Health Technology Assessment

HTA Report

Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS)

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Cardiac Stents: Comparison of Drug Eluting Stents (DES) with Bare Metal Stents (BMS)

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

EXECUTIVE SUMMARY

Introduction

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD), is the single leading cause of death for both men and women in the U.S. and is the most common form of cardiovascular disease. The symptoms of CAD have poor specificity and sensitivity for CAD, so other modalities must be used to confirm or refute a clinical suspicion of CAD. Most of the diagnostic testing for IHD evaluates the impact of ischemia on the myocardium. Only angiography and coronary artery ultrasound provide direct information on the condition of the coronary arteries. Findings from these studies assist in risk assessment and decision making regarding treatment.

Based on patient presentation and risk assessment various treatment options are considered and may include medical therapy and life-style management, percutaneous coronary intervention (PCI) with or without stenting, and coronary artery bypass grafting (CABG).

Balloon angioplasty initially was termed "percutaneous transluminal coronary angioplasty" (PTCA). The term "percutaneous coronary intervention" (PCI) includes balloon angioplasty, stenting and artherectomy. PTCA was first introduced in 1977. The high rates of acute vessel closure and restenosis following PTCA were the predominant factors that led to the development of bare-metal stents (BMS). The continued difficulties with early restenosis and thrombosis with BMS led investigators to explore ways to modify the stent to minimize these adverse outcomes, leading to the conception of drug-eluting stents (DES). DES are essentially BMS that have been coated with a polymer containing an anti-proliferative drug. These drugs inhibit vascular smooth cell proliferation and migration and are released from a non-resorbable polymer into the local environment to achieve high local drug concentrations. The drug is intended to prevent the neo-intimal hyperplasia that appeared to cause the restenosis observed with BMS implantation. In this report, PCI will be used to refer to PCI which includes placement of either DES or BMS unless otherwise noted.

Despite the reduction in restenosis rates, reports of high rates of subacute in-stent thrombosis (clot formation) after DES placement became cause for concern soon after FDA approval of these devices. Thrombosis is a serious complication that often results in acute MI or death. The FDA convened an advisory panel meeting in 2006 to review the data on DES and concluded that DES did not increase the risk of in-stent thrombosis if used for their approved indications: lesions that were newly diagnosed, less than 28-30mm long, and in clinically stable patients without other serious medical problems.

The focus of revascularization should be the improvement in health outcomes (e.g. mortality, freedom from MI, quality of life). Cardiac stenting with DES has been viewed as less invasive solution than CABG to achieving these goals and it is believed by many clinicians and patients that PCI with stenting may provide an attractive solution for alleviating and preventing future CAD-related events and for relief of angina. In light of

the possible benefits of PCI, the potential impact of its use on health care costs and uncertainties regarding the evidence of effectiveness and safety in the short and long term, patients, clinicians, and payers will benefit from a structured, systematic appraisal of the comparative effectiveness, safety, and economic impact of DES with BMS. Thus, the objective of this technology assessment is to critically appraise and analyze research evidence on the efficacy/effectiveness and safety comparing DES with BMS in patients with ischemic heart disease and to the extent possible, consider the potential financial impact.

To that end, the following key questions developed by the Washington State Health Technology Assessment Program will be addressed:

In patients with CHD undergoing stenting of coronary vessels:

1. What is the evidence of efficacy and effectiveness of drug eluting (DES) versus bare metal stents (BMS)?
   - Including any effects on special populations, such as patients with and without diabetes, after myocardial infarction and not after myocardial infarction; and in different vessel and lesion characteristics.

2. What is the evidence related to the safety profile of DES versus BMS?
   - Including in patients with and without continuation of anti-platelet medications.

3. What is the evidence of cost effectiveness and cost implications of DES versus BMS?
   - Including any effects of pharmacologic therapy and reintervention.

Methods for evaluating comparative effectiveness

Spectrum Research, Inc.'s (SRI) method for technology assessment involves formal, structured systematic search of the peer-reviewed literature across a number of databases in addition to searches of pertinent databases related to clinical guidelines and previously performed assessments. Included systematic reviews, previous health technology assessments (HTAs), meta-analyses and individual studies are critically appraised using appropriate checklists and/or SRI's Level of Evidence (LoE) system which evaluates the methodological quality based on study design as well as factor which may bias studies. An overall Strength of Evidence (SoE) combines the LoE with consideration of the number of studies and consistency of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Previously published formal HTAs or similar reports comparing DES with BMS provided an initial basis for this HTA with the most recently performed reports considered to be the most up-to-date and relevant. Results and conclusions from these reports are summarized. Individual studies and meta-analyses reviewed in these reports

were not re-evaluated. Meta-analyses published in peer-reviewed journals after the HTAs which compared DES with BMS were considered to provide the highest quality of new evidence. Those that were most complete and methodologically rigorous provided the primary focus. Comparative studies from peer-reviewed journals that were not previously included in HTAs or meta-analyses were also reviewed for inclusion, again with a focus on the highest level of available evidence.

Throughout the process, SRI sought clinical review to assure that the clinical components are accurately represented. In addition, peer-review by clinical experts, health services researchers and those with expertise in economic and outcomes evaluation provided an assessment of the systematic review methodology, analyses and report conclusions at the time of the publication of the public draft.

Summary and Implications

Summary with regard to efficacy and effectiveness of drug eluting stents (DES) compared with bare metal stents (BMS)

Efficacy

- Findings regarding efficacy described in this technology assessment report are primarily taken from previously done health technology assessments (HTAs) and the most complete, recently published meta-analyses of randomized controlled trials (LoE I/II studies) comparing DES with BMS. There is a very large degree of overlap across HTAs and meta-analyses with regard to trials included in their analyses.
- The overall strength of evidence (SoE) is high, meaning that further research is unlikely to change confidence in the effect estimates, based on the large number of high quality studies and consistency of estimates.
- Death overall, cardiac death and myocardial infarction were used as the primary clinical measures of efficacy. Technology assessments and conventional meta-analyses of between 14 and 24 head to head randomized controlled clinical trials comparing DES with BMS indicate that DES are no better at preventing death, cardiac death or myocardial infarction than BMS.
- Network meta-analysis of 38 randomized controlled trials (RCTs) and the corresponding conventional meta-analysis indicate that DES are no better at preventing death or cardiac death than BMS with no statistically significant differences between treatments based on cumulative incidence to 4 years. Rates for overall mortality were 4.1% for DES and 4.7% for BMS. Rates of cardiac death were 2.4% for DES and 2.7% for BMS.
- Based on conventional meta-analysis there was no statistically significant difference between DES and BMS with regard to myocardial infarction (4 years follow-up), HR, 0.86 (0.67, 1.09). SES (sirolimus-eluting stents) were associated with less risk of myocardial infarction compared with BMS in this network meta-analysis (HR 0.81 (0.66, 0.97). The absolute differences in risk were however small, 1% (0.15% -1.9%).

- Target lesion revascularization (TLR) was considered a secondary, intermediate outcome and not a primary clinical measure of efficacy. DES were consistently associated with lower risk of target lesion revascularization. The absolute differences in risk ranges from 10% to 16.7% comparing DES versus BMS based on data from RCTs. Rates of TLR may have been influenced by protocol-driven angiographic follow-up and not based on clinical presentation and symptoms and may therefore be an over-estimate of rates in a general population.
- Results from recent reports of long-term follow-up to previously reported RCTs show no differences in death, cardiac death or myocardial infarction between patients treated with DES and those treated with BMS.

Effectiveness

- Findings regarding effectiveness described in this technology assessment report are primarily taken from pooled results reported the previously done HTA completed by the Ontario Ministry of Health & Long Term Care.
- The overall strength of evidence (SoE) is considered low, meaning that further research is very likely to impact confidence in the effect estimates, and very likely to change the estimates. This is based on the overall lower quality of registry and non-randomized studies and heterogeneity across studies which suggest inconsistency of estimates.
- The evidence from past HTA reviews of registry data suggest that mortality and MI rates do not differ between DES and BMS patients. Heterogeneity across studies is possible. Results from recently published registry studies are mixed, some favoring DES, other showing now difference for mortality or for MI. Rates for mortality ranged from 4.5% - 8.5% for DES and 6.1% - 17% for BMS in studies with >1 year follow-up. Rates for MI were ranged from 1.7% - 12.7% for DES and from 2.0- 11.5% for BMS in studies with > 1 year follow-up.
- Rates of revascularization are lower for DES patients, but there is substantial heterogeneity between the studies included in the Ontario meta-analysis. Most HTAs express a need for longer follow-up and more specific definitions of the outcomes from registry data.
- More recently published registry reports are consistent with these findings, describing significant differences in TLR or TVR when DES are compared with BMS.
- Rates for revascularization ranged from 5.2% - 14.2% for DES and from 8.1% - 24.4% for BMS in studies with > 1 year follow-up.
- The overall quality, differences in adjustment methods, variations in outcome definition of these nonrandomized studies precludes drawing definitive conclusions.

Summary with regard to the safety of DES compared with BMS

- Findings regarding safety described in this technology assessment report are primarily taken from previously done HTAs and the most complete, recently published meta-analyses of randomized controlled trials (LoE I/II studies) comparing DES with BMS. There is a very large degree of overlap across HTAs and meta-analyses with regard to trials included in their analyses.
- In December 2006, the FDA convened a meeting of the Circulatory System Devices Advisory Panel that featured presentations by regulators, academic physicians, patients, industry representatives, and medical professional societies. The FDA concluded that the widespread use of DES for off-label indications is the primary cause for the increased incidence of stent thrombosis, as such uses are associated with higher rates of early and late stent thrombosis, MI, and death. The FDA also recommended a longer course of dual anti-platelet therapy than was originally used in the pivotal trials. Instead of 3 to 6 months, patients were advised to continue dual anti-platelet therapy for 1 year (and then aspirin for life) following DES implantation. The FDA currently recommends twelve months of dual anti-platelet therapy for patients not at high-risk for bleeding following DES implantation in order to decrease the risk of stent thrombosis.
- Most previous HTAs indicate that there were no statistically significant differences in stent thrombosis for use of DES compared with BMS, but note that studies may be underpowered. One review specifically on safety concluded that the majority of evidence suggests that there is an increased risk of stent thrombosis with DES compared to BMS.
- Based on the Academic Research Consortium (ARC) definition of definite thrombosis, rates from the most recent meta-analysis based on up to 4 years of follow-up were 1.4% for SES (sirolimus-eluting stents), 1.7% for PES (paclitaxel eluting stents) and 1.2% for BMS. No statistically significant difference in stent thrombosis was seen between treatments based on follow-up to 4 years.
- In the most recent meta-analysis for RCT data, a statistically significant difference in ARC-defined definite stent thrombosis was seen between > 30 days and 4 years when PES were compared with BMS., HR 2.11 (0.19, 4.23). Wide confidence intervals and moderate heterogeneity across included studies were noted. No statistically significant differences for the SES versus BMS comparison were seen for this same (or any other) time period.
- The overall strength of evidence (SoE) is moderate with regard to stent thrombosis, meaning that further research is likely to change confidence in the effect estimates and may change the estimates. There is some inconsistency in findings and heterogeneity across studies in meta-analyses. Even the larger meta-analyses may have been underpowered to detect significant differences in rare events such as late stent thrombosis.
- Rates of stent thrombosis in nonrandomized studies ranged from 0% - 2.9% for DES and from 0.1% - 3.5% for BMS.

- The overall evidence is very low with respect to bleeding related to prolonged course of dual anti-platelet therapy and stent fracture since no comparative studies were found. Based on 3 case series, cumulative incidence for bleeding ranged from 1.8%-4.0% up to 18 months of follow-up. Rates for stent fracture from 6 case series ranged from 1.9%-7.7% and one case series reported 18% in patients with in-stent stenosis

Summary with regard to efficacy and effectiveness and safety of DES compared with BMS in special populations

Diabetic patients

- Findings regarding safety described in this technology assessment report are the most complete, recently published meta-analyses of randomized controlled trials (LoE I/II studies) comparing DES with BMS. Previous HTAs or similar reports provide few conclusions and only limited evaluation on diabetic patients or special populations. There is some degree of overlap across HTAs with regard to studies with data on diabetic patients included in different meta-analyses.
- Overall strength of evidence is rated at moderate for efficacy related to death, cardiac death and MI since there is some inconsistency across analyses, part of which may be due to differing durations of anti-platelet therapy.
- The most comprehensive meta-analysis published since then reported a two-fold increase in overall mortality and cardiac mortality among patients receiving DES compared with BMS in those who had less than six months of dual anti-platelet therapy pointing to the importance of longer-term therapy. Three recently published meta-analyses indicate that, overall, mortality risk among diabetic patients is similar whether DES or BMS are used.
- No differences in the risk of myocardial infarction were seen in diabetic patients, regardless of dual anti-platelet therapy in the largest and most complete recent meta-analysis at up to 4 years of follow-up. MI rates were 5.8% for DES and 7.4% for BMS in the network meta-analysis among diabetic patients with ≥ 6 months of dual anti-platelet therapy. Two analyses with fewer trials suggest that at shorter follow-up times (6-24 months), DES may result in a lower risk of MI. Differences in the number and types of included trials and definitions of MI may contribute to difference found between the analyses.
- Outcomes for diabetic patients were examined in 3 HTAs, 4 meta-analyses and 1 RCT included in this report. Results suggest that both TLR and TVR rates are significantly lower in diabetic patients treated with DES than those treated with BMS between 6 months and 4 years following stenting. Cumulative incidences of TLR in the network meta-analysis were 9.7% for DES and 22% for BMS in diabetic patients having ≥ 6 months dual anti-platelet therapy.

- No statistically significant differences in stent thrombosis were seen between treatments either early (0-30 days) or late (>30 days to 4 years) in network meta-analysis restricted to those who had ≥ 6 months dual anti-platelet therapy. However, wide confidence intervals indicate lack of estimate stability and small numbers of events. Rates of thrombosis from 0-4 years were 1.6% for DES and 2.3% for BMS among diabetic patients with ≥ 6 months of dual anti-platelet therapy in the network meta-analysis.
- Overall strength of evidences regarding late stent thrombosis in diabetic populations is low given the wide confidence intervals around estimates.

Patients with acute MI

- Results from one recent HTA, a meta-analysis of 8 RCTs and three recent RCTs suggest no statistical difference in the risk of overall mortality in patients with acute MI comparing DES with BMS.
- Based on pooled estimates from 8 RCTs, there is not a statistically significant difference in risk of re-infarction when DES are used compared with BMS. Data on type and duration of antiplatelet therapy are not described.
- Across reports, DES implantation is associated with a statistically significant decrease in TLR compared with BMS in patients with acute MI.
- Overall strength of evidence with regard to the above outcomes is high.
- Randomized controlled trials assessing safety were summarized in one previous health technology assessment and two meta-analyses. In addition, three recent RCTs provided data on stent thrombosis in patients who received DES versus those who received BMS for acute MI. All report no statistically significant difference in rates of stent thrombosis between DES and BMS groups. Two non-randomized trials also reported no statistical difference between groups.
- Overall strength of evidence for safety is low, based on the likelihood that trials may have had insufficient power to detect differences between treatments particularly for late stent thrombosis and the effect of duration dual anti-platelet therapy was not evaluated.

Intermediate lesions

- Data from the one small meta-analysis of four trials (N = 167) were available.
- There were no differences in cardiac mortality at any follow up time. At 1 year, the incidence of myocardial infarction was 3.4% in the DES group and 5.4% in the BMS group; this difference was not statistically significant.
- No TLR was done by 30 days in either stent group. Data for 1 year for TLR/TVR are as follows: DES: (1.2%, 3.4%), BMS: (20.3%, 20.3%) (P = 0.0004, P < 0.0001, respectively).
- At 1 year, no subjects had suffered a thrombotic event. Given that thrombosis is generally a relatively rare event, it is likely that this study is underpowered to detect a difference in risk between the two types of stents studied.

- Overall strength of evidence for this population is very low for efficacy, effectiveness and safety based on the small number of patients available for analysis.

Summary with regard to economic studies

- The evidence from HTA reviews of 43 cost effectiveness studies, and from 5 additional full cost effectiveness analyses suggest that DES in comparison with BMS are not cost effective across populations.
- Incremental Cost Effectiveness Ratios (ICER) ranged from a low of $27,540 to a high of €1,099,858 or more per Quality Adjusted Life Year (QALY) and from $1650 to $7,000 per repeat revascularization avoided.
- Information from some previous HTAs suggests that DES may be cost effective in selected groups of higher risk patients with multiple risk factors, such long lesions, narrow vessels, complex lesions, diabetics and patients recently post MI.
- Nearly all the studies have taken the perspective of the health care payer. Few have addressed a societal perspective.
- The majority of studies have been conducted outside of the U.S. and differences in payment systems and policy need to be considered.
- Quality of life measures have received limited attention in the cost effectiveness studies, most using values from other studies, and the impact of more precise measurement is unknown.
- Until there is more agreement on efficacy and effectiveness measures and rates with DES versus BMS, there will continue to be great variability among cost effectiveness studies due to variations in parameters used. Methodologically rigorous, U.S.-based studies could facilitate better understanding of the cost-effectiveness.

Table 1. Overall Strength of Evidence (SoE) Criteria

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Table 2. Summary of evidence for each Key Question 1.

Key Question 1: Evidence of effectiveness of DES compared with BMS			
Outcome	**Efficacy**	**Effectiveness**	**Sources/Results**
Overall mortality up to 4 years	**1 neither favored**	**3 neither favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS consistently report no statistically significant difference in mortality. • Pooled rates for DES were 4.1% and 4.7% for BMS up to 4 years follow-up • There is significant overlap in the trials used for HTAs and meta-analysis Effectiveness: • Data from one previously published HTA's meta analysis of 6 nonrandomized comparative studies and 8 more recently published studies suggest no statistically significant difference in mortality for DES compared with BMS • Of 10 recently published studies, seven reported no statistically significant difference up to 3 years, one reported a statistically significant difference up to 1 year of follow-up favoring DES and three reported higher mortality among BMS patients, two at two years follow-up and one at up to 4.5 years follow-up • Heterogeneity across studies suggested in the meta analysis and diversity of findings in newer studies indicates inconsistency in findings making definitive conclusions difficult. • Overall mortality rates for mortality ranged from 4.5% - 8.5% for DES and 6.1% - 17% for BMS in studies with >1 year follow-up.
Cardiac mortality up to 4 years	**1 neither favored**	**3 neither favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS consistently report not statistically significant difference in cardiac mortality • Pooled rates for DES were 2.4% compared with 2.7% for BMS • There is significant overlap in the trials used for HTAs and meta-analysis Effectiveness: • Data from one previously published HTA's meta analysis of 6 nonrandomized comparative studies suggest no statistically significant difference in cardiac mortality for DES compared with BMS up to 1 year. Heterogeneity across studies prevents drawing firm conclusions. • Only 1 recently published study reported adjusted relative risk estimates for cardiac death: a significant difference in risk of cardiac death was seen between DES and BMS • Cardiac mortality rates ranged were 0.6% and 0.5% at one year in the one new study reporting on this.
MI up to 4 years	**1 neither favored**	**3 neither favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS with follow-up to 4 years consistently report not statistically significant difference in myocardial infarction based on the conventional meta-analysis which is may be more conservative HR, 0.86 (0.67-1.09) • Pooled rates for MI from the network meta-analysis were 4.5% for DES compared with 5.2% for BMS based on cumulative incidence up to 4 years. • There is significant overlap in the trials used for HTAs and meta-analysis Effectiveness: • Meta-analysis in one HTA suggests that there is no significant difference in the risk of MI with the use of DES compared with BMS. • No statistically significant differences at any time up to 3 years were reported in seven of the eight new studies, with one reporting higher MI rates for BMS patients. • Rates ranged from 1.7% - 12.7% for DES and from 2.0- 11.5% for BMS in studies with > 1 year follow-up.
Target vessel revascularization up to 4 years	**1 DES favored**	**3 DES favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS consistently report a statistically significant decrease in TVR or TLR favoring DES • There is significant overlap in the trials used for HTAs and meta-analysis • TVL and TLR rates in RCTs may be partially a reflection of protocol driven

			angiographic follow-up • Rates of TVR ranged from 6% - 9% for DES and were estimated at 19% for BMS based on cumulative incidence up to 4 years. Rates after the first year were lower for all stent types. Effectiveness: • TVR was statistically significantly less common with DES than with BMS in one HTA's meta-analysis, however heterogeneity across studies suggest that pooled results be interpreted cautiously. • One new study found no statistically significant difference at 30 days, whereas 9 others reported statistically significant differences from 30 days up to 3 years. • Rates of TVR or TLR for DES ranged from 0.4 %- 2.5 at ≤ 30 days and from 3.5% - 14.2% from 31 days up to 2 years, compared with BMS ranges from 0.6 %-2.4% at ≤ 30 days and 6.0- 24.4% for up to 3 years in 6 recent studies.
Key Question 1: Evidence of effectiveness of DES compared with BMS- in special populations			
Outcome	**Efficacy**	**Effectiveness**	**Sources/Results**
Overall mortality up to 4 years	**2 unclear**	**4**	Efficacy: Diabetic Patients • Previously published HTAs provide little data on special populations • The largest recently published meta-analyses suggest that a 2 fold increase in morality was associated with SES use compared with BMS if patients had less than 6 months of dual anti-platelet therapy. No significant differences in morality were found between treatment groups when 6 or months of anti-platelet therapy were used. • In patients having ≥ 6 months dual anti-platelet therapy, cumulative rates were 7.5% for DES and 7.6% for BMS. • There is some overlap in the trials used for in meta-analysis Effectiveness: Diabetic Patients • Specific discussion of overall mortality in diabetic patients was found in two technology assessments, one which relied on previously done meta-analyses [KCE] and the other which performed their own meta-analysis [Ontario 2007]. Results from these and two recently published registry studies are mixed with respect to overall mortality and cardiac death comparing DES and BMS.
Cardiac mortality up to 4 years	**2 unclear**	**4**	Efficacy: Diabetic Patients • Previously published HTAs provide little data on special populations • The largest recently published meta-analysis suggests a 2 fold increase in cardiac morality was associated with SES use compared with BMS if patients had less than 6 months of dual antiplatelet therapy. No significant differences in morality were found between treatment groups when 6 or months of anti-platelet therapy were used. • Cumulative rates of cardiac death in the network meta-analysis were 4.8% for DES and 4.2% for BMS in patients with ≥ 6 months anti-platelet therapy Effectiveness: Diabetic Patients • Specific discussion of overall mortality in diabetic patients was found in two technology assessments, one which relied on previously done meta-analyses [KCE] and the other which performed their own meta-analysis [Ontario 2007]. Results from these and two recently published registry studies are mixed with respect to overall mortality and cardiac death comparing DES and BMS.
MI up to 4 years	**2 unclear**	**4**	Efficacy: Diabetic Patients • No differences in the risk of myocardial infarction were seen in diabetic patients, regardless of dual anti-platelet therapy in the largest and most complete recent meta-analysis at up to 4 years of follow-up. Two analyses with fewer trials suggest that at shorter follow-up times (6-24 months), DES may result in a lower risk of MI. Differences in the number and types of included trials and definitions of MI may contribute to difference found between the analyses. • Cumulative MI rates were 5.8% for DES and 7.4% for BMS patients with ≥ 6 months anti-platelet therapy. Effectiveness: Diabetic Patients • Two registry studies report no statistical difference between DES and BMS.

Target vessel revascularization up to 4 years	**1 DES favored**	**3 DES favored**	Efficacy: Diabetic Patients • Outcomes for diabetic patients were examined in 3 HTAs, 4 meta-analyses and 1 RCT suggest that both TLR and TVR rates are significantly lower in diabetic patients treated with DES than those treated with BMS between 6 months and 4 years following stenting. • Cumulative TLR rates form the network meta-analysis were 9.7% for DES and 22% for BMS among diabetic patients with ≥ 6 months anti-platelet therapy. Effectiveness: • One report describes findings from RCT sub-analyses and one registry study [Hayes]. Findings from both types of studies suggest that TVR is less frequent among diabetic patients who received DES compared with those who received BMS

Table 3. Summary of evidence for each Key Question 2.

Key Question 2: Evidence of safety		
Outcome	**Safety**	**Sources/Results**
Stent thrombosis up to 4 years	**2**	Safety • Previously published HTAs and recently published meta-analyses of up to 35 RCTS draw somewhat different conclusions. Most HTAs indicate that that there were no statistically significant differences in stent thrombosis when DES were compared with BMS, particularly at longer follow-up times, several note that studies and even some meta-analyses may have been underpowered to detect statistically significant differences between treatment groups. In the most recent meta-analysis no statistically significant differences in stent thrombosis in studies with up to 4 years follow-up. • Small numbers of events coupled with heterogeneity across included trials suggest that estimates could change as additional data are collected. • There is significant overlap in the trials used for HTAs and meta-analyses. • Based on ARC definition of definite thrombosis, rates from the most recent meta-analysis based on up to 4 years of follow-up were 1.4% for SES, 1.7% for PES and 1.2% for BMS.
Late Stent thrombosis	**2**	• Previously published HTAs and recently published meta-analyses of up to 35 RCTS draw somewhat different conclusions. Many HTAs concluded that significant differences between treatment groups may not have been evident because of small sample size and suggest DES are associated with long term risk of stenosis. • In the most recent meta-analysis for RCT data, a statistically significant differences in ARC defined definite stent thrombosis was seen between > 30 days and 4 years when PES were compared with BMS., HR 2.11 (0.19, 4.23). Wide confidence intervals and moderate heterogeneity across included studies were noted. No statistically significant differences for the SES versus BMS comparison were seen for this same (or any other) time period. • Rates in 5 recent non-randomized studies ranged from 0- 0.9% for DES and 0.1%-3.5% for BMS
Bleeding with prolonged anti-platelet therapy	**4**	• No comparative studies were found. • From 3 case series, cumulative incidence for bleeding ranged from 1.8%-4.0% up to 18 months of follow-up
Stent fracture	**4**	• No comparative studies were found • Rates for stent fracture from 6 case series ranged from 1.9%-7.7% and one case series reported 18% in patients with in-stent stenosis
Key Question 2: Evidence of safety – Special populations		
Outcome	**Safety**	**Sources/Results**
Stent thrombosis up to 4 years	**3**	Safety –Diabetic patients • Previous HTAs provide little information on the risk of stent thrombosis (acute, sub-acute or late) in diabetic patients. • Recent meta-analyses consistently report no statistically significant difference in stent thrombosis by last follow-up regardless of dual anti-platelet therapy duration based on cumulative incidence of events from 0-4 years. Cumulative rates were 1.6% for DES and 2.3% for BMS in patients with ≥ 6 months anti-platelet therapy. • It is possible that even this largest meta-analysis had insufficient power to detect a difference between DES and BMS in the risk of late stent thrombosis in particular, given that it is a relatively rare event. • One previous report describes data from one large registry of 708 consecutive diabetic patients. While the authors state that in-stent thrombosis was more frequent in DES patients (2.4%-4.4%) versus BMS recipients (0.8%) they don't provide results of any statistical testing.
Late Stent thrombosis	**3**	Safety –Diabetic patients • No statistically significant differences in stent thrombosis were seen between treatments either early (0-30 days) or late (>30 days to 4 years) in network meta-analysis restricted to those who had ≥ 6 months dual anti-platelet therapy. However, wide confidence intervals indicate lack of estimate stability and small numbers of events. • No data from recent non-randomized studies were found for late stent thrombosis in diabetic populations

Table 4. Summary of evidence for each Key Question 3.

Key Question 3 Conclusions from economic analyses		
Outcome	**Cost-effectiveness**	**Sources/Results**
ICER	**4**	Economic analyses • HTA reviews of 43 cost effectiveness studies, and from 5 additional full cost effectiveness analyses suggest that DES in comparison with BMS are not cost effective across populations. • There is significant variability with regard to methodological quality and consistency of findings across studies • The ranges for ICERs are large, depending on modeling, outcomes chosen and perspective • Most HTAs concluded that DES may be cost effective in selected groups of higher risk patients, with multiple risk factors, such as long lesions, narrow vessels, complex lesions, diabetics and patients recently post MI. • Methodologically rigorous studies that are US-based are needed

APPRAISAL

Comparison of Drug Eluting Stents with Bare Metal Stents in Coronary Artery Revascularization

Final Scope

Rationale for the Appraisal

Cardiac stents provide one option for treating coronary artery disease. Since their inception, they have become used widely for a variety of indications and lesion characteristics and much research has been done on both BMS and a variety of DES. The literature overall is voluminous and complex. The technology has undergone rapid change in the past decade. The current literatures provide a snap shot of the technology and it is recognized that, as with all technologies, reports in the medical research literature lag a bit behind the changes.

Stents are typically indicated for patients with symptomatic ischemic heart disease associated with stenotic lesions in native coronary arteries. The current FDA approved indication is for the placement of a single stent in arteries with newly identified lesions less than 28-30 mm in length and ranging from 2.5 - 5.0 mm in diameter. The specific indications for lesion length and diameter vary for different brands of stents. Stents are not indicated for patients who are allergic to the stent materials or cannot tolerate angioplasty or anti-platelet medications.[1, 2.] A brief evaluation of patient characteristics involved in clinical trials for FDA-approved cardiac stents revealed the following: 60-70% of patients were male, the mean age was 60-70 years, more than half of patients had hypertension, and/or hypercholesterolemia. Although pivotal RCTs of drug eluting stents restricted enrollment to single-vessel stenosis, some studies included patients with multi-vessel disease. In these studies, approximately 60-70% of patients had one vessel involved, 20% had two, and 10% had three.[3]

Characteristics of patients encountered commonly in clinical practice may or may not differ from those of patients enrolled in the FDA trials. One or more vessels may be involved and/or narrowing may not be confined to a small or isolated region of a vessel in a large percentage of patients seen in a cardiology practice. Use of stents in multiple vessels, use of multiple stents in the same vessel or in vessels with diameters or lesion lengths not currently included in the FDA approved indications have become increasingly common. Such uses account for as much as 70% of all stent placements even though such uses are not part of the originally approved situations and the related research on the safety and efficacy. Thus, there are some uncertainties regarding the evidence for use of cardiac stents (bare-metal or drug-eluting) for more complex indications outside of the uses studied and approved by the FDA including the following:

1. The effectiveness of stent use in multiple vessels or multiple stents in the same vessel or in vessels with different vessel diameter or lesion length compared with

approved indications and with other methods of treatment in patients with intermediate disease.
2. The safety of implanting multiple stents in such patients and the comparative safety with regard to other treatment options.
3. How to identify patients or sub-populations who might benefit most (or least) from use of stents for situations outside of those studied for FDA approval and what decision points may be important to consider when weighing treatment options in patients with intermediate disease in particular.
4. The impact of patient preferences and physician self-referral.
5. The budget impact and cost-effectiveness of uses of stents outside of those approved by the FDA and studied in the trials leading to approval including downstream costs related to better outcomes or increased complications and quality of life.
6. How clinical guidelines or pre-authorization criteria describe use of stents outside of the original FDA indications.

These and other questions about stent use overall and the evidence base related to various uses of stents are important and beyond the scope of this report.

As a first step in understanding the potential benefits, limitations, safety, and uses of cardiac stenting, this report focuses on comparison of bare metal stent (BMS) with drug eluting stents (DES) in patients. Specific questions related to this focus include the following:

1. Are there any differences in clinical outcomes related to efficacy or safety (e.g based on clinical outcomes such as mortality, myocardial infarction, thrombosis) when DES are used compared with BMS?
2. What is the budget impact and cost-effectiveness of DES compared with BMS?
3. Are there special populations that may benefit from the use of DES instead of BMS?

Objective

The primary aim of this assessment was to systematically review, critically appraise and analyze research evidence comparing the safety and efficacy of bare metal stent (BMS) with drug eluting stents (DES). Available information on the economic impact of this will also be summarized and critically appraised.

Key questions

Specific key questions, as formulated by the HCA/Agency to be addressed are listed below:

In patients with CHD undergoing stenting of coronary vessels:

1. What is the evidence of efficacy and effectiveness of drug eluting (DES) versus bare metal stents (BMS)?
   - Including any effects on special populations, such as patients with and without diabetes, after myocardial infarction and not after

myocardial infarction; and in different vessel and lesion characteristics.

2. What is the evidence related to the safety profile of DES versus BMS?
   - Including in patients with and without continuation of anti-platelet medications.

3. What is the evidence of cost effectiveness and cost implications of DES versus BMS?
   - Including any effects of pharmacologic therapy and reintervention.

Outcomes

The issues of safety and efficacy are intertwined and difficult to separate. This is particularly true for DES since the use of anti-proliferative drug which are an integral part of DES provide both the mechanism which can lead to the prevention of in-stent stenosis (as intended) and potentially the mechanism by which thrombosis may occur due to the interaction between the coagulation process and a non-endotheliazed stent[4]. The separation of efficacy and safety outcomes in this reports is thus, some what artificial.

The primary focus of revascularization should be the improvement in clinical health outcomes (e.g. mortality, freedom from MI). Such outcomes have been a primary focus in many technology assessments and meta-analyses and they are the primary outcomes reported in this assessment.

For purposes of this report the following outcomes will be discussed under efficacy and effectiveness for studies comparing DES versus BMS:

- Primary outcomes: Death, cardiac death, myocardial infarction
- Secondary outcomes: target lesion revascularization or target vessel revascularization

The following outcomes will be discussed under safety for studies comparing DES versus BMS:

- Thrombosis
- Peri-procedural complications (MI, stroke)
- Bleeding following anti-platelet therapy
- Stent fracture

The primary endpoints for most clinical trials have been composite outcomes, target vessel revascularization or lumen loss and by design, powered to find differences with respect to those endpoints.

Composite outcomes reported in different studies of DES versus BMS were defined differently by different trials and reviews, combined critical outcomes like death with less serious outcomes like nonfatal MI, and included potentially non-objective outcomes which may have been protocol driven like revascularization. For these reasons, and to

avoid obscuring results of important component outcomes, in this assessment we are reporting the results of individual components, rather than composite outcomes.

Key considerations highlighted by clinical experts:

1. **Interventions**

   While it is true that medical technology is always evolving, and this year's stent may differ slightly from last year's it does not follow that this year's device is better than the last year's device. Often, the differences are of no clinical significance. Thus, without actual data to show that the latest technology is better than the previous one, one cannot make this assumption. It is equally true that the latest technology may have risks not present in the previous versions.

   What is most notable about stents in general and DES in particular, is that their adoption has outpaced the clinical evidence of benefit. Stenting does not improve clinical outcomes compared with medical therapy for stable CAD, yet the use of stents for this indication has grew[5-7.] In addition, after the introduction of DES in 2003, they rapidly grew to 90% of the stent market in a few years. Despite the lack of data of benefit of use in stable CAD and in situations outside FDA approved indications had increased[8-11]. The majority of DES is currently used "off-label".

   Data of benefit is strongest in the highest risk population – STEMI and ACS. Yet, most stents are used in stable CAD and in a growing number of asymptomatic patients who have no known benefit from this technology[5, 12]. Both internists and cardiologists may favor stents to medical therapy for patients with no or atypical symptoms of CAD, despite acknowledging that no studies have shown a clinical benefit for these indications. Doctors cite many reasons for such behavior, including: fear of being sued, belief that patients prefer stents, belief that an open artery is better than medical therapy and ease of insertion of a stent once patient is in cath lab. The fact that cath/PCI is almost always done as one procedure in one sitting with one consent process may have contributed to increased use of PCI for stable CAD that used to be treated with medical therapy in previous years. [13]

   The reproducibility and variability of percent luminal stenosis by angiography is poor. In addition, disparities are seen between intravascular ultrasound findings and coronary angiography, leading some to question the reliability of coronary angiography.

   Conventional meta-analyses with long term follow-up have not found a significant difference in death or MI with SES or PES compared with BMS. Meta-analyses consistently found significantly decreased risks of revascularization with SES or PES compared with BMS. Meta-analyses found increased risks of thrombosis with SES or PES compared with BMS from 1 to 4 years after stent placement; however, most of these increased risks did not reach statistical significance. The decreased risks of

revascularization with DES must be balanced against the increased risks of stent thrombosis[11]. The trade-offs involved may be valued differently by different patients, and should be discussed with them.

One approach is comparing the absolute incidences of revascularization and thrombosis. Since differences in thrombosis rates do not present for at least 1 year after stent placement, those trials or meta-analyses with longer follow-up times should be used for those comparisons. For example, Stone et al[14] provide incidence rates for target lesion revascularization of 7.8% with SES vs 23.6% with BMS ($p < 0.001$) and 10.1% with PES vs 20.0% with PES ($p < 0.001$) during 4 years after stent placement. In contrast, they report incidence rates for thrombosis of 1.2% with SES versus 0.6 with BMS ($p = 0.20$) and 1.3% with PES versus 0.9% with BMS ($p = 0.30$) during 4 years after sent placement. Although the relative risks of thrombosis with DES versus BMS (as presented in the results) appear large, the absolute risks are small.

Another approach is comparing a short-term benefit with a future risk. Some patients may feel short term time is more valuable than future time, so a lower risk of revascularization in the short term would seem more desirable than a higher risk of thrombosis in the future.

Yet another approach is considering the clinical importance of revascularization compared with thrombosis. Revascularization occurs in 10% to 20% of patients, but is associated with about 3.5% risk of death or nonfatal MI. Stent thrombosis occurs in about 1% of patients, but is associated with about 90% risk of death of nonfatal MI[15]. Some patients would rather avoid a rare but serious outcome more than a frequent but benign outcome.

2. **Costs:**
   Costs of DES compared to BMS are significant. Evaluation of cost-effectiveness is a complex process and there are conflicting results across studies. A recent cost-effectiveness analysis done by NICE in Great Britain found that use of DES was not cost-effective for most stable CAD. In contrast, some studies have suggested that DES may be cost effective in certain populations.

3. **Patient considerations**
   Relief of symptoms and a desire to avoid extensive procedures may be the most important factors to patients. Placement of stents during angiography instead of having a separate procedure may be attractive to many patients.

   It has been shown that patients have an inaccurate and at best incomplete understanding of the benefits and risks of PCI. For example, 75% of patients believed that PCI would prevent heart attacks[16]. A study of patients undergoing elective stenting showed that many believed it had to be done on an emergency basis, and more than two thirds believed that stenting would prevent heart attacks. Two thirds of patients getting PCI for stable CAD said they had not been offered any alternative.

Data on informed decision making show that patients are less likely to choose PCI when fully informed of the benefits and risk of PCI versus medical therapy. Groups such as the Foundation for Medical Decision Making (FMDM) and Health Dialog have developed and use patient decision making aids for stable CAD.

4. **Professional considerations:**
The American College of Cardiology Foundation (ACCF) Appropriateness Criteria Task force, together with the American Heart Association (AHA), Society for Cardiovascular Angiography and Interventions (SCAI), have shown leadership in the development of professional guidelines in general, and in guidelines for use of PCI in particular. There have been several sets of guidelines for use of PCI.[17, 18] these guidelines have been helpful in codifying the data, but have been criticized as being purposely vague and clinical scenarios not well-defined. To offer more specific criteria for appropriate use of PCI, the ACC/AHA/SCAI recently[19] published Appropriateness Criteria for Coronary Revascularization (ACCR). In the report, risk stratification for traditional exercise testing is as follows:
   - **Low risk** stress test findings are associated with a cardiac morality of < 1% per year.
   - **Intermediate-risk** findings are associated with a 1%-3% per year cardiac mortality.
   - **High-risk** findings are associated with >3% per year cardiac mortality.

   Implicit in the above stratification is determination of the extent of myocardial ischemia or myocardium at risk. However, Lin et al have found that the majority of patients undergoing elective PCI do not have any assessment of myocardial ischemia prior to the procedure[8.] Analysis of the National Cardiovascular Data Registry has shown that patients that get appropriate PCI have better outcomes than inappropriate ones.[20]

   There is great variation in PCI volume between operators, which is correlated to procedural outcomes. Cardiac surgeons complain of being left out of the decision making process of PCI vs CABG, which often occurs in the cardiologists office.

   For some clinicians, legal concerns about not actively addressing obstructive disease may influence use of stents.[13]

5. **Ethical considerations**
Patients often sign a consent for "cardiac catheterization, possible PCI" without understanding the benefits and risk of their treatment choices – medical therapy, PCI and CABG. Generally, the consent for PCI is obtained before the patient is sedated for the cardiac catheter, and the patient is not woken up to discuss treatment options before proceeding to PCI in the same catheter lab setting. Some have suggested that catheter and PCI should not be done as one procedure, to allow an informed discussion of patient choices after anatomy is determined by angiography. The

SYNTAX trial provides a possible model for patient risk assessment and cross-disciplinary evaluation of treatment options.[21]

1. Background

More detailed background information is found in Appendix N.

1.1 The Condition: Coronary artery disease

Coronary artery disease (CAD) is a condition characterized by slow deposition of plaques on the arterial walls and sudden plaque disruption leading to thrombosis below the plaquea.[22] These features cause narrowing (stenosis) of the coronary arteries, impairing the blood supply (ischemia) critical to the wellbeing of heart muscle (myocardium). CAD is the fundamental condition of ischemic heart disease (IHD), characterized by an imbalance between the blood supply to the myocardium and the requirements of the myocardium for oxygenated blood. IHD syndromes include chest pain (angina, stable and unstable), myocardial infarct (MI), heart failure (HF), arrythmias and sudden death. Coronary artery stents have been developed specifically to address the narrowing caused by plaque formation in CAD.

1.2 Epidemiology of CAD

Coronary artery disease (CAD), also referred to as coronary heart disease (CHD), is the single leading cause of death for both men and women in the U.S. and is the most common form of cardiovascular disease. According to the American Heart Association, more than 13 million people have CAD, and approximately 650,000 deaths were due to CAD in the U.S. in 2003, with 221,000 of those resulting from myocardial infarctions (MI). Furthermore, approximately 900,000 Americans are estimated to have a heart attack each year, and approximately 400,000 Americans have stable angina. Men have a 1 in 2 lifetime risk of developing CAD after the age of 40 and women have a 1 in 3 risk; CAD incidence in women lags behind men by 10 years. Although some genetic factors play a role, the major risk factors for CAD development include tobacco use, hypertension, elevated blood cholesterol, and diabetes mellitus. The total of direct and indirect costs of CAD in 2006 was $142.5 billion, with $11.6 billion paid to Medicare beneficiaries ($11,308 per hospital discharge for coronary atherosclerosis)[23.] Reduction in the prevalence, morbidity and mortality related to CAD is an important public health goal given the significant disease burden and contribution to total health care costs.

1.3 Pathogenesis of CAD

An understanding of the basic pathophysiology of IHD and CAD may facilitate appreciation of the strengths and limitations of various treatment options.

CAD begins with the slow deposition of cholesterol, other lipids, calcium, and fibrous tissue including collagen onto the arterial wall. Plaque development can begin in childhood and eventually causes narrowing of the lumen of the coronary vessels, thus restricting blood flow to the myocardium. Coronary artery plaques are responsible for

over 90% of IHD[22]. CAD may be asymptomatic for many years and the onset of symptoms depends on the location and severity of these obstructions; however, the severity of the lesions is poorly correlated with symptoms.

The partial stenosis due to plaque can quickly be transformed into a critical obstruction if there is disruption at the end of a stable plaque. A disruption may lead to bleeding and thrombus formation that can quickly obstruct a narrowed lumen and may result in myocardial death. Disrupted lesions are usually eccentric. They are more likely to be moderately stenotic (50-75% obstructed) and thus less likely to have caused stable angina. Coronary atherosclerotic plaque disruption and associated intraluminal platelet-fibrin thrombus formation are responsible for the acute coronary syndromes of acute MI, unstable angina (UA), and probably for sudden death. Table 1 compares the relative impact of stenosis, thrombosis, and plaque disruption to several IHD syndromes.[22]

Table 5. Comparison of stenosis, thrombosis, and plaque disruption in IHD syndromes[22]

Syndrome	Stenoses	Plaque Disruption	Plaque-Associated Thrombus
Stable angina	> 75%	No	No
Unstable angina	Variable	Frequent	Nonocclusive, often with thromboemboli
Transmural myocardial infarction	Variable	Frequent	Occlusive
Subendocardial myocardial infarction	Variable	Variable	Widely variable, may be absent, partial/complete or lysed
Sudden death	Usually severe	Frequent	Often small platelet aggregates or thrombi and/or thromboemboli

Other physiologic processes may mitigate the impact of atherosclerosis and plaque disruption. Such processes include compensatory arterial vasodilation and development of collateral vessels. Medications that slow the development of plaque or stabilize the plaque (e.g. statins) and medications that impair the formation of thrombosis (e.g. aspirin) have come to play an increasingly important role in controlling CAD.

Angina

The clinical impact of IHD depends on the number, distribution and degree of narrowing by the atheromatous plaques, but the symptoms are not strongly predicted by these features. The most common symptom is chest pain (angina). Classic angina is characterized by retrosternal chest discomfort, often described as a crushing pressure. The discomfort may radiate to the jaw, neck, back, shoulder or arm. It can be accompanied with dyspnea, diaphoresis, nausea and syncope. If the discomfort presents (1) in a predictable pattern, (2) is brought on by physical or mental stress, and (3) subsides with rest or angina medication such as nitroglycerin, it is called **stable angina**.[24] The development of angina suggests that at least one artery has a 75% or greater stenosis. Up to 50% of patients with coronary artery disease present first with angina. Other common symptoms associated with coronary ischemia include dyspnea or early fatigue with exertion, indigestion, palpitations, tightness in the throat, or neck pain. These

symptoms, when documented to be associated with CAD, are called "anginal equivalents." These symptoms are also seen in many common noncardiac conditions including gastroesophageal reflux, esophageal spasm and cervical disc disease. However, many patients have no symptoms at all.

Women and persons with diabetes are less likely to experience classic angina, making early diagnosis of CAD difficult[25.] Because of the poor correlation between symptoms and CAD, clinicians must rely on a careful history and other modalities to detect and confirm a suspicion of CAD. The Canadian Cardiovascular Society has developed a classification system for angina that facilitates quantifying angina for clinical assessment and treatment, Table 6.[26]

Unstable angina (U/A), NonSTwave elevation myocardial infarction (NSTEMI)
Unstable angina is now classified as part of acute coronary syndrome (ACS). A change in the anginal pattern may signal a significant decrease in coronary perfusion. Angina that occurs with less exertion, causes greater discomfort, or takes longer than 20 minutes to subside may be an ominous warning of critical ischemia and has been termed unstable angina. Electrocardiographic (ECG) changes of ST depression noted during angina suggest ischemia. The location of the ST depression indicates which arteries are involved. Unstable angina is defined by the clinical syndrome described above plus ST-T wave depression, T wave inversion, and increase in troponins. Another syndrome with similar clinical presentation to UA, but results in death of the myocardium (myocardial infarction (MI)), is called non-ST wave elevation myocardial infarction (NSTEMI). The symptoms, ECG, and labs on presentation are similar for UA and NSTEMI, so they are often grouped together for clinical assessment and management.

