Two-Year Outcome of a Randomized Trial Comparing Second-Generation Drug-Eluting Stents Using Biodegradable or Durable Polymer

Recent network meta-analyses have raised concerns about the safety of biodegradable polymer drug-eluting stents (BP-DES) compared with durable polymer everolimus-eluting stents (DP-EES). The NOBORI Biolimus-Eluting vs XIENCE/PROMUS Everolimus-Eluting Stent Trial (NEXT) is a 98-center, randomized, open-label, noninferiority trial evaluating the efficacy and safety of biodegradable polymer biolimus-eluting stents (BP-BES) vs DP-EES. The primary efficacy outcome of target-lesion revascularization (TLR) at 1 year demonstrated noninferiority of BP-BES compared with DP-EES. The primary safety outcome, a composite of death and myocardial infarction (MI), will be reported at 3 years. However, because the advantages of BP-BES could emerge beyond 1 year when polymer has fully degraded, we report the interim 2-year results.

Table. Clinical Outcomes at 2 Years of Follow-up in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%) of Patients With ≥1 Event</th>
<th>Bivariable HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or myocardial infarction</td>
<td>126 (7.8)</td>
<td>124 (7.7)</td>
<td>1.02 (0.79-1.30) .003</td>
</tr>
<tr>
<td>Target-lesion revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>98 (6.2)</td>
<td>94 (6.0)</td>
<td>1.04 (0.78-1.38) &lt;.001</td>
</tr>
<tr>
<td>Clinically driven</td>
<td>68 (4.4)</td>
<td>67 (4.3)</td>
<td>1.01 (0.72-1.42) .95</td>
</tr>
<tr>
<td>Target-vessel revascularization</td>
<td>154 (9.8)</td>
<td>136 (8.6)</td>
<td>1.14 (0.90-1.43) .28</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>285 (18.1)</td>
<td>269 (17.0)</td>
<td>1.06 (0.90-1.25) .50</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>12 (0.8)</td>
<td>20 (1.3)</td>
<td>0.60 (0.28-1.21) .16</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>59 (3.7)</td>
<td>56 (3.5)</td>
<td>1.05 (0.73-1.52) .78</td>
</tr>
<tr>
<td>Q-wave</td>
<td>11 (0.7)</td>
<td>12 (0.8)</td>
<td>0.92 (0.40-2.09) .83</td>
</tr>
<tr>
<td>Target vessel</td>
<td>50 (3.1)</td>
<td>49 (3.0)</td>
<td>1.02 (0.69-1.51) .92</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>46 (2.9)</td>
<td>58 (3.7)</td>
<td>0.79 (0.54-1.16) .24</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>35 (2.2)</td>
<td>37 (2.3)</td>
<td>0.95 (0.60-1.51) .82</td>
</tr>
<tr>
<td>Ischemic</td>
<td>20 (1.3)</td>
<td>22 (1.4)</td>
<td>0.91 (0.49-1.67) .76</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>15 (1.0)</td>
<td>15 (1.0)</td>
<td>1.00 (0.49-2.07) .99</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI major</td>
<td>35 (2.3)</td>
<td>31 (2.0)</td>
<td>1.13 (0.69-1.83) .63</td>
</tr>
<tr>
<td>TIMI minor or major</td>
<td>56 (3.6)</td>
<td>50 (3.2)</td>
<td>1.12 (0.76-1.64) .56</td>
</tr>
<tr>
<td>TIMI minimal, minor, or major</td>
<td>102 (6.4)</td>
<td>108 (6.8)</td>
<td>0.94 (0.72-1.24) .67</td>
</tr>
<tr>
<td>GUSTO severe</td>
<td>37 (2.4)</td>
<td>32 (2.1)</td>
<td>1.15 (0.72-1.86) .55</td>
</tr>
<tr>
<td>GUSTO moderate or severe</td>
<td>56 (3.6)</td>
<td>50 (3.2)</td>
<td>1.12 (0.76-1.64) .57</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>5 (0.31)</td>
<td>3 (0.19)</td>
<td>1.67 (0.41-8.14) .48</td>
</tr>
<tr>
<td>Acute (0-1 d)</td>
<td>0</td>
<td>1 (0.06)</td>
<td></td>
</tr>
<tr>
<td>Subacute (2-30 d)</td>
<td>2 (0.12)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Late (31-365 d)</td>
<td>2 (0.12)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Very late (&gt;365 d)</td>
<td>1 (0.07)</td>
<td>2 (0.11)</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>22 (1.4)</td>
<td>18 (1.1)</td>
<td>1.22 (0.66-2.31) .53</td>
</tr>
<tr>
<td>Definite or probable</td>
<td>5 (0.31)</td>
<td>3 (0.19)</td>
<td>1.67 (0.41-8.14) .48</td>
</tr>
<tr>
<td>Definite, probable, or possible</td>
<td>27 (1.7)</td>
<td>21 (1.3)</td>
<td>1.29 (0.73-2.30) .38</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary arteries; TIMI, Thrombolysis in Myocardial Infarction.

