Long-Term Efficacy and Safety of Biodegradable-Polymer Biolimus-Eluting Stents

Main Results of the Basel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination II (BASKET-PROVE II), A Randomized, Controlled Noninferiority 2-Year Outcome Trial

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Background—Biodegradable-polymer drug-eluting stents (BP-DES) were developed to be as effective as second-generation durable-polymer drug-eluting stents (DP-DES) and as safe >1 year as bare-metal stents (BMS). Thus, very late stent thrombosis (VLST) attributable to durable polymers should no longer appear.

Methods and Results—To address these early and late aspects, 2291 patients presenting with acute or stable coronary disease needing stents ≥3.0 mm in diameter between April 2010 and May 2012 were randomly assigned to biolimus-A9–eluting BP-DES, second-generation everolimus-eluting DP-DES, or thin-strut silicon-carbide–coated BMS in 8 European centers. All patients were treated with aspirin and risk-adjusted doses of prasugrel. The primary end point was combined cardiac death, myocardial infarction, and clinically indicated target-vessel revascularization within 2 years. The combined secondary safety end point was a composite of VLST, myocardial infarction, and cardiac death. The cumulative incidence of the primary end point was 7.6% with BP-DES, 6.8% with DP-DES, and 12.7% with BMS. By intention-to-treat BP-DES were noninferior (predefined margin, 3.80%) compared with DP-DES (absolute risk difference, 0.78%; −1.93% to 3.50%; \( P \) for noninferiority 0.042; per protocol \( P=0.09 \)) and superior to BMS (absolute risk difference, −5.16; −8.32 to −2.01; \( P=0.0011 \)). The 3 stent groups did not differ in the combined safety end point, with no decrease in events >1 year, particularly VLST with BP-DES.

Conclusions—In large vessel stenting, BP-DES appeared barely noninferior compared with DP-DES and more effective than thin-strut BMS, but without evidence for better safety nor lower VLST rates >1 year. Findings challenge the concept that durable polymers are key in VLST formation.

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Key words: antiplatelet drugs ■ clinical trial ■ coronary artery disease ■ coronary thrombosis ■ drug-coated stents ■ drug-eluting stents

Drug-eluting stents (DES) with biodegradable polymers were developed to be as effective as second-generation durable-polymer drug-eluting stents and as safe after 1 year as bare-metal stents (BMS). Thus, very late stent thrombosis (VLST: beyond 1 year after implantation), which has been associated with the durable polymer of first-generation DES,
should no longer appear. Polymers serve as matrix for controlled drug diffusion into the vessel wall and modulation of drug release. Thereafter, polymers lose their function but, by disintegration and absorption, may induce local inflammation, hypersensitivity reactions, neointernalertherosclerosis and VLST, myocardial infarction, or cardiac death. To overcome this perceived deficiency of durable-polymer stents, DES with polymers that are degraded biologically within 2 to 15 months have been introduced. The rationale postulated for biodegradable-polymer DES was, therefore, that they would also reduce the risk of VLST or late clinical events related to stent thrombosis beyond the first year, when the polymer has dissolved. Recently, several meta-analyses of early comparative trials suggested that biodegradable-polymer DES are noninferior in efficacy compared to first- and second-generation durable-polymer DES up to 1 year. However, findings on late safety outcomes were inconsistent. In follow-up studies, no further increase in VLST was noted, but no trial focused on this late outcome nor in a broad population of patients compared with BMS, which still are considered the gold-standard for low VLST rates. In addition, all these findings were obtained on standard clopidogrel-based dual antiplatelet therapy despite the fact that newer, more potent antithrombotic drugs like prasugrel and ticagrelor are available. These drugs were shown to be more effective to prevent stent thrombosis–related events in patients with acute coronary syndrome, however at the price of an increased bleeding risk.

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The aim of the present BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination II (BASKET-PROVE II) was to evaluate the long-term performance profile of a current biodegradable-polymer DES compared with the currently most widely used durable-polymer DES for efficacy and safety and to a last-generation thin-strut coated BMS for late safety in a representative sample of patients, on a background of dual antiplatelet therapy including prasugrel.