Table 6. Grading of Angina pectoris by the Canadian Cardiovascular Society Classification System[26]

Angina Class	Effect of angina on activity level	Causes of angina
Class I	Ordinary physical activity, such as walking or climbing stairs, does not cause angina.	• Strenuous, rapid, or prolonged exertion
Class II	Some limitations of regular activity	• Walking; • Climbing stairs; • Rapidly walking uphill; or • Walking or climbing stairs: o after meals o in cold o in wind o only within the first few hours after awakening o Walking more than 2 blocks (level); and o Climbing more than one flight of stairs at a normal pace and in normal condition
Class III	Significant limitations of normal physical activity	• Walking 1-2 blocks; and • Climbing 1 flight of stairs under normal conditions and at normal pace
Class IV	Inability to carry on any normal physical activity without discomfort.	• Angina may occur while at rest

Myocardial infarction (MI)

MI is defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Criteria for an MI include any of the following:

- detection of rise and or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile with symptoms of ischemia, ECG changes, development of Q-waves or imaging evidence of a new loss of viable myocardium or new regional wall motion defect.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, ST elevation, new left bundle branch block (LBBB), or fresh thrombus on angiography or autopsy.
- PCI with normal baseline troponin PLUS post-procedural elevation of the troponin level three times greater than the 99th percentile suggesting peri-procedural myocardial necrosis.
- CABG with normal baseline troponin PLUS post-procedural elevation of the troponin level five times greater than the 99th percentile, new pathological Q-waves or new LBBB, new graft or coronary artery occlusion, or imaging evidence of new loss of viable myocardium. All these would be suggestive of a peri-procedural myocardial necrosis.
- Pathologic findings of an acute myocardial infarction.

A prior MI can be detected by the development of new Q-waves, imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, or pathological findings of a healed or healing myocardial infarction.[27]

An acute MI is suggested by ST elevation, and thus is called ST elevated MI (STEMI). The EKG changes can begin within minutes of the onset of the severe, acute ischemia and evolve over several days as the myocytes die (see diagnostic tests). Within a few minutes, the dying cells will leak cardiac biomarkers (troponin) into the serum, which generally increase over the next 24 hours, then resolve back to normal over 3-5 days. Immediate coronary angiography may show the stenosis or blockage. Immediate echocardiography may show decreased (hypokinesis) or absent muscle function of the affected area, and may even show the development of a ventricular wall aneurysm. Radionucleotide imaging will show a new perfusion defect in the damaged area. MI may be the first presentation of CAD and IHD. Up to a third of persons with MI report no prior diagnosis of CAD or angina.

Acute Coronary Syndrome (ACS)

UA, NSTEMI and STEMI all signal a severe potential threat to the myocardium and are often grouped together as acute coronary syndrome (ACS) for clinical assessment and management.

Arrythmias and sudden death

Other symptoms associated with coronary artery disease may include palpitations, syncope and sudden death. Palpitations and syncope are non-specific signs and are not always associated with CAD.

Heart failure

Fluid retention in the ankles (pedal edema) and lungs (pulmonary edema) may signal that CAD has damaged the heart muscle, causing heart failure.

1.4 Diagnostic testing for CAD and IHD

The symptoms of CAD have poor specificity and sensitivity for CAD, so other tests must be used to confirm or refute a clinical suspicion of CAD. Most of the diagnostic testing for IHD evaluates the impact of ischemia on the myocardium. Only angiography and coronary artery ultrasound provide direct information on the condition of the coronary arteries. Multi-slice cardiac computed tomography angiography (CCTA) may provide information on cardiac vessels as well as an adjunct to other non-invasive tests. Findings from these studies assist in risk assessment and decision making regarding treatment. Tests commonly used in evaluation of CAD include:

- Electrocardiography (ECG)
- Cardiac biomarkers
- Echocardiography (including stress echocardiography)
- Radionucleotide imaging
- Angiography
- Computed tomography angiography

Additional detail on these is found in Appendix N.

1.5 Risk Conditions associated with CAD

The risk of developing CAD is increased with age, male sex, tobacco use, high blood pressure, high serum total cholesterol and low-density lipoprotein (LDL) cholesterol, low serum high-density lipoprotein (HDL) cholesterol, and family history of premature CAD, especially if it occurs in men under the age of 55 years or in women under the age of 65 years. Diabetes mellitus, metabolic syndrome, physical inactivity and obesity are also associated with an increased risk of CAD. Other risk factors include non-white ethnicity and stress[26, 28-30]. A number of risk stratification systems have been developed to help patients and clinicians in the complex decision making associated with IHD.

Framingham Risk Scoring System – This cardiovascular event risk scoring system was developed from a prospective, longitudinal, observational study of a community in the Boston area conducted by the National Institutes of Health[31]. The risk of developing a "hard" cardiovascular event of MI or cardiovascular death in the next 10 years can be calculated based on age, sex, tobacco use, blood pressure, total cholesterol, HDL cholesterol, prior MI and the presence of diabetes[32]. However, the study population consisted of white patients and may not predict accurate risk for non-white populations. Risk assessments can guide both primary and secondary prevention efforts for hypertension and lipid management, but are not accurate enough to provide specific guidance on which patients should be evaluated further for CAD. This risk assessment scoring system is available on the web[29]. Framingham: http://hp2010.nhlbihin.nte/atpiii/calculator.sap?usertype=prof

Other risk systems have been developed to assist management of a patient on presentation with ACS. These tools can provide guidance on surveillance and treatment measures. All three may be used at hospital admission.

TIMI Risk Score – The Thrombolysis in Myocardial Infarction (TIMI) Risk Scoring system was developed during a clinical trial of patients with UA/NSTEMI (non-ST elevation MI) to predict the 14-day risk of all cause mortality, MI and the need for urgent revascularization. The system uses data that is readily available at the time of presentation to an emergency room and requires a simple addition of dichotomous variables. The scoring system is highly predictive of a range of outcomes and has been used to assign treatment[20, 24, 33].

GRACE Risk Model – The Global Registry of Acute Coronary Events (GRACE) Risk Model was developed on the basis of patients in GRACE and predicts in-hospital mortality, composite of in-hospital mortality or MI, and 6 month risk of all-cause mortality in patients presenting with NSTEMI-ACS, STEMI or, UA. It is used to provide a basis for guiding treatment type and intensity.[20, 34, 35]

PURSUIT Risk Model – The Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Risk Model is based on patients enrolled in the PURSUIT trial presenting with NSTEMI-ACS. The model is used to provide a basis for therapeutic decision making and evaluates critical factors associated with an increased 30-day risk of death and the composite of death or (re)MI. [20, 24, 36]

Table 7. Risk stratification tools for ACS at presentation to hospital

Risk stratification tool	When used	Patient presentation	Factors considered in risk assessment	Predicts
TIMI Risk Score[20, 24, 33]	At hospital admission, used to provide basis in therapeutic decision making	NSTE-ACS	1 point given for each of the following variables at admission: • Age ≥65 years • ≥3 risk factors for CAD • Prior coronary stenosis of ≥50% • ST-segment deviation on ECG presentation • ≥2 anginal events in prior 24 hours • Use of aspirin in prior 7 days • Elevated serum cardiac biomarkers	14-day risk of composite outcomes: • All-cause mortality • New or recurrent MI • Severe recurrent ischemia requiring urgent revascularization
PURSUIT trial Risk Model[20, 24, 36]	At hospital admission, used to provide basis in therapeutic decision making	NSTE-ACS	Associated with increased risk (in order of strength): • Age • Heart rate • Systolic blood pressure • ST-segment depression • Signs of heart failure • Elevated cardiac enzymes	30-day risk of: • Death • The composite risk of death or (re)MI
GRACE study Risk Model[20, 34, 35]	At hospital admission, used to provide basis in guiding treatment type and intensity	NSTE-ACS, STEMI	• Older age • Killip class • Systolic blood pressure • ST-segment deviation • Cardiac arrest during presentation • Serum creatine level • Positive initial cardiac markers • Heart rate	• In-hospital mortality • Composite risk of In-hospital mortality or MI • 6-month risk of all-cause mortality

GRACE: Global Registry of Acute Coronary Events, NSTE: Non-ST-segment elevation acute coronary syndrome (includes UA/NSTEMI), TIMI: Thrombolysis in Myocardial Infarction, PURSUIT: Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy.

1.6 Treatment of CAD

Primary Prevention of CAD:
The American Heart Association recommends that everyone over the age of 40 be assessed for absolute risk of developing CAD at least every 5 years[30.] The Framingham risk scoring system provides a useful framework to discuss the risk and identify modifiable risk factors[37.] High quality evidence supports recommendations for smoking cessation, blood pressure, and lipid control to reduce the risk of developing CAD. Persons over age 50 can reduce their risk of sudden death due to CAD by taking an aspirin 81 mg-325 mg every day.

Secondary Prevention of CAD/IHD:
Once a person is diagnosed with CAD, should obtain baseline evaluation including an ECG, blood pressure determination, fasting lipid and glucose levels, and a risk factor assessment. Modifiable risk factors should be addressed.[18]

Evaluation with echocardiogram may identify patients with long-standing hypertensive heart disease or heart failure. A stress test (exercise or pharmacologic) will identify the degree and location of ischemia. A negative stress test may suggest that the symptoms are due to some other cause. Further evaluation will depend on the patient's symptoms, risk factors, and findings on stress testing and will be discussed below.

In general, persons with angina already have CAD lesions with at least 75% obstruction and are at increased risk of MI, heart failure and sudden death due to plaque destabilization and thrombosis. Evidence-based recommendations for medical management are now advised for all persons with CAD[38.] Medical management includes:

- Aspirin - to provide antithrombotic effect.
- Beta blocker - to decrease the sympathetic system that may set off a plaque disturbance.
- Statin to reduce further buildup of plaque and provide stabilization of the endothelium.
- ACE-inhibitors should be considered for those with metabolic syndrome, diabetes, or heart failure. This medication has been shown to slow kidney decline and improve heart failure management.
- Blood pressure control – should start with beta blockers as noted above. ACE inhibitors and calcium channel blockers can be added as needed.

The ACC/AHA suggests the goals for treatment of stable angina are to (1) prevent MI and death and (2) reduce the occurrence of ischemia and (3) eliminate (or nearly eliminate) the symptoms of angina so that the patient can resume normal activities. The latter goal is often the patient's greatest concern[26.] Patients should be given nitrates and

clear instructions on how to use them. Patients should be encouraged to maintain an active life style. Issues around exertion, and sexually activity should be discussed and patient concerns addressed.

Tertiary prevention

The management of patients with advanced CAD and IHD has been addressed in a number of guidelines by professional organizations. Both the disease and intervention guidelines describe the stent technology that is the focus of this assessment.

The evolution of percutaneous coronary intervention (PCI) from balloon angioplasty to stenting

PCI relieves coronary narrowing by utilizing a mechanical device (usually a balloon) at the end of a catheter to dilate an area of stenosis within the coronary artery. Access to the heart and coronary arteries is typically obtained through the femoral artery. The catheter is advanced into the ascending aorta and then threaded into the coronary artery. Angiography is then performed by injecting radiopaque dyes through the catheter tip to delineate the coronary artery anatomy and identify possible areas of stenosis. If a significant stenotic area is identified, the catheter tip can be advanced to that area and the balloon inflated to dilate the arterial lumen and compress the plaque. The balloon is then deflated and the catheter removed. This process, called a balloon angioplasty, was initially termed "percutaneous transluminal coronary angioplasty" (PTCA). The term "percutaneous coronary intervention (PCI)" is often used to include balloon angioplasty, stenting and artherectomy. Except where noted, PCI will be used in this document to refer to PCI with stenting.

PTCA was first introduced in 1977 as the first non-surgical means of dilating the coronary artery.[39] Initially, the success rate was only 64%, with emergency CABG required in 14%, but over time, with increasing experience, the success rate grew to around 90%.[40] However, balloon dilation injures the vascular wall, resulting in a variety of morphological changes, including (1) endothelial denudation and rapid accumulation of platelets and fibrin; (2) plaque disruption, causing intimal dissection, medial tearing, and aneurismal dilation of the media and adventia; (3) elastic recoil; and (4) post-injury arterial narrowing (constrictive negative remodeling). These changes or "controlled injuries" are responsible for acute vessel closure and restenosis, two of the major disadvantages of PTCA. Acute vessel closure typically occurs in 6-8% of cases within 24 hours following PTCA. Restenosis, defined as greater than 50% reduction in post-procedural luminal diameter, often manifests within the first 6 months after PTCA with rates ranging from 30% to 50%.[41]

The high rates of acute vessel closure and restenosis following PCI were the predominant factors that led to the development of bare-metal stents (BMS), as well as to widen the lumen and ensure a uniform shaped opening of the artery at the site of the plaque. A stent is a stainless mesh tube that can be collapsed and attached to the end of a balloon catheter. When the catheter tip is floated to an area of stenosis, the balloon is inflated to

expand the stent. The balloon is then deflated and detached from the stent. The stent remains in the artery permanently to act as a physical scaffold to help keep the artery open. BMS were first introduced in 1986[42] and approved by the U.S. Food and Drug Administration (FDA) in 1993.[41]

As reported by Newsome et al 2008, a 10% decrease in restenosis rates, 22% to 32%, was observed in patients receiving BMS (versus PCI alone) in premarket clinical trials that led to FDA-approval of these devices. Although many efforts were made to further decrease the incidence of restenosis, rates within six months of BMS implantation remain high at 20-25%. These rates are even higher in patients with complex lesions or other serious disorders (diabetes, renal insufficiency) and the incidence has been reported to approach 80% in such populations. Furthermore, approximately 60-80% of restenotic lesions require repeat revascularization[43.] As stated previously, restenosis is caused primarily by elastic recoil and neoinitimal hyperplasia. Because stents were designed to prevent elastic recoil and negative remodeling, restenosis following a BMS is primarily caused by neointimal proliferation, an inflammatory response that results in vessel lumen encroachment.[18] Another complication of BMS is subacute stent thrombosis (blood clot formation) which initially occurred in 4-24% of BMS patients.[44-49] However, addition of dual-antiplatelet therapy (clopidogrel and aspirin) as well as refinement of the stent placement procedure reduced the occurrence of BMS thrombosis to the current rate of 1.2%.[50-52]

The continued difficulties with early restenosis and thrombosis with BMS led investigators to explore ways to modify the stent to minimize these adverse outcomes, leading to the conception of drug-eluting stents (DES). DES are essentially BMS that have been coated with a polymer containing an antiproliferative drug. These drugs inhibit vascular smooth cell proliferation and migration and are released from a non-resorbable polymer into the local environment to achieve high local drug concentrations. The drug is intended to prevent the neo-intimal hyperplasia that appeared to cause the restenosis observed with BMS implantation. According to Newsome et al, when compared with BMS, DES have been shown to reduce neointimal hyperplasia, restenosis, and reintervention at 6 to 12 months, with a continued 74% reduction in restenosis at 4 years.[41]

However, despite the reduction in restenosis rates, reports of high rates of subacute in-stent thrombosis (clot formation) after DES placement became cause for concern soon after FDA approval of these devices.[53, 54] Thrombosis is a serious complication that often results in acute MI or death. The FDA convened an advisory panel meeting in 2006 to review the data on DES and concluded that DES did not increase the risk of in-stent thrombosis if used for their approved indications (on-label use): lesions that were newly diagnosed, less than 28-30mm long, and in clinically stable patients without other serious medical problems. The risk of in-stent thrombosis reported ranged from < 1% to approximately 5% in patients with complex lesions and those with renal dysfunction or diabetes and indicate that premature discontinuation of anti-platelet therapy is an independent risk factor[2.] It is estimated that at least 60% of DES use is off-label,

meaning that stents are implanted in patients who do not meet the criteria of the premarket clinical trials. The FDA concluded that off-label use of DES, such as implantation in complex lesions (e.g., bifurcation lesions, lesions requiring overlapping stents, or lesions from acute MI) or in patients with conditions such as renal dysfunction or diabetes contributed to increased rates of stent thrombosis.[2, 44, 47, 55] Thrombotic occlusion of stents has been and remains a concern since the early days of stenting.

In 2002, all stents were BMS. Within a year after the FDA approval of the first DES stent, 75% of all PCI utilized a DES stent,[56] and by 2005 nearly 90% of all PCI utilized a DES.[57] DES were used in approximately 80% of PCI procedures in the U.S. [2] By 2003, an estimated 84% of PCI patients received a stent,[23] and today, virtually all PCI procedures involve placement of a stent.[55]

To date, the FDA has approved four DES to treat symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries. The first DES to be approved by the FDA were sirolimus- and paclitaxel-eluting stents (Cypher©, Cordis Corporation and Taxus©, Boston Scientific) in 2003 and 2004. Sirolimus is a macrolide immunosuppressant that also inhibits mammalian target of rapamycin (mTOR) thereby blocking cell division by interfering at the transition from G1 to S phase.[58] Paclitaxel is a derivative of the yew plant that inhibits the cell cycle by stabilizing microtubules and has been used as an anti-proliferative drug in the treat of breast, lung and ovarian cancer.[59] In 2008, two other DES were approved: zotarolimus- and everolimus-eluting stents (Endeavor©, Medtronic Vascular and Xience©, Abbott Vascular). Zotarolimus is a tetrazole-containing immunosuppressant. Its mechanism of action has not been established conclusively but *in vitro* research suggests that zotarolimus binds to FKBP-12, leading to the formation of a trimeric complex with the protein kinase mTOR inhibiting its activity thus halting cell division, much like sirolimus.[60] Everolimus is a novel semi-synthetic macrolide immunosuppressant synthesized by chemical modification of rapamycin (sirolimus). At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, it binds to and interferes with FKBP-12, leading to the inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 phase.[61]

Indications, contraindications for FDA-approved DES and BMS
Detailed product information by stent type is provided in Appendix N.

FDA indications for the four FDA-approved DES are for the treatment of symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries with lesion lengths ranging from ≤ 2.8 mm – 3.0mm, and vessel diameters from 2.5 mm-4.25mm, depending on the specific stent.

Contraindications for FDA-approved DES include.[60-63]

- Patients with a hypersensitivity to stent components, including the drugs and their derivatives, polymers used to coat the stent, and the metals the stent is composed of.

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.

To date, the FDA has approved nine BMS, to include two coated stents, to treat symptomatic ischemic disease in patients with *de novo* lesions in native coronary arteries with lesion lengths ≤ 18mm – 30mm and vessel diameters of 2.75mm -5.0 mm, depending on the specific stent.

Complications
Major complications associated with PCI with stent placement (both BMS and DES) include death, acute MI, and stroke. Other complications include aneurysm, arrythmias, coronary perforation or dissection, distal emboli, intracoronary thrombosis, heart failure, infection, pericardial effusion, prolonged angina, renal failure, respiratory failure, tamponade, and vessel trauma requiring surgical repair.[18] In addition, abrupt stent closure, stent compression, stent facture, stent migration, incomplete stent apposition, failure to deliver the stent to the intended site, and allergic or drug reactions may occur.

Multiple Stents
In practice, stent placement has become increasingly common in situations outside FDA approved indications. Characteristics of patients encountered commonly in clinical practice may differ from those of patients enrolled in the FDA trials. One or more vessels may be involved and/or narrowing may not be confined to a small or isolated region of a vessel in a large percentage of patients seen in a cardiology practice. Use of stents in multiple vessels, use of multiple stents in the same vessel, in left main disease; placement at a branch; emergent clinical presentation; or in vessels with diameters or lesion lengths not currently included in the FDA approved indications. Such uses were generally not part of the currently approved indications and the related research on safety and efficacy. There are uncertainties regarding the evidence for use of cardiac stents (bare-metal or drug-eluting) for more complex indications outside of the uses studied and approved by the FDA.

Comparators
The focus of the health technology assessment is comparison of DES with BMS, both of which have been previously described. The use of stents is one option for tertiary prevention and treatment of CAD. Depending on patient presentation and risk assessment, medical therapy and coronary artery bypass grafting (CABG) are options for treatments. These are briefly discussed in Appendix N which has more detailed background information.

1.7 Clinical Guidelines

Overview

A number of clinical guidelines for treating patients with CAD are available on the National Guideline Clearinghouse (NGC), the primary repository for evidence-based clinical guidelines [http://www.guideline.gov]. These guidelines include those on stable CAD, UA/NSTEMI and STEMI, and use of PCI. Another guideline on the appropriateness of revascularization (PCI or CABG) was published in January of 2009 and was not yet available on the NGC at the final editing of this HTA but is available on Pubmed.[19] Unfortunately, no guidelines for clinical care or appropriateness have been published regarding the use of BMS versus DES, the central focus of this technology assessment. However, the guidelines on CAD management provide an important perspective on the setting and issues involved in the decisions leading to coronary stent placement. The guidelines address some of the broader questions raised by the Washington State Health Technology Assessment Program as outlined in the background of this document. Thus, a brief overview of these guidelines is found in Appendix N.

National Guideline Clearinghouse (NGC)

The NGC includes 36 potentially relevant guidelines for CAD management, including clinical management of various symptoms, clinical conditions and interventions. The most extensive and detailed guidelines were formulated by combined efforts of the American College of Cardiology (ACC) and American Heart Association (AHA) in conjunction with other US-based professional societies. These appear to be the most salient for patient care in Washington State. The most recent ACC/AHA guidelines with focused updates are listed in the Table below.

Table 8. ACC/AHA guidelines

Guideline Topic	Reference
Chronic Stable Angina	Initial guideline, 1999[26]
	Update 2002[28]
	Update 2007 on medical therapy[38]
UA/NSTEMI	Initial guideline, 2000[64]
	Update 2002[65]
	Update 2007[20]
STEMI	Initial guideline, 2004[66]
	Update 2007[33]
PCI	Initial guidelines 2001[17]
	Update 2005[67]
	Focused update, 2007[24]
Special Populations	NSTEMI in the elderly, Part I [68]
	STEMI in the elderly, Part II[69]
	Women

Selected recommendations from ACC/AHA clinical guidelines relevant to stenting are briefly summarized in the appendix. *The reader is advised to consult the published guidelines.*

1.8 Medicare and Representative Private Insurer Coverage Policies

Variations exist in coverage policies for coronary stents for CMS and selected third-party payers. Table 9 provides and overview of policy decisions.

- **Medicare (National Coverage Determination)**
  The Centers for Medicare and Medicaid Services (CMS) will cover PCI both with and without the placement of a stent when used in accordance with FDA-approved protocols for treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary bypass surgery and who have angina refractory to OMT, objective evidence of myocardial ischemia, lesions amenable to angioplasty. Coverage for all other is at the discretion of local CMS contractors.

- **Medicare (Regional Coverage Determination)**
  The local regional CMS does not have a formal coverage determination for stent implantation. However, the local provider last updated their billing guidance in 2007, which includes two Healthcare Common Procedure Coding System (HCPCS) codes, G0290 and G0291, which include transcatheter placement of ≤1 DES for a single (G0290) and each additional (G0291) vessel.

- **Aetna**
  Aetna considers paclitaxel- and sirolimus-eluting stents medically necessary for members with angina pectoris or silent ischemia and >50% stenosis of one or more coronary arteries. All other indications are considered experimental. No information regarding the coverage of BMS was found.

- **Cigna**
  Cigna considers the use of DES medically necessary for treatment of symptomatic ischemic heart disease due to de novo lesions in native coronary arteries or stenosis within a previously placed BMS. Any investigational, experimental, or unproven uses, including DES for acute MI, unprotected LMCA disease, SVG disease, are not covered.

Table 9. Summary of CMS and other payer policies regarding PCI with stent

Payer (year)	Stent(s) evaluated	Evidence base available*†	Specific evaluation of DES vs. BMS stent use?	Policy	Rationale
Centers for Medicare & Medicaid Services (CMS): **Pub 100-03 National Coverage Determinations: 20.7 - PTA**	NR	NR in current publication of policy	no	• PTA (with and without the placement of a stent) is covered when used in accordance w/ FDA-approved protocols for treatment of atherosclerotic lesions of a single coronary artery for patients for whom the likely alternative treatment is coronary bypass surgery and who exhibit the	Rationale not provided

Payer (year)	Stent(s) evaluated	Evidence base available*†	Specific evaluation of DES vs. BMS stent use?	Policy	Rationale
(2008)				following characteristics: (1) angina refractory to optimal medical management; (2) objective evidence of myocardial ischemia; and (3) lesions amenable to angioplasty. Coverage for all other indications for coronary PTA with stenting is at local Medicare contractor discretion.	
CMS Regional Coverage Article (A29387) (Washington, Oregon, Nevada, Hawaii, Alaska, American Samoa, Guam, and Northern Mariana Islands), administered by Noridian Administrative Services **(2007)**	NR	NR	no	• HCPCS code G0290: Transcatheter placement of a drug-eluting intracoronary stent(s), percutaneous, with or without any other intervention for a single vessel • HCPCS code G0291: Transcatheter placement of a drug-eluting intracoronary stent(s), percutaneous, with or without any other intervention for each additional vessel	Rationale not provided
Aetna Clinical Policy Bulletin number 0621 (2008)	Cypher, Taxus Express, Taxus Express	4 RCTs (9-12 months f/u (NR for 1 study); % f/u NR); N = 2667 1 cohort study (36 months f/u, % f/u NR); N = 3751 pairs of matched patients 1 case series (f/u NR, % f/u NR); N= NR 4 meta-analyses (f/u NR, N = 31,826, 62 trials; N's and number of trials not reported for one meta-anaylsis)	yes	• Paclitaxel-eluting stents and sirolimus-eluting stents are considered medically necessary for members with angina pectoris or silent ischemia and >50% stenosis of one or more coronary arteries. • All other indications are considered experimental. • Transcatheter placement of a drug eluting intracoronary stent(s) in one or more vessels is covered if selection criteria are met (HCPCS codes G0290, G0291). •	• Policy is in accordance with FDA-approved indications for sirolimus-eluting stents (Rx Velocity, Cordis, Johnson & Johnson) and paclitaxel-eluting stents (Taxus Express, Boston Scientific Corporation). • The use of stents improves PCI outcomes, although in-stent restenosis occurs in 15-20% of stent patients. • Compared with BMS, DES are associated with a lower rate of repeat procedures (PCI or CABG), restenosis • Compared with BMS, DES are associated with a similar or lower rate of adverse events, such as MI and death, although other studies and meta-analyses warn that DES may lead to an increased risk of MI, thrombosis, and non-cardiac-related death Physicians urged to meet SCAI guidelines for stent implantation Rates of stent thrombosis may be higher in "real-world" patients than reported in RCTs Well-designed RCTs assessing bifurcation techniques for stenting are needed.
Cigna HealthCare Coverage Position number 0092 (2008)	Cypher, Raptorrail, Taxus Express2, Endeavor, Xience V, bioabsorb-able evero-limus-	23 RCTs 10 non-randomized single arm, observational, or retrospective studies (4 include analysis against	yes	• Covers the use of DES as medically necessary for treatment of symptomatic ischemic heart disease due to de novo lesions in native coronary arteries or stenosis within a previously placed BMS. Does not cover DES for acute MI, unprotected LMCA disease, SVG disease, or other experimental,	• Compared with BMS, the use of DES reduces restenosis rates in selected patients. • The safety and efficacy of DES in the treatment of complex lesions (small vessels, long lesions, multi-vessel disease) has also been established in RCTs, although emerging data has demonstrated

Payer (year)	Stent(s) evaluated	Evidence base available*†	Specific evaluation of DES vs. BMS stent use?	Policy	Rationale
	eluting stent	historical control) 12 meta-analyses		investigational, or unproven uses.	that DES use in more complex lesions may be associated with poor outcomes. Larger studies with long-term follow-up are needed to establish whether DES use increases the risk of stent thrombosis, death, and MI. • Additional research is needed to assess the relative benefits and risks of off-label use of DES (such as in patients with long lesions, bifurcation lesions, or acute MI) compared to the use of BMS or CABG. • Well-designed clinical trials have shown the effectiveness of DES in improving clinical and angiographic outcomes in the treatment of restenosis within a previously placed BMS, although additional follow-up is needed to assess long-term efficacy. • Well-designed clinical trials are needed to establish the efficacy, safety, and long-term outcomes of DES used for acute MI and unprotected LMCA disease. • Transcatheter placement of drug eluting stent(s) in one or more vessels is covered when medically necessary with or without other therapeutic intervention (CPT codes 92980, 92981).
Civilian Health and Medical Program of the Department of Veterans Affars (CHAMPVA) **(2002)**	NR	NR	no	• PTCA is covered for treatment of stenotic lesions of one or more coronary arteries when the likely alternative is CABG. For coverage there must be at least one of the following characteristics: (1) angina refractory to optimal medical management; (2) objective evidence of myocardial ischemia; or (3) lesions amenable to angioplasty. • PTCA, with or without placement of an intravascular stent, for other conditions may be considered for cost sharing when determined to be medically necessary and generally acceptable medical practice.	Rationale not provided
Regence of Oregon and Utah; Regence of Idaho and select counties of Washington Medical Policy number 119 (2007)	Cypher, Taxus	NR	no	• PTA, with or without stenting, may be considered medically necessary for the treatment of single or multiple vessel coronary artery stenoses. • All other indications are considered investigational.	• Stents used as an adjunct to angioplasty to prevent vessel wall collapse. • DES are intended to prevent restenosis. • Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method, single vessel (CPT 92980); each additional vessel (CPT 92981) • Percutaneous transluminal coronary balloon angioplasty, single vessel

Payer (year)	Stent(s) evaluated	Evidence base available*†	Specific evaluation of DES vs. BMS stent use?	Policy	Rationale
					(CPT 92982); each additional vessel (CPT 92984)
BlueCross BlueShield of North Carolina Evidence Based Guidline number EBG.SUR6215 (2008)	Cypher, Taxus	NR	no	• The CYPHER sirolimus and the Taxus paclitaxel-eluting coronary stents may be appropriate for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions with 70-99% occlusion of length ≤ 30mm in native coronary arteries with a reference vessel diameter of ≥ 2.5 to ≤ 3.5mm. • The use of any stent that is not FDA approved and not listed here as a covered stent is considered investigational. • Drug eluting coronary stents are not recommended for patients with a hypersensitivity to stent materials, patients in whom antiplatelet and/or anticoagulation therapy is contraindicated, patients judged to have a lesion that prevents complete infiltration of an angioplasty balloon, or for non-coronary arteries.	• Stents prevent restenosis by preventing elastic recoil and vessel remodeling. • DES additionally prevent restenosis by eluting anti-proliferation drugs. • Applicable billing codes: G0290, G0291 (details not provided).

BMS: bare-metal stent(s), CABG: coronary artery bypass grafting, CAD: coronary artery disease, DES: drug-eluting stent(s), LMCA disease: left main coronary artery disease, MACE: major adverse coronary events, MI: myocardial infarction, MVD: multivessel disease, NR: not reported, PTA: percutaneous transluminal angioplasty, PTCA: (same as PCI with no stents), SVG: saphenous vein graft, TVF: target vessel failure.
* Percent follow-ups are weighted based on sample size, and were calculated using the N reported in the assessment. Note that for many studies, there were different rates of follow-up for different outcomes, and the lowest of those percentages are reported here for simplicity. Ranges of follow-up times are reported here.
† N reflects numbers as reported in the assessment before loss to follow-up.
‡ One % follow-up is a reasonable estimation based on the given data, as the exact % f/u was not provided.
****** follow-up was only reported for angiographic (but not other) endpoint results for at least one study.

- **Department of Veterans Affairs (VA)**
  The medical program for the VA covers PCI for treatment of stenotic lesions of one or more coronary arteries when the likely alternative is CABG if at least one of the following criteria are met: angina refractory to OMT, objective evidence of myocardial ischemia, or lesions amenable to angioplasty. PCI for any other conditions may be considered for cost sharing when determined to be medically necessary and generally acceptable medical practice

- **Regence (Regional Medical Policy)**
  Regence's local medical policy for the states of Oregon, Idaho, Utah, and select counties of Washington consider PCI with or without stenting to be medically necessary for the treatment of single or multiple vessel coronary artery stenoses. All other indications are considered investigational.

1.9 Select International Coverage Recommendations

- **NHS (National Institute for Clinical Excellence) (UK) (2008)**

The NHS recommends the routine use of stents when PCI is clinically appropriate for patients with either stable or unstable angina or with acute MI. DES are recommended for the treatment of CAD according to their instructions for use if (1) the target artery is less than 3 mm in diameter or longer than 15 mm; and (2) there is no more than £300 price difference between DES and BMS. Conditions that are sufficiently managed with OMT, including many cases of stable angina, are excluded.

- **Ontario Health Technology Advisory Committee (OHTAC) (2005)**
  OHTAC recommends DES be offered to patients considered for stent placement with at least two of the following: (1) long lesions (> 20 mm); (2) narrow lesions (< 2.75 mm); or (3) diabetes. By targeting DES to high-risk patients, OHTAC expects to decrease the number of patients managed with DES. In addition, they noted that DES have a high incremental cost per quality adjusted life year gained.

1.10 Washington State Data

Data from two Washington State Agencies and from the Clinical Outcomes Assessment Program (COAP) were provided by the Health Technology Assessment Program.

Estimates for costs and utilization from the Uniform Medical Plan and Washington State's Medicaid program are presented below in Table 10. They provide an estimate of base costs and may not include all costs for stent-related procedures and treatment.

The Clinical Outcomes Assessment Program (COAP) is a Washington State initiative designed to produce clinical information needed to improve quality of care and meet the growing demand for accountability in the health care industry. COAP's physician led Management Committee, in partnership with State officials and key stakeholders, has created this program as a model of collaboration in which Washington State's cardiac community can work together toward a common goal of improving patient care and health outcomes. COAP operates under the auspices of the non-profit Foundation for Health Care Quality.

Table 10. Cardiac stent procedure cost and utilization: 2004-2007, State of Washington

Cardiac Stent Procedure Utilization: 2004-2007
State of WA

	2004	2005	2006	2007
Total Costs*	**$14,263,103**	**$15,505,519**	**$17,218,988**	**$16,544,589**
Total Procedures**	**988**	**1010**	**1040**	**954**
*Bare Metal****	*175*	*80*	*117*	*283*
*Drug-Eluting****	*781*	*919*	*904*	*650*

* Inpatient, outpatient, Medicaid and Uniform Medical Plan as primary and secondary payors
** Procedure codes 36.06, 36.07, 92980, 92981, G0290 and G0291 performed as primary or secondary procedure
*** Excludes patients who received both types in same procedure

Cardiac Stent Procedure Costs and BMS/DES Cost Differential
State of WA

2009 Procedure Costs†	Costs	Differential
Medicaid		
Inpatient		
Bare Metal	$13,024	
Drug-Eluting	$16,670	$3,646
Outpatient		
Bare Metal	$4,863	
Drug-Eluting	$6,615	$1,752
Uniform Medical Plan		
Inpatient		
Bare Metal	$22,360	
Drug-Eluting	$26,497	$4,137
Outpatient		
Bare Metal	$13,038	
Drug-Eluting	$17,345	$4,307

† Inpatient costs based on APDRGs 852 and 854. Outpatient costs based on weighted facility fees for CPT code 92980 and HCPCS code G0290

COAP maintains a registry on all PCI procedures and cardiac surgeries from all hospitals in Washington State that perform these. The COAP data base is potentially a very rich source of information about these procedures and their outcomes. Beginning in 2008, all Washington State hospitals contribute data to COAP, with the addition of Madigan in 2008. There are 31 sites that do PCI, 19 of which have cardiac surgery backup.

Data on PCI have been collected since 1999 and data by stent type (DES or BMS) have been collected since 2004. The table below describes PCI utilization from 2004- 2007 across hospitals in Washington State. [70]

Table 11. Cardiac stent procedure utilization: 2004-2007, Clinical Outcomes Assessment Program (COAP)*

Year	2004	2005	2006	2007
Total PCI Procedures**	**15,158**	**15,330**	**15,686**	**14,164**
No Prior PCI	*10,022*	*10,146*	*10,265*	*9,135*
Repeat Procedures	*5,136*	*5,184*	*5,421*	*5,029*
% Repeat Procedures	*34%*	*34%*	*35%*	*36%*
PCI Procedures with Stents	**13,348**	**14,104**	**14,542**	**13,032**
% stented PCIs	*88%*	*92%*	*93%*	*92%*
Count of All Stents	*18,860*	*19,931*	*21,048*	*19,688*
Count of Bare Metal Stents	*3,224*	*1,408*	*2,122*	*5,214*
Count of Drug-Eluting Stents	*15,636*	*18,523*	*18,926*	*14,474*
% Bare Metal Stents	*17%*	*7%*	*10%*	*26%*

* A program of the Foundation for Healthcare Quality in WA state

** Inpatient and outpatient procedures

From 2004-2006, an increase in the total number of PCI procedures was seen, with a decline seen in 2007. The number of DES used has been consistently higher than the number of BMS, but a sharp decline in the proportion of DES use was seen in 2007. These data are from an unselected patient population and represent overall stent use in Washington State. It should be noted that the number of repeat procedures includes any type of PCI, i.e. with or without stenting, and may include other procedures under the general term PCI (e.g. angioplasty). There is no unique patient identifier so patients may be represented more than once in a given year and may be represented in more than one year. Repeat procedures may include procedures done to the same vessel or additional vessels.

Several other features of the above data need to be considered in order to put these data in context:

- The data are cross-sectional by year. Since there in not a unique patient identifier that can be used to follow a given patient across years, the data are not longitudinal.
- The data represent numbers of procedures and numbers of stents, not the number of patients. Multiple stents may have been used in a single patient.

Additional information about COAP and PCI data from this source can be found in Appendix K.

2. The Evidence

2.1 Systematic Literature Review

Objectives

The primary aim of this assessment was to systematically review, critically appraise and analyze research evidence comparing the safety and efficacy of bare metal stent (BMS) with drug eluting stents (DES). Available information on the economic impact of this will also be summarized and critically appraised.

2.2 Methods

Inclusion/exclusion

- **Previously published formal HTAs or similar reports** comparing DES with BMS formed the initial basis of this HTA with the most recently performed reports considered to be the most up-to-date. Reports that were publically available or available via Spectrum's contract with the State were used. Earlier HTA reports and those which do not explicitly provide data comparing BMS with DES were used if unique and relevant information which pertains to the key questions and outcomes of interest was presented.
- **Meta-analyses published after the HTAs** which compare DES with BMS were considered to present a higher level of evidence than individual trials or studies. The report focuses on the most complete and methodologically rigorous meta-analyses. Since meta-analyses of RCTs are considered to provide a higher overall quality of evidence, they provide the focus for new evidence since HTA publication. In general, methodologically rigorous meta-analyses include formal systematic review and inclusion of literature pertinent to the study questions.
- Summary of inclusion and exclusion criteria for individual **studies published after the currently available HTA** search dates or publication are in the following table:

Table 12. Summary of inclusion and exclusion criteria for new individual studies

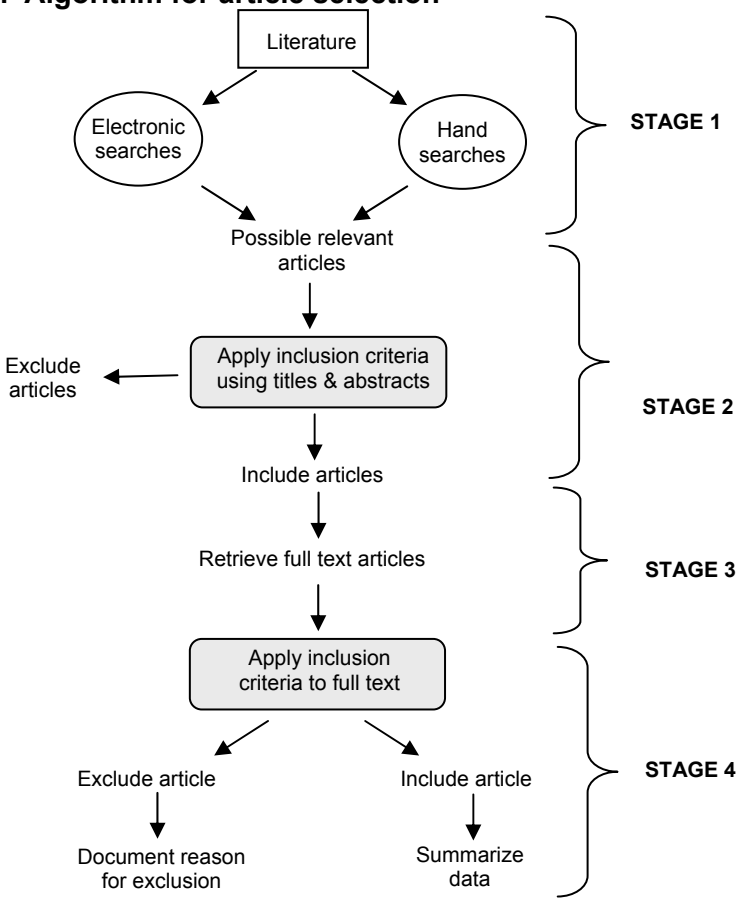
Study Component	Inclusion	Exclusion
Participants	• Patients with CHD undergoing stenting of coronary vessels	• Patients in whom stent placement would be contraindicated • Patients presenting for treatment of restenosis, stent thrombosis or revascularization after initial PCI or CABG or rescue PCI
Intervention	• FDA approved stents • Bare-metal and drug-eluting stents	• Non FDA Approved stents
Comparators	• BMS vs. DES	• Studies comparing different DES types which do not compare to BMS • Studies comparing pharmacologic regimens, anti-platelet medications or fibrinolysis or adjunctive devices • Studies in which < 70% of patients received stenting as

		the PCI intervention will be excluded
Outcomes	Studies reporting the following outcomes Primary clinical outcomes • overall mortality and cardiac death • myocardial infarction (MI) Secondary outcome (if reported) • revascularizations • functional outcomes • patient-reported outcome, quality of life • pain/relief of symptoms Safety • thrombosis • surgical or procedural complications • bleeding, stent fracture Economic • economic parameters (e.g. ICER)	
Study Design	• Only comparative studies (e.g. randomized controlled trials (RCTs), cohort studies with concurrent controls) will be considered for questions 1 and 2. o For nonrandomized studies, the focus will be on those which evaluate and appropriately control for specific potentially confounding factors will be considered for inclusion (e.g. age, smoking status) • Formal, full economic studies will be sought for question 3	• For question 1 and 2, studies other than comparative studies with concurrent controls will be excluded • Studies of fewer than 50 patients per treatment arm • Case reports • Case series • Costing studies, partial economic analyses
Publication	• Studies published in English in peer reviewed journals or publically available FDA reports • For Key Question 3- Full formal economic analyses (e.g. cost-utility studies) published in English in a peer-reviewed journal published after those represented in previous HTAs.	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Meeting abstracts, presentations or proceedings • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Incomplete economic evaluations such as costing studies

Data sources and search strategy

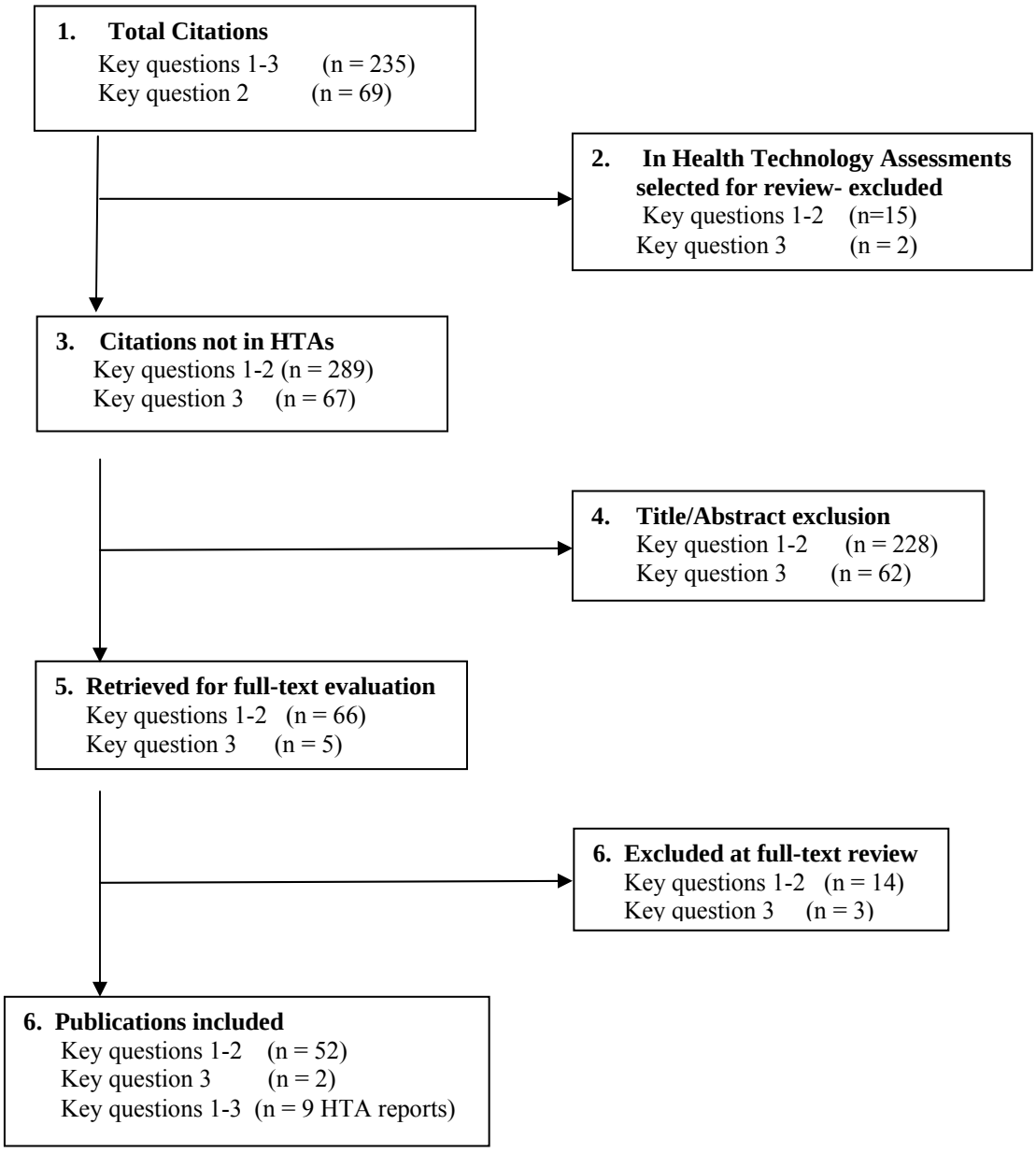
The reports and clinical studies included in this report were identified using the algorithm shown in Figure 1 below. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by two individuals. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria. Those articles selected form the evidence base for this report.

