TITLE: Drug Eluting Stents for Patients with Diabetes and Coronary Artery Disease: A Review of the Clinical Evidence and Guidelines

DATE: 18 October 2012

CONTEXT AND POLICY ISSUES

Diabetes is strongly associated with atherosclerosis of coronary blood vessels and has a large impact on Canadian health; in 2009-2010, 22.7% of Canadians ≥ 20 years old with diabetes had heart disease, compared to 6% in the population without diabetes.1,2

Strategies for coronary revascularization in patients with diabetes include medical treatment, percutaneous coronary intervention (PCI) with placement of a drug-eluting stent (DES) or bare-metal stent (BMS), and coronary artery bypass grafting (CABG).3-7 The most common DES include sirolimus-, paclitaxel-, everolimus-and zotarolimus-eluting stents.

There is a continued increase in revascularization procedures in Canada, with over 18,300 patients undergoing a PCI with placement of a DES or BMS in Ontario between December 2003 and March 2005.8,9 While DES have been shown to reduce the risk of restenosis in patients with coronary artery disease, the relative efficacy of various DES to BMS and CABG is not well defined. The objective of this study is to conduct a review of the clinical evidence regarding drug eluting stents for patients with diabetes and coronary artery disease compared to BMS and CABG. The evidence-based guidelines for the use of DES in patients with diabetes will also be reviewed.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of drug eluting stents in adults with both diabetes and coronary artery disease?

2. What are the evidence-based guidelines for the use of drug-eluting stents in adults with both diabetes and coronary artery disease?
KEY MESSAGE

In adults with diabetes and coronary artery disease, findings from both randomized and non-randomized controlled trials showed consistently that the clinical effectiveness, as measured by the need for a repeat revascularization of the target vessel, is the best with CABG, followed by DES, then BMS. Findings on safety outcomes such as risk of death and myocardial infarction are similar between DES and BMS up to 2.5 years follow-up and in favour of DES with longer follow-up times. Findings on comparisons between DES and CABG are inconsistent on safety outcomes. There was no evidence found on guidelines for the use of DES in adult patients with both diabetes and coronary artery disease.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (Sept 2012), University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 2007, and September 11 2012. Internet links were provided, where available.

Literature Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

<table>
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<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td>Population</td>
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<td>Intervention</td>
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<td>Comparator</td>
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<td>Outcomes</td>
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<td>Study design</td>
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Literature Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2007, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.
Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the AMSTAR tool,\textsuperscript{10} and observational studies were assessed using the Downs and Black checklist.\textsuperscript{11} Numerical scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Available Evidence

The literature search yielded 550 citations. Eight additional studies were identified by searching the grey literature. After screening of abstracts, 23 potentially relevant studies were selected for full-text review. Fourteen studies were included in the review.

The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

Study design

Two systematic reviews,\textsuperscript{12,13} nine retrospective observational studies,\textsuperscript{14-22} and three prospective observational studies\textsuperscript{23-25} were included in this report.

Population

The population of the included studies was patients with both diabetes and coronary artery disease. Glycated hemoglobin (HbA1c) levels were not reported. Three studies were from the US,\textsuperscript{15,17,20} and one study each from Canada,\textsuperscript{19} The Netherlands,\textsuperscript{23} North America,\textsuperscript{14} Sweden,\textsuperscript{16} China,\textsuperscript{24} Denmark,\textsuperscript{18} Japan,\textsuperscript{25} Israel,\textsuperscript{21} and Korea.\textsuperscript{22} One systematic review was from the US and Germany\textsuperscript{12}, and the second was from China.\textsuperscript{13} The systematic review comparing patients receiving DES with patients receiving bare metal stents\textsuperscript{12} included 10,714 patients. The systematic review comparing patients receiving DES with patients undergoing CABG\textsuperscript{13} included 4,284 patients. Observational study size ranged from 255 patients\textsuperscript{23} to 7,644 patients.\textsuperscript{16}

Interventions and comparators

One systematic review,\textsuperscript{12} two prospective studies,\textsuperscript{23,24} and seven retrospective studies\textsuperscript{14-20} compared DES with bare metal stents. One study\textsuperscript{23} included only sirolimus-eluting stents, three studies\textsuperscript{7,20,24} included both sirolimus- and paclitaxel-eluting stents, and the remainder of the studies did not specify the type of DES. The systematic review\textsuperscript{12} included studies with sirolimus-, paclitaxel-, everolimus-, or zotarolimus-eluting stents.

One systematic review,\textsuperscript{13} two prospective studies,\textsuperscript{23,25} and two retrospective studies\textsuperscript{21,22} compared DES with CABG. Two studies\textsuperscript{23,25} included only sirolimus-eluting stents, one study\textsuperscript{22} included sirolimus- and paclitaxel-eluting stents, and one study\textsuperscript{21} did not specify the type of DES. One of the studies that compared DES with CABG\textsuperscript{25} also compared DES with bare metal stents. The systematic review did not specify the type of DES included.
Outcomes

Clinical outcomes reported for all studies were similar, and included target vessel revascularization, death, and myocardial infarction.

A more detailed summary of the characteristics of the included studies is provided in Appendix 2.

Summary of Critical Appraisal

Two of the included studies\textsuperscript{12,13} were systematic reviews (SRs). The SR by Bangalore \textit{et al.}\textsuperscript{12} included only RCTs, whereas the SR by Gao \textit{et al.}\textsuperscript{13} included mainly observational studies. Both SRs clearly defined inclusion and exclusion criteria, and assessed the rigour of the included studies. The SR by Bangalore \textit{et al.}\textsuperscript{12} relied on data from multiple sources, minimizing the possibility of publication bias, whereas Gao \textit{et al.}\textsuperscript{13} comment on the possibility of publication bias in their meta-analysis.

