 0.31 [0.10–0.90], P=0.03), as compared with other limus-family DES, such as SES, EES and R-ZES (3.2% vs. 3.2% respectively, OR [95% CI] 1.04 [0.85–1.29], P=0.69, p-interaction=0.03).

As reported in Figure 2B, a total of 270 patients (2.2%) died. There was no significant difference in the risk of death between patients randomized to the Nobori BES or other DES (2.2% vs. 2.3% respectively, OR [95% CI] 0.98 [0.78–1.28], P=0.98). No significant heterogeneity was noted (I²=0%; p het =0.75).

As shown in Figure 2C, a total of 292 patients (2.4%) had MI. The risk of MI was similar between the Nobori BES and other DES (2.6% vs. 2.2% respectively, OR [95% CI] 1.10 [0.87–1.40], P=0.42). No significant heterogeneity was found (I²=0%; p het =0.73).

Figure 2D summarizes risk estimates for definite/probable ST, which was reported in 63 patients (0.52%). No significant difference in terms of definite/probable ST was found between the Nobori BES and other DES (0.53% vs. 0.50% respectively, OR [95% CI] 1.01 [0.45–2.25], P=0.99). A high heterogeneity was present (I²=46%; p het =0.11).

Sensitive Analysis and Small-Study Effects

No single study significantly altered the summary ORs, because one-at-a-time study omission did not result in a movement of the point estimate outside the 95% CIs (data not shown).

Visual inspection of the funnel plot did not reveal a skewed distribution for the study endpoints, suggesting the absence of small-study effects. Furthermore, neither the Harbord nor the Peters test was significant (Figure S1A–D).

Sample Size

For the TLR evaluation, only 39% (12,090 of 31,251 patients) of the required sample size was accrued in this meta-analysis. However, as shown in Figure S2, the cumulative Z curve crossed the boundaries for futility, supporting the noninferiority of the Nobori BES to other DES.
Figure 2. Odds ratio of target lesion revascularization (TLR, A), all-cause mortality (B), myocardial infarction (C) and definite/probable stent thrombosis (D) associated with the Nobori biolimus-eluting stent vs. other drug-eluting stents.
Discussion

The main findings of this meta-analysis are that the Nobori BES has a similar safety and efficacy profile to currently approved, permanent polymer DES, without significant differences in the risk of death, MI, TLR or ST up to 1-year follow-up. Although the Nobori BES has comparable efficacy to limus-family DES, such as SES, EES and R-ZES, it is superior to PES in reducing the risk of TLR. The overall effect showed no significant difference for any of the analyzed endpoints, which is in line with the results from any individual trial included in the analysis.

Permanent polymer coatings are the most likely cause of hypersensitivity vasculitis at the site of stent implantation and have been associated with chronic inflammation and delayed arterial healing, increasing the risk of thrombotic events such as very late ST. Animal studies suggested different patterns of chronic inflammation induced by permanent polymers. SES and PES have been associated with diffuse granulomatous inflammation and para-strut fibrin deposition, respectively. On the other hand, persistent inflammation induced by permanent polymer DES may act as a primary driver of late restenosis via the vehicle of neointimal proliferation, leading to a "catch-up phenomenon". Contrariwise, the absence of a permanent polymer from the DES platform seems to mitigate this late reduction in anti-restenotic efficacy. These findings prompted the development of biodegradable polymer DES as an alternative strategy to overcoming the problems deriving from the use of permanent polymers. Indeed, after their function has been accomplished, biodegradable polymers are broken down into inert monomers and, finally, converted to water and carbon dioxide, leaving in situ only the metal stent backbone.

Among the biodegradable polymer DES, those eluting biolimus, which is characterized by a high lipophilicity (~10-fold higher than sirolimus), have been widely studied in animal and preclinical models, and have undergone investigation in different clinical settings. The Nobori BES is coated only abuminally with a matrix containing Biolimus A9 (Biosensors, Newport Beach, CA, USA) and PLA (15.6 μg each 1-mm stent length in 1:1 ratio), aiming to allow a drug reservoir released directly into the surrounding coronary tissue. Biolimus A9 is eluted in a 2-phase process: the first phase is a burst release (~40%) immediately after stent deployment, followed by sustained drug release and polymer degradation over a period of 6–9 months.