Figure 1. Algorithm for article selection



For this HTA, the search for new literature was limited to studies published since June 2005 for meta-analyses, comparative studies and safety, since July 2007 for registries, and from 2007-2009 for economic studies, based on search dates reported in the most recent HTAs. Citations for meta-analyses, RCTs and comparative non-randomized studies (e.g. registry studies) that directly compared DES with BMS were checked against a list of citations previously reported in one or more of the HTAs. Citations for RCTs and non-randomized comparative studies were also checked against a list of studies previously reported in meta-analyses that were either part of previous HTAs or included in new meta-analyses. Only citations that met the inclusion criteria set a priori that had not been included in another published HTA or meta-analysis were retained. A list of trials and studies which were included in HTAs and meta-analyses is found in APPENDIX C.

Figure 2. Flow chart showing results of literature search for DES versus BMS



Categorization of studies and outcomes

"Efficacy" refers to health benefits that occur under ideal conditions with ideal patient populations, the situation typically reported in randomized controlled trials (RCTs). "Effectiveness" refers to health benefits that occur under real world conditions with diverse patient populations, the situation typically reported by registries in observational studies. Sub-analyses of RCTs are considered as cohort studies since randomization is

generally not preserved in analysis. "Safety" refers to complications and/or adverse events that may occur whether reported in RCTS or observational studies. Formal economic analyses those which formally evaluate the incremental costs and benefits for outcomes related to treatment efficacy and could include cost-utility analyses, cost-effectiveness analyses and cost-benefit analyses. Studies which provide only costing information are not considered full economic analyses.

The issues of safety and efficacy are intertwined and difficult to separate. This is particularly true for DES since the use of anti-proliferative drug which are an integral part of DES provide both the mechanism which can lead to the prevention of in-stent stenosis (as intended) and potentially the mechanism by which thrombosis may occur due to the interaction between the coagulation process and a non-endotheliazed stent[4.] The separation of efficacy and safety outcomes in this reports is thus, some what artificial.

Since the primary focus of revascularization should be the improvement in clinical health outcomes (e.g. mortality, freedom from MI) and since such outcomes have been a primary focus in most technology assessments, they are the primary outcomes reported in this assessment.

For purposes of this report the following outcomes are discussed under efficacy and effectiveness for studies comparing DES versus BMS:

- Primary outcomes: Death, cardiac death, myocardial infarction
- Secondary outcomes: target lesion revascularization or target vessel revascularization

The following outcomes are discussed under safety for studies comparing DES versus BMS:

- Thrombosis
- Peri-procedural complications (MI, stroke) if reported
- Bleeding following anti-platelet therapy
- Stent fracture

Outcomes from formal economic analyses may include various incremental cost-effectiveness ratios and related parameters, e.g. cost per quality of life year gained.

Data extraction

Reviewers extracted data from the included previously done HTA and meta-analyses for each common outcome of interest. General characteristics of the HTA or meta-analyses were abstracted and general population and treatment-specific information were abstracted if provided. Interested readers should consult the original publications for detailed information.

For new clinical studies: study population characteristics, study type, study interventions, study outcomes, follow-up time, complications, and adverse events.

Study quality assessment: Quality of systematic reviews, meta-analyses and level of evidence (LoE) evaluation

Details of assessment of study quality are found in Appendix B.

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine, [71] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group, [72] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[73]

Table 13. Definition of the different levels of evidence for articles on therapy

Level	Study type	Criteria
I	Good quality RCT	• Concealment • Blind or independent assessment for important outcomes • Cointerventions applied equally • F/U rate of 85% + • Adequate sample size • Intent-to-treat
II	Moderate or poor quality RCT	• Violation of one or more of the criteria for a good quality RCT
	Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Cointerventions applied equally • F/U rate of 85% + • Adequate sample size • Controlling for possible confounding†
III	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
	Case-control	
IV	Case-series	

*Reliable data are data such as mortality or reoperation.
†Authors must provide a description of robust baseline characteristics, and control for those potential prognostic variables that are unequally distributed between treatment groups.

The methodological characteristics of previously done HTAs (similar reports) and of meta-analyses were assessed using a checklist which incorporates aspects of the AMSTAR checklist[74] and areas for critical appraisal outlined by "Users Guides" developed by the evidenced – based working groups at McMaster University[75] (See appendix B).

Table 14. Assessment check list for HTAs, systematic reviews and meta-analyses

Methodological Principle*	Example
Purpose, aim, study question, and/or hypothesis stated	■
Literature search described	■
Unpublished sources sought	■
Inclusion/exclusion criteria stated	■
Characteristics of included studies provided	
Quality of included studies formally assessed and method described	■
Overall quality of included studies (LoE) given primary purpose/aim	LoE I/II
Quantitative analysis	
• Studies appraised critically	
• Magnitude and direction of effect sizes evaluated	■
• Consistency of effect sizes evaluated	■
• Stability of effect sizes (e.g. confidence intervals) evaluated	■
• Scientific quality of studies considered in conclusions	
• Methods to enhance objectivity incorporated	■
Quantitative analysis	
• Heterogeneity evaluated	■
• Heterogeneity explored, if present	NA
• Missing data handled appropriately	
• Effect sizes pooled appropriately	■
• Sensitivity analysis conducted	
• Publication bias explored	
Potential conflict of interest stated	

Since it was beyond the scope of this report to evaluate individual studies described in previous HTAs or meta-analyses, the following algorithm was followed. If meta-analyses used randomized trials as their basis, the overall quality of the included studies was considered to be LoE I or II. Sub-analyses of RCTs generally do not preserve the randomization of the original trial and therefore were considered cohort studies, LoE II or III. Registry studies and retrospective cohort studies were considered LoE III, based on their general methodological limitations.

There is no universally accepted, standardized approach to critical appraisal of economic evaluation studies. The criteria described in the Quality of Health Economic Studies (QHES) tool[76] provided a basis for the critical appraisal of included economic studies and was augmented with the application of epidemiologic appraisal precepts (see Appendix B). The QHES employs widely accepted criteria for appraisal, such as choice and quality of cost and outcomes measures, transparency of model and presentation, use of incremental analysis, uncertainty analysis, and discussion of limitations and funding source and was primarily used to facilitate description of primary strengths and limitations of the studies. A weighted global score can be obtained based on these

measures with a possible range of scores from 0 (worst) to 100 (best), theoretically providing a common metric to compare study quality. This tool and the weighted score have not yet undergone extensive evaluation for broad use but provide a valuable starting point for critique.

Overall quality of strength of a body of evidence was assessed using the criteria below in Table 15.

Table 15. Overall Strength of Evidence (SoE)

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Data analysis

2.3 Quality of literature available

The literature search resulted in 304 potentially relevant citations for reports or studies using search strategies outlined in Appendix A.

A total of 10 HTAs or similar reports were found. Of the 9 HTAs or similar reports found, six were retained based on publication in 2007-2008 [77-82] and three published before 2006 were consulted for supplemental information or context only[83, 84]. One HTA performed meta-analysis of registry studies and was retained.[85]

A total of 12 meta-analyses or pooled analysis of RCTs published since the HTAs were retained, five of which included RCT populations in general [14, 86-89] and seven which provided analysis of special populations[90-95]. One meta-analysis of non-randomized studies was found.[96]

Individual comparative clinical studies that were not contained in HTAs or meta-analyses that met the inclusion criteria fell into the following categories: 13 reports of long-term follow-up or subanalysis of previously reported RCTs or new RCTs[97-107] and 26 non-randomized or registry studies.[108-135]

During the final editing of this report the authors were made aware of a large registry study in elderly patients that was presented at the American College of Cardiology meetings, March 28, 2009. Data from the uncorrected journal proof [136] are included for informational purposes only since there was not sufficient time for full critical appraisal and inclusion. This study, together with any new evidence will be evaluated when this HTA is reviewed at a later date.

One full economic study[137] and one new systematic review [138]were found and included.

Quality of studies retained- previously reported HTAs

Data from HTAs or similar reports published in 2007- 2008 generally relied on RCTs published in peer-reviewed journals as the basis of their conclusions. One report focused solely on registry studies and included some non-published abstracts[85.] Only two previously reported HTAs performed their own meta-analyses of RCTs.[79, 81] The EUnetHTA report updated a previously performed meta-analysis of RCTs done by two of the authors. This report was a pilot assessment and the authors caution that as such, it should not be used for decision making as it may not be complete. The KCE-Belgian report selectively cites meta-analyses of RCTs to describe efficacy and selectively cites information from non-randomized studies.[4] Economic evaluation was the primary focus of the Ontario, Hill, KCE and FinOHTA reports.[4, 81, 82, 85] The Hayes, CTAF and ECRI reports are primarily systematic narrative reviews and provide data selectively.[77-79]

The only publically available full HTA that conducted a full systematic review and original meta-analysis of RCTs was conducted by Hill.[81] The KCE-Belgium report performed a systematic search review of the literature.[4]

Only one HTA, prepared for the Ontario Ministry of Health & Long Term Care (Ontario) included any pooling of data from registry studies, although tests for heterogeneity were significant.[85] Hill (NICE/NHS 2007) reviewed reports from 24 registries and identified 18 with sufficient information to discern use of DES but concluded it was inappropriate to pool data due to inconsistencies across registries.[81] The Belgian Health Care Knowledge Center (KCE 2007) reviewed 29 registry reports but also did not pool the results. They did report some rates and conclusions from their review.[4] The California Technology Assessment Forum (CTAF 2007) report is a narrative review focused mainly on stent thrombosis and anti-platelet therapy.[77] They referenced some registry studies, but did not report any rates. The Hayes Directory (2007) report included rates from one registry study (SCAAR) where there was a comparison of DES to BMS and we have included those here. [78]

Quality of studies retained-meta-analyses published after HTAs

With the exception of one meta-analysis, [96] all other meta-analyses were of RCTs.

Two network meta-analyses published by Stettler, et al, one which includes 38 RCTS (18,023 patients) published in 2007[88], and the other which includes 35 trials and describes outcomes separately for diabetic patients (N = 3852 and non-diabetic patients

(N = 10,947), provide the most complete overall analyses comparing DES with BMS to update information presented in previous HTAs or meta-analyses and were more methodologically rigorous than other recently published reports. The same trials are represented in both analyses with the exception of three RCTs. Since the 2007 report evaluates outcomes for all patients as included in the original RCTs without regard to diabetic status or other patient characteristics or presentation, it comprises the basis for the update on efficacy and safety in general with the 2008 report forming the basis for discussion of DES versus BMS in diabetic patients.[59] Other meta-analyses and pooled analyses published after the technology assessments previously described included fewer trials, generally did not include sensitivity analyses or exploration of heterogeneity and were frequently focused specific trials or special populations. Details of these reports are found in Appendix F.

Network meta-analysis (also referred to as mixed treatment comparison) differs from conventional meta-analysis in that it allows for both direct and indirect comparison of treatment groups using data from head to head trials of DES and BMS as well as head to head trials comparing different DES while fully respecting the randomization[88.] This allows for the inclusion of a broader range of trials into the "network" of data for the comparison of any two treatment pairs. The "network" refers to the groups or "networks" of comparisons, some of which are direct, some of which are indirect[139.] By contrast, conventional meta-analysis relies on comparisons made in head to head trials, thus only direct, within trial comparison is possible. In Stettler 2007[88], there were 38 included trials, 26 of which were head to head comparisons of either SES or PES with BMS. In the 2008 report[59], of the 35 included trials, 23 were head to head comparisons of either SES or PES with BMS. Appendix C provides information on which head to head trials are included in each meta-analysis. While use of larger numbers of trials and patients in network meta-analysis may result in greater statistical precision, however, not all comparisons are direct. Thus, results for both the network meta-analysis and conventional meta-analysis are presented, where data are provided by the authors. Additional data and information were provided by the authors in online appendices, which added to the transparency of these analyses.

A primary methodological strength of the Stettler meta-analyses was the extraction of data from trials based on standardized definitions of the pre-specified outcomes. Data for 29 trials were provided by investigators or manufacturers. One of the limitations of many meta-analyses is variation across trials with regard to how outcomes are defined, leading to misclassification of outcomes across trials.

Unlike most of the other meta-analyses found, Stettler et al provide extensive information related to evaluation of heterogeneity and model fit and provide results from sensitivity analysis based on aspects of the methodological quality (e.g. blind adjudication of clinical outcomes) of included trials as well as on aspects of stent design (e.g. strut thickness, platform).

Quality of studies retained –new clinical studies

New RCTs or longer term follow-up reports from previous RCTs were graded as LoE I/II. Subanalyses of RCTs were graded LoE II/III since randomization is not preserved and they are essentially prospective cohort studies.

Nonrandomized studies from registry data have number of limitations. First, the treatment modality is selected by the attending physician and is subject to guidelines in place at the time of the PCI. Often there is no comparison group and there can be considerable selection bias. It is not possible to determine follow-up rates. Several issues did indeed limit the ability to compare rates between registries or to pool data from registries. These included different inclusion criteria, classifications of vessel lesions, and different definitions of outcomes such as myocardial infarction, revascularization or MACE. The degree of detail recorded in terms of patient and lesion characteristics also varied across registries. Differing follow- up times, completeness of follow-up and source of information on outcomes (from direct follow-up versus matching with health care or governmental vital statistic records) also limited the ability to make comparisons. Finally, temporal and regional trends in stent use are reflected in registries, including changing indications for use of stents proportion of patients receiving DES (or PES or SES) versus BMS. In some cases the registry studies used historical BMS controls, usually from a year prior to the DES cases. For these reasons, all registry studies are classified as LoE III.

Study quality assessment- previously reported HTAs

The following provides an overview of components of methodological quality for these assessments based on what was reported by the authors.

Table 16. Appraisal checklist for health technology assessments or similar reports

	Source						
Methodological Principle*	EUnet-HTA 2008	Hill (NICE/ NHS) 2007	Hayes 2007	KCE-Belgium 2007	ECRI 2006	CTAF 2007	Ontario 2007
Purpose, aim, study question, and/or hypothesis stated	■	■	■	■	■	■	■
Literature search described	■	■	■	■			■
Unpublished sources sought	■	■	■				■
Inclusion/exclusion criteria stated	■	■		■			■
Characteristics of included studies provided		■	■	■			■
Quality of included studies formally assessed and method described†	■	■					
Overall quality of included studies (LoE) given primary purpose/aim	LoE I/II	LoE I/II	LoE I/II	LoE I -III	LoE I/II	UA	LoE III
Quantitative analysis							
• Studies appraised critically †		■	■				
• Magnitude and direction of effect sizes evaluated	■	■	■			■	■

• Consistency of effect sizes evaluated	■	■			■	■	■
• Stability of effect sizes (e.g. confidence intervals) evaluated	■	■					■
• Scientific quality of studies considered in conclusions							
• Methods to enhance objectivity incorporated	■	■					
Quantitative analysis							
• Heterogeneity evaluated	■	■					■
• Heterogeneity explored, if present	NA						■
• Missing data handled appropriately							
• Effect sizes pooled appropriately	■	■					■
• Sensitivity analysis conducted							
• Publication bias explored							
• Potential conflict of interest stated				■			

*Not all criteria will be applicable to all types of reports. For instance, formal meta-analyses should meet criteria for both qualitative and quantitative analysis while a systematic review to generate a research questions might only meet criteria

†Evaluation of whether the report describes the method(s) of critical appraisal. Report may have done critical appraisal to arrive at conclusions but methodology may not have been described as part of the report.

CTAF is California Technology Assessment Forum; ECRI is Emergency Care Research Institute; EUnetHTA is the European Network for Health Technology Assessment; KCE-Belgium is Belgian Health Care Knowledge Centre; NA is not applicable; NICE/NHS is National Institute for Health and Clinical Excellence/National Health Service; UA is unable to assess.

Study quality assessment- meta-analyses published after HTAs
Recent meta-analyses

Table 17. Appraisal Checklist for Meta-Analyses Dealing with General Patient Populations

	Source			
Methodological Principle*	Stettler 2007	Fuchs 2008	de Lemos 2007	Moreno 2007 Am J Card
Purpose, aim, study question, and/or hypothesis stated	■	■	■	■
Literature search described	■	■	■	■
Unpublished sources sought	■	■	■	■
Inclusion/exclusion criteria stated	■	■	■	■
Characteristics of included studies provided	■	■		■
Quality of included studies formally assessed and method described†	■		■	
Overall quality of included studies (LoE) given primary purpose/aim	LoE I/II	LoE I/II	LoE II	LoE I/II
Qualitative analysis				
• Studies appraised critically †	■		■	
• Magnitude and direction of effect sizes evaluated	■	■	■	■
• Consistency of effect sizes evaluated	■	■	■	■
• Stability of effect sizes (e.g. confidence	■	■	■	■

intervals) evaluated				
• Scientific quality of studies considered in conclusions	■		■	
• Methods to enhance objectivity incorporated	■		■	
Quantitative analysis				
• Heterogeneity evaluated	■	■	■	■
• Heterogeneity explored, if present	■	NA		NA
• Missing data handled appropriately	■			
• Effect sizes pooled appropriately	■	■	■	■
• Sensitivity analysis conducted	■		■	■
• Publication bias explored		■		
Potential conflict of interest stated	■			

NA = applicable (eg, heterogeneity was evaluated, but none was present), UA = unable to assess.
*Not all criteria will be applicable to all types of reports. For instance, formal meta-analyses should meet criteria for both qualitative and quantitative analysis while a systematic review to generate a research questions might only meet criteria.
†Evaluation of whether the report describes the method(s) of critical appraisal. Report may have done critical appraisal to arrive at conclusions but methodology may not have been described as part of the report.

Table 18. Appraisal Checklist for Reviews Addressing Patients with Diabetes Mellitus

	Source			
Methodological Principle*	Stettler 2008	Kumbhani 2008	Patti 2008	Kirtane 2008
Report type	MA	MA	MA	PA
Purpose, aim, study question, and/or hypothesis stated	■	■	■	■
Literature search described	■	■	■	
Unpublished sources sought	■	■	■	
Inclusion/exclusion criteria stated	■	■	■	
Characteristics of included studies provided	■	■	■	■
Quality of included studies formally assessed and method described†	■	■	■	
Overall quality of included studies (LoE) given primary purpose/aim	LoE I/II	LoE I/II	LoE I/II	LoE I/II
Qualitative analysis				
• Studies appraised critically †	■	■	■	
• Magnitude and direction of effect sizes evaluated	■	■	■	■
• Consistency of effect sizes evaluated	■	■	■	■
• Stability of effect sizes (e.g. confidence intervals) evaluated	■	■	■	■
• Scientific quality of studies considered in conclusions	■			
• Methods to enhance objectivity incorporated	■	■	■	
Quantitative analysis				
• Heterogeneity evaluated	■	■	■	■
• Heterogeneity explored, if present	■		NA	NA
• Missing data handled appropriately				
• Effect sizes pooled appropriately	■	■	■	■
• Sensitivity analysis conducted	■			
• Publication bias explored		■	■	
Potential conflict of interest stated	■	■		■

MA = meta-analysis, PA = pooled analysis, UA = unable to assess

*Not all criteria will be applicable to all types of reports. For instance, formal meta-analyses should meet criteria for both qualitative and quantitative analysis while a systematic review to generate a research questions might only meet criteria.

†Evaluation of whether the report describes the method(s) of critical appraisal. Report may have done critical appraisal to arrive at conclusions but methodology may not have been described as part of the report.

Table 19. Appraisal Checklist for Reviews Addressing Patients with Special Characteristics

Methodological Principle*	Acute MI		
	Pasceri 2007	Kastrati 2007	Moses 2006
Report type	MA		PA
Purpose, aim, study question, and/or hypothesis stated	■	■	■
Literature search described	■		
Unpublished sources sought	■		
Inclusion/exclusion criteria stated	■		
Characteristics of included studies provided	■	■	■
Quality of included studies formally assessed and method described†			
Overall quality of included studies (LoE) given primary purpose/aim	LoE I/II	LoE I/II	LoE/I/II
Qualitative analysis			
• Studies appraised critically †			
• Magnitude and direction of effect sizes evaluated	■	■	■
• Consistency of effect sizes evaluated	■	■	■
• Stability of effect sizes (e.g. confidence intervals) evaluated	■	■	■
• Scientific quality of studies considered in conclusions			
• Methods to enhance objectivity incorporated	■		
Quantitative analysis			
• Heterogeneity evaluated	■	■	■
• Heterogeneity explored, if present	■	NA	NA
• Missing data handled appropriately			
• Effect sizes pooled appropriately	■	■	■
• Sensitivity analysis conducted	■	■	■
• Publication bias explored	■		
Potential conflict of interest stated		■	■

MA = meta-analysis, PA = pooled analysis, UA = unable to assess

*Not all criteria will be applicable to all types of reports. For instance, formal meta-analyses should meet criteria for both qualitative and quantitative analysis while a systematic review to generate a research questions might only meet criteria

†Evaluation of whether the report describes the method(s) of critical appraisal. Report may have done critical appraisal to arrive at conclusions but methodology may not have been described as part of the report

Study quality assessment- RCTs and comparative studies published after and not included in previous HTAs or meta-analyses

The quality of new RCTs or long-term comparative studies was considered to be LoE III. Follow-up of previously reported RCTs is given a Level of Evidence (LoE) of II/III since randomization isn't preserved and they are essentially prospective cohort studies.

With regard to registry studies, several issues did indeed limit the ability to compare rates between registries or to pool data from registries. These included different inclusion criteria, classifications of vessel lesions, and different definitions of outcomes such as myocardial infarction, revascularization or MACE. The degree of detail recorded in terms of patient and lesion characteristics also varied across registries. Differing follow- up times, completeness of follow-up and source of information on outcomes (from direct follow-up versus matching with health care or governmental vital statistic records) also limited the ability to make comparisons. Finally, temporal and regional trends in stent use are reflected in registries, including changing indications for use of stents proportion of patients receiving DES (or PES or SES) versus BMS. In some cases the registry studies used historical BMS controls, usually from a year prior to the DES cases.

2.4 Description of study populations

Study populations are not well-summarized by previous done HTAs, but most include detailed tables for included studies and the interested reader should consult these sources.

The primary meta-analyses used in this report for efficacy, safety and evaluation of diabetic patients are those by Stettler[59, 88.] Population information as available in the reports or accompanying appendices is summarized below:

Table 20. Characteristics of trials included in Stettler et al. 2007 meta-analysis

		PES vs BMS	SES vs BMS	SES vs PES†
Number of trials*		8	17	15
No. patients		5138	5818	8719
Follow-up, months; no. studies	12	2	7	4
	24	2	4	4
	36	1	1	6
	48	3	5	1
Demographics/patient characteristics				
Gender				
% male, range		69-90	34-85	64-82
% female, range		10-31	15-66	18-36
Age, years; range		61-66	59-73	56-68
Diabetes, %; range		11-32	13-31	0-34
			100 (3 trials)	100 (1 trial)
Previous stent or coronary artery bypass		-	1	1
Lesion characteristics				
Lesion length, mm (no. trials)		10-46 (3)	15-32 (3)	< 20 (1)
		≤ 12 (2)	≤ 18 (1)	> 15 (1)
			≤ 28 (1)	≥ 16 (1)
			≤ 30 (1)	> 20 (1)
			≤ 33 (1)	≥ 25 (1)
			≤ 42 (1)	
			≤ 66 (1)	

		≥ 15 (1)§	
No restrictions, no. trials	2	5	6
NA, no. trials	1	2	4
Lesion diameter, mm (no. trials)	2.25-4.0 (5) > 2.5 (1) ≥ 4 (1)	2.25-4.50 (8) < 2.75 (1) < 4.0 (1) ≥ 4 (1)	2.25-4.00 (4) < 2.5 (2) < 2.8 (1) ≥ 2.5 (1) ≥ 4 (1)
No restrictions, no. trials	-	3	3
NA, no. trials	1	3	3
Indications, no. trials			
Stable or unstable angina pectoris	6	10	7
Angina pectoris and/or positive stress test	-	1	4
Silent ischemia	5	6	5
Acute coronary syndrome	-	3	2
Acute myocardial infarction	3	5	5
No acute myocardial infarction	-	-	8
Chronic total occlusion	-	1	-
No restrictions	-	-	1
Source of funding, no. trials			
Stent manufacturer	5	7	1
Non-profit	1	7	11
NA	2	3	3

NA = not applicable.
*The number of studies/patients for PES vs BMS, SES vs BMS, and SES vs PES includes one study (BASKET, N = 826) which looked at PES vs DES vs BMS.
†Because the Stetter 2007 network analysis includes data from SES vs PES trials for indirect comparisons the trial characteristics were included for informational purposes.
§Or bifurcation, ostial location, or angulation.

Stettler et al 2007[88] did not report on the use of anti-platelet therapy. In the PES versus BMS arm, the number of centers involved ranged from 1-3 in four trials and 38-73 in four. In the SES versus BMS arm, the number of centers ranged from 1-4 in nine trials, 8-19 in three, and 20-53 in four. In the SES versus PES arm, the number of centers ranged from 1-5 in all but one study which included 90 centers.

Another network meta-analysis by Stettler et al 2008[59] compared the efficacy and safety of SES, PES, and BMS in patients with and without diabetes mellitus using basically the same study population as Stettler 2007, shown in Table 20. The study included 35 trials in 3852 patients with diabetes and 10,947 patients without diabetes. No major differences were seen between the study characteristics with the exception of clopidogrel use. In the PES versus BMS arm, seven studies reported using clopidogrel for 6 months and one study reported using it for 9 months. In the SES versus BMS arm, clopidogrel was used for a duration of 2 months in five trials, 3 months in three, and 6 and 12 months in four trials each.

Additional characteristics of the trials included in Stettler 2007 are described below
Trials with follow-up from one to four years were included. Of the 38 included trials,

- Nine trials reported follow-up up to 4 years.
- Eight trials up to 3 years.
- Eight trials to 2 years.
- Thirteen trials to 1 year.

With regard to methodological quality, of the 38 include trials

- 29 trials described appropriate methods for concealment of allocation.
- 28 trials reported blinded adjudication of clinical outcomes.
- 31 trials - the authors were able to include all randomized patients in the analyses based in intention to treat.
- 22 trials met all three of the above (i.e. concealed allocation, blind adjudication and intention to treat).

With regard to safety, an additional meta-analysis by Fuchs, et. al[86] is summarized. General characteristics of this report a described in Table 21 below.

The authors report including 28 trials, 21 comparing DES versus BMS and seven comparing BMS versus balloon angiography. However, in Table 1 of the original article, demographics and characteristics were only available for 15 of the 21 studies comparing DES versus BMS; thus, the data does not accurately reflect the entire population and the total number of patients included in the DES versus BMS trials was unable to be determined. Also not reported were indications for PCI such as stable or unstable angina, silent ischemia, acute coronary syndrome, and chronic total occlusion. Lesion diameter was also not included.[86]

Table 21. Characteristics of trials included in Fuchs et al. 2008 meta-analysis*

		DES vs BMS
Number of trials		21
No. patients		NR
Follow-up, months; no. trials	6-9	9
	12	4
	24	1
	60	1
Demographics/patient characteristics		
Gender		
% male, range		62-94
% female, range		6-38
Age, years; range		58-67
Diabetes, %; range		10-33
		100 (1 trial)
NR, no. trials		1†
NA, no. trials		1
Current smoker, %; range		14-54
Previous MI, %; range		7-64
NA, no. trials		1
Antiplatelet therapy		
GP IIb/IIIa inhibition, months; range		6-60
NA, no. trials		6§
Lesion characteristics		
Lesion length, mm; range		8-16
NA, no. trials		1

GP = glycoprotein.
NA = not applicable.
NR = not reported.
*Data only reported for 15/21 RCTs comparing DES vs BMS.
†Percentage of diabetics was not reported for the DES arm in the RCT by Morice et al 2002 (RAVEL).
§Only GP IIb/IIIa inhibition for the DES arm of the trial by Gershlick et al 2004 (ELUTES) was reported.

Characteristics for randomized controlled trials (RCTs)
Randomized trial reports published since the HTAs and meta-analyses previously discussed fell into three categories: Extended follow-up on previously reported trials which have been included in HTAs and/or meta-analyses, sub-analyses of previously reported trials (some of which were included in the extended follow-up report) and new studies (all of which were for groups considered under the special populations section).

Table 22. Patient characteristics and overview of treatment for previously reported RCTs with longer term follow-up

	Pfisterer (2009) [BASKET]		Morice (2007)* [RAVEL]		Grube (2007) [TAXUS VI]	
Variable	DES (n = 545)	BMS (n = 281)	DES (n = 120)	BMS (n = 118)	DES (n = 219)	BMS (n = 227)
Patient demographics						
Gender						
No. males (%)	422 (79)	223 (79)	84 (70)	96 (81)	167 (76.3)	173 (76.2)
No. females (%)	123 (21)	58 (21)	36 (30)	22 (19)	52 (23.7)	54 (23.8)
Age, years; mean (SD)	64 (11)	64 (11)			61.8 (9.7)	63.4 (9.9)
Number diseased vessels (n)						
One	NR	NR	NR	NR	NR	NR
Two	NR	NR	NR	NR	NR	NR
Three	NR	NR	NR	NR	NR	NR
Comorbidities/Characteristics (n)						
Diabetes	17% (93)	22% (61)	16%	21%	17.8% (39)	22.0% (50)
Hyperlipidemia	76% (414)	76% (214)	38%	43%	70.3% (149)	73.4% (163)
Hypertension	66% (358)	68% (192)	62%	61%	57.5% (126)	58.1% (132)
Prior MI	28% (151)	27% (75)	38%	34%	NR	NR
Prior PCI or CABG	30% (161)	27% (77)	NR	NR	17.9% (39)	20.7% (47)
Treatment						
No. stents per lesion	NR	NR	NR	NR	NR	NR
GP IIb/IIIa (duration)	26% (NR) n = 141	25% (NR) n = 71	10.1% (NR)	9.5% (NR)	use at the discretion of the physician (NR)	use at the discretion of the physician (NR)
Other anti-platlet (duration)	aspirin and clopidogrel (6 months) aspirin (indefinitely)	aspirin and clopidogrel (6 months) aspirin (indefinitely)	aspirin 325 mg daily (indefinitely) clopidogreal 75 mg daily or ticlopidine 250 mg twice daily for 8 weeks	aspirin 325 mg daily (indefinitely) clopidogreal 75 mg daily or ticlopidine 250 mg twice daily for 8 weeks	aspirin ≥ 75 mg daily (≥ 6 months) clopidogrel 75 mg daily (≥ 6 months)	aspirin ≥ 75 mg daily (≥ 6 months) clopidogrel 75 mg daily (6 months)

CABG: coronary artery bypass graft.
GP IIb/IIIa = glycoprotein IIb/IIIa inhibitor.
MI = myocardial infarction.
NR = not reported.
PCI = percutaneous coronary intervention.
*Demographics are as reported from the original trial.

Table 23. Patient characteristics and overview of treatment for new RCTs in patients with acute MI/STEMI and or new left bundle branch block LBBB

Variable	Kelbaek (2008) [DEDICATION] DES (n = 313)	Kelbaek (2008) [DEDICATION] BMS (n = 313)	Valgimigli (2008) [MULTISTRATEGY] DES (n = 372)	Valgimigli (2008) [MULTISTRATEGY] BMS (n = 372)	Diaz del Llera (2007) DES (n = 60)	Diaz del Llera (2007) BMS (n = 54)
Patient demographics						
Gender						
No. males (%)	228 (72.8)	230 (73.5)	281 (75.6)	284 (76.3)	48 (80.0)	47 (78.3)
No. females (%)	85 (27.2)	83 (26.5)	91 (24.4)	88 (23.7)	12 (20.0)	7 (21.7)
Age, years; mean (SD)	61.8	62.6	63	65	64 (12)	65 (13)
Number diseased vessels (n)						
One	65%	60%	47.1% (175)	42.8% (159)	55.0% (33)	51.7% (31)
Two	25%	29%	33.6% (125)	34.7% (129)	31.7% (19)	31.7% (19)
Three	10%	11%	18.0% (67)	21.0% (78)	13.3% (8)	16.7% (10)
Comorbidities/Characteristics (n)						
Diabetes	9.3%	11.5%	14.3% (53)	14.8% (55)	26.7% (16)	28.3% (17)
Hyperlipidemia	18.5%	21.4%	51.6% (192)	54.9% (204)	NR	NR
Hypertension	32.3%	33.9%	55.3% (206)	59.1% (220)	NR	NR
Prior MI	6.1%	7.0%	7.5% (27)	8.1% (30)	5.0% (3)	10.0% (6)
Prior PCI or CABG	4.4%	5.4%	7.0% (26)	5.9% (25)	5.0% (3)	8.4% (5)
Treatment						
No. stents per lesion	1.3 ± 0.62	1.3 ± 0.62	1	1	NR	NR
GP IIb/IIIa (duration)	97% (NR)	96% (NR)	100% (12-24 hours) n = 372	100% (12-24 hours) n = 372	100% (12 hours) n = 60	100% (12 hours) n = 54
Other antiplatlet (duration)	clopidogrel (12 months) aspirin (indefinitely)	clopidogrel (12 months) aspirin (indefinitely)	aspirin (160-325 mg orally or 250 mg by IV then 80-125 mg/daily indefinitely) clopidogrel (300 mg orally then 75 mg/daily for 3 months)	aspirin (160-325 mg orally or 250 mg by IV then 80-125 mg/daily indefinitely) clopidogrel (300 mg orally then 75 mg/daily for 3 months)	aspirin (300-500 mg orally then 100 mg daily indefinately) clopidogrel 300-600 mg orally then 75 mg daily for 1-9 months)	aspirin (300-500 mg orally then 100 mg daily indefinately) clopidogrel 300-600 mg orally then 75 mg daily for 1-9 months)

CABG: coronary artery bypass graft.
GP IIb/IIIa = glycoprotein IIb/IIIa inhibitor.
MI = myocardial infarction.
NR = not reported.
PCI = percutaneous coronary intervention.

One new RCT describing stent use in diabetic patients was found.

Table 24. Patient characteristics and overview of treatment for RCTs in diabetic patients

	Maresta (2008) [DESSERT]	
Variable	DES (n = 75)	BMS (n = 75)
Patient demographics		
Gender		
No. males (%)	47 (63)	37 (49)
No. females (%)	28 (37)	38 (51)
Age, years; mean (SD)	71 (9)	69 (9)
Number diseased vessels (n)		
One	28% (21)	35% (26)
Two	38% (29)	34% (26)
Three	34% (25)	31% (23)
Comorbidities/Characteristics (n)		
Diabetes	100% (75)	100% (75)
Hyperlipidemia	47% (35)	52% (39)
Hypertension	77% (58)	75% (56)
Prior MI	36% (27)	25% (19)
Prior PCI or CABG	12% (9)	9% (7)
Treatment		
No. stents per lesion*		
One	96 (88%)	101 (93%)
Two	12 (12%)	8 (7%)
GP IIb/IIIa (duration)	100% (NR) n = 75	100% (NR) n = 75
Other antiplatlet (duration)	aspirin 100mg daily (NR) clopidogrel 75 mg daily (6 months) 70-IU/kg IV heparin (bolus)	aspirin 100mg daily (NR) clopidogrel 75 mg daily (NR) 70-IU/kg IV heparin (bolus)

CABG: coronary artery bypass graft.
GP IIb/IIIa = glycoprotein IIb/IIIa inhibitor.
MI = myocardial infarction.
NR = not reported.
PCI = percutaneous coronary intervention.
*Percentages are based on number of lesions, n = 109.

2.5 Description of study outcomes

The issues of safety and efficacy are intertwined and difficult to separate. This is particularly true for DES since the use of anti-proliferative drug which are an integral part of DES provide both the mechanism which can lead to the prevention of in-stent stenosis (as intended) and potentially the mechanism by which thrombosis may occur due to the interaction between the coagulation process and a non-endotheleized stent [KCE].[4] The separation of efficacy and safety outcomes in this reports is thus, some what artificial.

Outcomes:
Since the primary focus of revascularization should be the improvement in clinical health outcomes (e.g. mortality, freedom from MI) and since such outcomes have been a

primary focus in technology assessments, they are the primary outcomes reported in this assessment

For purposes of this report the following outcomes will be discussed under efficacy and effectiveness for studies comparing DES versus BMS:

- Primary outcomes: Death, cardiac death, myocardial infarction
- Secondary outcomes: target lesion revascularization or target vessel revascularization

The following outcomes will be discussed under safety for studies comparing DES versus BMS:

- Thrombosis
- Peri-procedural complications (MI, stroke)
- Bleeding following anti-platelet therapy

Stettler et. al specified the following primary outcomes using standardized definitions[122]:

- Overall mortality
- Cardiac death, defined as any death due to cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia), procedural relate deaths and deaths related to concomitant treatment and death of unknown cause.
- Myocardial infarction, including fatal and non-fatal non-Q-wave or Q-wave myocardial infarction
- Composite of death or myocardial infarction
- Definite stent thrombosis within the stented segment, confirmed by angiography or post-mortem based on the Academic Research Consortium (ARC) criteria. Authors ensured that secondary stent thrombosis occurring after a patient had undergone target vessel revascularization was included. This outcome will be discussed under the safety section.

Target vessel revascularization (TVR) was considered a secondary outcome and was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel done for restenosis or other complications of the target lesion (ranging from 5 mm proximal to 5 mm distal to the stent. Since rates of TVR were not available for three trials, target vessel revascularization was used as a proxy measure.

Composite outcomes reported in different studies of DES versus BMS were defined differently by different trials and reviews, combined critical outcomes like death with less serious outcomes like nonfatal MI, and included potentially non-objective outcomes which may have been protocol driven like revascularization. For these reasons, and to avoid obscuring results of important component outcomes, in this assessment we are reporting the results of individual components, rather than composite outcomes.

3. Results

Results will be presented in the following order:

- Evidence for efficacy and effectiveness from HTAs, meta-analyses and recently published studies across populations (i.e. general populations as included in the studies).
- Evidence for safety from HTAs, meta-analyses and recently published studies across populations.
- Evidence for efficacy, effectiveness and safety among special populations (e.g. diabetic populations, those with acute myocardial infarction).
- Evaluation of formal economic analyses.

For each section, conclusions from previously done HTAs (or similar reports) will be presented first followed by results of the most comprehensive and methodologically rigorous meta-analyses published after the completion of the HTAs. New studies will be presented last with a focus on findings from randomized controlled trials or in the case of economic studies, full economic studies based on clinical outcomes.

3.1 Key question 1 – What is the evidence of efficacy and effectiveness of drug eluting (DES) versus bare metal stents (BMS)?

Efficacy

Overall (all cause) death, cardiac death and myocardial infarction were used as the primary clinical measures of efficacy. Technology assessments and conventional meta-analyses of between 14 and 24 head to head randomized controlled clinical trials and three reports of longer-term follow-up to three previously reported randomized controlled trial comparing DES with BMS consistently indicate that DES are no better at preventing death, cardiac death or myocardial infarction than BMS.

Target lesion revascularization was considered a secondary, intermediate outcome and not a primary clinical measure of efficacy. DES were consistently associated with statistically significant lower risk of target lesion revascularization in the HTAs and meta-analyses. Rates of TLR may have been strongly influenced by protocol-driven angiographic follow-up and not based on clinical presentation and symptoms and may therefore be an over-estimate of rates in a general population.

Overall mortality and cardiac death

Based on information from previously done HTAs, current meta-analyses and trials with additional 2-5 year follow-up, no statistically significant differences in risk for overall mortality or cardiac death at any time for use of DES compared with BMS.

Conclusions from previous HTAs or similar reports (Table 25)

There is general agreement across HTAs (or similar reports) that there were no statistically significant differences in mortality between those who received DES compared with those who received BMS. There is significant overlap across these reports with regard to the specific trials used for meta-analysis or cited. In other words, many of the same trials are used across all reports, so, as expected, there is consistency

across reports. Appendix C lists the trials that were analyzed or cited in the various reports.

Table 25. Summary of results reported in previous HTAs related to mortality (death, cardiac death, or non-cardiac death)

Author (year)	Evidence Base and Approach	Effect size	Conclusions	Comments
Hill (NICE/NHS) (2007)	Systematic literature review and meta-analysis performed on 17 RCTs comparing DES to BMS Not all studies reported all outcomes. N = 3431 for comparisons of SES or PES with BMS for mortality. N for ENDEAVOR vs. BMS not provided	OR (95% CI) for DES vs BMS at 6-9 months: 0.87 (0.58 - 1.31) at 1 year: 1.31 (0.78 - 2.20) at 2 years: 0.96 (0.55 - 1.68) at 3 years: 1.64 (0.94 - 2.87) for SES vs BMS: at 6 months: 0.78 (0.43 - 1.42) at 1 year: 1.45 (0.67 - 3.15) at 2 years: 1.26 (0.49 - 3.23) at 3 years: 1.50 (0.84 - 2.68) for PES vs BMS: at 6-9 months: 0.86 (0.47 - 1.59) at 1 year: 0.89 (0.37 - 2.17) at 2 years: 0.82 (0.41 - 1.66) at 3 years: 7.25 (0.36 - 147.05)	There was no statistically significant difference in mortality at any time.	There was no heterogeneity between studies. Meta-analysis used results on cardiac or all-cause mortality, depending on data available in RCTs. To compare DES with BMS, Hill combined results for SES with PES. In a separate analysis, Hill et al compared SES to PES, and found no significant difference in mortality. Odds ratio for mortality with PES at 3 years is based on 1 study with few patients at that time point, and confidence intervals are wide.
KCE-Belgium (2007)	Systematic narrative review of meta-analyses of which 5 large, recent meta-analyses, 2 recent RCTs, and registry data provide the focus for describing efficacy, effectiveness and safety Additional meta-analyses were cited in the report The report focuses on economic analysis based on Belgian registry data	*Death:* HR (95% CI) for SES vs BMS: Kastrati: 1.03 (0.8 - 1.30) S-ne: NS difference Spaulding: 1.24 (0.84 - 1.84) Stettler: NS difference *Cardiac death*: Stettler: NS difference	There was no evidence that DES improves overall mortality or cardiac mortality compared with BMS.	KCE-Belgium did not report specific numbers for Stone or Stettler A systematic review by Nordmann found a slight increase in non-cardiac death (eg, due to cancer, stroke, or lung disease) with DES compared with BMS during 4 years after stent placement.
EUnetHTA (2008) Pilot assessment*	Partial systematic review, used update of a previous meta-analyses 17 RCTs comparing DES to BMS done by two of the report authors Not all studies reported all outcomes	RR (95% CI) for SES vs BMS: at 1 year: 0.94 (0.53 - 1.65) at 2 years: 1.31 (0.74 - 2.32) at 3 years: 1.45 (0.90 - 2.34) for PES vs BMS: at 1 year: 1.02 (0.67 - 1.54) at 2 years: 0.97 (0.60 - 1.56) at 3 years: 1.09 (0.72 - 1.65) for either DES vs BMS: at 1 year: 0.99 (0.71 - 1.39) at 2 years: 1.10 (0.76 - 1.58) at 3 years: 1.23 (0.90 - 1.69)	There was no significant difference in mortality between DES and BMS at any time. In other comparisons, no significant difference in cardiac or noncardiac mortality with either stent. However, there was a nonsignificant trend for increasing non-cardiac mortality with SES (RR 1.06 at 1 year, 2.13 at 2 years,	There was no heterogeneity between studies. The trend for increasing mortality with SES is largely due to increasing non-cardiac mortality with SES.

Author (year)	Evidence Base and Approach	Effect size	Conclusions	Comments
			and 1.95 at 3 years)	
Hayes (2007)	Systematic narrative review of 25 RCTs with 4 secondary analyses, 17 meta-analyses, and 24 observational studies Not all studies reported all outcomes.	No trial reported a significant difference in death or cardiac death from in-hospital - 1 year with SES compared with BMS. No trial reported a significant difference in death or cardiac death from 30 days - 1 year with PES compared with BMS overall or among patient subgroups.	No significant increased risk of death with DES compared with BMS when used for FDA-approved indications.	
ECRI (2008)	Review of 17 RCTs and 1 meta-analysis. Results summarized by vote count.	There were too few deaths - compare in-hospital or 1-month mortality rates Among 14 RCTs, none found a significant difference in mortality rates from 0 - 12 months after stent placement: 10.9/1000 with DES, 12.8/1000 with BMS	There was too little evidence with too few events to calculate mortality in ECRI's meta-analysis.	No numerical synthesis of results is reported.
CTAF (2007)	Narrative review citing meta-analyses with a focus on safety of DES	Not reported	Not discussed	

* The EUnetHTA is described as a pilot assessment to test a European collaborative model for formulating HTAs, using a novel perspective. They indicate that the report is not intended for actual decision making as it may be partially incomplete and partially outdated.