Only three of the included studies were prospective observational studies\textsuperscript{23-25} the remaining studies were retrospective.\textsuperscript{14-22} The studies appeared to include patients that were representative of the specific population (patients with diabetes and coronary artery disease), and confounders were considered in all studies. The main limitations were the lack of randomization and blinding in all studies.

A more detailed summary of the critical appraisal conducted for selected studies can be found in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the clinical effectiveness and safety of drug eluting stents in adults with diabetes and coronary artery disease?

Clinical effectiveness and safety of DES compared with BMS, in adults with diabetes and coronary artery disease

One meta-analysis of randomized controlled trials\textsuperscript{12} and nine non-randomized controlled trials\textsuperscript{14-20,23,24} examined the efficacy and safety of DES in patients with diabetes and coronary artery disease, compared with BMS. Data from all studies agreed on a significant reduction of the need for a repeat revascularization of the target vessel with the use of current DES, compared with BMS. Most studies found similar safety outcomes between DES and BMS.

The meta-analysis, conducted in 2012, included 20 randomized controlled trials that compared various currently used DES to BMS.\textsuperscript{12} As a measure of efficacy outcome, all DES were associated with a statistically significant 37% to 69% range of reduction of target vessel revascularization rate. Risks of death, MI, and stent thrombosis were similar between DES and BMS. The authors concluded that DES compared with BMS was efficacious without compromising safety of patients with diabetes and coronary artery disease.
Included non-randomized controlled studies that reported the rates of target vessel revascularization as an efficacy outcome found the need for revascularization was statistically reduced with the use of DES as compared to BMS.\(^{14,15,17-20,23,24}\) In terms of safety outcomes, all studies with mean follow-up times up to 2.5 years found similar rates of death, MI, thrombosis and composite outcome (death/MI) between DES and BMS,\(^{14-16,18-20,24}\) while the studies with longer mean follow up times (from three years up to five years) found smaller rates of MI or composite outcome (death/MI/stroke/revascularization) with DES use compared with BMS.\(^{17,23}\)

**Clinical effectiveness and safety of DES compared with CABG, in adults with diabetes and coronary artery disease**

One meta-analysis of randomized and non-randomized controlled trials,\(^{13}\) and four non-randomized controlled trials\(^{21-23,25}\) compared the efficacy and safety of DES to CABG in patients with diabetes and coronary artery disease. Data from all studies agreed on a higher risk of repeat revascularization with DES use compared with CABG. Comparisons on safety outcomes were inconsistent between studies.

The meta-analysis in 2012 included two randomized and nine non-randomized controlled trials that compared various DES to CABG.\(^{13}\) Findings showed a four-fold increase in risk for repeat revascularization rate but a 21% decrease in risk for a composite outcome of death/MI/cerebrovascular events in patients with DES placement compared with CABG.

All included non-randomized controlled trials reported lower repeat revascularization rates with CABG.\(^ {21-23,25}\) Mortality rates were found to be similar with DES or CABG in three trials,\(^ {22,23,25}\) but were in favour of CABG in one trial.\(^ {21}\) Composite end point (death/MI/stroke) was similar with the use of DES or CABG in one trial,\(^ {22}\) and in favour of off-pump CABG in another.\(^ {25}\)

2. **What are the evidence-based guidelines for the use of drug-eluting stents in adult patients with diabetes and coronary artery disease?**

There were no evidence-based guidelines found regarding the use of drug-eluting stents in adult patients with diabetes and coronary artery disease.

**Limitations**

The evidence comparing DES with BMS is relatively strong, based on systematic review/meta-analysis that included only RCTs. The evidence is further confirmed by the concordance to the findings of the non-RCTs. On the other hand, the evidence comparing DES to CABG is not as strong, due to the systematic review/meta-analysis that included both RCTs and non-RCTs. The variation in study design in the systematic review comparing DES to CABG is a limiting factor, due to the fact that the majority of included trials were non-RCTs, the selection of the type of revascularization was driven by clinical judgment. Neither systematic review conducted risk stratification according to patients' coronary anatomical type, which could have limited bias due to confounding and provided additional valuable information. Finally, the follow-up time of the included studies ranges from one to five years, thus may not detect the true long-term differences between different revascularization strategies. The large population covered in this review gives confidence to the generalizability of the findings to adults patients with diabetes and coronary artery disease. There were no evidence-based guidelines found regarding the use of drug-eluting stents in adult patients with diabetes and coronary artery disease.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In adults with diabetes and coronary artery disease, both randomized and non-randomized controlled trials consistently found that the clinical effectiveness, as measured by the need for a repeat revascularization of the target vessel, is the best with CABG, followed by DES, then BMS. Findings on safety outcomes, such as risk of death and myocardial infarction are similar between DES and BMS up to 2.5 years follow-up and in favour of DES with longer follow-up times. Comparisons between DES and CABG are inconsistent on safety outcomes. There was no evidence found on guidelines for the use of DES in adult patients with diabetes and coronary artery disease. Findings from our review are in accordance with results from a study on Ontario’s population who underwent percutaneous coronary interventions with placement of DES or BMS (including those with diabetes),\(^9\) with DES reducing the need for repeat revascularization without a compromise on safety outcomes, as compared to BMS.

