Drug Eluting Stents in Belgium: Health Technology Assessment

KCE reports 66C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
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Executive Summary

AIM OF THIS REPORT

Percutaneous Coronary Interventions (PCI) have revolutionised the world of cardiac interventions. Introduced in the late seventies of the previous century as an alternative to open heart Coronary Artery Bypass Grafting (CABG), these techniques have rapidly evolved from heroic experimental endeavours into well-established mainstream interventions.

The early balloon dilatations suffered from important restenosis problems and therefore repeat revascularisations through PCI or CABG were often required. To counter these restenosis problems, stenting was introduced in the late eighties, and during the nineties Randomised Clinical Trials (RCTs) showed that implanting a metal stent during PCI significantly reduced the incidence of restenosis. Because of this observation, stenting became almost routine use in most PCIs.

However, thrombotic occlusion of stents has been and remains a concern since the early days of stenting. During the nineteen nineties several regimens of anti-coagulation therapies have been tried that aim to prevent thrombotic occlusion of stents while limiting the risk for bleeding complications. At this moment there is consensus that a combination therapy of aspirin with a thienopyridine anti-platelet drug, the so called dual anti-platelet therapy, is the best option to achieve this goal.

Although it was clear that stenting reduced the occurrence of acute mechanical complications and reduced the risk of restenosis, in-stent restenosis remained a major challenge to interventional cardiologists. In-stent restenosis is usually due to an excessive growth of tissue in and around the stent as a reaction to injury, and stenting with the original *'bare metal stents'* (BMS) can even exacerbate this. Therefore, *'drug eluting stents'* (DES) were introduced into clinical practice in the beginning of this century, to try and antagonize this cellular reaction, thereby aiming to reduce the occurrence of in-stent restenosis after PCI.

This Health Technology Assessment (HTA) report summarizes the current available *clinical evidence on efficacy and safety of DES compared to BMS* for the treatment of coronary heart disease (CHD). We focused on the comparison of DES with BMS because direct comparisons between DES and medical treatment of CHD have never been done. We also chose to consider DES as a group, because evidence from follow-up of different types of DES in head-to-head trials is limited. The reader should be aware that the majority of RCTs comparing DES to BMS have been conducted in patients with simple coronary lesions in native vessels, called *'on-label use'*. In daily practice, however, DES became frequently used for other indications, such as more complex lesions or acute coronary syndromes, which became known as *'off-label use'*. It is not yet clear whether efficacy and safety evidence for DES obtained from RCTs in patients with stable angina can simply be extrapolated to these more specific patient populations. In the absence of further data, we had to assume this could be done.

This HTA also considers the *cost-effectiveness of DES compared to BMS.* We analysed the health economic literature on DES compared to BMS and we also analysed observational data from the Belgian PCI registry for the year 2004, the first full year that an additional DES reimbursement in patients with treated diabetes was introduced. The registry data were linked to health use reimbursement data of one year previous till one year post PCI. Subsequently, an economic model was developed using both registry and cost data from Belgium and effectiveness data from RCTs, to evaluate the balance between additional costs and additional benefits of using DES compared to BMS.

CORONARY HEART DISEASE AND ITS TREATMENT

Coronary heart disease (CHD) is a major cause of disability and mortality of both women and men in Europe. It is caused by the narrowing of the coronary arteries, i.e. the blood vessels supplying the heart with blood and oxygen due to a process known as atheromatosis. Treatment of CHD can be accomplished either by means of medical treatment or through myocardial revascularisation. Medical treatment can be effective in reducing symptoms, preventing the occurrence of myocardial infarction, slowing down the progression of the atheromatous disease and prolonging life (see also KCE report 14 on the variation of treatment of MI in Belgium).

The restoration of the blood flow to jeopardized parts of the myocardium is known as "revascularisation", which leads to a reduction of ischemia related symptoms and, depending on the nature of the underlying coronary disease, in some patients to an increase of life expectancy. Myocardial revascularization can be accomplished surgically through CABG or minimal invasively through PCI. Even while the surgical approach in recent years has become less traumatic by the introduction of off-pump and robotic surgery, it remains an invasive procedure requiring global anaesthesia and a considerable recovery period for the patients involved. The percutaneous intervention on the other hand can be safely accomplished under local anaesthesia, almost on an ambulatory basis and provoking little discomfort to the patient.

While the overall number of CABGs is declining worldwide, there has been a steep increase of PCI procedures since their introduction in 1977. In recent years, the yearly total number of revascularisations in Belgium was above 30 000 which is high as compared to countries with a similar CHD prevalence. Of these, over 23 000 were PCIs; around 2 000 were performed without stenting (plain balloon angioplasty), around 16 000 with a BMS and over 5 000 using a DES. About 8 000 CABGs are performed every year in Belgium.

Worldwide more than 2 million PCIs are performed every year. Although millions of patients have been treated with one of these revascularisation modalities, the preferable mode of revascularisation in a given patient often remains unclear and treatment is dependent on the personal opinion of the attending cardiologist.

EFFICACY AND SAFETY OF DES COMPARED TO BMS

The treatment of CHD has two main goals: improving prognosis and minimizing symptoms. PCIs in general have shown to improve survival compared to medical therapy only in the early treatment of ST-elevation myocardial infarction (STEMI), where PCI performs better than intravenous thrombolysis, provided it is performed early after the onset of symptoms and by an experienced team. CABG on the other hand improves life expectancy as compared to medical treatment in symptomatic patients with left main coronary disease and in three vessel coronary disease in combination with an impaired left ventricular function. A similar improvement has not been demonstrated for PCI so far.

The efficacy of DES has largely been studied in comparison with BMS but not in comparison with medical therapy. There is very little evidence that overall mortality and myocardial infarction (MI) rates differ after implantation of DES in comparison with BMS. This has been best substantiated in RCTs including patients with stable or unstable angina and single vessel interventions with sirolimus-eluting (SES) and paclitaxel-eluting (PES) stents, implanted in de novo lesions in native coronary vessels.

Thus, clinical effectiveness of DES essentially refers to the question whether their use results in a better symptomatic improvement compared to BMS in patients with angina pectoris and subsequently can lead to a reduced number of revascularisation procedures. Despite the worldwide implantation of millions of DES, the currently available evidence does not allow to unequivocally answer this question. Not more than two small RCTs partially reported the effect of DES vs. BMS on angina pectoris recurrence and therefore, the strength of the evidence that DES achieves lower angina recurrence rates than BMS is low (see chapter 3). This means that one has to rely mainly on intermediate endpoints such as angiographic coronary restenosis and target lesion revascularisations (TLR) to assess clinical effectiveness.

DES have been shown in RCTs and in several meta-analyses of these RCTs, to reduce the rate of restenosis following PCI as compared to BMS. This risk reduction varied from about half to up to two thirds reduction of the revascularisation rate in follow-up up to 4 years in RCTs (see chapter 3). This diminished rate of restenosis is reflected in a reduced number of repeat revascularisations, either through PCI or CABG. Most repeat revascularisations following PCI are repeat PCI and not CABG, and there is little evidence that DES reduces the need for future CABG. Moreover, in most trials, revascularisation was driven, at least partly, by a mandatory control angiography, around six months post implant. This is suggested by a sudden increase in so-called major adverse coronary events (MACE), which include revascularisations in many trials, around this follow-up time.

In order to assess the effectiveness of DES in everyday clinical practice, one should ideally combine the results obtained from the early RCTs with these from RCTs with off-label DES indications and with results from real-world registries. In absolute terms, there is a clear difference in the effect estimate of DES vs. BMS between the results from these different study levels. This can be due to several mechanisms such as an overestimation of the clinical *absolute benefit* of DES vs. BMS induced by a mandatory follow-up angiography in RCTs, an expansion of indications from a single stent in a simple stenosis towards multiple stents ('full metal jacket') in complex and diffuse lesions, and an underestimation of the performance of current BMS and stenting techniques as compared to the results obtained in comparison with previous BMS in the early DES trials.

Several clinical series suggest that off-label use of DES may be around 50-60% of patients undergoing DES placement. Restenosis rates in such series are reported to be higher than in RCTs. The effectiveness of SES compared to BMS has been investigated in several RCTs with off-label use of SES and the relative effect was comparable to the results obtained in the pivotal SES trials. TLR was reduced by 62 to 72% with SES relative to BMS in these studies. Also in observational studies (registries) most re-interventions appear to occur within one year following the original stenting as in RCTs. At one year, revascularisation rates for DES range from 2.0% to 9.5% and for BMS from 5.1% to 14.1% (see chapter 3).

In patients with diabetes mellitus certain clinical and angiographic features may lead to a worse prognosis following PCI. These patients have more generalized atherosclerotic disease, more often co-morbid conditions and a more severe and diffuse pattern of coronary disease. It therefore comes as no surprise that they are at an increased risk of complications following PCI and have an increased rate of in-stent restenosis. This has reportedly been the main reason why regulatory bodies in Belgium so far have limited the reimbursement of DES to patients with diabetes. But, there have been no long-term studies that exclusively enrolled diabetic patients to compare DES with BMS. Post hoc subgroup analyses of RCTs suggest that DES are also effective in reducing the incidence of in-stent restenosis in these patients but concerns still remain on the possible increased risk of late stent thrombosis.

With the introduction of DES, restenosis no longer was the Achilles' heel of PCI but unfortunately, this problem was replaced by another potential problem, '*late stent thrombosis*' (LST), a rare but potentially fatal adverse event. Several factors that can explain this morbid process have been identified: stent thrombogenicity, patient and lesion characteristics and factors related to the PCI procedure.

The use of dual anti-platelet therapy, using optimally sized stents and stent deployment with high balloon pressures, sometimes guided by intravascular ultrasound, have solved this problem only partially.

In response to conflicting results in different trials and meta-analyses on the occurrence of LST, individual patient level data of RCTs were re-analysed and new uniformly adopted definitions of stent thrombosis were used. The re-adjudication of stent thrombosis led to an apparent increase of stent thrombosis in both DES and BMS arms of RCTs but the increase in the BMS population was relatively more important than in the DES arms of the RCTs. In the most recently published meta-analysis, the incidence of overall stent thrombosis was not (statistically significantly) different between BMS and DES: it was 1.5% in the SES group versus 1.7% in the BMS group and 1.8% in the PES group versus 1.4% in the BMS group (see chapter 3). The incidence of stent thrombosis occurring 1 to 4 years after implantation in the same review was 0.9% in the SES group versus 0.4% in the BMS group and 0.9% in the PES group versus 0.6% in the BMS group. Discontinuation of one or both antiplatelet drugs is one of several risk factors related to stent thrombosis. So far, there is no definitive clinical evidence about the optimal length of dual anti-platelet therapy after DES implant. Both the most recently issued ESC and the joint ACC/AHA/SCAI guidelines recommend dual anti-platelet therapy for at least 1 month after BMS, 3 months after SES implantation, and 6 months after PES implantation, and in the absence of high bleeding risk, preferably up to 12 months in all DES patients.

PCI IN BELGIUM

In the US only 2 DES have currently been approved by the FDA. In Europe, however, 19 DES have received a CE label. Of these, 9 have also been approved for clinical use in Belgium. Not all of these DES underwent a thorough scientific evaluation so far.

For this report we analysed the registry data from the Belgian Working Group of Interventional Cardiology (BWGIC) for the year 2004 and linked those to the reimbursement data from one year previous to one year after the index PCI. In 2004 only the Taxus (PES) and the Cypher (SES) stents were available for clinical use. For patients with treated diabetes the hospital received an additional reimbursement from the RIZIV/INAMI since November 2003 when a DES was used. These environmental factors are obviously reflected in results from the registry, and extrapolation to the situation today should be done with care.

The data show that in the overall population in about 24% of PCIs with stenting, the stent used was a DES, about equally distributed between Cypher and Taxus. The major determinant for using a DES was obviously the indicator diabetes. However, in treated diabetics a BMS was chosen in more than 20% of interventions, while in non-diabetics a DES was used in almost 12% of PCIs, although this was apparently a net 'out of pocket' expense for the hospital. Apart from diabetes as the major determinant, there were however a series of other determinants for using DES in non-diabetics or using a BMS in diabetics. In a multivariate analysis, choice for DES is shown to be associated, both in diabetics and non-diabetics with a single lesion, lower age, stable CHD and proximal LAD lesion, while on the other hand acute MI or failed thrombolysis and male gender are associated with a lower probability to receive a DES.

Some of the determinants, however, are specific for the non-diabetic patients only: choice for DES is additionally determined by left main disease, previous PCI, small vessels and long lesions, but also, intriguingly, by the choice for a private or a two person hospital room. Obviously, we could only correct this analysis for what was measured in the analysis and there is undoubtedly residual confounding present in the analyses.

Re-intervention rates for restenosis are lower for both the diabetic and the non-diabetic patients in the DES group compared to the BMS group. Overall rates were 6.1% re-PCIs in the BMS group and 5.0% in the DES group (more detailed figures are given in chapter 5 and 6). This is obviously a much smaller difference than what is

observed in clinical trials, and derives from the observational nature of this analysis: interventional cardiologists use their clinical insight in deciding which stent to use, and this cannot be fully captured through a registry system.

During the index hospitalisation for PCI, on average 1.3 stents were used, but in approximately 5% of PCIs subsequent, staged PCI can be assumed. This means that, because of the lump sum reimbursement method for PCI material, this cost can be charged only once per hospitalisation. There is therefore a financial incentive to delay interventions in other coronary arteries. Because of this staging, the average number of stents that would have been needed during the index hospitalisation, would staging not have occurred, increases slightly. In the economic model we presented results with and without correction for this staging phenomenon.

The average cost for the original PCI hospital stay is almost €7 400 for the health care payer and for those patients needing repeat PCI in the year following the initial PCI the cost is around €6 500. The average health care payer cost in the 365 days following the original PCI is around €18 000 for diabetic patients and around €14 000 for non-diabetics. Although we did observe lower follow-up costs (around €1 300 taking into account observed patient characteristics) in non-diabetics receiving a DES, it is inappropriate to interpret these differences as causal, due to the observational nature of this registry leading to a probable selection bias and the many clinical and environmental factors that influence the choice of DES or BMS that remain unobserved in registry data.

ECONOMIC EVALUATION

For the economic evaluation of DES compared to BMS we first performed a literature analysis and subsequently developed a mathematical economic model. For this model we used Belgian PCI observational registry data for the year 2004 coupled with intervention and follow-up costs. Subsequently we combined this with efficacy data from literature.

Our literature search found a multitude of previous analyses comparing the cost-effectiveness of DES with BMS. Both favourable and unfavourable conclusions were reached. However, one of the important conclusions in most studies is that the utility gain (expressed as Quality Adjusted Life Years or QALYs) is small, and since there is no documented survival gain no metric using Life Years Gained (LYG) can confidently be applied. This low utility gain is a result of the combination of a small Quality of Life (QoL) gain for a very short period in a limited number of individuals. Combined with a substantial price difference this often leads to very unfavourable incremental cost-effectiveness ratios (ICERs) and the use of DES is therefore, according to literature, definitely not cost saving compared to BMS. Some of the studies try to circumvent this problem by using cost per revascularisation (most often a re-PCI) avoided. However, those results are difficult to interpret as they are not comparable to other interventions that might have a larger impact on QoL or that might even be life saving. As long as the *'Willingness to Pay'* to avoid a revascularisation is not determined through a societal debate, this metric largely remains not interpretable.

Our economic model was based on observational outcome from the Belgian BWGIC registry for the year 2004 and coupled cost data. We analysed and used these observational data for a total of 16 subgroups of patients. We compared the current situation with the presumed outcomes of these patients, *'if they would have received the other type of stent'*, i.e. DES rather than BMS or the other way round. For this analysis we used the same relative risk reduction obtained from RCTs, regardless whether this was on-label or off-label use since currently no better data are available. According to a recent review from Stone et al., the estimated hazard ratios for Target Vessel Revascularisation (TVR) after a median duration of follow-up of 4 years were as follows: SES vs. BMS: 7.8% vs. 23.6% (hazard ratio 0.29, 95% CI 0.22-0.39) and PES vs BMS: 10.1% vs. 20.0% (hazard ratio 0.46, 95% CI 0.38-0.55). We used an average of these estimates in the economic model.

The subgroups analysed were a combination of DES or BMS, diabetes or no diabetes, single vessel disease or multi vessel disease and complex lesions vs. no complex lesions, all in all 16 subgroups. For none of the subgroups that currently are treated with BMS, using either real stent costs or RIZIV/INAMI stent cost (assuming the same reimbursement amount as today for diabetes patients) switching from BMS to DES would be far from cost-effectiveness as commonly defined: mean ICERs are in the range of €860 000 to even €3 370 000 per QALY gained depending on subgroup. The analysis of switching those patients currently receiving a DES back to BMS is slightly more complicated: for all subgroups in the 'real stent cost' scenario this would result in slightly less benefits but in important monetary savings. Only in the current RIZIV/INAMI reimbursement scenario this would result in extra costs and health lost for the diabetic patients with both multivessel disease and complex lesions, assuming current reimbursement of DES. To enable comparison with some of the published studies we also presented costs per revascularisation avoided, although as said previously, the numbers are not interpretable as such. For the subgroups going from BMS to DES, the cost per reintervention avoided ranges from €11 000 to €41 000 depending on the specific subgroup.

With current ranges of uncertainty on the input variables in our model, probabilistic sensitivity analysis has shown that results are mainly dependent on the discount received by the hospitals (influencing the price differential between BMS and DES), the relative risk of re-PCI of DES vs. BMS and on the proportion of re-PCI that is truly due to restenosis. Of these, the price differential has a major impact. There is a small health benefits from switching from BMS to DES, but the large price difference is out of proportion with this small benefit.

From a budget impact point of view, switching from current use to total DES use for the index PCI and reimbursing it at current reimbursement levels would directly cause an additional expense of €12 million without much health benefit. Obviously, since the numbers are much smaller, switching current DES use in diabetics to BMS use would cause a saving of around €2 million.

CONCLUSIONS AND RECOMMENDATIONS

- Drug Eluting Stents compared to Bare Metal Stents do reduce the risk for restenosis and thereby the need for a repeat revascularisation. There is, however, no evidence that DES compared to BMS reduce (or increase) the risk of MI or death. The potential risk for late stent thrombosis appears to be small but real. Current evidence does not allow for further speculation about long term (after 4 years) effect on fatal or non-fatal side effects.
- In absolute numbers only a small proportion of patients will suffer from restenosis after stenting with either BMS or DES, and BMS are quite successful in avoiding restenosis. The health benefit from avoiding restenosis is small and for only a short period of time. Therefore, the possible gain expressed as *'Quality Adjusted Life Years'* (QALYs) is low in absolute numbers when comparing DES to BMS.
- The absolute price difference between DES and BMS (list price) is about €1 500. Although most hospitals receive important discounts, the price difference between DES and BMS remains important even taking into account these discounts. Adding to this the limited therapeutic added value, a readjustment of the reimbursement price by health insurance of DES more towards the levels of BMS reimbursement should be considered.
- The combination of a substantial price difference between DES and BMS, with a low QALY gain for a small number of people leads to very high *'Incremental Cost Effectiveness Ratios'* (ICERs). Using real stent cost (with discounts) those ICERs are on average above 1 million € per QALY gained, far above conventional cost-effectiveness thresholds. Switching completely from current practice to "DES-only" usage in first PCIs (as is the case in many countries) would cost an additional €12 million, without much health benefit.
- The data from the Belgian registry show that the differences in restenosis rates are much smaller than would be anticipated from the evidence from clinical trials comparing DES with BMS, for both diabetics and non-diabetics. Based on Belgian registry data we could not identify specific subgroups where ICERs for going from BMS to DES would be cost-effective using conventional cost-effectiveness thresholds.
- Current financing mechanisms lead in daily practice to a splitting-up of some of the PCI procedures because of financial reasons, leading to additional subsequent hospital stays. The financial incentives that stimulate these staged procedures should be abolished.
- The BWGIC registry provides a huge database and represents a useful tool for assessing the practice of interventional cardiology in Belgium, especially when these data are linked to cost and survival data, as has been done in the current report. This mandatory registration of PCI patients should be further continued and the interventional centres should be encouraged to provide peer review and quality control of the data reported.

Scientific summary

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ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ARC	Academic Research Consortium
BACTS	Belgian Association for Cardio-Thoracic Surgery
BMS	Bare Metal Stent
BWGIC	Belgian Working Group of Interventional Cardiology
CABG	Coronary Artery Bypass Grafting
CCTR	Cochrane Controlled Trial Register
CDC	Centers for Disease Control and Prevention
CHD	Coronary Heart Disease
CHMP	Committee for Medicinal Products for Human Use
CTO	Chronic Total Occlusion
CVD	Cardiovascular Disease
DAPT	Dual Anti-Platelet Therapy
DDD	Defined Daily Dose
DES	Drug Eluting Stent
ECG	Electrocardiogram
EMEA	European Medicines Agency
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
FU	Follow-up
IMA - AIM	Intermutualistisch Agentschap – Agence Intermutualiste
IPD	Individual Patient Data (for meta-analyses)
IR	Incidence Rate
IRA	Infarct Related Artery
ITT	Intention-To-Treat (population)
LAD	Left Anterior Descending Artery
LE	Life Expectancy
LOS	Length of Stay
LST	Late Stent Thrombosis
MACE	Major Adverse Cardiac Event
MI	Myocardial Infarction
MS	Member State (EU)
MVD	Multi Vessel Disease (more than 1 coronary vessel affected)
NSTEMI	Non ST Elevation Myocardial Infarction
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel Eluting Stent
POBA	Plain Old Balloon Angioplasty

PP	Per-protocol (population)
PTCA	Percutaneous Transluminal Coronary Angioplasty
PY	Person Years
QALY	Quality Adjusted Life Year
RCA	Right Coronary Artery
RCT	Randomized Controlled Trial
SES	Sirolimus Eluting Stent
ST	Stent Thrombosis
STE	ST segment Elevation
STEMI	ST Elevation Myocardial Infarction
TLR	Target Lesion Revascularisation
TVR	Target Vessel Revascularisation
UA	Unstable Angina
USA	United States of America
WHO	World Health Organisation

SCOPE OF THIS REPORT

This Health Technology Assessment report summarises current clinical evidence supporting the use of drug eluting stents (DES) for the treatment of coronary heart disease. The cost effectiveness of these stents is assessed, by systematically reviewing the literature and by constructing an economic model, incorporating Belgian clinical and cost data retrieved from a nationwide comprehensive registry in 2004.

We compared the efficacy and effectiveness of DES with bare metal stents (BMS) because direct comparisons between DES and medical treatment, both in stable angina and acute coronary syndromes (ACS), have never been done. We chose to consider DES as a group, because long term follow-up of patients enrolled in large trials with head-to-head comparisons of different DES are not available yet.

Currently, 19 different DES have received a CE conformity marking in Europe, and 9 are approved by the Belgian health authorities. Not all of these stents underwent the same extensive scientific evaluation in large trials. Since long term safety effects have turned out to be of major importance in the overall effectiveness evaluation of DES, we decided to concentrate on the DES for which most extensive long term evidence is available from randomised clinical trials (RCT), and those are the sirolimus and paclitaxel eluting stents. In addition, however, we discussed the evidence on zotarolimus and everolimus eluting stents that are also on the market in Belgium.

The majority of RCTs enrolled patients with stable coronary heart disease. The first pivotal trials studied patients with simple coronary lesions in native vessels, an indication which became known as 'on-label use'. Later on, patients with more complex coronary lesions were also included. Few trials focused on patients with acute coronary syndromes but nevertheless, DES became frequently used in daily practice for those other indications ('off-label use'). It is as yet not clear whether the efficacy and safety of DES obtained from trials in patients with stable angina can be simply extrapolated to specific patient populations that are characterized by an important intracoronary thrombus load.

In our economic model, based on observational data from the Belgian registry, events that took place in either stent subgroup (DES or BMS) were fully accounted for. In order to estimate the difference in effect and cost of both stent types, we calculated the presumed outcomes of the patients, if they had received the other stent type. For these calculations, relative risks obtained from RCTs were applied, using the same relative risk reductions for all patients, although we can not be fully confident that these probabilities can simply be transferred from an RCT environment towards real world practice that includes an important proportion of off-label use.

A time window of 1 year was considered in our economic model for two main reasons: first because we only had 1-year follow-up data from the Belgian registry combined with reimbursement data, and second because long term effectiveness and safety of DES compared to BMS remains unclear.

1 CORONARY HEART DISEASE

1.1 CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) encompasses any disease affecting the heart or blood vessels. The most common manifestation of CVD is coronary heart disease (CHD). Other forms of CVD include stroke, transient ischeamic attack and peripheral artery disease. Apart from CHD, cardiac disease may also be consequential to high blood pressure, valvular dysfunction, congenital abnormalities, primary cardiac muscle problems, and other pathologies.

CHD is caused by the narrowing of the coronary arteries, the blood vessels supplying the heart with blood and oxygen. The impedement of blood flow is due to a gradual build-up of fatty material that leads to the formation of atheromatous plaques. This can give rise to a myocardial infarction, angina pectoris, sudden cardiac death, and heart failure. In affluent societies, CHD causes severe disability and more death than any other disease, including cancer.[1]

Two coronary arteries carry oxygenated blood to the heart muscle: the right and the left coronary artery. The first part of the left coronary artery is known as the main stem or left main coronary artery which divides shortly after its origin in two branches: the circumflex artery (Cx) and the left anterior descending artery (LAD). When a plaque produces a >50% diameter stenosis (or >75% reduction in cross sectional area), reduced blood flow through the coronary artery during exertion may lead to ischaemia. Acute coronary events usually arise when thrombus formation follows disruption of a plaque. Intimal injury causes denudation of the thrombogenic matrix or lipid pool and triggers thrombus formation.[1] Depending on whether one, two or three coronary arteries are significantly narrowed due to the atheromatous proces, the labels single-double or triple vessel disease are attributed.

The main risk factors for CVD development are tobacco use, raised blood pressure, raised blood cholesterol, and diabetes mellitus. Several interventions aiming to prevent CVD have been well documented, ranging from lifestyle changes to a daily and lifelong intake of drugs. The best documented preventive interventions are smoking cessation, blood pressure lowering, anti-platelet aggregation therapy (low-dose aspirin) and pharmaceutical lipid management (statins).

This report essentially considers the treatment of patients in whom CHD has already manifested itself, most often either as stable angina pectoris or as an acute coronary syndrome (ACS). Stable angina pectoris is a clinical syndrome characterised by chest discomfort occurring at exertion or emotional stress and relieving when the exercise is stopped. It is caused by a temporary imbalance of the blood supply to the heart muscle through narrowed coronary blood vessels and the increased demand induced by exercise or emotion.

A myocardial infarction (MI) is a condition in which myocardial tissue is damaged and lost due to prolonged ischeamia due to an abrupt occlusion (mostly due to thrombus formation) of a coronary blood vessel. Whereas traditionally a substantial amount of myocardial tissue had to be destroyed before the diagnosis of MI could be made, recent developments in the detection of small quantities of myocardial necrosis using serum cardiac troponin levels have prompted a new definition of myocardial infarction. According to the Joint European Society of Cardiology (ESC) / American College of Cardiology (ACC) Committee, any amount of myocardial necrosis caused by ischemia should be labeled as an infarction.[2] This led to a paradigm shift in CHD in which MI was looked upon as being part of a broad spectrum of acute ischeamic heart diseases denoted as Acute Coronary Syndromes (ACS). These extend from AMI, through minimal myocardial injury to unstable angina (UA), the latter referring to a syndrome of cardiac ischemia clinically manifestating as prolonged chest pain, in which no myocardial necrosis can be documented.

Patients presenting with acute chest pain, in which the attending physician suspects cardiac ischeamia, are considered as suffering an ACS. If the electrocardiogram (ECG) shows a typical ST-segment elevation, the patient is classified as having a STE-ACS (ST-segment elevation acute coronary syndrome). Later on, when biomarkers indicate myocardial necrosis, the patients can be fully classified as ST-segment elevation MI or STEMI. Patients with prolonged chest pain and no ST-segment elevation on ECG are classified as NST-ACS. If later on biomarkers indicate a loss of myocardial tissue, they are classified as non-STEMI; if not, they are considered as unstable angina.

Diagnosis of CHD can often be made by history taking alone. Several non-invasive diagnostic tests are available to confirm a suspected diagnosis or to detect asymptomatic individuals: ECG at rest, exercise testing, stress echocardiography, multislice-CT-angiography and radionuclide myocardial perfusion imaging. The only absolute way to document CHD is by means of cardiac catheterisation and coronary angiography by which contrast material is injected into the coronary arteries. If needed, the diagnostic examination can be further supplemented by a therapeutic intervention during which a coronary stenosis is dilated by means of a balloon (mostly combined with the insertion of a supporting stent) mounted on a catheter, i.e. the percutaneous coronary intervention or PCI.

1.2 EPIDEMIOLOGY

1.2.1 Europe

CVD is the number one cause of death among women and men in Europe. It is also a major cause of disability and of reduced quality of life. While CVD mortality, incidence and fatalities are falling in most Western European countries, they are either not falling as fast or are even rising in some Central and Eastern European countries.[3] Cardiovascular disease is killing more people than all cancers combined, with a higher percentage of women (55% of all deaths) than men (43% of all deaths), and a higher mortality among men and women with a lower socio-economic position.[4] Even though western countries are experiencing declining rates of mortality from CVD, an increasing number of men and women are now living with CVD. This apparent paradox relates to increasing longevity and improved survival of people suffering from CVD. In the UK, age specific mortality for males aged 55-64 years halved from 1968 through 1997.[5]

1.2.2 Belgium

A decline in the occurrence of CHD has also been demonstrated for Belgium, where for both men and women a 36-37% decline of age standardized death certification rate for CHD occurred between 1965 and 1995.[3]

Regional differences in the occurrence of AMI between the north and the south of the country are prominent. This has been documented in the WHO-MONICA project where acute coronary events have been registered from 1983 on in two cities: Gent (north) and Charleroi (south). Important differences in CHD incidence and trends between the two cities were observed. In Charleroi, the incidence of CHD was substantially higher and the declining trend less steep as compared to Gent.[6, 7]

1.3 TREATMENT OPTIONS

Treatment of CHD aims at two different objectives: (1) to minimize symptoms or (2) to improve prognosis by preventing MI and death.

Symptomatic treatment of stable angina can be implemented by medical treatment (nitrates, beta-blockers, calcium-blockers, antiplatelets, etc.), by lifestyle changes (smoking cessation, physical activities, …), or through myocardial revascularization. In patients with an ACS, early treatment is primarily directed at treating complications and improving prognosis by limiting loss of myocardial tissue by means of drugs and/or revascularisation. In all patients with CVD, treatment is further supplemented with secondary preventive measures, including life style changes and drug treatment, in an attempt to prevent recurrent events and improve life expectancy.

Myocardial revascularization can be accomplished surgically (coronary artery bypass grafting – CABG) or percutaneously (percutaneous coronary intervention – PCI). Both methods are facing rapid development with the introduction of minimally invasive and off-pump surgery and by the development of new types of stents including drug eluting stents (DES). PCI has shown to be effective in reducing angina in patients with symptomatic CHD and to reduce mortality in patients with an acute STEMI provided the procedure is performed early and fast by an experienced team.[8, 9] CABG is highly effective in relieving symptoms and improving life expectancy in symptomatic patients with certain anatomical patterns of disease such as left main disease and three vessel disease, especially in combination with an impaired left ventricular function.[10] While the overall number of CABG is declining worldwide, there has been a steep increase of PCI procedures which was performed for the first time in a human being exactly 30 years ago by Andreas Grüntzig in September 1977. Actually, worldwide more than 2 million such procedures are performed annually.[11] Analysts estimate that the total number of DES implanted in 2010 will go beyond 4.5 million.[12]

Because of the different effects on outcome, invasive treatment options of CHD will be discussed separately in patients presenting with stable angina and those with an ACS.

1.3.1 Treatment of stable angina

Although guidelines advocate an initial approach with intensive medical therapy, a reduction of risk factors and lifestyle interventions, PCI became common practice in the initial management strategy for patients with stable CHD, even in those with multivessel disease.

In a 2005 paper, Taggart reported on ten RCTs that have compared PCI and CABG in patients with multivessel CHD.[13] Overall, the trials broadly agreed that survival was similar with both interventions but that surgery greatly reduced the need for further intervention (from 20% with PCI to 5% with CABG). Survival was similar with both interventions but Taggart argues that by largely excluding patients with severe three-vessel CHD, who predominantly constitute the population having surgery in the real world, the trials were inherently biased against the prognostic benefit of surgery.[13]

Very recently, the 5-year follow-up results of the MASS II trial were published, an RCT comparing medical treatment, PCI and CABG for multivessel CHD in 611 patients with stable angina, multi-vessel disease and preserved left ventricular function.[14] All 3 treatment regimens yielded comparable, relatively low rates of death. Medical therapy was associated with an incidence of long-term events and rate of additional revascularization similar to those for PCI. CABG was superior to medical therapy in terms of the prevention of major adverse cardiac events (MACE).

A much larger trial, reporting on 2287 patients and comparing optimal medical therapy with or without PCI for stable CHD was also published this year.[15] The primary outcome was death from any cause and nonfatal MI during a median follow-up period of 4.6 years. Nearly 70% of patients had multi-vessel disease and in more than 30% the proximal left anterior descending artery (LAD) was involved. The 4.6-year cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical therapy group (hazard ratio for the PCI group, 1.05; 95% CI 0.87-1.27). There were no significant differences between the PCI group and the medical therapy group in the composite of death, MI and stroke. PCI resulted in a better symptomatic outcome. Nearly 33% of patients crossed from medical therapy to revascularisation during the 4.6 year period, but since there was no increased risk of death or MI and no significant difference in hospitalization for ACS, the conclusion of the trialists that PCI can be safely deferred in patients with stable angina stood firm, provided optimal medical therapy is instituted and maintained.

1.3.2 Treatment options in ACS

Preserving myocardial tissue by limiting infarct size is one of the major immediate concerns in treating patients with ACS. In STEMI this is aimed at by early reperfusion of the infarct related artery (IRA) which is completely blocked by a thrombus. The thrombus inside the blood vessel can be resolved chemically or removed mechanically resulting in a recanalization of the IRA. In non-STEMI there is also thrombus inside the IRA which does however not completely block blood flow through that vessel. Here, thrombolysis is no therapeutic option but sooner or later PCI can be performed in patients with ongoing ischemia or with hemodynamic problems.[16]

For patients with STEMI, immediate PCI ("primary PCI") is the treatment of choice in patients who are admitted to a hospital with PCI facilities and an experienced team. The superiority of primary PCI over in-hospital thrombolysis seems to be especially clinically relevant for the time interval between 3 and 12 hours after the onset of symptoms.[8] When the patient is being admitted to a hospital without a cath-lab, immediate (or pre-hospital) thrombolysis is generally the preferred treatment.[17, 18] In patients with ACS with unstable angina or non-STEMI, a clear benefit from early angiography (<48 hours) and, when needed PCI or CABG, has only been reported in high-risk subgroups such as patients with recurrent chest pain, dynamic ST-segment changes, elevated biomarkers, heart failure or major arrhythmias.[8]

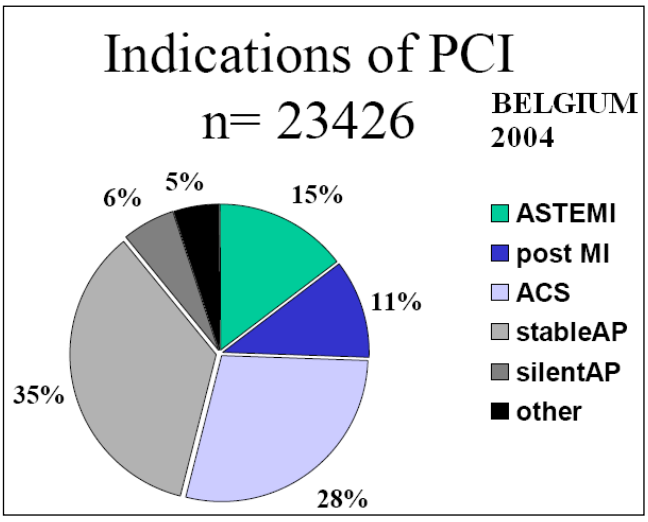
In patients in whom the IRA is completely occluded after the acute phase of a MI, percutaneous opening of this vessel later on (i.e. 3 to 28 days after the acute event) does not clearly affect prognosis. In 2166 stable high-risk patients the 4-year cumulative primary event rate was 17.2% in the PCI group and 15.6% in the medical therapy group (hazard ratio for death, reinfarction, or heart failure in the PCI group as compared with the medical therapy group, 1.16; 95% CI, 0.92 -1.45).[19]

1.3.3 Invasive treatment of CHD in Belgium

1.3.3.1 PCI

Figure 1.1 demonstrates the use of PCI in the year 2004 in Belgium, according to the Belgian Working Group of Interventional Cardiology (BWGIC). In 2004, 43% of PCIs in Belgium were performed for ACS. 15% (n=3514) were primary PCIs for acute STEMI. A comprehensive analysis of the 2004 Belgian PCI-data is reported further in this report. Note that the BWGIC registry is based on a voluntary data entry by participating centres and the data were not externally validated.

Figure 1.1: PCI indications in 2004 in Belgium according tot the BWGIC-data.



ASTEMI: primary PCI. Post MI: PCI after the acute phase of a MI. ACS: acute coronary syndrome. AP: angina pectoris. silentAP: silent ischeamia.

In 2005, we reported on the use of invasive therapy of AMI in Belgium during the years 1999-2001, based on a nationwide administrative database, including nearly 35.000 patients presenting with acute MI.[20, 18] The propensity to undergo early invasive treatment in patients with AMI (combined STEMI and non-STEMI) was dependent on whether or not the hospital to which the patient was transferred was equipped with an interventional cath-lab (table 1.1). Overall reperfusion rates were similar in both types of hospital but whether reperfusion was accomplished chemically (thrombolysis) or mechanically (primary PCI) was dependent on the availability of a cath-lab.

There was also an important difference between the type of hospital in the use of revascularization therapy after the acute phase of the AMI. Overall, 40.7% of patients admitted to any Belgian hospital with an AMI were treated invasively within 2 months: 82% by means of PCI and 18% surgically.

Table 1.1: Immediate and early treatment of patiens admitted to a Belgian hospital in 1999-2001 with an AMI by type of admission hospital.

	A (%)	B1 (%)	B2-B3 (%)	All Patients (%)
Number of Index Admissions	15205	6367	13389	34961
During the Index Admission				
Reperfusion	36.2	34.0	38.0	36.5
Thrombolysis	36.0	33.9	20.6	29.7
Urgent PCI	0.3	0.2	19.7	7.7
During the Episode of Care				
Revascularization during Episode	32.4	33.1	53.7	40.7
PCI	25.1	25.8	46.5	33.4
CABG	7.5	7.5	8.1	7.7

A-type hospital: has no cath-lab; B1: peforms only diagnostic catheterisations; B2-B3: both diagnostic and interventional procedures.

1.3.3.2 CABG

Table 1.2 shows data on the use of CABG in Belgium during the years 2001-2005. From a total of 32 186 myocardial revascularisations being performed in 2004, 8760 (27%) were CABGs and 23426 (73%) PCIs. In other words, in Belgium PCI was done three times as often as CABG.

Table 1.2: Myocardial revascularisations in Belgium.

	2001	**2002**	**2003**	**2004**	**2005**
Plain balloon angioplasty	5 076	3 863	4 718	2 108	1 640
BMS	14 448	16 008	13 906	15 696	15 858
DES	0	0	1 000	5 622	5 532
TOTAL PCI	19 524	19 871	19 624	23 426	23 030
CARDIAC OPERATIONS	11 437	12 773	13 635	13 694	12 920
Isolated CABG	7 008	7 661	7 785	7 422	6 654
CABG+Valve	859	1 074	1 292	1 338	1 315
TOTAL CABG	7 867	8 735	9 077	8 760	7 969
TOTAL REVASCULARISATIONS	27 391	28 606	28 701	32 186	30 999
PROPORTION PCI	0,71	0,69	0,68	0,73	0,74

Data from BWGIC (Belgian Working Group of Interventional Cardiology) and BACTS (Belgian Association for Cardio-Thoracic Surgery) kindly provided by V. Legrand and I. Rodrigus. 2003 PCI data are estimates.

Key points

- **Cardiovascular disease is the number one cause of death among women and men in the Western world.**
- **Invasive treatment has become very common, even as a first step management of patients with CHD. After 40 years of CABG and 30 years of PCI, with millions of patients being treated with both techniques, the body of evidence for strategy selection in CHD is still limited.**
- **Invasive treatment of CHD can be accomplished either surgically (CABG) or by an endovascular approach (PCI). Both methods are facing rapid development with the introduction of minimally invasive and off-pump surgery and by the development of new types of stents including drug eluting stents.**
- **Worldwide more than 2 million PCIs are being performed. In Belgium yearly more than 30 000 cardiac revascularisations are done, 75% of which by means of PCI.**

2 HISTORY OF PERCUTANEOUS CORONARY INTERVENTIONS (PCI)

2.1 PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)

Percutaneous transluminal coronary angioplasty (PTCA) is a common intervention intended to dilate coronary arteries that are narrowed due to atherosclerois. The technique has been introduced by Andreas Grüntzig[21] in 1977 as an extension of the work of Dotter and Judkins who introduced the procedure for transluminal recanalization of arteriosclerotic obstructions in lower limb arteries.[22] In this way, surgical revascularisation by means of coronary artery bypass grafting (CABG) could be prevented in some patients.

An important limitation of PTCA is the risk of an acute vessel closure provoked by the injury on the vessel wall resulting in intimal and medial flaps projecting into the vessel lumen. Even after succesful dilatation, restenosis of the dilated vessel later on occurs in 30 to 40% of patients.[23, 24] Several mechanisms may contribute to the process of restenosis: elastic recoil, platelet adherence to the injury site, inflammation of the vessel wall, neointimal hyperplasia and vascular constrictive remodelling.

2.2 STENTING

In order to try to prevent these shortcomings, coronary stenting was introduced, a technique in which a metal scaffolding is fit into the coronary artery on the site of the dilated lesion. It has first been used in 1986 by Sigwart and Puel who described the technique for treating acute vessel closure due to blood vessel wall dissection and the impairment of bloodflow by projecting intimal flaps.[25] In 1993 two trials, BENESTENT and STRESS,[23, 24], comparing combined PTCA and stenting with PTCA-only demonstrated that intracoronary stents significantly reduced the incidence of restenosis. Gradually, coronary stents became almost routinely used in most angioplasties, since they led to better immediate post-intervention results and less reinterventions. Some consensus panels endorsed the clinical enthusiasm even before a large body of high-quality evidence was available, although this evidence appeared later.[26, 27] By 1999, stenting comprised more than 80% of percutaneous coronary interventions.[28] In a meta-analysis of data from 25 trials Brophy et al.[26] calculated that stenting was associated with an 48% reduction in restenosis rate. In absolute terms, stenting reduced the angiographic restenosis rate by 14.5%. However, routine coronary stenting was associated with only limited reductions in rates of mortality, acute myocardial infarction or CABG compared with standard PTCA, and this benefit seemed to be limited to stents used in conjunction with glycoprotein IIb/IIIa inhibitors.[27] Stents compared to PTCA reduced target vessel revascularizations, but increased the risk of bleeding complications.[27]

Early thrombotic occlusion of freshly deployed stents has been a concern since their introduction in 1986. Such thrombotic events result in serious clinical catastrophes in a considerable number of patients and can lead to death (20-25%), MI (60-70%) and emergency CABG. The unacceptably high rates (up to 24%) of thrombotic events seen in early clinical experience were first approached pharmacologically by aggressive anticoagulation and involved pharmacological regimens combining heparin, oral anticoagulant, and aspirin, but these were hampered by a high rate of complications, especially bleeding requiring blood transfusion and puncture site complications requiring surgical repair. Despite heparin and warfarin, subacute thrombosis still occurred in at least 3% to 4% of patients.[29] From 1996 on, several trials have shown that a combination therapy with aspirin plus ticlopidine, a thienopyridine antiplatelet drug, is superior to aspirin combined with heparin and/or coumarin in preventing stent thrombosis.[30] These antiplatelet agents have a different mode of action and there combined use seemed to be additive.

The ticlopidine-aspirin combination leads to fewer hemorrhagic or peripheral complications than the conventional regimen combining oral anticoagulant with aspirin. Moreover, the dual antiplatelet approach showed better efficacy than aspirin alone. Thus, during the late nineties, the combination of ticlopidine and aspirin during the first weeks following PCI became the reference antithrombotic therapy after coronary stenting.

2.3 DRUG ELUTING STENTS

2.3.1 Rationale

Although it was clear that stenting reduced the occurrence of acute mechanical complications of angioplasty and diminished the rate of restenosis, both stent thrombosis and a residual late restenosis remained a major challenge to interventional cardiologists. In-stent restenosis is usually due to neointimal hyperplasia, an excessive growth of tissue in and around the stent as a reaction to injury. This process which also occurs following standard PTCA, is not prevented by the original bare metal stents (BMS); on the contrary, they actually exacerbate it. Drug eluting stents (DES) have been developed to try to antagonize this cellular reaction. The components of a DES can be divided into a platform (the stent), a carrier (usually a polymer) and an agent (the drug). The carrier facilitates a gradual release of the embedded drug into the local tissue. Several drugs have been studied but the current generation of DES are coated with a polymer embedded with an antiproliferative drug. The theory base is that this drug will inhibit cell proliferation and therefore reduce in-stent restenosis. The agents that have been the subject of the most extensive research are sirolimus (rapamycin) and paclitaxel. Sirolimus is a macrolide immunosuppressant used systemically to treat renal transplant rejection and that also halts proliferation of smooth muscle cells. Sirolimus is incorporated in the Cypher stent, manufactured by Cordis.[31] Paclitaxel is a derivative of the yew plant. It also inhibits the cell cycle and has been used as an anti-proliferative drug in the treatment of breast, lung and ovarian cancer.[32] This drug is used in the Taxus stent that is manufactured by Boston-Scientific.[33] Both these DES are generally referred to as "first generation stents". Although there seems to be no general agreement on the definition of these terms, second and third generation DES would be stents with specialized designs for complex anatomy, bioabsorbable polymers and "no polymer" systems and DES with a combination of different drugs to further reduce neointimal growth.[34] Many of these newer DES are currently under investigation.[12]

2.3.2 Short-term efficacy

The first major trial (238 patients) that compared DES with BMS was the RAVEL study in which patients with angina were randomized to a sirolimus eluting stent (SES) or a BMS for treatment of single, primary lesions in native coronary arteries.[35] The primary endpoint was in-stent late luminal loss, i.e. the difference between the angiographically measured minimal diameter immediately after the procedure and this diameter at six months. Late luminal loss was significantly lower in the DES group compared to the BMS group: at 6 months follow-up restenosis (i.e. stenosis >50%) occurred in not a single patient in the DES group and in 26.6% of patients in the BMS group.

In the following years, different DES were tested in patients with more complex lesions and also in the clinical context of acute coronary syndromes. From a meta-analysis of all RCTs comparing paclitaxel (and analogues) and sirolimus (and analogues) with BMS (follow-up between 6 months to 1 year), Roiron et al. concluded that the major adverse cardiac events (MACE) occurrence was highly reduced with DES compared to BMS from 19.9% to 10.1%.[36] MACE was defined as a composite of death, myocardial infarction and revascularisation and the difference in outcome between DES and BMS was mainly determined by revascularisations that were often angiographically driven by the study protocol itself and therefore not necessarily reflecting a clinical need for revascularisation. Mortality, MI and stent thrombosis alone were not significantly different between DES and the BMS.

In the meantime, a widely held belief developed that the problem of restenosis had been "cured" by using DES which resulted in a new paradigm in the treatment of CHD with a dramatic shift away from CABG and an increase in the complexity of PCIs leading to, at least in some countries, a virtual replacement of BMS by DES.[34] In 2003, in the New York State database the ratio of PCI vs. CABG had increased to 3.5/1 whereas in 2001 it was 1.9/1.[34]

In 2002, BMS were used for all PCIs in the US, while in 2004 this had decreased to 25%.[37] In 2005, in the US, 90% of stents were DES.[34] Thus, cardiologists worldwide quickly embraced this new technology, and millions of DES were implanted, both for indications that had thoroughly been tested in RCTs such as simple coronary lesions as for less well studied complex and multivessel interventions, despite the fact that few data on long term follow-up of efficacy and safety were publicly available at that time.[38] Only recently, evidence about off-label use has started to appear during the current debate about long-term safety.[39, 40]

2.3.3 Long-term efficacy and safety

Important potential side-effects, some of which typically related to the action of antiproliferative agents, have drawn particular attention of clinicians when using DES. In some cases, endovascular healing was completely inhibited, not only preventing endothelialisation of the stent but also sometimes inducing incomplete apposition of the stent angainst the vessel wall.[41] These effects may lead to late stent thrombosis (LST) which constitutes a major problem because it can lead to increased mortality.[42] Unlike restenosis which seems to be largely prevented by DES, thrombosis is a rare but potentially life-threatening complication of coronary stents. The clinical consequences are often catastrophic, including short-term mortality rates of up to 25% and major myocardial infarction in 60% to 70% of cases.[43] Stent thrombosis usually occurs before reendothelialization has been completed. It rarely occurs beyond 2 to 4 weeks for BMS,[44] but is a matter of concern in DES because of the delayed endothelialization. It is likely that the occurrence of LST is related to a delayed healing of the injury caused by the mechanical dilatation of the coronary vessel and a continued presence of a foreign body inside the blood vessel, predisposing to thrombus formation. This thrombotic tendency can be more pronounced in complex coronary lesions, but also in patients who stopped one or both of the antiplatelet drugs that were instituted following the DES implant.

LST and mortality have been the subject of long-term follow-up reports of previous trials and in real-world registries of unselected patient groups. Premature antiplatelet therapy discontinuation has been shown to be one of several risk factors for LST. The early RCTs with follow-up often limited to 1 year, suggested that thrombosis following DES placement is not more frequent than following BMS at up to one year after the procedure. But, in an observational study within the BASKET trial, Pfisterer et al. noticed that the (per protocol) discontinuation of clopidogrel six months after DES implant was followed by a doubling of documented LST in DES (2.6%) vs. BMS (1.3%).[45] In another prospective observational study, with follow-up at 9 months after DES implant, stent thrombosis occurred in 29 of 2 229 patients (1.3%). LST occurred in 5 of 17 patients (29%) who prematurely discontinued dual antiplatelet therapy. Other independent predictors of stent thrombosis in this study were renal failure, bifurcation lesions, diabetes and a low ejection fraction.[46]

At the Barcelona meeting of the World Congress of Cardiology in September 2006, two separate meta-analyses caused great concern. These studies have since then been published.[47, 48] Nordmann et al. conducted a systematic review on mortality outcomes in randomized trials that compared DES with BMS.[47] They not only included peer-reviewed publications but also incorporated unpublished results from long-term follow-up of existing studies presented at scientific meetings and follow-up information obtained directly from the principal investigators and manufacturers. They concluded that DES implantation does not reduce total mortality when compared with BMS. In addition to cardiac untoward effects, the Nordmann study also hinted at the possibility of an increase in non-cardiac late mortality with sirolimus eluting stents.[47]

In the meta analysis by Camenzind et al. a small but significant increase in the risk of death or Q-wave MI was found throughout a period of 3 years after implantation of a sirolimus eluting stent.

A presentation slide from the ACC conference in 2006 depicting these alarming reports is shown in figure 2.1.

Figure 2.1: Early results of trials and meta-analyses giving rise to the 2006 DES scare.

Clinical Outcomes with Drug-eluting Stents: Long-term Follow-up

Trial	Endpoint	Follow up	Incidence (%)		P value	NNH	Probability of harm
			DES	BMS			
Camezind Meta-analysis (1)							
SES vs BMS	Death	4 y	6.5%	5.1%	0.22	71	89%
SES vs BMS	Death or MI	3 y	6.0%	4.0%	0.06	50	97%
SES vs BMS	Death or MI	Last f/u	6.3%	3.9%	**0.03**	**71**	**99%**
PES vs BMS	Death or MI	3 y	3.5%	3.1%	0.60	250	70%
SIRIUS (2)	Death	4 y	6.0%	4.6%	0.30	71	85%
	Death or MI	4 y	8.4%	6.7%	0.27	59	87%
RAVEL (3)	Death	5 y	12.1%	7.1%	0.26	20	87%
	Death or MI	5 y	18.9%	10.5%	0.09	12	96%
BASKET (4)	Death or MI	18 m	8.4%	7.5%	0.63	111	68%

DES: drug-eluting stent; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent ; BMS : bare-metal stent ; MI : myocardial infarction; Reported P values are based on Fisher's Exact test; NNH: numbers needed to harm (inverse of absolute risk difference); Probability of harm is estimated as 1 minus one-sided P value based on Bayesian principles; threshold probability of significance = 97.5%.

Source: Cardiosource. American College of Cardiology.[49]

In a reaction to these conflicting data from meta-analyses and registries, the FDA convened an advisory panel meeting to review the data. Furthermore, new meta-analyses that pooled data on individual patient level and incorporated long-term follow-up data (up to 4 years and more) were published. These are further discussed in the chapter on efficacy and safety of DES.

2.4 REGULATORY STATUS

2.4.1 US

In the US, DES need to be approved by the Food and Drug Administration (FDA) and only two DES are currently approved: the sirolimus eluting stent Cypher in April 2003 (Cordis Inc.) and the paclitaxel eluting stent Taxus in March 2004 (Boston Scientific).[50] No other DES are currently marketed in the US. Also in the scientific literature most data from clinical trials are related to these two devices. Recently, both Medtronic and Abbott have filed applications with the FDA for approval of the Endeavor and Xience-V drug eluting stents respectively. In October 2007, the FDA Circulatory System Devices Panel voted in favour of a conditional approval of the Endeavor stent.[51]

2.4.2 Europe

2.4.2.1 Procedure

In Europe the situation is completely different from the US. Since DES are considered combination products composed of a medicinal product(s) and a medical device and since the medicinal product(s) has an ancillary function to the device they are in accordance with the Council Directive 93/42/EEC classified as medical devices.[52] Unlike the pharmaceutical sector, where new pharmaceuticals have to undergo series of regulatory clinical trials during development, the evaluation and timing of health technologies such as medical devices is less demarcated. For instance, no pre-market clinical trials are required for obtaining "CE marking"[a] of medical devices.[53] But, as a general rule, confirmation of conformity with the requirements concerning the characteristics and performances under the normal conditions of use of the device and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio must be based on clinical data in particular in the case of implantable devices and devices in class III (high risk).

The European Agency for the Evaluation of Medicinal Products (EMEA) is not directly involved in this procedure. Producers of DES have to apply for CE marking through a 'Notified Body'. A Notified Body is an organization that has been nominated by a member state and notified by the European Commission. A Notified Body will be nominated based on designated requirements, such as knowledge, experience, independence and resources to conduct the conformity assessments. Notified bodies are designated to assess the conformity with the essential requirements, and to ensure consistent technical application of these requirements according to the relevant procedures in the directives concerned (cfr. supra).[53] This Notified Body has to consult one of the competent bodies of the Member States or the EMEA with regards to the quality, safety and usefulness of the medicinal substance incorporated as integral part of the device, taking into account the intended purpose of the device.[54] In short, however, the procedure is easier than it is in the US. Precisely because DES are a combination product and as such at the borderline of being both a drug and a device, the Committee for Medicinal Products for Human Use (CHMP) is currently working on a guideline on the development of medicinal substances contained in drug eluting coronary stents.[54]

2.4.2.2 Conformity marking (CE Label)

In April 2002, Cordis Inc. received CE conformity marking in the European Union for the Cypher stent and in January 2003 the Taxus stent received CE conformity marking (CE Label) for treatment of de novo coronary artery lesions in native coronary arteries.[55] Other companies have since applied and obtained CE conformity marketing and therefore many more DES are on the market in EU member states than in the US.

2.4.2.3 DES marketed in Belgium

Currently, 19 different DES have received a CE marking. In some European countries including Belgium, additional approval by local authorities is needed to market medical devices. Accordingly, 9 DES have been approved for clinical use in Belgium. Not all these DES underwent the same thorough scientific evaluation so far. Because long term safety effects have proven to be of major importance in the overall effectiveness of DES, this report concentrates on DES for which ample long term evidence is available: sirolimus (Cypher) and paclitaxel (Taxus) eluting stents.

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[a] By affixing the CE marking, the manufacturer, its authorized representative, or person placing the product on the market or putting it into service asserts that the item meets all the essential requirements of all applicable EU directives and that the applicable conformity assessment procedures have been applied.

Table 2.1 lists the DES on the market in Belgium (status on September 12th, 2007).