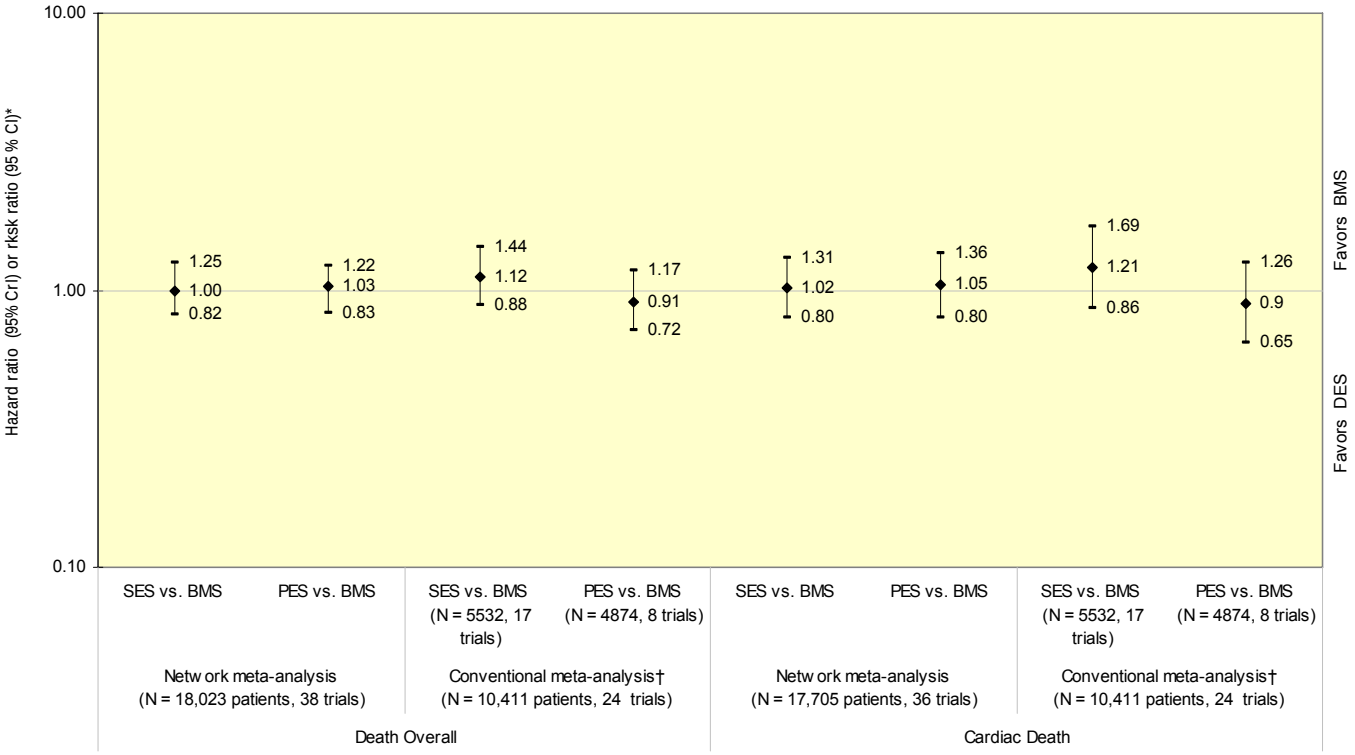
Results from recent meta-analyses

The 2007 meta-analysis by Stettler, et al[88] was the most complete and methodologically rigorous report found.

Rates for overall mortality for SES (4.0%), PES (5.3%) and BMS (4.7%) were similar, based on combined data all trials described in the Stettler 2007[88] across trials with one to 4 years' follow-up. The results of both the network meta-analysis (38 trials, 18,023 patients) and conventional meta-analysis (24 trials, 10, 411 patients) consistently showed no statistically significant difference between DES and BMS in the relative risk estimates (hazard ratio or risk ratio) of either overall mortality or cardiac mortality. The two analyses are based on different approaches to evaluation of many of the same RCTS. The show similar results and lead to the same conclusions. As previously described, network meta-analysis allows for the use of trials that are not head to head comparisons of DES with BMS (i.e. allows for inclusion of DES versus DES trials) while respecting the randomization, whereas the conventional analysis includes only head to head trials. Although the point estimates vary slightly based on meta-analytic method, the conclusion of no difference is the same regardless of method. Confidence intervals for the conventional analysis are somewhat wider than the credibility intervals for the network meta-analysis. Sensitivity analysis consisted of restricting the network analysis to trials

of specific methodological quality as well as adjustment for stent platform and strut thickness as previously described. None of these factors influenced the magnitude, direction or conclusions related to the estimates. Based on data provided in the authors' appendices, there was no inconsistency across trials included in the network, no statistical evidence of between-trial heterogeneity and assumptions for model goodness of fit were satisfied for both overall mortality and cardiac mortality. While statistical evaluation of heterogeneity provides information about the comparability of trials based on data and variance in the data, it doesn't address aspects of clinical heterogeneity and variations in population characteristics across trials which may be important to consider.

Figure 3. Relative risk estimates* for overall mortality and cardiac death comparing drug eluting stents with bare metal stents based on network meta analysis and conventional meta analysis for trials with 1 to 4 years follow-up[88]



SES = sirolims eluting stent, PES = paclitaxel eluting stent, BMS = bare metal stent
*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis
† Conventional meta-analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text)

There were no significant differences in overall mortality or cardiac death based on time after initial procedure although the incidence in all groups increased with time.

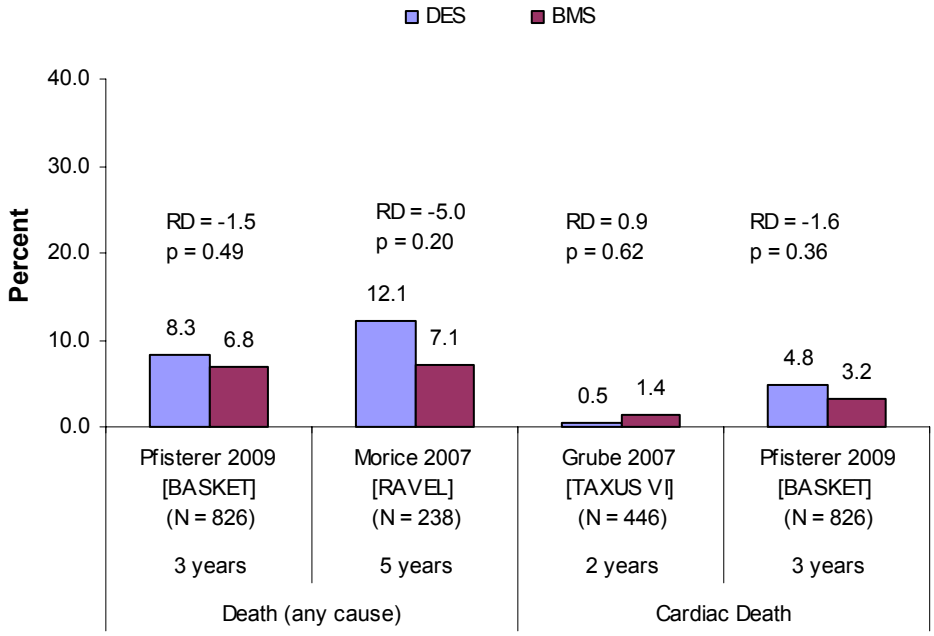
No statistically significant differences in overall mortality or cardiac death were found in other meta-analyses or pooled analyses published since 2006.[1, 77, 79, 80, 123] All of these reports included fewer trials. Additional information from these reports may be found in Appendix F and general characteristics of trials included meta-analyses can be found in Appendix C.

Results from recently published RCTs

Longer term follow-up (2-5 years) to three previously published trials [140-142] were found. No statistically significant differences in either overall mortality or cardiac-specific mortality were found and risk differences between BMS and DES were small. Two of the reports in particular may have been underpowered to detect a difference between

treatments.[140, 141] The findings are consistent with what is reported in the most recent meta-analyses of overall trial populations. Given that such meta-analyses have greater statistical power, it is unlikely that the addition of these findings would influence the general conclusions for these outcomes.

Figure 4. Rates of death (any cause) and cardiac death for longer-term follow-up on previously reported trials comparing DES with BMS



Myocardial infarction

There is no statistically significant difference in risk of myocardial infarction between DES or BMS, based on information in previous HTAs, results from conventional meta-analysis and data from recent reports from trials with 2-5 year follow-up.

Conclusions from previous HTAs or similar reports (Table 26)

There is general agreement across HTAs (or similar reports) that there were not significant differences in rates of acute myocardial infarction between those who received DES compared with those who received BMS.

Table 26. Summary of results reported in previous HTAs related to acute myocardial infarction (MI)

Author (year)	Effect size	Conclusions	Comments
Hill (NICE/NHS) (2007)	OR (95% CI): at 6-9 months: 0.84 (0.67 to 1.07) at 1 year: 0.73 (0.52 to 1.03) at 2 years: 0.92 (0.62 to 1.37) at 3 years: 0.89 (0.52 to 1.50) for SES vs BMS: at 6 months: 0.71 (0.47 to 1.09) at 1 year: 0.85 (0.46 to 1.57) at 2 years: 1.26 (0.58 to 2.74) at 3 years: 0.89 (0.52 to 1.50) for PES vs BMS: at 6-9 months: 0.96 (0.70 to 1.31) at 1 year: 069 (0.41 to 1.14) at 2 years: 0.83 (0.52 to 1.31) at 3 years: not estimable	There was no statistically significant difference in myocardial infarction at any time.	Results are for acute MI. Some heterogeneity between studies of PES.
KCE-Belgium (2007)	HR (95% CI) from previous meta-analyses Kastrati: Not reported Stone: NS difference Spaulding: Not reported Stettler: SES vs BMS: 0.81 (0.66 to 0.97) PES vs BMS: 0.83 (0.71 to 1.00)	There is no evidence that DES improves rates of subsequent myocardial infarction compared with BMS.	Kastrati and Spaulding and compared only SES with BMS Exact numbers are not reported for meta-analysis by Stone
EUnetHTA* (2008)	RR (95% CI) for SES vs BMS: at 1 year: 0.69 (0.44 to 1.08) at 2 years: 0.97 (0.62 to 1.51) at 3 years: 0.90 (0.60 to 1.37) for PES vs BMS: at 1 year: 0.96 (0.73 to 1.26) at 2 years: 1.04 (0.73 to 1.47) at 3 years: 0.99 (0.67 to 1.46) for either DES vs BMS: at 1 year: 0.87 (0.69 to 1.08) at 2 years: 1.01 (0.77 to 1.33) at 3 years: 0.95 (0.73 to 1.24)	No statistically significant difference in non-fatal MI with SES or PES at any time.	Results are for non-fatal MI There was no heterogeneity between studies.
Hayes (2007)	Most RCTs found NS difference in MI, Q-wave MI, non-Qwave MI, or recurrent MI from 30 days to 1 year: • for SES vs BMS.- Only significant difference reported was for patients with small coronary arteries at 8 months (1.6% with SES vs 7.8% with BMS; p=0.04) (SES-SMART study). • for PES vs BMS -Only significant differences reported were for a broad spectrum of patients at 9 to 12 months (0 with PES vs 1.1% with BMS; p=0.007) and for women at 1 year (2.7% with PES vs 7.9% with BMS; p=0.03).	No increased risk of myocardial infarction when used for FDA-approved indications	
ECRI (2008)	Among 5 RCTs, none found a significant difference in myocardial infarction in-hospital or at 1 month after placement Among 14 RCTs, 12 found no significant difference in myocardial infarction, while 2 found significantly fewer with DES compared with BMS from 0 to 12 months after placement	There was no statistically significant difference in acute MI up to 12 months after placement based on ECRI's meta-analysis.	No numerical synthesis of results is reported.
CTAF (2007)	Not reported	Not discussed	

* The EUnetHTA is described as a pilot assessment to test a European collaborative model for formulating HTAs, using a novel perspective. They indicate that the report is not intended for actual decision making as it may be partially incomplete and partially outdated.

Results from recent meta-analyses (Figure 4)

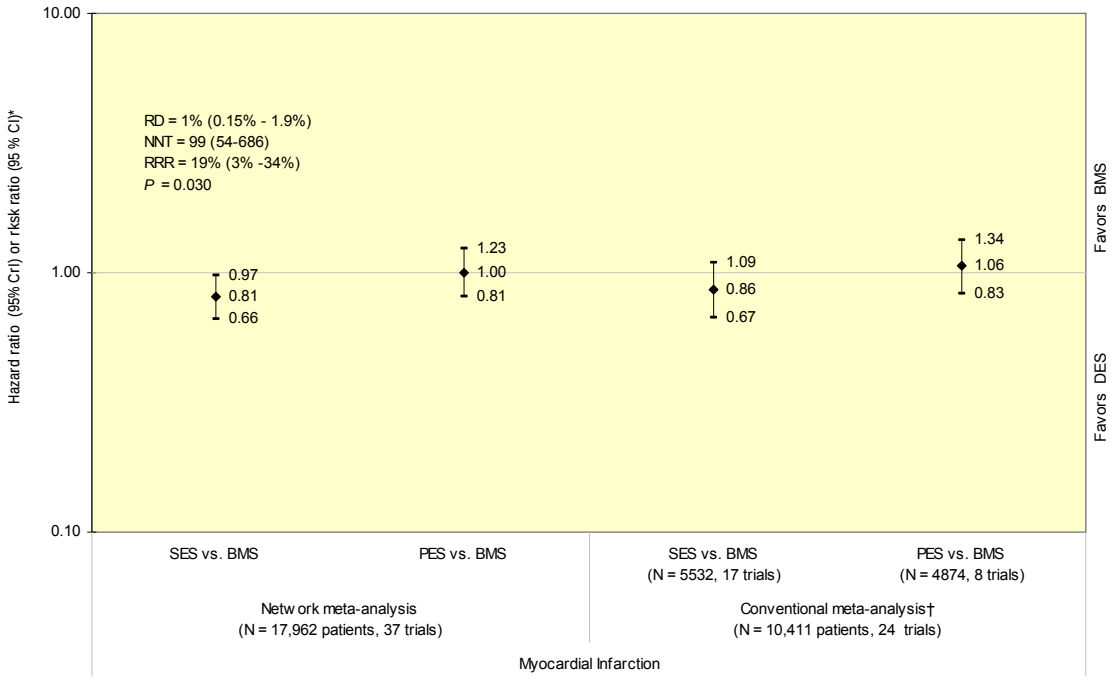
Rates for myocardial infarction (defined to include fatal and non-fatal non-Q-wave or Q-wave myocardial infarction) were somewhat lower for SES (4.1%) than for PES (5.1%) and BMS (5.2%), based on combined data trials described in the Stettler 2007[88] across trials with one to 4 years' follow-up. Overall, when SES and PES events are combined, 4.6 % (594/12,971) of DES patients experienced MI compared with 5.2% (256/4891) of BMS patients. For the network analysis, 37 trials (N = 17,962 patients) were represented and 24 head to head trials (N = 10,411 patients) were used for the conventional analysis. The incidence of myocardial infarction increased most in the period between the index procedure and first year of follow-up for all groups.

There was no statistically significant difference in MI when conventional analysis using head to head trials only was done (RR = 0.86, 95 % CI 0.67, 1.09). By contrast, Stettler's network meta-analysis estimate of relative risk suggests a lower risk of MI with SES compared with BMS, HR = 0.81 (95% CrI 0.66, 0.97, *P* = 0.030). The number needed to treat (NNT) reported by the authors was 99 patients (54-686). In other words, 99 patients would need to be treated with SES instead of BMS to avoid one MI. In terms of absolute risk, this translates in to a small risk difference between treatment groups of 1% (0.15% - 1.9%). NNT were derived from the cumulative incidence in the network meta-analysis. Direct comparisons from head to head trials may be more reliable.[139]

Sensitivity analysis was done (for all outcomes) by restricting network analyses according to features of methodological quality (concealment of allocation, blinded adjudication of outcomes, intention to treat analyses and those trial who included all three) as well as stent features (stent platform and strut thickness). From these analyses, restricting network analysis to trials which reported results according to intention to treat principles for myocardial infarction yielded an estimate of 0.86 (95% CrI 0.72, 0.98), which was closest to the estimate which included all trials. Estimates for other sensitivity analyses showed no statistically significant difference in relative risk for MI.

Comparison of PES with BMS revealed no difference between these stent types with regard to relative risk for MI for either the network or the conventional analysis. For the comparison of SES versus PES, SES was favored over PES, HR = 0.83 (0.71, 1.00, *P* = 0.045). Between-trial heterogeneity (statistical) was low for the network analysis and none was present in the conventional analysis for all treatment comparisons and no inconsistency across network trials was found.

Figure 5. Relative risk estimates* for myocardial infarction (fatal and non-fatal non-Q-wave or Q-wave MI) comparing drug eluting stents with bare metal stents based on network meta-analysis and conventional meta-analysis for trials with one up to 4 years follow-up[88]



SES = sirolimus eluting stent, PES = paclitaxel eluting stent, BMS = bare metal stent
NNT = number needed to treat to avoid one myocardial infarction over 4 years; RRR = relative risk reduction which is the proportional decrease in the patients experiencing myocardial infarction comparing DES with BMS
*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis
† Conventional meta-analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text)

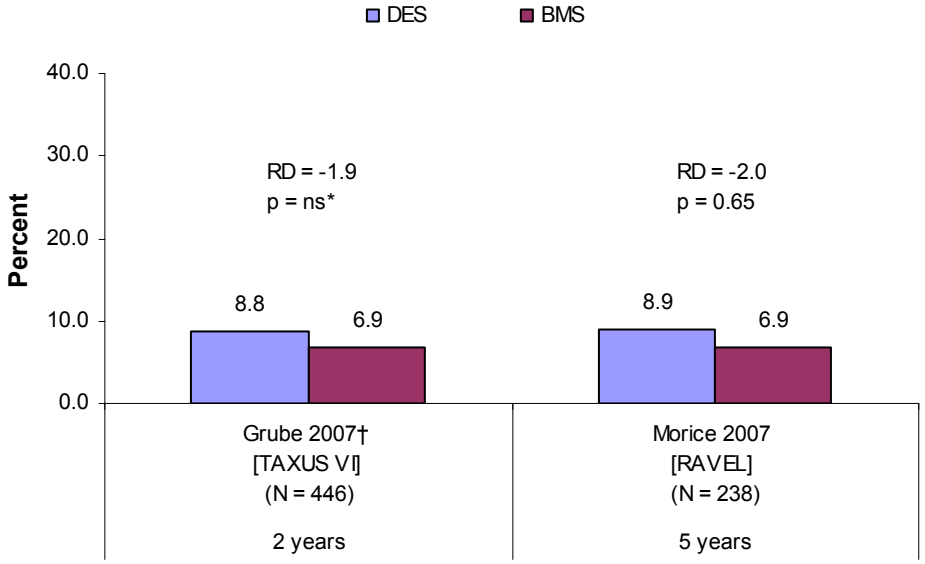
One recent meta-analysis of 25 trials by Moreno, et al reporting follow-up from 6 -12 months reported the risk of MI was significantly lower among patients who received DES (3.3%) compared with those who received BMS (4.2%), OR 0.79, 0.64, 0.97, P = 0.03 when both Q-wave and non-Q-wave MI were pooled. No statistically significant difference was seen when the two types of MI were considered separately.[143]

No other recently published meta-analyses or pooled analysis found a statistically significant difference in myocardial infarction with either SES or PES when directly compared with BMS.

Results from recently published RCTs

No differences in rates of Q-wave or non-Q-wave MI between DES and BMS were found based on long-term follow-up from two previously published trials.[140, 141] Both analyses may have been underpowered to detect a difference between treatments.

Figure 6. Rates of MI in two recently published RCTs



*Q-wave MI, p = 1.0; non-Q-wave MI, p = .44
†MI includes Q-wave MI and non-Q-wave MI

Target lesion or target vessel revascularization
Conclusions from previous HTAs and current meta-analysis indicate that DES are consistently associated with reduced rates of target lesion revascularization. In two of the previously reported RCTs with long term follow-up (3-5 years), this was not the case.

Conclusions from previous HTAs or similar reports (Table 27)
There is general agreement across HTAs (or similar reports) that DES use significantly decreased the need for target lesion and/or target vessel revascularization compared with BMS. Most also indicate that the rates may be inflated compared with rates general populations since most trials required repeat angiography as part of the study protocol and the decision for revascularization may have been driven by angiographic findings instead of patient symptoms and presentation.

Table 27. Summary of results reported in previous HTAs related to revascularization (in target lesion or target vessel) or restenosis

Author (year)	Effect size	Conclusions	Comments
Hill (NICE/NHS) (2007)	OR (95% CI) Target lesion revascularization for SES vs BMS: at 6 months: 0.21 (0.15 to 0.30) at 1 year: 0.17 (0.12 to 0.25) at 2 years: 0.22 (0.15 to 0.30) at 3 years: 0.25 (0.17 to 0.36) for PES vs BMS: at 6-9 months: 0.37 (0.28 to 0.49) at 1 year: 0.26 (0.18 to 0.39) at 2 years: 0.28 (0.20 to 0.40) at 3 years: 0.13 (0.01 to 2.69) for either DES vs BMS: at 6-9 months: 0.30 (0.25 to 0.37) at 1 year: 0.21 (0.16 to 0.27) at 2 years: 0.24 (0.19 to 0.31) at 3 years: 0.25 (0.17 to 0.35) Target vessel revascularization for PES vs BMS: at 6-9 months: 0.54 (0.43 to 0.68) at 1 year: 0.40 (0.29 to 0.55) at 2 years: 0.45 (0.34 to 0.59) at 3 years: 0.32 (0.03 to 3.29)	DES achieved statistically significantly improved rates of target lesion revascularization and target vessel revascularization up to 3 years.	No further reductions in TLR after 1 year. Data for TVR were synthesized only for PES; data for TVR were available only for single trials at 1 year and 3 years and are not included in our table.
KCE-Belgium (2007)	HR (95% CI) from previous meta-analyses Kastrati: effect size not reported Stone: SES vs BMS: 7.8% vs 23.6% HR 0.29 (0.22 to 0.39) PES vs BMS: 10.1% vs 20.0% HR 0.46 (0.38 to 0.55) Spaulding: effect size not reported Stettler: effect size not reported	DES improves the rates of restenosis and need for revascularization. However, the need for revascularization is driven by protocol driven angiographic follow up in RCTs.	Registry rates at 1 year range from 2.0% to 9.5% with DES and from 5.1% to 14.1% with BMS (see effectiveness section of report)
EUnetHTA* (2008)	RR (95% CI) for SES vs BMS: at 1 year: 0.30 (0.15 to 0.59) at 2 years: 0.28 (0.14 to 0.56) at 3 years: 0.32 (0.23 to 0.44) for PES vs BMS: at 1 year: 0.56 (0.43 to 0.73) at 2 years: 0.53 (0.42 to 0.65) at 3 years: 0.47 (0.32 to 0.70) for either DES vs BMS: at 1 year: 0.46 (0.34 to 0.61) at 2 years: 0.43 (0.32 to 0.59) at 3 years: 0.39 (0.29 to 0.52)	Both SES and PES significantly improved target lesion revascularization compared with BMS. The improvement was greater with SES than PES during the first 2 years, although results were heterogeneous.	

Author (year)	Effect size	Conclusions	Comments
Hayes (2007)	Most RCTs, overall results and subgroup analyses found significantly fewer rates of target vessel revascularization, target lesion revascularization, and/or target vessel failure with SES compared with BMT from 7 months to 1 year after stent placement. Other comparisons (e.g., with different patient populations) were nonsignificant, but favored SES. Most studies and subgroup analyses found significantly fewer rates of target vessel revascularization, target lesion revascularization, and/or target vessel failure with PES compared with BMS from 6 months to 1 year after stent placement. Other comparisons (eg, with different patient populations or using different types of PES) were nonsignificant, but favored PES, except for one dose-ranging trial (ELUTES). No RCT comparing PES to BMS found a significant difference in target vessel revascularization at 30 days.	DES decreased restenosis and revascularization when used for FDA-approved indications.	Registry data show decreased risk of revascularization and restenosis when DES are used for indications not approved by FDA. (See effectiveness section results)
ECRI (2008)		Decreased rates ot TLR/TVR with DES vs BMS were seen up to 2 years after stent placement	No numerical synthesis of results is reported.
CTAF (2007)	Previous meta-analysis by Roiron found angiographic restenosis rates as 10.5% with DES vs 31.7% with BMS (P<0.001; OR 0.25; 95% CI, 0.22 to 0.29) Babapulle found DES decrease rates of restenosis compared with BMS.	"DES are more effective than BMS in reducing early stent restenosis and the need for target vessel revascularization."	Based on the findings, CTAF recommended that DES be used only in patients with indications similar to FDA's indications for labeling; and in other patients (off-label use) only in limited circumstances However, the CTAF panel voted in favor of only the first recommendation and opposed the other.

* The EUnetHTA is described as a pilot assessment to test a European collaborative model for formulating HTAs, using a novel perspective. They indicate that the report is not intended for actual decision making as it may be partially incomplete and partially outdated.

Results from recent meta-analyses

Rates for target lesion revascularizaiton (defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel done for restenosis or other complications of the target lesion) were lower for SES (6.9%) than for PES (9.0%) and both were lower compared with BMS (19.0%), based on combined data across all trials described in the Stettler 2007[88] across trials with one to 4 years' follow-up. A total of 37 trials (n = 17,712 patients contributed to the network meta-analysis and 24 trials (N = 10,411 patients) were included in the conventional analysis. Since 3 trials did not report TLR, target vessel revascularization was used as a proxy. The authors report that similar results were obtained when these three trials were excluded from the analysis, but do not provide the data. After an initial increase in TLR in all groups between the time of the procedure and first year, the incidence of TLR remained fairly constant from years 2 to 4.

Both the network and conventional meta-analyses indicate that DES results in fewer revascularizations than BMS. The estimates are based on cumulative incidence from 0 days to 4 years after the procedure. Not all trials had data for four year follow-up. Based on included trials, to avoid one revascularization 7 (6-8) or 8 (7-10) would need to be treated with SES or PES respectively instead of BMS. This translates into risk differences of 14.3% (12.5%-16.7%) and 16.7% (10.0%-14.3%) respectively.

For TLR, there was moderate heterogeneity between trials for both the SES versus BMS and PES versus BMS comparators with I^2 estimate of 46% and 38% respectively suggesting that in the conventional analysis, this proportion of the variability in the pooled effect size could be due to heterogeneity across trials versus chance. Forest plots which provide information on the direction and magnitude of the effect size estimate as well as confidence intervals would be helpful in assessing the overall consistency of the individual trial estimates, but were not provided by the authors. All pooled estimates should be interpreted with some caution since heterogeneity will most likely be present regardless of the results of statistical testing. Heterogeneity between trials may suggest that the relative treatment effects may not arise from the same distribution and perhaps should not be combined.

Consistency among trials in the network means that indirect comparisons of treatment pairs are reasonable. Stettler reports some inconsistency across trials in the network meta-analyses with regard to TLR, which the authors suggest could be due to chance. The goodness of fit parameters for the TLR model, however, were not optimal. The estimates from the network meta-analysis for TLR remained stable based on results from the sensitivity analysis involving trial quality and stent features, however, suggesting that other sources of inconsistency or heterogeneity (statistical, methodological and/or clinical) may be present and should be considered.

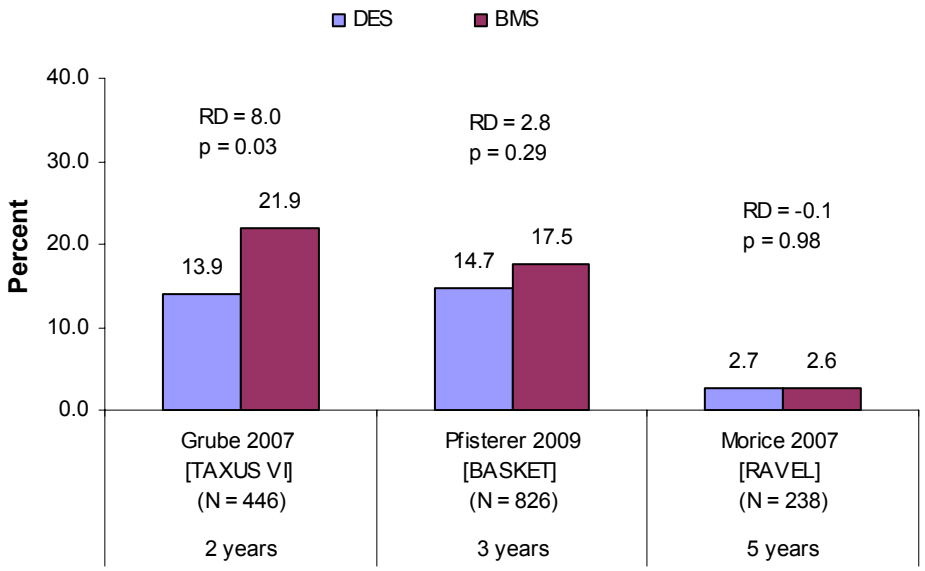
The lower risk of revascularization overall for DES compared with bare metal stents found in the Stettler analyses is consistent with the findings reported across HTAs, other meta analyses and most clinical trials, remembering that there is a significant overlap in the trails included in these reports.

To put these findings in context, several factors should be considered. Data on TVR and TLR are largely derived from trials where restenosis was defined based on protocol-driven angiography and the decision to do repeat revascularization was not always based on clinical symptoms, most likely resulting in artificially large estimates than those in every day clinical practice, thus, a higher NNT and lower absolute risk would be expected in the general population.[4, 88] In addition, the degree of obstruction from angiography may be subjective and vary between observers. Thus, the absolute difference in revascularization rates in real world practice is not clear.[4]

Results from recently published RCTs

Two-year results from the TAXUS IV trial suggest that target vessel revascularization is statistically significantly lower among patients receiving DES[140.] The trials with 3-5 year follow-up[103, 142] show no difference in TVR rates which may be consistent with the network meta-analysis data which suggest that after the first year, TVR rates for all stent types decline and appear to be similar. Given the greater statistical power for the meta-analyses, it may be unlikely that the findings from these RCTS will strongly influence the pooled estimates or conclusions.

Figure 7. Target vessel revascularization in recent published RCTs



Other meta-analyses consistently found significantly fewer revascularizations with SES or PES compared with BMS.

Effectiveness

The evidence from published HTAs or similar reports which included registry data suggest that mortality and MI rates do not differ between DES and BMS patients. Rates of revascularization are lower for DES patients, but there is substantial heterogeneity between the studies included. Most HTAs express a need for longer follow-up and more specific definitions of the outcomes from registry data.

Registries provide the opportunity to assess outcomes from a broader "real world" patient population than those included in clinical trials and also may have greater power to detect rare adverse events. There are limitations however to drawing conclusions from registry data. The treatment modality is selected by the attending physician and is subject to

guidelines in place at the time of the PCI. Often there is no comparison group and there can be considerable selection bias. It is not possible to determine follow-up rates. For these reasons, all registry studies are classified as LoE III. Analyses to control for selection bias or potentially confounding factors are only as good as the completeness of the data used for classification. If something is not measured, it cannot be controlled for. Although many studies report adjusted estimates, some using propensity scores, it is not always clear which factors were included or how scores were derived.

Only one HTA, the Ontario Ministry of Health & Long Term Care (Ontario) [85] included any pooling of data from registry studies, although tests for heterogeneity were significant. Hill (NICE/NHS 2007)[81] reviewed reports from 24 registries and identified 18 with sufficient information to discern use of DES but concluded it was inappropriate to pool data due to inconsistencies across registries. The Belgian Health Care Knowledge Center (KCE 2007) reviewed 29 registry reports but also did not pool the results.[4] They did report some rates and conclusions from their review. The California Technology Assessment Forum (CTAF 2007) report is a narrative review focused mainly on stent thrombosis and anti-platelet therapy.[77] They referenced some registry studies, but did not report any rates. The Hayes Directory (2007) report included rates from one registry study (SCAAR) where there was a comparison of DES to BMS and we have included those here.[78] Although many of the HTAs did obtain and review registry studies, often they did not report detailed information or analyses from them. In some cases their goal was to obtain more real world estimates to supplement RCT evidence for use in economic analyses.

Details of registry and nonrandomized studies are found in Appendix H.

Overall mortality and cardiac death

The evidence from past HTA reviews of registry data suggest that mortality and MI rates do not differ between DES and BMS patients. Data from more recently published nonrandomized studies are overall consistent with this finding.

Conclusions from previous HTAs or similar reports (Table 28)

Ontario performed a pooled analysis and a meta-analysis of data on all cause mortality from 13 non-randomized, comparative studies and found no significant differences in mortality risk between DES and BMS[85.] They also found no trend in mortality difference increasing with time. However, there was heterogeneity between studies (p=.07). This finding was echoed in two [4, 81] of the three other HTA reviews that addressed mortality from the registry studies. The Hayes HTA reported DES versus BMS results from one registry, SCAAR (Sweden), where authors found an increased mortality risk after 6 months and also at 3 years (RR = 1.18, 95% CI 1.14-1.35).[78] Cardiac death was only reported by one HTA (Ontario) from one small registry study and not mentioned further.[85]

Table 28. Summary of conclusions from previous HTAs or similar reports

Author (Year)	Evidence Base and Approach	Effect Size Mortality	Conclusions	Comments
Ontario (2007)	13 comparative studies thru 2006, 41,664 pts total; follow-up 9-12 mo (10 studies), 24 mo (1), 36 mo (2). Pooled Relative Risk, Meta-analysis, DerSimonian & Laird random effects models, heterogeneity using Mantel-Haenszel model.	RR (95% CI) DES vs BMS: <= 12 mo: 0.77 (0.54-1.09) 13-24 mo: 0.81 (0.50-1.31) >24 mo: 0.95 (0.86-1.06) Combined 36 mo: 0.87 (0.70-1.09). Risk Difference DES (95% CI) At 12 mo: -0.7% (-1.9% to 0.6%) 24 mo: -0.6% (-3.5% to 2.3%) 36 mo: -0.3% (-1.1% to 0.5%) Cardiac death at 12 mo: Reported in one study (n=505) RR 4.99 (0.58-41.80)	No significant difference in mortality risk or risk differences between DES and BMS. No trend in mortality difference increasing with time when combining registry studies.	There was heterogeneity between studies (p=.07). Some used historical controls, some concurrent. The RR for mortality within studies favored BMS in five studies, DES in 5 studies, neither in 2, not significant except one (Williams, favored DES, 12 mo RR 0.47, (95% CI 0.35-0.81). Full information regarding patients and outcomes were not available from all studies (4 were abstracts). Few studies reported outcomes longer than 12 mo. Lesion characteristics were not reported for most. There was selection bias. Patients selected for DES had a higher rate of pre-existing co-morbidities, were more likely female (% male: DES 69% vs BMS 70.9%, p=0.016). DES was more commonly used in patients who had diabetes (DES 27.2%, BMS 17.1%, p=0.035), previous PCI (DES 16.1%, BMS 10.8%, p=0.007) and multi-vessel disease (DES 48.7%, BMS 46.7%, p=0.001).
Hill (NICE/NHS) (2007)	Review of reports from 24 Registries identified, 18 with sufficient data to discern use of DES. Number of participants varied from 183 to >15,000	Rates not provided	No statistically significant differences in death were detected between DES and BMS. Inappropriate to pool data due to inconsistencies across registries. Severity of disease of patients treated has increased over time.	First conclusion is general, applying to RCT analysis as well as additional review. Most registries related to one type of DES and had commercial sponsorship by manufacturer or distributor of the DES being utilized.
KCE (2007)	29 Registries identified, published since 2005	Rates not provided	DES do not significantly influence mortality rates.	Conclusion of no significant difference in mortality between DES vs BMS is from RCT evidence. Pooled analysis of registry data not performed
CTAF (2007)	Review relating to late stent thrombosis which included studies from registry data	Not reported	Late stent thrombosis often leads to death	Report is a narrative review.
Hayes (2007)	Review comparing DES to BMS of one study from SCAAR registry	RR (95% CI) At 3 yrs: 1.18 (1.04-1.35) Propensity score adjusted cumulative event rate after 1st 6 mo: 1.32 (1.11-1.57)	SCAAR: Increased long term risk of death for DES vs BMS.	3 year RR is based on Cox regression model at mean propensity score. No details provided in review of factors included in propensity score. Limitations include observational study design, possible selection bias and possible physician bias in stent selection.

No registry assessments were made in the other HTAs or similar reports.

Results from recent meta-analyses

No other pooled analyses of registries were found.

Results from recently published registry or nonrandomized studies

Rates for overall mortality across recently published registry reports ranged from 4.5% to 8.5% for DES and 4.8% to 17.0% for BMS at the latest follow-up up to 2 years. Two studies reported outcomes at greater than 2 years follow-up. Only one study reported rates for cardiac mortality at two years: 4.4% for DES and 4.3% for BMS (Table 29).

Table 29. Rates of overall and cardiac mortality reported in registry or nonrandomized studies

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Overall mortality			
≤ 30 days	6 [108, 110, 115, 121, 122, 133]	0.7-1.2	0.9-3.3
30 days-1 year	6 [108, 110, 121, 122 131, 133]	2.7-6.1	3.1-8.6
1 year-2 years*	6 [110, 112, 115, 117 131, 133]	4.5-8.5	6.1-12.6
> 2 years†	2 [122 135]	5.7-8.0	4.8-17.0
Cardiac mortality			
≤ 30 days	1 [134]	2.1	1.2
At 1 year	1 [134]	0.6	0.5

*One study, Harjai et al 2008, reported different mean follow-up periods for the DES and BMS arms; the BMS group had almost one more year of follow-up than the DES group. The follow-up period here reflects a pooled mean of these two follow-up periods.
** Rates for one study, Roy et al 2008, were estimated from author figures.
†One study reported outcomes for > 2 years (3 year follow-up), the other for up to 4.5 years [Shishehbor].
§Only two studies reported cardiac mortality.

Adjusted relative risk estimates for overall death at the longest available follow-up (12 months to > 2 years) mixed, with six suggesting that there is no significant difference in risk of overall death between DES and BMS, one showing increased risk for DES and three showing higher risk for BMS. Of the recently published studies which provided adjusted estimates of relative risk:

- No statistically significant difference in overall mortality was seen at:
  - 30 days in one study [108]
  - 30 days to 1 year in three studies [108, 122, 134]
  - 1 year to 2 years in four studies [112, 117, 131, 134]
  - > 2 years in one study [122]

- Statistically significant difference (higher risk for BMS) in overall mortality was seen at:
  - ≤ 30 days in one study [121]
  - 30 days to 1 year in one study [121]
  - 1 year to 2 years in two studies [132, 133]
  - Up to 4.5 years in one study [135]

Ten [108, 110, 112, 115-117, 122, 131, 134, 144] of the fifteen studies [108, 110, 112, 115-117, 121-123, 131-135, 144] on "general" populations reported no significant difference in mortality between BMS and DES treated patients. Applegate, et al, [144] separated patients into those presenting with on-label versus off-label indications and found an unadjusted lower risk of mortality among off-label patients but did not report an adjusted rate individually. Two Canadian registries showed a higher risk of death for BMS. Philpott[121] showed risk adjusted ORs for death to favor DES at points up to one year. The odds of death were not significantly different between DES and BMS for patients with non-acute coronary syndromes. Time dependent spline analysis showed an initial survival benefit with DES which diminished over time to show benefit with BMS. Tu, et al, [123] matched DES patients by diabetes presence and propensity score to concurrent patients receiving BMS, with 3751 patients in each arm. The Kaplan Meier survival analysis favored DES over three years follow-up. One quarter of the patients in the registry were not eligible for the match, however, due to insufficient data to calculate the propensity score or obtain follow-up information. Mauri 2008, Austin 2008 and Shishehbor 2008 found higher risk of mortality for BMS in propensity matched cohorts. Significant observations are lost in the process of propensity matching although the resulting cohorts showed reasonable balance of risk factors. Residual confounding could not be ruled out, Cardiac death was reported in two of the general studies[117, 134] and the unadjusted risk was not significantly different between DES and BMS. Only one of the three studies of STEMI patients showed a mortality difference between DES and BMS. Kornowski, et al, [113] in a matched case-control study (DES n=122, BMS n=506) found lower mortality in the DES group at one and 6 months, but not at 12 mo. Among patients with unprotected left main coronary artery stenosis, Palmerini, et al,[120] found the risk of cardiac death was significantly lower in the DES group over two years (aHR=0.48 (95% CI 0.31-0.74). In analysis looking at separate time periods, after 180 days, there was not a significant difference in cardiac death (181-360 days; aHR = 1.249 (0.316-4.932). The size of the confidence interval suggests the small number of BMS patients in the analysis may limit the power.

Only one study reported adjusted relative risk estimates for cardiac death at the latest follow-up period.[120] At 2 years, a significant difference in risk of cardiac death was seen between DES and BMS (HR = 0.48, CI, 0.31-0.74).

Myocardial infarction

The risk of MI from DES versus BMS was not significantly different up to 36 months post PCI according to findings from the Ontario HTA pooled analysis. This conclusion was echoed by the remaining HTAs that provided evidence from registry studies. In two of the reports the conclusion is based on combined RCT and registry outcomes. Some limitations of identifying MI outcomes are that not all studies report them uniformly nor do they all provide breakdowns of type of MI. The Ontario pooled results did provide results for Q-wave MI and non-Q-wave MI separately, with Q-Wave MI Relative Risk at 12 months slightly favoring DES (0.12 (0.01-0.99, p= 0.05)). Results beyond 24 months for this breakdown of MI were not available. There was no significant difference in risk of myocardial infarction (MI) in seven newer studies that reported ratios adjusted for differences in patient characteristics at various follow-up times. [108, 115-117, 122, 123, 132]

However, three studies showed a statistically significant difference favoring DES at some time point.[131, 133, 134]

Conclusions from previous HTAs or similar reports (Table 30)
Pooled analyses in the Ontario HTA suggest that there is no significant difference in the risk of MI with the use of DES compared with BMS. In two of the reports the conclusion is based on combined RCT and registry outcomes. Some limitations of identifying MI outcomes are that not all studies report them uniformly nor do they all provide breakdowns of type of MI. The Ontario pooled results did provide results for Q-wave MI and non-Q-wave MI separately, with Q-Wave MI Relative Risk at 12 months slightly favoring DES (0.12 (0.01-0.99, p =0.05)). Results beyond 24 months for this breakdown of MI were not available.

Table 30. Summary of conclusions from previous HTAs or similar reports

Author (Year)	Evidence Base and Approach	Effect Size Myocardial Infarction	Conclusions	Comments
Ontario (2007)	6 comparative studies reporting MI thru 2006; follow-up 9-12 mo (6), 24 mo (1), 36 mo (2).	DES RR (95% CI) 12 mo MI-all 1.1 (0.8-1.5) MI-Q-Wave 0.12 (0.01-0.99) MI-non Q-wave 1.3 (0.8-1.9) 13-24 mo MI-all 0.8 (0.5-1.3) >24 mo MI-all 1.15 (0.5-2.6)	Risk of MI from DES vs BMS not significantly different up to 36 months post PCI	Few studies reported outcomes beyond 12 months. Not all studies reported all outcomes uniformly. Some used historical controls for BMS and some concurrent. Selection bias was present (see details under mortality). Data pooled for relative risk, but insufficient data for formal meta analysis.
Hill (NICE/NHS) (2007	Reports from 18 registries with sufficient data to discern use of DES.	Rates not provided	No statistically significant differences in AMI were detected between DES and BMS, within either DES subgroups or pooled analyses.	First conclusion is general, applying to RCT analysis as well as additional review. Most registries related to one type of DES and had commercial sponsorship by manufacturer or distributor of the DES being utilized.
KCE (2007)	29 Registries identified, published since 2005	Rates not provided	DES do not significantly influence rates of MI.	Conclusion of no significant difference in mortality between DES vs BMS is from RCT evidence.
CTAF (2007	Review relating to late stent thrombosis	Not reported	Late stent thrombosis risk higher in patients having DES implanted which often can lead to MI	"prudent to reserve DES for uses studied in pivotal RCTs"
Hayes (2007)	One study: SCAAR compared DES and BMS: Propensity score adjusted cumulative event rate	RR (95% CI) DES vs BMS >6 mo 1.12 (0.95-1.32)	No significant difference	Observational study, possible selection bias and physician bias in stent selection. Analysis may not totally account for differences.

Results from recent meta-analyses
No other pooled analyses of registries were found.

Results from recently published registry or nonrandomized studies

Rates for myocardial infarction across recently published registry reports ranged from 1.7% to 12.7% for DES and 2.0% to 11.5% for BMS at the latest follow-up (Table 31).

Table 31. Rates of myocardial infarction reported in registry or nonrandomized studies

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Myocardial infarction*			
≤ 30 days**	5[108, 110, 122 133, 134]	0.9-2.5	0.9-3.5
30 days-1 year**	6[108, 110, 122, 131, 133, 134]	2.7-8.5	2.0-8.4
1 year-2 years†	4 [110, 112, 115, 117]	1.7-12.7	2.0-11.5
> 2 years§	1 [122]	6.2	2.7

*For the study by Campolo et al 2007 Q-wave and non-Q wave myocardial infarction rates were summed to get overall myocardial infarction rates.
†One study, Harjai et al 2008, reported different mean follow-up periods for the DES and BMS arms; the BMS group had almost one more year of follow-up than the DES group. The follow-up period here reflects a pooled mean of these two follow-up periods.
§Only one study reported outcomes for > 2 years (3 year follow-up).
**Rates for Roy et al 2008, were estimated from author figures

There was no significant difference in risk of myocardial infarction (MI) in the studies that reported ratios adjusted for differences in patient characteristics at various follow-up times in seven studies. [108, 115-117, 122, 123, 132] However 3 studies showed a statistically significant difference at least on follow-up time. [131, 133, 134]

- No significant difference in the risk of myocardial infarction in DES versus BMS at any of the time points reported.
  - Two studies did not report adjusted MI rates, but stated there was no difference in unadjusted MI rates.[110, 112]
  - Two studies did not report MI rates separately[121, 144]
  - Marroquin, et al, also reported adjusted MI rates for off-label versus on-label indications between DES and BMS and also found no difference in MI rates.[116]
- Three studies reported statistically significant differences in MI favoring DES:
  - Statistically significant decrease in MI with DES was reported at 12 months in one study.[134]
  - Anstrom reported no difference at 12 months, but a statistically significant difference at 24 months.[131]
  - Mauri's results were significant at all follow-up times.[133]

Target lesion or target vessel revascularization

All the HTA analyses and reviews found that revascularization rates, particularly reported as target vessel revascularizations, were lower in DES patients than those treated with BMS. Overall, the authors of previous HTAs and others have noted that revascularization rates were higher in the BMS arms of randomized trials than is seen in common clinical practice, suggesting that patients were higher risk in the trials included or that revascularization rates were driven by protocol-mandated angiograms.[4, 81, 88]

Conclusions from previous HTAs or similar reports (Table 32)
In the pooled Ontario analysis, the RR for TVR at 9-12 months was 0.54 (95% CI 0.41-0.71), although there was heterogeneity. They noted that most of the registries were related to one type of DES and had commercial sponsorship by a manufacturer or distributor of the DES being utilized[85]. Rates were not provided from the HTA registry reviews for subgroups defined by patient characteristics.