A cost-effectiveness analysis of DES compared to BMS, based on data from over 16,000 patients undergoing percutaneous coronary interventions in Ontario, was published in 2007.\(^{26}\) The report found that the most favourable incremental cost-effectiveness ratio for DES compared to BMS was for non-post myocardial infarction diabetic patients with very long and narrow lesions, in which the revascularization rate for DES was the most advantageous compared to BMS over a two year period ($64,394 per quality-adjusted life year [QALY] gained). In terms of incremental cost per revascularization avoided, the same subgroup of patients had the most effective result with DES, with $2,630 per revascularization procedure averted.

In face of an expansion in percutaneous coronary intervention procedures in Canada and funding restrictions, benefits and risks of each revascularization strategy have to be considered to justify the choice. The Canadian Association of interventional cardiology and the Canadian Cardiovascular Society issued a joint statement on drug-eluting stents in 2007:\(^{27}\)

“Recommendations for DES use
1. Physicians should always carefully consider the benefits and risks on an individual patient basis when choosing between DES and BMS.
2. Physicians should weigh the benefits and risks especially carefully when considering DES use for unapproved (off-label) indications. While many of these patients may benefit from the significant reduction in restenosis and the need for repeat revascularization through DES implantation, it may be at the expense of a higher risk of very late stent thrombosis…” (p 121)

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REFERENCES


Appendix 1: Selection of Publications

550 citations identified from electronic literature search and screened (abstracts)

8 potentially relevant reports retrieved from other sources (grey literature, hand search)

535 citations excluded

23 potentially relevant articles retrieved for scrutiny (full text)

9 reports excluded

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

#### Table A1: Characteristics of Included Clinical Studies

<table>
<thead>
<tr>
<th>First Author, Year, Country, Study Design, Length of Study</th>
<th>Population, Number of patients (n)</th>
<th>Intervention; Number of patients (n)</th>
<th>Comparator; Number of patients (n)</th>
<th>Clinical Outcomes</th>
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<tbody>
<tr>
<td><strong>Drug Eluting Stents versus Bare Metal Stents</strong></td>
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<tr>
<td>Bangalore, 2012US; Germany Systematic review RCTs published from 2003-2011</td>
<td>42 RCTs of patients with diabetes mellitus n = 10,714</td>
<td>Sirolimus, paclitaxel, everolimus, or zotarolimus eluting stents</td>
<td>Bare metal stents or other drug eluting stents</td>
<td>Target vessel revascularization; death; myocardial infarction; stent thrombosis</td>
</tr>
<tr>
<td>Onuma, 2011 The Netherlands Non-randomized, open-label study 5 years</td>
<td>Patients with diabetes mellitus and multivessel disease n = 271</td>
<td>Sirolimus eluting stents; n = 159</td>
<td>Bare metal stents; n = 112</td>
<td>Target vessel revascularization; death; myocardial infarction</td>
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<tr>
<td>Rana, 2010 North America Retrospective observational study of a prospectively populated registry (multicentre) 1 year follow-up of individual patients from 1997-2006</td>
<td>Patients with diabetes n = 1,387</td>
<td>Drug eluting stents (drug not specified); n = 592</td>
<td>Bare metal stents; n = 795</td>
<td>Target vessel revascularization; death; myocardial infarction</td>
</tr>
<tr>
<td>Ramanath, 2010US Retrospective observational study of a prospectively populated registry (single centre) Up to 5 years follow-up of individual patients from 2000-2008</td>
<td>Patients with type I or II diabetes mellitus n = 1,319</td>
<td>Drug eluting stents (drug not specified); n = 770</td>
<td>Bare metal stents; n = 549</td>
<td>Target vessel revascularization; survival</td>
</tr>
<tr>
<td>Stenestrand, 2010 Sweden Retrospective observational study of a prospectively populated registry (multicentre) Up to 4 years follow-up of individual patients from 2003-2006</td>
<td>Patients with diabetes mellitus n = 7,644</td>
<td>Drug eluting stents (drug not specified); n = 4,045</td>