Table 2.1: Drug Eluting Stents marketed in Belgium

Identificatiecode/Code d'identification	Verdeler/Distributeur	Productnaam /Nom du produit
110003000012	Cordis (a Johnson & Johnson Company)	Cypher sirolimus eluting stent
110003000021	Boston Scientific Benelux	Taxus Express 2
110003000037	Cordis (a Johnson & Johnson Company)	Cypher Select
110003000046	Medtronic	Endeavor Drug Eluting Stent System
110003000055	Boston Scientific Benelux	Taxus Liberté TM
110003000073	Cordis (a Johnson & Johnson Company)	Cypher Select + sirolimus eluting stent
110003000082	Abbott Vascular	Xience V
110003000091	Boston Scientific Benelux	Promus
110003000107	B. Braun Medical	Coroflex Please Drug Eluting Stent

Source:http://www.riziv.fgov.be/care/nl/other/implants/general-information/circulars/2007/pdf/200707annexe1part1.pdf, accessed on 12 September 2007

2.5 CURRENT USE OF DES

2.5.1 US

In the US there is an almost universal use of DES in favour of BMS. In 2003, the year of its introduction; the Cypher stent accounted for roughtly half of the 800 000 annual stent implantations in the US.[50] By the end of 2004, DES were used in nearly 80% of PCI and in 2005, 90% of stents used in the US were DES.[38] In 2003, in the New York State database the ratio of PCI vs. CABG had increased to 3.5/1 whereas in 2001 it was 1.9/1.[34] This lead, obviously, to the use of millions of DES both for 'on-label' indications as for 'off-label' conditions. Only recently, evidence about off-label use has started to appear during the current debate about long-term safety.[39, 40]

2.5.2 Belgium

In Belgium, DES received an additional reimbursement (on top of BMS reimbursement) in November 2003, but only for patients with treated diabetes mellitus. An additional requirement for the reimbursement of all PCI was the introduction of a mandatory PCI register organised by the Belgian Working Group of Interventional Cardiology (BWGIC). No PCI can be reimbursed in Belgium when the intervention is not registered. As a result sound PCI data are available since late 2003. For the current report we made a detailed analysis of the registry data for the year 2004 with follow-up of reimbursement data from one year previous to one year after the index intervention. Current use of DES in Belgium is mainly driven by the one and only approved indication of reimbursement, "patients with treated diabetes", i.e. patients that are medically treated with insulin or oral hypoglycemic agents. Overall, DES were used in approximately 23% of PCIs in 2004, mainly in diabetics, and this proportion is slightly rising in subsequent years. Detailed data can be found further in this report. DES are also used in non-diabetics (about 14% of non-diabetics received DES or a combination of DES and BMS during their PCI in 2004) but in these cases the hospitals have to bear the additional cost themselves. Detailed information about the precise indications is lacking but are reported to include conditions with high risk of restenosis, such as chronic total occlusion, in-stent restenosis after prior BMS, multivessel stenting, etc (expert opinion from external expert group). The fact that hospitals are not able to recuperate this extra cost of DES in these indications induced us to make additional analyses of potential financial incentive and barriers for patients undergoing PCI.

In the US, it has been reported that financial barriers to health care services and medications are associated with worse recovery after AMI, manifested as more angina, poorer quality of life, and higher risk of rehospitalization.[56] Another possible consequence of current reimbursement schemes is the so-called 'staging' of PCI interventions. Since only one PCI can be reimbursed during a single hospital stay, some hospitals might be tempted to conduct PCIs on multiple vessels in consecutive hospital stays.

Key points

- **Percutaneous transluminal coronary angioplasty has been introduced into clinical practice in 1979 as an alternative for surgical myocardial revascularisation.**
- **Major shortcomings of plain balloon angioplasty are acute vessel closure and late restenosis of the dilated vessel. Acute closure has been overcome by implanting bare metal stents (BMS) whereas restenosis is more reduced by drug eluting stents (DES). However, BMS and especially the newer BMS systems are also quite effective in avoiding restenosis.**
- **In recent years DES have shown to be prone to late (>1 year) stent thrombosis, a rare but serious complication. It became a major source of concern for both scientific and regulatory communities. Through recent meta-analyses, the prevalence of this adverse event has been better defined and is discussed further in this report.**
- **Prolonged dual antiplatelet therapy has been recognised as a potential means of reducing the risk of late stent thrombosis in DES.**

3 EFFICACY, EFFECTIVENESS AND SAFETY OF DES VERSUS BMS

3.1 SEARCH STRATEGY

A large series of RCTs have been conducted that either compared a specific DES against BMS, or a specific DES against another DES. Most of those studies, however, were relatively small and often only limited follow-up was published for each study separately. A large number of meta-analyses have been published that include several of those trials, enabling more solid inference of efficacy and safety based on larger datasets.

Therefore we have focussed this review of efficacy and safety on the most complete meta-analyses, preferentially those based on individual patient data. However, those meta-analyses were mainly conducted for those DES that are currently marketed in the US, i.e. the Cypher and Taxus stents. For this reason we will also briefly discuss a few trials that were not included in the large meta-analyses but that concern DES currently on the market in Belgium. Details of the search strategy can be found in the appendix. In addition to data from RCTs we also searched the literature for 'real world' DES experience from registers, to assess effectiveness and safety of DES in clinical practice, including both on- and off-label indications. Again, we limited the search to marketed DES with anti-proliferative agents, excluding for example steroid-eluting stents.

3.2 RANDOMISED CLINICAL TRIALS

Table 3.1 lists the RCTs that were included in one or more meta-analyses published between 2004 and 2007. More details about those meta-analyses and the trials included in them can be found in appendix.

Table 3.1: Major randomised controlled trials comparing DES to BMS or head to head DES vs. other DES that were included in meta-analyses.

Acronym	DES	Intervention n	Control n	Total n
RAVEL	Sirolimus	120	118	238
SIRIUS	Sirolimus	533	525	1 058
C-SIRIUS	Sirolimus	50	50	100
E-SIRIUS	Sirolimus	175	177	352
TAXUS I	Paclitaxel	31	30	61
TAXUS II MR	Paclitaxel	266	270	536
TAXUS IV	Paclitaxel	662	652	1 314
TAXUS V de novo	Paclitaxel	577	579	1 156
TAXUS VI	Paclitaxel	219	227	446
ASPECT	Paclitaxel / Non polymeric	117	59	176
ELUTES	Paclitaxel / Non polymeric	152	38	190
DELIVER I	Paclitaxel / Non polymeric	517	512	1 029
FUTURE I	Everolimus	27	15	42
FUTURE II	Everolimus	21	43	64
SES-SMART	Sirolimus	129	128	257
ENDEAVOR II	Zoterolimus	598	599	1 197
PATENCY	Paclitaxel / Non polymeric	24	26	50
SCORE	QP2	128	138	266
BASKET	Sirolimus	545	562	1 107
DIABETES	Sirolimus	80	80	160
SCANDSTENT	Sirolimus	163	159	322
PRISON II	Sirolimus	100	100	200
TYPHOON	Sirolimus	355	357	712
DECODE	Sirolimus	54	29	83
Pache et al.	Sirolimus	250	250	500
SCORPIUS	Sirolimus	95	98	193
SESAMI	Sirolimus	160	60	220
STRATEGY	Sirolimus	87	88	175
JUPITER II	Tacrolimus	166	166	332
SPIRIT I	Everolimus	28	32	60
STEALTH	Biolimus A9	80	40	120
SIRTAX	Cypher/Taxus	503	509	1 012
TAXI	Cypher/Taxus	102	100	202
REALITY	Cypher/Taxus	684	669	1 353
ISAR-DIABETES	Cypher/Taxus	125	125	250
DIRECT	Sirolimus	225	0	225
SVELTE	Sirolimus	101	0	101
ACTION	Actinomycin	241	119	360
ISAR-DESIRE	Cypher/Taxus	100	100	200
CORPAL	Rapamycin/Paclitaxel	261	254	515
ISAR-SMART	Cypher/Taxus	180	180	360
RESEARCH	Rapamycin/Paclitaxel	508	450	958
IMPACT	MPA	100	50	150

3.3 META-ANALYSES

Our literature search identified 29 meta-analyses published since 2004. Table 3.2 gives an overview of the basic characteristics of these meta-analyses and their references. A more detailed description, and the RCTs included in each of those meta-analyses can be found in the appendix.

Table 3.2: Meta-analyses published since 2004

Acronym	Year	IPD	Follow-Up	Subgroup	Comparison	Nbr RCTs	Patients included
Stettler and Wandel[57]	2007	No	Up to 4 years		SES/BMS PES/BMS SES/PES	38	18 023
Spaulding[58]	2007	Yes	4 years		SES/BMS	4	1 748
Stone[59]	2007	Yes	4 years		DES/BMS	9	5 261
Mauri[60]	2007	Yes	4 years		DES/BMS	8	4 545
Kastrati[61]	2007	Yes	1 – 4.9 years		SES/BMS	14	4 958
Moreno[62]	2007	No	6 - 12 months		DES/BMS	25	9 791
Ellis[63]	2007	Yes	1 - 3 years		PES/BMS	4	3 445
Camenzind[48]	2007	No	6 mo – 4 y		SES/BMS PES/BMS	9	5 112
Boyden[64]	2007	No	6 to 9 mo	diabetes	DES/BMS	8	1 520
Roiron[36]	2006	No	6 mo - 12 mo		DES/BMS	20	8 987
Nordmann[47]	2006	No	1-4 year		DES/BMS	17	8 221
Stettler[65]	2006	No	6 mo to 24 mo	diabetes: yes/no	SES/PES	10	4 513
Sidhu[66]	2006	No	6 mo - 9 mo		SES/PES	4	2 704
Schampaert[67]	2006	Yes	2 years		SES/BMS	3	1 510
Kereiakes[68]	2006	Yes*	1 year	stent overlap	SES/BMS	5	1 747
Holmes[69]	2006	Yes	2 to 3 year		SES/BMS	4	1 748
Bavry[70]	2006	No	8 mo up to 4 years		DES/BMS	14	6 675
Bavry (JACC)[71]	2005	No	30 days up to 12 mo		PES/BMS	8	3 817
Bavry (AJC)[72]	2005	No	8 tot 13.5 mo		SES/BMS	6	2 963
Biondi Zoccai[73]	2005	No	6 - 12 mo		SES/PES and other DES	17	6 440
Indolfi[74]	2005	No	6 - 12 mo		DES/BMS	8	3 860
Kastrati[75]	2005	No	6 mo and more		SES/PES	6	3 669
Katritsis[76]	2005	No	6 to 12 mo		DES/BMS	10	5 066
Kittleson[77]	2005	No	9 mo to 1 year		SES/PES	10	5 041
Li[78]	2005	No	6 mo to 3 year		DES/BMS	25	12 059
Lord[79]	2005	No	9 mo to 12 mo	diabetes/ long lesions and small vessels	DES/BMS	7	3 390
Moreno[80]	2005	No	6 mo to 12 mo	stent length	DES/BMS	10	5 030
Shafiq[81]	2005	No	up to 12 mo		DES/BMS	13	4 372
Babapulle[82]	2004	No	6-12 mo		DES/BMS	11	5 103

As can be seen from this table and the tables in appendix, there is a large heterogeneity between those meta-analyses. The older ones mainly report on short term follow-up periods and have used summary data. Only in 2006 and especially in 2007 meta-analyses appeared that cover follow-up periods of up to 4 years and a few meta-analyses were published that are based on individual patient data (IPD), rather than solely on summary statistics.

Therefore, we will mainly use the information from those large and recent meta-analyses and use individual studies or older meta-analyses only when they contribute additional relevant information.

3.4 MAIN RESULTS

In most RCTs, the use of DES did not affect overall survival, cardiac mortality or the occurrence of MI when compared to BMS.

The use of DES has been shown to be succesful for the prevention of restenosis after PCI. The favourable effect of DES compared to BMS in reducing the need for repeat revascularisation, this is the revascularisation of the same lesion (TLR) or of the same vessel (TVR), has been well documented in many RCTs. The absolute magnitude of this difference in real life, however, is less clear since most data were derived from trials where restenosis was identified by compulsory angiography, and where revascularisation was therefore not always based on clinical symptoms and may have been inflated artificially.

The major clinical problems associated with the use of coronary stents are the risk of restenosis for BMS and the risk for late thrombosis for DES.[83, 84] The addition of an antiproliferative drug to a stent can lead to the prevention of in-stent restenosis, which is an intended effect, but it can in theory also lead to thrombosis due to a persisting interaction between coagulation processes and the non-endothelialized stent. This dual effect of DES explains why efficacy and safety issues of DES are largely intertwined and why they can not strictly be separated as they relate to the same mechanism of action.

In 2006 concerns emerged on the safety of DES induced by reviews of long term results of pivotal trials and registries reporting late clinical outcomes in unselected patients suggesting that the implantation of a DES may be associated with a small increased late mortality that was attributed to a risk of late stent thrombosis. In a response to this, the US Food and Drug Administration (FDA) convened a meeting of its Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to examine the safety of these devices.[85, 86] A few months later, an issue of the New England Journal of Medicine (N Engl J Med 356;10 March 8, 2007) was almost entirely devoted to DES, reporting on four different meta-analyses and one registry. The results of these meta-analyses have been used in the current report as the latest source of information on safety and efficacy of DES. These papers represent the most up-to-date comprehensive and peer-reviewed evidence on efficacy and safety of DES and they allow to overcome some of the limitations encountered in previously published reviews: they provide long term follow-up data of pivotal RCTs, the pooled analyses are based upon individual patient level data and they make use of a uniform new definition of stent thrombosis, the so-called "Academic Research Consortium ARC definitions". These papers however do not elucidate the effect on outcomes related to the cross-over of patients from BMS to DES in the different trials, simply because the number of cross-overs are not reported in the RCTs.

The major characteristics of the four analyses published in the March 8, 2007 NEJM are depicted in table 3.3. Some of these papers deal with both efficacy and safety aspects, while others focus mainly on one of these specifically.

Table 3.3: Characteristics of DES meta-analyses from NEJM March 8, 2007

AUTHOR	REF	SCOPE	FOLLOW-UP	N RCTs, n DES-pts	ENDPOINTS
Spaulding	[58]	SES vs BMS	4 years	N=4, n=878	(prim) all-cause mortality at 4 years; (sec) specific causes of death; stent thrombosis per protocol and ARC;
Stone	[59]	DES vs BMS	4 years	SES: N=4, n=878 PES: N=5, n=1 753	short-term and long-term safety and efficacy; stent thrombosis per protocol;
Mauri	[60]	DES vs BMS	4 years	SES: N=4, n=878 PES: N=4, n=1 400	stent thrombosis (per protocol and ARC);
Kastrati	[61]	SES vs BMS	1 to 4,9 years	N=14, n=2 486	(prim) all-cause death; (sec) death+MI, MACE, stent thrombosis (per protocol)

When performing a meta-analysis it has been widely recommended to use individual patient data (IPD). This can however be accomplished more or less thorougly, related to the objectives of the investigator and the readiness of the owner of the original patient data (sometimes the manufacturer) to release them. Although the use of IPD is claimed by all authors mentioned in table 3.3, the exact procedure that has been followed by each of them to have access to these data is not completely clear. This might explain slight numeric differences in reported outcomes between different reviews.

A fifth and very recently published meta-analysis was performed by Stettler and Wandel et al. which was first presented at the Euro PCR 2007 meeting by Jüni and Windecker. This analysis is the largest meta-analysis reported so far and includes data from 38 RCTs on 18 023 patients and we also will briefly report on it.[57]

We will first mainly focus on efficacy aspects, i.e. the impact of DES on symptoms of angina, the need for subsequent revascularisations, the prevention of MI and related to the latter (but to safety aspects as well) survival of patients. In a second part we will focus on safety aspects mainly related to the problem of stent thrombosis.

3.5 REPORTED EFFICACY

3.5.1 Kastrati et al.

Kastrati et al. performed an analysis on individual patient data of 4958 patients enrolled in 14 RCTs comparing SES with BMS for which a follow-up period of at least 1 year was available (mean follow-up interval was 1 to 4.9 years).[61] The primary end point was death from any cause. Other outcomes were stent thrombosis, the composite end point of death or MI, and the composite of death, MI, or reintervention. In all but one (the BASKET trial) of the 14 trials, a follow-up angiogram was protocol-mandated.

The overall risk of death (hazard ratio, 1.03; 95% CI, 0.8-1.30) and the combined risk of death or MI (hazard ratio, 0.97; 95% CI, 0.8-1.16) were not significantly different for patients receiving SES versus BMS. In total, 331 patients with SES died, had a MI, or required reintervention, as compared with 649 patients with BMS. Overall, the use of SES was associated with a hazard ratio for the combined outcome of death, MI, or reintervention of 0.43 (95% CI, 0.3-0.54; P<0.001), as compared with the use of BMS. This effect on this combined outcome was mainly driven by a sustained reduction in the need for reintervention.

There was no significant difference in the overall risk of stent thrombosis (ST) with SES versus BMS. However, there was evidence of a slight increase in the risk of stent thrombosis associated with SES after the first year. The effect on stent thrombosis resulting from this meta-analysis is discussed in more detail in the next part.

3.5.2 Stone et al.

Stone et al. performed a pooled analysis of four SES vs BMS trials incorporating 1748 patients (RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS) and five trials in which 3513 patients were randomly assigned to receive either PES or BMS: TAXUS I, TAXUS II, TAXUS IV, TAXUS V and TAXUS VI.[59] These trials were selected because they served as the basis for the approval of DES in both the United States and in Europe. The major clinical end points of the trials were analysed, based on individual patient level data. Stent thrombosis was defined as in the original study protocols. Clinical follow-up was available for up to 4 years for almost all patients enrolled in SES trials and for almost all patients in 3 out of 5 PES trials. Routine angiographic follow-up was done in almost all patients in 8 out of 9 trials. In one trial (TAXUS IV) routine angiographic follow-up was done at 9 months in part of the patients (42.5%).

Both DES types markedly reduced the rates of target-lesion revascularization at 4 years: SES vs BMS: 7.8% vs 23.6% (hazard ratio 0.29, 95% CI 0.22-0.39) and PES vs BMS: 10.1% vs 20.0% (hazard ratio 0.46, 95% CI 0.38-0.55). The absolute difference in the rates of restenosis peaked during the first year and then remained stable through 4 years of follow-up, meaning that there was no indication of catch-up restenosis. The rates of death or MI did not differ significantly between the groups with DES and those with BMS.

Stent thrombosis after 1 year was more common with both SES and PES than with BMS but the absolute number of events was very low: 14/2633 in DES patients and 2/2628 in BMS patients.

3.5.3 Spaulding et al.

In this meta-analysis,[58] the results of four RCTs comparing SES vs BMS were analysed, based on individual patient level data: RAVEL, SIRIUS, E-SIRIUS and C-SIRIUS. These RCTs compared a SES (Cypher) with a BMS of identical design (Bx Velocity, Cordis), implanted in single, previously untreated lesions in native coronary arteries. The trials totalled 1748 patients and follow-up information was available from all four studies over 4 years. A total of 428 patients with diabetes (treated through diet, with an oral hypoglycemic agent, or with insulin) were included. The primary safety end point of this meta-analysis was survival at 4 years.

The survival rate at 4 years was 93.3% in the SES group, as compared with 94.6% in the BMS group (hazard ratio for death, 1.24; 95% CI, 0.84-1.83).

3.5.4 Stettler and Wandel et al.

This paper was published on September 15th, 2007 during the final editing of this report.[57] In this meta-analysis from 38 RCTs on 18 023 patients, no difference in the rates of death or cardiac death between DES and BMS was found. After mixing the results of subgroup analyses in the DES vs BMS trials, and head-to-head comparisons of PES vs SES using a particular statistical technique ('network analysis'), SES were associated with a lower risk of MI: HRs were 0.81 vs BMS (95% CI: 0.66-0.97) and 0.83 vs PES (95% CI: 0.71-1.00). The HR of stent thrombosis was not statistically different for SES vs. PES. However, in another recently published meta-analysis of 16 RCTs specifically comparing SES with PES in head-to-head trials, no statistically significant difference in the risk of MI was found (HR 0.84; 95% CI 0.69-1.03) after a follow-up period of 9 to 37 months.[87] In this review, SES showed a statistically significantly lower risk of stent thrombosis (HR 0.66; 95% CI 0.46 -0.94) without significantly impacting on the risk of death (HR 0.92; 95% CI 0.74-1.13) or MI (HR 0.84; 95% CI 0.69-1.03). In a recently published series based on real-world experience, multivariable analysis showed no association of stent type (PES as compared to SES) with MACE (OR 1.03; 95% CI 0.77-1.38) and TLR (OR 1.08; 95% CI 0.81-1.44).[88]

3.6 REPORTED SAFETY ASPECTS

3.6.1 Introduction

The most problematic side effect of stenting in general and of DES in particular, is late stent thrombosis (LST). Management strategies have been focussing primarily at antithrombotic therapies but conditions other than platelet function appear to play a role in LST.

The phenomenon of LST had first become apparent with the introduction of coronary brachytherapy in patients with in-stent restenosis. This was attributed to a delayed endothelialisation caused by the radiotherapy. Virmani et al. documented through pathologic studies of patients dying after stent implantation that DES also caused delayed endothelialisation.[89-91] Because of previous experience with brachytherapy and those pathological findings, trial protocols with DES mandated more prolonged antiplatelet therapy than the earlier trials with BMS. Extended dual antiplatelet therapy was given for two to three months with SES and for six months with the PES. This may explain why LST has not been prominent in the early reports of trials with DES, since those early reports mainly reported on short term (i.e. up to 1 year) follow-up.

Besides the problem of stent thrombosis, a concern of an increased non-cardiac mortality with DES was raised in 2006 by Nordman et al.[47] These authors conducted a systematic review of all RCTs comparing DES with BMS, incorporating not only articles published in peer-reviewed journals but also retrieving information from websites, conference reports and contacts with trials investigators and stent manufacturers. They found a trend towards an increased risk for overall mortality in patients treated with DES compared with BMS among trials providing data from the second to the fourth year of follow-up. Although there was no difference in cardiac mortality, non-cardiac mortality (cancer, stroke, lung disease) appeared to be slightly higher among patients treated with DES than among patients treated with BMS. These findings cannot be considered as hard evidence for an increased risk for non-cardiac mortality with DES, but they at least make long-term follow-up and assessment of cause-specific death in patients receiving DES mandatory.

3.6.2 Definition of stent thrombosis: original vs. ARC

In the original study protocols, stent thrombosis was defined as angiographic confirmation of in-stent thrombus or unexplained death within 30 days after the procedure. Detailed stent thrombosis definition varied across trials when myocardial infarction was present without angiographic confirmation of target-vessel involvement. The definition in PES trials was considered somewhat more inclusive than the SES trials definition.

Thrombotic occlusion of the study stent subsequent to repeated percutaneous treatment of the target lesion did not qualify as stent thrombosis, due to the fact that these patients often underwent brachytherapy, known to predispose to LST.[92]

Following the previously cited alarming reports in 2006 on the alleged increased risk of LST in DES, and in order to better be able to compare the results of different trials, a common definition of stent thrombosis was developed by the Academic Research Consortium (ARC) of academic investigators, regulators, and industry representatives.[93] These definitions were proposed to serve as standard criteria for stent thrombosis for the comparison of event rates across different trials and studies in an attempt to establish uniformity, eliminate inappropriate censoring and improve sensitivity. According to the ARC definitions, stent thrombosis was classified as acute if it occurred within 24 hours after the index procedure, subacute if it occurred between 1 and 30 days after, late if it occurred between 31 days and 1 year after, and very late if it occurred more than 1 year after the procedure. Furthermore, stent thrombosis was considered definite if there was angiographic or autopsy evidence of thrombus or occlusion, 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.[93] Stent thrombosis was classified as probable if unexplained death occurred within 30 days after the index procedure or if a MI, occurring at any time after the index procedure, was documented in an area irrigated by the stented vessel in the absence of angiographic confirmation of stent thrombosis. Stent thrombosis was classified as possible if unexplained death occurred more than 30 days after the index procedure.

As opposed to the initial trial definition, events occurring after a repeat target-lesion revascularization were no longer censored but where considered as stent thrombosis.

3.6.3 Mauri et al

Mauri et al applied the ARC classification of stent thrombosis across eight RCTs involving 878 patients treated with SES, 1400 treated with PES, and 2267 treated with BMS and then pooled 4 years of follow-up data. The included trials were the same as those studied by Spaulding[58] (only SES trials) and Stone[59] (except for the TAXUS VI trial) in their respective meta-analyses.

The incidence of definite or probable stent thrombosis as defined by the ARC was 1.5% in the SES group versus 1.7% in the BMS group (absolute difference -0.2; 95% CI -1.5 to 1.0) and 1.8% in the PES group versus 1.4% in the BMS group (absolute difference 0.4; 95% CI, -0.7 to 1.4). The incidence of definite or probable events occurring 1 to 4 years after implantation was 0.9% in the SES group versus 0.4% in the BMS group and 0.9% in the PES group versus 0.6% in the BMS group (No confidence intervals were provided for these long term events, occuring after >360 days). The authors concluded that the incidence of stent thrombosis did not differ significantly between patients with DES and those with BMS in RCTs, although the power to detect small differences in rates was indeed limited.

3.6.4 Spaulding et al.

As already discussed (cfr 3.5.3) survival rate and rates of MI were similar in the SES and BMS groups.[58] Furthermore, no significant difference were found between the two treatment groups in stent thrombosis. According to the protocol definitions, there were 10 stent thromboses in the SES and 5 in the BMS group (hazard ratio, 2.00; 95% CI 0.68-5.85). Five of the thromboses in the SES group, but none in the BMS group, occurred after 1 year. In contrast, according to the ARC definitions, there were 30 stent thromboses in the SES group and 28 in the BMS group (hazard ratio, 1.07; 95% CI 0.64-1.79). Stent thrombosis was more frequent in the BMS group in the first year (14 vs. 6 in the SES group), whereas very late stent thrombosis (occurring after the first year) was more frequent in the SES group (23 vs. 14 in the BMS group).

3.6.5 Kastrati et al

In this meta-analysis that we already reported on in the previous chapter on stent efficacy (3.5.1) the overall risk of death was not significantly different for patients receiving SES versus BMS,[61] and the suggestion of a possible increased rate of death associated with DES use by previous reports,[47, 48] could not be confirmed by this analysis. No significant difference in the overall risk of stent thrombosis with SES versus BMS was found. However, there was evidence of a slight increase in the risk of stent thrombosis associated with SES after the first year.

Stent thrombosis was defined as in the original trial protocol and was observed in 65 patients (34 with SES and 31 with BMS). The hazard ratio for stent thrombosis was 1.09 (95% CI, 0.64-1.86). Over the full 4-year period and after the first year following the procedure, stent thrombosis occurred in nine patients, eight of whom had SES. The overall risk of stent thrombosis in this period was 0.6% (95% CI, 0.3-1.2) in the SES group and 0.05% (95% CI, 0.01-0.4) in the BMS group (P=0.02). This difference is chronologically associated with the end of the protocol-specified interval of dual antiplatelet therapy with thienopyridines and aspirin. Although the absolute number of fatal events is low and an accurate assessment could not be made without knowledge of the actual timing of discontinuation of dual antiplatelet therapy in individual patients, it has been suggested that their may be a need for a longer duration of dual antiplatelet therapy in patients receiving SES.

In a very recent editorial, Kastrati reported a more complete up-to-date meta-analysis (contrary to the analysis reported above, including also trials with less than 1 year follow-up) of 17 RCTs comparing SES vs BMS in 5606 patients.[84] Using the protocol-defined criteria for stent thrombosis, there were 37 cases of stent thrombosis with SES and 38 with BMS, corresponding to a pooled relative risk of 0.99 (95% CI 0.61-1.61).

3.6.6 Stone et al.

In the four SES vs. BMS trials included in this meta-analysis (cf 3.5.2), a total of 15 protocol-defined stent thromboses occurred, whereas in the five PES vs BMS trials, a total of 34 protocol-defined stent thromboses were reported.[59] The 4-year rates of stent thrombosis were 1.2% in the SES group versus 0.6% in the BMS group (P=0.20) and 1.3% in the PES group versus 0.9% in the BMS group (P=0.30). However, after 1 year, there were five episodes of stent thrombosis in patients with SES versus none in patients with BMS (P=0.025) and nine episodes in patients with PES versus two in patients with BMS (P=0.028). In this respect, Kastrati however argues that in the SES trials included in this meta-analysis, 5 cases of stent thrombosis occurred among BMS patients after they had a repeat revascularisation (resulting in their censoring from the life table analysis).[61, 84]

3.6.7 FDA Advisory Panel

As a consequence of alarming reports in 2006 on the potential increased mortality following the implantation of DES, the FDA convened an advisory panel meeting to review the data. The panel agreed, that when DES are used for their approved indications, the risk of thrombosis does not outweigh their advantages over BMS in reducing the rate of repeated revascularization. But the panel also concluded that, as compared with on-label use, off-label use is associated with increased risks of both early and late stent thrombosis, as well as death or MI.[85, 86, 94]

ON-LABEL USE OF DES.

The current FDA-approved indications for DES are as follows:[85, 86, 94]

- The CYPHER Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of length ≤ 30 mm in native coronary arteries with reference vessel diameter of ≥2.5 mm to ≤3.5 mm.
- The TAXUS Express Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter for the treatment of de novo lesions ≤28 mm in length in native coronary arteries ≥2.5 to ≤3.75 mm in diameter.

At the Panel,[85] the results of the Camenzind and Nordmann analyses were confronted with additional and methodological more stringent meta-analyses: (1) the Cardiology Research Foundation patient level analysis[95] (presented by Stone and corresponding to the paper published later on in the New England Journal of Medicine[59]), (2) an extended follow-up from the SIRIUS[96] and TAXUS[97] trials, presented by representatives of the manufacturers. The latter provided additional data, a.o. a readjucation of stent thrombosis according the ARC definitions.[93]

These analyses demonstrated no significant differences in the rate of death, MI, or death/nonfatal MI for either SES (follow-up ≈ 4 years) or PES (mean follow-up 3.2 years) when compared with BMS. The cumulative incidence of stent thrombosis at 4 years was not significantly different between SES and BMS, either by the protocol-defined definition (SES 1.2% vs. BMS 0.6%) or by the ARC definition (SES 1.5% vs. BMS 1.8%). The same holds true for PES vs. BMS: stent thrombosis by the per-protocol definition occurred in 1.3% in PES versus 0.9% in BMS and in 1.9% in PES and 1.5% in BMS according the ARC definitions. The time distribution of events however appeared different for BMS compared with DES. There were numerically more BMS thromboses in the 30-day to 1-year time period, and numerically more DES thromboses in the time period from 1 to 4 years. The total numbers of very late stent thrombosis were very low in all patient groups. The differences between DES and BMS were statistically different if the number of events were based on per-protocol definitions but no longer when based on ARC definitions. These data are summarized in Figure 3.1, retrieved from Laskey et al.[98]

Figure 3.1: Timing and Frequency of DES and BMS stent thrombosis (ST), table 4 from Laskey at al.[98]

TABLE 4. Timing and Frequency of DES ST in Clinical Trials

	0 to 4 Years		1 to 4 Years	
Stent and Definitions	DES, % (ST/N)	BMS, % (ST/N)	DES, % (ST/N)	BMS, % (ST/N)
SES				
On-protocol	1.2 (10/870)	0.6 (5/878)	0.6* (5/870)	0.0* (0/878)
ARC†	1.5 (13/848)	1.8 (15/843)	0.9 (8/848)	0.5 (4/843)
PES				
On-protocol	1.3 (20/1755)	0.9 (14/1758)	0.5*‡ (9/1755)	0.1*‡ (2/1758)
ARC†§	1.9 (22/1400)	1.5 (18/1397)	1.0 (10/1400)	0.7 (7/1397)

N indicates number at risk. Percentages represent life table analysis except where indicated.
*$P<0.05$ for DES vs BMS comparison.
†According to ARC categories definite and probable.
‡Does not represent life table analysis.
§Includes Taxus SR stent studies only.

The FDA panel concluded that in total, the data were consistent with a numerical increase in very late (>1 year after implant) stent thrombosis associated with DES compared with BMS, but that the true magnitude of the risk and the duration of the risk were uncertain. Given the convincing and persistent reduction in target vessel failure and TVR with DES, as well as evidence that indicates that mortality and MI rates are not different between DES and BMS patients, the panel agreed that, when used in accordance with their labeled indications, both the SES and the PES are safe and effective.[98]

OFF-LABEL USE OF DES.

To assess effectiveness and safety of DES in off-label use, the FDA Panel reviewed data from a number of RCTs that enrolled patients for off-label DES use as well as several registries.[85] From a methodological point of view, these data provide less compelling evidence than RCTs due to patient selection bias and less stringent follow-up and post hoc analyses.

Compared with on-label use, off-label DES use (like off-label BMS use) is associated with an increased risk of adverse events, such as death or the combined end point of death or nonfatal MI, which likely reflects the increased complexity of the lesions and the co-morbidity of the patients. The majority of registries suggested that no significant mortality differences existed between patients who received DES and those who received BMS.

3.6.8 Stettler and Wandel et al.

The results of this recently published meta-analysis were previously presented at the Euro PCR 2007 meeting and the authors found no difference in the rate of death or cardiac death between SES, PES and BMS.[57]

3.6.9 Conclusion on antiplatelet therapy

As discussed before, the combination of a thienopyridine and aspirin during the first weeks following PCI became, during the late nineties, the reference antithrombotic therapy after BMS implantation. Because DES were shown to cause delayed endothelialisation, and the related problems of acute thrombosis following brachytherapy kept in mind, trial protocols with DES mandated more prolonged antiplatelet therapy than earlier trials with BMS. Although initial studies highlighting the benefits of dual antiplatelet therapy used aspirin and ticlopidine, clopidogrel is used more often because it is associated with a lower rate of side effects. Its beneficial effect following stent implantation however has not been fully documented in RCTs which explains that regulatory bodies in Belgium and in the US as well, have not yet approved the use of clopidogrel in dual antiplatelet therapy following DES.[99]

Pivotal trials with PES typically demanded dual antiplatelet therapy to be maintained for at least 6 months whereas in SES-trials this was 2 to 3 months, aspirin being prescribed indefinitely. The increased occurrence of late stent thrombosis which seemed to be at least partly related to the cessation of the thienopyridine led to recommendations to prolong the period of mandatory dual antiplatelet therapy period to one year by some authorities.[8, 100] The FDA Advisory Panel confirmed that up to now, there is no definitive clinical evidence to guide recommendations about the optimal length of dual antiplatelet therapy after DES use. It corroborated the joint ACC/AHA/SCAI 2005 guideline[100] in recommending dual antiplatelet therapy for at least 1 month after BMS (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks), 3 months after SES implantation, and 6 months after PES implantation, and ideally up to 12 months in patients who are not at high risk of bleeding.[92]

The downside of dual antiplatelet therapy is a substantial increased risk of bleeding. For example, in the ACTIVE trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events), which involved patients with atrial fibrillation, the risk of bleeding complications with dual antiplatelet treatment was as high as that associated with oral anticoagulation.[101] Patients should therefore be evaluated for bleeding risk before implanting a DES instead of a BMS in order to assess whether long term thienopyridine treatment and lifelong aspirin treatment can be envisaged.

Patients who cannot comply with extended dual antiplatelet therapy, or who have planned procedures requiring early discontinuation of antiplatelet therapy may therefore not be good candidates for drug eluting stents.[94]

3.7 DES IN DIABETES

Diabetes is known to substantially elevate the risk of in-stent restenosis (>50% post BMS) and increase the risk of complications.[102, 103] Of the RCTs comparing DES to BMS, only one trial strictly limited enrollment to patients with diabetes and compared SES with BMS in de novo lesions in native coronary arteries.[104] In this trial, the primary end point was in-segment late lumen loss as assessed by quantitative coronary angiography at 9-month follow-up. It was reduced from 0.47±0.5 mm for BMS to 0.06±0.4 mm for SES ($p<0.001$). TLR rates were significantly lower in the sirolimus group. Five other trials (TAXUS IV, TAXUS V, RAVEL, SIRIUS, and SES-SMART) reported data for diabetic patients separately in subgroup analyses, with a considerably variation in the proprotion of patients with diabetes. Four of these showed a statistically significant reduction in TLR rates in patients receiving DES. Thus, current evidence suggests that DES use is likely effective in reducing the incidence of in-stent restenosis in patients with diabetes.[105]

In the meta-analysis done by Kastrati et al, the survival rate for patients with diabetes was significantly lower in the SES group (87.8% vs 95.6% in the BMS group; HR for death, 2.90; 95% CI 1.38-6.10).[61] In the as yet unpublished Stettler meta-analysis, 29 trials (3762 patients) contributed to a subgroup analyses of diabetic patients.[57] Among diabetic patients, a total of 267 had died, 78/1 199, 87/1151 and 102/1 329 in the BMS, PES and SES groups, respectively. HRs for overall mortality were 1.24 for SES versus BMS (0.74-1.87) and 1.16 for PES versus BMS (0.78-1.84). The authors do not compare all DES vs BMS in diabetics but from their data it can be calculated that 189 out of 2 480 diabetics receiving a DES died (7.62%) vs 78 out of 1 199 diabetics who received a BMS (6.51%).[57]

In a real world registry of 708 consecutive diabetic patients, two-year cumulative incidence of mortality was not statistically different between SES (13.3%), PES (11.5%) and BMS (9.8%) patients.[106] The incidence of stent thrombosis was high in both DES groups: it occurred in 4.4% of the SES patients, compared with 2.4% in the PES group and only 0.8% in the BMS group. Interestingly, of the total of 17 patients with stent thrombosis, two died, seven presented with a MI and 12 patients were still on dual antiplatelet therapy at the time of the event.[106]

In a narrative review, Seabra-Gomes argues that there are still some concerns over the use of DES for PCI in diabetics, related to possible LST that, in real life, may be higher than in other subgroups of patients.[103]

3.8 RCTS NOT INCLUDED IN META-ANALYSES

In the US, only the Cypher and Taxus stents are currently on the market and most information, both in individual RCTs as in meta-analyses can be found for those SES and PES respectively. However, some other DES are currently on the market in Belgium and two companies, Abbot and Medtronic, have also introduced a request to the FDA in order to obtain market approval to the US for the Xience V and Endeavor DES respectively. In this part we will discuss the trials considering those two DES. Apart from searching the literature, we asked for additional information from the companies through Unamec, the Belgian professional organisation of producers, importers and distributors of medical devices.[107]

3.8.1 Endeavor Trials

The Endeavor stent is a DES with zotarolimus as eluting drug and marketed by Medtronic. It has been evaluated in a series of Endeavor trials and is on the market in the EU but not in the US. The Endeavor I was a first in man trial (~100 participants) with follow-up up to 4 year presented at conferences. For the 'pivotal' Endeavor II trial (~1 197 participants) 3 year results are available and were presented at EuroPCR in June 2007. Based on these 36 month results Medtronic filed an application with the FDA to ask for market approval in the US. In the literature we only found the 9 month results published in 2006.[108] Other Endeavor trials are underway to evaluate efficacy and safety, including several head tot head trials with either the Cypher or the Taxus DES. Current results seem to indicate a good efficacy and safety profile but there are no clear proofs that efficacy or safety results from those trials are either inferior or superior to Cypher or Taxus results, and the number of subjects included in the trials are relatively small. Future RCT results and meta-analyses including those stents will need to clarify this.

3.8.2 Xience V trials

Abbott is also on the DES market in Europe with its XIENCE V everolimus eluting stent, but not on the US market. Data on efficacy and safety were collected through the SPIRIT RCT program, including the "First In Man SPIRIT I" trial (~60 participants), the SPIRIT II (n=300) and III (n=1 002) trials that where head to head comparisons with the Taxus DES. Those data were used by Abbott to file an application with the FDA to obtain market approval in the US. Current results indicate no inferiority to the TAXUS stent for several primary efficacy endpoints and a good safety profile. Again, numbers are relatively small and follow-up is relatively short (up to 3 years for SPIRIT I, but only 9 months for SPIRIT III), and no meta-analyses are available yet.

3.9 REGISTRIES

Most information on efficacy and safety of DES vs. BMS is based on RCTs. Those RCTs have shown that DES in general have an acceptable safety profile, and that, although they do not significantly influence rates of death or MI, they do significantly reduce the need for target lesion revascularisation (TLR), mainly during the first year and sustained up to 4 years after PCI, meaning that there is no apparent catch-up phenomenon after the first year. However, these trials are usually performed in large and experienced medical centers, with high volumes of PCI. On the other hand, they usually enrolled relatively small numbers of patients, with many specific in- and exclusion criteria leading to a relatively healthy patient population with a better prognosis than average. Therefore, these populations are probably not representative for the majority of patients that are treated with PCI in the real world, including off-label use of DES. Moreover, the design of the RCTs usually include mandatory angiographic follow-up which is known to artificially increase the rates of reported TLR, usually about doubling the rates of TLR.[109] Therefore, both the relative reduction of TLR as the absolute level of restenosis requiring revascularisation in BMS and DES could be overestimated in those RCTs.

We searched the literature for registries of the use of DES in 'real world' conditions including on- and off-label use. We identified 29 DES registries published since 2005. However, not all of the publications provided relevant data for our purposes. In table 3.4 the selected references are listed with the major study characteristics.

Table 3.4: Publications from Registries published since 2005

Population	Publication	Registry	Year	Main comparison	Follow-up	Total n
Consecutive Patients	Abbott et al.[110]	NHLB Dynamic Registry	2007	DES/BMS Gender differences in efficacy and safety	in-hospital and 1 year	3 223
Consecutive Patients	Daemen et al.[111]	Rotterdam / Bern	2007	SES/PES Safety	up to 3 years	8 146
Consecutive Patients	Biondi-Zoccai et al.[112]	TRUE (Taxus)	2007	PES	in hospital	1 065
Consecutive Patients	Lagerqvist et al.[113]	SCAAR	2007	DES/BMS	up to 3 year	19 771
Consecutive Patients	Abizaid et al.[114]	WISDOM	2006	PES	up to 1 year	778
Consecutive Patients	Daemen et al.[115]	RESEARCH	2006	SES	up to 3 year	958
Consecutive Patients	Kumar et al.[116]	ORCHID	2006	SES/PES	6 months	312
Consecutive Patients	Urban et al.[109]	e-Cypher	2006	SES	30 days, 6 month and 1 year	15 157
Consecutive Patients	Williams et al.[117]	DESCOVER	2006	SES/PES DES/BMS	1 year	6 906
Consecutive Patients	Zahn et al.[118]	German Cypher Registry	2006	SES	6.6 mo	7 445
Consecutive Patients	Ong et al.[119]	RESEARCH	2005	PES/SES	1 year	1 082
Practice Description	Mühlberger et al.[120]	Austrian PCI Registry	2007	Current Practice	None	16 880
Practice Description	Huang et al.[37]	ACC-NCDR	2006	Current Practice	None	1 276 582
Practice Description	López-Palop et al.[121]	Registro Español de Hemodinámica y Cardiologia Intervencionista XV Informe Oficial	2006	Current Practice	None	80 569
Practice Description	Zahn et al.[122]	CAS-ALKK	2005	Current Practice	in hospital registry	1 888
Subgroup (Bypass graft disease)	Costa et al.[123]	SECURE	2005	SES	8 months	252
Subgroup (diabetes and IIb/IIIa)	de Araujo Goncalves et al.[124]	de Araujo Goncalves et al.	2006	SES in diabetes. Use of SES with or without IIb/IIIa	1 year	203
Subgroup (discont. DAPT)	Spertus et al.[125]	PREMIER	2006	Premature discontinuation of Thienopyridine after PCI with at least 1 DES	1 year	500
Subgroup (in-stent restenosis)	Liistro et al.[126]	TRUE (Tuscany)	2006	SES	9 mo	244
Subgroup (in-stent restenosis)	Neumann et al.[127]	TROPICAL	2005	SES	9 mo	162

Subgroup (Left Main CAD)	Valgimigli et al.[128]	RESEARCH / T-SEARCH	2006	SES AND PES but analysis on single vessel vs bifurcation vessel	587 days	94
Subgroup (Left Main CAD)	Valgimigli et al.[129]	RESEARCH / T-SEARCH	2006	DES	587 days	130
Subgroup (Left Main CAD)	Valgimigli et al.[130]	RESEARCH / T-SEARCH	2005	DES / BMS	503 days	181
Subgroup (Left Main CAD)	Voudris et al.[131]	ONASSIS	2005	SES	almost 1 year	928
Subgroup (Prox LAD)	Khattab et al.[132]	German Cypher Registry	2007	SES	6-8 months (median 6.6 mo)	2 274
Subgroup (small vessels)	Rodriguez-Granillo et al.[133]	RESEARCH	2005	PES/SES	1 year	197
Subgroup (STEMI)	Daemen et al.[134].	RESEARCH / T-SEARCH	2007	SES / historic control BMS; STEMI analysis	up to 3 year for SES and up to 2 year for PES	505
Subgroup (STEMI)	Percoco et al.[135]	REAL	2006	SES in STEMI	1 year	1 617
Subgroup (unprotected Left Main Stenosis)	Palmerini et al.[136]	Bologna Registry	2006	PCI vs CABG	430 days	311

Registries are particularly useful because they aim at providing 'real world' data on stenting practice, including all sorts of patients with on- and off-label DES use, they do not have mandatory follow-up that might artificially increase revascularisation rates in RCTs, and patients are not followed-up so rigidly, avoiding the many censoring issues in RCTs. Also for safety issues they can provide important information because patients included in those registries might have lower compliance with, for example, dual-antiplatelet therapy.

Revascularisation rates obtained through registries are generally lower than in RCTs, but may therefore better reflect the effectiveness in daily practice. A problem, however, is that several registries report revascularisation differently, sometimes as revascularisation (PCI and/or CABG) rates, and sometimes as either target vessel or target lesion revascularisation. Also the period of follow-up is different making rates difficult to compare. For the purpose of this report we have mainly used the clinically driven revascularisation rates to compare them to the revascularisation rates found in RCTs. For reference purposes we listed revascularisation rates and MACE in table 3.5.

The selection bias that is typically encountered in registries can have very different characteristics between various registries. In some, such as SCAAR, it is left to the discretion of the cardiologist to make a choice between a BMS or a DES whereas in other registries, cardiologists a priori decide to implant a DES, but can choose between different types of DES.

Table 3.5: Revascularisation rates and MACE from registries

Publication	Registry	Repeat PCI in DES	Repeat PCI in BMS	MACE IN DES	MACE IN BMS
Abbott et al.[110]	NHLB Dynamic Registry	At 1 year: women 9.5% and men 8.8%	At 1 year: women 14.1% and men 12.0%	1 year 15.7% in women, 15.6% in men	1 year: 22.1% in women 20.2 % in men
Biondi-Zoccai et al.[112]	TRUE (Taxus)	In hospital 0.5% TVR	NA	In hospital 3.7% MACE	NA
Lagerqvist et al.[113]	SCAAR	At 3 year: 14.7% new PCI; clinical restenosis: 3.6% (shorter fup)	At 3 year: 14.5% new PCI; clinical restenosis: 5.9% (shorter fup)	NA	NA
Abizaid et al.[114]	WISDOM	TLR at 1 year: 2.0%	0	At 1 year: 5.2%	0
Daemen et al.[115]	RESEARCH	At 3 year: TLR 7.5%; TVR 9.4%	At 3 year: TLR 12.6%; TVR 16.6%	At 3 year: 18.9%	At 3 year: 24.7%
Kumar et al.[116]	ORCHID	At 6 mo: TVR is 1.9% in SES and 2.6% in PES		At 6 mo: 4.5% SES and 3.2% PES	0
Urban et al.[109]	e-Cypher	TLR: .at 30d 0.34%, at 6 mo 1.49% at 1 year 3.07%	NA	at 30 days: 1.36%, at 6 mo 3.38% and at 1 year 5.8P%	0
Williams et al.[117]	DESCOVER	TVR at 1 year (inclusive CABG): 6.3% SES, 5.5% PES / Any repeat PCI: 8.4%	TVR at 1 year: 9.5% inclusive CABG); Any repeat PCI: 9.3%	NA	NA
Ong et al.[119]	RESEARCH	clin driven TVR 3.7% for SES and 5.4 % for PES	0	10.5% for SES and 13.9 % for PSE	0
Liistro et al.[126]	TRUE (Tuscany)	at 9 mo: ischemia driven TLR 4.9%	0	0	0
Valgimigli et al.[130]	RESEARCH / T-SEARCH	TVR: 6%	TVR: 23%	0,24	0,45
Voudris et al.[131]	ONASSIS	TLR: 2.1%	TLR: 10.1%	0	0
Khattab et al.[132]	German Cypher Registry	At 6.6 months: TVR 7.9%	NA	At 6.6 months: MACE 10.5%	0
Rodriguez-Granillo et al.[133]	RESEARCH	0	0	5.6% for SES and 17.9% for PES	0
Daemen et al.[134].	RESEARCH / T-SEARCH	TVR at 3 year 8.0% for SES / TVR at 3 year 7.7% for PES	TVR at 3 year 12.0%	MACE at 3 year 17.9% for SES / MACE at 3 year 20.6% for PES	MACE at 3 year 25.5%
Percoco et al.[135]	REAL	at 396 days: TVR 3.4 %	at 396 days: TVR 5.1 %	at 396 days: 14 %	at 396 days: 20.3 %

As in the RCTs, most revascularisations (TVR, TLR) occurred within the first year after the original stenting, and this reduction was sustained during the following years with no indication for catch-up restenosis. At 1 year, revascularisation rates for DES varied widely in those registries ranging from 2,0% to 9.5%, and for BMS they ranged from 5.1% to 14,1%.

3.10 BELGIAN REGISTRY (BWGIC)

As indicated previously, we used data from the Belgian registry organised by the BWGIC for the economic analysis in this HTA. Data on outcomes of this observational study can be found in chapter 5 describing those data.

Key points

- **There is no published evidence from RCTs that the use of DES compared to BMS improves overall mortality, cardiac mortality or MI outcomes.**
- **One very large meta-analysis suggests that there might be a lower risk for MI with SES as compared to PES. This is not confirmed in another meta-analysis that was restricted to RCTs with head-to-head comparisons of SES vs PES.**
- **DES, compared to BMS, have been shown to be more effective in reducing the occurrence of restenosis, thereby reducing the need of repeat revascularisation. But, because of the lack of enough data from RCTs we have pooled data from DES and from BMS for the purpose of this analysis, thereby obscuring the differences in effectiveness within the DES and BMS groups.**
- **The absolute reduction of repeat revascularisations is artificially inflated in RCTs due to compulsory follow-up angiography leading to revascularisations that are not associated to clinical symptoms.**
- **SES and PES and other DES appear to be successful in reducing the need for repeat revascularisation due to restenosis. Although some recent publications suggest a better efficacy for SES compared to PES, data about the relative performance of different DES remain largerly inconclusive due to the small numbers of events in RCTs.**
- **Stent thrombosis infrequently occurs after both BMS and DES implants. Cumulative incidence at 4 years does not appear to be different between DES and BMS. However, the time distribution of events appears to be different with more BMS thromboses in the 30-day to 1-year time period and more DES thromboses in the >1-year time period, possibly associated to the timing of discontinuation of dual antiplatelet therapy.**

4 REVIEW OF LITERATURE OF ECONOMIC EVALUATIONS

Based on current evidence, using Drug Eluting Stents (DES) does not reduce the occurrence of death or MI compared with Bare Metal Stents (BMS). But, several trials have shown that DES substantially reduce rates of restenosis, and thus the need for repeat revascularization after PCI compared with conventional BMS. DES, however, are considerably more expensive than BMS. At current list prices, DES are more than twice as expensive as BMS. In the current Belgian reimbursement schedule, the RIZIV/INAMI procedure cost for DES in diabetics is €1 000 more than for BMS. In an era of increasing health expenditures, this obliges health care payers to question how far the use of DES should be supported and for which indications.

In this chapter we provide a systematic literature review and a detailed and critical appraisal of the results. In a later chapter we will describe the economic model we developed to calculate cost-effectiveness of DES versus BMS specifically for the Belgian health care payer.

4.1 SELECTION OF ECONOMIC LITERATURE

A comprehensive review of the literature was undertaken to identify all literature that may provide evidence with regard to the cost effectiveness of DES. An overview of the search strategy and the results are provided in appendix. As a result, 22 articles were included in our review on economic evaluations. Table 4.1 presents an overview of these articles.

Table 4.1: economic evaluations on DES

Authors	Title
Bagust A, Grayson AD, Palmer ND, Perry RA, Walley T.[137]	Cost effectiveness of drug eluting coronary artery stenting in a UK setting: cost-utility study.
Bakhai A, Stone GW, Mahoney E, Lavelle TA, Shi C, Berezin RH, Lahue BJ, Clark MA, Lacey MJ, Russell ME, Ellis SG, Hermiller JB, Cox DA, Cohen DJ.[138]	Cost effectiveness of paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization: results from the TAXUS-IV Trial.
Bowen J, Hopkins R, He Y, Blackhouse G, Lazzam C, Tu J, Cohen E, Tarride J, Goeree R.[139]	Systematic review and cost-effectiveness analysis of drug eluting stents compared to bare metal stents for percutaneous coronary interventions in Ontario.
Brophy J, Erickson L.[140]	An economic analysis of drug eluting coronary stents: a Quebec perspective.
Brophy JM, Erickson LJ.[141]	Cost-effectiveness of drug eluting coronary stents in Quebec, Canada.
Cohen DJ, Bakhai A, Shi C, Githiora L, Lavelle T, Berezin RH, Leon MB, Moses JW, Carrozza JP, Zidar JP, Kuntz RE.[142]	Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: Results from the sirolimus-eluting balloon expandable stent in the treatment of patients with de novo native coronary artery lesions (SIRIUS) trial.
Ekman M, Sjogren I, James S.[143]	Cost-effectiveness of the Taxus paclitaxel-eluting stent in the Swedish healthcare system.
Elezi S, Dibra A, Folkerts U, Mehilli J, Heigl S, Schomig A, Kastrati A.[144]	Cost Analysis From Two Randomized Trials of Sirolimus-Eluting Stents Versus Paclitaxel-Eluting Stents in High-Risk Patients With Coronary Artery Disease.
Greenberg D, Bakhai A, Cohen DJ.[145]	Can we afford to eliminate restenosis? Can we afford not to?
Hill R, Bagust A, Bakhai A, Dickson R, Dundar Y, Haycox A, Mujica Mota R, Reaney A, Roberts D, Williamson P, WalleyT.[32]	Coronary artery stents: a rapid systematic review and economic evaluation.
Ikeda S, Kobayashi M.[146]	Economic evaluation of drug eluting stents in Japan.
Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A, Bernheim A, Zutter A, Zellweger M, Grize L, Pfisterer ME.[147]	Incremental cost-effectiveness of drug eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET).
Lord SJ, Howard K, Allen F, Marinovich L, Burgess DC, King R, Atherton JJ.[79]	A systematic review and economic analysis of drug eluting coronary stents available in Australia.
Medical Services Advisory Committee.[148]	Drug eluting stents.
Mittmann N, Brown A, Seung SJ, Coyle D, Cohen E, Brophy J, Title L, Oh P.[149]	Economic evaluation of drug eluting stents.
Ong ATL, Daemen J, van Hout BA, Lemos PA, Bosch JL, van Domburg RT, Serruys PW.[150]	Cost-effectiveness of the unrestricted use of sirolimus-eluting stents vs. bare metal stents at 1 and 2-year follow-up: results from the RESEARCH Registry.
Polanczyk CA, Wainstein MV, Ribeiro JP.[151]	Cost-effectiveness of sirolimus-eluting stents in percutaneous coronary interventions in Brazil.
Rinfret S, Cohen DJ, Tahami Monfared AA, Lelorier J, Mireault J, Schampaert E.[152]	Cost effectiveness of the sirolimus-eluting stent in high-risk patients in Canada: an analysis from the C-SIRIUS trial.
Russell S, Antonanzas F, Mainar V.[153]	Economic impact of the taxus coronary stent: implications for the Spanish healthcare system.
Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA.[154]	Economic evaluation of sirolimus-eluting stents.
Tarricone R, Marchetti M, Lamotte M, Annemans L, de Jong P.[155]	What reimbursement for coronary revascularization with drug eluting stents?
Van Hout BA, Serruys PW, Lemos PA, Van Den Brand MJBM, Van Es G-A, Lindeboom WK, Morice M-C.[156]	One year cost effectiveness of sirolimus eluting stents compared with bare metal stents in the treatment of single native de novo coronary lesions: An analysis from the RAVEL trial.

Some other studies were not included for a variety of reasons. The study of Greenberg and Cohen,[157] published in 2002, was not included since these authors published a new paper in 2004 based on the same model with more up-to-date data. In the 2002 publication, the model was based on the assumption that a coated stent would reduce the incidence of clinical restenosis by 90%. In the 2004 publication, an 80% reduction in TVR with DES was assumed. A cost and threshold analysis of Oliva and colleagues was excluded since this report did not present results from a cost-effectiveness or cost-utility analysis.[158] The threshold analysis of Ward[159] was excluded for the same reason. Cost neutrality will be discussed separately. Finally, two studies performing the analysis from a hospital perspective and estimating budget impact or profit/loss were not taken into account because they are not considered as full economic evaluations.[160, 161] Results, however, are presented shortly when the perspective of the analysis is discussed.