Table 32. Summary of conclusions from previous HTAs or similar reports

Author (Year)	Evidence Base and Approach	Effect Size Revascularizations	Conclusions	Comments
Ontario (2007)	Pooled analysis for 7 studies reporting outcome: up to 12 mo (7 studies), 13-24 mo (0), >24 mo (1) Meta-analysis of 8 studies with up to 36 months follow-up.	RR (95% CI) (#studies) DES 9-12 mo: TLR 0.53 (0.26-1.05)(3) TVR 0.54 (0.41-0.71)(7) TVR by CABG 0.39 (0.22-0.68)(2) Up to 36 mo: RR (95% CI) (8 studies) 0.55 (0.44-0.69)	Lower rate of TVR for patients treated with DES vs those treated with BMS.	• There was heterogeneity. • Few studies reported outcomes beyond 12 mo. Two studies showed no statistically significant differences in TVR: Karjalainen, using TITANOX compared to PES and Halkin et al, in small sample of patients with renal insufficiency.
Hill (NICE/NHS) (2007	Reports from 18 registries with sufficient data to discern use of DES.	Not reported	Major differences in revascularization rates in favor of DES. Rates in BMS arm far higher than is seen in common clinical practice. Suggested that either only very high-risk patients were entered into the trial or revascularization rates were driven by protocol-mandated angiogram in all studies except BASKET.	• Conclusion is general, applying to RCT analysis as well as additional review. • Most registries related to one type of DES and had commercial sponsorship by manufacturer or distributor of the DES being utilized.
KCE (2007)	29 Registries identified, published since 2005	At one year: Revascularization rate ranges: DES 2.0% - 9.5% BMS 5.1% - 14.1%	Revascularization rates obtained through registries are generally lower than in RCTs but may better reflect effectiveness in daily practice.	• No pooled analysis of registry data was performed. Revascularizations are reported differently, such as PCI and/or CABG rates, or TVR or TLR. Period of follow-up is different. There is selection bias in terms of choice of BMS or DES by physicians.
Hayes (2007)	SCAAR registry study, Propensity score methods to adjust for differences, Cox	RR (95% CI) DES New PCI: 0.90 (0.82-0.98) CABG: 0.54 (0.42-0.70)	Significantly lower risks of revascularization and restenosis in	• Observational study, possible selection bias and physician bias in stent selection. Propensity analysis

	regression with adjustment for background factors	TVR: 0.84 (0.77-0.92) Restenosis: 0.40 (0.31-0.51)	DES group	may not adjust for all differences.

Results from recent meta-analyses

Biondi-Zoccai et al[96] compared DES with BMS and DES with CABG for patients with disease in an unprotected left main coronary artery. Traditionally, this has been an indication for CABG, rather than percutaneous intervention. They reportedly found no randomized trials including such patients. Their analysis is based on registry data and nonrandomized comparisons. Consistent with other registry studies, pooled estimates for TVR (OR = 0.34 [0.12-0.94], P = .04, I 2 = 0%) and MACE ([OR] = 0.34 [0.16-0.71], P = .004, I 2 = 45.3%) favor DES based on three nonrandomized studies (LoE III) two of which were retrospective, representing, a total of 396 patients. The authors do not report rates for clinical outcomes such as survival or myocardial infarction which are usually components of the composite measure, thus it is unclear to what extent the MACE estimates are driven by the TVR rates. They do not report on thrombosis or other safety-related outcomes. Since the included studies are LoE III, no firm conclusions regarding the stability of the pooled estimates is possible and results should be interpreted cautiously.

Results from recently published registry or nonrandomized studies

Thirteen of the studies in general populations reported adjusted revascularization rates, with follow-up times from 30 days up to 3 years. [108, 110, 112, 115-117, 122, 123, 131-134, 144] All showed lower risk of revascularization for DES, with a range of adjusted ratios of 0.35 to 0.68. One study, Ajani 2008,[108] reported non-significant revascularization rates at 30 days (1.31; 95% CI (0.86-2.33)).

Rates for target lesion revascularization and target vessel revascularization across recently published registry reports ranged from 5.2% to 14.2% for DES and 8.1% to 24.4% for BMS, respectively, at the follow-up times > 1 year (Table 33).

Table 33. Rates of revascularization reported in registry and nonrandomized studies

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Revascularization*			
TLR			
≤ 30 days	3[108, 110 134]	0.4-- 1.7	0.6-1.4
30 days-1 year	3[108, 110 134]	3.5-7.8	6.0-16.4
1 year-2 years	2 [110, 117]	5.2-5.8	8.1-9.9
TVR			
≤ 30 days	4[108, 110 133, 134]	0.6-2.5	1.2-3.2
30 days-1 year	6[108, 110, 122 131, 133, 134]	4.8-13.1	7.4-20.2

1 year-2 years†	6 [110, 112, 117 131-133]	6.6-11.5	12.8-19.0
> 2 years§	1 [122]	14.2	24.4

TLR = target lesion revascularization.
TVR = target vessel revascularization.
*One study, Mack et al 2008, did not differentiate between TLR and TVR at 18 months. Revascularization rate reported was 12.1% for DES and 14.9% for BMS.
† One study, Harjai et al 2008, reported different mean follow-up periods for the DES and BMS arms; the BMS group had almost one more year of follow-up than the DES group. The follow-up period here reflects a pooled mean of these two follow-up periods.
§Only one study reported outcomes for > 2 years (3 year follow-up).
Rates for Roy et al 2008, were estimated from author figures

Adjusted relative risk estimates for revascularization at the longest available follow-up (12 months to > 2 years) suggest a significant difference in the risk of target vessel revascularization (TVR) and target lesion revascularization (TLR) between DES and BMS in all studies. Only one study reported TLR. Of the recently published studies which provided adjusted estimates of relative risk:

- No statistically significant differences in TVR and TLR were seen at:
  - 30 days in one study.[108]
- Statistically significant difference in TVR was seen at:
  - 30 days to 1 year in three studies[108, 110, 122, 132-134]
  - 1 year to 2 years in six studies [110, 112, 117, 131-133]
  - > 2 years in one study[122]
- Statistically significant difference in TLR was seen at:
  - 30 day to 1 year in one study (HR = 0.57, CI, 0.39-0.82)[108]

3.2 Key question 2 -What is the evidence related to the safety profile of DES versus BMS

- Including in patients with and without continuation of anti-platelet medications

Safety

Stent thrombosis, particularly late stent thrombosis, is an important safety issue. While most HTAs indicate that that there were no statistically significant differences in stent thrombosis when DES were compared with BMS, particularly at longer follow-up times, several note that studies and even some meta-analyses may have been underpowered to detect statistically significant differences between treatment groups. Data from the most recent and complete meta-analysis suggests that there are no statistically significant differences in stent thrombosis in studies with up to 4 years follow-up, however, heterogeneity across trials combined with wide confidence intervals around estimates for late stent thrombosis in particular suggest that additional monitoring is needed.

No comparative studies evaluating bleeding following prolonged dual anti-platelet therapy or stent fracture were found. Rates from case series are presented.

Thrombosis

Overall rates of stent thrombus following placement of either DES or BMS are low. Based on ARC definition of definite thrombosis, rates from the most recent meta-analysis based on up to 4 years of follow-up were 1.4% for SES, 1.7% for PES and 1.2% for BMS. While most meta-analyses show no statistically significant difference in risk of stent thrombosis when DES and BMS are compared, some trials and even meta-analyses may have been underpowered to detect statistically significant differences particularly since the number of trials (and patients with and without events) with longer-term follow-up is small.

Conclusions from previous HTAs or similar reports (Table 34)

While most HTAs indicate that that there were no statistically significant differences in stent thrombosis when DES were compared with BMS, particularly at longer follow-up times, several note that studies and even some meta-analyses may have been underpowered to detect statistically significant differences between treatment groups. One report focusing on safety concluded, however, that the majority of evidence suggests that there is an increased risk of stent thrombosis with DES compared to BMS. Two reports conclude that there is a significantly higher risk of stent thrombosis after one year. There is significant overlap across these reports with regard to the specific trials used for meta-analysis or cited. In other words, many of the same trials are used across all reports, so, as expected, there is consistency across reports. Appendix C lists the trials that were analyzed or cited in the various reports.

Table 34. Summary of results reported in previous HTAs related to thrombosis

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Hill (NICE/ NHS) (2007)	Systematic literature review and meta-analysis performed on 17 RCTs comparing DES to BMS Not all studies reported all outcomes and total N for outcomes is not provided	OR (95% CI) • 1 month: 0.85 (0.47–1.56) • 6–9 months: 0.59 (0.32–1.10) • 1 year: 0.89 (0.35–2.25) • 2 years: 1.93 (0.69–5.43) • 3 years: incalculable	No statistically significant difference (NS) differences at any time.	• Fixed-effect (FE) model primarily used. • Random-effects (RE) model results included if heterogeneity* present. • Individual study estimates were not presented on effect direction and statistical significance, so pooled data should be interpreted with caution. • Quantitative heterogeneity* NS
KCE (2007)	Systematic review; Described 4 meta-analyses: *Mauri et al. (2007):* 8 RCTs (N = 4545) (DES vs BMS) *Spaulding et al. (2007):* 4 RCTs (N = 1748) (SES vs BMS) *Kastrati et al. (2007)*: 14 RCTs (4958) (SES vs BMS) *Stone et al. (2007):* 9 RCTs (N = 5261) (DES vs BMS)	*Mauri*: Definite or probable thrombosis (ARC), 4 year rates: • (SES, BMS): (1.5%, 1.7%), (95% CI -1.5 to 1.0) • (PES, BMS): (1.8%, 1.4%), (95% CI -0.7 to 1.4) Definite or probable thrombosis after first year (ARC): • (SES, BMS): (0.9%, 0.4%), (CI NR)) (PES, BMS): (0.9%, 0.6%), (CI NR)) *Spaulding*: Thrombosis (protocol), 4 year rates: • (SES, BMS): (1.1%, 0.6%) (hazard ratio, 2.00; 95% CI 0.68–5.85); • (5, 0 cases) occurred after first year (% NR) Definite or probable thrombosis (ARC): • (SES, BMS): (3.4%, 3.2%) (hazard ratio, 1.07; 95% CI 0.64–1.79); • (6, 14 cases) in first year (% NR); • (23, 14 cases) after first year (% NR) *Kastrati*: Thrombosis (protocol), 4.9 year rates: • (SES, BMS): (1.4%, 1.3%) (hazard ratio, 1.09; 95% CI 0.64–1.86); • After first year: (8, 1 cases) (% NR) Overall risk of stent thrombosis in this period: • SES: 0.6% (95% CI 0.3–1.2) • BMS: 0.05% (95% CI 0.01-0.4) *Stone*: Thrombosis (protocol), 4 year rates: • (SES, BMS): (1.2%, 0.6%) • (PES, BMS): (1.3%, 0.9%); After first year: • (SES, BMS): (5, 0 cases) (% NR) (P = 0.025) • (PES, BMS): (9, 2 cases) (% NR) (P = 0.028)	*Mauri*: NS difference Limited power to detect small differences in rates *Spaulding*: NS difference whether protocol or ARC definition of thrombosis was used. *Kastrati*: Slight increase in risk of thrombosis in SES group after the first year (*P* = 0.02), may be due to discontinuation of dual antiplatelet therapy. NS difference in the overall 4-year risk of thrombosis. *Stone*: Slight increase in risk of thrombosis in both DES groups after the first year (*P* = 0.025–0.028). NS difference	• Data from meta-analyses described but not analyzed. • All 4 meta-analyses claimed to use individual patient data. • • RCTs analyzed by Mauri were the same as those used by Spaulding (only SES trials) and Stone (except for TAXUS VI trial).
EUnetHTA (2008) Pilot assessment*	Partial systematic review, report of meta-analyses Decribe 5 meta-analyses and 2 observational	*Meta-analyses:* Data NR *Cohort studies:* • Incidence of late stent thrombosis: (DES, BMS): (2.6%, 1.3%)	NS difference in the incidence of stent thrombosis at 4 years. Discontinuation of dual antiplatelet therapy is associated with increase	Data only very briefly described. Studies were insufficiently powered.

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
	studies	• Incidence of stent thrombosis in DES patients after premature discontinuation of anti-platelet therapy: 29% (compared to 9 month risk of 1.3% in all DES patients).	thrombosis risk. Unclear whether the benefits of DES outweigh their risks, especially for "off-label" uses.	
Hayes HTA (2007)	Systematic narrative review Described 10 RCTs, 3 RCT substudies, 15 meta-analyses, 4 registry studies, and 3 cohort studies.	*RCTs:* • Incidence of stent thrombosis ranged from 0–3%; most reported between 8–12 months follow-up. • Meta-analyses: • Incidence of stent thrombosis was similar to that in RCTs, follow-up ranged from 6–12 months to 4 years. *Registry studies:* • Low rates of stent thrombosis (< 1%) with DES.	Most studies found no significant differences in overall thrombosis rates between DES and BMS. Three meta-analyses detected a significantly higher risk of stent thrombosis after the first year with DES.	• Data described but not analyzed. • All RCTs were industry-sponsored except one, in which the authors had financial interests in industry. • RCTs had relatively short follow-up. • Protocol definition of thrombosis varied, making it difficult to determine the "true rate" of events. • Overlap in the studies used for the meta-analyses. • Most studies, including the meta-analyses, were underpowered to detect any significant difference in thrombosis rates between the two groups.
ECRI (2008 update to 2006 report)	Described 14 RCTs and 1 meta-analysis. Generated pooled estimates of thrombosis rates for 1 and 12 month follow-ups only using 10 and 13 RCTs, respectively.	*In hospital:* • 12 RCTs (N = 5981) • Only 1 of 12 RCTs showed a statistically significant difference between DES and BMS groups. • 7 of 12 RCTs reported zero events. *1 month:* • Pooled data from 10 RCTs (N = 5372) show no significant difference in thrombosis rates between BMS and DES groups. • Incidence of stent thrombosis was 4.5 per 1000 in the DES group and 5.2 per 1000 in the BMS group. *0–12 months:* • 13 RCTs (N = 6463) • Only 1 of 13 RCTs showed a statistically significant difference between DES and BMS groups out to 6–12 months follow-up. • Meta-analyses: NS difference *12–24 months:* • Bavry et al. (2006): meta-analysis of 14 RCTs (N = 6463) showed that the incidence of stent thrombosis was 5.0 per 1000 in the DES group and 0 per 1000 in the BMS group. • Only 1 of 13 RCTs showed a statistically significant difference between DES and BMS groups out to 6–12 months follow-up.	*Overall conclusions:* ECRI's meta-analysis showed NS difference at 12 months. Bavry's meta-analysis showed a significantly increased risk of thrombosis at 2 years follow-up. DES are associated with a long-term risk of stent thrombosis.	• Data analyzed and described. • Details of meta-analysis are in the 2006 report, which is not freely available. • Clinical studies and FDA-monitored registries with longer term follow-up are needed.
CTAF HTA (2007)	Narrative review citing meta-analyses with a	*Meta-analysis:* Data only reported for one meta-analysis. • Incidence of late stent thrombosis: 5.0 events per 1,000 DES	The majority of evidence suggests that there is an increased risk of stent thrombosis with DES	Results from published studies described but not analyzed.

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
	focus on safety of DES Described 2 meta-analyses and 1 prospective cohort	• No events reported for BMS. • RR 5.02 (95% CI, 1.29 to 19.52) (P = 0.02). *Cohort study:* • of late stent thrombosis at 18 months in patients had survived the first 6 months after stenting, had no major clinical events, and Incidence had discontinued clopidogrel: (DES, BMS): (2.6%, 1.3%)	compared to BMS. There is an approximately 0.2% increase in the risk of late stent thrombosis per year with DES compared to BMS.	
HTA report of Registry studies				
Ontario (2007)	Pooled estimates from 3 registry studies	*Pooled for 3 registries:* *Goy*: • DES: 0.7% (0.5%–3.4%) • BMS: 1.0% (0.8%-1.1%) • RR=0.553; CI, 0.279–1.096) (P = 0.089)	NS difference in rates of stent thrombosis up to 1 year in pooled estimates from 3 registry studies.	Only ~10% of patients received BMS.

* The EUnetHTA is described as a pilot assessment to test a European collaborative model for formulating HTAs, using a novel perspective. They indicate that the report is not intended for actual decision making as it may be partially incomplete and partially outdated.

All recent HTAs give an overview of the concerns raised regarding the possibility of increased late thrombotic events and other adverse outcomes in patients who received DES based on long term results of pivotal trials and registry reports in 2006. Results from trials and meta-analyses were, however, conflicting in part due to how stent thrombosis was defined in various trials. Stent thrombosis was defined in the original trials as angiographic confirmation of in-stent thrombus or unexplained death up to 30 days after implantation; some also included MI in the absence of angiographic confirmation of target-vessel involvement, although the details varied between trials and was considered to be more inclusive in PES than SES trials. Stent thrombosis was considered to be acute if it occurred within 24 hours of implantation, subacute if it occurred between 1 and 30 days post-procedure, and late if it occurred more than 30 days after the index procedure. Any patient who developed secondary stent thrombosis, or thrombosis after repeat revascularization, was censored since these patients often underwent brachytherapy, an independent risk factor for LST.[145] In order to standardize the results of different trials, the Academic Research Consortium (ARC) generated a uniform definition of stent thrombosis. This definition would serve as the new standard definition for stent thrombosis in order to effectively compare event rates across different studies and would also improve sensitivity. The ARC definitions of stent thrombosis are summarized as follows:[146]

- Acute stent thrombosis: occurs within 24 hours after the index procedure.
- Subacute stent thrombosis: occurs between 1 and 30 days after the index procedure.
- Late stent thrombosis: occurs between 31 days and 1 year after the index procedure.
- Very late stent thrombosis: occurs more than 1 year after the procedure.
- Definite stent thrombosis: there is angiographic or autopsy evidence of thrombus or occlusion, is associated with clinical or electrocardiographic signs of acute

ischemia or elevation of creatine kinase levels to twice the normal value within 48 hours of angiography.
- Probable stent thrombosis: unexplained death occurred within 30 days of the procedure or if a MI occurred at any time after postprocedure and was confirmed to originate in an area irrigated by the stented vessel.
- Possible: unexplained death occurred more than 30 days after the index procedure.

In addition, the new ARC definition no longer censored thrombotic events that occurred following a repeat target-lesion revascularization, in contrast to the original protocol definitions of stent thrombosis.

In response to safety concerns, the FDA released a statement in September of 2006 that noted "the data we currently have do not allow us to fully characterize the mechanism, risks, and incidence of DES thrombosis".[147] In December 2006, the FDA convened a meeting of the Circulatory System Devices Advisory Panel that featured presentations by regulators, academic physicians, patients, industry representatives, and medical professional societies. The discussions at the meeting focused on safety issues and the use of dual antiplatelet therapy in addition to on-label versus off-label use of DES. The FDA concluded that the widespread use of DES for off-label indications is the primary cause for the increased incidence of stent thrombosis, as such uses are associated with higher rates of early and late stent thrombosis, MI, and death. Furthermore, when used for their approved indications, DES pose a low risk for thrombosis (< 2% for the first 3 years) that does not outweigh their benefit of reducing revascularization rates.[2] Based on data from nonrandomized studies, the FDA also recommended a longer course of dual anti-platelet therapy than was originally used in the pivotal trials. Instead of 3 to 6 months, patients were advised to continue dual anti-platelet therapy for 1 year (and then aspirin for life) following DES implantation assuming they were not at high risk for bleeding, although the optimal duration of this therapy has not been rigorously tested.

In response to the controversy surrounding the safety of DES, the NEJM published five studies in 2007 that are representative of the presentations and discussions from the 2006 FDA panel meeting. Three of these articles are meta-analyses of 4-year follow-up data from the pivotal RCTs;[14, 148, 149] another is a meta-analysis of all of the Cypher stent RCTs,[150] and the last is an analysis of the very large Swedish registry (SCAAR), which includes data of all the patients in Sweden who received stents between 2003 and 2004.[78]

Results from recent meta-analyses (Table 35, Figures 7-10)
The 2007 and 2008 network meta-analyses by Stettler, et al[59, 88] were the most complete and methodologically rigorous reports found. The 2007 report evaluates full trial populations from the included trials. The 2008 meta-analysis presents data separated by diabetes status as well as by duration of anti-platelet therapy.

Rates for definite stent thrombosis by stent type, based on the ARC definition are presented in Table 35. A total of 188 definite thrombi (1.4%) were identified based on combined data all trials described in the Stettler 2007[88] across trials with one to 4 years' follow-up.

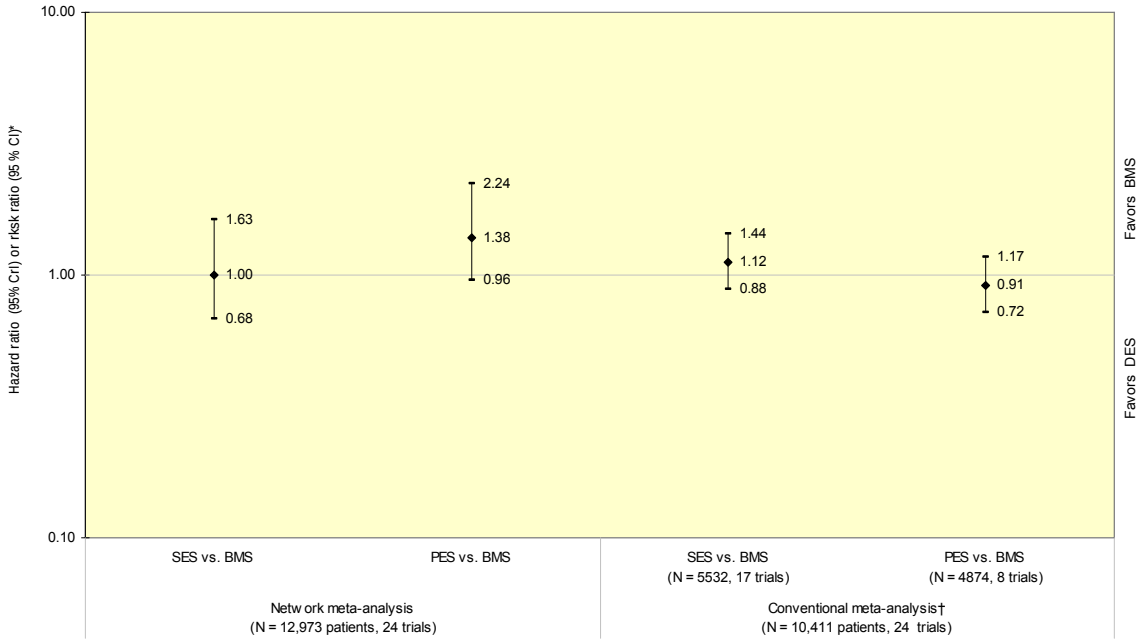
Table 35. Rates of definite stent thrombosis based on ARC definitions for all included trial populations from 2007 analysis[88]

Outcome	Trials N	Patients N	Experienced outcome (n)	Rates % (n/N) SES	PES	BMS
Definite stent thrombosis*	24	12, 937				
0 days – 4 years (cumulative)			188†	1.4% 66/4643	1.7% 72/4327	1.2% 50/4003
0 to 30 days			94	0.8% 36/4643	0.7% 30/4327	0.7% 28/4003
>30 days to 4 years			94	0.6% 30/4643	1.0% 42/4327	0.5% 22/4003

*Based on ARC criteria. No events occurred in 3 trials of the 27 reporting this outcome so only 24 trials contributed to analysis of this outcome.
†A cumulative total of 188 events occurred, 94 with in the frits 30 days following stent implantation and 94 after 30 days

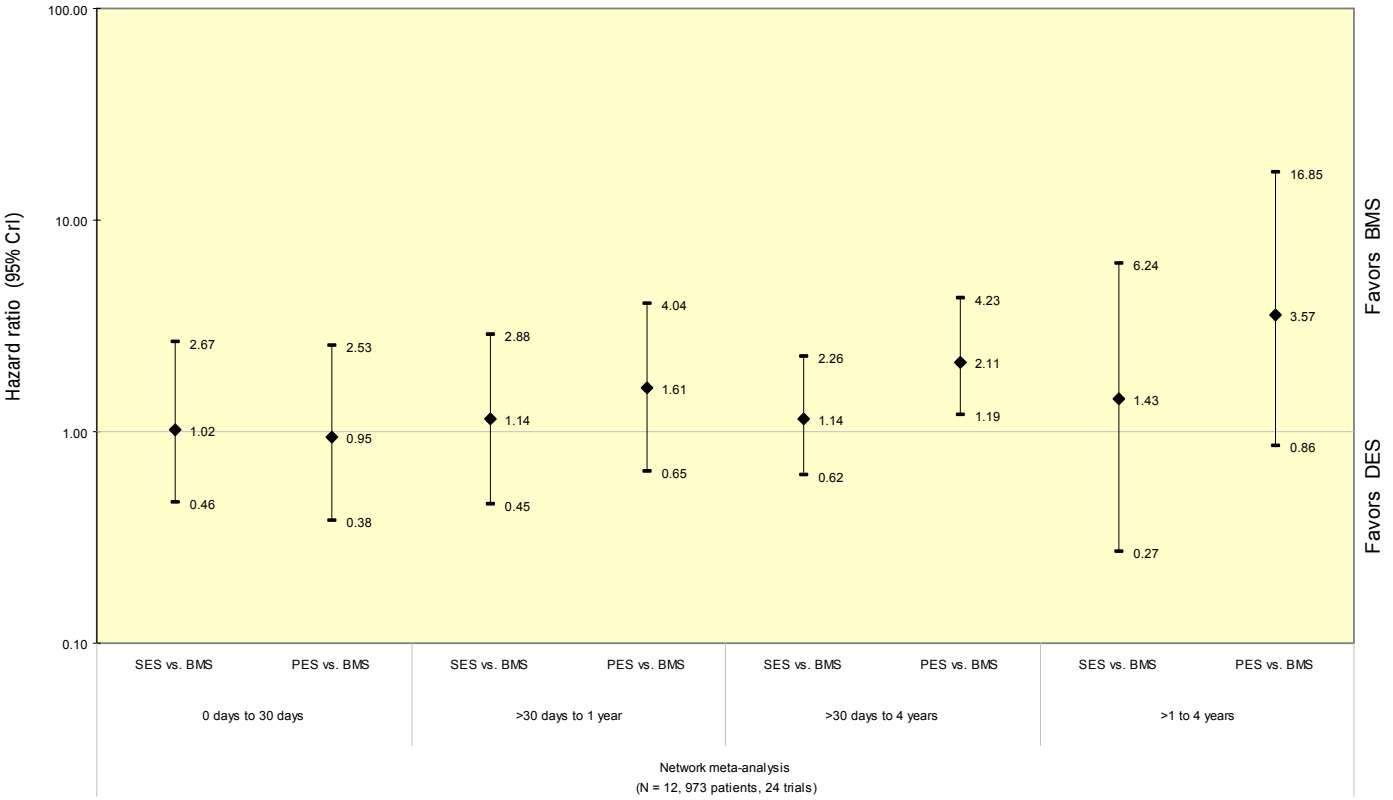
The results of both the network meta-analysis (24 trials, 12,973 patients) and conventional meta-analysis (24 trials, 10, 411 patients) showed no statistically significant difference between DES and BMS in the relative risk estimates (hazard ratio or risk ratio) based on the cumulative incidence of thrombosis up to 4 years of follow-up, Figure 7. No statistically significant differences between treatments were seen up to 30 days following stent placement, however a two-fold increase in the risk of late stent thrombosis was seen in the PES compared with the BMS group, HR = 2.11 (95% CrI 1.19, 4.23) based on the network meta-analysis (results for conventional analyses were not provided), Figure 8. SES were associated with a corresponding lower risk of late stent thrombosis compared with PES (data not shown), HR = 0.54 (0.26, 0.98, P = 0.041). There was no statistically significant difference in risk of late stent thrombosis comparing SES with BMS. Wide confidence intervals for estimates from 1-4 years may reflect small numbers of events during that time period. Although trials with follow-up from one to four years were included, of the 38 included trials included in the full meta-analysis, 25 reported follow-up past one year. The total number of trials and patients available for follow-up past one year that contributed to the determination of late stent thrombosis is not given by the authors.

Figure 8. Relative risk estimates* for ARC-defined definite stent thrombosis comparing drug eluting stents with bare metal stents based on network meta analysis and conventional meta analysis for trials with 1 to 4 years follow-up[88]



SES = sirolims eluting stent, PES = paclitaxel eluting stent, BMS = bare metal stent
*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis
† Conventional meta-analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text)

Figure 9. Relative risk estimates for ARC-defined definite stent thrombosis comparing drug eluting stents with bare metal stents based on network meta analysis with respect to timing of thrombotic events [88]

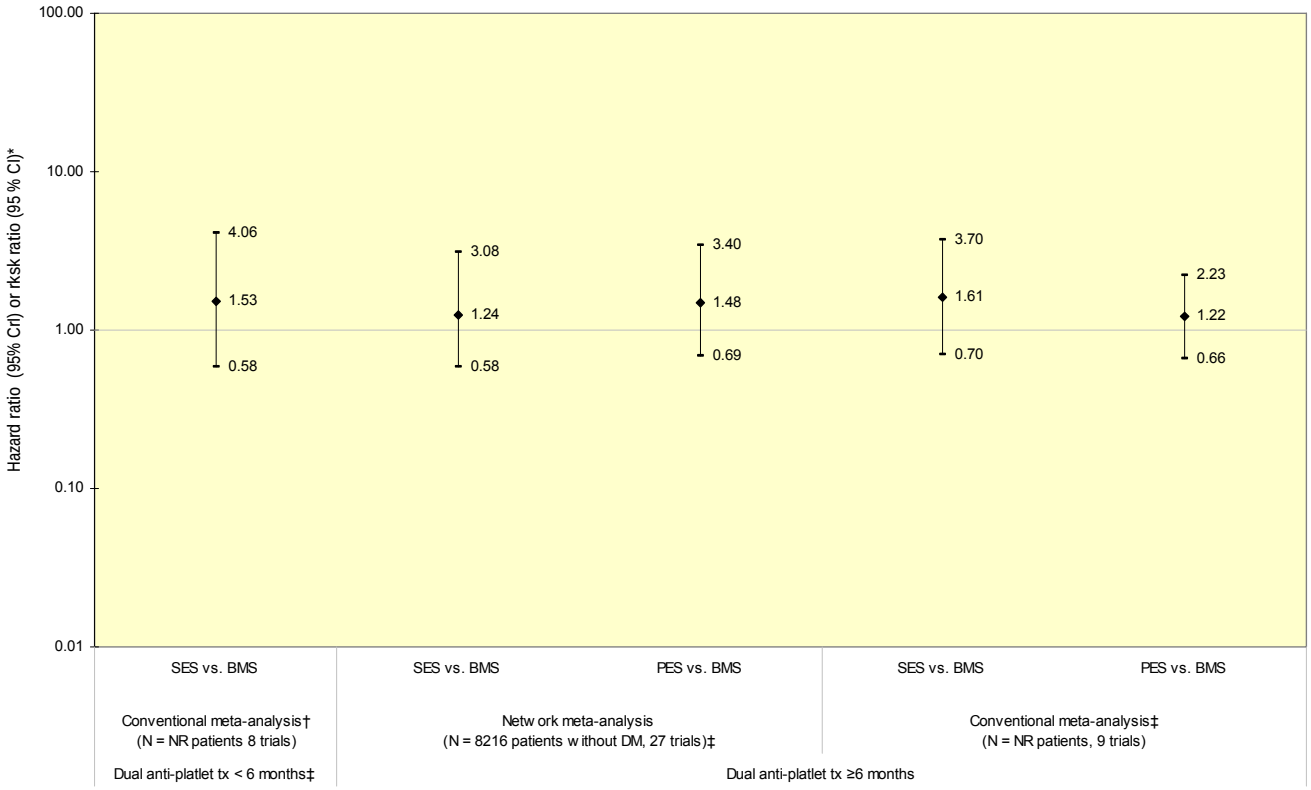


SES = sirolims eluting stent, PES = paclitaxel eluting stent, BMS = bare metal stent

The 2008 meta-analysis by Stettler[59] analyzed data for diabetic and non-diabetic patients separately as a result of their exploration of heterogeneity and inconsistency across the network of included studies. Further exploration prompted them to provide analyses based on duration of dual anti-platelet therapy separately for diabetic and non-diabetic patients. The authors considered the report to be an expanded and updated version of their 2007 meta-analysis. Compared to the earlier study, the 2008 meta-analysis included five additional trials. Results for diabetic patients are described in the special populations section. The results among those without diabetes indicated that there is no difference between DES and BMS with regard to stent thrombosis occurring between 0 and 4 years of follow-up (Figure 9) regardless of whether less than 6 months or more than 6 months of dual anti-platelet therapy were used, based on protocol. Adherence to anti-platelet therapy; however is not well reported in the trials. The authors note that there was moderate heterogeneity between trials for the stent thrombosis in the non-diabetic patients but model fit was considered adequate. Results for the conventional and network meta-analysis approaches were similar. With respect to timing of thrombosis among non-diabetic patients there were no statistically significant differences between DES and BMS at any time period based on network meta-analysis restricted to those who had at

least 6 months of dual anti-platelet therapy, Figure 10. When per protocol definition of stent thrombosis was used, the risk of late stent thrombosis (> 30 days – 4 years) was not statistically significant when SES was compared with BMS (HR 2.29 (0.83, 7.77) among non-diabetic patients who had greater than 6 months of dual anti-platelet therapy but there was a four fold increase in risk when PES was implanted compared with the BMS , HR = 4.12 (95% CrI 1.55, 13.1) however the wide confidence interval suggests a small number of individuals for the analysis. Data for conventional analyses were not provided with respect to timing of thrombosis.

Figure 10. Relative risk estimates* for ARC-defined definite stent thrombosis comparing drug eluting stents with bare metal stents based on conventional and network meta analysis for non-diabetic patients based on duration of anti-platelet therapy from 0 to 4 years[88]

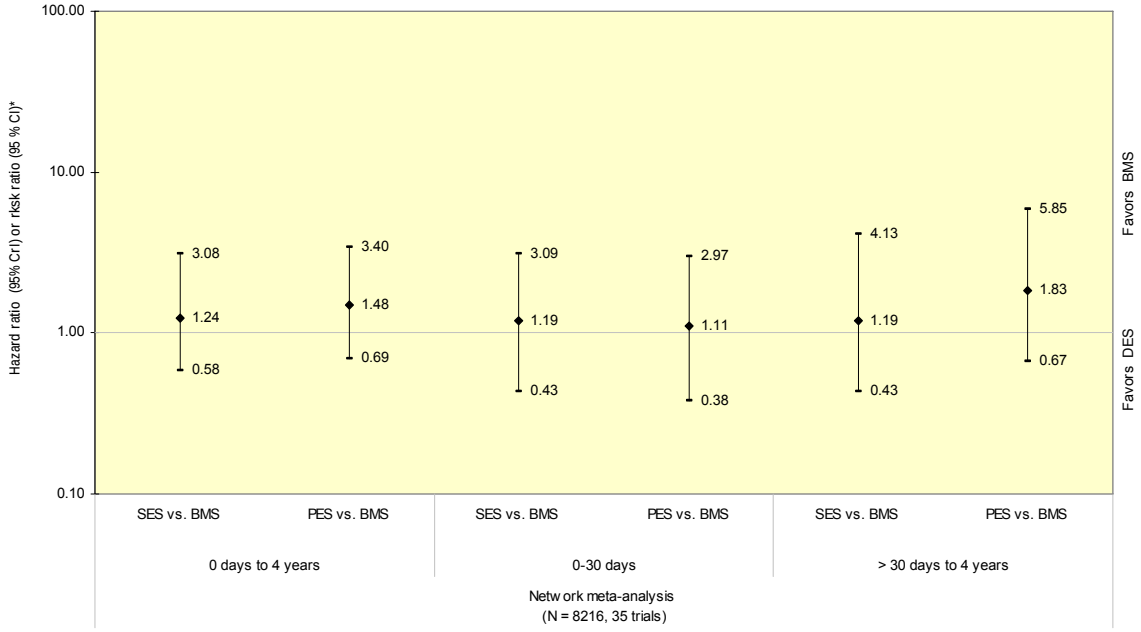


SES = sirolims eluting stent, PES = paclitaxel eluting stent, BMS = bare metal stent
*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis

† Only conventional meta-analysis was reported for those with less than 6 months therapy. Conventional analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text).

‡The precise number of patients and trials that contributed to each outcome for the restricted analysis among pattients with 6 or more months of dual anti-platelet therapy is not provided. Numbers for the conventional analysis of < 6 months therapy are suggested in the text (17 original trials with SES vs BMS minus 8), patient numbers for all outcomes are not reported (NR) and none are reported for those with ≥ 6 months therapy. Numbers listed for the network analysis are based on subraction of 8 trials from the 35 originally included and extimated from authors' figures for the network meta-analysis. Numbers for the conventional analysis are not reported.

Figure 11. Relative risk estimates* for ARC-defined definite stent thrombosis comparing drug eluting stents with bare metal stents based on network meta analysis for non-diabetic patients who had at least 6 months of dual anti-platelet therapy[88]



SES = sirolims eluting stent, PES = paclitaxel eluting stent, BMS = bare metal stent
*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis

Another recently published meta-analysis by Fuchs et al.[86] assessed the incidence of stent thrombosis using data from 21 clinical trials that evaluated DES versus BMS (N = 10,252). Trials were identified by a formal literature search for RCTS that evaluated DES, BMS, and balloon angioplasty. Stent thrombosis was redefined with the ARC definition and reported as subacute (SAT), occurring between 1 and 30 days after the index procedure, or late (LST), occurring 31 days to 1 year after stenting. However, because follow-up data were available for a range of 6 to 60 months (mean of 16 months), the number of patients available for each time point was not clear. Furthermore, the authors also reported on trials that compared BMS to balloon angioplasty, and the number of patients in the DES versus BMS trials could not accurately be determined. Baseline patient characteristics were only provided for 15 of the 21 trials. Odds ratios were calculated using the fixed effects model and individual patient data were not used.

Fuchs et al provide absolute incidence of thromboses as follows[86]:

- 1 day to 1 year after placement, 1.01% with DES versus 1.10% with BMS
- 1 to 30 days, 0.43% with DES versus 0.53% with BMS
- 31 days to 1 year, 1% with DES versus 0.8% with BMS.

No significant difference in the overall risk of stent thrombosis between DES and BMS groups was identified (OR = 0.86 (0.58, 1.3), $P < 0.48$). Similarly, there was no difference in the rates of sub-acute (SAT) and late stent thrombosis (LST) between groups (OR = 0.86 (0.50, .15), $P < 0.6$ and OR 0.92 (0.50, 1.68), $P < 0.78$, respectively). There was a non-significant trend towards increase LST rates with DES (27 LST cases versus 20 SAT cases). The overall rate of stent thrombosis was 1.05% (107 cases), and rates ranged from 0% to 3.6% among studies. Forest plots were depicted for overall and sub-acute stent thrombosis, though not for late stent thrombosis, and showed that although some studies favored DES and others favored BMS, none of the individual studies appeared to have statistically significant differences in the rates of overall or sub-acute thrombosis between groups. The variation in estimate direction suggests estimates were not consistent across trials even though authors report that overall study results were homogenous by Cochran's *Q* statistic for heterogeneity. Statistical test results were not provided for the *Q* or a determination of I^2. Funnel plots showed no evidence of publication bias. Although over 10,000 patients were included in this meta-analysis, it may have been underpowered to detect the true rate of thrombotic events since thrombosis was a rare event. Another limitation of the analysis is that individual patient data were not used.

Results from smaller, less rigorous pooled analyses also suggest no difference in risk for stent thrombosis between DES and BMS; however they may have been underpowered to detect a difference. Information on these analyses is provided in Appendix F. One pooled analysis of the four primary TAXUS trials (N = 2445, n = 30 with thrombosis) explored risk factors for 3 year risk of stent thrombosis. Based on multivariate analyses, independent risk factors included: nonuse of clopidogrel or ticlopidine at discharge ($P = 0.009$), male gender ($P = 0.023$), current smoking ($P = 0.035$), and possibly the use of multiple non-overlapping stents ($P = 0.062$). Non-adherence with recommended clopidogrel or ticlopidine therapy at one month was additionally associated with an increased risk of stent thrombosis ($P = 0.004$).[151]

Results from recently published RCTs

Three relevant RCTs were identified that were not included in any of the previously discussed HTAs or meta-analyses.[140-142] All were updates to previously published RCTs and reported results from longer periods of follow-up. All of these studies used different definitions of stent thrombosis and were likely insufficiently powered to detect the true rate of stent thrombosis.

Morice [141] reported five-year results from the RAVEL trial, (N =238 patients with a single de novo coronary lesion who were randomized to SES or BMS). Stent thrombosis rates were reported using the protocol as well as the ARC definition of stent thrombosis. According to the protocol criteria, stent thrombosis was defined as all MIs related to the target vessel as with angiographic evidence of vessel occlusion. The ARC definitions were previously discussed. There was only one incidence of per-protocol stent thrombosis, which occurred in a SES patient more than one year the index procedure (protocol: SES 0.8%, BMS 0%). When the ARC definition of stent thrombosis was applied, there were a total of 12 cases (5.0%) of definite, probable, or possible stent

thrombosis over the five years post-procedure (SES 4 (3.3%), BMS 8 (6.8%)). These rates are higher than those reported in studies included in the HTAs and meta-analysis. However, ARC-defined stent thrombosis is most often reported so that only definite or probable cases are counted. Excluding cases of possible stent thrombosis leaves a total of 5 (2.1%) cases (SES 2 (1.7%), BMS 3 (2.5%)). These rates are more consistent with previous reports. All ARC-defined cases of stent thrombosis were considered late or very late, meaning they occurred more than one month following stenting.

Grube [140] published two-year outcomes from the TAXUS VI trial, which evaluated PES versus BMS in 446 patients with complex lesions (Figure B). Treated lesions were long (mean length of 20.6 mm), and could be covered by up to two overlapping stents. Stent thrombosis was reported according to protocol critera as an ACS with angiographically-confirmed stent thrombosis, AMI in the distribution of the stented vessel, or death of unknown cause within 30 days after the index procedure. There were a total of 4 cases (0.9%) of stent thrombosis up to 2 years following stenting (PES 2 (0.9%), BMS 2(0.9%)). One PES case occurred after the first year, and the remaining cases occurred within the first 30 days following stenting. These rates are similar to rates of protocol-defined stent thrombosis in the HTAs and meta-analyses, which were typically lower than those of ARC-defined stent thrombosis.

Finally, Pfisterer[142] published data from three-years of follow-up from the BASKET trial, in which 826 patients were randomized 2:1 to DES or BMS (Figure C). Stent thrombosis was defined according to the ARC criteria, and the authors reported a composite of "definite", "probable", and "possible" stent thrombosis. Stent thrombosis was reported in 8.5% of patients (N = NR) (DES 9.0%, BMS 7.5%, $P = 0.51$). There was no significant difference in the rates of stenting between DES and BMS groups either in the first 6 months (DES 2.9%, BMS 3.9%, $P = 0.45$) or between 7 months and 3 years after the index procedure (DES 6.5%, BMS 3.6%, $P = 0.08$), although the latter had a marginally significant increase in the rate of stent thrombosis in DES patients. These rates are higher than those typically reported in the HTAs and meta-analyses, which may be due to the fact that the authors included "possible" stent thrombosis in the total numbers.

Results from recently published registry and non-randomized studies

Ten registry or nonrandomized studies not included in the systematic reviews previously discussed were identified that reported on stent thrombosis following DES versus BMS implantation. These studies are LoE III. Some studies define stent thrombosis by the ARC criteria, and others by different definitions; the course of dual antiplatelet therapy also varied. A summary of findings from these studies is given in Table 36.

As in the RCTs, rates of stent thrombosis were relatively low, ranging from 0 to 4.5%, and there was no significant difference between groups except in one study, which found significantly more very late stent thrombosis in DES patients.[117] Odds or hazard ratios were calculated in a few studies, sometimes were adjusted, and in no cases were there significant differences between groups.

In addition, three registry studies [114, 125, 152] reported on predictors of stent thrombosis, which included: renal failure, ACS at index procedure, absence of clopidogrel at 30 days, DM, long stent length (≥20 mm), ostial lesions, and bifurcation lesions. Predictors of DES stent thrombosis included absence of clopidogrel at 30 days, DM, renal failure, ACS at index procedure, and ostial lesions, PCI for bifurcation lesions, multivessel PCI, more than one stent in initial PCI. Predictors of BMS stent thrombosis included initial PCI for AMI.

One study separated outcomes based on whether a patient received a stent for "on-label" versus "off-label" indications.[144] "On-label" use was defined very similarly to the manufacturers' indications for Cypher and Taxus DES. Interestingly, incidences of stent thrombosis occurred up to 2 years follow-up when either DES or BMS were used for "on-label" indications (N = 530). There was no significant difference in overall rates of stent thrombosis between BMS and DES "off-label" groups, although there was significantly more very late stent thrombosis (>1 year) in DES patients.

Table 36. Summary of stent thrombosis events from new registry studies

Stent thrombosis	No. of studies	No. patients with complications		Range of rates reported		Effect size (95%CI)
		DES	BMS	DES	BMS	
Acute (< 24 hours)	2 [117, 122]	NR	NR	0%-0.4%	0.1%-1.3%	NR
Subacute (1–30 days)	6† [110, 117, 122, 125, 129, 152]	1-20 (NR for 2 studies)	4-28 (NR for 2 studies)	0-1.0%	0.3%-3.5%	OR 2.18 (95% CI 0.69-6.87)[119] NR for 4 studies
Late (31 days–1 year)	5 [108, 110, 117, 122, 125]	4-16 (NR for 2 studies)	14-42 (NR for 2 studies)	0%-0.9%	0.1%-3.5%	OR (95% CI) 0.74 (0.38-1.46)[101] OR 0.85 (95% CI 0.41-1.76)[119] OR (adjusted) (95% CI) 0.55 (0.23-1.27)[101] NR for 4 studies
Very late (>1 year)	3 [110, 117, 122]	2 (NR for 2 studies)	2-9 (NR for 1 study)	0.3%-0.4%	0.1%-0.2%	NR
Other time frames :						
0 – 18 months	1 [115]	65	19	2.9%	4.2%	NR
0 – 2 years	1 [153]	17	16			HR 0.97 (0.49-1.91) (0.55-2.30)[153]
0 – 2 years (mean) (range 6 months – 5 years)	1 [112]	14	23	2.9%, 2.9% (adjusted)	2.6%, 2.4% (adjusted)	HR (adjusted for baseline characteristics) (95% CI) 1.2 (0.50-2.90)[112] HR (adjusted for lesion characteristics) (95% CI) 1.13 (0.55-2.30)[112]
0 – 51 months	1 [114]	16	36	1.3%	1.6%	NR

*One study, Marzocchi, reported very late thrombosis as > 6 months to 2 years[117]
†Yan and Ong reported subacute stent thrombosis rates from 0-30 days.[125, 152]

Bleeding

The FDA currently recommends twelve months of dual antiplatelet therapy for patients not at high-risk for bleeding following DES implantation in order to decrease the risk of stent thrombosis. No studies comparing DES with BMS with regard to this outcome were found.