Methods

Study Design

BASKET-PROVE II was a randomized, multicentre, single- and assessor-blind, noninferiority trial with primary end point assessment after 2 years. The study design and protocol have been described in detail before. All patients were treated with bleeding risk–adjusted prasugrel-based dual antiplatelet therapy irrespective of clinical indication and stent type. Follow-up angiography and revascularization were only allowed if clinically indicated. Eight centers in Switzerland, Denmark, Germany, and Austria contributed patients (see online-only Data Supplement). The study was conducted according to the declaration of Helsinki, approved by all local ethics committees, and all patients gave written informed consent. Acute coronary syndrome patients gave oral consent before the procedure, documented on the informed consent form by a medical person independent of the trial; written informed consent was obtained afterward. BASKET-PROVE II was an investigator-initiated and -performed trial independently from any device industry.

Patients

Eligible patients presented between April 1, 2010, and May 21, 2012 with chronic or acute coronary artery disease requiring angioplasty and stenting with stents ≥3.0 mm in diameter by visual assessment. No restrictions applied to the number of treated lesions or vessels, length of treated lesions, or number of stents implanted. Patients with cardiogenic shock, in-stent restenosis or thrombosis, unprotected left main coronary artery or bypass-graft disease, planned surgery within 12 months, need for oral anticoagulation, increased bleeding risk, known intolerance to or suspected noncompliance with long-term antiplatelet drug therapy, history of transient ischemic attack or stroke, or circumstances that would have made follow-up impossible were excluded.

Randomization and Masking

Eligible patients were randomized in a 1:1:1 ratio to either of the following stents: a second-generation biolimus-A9–eluting biodegradable-polymer stainless-steel DES (Nobori, Terumo), a second-generation everolimus-eluting durable-polymer cobalt-chromium DES (Xience Prime, Abbott Vascular), or a newest-generation thin-strut BMS coated with a biocompatible silicone-carbide layer (ProKinetik, Biotronik). Randomization using computer-generated allocation sequences was carried out in blocks of 12 for each center with the use of sealed envelopes.

Study Procedures

Angioplasty and stenting were performed according to standard techniques at the discretion of interventional cardiologists. The allocated stent type was used for all lesions in patients with multiple lesions and in those undergoing staged procedures (within 3 months). All patients were prescribed acetylsalicylic acid 75 to 100 mg daily long-term. All patients received a loading dose of 60 mg prasugrel with a maintenance dose of 10 mg daily, risk-adjusted to 5 mg in patients aged >75 years or body weight <60 kg. Prasugrel was prescribed for 12 months after stenting with DES and for patients with acute coronary syndrome and for 4 weeks after elective stenting with BMS. To assure adherence to antiplatelet therapy, patients were given the drug in monthly packages at regular intervals from the study centers. No further prasugrel was provided after 12 months. All other concomitant treatments were prescribed according to current guidelines.

Clinical follow-up using dedicated questionnaires was performed after 24±2 months. Outcome data were collected by local investigators, recorded on dedicated electronic case report forms, and transmitted via internet to the central database at the University of Basel. A central monitoring team checked all submitted information, verified with source documents at regular on-site visits.

End Points and Definitions

The primary end point was major adverse cardiac events (ie, a combination of cardiac death, nonfatal myocardial infarction, or clinically driven nonmyocardial infarction–related target vessel revascularization) within 2 years. The main secondary end point, the safety end point, was a combination of definite or probable stent thrombosis, myocardial infarction, or cardiac death. Other secondary end points included individual components of the primary end point as well as definite or probable stent thrombosis subdivided for events occurring within the first and second year. Cardiac death was defined as any death without a clear extracardiac cause. Myocardial infarction required a clinical event with typical electrocardiographic or enzymatic changes as described previously. Stent thrombosis was defined according to the criteria of the Academic Research Consortium. All events were adjudicated by a Critical Events Committee blinded to the stent types used.