It is remarkable that in such a short time period, so many economic evaluations have been published. Not only countries traditionally involved with HTA, such as UK, US, Canada and Australia, but also the Netherlands, Germany, Spain, Italy, Switzerland, Sweden, Brazil and Japan have published such analyses. This is a clear indication of the world-wide attention this technology is currently receiving.

4.2 DESCRIPTION OF ECONOMIC LITERATURE

Comparative tables by study can be found in appendix providing the following details: column 1) authors, country, year of publication, conflict of interest, perspective, analytical technique, time window, discount rate; column 2) population, comparator, on which trial did the study rely, utilities (if relevant); column 3) year of costs and currency, cost details, average number of stents per procedure; column 4) mean restenosis rate, relative risk reduction with DES, type of repeat procedure; column 5) cost-effectiveness results, subgroup analysis; column 6) conclusions, sensitivity-, and threshold analysis (if present).

The studies of the Australian Medical Services Advisory Committee[148] (MSAC) and Lord and colleagues[79] are considered as one. The first report is a full HTA prepared by MSAC with the assistance of authors from the latter. The two studies of Brophy and Erickson[140, 141] were also regarded as one. The main difference between the two studies is the relative risk for restenosis of high-risk patients selected to receive DES versus the current average rate of restenosis. This was 2.67 in the full report and 2.5 in the journal publication. In our comparative table, we included input and results from the full report.

For practical reasons costs and ICERs will be presented as published originally. To improve comparability, some costs are also recalculated to 2006 euros in Belgium using consumer price indices (CPI) and purchasing power parities (PPP). Conversion factors are provided in table 4.2.

Table 4.2: increase in CPI, PPP and conversion factors

Study	Country	Currency	Year of costing	Increase of CPI**	PPP vs Belgian €	Conversion factor
Bagust et al.[137]	UK	£	2003	5.84%	1.39	1.47
Bakhai et al.[138]	US	$	2004	6.73%	0.86	0.91
Bowen et al.[139]	Canada	CAD	2003-2004	4.29%	0.70	0.73
Brophy et al.[140]	Canada	CAD	2003	6.20%	0.70	0.74
Cohen et al.[142]	US	$	2002	12.07%	0.86	0.96
Ekman et al.[143]	Sweden	SEK	2004	1.82%	0.09	0.10
Elezi et al.[144]	Germany	€	(2005)*	1.71%	0.98	1.00
Greenberg et al.[145]	US	$	2003	9.59%	0.86	0.94
Hill et al.[32]	UK	£	2001-2002	7.28%	1.39	1.49
Ikeda et al.[146]	Japan	JPY	2005	0.24%	0.00688	0.00690
Kaiser et al.[147]	Switzerland	€	2003-2004	2.24%	/***	1.02
Lord et al.[79]	Australia	AUD	2001-2002 and 2004	6.30%	0.62	0.65
Mittmann et al.[149]	Canada	CAD	2002-2003	6.20%	0.70	0.74
Ong et al.[150]	the Netherlands	€	2001-2002	6.34%	0.99	1.05
Polanczyk et al.[151]	Brazil	Brazilian reals	2003	18.69%	0.78	0.92
Rinfret et al.[152]	Canada	CAD	2003	6.20%	0.70	0.74
Russell et al.[153]	Spain	€	(2005)*	3.52%	1.11	1.15
Shrive et al.[154]	Canada	CAD	2002	9.14%	0.70	0.76
Tarricone et al.[155]	Italy	€	2003	6.42%	1.00	1.06
Van Hout et al.[156]	the Netherlands	€	(2004)*	2.87%	0.99	1.02

CPI: consumer price index; PPP: purchasing power parities
* if not explicitly mentioned, the year before the time of publication was taken into account; ** Between year of costing and 2006 (Source: stats.oecd.org, accessed on 16th July, 2007);
*** results already expressed in Euro and not in Swiss Francs.

4.2.1 Perspective

4.2.1.1 Health care payer perspective

To know whether DES offer value for money, the increased initial costs of the device are compared with the expected later savings from not having to treat restenosis. This cost difference is then compared with the health gains due to the alternative intervention. The cost issue can be examined from several perspectives such as that from the health care payer, society, hospitals, or patients. The perspective applied in the studies is mainly that of the health care payer.

4.2.1.2 Societal perspective

Two studies mentioned that they applied a societal perspective.[142, 138] In these studies, costs were assessed by a combination of "bottom-up" and "top-down" methods applying cost-to-charge ratios to transform hospital billing data to costs. It is important to note that a societal perspective, in theory, usually takes more cost items into account such as transportation costs borne by the patient or costs to employers due to absence from work or reduced productivity. Inclusion of these indirect costs in an economic analysis could result in a greater offset of the higher initial costs associated with DES. These indirect societal costs were not included in the two mentioned studies. The authors just wanted to indicate that the value of included items was calculated from a different perspective.

4.2.1.3 Hospital perspective

Several studies mentioned to perform an analysis from the hospital's perspective. The meaning of hospital perspective should be interpreted with caution. In some studies[149, 156, 153] the authors want to indicate that costs occurring in the hospital were taken into account. The value of these cost items, however, was appraised from the payer's perspective.

In contrast to these studies, several authors calculated net profits/losses from the hospital's perspective. Whereas cost-effectiveness analysis seeks to determine if a technology provides good value for money, the economic impact of DES on hospitals compares revenues and incomes: does the reimbursement level offset the costs of this new technology? Since only costs are regarded, they are not regarded as full economic evaluations. Although we do not include these studies in our systematic literature review of economic evaluations, we shortly present some results of these studies.

Kong et al. (US) calculated that, with 85% of stent procedures shifted to DES and with no changes in reimbursement policy, a hospital with a catheterization laboratory volume of 3 112 patients yearly converted from a $2.01 million (M) annual profit to an $8.10M loss in the first year (with a very small 95% CI: 8.09M to 8.12M) and $8.7M annual losses in later years. This represented an overall change in cash flow of $55.71M (95% CI: 55.66M to 55.76M) away from the hospital over 5 years. Although Medicare has proposed to increase reimbursement to ease the impact of DES on hospitals, this increase would not totally offset the costs.[161]

The study from Bakhai et al. (US) also performed a secondary analysis in which costs were assessed from a hospital perspective. Net profit per patient was actually slightly lower with PES than BMS ($6 605 vs. $7 064; 95% CI: 1 120 less to 201 more).

Another US study mentioned that the Centers for Medicare and Medicaid Services approved a $1,800 increase in reimbursement for BMS to compensate in part for the increased cost. While the increase provides full reimbursement for the incremental cost of placing one stent, it does not cover the cost of two or more stents.[162] The more stents that are required to treat a specific patient, the greater the financial burden imposed on hospitals by DES adoption.[163]

Brophy found a negative impact on the necessary budget for a specific Canadian hospital and advised that, despite good evidence supporting the efficacy of coated stents to reduce the rate of restenosis, the current budget of the hospital should not be redistributed to permit the routine acquisition of DES. Furthermore, the authors argue that in the absence of a specially dedicated provincial budget for this technology, coated stents should not be provided by this hospital except for specific circumstances.[160]

In general, according to these studies, DES are a loss-making technology for hospitals due to the substantially higher costs and inadequate reimbursement for those higher costs and possible decreasing future revenues due to fewer bypasses and repeat interventions for restenosis.[164] However, we need to emphasise that those studies particularly apply to North America.

4.2.2 Analytical technique

One of the main outcomes of an economic evaluation is the incremental cost-effectiveness ratio (or ICER). The ICER is a measure of the additional cost of the new technology (DES) over and above the comparator (BMS) as compared with the difference in outcome between these two technologies. In other words, what is the additional cost per unit of health gained?

4.2.2.1 Cost per LYG

There is, however, currently no evidence that using DES decreases mortality. Without this benefit, assessment of cost-effectiveness expressed as cost per LYG is not possible.

4.2.2.2 Cost per QALY

It is nonetheless reasonable to assume that lower rates of clinical restenosis and repeat interventions in patients treated with DES can have a positive impact on their Quality of Life (QoL).[145] As such, results could be expressed as costs per quality-adjusted life years (QALYs). This metric includes both length and quality of life and allows comparisons with other interventions.

4.2.2.3 Cost per repeat revascularization avoided

The QALY measure, however, has several drawbacks for the analysis of DES versus BMS. The benefit of DES over BMS involves the avoidance of interventions rather than avoiding death or repeat cardiac events. DES would only be associated with a very short-term utility improvement. Due to this limitation, several studies have used a disease-specific cost-effectiveness outcome, i.e. cost per repeat revascularization avoided.

The advantage of such a disease-specific outcome is that it is easy to measure and is easy to interpret by clinicians.[157] The primary limitation of this surrogate end point, however, is that it is specific to the field of coronary revascularization and that it cannot be compared with cost-effectiveness ratios for other conditions and interventions, or against cost-effectiveness analyses for the same conditions and interventions but using different outcome measures.[145] Therefore, it can be considered as not very useful to decision makers.

4.2.3 Target vessel/lesion revascularisation & angiographic follow-up

Most stent trials have not reported the most important outcome for patients, clinicians, and health care funders: the risk of any repeat revascularisation (irrespective of lesion or vessel involved).[137] As many as 40% of the repeat revascularizations in the first year may not have been attributed to clinical restenosis but, rather, to disease progression. It was reported that in subsequent years disease progression is 4 times more likely than stent restenosis to be responsible for adverse clinical outcomes (hazard ratio 6.3% v. 1.7%).[165] Taking repeat revascularization as endpoint is therefore likely to bias results in favor of DES.

4.2.3.1 Target vessel/lesion revascularisation

Publications from RCTs report angiographic restenosis (not all necessarily clinically significant) and event rates specific to the lesion or vessel initially revascularised. Since it is widely reported, target vessel revascularisation (TVR) and target lesion revascularisation (TLR) are used as proxies for overall revascularisation. A TVR is the need for repeat revascularization (percutaneous or surgical) for re-narrowing anywhere in the treated (target) coronary vessel. In contrast, a TLR was defined as repeated revascularization for recurrent narrowing anywhere in the stent or within the 5 mm border proximal or distal to the stent.[166]

This selective reporting, however, omits other interventions and exaggerates the apparent benefit attributable to DES,[137] because PCI does not stop the progression of disease.

4.2.3.2 Angiographic follow-up

A second bias, favouring results of DES, is caused by the intensive follow up in trials. Trials report angiographic outcomes because the follow-up angiogram is an important part of the investigation of the safety and efficacy of a DES.[167] In most trials routine angiography is conducted 6 to 9 months after the index procedure to assess in-stent restenosis. As mentioned by Lord et al.,[79] only three trials specified that revascularisation events must be clinically driven,[168-170] and two of these trials reported that asymptomatic patients with ≥70% vessel diameter stenosis by quantitative coronary angiography were included in the definition of "clinically driven".[168, 169] On the one hand, this bias applies both to patients receiving DES or BMS and will possibly not bias estimates of relative risk reduction. However, it is argued that angiographic restenosis is more frequent with BMS than with DES and therefore causes a bias in favour of DES.[85] Furthermore, angiographic follow-up may increase the baseline risk of restenosis, i.e. the risk of restenosis when BMS are applied. An identical relative risk reduction in combination with a higher baseline risk will inflate estimates of absolute risk reduction, which are used to estimate cost-effectiveness. Protocol driven follow up angiography overestimates the risk of recurrence and the benefit of using DES.

As mentioned by Hill,[32] some have argued that this bias would be counteracted since some of those stenoses classified as angiographically driven at 6 months would have progressed by 12 months or later to become symptomatic and requiring a clinically driven revascularisation. This should, however, be investigated in further research.

Several authors tried to perform a correction for this bias. To limit contamination of clinical outcomes by the performance of routine angiographic follow-up, Cohen et al.[142] only included clinically indicated repeated revascularization procedures. All repeat revascularization procedures were reviewed by an independent events committee and repeat revascularization was considered clinically indicated if there was evidence of symptomatic myocardial ischemia, after provocative testing, or both.[142]

The study of van Hout et al.,[156] based on the RAVEL study which had a protocol mandated angiogram scheduled at 5–7 months of follow-up, addressed this issue with estimates of the effect of angiographic follow-up from the earlier BENESTENT II study.[171] On average, the inclusion of angiographic follow-up increased the number of repeat revascularisations by a factor 1.6 and decreased the number of subsequent unscheduled angiograms by a factor of 0.6. After correction of the RAVEL data according to the expected effects of angiographic follow up, the difference in the number of repeat procedures was then estimated at 11.8% instead of 23.6%. Moreover, the difference in the number of unscheduled angiograms was estimated at 3.8% instead of 1.9%.[156]

Hill et al.[32] also mentioned to have adopted a BENESTENT II-type correction for rates of revascularisation in calculating the cost-effectiveness of stenting as they think this is a conservative and the most appropriate approach.

In the study of Kaiser et al.[147], performed alongside the Basel stent cost-effectiveness trial (BASKET), patients did not undergo protocol-mandated follow-up angiography.

Finally, the study of Bowen et al[139] was a field evaluation not influenced by protocol driven coronary angiograms and subsequent revascularization procedures.

4.2.4 Population

Results of a study should be considered specific to the trial population and may not be applicable to the full spectrum of PCI patients.[138] In economic evaluations, however, the study population is often wider than the selected trial population. Extending the analysis to other populations is based on the assumption that the relative benefits of DES are preserved. However, on the one hand, the incremental costs of DES may differ substantially according to patient characteristics: more stents are implanted on average for long lesions or patients undergoing multivessel revascularization. On the other hand, due to a different initial risk on restenosis with BMS, the same relative risk reduction will translate in a different absolute risk reduction, which influences the ICER. These differences in incremental costs and absolute health gains reflect the importance of subgroup analysis. Results should not be generalized to the PCI population as a whole.

Several studies performed subgroup analysis based on several risk factors (see tables in appendix). The following variables, or a combination of these variables, were used to differentiate populations: diabetes status,[142, 145, 32, 155, 139, 154, 143, 144, 153] reference vessel diameter,[142, 145, 32, 155, 139, 147, 137, 143, 153] lesion length,[142, 145, 32, 155, 139, 147, 143, 153] single- or multi-vessel disease,[32, 155, 147] number of stents used,[137] de novo vs. restenotic lesions,[137, 144] prior CABG,[137] age,[147, 154] elective or non-elective surgery,[137] post or non-post MI[139] and clinical follow-up alone or not.[138]

4.2.5 Comparator

With the exception of one study, all economic evaluations compare DES with BMS. The agents that have been the subject of the most extensive research are sirolimus and paclitaxel.[172] As shown in table 4.3, most economic studies explicitly state whether the DES is a Paclitaxel (PES) or a Sirolimus Eluting Stent (SES). Only a few economic studies,[147, 156] explicitly mention which type of BMS was used.

Only one economic evaluation directly compared the two most common types of DES. As mentioned by Bakhai et al.[138] it is important to notice that at the time the economic evaluations were performed, both stent types had not been compared in a single trial. Even though both the PES and SES were compared with an approved BMS in several trials, results should be interpreted with caution. The BMS used in the trials may have different characteristics (such as stent geometry and strut thickness) and clinical outcomes may differ in the BMS-control population. Thus, it is not possible to directly compare the cost effectiveness of these alternative DES designs based on current available data.

Table 4.3: Applied comparators

Economic evaluation	BMS	DES	PES	SES
140, 145, 32, 139, 147	Y	Y		
147, 79, 149, 137, 138, 143, 153	Y		Y	
173, 142, 155, 147, 79, 149, 154, 156, 137, 150, 152, 151	Y			Y
144			Y	Y

BMS: bare-metal stent; DES: drug eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

4.2.6 Time horizon and discount rate

Most studies evaluated the costs and effects over a short period of one year or even less. Five studies applied both the short one-year analysis and a longer two-year[143, 150, 153], 5-year[32], or even a lifetime[151] analysis. Three other studies performed their analysis with a two-year,[145] three-year,[146] and lifetime-[154]horizon.

The main argument to apply a short time horizon is based on the finding that most repeat interventions due to restenosis would be expected to occur within the first 12 months.[174] Later events are related predominantly to atherosclerosis progression, which would be unlikely to be altered by a drug eluting stent.[142] The risk of late thrombosis and the related dependence on clopidogrel treatment, however, have not been taken into account due to a lack of evidence at the time of writing of those economic evaluations. Recently, longer follow-up and meta-analyses have been published.

The majority of studies applied no discounting. Due to the short time window, whether or not applying a discount rate will not have a major impact on results. Only four studies applying a time horizon that is longer than one year discounted cost and/or outcomes. Hill and colleagues only did this in the 5-year analysis (not mentioning which rate was applied) but not in their simplified model.[32] Russell et al.[153] discounted future costs at an annual rate of 3%. Polanczyk et al.[151] and Shrive et al.[154] applied a discount rate of 3% on both costs and benefits.

4.2.7 Costs

4.2.7.1 BMS versus DES

The procedural cost of PCI with DES is higher than with BMS primarily due to the additional cost of the device itself.[175] Very different prices for BMS and DES have been reported (table 4.4). This may be due to country differences, the year of pricing, type of BMS or DES, whether or not manufacturers gave discounts in specific countries or to specific customers, etc. Comparing the prices over several studies and years is therefore very difficult.

The price difference is much larger in the US, Canadian, Dutch and Italian studies in comparison with those for the UK, Australia, Spain and Japan. The relatively high price for BMS in the Japanese study is also noteworthy. With the exclusion of the Japanese (which has very high prices for both BMS (€2 193) and DES (€2 904)) and Brazilian study (in which it was not clear what exactly was included in the "mean stent cost"), the price for BMS varies between €380 and €1 288 and for DES between €1 338 and €2 784. The price difference is minimum €690 and maximum €1 920.

It must be noted that the study of Tarricone et al.[155] does not include a higher cost for DES versus BMS. The reimbursement system for stenting procedures in Italy did not differentiate between SES and BMS at the moment of the analysis. Although a SES costed about €1 400 more than a BMS the authors argue not to increase the acquisition cost for DES. This is in contrast to the other studies in this review. Even though the reimbursement system does not (yet) differentiate between an existing and a new technology, not including the cost difference may lead to wrong conclusions. If the purpose of the analysis is to support reimbursement decisions for all DES vs. all BMS or for different categories of DES and BMS, an extra cost of the new technology (e.g. the acquisition cost) should be taken into account.

Table 4.4: Cost (difference) of BMS versus DES

Study	Stent	Price	Price difference	Source	Price in 2006 Belgian €*	Price (in €) difference
UK						
Bagust A et al.[137]	BMS	£370		Market average	543	
	DES	/	£500	List price difference	/	733
Hill R et al.[32]	BMS	£380		(medium estimate) from industry submission	565	
	DES	£900	£520		1 338	773
US						
Bakhai A et al.[138]	BMS	$800		Average hospital acquisition costs as of April 2004[176]	731	
	PES	$2 700	$1 900		2 468	1 737
Cohen D et al.[142]	BMS	$900		National survey of US hospitals in September 2003	864	
	SES	$2 900	$2 000		2 784	1 920
Greenberg D et al.[145]	BMS	$700		List price with volume discounts	657	
	DES	$2 700	$2 000		2 534	1 877
Canada						
Bowen et al.[139]	BMS	CAD600		Stent manufacturers	436	
	DES	CAD1 899	CAD1 299		1 379	944
Brophy J et al.[140]	BMS	CAD700		Hospital finance department	518	
	DES	CAD2 600	CAD1 900		1 923	1 405
Mittmann N et al.[149]	BMS	CAD608		Stent manufacturers	450	
	DES	CAD2 400	CAD1 792		1 775	1 326
Rinfret et al.[152]	BMS	CAD700		Hospital cath lab billing	518	
	SES	CAD2 700	CAD2 000		1 997	1 479
Shrive F et al.[154]	BMS	CAD500		Estimation (referring to Cordis document[177])	380	
	SES	CAD2 900	CAD2 400		2 204	1 824
The Netherlands						
Ong A et al.[150]	BMS	€692		Price paid by hospital in April 2002	727	
	SES	€1 929	€1 237		2 027	1 300
Van Hout B et al.[156]	BMS	€672		Stent manufacturer	683	
	SES	€2 000	€1 328		2 033	1 350

Italy						
Tarricone R et al.[155]	BMS	/		National charges		
	SES	/	€1 400			1 490
Switzerland						
Kaiser C et al.[147]	BMS	€1 260		List prices for stents	1 288	
	SES[a]	€2 380	€1 120		2 433	1 145
	SES[b]	€2 145	€885		2 193	905
	PES	€1 935	€675		1 978	690
Sweden						
Ekman M et al.[143]	BMS	/		Hospital list price		
	PES	/	SEK9 600			913
Australia						
Lord S et al.[79]	BMS	AUD850		Average selling price (state survey)	556	
	DES	AUD2 400	AUD1 550		1 571	1 015
Brazil						
Polanczyk et al.[151]	BMS	R$2 707 or 4 527[c]		The market price	2 493 or 4 169	
	SES	R$10 320	R$7 613 or 5 793		9 505	7 012 or 5 335
Japan						
Ikeda et al.[146]	BMS	¥318 000		(probably) market price	2 193	
	SES	¥421 000	¥103 000		2 904	710
Spain						
Russell S et al.[153]	BMS	/		Stent manufacturer		
	PES	/	€712			821

BMS: bare-metal stent; DES: drug eluting stent; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stent;
*: conversion factor: see table 4.2
a: until November 23, 2003; b: after November 24, 2003; c: depending on which perspective was taken (see table in appendix)
One study did not explicitly mentioned the cost or cost difference for SES versus PES.[144]

4.2.7.2 *Number of stents per procedure*

Because many PCI procedures require more than one stent (both to cover long lesions and to treat multiple lesions and vessels), this incremental unit price of DES versus BMS does not represent the true incremental cost of DES use.[163] The initial incremental cost of DES versus BMS is determined by both the price difference and the number of stents used in the procedure. A lower number of stents per PCI leads to a better cost-effectiveness ratio, and the other way round.

The studies included in this overview use an average number of stents per PCI between 1.1[144] and 1.9[147]. This relative large difference should be taken into account when discussing results. Two other studies avoid the discussion of the average number of stents implanted by providing results under the assumption that respectively 1, 2 or 3 stents are implanted.[32, 137]

In a UK dataset, an average number of 1.3 stents was used per procedure for single-vessel disease and 2.4 stents per procedures for two-vessel disease.[32] Tarricone et al.[155] also distinguished between these two groups implanting on average 1.2 and 2.6 stents for single- and multi-vessel disease, respectively. The latter study, however, assumed that in multi-vessel disease patients received 1.2 SES and 1.4 BMS. In contrast, Bagust et al.[137] assumed that cardiologists do not mix stent types when treating a patient, since it is not clear from clinical evidence whether mixing stents may compromise the effectiveness of the more efficacious device.

Finally, it is argued that the number of stents per procedure is higher in clinical practice versus trials since longer lesions and more vessels per patient are treated than in trials. Previous studies might therefore underestimate the true cost of DES procedures, which leads to an overly optimistic view of DES cost-effectiveness.[178] It is also noteworthy that the study with the highest average number of stents (1.9)[147] included unselected patients, as treated in everyday practice. This may partly reflect the difference between trial settings and real-world conditions.

4.2.7.3 *Other costs*

Costs of avoided subsequent procedures are also of importance. In table 4.5, we present the CABG costs (if mentioned) for the economic evaluations included in our review. The US studies reported aggregate costs and did not mention specific CABG cost separately for their cost-effectiveness analysis.[142, 145, 138] When discussing budget impact, one of the studies mentioned an approximate cost of about $25 000 (€23 500 in 2006 values) for CABG.[145]

Rinfret et al.[152] note repeat revascularization costs are substantially higher in the US, which makes results hard to generalize to the Canadian or other healthcare systems. Specifically for the Canadian studies, this is true for three studies.[140, 149, 152] The fourth study,[154] however, applied costs similar to the US CABG costs, i.e. CAD32 000 (€24 300 in 2006 values). Different CABG costs, in combination with different absolute reduction of repeat procedures and other proportions of PCI versus CABG for repeat procedures (see summary tables in appendix), may provide completely different results.

Table 4.5: Cost for CABG

Study	Description variable	Cost in original study	Cost in 2006 €*
UK			
Bagust et al.[137]	Elective CABG	£7 750	11 365
	Non-elective CABG	£9 460	13 872
Hill et al.[32]	CABG	£8 368	12 438
Canada			
Bowen et al.[139]	CABG	CAD18 799	13 656
Brophy et al.[140]	CABG (incl. medical fees)	CAD15 025	11 114
		(9 825-17 025)[a]	(7 268-12 594)
Mittmann et al.[149]	CABG	CAD19 618	14 512
Rinfret et al.[152]	CABG (hospital cost and physician fees)	CAD14 402	10 653
Shrive et al.[154]	CABG	CAD32 009	24 332
		(20 750-40 072)[b]	(15 773-30 461)
Sweden			
Ekman et al.[143]	CABG	SEK134 507	12 797
Japan			
Ikeda et al.[146]	Inpatient care CABG		
	1-vessel lesion	¥3 912 033	26 981
	2-vessel lesion	¥4 989 161	34 409
	3-vessel lesion	¥4 255 033	29 346
Switzerland			
Kaiser et al.[147]	CABG	€7 095	7 254
Australia			
Lord et al.[79]	CABG	AUD19 550	12 796
The Netherlands			
Ong et al.[150]	CABG	About €17 170[c]	18 039
Spain			
Russel et al.[153]	CABG	€14 068	16 230
Italy			
Tarricone et al.[155]	CABG	€16 992	18 089
Brazil			
Polanczyk et al.[151]	Elective CABG	R$5 967 or 21 826[d]	5 496 or 20 102
	Non-elective CABG	R$8 950 or 26 214	8 243 or 24 143

CABG: coronary artery bypass graft
*: conversion factor: see table 4.2
[a] range for sensitivity analysis; [b] interquartile range
[c] results were expressed on a per patient basis: 2.3% of events in the BMS group corresponds to a cost of €393 per patient. 0.4% of events in the SES group corresponds to a cost of €69 per patient. The cost of CABG is therefore around €17 087 – €17 250;
[d] depending on which perspective was taken (see table in appendix)

Costs for medical treatment also differ largely when comparing the studies in this review. Faithfully taking aspirin and clopidogrel is a key strategy for preventing blood clots, the so-called dual antiplatelet aggregation therapy. The optimal duration of this combination therapy is unknown, but according to the device leaflets it should be one month for BMS, 3 months for SES and 6 months for PES.[179] Some studies take this difference in antiplatelet treatment duration into account. Although both treatment groups in the Taxus IV trial received 6 months of clopidogrel (300 mg loading dose followed by 75 mg daily), the primary analysis of Bakhai et al. assigned patients in the control group a cost for only 1 month of clopidogrel to reflect as closely as possible standard practice after BMS implantation at the time of the study.[138]

A similar approach was applied in the study of Cohen et al. using data from the SIRIUS trial (Cohen and Bakhai are co-authors from these two studies). Although both treatment groups received 3 months of clopidogrel, patients in the control group were assigned a cost for only 1 month of clopidogrel because this is the predominant practice after BMS implantation.[142] In the study of Ekman et al.[143] the use of clopidogrel is assumed to be 3 months post BMS stenting, and 6 months post Taxus stenting. This is one month for BMS and at least 6 months for PES in the Spanish study from Russell.[153] Finally, in the evaluation of Ong et al.[150] at least 1-month clopidogrel treatment was recommended for patients with BMS and at least 3 months for patients with SES, which was maintained for at least 6 months under certain conditions (multiple SES implantation (>3 stents), total stented length >36 mm, chronic total occlusion, and treatment of bifurcation lesions).

Other studies included equal treatment duration for both BMS and DES. Two Canadian studies included prescription costs of clopidogrel for one year as long-term medication management in this patient population.[149, 152] One UK study included clopidogrel therapy for 4 weeks postdischarge.[32]

4.2.8 Utilities

In our systematic review we detected ten studies performing a cost-utility analysis. Table 4.6 provides an overview of those studies and includes the utility values and sources from which these data are retrieved.

Table 4.6: Utilities applied in economic evaluations

Economic evaluation	Utility values	Source for utility data
Bagust et al.[137]	Annual QALYs lost: Angina: 0.135 (0.122 to 0.148) per PTCA: 0.0056 (0.0051 to 0.0062) per CABG: 0.033 (0.031 to 0.035)	ARTS & SoS[a] trial
Bakhai et al.[138]	A mean quality-adjusted life expectancy for patients with and without repeat revascularization during follow-up (0.78[b] vs 0.86, p<0.001) was applied to the TAXUS-IV study population, along with a short-term disutility "toll" for patients who required bypass surgery.	Stent-PAMI trial
Bowen et al.[139]	EQ-5D utility values observed in the ARTS trial for resp. stent and CABG. Baseline: 0.69 / 0.68 1 month: 0.84 / 0.78 6 months: 0.86 / 0.86 12 months: 0.86 / 0.87 Waiting times (in days) for resp. PCI and CABG: Non-Post MI, no diabetes: 16.32 / 21.97 Non-Post MI, diabetes: 17.76 / 15.53 Post MI, no diabetes: 12.78 / 24.46 Post MI, diabetes: 8.65 / 13.10 One-year QALYs by clinical pathways for respectively No revascularization, PCI with or without stent and CABG: Non-Post MI, no diabetes: 0.860 / 0.819 / 0.804 Non-Post MI, diabetes: 0.860 / 0.820 / 0.801 Post MI, no diabetes: 0.860 / 0.823 / 0.805 Post MI, diabetes: 0.860 / 0.822 / 0.800	ARTS trial
Brophy et al.[140]	QALYs lost: Return of anginal symptoms: 0.013 Traditional balloon angioplasty: 0.04 Primary stenting: 0.02	Yock et al.[180]
Cohen et al.[142]	No details mentioned[c]	Stent-PAMI trial
Ekman et al.[143]	It is assumed that patients live with restenosis for 1 month before undergoing a repeat procedure. Utility weight post repeat procedure: 0.86 Utility weight with restenosis: 0.69 Post Revascularization: (1 x 0.86) = 0.86 QALYs Restenosis and repeat revascularization: ((1/12)x0.69+ (11/12)x0.86)= 0.846 QALYs Utility loss due to:[32] PCI repeat procedure = 0.0035 QALYs CABG repeat procedure =0.012 QALYs	ARTS trial
Hill et al.[32]	Baseline value (asymptomatic CHD): 0.86 Using the ARTS results for surviving post-CABG patients (EQ-5D 0.68 at baseline versus 0.86 at 6 months), we estimate a disutility of 0.012 QALY spread over 13 weeks, compared with 0.0035 QALY for surviving stented patients (based on EQ-5D 0.69 at baseline versus 0.86 at 6 months) spread over 6 weeks.	ARTS trial
Kaiser et al.[147]	Mean EQ-5D scores increased similarly in both groups (DES from 0.84 [SD 0.21] to 0.91 [0.17], p<0.0001; BMS from 0.83 [0.22] to 0.89 [0.20], p=0.004) whereas the mean visual analogue scale increased more in the DES group (from 0.68 [0.23] to 0.75 [0.20], p<0.0001) than in the BMS group (from 0.68 [0.21] to 0.70 [0.20], p=0.21; all Mann-Whitney U test).	BASKET
Lord et al.[79]	Utility weights: 0.77 for patients who experienced an event and 0.85 for patients who experienced no events. Utility weights were varied to 0.80 for patients who required a repeat revascularisation and to 0.86 for patients who required no repeat revascularisation, based on the results of the Stent-PAMI trial.	APPROACH
Shrive et al.[154]	The EQ-5D utility scores were higher among event-free patients than among patients who underwent a second procedure to manage restenosis (overall cohort, 0.85 v. 0.77, p < 0.001).	APPROACH

[a] The authors mentioned data from the SoS trial was obtained through personal communication. No further details or references were mentioned. Therefore, these data could not be checked.
[b] remark: in the original study, this value was 0.80.
[c] Based on the description of quality-of-life adjustments and since Cohen and Bakhai are co-authors of both studies, it is very probably that the same quality-of-life values are used as in the study of Bakhai et al.[138]

Different values are included in the cost-utility analyses. These values are based on trials or databases. In table 4.7 some further information on these sources is given. No details are provided on the SoS trial since these data were included in the study based on personal communication. Brophy et al.[140] based his QoL data on a study of Yock et al.[180] The QALY estimates from the latter study were based on previous studies: recurrence of anginal symptoms: -0.013 (-0.01 to -0.02),[181-184] traditional balloon angioplasty: -0.04 (-0.03 to -0.05),[185] and primary stenting: -0.02 (-0.01 to -0.03).[185] Retrieving these studies showed that these data are again based on older studies. For example, Cohen et al.,[185] mentioned that each year of life with significant angina is valued at 0.7 since previous studies have demonstrated that patients are generally willing to "trade" 1 year of life with severe angina for 0.7 years of perfect life. The authors refer to two studies published in 1981 and 1985.[186, 187] Furthermore, the authors assumed that patients with symptomatic restenosis would have a utility of 0.8 (QALY per year). QoL input from studies referring to others studies, that refer to other studies, which have made assumptions about inputs, etc… should be used with caution.

We also may remark the discrepancy between the baseline QoL value with BMS (0.78) applied in the study of Bakhai et al.[138] (and therefore probably also in the similar study of Cohen et al.[142]) and the original published QoL data (0.80),[188] increasing the QoL difference between BMS and DES and thus favouring the outcome. It is also not clear which value is appointed to the short-term disutility "toll" for patients who required bypass surgery.

Table 4.7: Description population for retrieving utilities

Trial	Population	Utility data
Stent-PAMI trial	Between December 1996 and November 1997, 900 patients were enrolled in the Stent-PAMI trial, a randomized trial to compare the clinical and angiographic outcomes of stenting versus PTCA in patients undergoing direct angioplasty for AMI.[188]	Serial utility assessment during the 1-year follow-up period demonstrated a difference of 0.015 quality-adjusted life years (QALYs) in favor of the stent group (0.85+0.18 versus 0.83+0.19, P=0.27). This difference was largely due to better quality-adjusted life expectancy for those patients who did not require repeat revascularization compared with those who did (0.86+0.18 versus 0.80+0.19 QALYs, P=0.003).[188]
ARTS	The Arterial Revascularization Therapy Study (ARTS) was designed to compare coronary artery bypass grafting (CABG) and stenting for the treatment of patients with multivessel coronary disease (MVD).[189, 190]	Quality of life among surviving patients: stenting group:[189] base line: 0.69±0.20 after intervention: after 1 month: 0.84±0.16 after 6 months: 0.86±0.16 after 12 months: 0.86±0.16 There were no differences in quality of life as assessed by the self-rated EQ-5D questionnaire between 1 and 3 years among patients allocated to stenting or bypass surgery. More specifically, the benefit observed after CABG in specific domains such as "mobility" and "anxiety or depression" at 1 year disappeared by 3 years.[190]
BASKET[147]	Unselected patients, as treated in everyday practice. The Basel stent cost-effectiveness trial (BASKET) included 826 consecutive patients treated with angioplasty and stenting for 1281 de-novo lesions, irrespective of indication for angioplasty. Patients were randomised to one of two DES (Cypher, n=264; Taxus, n=281) or to a cobalt-chromium-based BMS (Vision, n=281)	Mean EQ-5D scores increased similarly in both groups (DES from 0.84 [SD 0.21] to 0.91 [0.17], p<0.0001; BMS from 0.83 [0.22] to 0.89 [0.20], p=0.004) whereas the mean visual analogue scale increased more in the DES group (from 0.68 [0.23] to 0.75 [0.20], p<0.0001) than in the BMS group (from 0.68 [0.21] to 0.70 [0.20], p=0.21; all Mann-Whitney U test).
APPROACH	The APPROACH database, a prospective cohort initiative that captures data for all patients undergoing cardiac catheterization in Alberta. To increase the precision of the estimates of long-term survival after specific events, the authors used an expanded cohort of 8 528 APPROACH patients undergoing conventional stenting in 1995–2000. HRQoL was estimated in 1 954 patients of the APPROACH 1998–2000 cohort from self-reported EuroQol EQ-5D utility scores obtained 1 year after catheterization.	EUROQoL EQ-5D utility scores: 'Event' versus 'Event-free' scores: Overall cohort: 0.77 vs 0.85 According to age: < 65: 0.77 vs 0.86 65–75: 0.79 vs 0.84 > 75: 0.74 vs 0.78 Diabetes mellitus status: No diabetes: 0.78 vs 0.86 Diabetes: 0.72 vs 0.78

APPROACH: Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; ARTS: arterial revascularisation therapies study; Stent-PAMI trial: Stent Primary Angioplasty in Myocardial Infarction trial

Another problem is the discrepancy between populations in several trials for which QoL utilities have been estimated and the BMS/DES study population. In the stent-PAMI trial, the clinical and angiographic outcomes of stenting versus balloon PTCA in patients undergoing direct angioplasty for AMI are compared. Results, however, were reported for patients not requiring repeat revascularization compared with those who did. On the one hand, as mentioned by Tung et al.[44], extrapolating QALY data from a previous trial of BMS for reperfusion therapy for MI (Stent-PAMI) to the SIRIUS or TAXUS cohort of elective stenting, as performed respectively by Cohen et al.[142] and Bakhai et al.[138], may not be applicable. On the other hand, working with the best available data (and mentioning its limitations) is better than having no data at all.

Furthermore, estimates for recurrent angina from ARTS and SoS strictly relate to patients with multivessel disease and may overstate the effect for patients with less complex disease treated percutaneously.[137] Hill et al.[32] also noticed the underlying trial does not indicate how utility is affected by the return of symptoms of a severity sufficient to warrant a second intervention, or how the positive effect of a successful second (or third) procedure compares with the index intervention.

Next, ARTS does not allow us to retrieve QoL data for patients with single-vessel disease since they were excluded from the trial. Nor does ARTS provide results for specific subgroups such as diabetic patients and those with long lesions or small diseased vessels.[32]

The APPROACH database gives QoL data for both 'event' and 'event free' outcomes, categorized according to age and diabetes status. These self-reported EuroQol EQ-5D utility scores were obtained 1 year after catheterization. It is, however, not clear how long differences in utility persist.

Finally, the BASKET trial, including unselected patients as treated in everyday practice, provides data which show that mean EQ-5D scores increased similarly in both DES and BMS groups.

4.2.9 Health improvement

Table 4.8 gives an overview of the modelled health improvements in economic evaluations comparing BMS with DES (PES or SES). The studies of Ekman et al.[143] and Russell et al.[153] use exactly the same input data and are considered as one in this table. The study of Elezi et al.[144] is not shown since it did not use BMS as comparator.

A first problem to compare data is the difference in outcome. Because TVR encompasses not only the original target lesion, but also new lesions developing elsewhere in the "target vessel," it can occur at a higher incidence than TLR in a given population.[149] As mentioned by Mittmann, TVR is an end point that is theoretically more meaningful, because it captures additional events that could be interpreted as complications of the original procedure. In practice, however, most TVR interventions are done on the target lesion, so the numeric difference in number between TLR and TVR tends to be small.[149]

Hill et al. mention all revascularizations should be considered together. They argue it is difficult from routine data sources to distinguish the precise location and nature of an intervention to allow separate analysis and costing. Furthermore, changes in symptoms cannot be allocated between two lesions which are revascularised at the same time (e.g. one undergoing a repeat intervention and the other a separate de novo intervention in another vessel).[32] The authors refer to the 12-month follow-up results from the STRESS I study[191] which show that although TLR is reduced by 32% as a result of stenting, all revascularisations fell by only 17%. This indicates that interventions which benefit disease in specific vessels do not lead to equivalent changes in the number of patients needing repeat treatment since other problems remain to be treated in many of the same patients. Therefore, Hill et al. believe that large reductions in TLR/TVR rates in trials cannot be directly converted to fewer patient admissions in actual clinical practice without some means of estimating the downgrading of these figures.[32]

Table 4.8: Health improvement used in the economic evaluations

Economic evaluation	Time window	Health improvement			
		Outcome	RR (reduction)	BMS baseline risk	DES risk
Bagust et al.[137]	12 months	TVR	SES: RR reduction of 69.8% (95%CI: 59.3% to 77.7%, p<0.001) PES: RR reduction of 55.3% (95%CI: 40.3% to 66.5%, p<0.001)	24.9% 16.3%	SES: 7.5% PES: 7.3%
Bakhai et al.[138]	12 months	TVR	PES: The need for 1 or more repeat TVR procedures was reduced by 60%	16.6%	PES: 6.6%
Bowen et al.[139]	12 months	Repeat revascularization	/	Non-post MI, non diabetes All: 7.2% Long and narrow: 10.9% Long: 9.0% Short: 6.4% Narrow: 10.7% Wide: 5.9% Long or narrow: 9.5% Short and wide: 5.1% Non-post MI, diabetes All: 10.0% Long and narrow: 20.6% Long: 18.6% Short: 6.7% Narrow: 11.9% Wide: 7.9% Long or narrow: 14.3% Short and wide: 5.5% Post MI, non diabetes All: 6.1% Long and narrow: 15.9% Long: 8.1% Short: 4.9% Narrow: 6.1% Wide: 5.5% Long or narrow: 7.5% Short and wide: 4.5% Post MI, diabetes	DES: 5.4% 5.8% 4.7% 5.3% 6.4% 4.8% 5.4% 5.4% DES: 6.7% 6.0% 7.9% 5.2% 5.7% 5.7% 6.9% 5.1% DES: 3.8% 5.8% 3.0% 4.2% 6.0% 2.8% 4.8% 2.8%

				All	12.1%	DES:	5.8%
Brophy et al.[140]	9 months	Repeat revascularization	Repeat revascularization risk reduction: DES: 0.74 (0.48-0.89) (following 1st intervention)	12.8% (9.7 -20%) (following 1st intervention)		/	
Cohen et al.[142]	12 months	Repeat revascularization	Repeat revascularization risk reduction: 52%	28.4%		SES: 13.3%	
Ekman et al.[143] and Russel et al.[153]	12 months	TLR	/	Total population:	15.1%	PES:	4.4%
				Diabetes:	19.6%		7.1%
				Small vessel:	20.6%		5.6%
				Long lesion:	22.1%		5.5%
	24 months	TLR	/	Total population:	17.4%	PES:	5.6%
				Diabetes:	22.0%		8.0%
				Small vessel:	25.4%		6.1%
				Long lesion:	22.4%		8.9%
Greenberg et al.[145]	24 months	TVR	An 80% reduction in TVR with DES is assumed.	14%		/	
Hill et al.[32]	12 months	Repeat revascularization	ARR was mentioned Single-vessel, non-diabetic: 6.0% Two-vessel, non-diabetic: 7.9% Single-vessel, small diameter: 10.0% Single-vessel, long lesion, non-diabetic: 10.1% Single-vessel, long lesion, diabetic: 12.6%				
Ikeda et al.[146]	36 months	Repeat revascularization	PTCA required for revascularization would be 0.224 times in SES implantation versus BMS implantation.	19.2%		SES: 4.3%	
Kaiser et al.[147]	6 months	MACE	DES reduced the rate of major adverse cardiac events by 44% (odds ratio: 0.56; 95%CI: 0.35–0.91, p=0.02)	12.1%		DES: 7.2% SES: 5.7% PES: 8.5%	
		TVR	… mainly due to a lower rate of TVR (0.57; 0.31–1.02), i.e. RRR of 43% on average	7.8%		DES: 4.6% SES: 3.0% PES: 6.0%	
Lord et al.[79]	12 months	TLR	RR: 0.29 (95% CI, 0.20–0.43) for PES. RR: 0.20 (95% CI, 0.13–0.29) for SES.	14.6% 20.5%		PES: 4.3% SES: 4.0%	
Mittmann et al.[149]	12 months	TLR	/	14.2% (Beta (349, 2 107))		4.8% Beta (127, 2 520)	
Ong et al.[150]	12 months	TVR	/	10.4%		SES: 3.65%	
	24 months	TVR		14.7%		SES: 6.4%	
Polanczyk et al.[151]	12 months		Relative risk reduction of 80%.	30% (10% - 50%)		SES: 6% (2% - 15%)	
Rinfret et al.[152]	12 months	Repeat revascularization	The use of SES was associated with an 82% relative	22%		SES: 4%	

			reduction in the need for repeat revascularization.			
Shrive et al.[154]		The probability of a second procedure (catheterization, PCI or CABG)	The relative risk of clinical restenosis was estimated at 0.23.		Repeat catheterization for restenosis: with revascularization procedure: 8.2%; without revasculirization procedure: 12.2%	/
Tarricone et al.[155]	12 months	TLR	Efficacy on TLR:			
			Overall population:			
			Single-vessel disease:			
			Normal:	94%	13.0%	0.72%
			Small vessel:	94%	14.4%	0.83%
			Long lesion:	75%	20.0%	4.9%
			Multivessel disease:	75%	22.3%	5.5%
			Diabetic population:			
			Single-vessel disease:			
			Normal:	94%	15.21%	0.91%
			Small vessel:	94%	16.9%	1.0%
			Long lesion:	68%	26.4%	8.4%
			Multivessel disease:	68%	22.3%	5.8%
Van Hout et al.[156]	12 months	MACE	With angiographic follow-up:		28.8%	SES: 5.8%
			Withouth angiographic follow-up:		16.9%	5.8%
		TLR	With angiographic follow-up:		23.6%	SES: 0.8%
			Withouth angiographic follow-up:		11.8%	0.8%

MACE: major adverse cardiac events; RR: relative risk; TLR: target lesion revascularization; TVR: target vessel revascularization.

Table 4.8 shows that there is a great variation in *relative risk reduction* when comparing the economic evaluations in this review. The lowest risk reduction was seen in the study of Kaiser. Compared with BMS, the use of DES reduced the rate of major adverse cardiac events (MACE) by 44% (odds ratio: 0.56; 95%CI: 0.35–0.91, p=0.02), which was mainly due to a lower rate of TVR (odds ratio: 0.57; 95%CI: 0.31–1.02).[147] We may remark that this study reflected a real-world situation (cfr. patient population and no angiographic follow-up). The highest risk reduction was 94% for certain subpopulations (normal and small-vessel disease in both the overall and diabetic population).[155]

The *baseline risk* of repeat revascularization with BMS also differs greatly among and within studies. The field evaluation study of Bowen et al.[139] shows there is a variation in baseline risk and relative risk reduction (and consequently absolute risk reduction) when comparing different subpopulations, with the highest improvement seen in long and narrow vessels. Looking across studies, especially the studies of Bagust[137] and Cohen[142] included a high baseline risk for TVR of 24.9% and 28.4%, respectively. This was only 7.8% for TVR with BMS, after only 6 months of follow-up, in the study of Kaiser et al.[147] In combination with the relative risk reduction, this results in completely different absolute risk reduction, which drives the cost-effectiveness results. For example, a relative low risk reduction of 52% still results in an absolute risk reduction of about 15% in the study of Cohen due to the high baseline risk of repeat revascularization with BMS. This ARR is even higher in several other studies,[79, 137, 143, 153] whether or not depending on which subpopulation is taken into account. This is in contrast with the absolute risk reduction of 3.2% for DES versus BMS in the study of Kaiser, which even decreases to 1.8% when only looking at PES. If both PES and SES are considered, the relative and absolute risk reductions are in favour of SES.[147, 79, 137, 144] However, no direct comparison between PES and SES was available at that time.

The relatively low baseline risk with BMS for both MACE and TVR is due to a combination of several factors. The *influence of angiographic follow-up* is the most important factor. This is clearly shown in the study of Van Hout et al.[156] The risk probabilities are not changed for SES. The baseline risk with BMS (for both MACE and TLR), however, are about 12 percent lower in absolute numbers without versus with angiographic follow-up. The absolute risk reduction for MACE becomes 11.1% (16.9% minus 5.8%) instead of 23% (28.8% minus 5.8%) and 11% (11.8% minus 0.8%) instead of 22.8% (23.6% minus 0.8%) for TLR. Furthermore, in the APPROACH database (Brophy et al.), the frequency of repeat revascularization was 8.2%, whereas RCTs, with their compulsory protocol angiograms, suggest a 3-fold higher rate.[192] The exact rate of lowering revascularisations which is clinically driven is very uncertain for the other economic evaluations.

Finally, the *follow-up time* may also have an influence on the baseline risk and absolute risk reduction. Restenosis, however, occurs mainly during the first year. After one year, disease progression would become more important. Therefore, the ARR should not increase much further after one year. The studies of Ong,[150] Ekman,[143] and Russel,[153] show that the risk for TVR increases for both the BMS and DES population when comparing input data for 12 and 24 months.

4.3 RESULTS

Table 4.9 presents the results of the economic evaluations included in this overview. For practical reasons, original numbers without conversion factor are provided. Furthermore, the general conclusions of these studies are reproduced.

Table 4.9: results of the economic evaluations included in this overview

Economic evaluation	Cost-effectiveness			
Bagust et al.[137]	DES versus BMS: mean cost per QALY gained			
	For elective surgery risk groups:			
		Number of risk factors		
	0	1	2	3 or 4
SES	£238 900	£179 700	£85 200	£51 600
PES	£324 400	£249 700	£130 200	£87 900
	For non-elective surgery risk groups:			
		Number of risk factors		
	0	1	2	
SES	£133 600	£30 600	-£23 700	
PES	£195 800	£65 700	-£3 000	
Bakhai et al.[138]	PES versus BMS:			
	Overall population: ICER of $4 678 per TVR avoided and $47 798/QALY gained.			
	Patients assigned to clinical follow-up alone: ICER of $760 per TVR avoided and $5 105/QALY gained.			
	Subgroup analysis: cost per TVR avoided			
	Diabetes	Dominant	No diabetes	$9 387
	LAD	$2 764	No LAD	$8 746
	Diameter		Length	
	<2.5mm	Dominant	≤20mm	$6 700
	2.5-3.0mm	$5 089	>20mm	$4 972
	≥3mm	$25 571		
Bowen et al.[139]	DES versus BMS:			
	ICERs of the probabilistic analysis (deterministic result available in appendix):			
		Non-post MI, non diabetes		Non-post MI, diabetes
		CAD/Rev.	CAD/QALY	CAD/Rev.	CAD/QALY
	All	97 832	2 275 668	51 214	1 170 050
	Long and narrow	40 384	893 610	8 405	194 276
	Long	42 616	982 469	11 943	274 002
	Short	159 533	3 731 167	105 641	2 421 431
	Narrow	43 448	1 004 577	25 891	593 503
	Wide	172 933	4 020 399	65 174	1 500 389
	Long or narrow	42 797	995 367	20 232	465 438
	Short and wide	Dominated	Dominated	323 016	7 163 108
		Post MI, non diabetes		Post MI, diabetes	
		CAD/Rev.	CAD/QALY	CAD/Rev.	CAD/QALY
	All	71 189	1 720 737	17 243	429 035
	Long and narrow	10 904	273 498	/	/
	Long	29 896	708 163	/	/
	Short	320 322	7 857 601	/	/
	Narrow	Dominated	Dominated	/	/
	Wide	54 184	1 309 047	/	/
	Long or narrow	65 632	1 569 126	/	/
	Short and wide	83 457	2 045 644	/	/
Brophy et al.[140]	DES versus BMS:				
	DES penetration:	20%	60%	100%	
	Cost per revasc. avoided	CAD7 200	CAD15 000	CAD23 000	
	Cost per QALY	CAD96 523	/	/	
Cohen et al.[142]	SES versus BMS:				
	Overall population: ICER of $1 650 per repeat revascularization event avoided or $27 540 per QALY gained.				
	Subgroup analysis: cost per repeat revascularization avoided				
	Diabetes	$2 376	Diameter		
	No diabetes	$1 973	<2.5mm	Dominant	
	Predicted TLR		2.5-3.0mm	$1 345	
	10-15%	$3 727	>3mm	$6 206	
	15-20%	$5 789	Length		
	20-25%	$509	<15mm	$4 265	
	25-30%	Dominant	15-20mm	$4 459	
			>20mm	Dominant	

Ekman et al.[143]		PES versus BMS:		
		Total population		
	Follow-up:	12 months	24 months	
	Cost per revasc. avoided	€5 126	€3 900	
	Cost per QALY	€257 486	€197 827	
	High-risk group			
	Cost per revasc. avoided	€838	Dominant	
	Cost per QALY	€41 791	Dominant	
Elezi et al.[144]		SES versus PES:		
	SES is dominant compared to PES(for all subgroups: whole study cohort, diabetic and nodiabetic patients, de novo lesions, and restenotic lesions)			
Greenberg et al.[145]		DES versus BMS:		
	The ICER is about $7 000 per repeat revascularization avoided.			
	The ICER is less than $10 000 per repeat revascularization avoided for virtually all diabetic patients and for non-diabetic patients with smaller vessels (reference vessel diameter <3.0 mm) and longer lesions (lesion length >15 mm).			
Hill et al.[32]		DES versus BMS:		
	Single-vessel (SV) disease in function of time from initial procedure			
	Cost per QALY	1 year	£1 099 858	
		2 year	£825 512	
		3 year	£780 442	
		4 year	£771 347	
		5 year	£769 434	
	Simplified model, cost per QALY			
	Number of stents	1 stent	2 stents	3 stents
	SV, non diabetic (ND)	£94 179	£289 239	£484 300
	SV, small diameter	£16 155	£133 191	£250 227
	SV, long lesion, ND	£9 531	£119 942	£230 353
	SV, long lesion, diabetic	-£4 157	£92 567	£189 291
	Two-vessel, ND	/	£195 413	£343 560
Ikeda et al.[146]		SES versus BMS:		
		SES is dominant		
Kaiser et al.[147]		DES versus BMS:		
		DES	SES	PES
	Cost per MACE avoided	€18 311	€19 264	€16 694
	Cost per QALY			
	EQ-5D	€73 283		
	Visual analogue scale	€54 546		
	No specific results provided for subgroups.			
Lord et al.[79]		DES versus BMS:		
		SES	PES	
	Cost per revasc. avoided	AUD3 746	AUD6 117	
	Cost per QALY	AUD46 829	AUD76 467	
Mittmann et al.[149]		DES versus BMS:		
	Cost per TLR avoided:	SES		
	Hospital perspective		CAD12 527 – 16 600	
	Provincial perspective		CAD11 133 – 15 192	
		PES		
	Hospital perspective		CAD26 562 – 29 048	
	Provincial perspective		CAD25 202 – 27 687	
Ong et al.[150]		SES versus BMS:		
	Cost per revasc. avoided			
	1 year follow-up		€29 373 (14 659; 83 884)	
	2 years follow-up		€22 267 (10 737; 65 978)	
Polanczyk et al.[151]		SES versus BMS:		
	Under the “supplementary medical system (SMS)” (health plans and private patients) or under the "public health (SUS)" perspective:			
		SMS	SUS	
	Cost per event avoided	R$27 403	R$47 529	
Rinfret et al.[152]		SES versus BMS:		
	The ICER was CAD11 275 per repeat revascularization avoided.			
Russel et al.[153]		PES versus BMS:		
	Cost per revasc. avoided	Total population	High-risk population	

	1 year follow-up	€811	Cost saving	
	2 years follow-up	€1 568	Cost saving	
Shrive et al.[154]	SES versus BMS:			
	Cost per QALY:			
	Overall:	CAD58 721	Age, yr	
	Diabetes status		< 65	CAD72 464
	No diabetes	CAD63 383	65–75	CAD47 441
	Diabetes	CAD44 135	> 75	CAD40 129
Tarricone et al.[155]	SES versus BMS: SES is a Dominant treatment strategy.			
Van Hout et al.[156]	SES versus BMS			
	Costs per MACE-free survivor were estimated at €234 with an upper 95% limit of €5 679.			

LAD: left anterior descending coronary artery; MACE: major adverse cardiac events; revasc.: revascularization

In the study of Bagust et al.[137] (UK), results depend on the number of risk factors present. The risk factors for elective treatment are: calcification, angulation >45°, restenotic lesion, and triple vessel disease. For non-elective treatment this is: vessel diameter <2mm and prior CABG. In table 4.9 mean results are presented. DES is only cost effective (<£30 000/QALY gained), and even cost saving, in the non-elective surgery risk group with both vessel diameter <2mm and prior CABG. In the original paper, results are also provided in function of the number of stents used (1, 2 or 3). In that case, cost-effectiveness is achieved for elective treatment only if a single DES is implanted in a patient with two or more risk factors. For non-elective treatment, a single DES is cost-effective if at least one risk factor is present. Up to two (PES) or three (SES) stents is cost effective if both risk factors apply. The authors concluded that considering the UK cost-effectiveness threshold of £30 000 per QALY, the use of DES would only be cost effective for about 4% of the patients, despite the evident effectiveness of DES in preventing restenosis.