Conclusions from previous HTAs or similar reports

Data for this outcome was not discussed in previous HTAs or similar reports.

Results from recent meta-analyses

No meta-analyses comparing DES with BMS included this outcome.

Results from recently published RCTs

No reports were found.

Results from recently published registry and non-randomized studies

One multicenter single-arm observational study evaluated the risk of bleeding in 2355 consecutive DES patients with a prolonged course of dual antiplatelet therapy.[154] Because there was no BMS control, this study was not abstracted, but results are provided here in order to provide some context regarding bleeding complications. In this study, patients were recommended 100 mg/day aspirin indefinitely, and either 75 mg/day clopidogrel or 250 mg/day ticlopidine for at least 3 months (SES patients) or at least 6 months (PES patients). The median duration of dual antiplatelet therapy was 209 days.

Rates presented represent cumulative incidence between 30 days and 18 months. Overall, 3.1% (N = 75) of patients experienced bleeding events. Major bleeding complications, which were defined as intracranial bleeding or a clinically overt hemorrhage with a decrease in hemoglobin (> 5 g/dl) or hemocrit (> 15%), occurred in 45 (1.9%) of patients at a median of 263 days. Of these patients, 42 were on dual antiplatelet therapy at the time of the event. These patients had a significantly higher risk of death ($P < 0.01$) and Q wave MI ($P = 0.02$) than patients who did not experience major bleeding; these events occurred at a median of 11.5 days after experiencing major bleeding. Multivariate analysis found that dual antiplatelet therapy use (hazard ratio 19.8 (95% CI 3.69-106.34) ($P < 0.001$) and age older than 65 years (hazard ratio 2.15 (95% CI 1.16-4.00) ($P = 0.02$) were significantly predictors of major bleeding. Minor bleeding events comprised all other bleeding events occurred in 26 (1.1%) of patients. The incidence of bleeding in patients on dual antiplatelet therapy remained constant over the 18-month follow-up period. Dual anti-platelet therapy was discontinued prematurely in 6.7% of patients for a variety of reasons, including bleeding (26.6%), surgical procedures (24.7%), and gastritis/gastroesophageal reflux (19.0%).

Ajani reported peri-procedural rates of major bleeding of 1.8%; these rates were not given separately for DES compared to BMS.[108]

The bleeding rates in these three different studies ranged from 1.8% to 4.0%. However, each study reported bleeding complications for different follow-up periods, making it difficult to compare results (Latib reported rates between 30 days and 18 months; Ndrepepa between 0 and 30 days; Ajani only reported peri-procedural major bleeding).[108, 154, 155] Finally, none of these studies reported rates of bleeding for patients who received DES compared to those who received BMS.

Stent strut fracture

Drug-eluting stent fracture is a complication that was not reported in most clinical trials or any of the HTAs included here. Stent strut fracture is defined as the separation of stent struts or segments. No studies comparing DES with BMS were found, but 8 case series were identified that reported rates of stent strut fracture following DES implantation. Follow-up imaging (conventional coronary angiography, CT angiography, plain fluoroscopy, or IVUS) was performed in most studies between 6 and 9 months after stenting (range: 7 days - 30 months). From 6 case series, rates for stent fracture ranged from 1.9% to 7.7% (N = 2047). [156-161] In patients w/ in-stent restenosis, fractures occurred in 18.6% lesions in 1 case series (N = 188);[162] in patients with long lesions (≥25 mm), fractures occurred in 1.7% lesions in 1 case series (N = 415).[163]

Stent fracture was associated with in-stent restenosis [156, 158-162, 164], target lesion revascularization,[164], total stent length[160], the change in the angulation of the lesion after stenting,[160] stenting on a bend >75º,[162] SES (versus PES),[157, 162] overlapping stents, [162] and right coronary artery lesions. [160, 163] There may be a higher risk of stent strut fracture with SES compared to PES: in the 4 case series that reported on patients who received either SES or PES, 72% - 100% of fractures occurred in SES, [157, 158, 162, 163] while all the other case series evaluated patients with SES only.

Other complications

Conclusions from previous HTAs or similar reports

There was very limited reporting of any other adverse events in the HTAs. ECRI's 2008 HTA identified a retrospective study that reported a hypersensitivity reaction to DES in approximately 5% of patients.[79] The MSAC report noted that according to the FDA, most hypersensitivity reactions to DES were minor (e.g., skin rashes, itching), although some severe reactions (e.g., anaphylaxis) have occurred.[84] A brief section was also included on incomplete apposition, which occurs when the stent is not close enough to the vessel wall to prevent blood flow between the stent and the vessel wall. A RAVEL substudy found significantly greater incomplete apposition in the SES group (21% versus 4% BMS) at 6 months ($P < 0.001$) though no adverse events were associated with the incomplete apposition at 1 year.[165] In the SIRIUS trial, rates of post-procedure incomplete stent apposition were similar in patients treated with SES and BMS. However, new late incomplete apposition was detected at 8 months only in patients who received SES (9.7%) ($P < 0.05$).[166] Both of these reports were both limited to a small subset of patients who underwent IVUS (ultrasound) of the stented artery.

Results from recent meta-analyses. None

Results from recently published RCTs
Other safety issues (e.g., peri-procedural complications, bleeding, etc.) were not discussed in any of the other new RCTs.

3.3 Key Question 1 and 2 - Special populations- Efficacy, effectiveness and safety in

In this report information on the efficacy, effectiveness and safety for the following special populations is summarized:

- Diabetic patients
- Patients with acute MI
- Other special populations: patients with intermediate lesions

Efficacy in diabetic patients

Diabetic patients tend to have multi-vessel disease, smaller coronary arteries and longer lesions. Diabetic patients and those with long or otherwise complex lesions are considered special populations in stent research. While they are generally considered to be a higher risk for restenosis and other complications, data on these patients are lacking since they are often not enrolled in large numbers in effectiveness and safety studies on different types of stents.[167, 168] In a 2006 report, the FDA found that these patients were at higher risk of stent thrombosis, although this increase was small.[2] These risks were deemed highest in patients who did not continue with antiplatelet therapy post-procedure.[2] Conclusions from previous HTAs and similar reports provide limited data and conclusions regarding the efficacy of DES versus BMS in diabetic patients. They suggest that patients in these subgroups are more likely to benefit from a reduced rate of restenosis due to DES placement, but that they are higher risk of death and MI when DES are used as compared with BMS.[4, 77, 78] However, other reports have not found these elevated risks, or have found mixed results when examining the available data.[79, 81, 84, 85]

Overall mortality and cardiac death

Previous HTAs or similar reports provide few conclusions and only limited evaluation on diabetic patients or special populations. Citing a 2007 meta-analysis, the KCE - Belgian reports a statistically significant, two-fold increase in overall mortality in diabetic patients receiving DES compared with BMS, however review of the original meta-analysis did not confirm this.[4]

The most comprehensive meta-analysis published since then reported a two-fold increase in overall mortality and cardiac mortality among patients receiving less than six months of dual anti-platelet therapy pointing to the importance of longer-term therapy. Three recently published meta-analyses indicate that, overall, mortality risk among diabetic patients is similar whether DES or BMS are used. They were, however, smaller in scope.

Conclusions from previous HTAs or similar reports (Table 37)
Specific discussion of overall mortality in diabetic patients was found in two reports, both of which relied on previously done meta-analyses[4] or specific one RCT.[78]

Table 37. Summary of conclusions from previously reported HTAs or similar report related to overall mortality in diabetic patients comparing DES with BMS

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
KCE-Belgian (2007)	Previously published meta-analyses – four of which are highlighted for safety	Mortality Kasrati 2007 meta-analysis is quoted as showing an increased risk • HR (95% CI): 2.90 (1.38, 6.10) • Consultation with original meta-analysis gives HR 1.27 (0.83, 1.95)	Mortality • The HR value for one meta-analysis cited in the KCE report is not consistent with data in the original meta-analysis • Based on the original meta-analysis, there is no increased risk of death with SES compared with BMS	• The Kastrati meta-analysis contained 14 trials, N = 4958 total patients, n = 1411 with diabetes; results up to 5 years: o 8.7% mortality for SES o 7.6% mortality for BMS
Hayes (2007)	Literature review and critique of available RCTs, meta-analyses, and registries. Two studies enrolled only diabetic subjects; one (DIABETES) compared DES vs. BMS, while the other compared two different types of DES. Results for subgroup analyses from meta-analyses also presented.	Mortality (Sabate, DIABETES trial) • OR (95% CI): 1.27 (NS)	Mortality • NS differences reported from meta-analysis.	• The authors describe several subgroup analyses in the text of the file indicating that DES performed better in diabetic patients than BMS, however statistical evidence regarding the strength of these associations was not included. • The authors conclude that DES are more effective in special populations, including patients with diabetes and long lesions, but that results on safety endpoints are mixed and inconclusive.

Results from recent meta-analyses
Three recently published meta-analyses[59, 91, 94] and one pooled analysis[90] that reported on outcomes for diabetic patients were found. One pooled analysis was excluded as it compared intravascular ultrasound and angiographic findings but not on the outcomes relevant to this report.[169] There is significant overlap with respect to the trials used in the individual analyses (Appendix C). A few trials enrolled only diabetic patients. The 2008 meta-analysis by Stettler, et al was the most complete and methodologically rigorous report found.[59] It included standardized definitions of outcomes and evaluated the influence of anti-platelet therapy duration.

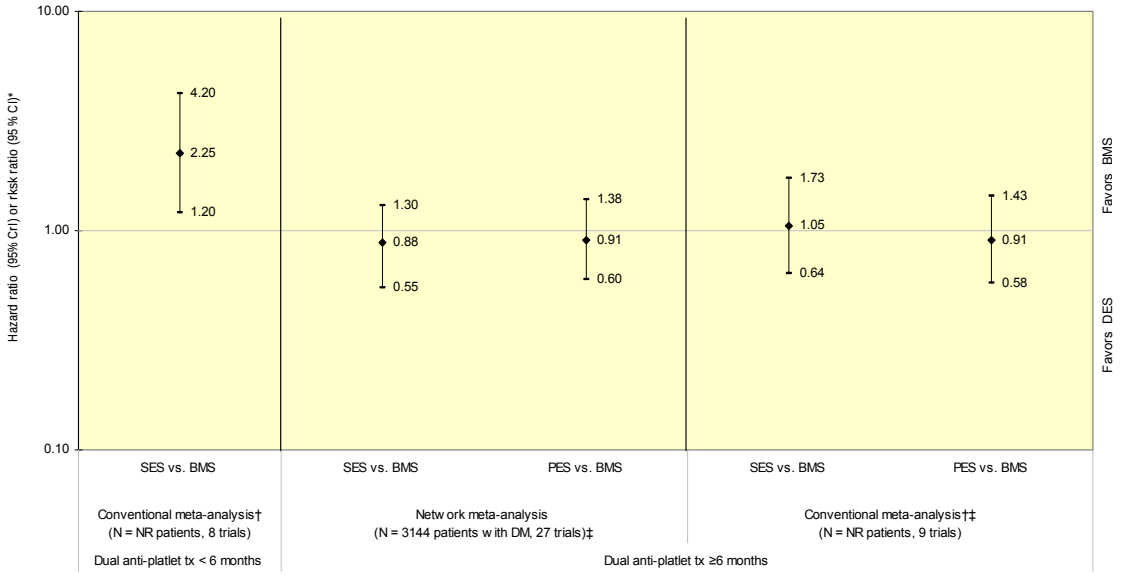
The 2008 network meta-analysis by Stettler[59], et al analyzed data for diabetic and non-diabetic patients separately as a result of their exploration of heterogeneity and inconsistency across the network of included studies. Further exploration prompted them to provide analyses based on duration of dual anti-platelet therapy separately for diabetic and non-diabetic patients. The authors considered the report to be an expanded and updated version of their 2007 meta-analysis.[88] Compared with the earlier study, the 2008 meta-analysis included five additional trials. The entire network meta-analysis included

35 trials with 3852 people with diabetes and 10, 947 without diabetes contributing to the analysis. Not all trials and patients contributed to sub-analyses based on duration of dual anti-platelet therapy, however.

Rates for overall mortality or cardiac mortality among diabetic patients are not provided by the authors. Among those who had at least 6 months of dual anti-platelet therapy, the total number of deaths for SES, PES and BMS respectively were 78, 98 and 69 across the network of 27 trials from 0 to 4 years of follow-up. Diabetic patients in whom SES were implanted had a statistically significant two-fold increase in the risk of overall mortality (RR 2.25 (95% CI 1.20, 4.20) compared with those who had BMS if the duration of dual antiplatelet therapy was less than 6 months, based on conventional meta-analysis of eight head to head trials (Figure 11) and marginally insignificant two-fold increase in the risk of cardiac death, RR 2.14 (1.00, 4.62) (Figure 12). All trials reporting less than 6 months of therapy compared SES with BMS so risk comparing PES with BMS is not known. By contrast, no statistically significant differences in the risk of overall mortality or cardiac death between either SES or PES and BMS were seen in diabetic patients who had six or more months of dual anti-platelet therapy in either the network meta-analysis (N = 2898 diabetic patients in 27 trials) or the conventional analysis (N not reported for 9 trials). There was no evidence of heterogeneity for the conventional analysis. Heterogeneity was low for overall mortality and cardiac death for trials and inconsistency across the network of trials requiring six or more months of therapy were low and model fit was adequate. From these analyses, it appears that duration of anti-platelet therapy in diabetic patients for six or more months is an important factor in preventing mortality following stent placement. Adherence to therapy, however, is not well described and reports of adherence in trials may relate to duration of follow-up. Not all trials contributed data across all four years but specifics are not provided by the authors.

For non-diabetic patients, there were no statistically significant differences in overall mortality or cardiac mortality regardless of duration of anti-platelet therapy (data not shown here). There was no evidence of heterogeneity across trials in with the conventional analysis for either outcome or duration of therapy, but there was significant amount of heterogeneity for cardiac death for the SES versus BMS comparison for non-diabetic patients with ≥ 6 months therapy.

Figure 12. Relative risk estimates* for overall mortality among diabetic patients according to duration of dual anti-platelet therapy

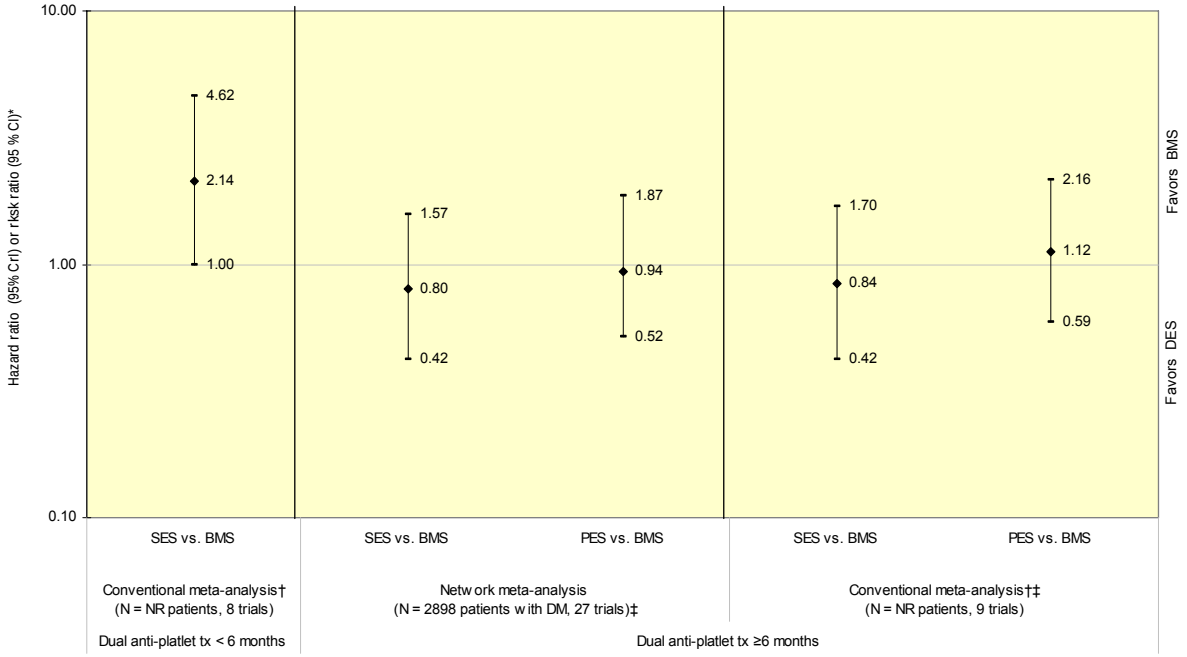


*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis

† Only conventional meta-analysis was reported for those with less than 6 months therapy. Conventional analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text).

‡The precise number of patients and trials that contributed to each outcome for the restricted analysis among patients with 6 or more months of dual anti-platelet therapy is not provided. Numbers for the conventional analysis of < 6 months therapy are suggested in the text (17 original trials with SES vs BMS minus 8), patient numbers for all outcomes are not reported (NR) and none are reported for those with ≥ 6 months therapy. Numbers listed for the network analysis are based on subtraction of 8 trials from the 35 originally included and estimated from authors' figures for the network meta-analysis. Numbers for the conventional analysis are not reported.

Figure 13. Relative risk estimates* for cardiac death among diabetic patients according to duration of dual anti-platelet therapy



*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis

† Only conventional meta-analysis was reported for those with less than 6 months therapy. Conventional analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text).

‡The precise number of patients and trials that contributed to each outcome for the restricted analysis among patients with 6 or more months of dual anti-platelet therapy is not provided. Numbers for the conventional analysis of < 6 months therapy are suggested in the text (17 original trials with SES vs BMS minus 8), patient numbers for all outcomes are not reported (NR) and none are reported for those with ≥ 6 months therapy. Numbers listed for the network analysis are based on subtraction of 8 trials from the 35 originally included and estimated from authors' figures for the network meta-analysis. Numbers for the conventional analysis are not reported.

Results from other recently published meta-analyses[91, 94] and the pooled analysis[90] which specifically evaluated mortality in diabetic patients were comparable to those reported by Stettler for patients who had at least six months of dual anti-platelet therapy.

Table 38. Summary of mortality from other recent meta-analyses in diabetic patients

Author (Year)	Number of Trials (N diabetic patients)	Relative Risk Estimate
Patti (2008)	9 RCTs, N = 1,141 diabetic patients	Overall Mortality OR (95% CI): 1.05 (0.46, 2.35)
Kumbahni (2008)	12 RCTs, N = 1,879 diabetic patients	Overall Mortality RR (95%): 0.64 (0.32, 1.28)
Kirtane (2008)	5 trials, N = 827 diabetic patients	Overall Mortality HR (95% CI): 0.88 (0.53, 1.45) Cardiac Mortality

	HR (95% CI): 1.10 (0.53, 2.28)

Results from recently published RCTs
One RCT of 150 diabetic patients that has not been included in previous reports was found.[102] No statistically significant difference in overall mortality risk (OR = 0.64, 95% CI, 0.07-4.89) were reported at 12 months, based on a 76% follow-up rate in this LoE II study.

Myocardial infarction
No differences in the risk of myocardial infarction were seen in diabetic patients, regardless of dual-antiplatelet therapy in the largest and most complete recent meta-analysis at up to 4 years of follow-up. Two analyses with fewer trials suggest that at shorter follow-up times (6-24 months), DES may result in a lower risk of MI. Differences in the number and types of included trials and definitions of MI may contribute to difference found between the analyses.

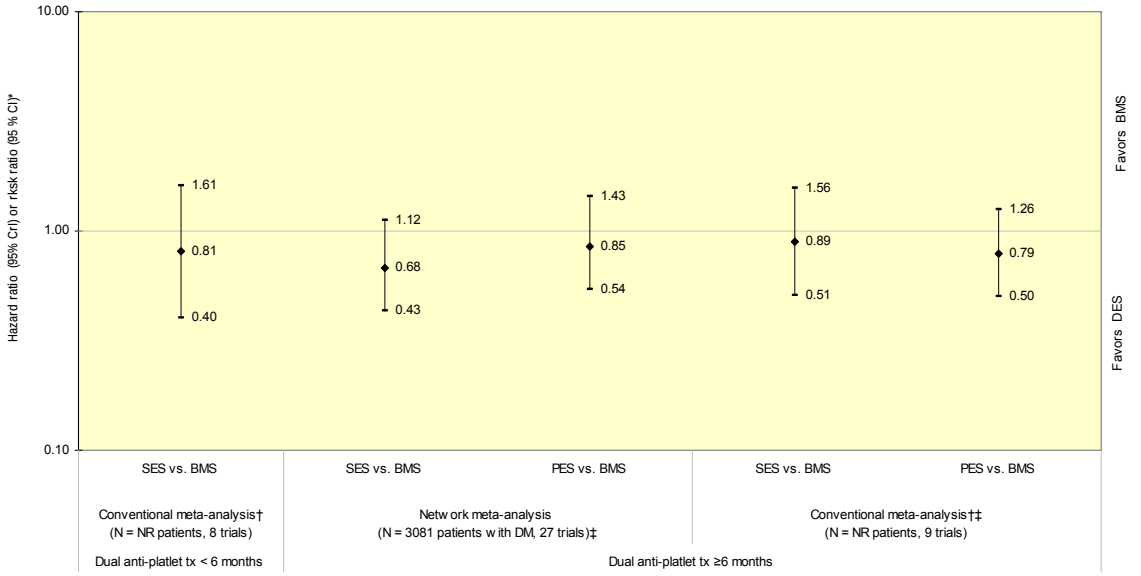
Previous HTAs: No previous health technology assessments provided data on the risk of myocardial infarction in patients with diabetes mellitus who received DES vs. those who received BMS.

Results from recent meta-analyses

No differences in the risk of myocardial infarction from 0 to 4 years were seen when DES were compared with BMS among diabetic patients regardless of duration of dual anti-platelet therapy for either the conventional or the network meta-analysis reported in the 2008 report by Stettler, et al[59] (Figure 13). Overall rates of myocardial infarction for all diabetic patients were not provided. For the conventional analysis of those with less than six months dual anti-platelet therapy, heterogeneity was very low but authors do not report heterogeneity for those with more than six months of therapy. For the network analysis, there was low to moderate inconsistency across trials of patients who had six or more months of dual anti-platelet therapy but this may be due to chance.

In both the conventional and network analyses of non-diabetic patients, there was no statistically significant differences in MI risk between patients who received DES and those who had BMS, regardless of duration of dual anti-platelet therapy (data not shown).

Figure 14. Relative risk estimates* for myocardial infarction among diabetic patients according to duration of dual anti-platelet therapy



*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis.

† Only conventional meta-analysis was reported for those with less than 6 months therapy. Conventional analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text).

‡The precise number of patients and trials that contributed to each outcome for the restricted analysis among patients with 6 or more months of dual anti-platelet therapy is not provided. Numbers for the conventional analysis of < 6 months therapy are suggested in the text (17 original trials with SES vs BMS minus 8), patient numbers for all outcomes are not reported (NR) and none are reported for those with ≥ 6 months therapy. Numbers listed for the network analysis are based on subtraction of 8 trials from the 35 originally included and estimated from authors' figures for the network meta-analysis. Numbers for the conventional analysis are not reported.

For the conventional meta-analysis in patients with less than 6 months of dual anti-platelet therapy, heterogeneity was low. Between-trial variance among those with 6 or more month's therapy was also low in the network analysis and model fit was considered to be adequate.

In contrast to Stettler's findings, results from two other recently published meta-analyses[91, 94] suggest that use of DES may confer a lower risk of MI in diabetic patients. Both contained fewer trials than Stettler were based on shorter length of follow-up and Stettler segregated analyses based on duration of dual anti-platelet therapy. The meta-analysis by Patti, et al,[94] reported a 52% lower risk of MI among patients who had DES implanted compared with patients receiving BMS, OR 0.48 (0.26, 0.87), a statistically significant finding, based on data from 7 trials, including the DIABETES trial which enrolled diabetic patients exclusively. No significant heterogeneity across trials was found. Although the authors report that there was no evidence of publication bias, compared with the Stettler 2008 analysis, two head to head trials of SES versus BMS that exclusively enrolled diabetic patients were not part of Patti's analysis, namely the

DECODE (N = 83) and the SCORPIUS (N = 250) trials. Data on diabetic patients from an additional 15 head to head trials were part of the Stettler analysis and relative risk was determined from cumulative incidence up to 4 years of follow-up. Follow-up times for trials included in Patti, et al were 8 months (1 trial), 12 months (2 trials) and 24 months (4 trials). Kumbahni, et al report a marginally significant difference in non-Q-wave MI only favoring DES, RR 0.57 (0.32, 0.99, $P = 0.046$) and no significant difference for Q-wave MI for follow-up periods from 6- 12 months following stent implantation.[91] This analysis also included data from six meeting abstracts that apparently were not reflected in the peer-reviewed literature. Differences in the number of included trials, length of and in MI definition may contribute to differences in the results reported. A listing of which RCTS are included in which meta-analyses can be found in Appendix C.

A pooled analysis of PES trials[90] was consistent with Stettler's findings, neither showing a difference in risk of myocardial infarction whether DES or BMS was used.

Table 39. Summary of myocardial infarction findings from other recent meta-analyses in diabetic patients

Author (Year)	Number of Trials (N diabetic patients)	Effect Estimates
Patti (2008)	7* RCTs, with follow-up from 8-24 months; compulsory angiographic follow-up 6- 9 months N = 1,141 diabetic patients	Myocardial Infarction DES: 3.5%, BMS: 7.2% OR (95% CI): 0.48 (0.26, 0.87)
Kumbahni (2008)	12 RCTs (or less), N = 1,879 (or less) with follow-up from 6-12 months	Non-Q-Wave Myocardial Infarction DES: 3.1% , BMS:5.9% RR (95% CI): 0.57 (0.32, 0.99); p = 0.046 RD (95% CI): 2.6% (0.24%, 5.0%), p = 0.03 Q-Wave Myocardial Infarction DES: 0.7%, BMS:1.0% RR .072, (95% CI 0.25, 2.07
Kirtane (2008) (pooled analysis of PES trials only)	5 trials, N = 832 diabetic patients PES only	Myocardial Infarction PES: 6.9% (24), BMS: 8.9% (35) HR (95% CI): 0.70 (0.41, 1.17)

*Authors indicate that 9 trials were used, however, for mortality, only 7 trials are listed

Results from recently published RCTs

No statistically significant difference in either Q wave or non-Q-wave MI were seen when DES and BMS were compared in this small trial at 12 months. Event rates and effect estimates are given below.[102]

	SES	BMS	OR (95% CI)
Q-wave-MI	1.5% (n = 1)	4.3% (n = 3)	OR = 3.00, 95% CI, 0.27-76.03)
Non-Q-wav-MI	15.7% (n = 11)	14.7% (n = 10)	OR = 1.08, 95% CI, 0.39-3.01

Target lesion revascularization

Outcomes for diabetic patients were examined in 3 HTAs, 4 meta-analyses and 1 RCT included in this report. Results suggest that both TLR and TVR rates are significantly lower in diabetic patients treated with DES than those treated with BMS between 6 months and 4 years following stenting.

Conclusions from previous HTAs or similar reports (Table 40)
Revascularization rates were lower for diabetic patients treated with DES compared with BMS. Results were statistically significant.

Table 40. Summary of results reported in previous HTAs in diabetic patients

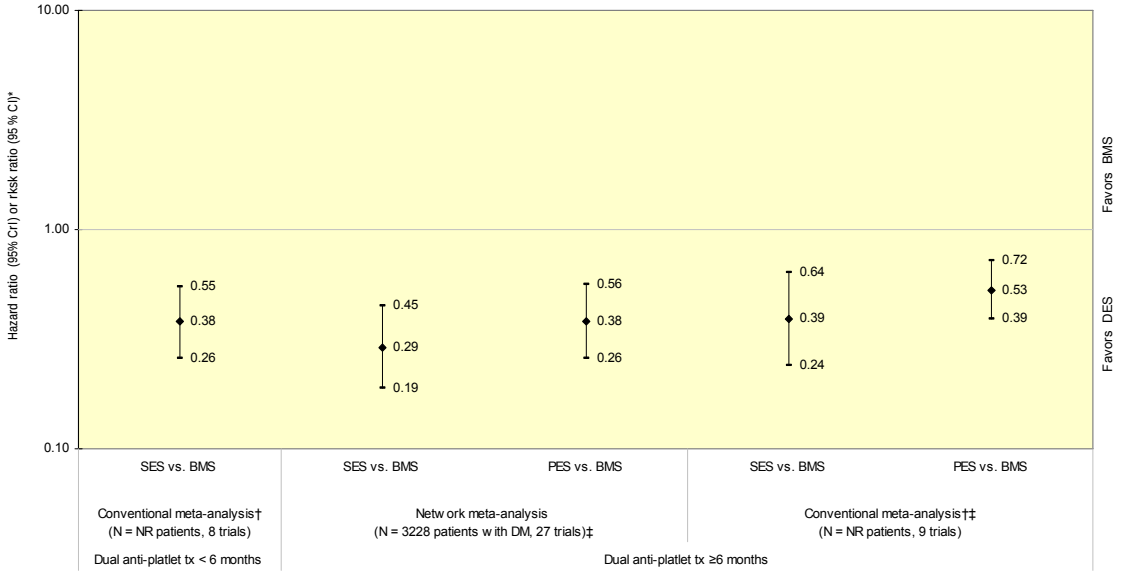
Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
KCE-Belgian (2007)	Review of previously published meta-analyses, RCTs, and registries. One study that compared DES vs. BMS enrolled only diabetic subjects (DIABETES) (N = NR). Subgroup analyses of 5 RCTs (TAXUS IV, TAXUS V, RAEL, SIRIUS, SES-SMART) (N = NR).	Data NR for RCT or RCT subanalyses.	• TLR rates were significantly lower in the SES (versus BMS) group of the DIABETES trial (data NR). • TLR rates were significantly lower in patients receiving DES (versus BMS) in subgroup analyses of 5 RCTs (data NR).	• Data described but not analyzed.
Hayes (2007)	Literature review and critique of available RCTs, meta-analyses, and registries. One study enrolled only diabetic subjects (DIABETES) (N = 160). Results from 2 subgroup analyses: SIRIUS (Moussa 2004) (N = 279), TAXUS IV (Hermiller 2005) (N = 1314) and 1 registry (Aoki 2005) (N = 230) also presented.	RCTs: • Rates of TLR at 9 months in patients with diabetes were 6.3% for DES and 31.3% for BMS (P < 0.001) (DIABETES). Subanalyses of RCTs: • Rates of TLR between 9-12 months in patients with diabetes ranged from 6.9-7.4 % for DES and 20.9-22.3% for BMS (P < 0.001 for both) (Moussa 2004, Hermiller 2005). • Rates of TVR between 9-12 months in patients with diabetes ranged from 9.9-11.3% for DES and 24.0-24.3% for BMS (P < 0.004 for both) (Moussa 2004, Hermiller 2005). Regsitries: • Rates of TVR at 1 year in patients with diabetes were 7.4% for DES and 19.3% for BMS (historical control) (P = 0.03) (Aoki). • Rates of repeat	• TLR rates were significantly lower in diabetic patients treated with DES compared to BMS.	• Data described but not analyzed. • All RCTs were industry-sponsored. • RCTs had relatively short follow-up. • Registry study uses pre-DES historical control.

		revascularization (type not specified) at 1 year in patients with diabetes were 10.2% for DES and 23.5% for BMS (historical control) (P = 0.007) (Aoki).		
MSAC (2004)	Described subgroup analyses of 3 RCTs (N = 459 (SIRIUS, RAVEL, TAXUS IV) (Holmes 2004, Abizaid 2004, Stone 2004)	*Subanalyses of RCTs:* • Rates of TLR at 9-12 months in patients with diabetes ranged from 0.0-6.9% for DES and 19.4-36.0% for BMS (P ≤ 0.006 for two studies, P = 0.07 for the other). • SIRIUS: RR (95% CI): 0.30 (0.15-0.62) (P < 0.0001) (12 months) (Holmes 2004)	• TLR rates were significantly lower in patients treated with DES versus BMS in 2 of 3 studies.	• Data described but not analyzed. •

Results from recent meta-analyses

DES use was consistently associated with a statistically significant decrease in the risk for target lesion revascularization among diabetic patients in both conventional and network meta-analyses by Stettler 2008,[59] regardless of duration of dual anti-platelet therapy (Figure 14). Among non-diabetic patients, the results were similar; indicating that, regardless of duration of dual anti-platelet therapy, the risk of revascularization was significantly less with DES than with BMS.

Figure 15. Relative risk estimates* for target lesion revascularization among diabetic patients according to duration of dual anti-platelet therapy



*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-analysis.

† Only conventional meta-analysis was reported for those with less than 6 months therapy. Conventional analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of

trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text).

‡The precise number of patients and trials that contributed to each outcome for the restricted analysis among patients with 6 or more months of dual anti-platelet therapy is not provided. Numbers for the conventional analysis of < 6 months therapy are suggested in the text (17 original trials with SES vs BMS minus 8), patient numbers for all outcomes are not reported (NR) and none are reported for those with ≥ 6 months therapy. Numbers listed for the network analysis are based on subtraction of 8 trials from the 35 originally included and estimated from authors' figures for the network meta-analysis. Numbers for the conventional analysis are not reported.

Results from two other recent meta-analyses[91, 94] and one pooled analysis[90] are consistent with the findings from Stettler (Table 41).

Table 41. Results for TLR/TVR from other meta-analyses of diabetic patients

Author (Year)	Number of Trials (N diabetic patients)	Relative Risk Estimate
Patti (2008)	9 RCTs, N = 1,141 diabetic patients	Overall TLR OR (95% CI): 0.23 (0.16-0.33) (*P* < 0.00001)
Kumbahni (2008)	12 RCTs (or less), N = 1,879 (or less)	Overall TLR RR (95% CI): 0.35 (0.27-0.46) (*P* < 0.0001)
Kirtane (2008)	5 trials, N = 832 diabetic patients	HR (95% CI) TLR Overall: 0.42 (0.30-0.60) (*P* < 0.0001) Overall TVR Overall: 0.67 (0.50-0.89) (*P* = 0.005)

Results from recently published RCTs

Statistically significant differences in TLR and TVR were seen when DES and BMS were compared in one small trial at 12 months. Event rates and effect estimates are given below.[102] Large confidence intervals for the odds ratio connote variability in the estimates possibly due to small numbers of patients experiencing events.

	SES	BMS	OR (95% CI)
TLR	5.9% (n =4)	30%% (n = 21)	OR = 6.86, 95% CI, 2.04, 25.37
TVR	15.7% (n = 11)	14.7% (n = 10)	OR = 5.40, 95% CI, 1.76, 17.72

Effectiveness in diabetic patients

Overall mortality and cardiac death

Specific discussion of overall mortality in diabetic patients was found in two technology assessments, one which relied on previously done meta-analyses[4] and the other which performed their own meta-analysis.[85] Results from these and two recently published registry studies are mixed with respect to overall mortality and cardiac death comparing DES and BMS.

Results from previous HTAs or similar reports (Table 42)

Data from the Ontario report suggest that timing and prior MI status influences risk of death among diabetic patients. At 6 months there was a statistically significant decrease in mortality among diabetic patients who received DES compared with BMS, regardless of whether they had had a prior MI. From 7-24 months, among those had a prior MI, there was not a statistically significant difference in MI risk between treatment groups, but among those had a prior MI, the lower risk of mortality remained statistically significant. These findings need to be considered in the context of possible heterogeneity across studies and of confounding by unmeasured variables.

Table 42. Summary of conclusions from previously reported HTAs or similar report related to overall mortality in diabetic patients

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
KCE-Belgian (2007)	29 DES registries identified; 1 registry's data cited	• N = 708 patients • Mortality: 2 year cumulative incidence • SES 13.3% • PES 11.5% • BMS 9.8%	• Two-year cumulative incidence of mortality was not statistically different between diabetic patients receiving DES and those receiving BMS. • In-stent thrombosis was higher in the DES group; however it is not stated whether this difference is statistically significant.	
Ontario (2007)	Literature review, data analysis of an observational study, and cost-effictiveness analysis	Mortality • RD (95% CI) Without prior MI • 6 months: -1.05% (-2.04%, -0.06%) • 7-24 months: -0.82% (-1.79%, 0.15%) With prior MI • 6 months: -4.21% (-7.98%, -0.44%) • 7-24 months: -1.58% (-2.86%, -0.30%)	• Patients without prior MI • At 6 months, patients in the DES group with diabetes, but without prior MI were less likely to die than those in the BMS group; this difference was statistically significant • At 7-24 months, patients in the DES group with diabetes, but without prior MI were less likely to die than those in the BMS group; this difference was not statistically significant • Patients with prior MI • At 6 months, patients in the DES group with diabetes and prior MI were less likely to die than those in the BMS group; this difference was statistically significant • At 7-24 months, patients in the DES group with diabetes and prior MI were less likely to die than those in the BMS group; this difference was statistically significant	While the authors found a reduced risk of mortality in the DES group, they urge caution as they were not able to identify the cause of death. In addition there are possible confounders that are unaccounted for, including unbalanced allocation of patients to DES and BMS group.

Results from recently published registry and non-randomized studies

Two recently published non-randomized studies involving diabetic patients were found. One found no significant difference in overall death, whether unadjusted or adjusted for 2-year propensity scores[119]. Another study found a lower rate of overall death after DES compared with BMS [6.7% vs 10.8%, aRR = 0.66 (0.44-0.99)] and this difference was significant for cardiac death (3.6% vs 7.2%, aRR = 0.53 (0.31-0.90)] but not for

noncardiac death [3.2% vs 3.8%, aRR = 0.97 (0.52-1.81), where aRR is the adjusted relative risk.[127]

Table 43. Cumulative rates of overall and cardiac mortality reported in registry or nonrandomized studies of diabetic populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Overall mortality			
≤ 30 days	1 [119]	1.6	1.7
30 days-1 year	2 [119, 127]	6.2-7.2	8.0-9.5
1 year-2 years	2 [119, 127]	6.7-10.2	10.8-12.3
Cardiac mortality			
at 2 years	1 [127]	3.6	7.2

Myocardial infarction

No previous health technology assessments provided data on the risk of myocardial infarction in patients with diabetes mellitus who received DES versus those who received BMS based on non-randomized studies. Two registry studies report no statistical difference between DES and BMS.

Previous HTAs: No technology assessments of non-randomized studies were found related to this outcome in diabetic patients.

Previous meta-analyses: No meta-analyses of non-randomized studies were found related to this outcome in diabetic patients.

Results from recently published registry and non-randomized studies

Two studies reported no significant difference in nonfatal myocardial infarction (MI) rates[119, 127]

Table 44. Cumulative rates of myocardial infarction reported in registry or nonrandomized studies of diabetic populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Myocardial infarction			
≤ 30 days	1 [119]	0.9	0.7
30 days-1 year	2 [119, 127]	4.8-6.6	4.7-7.0
1 year-2 years	2 [119, 127]	5.7-9.1	4.9-8.9

Target lesion revascularization

Previous HTAs: One report describes findings from RCT sub-analyses and one registry study.[78] Findings from both types of studies suggest that TVR is less frequent among diabetic patients who received DES compared with those who received BMS. Since sub-analyses of RCTs do not preserve randomization, they are included here. The Ontario HTA's meta-analysis of registry studies, patients with diabetes mellitus who had not had a prior MI and who received DES had statistically significantly lower rates for revascularization whereas the difference was not statistically significant among those who had a prior MI.

Table 45. Summary of conclusions for nonrandomized studies from previous HTAs with regard to TVR/TLR

Author (Year)	Evidence Base and Approach	Effect size	Conclusions	Comments
Ontario (2007)	Literature review, data analysis of an observational study, and cost-effictiveness analysis	Target Vessel Revascularization (TVR) • Log-rank p-value <0.01, favoring DES over BMS in patients without prior MI • Log-rank p-value=0.09, NS difference in patients with prior MI	• In patients without prior MI, DES was associated with lower rates of TVR; this difference was significant. • In patients with prior MI, DES was associated with lower rates of TVR; this difference, however, was not significant.	• There are possible confounders that are unaccounted for, including unbalanced allocation of patients to DES and BMS group.
Hayes (2007)	Literature review and critique . Results from 2 subgroup analyses: SIRIUS (Moussa 2004) (N = 279), TAXUS IV (Hermiller 2005) (N = 1314) and 1 registry (Aoki 2005) (N = 230) are presented.	*Subanalyses of RCTs:* • Rates of TLR between 9-12 months in patients with diabetes ranged from 6.9-7.4 % for DES and 20.9-22.3% for BMS (P < 0.001 for both). • Rates of TVR between 9-12 months in patients with diabetes ranged from 9.9-11.3% for DES and 24.0-24.3% for BMS (P < 0.004 for both). *Regsitries:* • Rates of TVR at 1 year in patients with diabetes were 7.4% for DES and 19.3% for BMS (historical control) (P = 0.03). • Rates of repeat revascularization (type not specified) at 1 year in patients with diabetes were 10.2% for DES and 23.5% for BMS (historical control) (P = 0.007).	• TLR rates were significantly lower in diabetic patients treated with DES compared to BMS.	• Data described but not analyzed. • All RCTs were industry-sponsored. • RCTs had relatively short follow-up. • Registry study uses pre-DES historical control.

Previous meta-analyses: No meta-analyses of non-randomized studies were found related to this outcome in diabetic patients.

Results from recently published registry and non-randomized studies
In one study, unadjusted rates of TVR were not significantly different at 30 days or one year but after propensity score adjustment, occurred less in the DES population than the BMS population [11.6% vs 15.0%, aHR = 0.66 (0.46-0.96)]. [110] The other study reported cumulative rates at 15 months of 5.1% for DES and 8.4% for BMS [aRR = 0.48 (0.33-0.71). [127]

Table 46. Cumulative rates of revascularization reported in registry and nonrandomized studies of diabetic populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Revascularization*			
TLR			
Cumulative to 15 months	1 [127]	5.1	8.4
TVR			
≤ 30 days	1 [119]	2.0	1.5
30 days-1 year	1 [119]	9.9	12.4
1 year-2 years	1 [119]	12.8	14.4

*TLR = target lesion revascularization.
TVR = target vessel revascularization.

Safety in diabetic patients

Stent thrombosis
Previous HTAs provide little information on the risk of stent thrombosis (acute, sub-acute or late) in diabetic patients.

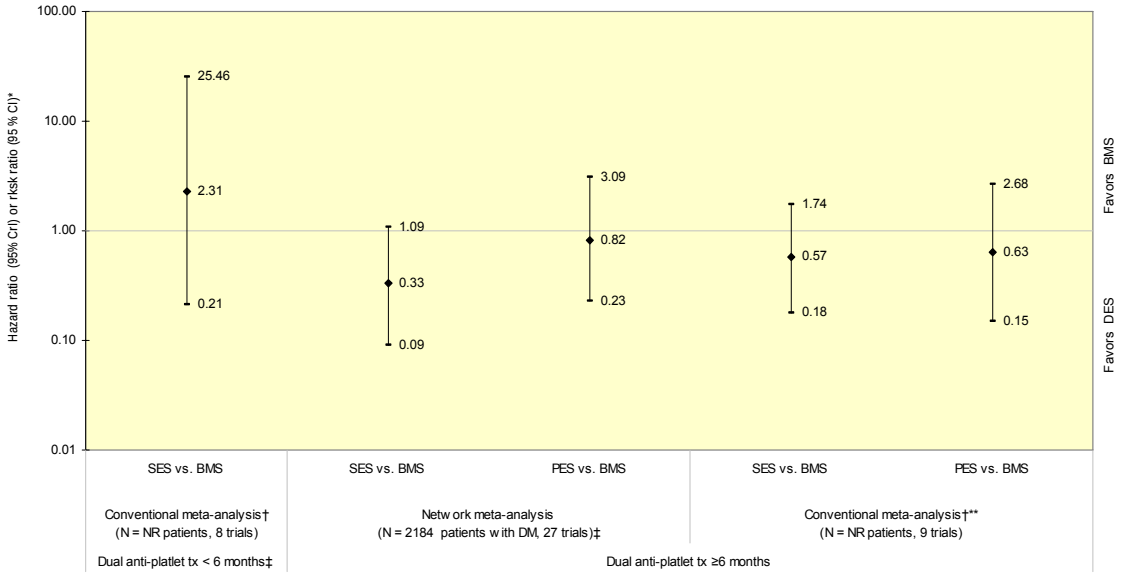
Recent meta-analyses consistently report no statistically significant difference in stent thrombosis by last follow-up. Only one report evaluates risk with respect to time and finds no statistically significant difference at any time. It is possible that even this largest meta-analysis had insufficient power to detect a difference between DES and BMS in the risk of late stent thrombosis in particular, given that it is a relatively rare event.

Conclusions from previous HTAs or similar reports
Only one previous HTA commented on stent thrombosis in diabetic populations.
One report noted that patients more likely to benefit from DES (e.g., patients with diabetes, small vessels, and chronic kidney disease) are at the same time at higher risk for developing late stent thrombosis.[77] An early report (2004) conclude that there is a lack of evidence on the risk of thrombosis in a more "clinically complex" patient.[84]

Results from recent meta-analyses
The report of Stettler, et al [59] again appears to provide the most complete evaluation. Although no statistically significant differences were seen in the relative risk of ARC-defined definite stent thrombosis in diabetic patients (regardless of duration of anti-platelet therapy) based on stent type in either the conventional or network meta-analyses

based on cumulative incidence up to 4 years, wide confidence intervals around the estimates suggest variability in the estimates that may be a reflection sample size. Only one study contributed to the conventional analysis of patients who had less than six months of dual anti-platelet therapy. A moderate degree of between-trial variance was seen for the network analysis among patients who had ≥ 6 months of dual anti-platelet therapy. Forests plots reflecting the direction and magnitude of estimates from individual studies were not provided.

Figure 16. Relative risk estimates* for stent thrombosis (ARC definition) from 0-4 years follow-up among diabetic patients according to duration of dual anti-platelet therapy



*The hazard ratio (HR) and 95% credibility interval (CrI) are given for the network meta-analysis and the risk ratio (RR) and 95% confidence interval (CI) are given for conventional meta-anlaysis.