Statistics

The sample size for the trial was estimated based on the findings of the BASKET-PROVE trial. Assuming an anticipated proportion of events of 7.6% for durable-polymer DES after 2 years as observed in the everolimus-eluting stent group of BASKET-PROVE, a non-inferiority margin of 3.8% absolute risk difference compared with the DES group was prespecified, considering a 50% relative excess of events or more in the biodegradable-polymer biolimus-A9–eluting...
stent patients as inferior. This noninferiority margin corresponded to that used in previous similar trials.19,20 It was determined that a sample size of 2×800 patients would have at least 80% power, declaring noninferiority if the upper limit of the 95% confidence interval (CI) of the absolute risk difference would be not larger than the noninferiority margin. Assuming an anticipated proportion of events of 7.6% for biodegradable-polymer DES and 12.9% for BMS after 2 years—as observed within the BASKET-PROVE trial17—the power for superiority was calculated to be >95%. Eight hundred patients per group was the primary goal, expecting a loss to follow-up rate of 10% in this clinical 2-year study. Based on the actual loss to follow-up observed of only ≈2%, which became apparent toward the end of the recruitment period based on very rigorous and continuously updated data monitoring, the Steering Committee decided to stop inclusion around 750 patients per group—in fact 765 per arm were included, similar to what was achieved in BASKET PROVE17—to shorten the duration of the recruitment phase.

Baseline characteristics are reported as counts and percentages or means±standard deviation. All analyses were performed on the intention-to-treat population. Withdrawal or loss to follow-up was addressed by censoring patients at the last available contact. In addition, a prespecified per protocol analysis, excluding major protocol violations, was performed for the noninferiority test and the results compared with the intention-to-treat analysis. The prespecified comparisons were those of biodegradable-polymer biolimus-A9–eluting versus durable-polymer everolimus-eluting stents (noninferiority), and biodegradable-polymer biolimus-A9–eluting versus bare-metal stents (superiority).

Noninferiority of biodegradable-polymer biolimus-A9–eluting compared with durable-polymer everolimus-eluting stent was established if the upper 95% CI of the absolute risk difference, applying a continuity-corrected modification of the Wilson’s score method,21 did not exceed the prespecified margin. Time-to-event analyses were carried out using the Kaplan–Meier estimator and Cox proportional hazards models, stratifying for center. In addition, because the assumption of constant hazard did not hold for all outcomes, time-independent logistic regressions were performed and odds ratios with 95% CIs are given. Landmark analyses were conducted for the major trial end points by splitting the entire follow-up period into 0 to 12 and 13 to 24 months. All analyses were performed by an independent statistical team of the Clinical Trial Unit of the University Hospital Basel using the statistical software system R, version 3.1.0.22

### Results

#### Patients and Follow-Up

A total of 2299 patients were enrolled in the trial, of whom 8 with acute interventions refused written consent after the procedure. The remaining 2291 patients with 2897 stented segments were randomly assigned to receive durable-polymer (n=765), biodegradable-polymer (n=765), or bare-metal (n=761) stents (Figure 1). Baseline characteristics in the 3 stent groups were similar (Table 1). Two thirds of patients presented with acute coronary syndromes, and half of these had myocardial infarction with ST-segment elevation. Angiographic and interventional parameters were similar between the 3 groups, too, with primary success rates of 95% to 96%. Five percent of patients received additional stents that were <3 mm in diameter. The median follow-up for surviving patients was 714 days, interquartile range 692 to 736 days, without differences between groups. At the end of the 2-year follow-up, survival status was known in 2256 patients (98.5%), but 17 were not reachable for a detailed final assessment (complete follow-up 97.7%).

#### Efficacy

Clinical outcomes after 2 years and hazard ratio estimates are shown in Table 2 and time-independent analyses in Table I in the online-only Data Supplement for all 3 stent groups. The primary end point occurred in 7.6% of patients receiving biodegradable-polymer, 6.8% of those receiving durable-polymer, and 12.7% with BMS. Noninferiority of the biodegradable-polymer stent compared with the durable-polymer drug-eluting stent was
established with an absolute risk difference of 0.78% (95% CI, -1.93% to 3.50%; \( P \) for noninferiority, 0.042). Noninferiority was formally no longer established if the more conservative per-protocol approach was used with an upper limit of the CI of 4.15% exceeding the predefined margin by 0.35% (\( P = 0.09 \)). The biodegradable-polymer stent was superior to the BMS regarding the primary end point after 2 years (absolute risk difference -5.16, 95% CI -8.32 to -2.01, \( p < 0.001 \)), a finding which was consistent with the use of the time-dependent proportional-hazard analysis (Table 2, Figure 2). This was mainly attributable to the difference of target vessel revascularizations not related to myocardial infarction. Landmark analyses showed that these effects appeared during the initial 12 months after stenting with an odds ratio for the comparison of the biodegradable-polymer versus the bare-metal stent for the primary end point of 0.42 (95% CI, 0.28–0.64; \( P < 0.0001 \)), but did not increase further after 12 months (odds ratio, 1.22; 95% CI, 0.63–2.37; \( P = 0.54 \); see Figure 2, and Table I and Figure I in the online-only Data Supplement).