Bakhai et al.[138] (US) presented results for both the overall population and for patients managed according to standard clinical practice without mandatory angiographic follow-up. In the latter, the cost per QALY was $5 105 whereas this was only $47 798 in the overall population. The 1-year follow-up cost offset with PES in the nonangiographic cohort was greater than that observed in the angiographic cohort ($1 894 per patient vs. $1 104 per patient). The authors tried to explain this counterintuitive results by the possibility that repeat revascularization procedures in the nonangiographic cohort were more challenging and resource-intensive compared with those procedures driven by angiographic findings alone. In their subgroup analysis, PES were economically dominant in patients with reference vessel diameters <2.5 mm and in patients with diabetes mellitus. The authors stated that although the cost savings were insufficient to fully offset the higher initial treatment costs, the overall results of their economic analysis suggest that use of PES may be reasonably cost-effective from a societal perspective over a broad range of patient and lesion characteristics.[138]

Another study in the US compared SES versus BMS.[142] Two co-authors, Cohen and Bakhai, are the principal authors of this cost-effectiveness study and are also co-authors of the previous mentioned study comparing PES versus BMS.[138] For SES versus BMS, the cost per repeat revascularisation event avoided was $1 650 or $27 540 per QALY gained and SES were economically dominant in patients with reference vessel diameters <2.5 mm, lesion lengths >20 mm and predicted TLR 25-30%. Basically the same conclusion as in the previous mentioned analysis was drawn. Although use of SES was not cost-saving compared with BMS implantation, for patients undergoing PCI of complex coronary stenoses, their use appears to be reasonably cost-effective within the context of the US healthcare system.[142]

We also first discuss the results of Greenberg et al.[145] (US) since the second and third author of this study are Bakhai and Cohen and, not surprisingly, results and conclusions are similar to the previous two studies. Compared with BMS, DES are cost saving for only a modest proportion of the current PCI population in the United States. Over a two-year follow-up period, the ICER of DES versus BMS is about $7 000 per repeat revascularization avoided. They also suggest that DES are economically attractive (i.e., cost-effectiveness ratio <$10 000 per repeat revascularization avoided) for virtually all-diabetic patients and for non-diabetic patients with smaller vessels (reference vessel diameter <3.0 mm) and longer lesions (lesion length >15 mm).[145]

Bowen et al.[139] (Canada) presented results for 22 subgroups. The primary cost-effectiveness outcome was the incremental cost per QALY gained of DES versus BMS. The secondary outcome was the incremental cost per revascularization avoided. In both the probabilistic and deterministic analysis, the ICER was high for all 22 cohorts with the most favourable ratio being CAD194 276 per QALY gained in the probabilistic analysis for the non-post MI diabetes, long and narrow lesions cohort. In terms of incremental cost per revascularization avoided, the most cost effective result was CAD8 405 per revacularization procedure averted for the same cohort.

Brophy and Erickson[140] (Canada) calculated, in the base scenario with 20% of DES penetration (i.e. for high-risk patients) and a RR of selected patients of 2.67 versus the average risk of restenosis, the average cost is CAD7 200 per avoided procedure. The cost per revascularization avoided would increase to about CAD23 000 at 100% DES penetration. As mentioned by the authors, this is a classic example of diminishing returns from increased implementation of a more effective, yet more expensive health technology if a subgroup of high-risk patients can be selected for limited implementation of this technology.[140] The cost per QALY gained is estimated at CAD96 523 in the base scenario. The authors conclude that the universal introduction of DES would greatly increase expenditures with relatively limited benefits. At the present stent costs, there appears to be little cost-effectiveness justification for high rates of DES implementation, due to low baseline restenosis rates with BMS and diminishing returns with increased use of DES.

The Swedish study of Ekman et al.[143] distinguished results for the overall population and a high risk subgroup, defined as patients with medically treated diabetes, small vessels (<2.5 mm), and long lesions (>20 mm). For the total population, PES was not cost effective with a cost per QALY of about €257 000 and €198 000 using one- or two-year follow-up data respectively. For the high risk subgroup, the ICER is €41 791 per QALY with one year follow-up data and became dominant with two-year follow-up data. The authors conclude that the Taxus stent is cost-effective in high risk patients, particularly at 24 months and less cost-effective for the general population.

In contrast to all other analyses, the study of Elezi et al.[144] (Germany) evaluates the cost of percutaneous coronary interventions with use of sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES). According to this study, the use of SES is economically more attractive than PES in patients with coronary artery disease presenting with high clinical and angiographic risk profiles.[144]

In the UK study of Hill et al.[32] ICERs were expressed as cost per QALY gained. For single-vessel disease, DES was not cost effective versus BMS with an ICER between £1 100 000 and £769 000 changing the time from initial procedure between 1 and 5 years, respectively. The authors also constructed a simplified model since the comparison of DES and BMS for single-vessel disease does not involve any question of mortality. Results were estimated for five subgroups: 1) single-vessel, non-diabetic; 2) single-vessel, small diameter; 3) single-vessel, long lesion, non-diabetic, 4) single-vessel, long lesion, diabetic; and 5) two-vessel, non-diabetic patients. If two or more stents were implanted, the best ICER was obtained for the 'single-vessel, long lesion and diabetic' subgroup (£92 500/QALY) and could be considered as not cost effective. If only one stent was implanted, the ICER was below £20 000 for the second (£16 150/QALY) and third (£9 500/QALY) subgroup and even cost-saving for the fourth subgroup.

The authors conclude that the use of DES for elective treatment of uncomplicated single-vessel disease cannot be justified since the claimed reduction in the need for repeat interventions has not been shown to result in more than very minor and uncertain utility gains, but certainly incur substantial additional net treatment costs. DES might be considered cost-effective if one or more of the following options apply: the additional cost of DES (compared with ordinary stents) was substantially reduced, the outcome benefits from the use of DES are much improved, the use of DES is targeted on the subgroups of patients with the highest risks of requiring reintervention.[32]

In the Japanese study of Ikeda et al.[146], SES was dominant in comparison with BMS.

In the Swiss study of Kaiser et al.[147] the ICER of DES compared with BMS to avoid one major event was €18 311. This cost-effectiveness ratio was similar for Cypher versus BMS (€19 264) and for Taxus versus BMS (€16 694). Costs per QALY gained were more than €50 000 when calculated from the EQ-5D index (€73 283) or the visual analogue scale (€54 546). Subgroup analyses of parameters predicting MACE regarding cost-effectiveness ratios indicate that DES might be cost-effective in high-risk patients such as: three-vessel disease, age older than 65 years, more than one segment treated, small stent sizes, or stent length greater than 20 mm. The authors conclude that the use of stents could be restricted to patients in such high-risk groups.[147]

The Australian study by Lord et al.[79] evaluated both SES and PES versus BMS. The cost per revascularisation avoided by using DES was AUD3 750–AUD6 100, with an estimated cost per QALY gained of AUD46 829–AUD76 467 for respectively SES and PES. The authors state that DES are cost-effective if a cost of AUD3 750–AUD6 100 is considered acceptable to avoid revascularisation of the target lesion.

The Canadian study of Mittmann et al.[149] calculated results for both SES and PES versus BMS. The analysis from a hospital perspective included acquisition costs for stents and drugs, costs for hospitalization (including the costs of repeat vascularization) and costs for rehabilitation. The analysis from a provincial payer perspective included all these costs, plus physician fees and charges for laboratory and diagnostic testing. The cost per TLR avoided ranged between CAD11 133 and CAD16 600 for SES and between CAD25 202 and CAD29 048 for PES. However, in conclusion, the authors mention there is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective in a Canadian context.

Ong et al.[150] (the Netherlands) performed their economic evaluation on the RESEARCH (Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry. This is a single-centre registry conducted with the main purpose of evaluating the safety and efficacy of SES implantation for patients treated in daily practice. Based on their analysis, the ICER per TVR avoided was €29 373 (14 659; 83 884) at 1 year, and €22 267 (10 737; 65 978) at 2 years. The authors conclude the use of SES, while significantly beneficial in reducing the need for repeat revascularization, was more expensive and not cost-effective in the RESEARCH registry at either 1 or 2-years when compared with BMS.

In the Brazilian study,[151] the cost effectiveness was calculated from both the "supplementary medical system (SMS)" (health plans and private patients) and the public health (SUS) system. The ICER was respectively R$27 403 and R$47 529 per event avoided in one year. In their conclusions, the authors mention the cost-effectiveness ratios for SES were elevated.

Rinfret et al.[152] (Canada) estimated the cost effectiveness of SES versus BMS for high-risk patients with single long (15-32mm in length) de novo lesions in small (2.5-3.0mm in diameter) coronary arteries. The ICER was CAD11 275 per repeat revascularization avoided. The authors suggest this is borderline cost effective compared with the implicit willingness-to-pay (WTP) of CAD12 551 for such health benefit in Canada. The societal WTP to avoid a repeat revascularization procedure in Canada was based on the ICER of BMS versus conventional balloon angioplasty. They conclude the ICER for SES compares favorably with the currently accepted comparator, i.e. BMS, to reduce coronary restenosis - at least for higher risk patients undergoing single-vessel revascularization.

The analysis of Russell et al.[153] (Spain) considers the general patient population and a high-risk subpopulation (medically treated diabetic patients, small vessels (<2.5 mm), long lesions (>20 mm)). The cost for each repeat revascularization avoided due to the use of PES is calculated as €1 568 at 12 months and €811 at 24 months. In the high-risk subpopulation, PES was overall cost saving as compared to BMS both at 12 months and 24 months. The authors concluded the cost-effectiveness relationship could be acceptable in the general patient population and is dominant in the high-risk subpopulation.[153]

Shrive et al.[154] (Canada) found that SES use was associated with a cost per QALY gained of CAD58 721 and that SES use was more cost-effective in patients with diabetes (CAD44 135/QALY gained) and in those >75 years of age (CAD40 129/QALY gained). For patients <65 years of age and those without diabetes, SES use was substantially less cost effective (CAD72 464 and CAD63 383/QALY gained, respectively). The authors concluded that the use of SES is associated with a cost per QALY that is similar to or higher than that of other accepted medical therapies and argued that DES might be economically more attractive for patients at higher risk of restenosis or death if a second revascularization procedure were to be required.

In the Italian study of Tarricone et al.[155], the incremental costs of SES versus BMS are all negative values and SES is always considered as a dominant strategy. Comparisons with other study results are nevertheless meaningless since this study did not take into account the difference in acquisition costs of SES versus BMS. The argument of the authors is that the Italian Health Care System did not differentiate between both stent types. In contrast, all other studies included an incremental cost for DES, even though the health care system did not make this difference (yet).

In the Dutch study of Van Hout et al.[156] costs per MACE-free survivor were estimated at €234 with an upper 95% limit of €5 679. Authors suggest this is an attractive balance between costs and effects for SES in the treatment of single native de novo coronary lesions.

Having a first look at these results, it is noteworthy that results are very diverse from being cost saving to not cost-effective at all. Most of the times, the results of studies expressing results as cost per QALY gained indicate that DES are not cost effective for the overall population. For high risk subgroups such as diabetics and patients with small vessel disease and/or long lesions, results are more favourable and sometimes even dominant. A lot of studies also express results in a disease-specific metric such as cost per TVR avoided. With respect to the question whether the technology offers value for money, it is difficult to interpret these results.

Finally, results were most of the times more favourable for SES than for PES (if both were included in the same analysis), more favourable (and sometimes even cost saving) for high risk subgroups (e.g. diabetics, small vessel disease: long lesions), better if DES penetration was lower (i.e. restricted to high-risk patients), better when less stents were implanted, and (with the exception of one study) improved with longer follow-up time.

4.4 DISCUSSION

In the following part we discuss the sensitivity of results towards the input variables. Next, results of threshold approaches applied in several economic evaluations to reach cost neutrality are presented. Furthermore, the problem with the WTP value is discussed. We also talk about the possible bias in the interpretation of results and formulation of conclusions due to possible conflicts of interest. Finally, we mention the transferability problem of results.

4.4.1 Sensitivity analysis

Most of the studies also performed sensitivity analysis. Only one study applied multivariable probabilistic sensitivity analysis.[140] This is theoretically the preferred method compared to one- or two-way sensitivity analysis since variables are not solely uncertain at the same time. In their study, however, the authors always applied triangular distributions from the base case value to extreme values, while, for example, beta distributions for probabilities are preferable.

Not surprisingly, one of the main determinants of cost effectiveness is the price premium for DES compared with that for BMS.[79, 154, 137, 143, 153, 151] A smaller difference in stent prices results in more cost effective outcomes. On the cost side, other variables which have a relatively important impact on the outcomes are the cost of hospitalization for repeat revascularization,[138, 151] the number of stents per procedure,[140, 79] and the duration of clopidogrel treatment.[142, 138, 143, 153] Results are more favourable with higher costs for repeat procedures, lower number of stents used and a lower difference (or even no difference) in the duration of clopidogrel treatment between the DES and BMS group.

On the effectiveness side, results are mainly sensitive to the baseline revascularization rate with BMS and the effectiveness of DES.[140, 79, 154, 143, 153, 151] One study, expressing the results in costs per QALY gained, also mentioned that the results are sensitive to the disutility and waiting time with restenosis.[143]

The impact of this uncertainty on the outcome and conclusions are clearly important when looking at some results of these sensitivity analyses. For example, in the study of Lord et al.,[79] results are sensitive to changes in estimates of true effects in clinical practice, market price and number of stents used per patient and varied between being cost-saving to costing AUD25 150 per revascularisation avoided or AUD314 385 per QALY gained. Another example, in the study of Cohen et al.,[142] if patients in both the sirolimus and control groups would be treated with 1 year of postprocedure clopidogrel, use of SES was projected to be cost-saving over the 1-year follow-up period instead of an ICER of $1 650 per repeat revascularization event avoided or $27 540 per QALY gained.

4.4.2 Threshold analysis: cost-neutrality

Several studies performed a threshold analysis to calculate the price of DES to reach cost-neutrality. This makes sense since the price difference between DES and BMS is one of the main determinants of results and because this factor can be manipulated by industry. Studies concluding DES are a cost-saving strategy compared to BMS did not perform such an analysis since the price premium is already justifiable.

A general formula, which approaches the break-even price, is the following:

$$\text{Break - even price DES} = \text{price BMS} + \frac{\text{ARR repeat procedure} \times \text{cost repeat procedure}}{\text{number of stents}}$$

Changing probabilities for the type of repeat PCI (e.g. more DES in the repeat procedure if DES was implanted in the initial procedure), or other aspects, may result in slightly different break-even prices than with applying this formula. It is clear that a higher break-even price for DES is acquired if 1) the price of BMS is high; 2) the absolute risk reduction, which drives cost-effectiveness, is high; 3) the cost of repeat procedures is high; and 4) the number of stents used is low.

Very different price premiums were calculated. According to the study of Bagust et al.[137], for more than 50% usage of SES, the price premium should be less than £146 and for 90% usage no more than £80. For PES the price premiums are even lower. In a Canadian study, the investigators also calculated the price at which DES use would be cost neutral assuming different DES penetration rates and the cost for BMS to be CAD700. With a 20% use in patients at highest risk, the break-even cost for DES would be CAD1 663; at 60%, it would be CAD1 266; and at 100%, it would be CAD1 161 (instead of CAD2 600).[140] Comparable price premiums were found in another Canadian study. With a stent/lesion ratio of 1.5, the cost of the SES would have to fall below CAD1 147 (with a BMS cost of CAD500) to achieve cost savings. Assuming 1.2 stents per lesion, the SES price has to fall below CAD1 309 to save money.[152] A Dutch study calculated that, at a price of €692 per BMS, the cost neutral price for the DES would be €1 023 with the 1-year results and €1 069 at 2 years. Given a BMS price of €400, which would not be unreasonable according to the authors, a DES would have to fall to €779 to be cost-neutral.[150]

In contrast to other studies, Tarricone et al.[155] did not calculate the break-even price for the SES but the break-even charge for the procedure. i.e., how much the reimbursement value of SES-based revascularization has to increase to cover the extra hospital costs by the use of SES. The break-even additional charge was €1 371 for overall population and €1 404 for diabetics.

Next to these studies included in our review, several other studies, which did not publish cost-effectiveness results, performed threshold analysis. In the study of Oliva et al.[158] the value required for the new stent to avoid increasing the overall cost estimate of the conventional stent would be €1 448 instead of €2 000, whereas a BMS costs €1 000. In the Australian study of Ward[159] DES will only be cost neutral for 'high risk' lesions when the premium for DES reduces to AUD617 (instead of AUD1 500) and for all lesions at AUD452. 'High Risk' lesions were defined as those in diabetic patients, saphenous vein grafts, small vessels ($\leq$2.5mm diameter), long lesions ($\geq$25mm in length), ostial lesions or instent restenotic lesions. We have to remark that in this analysis TLR in patients receiving DES was assumed to be 0%, which is very optimistic. Finally, Galanaud et al.[193] calculated the break-even price of SES ranged from €1 291 to €1 489 in France (retail price, €2 100), €2 028 in the Netherlands (retail price, €2 300), and €2 708 in the United States (retail price, €3 150).

Several studies also calculated the price to reach a certain threshold expressed as cost per revascularization event avoided. However, we have to remark we do not have accepted thresholds for the value of a revascularization event avoided. Therefore, we judge these threshold analyses as less meaningful.

In conclusion, very different price premiums are calculated. Whereas several studies already indicated DES would be cost saving with prices available at the moment of their analysis, other studies calculate very small price premiums to reach cost neutrality.

4.4.3 Willingness to pay

There is no proof that DES will alter mortality or that preventing restenosis prolongs life. As a result, assessment of cost-effectiveness expressed as cost per LYG is precluded. Results could be expressed as costs per QALYs. However, DES would only be associated with a very short-term utility improvement. As mentioned before, due to this limitation, several studies have used a disease-specific cost-effectiveness outcome, i.e. cost per repeat revascularization avoided. The main problem, however, is that this surrogate end point is specific to the field of coronary revascularization and cannot be compared with cost-effectiveness ratios for other conditions.[157] Furthermore, we do not have accepted thresholds for the value of a revascularization event avoided.

Several authors have tried to solve this problem by calculating how much society is prepared to pay to prevent repeat revascularization.

Greenberg, Bakhai, Neumann and Cohen[194] used a contingent valuation approach to evaluate the willingness to pay (WTP) among participants in two large clinical trials evaluating new PCI devices. The baseline scenario described a 30% probability of repeat revascularization following the initial procedure. Patients were asked to indicate, using a close-ended (referendum) question, their out of pocket WTP for an improved treatment that would reduce this risk. Three different prices ($500, $1000, and $1500) and three levels of absolute risk reduction (10, 20, and 30%) were randomly varied creating nine sub-samples of patients. 1642 patients completed the WTP question. The WTP medians for the 10 and 20% risk reductions were $273 and $366, respectively. The median WTP for the 30% risk reduction was significantly higher at $1 162 ($P < 0.001$). Higher household income (OR = 1.57,$P < 0.001$) was independently associated with a higher WTP. The authors concluded that avoidance of coronary restenosis, although short-lived, may have considerable value to patients undergoing PCI and that these findings may have important implications for emerging technologies such as DES.[194]

However, in other publications, these authors use a much higher acceptability threshold. According to Greenberg, it appears that most technologies with C/E ratios <$10 000 per repeat revascularization procedure avoided (e.g., brachytherapy, routine coronary stenting) have been widely adopted within the U.S. health care system and are currently reimbursed by most third-party payers. Therefore, they suggest that a C/E ratio <$10 000 per repeat revascularization is a reasonable threshold for cost-effectiveness of treatments that reduce coronary restenosis.[157]

In a study of Rinfret et al.,[152] in which Cohen was the second author, one of the objectives of the study was to evaluate the societal WTP to avoid a repeat revascularization procedure in Canada based on the ICER of BMS versus conventional balloon angioplasty. According to their calculations, this was associated with an ICER of about CAD12 500 per repeat revascularization avoided. Given the widespread adoption of stenting in current practice, the authors believe that this ratio represents a reasonable approximation of the amount of money the Canadian public healthcare system is currently WTP for such a health benefit (the authors suggest this may be considered as a form of 'revealed preference').[152]

We have to be very careful with such an approach. First of all, the discrepancy between the WTP of $1 162 for a 30% absolute risk reduction (with a baseline scenario with a 30% probability of repeat revascularization following the initial procedure) and the suggested WTP of $10 000 per repeat revascularization avoided has never been explained by the authors. Furthermore, a comparison with other established (and reimbursed) technologies that can prevent coronary restenosis has been suggested to serve as a useful benchmark.[145] Reimbursing a technology, however, does not automatically mean this technology is cost effective. Economic considerations, especially in the past, have not always been taken into account by decision makers. Standard metrics such as costs per LYG or per QALY gained remain preferable to support decisions. Conclusions based on comparisons with other 'widely adopted technologies' or 'reimbursement decisions of the past' should be regarded with caution. Following these arguments, reimbursing non cost effective technologies in the past could lead to the reimbursement of non cost effective technologies in the present.

4.4.4 Conflicts of interest

Based on a pooled analysis comparing statins versus no treatment for the prevention of cardiovascular disease, Franco et al.[195] suggested conflict of interest to be an explanatory variable for more favourable outcomes of economic evaluations performed by industry. Also for DES, authors have argued several studies funded by stent manufacturers have methodologic weaknesses, including interpretive biases due to conflicts of interest with industry.[44]

Assessing the validity of any model assumptions remains primordial. For example, the number of stents used per procedure is on average 1.4,[154] 1.5,[79] 1.62,[146] 1.7,[140] 1.9[147], between 1.23 and 2.26 according to lesion characteristics,[139] or respectively 1, 2 or 3[32, 137] in studies not sponsored by industry. This was on average between 1.02 and 1.4 in more than half of the studies sponsored by industry.[142, 145, 155, 156, 138, 143, 144]

Another study sponsored by industry assumed 1.2 stents for single vessel disease and 2.6 for multi-vessel disease.[155] However, for the latter, only 1.2 stents were SES and the remaining 1.4 BMS resulting in more favourable outcomes for the calculated break-even charge for the procedure. Finally, several studies sponsored by industry also performed scenario analysis assuming the mean number of stents per patient decreases due to the availability of longer stents.[142, 152] However, an opposite scenario, in which this average number of stents increases due to the treatment of more complex lesions, is not discussed.

Looking at the conclusions, results of industry-sponsored studies are rather more optimistic than results of studies not mentioning conflict of interest. In the latter group, only one study concludes SES is a cost-saving option as compared with BMS implantation within the context of the Japanese healthcare system.[146] Another study mentions the use of DES could be restricted to patients in high-risk groups.[147] One study leaves the debate open by declaring that DES are cost-effective if a cost of AUD3 700 – 6 200 is considered acceptable to avoid revascularisation of the target lesion.[79] According to another non-industry sponsored study, the use of SES is associated with a cost per QALY that is similar to or higher than that of other accepted medical forms of therapy and is associated with a significant incremental cost.[154] The remaining non-industry sponsored studies are not favourable at all for DES:

- The most favourable cost-effectiveness ratio for DES compared to BMS was CAD194 276/QALY for non-post MI, diabetes patients with long and narrow lesions.
- DES would only be cost effective for about 4% of the patients, despite the evident effectiveness of DES in preventing restenosis;[137]
- there appears to be little cost-effectiveness justification for high rates of DES implementation;[140] and
- DES may not generally be considered a cost-effective alternative to BMS in single-vessel disease.[32]

Whereas the majority of conclusions are not very favourable in non-industry sponsored studies, the tendency is more favourable in studies mentioning conflict of interest. In only one analysis, based on the RESEARCH registry, the use of SES was more expensive and not cost-effective when compared with BMS.[150] Another study mentions there is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective in a Canadian context.[149] Polanczyk et al.[151] mention the cost-effectiveness ratios are elevated. All other study results have a relatively positive connotation:

- PES may be reasonably cost-effective over a broad range of patient and lesion characteristics;[138]
- the use of SES appears to be reasonably cost-effective within the context of the US healthcare system;[142]
- PES is cost-effective in high risk patients. Although it may be less cost-effective for the general population, there is still a substantial offset of initial procedure costs;[143]
- DES will be reasonably cost effective for the majority of patients and even cost saving for a large subgroup of patients;[145]

- the ICER for SES compares favorably with the currently accepted comparator, i.e. BMS, to reduce coronary restenosis - at least for higher risk patients undergoing single-vessel revascularization;[152]
- given the decrease in the number of repeat revascularizations with PES, the cost-effectiveness relationship could be acceptable in the general patient population and is dominant in the high-risk subpopulation;[153]
- SES is a cost-saving strategy in the perspective of the Italian Health Care System that could therefore support the introduction of the new technology by reimbursing about 80% of its current incremental acquisition cost;[155] and finally,
- the one year data from RAVEL suggest an attractive balance between costs and effects for SES in the treatment of single native de novo coronary lesions.[156]

The possible bias in conclusions and/or recommendations may be due to different forms of bias such as interpretive bias or publication bias. There is, however, no hard evidence to prove this. Conclusions, however, should be critically appraised. In the first place, the validity of input variables to the real-world situation should be checked.

4.4.5 Transferability

There may be a number of concerns about direct application of the results of the included studies in this review. The economic evaluations are performed in the UK (2), US (3), Canada (5), the Netherlands (2), Sweden, Germany, Switzerland, Spain, Italy, Australia, Brazil and Japan. The health care systems and costs in these countries may not reflect the Belgian situation. Differences in intervention costs, stent prices, clinical practice, etc. between countries may limit transferability of study results to the Belgian context.

Furthermore, due to the contradictory results of the studies, it is not possible to make clear conclusions based on this review. Both positive and negative conclusions were drawn. It is not clear at all which study would best reflect real world Belgian practice or Belgian costs.

4.5 CONCLUSION

With respect to cost-utility analyses, both positive and negative conclusions were drawn. However, as mentioned by Hill et al., "*the projected utility gain is extremely small since it arises only from reduced HRQoL in patients requiring repeat revascularisation in a short period before and after the additional intervention. Without any confirmed survival benefit, the identifiable QALY gain achievable is very limited. … Claims to large QALY benefits, by avoidance of adverse events and in the absence of mortality gains, are likely to be unfounded.*"[32] According to non-industry sponsored studies DES was not considered a cost-effective alternative to BMS for the whole population. Only for high-risk populations, defined by diabetes status, vessel diameter and lesion length, DES could be cost effective. However, an economic evaluation using input data from a field evaluation and reflecting real world conditions did not reach favourable cost-effectiveness levels for 22 analysed subgroups, including high-risk subgroups.

Results expressed as cost per repeat revascularization avoided or other similar outcomes are difficult to interpret. It is not clear how much value society attaches to the avoidance of a repeat revascularization. Whereas the same criticism applies to a general cost-effectiveness threshold, the preference should be given to more generally accepted metrics such as cost per LYG and cost per QALY gained. Trying to convince policy makers that DES is cost-effective by comparing with disease specific thresholds diverts the attention of real health related QoL gains.

In general, while DES significantly reduces the need for repeat revascularization, most studies suggest that the resulting savings only partially offset the higher initial cost of the stent procedure. DES are considered too expensive to be used in all patients undergoing PCI. Conclusions may alter for specific subgroups of high-risk patients.

Results were most sensitive to the DES versus BMS price difference, number of stents used, relative benefit of DES versus BMS, and cost of repeat procedures.

Key points

Based on the results of the economic literature review:

- **Although DES significantly reduce the need for repeat revascularization compared to BMS, DES are not cost saving.**
- **DES have no impact on mortality and their effect on quality of life is very modest. As a result, DES are associated with a high cost per QALY gained.**
- **Some studies use the cost per avoided revascularization as an alternative to QALYs. But, there is no consensus on society's willingness to pay for avoiding repeat revascularizations. As a result, results expressed in such a metric are more difficult to interpret.**
- **The current economic analyses do no consider cost of potential adverse effects such as Stent Thrombosis (ST) mainly because no reliable data were available**
- **For the general population, based on the 'cost/QALY gained' metric, DES are not considered cost effective.**
- **DES might be cost-effective for high-risk populations based on diabetic status, vessel diameter and lesion length.**
- **Cost-effectiveness results using clinically driven revascularisation rates make results less favourable.**
- **Cost-effectiveness results might improve by decreasing the price difference between DES and BMS.**

5 ANALYSIS OF BELGIAN PCI REGISTRY COST AND OUTCOME DATA

The purpose of this chapter is to give a detailed description of the Belgian cost data that are used in the economic evaluation in the next chapter. Registration data of the Belgian Working Group of Interventional Cardiology (BWGIC) were linked with patient reimbursement data of the different sickness funds obtained from the Intermutualistisch Agentschap (IMA). The use and matching of the two data sources was approved by the Belgian privacy commission.[196] Paragraphs 5.1, 5.2 and 5.3 give a description of the data sources, the matching procedure and methodology. Overviews are presented in figures 5.1 and 5.2, while paragraph 5.4 describes the results.

We analysed current use in 2004 of PCI and the use of DES and BMS in Belgium, with a main emphasis on costs involved. For this the data of the BWGIC registry for the year 2004 had to be linked to the reimbursement cost data from social security. The aim is to collect cost data from 1 year previous till 1 year past the index PCI date. Those data are intended to include hospital stays, ambulatory care and medication. Additionally, vital statistics are collected until 1 year after the index PCI.

5.1 DESCRIPTION OF DATA SOURCES

5.1.1 IMA databases

IMA selected patients undergoing a PCI in 2004 on the basis of the nomenclature codes 589013-589024 for this intervention.[b] IMA has detailed information on medical costs. Information on reimbursements, co-payments and supplements of all reimbursed medical interventions (as specified in the nomenclature) is available. In this analysis we consider the first PCI in 2004 as the index-PCI. A first database contains cost information from 365 days before until 365 days after the day of the index PCI. Data are aggregated per month and for aggregates of medical interventions. Additional databases with information on the consumption of medicines is available on ATC-code level (Farmanet data and hospital database) and with information on medical consumption related to the PCI on nomenclature code level. Additional data are also available per hospital stay: for the hospitalization related to the index-PCI, and for repeat-hospitalizations within one year after the index-PCI. We will refer to the hospitalization related to the index-PCI as the index-hospitalization.

Apart from the cost databases, IMA also has a database with information of population characteristics such as age, gender, insurance status, place of residence, vital status (month of death) etc.

5.1.2 BWGIC DATABASE

The PCI-database of the BWGIC contains detailed clinical information on all registered PCI-interventions from 1st of November 2003 onward. Information relates to medical conditions before the intervention, details with respect to the intervention (location of the stenosis or narrowing, number and type of stents used, complications). This database captures almost all Belgian PCIs as registration is a prerequisite for reimbursement of the PCI by the RIZIV. The available dataset was up-to-date until the 31st of October 2005. The database is an administrative database; the validity of the data as registered by the centers is not checked.

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b The nomenclature code is described as follows: 'Percutane endovasculaire dilatatie met of zonder plaatsing van stent(s) onder controle door medische beeldvorming van een vernauwing en/of occlusie van een kransslagader, inclusief de manipulaties en controles tijdens de behandeling en al het gebruikte materieel, met uitsluiting van de dilatatiecatheter, de farmaca en de contrastmiddelen voor het geheel van de kransslagaders'.

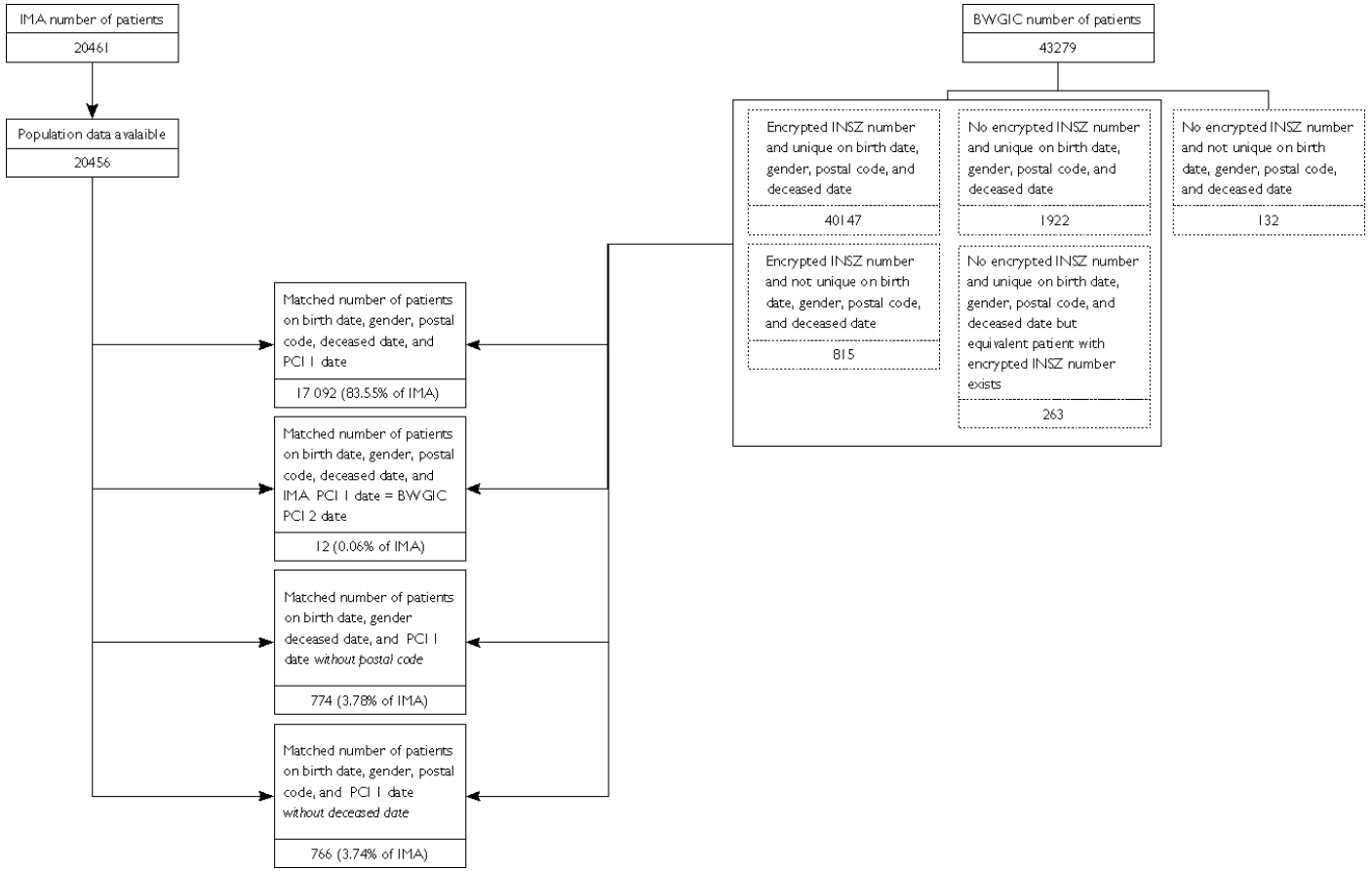
A total of 48 482 *PCIs* have been registered in the period between November 1st 2003 and October 31 2005; including 24 827 PCIs in the year 2004.

The total number of *patients* undergoing at least one PCI in the total period is 43 279. The number of patients undergoing a PCI in 2004 is 21 308.

5.2 DATA MATCHING PROCEDURE

In the reimbursement data from 2004, the nomenclature code for PCI was used in 20 461 unique patients, and for virtually all (20 456) we also obtained the population data. Since no unique identical patient identifier is available in both databases, those patients were coupled through probabilistic matching to the data from the BWGIC database with PCIs performed between Nov 2003 and Nov 2005. Through this process data from 18 644 patients (91% of PCIs performed in 2004) could be uniquely linked. Figure 5.1 shows the details of this data matching process.

Figure 5.1: Data matching results



5.3 METHODOLOGY

5.3.1 Patient selection

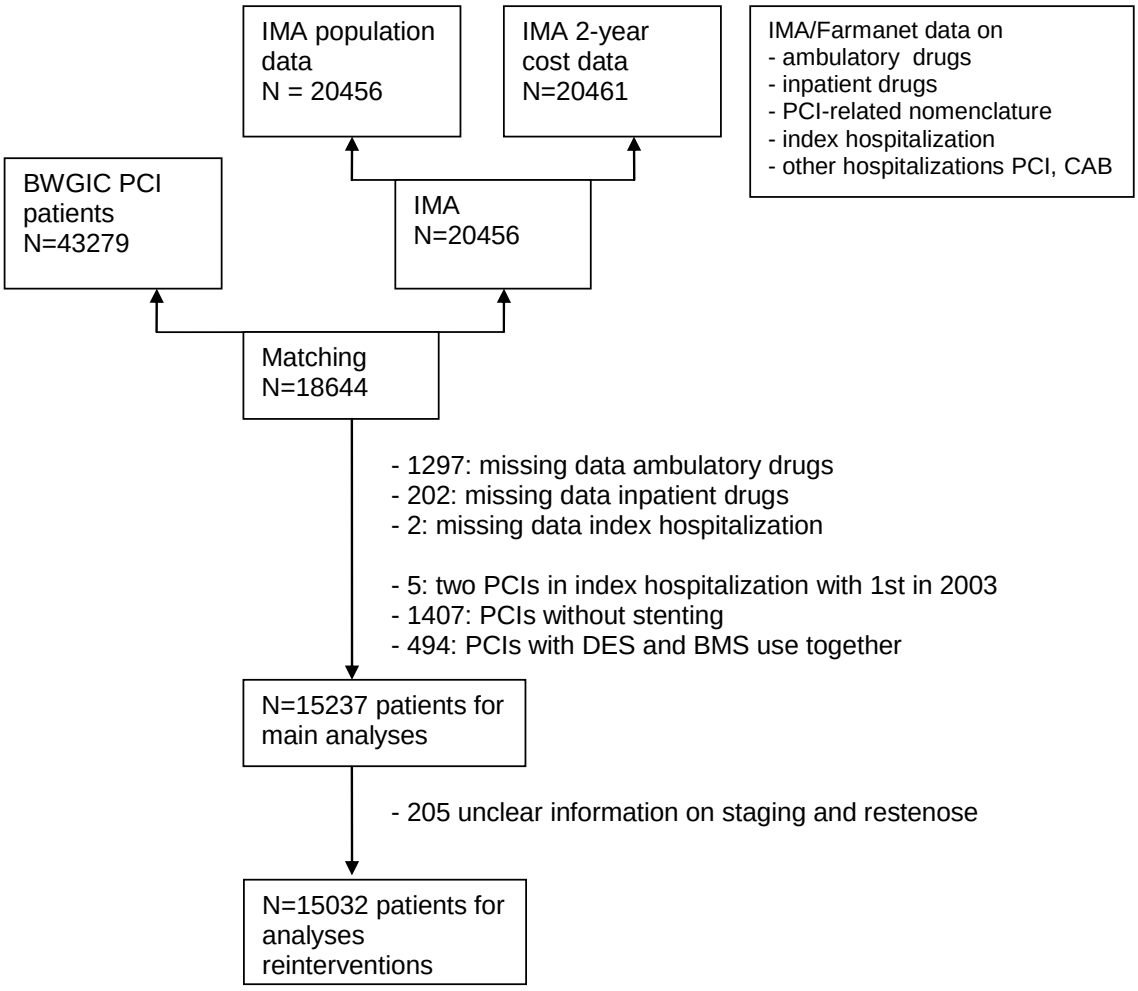
The patient selection is illustrated in the flow chart in figure 5.2. For self-employed people insurance for ambulatory medical consumption is not compulsory. In this case, IMA data do not contain this consumption and we are by no means able to capture or estimate an important part of these individuals' follow-up costs and we chose to exclude this group from the analyses. We therefore excluded all patients not reporting any ambulatory consumption on medicines. We realize that by doing this there is a risk of incorrectly excluding non self- employed people without any ambulatory drug consumption but we argue that the chance that a patient undergoing a PCI does not consume any ambulatory medicines during the year before and the year after his PCI is indeed very low. This way, we excluded 1 297 patients.

A further 202 patients were excluded because of lacking information on in-patient medicines. Two more patients were excluded because of lacking or erroneous information on the index-hospitalization.

Five patients who received a stent in both the years 2003 and 2004 within one and the same hospitalization were excluded as well, because both ignoring the 2003 stenting procedure as well as including the 2003 stenting procedure would infringe our concept of "first PCI-intervention in 2004". Note that patients starting their hospitalization in 2003 and receiving their first stent of that hospitalization in 2004 are not excluded from the analysis.

The main goal of this analysis is to describe and interpret current practice (2004) and the relation of the type of stent used during the index-intervention with costs and outcomes. Therefore, receiving one or more BMS or one or more DES during the index procedure is a criterion for inclusion. Note however that patients undergoing PCI without stenting (1 407 patients) as well as patients receiving both a BMS and a DES during the index procedure (494 patients) were excluded.

Figure 5.2: Data and patient selection



Finally, a total of 15 237 patients were included in the analysis and the database used for analysis contains all information on patients:

1. Undergoing at least one PCI with stenting in 2004
2. Receiving only one type of stents during the index-PCI (BMS or DES)
3. With complete follow-up data on the consumption of pharmaceuticals
4. Not receiving a stent in both 2003 & 2004 during one and the same hospitalization.

For the determination of the re-interventions we were forced to drop another 205 patients, because the proxy variables for staging and restenosis were calculated based on the first PCI reported in the BWGIC-database. As the BWGIC-database includes the period November 2003-October 2005, we had to make sure that all the reference interventions on which the proxy variables would be based took place in the year 2004. We therefore had to exclude all 205 patients undergoing a PCI in November/December 2003. A total of 15 032 patients have thus been retained for the analysis of the re-interventions. For the calculation of the costs of the re-PCIs according to stent type (no stent, BMS, DES or mixed), the re-PCIs in the IMA and BWGIC databases have to be matched at PCI-level (in addition to patient level). Only 1 674 re-PCI of the total number of 2 587 re-PCI in the IMA data (64.71%) matched with a PCI in the BWGIC database and were used for the detailed cost calculations.

5.3.2 Data preparation

The IMA-data do not include the full part of the 'nursing day cost' (which is not paid to the hospital per diem, but as a lump sum per month). In our analysis we therefore used the average nursing day cost as estimated by the Belgian department of Health (Federale Overheidsdienst Volksgezondheid, Veiligheid van de voedselketen en Leefmilieu).[c] The price applied is the mean of the prices of the 1st of January 2004 (€ 284.86) and the 1st of July 2004 (€ 289.89). The calculated average price per day is thus €287.23. The number of hospital days per hospitalization has been calculated as the number of times the per diem out-of-pocket expense for medicines was charged.[d]

5.4 RESULTS

For these results we will first give a general overview of the patient characteristics of the patients who were selected for analysis: 15 237 patients undergoing PCI with stenting in 2004. Information is obtained from the BWGIC directory as well as from the IMA data. In addition we will give some general information on the index procedure and the related hospital stay. We will further describe events and costs during the one-year follow-up period.

5.4.1 Socio-demographic characteristics of the population

Table 5.1 shows that almost 82% of the 15 237 patients undergoing PCI with stenting do not have diabetes. Given the importance of diabetes for PCI intervention and the selection of stent type, all analyses will be shown for the total sample and for the diabetic and non-diabetic population separately. Sizes of both groups are still large enough to be meaningful: there are 12 442 non-diabetic patients and 2 795 diabetic patients included in the analysis.

c Personal communication.

d It could not be calculated on the basis of the hospitalization dates. Hospitals can charge the nursing day costs depending on the hour of admission and/or discharge, and these were not available. This rule is similar for the per diem for drugs, so this could be used.

Table 5.1: Diabetes mellitus

	Number	%
No diabetes	12 442	81.7%
Diabetes	2 795	18.3%

The majority of the patients is male (see table 5.2). In the diabetic population almost 62% is male whereas it is about 75% in the non-diabetic group.

Table 5.2: Gender

	General		Diabetics		Non-diabetics	
	N	%	N	%	N	%
Men	10 994	72.2%	1 726	61.8%	9 268	74.5%
Women	4 243	27.8%	1 069	38.3%	3 174	25.5%

The age of the patients receiving a PCI varies between a minimum of 23 years to a maximum of 100 years. The average age is 65 years; the median 67. In the diabetic group the mean and median age are slightly higher: 67 and 68 years respectively, see table 5.3. The age distribution of both patient groups is given in figure 5.3. Overall the distribution looks relatively similar. The non-diabetics have relatively higher frequencies for ages up to 59 and above 81 years and the diabetics are more represented in the range 66-80 years.

Table 5.3: Age in years

	General	Diabetics	Non-diabetics
Average age	65	67	65
Minimum age	23	23	26
25th percentile	57	60	57
75th percentile	74	74	74
Median age	67	68	66
Maximum age	100	91	100
Number	15 237	2 795	12 442

Figure 5.3: Age distribution of patients undergoing PCI

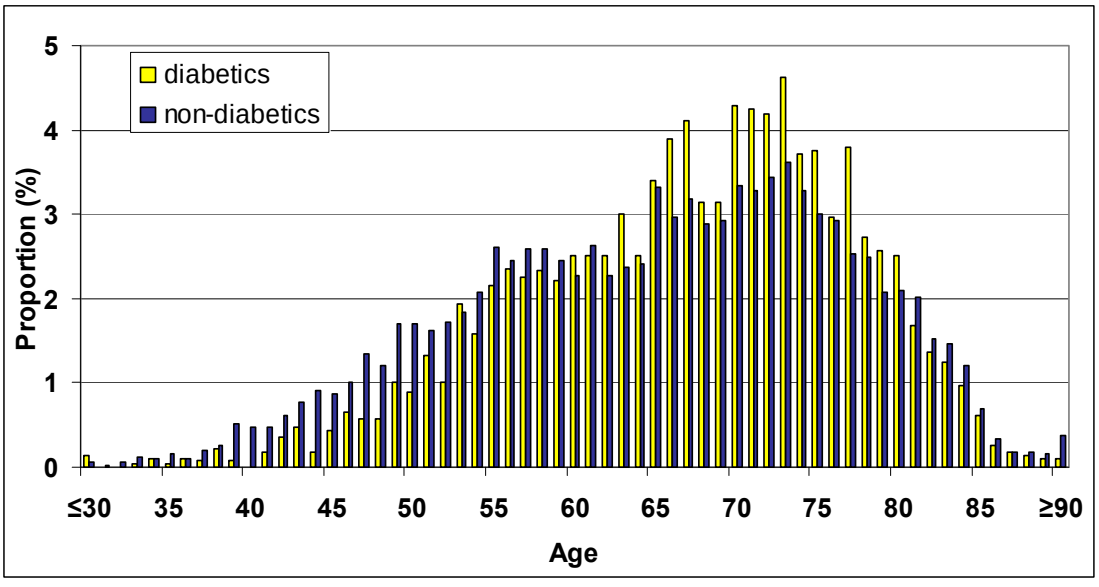


Table 5.4 describes the social security status of the patients. More then 96% of the population is insured through the general scheme. This low proportion of self-employed is obviously a result of the selection with the a-priori exclusion of patients without registered pharmaceutical consumption. From this population, 25% benefits from a preferential low co-payment in health care.

There is a big difference between the diabetic and the non-diabetic subgroup. 34% of the diabetic have preferential treatment while this is only 24% in the non-diabetic subgroup.

Table 5.4: Social security status

	General		Diabetics		Non-diabetics	
	N	%	N	%	N	%
General scheme	14 567	96.1%	2 669	96.0%	11 898	96.1%
Self-employed	587	3.9%	110	4.0%	477	3.9%
Preferential treatment	3 851	25.4%	944	34.0%	2 907	23.5%

Table 5.5 gives the geographical distribution of patients: 60% are living in Flanders, 6% in Brussels and 33% in Wallonia.[e] The distribution at provincial level is also shown in table 5.5. Relatively less diabetic patients live in Antwerpen and relatively more in Brussels.

Table 5.5: Province of residence

Province	General	Diabetics	Non-diabetics
Abroad or unknown	0. 7%	0.8%	0.7%
Flanders	60.3%	56. 5%	61.2%
Antwerpen	17.7%	15. 8%	18.2%
Vlaams Brabant	9.5%	8.9%	9.6%
West-Vlaanderen	11.3%	10.6%	11.4%
Oost-Vlaanderen	11.3%	11.1%	11.4%
Limburg	10.5%	10.1%	10. 6%
Brussels	6.4%	8.5%	6.0%
Wallonia	32.6%	34.3%	32.3%
Brabant-Wallon	2.6%	2.8%	2. 6%
Hainaut	11.5%	12.3%	11.3%
Liège	10. 8%	10.9%	10.8%
Luxembourg	2.1%	2.3%	2.0%
Namur	5.7%	6.1%	5.6%

5.4.2 Clinical characteristics of the population

Table 5.6 shows the prevalence of patient risk factors before intervention. A sizeable portion of the patients in our database already had cardiac problems before the PCI intervention: 17% already had a prior myocardial infarction (MI), 20 % had a prior PCI and 11% previously underwent CABG. We defined 70% of the patients as 'clean', meaning that they had no prior PCI or CABG (i.e. no prior revascularization). In addition, 3% of the population suffered from renal dysfunction (defined as creatinine level >2.2 mg/dl) and 12% had peripheral vascular disease. Renal dysfunction and peripheral vascular disease are more prominent in the diabetics group. Interventions on small vessels are operationalised as interventions on peripheral coronary vessels defined by segment number (distal vessels). This definition was used for 15% of the interventions. In 6% of PCIs patients had long lesions, operationalized as more than 1 stent needed in the same segment. In diabetics this was only 5%. The proportion of complex lesions, defined as either long lesions or small vessels amounted to 20%. Two percent of interventions were in the left main coronary, while 17% were in proximal LAD (segments 6 and 7), 15% in diabetics and 17% in non-diabetics respectively.

e In the BWGIC database, before the matching and patient selection, much more patients were from Brussels.

Tabel 5.6 also shows underlying CHD. The variables described are not exclusive and overlap. Of the index PCIs, 16% were primary PCIs for acute infarction, 3.5% was after failed thrombolysis (rescue PCI), 11% were after a previous MI (in the previous 14 days), 31% was for acute coronary syndrome (ACS), 34% for stable coronary artery disease, 5% for asymptomatic disease and in 2.2% of interventions there was cardiogenic shock.

Table 5.6: Clinical parameters

	General	Diabetics	Non-diabetics
Any prior MI	17.3%	19.2%	17.0%
Prior PCI	19.9%	23.3%	19.1%
Prior CABG	11.4%	13.9%	10.8%
Clean (no Prior PCI or CABG)	70.1%	66.0%	71.0%
Renal dysfunction	2.7%	5.0%	2.2%
Peripheral vascular disease	11.5%	15.8%	10.5%
Number of diseased vessels			
1	45.0%	39.4%	46.3%
2	31.6%	31.3%	31.7%
3	23.4%	29.3%	22.0%
Small vessel	14.8%	15.0%	14.7%
Long lesion	6.4%	4.7%	6.8%
Complex (long or small)	20.2%	19.1%	20.4%
Left main	1.6%	1.6%	1.5%
Proximal LAD	16.8%	15.2%	17.1%
Acute MI	16.2%	11.3%	17.3%
Failed thrombolysis	3.5%	2.2%	3.8%
Post MI (within 14 days)	11.4%	9.4%	11.9%
ACS	30.6%	30.0%	30.7%
Stable CHD	34.4%	38.4%	33.5%
Asymptomatic disease	5.3%	6.5%	5.1%
Cardiogenic shock	2.2%	2.6%	2.1%

Variables are not exclusive and definitions overlap.

5.4.3 Characteristics of the index PCI

The index PCI is performed in 34 different centers. The number of PCIs performed in each of the centers is shown in table 5.7. It is clear that the number of interventions varies greatly per center. Eighteen centers perform less than 400 interventions per year and their 'market share' amounts to only 22%, equal to the market share of the three biggest centers. The two smallest centers do not have any diabetic patients. For the other centers, the proportion of diabetic patients varies from 9% to 29%.

Table 5.7: Number of PCIs per center and share of diabetic and non-diabetic patients

Center	Number of PCI-interventions	% of total	% of interventions in diabetic patients
1	4	0.0	0.0
2	5	0.0	0.0
3	44	0.3	9.1
4	88	0.6	25.0
5	119	0.8	26.9
6	132	0.9	28.8
7	142	0.9	22.5
8	155	1.0	16.1
9	171	1.1	21.1
10	177	1.2	24.3
11	181	1.2	22.1
12	267	1.8	17.2
13	293	1.9	17.6
14	296	1.9	19.6
15	313	2.1	25.2
16	316	2.1	20.3
17	329	2.2	23.4
18	371	2.4	19.7
19	428	2.8	18.2
20	515	3.4	17.3
21	543	3.6	14.6
22	570	3.7	18.8
23	579	3.8	18.1
24	640	4.2	19.4
25	648	4.3	16.7
26	656	4.3	14.3
27	657	4.3	16.6
28	794	5.2	18.0
29	801	5.3	24.6
30	832	5.5	15.5
31	866	5.7	16.4
32	1 043	6.9	18.0
33	1 060	7.0	17.6
34	1 202	7.9	16.2

Patients stay in a common room, in 77% of cases, 16% in a two-person room and only 7% choose a single room (see table 5.8). The room type shown is the room chosen by the patient at admission, not the actual room occupied. The choice of room is important for the supplements patients have to pay. Patients are most protected from supplements in a common room and least in a single room.

Table 5.8: Room choice

	General		Diabetics		Non-diabetics	
	N	%	N	%	N	%
Single room	1 029	7.0%	177	6.7%	852	7.1%
2-person room	2 323	15.9%	451	17.0%	1 872	15.7%
Common room	11 257	77.1%	2 021	76.3%	9 236	77.2%

Table 5.9 shows the distribution of procedure type. The index PCI is elective, i.e. a planned intervention after previously performed diagnostic coronarography, in 32% of the cases overall and in 35% and 31% of the diabetic and non-diabetic patients respectively. Four percent of the interventions are 'referred' (elective PCIs after previous diagnostic coronarography performed elsewhere). The remainder of the procedures are unplanned interventions, following immediately a diagnostic procedure (ad hoc). In 41% of the interventions there is direct placement of a stent without prior balloon dilatation (direct stenting).

Table 5.9: Type of procedure

	General	Diabetics	Non-diabetics
Elective	31.7%	35.2%	30.9%
Ad Hoc	64.5%	60.9%	65.4%
Referred	3.7%	3.9%	3.7%
Direct stenting	41.3%	37.0%	42.3%

During the index hospitalization, patients stay on average 5.5 days in hospital[f]; the median number of days is only 3. There is a wide range. Almost 2% of procedures are performed in day-hospital (0 nights) and an additional 10% of patients leave the hospital after one night. At the other end of the scale are some outliers who remain in hospital for a very long time: 17 cases (0.15%) stay more than 100 days. Additional frequencies are presented in table 5.10. A graphical representation of the frequency distribution of length of stay (LOS) of diabetics and non-diabetics is presented in figure 5.4. From the figure it is very clear that the distribution is skewed to the right. The figure also shows that a higher proportion of diabetic patients have more extreme LOS. The average LOS for diabetics is 6.4 days. The median value is similar however (3 days). Figures 5.5, 5.6 and 5.7 show boxplots of the LOS according to the type of intervention (elective, ad hoc or referred, figure 5.5) and according to the type of stent (DES or BMS) for respectively diabetic patients (figure 5.6) and non-diabetic patients (figure 5.7).

Table 5.10: Length of stay during index hospitalization

	General	Diabetics	Non-diabetics
0	1.9%	1.4%	2.1%
1	10.1%	8.4%	10.5%
2	26.9%	28.6%	26.5%
3	15.8%	15.0%	16.0%
4	8.3%	6.9%	8.6%
5	6.6%	5.4%	6.8%
6	5.6%	4.5%	5.8%
7	4.5%	4.4%	4.6%
8-10	9.3%	9.5%	9.2%
11-20	7.9%	11.1%	7.2%
>20	3.2%	4.7%	2.8%

[f] Figures calculated on the basis of the IMA-data as the number of times the per diem for drugs is charged.