* Cumulative incidence rates were estimated using the Kaplan-Meier method.

b The HRs and 95% CIs were estimated using the Cox proportional hazard model.

c Indicates noninferiority P value. The other P values indicate superiority because noninferiority analyses for the secondary outcomes were not prespecified.
Methods | The study design and baseline characteristics were previously described. 4 Between May and October 2011, patients scheduled for DES implantation were enrolled without any exclusion criteria and randomly assigned to BP-BES or DP-EES implantation in all target lesions scheduled for stenting. Ethics committees at each center approved the study and participants provided written informed consent.

The 2-year follow-up concluded in December 2013 and was planned as a noninferiority analysis of the primary safety and efficacy outcomes. The 2-year report had 71% power at a 1-sided α level of .006 for demonstrating noninferiority of BP-BES relative to DP-EES for the primary safety end point of death or MI with a 2.9% noninferiority margin for the anticipated event rate of 8.1%. 4 The analysis had 98% power at a 1-sided α level of .006 for demonstrating noninferiority of BP-BES relative to DP-EES for the primary efficacy end point of TLR with a 3.4% margin for the anticipated event rate of 6.9%. 4

Variables were compared with the χ² test or Fisher exact test, and the t test or the Wilcoxon rank sum test as appropriate. Clinical outcomes were analyzed as intention to treat. Patients who did not complete the 2-year follow-up were censored at drop out. Each end point was assessed by the Kaplan-Meier method and compared by the log-rank test or Cox proportional hazards model. Statistical analyses were performed with JMP version 10 and SAS version 9.3 (SAS Institute Inc). All P values were 2-sided and P < .05 was regarded as statistically significant, except for the 1-sided P values in the noninferiority analysis.

Results | Of 3235 patients with 4069 lesions, 1617 were assigned to receive BP-BES and 1618 to DP-EES. Two-year follow-up was completed in 3184 patients (98.4%). Dual antiplatelet therapy was maintained in a large proportion of patients at 2 years in both groups (69% vs 70%, P = .58). Treatment with BP-BES was demonstrated to be noninferior to DP-EES for death or MI (7.8% vs 7.7%, respectively; difference of 0.14% [upper 99.4% CI, 2.5%]; noninferiority P = .003) and TLR (6.2% vs 6.0%, respectively; difference of 0.28% [upper 97.5% CI, 2.0%]; noninferiority P < .001).

The cumulative 2-year incidence rates of death or MI and TLR were not significantly different between the groups (Table and Figure). No differences were found in prespecified secondary outcomes between groups (Table).