<table>
<thead>
<tr>
<th>Stents</th>
<th>BP-DES</th>
<th>DP-DES</th>
<th>BMS</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>765</td>
<td>765</td>
<td>761</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62±11</td>
<td>62±11</td>
<td>63±11</td>
<td>0.78</td>
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<tr>
<td>Male sex, n (%)</td>
<td>600 (78)</td>
<td>610 (80)</td>
<td>570 (75)</td>
<td>0.06</td>
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<td>Cardiac risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>161 (21)</td>
<td>127 (17)</td>
<td>141 (19)</td>
<td>0.08</td>
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<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>38 (5.0)</td>
<td>37 (4.8)</td>
<td>35 (4.6)</td>
<td>0.94</td>
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<td>Arterial hypertension</td>
<td>506 (66)</td>
<td>507 (66)</td>
<td>510 (66)</td>
<td>0.93</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>494 (65)</td>
<td>484 (63)</td>
<td>471 (62)</td>
<td>0.55</td>
</tr>
<tr>
<td>Current smoker</td>
<td>271 (35)</td>
<td>267 (35)</td>
<td>280 (37)</td>
<td>0.73</td>
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<tr>
<td>Previous myocardial infarction</td>
<td>71 (9.0)</td>
<td>65 (9.0)</td>
<td>75 (10)</td>
<td>0.65</td>
</tr>
<tr>
<td>Previous coronary artery intervention</td>
<td>98 (13)</td>
<td>94 (12)</td>
<td>115 (15)</td>
<td>0.23</td>
</tr>
<tr>
<td>Previous coronary artery bypass-grafting</td>
<td>23 (3)</td>
<td>22 (3)</td>
<td>14 (2)</td>
<td>0.29</td>
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<tr>
<td>Clinical presentation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>274 (36)</td>
<td>271 (35)</td>
<td>300 (39)</td>
<td>0.20</td>
</tr>
<tr>
<td>NSTEMI*</td>
<td>263 (34)</td>
<td>271 (35)</td>
<td>253 (33)</td>
<td>0.67</td>
</tr>
<tr>
<td>ST-segment–elevation myocardial infarction</td>
<td>228 (30)</td>
<td>223 (29)</td>
<td>208 (27)</td>
<td>0.54</td>
</tr>
<tr>
<td>Treated vessels, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main artery (protected)</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>3 (0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Left anterior descending artery</td>
<td>475 (62)</td>
<td>483 (63)</td>
<td>491 (65)</td>
<td>0.61</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>268 (35)</td>
<td>264 (35)</td>
<td>252 (33)</td>
<td>0.72</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>396 (52)</td>
<td>403 (53)</td>
<td>394 (52)</td>
<td>0.92</td>
</tr>
<tr>
<td>Complexity of coronary artery disease, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>283 (37)</td>
<td>296 (39)</td>
<td>299 (39)</td>
<td>0.63</td>
</tr>
<tr>
<td>Treated bifurcations</td>
<td>33 (4)</td>
<td>43 (6)</td>
<td>45 (6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Treated chronic total occlusions</td>
<td>33 (4)</td>
<td>27 (4)</td>
<td>26 (3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Stents &lt;3.0 mm</td>
<td>30 (4)</td>
<td>49 (6)</td>
<td>20 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>GPIIb/IIIa blocker use</td>
<td>93 (12)</td>
<td>98 (13)</td>
<td>93 (12)</td>
<td>0.91</td>
</tr>
<tr>
<td>Procedural characteristics, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated segments per patient, n</td>
<td>1.2±0.5</td>
<td>1.3±0.6</td>
<td>1.3±0.5</td>
<td>0.38</td>
</tr>
<tr>
<td>Stents per patient, n</td>
<td>1.5±0.8</td>
<td>1.5±0.9</td>
<td>1.5±0.8</td>
<td>0.18</td>
</tr>
<tr>
<td>Number of stented segments</td>
<td>956</td>
<td>979</td>
<td>962</td>
<td></td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>25.7±16.7</td>
<td>27.1±18.4</td>
<td>25.1±15.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Stent length per lesion, mm</td>
<td>20.3±8.8</td>
<td>20.9±10.1</td>
<td>19.7±7.9</td>
<td>0.33</td>
</tr>
<tr>
<td>Max. deployment pressure, mmHg</td>
<td>14.3±3.7</td>
<td>14.3±3.4</td>
<td>14.6±3.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Staged procedures</td>
<td>38 (5)</td>
<td>64 (8)</td>
<td>45 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Lesions with angiographic success</td>
<td>922/956 (96)</td>
<td>938/979 (96)</td>
<td>917/962 (95)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Plus-minus values are means±SD. \( P \) values for continuous variables were calculated using a Kruskal–Wallis rank sum test and for categorical variables using a \( \chi^2 \) test if there were \( \geq 5 \) observations in each group, otherwise Fisher exact test was applied. \( P \) values were not adjusted for multiple comparisons. BMS indicates bare-metal stent; BP-DES, biodegradable-polymer drug-eluting stent; DP-DES, durable-polymer drug-eluting stent; GPIIb/IIIa, glycoprotein IIb/IIIa; and NSTEMI: non–ST-segment–elevation myocardial infarction.