Figure 5.4: Distribution of length of stay of index hospitalization

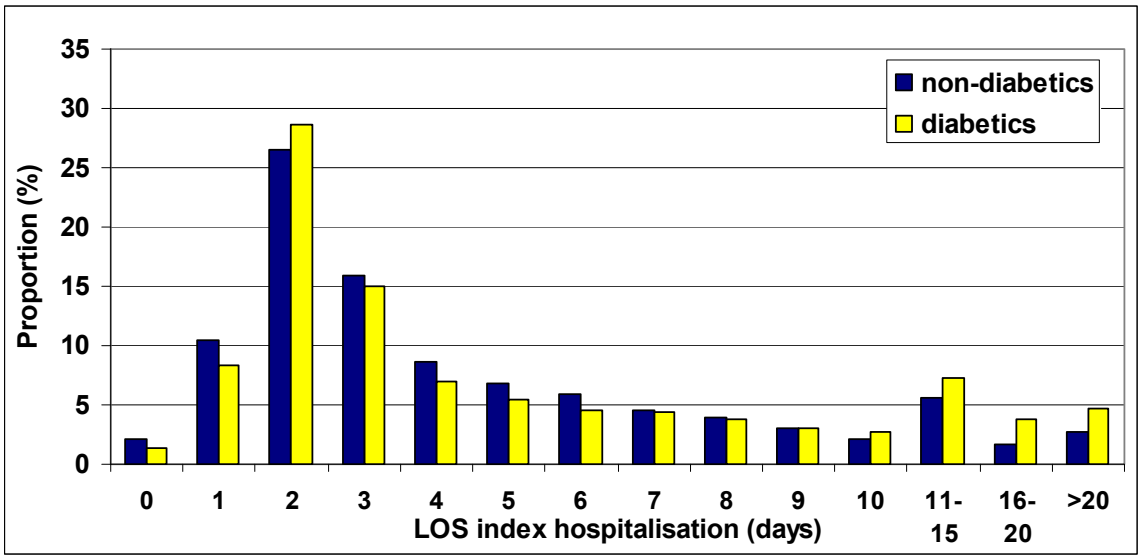
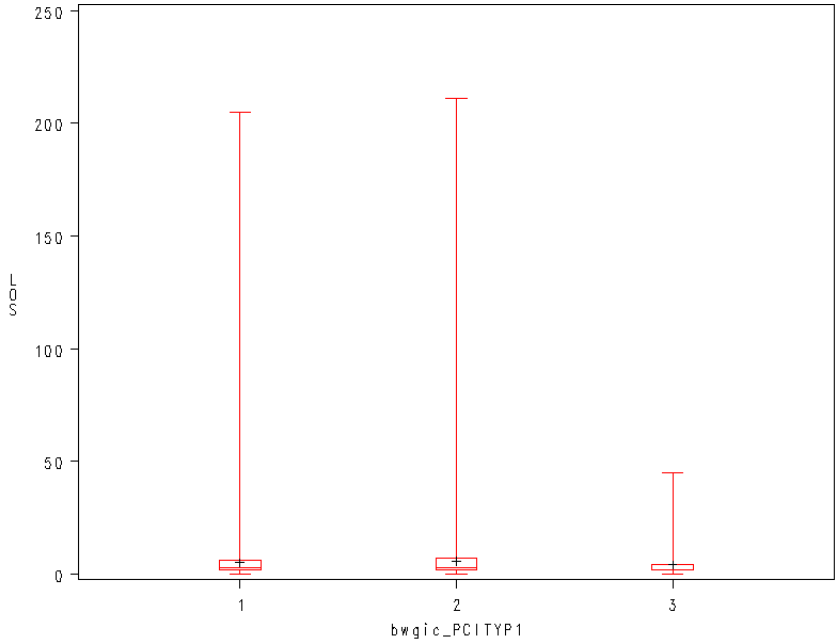
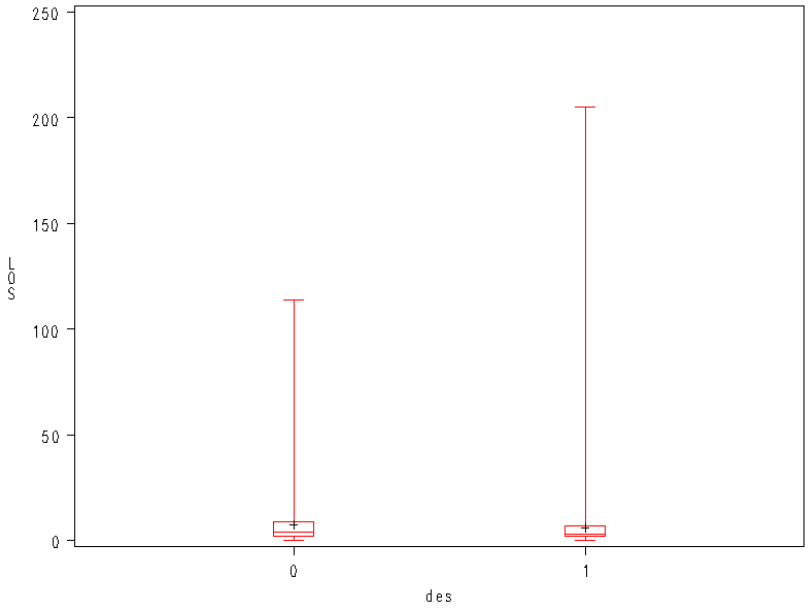


Figure 5.5: Boxplot of Length of stay of index hospitalization for elective, referred and ad hoc procedures



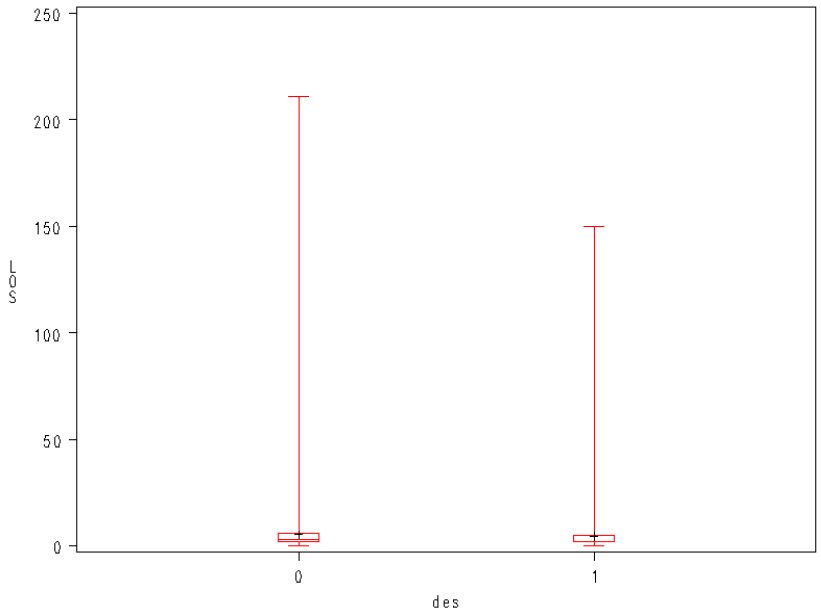
1= elective; 2= ad hoc; 3= referred

Figure 5.6: Boxplot of Length of stay of index hospitalization according to stent type for diabetic patients



0=BMS; 1=DES

Figure 5.7: Boxplot of Length of stay of index hospitalization according to stent type for non-diabetic patients



0= BMS; 1= DES

5.4.4 Staging

Reimbursement of coronary stents in Belgium is on a lump sum basis. The hospital can only charge this lump sum once per hospitalization, irrespective of the number of stents used during PCI or the number of PCI procedures during this hospital stay. This mechanism obviously creates an incentive for the staging of PCIs, whereby stenting in case of multivessel disease is performed during separate hospitalizations, when the lump sum can be charged during each separate hospitalization.

In the BWGIC-database proxy variables for potential staging were defined. If a patient suffers from multivessel disease and he has a second PCI in another vessel than during the index PCI performed less or equal to 45 days after the index PCI (or a third PCI within 45 days after a staged PCI, in other vessel than the index PCI and the first staged procedure) staging is assumed. Of the 2 587 repeat-PCI interventions within one year after index PCI, 734 (28%) could be considered as part of a staged procedure related to the index-procedure rather than as a re-intervention because of restenosis or new lesions. This means that about 5% of index-PCIs are followed by a staged PCI, a proportion that is similar in most subgroups as shown in table 5.11.

Table 5.11: Staged procedures: number and % of index PCI interventions.

		N index	N staged procedures	staged procedures as % of index
BMS	Non-Diabetics	10 852	526	4.8%
	Diabetics	601	29	4.8%
DES	Non-Diabetics	1 435	52	3.6%
	Diabetics	2 144	127	5.9%
BMS		11 453	555	4.8%
DES		3 579	179	5.0%
ALL		15 032	734	4.9%

5.4.5 Number and type of stents

BMS are used in 76% of all index procedures. The distribution is completely different for diabetic and non-diabetic patients, which is obviously related to the current Belgian reimbursement rules. A great majority of diabetic patients (78%) receive a DES whereas an even greater majority of non-diabetic patients receive a BMS (88%), as shown in table 5.12. Of the DES index PCIs, 43% were with Cypher and 44% Taxus. In the next paragraph we further analyze the choice of PCI type (DES or BMS).

Table 5.12: Type of stents used during index procedure

	General		Diabetics		Non-diabetics	
	Number	%	Number	%	Number	%
BMS	11 576	76.0%	606	21.7%	10 970	88.2%
DES	3 661	24.0%	2 189	78.3%	1 472	11.8%
Cypher	1 596	10.5%	849	30.4%	747	6.0%
Taxus	1 629	10.7%	1 168	41.8%	461	3.7%
Study	49	0.3%	2	0.1%	47	0.4%
Other	11	0.1%	0	0.0%	11	0.1%
Mixed*	37	0.2%	29	1.0%	8	0.1%
Unknown	339	2.2%	141	5.0%	198	1.6%

* combination multiple segments

Only one stent was used in 79% of patients during the index hospitalization, 18% received two stents and 4% three or more (table 5.13). The aggregated average number of stents used during PCI with stenting is 1.26 stents per hospitalization**.** This average number of stents is higher with BMS than with DES. If we take into account staged procedures the average number of stents used is 1.30, again higher with BMS than with DES.

Table 5.13: Number of stents used during the index procedure

	General	Diabetics	Non-diabetics
1	78.6%	83.3%	77.5%
2	17.5%	14.3%	18.2%
3	3.1%	1.9%	3.4%
More than 3	0.8%	0.5%	0.9%
Average number of BMS	1.29	1.29	1.30
Average number of DES	1.19	1.22	1.17
After taking into account staging			
Average number of BMS	1.32	1.33	1.32
Average number of DES	1.23	1.22	1.24

5.4.6 Choice of stent type

As described above, 76% of the patients in the sample received a BMS and 24% a DES. Since this is an observational study population, the type of stent a patient receives is certainly not a random variable. DES is only reimbursed for diabetic patients and this is therefore the most important variable determining the choice of DES versus BMS. But not all diabetics receive a DES and likewise not all non-diabetics receive a BMS. So other variables play a role as well. In this paragraph, we will first look at the distribution of patient characteristics in both 'treatment' groups. Next we will analyze the determinants of DES choice in a multivariate logistic regression.

Table 5.14 summarizes the results of the bivariate analyses. The table gives for the index hospitalization with BMS or with DES the proportion of patients who have the specified characteristic (for the categorical variables) or the mean value of the variable (for continuous variables). This is done separately for the diabetic patients (columns 2 and 3) and for of the non-diabetic patients (columns 5 and 6). A χ^2 (categorical variables) or a t-test (continuous variables) was performed to test for the significance of the differences between DES and BMS and the significance level is written in columns 4 and 7. The first row in the table shows that almost 67% of diabetic patients receiving a BMS are male and 60% of diabetic patients receiving a DES. Comparing these percentages we can derive that male diabetic patients are more likely to receive a BMS then female diabetic patients and this difference is significant (P=0.00). The same holds for the non-diabetic patients. The history and risk of the patient are relevant as well. Diabetic as well as non-diabetic patients with a high mortality risk (cardiogenic shock, acute MI or PCI for failed thrombolysis) and those needing more than 1 stent more frequently receive a BMS. Also diabetic patients with renal dysfunction and peripheral vascular disease more frequently receive a BMS. Diabetic patients with long lesions receive more frequently a BMS. A DES is relatively more frequently given if the patient is considered at low risk (stable CHD or asymptomatic ischemia), if the patient already had a prior PCI and when the intervention is ad hoc or upon referral (diabetic as well as non-diabetic patients). The age of the patients receiving a DES is significantly lower than those in whom a BMS is implanted. For non-diabetic patients with intermediate risk (ischemic post MI or ACS) or treating left main and proximal LAD lesions increases the choice for DES. More experienced physicians are more inclined to use BMS, and although the differences are small they are nevertheless significant. The scale of the center has no significant influence, but there are significant differences in PCI choice between the centers (31 center dummies; values not shown). The room type chosen by the patient exerts a significant impact in non-diabetic patients. Six percent of patients receiving a BMS are in a single room while this is 12% for patients receiving a DES. Single or multivessel disease or small vessels do not have a significant impact on PCI type. The latter is remarkable since small vessels are considered an indication for DES. We have to keep in mind, however, that we approximate small vessels as peripheral vessel defined by segment number.

Table 5.14: Choice of BMS or DES in diabetic and non-diabetic patients: a bivariate analysis

	Diabetic patients			Non-diabetic patients		
Patient characteristic	**BMS**	**DES**	**p**	**BMS**	**DES**	**p**
Male gender	66.8	60.4	.00	74.8	72.0	.02
Prior PCI	19.0	24.4	.01	17.3	32.4	<.0001
Number of stents >1	25.3	14.3	<.0001	23.0	18.5	<.0001
Renal dysfunction	7.6	4.3	.00	2.1	2.7	.16
1 vessel disease	41.6	38.8		46.3	45.8	
2 vessel disease	27.9	32.3		31.7	31.5	
3 vessel disease	30.5	28.9	.12	22.0	22.7	.82
Peripheral vascular disease	18.7	15.0	.04	10.4	11.2	.38
AMI or failed thrombolysis	14.5	8.6	<.0001	16.3	7.6	<.0001
Post MI or ACS	40.7	38.0	.23	41.1	46.4	<.0001
Stable CHD or asymptomatic patients	36.1	47.0	<.0001	37.9	42.1	.00
Cardiogenic shock	5.2	1.9	<.0001	2.3	0.9	.00
Operator > 125 PCIs /year	76.9	72.8	.05	75.9	71.1	<.0001
Operator > 75 PCIs /year	91.9	90.0	.15	91.0	89.3	.03
Operator > 20 MI / year	78.7	70.9	<.0001	75.2	70.2	<.0001
Center > 400 PCIs/year	88.9	90.6	.21	92.3	93.1	.30
Center > 60 MI/ / year	89.6	88.3	.37	90.2	92.0	.03
PCI=elective	40.8	33.7		31.3	28.2	
PCI=ad hoc	57.1	61.9		65.2	66.7	
PCI=referred	2.2	4.4	.00	3.5	5.1	.00
Small vessel	14.4	15.2	.62	14.7	15.0	.77
Long lesion	7.7	3.9	.00	6.8	6.7	.86
Left main	1.5	1.6	.78	1.3	3.6	<.0001
Proximal LAD	14.0	15.5	.36	16.2	24.3	<.0001
Single room	6.0	6.9		6.4	12.3	
2-person room	16.5	17.2		15.0	20.5	
Common room	77.5	76.0	.69	78.6	67.2	<.0001
Center dummies			<.0001			<.0001
Age	68.6	66.6	<.0001	65.2	63.7	<.0001

To understand the characteristics of the patients receiving a DES better, we further performed a multivariate logistic regression analysis in which the dependent variable is a discrete variable, taking the value of one if the individual received a DES and with relevant characteristics as explanatory variables. The resulting odds ratios are shown in table 5.15. These can be interpreted as the relative probability of belonging to the group receiving a DES; if the number is less than one, this means that the probability of receiving a DES is smaller than in the reference group, and the opposite is true for an odds ratio larger than one. In order to get the relative probability of subgroups defined by more than one variable, the product of the relevant odds ratios can be taken.

We started the regression analyses with all significant variables from the bivariate analyses in addition to the dummy for small vessels. Although this variable is not significant in the bivariate analysis, it is introduced, since it is generally seen as an important indication for DES use.[197] In a second step, variables with no significant impact in diabetic patients as well as in non-diabetic patients were removed[g]; dummy variables indicating the center (many of them significant) and the dummy for small vessels and long lesions were kept.

First we discuss the results of the diabetic patients. The global null hypothesis (that all coefficients are not significantly different from zero) is firmly rejected ($p<.0001$) and 80% of the cases are correctly classified when taking a cut-off probability of 0.5. Several patient characteristics significantly determine DES choice. The smallest relative probability (0.47) to receive a DES is found in patients needing more than one stent. Male patients are only 0.6 times as likely to receive a DES in comparison to female patients and a similar relative probability is found for patients stented for an AMI or after failed thrombolysis. Age also influences the probability negatively. An increased relative probability is found for patients with stable coronary artery disease or asymptomatic disease and for proximal LAD ($p=0.09$).

Also for the non-diabetic patients the regression is highly significant and almost 90% of the cases are correctly classified. Odds ratios smaller than 1 are found for age, male gender, number of stents above 1 and for patients stented for an AMI or after failed thrombolysis. Stable coronary artery disease or asymptomatic ischemic disease, small vessels and proximal LAD interventions increase the relative probability to receive DES. This is even more pronounced for left main lesions, with an odds of 4.5. Remarkably also room choice remains significant in this regression. Patients in a two-person room have a 1.3 times higher probability to receive a DES in comparison to persons in a common room. For patients in a single room the relative probability to receive a DES in comparison to patients in a common room is almost double (1.9).

These results suggest that patient characteristics effectively guide the choice of stent type. Not all effects however are as expected. Although in general it is more recommended to use DES for patients with small vessels and long lesions, the association is only found for non-diabetic patients, and is not very strong (odds ratio of about 1.3) and less significant ($p=0.01$ for small vessels and $p = 0.09$ for long lesions). We should keep in mind however that there could be measurement errors in these variables as these are only proxy variables. In addition we find evidence that financial considerations play a role as well. In Belgium we have a lump sum reimbursement for PCI (fixed reimbursement irrespective of the number of stents used) which is identical for BMS or DES, unless the patient is diabetic. This reimbursement rule appears to explain part of the preponderance to use DES in diabetics and the reluctance to use it in case the number of stents needed is larger than 1. Also the significance of the room choice of the patient can be interpreted in this sense. Although DES use will only be reimbursed at the level of BMS reimbursement for non-diabetic patients, room supplements and fee supplements can be charged to patients choosing two-person rooms and especially to those choosing single rooms. With this mechanism, extra revenues can be generated from these patients, compensating the 'deficit' on the device. On the other hand, there is a social stratification in room choice: individuals with higher socio-economic status more often opt for a single room. It could therefore also be argued that the use of DES is influenced by the socioeconomic status of the individual which is indirectly reflected in room choice. Increased reimbursement, as in the case of diabetic patients, appears to neutralize the influence of room type.

g The results are only marginally affected.

Table 5.15: Choice of BMS or DES in diabetic and non-diabetic patients: a multivariate logistic regression analysis

	Diabetic patients				Non-diabetic patients			
Independent variable	**Odds Ratio**	**95% confidence interval**		**p**	**Odds ratio**	**95% confidence interval**		**p**
Male gender	0.61	0.49	0.76	<.0001	0.77	0.67	0.89	.00
Prior PCI	1.16	0.90	1.50	0.26	2.31	2.00	2.67	<.0001
number of stents>1	0.47	0.35	0.64	<.0001	0.56	0.46	0.68	<.0001
Age (in years)	0.97	0.96	0.99	<.0001	0.98	0.97	0.98	<.0001
Acute MI or failed thrombolysis	0.61	0.43	0.86	0.01	0.41	0.32	0.51	<.0001
stable CHD or asymptomatic	1.55	1.24	1.94	0.00	1.28	1.12	1.47	0.00
Small vessel	1.03	0.77	1.38	0.85	1.25	1.05	1.49	0.01
Long lesion	0.86	0.52	1.42	0.56	1.30	0.96	1.77	0.09
Left main	1.49	0.62	3.57	0.37	4.52	3.08	6.64	<.0001
proximal LAD	1.30	0.96	1.75	0.09	1.86	1.60	2.17	<.0001
Single room	0.98	0.64	1.52	0.94	1.91	1.56	2.35	<.0001
2-person room	0.97	0.72	1.29	0.81	1.25	1.05	1.49	.01
Center	Coefficients not shown				Coefficients not shown			
	N = 2604 global null hypothesis likelihood ratio = 365, p value <.0001 at p=0.5, 80% correctly classified				N=11652 global null hypothesis likelihood ratio = 1878 p value <.0001 at p=0.5, 89% correctly classified			

5.4.7 Cost of index hospitalization

In the next three paragraphs the focus is on costs. These costs are derived from the IMA data. We will first describe the costs of the index hospitalization. The index hospitalization is the hospitalization during which the index intervention took place. We defined the day of the index PCI-intervention as 'day 0'. Sometimes admission of the patient is before this 'day 0', but these days and the related costs are counted as well since we consider the complete hospitalization. Costs of diagnosis are included if performed during the index hospitalisation.

The average total reimbursed cost of the index hospitalization is €7 112. In addition there is an average patient co-payment (remgeld, ticket modérateur) of €268 and an average supplement of €271. This means that 93% of the hospital bill is paid by the health insurance and the remaining 7% is an out-of-pocket (OOP) payment of the patient. All these figures deviate rather strong from those of a general hospital stay.[198] LOS of the index hospitalization is somewhat smaller (5.5 days in comparison to 6.9 days on average in 2003), but RIZIV-reimbursements per stay are much larger (€7 112 in comparison to €2 763[h]) as well as OOP (€540 in comparison to €421). Table 5.16 gives further details on the composition of these costs.

Reimbursement for PCI material and fees are 41% of the total reimbursements, while the reimbursements for nursing day amount to 22%. These categories alone already lead to an amount of €4 468. In addition drug costs are relatively large; a total of €608. Table 5.17 gives mean, median, 25th percentile and 75th percentile values of the sum of reimbursements and co-payments for different subgroups. The cost of the index hospitalization is very similar for diabetic patients receiving a DES vs a BMS despite the fact that reimbursement of PCI material is €1000 higher for DES in this group. The costs of the index hospitalization for non-diabetics is lower for patients receiving a DES vs a BMS in the current situation with an equal reimbursement price for the two types of PCI.

h RIZIV costs are not fully comparable since the nursing day cost is approximated in a different way.

Table 5.16: Cost of index hospitalization (in €, 2004 prices, N=15237)

	Reimbursement		Co-payment	Supplement	TOTAL
	€	%	€	€	€
Material PCI	1 941.4€	27.30%	0€	0.1€	1 941.5€
Fees PCI	939.9€	13.22%	0.0€	57.9	997.8€
Additional fees PCI	101.2€	1.42%	0.0€	5.5€	106.7€
Heart catheterisation	153.7€	2.16%	0.0€	9.1€	162.8€
Coronarography	130.6€	1.84%	0.0€	8.5€	139.1€
Clinical biology	241.3€	3.39%	8.9€	1.9€	252.1€
Other fees	430.5€	6.05%	20.9€	17.5€	468.9€
Other implants	258.6€	3.64%	0.6€	32.0€	291.2€
Delivery margin implants	0	0.00%	141.3€	0€	141.3€
Nursing day	1 586.8€	22.31%	0€	0€	1 586.8€
Lump sum day-hospital	21.9€	0.31%	0€	0€	21.9€
Out-of-pocket nursing day	0	0.00%	70.2€	33.4€	103.5€
IIbIIIa inhibitors	244.2€	3.43%	0.4€	0€	244.5€
Other drugs	364.0€	5.12%	4.5€	0€	368.5€
Diverse costs	0 .00€	0.00%	0.3€	71.6€	71.9€
Other	697.7€	9.81%	20. 9€	34.0€	752.5€
Total	**7 111.6€**	**100%**	**268. 0€**	**271.5€**	**7 651.0€**

In the appendix for this chapter a description of the cost categories is given

Table 5.17: Cost of index hospitalization for different subgroups (reimbursements + co-payment in €, 2004 prices)

		N	Mean	median	25th perc.	75th perc.
BMS	Non-Diabetics	10 970	7 310.9 €	6 221.3 €	5 142.4 €	7 960.9 €
	Diabetics	606	8 272.0 €	6 756.1 €	5 391.0 €	9 126.2 €
DES	Non-Diabetics	1 472	6 410.3 €	5 406.2 €	4 733.9 €	6 948.1 €
	Diabetics	2 189	8 128.7 €	6 776.2 €	5 898.2 €	8 877.6 €
BMS		11 576	7 361.2 €	6 246.9 €	5 152.6 €	8 009.5 €
DES		3 661	7 437.8 €	6 312.0 €	5 230.5 €	8 140.2 €
ALL		15 237	7 379.6 €	6 268.2 €	5 169.6 €	8 043.3 €

5.4.8 Cost during follow-up

5.4.8.1 Medication

In order to prevent thrombosis, patients must take a second antiplatelet drug (one of either thienopyridine derivative, clopidogrel or ticlopidine) in addition to aspirin for one to six or more months after stenting and with a longer duration when a DES was used. Following BMS, dual antiplatelet therapy is mandatory during one month, whereas after DES implantation three to six months of dual antiplatelet therapy is advised. From 2006 onward, reports of an increased risk of late stent thrombosis occurring in DES have prompted cardiologists to extend this period up to 12 months, particularly in patients with a low bleeding risk. For aspirin, there is no reimbursement in Belgium, whereas currently only ticlopidine is being reimbursed for one month following coronary stenting. Some patients, however, can obtain reimbursement of either thienopyridine following ACS whether or not a PCI was performed.

Table 5.18 gives the reimbursements + co-payments for clopidogrel and ticlopidine[i]. It amounts to €341 in case of BMS and €456 in case of DES. This corresponds to a number of the Defined Daily Doses (DDDs)[j] of about 170 and 230 for BMS and DES respectively. This is much higher than the standard reimbursement duration of 30 days so patients obviously obtained longer reimbursement on the basis of co-morbidity, but it probably remains an underestimate of true consumption.

Table 5.18: Cost of clopidogrel / ticlopidine(reimbursement + co-payment) and DDD for clopidogrel in the period up to 12 months after index procedure

	Clopidogrel	# DDD Clopidogrel *	Ticlopidine
BMS	327.6 €	167.5	13.1 €
DES	444.9 €	227.5	10.6 €

* DDD of 75 mg

5.4.8.2 Re-interventions

As explained in the data section, re-interventions are only analyzed for patients with a first intervention in the BWGIC-database in 2004 (15 032 patients). We analysed re-interventions during a one-year follow-up. As the data did not allow us to determine the exact date of the re-intervention, we considered a re-intervention as "within one year from the day of index-procedure" if the end-day of the hospitalization related to the re-intervention was within 365 days from the day of the index-procedure. We preferred this conservative definition over the choice of begin-day of the related hospitalization as benchmark. Re-interventions can be necessary in case of restenosis and can be performed either by re-PCI or by CABG. Indicators of restenosis, however, are not readily available in our database. We operationalized restenosis as re-PCI in the same vessel as the index PCI within one year after the initial intervention. The percentage of people with a treated restenosis calculated in this way is 5.8%. We see that people initially receiving a DES are, in this observational setting, less likely to undergo a re-PCI due to restenosis (5.0%) than people initially receiving a BMS (6.1%). Especially in the diabetes subgroup this difference is remarkable. Diabetics initially receiving a DES have 5.3% chance to undergo a re-PCI due to restenosis within one year compared with 10.0% for diabetic patients initially receiving a BMS. Firm conclusions however cannot be drawn from these observations because of the a priori biased patient selection. Revascularisation with CABG was performed in 2.3% of the patients within one year from the day of the index-procedure. Also for CABG we found that the patients receiving a DES have lower revascularization rates. Table 5.19 shows overall results and results for specific subgroups.

i The data only relate to reimbursed drugs; we don't have information on non-reimbursed drugs.

j The number of DDDs for Ticlopidine cannot be derived easily from the expenditures data because there are different brands and prices. They are very small however.

Table 5.19: Patients undergoing a re- PCI intervention due to restenosis and a CABG within one year after the index PCI

			Re-PCI (restenosis)		CABG	
		N index	Number	% of index-PCI	Number	% of index-PCI
BMS	Non-Diabetics	10 852	636	5.9%	267	2.5%
	Diabetics	601	60	10.0%	14	2.3%
DES	Non-Diabetics	1 435	67	4.7%	15	1.0%
	Diabetics	2 144	113	5.3%	43	2.0%
BMS		11 453	696	6.1%	281	2.5%
DES		3 579	180	5.0%	58	1.6%
ALL		15 032	876	5.8%	339	2.3%

The total number of re-PCI during the one-year follow-up can be found in Table 5.20. About 17.2% underwent a new PCI-intervention (with or without stenting) within one year from the day of the index-procedure. The re-PCI can be due to restenosis, disease progression or staging. The respective shares can be found in the table for the whole population as well as for some specific subgroups. The proportion of restenosis in patients with DES is lower than in those with BMS but, especially in non-diabetics, the difference is much smaller than would be expected from RCT evidence. This probably reflects the clinical judgement of the interventional cardiologist who preferable implants a DES in patients with higher restenosis risk.

Table 5.20: Total number of re-PCIs within one year after index-PCI and % due to restenosis and staging

		N index	All re-PCI as % of index	Restenosis as % of all re-PCI	Restenosis as % of index	Staging as % of index
BMS	Non-Diabetics	10 852	16.8%	35.0%	5.9%	4.8%
	Diabetics	601	24.0%	41.7%	10.0%	4.8%
DES	Non-Diabetics	1 435	13.9%	33.7%	4.7%	3.6%
	Diabetics	2 144	19.7%	26.7%	5.3%	5.9%
BMS		11 453	17.2%	35.4%	6.1%	4.8%
DES		3 579	17.4%	28.9%	5.0%	5.0%
ALL		15 032	17.2%	33.9%	5.8%	4.9%

These data correspond to the restenosis rates used in the economic model for Belgium, chapter 6 (table 6.6 parts a and b)

To determine the type and number of stents used during the re-PCI and the associated cost by stent type we had to link the data on re-hospitalizations from the IMA (containing cost data) with the BWGIC-database (containing information on the type of stent used during the re-PCI). If patient ID numbers matched and the period of hospitalization from the IMA-data included the date of the PCI we considered observations as matching. This way, only 64.7% of the 2,587 re-PCI hospitalizations from the IMA-database could be directly matched with an observation in the BWGIC-database. Therefore, we performed the cost analysis on the matched 1,674 observations. The rather high number of non-matching observations can partly be explained by the fact that the available BWGIC-database was only up-to-date until October 2005. All re-interventions taking place in November or December 2005 will not have matched. Another reason is that the patient ID numbers in the BWGIC database are entered manually without any formal control, potentially leading to incorrect ID numbers.

The mean cost (reimbursements and co-payment) of a re-PCI was €6 473 and the average number of stents used during re-PCI was 1.07 (including the PCIs without stenting). Results for the subgroups are presented in Table 5.21.

When accounting for staging, the mean cost of a re-PCI is €6 767, and the average number of stents used is 1.03 (see table 5.21).

Table 5.21: Cost of re-PCI within one year after the initial PCI (reimbursements + co-payments) by stent type used during index PCI (with and without correction for staging)

		No correction for staging				
		N	mean cost	mean stents	median cost	Median stents
BMS	Non-Diabetics	1 156	6 272.7€	1.07	4 758.5€	1
	Diabetics	107	7 109.1€	1.06	5 553.9 €	1
DES	Non-Diabetics	134	6 021.5€	0.99	4 524.3€	1
	Diabetics	277	7 281.5€	1.12	5 805.3€	1
BMS		1263	6 343.6€	1.07	4 800.8€	1
DES		411	6870.7€	1.08	5 443.8€	1
ALL		1674	6473.0€	1.07	4 930.8€	1
		Corrected for staging				
		N	mean cost	mean stents	median cost	median stents
BMS	Non-Diabetics	880	6 526.2€	1.03	4 874.2€	1
	Diabetics	93	6 964.5€	1.03	5 631.6€	1
DES	Non-Diabetics	112	6 448.7€	0.94	4 558.8€	1
	Diabetics	208	7 868.5€	1.09	6 003.5€	1
BMS		973	6 568.1€	1.03	4 932.3€	1
DES		320	7 371.6€	1.04	5 504. 7€	1
ALL		1293	6 766.9€	1.03	5 078.2€	1

These cost data correspond to the cost for re-PCI used in the economic model for Belgium, chapter 6 (table 6.8 parts a and b)

Results for the cost of re-PCI interventions by type of stent used during the repeat intervention can be found in the appendix for this chapter.

We used the 339 identified CABG-procedures within one year after the index-PCI to calculate the mean cost of a CABG. This cost of €15 542 was used as an approximation for the cost of a CABG as a re-intervention since the data do not allow us to distinguish between re-intervention for the same lesion or progression of CHD in another location. Results are presented in Table 5.22.

Table 5.22: Cost CABG within one year after the initial PC (reimbursement and co-payment).

		N	mean cost	median	25th perc.	75th perc.
BMS	Non-Diabetics	267	15 161.8€	12 444.3€	10 465.2€	15 893.1€
	Diabetics	14	19 323.0€	15 853.4€	12 612.1€	18 582.0€
DES	Non-Diabetics	15	15 218.5€	12 048.4€	10 824.4€	16 072.5€
	Diabetics	43	16 787.5€	13 328.0€	11 257.7€	19 363.7€
BMS		281	15 369.2€	12 541.2€	10 507.2€	16 231.4€
DES		58	16 381.7€	12 854.5€	11 162.4€	18 772.3€
ALL		339	15 542.4€	12 550.6€	10 580.9€	16 575.5€

5.4.9 One-year cost post PCI-index date and its determinants

We analysed the full one-year cost since the index PCI at 'day 0'. Costs in this period are all costs generated by the patient, including the costs of the index-PCI and the hospitalizations, ambulatory follow-up costs, costs of complications or re-intervention and also all other non PCI-related costs of other illnesses, preventive activities etc. It is not possible to make a clear distinction between PCI-related costs and other costs. We will discuss costs from the viewpoint of the health care payer which means that we take RIZIV-INAMI reimbursements as well as patient co-payments.

Table 5.23 shows the RIZIV-INAMI reimbursements and co-payments of these one-year follow up costs for the diabetic and non-diabetic patients respectively, subdivided for patients who received a BMS or a DES. The one-year costs before the PCI implant were also added to allow for comparison. For the diabetics costs of the previous year are quite similar for patients with DES or BMS. For the non-diabetics this is not the case, both RIZIV reimbursements and co-payments are significantly different between BMS and DES patients. DES patients incur significantly higher costs in the year prior to their PCI implant. Costs of the previous year could be considered as a proxy for the health condition of the patient. Therefore this could be an indication that non-diabetics who receive a BMS were in better health during the year prior to the intervention than those who receive a DES, although this appears to be in contradiction with the indicators for DES use discussed previously in this chapter.

When we look at the one-year follow up costs it is obvious that the patients in our sample are very expensive. On average RIZIV reimbursements in 2004 amounted to €1 607 per individual (RIZIV, jaarverslag 2005, p 179)[199] while our patients are 5 to 10 times more expensive. Total health care payer costs amounted to €18 273 and €17 486 for BMS and DES respectively for the diabetic patients. For the non-diabetics the amounts were €13 908 and €12 157 respectively. It is striking that the non-diabetic patients who receive a DES have significantly lower costs than those who receive a BMS, and this difference is opposite to our findings for the costs prior to the PCI implant. For the diabetic patients there are no significant cost differences between BMS and DES patients. To try to get a better understanding of these costs we subdivided the total costs[k] in table 5.24.

k In the appendix for this chapter a description of the cost categories is given.

Table 5.23: Average 1-year costs before and after index day 0 for diabetics and non-diabetics (N = 15237)

	Diabetics				Non-diabetics			
	RIZIV-reimbursements		co-payments		RIZIV-reimbursements		co-payments	
	BMS	DES	BMS	DES	BMS	DES	BMS	DES
Total average cost one year before PCI	8 035.2€	7 958.3€	496.7€	520.2€	4 824.1€	5 446.0€	371.8€	443.3€
Difference	-76.9€		+23.4€		+621.9€		+71.5€	
p-value	0.886		0.216		0.002		<0.001	
Total average cost one year after PCI	17 332.0€	16 573.1€	941.1€	912.9€	13 083.1€	11 356.7€	825.0€	800.3€
Difference	-758.9€		-28.2€		-1 726.4€		-24.7€	
p-value	0.283		0.289		<0.001		0.074	

Diabetics – BMS: n=606 ; Diabetics – DES: n=2 189 ; Non-diabetics – BMS: n=10 970 ; Non-diabetics – DES: n=1 472

For the diabetics we mainly see differences in inpatient (IP) implants, nursing day and drug cost. As the implant cost is higher for the DES patients (DES is reimbursed for diabetic patients) and the nursing day and drug costs are higher for the BMS patients, these cost differences are largely neutralized. Further most inpatient cost categories are somewhat lower. As said before, the difference is not significant. When we look at the non-diabetic group we find the greatest cost differences for inpatient implants and nursing day costs. Implant and nursing day costs are lower for the DES patients. With the exception of outpatient drugs, costs of most other items are similar or somewhat lower as well; therefore total costs are lower for the DES-group in the non-diabetics. We should keep in mind however that these figures represent current reimbursement policies, which means reimbursement of DES equal to reimbursement of BMS for non-diabetic patients. Incremental material costs of DES are covered by the hospital, and this is not reflected in these reimbursement figures.

Table 5.24: Average 1-year costs after index day 0 for diabetics and non-diabetics per category (N = 15 237)

	Diabetics				Non-Diabetics			
	Reimbursement		Co-payment		Reimbursement		Co-payment	
	BMS	DES	BMS	DES	BMS	DES	BMS	DES
Fees GP OP	295.9	270.6	54.8	53.8	222.4	190.1	48.6	44.4
Specialist fees OP	430.1	437.8	48.0	52.9	417.3	419.3	56.6	63.2
Drugs OP	1847.1	1848.6	289.4	304.8	1261.6	1400.4	247.1	269.4
Paramedical fees OP	598.6	587.0	42.9	40.7	262.5	191.6	30.8	29.6
Dental care OP	40.9	53.5	8.3	9.1	54.1	64.0	10.0	11.9
Other OP except clinical biology, medical imaging, dialysis	367.2	399.4	25.4	16.3	214.1	155.2	28.8	20.8
Clinical biology OP&IP	697.2	627.4	34.2	34.6	491.0	433.2	29.5	27.9
Medical imaging OP&IP	861.0	834.2	15.3	16.9	806.9	786.7	17.2	16.0
Dialysis OP&IP	783.0	749.4	0.0	0.2	209.7	232.1	0.4	0.0
Surgical fees IP	710.6	563.1	0.0	0.0	566.4	426.9	0.5	3.6
Specialist fees 'special treatments' IP	1958.2	1786.5	20.8	20.1	1762.6	1618.2	19.8	17.1
Other fees IP	6.3	9.1	0.1	0.3	4.3	3.8	0.2	0.1
Implants IP	3004.6	3671.8	206.9	200.7	2772.3	2409.4	187.3	174.0
Nursing day IP	4247.8	3574.2	156.9	130.8	2956.2	2227.8	120.3	96.1
Drugs IP	1032.2	813.4	15.9	12.5	808.6	636.9	9.3	9.4
Other	451.2	347.2	22.1	19.3	273.0	161.1	18.7	16.8
Total	**17332.0**	**16573.1**	**941.1**	**912.9**	**13083.2**	**11356.7**	**825.0**	**800.3**

Diabetics – BMS: n=606; Diabetics – DES: n=2 189; Non-diabetics – BMS: n=10 970; Non-diabetics – DES: n=1 472

Direct comparison of the costs of both stent types would be inappropriate since our patients are not randomly allocated to the two treatments and the characteristics of the patients receiving DES or BMS are not similar. Taking into account the observed patient characteristics available in the database could partially correct for this observational bias but does not solve the problem of non-random allocation. We nevertheless tried this exercise of taking the differences of patient characteristics into account. This is done by explaining the costs on the basis of various patient characteristics and PCI type in an OLS regression. Several patient characteristics are taken into account when explaining costs (RIZIV-reimbursements + co-payments). First the PCI type (dummy DES=1) is included, next some demographic characteristics are incorporated: sex and age of the patient, the region where the patient lives and whether the patient survives the follow-up period. We further take into account a number of disease severity characteristics of the patients; whether the patient suffers from an acute infarction when admitted or after failed thrombolysis, whether he or she suffers from stable or asymptomatic coronary artery disease, the number of disease vessels of the patient, whether he or she suffers from renal dysfunction, from peripheral vascular disease, whether thrombocyte aggregation blockers are used during the hospitalization, whether the patient has small vessels or long lesions, whether the lesion is left main or proximal LAD and the number of stents that are placed; we further correct for the fact whether direct stenting is applied, for the center where the patient is admitted and for the total costs (RIZIV-reimbursements + co-payments) of one year before the hospitalization. The latter variable is introduced, as a proxy for the health status of the patient (other than vascular) for which we do not have other indicators.

Several models were fitted to identify the appropriate model in terms of statistical assumptions; we tried simple Ordinary Least Squares (OLS) and Generalized Linear Models (GLM) with a gamma error distribution and a log-link function. OLS performed better on the scaled deviance and therefore proved to have the best model fit. The results of the OLS regressions for the diabetic and the non-diabetic sub-samples are summarized in table 5.25.

Table 5.25: Determinants of one-year follow-up costs

		OLS	
		Diabetic patients	**Non-diabetic patients**
		(n=2 562)	**(n=11 135)**
Choice of PCI (DES)		-709.3	-1 309.7**
Demographic characteristics			
Age		42.3	37.9**
Male gender		-1 272.1*	-775.3**
Region Flanders vs Walloon region		1 800.5	-192.7
Brussels + abroad vs Walloon region		1 958.5	1 806.8**
Death in quarter 1 vs alive		-11 280.1**	-4 385.2**
Death in quarter 2 vs alive		6 281.5*	4 969.4**
Death in quarter 3 vs alive		8 539.0**	11 084.6**
Death in quarter 4 vs alive		8 552.4**	16 348.6**
Disease severity			
Acute infarct/thrombolysis		4 938.9**	4 897.4**
Stable/asymptomatic coronary artery disease		-1 202.4*	-1 365.6**
Number of diseased vessels	2 vs 1	351.5	1 079.3**
	3 vs 1	2 299.8**	2 240.7**
Renal dysfunction		8 900.6**	6 422.4**
Peripheral vascular disease		-137.3	1 491.9**
IIb/IIIa inhibitors		2 414.5**	990.7**
Small vessel		-145.3	-361.4
Long lesion		808.0	-284.1
Left main		-1 991.5	1 304.5
proximal LAD		1 260.6	1 565.5**
Number of stents		-836.7	539.2*
Other			
Direct stenting		-11 11.4*	-356.8

Costs of previous year	0.65**	0.61**
Center	Not shown	Not shown
Constant term	6 970.0	6 670.9**
R-square	0.34	0.22
F	24.06**	54.30**

* significant at the 5% level
** significant at the 1% level

We will first comment on the results for the diabetic patients. The coefficients of the binary variables can be interpreted as the change in costs (in €) when the binary characteristic is present vs. absent. The coefficients of the continuous variables give the change in costs per unit increase of the variable. The OLS results show that the difference in total one-year follow up costs between diabetic patients that receive a DES or BMS amounts to €-709; therefore diabetics who receive a DES are less expensive during the first year of follow-up. The difference is however not significantly different from zero. Some other characteristics explain the difference in costs more importantly. Male patients have €1 272 less costs than female patients. Diabetic patients who die in the first quarter incur lower costs than patients who survive the first year after PCI implant, patients who die in the 2nd, 3rd or 4th quarter are significantly more expensive[l]. Patients who had a PCI after an acute infarction or after thrombolysis have significantly higher costs, patients with stable or asymptomatic disease incur lower costs. It is also found that patients with 3 vessel disease compared to 1 have significantly higher costs (€2 300). Patients with renal failure or that need thrombocyte aggregation blockers during their hospitalization also generate more costs (€8 901 and €2 415 respectively). Direct stenting provides a saving of €1 111. Finally it is found that a patient's cost in the previous year is a good predictor for future costs. It was also found that some centers are more expensive than other centers.

For the non-diabetic patients results are quite similar. An important difference however is that for this group of patients we do find a significant cost difference between DES and BMS. Patients who receive a DES have €1 310 less costs in the follow-up period than patients who receive a BMS. For the non-diabetics also a great cost difference between DES and BMS was found without taking patient characteristics into account. In agreement with the results for the diabetic patients it is found that male patients are less expensive. Patients who die in the first quarter have lower and patients who die in the other quarters have higher costs than survivors[1], patients who had an acute infarction when admitted or after failed thrombolysis, patients who had more than one diseased vessel, renal failure, are treated with IIb/IIIa inhibitors have significantly higher costs. Patients with stable or asymptomatic disease incur lower costs. The costs of the previous year are again a good predictor for future costs. For the non-diabetics, in addition to these significant variables, other determinants have a significant impact as well. Elder patients are more expensive; patients suffering from peripheral vascular disease are €1 491.9 more expensive. Patients with proximal LAD generate an extra cost of €1 565.5, and patients who need more than one stent incur €539.2 more costs.

When we compare the results from the multivariate analysis (table 5.25) with the results of the simple cost comparison (tabel 5.23) we see that taking into account patient characteristics does not fundamentally change the cost difference between DES and BMS in diabetic patients and the difference remains insignificant. Taking into account patient characteristics for the non-diabetic group decreases the difference to about €1 300 in favor of DES and this difference remains significant.

l The fact that patients who die in the first quarter have lower costs could be explained by the fact that the follow-up period for them is far less than one year. For patients dying in quarter two or later, the shorter follow-up period is obviously dominated by higher costs related to the death of the patient.

However, still this does not allow us to conclude that DES lowers health care costs in comparison to BMS. In the regression analysis we could only correct for observed patient characteristics available in the database. But this does not solve the problem of non-random allocation. The variable of PCI choice in our regression is obviously an endogenous variable with resulting problems of selection bias induced by incorrectly omitted observable variables and unobserved factors.

5.4.10 Clinical outcomes and its determinants

We describe several clinical outcomes at one month and one year follow-up. We first give descriptive results for the 3 patient groups (general population, diabetic and non-diabetic patients), and subsequently we discuss the determinants of these outcome indicators in multivariate logistic regression analyses.

The clinical outcomes discussed are:

- Mortality
- CABG
- Renal dialysis (when this was not the case before the index PCI)
- Re-PCI
- Massive bleeding[m]
- Angiographically defined success
- Success without complications

Clinical outcomes are determined at one month after the PCI implant and at one year after the PCI implant except for the outcome 'angiographically defined success' which is available as a 1 month indicator only, because it can not be detected in the reimbursement data. Furthermore, we defined the variable success without complications (1 month and 1 year) as a PCI that was angiographically successful and where the patient had no complications, i.e. the patient did not die, had no CABG, no dialysis, no re-PCI and no massive bleeding within one month or one year after the index PCI. Re-PCI contains any re-intervention on the patient within 1 month or 1 year, i.e. restenosis, staging and intervention on new lesions due to progression of disease. This outcome indicator was chosen because it is the most important from a patient perspective. Since we do not know the exact date (only the month of the re-intervention or complication), we consider a re-intervention/complication within one month (one year) from the day of index-procedure if the end-day of the hospitalization related to the re-intervention or complication is within 30 or 365 days from the day of index-procedure. For death we know the month of death and we assume the patient died the last day of the month.

Frequencies for these outcome indicators for the population in general and for the diabetics and non-diabetics are presented in table 5.26.

m Specific nomenclature codes for blood transfusions were not available in the IMA database, therefore the following codes were used as a proxy for massive bleeding: 470271 470282 (medical supervision on a high risk transfusion) 555111 555122 (compatibility test for transfusion) 555155 555166 (search for irregular anti-erythrocyte-antibodies) 555531 555542 (compatibility test for massive transfusion of single donor leucocytes or thrombocytes if anti-HLA antibodies were detected in recipient) 752415 752426 (plasma for autolog transfusions). For a detailed description of these nomenclature codes see the appendix to this chapter. When one of these codes is present for a patient it is assumed that he/she had a massive bleeding. We did not include patients who had one of these codes for the index hospitalization as preventive compatibility tests are often performed preventively before a PCI.

Table 5.26: Outcome indicators of the index procedure

	General (n=15 237)	Diabetics (n=2 795)	Non-diabetics (n=12 442)
Death < 1month	1.4%	1.6%	1.4%
CABG < 1 month	0.58%	0.57%	0.59%
Renal dialysis < 1 month	0.20%	0.36%	0.17%
Re-PCI < 1 month	7.7%	8.6%	7.5%
Massive bleeding < 1 month	2.1%	3.2%	1.9%
Death < 1 year	4.3%	5.7%	3.9%
CABG < 1 year	2.6%	2.4%	2.7%
Renal dialysis < 1 year	0.64%	1.1%	0.54%
Re-PCI < 1 year	17.0%	19.0%	16.5%
Massive bleeding < 1 year	11.1%	13.6%	10.5%
Angiographic succes	95.9%	95.6%	96.0%
Angiographic succes + no compl < 1 month	85.8%	84.2%	86.2%
Angiographic succes + no compl < 1 year	68.9%	64.5%	69.9%

As expected, the outcome indicators of the diabetic patients are worse than those of the non-diabetics. Diabetics more often die, need more dialysis and re-PCIs and suffer from massive bleeding more frequently. Only for CABG at 1 year the results are reversed but the differences are very small and could be interpreted as due to an elevated surgical risk. Of all patients, 69% both survive the PCI and do not suffer from the considered complications within one year. For the diabetics and non-diabetics these proportions are 65% and 70% respectively.

Next we try to find the determinants of the 3 most important outcome indicators in multivariate logistic regression analyses. We investigate mortality, angiographic success and angiographic success without complications (1 month and 1 year). The results of these analyses can be found in tables 5.27, 5.28 and 5.29. The dependent variables in these logistic regressions are discrete variables taking the value of one when the patient dies, has angiographic success or has an angiographic success and no complications respectively (1 month and 1 year). The explanatory variables are relevant demographic and disease severity characteristics of the patients. Figures in the table represent odds ratios. Separate analyses were performed for the general population, the diabetics and the non-diabetics.

Table 5.27: Odds ratios for outcome parameters of the index procedure in the general population: results from a multivariate regression analysis (n=12 294)

	Mortality		'Succes'	Succes + no compl	
	1 month	1 year		1 month	1 year
PCI choice (DES=1)	0.81	1.02	1.09	1.27**	1.45**
Male	0.92	1.04	1.05	1.08	1.07
Previous PCI	1.10	0.92	0.95	1.35**	1.15**
Diabetes	1.27	1.48**	0.97	0.78**	0.67**
Number of stents	1.05	1.13	1.26	0.78**	0.92
Number of lesions 1 vs 3	0.85	0.74*	2.00**	3.25**	2.53**
2 vs 3	0.71	0.80°	1.27°	1.26**	1.29**
Age (per year)	1.07**	1.07**	0.99*	0.99**	0.99**
Renal dysfunction	3.32**	3.16**	0.97	0.74°	0.60**
IIb/IIIa inhibitors	0.91	0.89	0.77*	0.92	0.91°
Peripheral vascular disease	1.38	1.56**	0.91	0.92	0.73**
Acute MI or failed thrombolysis	5.40**	2.10**	0.70*	0.61**	0.79**
Stable/asymptomatic CHD	0.53*	0.56**	1.33*	1.15*	1.09°
Cardiogenic shock	16.23**	10.51**	0.36**	0.30**	0.35**
Small vessel	1.06	0.91	0.38**	0.61**	0.76**
Long lesion	1.36	0.84	0.47**	0.81°	0.88
Left main	4.39**	2.41**	0.56*	0.84	0.70*
Proximal LAD	1.72**	1.21	0.85	0.89	0.88*
Direct stenting	0.83	0.89	2.37**	1.61**	1.26**

° significant at the 10% level
* significant at the 5% level
** significant at the 1% level

From table 5.27 it is obvious that many characteristics influence the outcome measures studied. An important result is that the type of stent (BMS/DES) is not associated to mortality or angiographic success. It does, however, influence the 'success and no complications' variable. Patients that receive a DES have a 1.3 and 1.5 times higher probability to have an angiographic success and no complications after one month and one year respectively in comparison to patients with BMS. Again, it is unclear from these observational results whether this relation is causal.

Other important, although expected, results are that patients who were admitted for their initial PCI with an acute MI or who had a rescue PCI after failed thrombolysis or who presented with cardiogenic shock have a high probability to die and a low probability to have a successful PCI, whereas patients with a stable or asymptomatic CHD have a much better prognosis. It is also found that older people and patients who have more than one lesion have a lower probability of survival and success. Further we see that patients who need more than one stent have a lower probability to be 'successful without complications' within 30 days and the same holds for patients with PCIs in small vessels after both 30 days and one year. The latter also have a lower probability to be 'successfully stented'. Patients with renal dysfunction have a 3.3 and 3.2 times higher probability to die within one month and one year respectively. Patients who are treated with IIb/IIIa inhibitors have a lower probability to have an angiographically successful PCI. Patients who are treated for left main disease have a lower probability to survive and to be successful. Finally it can be derived from the table that diabetics have a 1.5 times higher probability to die within the year compared to non-diabetics. They also have a 0.8 and 0.7 times lower probability to have a successful PCI without complications at 1 month and 1 year respectively.

In general we can conclude that the type of stent used is significantly associated with the 'success rate without complications' but, again, this observational study does not allow for causal inference since results may be biased by selection. The results are derived from a naturalistic setting and the patients receiving a BMS versus a DES are not identical. In the analyses we do control for some obvious and measured patient characteristics but nevertheless results may be biased by unmeasured or unobservable confounding.

Table 5.28: Odds ratios for outcome parameters of the index procedure in the diabetic population: results from a multivariate regression analysis (n=2 256)

	Mortality		Succes	Succes + no compl	
	1 month	1 year		1 month	1 year
PCI choice (DES)	0.92	0.93	1.62°	1.21	1.70**
Male	1.39	1.15	1.37	1.09	1.17
Previous PCI	1.12	0.91	0.71	1.52*	0.97
Number of stents	2.02	1.01	1.13	0.77	0.95
Lesions treated 1 vs 3	1.47	0.97	1.74°	2.30**	2.21**
Lesions treated 2 vs 3	1.06	1.03	0.93	1.02	1.21
Age (per year)	1.11**	1.08**	1.00	0.98*	0.99*
Renal dysfunction	1.95	2.97**	0.99	0.62°	0.42**
IIb/IIIa inhibitors	2.18°	1.29	0.94	0.89	0.75*
Peripheral vascular disease	1.00	1.52°	0.98	1.29	0.88
Acute MI/ failed thrombolysis	3.07*	1.61°	1.32	0.57**	0.87
Stable/asymptomatic CHD	0.35	0.56*	1.50	1.23	1.12
Cardiogenic shock	21.44**	13.92**	0.11**	0.21**	0.18**
Small vessel	0.85	0.74	0.60°	0.82	0.93
Long lesion	1.94	1.02	0.48	0.87	0.77
Left main	3.30	1.56	0.55	0.73	1.28
Proximal LAD	1.49	1.03	1.34	1.09	0.90
Direct stenting	0.93	0.76	4.88**	1.99**	1.26*

° significant at the 10% level
* significant at the 5% level
** significant at the 1% level

Looking at the results for diabetic patients separately it is clear that fewer characteristics can be found that significantly explain the outcome indicators. This can be explained by the fact that having diabetes is in itself a very important explanatory characteristic. Diabetic patients with a DES have a 1.7 times higher probability to have an 'angiographically successful PCI and have no complications' within one year compared to patients with a BMS, probably due to the observation that diabetics with a poor prognosis more often receive a BMS (see earlier in this chapter). Diabetic patients with cardiogenic shock have a very high probability to die and or to have complications. Other important characteristics are the number of lesions, age, acute MI or failed thrombolysis, stable CHD and direct stenting.

Table 5.29: Odds ratios for outcome parameters of the index procedure in the non-diabetic population: results from a multivariate regression analysis (n=10 038)

	Mortality		Succes	Succes + no compl	
	1 month	1 year		1 month	1 year
PCI choice (DES)	0.82	1.10	0.89	1.29*	1.33**
Male	0.85	1.01	0.97	1.08	1.04
Previous PCI	1.09	0.92	1.07	1.31**	1.22**
Number of stents	0.85	1.14	1.30°	0.78**	0.92
Lesions treated 1 vs 3	0.76	0.67**	2.06**	3.54**	2.62**
Lesions treated 2 vs 3	0.65°	0.73*	1.35*	1.34**	1.32**
Age (per year)	1.06**	1.07**	0.99*	0.99*	0.99**
Renal dysfunction	4.02**	3.23**	1.00	0.79	0.71*
IIb/IIIa inhibitors	0.74	0.79°	0.75*	0.92	0.96
Peripheral vascular disease	1.54°	1.57**	0.91	0.84°	0.70**
Acute MI/ failed thrombolysis	6.32**	2.26**	0.64**	0.61**	0.76**
Stable/asymptomatic CHD	0.60°	0.56**	1.30*	1.13°	1.08
Cardiogenic shock	15.56**	9.94**	0.50**	0.33**	0.39**
Small vessel	1.14	0.99	0.34**	0.57**	0.72**
Long lesion	1.33	0.81	0.47**	0.79*	0.89
Left main	4.82**	2.61**	0.57°	0.88	0.64**
Proximal LAD	1.77*	1.26	0.80°	0.86°	0.88*
Direct stenting	0.80	0.94	2.09**	1.54**	1.26**

° significant at the 10% level
* significant at the 5% level
** significant at the 1% level

The results for the non-diabetic patients are very similar to those of the general population. Again it is found that patients who receive a DES have a higher probability (1.3 times resp.) to have 'angiographic success and no complications' within 30 days or one year.

