TITLE: Bioabsorbable Stents for Adults with Coronary Artery Disease: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

DATE: 10 December 2013

CONTEXT AND POLICY ISSUES

Heart disease is the leading cause of death in the United States in 2011, and was the second leading cause of death in Canada in 2009. Coronary artery disease includes stable angina or unstable angina and myocardial infarction. The acute coronary syndromes (ACS) encompass a spectrum of unstable coronary artery disease from unstable angina to transmural myocardial infarction (MI). Their common etiology is the formation of thrombi on an inflamed and complicated atheromatous plaque. Acute myocardial infarction (AMI) reflects a state of acute myocardial necrosis. It was estimated that in 2004 there were 1,565,000 hospitalizations for primary or secondary diagnosis of ACS: 669,000 for unstable angina and 896,000 for MI in USA. Despite the reduction of coronary heart disease mortality over the past 40 years, hospital admissions for ACS continue to increase.

One of the most common medical interventions performed in the treatment of CAD today is the percutaneous coronary intervention (PCI), which opens clogged or damaged coronary arteries. Since its development in 1977, PCI has been a widely used alternative to coronary artery bypass grafting (CABG), and it relieves patients of coronary arterial blockage 90-95% of the time. PCI procedures include percutaneous transluminal coronary balloon angioplasty and coronary vascular stents (or scaffolds) such as bare metal stents (BMS), and drug eluting stents (DES). Coronary vascular stents are metallic 'scaffolds' that hold a blocked vessel open to restore coronary artery blood flow. The earliest type of stent developed was bare metal stent (BMS). Later, drug eluting stents (DES) were developed and widely used for PCI. A drug-eluting stent (DES) is comprised of three components: a bare metal backbone (platform), the durable polymer, and anti-proliferative agents such as everolimus, biolimus, or sirolimus. The first-generation of DES, containing sirolimus or paclitaxel, was shown to reduce in-stent neointimal hyperplasia, reduce rates of clinical restenosis, and curtail the need for repeated PCI compared with BMS. However, the greater risk of late stent thrombosis (LST) raised safety concerns. Hypersensitivity reactions to the durable polymer component of the first generation DES can produce chronic inflammation which is thought to delay endothelial healing and favour stent thrombosis (ST). ST was further stratified as early (≤30 days), late (31 days to 1 year), or very late (beyond 1 year). The second-generation DES were thus developed using a thinner

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stent struts, permanent but biocompatible polymers to minimize inflammation or hypersensitivity reactions, and novel anti-proliferative agents.\textsuperscript{11}

The most recent innovation (the third generation) in stent technology is the development of bioabsorbable stents (also known as bioresorbable or biodegradable stents). Broadly speaking, bioabsorbable stents may include two main types: bioabsorbable polymer stents or stents with a bioabsorbable metallic backbone.\textsuperscript{10,13} With bioabsorbable polymer stent, a bioabsorbable polymer impregnated with anti-proliferative drug is designed to elute the drug from the metallic stent with the polymers gradually degraded after implantation.\textsuperscript{8,11}

It was suggested that certain patients are currently deemed unsuitable for bioabsorbable stents in treating coronary artery disease. These include those with extensive calcified blockages and blockages at the side of branches that come off the main vessels.\textsuperscript{9}

In some Canadian jurisdictions, it has been found that the use of bioabsorbable polymer stents is increasing with a decline of using durable (permanent or biocompatible) polymer DES. Bioabsorbable stents are expensive in comparison to durable polymer DES. The aim of this review is to evaluate the comparative clinical effectiveness, cost effectiveness comparing bioabsorbable stents with durable DES as well as to review the guidelines for DES use in patients with coronary artery disease (CAD).

**RESEARCH QUESTIONS**

1. What is the clinical effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease?

2. What is the cost-effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease?

3. What are the evidence-based guidelines regarding the use of bioabsorbable stents for adults with coronary artery disease?

**KEY FINDINGS**

The comparative effectiveness of BP-DES with DP-DES in patients with coronary artery disease who have undergone PCI is inconsistent and inconclusive, depending on the types of stents and the eluting drugs. Better designed RCTs and cost-effectiveness analysis in Canadian settings are needed to determine whether BP-DES could replace DP-DES in the treatment of patients with CAD requiring PCI.

**METHODS**

**Literature Search Strategy**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also
limited to English language documents published between January 1, 2008 and November 12, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td><strong>Population</strong></td>
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<td>Adult patients with ACS or coronary artery disease requiring coronary intervention</td>
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<tr>
<td><strong>Intervention</strong></td>
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<td>Bioabsorbable stents (such as bioabsorbable polymer stents)</td>
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<td><strong>Comparator</strong></td>
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<td>Drug-eluting stents (such as durable polymer DES, polymer free DES)</td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td>Safety, risk, clinical effectiveness, cost-effectiveness, guidelines, appropriate patient population</td>
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<tr>
<td><strong>Study Designs</strong></td>
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<tr>
<td>Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic evaluations, guidelines</td>
</tr>
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</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria or were included in a selected meta-analysis.

Critical Appraisal of Individual Studies

Network meta-analyses (NMA) were assessed with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Checklist. The methodological quality of the included meta-analyses were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. RCTs were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 2 (SIGN 50 Checklist 2). Non-randomized studies were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist (SIGN 50 checklist 3 and check list 4). A numeric score was not calculated for each study. Instead, the strengths and weakness of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 415 citations. Upon screening titles and abstracts, 381 citations were excluded, and 34 potentially relevant articles were retrieved for full-text review. In addition, five articles were identified by reference check. Therefore, total 39 potential articles were retrieved for full-text review. Of the 39 potentially relevant reports, 22 did not meet the inclusion criteria. Seventeen reports are included in this review. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Appendix 1). Three studies were network meta-analyses, one was a meta-analysis, two were pooled analyses of individual patient data from three RCTs, nine
reports25-33 representing six unique RCTs and two non-randomized studies34,35 were included to assess the comparative clinical effectiveness of bioabsorbable polymer DES compared with durable polymer or polymer free DES in adult patients with CAD requiring PCI. No studies were identified evaluating the cost-effectiveness of bioabsorbable polymer DES compared with durable polymer or polymer free DES for adults CAD. No guidelines regarding the use of bioabsorbable stents for adults with CAD were found.

**Summary of Study Characteristics**

1. *What is the clinical effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease?*

A summary of the study characteristics can be found in Appendix 2.

The study characteristics of BP-DES compared with DP-DES in patients with coronary artery disease undergoing PCI is briefly summarized as follows:

Three network meta-analyses12,20,21 were performed in multiple European and Asian countries,12,20 and the USA21 All network meta-analyses were based a systematic review of RCTs. All outcomes were assessed after up to one year follow-up. One meta-analysis was performed in Italy and the Netherlands.22 Two pooled analyses of individual patient data from three RCTs36-38 were performed in Switzerland, Germany and the Netherlands.23,24 One23 reported the findings for all patients undergoing PCI. The other24 was for the subgroup of patients with diabetes who undergone PCI. The outcome of the pooled analysis was assessed for up to four-year’s follow-up.

Nine reports25-33 representing six unique RCTs were conducted in multiple European countries,25,27,28,30 the USA and Germany,26 multiple European countries, USA and New-Zealand29 and China.31-33 Sample size ranged from 16733 to 1707.25,31 Trial duration was from six months in one study29 to five years.30 Four reports25,27,28,30 were based on the same RCT (LEADERS trial) and reported the outcomes assessed at one, two, three and five years respectively.