*Including patients with unstable angina.
Safety
The combined safety end point and all individual components were not significantly different between the 3 stent groups (Table 2). Landmark analyses showed that this was true during the first year on antiplatelet therapy as well as thereafter (Table I and Figure I in the online-only Data Supplement). Of note, the combined safety end point was not reduced in patients with biodegradable-polymer stents compared with patients with other stents (Figure 3), and no increase in stent thrombosis rates was observed after stopping prasugrel for any stent.

Discussion
In the present study, the biodegradable-polymer biolimus-A9–eluting stent proved to be as effective and noninferior by intention-to-treat to the best-in-class second-generation durable-polymer everolimus-eluting stent to prevent restenosis. In fact, both DES were superior to BMS regarding this primary end point, particularly by reducing target vessel revascularization. However, the biodegradable-polymer DES did not further reduce the rate of VLST, myocardial infarction, or cardiac death beyond 1 year. Overall, stent thrombosis rates were very low in BASKET-PROVE II with all 3 stents, possibly because of the prasugrel-based dual antiplatelet therapy in this study. The major strength of this study is the comprehensive assessment of the relative performance and value of a current biodegradable-polymer biolimus-A9–eluting stent compared with best-in-class durable-polymer drug-eluting stents observed here, seems to question the concept that durable polymers are key in late stent thrombosis formation.

Figure 2. Kaplan–Meier estimates of the primary end point cardiac death or nonfatal myocardial infarction or clinically driven target vessel revascularization. Comparison of biodegradable-polymer biolimus-eluting (BP-DES, green), durable-polymer everolimus-eluting (DP-DES, red), and bare-metal (BMS, blue) stent groups.
biodegradable-polymer compared with both a second-generation durable-polymer everolimus-eluting stent and a newest-generation thin-strut BMS as well as the assessment of both early efficacy and late safety. This was achieved in a single trial in a real-world population, including patients with stable and acute coronary artery disease and ST-segment-elevation myocardial infarction. It was a multicentre, randomized, investigator-driven, industry-independent trial with a primary end point after 2 years, sufficiently late to obtain long-term outcome results not biased by early outcome results. The only relevant selection was to enroll patients in need of large coronary stents ≥3 mm in diameter, a population expected to have lower restenosis rates and higher rates of myocardial infarction and death related to stent thrombosis.23,24 In such patients, the validity of the concept that biodegradable polymers would be safer without loss of efficacy versus durable-polymer stents should become particularly apparent. Finally, results were obtained on the background of prasugrel-based dual antiplatelet therapy shown to be more potent and consistent in its effect than clopidogrel-based therapy in patients with acute coronary syndromes.15 This fact has to be kept in mind when interpreting present results and may have been a reason for the low stent thrombosis rates in all 3 stent groups, which, however, cannot be verified without a randomized comparison with a clopidogrel-based therapy.