Key points

- **In 2004, almost 25 000 PCI were performed in over 21 000 patients.**
- **Due to reimbursement rules most diabetic patients receive a DES while most non-diabetics receive a BMS. However, other clinical and non-clinical parameters (for example the choice for a private hospital room) also influence the choice for DES vs. BMS.**
- **The average number of stents used during PCI is 1.3 (higher for BMS than for DES) but in approximately 5% of PCIs a subsequent staged procedure can be assumed.**
- **The average cost (reimbursement plus patient co-payment) for the original PCI hospital stay is over €7 000. For those patients needing re-PCI in the first year the re-PCI cost is around €6 500. The average health care payer cost in the 365 days after the original PCI is around €18 000 for diabetic patients and around €13 000 for non-diabetics.**
- **Direct comparisons of follow-up costs in patients treated with DES and with BMS are misleading in this observational and non-randomised setting because of differences in patient characteristics.**
- **Patient outcomes in real-world circumstances are different from trial conditions. In this Belgian registry 1-year mortality after PCI is 4.3% compared to approximately 1% in most DES trials, illustrating the different patient mix.**
- **The restenosis rates are lower in patients with a DES implant than in patients with a BMS implant but, especially in non-diabetics, the difference is much smaller than would be expected from RCT evidence. This is probably explained by the clinical judgement of interventional cardiologists who preferable uses a DES in patients with a higher risk of restenosis.**

6 ECONOMIC MODEL FOR BELGIUM

In this chapter we describe the economic model which is developed to calculate cost-effectiveness of DES versus BMS for the Belgian health care payer. The structure of the model, its input data, and other aspects are provided to assure transparency of the model. Results for several scenarios are calculated and discussed.

6.1 RATIONALE

The economic studies included in our review of cost-effectiveness studies (chapter 4) used data which were published in the 'pre-Barcelona' period. Since this conference in September 2006, a lot of new evidence on the use of DES has been published. Most of the studies have been performed in Canada, the US or UK. As shown in the literature overview, results are not always in the same line. Furthermore, there have been no published studies using Belgian data and costs which reflect current local practice. Therefore, we felt it essential to develop our own model to estimate the costs and benefits arising from the use of DES in the Belgian context. In this model, we took into account the results of recently published studies and include real-world data coming from the Belgian health insurance and the Belgian BWGIC registry.

Our objective is to assess the cost-effectiveness, i.e. the trade-off between additional costs and improved clinical outcome, of the use of DES versus BMS in patients with coronary heart disease (CHD).

6.2 METHODS

In an economic evaluation, some aspects (such as the population, intervention and comparator) are case specific. Other methodological decisions, however, are based on existing guidelines. For this Belgian HTA report, we follow the existing Belgian guidelines for pharmaco-economic evaluations.[200]

6.2.1 Perspective of the evaluation

In accordance with the Belgian pharmaco-economic guidelines, the analysis is performed from the perspective of the health care payer. This includes both costs paid by the standard health insurance and the patient out-of-pocket contribution.

6.2.2 Analytical technique

As shown in our economic review, several studies have performed cost-effectiveness (CEA) and/or cost-utility (CUA) analysis. No life years are gained and therefore the metric 'cost/LYG' can not be used. Through avoiding repeat procedures, utilities are gained. Therefore, we express our results in cost per QALY gained. An alternative approach used in several studies is to express results in the disease specific outcome 'cost per revascularization avoided'. We believe it is hard to rely on this metric. However, for reasons of comparability with previous economic evaluations, we also include this metric in our base case calculations. Nonetheless, we would like to stress that costs per QALY are more useful for decision makers.

6.2.3 Population

As for most health interventions, universal use of a specific technique may not be advisable. Depending on population characteristics, certain subgroups may gain relatively more than others. These differences should be taken into account to obtain a more optimal use of health interventions. For DES, the selection criteria most often used include diabetes, lesion length and vessel diameter, since they are associated with an increased risk of repeat revascularization. In contrast to *diabetic status*, no direct estimates for lesion length and vessel diameter were available in the Belgian registry. However, an approximation for *complex lesions* was taken into account (see definition in table 6.1).

Finally, the variable for *multi-vessel disease* (MVD) was also applied to construct subgroups. In combination with the *initial stent type* (DES/BMS), 16 subgroups were created.

Our analysis was performed separately for the complete population in our registry and for 'clean' patients, which are patients in our database without an interventional history. Furthermore, as discussed previously, the Belgium reimbursement system may encourage staging. The database contained the variable 'staging' to correct for this phenomenon (see definition in table 6.1). By doing so, staged procedures are seen as part of the index procedure. Taking this variable into account in an incremental economic evaluation has an influence on both the mean number of stents used in the initial procedure and the probability for repeat procedures. In our base case, we include this correction. The original database, without this correction, is applied in an alternative scenario analysis.

Other variables that could have an influence on the probability for repeat revascularization, such as age, sex, and others, were not included since this would result in small numbers of observations in several subgroups. As such we try to provide results for specific subgroups without creating unstable or unreliable results due to a lack of data. Table 6.1 gives an overview of population characteristics included in our model to create subgroups.

Table 6.1: population characteristics to determine subgroups

Characteristics	Description
DES/BMS	The type of stents that was implemented in the initial procedure
Diabetes	No treated diabetes versus diabetes treated with oral medication or insulin treated diabetes
Multivessel disease	More than 1 vessel affected diagnosed through coronarography
Complex lesion	Either small vessels (peripheral vessels defined by segment) or long lesions (operationalised as more than 1 stent needed in the same segment)
'Clean' patients	No interventional history (no PCI, no CABG)
Staging correction	Multivessel disease (MVD) plus second PCI in another vessel than the index PCI and less or equal to 45 days after index PCI (or third within 45 days after staged PCI, and other vessel than index PCI)

6.2.4 Intervention and comparator

The intervention and comparator under consideration are the implantation of DES versus BMS. Relying on observational data, no direct comparison is possible due to the different underlying characteristics of patients receiving BMS or DES. In our approach, we want to apply both strengths of observational data and meta-analysis of published literature. Initial probabilities (i.e. probabilities as observed in reality) for certain events are based on data from the Belgian registry and cost data come from the Belgian health insurance. Relative risk improvements are based on published meta-analyses. As such we initially set up the situation 'as it is' for both the BMS and DES subgroups. Then, we apply the relative improvement of applying DES on the BMS subgroups. Similarly, but in the opposite direction, we apply the relative deterioration on the DES subgroups to reflect the situation if they would have been treated with BMS.

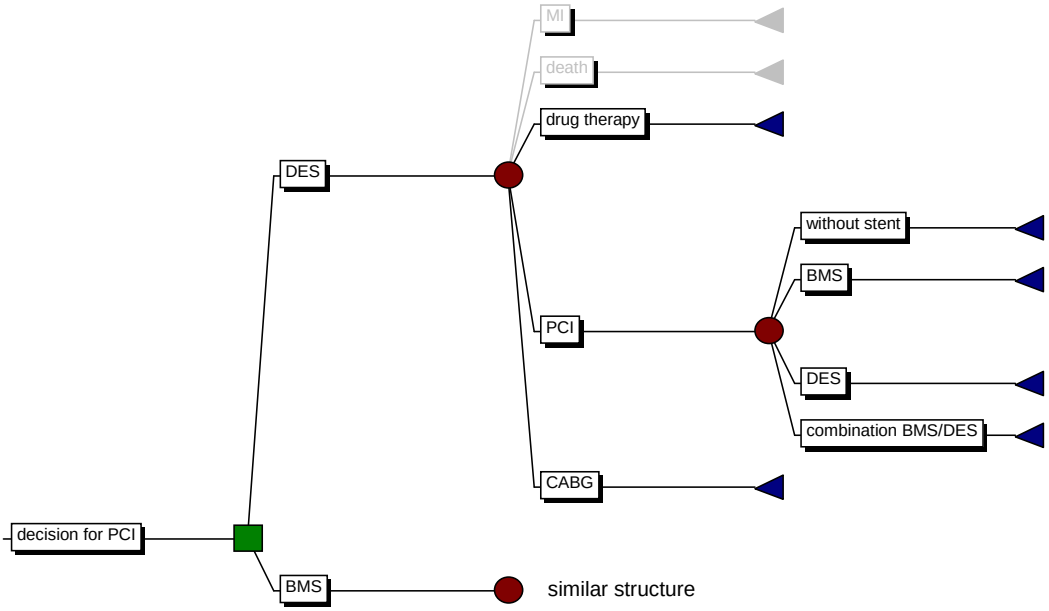
The idea for this approach is that the clinical report of a trial often indicates there is no evidence of difference between subgroups in terms of relative treatment effect. As mentioned by Drummond et al,[201] cost-effectiveness is driven by absolute benefit, and there may be important variation between subgroups in baseline event rates. This assumption of constant relative effects being applied to subgroup-specific baseline event rates is thus common in cost-effectiveness models.[201] As such, our model uses both strengths of observational data to reflect real-world situations, and from randomized controlled trials to determine relative improvements.

6.2.5 The model

6.2.5.1 Structure (The clinical pathway used for analysis)

The structure of the model is based on interventional cardiology clinical pathways based on expert opinion and the design of other decision analytic models included in our literature review (chapter 4). The design of the decision tree is shown in figure 6.1. The first node indicates the choice between DES and BMS. The structure for both arms of the decision model is the same for both BMS and DES. After the implantation of a DES/BMS, MI, death or other symptoms may occur. Since published randomized trials and meta-analyses have shown no difference in MI or death between DES and BMS, both treatment nodes are not further taken into account for calculations. All patients receive drug therapy, which may differ according to the type of stent implanted. If symptoms appear, a repeat procedure may be considered, which can be a PCI with stent (BMS, DES or a combination of both), PCI without stent (balloon angioplasty) or CABG. No difference between first, second, or third repeat interventions is made. Alternatively, we include the cumulative percentage for the probability of a repeat procedure. As such, we assume the same influence of DES versus BMS on a first, second or third repeat intervention.

Figure 6.1: Decision model for the choice of stent for PCI



BMS: bare metal stent; CABG: coronary artery bypass graft; DES: drug eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention
The square represents a decision node (DES or BMS), the circles represent chance nodes and costs are linked to the triangles. The rates of deaths or nonfatal MI have been shown to be identical for both arms and are therefore not taken into account in calculations. Probabilities and costs for all the arms of the decision model can be found in the part 'input parameters'.

6.2.5.2 Time window and discounting

The time horizon in an economic evaluation should extend far enough into the future to capture the major health and economic outcomes. Frequently, this means results are modelled up to lifetime. In this case however, based on published literature, no difference in long-term results is expected. Most recent published meta-analyses have a follow-up period of four years. Therefore, we initially thought to apply a 4-year time horizon. However, as mentioned by Cohen,[142] previous studies suggest that the restenosis process is largely complete after 12 months,[174] so later events are related predominantly to atherosclerosis progression, which would be unlikely to be altered by using DES. Furthermore, no conclusive evidence is available concerning the long-term events.

And finally, our Belgian registry contains data during a follow-up period of one year. As a result, we decided to model cost effectiveness of DES versus BMS over a one year period.

According to the Belgian pharmaco-economic guidelines, future costs and benefits are discounted at a yearly rate of 3% and 1.5% respectively in the base-case analysis.[200] Since the costs and benefits are only modelled over a one-year period and discounting would not alter results, we did not apply any discount rate.

6.2.5.3 Input parameters

In the following part we present the values of input parameters used in the model, shape of the distributions and ranges of the values for probabilistic modelling and probabilistic sensitivity analysis.

STENT COSTS

The costs for the initial procedure are calculated based on Belgian cost data. According to these data, differences are observed according to patient characteristics. As mentioned before, however, the BMS and DES groups can not be compared to calculate incremental costs and benefits since the underlying populations are different. In our approach we pose the questions: what would be the incremental cost and benefit for each subgroup if the BMS treatment groups would have been treated with DES and the other way round. As such, the only incremental costs for the initial procedure are caused by the difference in stent costs. Two scenarios are worked out. First of all, we use reimbursement costs for different type of stents. Secondly, we performed our analysis including real purchase stent costs.

An extra €1000 is reimbursed if DES is implanted in a patient with diabetes, no matter how much stents are implanted. There is no higher reimbursement price for non-diabetic patients if DES was implanted (table 6.2). Even though we are performing an economic evaluation from the health care payer's perspective, the extra cost for the intervention under consideration should be included. Therefore, we include the extra cost of DES if this type of stent was used for the initial PCI or repeat PCI. The analysis which uses this approach is indicated 'RIZIV/INAMI stent cost'.

Table 6.2: PCI reimbursement cost for Belgian Health Insurance

Cost for Belgian Health Insurance	
PCI without stent	1350 €
PCI with BMS	2050 €
PCI with DES	
non-diabetics	2050 €
diabetics	3050 €

BMS: bare metal stent; DES: drug eluting stent

Furthermore, one could expect that if the health care payer decides to reimburse a certain technology, the reimbursement price would follow the increased underlying treatment cost. Therefore, in an alternative scenario, the difference in treatment cost between DES and BMS is based on the mean cost per stent and the number of stents used.

The cost for DES and BMS is based on list prices obtained from four manufacturers: Boston Scientific, Cordis, Medtronic, and Abbott. To be able to guarantee confidentiality, we agreed not to publish individual list prices but to use a weighted average, rounded to the nearest hundred, without providing further details. For BMS, the weighted rounded average was €1 000. For DES we not only included prices for the paclitaxel and sirolumus eluting stent since keeping confidentiality with two numbers towards the two manufacturers would not be possible. Therefore, we also gathered prices of two other types of DES from the other manufacturers (which received a lower weight in our calculations). As such we calculated an average price for DES of €2500 (table 6.3).

Table 6.3: weighted average of official stent costs and disount percentage

Stent cost and discount %	mean	Beta distribution	
		Lower bound	Upper bound
BMS	1000 €	/*	/
DES	2500 €	/	/
discount (%)	50%	30%	70%

BMS: bare metal stent; DES: drug eluting stent

*: Mentioning lower and upper bounds is considered inappropriate to remain confidentiality of official stent prices received by the four manufacturers. The real stent cost varies by multiplying the official stent prices with the probabilistic discount percentage.

These average weighted prices are based on official list prices. In reality, however, actual market prices are considerably lower due to discounts. This discount mainly depends on the size of the department and the quantities of stents being bought. For larger departments, according to expert opinion, this price discount would be about 60-70%, while it would be about 30-35% for smaller institutes (expert opinion). In our model, we apply a Beta distribution with an average discount of 50% varying between 30% to 70% (table 6.3). We prefer to include this discount percentage since this is what realy happens in reality and we do not want to make a model for an individual (large or small) hospital. However, in a separate scenario analyis, we work with five different fixed real stent costs for DES (see further).

AVERAGE NUMBER OF STENTS

The average number of stents was calculated for each subgroup based on the Belgian registry. Table 6.4 provides an overview of the average number of stents for each subgroup. As mentioned before, the Belgian reimbursement system may encourage staging. Part a of table 6.4, i.e. our base case, gives an overview of the mean number of stents taking into account the correction for the staging phenomenon. Part b provides an overview for the input used in our alternative scenario without any correction for staging. Part c and d provide the same details for our 'clean' population. In our economic evaluation, since we have large numbers, we modelled the number of stents as a normal distribution and cut-off this distribution at the 1st and 99th percentile value to prevent unlogic values (+/-infinity) to be drawn from this distribution.

Table 6.4, part a: average number of stents with staging correction

Population characteristics		N	Mean	St. dev mean	Normal distribution	
					Lower bound	Upper bound
All patients		15032	1,30	0,0051	1	4
Type of stent						
BMS	all	11453	1,32	0,0060	1	4
	non-diabetics	10852	1,32	0,0061	1	4
	diabetics	601	1,33	0,0249	1	3
DES	all	3579	1,23	0,0092	1	3
	non-diabetics	1435	1,24	0,0143	1	3
	diabetics	2144	1,22	0,0119	1	4
BMS, non diabetics						
no MVD or complex lesion		4129	1,09	0,0047	1	2
no MVD but complex lesion		902	1,61	0,0246	1	4
MVD but no complex lesion		4523	1,29	0,0085	1	3
MVD and complex lesion		1298	1,97	0,0278	1	5
BMS, diabetics						
no MVD or complex lesion		199	1,11	0,0234	1	2
no MVD but complex lesion		49	1,71	0,1200	1	4
MVD but no complex lesion		277	1,29	0,0324	1	3
MVD and complex lesion		76	1,86	0,0929	1	5
DES, non-diabetics						
no MVD or complex lesion		526	1,05	0,0109	1	2
no MVD but complex lesion		139	1,63	0,0628	1	4
MVD but no complex lesion		613	1,21	0,0194	1	3
MVD and complex lesion		157	1,66	0,0638	1	5
DES, diabetics						
no MVD or complex lesion		703	1,05	0,0091	1	2
no MVD but complex lesion		131	1,36	0,0463	1	3
MVD but no complex lesion		1040	1,21	0,0164	1	3
MVD and complex lesion		270	1,64	0,0529	1	5

Table 6.4, part b: average number of stents without staging correction

Population characteristics		N	Mean	St. dev mean	Normal distribution	
					Lower bound	Upper bound
All patients		15032	1,26	0,0046	1	3
Type of stent						
BMS	all	11453	1,29	0,0055	1	3
	non-diabetics	10852	1,29	0,0057	1	3
	diabetics	601	1,30	0,0228	1	3
DES	all	3579	1,19	0,0080	1	3
	non-diabetics	1435	1,22	0,0135	1	3
	diabetics	2144	1,17	0,0097	1	3
BMS, non diabetics						
no MVD or complex lesion		4129	1,09	0,0047	1	2
no MVD but complex lesion		902	1,61	0,0246	1	4
MVD but no complex lesion		4523	1,23	0,0071	1	3
MVD and complex lesion		1298	1,90	0,0258	1	5
BMS, diabetics						
no MVD or complex lesion		199	1,11	0,0234	1	2
no MVD but complex lesion		49	1,71	0,1200	1	4
MVD but no complex lesion		277	1,25	0,0300	1	3
MVD and complex lesion		76	1,74	0,0757	1	3
DES, non-diabetics						
no MVD or complex lesion		526	1,05	0,0109	1	2
no MVD but complex lesion		139	1,63	0,0628	1	4
MVD but no complex lesion		613	1,16	0,0162	1	2
MVD and complex lesion		157	1,65	0,0638	1	5
DES, diabetics						
no MVD or complex lesion		703	1,05	0,0091	1	2
no MVD but complex lesion		131	1,36	0,0463	1	3
MVD but no complex lesion		1040	1,12	0,0105	1	2
MVD and complex lesion		270	1,57	0,0505	1	5

Table 6.4, part c: average number of stents with staging correction for 'clean' population

Population characteristics		N	Mean	St. dev mean	Normal distribution	
					Lower bound	Upper bound
All patients		6275	1,30	0,0078	1	4
Type of stent						
BMS	all	4889	1,32	0,0090	1	4
	non-diabetics	4663	1,32	0,0092	1	4
	diabetics	226	1,38	0,0439	1	3
DES	all	1386	1,25	0,0156	1	4
	non-diabetics	544	1,24	0,0240	1	3
	diabetics	842	1,25	0,0203	1	4
BMS, non diabetics						
no MVD or complex lesion		2028	1,07	0,0058	1	2
no MVD but complex lesion		440	1,62	0,0353	1	4
MVD but no complex lesion		1694	1,32	0,0141	1	3
MVD and complex lesion		501	2,03	0,0447	1	5
BMS, diabetics						
no MVD or complex lesion		87	1,11	0,0386	1	3
no MVD but complex lesion		19	1,84	0,2202	1	4
MVD but no complex lesion		96	1,35	0,0612	1	3
MVD and complex lesion		24	2,04	0,1653	1	4
DES, non-diabetics						
no MVD or complex lesion		248	1,04	0,0146	1	2
no MVD but complex lesion		62	1,63	0,0864	1	4
MVD but no complex lesion		180	1,23	0,0365	1	3
MVD and complex lesion		54	1,78	0,1306	1	5
DES, diabetics						
no MVD or complex lesion		325	1,05	0,0116	1	2
no MVD but complex lesion		61	1,38	0,0704	1	3
MVD but no complex lesion		355	1,25	0,0308	1	4
MVD and complex lesion		101	1,79	0,0965	1	5

Table 6.4, part d: average number of stents without staging correction for 'clean' population

Population characteristics		N	Mean	St. dev mean	Normal distribution	
					Lower bound	Upper bound
All patients		6275	1,27	0,0073	1	3
Type of stent						
BMS	all	4889	1,29	0,0086	1	3
	non-diabetics	4663	1,29	0,0086	1	3
	diabetics	226	1,34	0,0406	1	3
DES	all	1386	1,21	0,0137	1	3
	non-diabetics	544	1,23	0,0232	1	3
	diabetics	842	1,19	0,0172	1	3
BMS, non diabetics						
no MVD or complex lesion		2028	1,07	0,0058	1	2
no MVD but complex lesion		440	1,62	0,0353	1	4
MVD but no complex lesion		1694	1,26	0,0124	1	3
MVD and complex lesion		501	1,96	0,0424	1	5
BMS, diabetics						
no MVD or complex lesion		87	1,11	0,0386	1	3
no MVD but complex lesion		19	1,84	0,2202	1	4
MVD but no complex lesion		96	1,33	0,0582	1	3
MVD and complex lesion		24	1,79	0,1347	1	3
DES, non-diabetics						
no MVD or complex lesion		248	1,04	0,0146	1	2
no MVD but complex lesion		62	1,63	0,0864	1	4
MVD but no complex lesion		180	1,19	0,0313	1	3
MVD and complex lesion		54	1,76	0,1320	1	5
DES, diabetics						
no MVD or complex lesion		325	1,05	0,0116	1	2
no MVD but complex lesion		61	1,38	0,0704	1	3
MVD but no complex lesion		355	1,15	0,0202	1	2
MVD and complex lesion		101	1,71	0,0935	1	5

DRUG THERAPY

Costs for drug therapy were also included. These costs are not reimbursed for all patients and could therefore not be extracted from the Belgian database. Consequently, these costs are modeled theoretically. Usually, 75mg clopidogrel (Plavix) is given per day (loading dose, 300mg). In Belgium, 28 tablets of 75mg clopidogrel cost €53.1, i.e. about €57 per month (table 6.5). The optimal duration of this combination therapy (associated with asprin) is unknown. According to the device leaflets it should be one month for BMS, 3 months for SES and 6 months for PES.[179] In our model, in the base case analysis, we assume that this anti-platelet therapy was given for one month after BMS and for 6 months after DES. In alternative scenarios, we change this duration to 1, 3 and 12 months for DES.

Table 6.5: cost for underlying drug therapy

Drug therapy	mean
clopidogrel (Plavix, 75mg/day)	€56.89/month*
Duration after DES	
base case scenario	6 months
alternative scenarios	1, 3 and 12 months
Duration after BMS	1 month

* Source: www.bcfi.be, accessed 16 August, 2007

REPEAT INTERVENTIONS: PCI

Savings from avoided revascularization procedures are subtracted from the additional initial costs of the DES implant and extra costs for drug therapy after DES implantation to calculate the total incremental cost of DES versus BMS. In our model, the repeat intervention could be CABG and/or PCI with or without stenting. The probabilities and costs of these interventions are calculated using Belgian real-world data.

For repeat PCI, several probabilities were calculated: a) the probability of having a repeat PCI; b) the probability this was due to restenosis; and c) if a re-PCI was necessary, which percentage was performed without a stent or with DES, BMS or a combination of both. Concerning the probability for a repeat procedure, no distinction was made whether it was a first, second, or third repeat procedure. As such, a cumulative probability of having a repeat procedure was modeled (table 6.6). The probability this repeat procedure was due to restenosis was also determined in the Belgian database (table 6.6). Changing from BMS to DES could only have an influence on this part of repeat PCIs, which was modeled as a Beta distribution.

Table 6.6, part a: cumulative probability for a repeat PCI and the probability this was due to restenosis (population with staging correction)

Population characteristics		% re-PCI				% of re-PCI due to restenosis			
				Beta distribution				Beta distribution	
		N	%	alpha 1	alpha 2	N	%	alpha 1	alpha 2
All patients		15032	14,27%	2145	12887	2145	40,84%	876	1269
Type of stent									
BMS	all	11453	14,22%	1629	9824	1629	42,73%	696	933
	non-diabetics	10852	13,81%	1499	9353	1499	42,43%	636	863
	diabetics	601	21,63%	130	471	130	46,15%	60	70
DES	all	3579	14,42%	516	3063	516	34,88%	180	336
	non-diabetics	1435	12,13%	174	1261	174	38,51%	67	107
	diabetics	2144	15,95%	342	1802	342	33,04%	113	229
BMS, non-diabetics									
no MVD or complex lesion		4129	9,23%	381	3748	381	55,38%	211	170
no MVD but complex lesion		902	10,42%	94	808	94	58,51%	55	39
MVD but no complex lesion		4523	17,58%	795	3728	795	33,96%	270	525
MVD and complex lesion		1298	17,64%	229	1069	229	43,67%	100	129
BMS, diabetics									
no MVD or complex lesion		199	13,07%	26	173	26	61,54%	16	10
no MVD but complex lesion		49	12,24%	6	43	6	50,00%	3	3
MVD but no complex lesion		277	27,44%	76	201	76	42,11%	32	44
MVD and complex lesion		76	28,95%	22	54	22	40,91%	9	13
DES, non-diabetics									
no MVD or complex lesion		526	7,22%	38	488	38	55,26%	21	17
no MVD but complex lesion		139	7,91%	11	128	11	72,73%	8	3
MVD but no complex lesion		613	16,97%	104	509	104	24,04%	25	79
MVD and complex lesion		157	13,38%	21	136	21	61,90%	13	8
DES, diabetics									
no MVD or complex lesion		703	8,53%	60	643	60	38,33%	23	37
no MVD but complex lesion		131	12,98%	17	114	17	47,06%	8	9
MVD but no complex lesion		1040	20,10%	209	831	209	27,75%	58	151
MVD and complex lesion		270	20,74%	56	214	56	42,86%	24	32

Table 6.6, part b: cumulative probability for a repeat PCI and the probability this was due to restenosis (population without staging correction)

Population characteristics		% re-PCI				% of re-PCI due to restenosis			
				Beta distribution				Beta distribution	
		N	%	alpha 1	alpha 2	N	%	alpha 1	alpha 2
All patients		15032	17,21%	2587	12445	2587	33,86%	876	1711
Type of stent									
BMS	all	11453	17,16%	1965	9488	1965	35,42%	696	1269
	non-diabetics	10852	16,78%	1821	9031	1821	34,93%	636	1185
	diabetics	601	23,96%	144	457	144	41,67%	60	84
DES	all	3579	17,38%	622	2957	622	28,94%	180	442
	non-diabetics	1435	13,87%	199	1236	199	33,67%	67	132
	diabetics	2144	19,73%	423	1721	423	26,71%	113	310
BMS, non-diabetics									
no MVD or complex lesion		4129	9,23%	381	3748	381	55,38%	211	170
no MVD but complex lesion		902	10,42%	94	808	94	58,51%	55	39
MVD but no complex lesion		4523	23,17%	1048	3475	1048	25,76%	270	778
MVD and complex lesion		1298	22,96%	298	1000	298	33,56%	100	198
BMS, diabetics									
no MVD or complex lesion		199	13,07%	26	173	26	61,54%	16	10
no MVD but complex lesion		49	12,24%	6	43	6	50,00%	3	3
MVD but no complex lesion		277	30,32%	84	193	84	38,10%	32	52
MVD and complex lesion		76	36,84%	28	48	28	32,14%	9	19
DES, non-diabetics									
no MVD or complex lesion		526	7,22%	38	488	38	55,26%	21	17
no MVD but complex lesion		139	7,91%	11	128	11	72,73%	8	3
MVD but no complex lesion		613	20,55%	126	487	126	19,84%	25	101
MVD and complex lesion		157	15,29%	24	133	24	54,17%	13	11
DES, diabetics									
no MVD or complex lesion		703	8,53%	60	643	60	38,33%	23	37
no MVD but complex lesion		131	12,98%	17	114	17	47,06%	8	9
MVD but no complex lesion		1040	26,35%	274	766	274	21,17%	58	216
MVD and complex lesion		270	26,67%	72	198	72	33,33%	24	48

Table 6.6, part c: cumulative probability for a repeat PCI and the probability this was due to restenosis ('clean' population with staging correction)

Population characteristics		% re-PCI				% of re-PCI due to restenosis			
				Beta distribution				Beta distribution	
		N	%	alpha 1	alpha 2	N	%	alpha 1	alpha 2
All patients		6275	12,57%	789	5486	789	40,05%	316	473
Type of stent									
BMS	all	4889	12,52%	612	4277	612	42,65%	261	351
	non-diabetics	4663	12,31%	574	4089	574	42,86%	246	328
	diabetics	226	16,81%	38	188	38	39,47%	15	23
DES	all	1386	12,77%	177	1209	177	31,07%	55	122
	non-diabetics	544	10,29%	56	488	56	41,07%	23	33
	diabetics	842	14,37%	121	721	121	26,45%	32	89
BMS, non-diabetics									
no MVD or complex lesion		2028	7,69%	156	1872	156	64,10%	100	56
no MVD but complex lesion		440	8,18%	36	404	36	55,56%	20	16
MVD but no complex lesion		1694	17,24%	292	1402	292	29,11%	85	207
MVD and complex lesion		501	17,96%	90	411	90	45,56%	41	49
BMS, diabetics									
no MVD or complex lesion		87	5,75%	5	82	5	40,00%	2	3
no MVD but complex lesion		19	10,53%	2	17	2	50,00%	1	1
MVD but no complex lesion		96	26,04%	25	71	25	40,00%	10	15
MVD and complex lesion		24	25,00%	6	18	6	33,33%	2	4
DES, non-diabetics									
no MVD or complex lesion		248	6,85%	17	231	17	58,82%	10	7
no MVD but complex lesion		62	3,23%	2	60	2	100,00%	2	0
MVD but no complex lesion		180	17,22%	31	149	31	25,81%	8	23
MVD and complex lesion		54	11,11%	6	48	6	50,00%	3	3
DES, diabetics									
no MVD or complex lesion		325	7,08%	23	302	23	30,43%	7	16
no MVD but complex lesion		61	8,20%	5	56	5	80,00%	4	1
MVD but no complex lesion		355	18,59%	66	289	66	19,70%	13	53
MVD and complex lesion		101	26,73%	27	74	27	29,63%	8	19

Table 6.6, part d: cumulative probability for a repeat PCI and the probability this was due to restenosis ('clean' population without staging correction)

Population characteristics		% re-PCI				% of re-PCI due to restenosis			
				Beta distribution				Beta distribution	
		N	%	alpha 1	alpha 2	N	%	alpha 1	alpha 2
All patients		6275	15,11%	948	5327	948	33,33%	316	632
Type of stent									
BMS	all	4889	14,99%	733	4156	733	35,61%	261	472
	non-diabetics	4663	14,78%	689	3974	689	35,70%	246	443
	diabetics	226	19,47%	44	182	44	34,09%	15	29
DES	all	1386	15,51%	215	1171	215	25,58%	55	160
	non-diabetics	544	11,76%	64	480	64	35,94%	23	41
	diabetics	842	17,93%	151	691	151	21,19%	32	119
BMS, non-diabetics									
no MVD or complex lesion		2028	7,69%	156	1872	156	64,10%	100	56
no MVD but complex lesion		440	8,18%	36	404	36	55,56%	20	16
MVD but no complex lesion		1694	22,37%	379	1315	379	22,43%	85	294
MVD and complex lesion		501	23,55%	118	383	118	34,75%	41	77
BMS, diabetics									
no MVD or complex lesion		87	5,75%	5	82	5	40,00%	2	3
no MVD but complex lesion		19	10,53%	2	17	2	50,00%	1	1
MVD but no complex lesion		96	27,08%	26	70	26	38,46%	10	16
MVD and complex lesion		24	45,83%	11	13	11	18,18%	2	9
DES, non-diabetics									
no MVD or complex lesion		248	6,85%	17	231	17	58,82%	10	7
no MVD but complex lesion		62	3,23%	2	60	2	100,00%	2	0
MVD but no complex lesion		180	21,11%	38	142	38	21,05%	8	30
MVD and complex lesion		54	12,96%	7	47	7	42,86%	3	4
DES, diabetics									
no MVD or complex lesion		325	7,08%	23	302	23	30,43%	7	16
no MVD but complex lesion		61	8,20%	5	56	5	80,00%	4	1
MVD but no complex lesion		355	25,35%	90	265	90	14,44%	13	77
MVD and complex lesion		101	32,67%	33	68	33	24,24%	8	25

The type of re-PCI was different for the DES and BMS subgroups. The probabilities were modeled applying conditional Beta distributions, which reflect the uncertainty on all probabilities and make sure these probabilities aggregate to 100%.[n] The probabilities and arguments (alpha1-4) of these conditional Beta distributions are shown in table 6.7. Similar as before, calculations were made for all/'clean' patients and with or without correction for staging (part a-d). Due to the relatively limited observations in diabetic patients initially treated with BMS and non-diabetic patients treated with DES, we preferred not to split up these subgroups further according to MVD and complex lesion (numbers shown in italics in table 6.7, part a-d). In other words, the type of repeat PCI was assumed to be independent from these characteristics for these two subpopulations.

[n] Series of conditional beta distributions:[202] First π_1 is drawn from a beta $\left(\alpha_1, \sum_{j=2}^{k} \alpha_j\right)$. Next, for each π_j in turn, j = 2, …, k-1, draw φ_j from a beta $\left(\alpha_j, \sum_{i=j+1}^{k} \alpha_i\right)$, and then set $\pi_j = (1 - \sum_{i=1}^{j-1} \pi_i)\varphi_j$. Finally, set $\pi_k = 1 - \sum_{i=1}^{k-1} \pi_i$.

In our model, we assumed that after changing from BMS to DES, the probability of using DES in the repeat PCI procedure would increase to the distribution found in the DES population with the same characteristics (diabetics, MVD, complex lesion) and the other way round if we assumed that DES treated patients would have received BMS in the index procedure. We assume re-PCI costs did not differ according to whether or not this procedure was due to restenosis.

The cost of repeat PCI has been calculated separately for the 'RIZIV/INAMI stent cost' point of view and alternatively using real stent costs. For both approaches, costs for the Belgian health insurance for repeat PCI have been calculated (table 6.8, 'mean without correction'). For the 'RIZIV/INAMI stent cost' calculation, this cost has been adjusted for non-diabetic patients. In these subgroups, the DES reimbursement cost has been added for those patients who actually received DES. For example, in table 6.8 (part a), for non-diabetics initially treated with BMS, €6850 equals €6526 + (29.2% + 3.2%) x €1000. The percentages are those patients treated with DES in the re-intervention in this subgroup (table 6.8, lower right corner). Similarly for non-diabetics initially treated with DES, €6949 equals €6449 + (43.8% + 6.3%) x €1000.

For our real cost calculations, in a first step, the reimbursement cost for stents has been extracted from this RIZIV/INAMI cost. In a second step, the fixed costs for placing a stent have been added (i.e. costs for coronay balloon catheter, closure device, indeflator, .14" coronary guide wire, coronary guiding catheter, .35" guide wire, introducer sheat, pressure kit disposable, and other disposables). Depending on the discount given by suppliers, this cost is about €750. It has been included in our model with a Beta distribution ranging from €550 to €950. For example, the real cost of a procedure without stenting is €5338 in the non-diabetic population initially treated with BMS (table 6.8, part a), which equals €6850 – (16% x €1350) – (51.6% x €2050) – ((29.2% + 3.2%) x €3050) + €750. In a third step, the real stent costs are added. As such, in the same subgroup, the mean real cost for a procedure with BMS becomes €5938, which equals €5338 + €1000 (list price BMS) x 50% (discount) x 1.2 (average number of BMS stents). If a combination of BMS and DES was implanted, we assumed the proportion was 50/50. All these 'RIZIV/INAMI stent cost' and real costs can be found in table 6.8, part a-d for the several analysed subgroups. Similar as in table 6.7, data for diabetic patients initially treated with BMS and non-diabetic patients treated with DES were not split up, but details are provided (in italics).

Table 6.7, part a: type of re-PCI (in %) (population with staging correction)

Population characteristics			type of re-PCI				Conditional Beta distribution			
		N	% no stent	% BMS	% DES	Comb.	alpha 1	alpha 2	alpha 3	alpha 4
All patients		1293	15,93%	40,22%	39,52%	4,33%	206	520	511	56
Type of stent										
BMS	all	973	16,03%	48,51%	31,96%	3,49%	156	472	311	34
	non-diabetics	880	16,02%	51,59%	29,20%	3,18%	141	454	257	28
	diabetics	93	16,13%	19,35%	58,06%	6,45%	15	18	54	6
DES	all	320	15,63%	15,00%	62,50%	6,88%	50	48	200	22
	non-diabetics	112	22,32%	27,68%	43,75%	6,25%	25	31	49	7
	diabetics	208	12,02%	8,17%	72,60%	7,21%	25	17	151	15
BMS, non-diabetics										
no MVD or complex lesion		228	16,67%	46,49%	34,65%	2,19%	38	106	79	5
no MVD but complex lesion		57	22,81%	42,11%	33,33%	1,75%	13	24	19	1
MVD but no complex lesion		467	14,35%	55,89%	26,34%	3,43%	67	261	123	16
MVD and complex lesion		128	17,97%	49,22%	28,13%	4,69%	23	63	36	6
BMS, diabetics										
no MVD or complex lesion		*17*	*23,53%*	*23,53%*	*41,18%*	*11,76%*	*4*	*4*	*7*	*2*
no MVD but complex lesion		*4*	*0,00%*	*25,00%*	*75,00%*	*0,00%*	*0*	*1*	*3*	*0*
MVD but no complex lesion		*57*	*10,53%*	*21,05%*	*61,40%*	*7,02%*	*6*	*12*	*35*	*4*
MVD and complex lesion		*15*	*33,33%*	*6,67%*	*60,00%*	*0,00%*	*5*	*1*	*9*	*0*
DES, non-diabetics										
no MVD or complex lesion		*27*	*37,04%*	*11,11%*	*44,44%*	*7,41%*	*10*	*3*	*12*	*2*
no MVD but complex lesion		*7*	*57,14%*	*28,57%*	*14,29%*	*0,00%*	*4*	*2*	*1*	*0*
MVD but no complex lesion		*63*	*11,11%*	*36,51%*	*44,44%*	*7,94%*	*7*	*23*	*28*	*5*
MVD and complex lesion		*15*	*26,67%*	*20,00%*	*53,33%*	*0,00%*	*4*	*3*	*8*	*0*
DES, diabetics										
no MVD or complex lesion		35	8,57%	5,71%	80,00%	5,71%	3	2	28	2
no MVD but complex lesion		9	22,22%	22,22%	44,44%	11,11%	2	2	4	1
MVD but no complex lesion		126	12,70%	7,14%	73,81%	6,35%	16	9	93	8
MVD and complex lesion		38	10,53%	10,53%	68,42%	10,53%	4	4	26	4

Table 6.7, part b: type of re-PCI (in %) (population without staging correction)

Population characteristics			type of re-PCI				Conditional Beta distribution			
		N	% no stent	% BMS	% DES	Comb.	alpha 1	alpha 2	alpha 3	alpha 4
All patients		1674	13,56%	46,89%	35,54%	4,00%	227	785	595	67
Type of stent										
BMS	all	1263	13,78%	56,53%	26,60%	3,09%	174	714	336	39
	non-diabetics	1156	13,75%	59,60%	23,79%	2,85%	159	689	275	33
	diabetics	107	14,02%	23,36%	57,01%	5,61%	15	25	61	6
DES	all	411	12,90%	17,27%	63,02%	6,81%	53	71	259	28
	non-diabetics	134	18,66%	32,09%	44,03%	5,22%	25	43	59	7
	diabetics	277	10,11%	10,11%	72,20%	7,58%	28	28	200	21
BMS, non-diabetics										
no MVD or complex lesion		228	16,67%	46,05%	35,09%	2,19%	38	105	80	5
no MVD but complex lesion		57	22,81%	42,11%	33,33%	1,75%	13	24	19	1
MVD but no complex lesion		688	11,63%	65,55%	19,91%	2,91%	80	451	137	20
MVD and complex lesion		183	15,30%	59,56%	21,31%	3,83%	28	109	39	7
BMS, diabetics										
no MVD or complex lesion		*17*	*23,53%*	*23,53%*	*41,18%*	*11,76%*	*4*	*4*	*7*	*2*
no MVD but complex lesion		*4*	*0,00%*	*25,00%*	*75,00%*	*0,00%*	*0*	*1*	*3*	*0*
MVD but no complex lesion		*65*	*9,23%*	*24,62%*	*60,00%*	*6,15%*	*6*	*16*	*39*	*4*
MVD and complex lesion		*21*	*23,81%*	*19,05%*	*57,14%*	*0,00%*	*5*	*4*	*12*	*0*
DES, non-diabetics										
no MVD or complex lesion		*26*	*38,46%*	*11,54%*	*42,31%*	*7,69%*	*10*	*3*	*11*	*2*
no MVD but complex lesion		*7*	*57,14%*	*28,57%*	*14,29%*	*0,00%*	*4*	*2*	*1*	*0*
MVD but no complex lesion		*84*	*8,33%*	*41,67%*	*44,05%*	*5,95%*	*7*	*35*	*37*	*5*
MVD and complex lesion		*17*	*23,53%*	*17,65%*	*58,82%*	*0,00%*	*4*	*3*	*10*	*0*
DES, diabetics										
no MVD or complex lesion		34	8,82%	5,88%	79,41%	5,88%	3	2	27	2
no MVD but complex lesion		9	22,22%	22,22%	44,44%	11,11%	2	2	4	1
MVD but no complex lesion		186	10,22%	8,60%	73,66%	7,53%	19	16	137	14
MVD and complex lesion		48	8,33%	16,67%	66,67%	8,33%	4	8	32	4

Table 6.7, part c: type of re-PCI (in %) ('clean' population with staging correction)

Population characteristics			type of re-PCI				Conditional Beta distribution			
		N	% no stent	% BMS	% DES	Comb.	alpha 1	alpha 2	alpha 3	alpha 4
All patients		489	16,97%	39,88%	39,26%	3,89%	83	195	192	19
Type of stent										
BMS	all	365	17,81%	48,22%	31,23%	2,74%	65	176	114	10
	non-diabetics	339	17,70%	50,44%	28,91%	2,95%	60	171	98	10
	diabetics	26	19,23%	19,23%	61,54%	0,00%	5	5	16	0
DES	all	124	14,52%	15,32%	62,90%	7,26%	18	19	78	9
	non-diabetics	43	23,26%	30,23%	37,21%	9,30%	10	13	16	4
	diabetics	81	9,88%	7,41%	76,54%	6,17%	8	6	62	5
BMS, non-diabetics										
no MVD or complex lesion		102	17,65%	41,18%	40,20%	0,98%	18	42	41	1
no MVD but complex lesion		22	31,82%	40,91%	27,27%	0,00%	7	9	6	0
MVD but no complex lesion		170	14,71%	57,65%	24,12%	3,53%	25	98	41	6
MVD and complex lesion		45	22,22%	48,89%	22,22%	6,67%	10	22	10	3
BMS, diabetics										
no MVD or complex lesion		*2*	*50,00%*	*0,00%*	*50,00%*	*0,00%*	*1*	*0*	*1*	*0*
no MVD but complex lesion		*1*	*0,00%*	*0,00%*	*100,00%*	*0,00%*	*0*	*0*	*1*	*0*
MVD but no complex lesion		*18*	*16,67%*	*27,78%*	*55,56%*	*0,00%*	*3*	*5*	*10*	*0*
MVD and complex lesion		*5*	*20,00%*	*0,00%*	*80,00%*	*0,00%*	*1*	*0*	*4*	*0*
DES, non-diabetics										
no MVD or complex lesion		*14*	*42,86%*	*7,14%*	*35,71%*	*14,29%*	*6*	*1*	*5*	*2*
no MVD but complex lesion		*2*	*50,00%*	*50,00%*	*0,00%*	*0,00%*	*1*	*1*	*0*	*0*
MVD but no complex lesion		*23*	*8,70%*	*43,48%*	*39,13%*	*8,70%*	*2*	*10*	*9*	*2*
MVD and complex lesion		*4*	*25,00%*	*25,00%*	*50,00%*	*0,00%*	*1*	*1*	*2*	*0*
DES, diabetics										
no MVD or complex lesion		16	0,00%	6,25%	81,25%	12,50%	0	1	13	2
no MVD but complex lesion		4	50,00%	0,00%	50,00%	0,00%	2	0	2	0
MVD but no complex lesion		43	11,63%	4,65%	79,07%	4,65%	5	2	34	2
MVD and complex lesion		18	5,56%	16,67%	72,22%	5,56%	1	3	13	1

Table 6.7, part d: type of re-PCI (in %) ('clean' population without staging correction)

Population characteristics			type of re-PCI				Conditional Beta distribution			
		N	% no stent	% BMS	% DES	Comb.	alpha 1	alpha 2	alpha 3	alpha 4
All patients		631	14,58%	45,96%	35,82%	3,65%	92	290	226	23
Type of stent										
BMS	all	475	15,58%	55,16%	26,74%	2,53%	74	262	127	12
	non-diabetics	443	15,58%	57,56%	24,15%	2,71%	69	255	107	12
	diabetics	32	15,63%	21,88%	62,50%	0,00%	5	7	20	0
DES	all	156	11,54%	17,95%	63,46%	7,05%	18	28	99	11
	non-diabetics	52	19,23%	34,62%	38,46%	7,69%	10	18	20	4
	diabetics	104	7,69%	9,62%	75,96%	6,73%	8	10	79	7
BMS, non-diabetics										
no MVD or complex lesion		102	17,65%	41,18%	40,20%	0,98%	18	42	41	1
no MVD but complex lesion		22	31,82%	40,91%	27,27%	0,00%	7	9	6	0
MVD but no complex lesion		249	12,85%	64,66%	19,68%	2,81%	32	161	49	7
MVD and complex lesion		70	17,14%	61,43%	15,71%	5,71%	12	43	11	4
BMS, diabetics										
no MVD or complex lesion		*2*	*50,00%*	*0,00%*	*50,00%*	*0,00%*	*1*	*0*	*1*	*0*
no MVD but complex lesion		*1*	*0,00%*	*0,00%*	*100,00%*	*0,00%*	*0*	*0*	*1*	*0*
MVD but no complex lesion		*19*	*15,79%*	*26,32%*	*57,89%*	*0,00%*	*3*	*5*	*11*	*0*
MVD and complex lesion		*10*	*10,00%*	*20,00%*	*70,00%*	*0,00%*	*1*	*2*	*7*	*0*
DES, non-diabetics										
no MVD or complex lesion		*14*	*42,86%*	*7,14%*	*35,71%*	*14,29%*	*6*	*1*	*5*	*2*
no MVD but complex lesion		*2*	*50,00%*	*50,00%*	*0,00%*	*0,00%*	*1*	*1*	*0*	*0*
MVD but no complex lesion		*31*	*6,45%*	*48,39%*	*38,71%*	*6,45%*	*2*	*15*	*12*	*2*
MVD and complex lesion		*5*	*20,00%*	*20,00%*	*60,00%*	*0,00%*	*1*	*1*	*3*	*0*
DES, diabetics										
no MVD or complex lesion		16	0,00%	6,25%	81,25%	12,50%	0	1	13	2
no MVD but complex lesion		4	50,00%	0,00%	50,00%	0,00%	2	0	2	0
MVD but no complex lesion		64	7,81%	9,38%	76,56%	6,25%	5	6	49	4
MVD and complex lesion		20	5,00%	15,00%	75,00%	5,00%	1	3	15	1

Table 6.8, part a: cost of repeat PCI (population with staging correction)

Population characteristics		N	Mean without correction	St. dev mean	Normal distribution Lower bound	Normal distribution Upper bound	RIZIV/INAMI cost	mean real costs no stent	mean real costs BMS	mean real costs DES	mean real costs DES+BMS
All patients											
Type of stent											
BMS	all	973	6.568 €	173	2514	28541					
	non-diabetics	880	6.526 €	187	2588	32511	6.850 €	5.338 €	5.938 €	6.788 €	7.188 €
	diabetics	93	6.964 €	411	1993	28263	6.964 €	5.777 €	6.365 €	7.167 €	8.089 €
DES	all	320	7.372 €	365	2683	38306					
	non-diabetics	112	6.449 €	694	3371	36832	6.949 €	5.305 €	5.871 €	6.706 €	7.215 €
	diabetics	208	7.868 €	417	2432	38306	7.868 €	5.854 €	6.591 €	7.254 €	7.786 €
BMS, non-diabetics								**BMS, non-diabetics**			
no MVD or complex lesion		228	6.592 €	401	3466	45083	6.961 €	N (and %)	141 (16,0%)	454 (51,6%)	257 (29,2%)	28 (3,2%)
no MVD but complex lesion		57	6.750 €	639	3292	32511	7.101 €	Mean	/	1,20	1,16	2,11
MVD but no complex lesion		467	6.649 €	273	2514	28541	6.946 €	St. dev		0,46	0,4	0,31
MVD and complex lesion		128	5.862 €	260	1830	16770	6.190 €	LB & UB		1 3	1 3	2 3
BMS, diabetics								**BMS, diabetics**			
no MVD or complex lesion		*17*	*7.146 €*	*1121*	*1993*	*17444*	*7.146 €*	N (and %)	15 (16,1%)	18 (19,4%)	54 (58,1%)	6 (6,5%)
no MVD but complex lesion		*4*	*12.528 €*	*5763*	*5006*	*28263*	*12.528 €*	Mean	/	1,17	1,11	2,50
MVD but no complex lesion		*57*	*6.862 €*	*411*	*2118*	*17358*	*6.862 €*	St. dev		0,38	0,37	1,22
MVD and complex lesion		*15*	*6.079 €*	*638*	*3371*	*13947*	*6.079 €*	LB & UB		1 2	1 3	2 5
DES, non-diabetics								**DES, non-diabetics**			
no MVD or complex lesion		*27*	*5.710 €*	*632*	*3371*	*16180*	*6.228 €*	N (and %)	25 (22,3%)	31 (27,7%)	49 (43,8%)	7 (6,3%)
no MVD but complex lesion		*7*	*5.910 €*	*1214*	*3813*	*12435*	*6.052 €*	Mean	/	1,13	1,12	2,14
MVD but no complex lesion		*63*	*7.336 €*	*1188*	*3599*	*68450*	*7.860 €*	St. dev		0,34	0,33	0,38
MVD and complex lesion		*15*	*4.380 €*	*140*	*3294*	*5210*	*4.913 €*	LB & UB		1 2	1 2	2 3
DES, diabetics								**DES, diabetics**			
no MVD or complex lesion		35	7.250 €	543	2265	15132	7.250 €	N (and %)	25 (12,0%)	17 (8,2%)	151 (72,6%)	15 (7,2%)
no MVD but complex lesion		9	7.621 €	907	4664	12517	7.621 €	Mean	/	1,47	1,12	2,20
MVD but no complex lesion		126	7.498 €	481	2770	33406	7.498 €	St. dev		0,8	0,38	0,41
MVD and complex lesion		38	9.724 €	1523	2683	51591	9.724 €	LB & UB		1 4	1 3	2 3

Table 6.8, part b: cost of repeat PCI (population without staging correction)

Population characteristics		N	Mean without correction	St. dev mean	Normal distribution Lower bound	Normal distribution Upper bound	RIZIV/INAMI cost	mean real costs no stent	mean real costs BMS	mean real costs DES	mean real costs DES+BMS
All patients											
Type of stent											
BMS	all	1263	6.344 €	151	2514	28541					
	non-diabetics	1156	6.273 €	159	2588	28541	6.539 €	5.069 €	5.679 €	6.531 €	6.901 €
	diabetics	107	7.109 €	476	2118	28263	7.109 €	5.281 €	5.902 €	6.658 €	7.593 €
DES	all	411	6.871 €	273	1836	33406					
	non-diabetics	134	6.022 €	588	1807	36832	6.514 €	4.852 €	5.447 €	6.252 €	6.762 €
	diabetics	277	7.282 €	286	2432	33406	7.282 €	5.254 €	5.970 €	6.654 €	7.216 €
BMS, non-diabetics								**BMS, non-diabetics**			
no MVD or complex lesion		228	6.399 €	346	3466	41520	6.772 €	N (and %)	159 (13,8%)	689 (59,6%)	275 (23,8%)	33 (2,9%)
no MVD but complex lesion		57	6.750 €	639	3292	32511	7.101 €	Mean	/	1,22	1,17	2,09
MVD but no complex lesion		688	6.220 €	218	2461	28541	6.448 €	St. dev		0,47	0,45	0,29
MVD and complex lesion		183	6.166 €	338	1830	26820	6.418 €	LB & UB		1 3	1 3	2 3
BMS, diabetics								**BMS, diabetics**			
no MVD or complex lesion		*17*	*7.146 €*	*1121*	*1993*	*17444*	*7.146 €*	N (and %)	15 (14,0%)	25 (23,4%)	61 (57,0%)	6 (5,6%)
no MVD but complex lesion		*4*	*12.528 €*	*5763*	*5006*	*28263*	*12.528 €*	Mean	/	1,24	1,10	2,50
MVD but no complex lesion		*65*	*7.110 €*	*626*	*2118*	*39306*	*7.110 €*	St. dev		0,52	0,35	1,22
MVD and complex lesion		*21*	*6.341 €*	*550*	*3371*	*13947*	*6.341 €*	LB & UB		1 3	1 3	2 5
DES, non-diabetics								**DES, non-diabetics**			
no MVD or complex lesion		*26*	*5.748 €*	*655*	*3371*	*16180*	*6.248 €*	N (and %)	25 (18,7%)	43 (32,1%)	59 (44,0%)	7 (5,2%)
no MVD but complex lesion		*7*	*5.910 €*	*1214*	*3813*	*12435*	*6.052 €*	Mean	/	1,19	1,12	2,14
MVD but no complex lesion		*84*	*6.471 €*	*907*	*1807*	*68450*	*6.971 €*	St. dev		0,45	0,33	0,38
MVD and complex lesion		*17*	*4.323 €*	*130*	*3294*	*5210*	*4.911 €*	LB & UB		1 3	1 2	2 3
DES, diabetics								**DES, diabetics**			
no MVD or complex lesion		34	7.313 €	555	2265	15132	7.313 €	N (and %)	28 (10,1%)	28 (10,1%)	200 (72,2%)	21 (7,6%)
no MVD but complex lesion		9	7.219 €	702	4664	11161	7.219 €	Mean	/	1,43	1,12	2,24
MVD but no complex lesion		186	7.125 €	353	2770	33406	7.125 €	St. dev		0,74	0,37	0,44
MVD and complex lesion		48	7.876 €	831	2683	38306	7.876 €	LB & UB		1 4	1 3	2 3

Table 6.8, part c: cost of repeat PCI ('clean' population with staging correction)

Population characteristics		N	Mean without correction	St. dev mean	Normal distribution Lower bound	Normal distribution Upper bound	RIZIV/INAMI cost	mean real costs no stent	mean real costs BMS	mean real costs DES	mean real costs DES+BMS
All patients											
Type of stent											
BMS	all	365	6.361 €	243	2946	24221					
	non-diabetics	339	6.298 €	255	3018	24221	6.616 €	5.121 €	5.751 €	6.584 €	7.348 €
	diabetics	26	7.190 €	773	2118	17444	7.190 €	6.024 €	6.653 €	7.274 €	6.024 €
DES	all	124	7.464 €	731	2265	51591					
	non-diabetics	43	7.000 €	1541	3371	68450	7.465 €	5.862 €	6.481 €	7.429 €	7.612 €
	diabetics	81	7.732 €	770	1836	51591	7.732 €	5.674 €	6.424 €	7.051 €	7.881 €
BMS, non-diabetics								**BMS, non-diabetics**			
no MVD or complex lesion		102	6.168 €	295	3322	15668	6.580 €	N (and %)	60 (17,7%)	171 (50,4%)	98 (28,9%)	10 (2,9%)
no MVD but complex lesion		22	6.539 €	908	3292	21133	6.812 €	Mean	/	1,26	1,17	2,10
MVD but no complex lesion		170	6.468 €	450	2946	27476	6.745 €	St. dev		0,53	0,45	0,32
MVD and complex lesion		45	5.828 €	392	3555	13781	6.117 €	LB & UB		1 3	1 3	2 3
BMS, diabetics								**BMS, diabetics**			
no MVD or complex lesion		*2*	*11.353 €*	*6090*	*5263*	*17444*	*11.353 €*	N (and %)	5 (19,2%)	5 (19,2%)	16 (61,5%)	0 (0,0%)
no MVD but complex lesion		*1*	*5.006 €*				*5.006 €*	Mean	/	1,20	1,00	0,00
MVD but no complex lesion		*18*	*6.734 €*	*832*	*2118*	*12812*	*6.734 €*	St. dev		0,45	0	0
MVD and complex lesion		*5*	*7.673 €*	*1705*	*3998*	*13947*	*7.673 €*	LB & UB		1 2	1 1	0 0
DES, non-diabetics								**DES, non-diabetics**			
no MVD or complex lesion		*14*	*5.075 €*	*880*	*3371*	*16180*	*5.575 €*	N (and %)	10 (23,3%)	13 (30,2%)	16 (37,2%)	4 (9,3%)
no MVD but complex lesion		*2*	*8.124 €*	*4311*	*3813*	*12435*	*8.124 €*	Mean	/	1,23	1,25	2,00
MVD but no complex lesion		*23*	*8.748 €*	*2807*	*4002*	*68450*	*9.227 €*	St. dev		0,44	0,45	0
MVD and complex lesion		*4*	*4.876 €*	*185*	*4359*	*5210*	*5.376 €*	LB & UB		1 2	1 2	2 2
DES, diabetics								**DES, diabetics**			
no MVD or complex lesion		16	7.271 €	918	2265	14264	7.271 €	N (and %)	8 (9,9%)	6 (7,4%)	62 (76,5%)	5 (6,2%)
no MVD but complex lesion		4	9.720 €	1361	6251	12517	9.720 €	Mean	/	1,50	1,10	2,20
MVD but no complex lesion		43	6.161 €	502	1836	20557	6.161 €	St. dev		0,55	0,35	0,45
MVD and complex lesion		18	11.457 €	3018	2683	51591	11.457 €	LB & UB		1 2	1 3	2 3

Table 6.8, part d: cost of repeat PCI ('clean' population without staging correction)

Population characteristics		N	Mean without correction	St. dev mean	Normal distribution Lower bound	Normal distribution Upper bound	RIZIV/INAMI cost	mean real costs no stent	mean real costs BMS	mean real costs DES	mean real costs DES+BMS
All patients											
Type of stent											
BMS	all	475	6.221 €	219	2946	26820					
	non-diabetics	443	6.152 €	230	3018	26820	6.421 €	4.961 €	5.591 €	6.474 €	7.195 €
	diabetics	32	7.171 €	653	2118	17444	7.171 €	5.980 €	6.572 €	7.230 €	5.980 €
DES	all	156	6.559 €	511	1807	38306					
	non-diabetics	52	6.417 €	1289	1807	68450	6.878 €	5.251 €	5.863 €	6.756 €	7.001 €
	diabetics	104	6.630 €	422	2265	20557	6.630 €	4.557 €	5.311 €	5.933 €	6.772 €
BMS, non-diabetics											
no MVD or complex lesion		102	6.168 €	295	3322	15668	6.580 €				
no MVD but complex lesion		22	6.539 €	908	3292	21133	6.812 €				
MVD but no complex lesion		249	5.932 €	318	2946	27476	6.157 €				
MVD and complex lesion		70	6.790 €	753	3145	39319	7.005 €				
BMS, diabetics											
no MVD or complex lesion		*2*	*11.353 €*	*6090*	*5263*	*17444*	*11.353 €*				
no MVD but complex lesion		*1*	*5.006 €*				*5.006 €*				
MVD but no complex lesion		*19*	*6.652 €*	*791*	*2118*	*12812*	*6.652 €*				
MVD and complex lesion		*10*	*7.537 €*	*996*	*3998*	*13947*	*7.537 €*				
DES, non-diabetics											
no MVD or complex lesion		*14*	*5.075 €*	*880*	*3371*	*16180*	*5.575 €*				
no MVD but complex lesion		*2*	*8.124 €*	*4311*	*3813*	*12435*	*8.124 €*				
MVD but no complex lesion		*31*	*7.242 €*	*2116*	*1807*	*68450*	*7.693 €*				
MVD and complex lesion		*5*	*4.732 €*	*211*	*4119*	*5210*	*5.332 €*				
DES, diabetics											
no MVD or complex lesion		16	7.271 €	918	2265	14264	7.271 €				
no MVD but complex lesion		4	8.856 €	1008	6251	11161	8.856 €				
MVD but no complex lesion		64	5.744 €	326	1836	20557	5.744 €				
MVD and complex lesion		20	8.507 €	1715	2683	38306	8.507 €				

	BMS, non-diabetics	BMS, diabetics	DES, non-diabetics	DES, diabetics
N (and %)	69 (15,6%)	255 (57,6%)	107 (24,2%)	12 (2,7%)
Mean	/	1,26	1,21	2,08
St. dev		0,51	0,54	0,29
LB & UB		1 3	1 3	2 3
N (and %)	5 (15,6%)	7 (21,9%)	20 (62,5%)	0 (0,0%)
Mean	/	1,14	1,00	0,00
St. dev		0,38	0	0
LB & UB		1 2	1 1	0 0
N (and %)	10 (19,2%)	18 (34,6%)	20 (38,5%)	4 (7,7%)
Mean	/	1,22	1,20	2,00
St. dev		0,43	0,41	0
LB & UB		1 2	1 2	2 2
N (and %)	8 (7,7%)	10 (9,6%)	79 (76,0%)	7 (6,7%)
Mean	/	1,50	1,10	2,14
St. dev		0,71	0,34	0,38
LB & UB		1 3	1 3	2 3

REPEAT INTERVENTIONS: CABG

The probability of undergoing CABG as a repeat procedure is also modeled for all subgroups applying a Beta distribution. For CABG only the distinction between the complete (table 6.9, part a) and 'clean' population (table 6.9, part b) is made because the staging correction only has an influence on PCI interventions.