The two non-randomized studies34,35 were observational studies. One35 was prospective study conducted in China35 and the other was a retrospective study conducted in Poland and the USA.34

The populations of above all included studies were adult patients with coronary artery disease who required PCI. Bioabsorbable stents included bioabsorbable polymer-based DES such as bioabsorbable polymer (BP)-based biolimus-eluting stents (BES, BP-BES),12,20,25,27,28,30 bioabsorbable polymer sirolimus-eluting stents (BP-SES),29,32,35 bioabsorbable polymer paclitaxel eluting stents (BP-PES),34 and bioabsorbable rapamycin-eluting stents (BP-RES).31,33 As the comparator, the durable (or permanent, or biostable) polymer stents (DP-DES) included durable polymer sirolimus eluting stents (DP-SES),20,21,23-25,27,28,30,32,33 durable polymer paclitaxel eluting stents (DP-PES),21,29,34 durable polymer cobalt chromium everolimus eluting stents (DP-CoCr-EES),21 durable polymer platinum chromium everolimus eluting stents (DP-PC-EES),21 durable polymer zotarolimus-eluting Endeavor (DP-ZES-E),21 and durable polymer zotarolimus-eluting Resolute (DP-ZES-R).21 Three studies31-33 compared bioabsorbable DES with polymer free DES (PF-DES). The reported outcomes were major adverse cardiac events (MACE), which
is a composite of adverse cardiac events including cardiac mortality, myocardial infarction (MI), and target lesion revascularization (TLR) and target vessel revascularization (TVR); all-cause-mortality; cardiac mortality; MI; stent thrombosis (ST); late stent thrombosis (LST); TLR; and TVR.

2. What is the cost-effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease?

No study was identified examining the cost-effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease.

3. What are the evidence-based guidelines regarding the use of bioabsorbable stents for adults with coronary artery disease?

No guidelines regarding the use of bioabsorbable stents for adults with CAD were identified.

Summary of Critical Appraisal

The strengths and limitations of all included studies in the report are summarized in Appendix 3.

The included NMA reports met most ISPOR criteria and were considered high quality. All were based on well conducted systematic review to identify all relevant studies (comprehensive database search, and a duplicate process of study selection and data extraction). Validity of all individual studies was assessed. The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian network meta-analysis (NMA) WinBUGS 1.4.3). Both direct and indirect estimates of effect were provided. Heterogeneity and inconsistency were assessed. The outcome measurements were appropriate. Limitations were: none of the NMAs reported the patient characteristics in the included studies. Three NMAs did not provide a list of excluded studies. Publication bias was not assessed in two NMAs. The two pooled analyses were not based on a systematic review to identify the studies and whether the quality of included studies was considered in the analysis and conclusions was not clearly indicated.

The methodological quality of six RCT reports was considered high because the randomization method, allocation concealment, baseline characteristics, and intention to treat (ITT) analysis were well described. Although ITT analysis were not performed in two RCTs, the dropout rates were low and comparable in both treatment arms. The methodological quality of the two RCTs by Zhang et al. was considered moderate because the true ITT analysis was not reported. The RCT reported by Chen et al. was considered poor because the randomization method, allocation concealment, and ITT analysis were not well addressed. One study was not powered for clinical outcomes (death, MI, TLR, ST). The non-randomized control trial by Liu et al. and the observational study by Buszman et al. were considered poor methodologically because the patient selection process was not clearly reported, the outcome assessment was not blinded, confounding factors were not controlled, and the external validity was limited and uncertain on whether study patients were representative of all eligible patients.
Summary of Findings

1. What is the clinical effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease?

The main findings of the included studies are summarized below and in Appendix 4.

Bioabsorbable polymer DES vs. durable polymer DES

Findings from network meta-analyses and meta-analyses

The NMA by Navarese et al.\(^{20}\) compared the bioabsorbable polymer biolimus eluting stents (BP-BES) with durable polymer eluting stents including sirolimus (DP-SES), paclitaxel (DP-PES), everolimus (DP-EES), and zotarolimus-E eluting stents (DP-ZES-E). No statistically significant difference was found in any clinical outcome such as cardiac mortality, myocardial infarction and target vessel revascularization, with the exception that BP-BES experienced less target lesion revascularization (TLR) compared with DP-PES \([\text{odds ratio (OR), 95\% confidence interval (CI): 0.52 (0.32 to 0.80)}]\) and DP-ZES-E: \([\text{OR (95\% CI): 0.40 (0.20 to 0.77)}]\).

The NMA by Palmerini et al.\(^{12}\) compared BP-BES with durable polymer eluting stents including DP-PES, DP-SES, DP-EES (DP-CoCr-EES, DP-PtCr-EES) and DP-ZES (DP-PC-ZES, DP-Re-ZES). The author reported that BP-BES achieved statistically significant lower cardiac death/MI: \([\text{OR (95\% CI): 0.78 (0.64 to 0.96)}]\), MI: 0.73 (0.59 to 0.99) and TVR: 0.74 (0.55 to 0.99) compared with DP-PES after one year follow-up. Compared with DP-PC-ZES, there was a statistically significant difference in favor of BP-BES in TVR \([\text{OR (95\%CI): 0.67 (0.47 to 0.95)}]\), but not in cardiac death/MI or MI. However, more stent thrombosis (ST) was observed in BP-BES than with durable polymer cobalt-chromium everolimus-eluting stents \([\text{OR (95\%CI): 1.92 (1.02 to 3.45)}]\) after more than one year following up. No statistically significant difference was found in other clinical outcomes such as cardiac mortality/MI, MI or target vessel revascularization when BP-BES was compared with DP-PC-ZES, DP-Re-ZES, DP-PtCr-EES or DP-ZES.

In the NMA reported by Bangalore et al.\(^{21}\) a statistically significant decrease in stent thrombosis (ST) events was reported in BP-BES compared with DP-SES \([\text{rate ratio (RR) (95\%CI): 0.29 (0.10 to 0.82)}]\). Statistically significant fewer MI, TVR and ST events were also reported in BP-BES compared with DP-PES. The reported RRs (95\%CI) were 0.82 (0.68 to 0.97), 0.66 (0.57 to 0.78) and 0.61 (0.37 to 0.89) for MI, TVR and ST respectively. It was also observed that BP-BES had statistically significant lower TVR compared with DP-ZES-E: 0.69 (0.56 to 0.84).

In their MA, Lupi et al.\(^{22}\) did not find any significant difference between bioabsorbable DES including BP-BES or BP-SES, and durable DES including DP-PES, DP-SES, DP-ZES in terms of overall mortality, MI, late ST, and TLR.

Findings from pooled analysis of three RCTs

Stefanini et al.\(^{23}\) reported a pooled analysis of three RCTs\(^{36-38}\) comparing BP-DES, including BP-BES and BP-SES, with DP-DES, including DP-SES and DP-EES. It was found that, compared with DP-DES, BP-DES was associated with a statistically significant lower rate of MI \([\text{Hazard ratio (HR) (95\%CI): 0.59 (0.37 to 0.95)}]\) and ST \([\text{HR (95\%CI): 0.22 (0.08 to 0.61)}]\). However, no difference between BP-DES and DP-DES was indicated in other clinical outcomes
such as all-cause mortality, cardiac mortality, cardiac mortality/ML and TLR up to 4 years follow-up. The analysis by de Waha et al.\textsuperscript{24} focused on a subgroup patients with diabetes from the same three RCTs\textsuperscript{36-38} and identified a statistically significant lower rate of ST in BP-DES compared with DP-DES, [HR (95\%CI): 0.45 (0.22 to 0.92)]. No difference was found in mortality, MI and TLR.