Previous studies of biodegradable-polymer stents were recently summarized in 4 meta-analyses.5–8 The fact that 4 such comprehensive meta-analyses were published within 1 year in major journals points to the great interest in biodegradable-polymer DES. It also highlights the fact that differences are small, such that large numbers of patient data are needed to find significant differences between the different stents. The network type of analyses allowed indirect comparisons between all types of stents even if direct comparative trial data were limited. In fact, no trial evaluating biodegradable-polymer versus durable-polymer second-generation stents had a primary outcome assessment beyond 1 year up to the present trial.20,25,26 and follow-up reports are available only for a single trial as letter.5 Regarding biodegradable-polymer DES, findings of these meta-analyses indicate that biodegradable-polymer DES are superior in efficacy and safety compared with BMS and first-generation DES. Interestingly, compared with the second-generation durable-polymer everolimus-eluting stent used as standard in BASKET-PROVE II, there were inconsistent results: 3 meta-analyses found increased rates of stent thrombosis for biodegradable-polymer stents within 1 year,6–8 and 2 found a higher myocardial infarction rate,5,8 whereas the others described biodegradable-polymer stents as noninferior in these outcomes. With respect to events after 1 year, conclusions remain vague in view of the lack of direct trial comparisons; the direction of the results after 1 year did not, however, seem to diverge. These differences in the 4 meta-analyses may be attributable to different methodological details, trial selection, and different definitions, but also attributable to the lack of sufficient data with direct stent comparisons, particularly beyond 1 year. Here, BASKET-PROVE II adds important new information: it is the first trial with a 2-year primary end point and the first with a BMS control arm.

Several limitations need to be addressed. First, the trial was not powered for late safety, the main secondary end point. Because this is the first biodegradable-polymer drug-eluting stent trial with a 2-year primary end point, the expected rate of second-year VLST, myocardial infarction, or cardiac death was not really known at the time of the study design. Present results suggest that a trial of >20000 patients would be required to demonstrate a significant benefit of biodegradable-polymer drug-eluting stents given the observed differences in VLST. In view of the excellent late safety profile of the durable-polymer drug-eluting stent tested, any late benefit of biodegradable-polymer drug-eluting stents will be extremely difficult to demonstrate and is unlikely to be clinically meaningful. Another issue is the noninferiority margin, which may appear high at first sight. However, because the a priori definition of a noninferiority margin is somewhat arbitrary, we based our assumptions on results of the predecessor BASKET-PROVE trial with a similar design17 and defined a 50% relative excess of events or more in the biodegradable-polymer DES as inferior. This is in accordance with the sirolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization (LEADERS) trial,19 which first established

Figure 3. Kaplan–Meier estimates of the secondary safety end point cardiac death, nonfatal myocardial infarction, or definite or probable stent thrombosis overall (left) and subdivided for first and second year (right). Comparison of biodegradable-polymer biolimus-eluting (BP-DES, green), durable-polymer everolimus-eluting (DP-DES, red), and bare-metal stent (BMS, blue) groups.
noninferiority of these stents compared with a first-generation DES, and with the Nobori Biolimus-Eluting versus Xience/ Promus Everolimus-Eluting Stent Trial (NEXT) evaluating noninferiority compared with everolimus-eluting stents up to 1 year. Only the most recently published trials used a noninferiority margin of 42% and 44%, not much lower than the 50% used in BASKET-PROVE II. A further issue is the inconsistent findings for noninferiority depending on whether the intention-to-treat or the per-protocol set was used. All prior analyses cited were based on the intention-to-treat patient population despite the advice of the Consolidated Standards of Reporting Trials (CONSORT) statement to use the per-protocol set for noninferiority analyses. This information was added as complementary finding only in 2 trials. The present report demonstrates the importance of taking both these statistical approaches into account: noninferiority was no longer significant in the per-protocol analysis exceeding the predefined margin by 0.35%. This was attributable to the exclusion of primary end point events in 6 patients (0.003%) only: either no stent was implanted (n=2) or a history of transient ischemic attack was noted not recognized at enrollment (n=4), such that in fact 4/6 protocol violations were attributable to the antiplatelet regime of this trial and not the stents tested. Finally, the fact that all patients were treated with prasugrel-based dual antiplatelet therapy may question the generalizability regarding VLST and ischemic end points. To scrutinize the safety of this approach, especially regarding rates of major bleeding in stable coronary artery disease patients, a separate report has been submitted.