<td>Bare metal stents; n = 3,599</td>
<td>Death; myocardial infarction; restenosis</td>
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<tr>
<td>First Author, Year, Country, Study Design, Length of Study</td>
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<td>Dou, 2009&lt;sup&gt;18&lt;/sup&gt; China Non-randomized, open-label study 2 years</td>
<td>Patients with diabetes n = 1,565</td>
<td>Sirolimus (n = 1,095) or paclitaxel (n = 222) eluting stents; n = 1,317</td>
<td>Bare metal stents; n = 248</td>
<td>Target vessel revascularization; death; myocardial infarction; mortality; thrombosis</td>
</tr>
<tr>
<td>Garg, 2008&lt;sup&gt;17&lt;/sup&gt; US Retrospective observational study of a prospectively populated registry (multicentre) 3 years follow-up of individual patients from 2003-2004</td>
<td>Patients with diabetes mellitus n = 5,051</td>
<td>Sirolimus or paclitaxel eluting stents; n = 3,341</td>
<td>Bare metal stents; n = 1,710</td>
<td>Target vessel revascularization mortality; myocardial infarction</td>
</tr>
<tr>
<td>Maeng, 2008&lt;sup&gt;18&lt;/sup&gt; Denmark Retrospective observational study of a prospectively populated registry (multicentre) 15 months follow-up of individual patients from 2002-2005</td>
<td>Patients with diabetes mellitus n = 1,423</td>
<td>Drug eluting stents (drug not specified); n = 552</td>
<td>Bare metal stents; n = 871</td>
<td>Target-lesion revascularization; thrombosis; mortality</td>
</tr>
<tr>
<td>Ko, 2008&lt;sup&gt;19&lt;/sup&gt; Canada Retrospective observational study of a prospectively populated registry (multicentre) 2 years follow-up of individual patients from 2003-2005</td>
<td>Patients with diabetes n = 2,374</td>
<td>Drug eluting stents (drug not specified); n = 1,187</td>
<td>Bare metal stents; n = 1,187</td>
<td>Target vessel revascularization; myocardial infarction; mortality</td>
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<tr>
<td>First Author, Year, Country, Study Design, Length of Study</td>
<td>Population, Number of patients (n)</td>
<td>Intervention; Number of patients (n)</td>
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<tr>
<td>Daemen, 2007&lt;sup&gt;20&lt;/sup&gt; US Retrospective observational study of a prospectively populated registry (single centre) 2 years follow-up of individual DES patients from 2002-2004 and BMS pre 2002</td>
<td>Patients with diabetes mellitus n = 705</td>
<td>Sirolimus (n = 206) or paclitaxel (n = 250) eluting stents; n = 456</td>
<td>Bare metal stents; n = 252</td>
<td>Target vessel revascularization; myocardial infarction; death</td>
</tr>
<tr>
<td>Gao, 2012&lt;sup&gt;13&lt;/sup&gt; China Systematic review RCTs and cohort studies from 2007-2010</td>
<td>Patients with diabetes and left main or multivessel cardiac disease n = 4,284</td>
<td>Drug eluting stents (drug not specified); n = 2,145</td>
<td>CABG; n = 2,139</td>
<td>Target vessel revascularization; death; myocardial infarction; cerebrovascular events</td>
</tr>
<tr>
<td>Dohi, 2012&lt;sup&gt;25&lt;/sup&gt; Japan Non-randomized, open-label study Mean follow-up of 2.7 years from 2002-2008</td>
<td>Patients with diabetes mellitus and multivessel coronary artery disease n = 399</td>
<td>Sirolimus eluting stents; n = 140</td>
<td>CABG; n = 259</td>
<td>Target vessel revascularization; mortality; major adverse cardiac and cerebrovascular events</td>
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<tr>
<td>Moshkovitz, 2012&lt;sup&gt;21&lt;/sup&gt; Israel Retrospective observational study Mean follow-up of 62 months from 2002-2006</td>
<td>Patients with diabetes and multivessel CAD n = 497</td>
<td>Drug eluting stents (drug not specified); n = 271</td>
<td>CABG; n = 226</td>
<td>Target vessel revascularization; 5-year reintervention-free survival; major adverse cardiac events</td>
</tr>
<tr>
<td>Kim, 2012&lt;sup&gt;22&lt;/sup&gt; Korea Retrospective observational study of a single-centre prospective study Four to 7 years follow-up of individual patients from 2003-2010</td>
<td>Patients with diabetes mellitus and multivessel CAD n = 891</td>
<td>Sirolimus or paclitaxel eluting stents ; n = 489</td>
<td>CABG; n = 1,093</td>
<td>Target vessel revascularization; mortality; myocardial infarction; stroke</td>
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</table>
Table A1: Characteristics of Included Clinical Studies