**Findings from RCTs**

Four articles\textsuperscript{25,27,28,30} reported the findings from one RCT (LEADERS). After 3 year follow-up, Wykrzykowska et al.\textsuperscript{25,27} and Klauss et al.\textsuperscript{28} did not find a statistically significant difference between BP-BES and DP-SES in overall major adverse cardiac events (MACE: a composite of cardiac death, MI, TVR), cardiac mortality, MI, TLR and TVR, and ST. However, with up to 5-year follow-up, Serruys et al.\textsuperscript{30} reported a statistically significant reduction in very late ST (> 1 year) with BP-BES [(risk ratio (RR) (95\%CI): 0.26 (0.10 to 0.69), P = 0.0034)]. The authors concluded that the safety benefit of the bioabsorbable polymer BES, compared with the durable polymer SES, was related to a significant reduction in very late ST (>1 year) and associated composite clinical outcomes.\textsuperscript{30}

In their RCT, Krucoff et al.\textsuperscript{26} reported that BP-PES (CoStar DES) is “not noninferior” to the DP-PES (Taxus DES) based on per-patient clinical and per-vessel angiographic analyses. The relative benefit of DP-PES was primarily attributable to reduction in TVR. After follow-up to 9 months there was no apparent difference in death, MI, or stent thrombosis rates.\textsuperscript{26}

The remaining two RCTs\textsuperscript{29,31} did not find a statistically significant difference in clinical outcomes when comparing BP-DES (including BP-RES and BP-SES) with DP-DES (including DP-RES and DP-PES).

**Findings from non-randomized studies**

The two-year prospective observational study\textsuperscript{35} demonstrated that both of the BP-sirolimus-eluting stent (BP-SES) and the DP-sirolimus-eluting stent (DP-SES) had similarly reduced incidence of MACE after PCI in daily practice at two years follow-up. The one-year retrospective observational study\textsuperscript{34} did not find a statistically significant difference between bioabsorbable polymer PES and durable polymer PES in clinical outcomes such as MACE, MI, TLR and TVR.

**Bioabsorbable polymer stents vs. polymer free DES:**

Of the three RCTs\textsuperscript{31-33} comparing BP-DES with PF-DES, two\textsuperscript{31,33} compared bioabsorbable polymer rapamycin-eluting stents (BP-RES)\textsuperscript{31,33} with polymer free paclitaxel-eluting stents (PF-PES). One\textsuperscript{32} compared BP-PES with the polymer free dual eluting drug stents (PF-sirolimus and probucol eluting stents). It was reported that BP-RES are non-inferior to polymer free PES in terms of MACE, cardiac death, all-cause death, MI, TLR, TVR, and hospitalization after following up for one year\textsuperscript{33} and two years.\textsuperscript{31} However, it was reported that the BP-RES was statistically superior to the polymer free dual DES (PF-sirolimus and probucol eluting stents) in terms of restenosis, late loss, and TVR for patients with long lesions.

2. **What is the cost-effectiveness of bioabsorbable polymer drug eluting stents compared with durable polymer or polymer free drug eluting stents for adults with coronary artery disease?**

No information on the cost-effectiveness of bioabsorbable stents for adults with CAD was identified.
3. What are the evidence-based guidelines regarding the use of bioabsorbable stents for adults with coronary artery disease?

No evidence-based guidelines regarding the use of bioabsorbable stents for adults with CAD were identified.

Limitations

The overall methodological risk of bias of the included NMAs and the majority of RCTs was low. The methodological risk of bias of the RCT by Chen et al.\textsuperscript{32} and the two non-randomized studies\textsuperscript{34,35} were considered moderate to severe because the randomization method, allocation concealment, ITT analysis were not well addressed in the RCT,\textsuperscript{32} and the patient selection process was not clearly reported and the outcome assessment was not blinded in the non-randomized studies.\textsuperscript{34,35} In one study, confounding factors were not controlled.\textsuperscript{34} While the overall methodological quality of the overall body of evidence was considered high, several major limitations (clinical and methodological heterogeneities) should be emphasized in interpreting the body evidence presented in this review. Firstly, the duplicate presentations of the some studies were seen in the selected NMAs. Secondly, the extensive heterogeneity (such as stable vs. unstable CAD) of populations existed in all NMAs and RCTs. Although, it reflected the overall daily clinical practice scenario, whether the findings could be applied to particular patients (such as ACS vs. chronic CAD, stable vs. unstable coronary heart disease, single vessel blockage vs. multiple vessel blockages, de novo CAD vs. recurrent CAD, single vessel intervention vs. multiple vessel intervention, etc.) is uncertain. Thirdly, in most of the trials, the eluting drugs used in bioabsorbable polymer DES and bio-durable polymer DES were different, therefore, it was not clear the difference between BP-DES and DP-DES was due to different drugs or the different polymer or polymer free technology. Advanced experimental trials are needed to address this question. Finally, there was no RCT conducted in Canada. Only two RCTs (2 of 6) were conducted with the participation of the USA; so findings in this review may not be transferable to the Canadian setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Although various BP-DES and various DP-DES appear collectively to show a similar clinical effectiveness in terms of a composite of major adverse cardiac events, cardiac mortality, MI, TVR, or ST in patients with coronary artery disease who required PCI, the comparative effectiveness of BP-DES with DP-DES is inconsistent and inconclusive depending on the types of stents and the used eluting drugs. Better designed RCTs and cost-effectiveness analyses in Canadian settings are needed to determine whether BP-DES could replace DP-DES in the treatment of patients with coronary artery disease requiring PCI.
REFERENCES


Appendix 1: Selection of Included Studies

415 citations identified from electronic literature search and screened

381 citations excluded

34 potentially relevant articles retrieved for scrutiny (full text, if available)

5 potentially relevant reports retrieved from other sources (grey literature, reference check)

39 potentially relevant reports

22 reports excluded:
- irrelevant intervention (2)
- irrelevant comparator (3)
- irrelevant outcomes (1)
- irrelevant study design (3)
- Study included in an included-meta-analysis (13)