In conclusion, the apparent noninferiority of biodegradable-polymer Biolimus-eluting DES compared with durable-polymer everolimus-eluting DES in the intention-to-treat analysis described in the present study in patients with large vessel stenting confirms similar findings of early 1-year outcomes and extends them to a 2-year primary assessment. Present data do not offer any evidence, however, that VLST and related myocardial infarction or cardiac death may be reduced by the biodegradable-polymer Biolimus-eluting compared to the best-in-class durable-polymer everolimus-eluting stents. Accordingly, our findings challenge the concept that the polymer should be key in the perceived late deficiency of durable-polymer DES (ie, their propensity to VLST).

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Disclosures

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References


**CLINICAL PERSPECTIVE**

There is an ongoing controversy over the potential association of the durable polymer of durable-polymer drug-eluting stents (DP-DES) with very late stent thrombosis (VLST) and related myocardial infarction or death beyond 1 year after implantation. To overcome this perceived deficiency of durable polymers, DES with biodegradable polymers (BP-DES) were introduced. BP-DES have been shown to be noninferior compared with DP-DES during the initial year after implantation and superior to first-generation DP-DES thereafter, but no comparison of early efficacy and late safety of BP-DES to second-generation best-in-class everolimus-eluting DP-DES (Xience Prime) and to newest-generation thin-strut bare-metal stents (Prokinetik) within 1 trial have been performed. BAsel Stent Kosten-Effektivitäts Trial–PROspective Validation Examination II (BASKET-PROVE II) filled this gap, evaluating the biolimus-eluting BP-DES (Nobori) in 2291 patients with a follow-up of 2 years. The BP-DES proved to be as effective and noninferior by intention-to-treat to the DP-DES to prevent restenosis. In fact, both DES were superior to the bare-metal stents regarding this primary end point, particularly by reducing target-vessel revascularization. However, BP-DES did not further reduce the rate of VLST, myocardial infarction, or cardiac death beyond 1 year. Overall, stent thrombosis rates were very low in BASKET-PROVE II with all 3 stents, possibly because of the prasugrel-based dual antiplatelet therapy in this study. The lack of an improved late safety (ie, the lack of a reduction of VLST with BP-DES compared with best-in-class DP-DES observed here) seems to question the concept that durable polymers are key in late stent thrombosis formation; however, only a mega-trial may provide a definite proof for this.
Long-Term Efficacy and Safety of Biodegradable-Polymer Biolimus-Eluting Stents: Main Results of the Basel Stent Kosten-Effektivitäts Trial –PROspective Validation Examination II (BASKET-PROVE II), A Randomized, Controlled Noninferiority 2-Year Outcome Trial