<table>
<thead>
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<th>First Author, Year, Country, Study Design, Length of Study</th>
<th>Population, Number of patients (n)</th>
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<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onuma, 2011**&lt;sup&gt;++&lt;/sup&gt; The Netherlands Non-randomized, open-label study 5 years</td>
<td>Patients with diabetes mellitus and multivessel disease n = 255</td>
<td>Sirolimus eluting stents; n = 159</td>
<td>CABG; n = 96</td>
<td>Target vessel revascularization; death; myocardial infarction; stroke</td>
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### Appendix 3: Summary of Critical Appraisal of Included Studies

**Table A2: Critical Appraisal of Included Studies**

<table>
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<tr>
<th>First author, year</th>
<th>Strengths</th>
<th>Limitations</th>
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</table>
| Bangalore, 2012; Systematic review | - review addressed a clearly focused issue  
- literature search likely captured all important, relevant studies  
- flow chart for number of studies reviewed and included, and reasons for exclusion given  
- appropriate study design of included studies (RCTs)  
- clearly defined inclusion and exclusion criteria  
- rigour of included studies was assessed  
- any heterogeneity of results was examined  
- confidence intervals provided  
- many different data sources utilized, to minimize publication bias | - limited data available on some stents  
- not all included trials reported each of the assessed outcomes  
- confounding by indication cannot be ruled out |
| Dohi, 2012 | - prospective study  
- objective and main outcomes of the study clearly described  
- characteristics of the patients included in the study clearly described  
- distributions of principal confounders in each group of patients clearly described and considered  
- patients and facility representative of population | - no blinding of patients or assessors  
- patients not randomized to intervention groups  
- not apparent if there was adequate adjustment for confounding in the analysis from which the main findings were drawn |
| Gao, 2012 Systematic review | - review addressed a clearly focused issue  
- literature search likely captured all important, relevant studies  
- flow chart for number of studies reviewed and included, and reasons for exclusion given  
- appropriate study design of included studies (RCTs)  
- clearly defined inclusion and exclusion criteria  
- rigour of included studies assessed  
- most studies were observational  
- summarized event rates for each trial, instead of individual patient data was used, which could be subject to confounding and selection bias  
- specific type of DES could not be analyzed  
- follow-up durations of studies differed  
- possibility of publication bias | |
| Kim, 2012 | - objective and main outcomes of the study clearly described  
- characteristics of the patients included in the study clearly described  
- interventions of interest clearly described  
- distributions of principal confounders in each group of patients clearly described and considered  
- patients participating in the study likely representative of the population  
- analyses adjust for different lengths of follow-up of patients | - retrospective study  
- losses to follow-up not reported  
- no blinding of patients or assessors  
- patients not randomized to intervention groups  
- possibly inadequate adjustment for confounding by indication  
- separate results for specific types of DES not reported |
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Moshkovitz, 2012\(^1\) | • objective and main outcomes of the study clearly described  
• characteristics of the patients included in the study clearly described  
• interventions of interest clearly described  
• distributions of principal confounders in each group of patients clearly described and considered  
• characteristics of patients lost to follow-up described  
• patients in the study representative of the population  
• some adjustment for confounding in the analysis from which the main findings were drawn | • retrospective study  
• no blinding of patients or assessors  
• analyses do not appear to adjust for different lengths of follow-up of patients  
• patients not randomized to intervention groups  
• patients lost to follow-up were not included in the study results |
| Onuma, 2011\(^2\)^   | • prospective study  
• objective and main outcomes of the study clearly described  
• characteristics of the patients included in the study clearly described  
• interventions of interest clearly described  
• distributions of principal confounders in each group of patients clearly described and considered  
• patients in the study representative of the population  
• appears to be adequate adjustment for confounding in the analysis from which the main findings were drawn | • not reported if any patients were lost to follow-up  
• no blinding of patients or assessors  
• patients in different intervention groups recruited over the different periods of time (5-year time difference)  
• patients not randomized to intervention groups  
• study is subanalysis of 2 trials, and lacks sufficient power with limited number of patients |
| Ramanath, 2010\(^3\) | • objective and main outcomes of the study clearly described  
• characteristics of the patients included in the study clearly described  
• interventions of interest clearly described  
• distributions of principal confounders in each group of patients clearly described and considered  
• patients and facility representative of the population  
• adequate adjustment for confounding in the analysis from which the main findings were drawn | • retrospective study  
• specific types of DES could not be analyzed  
• not reported if any patients were lost to follow-up  
• no blinding of patients or assessors  
• patients not randomized to intervention groups  
• losses to follow-up not reported |
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Rana, 2010¹⁴      | • objective and main outcomes of the study clearly described  
                  • characteristics of the patients included in the study clearly described  
                  • interventions of interest clearly described  
                  • distributions of principal confounders in each group of patients clearly described and considered  
                  • patients and facilities representative of the population | • retrospective study  
                  • specific types of DES not reported  
                  • estimates of the random variability in the data not reported for all of the main outcomes  
                  • losses to follow-up not reported  
                  • no blinding of patients or assessors  
                  • patients not randomized to intervention groups  
                  • not apparent if adequate adjustment for confounding in the analysis from which the main findings were drawn |
| Stenestrand, 2010¹⁰ | • objective and main outcomes of the study clearly described  
                     • characteristics of the patients included in the study clearly described  
                     • interventions of interest clearly described  
                     • distributions of principal confounders in each group of patients clearly described and considered  
                     • adequate adjustment for confounding in the analysis from which the main findings were drawn  