17 reports included in review
### Appendix 2: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study Design, Length of Study</th>
<th>Patient Characteristics, Sample Size</th>
<th>Intervention</th>
<th>Comparators</th>
<th>Main Outcomes</th>
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<tbody>
<tr>
<td>Network met-analysis/Meta-analysis</td>
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<tr>
<td>Navarese EP, 2013, Multi-nations (European, USA and Asia)</td>
<td>Net-work Meta-analysis (NMA) of RCTs</td>
<td>Patients undergoing PCI</td>
<td>BP-BES</td>
<td>●DP-SES ●DP-PES ●DP-EES</td>
<td>(Assessed at ≥ 1 year) ●Death, MI, stent thrombosis (ST) ●Target lesion revascularization (TLR) and target vessel revascularization (TVR)</td>
</tr>
<tr>
<td>Palmerini T, 2013, Multi-nation (Canada, USA and European)</td>
<td>NMA) of RCTs</td>
<td>Patients undergoing PCI</td>
<td>BP-BES</td>
<td>●DP-DES ●BMS</td>
<td>(Assessed at 1 year) ●Cardiac death, MI, ST ●TLR, TVR</td>
</tr>
<tr>
<td>Bangalore S, 2013, USA</td>
<td>NMA) of RCTs</td>
<td>Patients undergoing PCI</td>
<td>BP-BES</td>
<td>●DP-SES ●DP-PES ●DP-CoCr-EES ●DP-PC-EES ●DP-ZES-E ●DP-ZES-R ●BMS</td>
<td>Assessed at ≥ 1 year) ●Cardiac death, MI, ST ●TLR, TVR</td>
</tr>
<tr>
<td>Lupi A, 2012, Italy and Netherlands</td>
<td>NMA) of RCTs</td>
<td>Patients undergoing PCI</td>
<td>●BP-BES ●BP-SES</td>
<td>●DP-PES ●DP-SES ●DP-ZES</td>
<td>Assessed at 1-4 year) ●Cardiac death, MI, ST ●TLR, TVR</td>
</tr>
<tr>
<td>de Waha, 2013, Germany, Switzerland and Netherlands</td>
<td>Pooled analysis (individual patients data from 3 RCTs)</td>
<td>Patients undergoing PCI (subgroup of diabetes)</td>
<td>BP-SES</td>
<td>DP-SES</td>
<td>(Assessed at 4 years) ●Cardiac death, MI, ST ●TLR</td>
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<tr>
<td>Stefanini GG, 2012, Switzerland, Germany and Netherlands</td>
<td>Pooled analysis (individual patients data from 3 RCTs)</td>
<td>Patients undergoing PCI</td>
<td>BP-SES</td>
<td>DP-SES</td>
<td>(Assessed at up to 4 years) ●Cardiac death, MI, ST ●TLR, TVR</td>
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<tr>
<td>Randomized controlled trials</td>
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<tr>
<td>Wykrzykowska JJ, 2009, Multi-countries (European)</td>
<td>RCT (LEADERS trial) Duration: 1 year</td>
<td>Patients undergoing PCI N=1707</td>
<td>BP-BES</td>
<td>DP-SES</td>
<td>(Assessed at 1 years) ●MACE (composite of cardiac death, MI) ●TLR, TVR</td>
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<tr>
<td>Klaus V, 2011, Multi-countries (European)</td>
<td>RCT (LEADERS trial) Duration: 2 years</td>
<td>Patients undergoing PCI N=1707</td>
<td>BP-BES</td>
<td>DP-SES</td>
<td>(Assessed at 2 years) ●MACE ●TLR, TVR</td>
</tr>
<tr>
<td>Wykrzykowska J, 2011, Multi-countries (European)</td>
<td>RCT (LEADERS trial) Duration: 3 years</td>
<td>Patients undergoing PCI N=1601</td>
<td>BP-BES</td>
<td>DP-SES</td>
<td>(Assessed at 3 years) ●MACE ●TLR, TVR</td>
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<tr>
<td>Serruys PW, 2013,</td>
<td>RCT (LEADERS trial)</td>
<td>Patients undergoing PCI</td>
<td>BP-BES</td>
<td>DP-SES</td>
<td>(Assessed at 5 years) ●MACE</td>
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<tr>
<td>First Author, Publication Year, Country</td>
<td>Study Design, Length of Study</td>
<td>Patient Characteristics, Sample Size</td>
<td>Intervention</td>
<td>Comparators</td>
<td>Main Outcomes</td>
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<tr>
<td>Multi-countries (European) trial)</td>
<td>Duration: 5 years</td>
<td>N=1601</td>
<td>BP-SES</td>
<td>DP-PES</td>
<td>● TLR, TVR</td>
</tr>
<tr>
<td>Ormiston JA, 2010, Multi-countries (USA, Europe, New-Zealand)</td>
<td>RCT (NEVO Res-Ellution I)</td>
<td>Duration: 6 months</td>
<td>Patients undergoing N=394</td>
<td>BP-SES</td>
<td>(Assessed at 6-month) ● MACE ● Death ● MI ● ST ● TLR</td>
</tr>
<tr>
<td>Krucoff MW, 2008, USA and Germany</td>
<td>RCT (COSTAR II trial)</td>
<td>Duration: 8 months</td>
<td>Patients undergoing PCI N= 1,675</td>
<td>BP-PES</td>
<td>(Assessed at 8-month) ● MACE ● TVR</td>
</tr>
<tr>
<td>Zhang Y, 2013, P.R.China</td>
<td>RCT Duration: 2 years</td>
<td>Patients undergoing PCI N=989</td>
<td>BP-RES</td>
<td>DP--RES Polymer free PES (PF-PES)</td>
<td>Assessed at 2 years ● MACE, cardiac death, MI, all cause death ● TVR ● ST</td>
</tr>
<tr>
<td>Zhang Y, 2013, P.R.China</td>
<td>RCT Duration: 1 year</td>
<td>Patients undergoing PCI N=167</td>
<td>BP-RES</td>
<td>PES (PF-PES)</td>
<td>Assessed at 1 year ● MACE, cardiac death, MI, all cause death ● TVR ● ST</td>
</tr>
<tr>
<td>Chen SL, 2013, P.R. China</td>
<td>RCT Duration: 1 year</td>
<td>Patients undergoing PCI N=346</td>
<td>BP-SES</td>
<td>PF-DES (PF-sirolimus and probucol stent)</td>
<td>Assessed at 1 year ● MACE, cardiac death, MI, all cause death ● TVR ● ST</td>
</tr>
<tr>
<td>Non-randomized /observational studies</td>
<td>Observation al study (Multicenter retrospective Registry) Follow-up: 1 years</td>
<td>Patients undergoing PCI N=392</td>
<td>BP-PES</td>
<td>DP-PES</td>
<td>(Assessed at 1 years) ● MACCE (composite of cardiac death, MI, stroke) ● TLR, TVR, ST</td>
</tr>
<tr>
<td>Buszmann PP, 2013, Poland and USA</td>
<td>Non-randomized study (a large single-center database) Follow-up: 2 years</td>
<td>Patients undergoing PCI N=1114</td>
<td>BP-SES</td>
<td>DP-SES</td>
<td>(Assessed at 2 years) ● MACE, death, MI ● TLR, TVR</td>
</tr>
</tbody>
</table>

ACS=acute coronary syndrome; AE=adverse events; AMI=acute myocardial infarction; BES=bioeluting stents; BMS =bare metal stent; BP=bioabsorbable (or bioreabsorbable or biodegradable) polymer; BP-BES= bioabsorbable polymer bioeluting stents; BP-DES= Biodegradable polymer drug eluting stents; BP-PES= Biodegradable polymer PES; BP-RES= biodegradable polymer-based rapamycin-eluting stents; CAD=coronary artery disease; CoCr-EES= cobalt-chromium everolimus-eluting stents; COSTAR = Cobalt Chromium Stent With Antiproliferative for Restenosis, the costar stents was discontinued in the market; DP=durable polymer; DP-BES= durable polymer bioeluting stents; DP-DES = durable polymer DES; DP-EES = durable everolimus-eluting stents ; DP-PES= durable polymer PES; DP-ZES-E= durable polymer zotarolimus eluting-Endeavor; DP-ZES-R = durable polymer zotarolimus eluting-Resolute; LST=late stent thrombosis; MA=meta-analysis; MACCE= major adverse coronary and cerebral events (composite of cardiac death, MI, stroke); MACE=major adverse cardiac events; NMA=Network meta-analysis; non-RCTs=non-randomized controlled trials including observational studies; PCI=percutaneous coronary intervention; PF=polymer free; RCT= randomized controlled trials; ST=stent thrombosis; TLR= target lesion revascularization; TVR=target vessel revascularization;
APPENDIX 3: Summary of Study Strengths and Limitations