Discussion | Network meta-analyses have suggested that BP-DES had an excess risk for stent thrombosis or MI compared with DP-EES. 1-3 Furthermore, one study suggested that BP-DES was associated with excess mortality beyond 1 year compared with DP-EES. 1 However, no randomized trials of BP-DES vs DP-EES have reported clinical outcomes beyond 1 year.

In NEXT, the safety and efficacy outcomes of BP-BES were noninferior to those of DP-EES at 2 years. However, 2 years is not long enough to confirm the long-term safety of BP-BES, and the study was underpowered for the interim analysis. Follow-up at 3 years will be important.

Possible reasons for the discrepancy between this study and the network meta-analyses include absence of trials comparing long-term outcomes of BP-DES with DP-EES directly, pooling of several different BP-DES as a class, different risk profiles of enrolled patients across trials, and the wide variation in the ages of the trials, with changes in clinical practices such as duration of dual antiplatelet therapy. Other limitations include that patients with MI were underrepresented in our sample and event rates were less than expected.
The suggestion is not consistent with the current National Comprehensive Cancer Network (NCCN) guidelines and the American Society of Clinical Oncology (ASCO) practice guidelines. The NCCN recommends intensive surveillance with annual enhanced computed tomography (CT) along with serum carcinoembryonic antigen (CEA) measurement every 3 to 6 months only for patients with stage III colon cancer.² The ASCO panel mentions that other than stage and subset, there is no single pathological feature or statistical model that can be used to build a surveillance strategy.³

Although there was little difference in detection rates of treatable recurrences among Dukes A (stage I), Dukes B (stage II), and Dukes C (stage III) colorectal cancers in the trial,⁴ this does not mean that intensive surveillance strategies are equally effective for any stage of colorectal cancer. In a randomized clinical trial recruiting 259 patients with stage II or stage III colorectal cancer, when compared with the simple strategy of CEA testing and physical examination, an intensive strategy with CT or ultrasound in addition to CEA testing was associated with higher overall survival (hazard ratio, 0.34; 95% CI, 0.12-0.98) in patients with stage II tumors but not in those with stage III tumors (hazard ratio, 0.71; 95% CI, 0.34-1.47).⁵ In a cohort of 600 patients who underwent hepatic resection for colorectal metastases with curative intent, only 48 (8%) had been diagnosed as having stage I colorectal cancer.⁶ Therefore, it may be reasonable to stratify the intensiveness of surveillance according to the tumor stage.

Tetsuji Fujita, MD

Author Affiliation: Department of Surgery, Jikei University School of Medicine, Tokyo, Japan.

Corresponding Author: Tetsuji Fujita, MD, Department of Surgery, Jikei University School of Medicine, 3-25-8 Nishinshimbashi, Tokyo, Minato-ku 105-8461, Japan (tetsu@jg8.so-net.ne.jp).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Fujita and Kozuma and Kimura reported being advisory board members of Terumo Japan and Abbott Vascular Japan. Dr Kozuma also reported receiving fees for giving lectures for Abbott Vascular Japan, Terumo, Boston Scientific Japan, Nipro, Medtronic Japan, and Orbis Neich; serving as a consultant to Terumo and Zenon Medical; and being an advisory board member for Nipro. No other disclosures were reported.

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Trial Registration: clinicaltrials.gov Identifier: NCT01303640


COMMENT & RESPONSE

Surveillance for Recurrence of Colorectal Cancer

To the Editor In interpreting the results of a randomized clinical trial comparing different surveillance strategies after curative resection of colorectal cancer, Dr Primrose and colleagues¹ suggested that “stage-specific follow-up strategies may not be necessary” because “although there are fewer recurrences with better-stage tumors, they are more likely to be curable.”

This study by Dr Primrose and colleagues² evaluated intensive follow-up strategies in patients with colorectal cancer. This subject deserves specific attention considering that surgical resection is now possible in metastatic disease, especially when metastases are localized to the liver or lungs.

We were surprised by the 15% overall death rate of patients with Dukes A (stage I) disease at 5 years, similar to the

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