                     • patients and facilities representative of the population  
                     • analyses adjust for different lengths of follow-up of patients | • retrospective study  
                     • results for specific types of DES not reported individually  
                     • no information on patients potentially lost to follow-up  
                     • probability values not reported  
                     • no blinding of patients or assessors  
                     • patients not randomized to intervention groups |
| Dou, 2009⁵⁵       | • prospective study  
                     • objective and main outcomes of the study clearly described  
                     • characteristics of the patients included in the study clearly described  
                     • interventions of interest clearly described  
                     • distributions of principal confounders in each group of patients clearly described and considered  
                     • patients in the study representative of the population  
                     • adequate adjustment for confounding in the analysis from which the main findings were drawn | • no information on patients potentially lost to follow-up  
                     • no blinding of patients or assessors  
                     • patients were not randomized to intervention groups |
| Garg, 2008⁷⁷      | • objective and main outcomes of the study clearly described  
                     • characteristics of the patients included in the study clearly described  
                     • interventions of interest clearly described  
                     • distributions of principal confounders in each group of patients clearly described and considered  
                     • patients and facilities in the study representative of the population  
                     • adequate adjustment for confounding in the analysis from which the main findings were drawn | • retrospective study  
                     • no blinding of patients or assessors  
                     • patients not randomized to intervention groups |
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Strengths</th>
<th>Limitations</th>
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</table>
| Maeng, 2008¹⁸     | • objective and main outcomes of the study clearly described  
|                   | • characteristics of the patients included in the study clearly described  
|                   | • interventions of interest clearly described  
|                   | • distributions of principal confounders in each group of patients to be completed clearly described  
|                   | • the characteristics of patients lost to follow-up described  
|                   | • patients and facilities in the study representative of the  
|                   | • adequate adjustment for confounding in the analysis from which the main findings were drawn | • retrospective study  
|                   | • patients and assessors not blinded  
|                   | • patients not randomized to intervention groups  
|                   | • results for specific types of DES not reported individually |
| Ko, 2008¹⁹        | • objective and main outcomes of the study clearly described  
|                   | • characteristics of the patients included in the study clearly described  
|                   | • interventions of interest clearly described  
|                   | • distributions of principal confounders in each group of patients clearly described and considered  
|                   | • patients and facilities in the study representative of the population  
|                   | • adequate adjustment for confounding in the analysis from which the main findings were drawn | • retrospective study  
|                   | • results for specific types of DES not reported individually  
|                   | • did not provide estimates of the random variability in the data for the main outcomes  
|                   | • losses to follow-up not reported  
|                   | • patients and assessors not blinded  
|                   | • patients not randomized to intervention groups  |
| Daemen, 2007²⁰    | • objective and main outcomes of the study clearly described  
|                   | • characteristics of the patients included in the study clearly described  
|                   | • interventions of interest clearly described  
|                   | • distributions of principal confounders in each group of patients clearly described and considered  
|                   | • patients and facilities in the study representative of the population  
|                   | • adequate adjustment for confounding in the analysis from which the main findings were drawn | • retrospective study  
|                   | • patients lost to follow-up not described  
|                   | • patients and assessors not blinded  
|                   | • patients not randomized to intervention groups  
|                   | • different time periods for the interventions |
### Appendix 4: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Bangalore, 2012(^{12})</td>
<td><strong>Target vessel revascularization (hazard ratio compared with BMS)</strong>&lt;br&gt;Sirolimus eluting stent: 0.38 (0.29 to 0.48)&lt;br&gt;Paclitaxel eluting stent: 0.47 (0.35 to 0.61)&lt;br&gt;Everolimus eluting stent: 0.31 (0.19 to 0.47)&lt;br&gt;Zotarolimus eluting stent: 0.63 (0.42 to 0.96)&lt;br&gt;<strong>Death (hazard ratio compared with BMS)</strong>&lt;br&gt;Sirolimus eluting stent: 1.00 (0.73 to 1.39)&lt;br&gt;Paclitaxel eluting stent: 0.96 (0.70 to 1.38)&lt;br&gt;Everolimus eluting stent: 0.83 (0.42 to 1.46)&lt;br&gt;Zotarolimus eluting stent: 1.14 (0.58 to 2.27)&lt;br&gt;<strong>MI (hazard ratio compared with BMS)</strong>&lt;br&gt;Sirolimus eluting stent: 0.71 (0.49 to 1.05)&lt;br&gt;Paclitaxel eluting stent: 0.82 (0.55 to 1.22)&lt;br&gt;Everolimus eluting stent: 0.52 (0.21 to 1.09)&lt;br&gt;Zotarolimus eluting stent: 2.16 (0.91 to 8.45)&lt;br&gt;<strong>Stent thrombosis (hazard ratio compared with BMS)</strong>&lt;br&gt;Sirolimus eluting stent: 0.64 (0.36 to 1.14)&lt;br&gt;Paclitaxel eluting stent: 0.78 (0.45 to 1.54)&lt;br&gt;Everolimus eluting stent: 0.56 (0.20 to 1.46)&lt;br&gt;Zotarolimus eluting stent: 2.75 (0.60 to 14.85)&lt;br&gt;</td>
<td>“Among patients with diabetes treated with coronary stents all currently available drug eluting stents were efficacious without compromising safety compared with bare metal stents” (p 1)</td>
</tr>
<tr>
<td>Onuma, 2011(^{13})</td>
<td><strong>At 5 years</strong>&lt;br&gt;<strong>Target vessel revascularization (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 33.2%&lt;br&gt;BMS: 43.7% (p 0.02)&lt;br&gt;<strong>Death(rate)</strong>&lt;br&gt;Sirolimus eluting stent: 9%&lt;br&gt;BMS: 13.6% (p 0.23)&lt;br&gt;<strong>MI (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 4.8%&lt;br&gt;BMS: 11% (p 0.04)&lt;br&gt;<strong>Death/stroke/MI/revascularization (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 40.5%&lt;br&gt;BMS: 53.8% (p &lt; 0.001)&lt;br&gt;</td>
<td>Sirolimus eluting stents had lower revascularization rate, myocardial infarction rate, and major adverse cardiac and cerebrovascular events than bare metal stents at 5-year follow up.</td>
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**Research question 1 (clinical effectiveness and safety of drug eluting stents in adults with diabetes and coronary artery disease)**