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Navarese EP, 2013, Multi-nations (European, USA and Asia) | • The rational and the objectives for the study were clearly described  
• The NMA was based on a systematic review to identify all relevant studies.  
• Validity of all individual studies was assessed using Cochrane Collaboration guidelines.  
• List of included studies was provided  
• ITT analysis  
• The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian network meta-analysis (NMA) WinBUGS 1.4.3).  
• Both indirect and indirect estimates of effect were provided (NWM analysis and pairwise comparison)  
• Heterogeneity and inconsistency were assessed,  
• The outcome measures assessed in the NMA were appropriate. | • Patient characteristics in the individual studies were not reported  
• List of excluded studies not provided  
• Potentially heterogeneous definitions of MI used across the trials  
• Publication bias was not assessed |
| Palmerini T, 2013, Multi-nation (Canada, USA and European) | • The rational and the objectives for the study were clearly described  
• The NMA was based on a systematic review to identify all relevant studies.  
• Validity of all individual studies was assessed  
• List of included studies was provided  
• Publication bias was assessed  
• The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian network meta-analysis (NMA) WinBUGS 1.4.3).  
• Both indirect and indirect estimates of effect were provided (NWM analysis and pairwise comparison)  
• Heterogeneity and inconsistency were assessed,  
• The outcome measures assessed in the NMA were appropriate. | • Patient characteristics in the individual studies were not reported  
• List of excluded studies not provided  
• Only FDA approved stents were included |
| Bangalore S, 2013, USA | • The rational and the objectives for the study were clearly described  
• The NMA was based on a systematic review to identify all relevant studies.  
• Validity of all individual studies was assessed  
• List of included studies was provided  
• The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian network meta-analysis (NMA) WinBUGS 1.4.3).  
• Both indirect and indirect estimates of effect were provided (NWM analysis and pairwise comparison) | • Patient characteristics in the individual studies were not reported  
• List of excluded studies not provided  
• Publication bias was not assessed |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Lupi A, 2012, Italy and Netherlands | • Heterogeneity and inconsistency were assessed,  
• The outcome measures assessed in the NMA were appropriate. | • Patient characteristics in the individual studies were not reported,  
• Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated |
| de Waha, 2013, Germany, Switzerland and Netherlands | • Research questions and selection criteria were defined and presented  
• Comprehensive literature search based on pre-defined criteria  
• 2 independent investigators performed study data extraction  
• Lists of included and excluded studies provided  
• Quality assessment of the included studies was described  
• Methods used to combine the findings was clearly reported  
• Publication bias was assessed  
• Conflict of interests declared | • No comprehensive literature search,  
• Data was pooled only from three trials  
• Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated  
• Publication bias was not assessed |
| Stefanini GG, 2012, Switzerland, Germany and Netherlands | • Research questions presented  
• Patients level pooled analysis  
• List of included studies provided  
• Quality assessment of the included studies was described  
• Methods used to combine the findings was clearly reported  
• Conflict of interests declared | • No comprehensive literature search.  
• Data was pooled only from three trials  
• Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated  
• Publication bias was not assessed |
| Wykrzykowska JJ, 2009, Multi-countries (European) | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• ITT analysis performed  
• Non-inferior margin was described  
• Drop-out rate were low and comparable in both arms (2% vs. 2%)  
• Drop-out (Quality assessment this report was based on companion publications 26-27,29,30,32) | • Blinding process was not clearly described  
• Eluting drugs were not the same in the intervention and comparator arms  
• Whether the results across all centers were comparable were not addressed |
| Klauss V, 2011, | • Research question was clearly defined  
• Randomization method was clearly described | • Blinding process was not clearly described  
• Eluting drugs were not the same in the |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Multi-countries (European)     | • Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• Non-inferior margin was described  
• ITT analysis performed  
• Drop-out rate were low and comparable in both arms (3% vs. 3%)  
• No drop-out  
(Quality assessment this report was based on companion publications 25,27,28,30,37) | intervention and comparator arms  
• Whether the results across all centers were comparable were not addressed |
| Wykrzykowska J, 27  
2011, Multi-countries (European) | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• Non-inferior margin was described  
• ITT analysis performed  
• Drop-out rate were low and comparable in both arms (5% vs. 5%)  
(Quality assessment this report was based on companion publications 25,27,28,30,37) | Blinding process was not clearly described  
• Eluting drugs were not the same in the intervention and comparator arms  
• Whether the results across all centers were comparable were not addressed |
| Serruys PW, 30  
2013, Multi-countries (European) | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• Non-inferior margin was described  
• ITT analysis performed  
• Drop-out rate were low and comparable in both arms (5% vs. 5%)  
(Quality assessment this report was based on companion publications 25,27,28,30,37) | Blinding process was not clearly described  
• Eluting drugs were not the same in the intervention and comparator arms  
• Whether the results across all centers were comparable were not addressed |
| Ormiston JA, 29  
2010, Multi-countries (USA, Europe, New-Zealand) | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Non-inferior margin was described  
• Drop-out rate were low (total 3%)  
• Single blinding process  
• Not powered for clinical outcomes (death, MI, TLR, ST)  
• Eluting drugs were different in the treatment and control groups  
• ITT analysis not performed  
• Whether the results across all centers were comparable were not addressed | |
| Krucoff MW, 26  
2008, USA and Germany | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Only difference between groups is treatment | Single blinding process  
• ITT analysis not performed  
• Whether the results across all centers were comparable were not addressed |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Zhang Y, 2013, P.R.China      | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline were comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• Non-inferior margin was described  
• ITT analysis performed  
• Drop-out rates were low and comparable in both arms (5% vs. 6%) | • Key patient characteristics at baseline were not comparable in the treatment and control groups  
• Blinding process was not clearly described  
• Eluting drugs were different in the treatment and control groups.  
• Whether the results across all centers were comparable were not addressed |
| Zhang Y, 2013, P.R.China      | • Research question was clearly defined  
• Randomization method was clearly described  
• Allocation concealment was reported.  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• Non-inferior margin was described  
• ITT analysis performed for clinical outcomes  
• Drop-out rates were low and comparable in both arms (8% vs. 6%) | • Blinding process was not clearly described  
• Eluting drugs were different in the treatment and control groups.  
• ITT analysis not performed  
• Single center trial |
| Chen SL, 2013, P.R. China     | • Research question was clearly defined  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Outcome was standard, valid and reliable  
• ITT analysis performed  
• Drop-out rates were low and comparable in both arms. (6% vs. 5%) | • Randomization method was not clearly described  
• Allocation concealment was not reported.  
• Eluting drugs were different in the treatment and control groups.  
• Blinding process was not clearly described  
• Whether the results across all centers were comparable were not addressed |
| Non randomized study/observational study assessed with SIGN 50 Check list 3 and 4 | • Research question (objective) was clearly stated  
• Demographics of each group well reported  
• Patient selection process was clearly reported  
• Reporting (intervention, control, outcomes and main findings) was clearly stated  
• Outcome measurement was valid and reliable  
• Confidence interval was reported  
• No drop-out  
• Long-term follow-up (> 1 year)  
• Statistical analyses were performed  
• Conflict of interest reported | • Based on retrospective registry database  
• Patient with ST segment elevation myocardial infarction (STEMI) excluded  
• Blind outcome assessment was not addressed  
• Confounding factors were not controlled  
• External validity limited; uncertain as whether study patients were representative of all eligible patients |
| Liu HB, 2009, P.R.China       | • Research question (objective) was clearly stated  
• Demographics of each group well reported. | • Patient selection process was not clearly reported  
• Outcome assessment was not blinded |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Source population baseline characteristics was compared between treatment and control group</td>
</tr>
<tr>
<td></td>
<td>- Reporting (intervention, control, outcomes and main findings) was clearly stated</td>
</tr>
<tr>
<td></td>
<td>- Outcome measurement was valid and reliable</td>
</tr>
<tr>
<td></td>
<td>- Confidence interval was reported</td>
</tr>
<tr>
<td></td>
<td>- Follow-up period: 2 years</td>
</tr>
<tr>
<td></td>
<td>- Statistical analyses were performed</td>
</tr>
<tr>
<td></td>
<td>- Conflict of interest reported</td>
</tr>
<tr>
<td></td>
<td><strong>Limitations</strong></td>
</tr>
<tr>
<td></td>
<td>- Confounding factors were not controlled</td>
</tr>
<tr>
<td></td>
<td>- Lost of follow-up at two years (BP-SES vs. DP-SES: 16% vs. 38%)</td>
</tr>
<tr>
<td></td>
<td>- External validity limited; uncertain as whether study patients were representative of all eligible patients</td>
</tr>
</tbody>
</table>