Table 6.9, part a: Percentage of reintervention with CABG (Complete population)

Population characteristics		N	Mean	Beta distribution	
				alpha 1	alpha 2
All patients					
Type of stent					
BMS	all	11453	2,45%	281	11172
	non-diabetics	10852	2,46%	267	10585
	diabetics	601	2,33%	14	587
DES	all	3579	1,62%	58	3521
	non-diabetics	1435	1,05%	15	1420
	diabetics	2144	2,01%	43	2101
BMS, non diabetics					
no MVD or complex lesion		4129	1,24%	51	4078
no MVD but complex lesion		902	1,88%	17	885
MVD but no complex lesion		4523	3,38%	153	4370
MVD and complex lesion		1298	3,54%	46	1252
BMS, diabetics					
no MVD or complex lesion		199	1,51%	3	196
no MVD but complex lesion		49	4,08%	2	47
MVD but no complex lesion		277	2,17%	6	271
MVD and complex lesion		76	3,95%	3	73
DES, non-diabetics					
no MVD or complex lesion		526	0,95%	5	521
no MVD but complex lesion		139	0,00%	0	139
MVD but no complex lesion		613	1,31%	8	605
MVD and complex lesion		157	1,27%	2	155
DES, diabetics					
no MVD or complex lesion		703	1,00%	7	696
no MVD but complex lesion		131	3,05%	4	127
MVD but no complex lesion		1040	2,50%	26	1014
MVD and complex lesion		270	2,22%	6	264

Table 6.9, part b: Percentage of reintervention with CABG ('clean' population)

Population characteristics		N	Mean	Beta distribution	
				alpha 1	alpha 2
All patients					
Type of stent					
BMS	all	4889	3,11%	152	4737
	non-diabetics	4663	3,11%	145	4518
	diabetics	226	3,10%	7	219
DES	all	1386	1,66%	23	1363
	non-diabetics	544	1,10%	6	538
	diabetics	842	2,02%	17	825
BMS, non diabetics					
no MVD or complex lesion		2028	1,63%	33	1995
no MVD but complex lesion		440	2,50%	11	429
MVD but no complex lesion		1694	4,49%	76	1618
MVD and complex lesion		501	4,99%	25	476
BMS, diabetics					
no MVD or complex lesion		87	0,00%	0	87
no MVD but complex lesion		19	5,26%	1	18
MVD but no complex lesion		96	5,21%	5	91
MVD and complex lesion		24	4,17%	1	23
DES, non-diabetics					
no MVD or complex lesion		248	0,40%	1	247
no MVD but complex lesion		62	0,00%	0	62
MVD but no complex lesion		180	2,22%	4	176
MVD and complex lesion		54	1,85%	1	53
DES, diabetics					
no MVD or complex lesion		325	0,31%	1	324
no MVD but complex lesion		61	1,64%	1	60
MVD but no complex lesion		355	3,94%	14	341
MVD and complex lesion		101	0,99%	1	100

The cost of CABG has been calculated for aggregated groups since the number of observations was relatively limited (only 14 observations in both diabetic patients initially treated with BMS and non-diabetic patients treated with DES). We preferred to keep the differences in CABG costs between diabetic and non-diabetic patients. These costs are taken into account applying a normal distribution which was truncated at the 1st and 99th percentile of the initial observations (table 6.10).

Table 6.10: cost of CABG

Population characteristics	N	Mean	St. dev mean	Normal distribution	
				Lower bound	Upper bound
All patients					
diabetics	57	17.410 €	1384	1341	52521
non-diabetics	282	15.165 €	572	7650	64111
'Clean' patients					
diabetics	24	17.439 €	2459	8742	52521
non-diabetics	151	15.319 €	804	7650	56287

(INVERSE) RELATIVE RISK

According to a recent review, as mentioned in the literature review on effectiveness, the estimated hazard ratios for TVR after a median duration of follow-up of 4 years were as follows: SES vs BMS: 7.8% vs 23.6% (hazard ratio 0.29, 95% CI 0.22-0.39) and PES vs BMS: 10.1% vs 20.0% (hazard ratio 0.46, 95% CI 0.38-0.55).[59] Based on these numbers, we included a hazard ratio with a 95% CI of 0.22-0.55. This was modelled as a normal distribution on the natural log, which was exponentiated afterwards. The mean hazard ratio could be deduced from this symmetric normal distribution, which was 0.34785. Our normal distribution was truncated at the 99% CI to prevent unlogic values (+/- infinity) to be drawn.

This improvement was applied to the populations initially treated with BMS. The influence of initially using DES instead of BMS only applied on those re-interventions caused by restenosis (see table 6.6). For the subgroups initially treated with DES, the opposite calculation was made, i.e. a deterioration of the situation if BMS would have been used instead of DES. In other words, how much higher would the number of repeat PCIs have been if BMS was used instead of DES.

In the base case, it is assumed that DES versus BMS usage only has an influence on PCI and not on CABG. In an alternative scenario, it is assumed that DES has the same influence on repeat interventions with CABG as for PCI.

CORRECTION ON PERCENTAGE OF RESTENOSIS IN THE DES GROUP

The percentages of restenosis in each subgroup are based on observed data. In our calculations, we assume changing from BMS to DES only has an influence on the reinterventions caused by restenosis. As a result, calculating the percentage of re-PCIs as if the DES patients would have been treated with BMS is not possible using the observed percentages of restenosis. To correctly calculate the health benefit, the percentage of restenosis has to be expressed towards the number of re-PCIs if patients would have been treated with BMS. Table 6.11 provides both the observed data which express the percentage of restenosis in patients initially treated with DES and this percentage if these patients would have been treated with BMS.

As an example, we explain how we calculate this percentage for non-diabetic patients with no MVD or complex lesion (all patients, with staging correction). In this group, a cumulative 7.22% of re-PCIs were noticed (see table 6.6, part a). It was observed that 55.26% were due to restenosis. As a result, 3.99% were due to restenosis and the remaining 3.23% not.

We assume that using DES or BMS only has an influence on restenosis-caused re-PCI. Using the inverse relative benefit of DES versus BMS, we can calculate that the initial percentage of re-PCI due to restenosis would have been 11.47% if BMS stents were used initially (i.e. 3.99%/0.34785). As such, the total percentage of re-PCI with BMS would have been 14.70% (i.e. 3.23% + 11.47%) of which 78.03% are due to restenosis (i.e. 11.47%/14.70%). This adjusted percentage of restenosis is used in our calculations.

Table 6.11: percentage of restenosis

Population characteristics	observed % of restenosis			
	all patients		clean patients	
	staging correction	no correction	staging correction	no correction
DES, non-diabetics				
no MVD or complex lesion	55,26%	55,26%	58,82%	58,82%
no MVD but complex lesion	72,73%	72,73%	100,00%	100,00%
MVD but no complex lesion	24,04%	19,84%	25,81%	21,05%
MVD and complex lesion	61,90%	54,17%	50,00%	42,86%
DES, diabetics				
no MVD or complex lesion	38,33%	38,33%	30,43%	30,43%
no MVD but complex lesion	47,06%	47,06%	80,00%	80,00%
MVD but no complex lesion	27,75%	21,17%	19,70%	14,44%
MVD and complex lesion	42,86%	33,33%	29,63%	24,24%
Population characteristics	Calculated % of restenosis			
	all patients		clean patients	
	staging correction	no correction	staging correction	no correction
DES, non-diabetics				
no MVD or complex lesion	78,03%	78,03%	80,42%	80,42%
no MVD but complex lesion	88,46%	88,46%	100,00%	100,00%
MVD but no complex lesion	47,64%	41,57%	50,00%	43,39%
MVD and complex lesion	82,37%	77,26%	74,19%	68,32%
DES, diabetics				
no MVD or complex lesion	64,12%	64,12%	55,71%	55,71%
no MVD but complex lesion	71,87%	71,87%	92,00%	92,00%
MVD but no complex lesion	52,48%	43,56%	41,35%	32,68%
MVD and complex lesion	68,32%	58,97%	54,76%	47,91%

QUALITY OF LIFE

As in the study of Bowen et al.[139] two different quality of life (QoL) impacts of revascularization are incorporated in the model: 1) impact of anginal symptoms occurring before the revascularization procedure; and 2) impact on QoL during the recovery time after the revascularization procedure.

No direct QoL data are available from studies comparing BMS versus DES. However, the Arterial Revascularization Therapies Study (ARTS) provided QoL data for both PCI and CABG, i.e. two states which occur in the model. In this trial, a total of 1205 patients were randomly assigned to undergo stent implantation (600) or bypass surgery (605). Secondary measures of efficacy were assessed by means of the EuroQol questionnaire regarding the QoL. Ratings were summarized after being weighted to account for differences in the importance of the various items to the patient.[189] Table 6.12 presents the summarized EuroQol data from the ARTS trial.

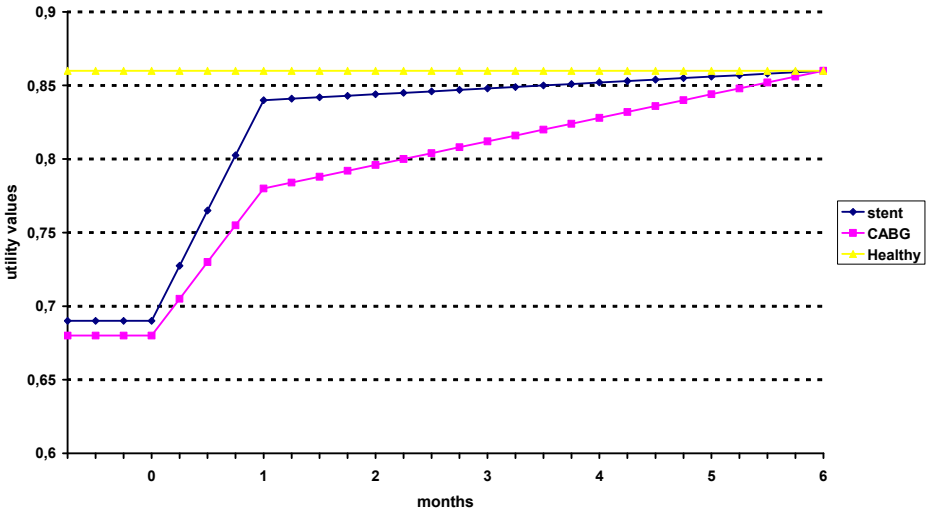
Table 6.12: summarized EQ-5D values observed in the ARTS trial[189]

	Baseline	1 month	6 months	12 months
Stenting Group (n=600)	0.69±20	0.84±16	0.86±16	0.86±16
CABG group (n=605)	0.68±20	0.78±17	0.86±15	0.87±16

means ±SD

Based on these data, utility values for a healthy patient was assumed to be 0.86. Lower utility values were assigned up to 6 months after PCI or CABG intervention. Linearity on QoL values was assumed between baseline and 1 month and between 1 and 6 months. Before these interventions, a short period with anginal symptoms may occur. In a Canadian field evaluation,[139] the duration of anginal symptoms was approximated by the average waiting time for revascularization procedures. This was between 8.65 (PCI, post MI, diabetes) and 24.46 (CABG, post MI, without diabetes) days, depeding on revascularization type and patient characteristics. In our model, we incorporate a proportion of one month (Beta distribution with values between 0.29 (i.e. 8.65/30) and 0.82 (i.e.24.46/30)), reflecting the period prior to the procedure with a lower QoL value which is equal to the baseline value from the ARTS trial. Figure 6.2 presents the mean QoL values incorporated in our model. The uncertainty around these mean values is summarized in table 6.13. In our model, based on the ARTS data, we assumed no further differences in QoL values after 6 months.

Figure 6.2: Mean utility values for healthy state, PCI and CABG



CABG: coronary artery bypass graft
Before stenting or CABG, a short period with anginal symptoms may occur. During this period, the same QoL value as for the baseline value was assumed.

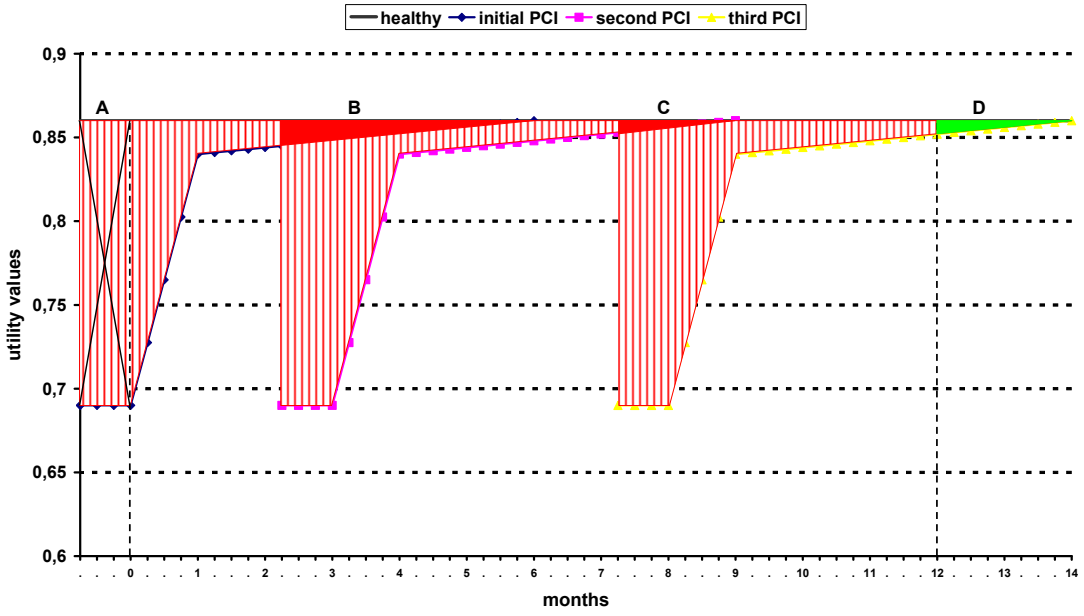
Table 6.13: Utility values for healthy state, PCI and CABG

Quality of Life states	mean	St. dev mean	distribution	Range (95%CI)	
				Lower bound	Upper bound
Healthy	0,86	0,0065	Beta	0,847	0,873
Stent					
baseline	0,69	0,0082	Beta	0,674	0,706
after 1 month	0,84	0,0065	Beta	0,827	0,853
after 6 months	0,86	0,0065	Beta	0,847	0,873
CABG					
baseline	0,68	0,0081	Beta	0,664	0,696
after 1 month	0,78	0,0069	Beta	0,766	0,794
after 6 months	0,86	0,0061	Beta	0,848	0,872
time before PCI or CABG					
QoL	see baseline values for respectively PCI and CABG				
duration	0,56 months		Beta	0,34	0,77

CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention; QoL: quality of life.

In our model, the initial loss of QoL before the initial procedure could be left out of consideration because it applies to all patients and does not influence the incremental calculations (figure 6.3, area A). For our calculations of QoL after the initial procedure, double counting has to be prevented. If a repeat procedure is observed within 6 months after the previous intervention, the lowest QoL is taken into account (which becomes zero in case of death). Adding all QoL differences without this correction would result in double counting (figure 6.3, area B and C). Furthermore, even though a repeat procedure may happen at the end of the year and have an influence on QoL up to six months later, we opt to restrict our time window up to 12 months. This is because, theoretically, costs and benefits should be calculated during the same time period.

Figure 6.3: avoiding double counting in utility values



Based on our Belgian database, we know in which month PCI, CABG or death occurred. We used these patient data to simulate the QoL for each patient in each subgroup. As such, performing 1000 simulations taking into account the uncertainty on the QoL values, we could calculate the average QoL for each subgroup.

The QoL improvement is calculated in three steps. First of all, QoL with the observed PCI, CABG and death events was calculated (i.e. QoL with no improvement). Secondly, QoL with only the initial PCI event and all CABG and death events was calculated (i.e. QoL with 100% improvement on re-PCI but no influence on CABG or death). These first two steps are performed in a separate model due to calculation limits (otherwise we would have 1000 simulations for all 1000 simulations for each scenario that is modeled). In the final step, which is integrated in the core model, the QoL improvement could be calculated by multiplying the average difference between those two extremes (i.e. 0% versus 100% avoidance of PCI) with the percentage of re-PCI procedures that could be prevented. The latter is based on the percentage of PCI due to restenosis and the relative benefit of DES versus BMS. These calculations are performed separately for each subgroup. In an alternative scenario, we also modeled the influence on QoL if DES could also prevent CABG events.

6.2.6 Sensitivity analysis

In an economic evaluation, the uncertainty of the output (IC, IE and ICERs) depends on the uncertainty and relative importance of the input variables. In contrast to deterministic modelling, multivariable *probabilistic modelling* takes into account the uncertainty around the values of all input variables at the same time, which is reflected in the uncertainty of the results. This is done by determining probability distributions, instead of point estimates, to the input variables (which are all shown in the previous tables). Then, simulations are performed. In each iteration, a random draw from the prespecified probability distributions is made to generate a result. After 1000 simulations, the uncertainty of the result can be measured. Results are presented with 95% confidence intervals.

In contrast to one-way sensitivity analysis, which sets the value of a specific variable at a certain alternative value, *probabilistic sensitivity analysis* on multiple variables reflects the combined implications of uncertainty in parameters. Using this approach, rank correlation coefficients are calculated between the output values (the ICERs) and the sampled input values to indicate the relative importance of variables (and their uncertainty) on results.

6.2.7 Scenario analysis

Several scenarios have been worked out in our model if different approaches or assumptions could be made (table 6.14).

First of all, concerning the *extra cost of DES versus BMS*, sales prices were included and multiplied with the mean number of stents used in both the initial procedure and for repeat procedures with stents. The reason is that even though an intervention is not reimbursed yet, the extra cost should be taken into account in an economic evaluation. An alternative approach is to include the fixed supplemental charge for DES above BMS. DES is currently only reimbursed for diabetic patients. One could expect that if DES would also be reimbursed for other subgroups of patients, the extra charge would be the same as it exists currently for the diabetic group, i.e. €1000. Secondly, the '*staging*' correction was included in the base case analysis and excluded in an alternative scenario. Since the 'staging' correction is an approximation of what happens in reality (and may not exactly reflect this reality), trueth might lie somewhere in between. The distinction between 'all patients' and 'clean patients' is also made. Next, whether or not DES would also have an *effect on CABG* was rather uncertain. In the base case, we assume the proportion of CABG interventions was not influenced by the initial stent type. In an alternative scenario, we assumed the relative influence on CABG was similar as the influence on PCI. Furthermore, the *duration of clopidogrel* was set at one and six months for respectively BMS and DES. We changed the latter to respectively one, three and 12 months. And finally, the real *stent cost was set fixed* for both stent types. The real stent cost for BMS was set at €500 (i.e. official stent price in combination with a 50% discount). For real costs of DES, five scenarios with different stent prices were modelled, i.e. respectively €1500, €1250, €1000, €750, and €500.

Table 6.14: Different scenarios in our model

	Description	
	Base case scenario	Alternative scenario
Incremental price of DES vs BMS (both in initial procedure and repeat intervention)	Sales prices are estimated (as a combination of official list prices (fixed weighted average) and a discount percentage (with uncertainty)).	Currently, an extra cost for DES is charged if it is implemented in diabetic patients. This charge is €1000 and is independent of the number of stents used. Therefore, in an alternative scenario, we include an extra cost of €1000 if BMS is replaced by DES or extract €1000 if DES is replaced by BMS.
Staging	A correction for the Belgian 'staging' phenomenon is included.	Calculations are also performed without any correction for staging
'Clean' patients	All patients are included	Only patients with no interventional history (no PCI, no CABG) are included
effect on CABG	DES versus BMS has no influence on CABG	DES has the same relative influence on PCI and on CABG
Drug therapy	Clopidogrel is given for 6 months with DES and 1 month with BMS	Three alternative scenarios are provided for the duration of clopidogrel treatment after DES implantation: 1, 3 and 12 months.
Real stent costs	Sales prices are estimated (as a combination of official list prices (fixed weighted average) and a discount percentage (with uncertainty)).	Fixed stent costs are used (i.e. without discount percentages). The BMS real stent cost is assumed to be €500 per stent. For DES, five scenarios are modelled with a real stent cost of respectively €1500, €1250, €1000, €750, and €500.

6.3 RESULTS

Base case results are given for all 16 subgroups (stratified for type of stent, diabetic status, MVD and complex lesion). Both scenarios with real stent costs and with RIZIV/INAMI stent costs are presented. For two selected subgroups (1 and 9), the cost-effectiveness plane and the results of the probabilistic sensitivity analysis are presented. For the first subgroup, results for the scenarios about staging, drug therapy and effect on CABG are also given. The results of the five scenarios with fixed real stent costs are provided for all subgroups.

6.3.1 Base case results

Table 6.15 gives an overview of the base case results for all 16 subgroups using real stent costs. Table 6.16 gives the same results using RIZIV/INAMI stent costs. Results in both tables were corrected for staging. In subgroup 1 to 8, results have to be interpreted as if one would change from BMS to DES in the index hospitalisation. In subgroup 9 to 16, it is the other way round. For the last two columns, i.e. the absolute percentage of events avoided and cost per event avoided, numbers are calculated for changing BMS to DES for all groups, since this is the only scenario that allows avoiding events.

As can be seen, the incremental costs for switching from BMS to DES (subgroup 1 to 8) are substantial while the utilities expressed as QALYs are indeed very small. This obviously leads to very high ICERs in all scenarios, ICERs that are of an order of magnitude of €1 million and more per QALY gained. The best ICER in the subgroups initially treated with BMS is for diabetic patients with multi-vessel disease but no complex lesions applying real stent costs. Even in this case, the ICER remains very high (€860 000/QALY).

In subgroup 9 to 16, changing from DES to BMS in the index hospitalisation would lead to cost savings with a small loss of QALYs. ICERs from our probabilistic model are not given if results are located in different quadrants of the cost-effectiveness plane.

To simplify comparison with the ICERs from the other subgroups, a proxy for the ICER is calculated by dividing the mean incremental cost by mean incremental QALYs (although we are aware that the ICER of the mean incremental cost (IC) and mean incremental effectiveness (IE) is not the same as the mean ICER of the 1000 simulated ICERs). ° When comparing with the previous eight subgroups, ICERs are more favourable but remain relatively high. However, when making calculations with RIZIV/INAMI stent costs, changing from DES to BMS would not be recommended from an economic point of view for diabetic patients with both MVD and complex lesion. In this subgroup, changing from DES to BMS would lead on average to extra costs while QALYs would be lost. This is not so when real stent costs are used, which in contrast to RIZIV/INAMI stent costs, is the calculation method which also takes the real number of stents used into account.

It is clear that, in our model, the proportion of events avoided is smaller in the subgroups initially treated with BMS in comparison with DES treated patients and for patients without MVD or complex lesions in comparison with those who have these unfavourable characteristics. Only for subgroup 6 this is not completely true (i.e. a smaller proportion of events avoided in comparison with subgroup 5). This is probably due to the fact that this is the smallest subgroup (49 patients) which implies greater uncertainty on input variables. This is also observed when looking at the cost per event avoided. The best results are seen in the group currently treated with DES with MVD and complex lesion.

° As mentioned by Briggs and colleagues,[202] "our interest is in the expected value of the output parameters (costs, effects and cost-effectiveness), but we will not obtain this expectation by evaluating the model at the expected values of the input parameters. For a nonlinear transformations g(.) (and models can be considered as nonlinear transformations), the expectation of the transformation does not equal the transformation of the expectation,[203] i.e. $E[g(.)] \neq g(E[.])$. For this reason, even if the decision maker is convinced that their only interest is in the expected value of the model, it is still necessary to consider uncertainty in the input parameters of a nonlinear model rather than simply employ the point estimates."

Table 6.15: IC, IE, ICER, % events avoided and cost per event avoided (real stent costs, correction for staging)

	incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)		*deterministic*	Absolute % events avoided		cost per event avoided (€)	
	2.5%	97.5%	2.5%	97.5%	2.5%	97.5%		2.5%	97.5%	2.5%	97.5%
BMS, non-diabetics											
no MVD or complex lesion	905		0,00046		1998543		*1953501*	3,29%		28244	
	638	1164	0,00033	0,00057	1260669	3093488		2,35%	4,13%	17381	43754
no MVD but complex lesion	1262		0,00057		2263373		*2201302*	3,92%		33453	
	861	1647	0,00039	0,00074	1351907	3466616		2,55%	5,35%	19119	54478
MVD but no complex lesion	1036		0,00044		2393028		*2334820*	3,84%		27671	
	711	1347	0,00031	0,00055	1458582	3805602		2,70%	4,87%	16579	43828
MVD and complex lesion	1474		0,00059		2559456		*2492373*	4,96%		30679	
	993	1960	0,00041	0,00075	1492798	4032080		3,38%	6,53%	17136	48928
BMS, diabetics											
no MVD or complex lesion	778		0,00073		1139797		*1069112*	5,18%		16890	
	448	1103	0,00044	0,00101	482011	2147753		2,66%	8,59%	5774	35520
no MVD but complex lesion	1291		0,00051		3371916		*2540066*	3,95%		52037	
	738	1820	0,00014	0,00094	934454	10830340		0,85%	9,54%	8602	182893
MVD but no complex lesion	773		0,00095		863011		*814607*	7,43%		11190	
	376	1142	0,00061	0,00129	325126	1645716		4,53%	10,61%	3885	21335
MVD and complex lesion	1198		0,00092		1482003		*1306372*	7,61%		18645	
	627	1809	0,00045	0,00146	473294	3290199		3,33%	13,37%	5241	45821
DES, non-diabetics											
no MVD or complex lesion	-567		-0,00097		*		*582249*	7,80%		9894	
	-973	10	-0,00185	-0,00039				15,58%	3,00%	-99	29749
no MVD but complex lesion	-787		-0,00146		*		*539677*	11,21%		10848	
	-1482	144	-0,00271	-0,00056				24,36%	3,65%	-758	37387
MVD but no complex lesion	-694		-0,00088		*		*787289*	7,96%		11490	
	-1140	-161	-0,00173	-0,00036				15,71%	3,15%	965	32034
MVD and complex lesion	-486		-0,00181		*		*268375*	16,16%		5078	
	-1286	784	-0,00351	-0,00073				34,21%	5,81%	-2456	19760
DES, diabetics											
no MVD or complex lesion	-647		-0,00067		*		*970400*	6,36%		13182	
	-1031	-188	-0,00124	-0,00026				12,13%	2,55%	1704	37145
no MVD but complex lesion	-471		-0,00132		*		*357517*	11,86%		6903	
	-1165	511	-0,00267	-0,00049				25,77%	3,79%	-2201	27114
MVD but no complex lesion	-465		-0,00110		*		*424128*	10,86%		5948	
	-1006	220	-0,00198	-0,00046				20,36%	4,48%	-1195	19619
MVD and complex lesion	-348		-0,00200		*		*173399*	17,29%		3580	
	-1222	847	-0,00369	-0,00084				33,93%	6,85%	-2681	16802

* The ICER of the probabilistic model is not mentioned if simulation results are spread over several quadrants of the cost-effectiveness plane (subgroup 9-16). As an alternative (in italics), we present the ICER calculated by dividing the mean incremental cost by the mean incremental benefit.

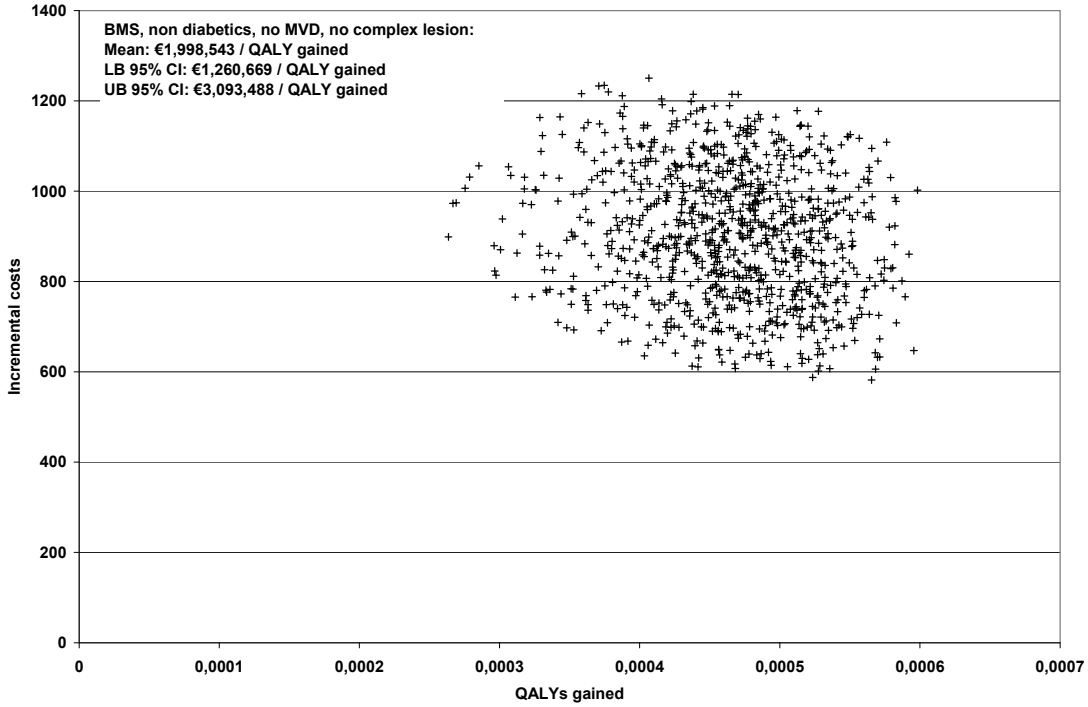
Table 6.16: IC, IE, ICER, % events avoided and cost per event avoided (RIZIV/INAMI stent costs, correction for staging)

	incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)		*deterministic*	Absolute % events avoided		cost per event avoided (€)	
	2.5%	97.5%	2.5%	97.5%	2.5%	97.5%		2.5%	97.5%	2.5%	97.5%
BMS, non-diabetics											
no MVD or complex lesion	1061		0,00046		2344566		*2290191*	3,29%		33145	
	992	1131	0,00033	0,00057	1761747	3444627		2,35%	4,13%	24295	47714
no MVD but complex lesion	1016		0,00057		1829543		*1772143*	3,92%		27065	
	896	1120	0,00039	0,00074	1241935	2802505		2,55%	5,35%	16840	43643
MVD but no complex lesion	1038		0,00044		2400948		*2339935*	3,84%		27770	
	959	1118	0,00031	0,00055	1747275	3519075		2,70%	4,87%	19760	41423
MVD and complex lesion	996		0,00059		1735754		*1683383*	4,96%		20807	
	884	1097	0,00041	0,00075	1186849	2667817		3,38%	6,53%	13644	31916
BMS, diabetics											
no MVD or complex lesion	944		0,00073		1379067		*1297156*	5,18%		20388	
	719	1119	0,00044	0,00101	742723	2519809		2,66%	8,59%	8368	41106
no MVD but complex lesion	999		0,00051		2640358		*1965136*	3,95%		41049	
	594	1225	0,00014	0,00094	690941	8395777		0,85%	9,54%	6268	140746
MVD but no complex lesion	804		0,00095		897475		*847168*	7,43%		11630	
	561	1003	0,00061	0,00129	449210	1633218		4,53%	10,61%	5302	22238
MVD and complex lesion	793		0,00092		1001823		*865316*	7,61%		12652	
	375	1099	0,00045	0,00146	277088	2391817		3,33%	13,37%	2850	32418
DES, non-diabetics											
no MVD or complex lesion	-757		-0,00097		*		*777800*	7,80%		12909	
	-1099	-230	-0,00185	-0,00039				15,58%	3,00%	1433	36501
no MVD but complex lesion	-536		-0,00146		*		*367244*	11,21%		8061	
	-1056	341	-0,00271	-0,00056				24,36%	3,65%	-1488	28596
MVD but no complex lesion	-769		-0,00088		*		*871970*	7,96%		12684	
	-1102	-244	-0,00173	-0,00036				15,71%	3,15%	1548	34584
MVD and complex lesion	-205		-0,00181		*		*113394*	16,16%		3036	
	-919	1045	-0,00351	-0,00073				34,21%	5,81%	-3276	15926
DES, diabetics											
no MVD or complex lesion	-863		-0,00067		*		*1294168*	6,36%		17264	
	-1142	-442	-0,00124	-0,00026				12,13%	2,55%	3636	44792
no MVD but complex lesion	-345		-0,00132		*		*261941*	11,86%		5881	
	-1001	802	-0,00267	-0,00049				25,77%	3,79%	-3330	25520
MVD but no complex lesion	-526		-0,00110		*		*479819*	10,86%		6696	
	-1000	192	-0,00198	-0,00046				20,36%	4,48%	-949	22153
MVD and complex lesion	333		-0,00200		*		*dominated*	17,29%		-550	
	-711	2101	-0,00369	-0,00084				33,93%	6,85%	-6811	10484

* The ICER of the probabilistic model is not mentioned if simulation results are spread over several quadrants of the cost-effectiveness plane (subgroup 9-16). As an alternative (in italics), we present the ICER calculated by dividing the mean incremental cost by the mean incremental benefit

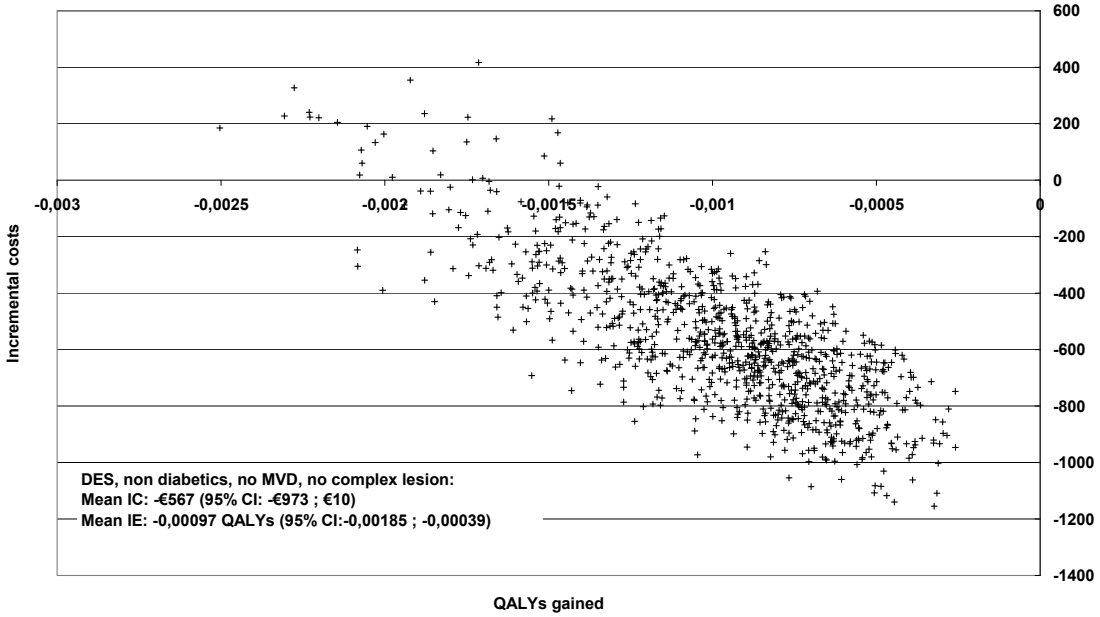
Figure 6.4 gives, as illustration, the cost-effectiveness plane for subgroup 1 (part a) and subgroup 9 (part b) resulting from the probabilistic Monte Carlo simulation using real stent costs. In the first figure, and similar for subgroups 2 to 8, simulation dots are oriented in the north-east quadrant of the plane, i.e. changing from BMS to DES results in extra costs and QALYs gained. In contrast, this is the south-west quadrant in the second figure, i.e. changing from DES to BMS results in cost savings but QALYs are lost.

Figure 6.4, part a: Cost-effectiveness plane for subgroup 1



LB: lower bound; UB: upper bound

Figure 6.4, part b: Cost-effectiveness plane for subgroup 9



6.3.2 Probabilistic sensitivity analysis

Figure 6.5 presents a tornado graph of our probabilistic sensitivity analysis for subgroup 1 and 9. Only the variables with a correlation coefficient above 0.2 are presented. We have to remark that the correlation coefficients of the QoL input values could not be calculated in our model since the QoL values and their uncertainty were used in a separate simulation of which the mean result were used in the core model (see above).

Figure 6.5, part a: Probabilistic sensitivity analysis for subgroup 1

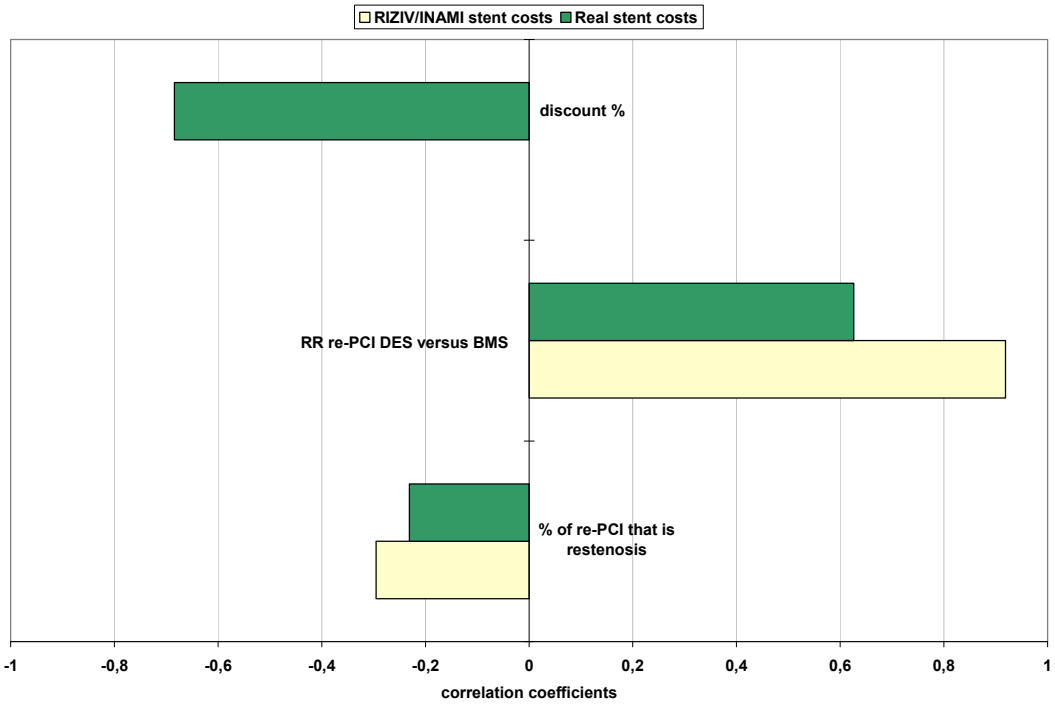
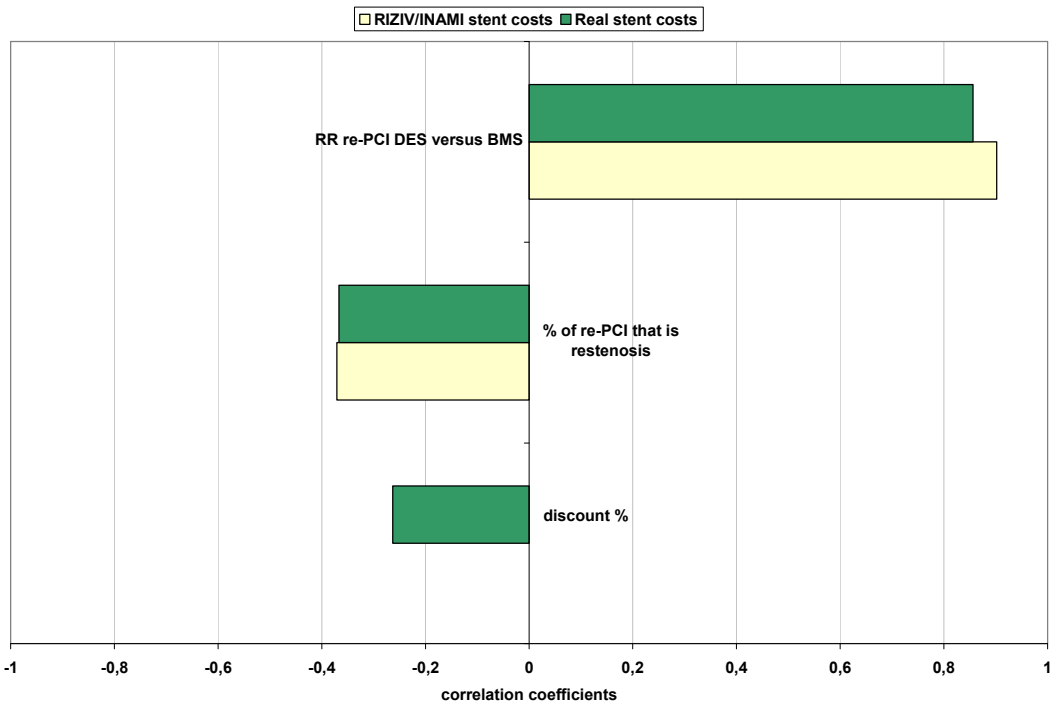


Figure 6.5, part b: Probabilistic sensitivity analysis for subgroup 9



The tornado graph contains results for both the 'RIZIV/INAMI stent cost' and 'real stent cost' approach. It is clear that the discount percentage only has an influence on ICER in the latter. This discount percentage is the most determining factor of the ICER in subgroup 1. This is not only because this is an important factor, but also because the uncertainty interval around this variable varies widely between 30% and 70%. The two other most determining input variables for the ICER are the relative risk of re-PCI with DES versus BMS and the percentage of re-PCI caused by restenosis. In subgroup 9, the same variables are identified in the probabilistic sensitivity analysis. However, the order of importance is different, with the relative risk as the variable with the largest correlation coefficient. This could be explained by the fact that in our model, the relative risk reduction is used twice in our calculations for subgroups initially treated with DES. Similar as for all subgroups, it is used to calculate the improvement in reinterventions if DES is used instead of BMS. Secondly, in subgroup 9 to16, it is also used to calculate the initial percentage of restenosis if patients initially would have been treated with BMS instead of DES (see part 'correction on percentage of restenosis in the DES group'). This explains why this variable has more impact on the results when comparing the tornado graphs of subgroup 1 and 9.

6.3.3 Alternative scenarios

As described previously, we also tested alternative scenarios. For the scenarios about staging, drug therapy and effect on CABG, results are presented for the first subgroup. The results of the five scenarios on fixed real stent costs are given for all subgroups.

6.3.3.1 Not correcting for staging or 'clean' patients

The correction for staging and the analysis of the subgroup of patients without interventional history has a minor influence on the ICERs. They remain very high as shown in table 6.17.

Table 6.17: Incremental costs, benefits and ICERs for subgroup 1 with and without staging correction and separately for patients without interventional history

	incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)	
	2.5%	97.5%	2.5%	97.5%	2.5%	97.5%
BMS, non-diabetics no MVD or complex lesion						
real stent costs						
All patients						
correction for staging	905		0,00046		1998543	
	638	1164	0,00033	0,00057	1260669	3093488
no correction for staging	914		0,00046		2016934	
	651	1178	0,00033	0,00057	1284546	3104199
Clean patients						
correction for staging	900		0,00045		2044452	
	642	1155	0,00032	0,00056	1262535	3163257
no correction for staging	905		0,00045		2054052	
	647	1160	0,00031	0,00057	1288617	3123655
RIZIV/INAMI stent costs						
All patients						
correction for staging	1061		0,00046		2344566	
	992	1131	0,00033	0,00057	1761747	3444627
no correction for staging	1068		0,00046		2359427	
	1005	1138	0,00033	0,00057	1754730	3472848
Clean patients						
correction for staging	1076		0,00045		2444778	
	1006	1143	0,00032	0,00056	1804335	3606206
no correction for staging	1077		0,00045		2448864	
	1006	1146	0,00031	0,00057	1794218	3689157

6.3.3.2 *Duration of dual-antiplatelet therapy*

In table 6.18 we evaluated different durations of dual-antiplatelet therapy, while in the base case 6 months duration was used. In our model, we did not incorporate any change in QoL or QALYs by changing the duration of dual-antiplatelet therapy. We found an expected important impact on both costs and ICERs. The incremental cost clearly decreases if the duration decreases. However, even if this therapy is given for only one month after DES is implanted, the ICERs remain very high.

Table 6.18: Incremental costs, benefits and ICERs for subgroup 1 in different scenarios of dual-antiplatelet therapy duration

	incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)	
	2.5%	97.5%	2.5%	97.5%	2.5%	97.5%
BMS, non-diabetics, no MVD or complex lesion						
real stent costs						
1 month	621		0,00046		1372642	
	353	880	0,00033	0,00057	695019	2301670
3 months	734		0,00046		1623003	
	467	994	0,00033	0,00057	922280	2614436
6 months	905		0,00046		1998543	
	638	1164	0,00033	0,00057	1260669	3093488
12 months	1247		0,00046		2749624	
	979	1506	0,00033	0,00057	1884888	4113191
RIZIV/INAMI stent costs						
1 month	777		0,00046		1718665	
	707	847	0,00033	0,00057	1260808	2579098
3 months	891		0,00046		1969026	
	821	960	0,00033	0,00057	1463476	2925309
6 months	1061		0,00046		2344566	
	992	1131	0,00033	0,00057	1761747	3444627
12 months	1403		0,00046		3095647	
	1333	1472	0,00033	0,00057	2367345	4483262

6.3.3.3 *Effect on CABG incidence*

In the base case scenario we assume no effect on CABG incidence because there is no conclusive evidence that CABG incidence is reduced due to DES use. However, if we assume a similar effect on revascularisation rates through CABG as through PCI, ICERs improve markedly (table 6.19). Similar as for the other scenarios, ICERs, however, remain very high since QALYs gained are very small and incremental costs remain relatively high.

Table 6.19: Incremental costs, benefits and ICERs for subgroup 1 with or without effect on CABG

	incremental cost (€)		incremental benefit (QALYs)		ICER (€ per QALY gained)	
	2.5%	97.5%	2.5%	97.5%	2.5%	97.5%
BMS, non-diabetics, no MVD or complex lesion						
real stent costs						
no effect	905		0,00046		1998543	
	638	1164	0,00033	0,00057	1260669	3093488
effect on CABG	838		0,00058		1482446	
	573	1113	0,00041	0,00071	888092	2386857
RIZIV/INAMI stent costs						
no effect	1061		0,00046		2344566	
	992	1131	0,00033	0,00057	1761747	3444627
effect on CABG	994		0,00058		1757841	
	911	1088	0,00041	0,00071	1281851	2651255

6.3.3.4 Real stent costs

In the initial scenario with real stent costs, the weighted average of the official stent prices is multiplied with a discount percentage which varies between 30% and 70%. In this scenario analysis, we included fixed stent prices. Five scenarios are modelled. In every scenario, we assume the real cost for BMS is €500. For DES, this is respectively €1500, €1250, €1000, €750, and €500. Results are presented in table 6.20 (part a and b).

Changing stent prices does not have an influence on incremental effects (i.e. the incremental benefit is the same as in table 6.15 and 6.16). As expected, results are more favourable if the price difference between BMS and DES decreases. However, it may be surprising that even with an equal price for both DES and BMS, results are not always cost saving. In subgroups 1 to 8 (table 6.20, part a), an equal DES and BMS stent cost only results in cost savings in four subgroups. This is because drug therapy costs are still higher. In our base case, clopidogrel therapy is followed for 1 month after BMS and 6 months after DES, resulting in an extra cost of €284. In combination with the fact that only a minority of patients may profit from DES by avoiding a reintervention, an equal DES and BMS price does not always automatically result in cost savings. We should also not forget that lowering stent prices does not only have an influence on the initial incremental costs of the index hospitalisation if BMS is replaced by DES, but also on the costs of the repeat PCI. Lowering stent prices decreases the cost of repeat PCI. This effect is also included in our model with real stent cost calculations. In general, due to the very small health gains, even a small price difference between DES and BMS results in unfavourable cost-effectiveness ratios.

In subgroups 9 to 16 (table 6.20, part b), i.e. those currently treated with DES in the index hospitalisation, results are more favourable. With equal stent prices, BMS is dominated by DES, i.e. changing from DES to BMS would result in extra costs while QALYs would be lost. From the moment the price difference increases, changing from DES to BMS would result in cost savings and relatively few QALYs lost.

Table 6.20, part a: Incremental costs, benefits and ICERs for subgroups 1 to 8 with fixed stent prices

stent cost			BMS = €500				
			DES = €1500	DES = €1250	DES = €1000	DES = €750	DES = €500
BMS, non-diabetics							
no MVD or complex lesion		IC	1176	905	634	363	92
IE: mean	0,00046	95%CI	1120 1241	850 967	580 693	310 421	40 147
2.5%	0,00033	ICER	2597121	2000185	1403249	806313	209377
97.5%	0,00057	95%CI	1987717 3771320	1512621 2940954	1033632 2101139	555207 1276190	74754 449544
no MVD but complex lesion		IC	1663	1262	861	460	58
IE: mean	0,00057	95%CI	1556 1761	1165 1352	771 947	373 543	-25 139
2.5%	0,00039	ICER	2986249	2268287	1550325	832363	*101807*
97.5%	0,00074	95%CI	2132951 4386750	1597290 3359214	1060760 2353599	524223 1368247	
MVD but no complex lesion		IC	1363	1036	708	381	54
IE: mean	0,00044	95%CI	1289 1438	968 1107	644 779	318 452	-7 124
2.5%	0,00031	ICER	3147402	2394247	1641093	887938	*121755*
97.5%	0,00055	95%CI	2354118 4517948	1770890 3488144	1181694 2458340	583259 1428535	
MVD and complex lesion		IC	1968	1474	980	486	-8
IE: mean	0,00059	95%CI	1846 2081	1362 1577	874 1077	385 580	-108 86
2.5%	0,00041	ICER	3419779	2564236	1708693	853151	*cost saving*
97.5%	0,00075	95%CI	2475999 4998705	1831872 3806538	1182249 2614372	523403 1409199	
BMS, diabetics							
no MVD or complex lesion		IC	1051	778	506	233	-40
IE: mean	0,00073	95%CI	816 1238	553 959	283 677	16 397	-255 116
2.5%	0,00044	ICER	1532685	1140577	748469	*320251*	*cost saving*
97.5%	0,00101	95%CI	835109 2779035	574202 2141383	303306 1488127		
no MVD but complex lesion		IC	1710	1291	873	455	36
IE: mean	0,00051	95%CI	1270 2072	881 1612	478 1144	80 677	-328 231
2.5%	0,00014	ICER	4432306	3380037	2327768	*894279*	*70968*
97.5%	0,00094	95%CI	1505649 13617440	1038972 10652300	568029 7687159		
MVD but no complex lesion		IC	1090	773	455	137	-180
IE: mean	0,00095	95%CI	825 1304	517 975	212 649	-97 324	-405 0
2.5%	0,00061	ICER	1210874	863333	515791	*144821*	*cost saving*
97.5%	0,00129	95%CI	648991 2121312	415836 1576711	170910 1038408		
MVD and complex lesion		IC	1658	1198	738	278	-182
IE: mean	0,00092	95%CI	1205 2021	769 1529	323 1044	-116 566	-562 89
2.5%	0,00045	ICER	2031890	1481795	931701	*302824*	*cost saving*
97.5%	0,00146	95%CI	868632 4390124	551590 3308601	234786 2244584		

The ICER of the probabilistic model with its 95% CI is not mentioned if simulation results are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), we present the ICER calculated by dividing the mean incremental cost by the mean incremental benefit.