**DES vs BMS**

Systematic Review (of randomized controlled trials)

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<td>“Among patients with diabetes treated with coronary stents all currently available drug eluting stents were efficacious without compromising safety compared with bare metal stents” (p 1)</td>
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**Trials (non-randomized controlled trials)**

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<td><strong>At 5 years</strong>&lt;br&gt;<strong>Target vessel revascularization (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 33.2%&lt;br&gt;BMS: 43.7% (p 0.02)&lt;br&gt;<strong>Death(rate)</strong>&lt;br&gt;Sirolimus eluting stent: 9%&lt;br&gt;BMS: 13.6% (p 0.23)&lt;br&gt;<strong>MI (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 4.8%&lt;br&gt;BMS: 11% (p 0.04)&lt;br&gt;<strong>Death/stroke/MI/revascularization (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 40.5%&lt;br&gt;BMS: 53.8% (p &lt; 0.001)&lt;br&gt;</td>
<td>Sirolimus eluting stents had lower revascularization rate, myocardial infarction rate, and major adverse cardiac and cerebrovascular events than bare metal stents at 5-year follow up.</td>
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<td><strong>Rana, 2010</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td><strong>At 1 year</strong>&lt;br&gt;Target vessel revascularization (rate)&lt;br&gt;DES: 9%&lt;br&gt;BMS: 13% (p &lt; 0.001)&lt;br&gt;Death/MI (rate)&lt;br&gt;DES: 7%&lt;br&gt;BMS: 7% (p 0.76)</td>
<td><strong>“In patients with diabetes undergoing PCI, the use of DES is associated with a reduced need of repeat revascularization when compared with balloon angioplasty or BMS use” (p 1976)</strong></td>
</tr>
<tr>
<td><strong>Ramanath, 2010</strong>&lt;sup&gt;(12839)&lt;/sup&gt;</td>
<td><strong>At mean 2.5 years</strong>&lt;br&gt;Target vessel revascularization (hazard ratio compared with BMS)&lt;br&gt;DES: 0.62 (0.43 to 0.90) (p 0.013)&lt;br&gt;Survival (hazard ratio compared with BMS)&lt;br&gt;DES: 0.72 (0.52 to 1.00) (p 0.053)</td>
<td><strong>“The use of DES when compared with BMS among diabetics undergoing PCI is associated with significant improvement in long-term TVR (target vessel revascularization), with an insignificant similar trend in all-cause mortality (p 473)”</strong></td>
</tr>
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<td><strong>Stenestrand, 2010</strong>&lt;sup&gt;(16)&lt;/sup&gt;</td>
<td><strong>At median 2.5 years</strong>&lt;br&gt;Death/MI(relative risk compared with BMS)&lt;br&gt;DES: 0.91 (0.77 to 1.06)&lt;br&gt;Mi (relative risk compared with BMS)&lt;br&gt;DES: 0.80 (0.66 to 0.96)&lt;br&gt;Restenosis (relative risk compared with BMS)&lt;br&gt;DES: 0.50 (0.35 to 0.70)</td>
<td><strong>“This real-life registry study shows that restenosis was halved by DES in diabetic patients with stable or unstable coronary disease, with similar risk of death or MI up to 4 years compared with BMS” (p 177)”</strong></td>
</tr>
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<td><strong>Dou, 2009</strong>&lt;sup&gt;(24)&lt;/sup&gt;</td>
<td><strong>At 2 years</strong>&lt;br&gt;Target vessel revascularization (rate)&lt;br&gt;DES: 5.48%&lt;br&gt;BMS: 11.69% (p 0.000)&lt;br&gt;Death/MI (rate)&lt;br&gt;DES: 3.73%&lt;br&gt;BMS: 4.03% (p 0.817)&lt;br&gt;Mi (rate)&lt;br&gt;DES: 1.98%&lt;br&gt;BMS: 3.63% (p 0.107)&lt;br&gt;Mortality(rate)&lt;br&gt;DES: 2.28%&lt;br&gt;BMS: 1.61% (p 0.508)&lt;br&gt;Thrombosis (rate)&lt;br&gt;DES: 0.46%&lt;br&gt;BMS: 0.81 (p 0.479)</td>
<td><strong>“…the use of DES is associated with long-term significant reductions in the risks of TVR (target vessel revascularization). There is no significant difference in all-cause mortality, MI, and thrombosis between DES and BMS…” (p 612)”</strong></td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Main Study Findings</td>
<td>Authors' Conclusions</td>
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<tr>
<td>Garg, 2008</td>
<td>At 3 years</td>
<td>« …DES were associated with reduced mortality, myocardial infarction, and revascularization rates at long-term follow-up compared with BMS » (p 2277)</td>
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<tr>
<td></td>
<td>Mortality (rate) DES: 17.5% BMS: 20.7% (p 0.02)</td>
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<td></td>
<td>MI (rate) DES: 13.8% BMS: 16.9% (p 0.02)</td>
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<td></td>
<td>Target vessel revascularization (rate) DES: 18.4% BMS: 23.7% (p &lt; 0.001)</td>
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<tr>
<td>Maeng, 2008</td>
<td>At 15 months</td>
<td>“…use of DESs reduced target-lesion revascularization in diabetic patients receiving routine clinical care. This result was obtained without increased risk of death, stent thrombosis, or MI) (p 165)</td>
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<td>Target-lesion revascularization (relative risk compared with BMS) DES: 0.48 (0.33 to 0.71)</td>
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<td></td>
<td>Thrombosis (relative risk compared with BMS) DES: 0.90 (0.53 to 1.52)</td>
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<tr>
<td></td>
<td>Mortality (relative risk compared with BMS) 0.66 (0.44 to 0.99)</td>
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<tr>
<td>Ko, 2008</td>
<td>At 2 years</td>
<td>“Drug-eluting stents are effective among diabetic patients in substantially reducing the need for repeat target vessel revascularization” (p 125)</td>
</tr>
<tr>
<td></td>
<td>Target vessel revascularization (rate) DES: 7.1% BMS: 14.4% (p &lt; 0.001)</td>
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<td>MI (rate) DES: 6.6% BMS: 4.5% (p 0.45)</td>
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<tr>
<td></td>
<td>Mortality (rate) DES: 7.6% BMS: 9.5% (p 0.086)</td>
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<tr>
<td>Daemen, 2007</td>
<td>At 2 years</td>
<td>Paclitaxel-eluting stents reduced target vessel revascularization and major adverse cardiac events compared with BMS</td>
</tr>
<tr>
<td></td>
<td>Target vessel revascularization (rate) Sirolimus eluting stent: 15.3% Paclitaxel-eluting stent: 9.7% BMS: 19.5% (difference was statistically significant to paclitaxel, not to sirolimus)</td>
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<td>Major adverse cardiac events (death/MI/target vessel revascularization) (rate) Sirolimus eluting stent: 28.9% Paclitaxel-eluting stent: 21.2% BMS: 29.7% (difference was statistically significant to paclitaxel, not to sirolimus)</td>
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</table>
### Table A3: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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<tbody>
<tr>
<td><strong>Mortality (rate)</strong></td>
<td>Sirolimus eluting stent: 13.3%</td>
<td>DES vs CABG Systematic Review (of randomized and non-randomized controlled trials)</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent : 11.5%</td>
<td>BMS: 9.8% (difference not statistically significant to both)</td>
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<tr>
<td><strong>Sirolimus eluting stent</strong></td>
<td>DES: 13.3%</td>
<td>“…the composite outcome was better in patients undergoing PCI with drug-eluting stent, despite a higher repeat revascularization rate.” (p 1)</td>
</tr>
<tr>
<td><strong>Paclitaxel-eluting stent</strong></td>
<td>CABG: 11.5%</td>
<td></td>
</tr>
<tr>
<td><strong>BMS</strong></td>
<td>CABG: 9.8%</td>
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</table>