MA=meta-analysis MTA=mixed treatment analysis; NWM=net-work meta-analysis; RCT=randomized controlled trial; AMSTAR=A Measurement Tool to Assess the Methodological Quality of Systematic Reviews; ITT=intention to treat.
### Appendix 4: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Network meta-analysis/ meta-analysis</strong></td>
<td></td>
<td>On page 1: &quot;The newer durable polymer everolimus-ES and Resolute zotarolimus-ES and the biodegradable polymer biolimus-ES maintain the efficacy of sirolimus-ES; however, for safety endpoints, differences become apparent, with everolimus-ES and Resolute zotarolimus-ES emerging as the safest stents to date.”</td>
</tr>
</tbody>
</table>
| **Navarese EP,** 2013, Multi-nations (European, USA and Asia) | Cardiac Mortality - Odds Ratio (95%CI)  
BP-BES vs. DP-SES: 1.00 (0.73, 1.38)  
BP-BES vs. DP-PES: 0.91 (0.62, 1.32)  
BP-BES vs. DP-EES: 1.09 (0.79, 1.51)  
BP-BES vs. DP-ZES-E: 0.80 (0.50, 1.30)  
DP-ZES-R vs. BP-BES: 0.73 (0.44, 1.19)  
MI - Odds Ratio (95%CI)  
BP-BES vs. DP-SES: 0.98 (0.42, 2.02)  
BP-BES vs. DP-PES: 0.54 (0.23, 1.30)  
BP-BES vs. DP-EES: 1.55 (0.69, 3.53)  
BP-BES vs. DP-ZES-E: 0.50 (0.15, 1.57)  
DP-ZES-R vs. BP-BES: 0.80 (0.22, 2.53)  
TLR - Odds Ratio (95%CI)  
BP-BES vs. DP-SES: 0.92 (0.62, 1.47)  
BP-BES vs. DP-PES: 0.52 (0.32, 0.80)  
BP-BES vs. DP-EES: 1.05 (0.66, 1.60)  
BP-BES vs. DP-ZES-E: 0.40 (0.20, 0.77)  
DP-ZES-R vs. BP-BES: 1.02 (0.54, 1.94)  
TVR - Odds Ratio (95%CI)  
BP-BES vs. DP-SES: 1.00 (0.68, 1.48)  
BP-BES vs. DP-PES: 0.68 (0.44, 1.05)  
BP-BES vs. DP-EES: 1.15 (0.77, 1.71)  
BP-BES vs. DP-ZES-E: 0.60 (0.34, 1.06)  
DP-ZES-R vs. BP-BES: 0.93 (0.47, 1.85) | |
| **Palmerini T,** 2013, Multi-nation (Canada, USA and European) | OR (95%CI)  
**BP-BES VS DP-PES:**  
1 year:  
Cardiac death/MI: 0.70 (0.50 - 1.01)  
MI: 0.81 (0.63, 1.05)  
TVR: 0.70 (0.50, 1.01)  
ST: 0.78 (0.41, 1.50)  
Long term (>1 year):  
Cardiac death/MI: 0.78 (0.64, 0.96)  
MI: 0.73 (0.59, 0.99)  
TVR: 0.74 (0.55, 0.99)  
ST: 0.60 (0.32, 1.05)  
**BP-BES VS DP-SES:**  
1 year:  
Cardiac death/MI: 0.99 (0.79, 1.25)  
MI: 1.0 (0.8, 1.28)  
TVR: 1.05 (0.76, 1.47)  
ST: 1.03 (0.59, 1.87)  
Long term (>1 year):  
Cardiac death/MI: 0.90 (0.75, 1.09)  
MI: 0.91 (0.75, 1.15)  
TVR: 1.00 (0.76, 1.32)  
ST: 0.74 (0.43, 1.27)  
**BP-BES VS DP-PC-ZES:**  
1 year:  
Cardiac death/MI: 0.89 (0.63 - 1.26)  
MI: 1.04 (0.72, 1.40)  
TVR: 0.57 (0.37, 0.88)  
ST: 0.60 (0.27, 1.25) | On page 2: "In this large-scale network meta-analysis, BP-BES were associated with superior clinical outcomes compared to BMS and first generation DES, similar rates of cardiac death/MI, MI, and TVR compared to second generation DP-DES, but higher rates of definite ST than CoCr-EES.” |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>BP-BES VS DP-ZES-R:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 year:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac death/MI: 1.17 (0.80 -1.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI: 1.20 (0.80, 1.79)</td>
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<tr>
<td></td>
<td>TVR: 0.97 (0.53, 1.76)</td>
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<tr>
<td></td>
<td>ST: 0.54 (0.14, 1.82)</td>
<td></td>
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<tr>
<td></td>
<td>Long term (&gt;1 year):</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac death/MI: 1.03 (0.74, 1.42)</td>
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<tr>
<td></td>
<td>MI: 1.07 (0.75, 1.57)</td>
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<tr>
<td></td>
<td>TVR: 0.99 (0.60, 1.63)</td>
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</tr>
<tr>
<td></td>
<td>ST: 0.61 (0.19, 1.92)</td>
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<tr>
<td></td>
<td><strong>BP-BES VS DP-CoCr-EES:</strong></td>
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<tr>
<td></td>
<td>1 year:</td>
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<tr>
<td></td>
<td>Cardiac death/MI: 1.12 (0.88 -1.43)</td>
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<tr>
<td></td>
<td>MI: 1.19 (0.95, 1.49)</td>
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<tr>
<td></td>
<td>TVR: 1.05 (0.75, 1.49)</td>
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</tr>
<tr>
<td></td>
<td>ST: 2.44 (1.30, 4.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long term (&gt;1 year):</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac death/MI: 1.03 (0.81, 1.27)</td>
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<tr>
<td></td>
<td>MI: 1.10 (0.89, 1.43)</td>
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<tr>
<td></td>
<td>TVR: 1.06 (0.80, 1.43)</td>
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<tr>
<td></td>
<td>ST: 1.92 (1.02, 3.45)</td>
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<tr>
<td></td>
<td><strong>BP-BES VS PtCr-EES:</strong></td>
<td></td>
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<tr>
<td></td>
<td>1 year:</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac death/MI: 1.32 (0.79 -2.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI: 1.59 (0.89, 3.03)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TVR: 1.08 (0.52, 2.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ST: 1.13 (0.24, 5.00)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long term (&gt;1 year):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac death/MI: 1.18 (0.77, 2.04)</td>