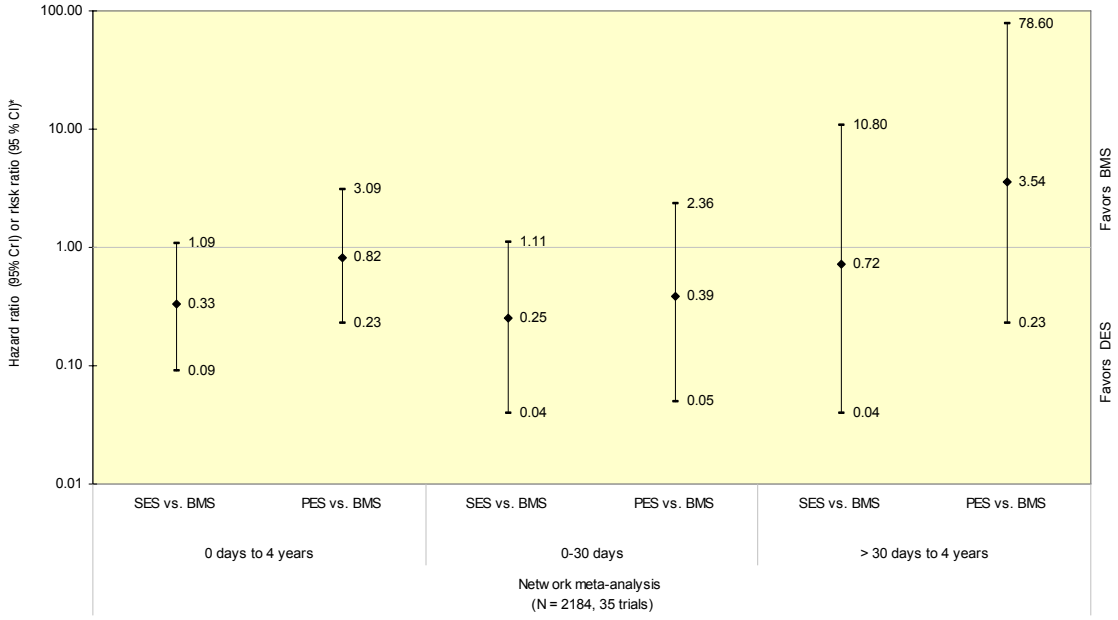
† Only conventional meta-analysis was reported for those with less than 6 months therapy. Conventional analysis is based on direct comparison of treatments as randomized in the trials and includes only those trials which directly compare treatments. The number of trials used for each outcome may vary and the N and number of trials in this graph reflect the overall (maximum) number of trials reported by Stettler, et. al. The N and number of trials in the conventional analyses were not provided for each outcome. One trial compared SES, PES and BMS. The network meta-analysis allows for direct and indirect comparison of treatments across all trials (which allows a greater number of trials to be included) while preserving randomization (see text).

‡Only one trial contributed to the analysis.

**The precise number of patients and trials that contributed to each outcome for the restricted analysis among patients with 6 or more months of dual anti-platelet therapy is not provided. Numbers for the conventional analysis of < 6 months therapy are suggested in the text (17 original trials with SES vs BMS minus 8), patient numbers for all outcomes are not reported (NR) and none are reported for those with ≥ 6 months therapy. Numbers listed for the network analysis are based on subtraction of 8 trials from the 35 originally included and extimated from authors' figures for the network meta-analysis. Numbers for the conventional analysis are not reported.

No statistically significant differences in stent thrombosis were seen between treatments either early (0-30 days) or late (>30 days to 4 years) in network meta-analysis restricted to those who had ≥ 6 months dual anti-platelet therapy. However, wide confidence intervals indicate lack of estimate stability and small numbers of events. It is likely that, because of the small number of events, particularly with later follow-up, even this pooled analysis was under-powered to detect a difference between treatments. The authors do not describe the heterogeneity, consistency across the network of included trials or the model fit for this set of analyses.

Figure 17. Relative risk estimates* for definite stent thrombosis (ARC definition) with respect to time among diabetic patients according to duration of dual anti-platelet therapy



Stettler's findings are consistent with the two other meta-analysis [91, 94] and the pooled analysis.[90] None of these other analyses provide information on the effect of duration of dual anti-platelet therapy.

Table 47. Summary of findings from other recent meta-analyses

Author (Year)	Number of Trials (N diabetic patients)	Effect Estimates
Patti (2008)	7* RCTs, with follow-up from 8-24 months; compulsory angiographic follow-up 6- 9 months N = 1,141 diabetic patients	Stent Thrombosis (12 mo. follow-up) • DES: 1.1%; BMS: 1.2% • OR (95% CI): 0.98 (0.31, 3.13)
Kumbahni (2008)	12 RCTs (or less), N = 1,879 (or less) with follow-up from 6-12 months	Stent Thrombosis (8-12 mo. follow-up) • DES: 0.4%; BMS: 1.4% • RR (95% CI): 0.41 (0.13, 1.27)
Kirtane (2008) (pooled analysis of PES vs. BMS trials only)	5 trials, N = 832 diabetic patients PES only	Stent Thrombosis (4 yr. follow-up) *ARC Definition (all)* • DES: 4.8% (15); BMS: 3.1% (11) • HR (95% CI): 1.38 (0.63, 3.00) *ARC Definition (definite/probable)* • DES: 2.2% (6); BMS: 1.4% (4) • HR (95% CI): 1.22 (0.37, 4.01)

*Authors indicate that 9 trials were used, however, for mortality, only 7 trials are listed

Results from recently published RCTs

No statistically significant difference any type of stent thrombosis were seen when DES (1.5%) and BMS (1.4%) were compared in this small trial at 12 months, RR = 0.97, 0.03,

36.37). This study is likely to be underpowered to detect a statistically significant difference between treatments.[102]

Results from previous HTAs regarding registry and non-randomized studies

One previous report[4] describes data from one large registry of 708 consecutive diabetic patients. While the authors state that in-stent thrombosis was more frequent in DES patients (2.4%-4.4%) versus BMS recipients (0.8%) they don't provide results of any statistical testing.

Table 48. Previous HTA of registries conclusions regarding stent thrombosis in diabetic patients

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
KCE-Belgian (2007)	29 DES registries identified; 1 registry's data cited	• N = 708 patients Stent thrombosis incidence • SES 4.4% • PES 2.4% • BMS 0.8%	• In-stent thrombosis was higher in the DES group; however it is not stated whether this difference is statistically significant. • Cited on report expressing concern about LST in diabetes being higher in other patient sub groups	• n = 17 In-stent thrombosis patients outcomes- 2 died, 7 presented with MI, 12 were still on anti-platelet therapy at the time

Results from recently published registry and non-randomized studies

Two recent studies reported no significant differences for stent thrombosis when comparing DES to BMS [Ortolani, Maeng].

Table 49. Cumulative rates of stent thrombosis reported in registry and nonrandomized studies of diabetic populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Stent thrombosis			
≤ 30 days	2 [119, 127]	0.5 – 0.5	0.3 – 1.6
To 1 year	2 [119, 127]	1.1 – 2.3	0.7 – 2.6
To 2 years	2 [119, 127]	1.5 – 2.4	0.7 – 3.2

Peri-procedural complications (bleeding, stroke, etc)

Periprocedural complications were not reported in either of the new non-randomized studies. [119]

Efficacy in patients with acute MI

Overall mortality and cardiac death

Results from one recent HTA, a meta-analysis and three recent RCTs suggest no statistical difference in the risk of overall mortality in patients with acute MI comparing DES with BMS.

Conclusions from previous HTAs or similar reports (Table 50)
Data specific to this population were provided in one report. While they did not conduct meta-analyses on all available data to investigate the risk of mortality, Hill [81] et al. included data from the STRATEGY study, which exclusively enrolled patients with acute STEMI. The trial was an open-label RCT with concealed allocation. No details were given in the HTA regarding the methods used to analyze the data for this individual study. The incidence of mortality over the 9 months of follow-up reported was 8.0% in the DES group, compared with 9.1% in the BMS group (HR (95% CI): 0.88 (0.30, 2.53)). However, the results of this study must be interpreted with caution, given the small sample size and the relatively low number of events.

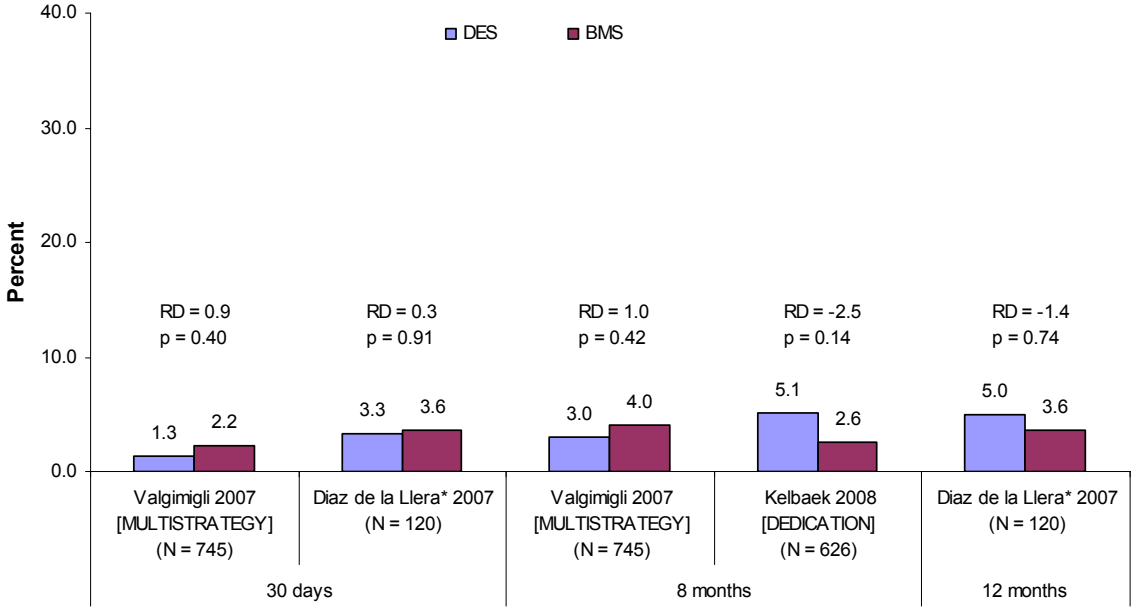
Table 50. Overall Mortality and Cardiac Mortality – Previous HTAs

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Hill (NICE/ NHS) (2007)	Results presented are from the STRATEGY study, which enrolled only subjects with acute STEMI [Valgimigi 2004]	All-cause mortality DES: 8.0% (7); BMS: 9.1% (8) HR (95% CI): 0.88 (0.30, 2.53)	All-cause mortality NS differences at 9 months of follow-up.	Results presented are from a single study which exclusively enrolled patients with acute STEMI. Trial was open label, but concealed allocation Dual antiplatelet therapy was indicated in the protocol; duration was not specified

Results from recent meta-analyses
Two recent meta-analyses [93], [95] were found only one of which [95] provides data for overall mortality separate from MACE or a composite of death or MI. This analysis of patient-level data from 8 RCTs (N = 2786) found no statistically significant difference in the risk of overall mortality in patients with acute STEMI who received DES (4.1%) compared with BMS (5.1%), HR 0.76 (0.53, 1.10). None of the individual trials showed a statistically significant difference between DES and BMS and all but one trial tended to favor DES. Sensitivity analyses were conducted by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Recommended duration of anti-platelet therapy was 3 months in one trial, 6 months in 4 trials, and 12 months in 3 trials. [95]

Results from recently published RCTs (Figure 18)
No statistically significant differences in mortality were seen between treatments in any of the new RCTs at any time period.[98, 100, 105] Results from these new trials are consistent with findings from trials included in meta-analysis by Kastrati.[95]

Figure 18. Overall mortality in recently published RCTs



* All deaths were considered cardiac unless otherwise documented

Re-infarction

The most complete set of data come from one meta-analysis.[95] Based on pooled estimates from 8 RCTs, there is not a statistically significant difference in risk of re-infarction when DES are used compared with BMS. Data on type and duration of antiplatelet therapy are not described.

Conclusions from previous HTAs or similar reports

Data or conclusions specific to this outcome were not reported.

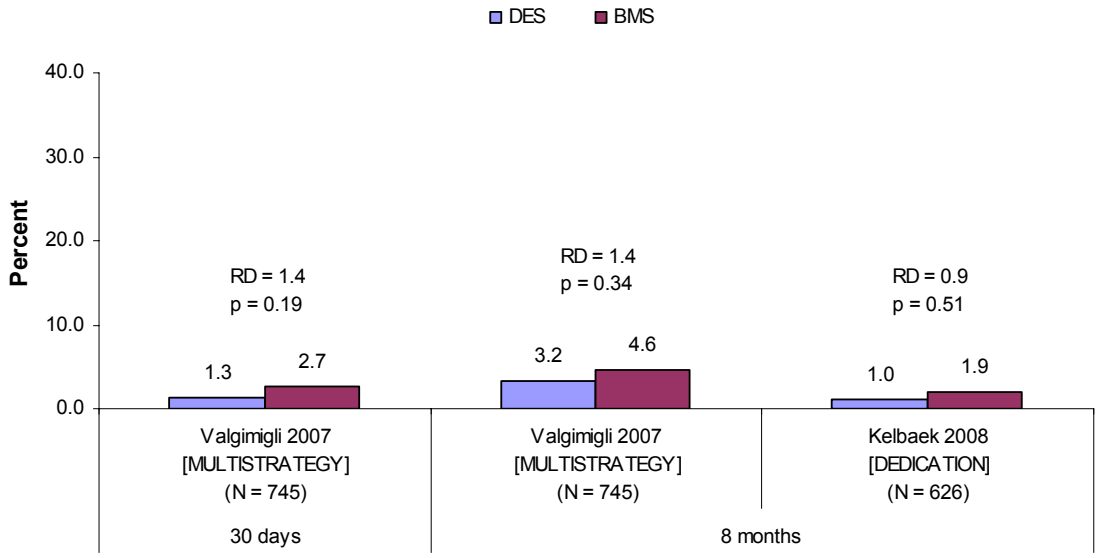
Results from recent meta-analyses

Only one of the two meta-analyses provided specific results for recurrence of myocardial infarction.[95] No statistically significant difference in MI recurrence was seen when DES (3.1%) were compared with BMS (4.0%), HR 0.72 (0.48, 1.08). There was no evidence of statistical heterogeneity between trials and all but one trial favored DES.

Results from recently published RCTs

There were no statistically significant differences in re-infarction rates between treatment groups in any of the new trials.[98, 100, 105]

Figure 19. Re-infarction rates in recently published RCTs



Target lesion revascularization

Across reports, DES implantation is associated with a statistically significant decrease in TLR compared with BMS in patients with acute MI.

Conclusions from previous HTAs or similar reports (Table 51)

Two previous reports used data from one RCT each to formulate conclusions about patients with acute MI.

Table 51. Conclusions from previous HTAs regarding TLR/TVR in acute MI patients

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Hayes (2007)	Literature review and critique of available RCTs, meta-analyses, and registries. 1 RCT evaluated patients with AMI with STEMI (Spaulding 2006) (N = 712) (TYPHOON)	*RCTs:* • Rates of clinically-driven TVR at 1 year in patients with AMI with STEMI were 5.6% for DES and 13.4% for BMS (P < 0.001).	• Rates of clinically-driven TVR were significantly lower in AMI STEMI patients treated with DES compared to BMS at 1 year, • TLR and TVR rates were significantly lower in ACS patients treated with DES compared to BMS at 1 year. • NS at 30 days.	• Data described but not analyzed. • Original trial was not designed to assess the relative effectiveness in patients with ACS. • All RCTs were industry-sponsored.
Hill (NICE/ NHS) (2007)	Pooled estimates from 17 RCTs comparing DES vs. BMS. One study enrolled only	**6-9 months f/u:** TLR: STRATEGY: SES: 5.7% BMS: 20.5% OR (95% CI): 0.24 (0.08-0.67) TVR:	• TLR and TVR rates significantly favor DES in STEMI patients at 6-9 months.	• Manufacturer-sponsored trial.

	subjects with STEMI (STRATEGY) (N = 175).	STRATEGY: SES: 5.7% BMS: 20.5% OR (95% CI): 0.29 (0.11-0.77)		

Results from recent meta-analyses

Both recent meta-analyses provided relative risk estimates for TLR. [93, 95] Pooled relative risk estimates were similar for both analyses. Pasceri's analysis included reports on one trial abstract and three scientific presentations, so not all were from peer-reviewed published sources.

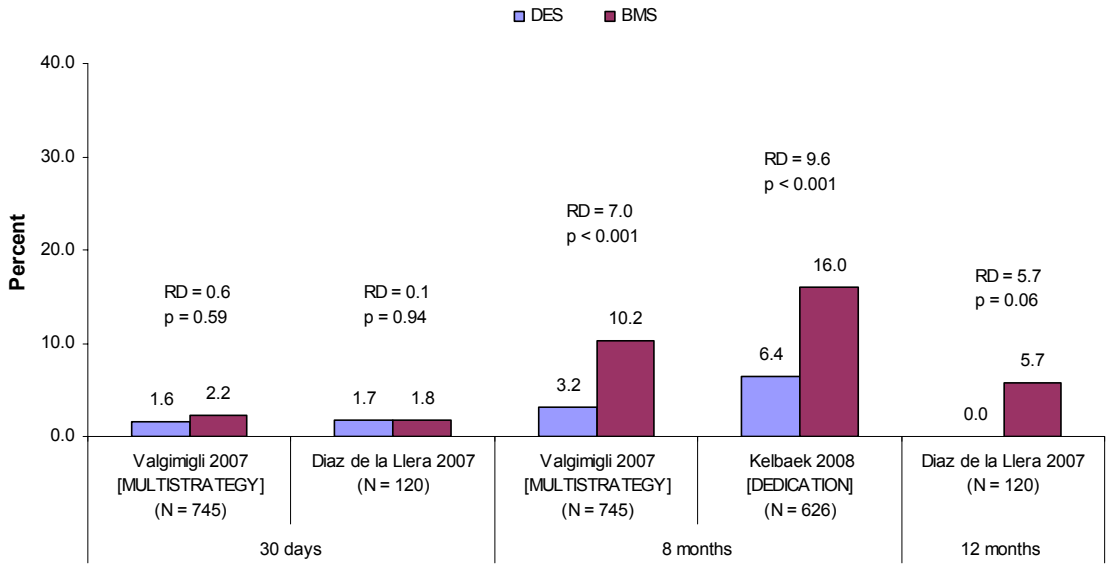
Table 52. Results from recent meta-analyses regarding TLR/TVR in acute MI patients

Author (Year)	Number of Trials (N diabetic patients)	Effect Estimates
Kastrati (2005)	8 RCTs, N = 2786	Reintervention DES: 5.1 %; BMS: 13.1% HR (95% CI): 0.0.38 (0.29, 5.0)
Pasceri (2007)	7 RCTs, N = 2357	TLR DES: 4.8%; BMS: 12.0% RR (95% CI): 0.40 (0.30, 0.54)

Results from recently published RCTs

Results from the two recent RCTS show no difference in TLR by 30 days [105] Diaz] [98]. At eight months, statistically significant decreases in TLR are seen in two trials.[100, 105] One small trial reported 12 month follow-up that approaches statistical significance. [98]

Figure 20. TLR rates in recently published RCTs



Effectiveness in patients with acute MI

Overall mortality and cardiac death
No previous health technology assessments or meta-analysis based on non-randomized studies provided data on the risk of overall mortality and cardiac death in patients with diabetes mellitus who received DES versus those who received BMS. Among three recent non-randomized studies, one case-control study suggests some benefit within 6 months favoring DES, but not at 12 months. The other two non-randomized studies report no statistical difference between DES and BMS.

Previous HTAs: No technology assessments of non-randomized studies were found related to this outcome in patients with acute MI.

Previous meta-analyses: No meta-analyses of non-randomized studies were found related to this outcome in patients with acute MI.

Results from recently published registry and non-randomized studies
Only one of the four studies of STEMI patients [113, 124, 129, 170] showed a mortality difference between DES and BMS. Kornowski et al [2008], in a matched case-control study (DES n=122, BMS n=506), found lower mortality in the DES group at one and 6 months, but not at 12 months. [113] Among patients with unprotected left main coronary artery stenosis, Palmerini found the risk of cardiac death was significantly lower in the DES group over two years [aHR=0.48 (95% CI 0.31-0.74)].[120] (Table 53).

Table 53. Cumulative rates of overall and cardiac mortality reported in registry or nonrandomized studies of STEMI and ULMCA stenosis populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Overall mortality			
≤ 30 days	2 [113, 124]	0-0.6	0.7-3.8
30 days-1 year	3 [113, 124, 170]	3.3-6.3	4.2-8.4
1 year-2 years*	3 [124, 129, 170]	6.2-8.0	6.4-13.7
Cardiac mortality			
at 2 years	1 [120]	6.9	17.6

*Percoco reported outcomes at a median of 396 days

Re-infarction-
No previous health technology assessments or meta-analysis based on non-randomized studies provided data on the risk of re-infarction (i.e. another MI in patients treated with stents for MI) in patients with who received DES versus those who received BMS for acute MI. Of three recent non-randomized studies, one suggests a slightly lower rate of re-infarction in the DES group (0% vs. 4.3%). The other two studies report no difference between groups.

Previous HTAs: No technology assessments of non-randomized studies were found related to this outcome in diabetic patients.

Previous meta-analyses: No meta-analyses of non-randomized studies were found related to this outcome in diabetic patients

Results from recently published registry and non-randomized studies
Of the three studies reporting adjusted MI rates for STEMI patients, Kornowski [113] found the rate of re-infarction was lower in the DES group ($P = 0.02$ at twelve months) whereas Percoco [129] found the risk was not significantly different [aHR = 1.11 (0.5-2.46)], as did Vlaar [124](overall $P = 0.31$) and Brodie ($P = 0.45$).

Table 54. Cumulative rates of myocardial infarction reported in registry or nonrandomized studies of STEMI and ULMCA stenosis populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Myocardial infarction			
≤ 30 days	2[113, 124]	0-1.0	1.1-3.4
30 days-1 year	3 [113, 124, 170]	0-2.7	4.3-6.1
1 year-2 years*	3 [124, 129, 170]	4.8-7.2	3.1-6.9

*Percoco reported outcomes at a median of 396 days

TLR or TVR
One previous health technology assessment and three recent non-randomized studies provided data on the risk of TLR or TVR in patients who received DES versus those who received BMS for acute MI. All report statistically lower rates of revascularization in the DES group.

Conclusions from previous HTAs
Hayes (2007)[78] reported the results of a subanalysis of 450 patients with acute coronary syndrome (ACS) (i.e., unstable angina or non-STEMI) from the TAXUS IV trial[171]. DES were significantly more effective at reducing both TLR and TVR rates than BMS at one year, while there was no difference at 30 days. However, the trial was not originally designed to evaluate outcomes in patients with ACS and is considered a cohort (non-randomized) study.

Table 55. Conclusions from previous HTAs evaluating TLR in patients with acute MI

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Hayes (2007)	1 substudy evaluated patients with acute coronary syndrome (ACS) (unstable AP, non-STEMI) (N = 450) (Moses 2005)	*Subanalyses of RCTs:* • Rates of TLR(TVR) at 30 days in patients with ACS were 0.0% (0.9%) for DES and 0.5% (0.0%) for BMS (NS for either). • Rates of TLR (TVR) at 1 year in patients with ACS were 3.9% (6.5%) for	• Rates of clinically-driven TVR were significantly lower in AMI STEMI patients treated with DES compared to BMS at 1 year, • TLR and TVR rates were significantly	• Data described but not analyzed. • Original trial was not designed to assess the relative effectiveness in patients with ACS. • All RCTs were industry-sponsored.

	(TAXUS IV substudy)	DES and 16.0% (17.7%) for BMS (P ≤ 0.0003 for both).	lower in ACS patients treated with DES compared to BMS at 1 year. • NS at 30 days.	

Previous meta-analyses: No meta-analyses of non-randomized studies were found related to this outcome in diabetic patients

Results from recently published registry and non-randomized studies
Three of the studies [113, 129, 170] of STEMI indications reported lower revascularization rates for DES; Percoco [129] reported an adjusted HR = 0.41 (0.2-0.85) for TVR. Vlaar [124] did not report adjusted revascularization rates; unadjusted rates were significantly lower for DES (TVR, P = 0.002; TLR P < 0.001).

Table 56. Cumulative rates of revascularization reported in registry and nonrandomized studies of STEMI and ULMCA stenosis populations

Outcome	No. Studies	Range of crude rates reported (%) DES	BMS
Revascularization*			
TLR			
≤ 30 days	1 [124]	0.8	2.4
30 days-1 year	2 [113, 124]	2.5-2.9	10.4-14.0
1 year-2 years	1 [124]	4.7	11.1
TVR			
≤ 30 days	1 [124]	1.1	2.4
30 days-1 year	2 [124, 170]	4.0-6.2	7.5-10.4
1 year-2 years†	4 [113, 124, 129, 170]	3.4-8.0	5.1-15.2

*TLR = target lesion revascularization.
TVR = target vessel revascularization.
†Percoco reported outcomes at a median of 396 days

Safety in patients with acute MI
Randomized controlled trials assessing safety were summarized in one previous health technology assessment and two meta-analyses. In addition, three recent RCTs provided data on stent thrombosis in patients who received DES versus those who received BMS for acute MI. All report no statistically significant difference in rates of stent thrombosis between DES and BMS groups. Two non-randomized trials also reported no statistical difference between groups.[129] The adjusted estimates were not statistically significant in a third study.[170]

Conclusions from previous HTAs or similar reports (Table 57)

Hayes (2007) reported the results of the TYPHOON study[149] which enrolled 712 patients with AMI with STEMI. At 1 year, there was no significant difference in the rates of stent thrombosis between groups (3.4% DES vs. 3.6% BMS). Hayes also described a subanalysis of 450 patients with acute coronary syndrome (ACS) (ie., unstable angina or non-STEMI) from the TAXUS IV trial.[171] At 1 year, rates of stent thrombosis were not

significantly different patients treated with DES versus BMS (0.8% DES vs. 0.9% BMS). There was also no difference at 30 days (0.8% DES vs. 0.5% BMS). Due to small sample sizes, the studies may have been underpowered, and results should be interpreted accordingly.

Table 57. Findings reported in previous HTAs regarding stent thrombosis in acute MI patients

Author (Year)	Evidence Base and Approach	Primary Outcomes and Effect size	Conclusions	Comments
Hayes (2007)	Literature review and critique of available RCTs, meta-analyses, and registries. 1 RCT evaluated patients with AMI with STEMI (Spaulding 2006) (N = 712) (TYPHOON) 1 substudy evaluated patients with acute coronary syndrome (ACS) (unstable AP, non-STEMI) (N = 450) (Moses 2005) (TAXUS IV substudy)	*RCTs:* 1 year: • SES: 3.4% • BMS: 3.6% • (P = NS) *Subanalyses of RCTs:* 30 days: • PES: 0.8% • BMS: 0.5% • (P = NS) 1 year: • PES: 0.8% • BMS: 0.9% • (P = NS)	• NS difference at 30 daysor 1 year.	• Data described but not analyzed. • Original trial was not designed to assess the relative effectiveness in patients with ACS. • All RCTs were industry-sponsored. • May have been underpowered. • Short-term follow-up.

Results from recent meta-analyses

Neither recent meta-analysis found a statistically significant increase in overall rates of stent thrombosis possibly due to lack of statistical power. [93, 95])

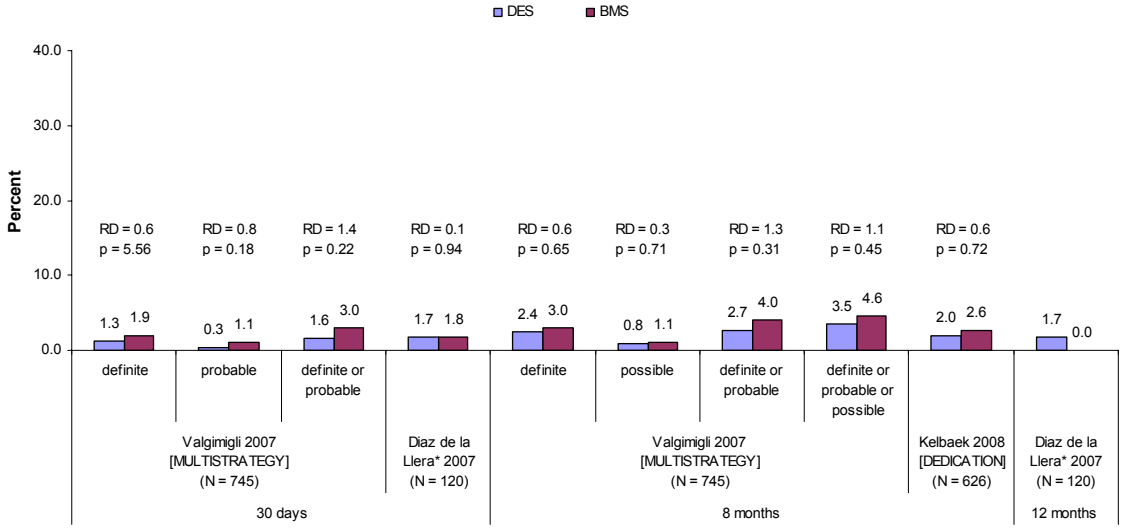
Table 58. Findings reported in recent meta-analyses regarding stent thrombosis in acute MI patients

Author (Year)	Number of Trials (N patients)	Effect Estimates
Kastrati (2007)	8 RCTs, N = 2786	Stent Thrombosis (12 mo. follow-up) DES: 3.1% (46); BMS: 4.0% (52) HR (95% CI): 0.72 (0.48, 1.08)
Pasceri (2007)	7 RCTs, N = 2357	Stent Thrombosis (8-12 mo. follow-up) DES: 2.3% (27); BMS: 2.6% (31) RR (95% CI): 0.87 (0.53, 1.45) *P* = 0.60

Results from recently published RCTs

Across three new RCTs, no statistically significant difference in the frequency of stent thrombosis was seen at any time period, however the longest follow-up was 12 months and none of these studies was likely powered to detect a significant difference for this rare outcome. [98, 100, 105]

Figure 21. Results recent published RCTs regarding stent thrombosis in acute MI patients



Results from recently published registry and non-randomized studies

Stent thrombosis

Three studies reporting stent thrombosis found less thrombosis in the DES group, but not a significant difference for adjusted rates. [113, 129, 170]

Table 59. Cumulative rates of stent thrombosis reported in registry and nonrandomized studies of STEMI and ULMCA stenosis populations

		Range of crude rates reported (%)	
Outcome	**No. Studies**	**DES**	**BMS**
Stent thrombosis			
≤ 30 days	2 [113, 129]	0-0.4	1.1-2.2
30 days-1 year	3 [113, 129, 170] [Brodie 2008, Kornowski 2008, Percoco 2006]	0.8-1.0	1.5-3.6
1 year-2 years	1 [170]	1.8	3.9

Any peri-procedural complications (bleeding, stroke, etc)

Periprocedural complications were not reported in four studies.[113, 120, 124, 129]

Efficacy in patients with intermediate lesions

Intermediate target lesions, defined as <50% diameter stenosis as defined by quantitative coronary angiography (QCA), were examined in no HTAs and one pooled analysis.

Results from one small pooled analysis[92] suggest no differences between treatments with regard to cardiac death or myocardial infarction. DES are more effective than BMS at reducing revascularization rates in patients with intermediate lesions the first year after stenting, although only 167 patients were analyzed. While this study provides useful information regarding the safety and effectiveness of DES versus BMS in this understudied patient population, the small sample size means that all results from the analyses should be interpreted with caution.

Overall mortality and cardiac death
Data from the one small meta-analysis of four trials (N = 167) are available and suggest that there are no differences in cardiac mortality at any follow up time [Moses].

Results from recent meta-analyses

Moses et al.[92] collected patient-level from four trials on subjects who were classified as having intermediate lesions (<50% diameter stenosis as defined by QCA). All four trials [SIRIUS, TAXUS-IV, and FUTURE-I and –II] required that patients have a lesion diameter stenosis >50% to be included in the trial; however when the lesion diameter stenosis was assessed quantitatively using QCA, 6.7% (167) of the subjects were found to have lesions with <50% stenosis. The authors used Cox proportional hazards regression to compare their results. Heterogeneity of the treatment effect was evaluated by including a treatment by study interaction term in the model; the significance of this variable was assessed using the likelihood ratio test. No deaths occurred within 30 days of the procedure. At 1 year (cumulative) the rates for cardiac death were: DES: 0% (0); BMS: 2.7% (2); p-value = 0.11.

Myocardial infarction
Results from the one recent meta-analysis were found. At 1 year, the incidence of myocardial infarction was 3.4% in the DES group and 5.4% in the BMS group; this difference was not statistically significant.[92]

Target lesion revascularization
Moses, et al report no TLR at 30 days in either stent group. Data for 1 year for TLR/TVR are as follows: DES: (1.2%, 3.4%), BMS: (20.3%, 20.3%) (P = 0.0004, P < 0.0001, respectively). [92]

Effectiveness in patients with intermediate lesions:
No reports were found.

Safety in other patients with intermediate lesions:
Data from the one small meta-analysis were available. At 1 year, no subjects had suffered a thrombotic event.[92] Given that thrombosis is generally a relatively rare event,

it is likely that this study is underpowered to detect a difference in risk between the two types of stents studied.

Effectiveness in elderly populations

The following study was brought to the HTA author's attention after the cut-off period for study inclusion and during the final editing process for the final HTA report. Since it appears to represent the largest registry-related study comparing DES with BMS to date, it is included here for informational purposes. The data are from an uncorrected proof of the study which appeared online following presentation at the recent American College of Cardiology meeting and therefore may not reflect the final, corrected, MEDLINE accessible version. As it is an AHRQ funded study, a press release related to the presentation was available as well. Because of the timing, there was insufficient time to do full critical appraisal or review and appropriate incorporation of this study into the final HTA report.

This study by Douglas, et al [136] linked Medicare data with information from the ACC-National Cardiovascular Data Registry (NCDR). Data for the primary outcomes of interest in this HTA are presented in the table below.

Table 60. Adjusted rates for outcomes in patients ≥ 65 years old based on linked Medicare and ACC-NCDR data in 262,700 patients at 30 months

Outcome	Experienced outcome (n)	Rates %		
		DES (n = 217,675)	BMS (n = 45, 025)	Risk difference
Overall mortality	21,254	13.5%	16.5%	3%
Cardiac death (only HR provided)	NR	NR	NR	
Myocardial infarction	10,528	7.5%	8.9%	1.4%
Target lesion revascularization	34,751	23.5%	23.4%*	0.1%

NR – not reported; HR – hazard ratio
* after risk adjustment, there was no statistically significant different in revascularization at 30 months- authors report that rates were lower in DES patients at 12 months, but there was a late "rebound" in revascularization between 12 and 30 months in the DES group.

Statistically significant differences in adjusted relative risk estimates favoring DES were reported for death, MI and revascularization based on time-to-event analysis. There were no statistically significant differences between treatment groups for revascularization, stroke and bleeding following risk adjustment.

Risk differences in outcomes based on pooled cumulative data (0-4 years) from the Stettler 2007 meta-analysis of RCTs for overall mortality (0.6%) and myocardial infarction (0.2%) and death or MI (1.0%) were lower compared with the above registry study, but higher for target lesion revascularization (10.9%). [Stettler 2007]

While this registry study adds important information regarding real world use of stents, the following, based on limited critical appraisal, should be considered. Data were from

Medicare patients who tended to be older and to have a higher proportion of females compared with the other studies such as the RCTs summarized by Stettler. In addition, as the authors point out, data quality in this study is dependent on the accuracy and completeness of both the registry and Medicare data sets and misclassification is possible. Assuming such misclassification is not differential by treatment group, the results may be biased to the null. The uneven distribution of patients in the two treatment groups suggests a potential for bias related to treatment selection. Although the investigators use several adjustment methods to account for factors which may influence treatment selection as well as demographic and other factors, incomplete adjustment of measured and unmeasured variables is still possible and may contribute to the observed results.

In the AHRQ press release that coincided with posting of this study, one study author suggests that the better outcomes among DES patients may in part be due to the requirement for use of anti-platelet medications (e.g. clopidogrel) for a long time following PCI where as patients receiving BMS are usually prescribed blood-thinning drugs for a shorter time period and may take the less frequently. He also suggests that more frequent physician visits and prescription of medications and therapies to lower cholesterol and manage other cardiac conditions among DES recipients compared with those who received BMS may contribute to the better outcomes observed in DES patients.[172]

The data reported here are from an uncorrected proof in the online version of the Journal of the American College of Cardiology (JACC). A more complete evaluation and inclusion of this new registry study will be needed when this HTA is re-reviewed.

3.4 Key question 4: What is the evidence of cost effectiveness and cost implications of DES versus BMS – including any effects of pharmacologic therapy and re-intervention?

Several previously published Health Technology Assessments (HTAs) summarized in this report did systematic reviews of published economic analyses and/or conducted cost effectiveness studies of their own. There is a great deal of overlap between the HTAs of the studies reviewed. Appendix D shows the specific studies reviewed by each HTA. This section includes

- A summary of the conclusions from previous HTAs, similar reports and recent systematic reviews based on their critical review of the economic literature. Because of changes in the technology and patterns of use of DES and BMS more emphasis has been placed on the more recent review, realizing many aspects of clinical practice may have changed since these studies were performed.
- Information on and critique of the economic analyses performed as part of the HTAs.
- Critique of and results from one new full economic analysis published since the HTAs is included. Only full economic analyses were considered for inclusion.

Recent reviews of formal economic analyses and one new cost effectiveness report conclude that DES are either not cost effective or only cost effective in high risk patients, most often defined as those having a combination of two or more factors such as needing stenting in small diameter, long length vessels or who have diabetes or have had a recent MI. Only one of the HTAs[4] in their analysis included a possible difference in costs or quality of life (QOL) when long term dual anti-platelet therapy and its potential complications or late stent thrombosis in DES were included in the clinical model. With the exception of the economic analyses conducted as part of HTAs, for which clinical outcomes such as survival and freedom from MI were the primary outcomes considered, most of the studies reviewed in previous HTAs focused more on the cost per revascularization avoided rather than cost per quality adjusted life years QALY. While this outcome is useful to consider when comparing alternative technologies for a specific intervention, repeat revascularizations are an intermediate point on the clinical pathway and, to date, the expected rates have been subject to a great deal of variation in specification and experience. In addition, they are specific to treatment of cardiac ischemia and do not allow comparisons with other alternative medical care. Cost per Quality Adjusted Life Years gained (QALY) is considered the more appropriate outcome for cost effectiveness analyses, particularly for consideration of decisions regarding alternative medical care expenditures in other areas. For example health care systems (or payers) may need to consider that spending for one technology or medical service in one area may preclude spending for a technology or service in another area since there are finite resources. Cost per QALY may provide one factor to consider together with the pros and cons, risks and benefits of technologies or services. Since revascularization is part of the clinical pathway (between the original stent placement and clinical outcomes) and is subject to great variations in specification, the QOL metric may be the more appropriate measure.[4] In general, the studies reviewed paid a great deal more attention to revascularization rates than to consideration of QOL values, their sources and variability.

The quality and methods of individual economic studies were variable. Conclusions across economic studies were also variable. The most methodologically rigorous studies are those done as part of previous HTAs which have been done in Europe and Canada. Differences in the health care systems, reimbursement policies and purchasing methods from one country to another should be considered when interpreting these analyses. Studies conducted primarily in other countries may not be directly applicable in the US without careful assessment of system differences. There is a need for methodologically rigorous economic studies using US data and system parameters.

Since there remains some uncertainty regarding efficacy, effectiveness, and safety of DES versus BMS, differing assumptions about those outcomes continue to contribute to variability in the economic analyses, primarily related to off-label use. Early studies, mainly supported by stent manufacturers and associated with pivotal RCTs, often found DES to be cost effective[173.] Analyses performed as part of health technology assessments found them not cost effective, or cost effective in only select sets of patients, especially as use of DES increased and expanded beyond the clinical indications in the early trials and as jurisdictions were able to compile data on real world experience.

Overall, the incremental cost effectiveness ratios (ICER) in the HTA literature reviews for DES ranged from a low of $27,540 to a high of €1,099,858 per QALY, the lower value coming from an early RCT trial supported by industry [Hill, MSAC]. The four recent economic analyses performed as part of HTAs reported ICERs which ranged from a low of $64,394 in the Ontario HTA to over £1 million in the KCE-Belgian HTA. The one additional study reviewed reported an ICER of €40,467.[137] ICERs for repeat revascularizations ranged from $1650 to $7000. Sensitivity analyses showed that ICERs were most influenced by the price premium of DES, the number of stents implanted in the index procedure and revascularization rates. Across all reports, conclusions were that DES might be cost effective in higher risk patients, if at all, and that they were not cost effective in low risk patients (non-diabetic, non-post MI, short length, wide vessel).

More recent analyses are the focus of this report. Except for one HTA analysis,[4] even these most recent analyses have not addressed changing patterns of clopidogrel use, duration of anti-platelet therapy and related complications or the probabilities of and costs of late stent thrombosis. In addition, it is important to consider the applicability of results found in countries where reimbursement policy or authorization to use a particular technology may actually be strongly associated with the proportion and/or types of patients receiving DES versus BMS, the associated costs and clinical pathway and thus affect findings in a cost effectiveness study.[4, 85] For example, in Belgium, coronary stents are reimbursed on a lump sum basis and the hospital can only charge this lump sum once per hospitalization, regardless of the number of stents used. This policy creates an incentive for the staging of PCIs, where stenting in multi-vessel disease is performed during separate hospitalizations. In Ontario, there was potential for allocation of the BMS in patients with an anticipated shorter life expectancy as a result of a finite amount of funding for DES, thus giving the appearance of higher mortality in the BMS group.[85]

Overview of economic analysis methods

To formally analyze the cost effectiveness of DES in comparison with BMS, it is necessary to begin by specifying the expected effectiveness of each as well as the associated costs over a certain time period (often called the time horizon). [174] Incremental cost effectiveness ratios (ICER)[174] are the difference in costs over a set time period between DES and BMS divided by the difference in effectiveness between the two interventions. To calculate the ICER, assumptions about patients, events and costs associated with specific clinical pathway(s) (are) modeled. In particular, the proportion of patients who will receive DES, their clinical presentation, and the probabilities of death, myocardial infarction, revascularization (PCI or CABG), complications and events such as stent thrombosis and the associated costs have to be specified. (More recent efficacy studies considering anti-platelet therapy and late stent thrombosis suggest these factors should be included in CE analyses but they were not usually characterized as different between DES and BMS in the studies reviewed). The analysis, using various statistical and decision analytic modeling techniques,[174] also allows one to vary these parameters to assess the impact of different costs or efficacy values on the results (called sensitivity analysis) allowing policy makers and others to assess the impact of alternative decisions.

In specifying the numerator, (i.e. difference in costs), most studies use the third party payer perspective and thus include direct medical costs, including costs of stents, tests, drugs, supplies, health care personnel and medical facilities including the initial hospitalization and clinical visits or repeat hospitalizations during the follow-up period. A few studies included patient out of pocket expense as well. Comparing DES with BMS the main differences in costs would be expected to be the initial treatment costs, the cost of the stents (DES versus BMS) and the costs associated with revascularizations. While rarely considered in the studies reviewed, recent issues regarding dual anti-platelet therapy and probability of late stent thrombosis are important considerations that should be included in future economic analyses. Costs can be hypothetically modeled based on pricing and set rates or they can be based on actual experience. Those based on experience of payers may more accurately reflect actual practice and costs, especially with regard to actual rates of DES or BMS use, number of stents implanted, or repeat revascularizations by CABG versus PCI, but also may be confounded by policy that drives rates artificially. For example, if DES requires pre-authorization the rate of DES may differ from an environment where pre-authorization is not required. Similarly, third party payers may obtain discount rates for devices or hospital costs, etc, that would not translate to another environment.

In specifying effectiveness, classic cost utility analysis uses the difference in "quality adjusted life years" or QALY (the utility) as the denominator. A QALY is the length of life expectancy (or a time horizon specified for the study) multiplied by the patient's rating of their quality of life on a 0 to 1 scale where 1 is perfect health and 0 is death. Ideally this measure is obtained at important milestones in the patient's course, but at least at baseline and some follow-up point. In the comparison of DES and BMS, most of the studies used an assumption that rates of mortality and myocardial infarction would not differ significantly between DES and BMS, based on results from RCTs and most nonrandomized studies. The QALY outcome therefore becomes primarily an estimate of the difference in quality of life (patient reported) between DES and BMS during the time horizon. Steps in the clinical pathway contribute to this estimate, most notably revascularizations, either CABG or PCI. The rates and costs of procedural complications as well the costs and complications of adjuctive therapies should also be part of the clinical pathway modeled but haven't been included to date as specific model parameters. It is important to use a quality of life measure (utility) that is sensitive to quality of life differences in patients with the particular condition being studied. Often the general population quality of life measures are not sensitive to small changes associated with a particular medical condition. The more general population measures are important for use in analyses informing decisions regarding funding allocations across populations.

Given that the DES are more expensive than the BMS, the primary question in the cost effectiveness analysis then becomes whether the increased initial costs of DES could be offset by the reduced costs from fewer repeat revascularizations (smaller numerator), or be justified by the gain in QoL (larger denominator). Based on clinical endpoints such as death and myocardial infarction the cost per QALY may be the more appropriate

measure. However, many studies report a cost per revascularization avoided as a primary endpoint or in addition to the cost per QALY.

Conclusions from previous HTAs or similar reports (Table 61)

Six previous HTAs included a systematic review and critical appraisal of the economic literature regarding cost effectiveness of DES versus BMS. There was a great deal of overlap between them in the included studies (Appendix D). Most of the economic evaluations were conducted from the third party payer or health care provider perspective on a general population for the country in which they were conducted for a one year follow-up period. The table below provides a summary of the parameters used and the results described in previous HTAs and reviews. In general, critical appraisals of the literature led authors of the previous HTAs to draw the following conclusions:

- DES may be more cost effective in higher risk patients.
- When more realistic assumptions and data values were used, DES may be cost effective only under very limited circumstances.
- Several of the studies reviewed were supported by industry.