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SUPPLEMENTAL MATERIAL

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**Table 1.** Clinical Outcomes after 0-12 and 13-24 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BP-DES (n=765)</th>
<th>DP-DES (n=765)</th>
<th>BMS (n=761)</th>
<th>BP-DES versus DP-DES OR (95% CI)</th>
<th>P-value</th>
<th>BP-DES versus BMS OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death – no. (%)</td>
<td>10 (1.3)</td>
<td>7 (0.9)</td>
<td>14 (1.8)</td>
<td>1.44 (0.54-3.79)</td>
<td>0.46</td>
<td>0.71 (0.31-1.62)</td>
<td>0.42</td>
</tr>
<tr>
<td>- months 0-12</td>
<td>7 (0.9)</td>
<td>5 (0.7)</td>
<td>8 (1.1)</td>
<td>1.41 (0.45-4.46)</td>
<td>0.56</td>
<td>0.88 (0.32-2.44)</td>
<td>0.80</td>
</tr>
<tr>
<td>- months 13-24</td>
<td>3 (0.4)</td>
<td>2 (0.3)</td>
<td>6 (0.8)</td>
<td>1.52 (0.25-9.12)</td>
<td>0.65</td>
<td>0.50 (0.12-2.00)</td>
<td>0.33</td>
</tr>
<tr>
<td>Non-fatal- MI – no. (%)</td>
<td>18 (2.4)</td>
<td>21 (2.7)</td>
<td>24 (3.2)</td>
<td>0.85 (0.45-1.61)</td>
<td>0.62</td>
<td>0.74 (0.40-1.38)</td>
<td>0.34</td>
</tr>
<tr>
<td>- months 0-12</td>
<td>8 (1.0)</td>
<td>12 (1.6)</td>
<td>18 (2.4)</td>
<td>0.66 (0.27-1.63)</td>
<td>0.37</td>
<td>0.44 (0.19-1.01)</td>
<td>0.053</td>
</tr>
<tr>
<td>- months 13-24</td>
<td>10 (1.4)</td>
<td>9 (1.2)</td>
<td>6 (0.8)</td>
<td>1.11 (0.45-2.75)</td>
<td>0.82</td>
<td>1.64 (0.59-4.53)</td>
<td>0.34</td>
</tr>
<tr>
<td>TVR – no. (%)</td>
<td>34 (4.4)</td>
<td>24 (3.1)</td>
<td>63 (8.3)</td>
<td>1.43 (0.84-2.45)</td>
<td>0.18</td>
<td>0.51 (0.33-0.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>- months 0-12</td>
<td>22 (2.9)</td>
<td>17 (2.2)</td>
<td>56 (7.4)</td>
<td>1.30 (0.68-2.47)</td>
<td>0.42</td>
<td>0.37 (0.22-0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- months 13-24</td>
<td>12 (1.7)</td>
<td>7 (1.0)</td>
<td>7 (1.0)</td>
<td>1.77 (0.69-4.54)</td>
<td>0.23</td>
<td>1.65 (0.64-4.22)</td>
<td>0.30</td>
</tr>
<tr>
<td>Event</td>
<td>No. (%)</td>
<td>Hazard Ratio (CI)</td>
<td>p-Value</td>
<td></td>
<td></td>
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<tr>
<td><strong>Cardiac death, MI or TVR – no. (%)</strong></td>
<td>58 (7.6)</td>
<td>1.12 (0.76-1.66)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- months 0-12</td>
<td>37 (4.8)</td>
<td>1.09 (0.68-1.76)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>- months 13-24</td>
<td>21 (2.9)</td>
<td>1.20 (0.63-2.27)</td>
<td>0.55</td>
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<tr>
<td><strong>Combined safety endpoint: Cardiac death, MI or definite/probable ST</strong></td>
<td>28 (3.7)</td>
<td>0.96 (0.57-1.64)</td>
<td>0.89</td>
<td></td>
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<tr>
<td>- months 0-12</td>
<td>15 (2.0)</td>
<td>0.83 (0.42-1.66)</td>
<td>0.60</td>
<td></td>
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<tr>
<td>- months 13-24</td>
<td>13 (1.8)</td>
<td>1.19 (0.53-2.67)</td>
<td>0.68</td>
<td></td>
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<tr>
<td><strong>Definite or probable stent thrombosis – no. (%)</strong></td>
<td>3 (0.4)</td>
<td>0.60 (0.14-2.53)</td>
<td>0.49</td>
<td></td>
<td></td>
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<tr>
<td>- months 0-12</td>
<td>2 (0.3)</td>
<td>0.50 (0.09-2.74)</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- months 13-24</td>
<td>1 (0.1)</td>
<td>0.98 (0.06-15.72)</td>
<td>0.99</td>
<td></td>
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</tbody>
</table>
The odds ratio of A versus B = (odds of A) : (odds of B). Patients may have had more than one event.

Abbreviations: BP-DES: biodegradable-polymer drug-eluting stent; DP-DES: durable-polymer drug-eluting stent; BMS: bare-metal stents; CI: confidence intervals; OR: odds ratio; MI: myocardial infarction; TVR: target-vessel revascularization.
SUPPLEMENT Figure 1

A) Cardiac death

B) non-fatal MI

C) non-MI-rel. TVR

0-24 months

0-12, 13-24 months
Kaplan-Meier estimates of the secondary endpoints cardiac death (panel A), non-fatal myocardial infarction (panel B), and non-myocardial infarction-related target vessel revascularization (panel C) overall (left) and separated for first and second year (right) for all the three stent groups.

SUPPLEMENT Figure 2

A) definite ST

Kaplan-Meier estimates of definite (panels A) and definite or probable (panels B) stent thrombosis overall (left) and separated for first and second year (right) for all the three sent groups.