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<tr>
<td></td>
<td>MI: 1.30 (0.69, 2.27)</td>
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<tr>
<td></td>
<td>TVR: 1.21 (0.67, 2.22)</td>
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</tr>
<tr>
<td></td>
<td>ST: 1.15 (0.29, 4.55)</td>
<td></td>
</tr>
<tr>
<td>Bangalore S, 21, 2013, USA</td>
<td><strong>Rate Ratio (95%Crl)</strong></td>
<td><strong>On page 1:</strong> “Biodegradable polymer drug eluting stents are superior to first generation durable polymer drug eluting stents but not to newer generation durable polymer stents in reducing target vessel revascularization. Newer generation durable polymer stents, and especially cobalt chromium everolimus eluting stents, have the best combination of efficacy and safety. The utility of biodegradable polymer stents in the context of excellent clinical outcomes with newer generation durable polymer stents needs to be proven.”</td>
</tr>
<tr>
<td></td>
<td><strong>BP-BES VS DP-SES:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤ 1 year:</td>
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</tr>
<tr>
<td></td>
<td>Death: 0.93 (0.74, 1.19)</td>
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</tr>
<tr>
<td></td>
<td>MI: 0.97 (0.79, 1.13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TVR: 0.92 (0.79, 1.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ST: 0.71 (0.49, 1.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At &gt;1 year:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death: 0.89 (0.69, 1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI: 0.69 (0.49, 1.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TVR: 0.79 (0.54, 1.08)</td>
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<td>ST: 0.29 (0.10, 0.82)</td>
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<td><strong>BP-BES VS DP-PES:</strong></td>
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<td>1 year:</td>
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<td>Death: 0.91 (0.71 -1.19)</td>
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<td>MI: 0.82 (0.68, 0.97)</td>
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*Bioabsorbable Stents for Adults with CAD*
<table>
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<th>First Author, Publication Year</th>
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<th>Author’s Conclusions</th>
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| Lupi A., 2012, Italy | TVR: 0.66 (0.57, 0.78)  
ST: 0.61 (0.37, 0.89)  
Long term (>1 year):  
Death: 0.99 (0.68, 1.36)  
MI: 0.63 (0.39, 1.13)  
TVR: 0.79 (0.53, 1.13)  
ST: 0.51 (0.16, 1.69)  
**BP-BES VS DP-CoCr-EES:**  
1 year:  
Death: 1.12 (0.87 -1.45)  
MI: 1.22 (1.06, 1.49)  
TVR: 1.03 (0.89, 1.21)  
ST: 2.04 (1.27, 3.35)  
Long term (>1 year):  
Death: 1.52 (1.02, 2.22)  
MI: 1.03 (0.67, 1.95)  
TVR: 1.15 (0.74, 1.72)  
ST: 1.81 (0.44, 7.09)  
**BP-BES VS DP-PtCr-EES:**  
1 year:  
Death: 1.13 (0.73 -1.75)  
MI: 1.31 (0.87, 1.82)  
TVR: 1.11 (0.79, 1.63)  
ST: 1.42 (0.58, 3.52)  
Long term (>1 year):  
Death: 2.03 (0.95, 4.08)  
MI: 0.74 (0.20, 2.51)  
TVR: 1.50 (0.62, 3.54)  
ST: 1.11 (0.12, 7.79)  
**BP-BES VS DP-ZES-E:**  
1 year:  
Death: 0.92 (0.68 -1.29)  
MI: 1.01 (0.78, 1.21)  
TVR: 0.69 (0.56, 0.84)  
ST: 0.91 (0.50, 1.47)  
Long term (>1 year):  
Death: 1.02 (0.73, 1.46)  
MI: 0.87 (0.50, 1.49)  
TVR: 0.97 (0.60, 1.46)  
ST: 1.39 (0.44, 5.62)  
**BP-BES VS DP-ZES-R:**  
1 year:  
Death: 1.16 (0.794-1.78)  
MI: 1.13 (0.84, 1.49)  
TVR: 1.07 (0.83, 1.44)  
ST: 0.80 (0.39, 1.96)  
Long term (>1 year):  
Death: 1.28 (0.71, 2.48)  
MI: 0.92 (0.42, 3.08)  
TVR: 1.02 (0.53, 2.04)  
ST: 1.68 (0.20, 15.70)  | On page 1 “Our present meta-analysis showed that BP-DES when compared with DP-DES significantly reduced LLL and TVR but without clear benefits on mortality, MI. **BP-BES VS DP-DES:** (BP BES including BES and SES vs. DR-DES) OR (95%CI) (up to 4 years) |
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| Netherlands                   | Overall mortality: 0.97 (0.73 - 1.29)  
MI: 1.13 (0.87, 1.46)  
Late ST: 0.64 (0.36, 1.16)  
TLR: 0.67 (0.47, 0.98) | and LST rates. |
| Stefanini GG, 2012, Switzerland, Germany and Netherlands | HR (95% CI) (up to 4 years)  
BP-DES VS DP-DES: (BP-DES including BP-BES and BP-SES VS. DP-DES including DP SES, DP-EES)  
Overall mortality: 0.85 (0.65 - 1.12)  
Cardiac mortality: 0.95 (0.64, 1.40)  
Cardiac mortality/Mi: 0.73 (0.53, 1.00)  
Mi: 59 (0.37, 0.95)  
ST: 0.22 (0.08, 0.61)  
TLR: 0.81 (0.60, 1.09) | On page 1214: “Biodegradable polymer DES improves safety and efficacy compared with durable polymer SES during long-term follow-up to 4 years.” |
| de Waha, 2013, Germany, Switzerland and Netherlands | HR (95% CI) at 4 years  
MACE (Cardiac death, Mi or TLR): 0.95 (0.74, 1.21) \( P=0.67 \)  
ST: 0.45 (0.22, 0.92), \( P=0.02 \)  
All-cause mortality: 0.84 (0.62, 1.15) \( P=0.28 \)  
Cardiac mortality: 0.92 (0.60, 1.41), \( P=0.71 \)  
Mi: 0.90 (0.58, 1.38), \( P=0.62 \)  
TLR: 0.89 (0.65, 1.22), \( P=0.47 \) | On page 5162: “In patients with diabetes, biodegradable polymer DES, compared to durable polymer SES, were associated with comparable overall clinical outcomes during follow-up to 4 years. Rates of stent thrombosis were significantly lower with BP-DES.” |