Table 61. Conclusions based on review and critical appraisal of economic studies reported in previous HTAs

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
Hill (NICE/NHS) (2007)	Review of 10 full economic evaluations: 4 CUAs, 6 CEAs: • Most used healthcare provider perspective, were set in UK, USA, Canada or Europe. • Time horizon 1 yr (7), 6 mo(1), 2 yrs(1) and patient's lifetime(1). • Price premiums for DES ranged from £233 to £1255, highest in US, Canada. • Outcomes from efficacy data – from meta-analyses to single trial data: values ranged from 23% relative risk reduction for repeat revascularization to 94% reduction in TLR.	• Incremental Cost Per QALY Can$27,540 to Can$96,523 for gen pop • ICER per RRA $1650 over 1 yr - $7000 over 2 yrs. • Other outcomes reported not comparable. • Study quality "reasonably high" except modeling methodology poorly described, sensitivity analysis not fully explained or justified.	DES more cost effective in higher risk patients	When more realistic assumptions and data values were used, DES may be cost-effective only under very limited circumstances. Authors report industry affiliation in 4 studies
KCE (2007)	Review of 22 articles: • Most use payer perspective • 1 year time frame • price premium for DES over BMS varied as much as 5 times (higher US) • used different # stents per proc 1.1-1.9	• $27,540/QALY-€1,099,858/ QALY for total study population • Highly variable results depending on parameters used,	• DES could be cost effective only for high risk populations, defined by diabetes status, vessel diameter	• Most studies suggest the savings from fewer revascularizations with DES only partially offset the

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
	• costs for avoided procedures varied (eg. CABG from €7254 – €24,332 • BMS baseline risk of revasc 12.1-30%, DES risk 5.8%-13.3%.	number of lesions, diabetes status, etc..	and lesion length	higher initial cost of the stent procedure
FinOHTA (2007)	13 studies 1/2004-1/2006: 3 CUA, 6 CEA, 4 not stated • Time horizon, perspective not reported, model parameters not reported • Rated study quality using Drummond (0-10 scale) • Classified conclusions of authors	Median study • quality score = 9, range 7-10 • Author conclusions: • 2 –DES cost eff • 6- DES may be cost effective in selected but not as single strategy • 4 – DES not cost-effective • 1 – no conclusion	• Quality score: Most studies did not adjust costs and consequences for differential timing. • 2 studies finding DES cost effective were from RCTs.	Supplemental Table 1 did not provide systematic information about studies, such as perspective, time horizon, parameters used in the models.
ECRI (2007	Narrative discussion of 7 studies, two from the US. No synthesis or assessment of quality. Payer perspective, most one year time horizon.	US studies: • $27,540/QALY-$47,798/QALY; $1,650/RRA	• Non-US studies: DES is CE in only selected higher risk pts (3); only in single de novo lesions (1); no concensus (1)	US studies were industry supported.
EUnetHTA (2008)	references FinOHTA assessment			
Ligthart (2006)	19 Cost effectiveness studies, 1/1/2000 – 7/31/2006 from third party payer perspective. • Outcome variable: whether the study's conclusion favored widespread use of DES. • Predictor variables: Study quality (10 pt checklist and QHES, ___), funding source, country, year of publication • Classification and regression tree (CART) model used for multivariate analysis	• 10 favored widespread use of DES • 9 favored restrained use • 1 of 9 high quality vs 9 of 10 lower quality studies favored widespread use(p=0.03) • Sponsored studies more likely to support widespread use (7/7 vs 3/12, p=0.003 • Studies from US more likely to endorse unlimited use (p=0.03) • Favoring	• Conclusions drawn by CE studies are associated with the study's quality, finding source and country of origin. • Studies favoring widespread use were more likely than those not favoring to be published early after introduction of DES. Later studies by HTAs were of higher quality	• While no cost/QALY threshold is established as "cost effective", $50,000 is often mentioned as a "rule of thumb". • • None of the studies reviewed considered the clinical and economic consequences of late stent thrombosis.

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
		widespread use associated with a threshold of $50,000/QALY in 9 studies reporting. QHES median score = 62, Sensitivity analysis confirmed results.	and that more focused approach concentrating on high-risk patients was indicated. Authors recommend vigilance when interpreting findings from CE analyses.	
Ontario (2007)	No systematic assessment of economic studies.			
CTAF (2007)	No systematic assessment of economic studies			
Hayes (2007)	No systematic assessment of economic studies			
CCOHTA (2006)	Narrative review of 1 study and several abstracts. Not systematic.			
AETMIS (2004)	Limited review, not systematic, less relevant to current practice			
MSAC (2004)	Search, brief review; details of models not reported, stated Greenberg report had limited information	Cohen- • $27,540/QALY • $1,650/RRA; • Greenberg • $12,500 (US$ 1998) /RRA	ICER sensitive to patient subgroup and predicted target lesion revascularization rate.	Industry supported. These studies were included in KCE and Hill where more thorough review was conducted.

TVR Target Vessel Revascularization
RRA Repeat revascularization avoided
QALY quality adjusted life years
ICER Incremental cost effectiveness ratio = difference in costs between two interventions divided by the difference in quality adjusted life years (QALY) or other outcome measure, such as repeat revascularization avoided. Interpreted as the cost per QALY or cost per RRA.
CUA Cost Utility Analysis = Cost per QALY
CEA Cost Effectiveness Analysis = Cost per Outcome such as RRA
Quality of Health Economic Studies (QHES) instrument [see Appendix ___]

Hill [81] and the KCE report[4] provided the most detailed critical appraisals of previous economic analyses. Input parameters for the cost effectiveness studies varied widely across studies according to the two reports. Hill reported a range of price premium for DES from €233 to €1255, with the highest differences in the US and Canada. The KCE review noted that the price premium varied as much as 5 times higher (€690-€5335). Average number of stents per procedure varied from 1.1 to 1.9 in the KCE review. Outcomes were mostly taken from efficacy data from RCTs, and ranged from 23% risk reduction for repeat revascularization to a 94% reduction in target lesion revascularization.[81] Baseline risk of revascularization for BMS ranged from 12.1 % to 30% and for DES from 5.8% to 13.3%.[4] Costs for avoided procedures varied, for example, for CABG from €7,254 to €24,332.[4]

Incremental cost effectiveness ratios (ICER) also had wide variation. The incremental cost per QALY ranged from $27,540 to €1,099,858 for a general population. The incremental cost per repeat revascularization avoided ranged from $1,650 over 1 year to $7,000 over 2 years.

Two of the reviews focused more on the relationship of the quality of the economic study and the recommendations made.[82,173] Kuukasjarvi, et al,[82] reviewed 13 studies published between January of 2004 and January 2006, rating the quality of the study using a scale developed by Drummond (0-10 scale)[175] and classified the conclusions of the authors. The reviewers reported that three studies were economic studies from the RCTs and ten were modeling studies. The median study quality was 9, with a range of 7 – 10. In the Drummond scale, the step most often rated not done was to adjust costs and consequences for differential timing. Only two authors, in studies from the RCTs (rated 9 and 8), found DES cost effective. The third study from an RCT (rated 9) and five modeling studies concluded they may be cost effective in selected situations, but not as a single strategy. Four modeling studies concluded they were not cost effective and one reached no conclusion. A table of the classifications of conclusions was not provided.

Ligthart[173] reviewed 19 studies published between January 1, 2000 and July 31, 2006, restricting the selection to studies conducted from a third party payer perspective. Quality was rated on a 10 point checklist developed by the authors based on previous published guidelines and recommendations. Studies with a score above the median of 10 were rated high quality and those below, lower quality. They also rated the studies according to the QHES.[76] Because only a minority of studies reported a cost/QALY outcome, they classified the conclusion of each study as favorable or not favorable to widespread use of DES. Their analysis found that the conclusions drawn by the cost effectiveness studies were associated with the study's quality, funding source and country of origin. Only 1 of 9 high quality studies supported widespread use versus 9 out 10 lower quality studies. All of the 7 studies sponsored by industry argued in favor of widespread use as compared with 3 of the 12 studies without sponsorship (p=0.03). Studies from the US were more likely to endorse widespread use than those from other countries (p=0.032). Repeating the analysis using the QHES scores for these studies, while not as significant, confirmed the findings. The median score, out of a possible 100, was 62 with a range of 18 to 94.

Of the studies included in the FinOHTA[82] review, 8 were also in the Ligthart[173] review. The same two studies from the RCTs noted in the FinOHTA review were classified as favoring widespread use and rated as lower quality in Ligthart's review.

Newer systematic literature review.

One systematic review of the literature was identified and is summarized below.
The RCTs and the two quality of life studies using 0 to 1 utility ratings were included in the reviews from the HTAs above, and thus it is not expected that this study will change conclusions already drawn. A true cost effectiveness analysis is not conducted.

Groeneveld, [138] reviewed four DES cost studies from RCTs reporting original health care costs and 8 studies reporting original quality of life (QOL) data on the effects of restenosis and TVR. They found that the heterogeneity of studies prevented formal meta-analysis and so provided a narrative review. They rated the quality of the studies on four questions, each of which was scored on a 1-5 scale, and calculated a summary score by averaging the four component scores. No reference was provided for the quality rating method. Three of the cost studies had summary scores of 4.0 and one was 2.9 due to a less direct method of estimating costs. Their findings, in 2006 dollars, were that DES had $1600-$3200 higher up-front costs than BMS and differences in total costs after one year ranged from $200 to $1200. The average cost of a repeat revascularization was between $1,800 and $36,900. Quality of life studies were scored lower than the costing studies, with only one assigned a summary score above 4 (4.5). Only two of the studies reported QOL on the basis of a 0 to 1 utility which is the metric used in cost per QALY studies. They reported that restenosis was associated with lower QOL by 0.06 – 0.08 QALY. Thus, the authors concluded if you had an ICER threshold set at $100,000/QALY, DES is only cost effective if cost per repeat revascularization is less than or equal to $8000. The usual cost per QALY threshold used as a rule of thumb is closer to $50,000. The authors received support from the Institute for Health Technology Studies which has industry funding.

Original economic analyses performed as part of previous HTAs

Four recent HTAs conducted cost effectiveness studies of their own, three using data from regional registries and one a model using local hospital cost data.

The HTAs own economic analyses' findings mirror those of the literature reviews above, that use of DES is not cost effective[4, 82] or is only likely to be cost effective in high risk patients,[81, 85] depending on the ICER threshold used. The Hill and Ontario studies did not take into account longer anti-platelet therapy for DES or different late stent thrombosis rates between DES and BMS in their analyses, although use of actual costs in "real world" practice may have partially included such factors. ICERs ranged from $64,394 in the Ontario HTA to over £1 million in the KCE HTA. Sensitivity analyses found that cost effectiveness ratios were most influenced by the price premium of DES, number of stents in the index procedure and revascularization rates. For example, if the difference in price for DES over BMS increased, it would increase the ICER and DES would be less cost effective. Similarly, if more stents are implanted initially, there are more stents that can restenose, thus higher incremental costs if DES stents are used in the revascularization.

Table 62. Summary of economic analyses performed as part of recent HTAs

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
Hill/NICE (2007)	CU analysis from perspective of NHS (payer), DES vs BMS • Population: Pts revascularized for angina, elective vs non-elective • Data source: RCTs, CTC Liverpool audit	• Cost per QALY £183,000-£562,000 • CE only achieved for	• Use of DES best targeted at subgroups of patients with highest risks of requiring	• Sensitivity analysis indicated that CE ratios influenced most.by

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
	• Time horizon: 12 months • Effectiveness: Reduced rate of repeat revascularizations within 12 mo: 2.95% to 4.99% • Benefit: Avoid QALY loss from repeat revascularization 0.00658 • price premium €563-€752, # stents per pt 1.454-1.615 • reduction in absolute risk of repeat intervention. 7.79%-10.15% • Sensitivity analysis –univariate and extreme value	non-elective pts who have previous CABG and small vessels, about 1/3100 of all pts treated with PCI	reintervention	• price premium • numbers of stents in index procedure • absolute risk reduction In repeat interventions • • QHES score = 94
KCE-Belgium (2007)	Economic Model for Belgium: • Perspective: health care payer (insurance and patient out of pocket); • Population subgroups include diabetes status, complex lesions, multivessel disease, no interventional history; • Data Source: analysis of Belgian Registry for 2004 • time horizon 1 year; • price premium DES ~€750; • avg, 1,3 stents per proc, • revasc rate 5.0% DES, 14.4% BMS; • QoL healthy .86, stent .69, 1 mo post stent .84, 6 mo post .86	• ICER's on magnitude of €1 million and more. • Best ICER is €860,000 in subgroup for diabetic patients with multi-vessel disease but no complex lesions. • Alternative scenarios assessed.	• DES are not cost saving or cost neutral. • No good economic justification to implant DES in patients currently receiving BMS. Alternative scenarios considered, ICER's remain unfavorably high.	• The analysis does not compare BMS to DES head to head, but considers outcomes if DES patients were to receive BMS. • Belgium provides reimbursement for DES in diabetic patients. • "Staging" (implanting one stent initially and another at some time later due to payment reimbursement policy) • • QHES score =100 • •
Ontario (2007)	CU analysis from perspective of Ontario Ministry of Health • Time horizon: 2 years • Population: 20,321 Pts receiving DES (36%) or BMS 12/2003-3/2005 • Subgroups: 44 groups -diabetes vs no, recent MI vs no, long vs short vessel, narrow vs wide vessel • Data source: CCN CARDIACCESS registry • Price premium DES: $1299 • Avg stents/proc:1.1-3.06 • Reduced rates revasc: +0.5 to -26.4 • QOL: from ARC: angina=0.68, healthy=0.86, post PCI decrement = -0.02	Cost / QALY • Most favorable ICER: $64,394 for non-post MI diabetic pts with long narrow vessel • All others $205,021-$387,146 Cost/Revasc avoid • Lowest is $2,630 in non-post MI diabetics with long narrow vessels • BMS dominates DES in non-	• Cost per QALY is high for all cohorts except • Non-post MI diabetics with very long and narrow lesions. • • DES reduces revascularization rates at 2 years in some but not all patient cohorts. • • No reduction in revasc rates for for pts with short and wide lesions, in pts with or without diabetes	• Based on Ontario real world data. • • Allocation bias could be present – budget limitations may influence physician selection for DES vs BMS. • • Data limited for adjusting for other factors affecting outcomes. • QHES score = 94

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
		post MI diabetics with short wide vessels		
FinOHTA (2007)	CU decision analysis model from perspective of health care provider • Time horizon: 2 years • Population: Pts receiving DES or BMS • Data source: Hospital costs from Cardiac Centre of Tampere University Hospital, 2006€ • Price premium DES: €1050 • Avg stents/proc: not stated • Reduced rates revasc: -10 • QOL: prePCI = 0.73, 6mo post PCI= 0.824, preCABG=0.75, post=0.86	• ICER / QALY = €98,827 • • ICER per revasc avoided = €4,794 • At €50,000 societal willingness to pay, probability of DES being acceptable = 13%.	Cost difference between DES and BMS is too large for DES to be cost-effective for small QOL gain.	Sensitivity analyses showed result sensitive to • cost difference between DES and BMS. At threshold of €498 or less, DES dominant • difference in revasc rate • QHES score = 88

Revasc: revscularization, MI: myocardial infarction, Pts: patients, Avg: average, QOL: quality of life
Dominates: lower cost, better outcome. ICER not calculated

Critical Appraisal, HTA Economic Analyses

Critical appraisal of each of the HTA economic analyses was done based on the items of the Quality of Health Economic Studies (QHES) instrument [See Appendix B] and epidemiologic principles. The QHES is a series of 10 multifactor questions aimed at evaluating the completeness of reporting, model specification and sensitivity analyses in economic studies. Each question has a yes or no answer and is weighted, with a possible score range of 0 to 100. The scores are reported under comments in Table 66 above. Weighted QHES scores were high with a range of 88 to 100 and a median of 94. This is in contrast to the Ligthart's HTA review[173] of the literature in the section above, where the median QHES score was 62. Thus the HTAs own economic analyses have higher ratings in general than the studies they reviewed. This may be partially due to improvement in reporting. One limitation of the QHES is that it rates whether a component was present in a report or analysis, but does not allow a "quality" of component rating. Thus the Hill, KCE and Ontario HTA reports are very lengthy, allowing detail to be included that is often not allowed in the peer reviewed literature.

The Hill report provided a great deal of detail on input parameters but did not provide a diagram of their model which would have indicated, for example, whether they accounted for more than one repeat revascularization for a patient. They also did not specify what type of statistical analysis was conducted, other than specifying a range of assumptions that were assessed. A strength of the study is that efficacy data were used from the RCTs and modified using the findings from two observational studies in Liverpool to provide rates that were closer to "real world". Quality of life values were taken from a continuing database of EuroQol surveys administered "a few weeks post discharge". While this gives values for a larger population than those included in the RCT trials, it is unclear whether the variable timing of the survey would give valid results. The authors also note

that the value for post-CABG was the same as the value post –PCI which wasn't expected. They attribute it to the EuroQol not being sensitive enough to the change in QOL after these procedures.

The KCE report from Belgium[4] earned a 100 score on the QHES, in part reflecting the thoroughness of their report. Since the policy was to pay a price premium only for diabetes patients undergoing PCI, they could not compare DES to BMS directly. Instead, using registry data, they analyzed the DES cohort as though it would receive BMS and the BMS cohort as though it would receive DES. Efficacy rates were taken from the RCTs and meta-analyses. Quality of life was taken from the ARTs RCT trial. It is not clear how well this approach of applying RCT rates would reflect real world practice. The ICERs from this study were the highest of all the HTAs in general.

The Ontario HTA's[85] economic analysis used the data from their field evaluation (from registries) divided into 44 cohorts to determine cost effectiveness, therefore they did not calculate an overall ICER for BMS vs DES, only that within cohorts. Their base case model assumes a mortality gain for DES, based on the registry data, although in their own report of the field study, they caution against putting much weight on that mortality difference, suggesting it may be due to allocation bias based on budget limits on DES use. These constraints may also affect the rates found in the registry data and types of patients getting DES versus BMS.

The FinOHTA economic analysis[82] used data from one hospital for direct hospital cost parameters. The analysis was a modeling study with parameters taken from the literature for the probabilities of revascularizations or repeat revascularizations, and the outcomes from those. Sensitivity analyses are conducted. The base case assumes that the difference in repeat revascularization rates between DES and BMS is 0.12 over 2 years. There is no subgroup analysis according to patient type, other than to evaluate the outcomes as a lower difference from BMS in revascularization probability ("DES low" = 0.062) and a higher difference ("DES high" = 0.188).

The Hill and KCE reports used a one year time horizon, as have many other studies. The argument for the 12 month time horizon is that most revascularization events occur in that time frame, which reflects the focus in these analyses on revascularizations avoided. The other, and most likely stronger, reason given for shorter followup is lack of data for a longer time frame. The Ontario and FinOHTA analyses use a two year time horizon. Whether late stent thrombosis or longer term antiplatelet therapy would alter the findings is unknown. The Hill, KCE and Ontario studies were based on observational data and could be subject to selections bias or bias due to unmeasured confounders.

While they presented the values used, and conducted sensitivity analyses for different values, none of the HTAs gathered their own QOL values. This can be problematic since there is a substantial body of evidence regarding the variation in QOL ratings depending on how they are elicited (in person, phone, mail, etc), what instrument is used, where they are collected, how they are scaled, and how sensitive they are to the differences in health states of the conditions being rated.[174]

Other Cost Effectiveness Studies Comparing DES with BMS

One additional study was identified that conducted a formal cost effectiveness analysis of DES versus BMS. Brunner-LaRocca et al, [137] used data from the BASKET trial to investigate cost effectiveness from a third party payer perspective. Patients receiving PCI between May, 2003 and May, 2004 at the University Hospital in Basel, Switzerland, were randomized 2:1 to a DES or BMS and followed for 18 months. More details of the study are given in the table below. They found DES to be associated with a cost of €40,467 per QALY gained. If one set a €40,000 threshold, DES would be cost effective only in those needing small vessel or bypass graft stenting. Their conclusion was that used in all patients, DES were not a good value, even with reduced prices.

Table 63. Additional Cost Effectiveness Studies Comparing DES to BMS

Author (Year)	Evidence Base and Approach	Results	Conclusions	Comments
Brunner-La Rocca (2007)	CE in BASKET trial • Perspective: Third party payer • Time horizon: 18 months • Population; All pts receiving PCI May 2003-May 2004, 66% off label • Subgroups: Low risk ≥3.0mm native vessel, high risk <3.0 mm stents/bypass graft stenting • Data source: Swiss medical tariff TARMED in 2004 • Price premium DES: €675 (PES), €1,015 SES • Avg stents/proc: 1.9 • Reduced rates revasc: -35% • QOL: EQ5D @ 6mo, 18mo. Pre-PCI assumed=0.9	Cost/QALY • ICER= €40,467 • At €40,000 threshold • low risk pts: 0.11 probability of DES being cost effective • high risk pts: 0.975 probability of DES being cost effective Cost/MACE avoided • ICER=€64,732 • ICER at 18 mo worse than 6 mo due to late stent thrombosis	Used in all patients, DES are not good value, even with reduced prices DES cost effective only in pts needing small vessel or bypass graft stenting	Sensitivity analysis considered wide range of scenarios. ICERs sensitive to DES pricing, event rates QHES score = 86

Off label: clinical indications different from RCT trial, more complex lesions, higher risk.
MACE: Major adverse cardiac event = death, myocardial infarction, or revascularization.

Critical appraisal of La Rocca analysis:

One strength of this study is that it provides 18 month follow-up from a randomized trial. One limitation of this study is that QOL was not measured at points in the clinical course when one might expect quality of life to be lowest. The authors assigned a QOL of 0.9 to everyone pre-PCI and values were measured at 6 and 18 months follow-up in 85% of patients. Other studies have measured or assumed QOL pre-PCI was lower due to angina, such as the ARTS value of 0.68. If the baseline value is set high, that does not allow a "reduced" quality of life for the period leading up to and perhaps just past the prodedure, so there is not a place to "improve" from.

Suggestions for further economic analysis:

There is a need for methodologically rigorous, full economic studies using US data and system parameters. Important elements of rigorous economic analysis would include:

- Directly elicited quality of life utility at important points along the clinical pathway that includes consideration of QOL impacts of pre-procedural symptoms, the index procedure, repeat revascularization by stenting or CABG, pharmacotherapy, MI, late stent thrombosis, and death.
    - For comparison of DES and BMS, a disease specific utility would be more sensitive to differences.
    - For funding policy decisions between cardiac care and other medical care, a general QOL utility such as the EQ5D, HUI III or the SF6D could be considered.
- US-based event probabilities and absolute rates, with sensitivity analyses that include the range of possible rates from published high quality studies based on most recent experience including on and off-label indications. Models might include
    - Consideration of indications for repeat revascularizations.
    - Incorporation of probability distributions of event rates, allowing more than one re-intervention.
    - Consideration of inclusion of patients receiving both DES and BMS in the same intervention and well as multiple stents of the same kind during the same intervention.
- Follow-up treatment regimens that reflect current best evidence, particularly regarding pharmacotherapy.
- Time horizon should include sufficient time to allow for observation of pertinent safety-related outcomes and clinically important longer-term outcomes such as death and MI.
- Costs that reflect current costs and reimbursement policies in the US and appropriate for the perspective taken.
    - For Societal perspective, costs to the patient and family should be included.
    - For payer perspective, costs to reflect actual costs to the payer.
    - Sensitivity analyses that cover a range of possible cost differences.

Summary and Implications

A summary of the overall strength of evidence for each key question can be found in Tables 64-67 below

Summary and Implications

Summary with regard to efficacy and effectiveness of DES compared with BMS

Efficacy

- Findings regarding efficacy described in this technology assessment report are primarily taken from previously done health technology assessments (HTAs) and the most complete, recently published meta-analyses of randomized controlled trials (LoE I/II studies) comparing DES with BMS. There is a very large degree of overlap across HTAs and meta-analyses with regard to trials included in their analyses.
- The overall strength of evidence (SoE) is high, meaning that further research is unlikely to change confidence in the effect estimates, based on the large number of high quality studies and consistency of estimates.
- Death overall, cardiac death and myocardial infarction were used as the primary clinical measures of efficacy. Technology assessments and conventional meta-analyses of between 14 and 24 head to head randomized controlled clinical trials comparing DES with BMS indicate that DES are no better at preventing death, cardiac death or myocardial infarction than BMS.
- Network meta-analysis of 38 randomized controlled trials (RCTs) and the corresponding conventional meta-analysis indicate that DES are no better at preventing death or cardiac death than BMS with no statistically significant differences between treatments based on cumulative incidence to 4 years. Rates for overall mortality were 4.1% for DES and 4.7% for BMS. Rates of cardiac death were 2.4% for DES and 2.7% for BMS.
- Based on conventional meta-analysis there was no statistically significant difference between DES and BMS with regard to myocardial infarction (4 years follow-up), HR, 0.86 (0.67, 1.09). SES (sirolimus-eluting stents) were associated with less risk of myocardial infarction compared with BMS in this network meta-analysis (HR 0.81 (0.66, 0.97). The absolute differences in risk were however small, 1% (0.15% -1.9%).
- Target lesion revascularization (TLR) was considered a secondary, intermediate outcome and not a primary clinical measure of efficacy. DES were consistently associated with lower risk of target lesion revascularization. The absolute differences in risk ranges from 10% to 16.7% comparing DES versus BMS based on data from RCTs. Rates of TLR may have been influenced by protocol-driven angiographic follow-up and not based on clinical presentation and symptoms and may therefore be an over-estimate of rates in a general population.
- Results from recent reports of long-term follow-up to previously reported RCTs show no differences in death, cardiac death or myocardial infarction between patients treated with DES and those treated with BMS.

Effectiveness

- Findings regarding effectiveness described in this technology assessment report are primarily taken from pooled results reported the previously done HTA completed by the Ontario Ministry of Health & Long Term Care.

- The overall strength of evidence (SoE) is considered low, meaning that further research is very likely to impact confidence in the effect estimates, and very likely to change the estimates. This is based on the overall lower quality of registry and non-randomized studies and heterogeneity across studies which suggest inconsistency of estimates.
- The evidence from past HTA reviews of registry data suggest that mortality and MI rates do not differ between DES and BMS patients. Heterogeneity across studies is possible. Results from recently published registry studies are mixed, some favoring DES, other showing now difference for mortality or for MI. Rates for mortality ranged from 4.5% - 8.5% for DES and 6.1% - 17% for BMS in studies with >1 year follow-up. Rates for MI were ranged from 1.7% - 12.7% for DES and from 2.0- 11.5% for BMS in studies with > 1 year follow-up.
- Rates of revascularization are lower for DES patients, but there is substantial heterogeneity between the studies included in the Ontario meta-analysis. Most HTAs express a need for longer follow-up and more specific definitions of the outcomes from registry data.
- More recently published registry reports are consistent with these findings, describing significant differences in TLR or TVR when DES are compared with BMS.
- Rates for revascularization ranged from 5.2% - 14.2% for DES and from 8.1% - 24.4% for BMS in studies with > 1 year follow-up.
- The overall quality, differences in adjustment methods, variations in outcome definition of these nonrandomized studies precludes drawing definitive conclusions.

Summary with regard to the safety of DES compared with BMS

- Findings regarding safety described in this technology assessment report are primarily taken from previously done HTAs and the most complete, recently published meta-analyses of randomized controlled trials (LoE I/II studies) comparing DES with BMS. There is a very large degree of overlap across HTAs and meta-analyses with regard to trials included in their analyses.
- In December 2006, the FDA convened a meeting of the Circulatory System Devices Advisory Panel that featured presentations by regulators, academic physicians, patients, industry representatives, and medical professional societies. The FDA concluded that the widespread use of DES for off-label indications is the primary cause for the increased incidence of stent thrombosis, as such uses are associated with higher rates of early and late stent thrombosis, MI, and death. The FDA also recommended a longer course of dual anti-platelet therapy than was originally used in the pivotal trials. Instead of 3 to 6 months, patients were advised to continue dual anti-platelet therapy for 1 year (and then aspirin for life) following DES implantation. The FDA currently recommends twelve months of dual anti-platelet therapy for patients not at high-risk for bleeding following DES implantation in order to decrease the risk of stent thrombosis.

- Most previous HTAs indicate that there were no statistically significant differences in stent thrombosis for use of DES compared with BMS, but note that studies may be underpowered. One review specifically on safety concluded that the majority of evidence suggests that there is an increased risk of stent thrombosis with DES compared to BMS.
- Based on the Academic Research Consortium (ARC) definition of definite thrombosis, rates from the most recent meta-analysis based on up to 4 years of follow-up were 1.4% for SES (sirolimus-eluting stents), 1.7% for PES (paclitaxel eluting stents) and 1.2% for BMS. No statistically significant difference in stent thrombosis was seen between treatments based on follow-up to 4 years.
- In the most recent meta-analysis for RCT data, a statistically significant difference in ARC-defined definite stent thrombosis was seen between > 30 days and 4 years when PES were compared with BMS., HR 2.11 (0.19, 4.23). Wide confidence intervals and moderate heterogeneity across included studies were noted. No statistically significant differences for the SES versus BMS comparison were seen for this same (or any other) time period.
- The overall strength of evidence (SoE) is moderate with regard to stent thrombosis, meaning that further research is likely to change confidence in the effect estimates and may change the estimates. There is some inconsistency in findings and heterogeneity across studies in meta-analyses. Even the larger meta-analyses may have been underpowered to detect significant differences in rare events such as late stent thrombosis.
- Rates of stent thrombosis in nonrandomized studies ranged from 0% - 2.9% for DES and from 0.1% - 3.5% for BMS.
- The overall evidence is very low with respect to bleeding related to prolonged course of dual anti-platelet therapy and stent fracture since no comparative studies were found. Based on 3 case series, cumulative incidence for bleeding ranged from 1.8%-4.0% up to 18 months of follow-up. Rates for stent fracture from 6 case series ranged from 1.9%-7.7% and one case series reported 18% in patients with in-stent stenosis

Summary with regard to efficacy and effectiveness and safety of DES compared with BMS in special populations

Diabetic patients

- Findings regarding safety described in this technology assessment report are the most complete, recently published meta-analyses of randomized controlled trials (LoE I/II studies) comparing DES with BMS. Previous HTAs or similar reports provide few conclusions and only limited evaluation on diabetic patients or special populations. There is some degree of overlap across HTAs with regard to studies with data on diabetic patients included in different meta-analyses.
- Overall strength of evidence is rated at moderate for efficacy related to death, cardiac death and MI since there is some inconsistency across analyses, part of which may be due to differing durations of anti-platelet therapy.

- The most comprehensive meta-analysis published since then reported a two-fold increase in overall mortality and cardiac mortality among patients receiving DES compared with BMS in those who had less than six months of dual anti-platelet therapy pointing to the importance of longer-term therapy. Three recently published meta-analyses indicate that, overall, mortality risk among diabetic patients is similar whether DES or BMS are used.
- No differences in the risk of myocardial infarction were seen in diabetic patients, regardless of dual-antiplatelet therapy in the largest and most complete recent meta-analysis at up to 4 years of follow-up. MI rates were 5.8% for DES and 7.4% for BMS in the network meta-analysis among diabetic patients with ≥ 6 months of dual anti-platelet therapy. Two analyses with fewer trials suggest that at shorter follow-up times (6-24 months), DES may result in a lower risk of MI. Differences in the number and types of included trials and definitions of MI may contribute to difference found between the analyses.
- Outcomes for diabetic patients were examined in 3 HTAs, 4 meta-analyses and 1 RCT included in this report. Results suggest that both TLR and TVR rates are significantly lower in diabetic patients treated with DES than those treated with BMS between 6 months and 4 years following stenting. Cumulative incidences of TLR in the network meta-analysis were 9.7% for DES and 22% for BMS in diabetic patients having ≥ 6 months dual anti-platelet therapy.
- No statistically significant differences in stent thrombosis were seen between treatments either early (0-30 days) or late (>30 days to 4 years) in network meta-analysis restricted to those who had ≥ 6 months dual anti-platelet therapy. However, wide confidence intervals indicate lack of estimate stability and small numbers of events. Rates of thrombosis from 0-4 years were 1.6% for DES and 2.3% for BMS among diabetic patients with ≥ 6 months of dual anti-platelet therapy in the network meta-analysis.
- Overall strength of evidences regarding late stent thrombosis in diabetic populations is low given the wide confidence intervals around estimates.

Patients with acute MI

- Results from one recent HTA, a meta-analysis of 8 RCTs and three recent RCTs suggest no statistical difference in the risk of overall mortality in patients with acute MI comparing DES with BMS.
- Based on pooled estimates from 8 RCTs, there is not a statistically significant difference in risk of re-infarction when DES are used compared with BMS. Data on type and duration of antiplatelet therapy are not described.
- Across reports, DES implantation is associated with a statistically significant decrease in TLR compared with BMS in patients with acute MI.
- Overall strength of evidence with regard to the above outcomes is high.

- Randomized controlled trials assessing safety were summarized in one previous health technology assessment and two meta-analyses. In addition, three recent RCTs provided data on stent thrombosis in patients who received DES versus those who received BMS for acute MI. All report no statistically significant difference in rates of stent thrombosis between DES and BMS groups. Two non-randomized trials also reported no statistical difference between groups.
- Overall strength of evidence for safety is low, based on the likelihood that trials may have had insufficient power to detect differences between treatments particularly for late stent thrombosis and the effect of duration dual anti-platelet therapy was not evaluated.

Intermediate lesions

- Data from the one small meta-analysis of four trials (N = 167) were available.
- There were no differences in cardiac mortality at any follow up time. At 1 year, the incidence of myocardial infarction was 3.4% in the DES group and 5.4% in the BMS group; this difference was not statistically significant.
- No TLR was done by 30 days in either stent group. Data for 1 year for TLR/TVR are as follows: DES: (1.2%, 3.4%), BMS: (20.3%, 20.3%) (P = 0.0004, P < 0.0001, respectively).
- At 1 year, no subjects had suffered a thrombotic event. Given that thrombosis is generally a relatively rare event, it is likely that this study is underpowered to detect a difference in risk between the two types of stents studied.
- Overall strength of evidence for this population is very low for efficacy, effectiveness and safety based on the small number of patients available for analysis.

Summary with regard to economic studies

- The evidence from HTA reviews of 43 cost effectiveness studies, and from 5 additional full cost effectiveness analyses suggest that DES in comparison with BMS are not cost effective across populations.
- Incremental Cost Effectiveness Ratios (ICER) ranged from a low of $27,540 to a high of €1,099,858 or more per Quality Adjusted Life Year (QALY) and from $1650 to $7,000 per repeat revascularization avoided.
- Information from some previous HTAs suggests that DES may be cost effective in selected groups of higher risk patients with multiple risk factors, such long lesions, narrow vessels, complex lesions, diabetics and patients recently post MI.
- Nearly all the studies have taken the perspective of the health care payer. Few have addressed a societal perspective.
- The majority of studies have been conducted outside of the U.S. and differences in payment systems and policy need to be considered.
- Quality of life measures have received limited attention in the cost effectiveness studies, most using values from other studies, and the impact of more precise measurement is unknown.

- Until there is more agreement on efficacy and effectiveness measures and rates with DES versus BMS, there will continue to be great variability among cost effectiveness studies due to variations in parameters used. Methodologically rigorous, U.S.-based studies could facilitate better understanding of the cost-effectiveness.

Table 64. Overall Strength of Evidence (SoE) Criteria

SoE	Description	Further Research Impact	Domain Criterion Met		
			Quality	Quantity	Consistency
1	High	Very unlikely to change confidence in effect estimate	+	+	+
2	Moderate	Likely to have an important impact on confidence in estimate and *may* change the estimate	+	-	+
			+	+	-
3	Low	Very likely to have an important impact on confidence in estimate and *likely* to change the estimate	+	-	-
			-	+	+
4	Very Low	Any effect estimate is uncertain	-	+	-
			-	-	+
			-	-	-

Table 65. Summary of evidence for each Key Question 1.

Key Question 1: Evidence of effectiveness of DES compared with BMS			
Outcome	**Efficacy**	**Effectiveness**	**Sources/Results**
Overall mortality up to 4 years	**1 neither favored**	**3 neither favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS consistently report no statistically significant difference in mortality. • Pooled rates for DES were 4.1% and 4.7% for BMS up to 4 years follow-up • There is significant overlap in the trials used for HTAs and meta-analysis Effectiveness: • Data from one previously published HTA's meta analysis of 6 nonrandomized comparative studies and 8 more recently published studies suggest no statistically significant difference in mortality for DES compared with BMS • Of 10 recently published studies, seven reported no statistically significant difference up to 3 years, one reported a statistically significant difference up to 1 year of follow-up favoring DES and three reported higher mortality among BMS patients, two at two years follow-up and one at up to 4.5 years follow-up • Heterogeneity across studies suggested in the meta analysis and diversity of findings in newer studies indicates inconsistency in findings making definitive conclusions difficult. • Overall mortality rates for mortality ranged from 4.5% - 8.5% for DES and 6.1% - 17% for BMS in studies with >1 year follow-up.
Cardiac mortality up to 4 years	**1 neither favored**	**3 neither favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS consistently report not statistically significant difference in cardiac mortality • Pooled rates for DES were 2.4% compared with 2.7% for BMS • There is significant overlap in the trials used for HTAs and meta-analysis Effectiveness:

			• Data from one previously published HTA's meta analysis of 6 nonrandomized comparative studies suggest no statistically significant difference in cardiac mortality for DES compared with BMS up to 1 year. Heterogeneity across studies prevents drawing firm conclusions. • Only 1 recently published study reported adjusted relative risk estimates for cardiac death: a significant difference in risk of cardiac death was seen between DES and BMS • Cardiac mortality rates ranged were 0.6% and 0.5% at one year in the one new study reporting on this.
MI up to 4 years	**1 neither favored**	**3 neither favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS with follow-up to 4 years consistently report not statistically significant difference in myocardial infarction based on the conventional meta-analysis which is may be more conservative HR, 0.86 (0.67-1.09) • Pooled rates for MI from the network meta-analysis were 4.5% for DES compared with 5.2% for BMS based on cumulative incidence up to 4 years. • There is significant overlap in the trials used for HTAs and meta-analysis Effectiveness: • Meta-analysis in one HTA suggests that there is no significant difference in the risk of MI with the use of DES compared with BMS. • No statistically significant differences at any time up to 3 years were reported in seven of the eight new studies, with one reporting higher MI rates for BMS patients. • Rates ranged from 1.7% - 12.7% for DES and from 2.0- 11.5% for BMS in studies with > 1 year follow-up.
Target vessel revascularization up to 4 years	**1 DES favored**	**3 DES favored**	Efficacy: • Previously published HTAs and recently published meta-analyses of up to 35 RCTS consistently report a statistically significant decrease in TVR or TLR favoring DES • There is significant overlap in the trials used for HTAs and meta-analysis • TVL and TLR rates in RCTs may be partially a reflection of protocol driven angiographic follow-up • Rates of TVR ranged from 6% - 9% for DES and were estimated at 19% for BMS based on cumulative incidence up to 4 years. Rates after the first year were lower for all stent types. Effectiveness: • TVR was statistically significantly less common with DES than with BMS in one HTA's meta-analysis, however heterogeneity across studies suggest that pooled results be interpreted cautiously. • One new study found no statistically significant difference at 30 days, whereas 9 others reported statistically significant differences from 30 days up to 3 years. • Rates of TVR or TLR for DES ranged from 0.4 %- 2.5 at ≤ 30 days and from 3.5% - 14.2% from 31 days up to 2 years, compared with BMS ranges from 0.6 %-2.4% at ≤ 30 days and 6.0- 24.4% for up to 3 years in 6 recent studies.
Key Question 1: Evidence of effectiveness of DES compared with BMS- in special populations			
Outcome	**Efficacy**	**Effectiveness**	**Sources/Results**

Overall mortality up to 4 years	**2 unclear**	**4**	Efficacy: Diabetic Patients • Previously published HTAs provide little data on special populations • The largest recently published meta-analyses suggest that a 2 fold increase in morality was associated with SES use compared with BMS if patients had less than 6 months of dual anti-platelet therapy. No significant differences in morality were found between treatment groups when 6 or months of anti-platelet therapy were used. • In patients having ≥ 6 months dual anti-platelet therapy, cumulative rates were 7.5% for DES and 7.6% for BMS. • There is some overlap in the trials used for in meta-analysis Effectiveness:Diabetic Patients • Specific discussion of overall mortality in diabetic patients was found in two technology assessments, one which relied on previously done meta-analyses [KCE] and the other which performed their own meta-analysis [Ontario 2007]. Results from these and two recently published registry studies are mixed with respect to overall mortality and cardiac death comparing DES and BMS.
Cardiac mortality up to 4 years	**2 unclear**	**4**	Efficacy: Diabetic Patients • Previously published HTAs provide little data on special populations • The largest recently published meta-analysis suggests a 2 fold increase in cardiac morality was associated with SES use compared with BMS if patients had less than 6 months of dual antiplatelet therapy. No significant differences in morality were found between treatment groups when 6 or months of anti-platelet therapy were used. • Cumulative rates of cardiac death in the network meta-analysis were 4.8% for DES and 4.2% for BMS in patients with ≥ 6 months anti-platelet therapy Effectiveness: Diabetic Patients • Specific discussion of overall mortality in diabetic patients was found in two technology assessments, one which relied on previously done meta-analyses [KCE] and the other which performed their own meta-analysis [Ontario 2007]. Results from these and two recently published registry studies are mixed with respect to overall mortality and cardiac death comparing DES and BMS.
MI up to 4 years	**2 unclear**	**4**	Efficacy: Diabetic Patients • No differences in the risk of myocardial infarction were seen in diabetic patients, regardless of dual anti-platelet therapy in the largest and most complete recent meta-analysis at up to 4 years of follow-up. Two analyses with fewer trials suggest that at shorter follow-up times (6-24 months), DES may result in a lower risk of MI. Differences in the number and types of included trials and definitions of MI may contribute to difference found between the analyses. • Cumulative MI rates were 5.8% for DES and 7.4% for BMS patients with ≥ 6 months anti-platelet therapy. Effectiveness: Diabetic Patients • Two registry studies report no statistical difference between DES and BMS.
Target vessel revascularization up to 4 years	**1 DES favored**	**3 DES favored**	Efficacy: Diabetic Patients • Outcomes for diabetic patients were examined in 3 HTAs, 4 meta-analyses and 1 RCT suggest that both TLR and TVR rates are significantly lower in diabetic patients treated with DES than those treated with BMS between 6 months and 4 years following stenting. • Cumulative TLR rates form the network meta-analysis were 9.7% for DES and 22% for BMS among diabetic patients with ≥ 6 months anti-platelet therapy. Effectiveness: • One report describes findings from RCT sub-analyses and one registry study [Hayes]. Findings from both types of studies suggest that TVR is less frequent among diabetic patients who received DES compared with those who received BMS

Table 66. Summary of evidence for each Key Question 2.

Key Question 2: Evidence of safety		
Outcome	**Safety**	**Sources/Results**
Stent thrombosis up to 4 years	**2**	Safety • Previously published HTAs and recently published meta-analyses of up to 35 RCTS draw somewhat different conclusions. Most HTAs indicate that that there were no statistically significant differences in stent thrombosis when DES were compared with BMS, particularly at longer follow-up times, several note that studies and even some meta-analyses may have been underpowered to detect statistically significant differences between treatment groups. In the most recent meta-analysis no statistically significant differences in stent thrombosis in studies with up to 4 years follow-up. • Small numbers of events coupled with heterogeneity across included trials suggest that estimates could change as additional data are collected. • There is significant overlap in the trials used for HTAs and meta-analyses. • Based on ARC definition of definite thrombosis, rates from the most recent meta-analysis based on up to 4 years of follow-up were 1.4% for SES, 1.7% for PES and 1.2% for BMS.
Late Stent thrombosis	**2**	• Previously published HTAs and recently published meta-analyses of up to 35 RCTS draw somewhat different conclusions. Many HTAs concluded that significant differences between treatment groups may not have been evident because of small sample size and suggest DES are associated with long term risk of stenosis. • In the most recent meta-analysis for RCT data, a statistically significant differences in ARC defined definite stent thrombosis was seen between > 30 days and 4 years when PES were compared with BMS., HR 2.11 (0.19, 4.23). Wide confidence intervals and moderate heterogeneity across included studies were noted. No statistically significant differences for the SES versus BMS comparison were seen for this same (or any other) time period. • Rates in 5 recent non-randomized studies ranged from 0- 0.9% for DES and 0.1%-3.5% for BMS
Bleeding with prolonged anti-platelet therapy	**4**	• No comparative studies were found. • From 3 case series, cumulative incidence for bleeding ranged from 1.8%-4.0% up to 18 months of follow-up
Stent fracture	**4**	• No comparative studies were found • Rates for stent fracture from 6 case series ranged from 1.9%-7.7% and one case series reported 18% in patients with in-stent stenosis
Key Question 2: Evidence of safety – Special populations		
Outcome	**Safety**	**Sources/Results**
Stent thrombosis up to 4 years	**3**	Safety –Diabetic patients • Previous HTAs provide little information on the risk of stent thrombosis (acute, sub-acute or late) in diabetic patients. • Recent meta-analyses consistently report no statistically significant difference in stent thrombosis by last follow-up regardless of dual anti-platelet therapy duration based on cumulative incidence of events from 0-4 years. Cumulative rates were 1.6% for DES and 2.3% for BMS in patients with ≥ 6 months anti-platelet therapy. • It is possible that even this largest meta-analysis had insufficient power to detect a difference between DES and BMS in the risk of late stent thrombosis in particular, given that it is a relatively rare event. • One previous report describes data from one large registry of 708 consecutive diabetic patients. While the authors state that in-stent thrombosis was more frequent in DES patients (2.4%-4.4%) versus BMS recipients (0.8%) they don't provide results of any statistical testing.
Late Stent thrombosis	**3**	Safety –Diabetic patients • No statistically significant differences in stent thrombosis were seen between treatments either early (0-30 days) or late (>30 days to 4 years) in network meta-analysis restricted to those who had ≥ 6 months dual anti-platelet therapy. However, wide confidence intervals indicate lack of estimate stability and small numbers of events. • No data from recent non-randomized studies were found for late stent thrombosis in diabetic populations

Table 67. Summary of evidence for each Key Question 3.

Key Question 3 Conclusions from economic analyses		
Outcome	**Cost-effectiveness**	**Sources/Results**
ICER	4	Economic analyses • HTA reviews of 43 cost effectiveness studies, and from 5 additional full cost effectiveness analyses suggest that DES in comparison with BMS are not cost effective across populations. • There is significant variability with regard to methodological quality and consistency of findings across studies • The ranges for ICERs are large, depending on modeling, outcomes chosen and perspective • Most HTAs concluded that DES may be cost effective in selected groups of higher risk patients, with multiple risk factors, such as long lesions, narrow vessels, complex lesions, diabetics and patients recently post MI. • Methodologically rigorous studies that are US-based are needed

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