**Trials (non-randomized controlled trials)**

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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<tbody>
<tr>
<td><strong>Dohi, 2012</strong></td>
<td><strong>At mean 2.6 years</strong></td>
<td>“…there was no difference between off-pump coronary artery bypass and sirolimus-eluting stent placement in all-cause mortality or cardiac death. However, the incidence of acute coronary syndrome, target vessel revascularization, and major adverse cardiac and cerebrovascular events were markedly lower in the patients undergoing off-pump coronary artery bypass than in those receiving sirolimus-eluting stent placement” (p 195)</td>
</tr>
<tr>
<td><strong>Mortality (hazard ratio compared to CABG)</strong></td>
<td>Off-pump CABG: 1.45 (0.47 to 4.42) (p 0.51)</td>
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<tr>
<td><strong>Target vessel revascularization (hazard ratio compared to sirolimus-eluting stent)</strong></td>
<td>Off-pump CABG: 0.08 (0.024 to 0.30) (p &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td><strong>Major adverse cardiac and cerebrovascular event (hazard ratio compared to sirolimus-eluting)</strong></td>
<td>Off-pump CABG: 0.14 (0.06 to 0.30) (p &lt; 0.0001)</td>
<td></td>
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<tr>
<td><strong>Trials</strong></td>
<td><strong>At mean 62 months</strong></td>
<td>“…significantly better long-term adjusted survival and outcomes of diabetic patients who underwent CAGB with BITA (bilateral internal thoracic artery) grafting compared with diabetic patients who underwent PCI with DES (p 1)”</td>
</tr>
<tr>
<td><strong>Target vessel revascularization (rate)</strong></td>
<td>DES: 33.6%</td>
<td></td>
</tr>
<tr>
<td><strong>CABG : 14.2% (p 0.000)</strong></td>
<td>5-year reintervention-free survival (rate)</td>
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<tr>
<td><strong>DES: 65% ± 3.1%</strong></td>
<td><strong>CABG: 86% ± 2.4% (p 0.001)</strong></td>
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<tr>
<td><strong>Major adverse cardiac events (rate)</strong></td>
<td>DES: 54% ± 3.2%</td>
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<tr>
<td><strong>CABG: 81% ± 2.7% (p &lt; 0.001)</strong></td>
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**Kim, 2012** | **At median 5.6 years** | “In diabetic patients… 5-year risk of death and the composite of death, MI, or stroke were similar in patients undergoing DES or CABG. However, the rate of repeat revascularization was significantly higher in the DES group” (p 1548) |
| **Target vessel revascularization (hazard ratio compared to CABG)** | DES : 3.69 (2.64 to 5.17)(p < 0.001) | |
| **Mortality (hazard ratio compared to CABG)** | DES: 1.01 (0.77 to 1.33) (p 0.96) | |
### Table A3: Main Study Findings and Authors’ Conclusions

<table>
<thead>
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<tr>
<td></td>
<td><strong>Death/MI/stroke (hazard ratio compared to CABG)</strong>&lt;br&gt;DES: 1.03 (0.80 to 1.31) (p 0.91)</td>
<td>CABG had lower revascularization rate, and cerebrovascular events rate than sirolimus-eluting stents at 5-year follow up. <em>“At 5-year follow-up, CABG has comparable safety and superior efficacy with BMS and SES in the treatment of diabetic patient with multivessel disease”</em> (p 317)</td>
</tr>
<tr>
<td></td>
<td><strong>At 5 years</strong>&lt;br&gt;<em>Target vessel revascularization (rate)</em>&lt;br&gt;Sirolimus eluting stent: 33.2%&lt;br&gt;CABG: 10.7% (p &lt; 0.01)</td>
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<td></td>
<td><strong>Death (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 9%&lt;br&gt;CABG: 8.6% (p 0.91)</td>
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<td></td>
<td><strong>MI (rate)</strong>&lt;br&gt;Sirolimus eluting stent: 4.8%&lt;br&gt;CABG: 5.2% (p 0.76)</td>
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**Research question 2 (evidence-based guidelines for the use of drug-eluting stents in adult diabetic patients with coronary artery disease)**

No studies identified for this research question

*BMS= bare metal stent; CABG= coronary artery bypass grafting; DES= drug eluting stent; MI= myocardial infarction*