The potential advantages of the Nobori BES are mainly related to the biodegradable polymer, which should decrease the risk of late and very late events (especially ST) and, in turn, the need for prolonged dual antiplatelet therapy and the risk of long-term bleeding events after PCI. However, despite any potential advantage of biodegradable polymer DES not emerging until the late follow-up period after polymer dissolution, it should be mandatory to demonstrate at least an equivalent efficacy and safety profile of the Nobori BES to currently approved DES at 1-year follow-up.

All individual studies included in the present meta-analysis were designed as noninferiority studies. As such, they were underpowered for testing superiority. Despite meta-analyses being usually associated with significantly higher precision than individual studies, the power of the present meta-analysis was low and therefore the absence of significant superiority is not informative. Two trials comparing the Nobori BES with EES were included in the present meta-analysis, totaling 5,942 patients, which represented approximately 45% of our study population. Recent network meta-analyses and PCI registries demonstrated that EES is associated with lower ST rates when compared with bare-metal stents at 1 year, thus making EES the new benchmark for safety. Hereby, these data support the hypothesis of a 1-year equivalent performance of the Nobori BES to the newer-generation DES, which have thinner polymers and stent struts, more uniform distribution of the coating, and less polymer webbing, bonding, and delamination.

With regard to the comparison of the Nobori BES with PES, in this meta-analysis we found a 69% reduction in the odds of TLR in favor of the Nobori BES. These results should be interpreted with caution because PES has a lower efficacy than other DES. However, because both the NOBORI I Phase 1 and 2 trials were powered only for a surrogate endpoint (late lumen loss), these results further confirm the clinical anti-proliferative performance of the Nobori BES over PES.

In the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial, a similar BES with a PLA polymer (BioMatrix Flex: Biosensors) was shown as noninferior to SES at 9 and 12 months, but at 5-year follow-up the definite very late ST was significantly lower with BES than with SES. Similarly, in a pooled analysis of patient-level data from 3 randomized trials, Stefani et al reported a significant reduction of TLR, MI, and very late ST with biodegradable DES compared with SES. Preclinical and imaging data were also supportive for the biocompatibility of the Nobori BES, because a lower inflammatory response in the stented segments, and rapid recovery of endothelial function with preserved endothelium-dependent vasomotion at adjacent stent segments were demonstrated for the Nobori BES as compared with the SES. The results of this meta-analysis are also in line with the 1-year data from the NOBORI 2 registry, in which a total of 3,067 patients were enrolled. Indeed, TLR and definite/probable ST rates were 2.2% and 0.7% in the NOBORI 2 registry, compared with 3.2% and 0.55%, respectively in the present study.

Study Limitations

First, this was a meta-analysis at the study level and we could not properly assess the role of confounding factors. Second, we examined the safety and efficacy of the Nobori BES at 1-year follow-up. Thus, long-term follow-up data are required to establish whether polymer degradation associated with Nobori BES implantation improves clinical outcomes. Third, a high heterogeneity was observed for TLR and ST. Although differing anti-restenotic performance among the permanent polymer DES arms is the most likely explanation of the TLR heterogeneity, the higher heterogeneity for ST deserves further investigation. Therefore, caution should be used in interpreting ST results, based on the observed low incidence of early to late ST. Fourth, both the NEXT and COMPARE II trials (Comparison of the Everolimus Eluting With the Biolimus A9 Eluting NOBORI® Stent in All-comers: a Randomized Open Label Study) trials had a lower than expected rate of the primary study endpoint. However, this together with the noninferiority design of the selected trials should strengthen the need for the present meta-analysis.

Conclusions

The results of this meta-analysis demonstrate the 1-year equivalence of the Nobori BES with currently approved, high-performing, permanent polymer DES in terms of safety and efficacy. Nobori BES use is associated with a greater reduction in the risk of TLR than with PES. Updated follow-up of current trials will shed light on the long-term outcomes of the Nobori BES compared with permanent polymer DES, contributing to

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a better definition of the role of biodegradable polymer DES in patients undergoing PCI.

Disclosures

There is no conflict of interest for any of the authors. No funding was received for the writing of this manuscript.

References


### Supplementary Files

#### Search Strategy

**Table S1.** Endpoints definition in the included RCTs of the nobori BES vs. permanent polymer DES in patients undergoing PCI

**Table S2.** Risk of bias assessment of the included RCTs of the nobori BES vs. permanent polymer DES in patients undergoing PCI

**Figure S1.** Funnel plots of (A) target lesion revascularization, (B) death, (C) myocardial infarction and (D) stent thrombosis.

**Figure S2.** Trial sequential analysis. TLR, target lesion revascularization.