**Randomized controlled trials**

| Wykrzykowska JJ, 2009, Multi-countries (European) | LEADERS assessed at 1 year  
BP-BES VS DP-SES:  
MACE: 17% vs. 14.6%  \( P=0.62 \)  
TLR: 12.4% vs. 6.0%  \( P=0.07 \)  
ST: 10.5% vs. 5.3%  \( HR=1.94, P=0.13 \) | On page 2: “BES and SES appear similar with respect to MACE in long lesions in this "all-comer" patient population. However, long lesions tended to have a higher rate of binary in-segment restenosis and TLR following BES than SES treatment.” |
| Klaus V, 2011, Multi-countries (European) | LEADERS assessed at 2 year  
BP-BES VS DP-SES:  
MACE (Composite of cardiac death, Mi, TVR) 12.8% vs. 15.2%;  \( HR=0.84 (0.65, 1.08) \)  
Cardiac death: 3.2% Vs. 3.9%;  \( HR=0.81 (0.49, 1.53); p=0.42 \)  
Mi: 6.3% Vs. 5.6%;  \( HR=0.91 (0.51, 1.63); p=0.56 \)  
TVR: 7.5% vs. 8.6%;  \( HR=0.86 (0.62, 1.20); P=0.38 \)  
ST: 2.2% vs. 2.5%;  \( P=0.73 \) | On page 887: “At 2 years of follow-up, the unrestricted use of BES with a biodegradable polymer maintained a similar safety and efficacy profile as SES with a durable polymer. (Limus Eluted From a Durable Versus Erodable Stent Coating.” |
| Wykrzykowska JJ, 2011, Multi-countries (European) | LEADERS assessed at 3 year  
DP-BES VS DP-SES:  
MACE (Composite of cardiac death, Mi, TVR) 15.7% vs. 19%;  \( HR=0.82 (0.65, 1.03) \)  
Cardiac death: 4.2% Vs. 5.2%;  \( HR=0.81 (0.52, 1.26); p=0.34 \)  
Mi: 7.2% Vs. 7.1%;  \( HR=0.73 (1.01, 1.44); p=0.97 \)  
TVR: 9.4% vs. 11.1%;  \( HR=0.84 (0.62, 1.12) \) | On page 2: “The findings of the three year follow-up support the claim that the biodegradable polymer biolimus-eluting stent has equivalent safety and efficacy to permanent polymer sirolimus-eluting stent in an all-comers patient population. Its performance is superior in some subpopulations such as in ST-elevation MI patients and event rates for BES are overall lower than for SES with a trend toward increasing divergence of outcomes over three years.” |
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<td><strong>Serruys PW, 2013, Multi-countries (European)</strong></td>
<td>LEADERS assessed at 5 year BP-BES VS DP-SES: MACE (Composite of cardiac death, MI, TVR) 22.3% vs. 26.1% ; RR (95%CI): 0.83 (0.68, 1.02) Cardiac death: overall mortality rate not reported MI: overall MI rate not reported Overall ST: 2.6% vs. 4.2%; RR(95%CI): 0.60 (0.35, 1.02) P=0.057 Very late ST(&gt;1 year): RR: 0.26 (0.10, 0.69), P=0.0034</td>
<td>On page 2: &quot;The safety benefit of the biodegradable polymer BES, compared with the durable polymer SES, was related to a significant reduction in very late ST (&gt;1 year) and associated composite clinical outcomes.&quot;</td>
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<td><strong>Ormiston JA, 2010, Multi-countries (USA, Europe, New-Zealand)</strong></td>
<td>(NEVO RES-I) Trial (at 6 months) BP-SES vs. DP-PES MACE (composite of cardiac death, MI, TVR) 4.0% vs. 7.4% ; P=0.19 Death: 0.5% vs. 1.6%; p=0.36 MI: 2.0% Vs. 2.6%; p=0.75 TLR: 3.5 % vs. 5.3%; P=0.46 TVR: 5.6 % vs. 7.4%, P=0.54 ST: 0% vs. 1.1%; P=0.24</td>
<td>On page 556: “This trial proved the superiority of NEVO SES over TAXUS Liberte PES for the primary angiographic end point of in-stent late loss. No stent thrombosis occurred in the NEVO SES group.”</td>
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<td><strong>Krucoff MW, 2008, USA and Germany</strong></td>
<td>COSTAR II Study: (at 8 months) Bioabsorbable polymer stents vs. biostable polymer stents (COSTAR vs. Taxus)* MACE (Composite of cardiac death, MI, TVR) 11.0 % vs. 6.9% p=0.005 Single vessel MACE: 9.9% vs. 6.1% P=0.015 Multi-vessel MACE: 15.4% vs. 9.7% P=0.0125) Death: 0.5% vs. 0.7%; P=0.541 MI: 3.4% Vs. 2.4% p=0.242 TVR: 8.1 % vs. 4.3%; P=0.02</td>
<td>On page 2: &quot;The CoStar DES is not noninferior to the Taxus DES based on per-patient clinical and per-vessel angiographic analyses. The relative benefit of Taxus is primarily attributable to reduction in TVR. Follow-up to 9 months showed no apparent difference in death, MI, or stent thrombosis rates.”</td>
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<td><strong>Zhang Y, 2013, P.R.China</strong></td>
<td>BP-RES vs. DP-RES vs. PF-PES) at 2 years MACE (Composite of cardiac death, MI, TLR) 6.58% vs. 7.24% vs. 6.17%; p=0.28 Cardiac death: 2.82% vs. 2.63% vs. 2.27%; p value: NR All cause death: 3.45% vs.3.29% vs. 2.92; p=0.93 MI: NR TVR: 3.45% vs.2.63% vs. 2.67; p value: NR ST: 2.19% vs.1.97% vs. 1.62%; p=0.87 Re-hospitalization: 12.85% vs.11.51% vs. 14.29%, p=0.59</td>
<td>On page 2646: &quot;In this multicentre, randomised, controlled clinical trial, PF paclitaxel-eluting stents and BD rapamycin-eluting stents were shown to be noninferior to PP rapamycin-eluting stents in two-year clinical outcomes for the treatment for CHD.”</td>
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<td><strong>Zhang Y, 2013, P.R.China</strong></td>
<td>BP-RES VS PF-PES at 1 year MACE (Composite of cardiac death, MI, TVR) 5.88% vs. 6.1% ; p=0.02 Cardiac death: 2.35% vs.2.44%; p value: NR All cause death: 3.53% vs.2.44%; p=0.67 MI: 2.35% vs. 2.44 %; p value: NR TVR: 3.53%vs.2.44%; p value: NR ST: 3.53%vs.1.22%; p=0.32</td>
<td>On page 2646: &quot;In this small randomized trial, polymer-free paclitaxel-eluting stents appear to be noninferior or equivalent to biodegradable polymer-based rapamycin-eluting stents.”</td>
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| Chen SL, 2013, P.R. China      | BP-SES vs. PF-sirolimus/probucol stent at 1 year  
MACE (Composite of cardiac death, MI, TLR) 6.9% vs. 14.5%; p=0.036  
Cardiac death: 0.6% vs. 0%, p=0.499  
All cause death: 0% vs. 0%, NS  
MI: 3.5% vs. 1.2%, p=0.283  
TLR: 1.7% vs. 9.2%; p=0.003  
TVR: 3.5% vs. 13.9%, p=0.001  
ST: 1.2% vs. 0%, p=0.499 | On page 193: “The Excel stent was statistically superior to the Dual DES in terms of restenosis, late loss, and TVR for long lesions.” |
| Buszman PP, 2013, Poland and USA | Bioabsorbable polymer PE stents vs. durable polymer PE stents (BP-PES vs. DP-PES)  
At 1 year:  
MACE: 17.6% vs. 14.4%; P=0.49  
TLR: 8.4% vs. 6%; P=0.36  
TVR: 11.4% vs. 8.4%; P=0.36  
ST: 2.15% vs. 3.4%; P=0.42 | On page E155: “In this observational analysis, BP-PES was comparable to DP-PES, with regard to incidence of repeated revascularizations, stent thrombosis and MACCE despite earlier DAPT discontinuation.” |
| Liu HB, 2009, P.R. China       | Bioabsorbable polymer SES vs. durable polymer SES (Excel stent vs. Firebird stent) at 2 year:  
MACE: 6.1% vs. 7.6%; HR(95%CI): 0.84 (0.50, 1.43)  
Death: 2.3% vs. 2.8%; HR(95%CI): 0.74 (0.30, 0.85)  
MI: 1.8% vs. 1.3%; HR(95%CI): 1.41 (0.45, 4.43)  
TLR: 1.5% vs. 1.8%; HR(95%CI): 0.86 (0.29, 2.55)  
TVR: 2.5% vs. 4.0%; HR(95%CI): 0.62 (0.28, 1.37) | On page 681: “Results from this long-term, relatively large size, single-center study showed that both of the EXCEL and the FIREBIRD sirolimus-eluting stent had similar and lower incidence of MACE after PCI in daily practice.” |

**Notes:**  
BES=biolimus bioabsorbable polymer stents; BP-DES= bioabsorbable drug eluting stents; BP-PES= Bioabsorbable polymer paclitaxol eluting stents. BP-RES= biodegradable polymer-based rapamycin-eluting stents; CoCr-EES= cobalt-chromium everolimus-eluting stents; DP-DES= durable drug eluting stents; DP-PES= durable polymer paclitaxol eluting stents; HR=hazard ratio; ITT=intention to treat; LST=Late stent thrombosis; MA=meta-analysis; NEVO RES-I Trial = NEVO RES-ELUTION I Trial; NWM=network meta-analysis; NR=not reported; NS=not statistically significant; OBS=observational studies; OR=Odds Ratio; PC-ZES= phospholipid-based zotarolimus-eluting stents; PES= Paclitaxol eluting stents; PtCr-EES= platinum chromium everolimus-eluting stents; RCT=randomized controlled trial; Re-ZES= Re-ZES; RR=Rate Ratio or risk ratio; SES=sirolimus permanent polymer stents; ST=stent thrombosis; TLR=target lesion revascularization; TVR=target vessel revascularization; ZES= zotarolimus-eluting stents; Zotarolimus-E = Zotarolimus-Endeavor; Zotarolimus-R= Zotarolimus-Resolute; 95% CI=95% confidence interval; 95% CrI=95% credibility interval.  
* Costar DES was discontinued in the market.