Table 6.20, part b: Incremental costs, benefits and ICERs for subgroups 9 to 16 with fixed stent prices

stent cost			BMS = €500				
			DES = €1500	DES = €1250	DES = €1000	DES = €750	DES = €500
DES, non-diabetics							
no MVD or complex lesion		IC	-824	-567	-310	-52	205
IE: mean	-0,00097	95%CI	-1149 -258	-888 -11	-627 237	-366 485	-105 733
2.5%	-0,00185	ICER	*846473*	*582261*	*318048*	*53835*	*dominated*
97.5%	-0,00039	95%CI					
no MVD but complex lesion		IC	-1187	-787	-387	13	413
IE: mean	-0,00146	95%CI	-1716 -308	-1295 77	-889 471	-483 854	-75 1236
2.5%	-0,00271	ICER	*813613*	*539452*	*265290*	*dominated*	*dominated*
97.5%	-0,00056	95%CI					
MVD but no complex lesion		IC	-1000	-694	-389	-83	222
IE: mean	-0,00088	95%CI	-1320 -468	-1014 -170	-703 122	-389 425	-82 733
2.5%	-0,00173	ICER	1435057	*787410*	*440905*	*94400*	*dominated*
97.5%	-0,00036	95%CI	263764 3657998				
MVD and complex lesion		IC	-892	-486	-79	327	734
IE: mean	-0,00181	95%CI	-1586 320	-1174 719	-749 1117	-326 1518	90 1913
2.5%	-0,00351	ICER	*492950*	*268341*	*43732*	*dominated*	*dominated*
97.5%	-0,00073	95%CI					
DES, diabetics							
no MVD or complex lesion		IC	-903	-647	-391	-135	121
IE: mean	-0,00067	95%CI	-1182 -475	-918 -234	-653 7	-389 258	-125 501
2.5%	-0,00124	ICER	1692058	*970732*	*586542*	*202351*	*dominated*
97.5%	-0,00026	95%CI	404985 4444049				
no MVD but complex lesion		IC	-787	-472	-156	159	474
IE: mean	-0,00132	95%CI	-1384 182	-1053 475	-718 769	-385 1062	-52 1346
2.5%	-0,00267	ICER	*596913*	*357795*	*118676*	*dominated*	*dominated*
97.5%	-0,00049	95%CI					
MVD but no complex lesion		IC	-757	-465	-173	119	410
IE: mean	-0,00110	95%CI	-1205 -91	-904 178	-602 457	-300 739	-3 1025
2.5%	-0,00198	ICER	*690560*	*424297*	*158034*	*dominated*	*dominated*
97.5%	-0,00046	95%CI					
MVD and complex lesion		IC	-735	-348	39	426	813
IE: mean	-0,00200	95%CI	-1495 428	-1085 786	-683 1142	-280 1512	123 1867
2.5%	-0,00369	ICER	*366784*	*173653*	*dominated*	*dominated*	*dominated*
97.5%	-0,00084	95%CI					

The ICER of the probabilistic model with its 95% CI is not mentioned if simulation results are spread over several quadrants of the cost-effectiveness plane. As an alternative (in italics), we present the ICER calculated by dividing the mean incremental cost by the mean incremental benefit.

6.4 BUDGET IMPACT

If decision makers decide to reimburse DES for other subgroups than currently eligible (patients with treated diabetes), more DES will probably be used. Therefore, we calculate the budget impact for subgroups 1 to 8 if BMS is replaced by DES in the index procedure. In this calculation, we only account for the extra stent cost in the initial procedure and not for cost differences afterwards. Similar but the other way round for diabetic patients currently treated with DES in the index procedure (subgroup 13 to 16), the budget impact of changing from DES to BMS is calculated. In these subgroups, DES are currently reimbursed. For subgroup 9 to 12, i.e. non-diabetic patients currently treated with DES (for whom DES currently are not reimbursed), the budget impact of reimbursing this stent is calculated.

First of all, we need an estimate of the number of patients with an index procedure during a year. In 2004, 21308 patients had a PCI (chapter 5). For 19.9% of this group (see table 5.6), this already was a re-PCI. As a result, about 17000 patients had a first PCI in 2004. Since there is a steady increase in the yearly number of PCIs (see chapter 1) this number should be seen as a minimum. These 17000 patients could be attributed to our 16 subgroups (table 6.21). In combination with the incremental real cost for stents (table 6.21) or the incremental RIZIV/INAMI stent cost (€1000), the budget impact could be calculated. Results are shown in the last two columns of table 6.21.

The results show that, obviously, the major budget impact would be if non-diabetic patients initially treated with BMS, which is the largest part of our population, would initially be treated with DES. This would result in an additional cost of more than €12 million. If DES would be reimbursed for non-diabetics currently receiving DES, this would cost about €1.5 million. The potential budget savings by replacing initially implanted DES by BMS for diabetic patients amount to about €2.4 million if calculations are made with RIZIV/INAMI stent costs.

Table 6.21: Budget impact

	incremental real cost for stents (€)		index PCIs in each subgroup (N = 17000)		budget impact per subgroup	
	2.5%	97.5%	% of patients in each group	index PCIs in each group	real stent costs	RIZIV/INAMI stent costs
BMS, non-diabetics					**12166446**	**12272751**
no MVD or complex lesion	817	1082	27,47%	4670	3817353 2567265 5051071	4669572
no MVD but complex lesion	1207	1603	6,00%	1020	1231666 829021 1635461	1020090
MVD but no complex lesion	967	1282	30,09%	5115	4948789 3343835 6556073	5115154
MVD and complex lesion	1477	1965	8,63%	1468	2168638 1464253 2884514	1467935
BMS, diabetics					**681424**	**679683**
no MVD or complex lesion	832	1102	1,32%	225	187349 126233 248027	225053
no MVD but complex lesion	1282	1748	0,33%	55	71044 46277 96862	55415
MVD but no complex lesion	968	1282	1,84%	313	303107 204844 401503	313265
MVD and complex lesion	1395	1884	0,51%	86	119924 80350 161897	85950
DES, non-diabetics					**1510907**	**1622871**
no MVD or complex lesion	788	1045	3,50%	595	468470 621922 316038	594864
no MVD but complex lesion	1223	1640	0,92%	157	192240 257742 129323	157198
MVD but no complex lesion	907	1203	4,08%	693	629110 834275 424665	693254
MVD and complex lesion	1245	1670	1,04%	178	221088 296568 147957	177555
DES, diabetics					**-2220009**	**-2424694**
no MVD or complex lesion	-788	-534	4,68%	795	-626114 -828135 -424223	-795037
no MVD but complex lesion	-1020	-680	0,87%	148	-151094 -201445 -100729	-148151
MVD but no complex lesion	-907	-611	6,92%	1176	-1067350 -1414384 -718587	-1176158
MVD and complex lesion	-1230	-834	1,80%	305	-375450 -499676 -254538	-305349

6.5 DISCUSSION

The results from RCTs comparing sirolimus and paclitaxel drug eluting stents with BMS are remarkable. An important number of re-interventions would be avoided due to the lower risk of restenosis with DES. Being more than twice as expensive as BMS, however, the major constraint to fully implement the use of DES is its higher cost. Furthermore, the reliability of RCT data in real-world conditions, may question the results and recommendations of economic analysis relying on RCT data. Especially the protocol-driven angiographic follow-up overestimates the base risk for restenosis. As such the absolute benefit, which drives the economic evaluation, is also overestimated resulting in overly optimistic results.

The major strength of our evaluation is the use of real-world observational data, estimating the base risk for re-PCI and the proportion due to restenosis. Also real cost data for re-interventions, both PCI and CABG, were obtained. A potential limitation of our data is that they are indeed 'just' observational data. The probabilities for restenosis for both BMS and DES groups could not be compared due to the possible underlying differences in both populations. However, in our approach, we avoid this problem by combining relative risk reductions (or the inverse when changing from DES to BMS) with base risks as observed in reality. To avoid any confusion, BMS and DES groups are not compared directly from our observational data. The relative benefits, based on RCTs and meta-analyses, were applied to the base risks to calculate the health benefits and cost savings during the year following the initial procedure. As such, our questions are the following: what would the costs and benefits be in the BMS subgroups if they would have been treated with DES (subgroup 1 to 8) and if the DES subgroups would have been treated with BMS (subgroup 9 to 16). As such, we do not cross subgroups to make comparisons and the strengths of both observational data and meta-analyses are combined.

Another possible limitation is that some variables were included as proxies. First of all, the definition of complex lesion was done by a proxy variable, defined as either small vessels (PCI segment, and therefore not necessarily corresponding to a clinically highly significant lesion) or long vessel (operationalised as needing more than one stent). Similarly, the variables used for the staging correction and to indicate whether or not a reintervention is due to restenosis are also proxy variables. Another proxy variable was included for the real cost of stents. Companies do not want their prices, and especially their discounts, to be made public and also hospitals are reluctant to mention how much they really pay for their devices. We had to convince the cooperating companies that we would not publish publicly their stent prices and therefore we used weighted averages instead. Doing so, we may have lost some transparency. However, we prefer and judge it very useful to include these proxies rather than not doing so.

Finally, the major limitation of our model is that its time window is limited to one year while up to 4-year follow-up data are available. We argue, however, that this is not a major problem since most re-interventions due to restenosis occur during the first year. Furthermore, we used a large Belgian database with coupled cost data that was limited to one-year of follow-up. As such, we are confident that, with our analysis, we are able to calculate real-world condition one-year ICERs of DES versus BMS. We are aware that late stent thrombosis, especially following the cessation of dual-antiplatelet therapy, may have a negative impact on efficacy and safety. However, limiting our analysis to one year and not including this safety problem is not a problem towards our conclusions and recommendations. Our one-year ICERs are already unfavourable and including this long-term safety problem would only worsen the ICERs further. As mentioned by Eisenberg, one could question whether it is ethical to subject large numbers of patients who are at low risk of restenosis to the small but real risk of late thrombosis known to be associated with DES. Moreover, the widespread use of DES and the ensuing risk of late thrombosis is creating a new clinical phenomenon: long-term dependence on clopidogrel.[178]

The Belgian pharmacoeconomic guidelines mention that the identification, measurement, and valuation of costs should be consistent with the perspective of the Belgian health care payer. In our analysis, the focus is on direct health care costs. In the case of DES, one could argue that there are indirect cost savings by avoiding reinterventions since, for example, less absenteeism from work could occur. Dealing with a rather older population, these possible indirect cost consequences have not been included in the economic evaluation. As such, following the Belgian guidelines, non-health care costs or unrelated health care costs are not included in the reference case analysis.

Comparing the input of our model with most previous published models, we need to discuss some differences. First of all, we used real world data while many models mainly rely on input from RCTs. Compared to most economic evaluations, the risk of having a reintervention is smaller when using Belgian observational data. Secondly, a distinction between re-PCIs was made based on whether or not this was caused by restenosis. We assume that changing from stent type would only have an influence on these re-PCIs and not on PCIs related to progression of CHD. This distinction was not always clearly made in previous models. Thirdly, our QALYs were calculated taking into account events such as CABG and death which are not avoided by changing stent type. If only QoL values for the initial PCI and re-PCI are taken into account, the QALYs gained may be overestimated. Using the Belgian observational data, we have monthly events of re-PCI, CABG and death at our disposal. As such we can more exactly calculate the QALYs gained by decreasing the number of reinterventions. It is not always clear how other models took into account that for example death could not be prevented by changing the stent type.

When comparing our results with the results of previous published economic evaluations, our results are quite similar to the results of the field evaluation published by Bowen[139] with very unfavourable ICERs towards DES. The reason is clear: important incremental costs and very small gains in QALYs. No life-years are gained and the small QoL gains only occur during short periods for a small part of the population.

The ICERs could improve if DES would further improve health benefits compared to BMS. However, this should be proven in the first place and secondly, we should not forget that new BMS types also may increase efficacy. Newer generation BMS may be superior to conventional BMS used in studies and consequently, the possibility exists that the differential benefit of DES may be reduced when compared against these newer BMS devices.[159, 150]

The factor which can be manipulated most easily is the price of both stent types. The ICERs could improve if the price difference between BMS and DES would decrease. One could expect that, with time, the cost of DES (and BMS) will further decrease. Especially the entry of new market players may increase competition. For example, in France, the price for the first DES was about €2 200. The introduction of a second stent on the market has lowered the price with about 30% (€1 600).[204] From a payer's perspective, one can hope prices will decrease further. However, we have to make some remarks. First of all, prices for BMS may also fall further and the price differential, which is of importance in economic evaluations, may remain rather constant or decrease at a slower pace. Secondly, Hodgson and colleagues remark that no considerable decrease in prices happened for more than 5 years after the introduction of BMS and only after three competitors had each been on the market for several years.[175] More competitors as such is no garuantee for increased price competition. Furthermore, if DES would be used for a larger group of patients, the demand for this implant would increase and considerable price drops may be questionable. And finally, we should not forget that longer clopidogrel treatment still results in extra costs. As a result, as long as the gain in QALYs remains relatively small, even small price differences do not automatically provide cost effective results.

As mentioned by Hodgson, from the patient's perspective, DES would ideally be used to treat all lesions for which there was even a small absolute benefit. Given the positive results of most of the DES studies reported in peer-reviewed journals and the media response to these results, it is not surprising that patients believe that DES should be used for all patients and for all indications.[175]

However, patients, health care providers and decision makers should be aware that health care budgets are not infinite. The opportunity loss of increasing expenses in one area should be taken into account. Reimbursing interventions regardless of costs because they are perceived to be better may do more harm than good. The harm, however, happens in another non-specified area, and is therefore not always taken into account. In the case of DES, the budget impact of replacing BMS in the initial treatment may increase expenses with up to €12 million. This could even be more if using DES instead of BMS for re-interventions would also increase. On the other hand, as mentioned by Ryan,[163] the use of DES for patients who currently undergo bypass (CABG) surgery at a cost of about €15600 in Belgium, could result in substantial short- and long-term cost savings, provided the long-term outcomes are not compromised by such a strategy. We calculated ICERs in an alternative scenario were DES had the same influence on CABG as for re-PCI, which resulted in better ICERs but remained very high. However, the subject of this Health Technology Assessment report is to determine the (economic) value of DES compared to BMS. Another HTA would be needed to explore the relative clinical and economic advantages of DES (or BMS) compared to surgical revascularization.

6.6 CONCLUSION

From the physician's perspective, it is attractive to offer patients the newest technology and spare them the frustration of additional revascularization procedures.[162] From the patient's point of view, better technologies may be desired regardless of their price. However, when comparing DES with BMS, DES are not cost saving or cost neutral. A substantial amount of money has to be spent to obtain a very modest clinical benefit. In patients receiving a BMS, on average and based on real-world Belgian data corrected for staging, there is a cumulative probability of about 15% to have a re-PCI in the first year, but less than half of these reinterventions are because of restenosis. If about two thirds of these restenosis-related re-PCIs could be prevented by changing from BMS to DES, this would on average prevent less than an absolute 5% decrease of re-PCIs. Moreover, no life years are gained for these patients. Only small QoL improvements for very short periods are gained. Together, this results in very unfavourable ICERs for DES compared to BMS.

In conclusion, based on our evaluation, there is no good economic justification to implant DES in patients currently receiving BMS. These resources would better be used to improve health care in other areas.

Key points

- **Due to the substantial increased cost combined with a very small incremental benefit (expressed as Quality Adjusted Life Years), the incremental cost-effectiveness ratios of using DES instead of BMS are very unfavourable.**
- **In alternate scenarios these ICERs become better when assuming an additional beneficial effect of DES on CABG rates but even then ICERs remain unfavourably high.**
- **The budget impact of using DES instead of BMS is substantial and the opportunity cost of the extra expenses for DES should be considered.**

7 APPENDICES

APPENDIX FOR CHAPTER ON EFFICACY AND SAFETY (CHAPTER 3)

LITERATURE SEARCH FOR META-ANALYSES OF CLINICAL EFFICACY AND SAFETY

We wanted to retrieve meta-analyses that compared the efficacy and safety of drug eluting stents (either PES or SES or both) with bare metal stents in patients with coronary heart disease, without a-priori language restriction and with a clinical follow-up of at least 6 months. In addition we search for publications from registries that compared the efficacy and safety of DES with BMS in the same group of patients. We searched Medline, Embase, and the Cochrane Database of Systematic Reviews (CDSR). Databases were searched during the month of June and July 2007.

Table A3.1: Search for meta-analyses in Medline, through OVID interface (June, 2007)

1	Stents/	22816
2	coronary.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	122634
3	coronary$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	122635
4	1 and 3	9413
5	meta-analysis.pt.	13071
6	4 and 5	87
7	paclitaxel.nm.	9686
8	sirolimus.nm.	4344
9	7 or 8	13663
10	6 and 9	28
11	limit 10 to yr="2004 - 2007"	28
12	from 11 keep 1-28	28

Table A3.2: Search for meta-analyses in Embase (June 4th, 2007)

1	('stents'/exp OR 'stents') AND [2004-2008]/py	15717
2	coronary AND [2004-2008]/py	59884
3	coronary* AND [2004-2008]/py	59884
4	#1 AND #3	7060
5	*eluting AND [2004-2008]/py	3604
6	#4 AND #5	2481
7	#5 AND [meta analysis]/lim AND [2004-2008]/py	158
8	#6 AND [meta analysis]/lim AND [2004-2008]/py	140

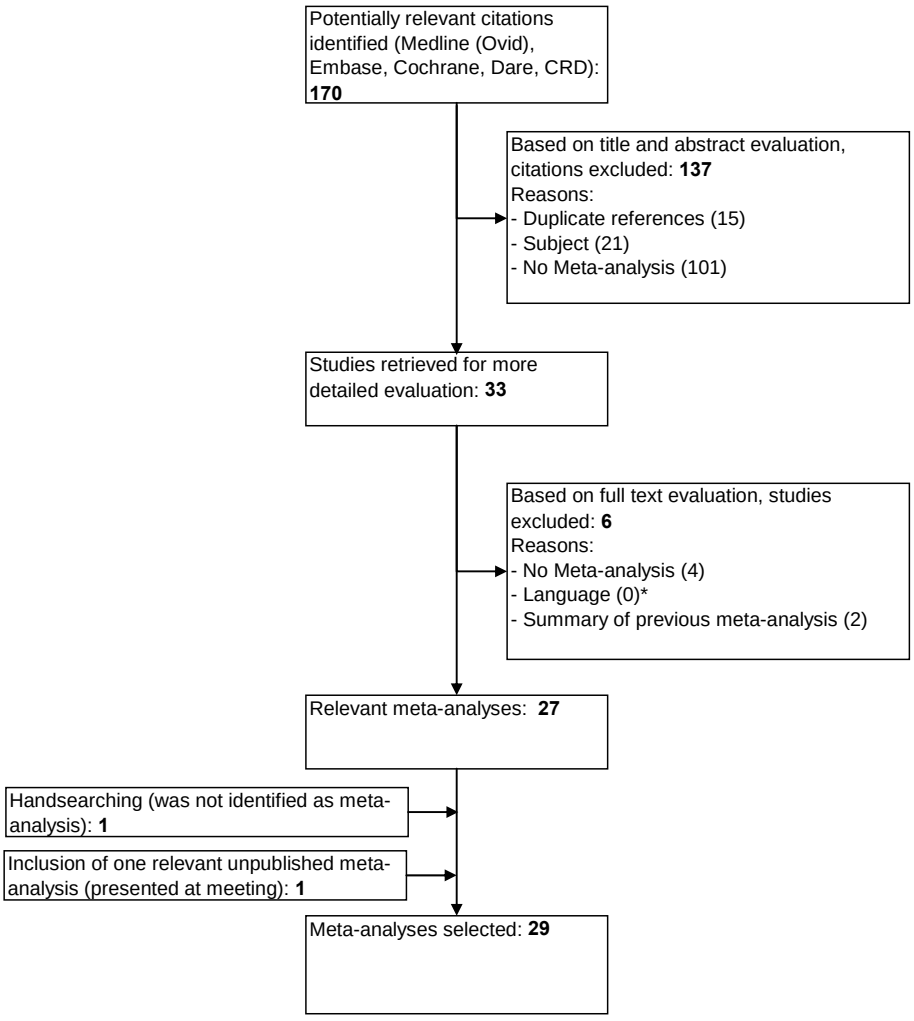
Table A3.3: Search for meta-analyses in CDSR (July, 2007)

#1	MeSH descriptor Stents, this term only	1685
#2	MeSH descriptor Coronary Disease explode all trees	9959
#3	*elut* OR *coat*	3701
#4	*elut*	421
#5	(#1 AND #2 AND #3)	250
#6	MeSH descriptor Meta-Analysis, this term only	378
#7	(#5 AND #6)	0
#8	meta-analysis	10114
#9	(#5 AND #8)	25
#10	(#9), from 2004 to 2007	23
	Selection on potential meta-analyses from #10	2

A total of 170 potential meta-analyses were thus selected. Subsequent sifting of references using title and abstract eliminated 137 articles, the majority because they were not meta-analyses. We retrieved 33 full-text articles for further selection to finally end up with 28 published meta-analyses and 1 metaanalysis that was only presented at the Barcelona EuroPCR meeting in June 2007. The flow-chart in figure xx represents the process of selection of evidence.

Figure A3.1: Flow chart of search for DES Meta-Analyses

DES Meta-analyses



*1 reference in Chinese (Li 2005) was kept for completeness since tables and abstract where in English

Table A3.4: Meta-analyses published in 2007: details of included RCTs

	Spaulding[58]	Stone[59]	Mauri[60]	Kastrati[61]	Moreno[62]	Ellis[63]	Camenzind[48]	Boyden[64]
n	1748	5261	4545	4958	9791	3445	5112	1520
RCTs	4	9	8	14	23	4	9	10
RAVEL	*	*	*	*	*		*	*
SIRIUS	*	*	*	*	*		*	*
C-SIRIUS	*	*	*	*	*		*	*
E-SIRIUS	*	*	*	*	*		*	*
TAXUS I		*	*		*		*	
TAXUS II MR		*	*		*	*	*	*
TAXUS IV		*	*		*	*	*	*
TAXUS V de novo		*	*		*	*	*	*
TAXUS VI		*			*	*	*	*
ASPECT								
ELUTES								
DELIVER I								
FUTURE I					*			
FUTURE II					*			
SES-SMART					*			*
ENDEAVOR II					*			
PATENCY								
SCORE								
BASKET				*	*			
DIABETES				*	*			*
SCANDSTENT				*	*			
PRISON II				*	*			
TYPHOON				*				
DECODE				*				
Pache et al.				*	*			
SCORPIUS				*				
SESAMI				*				
STRATEGY				*	*			
JUPITER I					*			
JUPITER II					*			
SPIRIT I					*			
STEALTH					*			
SIRTAX								
TAXI								
REALITY								
ISAR-DIABETES								
DIRECT								
SVELTE								
ACTION								
ISAR-DESIRE								
CORPAL								
ISAR-SMART								
RESEARCH								
IMPACT								

Table A3.5: Meta-analyses published in 2006: details of included RCTs

	Roiron[36]	Nordmann[47]	Stettler[65]	Sidhu[66]	Schampaert[67]	Kereiakes[68]	Holmes[69]	Bavry[70]
n	8987	8221	4513	2704	1510	1747	1748	6675
RCTs	20	16	10	4	3	5	4	14
RAVEL	*	*	*				*	*
SIRIUS	*	*	*		*	*	*	*
C-SIRIUS	*	*	*		*	*	*	*
E-SIRIUS	*	*	*		*	*	*	*
TAXUS I	*	*	*					*
TAXUS II MR	*	*	*					*
TAXUS IV	*	*	*					*
TAXUS V de novo	*	*						*
TAXUS VI	*	*	*					*
ASPECT	*	*						
ELUTES	*	*						
DELIVER I	*	*						
FUTURE I	*							
FUTURE II	*							
SES-SMART	*	*	*					*
ENDEAVOR II	*							
PATENCY	*							
SCORE	*							
BASKET		*						
DIABETES	*	*	*					*
SCANDSTENT	*	*						*
PRISON II								
TYPHOON								
DECODE								
Pache et al.								*
SCORPIUS								
SESAMI								
STRATEGY								*
JUPITER I								
JUPITER II								
SPIRIT I								
STEALTH								
SIRTAX				*				
TAXI				*				
REALITY				*				
ISAR-DIABETES				*				
DIRECT						*		
SVELTE						*		
ACTION								
ISAR-DESIRE								
CORPAL								
ISAR-SMART								
RESEARCH								
IMPACT								

Table A3.6: Meta-analyses published in 2004 and 2005: details of included RCTs, part 1

	Bavry (JACC)[71]	Bavry (AJC)[72]	Biondi Zoccai[73]	Indolfi[74]	Kastrati[75]	Katritsis[76]	Bavry (JACC)[71]
n	3817	2963	6440	3860	3669	5066	3817
RCTs	8	6	17	8	6	10	8
RAVEL		*	*	*		*	
SIRIUS		*	*	*		*	
C-SIRIUS		*	*	*		*	
E-SIRIUS		*	*	*		*	
TAXUS I	*		*	*		*	*
TAXUS II MR	*		*	*		*	*
TAXUS IV	*		*	*		*	*
TAXUS V de novo							
TAXUS VI	*		*				*
ASPECT	*		*			*	*
ELUTES	*		*			*	*
DELIVER I	*		*			*	*
FUTURE I			*				
FUTURE II			*				
SES-SMART		*	*	*			
ENDEAVOR II							
PATENCY	*		*				*
SCORE							
BASKET							
DIABETES							
SCANDSTENT							
PRISON II							
TYPHOON							
DECODE							
Pache et al.							
SCORPIUS							
SESAMI							
STRATEGY							
JUPITER I							
JUPITER II							
SPIRIT I							
STEALTH							
SIRTAX					*		
TAXI					*		
REALITY					*		
ISAR-DIABETES					*		
DIRECT							
SVELTE							
ACTION			*				
ISAR-DESIRE					*		
CORPAL					*		
ISAR-SMART							
RESEARCH		*					
IMPACT			*				

Table A3.7: Meta-analyses published in 2004 and 2005: details of included RCTs, part 2

	Kittleson[77]	Li[78]	Lord[79]	Moreno[80]	Shafiq[81]	Babapulle[82]	Kittleson[77]
n	5041	12059	3390	5030	4372	5103	5041
RCTs	10	25	7	10	13	11	10
RAVEL	*	*	*	*	*	*	*
SIRIUS	*	*	*	*	*	*	*
C-SIRIUS	*	*	*	*	*	*	*
E-SIRIUS	*	*	*	*	*	*	*
TAXUS I	*	*	*	*	*	*	*
TAXUS II MR	*	*	*	*	*	*	*
TAXUS IV	*	*	*	*	*	*	*
TAXUS V de novo		*					
TAXUS VI		*					
ASPECT	*	*		*	*	*	*
ELUTES	*	*		*	*	*	*
DELIVER I	*	*		*	*	*	*
FUTURE I		*			*		
FUTURE II		*					
SES-SMART		*					
ENDEAVOR II		*					
PATENCY		*			*	*	
SCORE		*			*		
BASKET							
DIABETES		*					
SCANDSTENT		*					
PRISON II							
TYPHOON							
DECODE							
Pache et al.							
SCORPIUS							
SESAMI							
STRATEGY							
JUPITER I							
JUPITER II							
SPIRIT I		*					
STEALTH							
SIRTAX		*					
TAXI							
REALITY		*					
ISAR-DIABETES		*					
DIRECT							
SVELTE							
ACTION		*					
ISAR-DESIRE							
CORPAL							
ISAR-SMART							
RESEARCH							
IMPACT							

LITERATURE SEARCH FOR REGISTRIES

In addition we search for publications from registries that compared the efficacy and safety of DES with BMS in the same group of patients. We searched Medline, Embase, and the Cochrane Database of Systematic Reviews (CDSR). Databases were searched during the month of June and July 2007.

Table A3.8: Search for registries in Medline, through OVID interface (July, 2007)

1	Stents/	23289
2	coronary.mp.	124507
3	1 and "3".mp. [mp=title, original title, abstract, name of substance word, subject heading word]	4527
4	Registries/	18382
5	3 and 4	77
6	from 5 keep 1-77	77

Table A3.9: Search for registries in Embase (July, 2007)

1	'stents'/exp AND [2004-2008]/py	15756
2	coronary* AND [2004-2008]/py	61535
3	coronary AND [2004-2008]/py	61535
4	#1 AND #3 AND [2004-2008]/py	7132
5	*eluting AND [2004-2008]/py	3743
6	#4 AND #5 AND [2004-2008]/py	2533
7	'registries'/exp AND [2004-2008]/py	7349
8	#6 AND #7 AND [2004-2008]/py	77

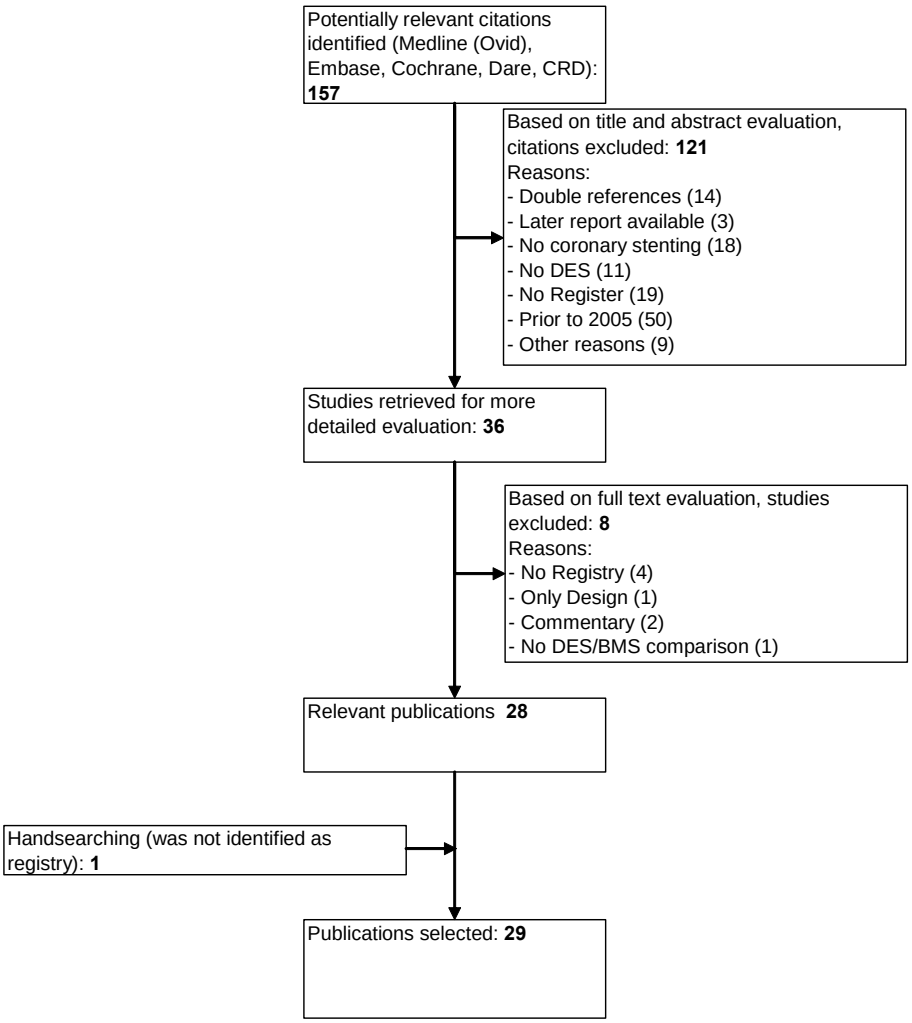
Table A3.10: Search for registries in CDSR (July, 2007)

#1	MeSH descriptor Stents, this term only	1685
#2	MeSH descriptor Coronary Disease explode all trees	9959
#3	*elut* OR *coat*	3701
#4	*elut*	421
#5	(#1 AND #2 AND #3)	250
#6	MeSH descriptor Registries, this term only	391
#7	(#5 AND #6)	3

A total of 157 potential reports on DES registries were thus selected. Since registry publications previous to 2005 added little additional information, publications from 2004 and previous years were excluded. This selection on publication year and subsequent sifting of references using title and abstract eliminated 104 articles. We retrieved 36 full-text articles for further selection to finally end up with 28 published reports on DES registries. Further hand-searching added 1 recent publication.Figure xx gives the flow-chart presenting this process of selection of the evidence.

Figure A3.2: Flow chart of search for DES Registries

DES Registries



APPENDIX FOR CHAPTER ON ECONOMIC EVALUATION (CHAPTER 4)

SEARCH FOR COST-EFFECTIVENESS STUDIES

Search strategy

Initially, websites of HTA institutes were consulted. The search of INAHTA's (International Network of Agencies for Health Technology Assessment) databases helped to identify assessment reports issued by national or regional HTA agencies on DES. This consultation was completed by a manual search of the websites of HTA institutes mentioned on the INAHTA website (table A4.1).

Table A4.1: List of INAHTA member websites searched

Organisation		Country
INAHTA	International Network of Agencies for Health Technology Assessment	International
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CAHTA	Catalan Agency for Health Technology Assessment and Research	Spain
CEDIT	Comité dÉvaluation et de Diffusion des Innovations Technologiques	France
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMT	Center for Medical Technology Assessment	Sweden
CRD	Centre for Reviews and Dissemination	United Kingdom
CVZ	College voor Zorgverzekeringen	The Netherlands
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DSI	Danish Institute for Health Services Research	Denmark
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
GR	Gezondheidsraad	The Netherlands
HAS	Haute Autorité de Santé	France
HunHTA	Unit of Health Economics and Health Technology Assessment	Hungary
IAHS	Institute of Applied Health Sciences	United Kingdom
ICTAHC	Israel Center for Technology Assessment in Health Care	Israel
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IHE	Institute of Health Economics	Canada
IMSS	Mexican Institute of Social Security	Mexico
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technonoly Assessment	Austria
MAS	Medical Advisory Secretariat	Canada
MSAC	Medicare Services Advisory Committee	Australia
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NCCHTA	National Coordinating Centre for Health Technology Assessment	United Kingdom
NHS QIS	Quality Improvement Scotland	United Kingdom
NHSC	National Horizon Scanning Center	United Kingdom
NOKC	Norwegian Knowledge Centre for Health Services	Norway
NZHTA	New Zealand Health Technology Assessment	New Zealand
OSTEBA	Basque Office for Health Technology Assessment	Spain
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UETS	Unidad de evaluacíon Technologias Santarias	Spain
VATAP	VA Technology Assessment Program	USA
VSMTVA	Health Statistics and Medical Technologies State Agency	Latvia
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands

Several HTA reports were identified. Some of them were written in German,[205] Swedish,[206] Norwegian,[207] and Spanish,[208, 209] and therefore excluded. Other full reports were only available for purchase.[210, 105] We purchased the most recent report from 2006 but it did not include an independent economic evaluation. We did not purchase the report from 2003 as we considered this to be obsolete.

An HTA report of AETMIS[140] (Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante) was published in August 2004, including cost-effectiveness studies up till May 2004. In another Canadian HTA report an independent literature search of MEDLINE was conducted until December 2003.[149] The UK HTA report published by Hill and colleagues in 2004 included literature until 2002 in their search strategy.[32] Finally, an Australian HTA report identified published papers of economic evaluations of DES to end August 2004.[148]

Since some of these HTA reports performed their systematic literature search until 2004, we conducted our search for subsequent years (2004-2007). Finally, a language restriction was imposed by which only English, Dutch or French manuscripts were considered.

In June 2007, the following databases were searched: Medline, Embase, DARE, NHS EED, HTA, and CDSR. The following five tables (A4.2 to A4.6) provide an overview of our search strategy.

Table A4.2: Search strategy and results for MEDLINE (performed on 18 June 2007) using the OVID interface

1	economics/	4294
2	exp "Costs and Cost Analysis"/	69090
3	"Value of Life"/ec [Economics]	151
4	Economics, Dental/	95
5	exp Economics, Hospital/	6358
6	Economics, Medical/	513
7	Economics, Nursing/	378
8	Economics, Pharmaceutical/	1399
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	76038
10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	164158
11	(expenditure$ not energy).tw.	6073
12	(value adj1 money).tw.	4
13	budget$.tw.	5921
14	10 or 11 or 12 or 13	170009
15	9 or 14	201658
16	letter.pt.	283232
17	editorial.pt.	123433
18	historical article.pt.	70065
19	16 or 17 or 18	471053
20	15 not 19	190856
21	Animals/	1512335
22	human/	4048884
23	21 not (21 and 22)	1014879
24	20 not 23	176197
25	(metabolic adj cost).ti,ab,sh.	249
26	((energy or oxygen) adj cost).ti,ab,sh.	857
27	24 not (25 or 26)	175370
28	Stent$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	29218
29	(coat$ or elut$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	50688
30	(Sirolimus or Paclitaxel).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	15868
31	(taxus or cypher or tacrolimus or zotarolimus).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	9468
32	28 or 29 or 30 or 31	99637
33	27 and 32	2451
34	(Myocardial or coronary).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	179400
35	33 and 34	628
36	limit 35 to yr="2004 - 2007"	232
37	limit 36 to (dutch or english or french)	**214**

Table A4.3: Search strategy and results for MEDLINE In-Process & Other Non-Indexed Citations (performed on 18 June 2007)

1	cost$.mp. [mp=title, original title, abstract, name of substance word]	7058
2	economic$.mp. [mp=title, original title, abstract, name of substance word]	2950
3	budget$.mp. [mp=title, original title, abstract, name of substance word]	426
4	expenditure$.mp. [mp=title, original title, abstract, name of substance word]	635
5	1 or 2 or 3 or 4	10024
6	Stent$.mp. [mp=title, original title, abstract, name of substance word]	1273
7	(coat$ or elut$).mp. [mp=title, original title, abstract, name of substance word]	5236
8	(Sirolimus or Paclitaxel).mp. [mp=title, original title, abstract, name of substance word]	509
9	(taxus or cypher or tacrolimus or zotarolimus).mp. [mp=title, original title, abstract, name of substance word]	291
10	6 or 7 or 8 or 9	6880
11	5 and 10	147
12	(Myocardial or coronary).mp. [mp=title, original title, abstract, name of substance word]	6109
13	11 and 12	16
14	limit 13 to yr="2004 - 2007"	14
15	limit 14 to (dutch or english or french)	**13**

Table A4.4: Search strategy and results for EMBASE (performed on 19 June 2007)

1	'socioeconomics'/exp	98802
2	'cost benefit analysis'/exp	4447
3	'cost effectiveness analysis'/exp	50123
4	'cost of illness'/exp	7613
5	'cost control'/exp	31124
6	'economic aspect'/exp	713205
7	'financial management'/exp	177526
8	'health care cost'/exp	119584
9	'health care financing'/exp	874
10	'health economics'/exp	386931
11	'hospital cost'/exp	16721
12	'finance'/exp	7888
13	'funding'/exp	1641
14	fiscal	4318
15	financial	107206
16	#12 OR #13 OR #14 OR #15	118143
17	'cost minimization analysis'/exp	1176
18	estimate*:ti,ab,de,cl	32718
19	cost*:ti,ab,de,cl	370898
20	variable*:ti,ab,de,cl	324848
21	unit:ti,ab,de,cl	219964
22	'#19 *4 #18' OR '#18 *4 #19'	158179
23	'#19 *4 #20' OR '#20 *4 #19'	15155
24	'#19 *4 #21' OR '#21 *4 #19'	77115
25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 OR #22 OR #23 OR #24	1085006
26	'drug eluting stent'/exp	2568
27	#25 AND #26 AND [2004-2007]/py	409
28	#27 AND [humans]/lim	383
29	'heart disease'/exp	832018
30	#28 AND #29	239
31	#30 AND ([dutch]/lim OR [english]/lim OR [french]/lim)	**227**

Table A4.5: Search strategy and results for CRD: DARE, NHS EED and HTA (performed on 18 June 2007)

1	MeSH Stents	382
2	coat* OR elut* OR "Sirolimus" OR "Paclitaxel" OR taxus OR cypher OR medicat*	3074
3	#1 and #2 RESTRICT YR 2004 2007	62
4	english:la OR french:la OR dutch:la	29150
5	#3 and #4	**51**

Table A4.6: Search strategy and results for CDSR (performed on 19 June 2007)

1	MeSH descriptor Stents, this term only	1637
2	coat* or elut*	3367
3	paclitaxel or sirolimus or taxus or cypher	1748
4	#1 OR #2 OR #3	6267
5	MeSH descriptor Costs and Cost Analysis explode all trees	22703
6	#4 AND #5	456
7	(#6), from 2004 to 2007	188
8	MeSH descriptor Coronary Disease explode all trees	9835
9	#7 AND #8	**69**

Results of search strategy

A total of 561 papers were identified: 227 with Medline, 227 with Embase, 51 with the NHS EED, DARE, and HTA databases, and 56 from the Cochrane Database of Systematic Reviews (the following categories were included: Technology Assessments, Economic Evaluations, and Other Reviews) (table A4.7). After removing 96 duplicates, 465 articles were left.

Table A4.7: search for cost-effectiveness studies: summary

Database	Years	References identified
MEDLINE	2004-2007	214
MEDLINE In-Process & Other Non-Indexed Citations	18 June, 2007	13
EMBASE	2004-2007	227
CRD	2004-2007	51
NHS EED		27
DARE		17
HTA		7
CDSR	2004-2007	56
Technology Assessments		7
Economic Evaluations		46
Other reviews		3
Clinical Trials (excluded)		(13)
Total references identified		561
Duplicates		96
Total		**465**

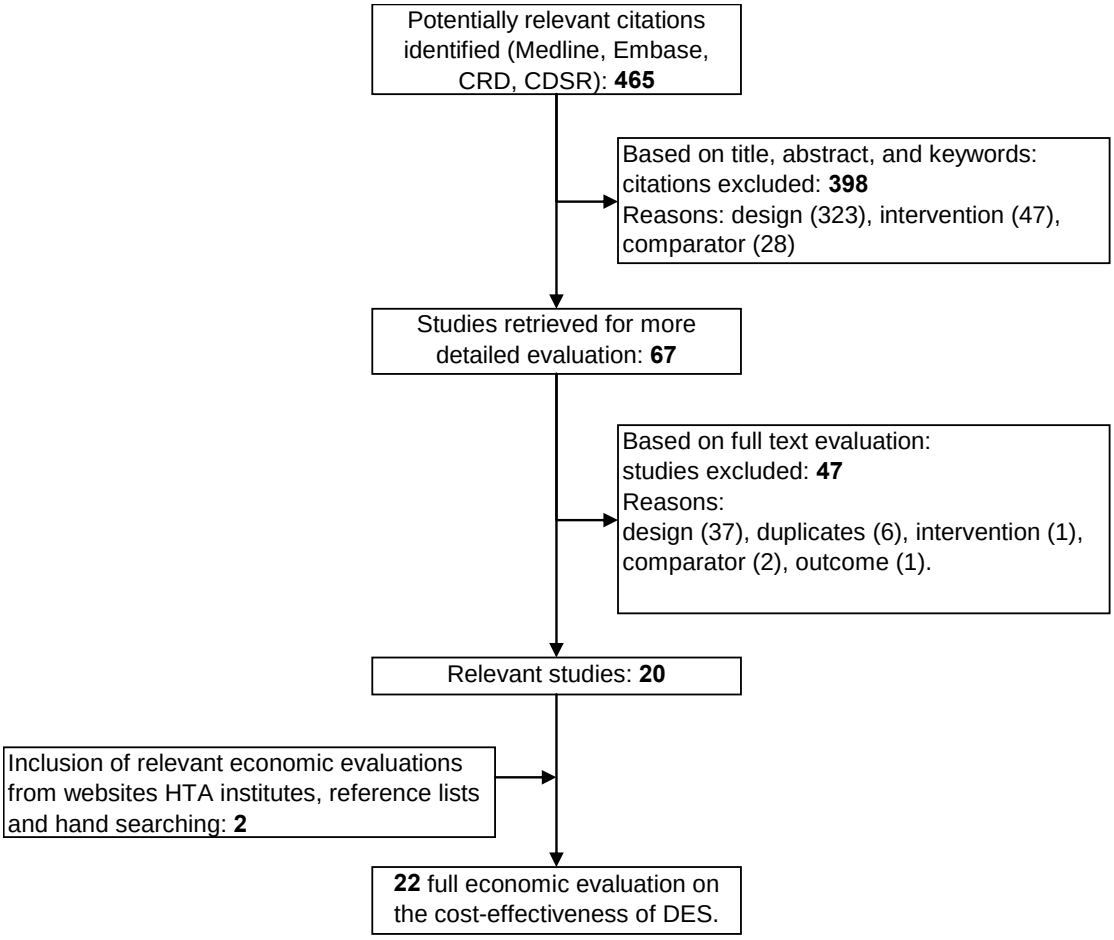
CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects; NHS EED: NHS Economic Evaluation Database; CDSR: Cochrane Database of Systematic Reviews

Inclusion and exclusion criteria

Papers fulfilling several selection criteria were included in the economic review. Full economic evaluations that compare two or more alternatives and consider both costs and consequences, including cost-effectiveness, cost-utility and cost-benefit analysis, were eligible. The populations described in the study are patients eligible for PCI, whether or not at high risk of restenosis. The intervention considered is the implantation of DES. Both bare-metal stents (BMS) and another type of DES are considered as possible comparators. The outcomes should be expressed as costs per life-years gained (LYG), costs per quality-adjusted life years (QALYs) gained, or any other appropriate disease-specific health outcome. The latter refers to the cost per revascularization avoided.

From the 465 articles, 398 were excluded based on title, abstract and keywords (figure A4.1). The majority of studies were no full economic evaluations. The remaining 67 studies were retrieved in full text. Twenty studies fulfilled our selection criteria. Reference lists of the initial 67 studies were hand searched for further references. Two additional references matched our inclusion criteria. The first report[139] was found by hand searching websites from HTA institutes. The second article,[153] categorised as a Spanish article but written in English, was retrieved after screening reference lists.

Figure A4.1: identification and selection of studies



CRD: Centre for Reviews and Dissemination; CDSR: Cochrane Database of Systematic Reviews; DES: drug eluting stents

SUMMARY TABLES OF ECONOMIC EVALUATIONS ON DES

In the following part, summary tables of the economic evaluations from our systematic review are provided including the following details: column 1) authors, country, year of publication, conflict of interest, perspective, analytic technique, time window, discount rate; column 2) population, comparator, on which trial did the study rely, utilities (if relevant); column 3) year of costs and currency, cost details, average number of stents per procedure; column 4) mean restenosis rate, relative risk reduction with DES, type of repeat procedure; column 5) cost-effectiveness results, subgroup analysis; column 6) conclusions, sensitivity-, and threshold analysis (if present).

Table A4.8: Bagust et al.[137]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Bagust A, Grayson AD, Palmer ND, Perry RA, Walley T. UK 2006 None declared	2 884 patients receiving PCI with stenting. Triple vessel disease: 12.0% and 16.0% for resp. elective and non-elective surgery. Diabetes: 13.2% and 12.9% for resp. elective and non-elective surgery.	2003, in £ Cost per uncoated stent £370 Price premium per DES £500 Cardiology First outpatient visit £130 Follow up outpatient visit £93 Angiogram £372 Elective PTCA £3.190 Non-elective PTCA £4.179 Elective CABG £7.750 Non-elective CABG £9.460 Cardiac surgery First outpatient visit £214 Follow up outpatient visit £172 Stents used initial procedure 1, 2 or 3 Repeat PTCA stents used Elective index PTCA 1.87 (1.62 to 2.15) Non-elective index PTCA 1.71 (1.50 to 1.97)	SES: meta-analysis leads to TVR of 7.5% (SES) versus 24.9% (BMS), a RR reduction of 69.8% (95%CI: 59.3% to 77.7%, p<0.001). PES: meta-analysis leads to TVR of 7.3% (PES) versus 16.3% (BMS), a RR reduction of 55.3% (95%CI: 40.3% to 66.5%, p<0.001). Type of repeat procedure After elective PTCA Balloon angioplasty: 36.6% (28.9% to 45.0%) Stented PTCA: 54.5% (46.0% to 62.7%) CABG: 9.0% (5.1% to 15.2%) After non-elective PTCA Balloon angioplasty: 27.4% (19.0% to 37.6%) Stented PTCA: 54.5% (44.2% to 64.9%) CABG: 17.9% (11.1% to 27.4%)	Cost-effectiveness of DES versus BMS after 12 months of follow up depending on: a) elective or non-elective surgery risk groups b) number of risk factors elective surgery: 0-3 risk factors (calcification, angulation >45°, restenotic lesion, triple vessel diameter) non-elective surgery: 0-2 risk factors (vessel diameter <2mm, prior CABG) c) number of stents used (1-3) Cost-effectiveness is achieved when: (exact numbers: see full paper) a) for elective treatment: a single DES is implanted in a patient with two or more risk factors. b) for non-elective treatment: a single DES if at least one risk factor is present. up to two (PES) or three (SES) stents if both risk factors apply.	Considering the UK cost-effectiveness threshold of £30 000 per QALY, the use of DES would only be cost effective for about 4% of the patients, despite the evident effectiveness of DES in preventing restenosis. One-way sensitivity analysis (with 95%CI) and combined extreme values analysis: Main determinant cost effectiveness: the price premium for DES versus BMS. Conclusions are robust for 99% of elective surgeries and 91% of non-elective surgeries. Threshold analysis: to achieve an ICER of £30000 or to achieve cost neutrality. For more than 50% usage of SES, the price premium should be less than £221 (cost effectiveness) or £146 (neutrality) and for 90% usage no more than £112 and £80, resp. Equivalent price thresholds for PES are lower.
Perspective **Analytic technique** **Time window** **Discount rate**	DES versus BMS sirolimus (Cypher) paclitaxel (Taxus)				
perspective of the NHS CUA 12 months no discounting	RAVEL, SIRIUS, TAXUS I, II & IV patient utilities: ARTS and SoS trials Annual QALYs lost angina 0.135 (0.122 to 0.148) per PTCA 0.0056 (0.0051 to 0.0062) per CABG 0.033 (0.031 to 0.035)				

Table A4.9: Bakhai et al.[138]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Bakhai A, Stone GW, Mahoney E, Lavelle TA, Shi C, Berezin RH, Lahue BJ, Clark MA, Lacey MJ, Russell ME, Ellis SG, Hermiller JB, Cox DA, Cohen DJ, on behalf of the TAXUS-IV investigators. US 2006 Study funding provided in part by a grant from Boston Scientific, Inc. Ms. Lahue, Ms. Clark, Mr. Lacey, and Dr. Russell are employees of Boston Scientific, Inc. Drs. Stone, Ellis, and Hermiller have served as consultants to Boston Scientific. **Perspective** **Analytic technique** **Time window** **Discount rate** societal perspective CEA and CUA 12 months no discounting	1 314 patients undergoing PCI randomized to either PES (N = 662) or BMS (N = 652) in the TAXUS-IV trial. Patients eligible if: PCI to a de novo lesion 10 to 28 mm in length, located in a native coronary artery with a reference vessel diameter 2.5 to 3.75 mm (by visual estimate). Diabetes mellitus: 23.4% and 25.0% in resp. the PES and control group. DES versus BMS PES (Taxus) BMS (Express) TAXUS IV patient utilities: Stent-PAMI trial A mean quality-adjusted life expectancy for patients with and without repeat revascularization during follow-up (0.78 vs 0.86, p<0.001) was applied to the TAXUS-IV study population, along with a short-term disutility "toll" for patients who required bypass surgery.	2004, in $ cost of BMS $800 cost of PES $2.700 PES versus BMS Initial procedure (p<0.001) $6 324 vs 4 336 Medications (p=0.16) $387 vs 442 Balloons/stents (p<0.001) $3 966 vs 1 924 Additional procedural costs (p=0.63) $1 972 vs 1 969 Professional fees (p=0.18) $1 889 vs 1 883 Hospital room/ ancillary/ nursing (p=0.35) $2 882 vs 2 849 follow-up costs (p<0.001) $3 487 vs 4 944 Hospitalizations (p<0.001) $2 241 vs 3 749 Physician fees (p=0.001) $432 vs 780 Outpatient services/ medications (p0.001) $814 vs 414 Aggregate 1-yr costs $14 583 vs 14 011 (difference: $572 (-346 to 1 478), p<0.001) stents All, p=0.70 1.3 ± 0.7 vs 1.3 ± 0.8 Study, p=0.81 1.1 ± 0.3 vs 1.1 ± 0.3 Nonstudy, p=0.76 0.3 ± 0.7 vs 0.3 ± 0.8	Overall The need for 1 or more repeat TVR procedures was reduced by 60% in the PES group compared with the BMS group (6.6% vs. 16.6%, p < 0.001). repeat TVR PES versus BMS 6.6% vs 16.6% (-9.9 (-13.3 to -6.5), p<0.001) CABG 1.7% vs 3.8% (-2.2 (-3.9 to -0.4), p=0.02) PCI 5.1% vs 13.3% (-8.2 (-11.3 to -5.1), p<0.001) Patients assigned to clinical follow-up alone: At 1-year follow-up, randomization to PES was associated with a 62% relative reduction in TVR (5.2% vs. 13.9%, p < 0.001).	Overall ICER of $4 678 per TVR avoided and $47 798/QALY gained. 86% of the resulting ICERs were <$10 000 per TVR avoided. 14.8% of bootstrap replicates showed economic dominance and 56.8% of the results <$50 000/QALY gained. Patients assigned to clinical follow-up alone ICER of $760 per TVR avoided and $5 105/QALY gained. 90% of the resulting ICERs were <$10 000 per TVR avoided. cost-utility ratio was <$50 000/QALY gained in 76.3%. Subgroup analyses: diabetes mellitus, vessel size and lesion length. PES less attractive for: reference vessel diameters >3.0 mm (~$25 000/TVR avoided). PES economically dominant for: reference vessel diameters <2.5 mm and diabetes.	Although the cost savings were insufficient to fully offset the higher initial treatment costs, the authors conclude that use of PES may be reasonably cost-effective from a societal perspective over a broad range of patient and lesion characteristics. The findings were sensitive to the cost of hospitalization for repeat revascularization. Secondary analyses: Hospital perspective: net profit (i.e., revenue-cost) per patient was lower with PES than BMS ($6 605 vs 7 064). Third-party payer perspective: aggregate 1-year costs were slightly lower for PES than for BMS ($18 818 vs 19 045). Scenario analysis on clopidogrel use: results improved substantially if all patients received 12 months clopidogrel (assumption).

Table A4.10: Bowen et al.[139]

Authors / Country / Year of publication / Conflict of interest

Bowen J, Hopkins R, He Y, Blackhouse G, Lazzam C, Tu J, Cohen E, Tarride JE, Goeree R.

Canada

2005

None declared

Perspective / Analytic technique / Time window / Discount rate

The analysis was taken from the perspective of the Ontario Ministry of Health.

CEA and CUA.

One year.

No discounting.

Population / Comparator / Data from trial / QALYs

Patients undergoing a PCI that included the insertion of coronary stent(s).

All analyses were carried out separately for Non-Post MI and Post-MI patients. In order to account for patient groups at higher risk of revascularization, groups were further stratified according to diabetes status, lesion length and lesion diameter (except for the Post–MI group with diabetes due to small sample size). In total, the cost-effectiveness of DES versus BMS was determined for 22 different cohorts of patients.

DES versus BMS

Results from a field evaluation were used to derive the probabilities of revascularization, the type of revascularizations (e.g. PCI stent, PCI without stent, CABG) and the number of stents (initial and follow-up stents).

Data from the ARTS trial was used to calculate QALYs.

Two different quality of life impacts of revascularization were incorporated in the model and reflected in the QALY calculations: 1) quality of life impact of anginal symptoms occurring before the revascularization procedure; and 2) quality of life impact of recovery time post revascularization procedure.

EQ-5D utility values observed in the ARTS trial for resp. stent and CABG.

baseline	0.69 / 0.68
1 month	0.84 / 0.78
6 month	0.86 / 0.86
12 month	0.86 / 0.87

Waiting times (in days) for resp. PCI and CABG:

Non-Post MI:	
no diabetes	16.32 / 21.97
diabetes	17.76 / 15.53
Post MI:	
no diabetes	12.78 / 24.46
diabetes	8.65 / 13.10

One-year QALYs by clinical pathways for respectively No revascularization, PCI with or without stent and CABG.

Non-Post MI:	
no diabetes	0.860 / 0.819 / 0.804
diabetes	0.860 / 0.820 / 0.801
Post MI:	
no diabetes	0.860 / 0.823 / 0.805
diabetes	0.860 / 0.822 / 0.800

Year costs, currency / Costs details / Number of stents

2003/2004, in Canadian Dollars (CAD)

BMS	CAD600
DES	CAD1899

Hospital Cost of Revascularizations (hospital costs, physician fees and stent costs).

PCI with stent	CAD7 117 + stent cost
PCI with no stent	CAD7,015
CABG	CAD18,799

Mean number of stents according to lesion characteristics.

Non-Post MI	Non-diabetes and diabetes
All	1.48 / 1.54
Long & Narrow Lesions	2.21 / 2.26
Long	1.78 / 1.89
Short	1.35 / 1.36
Narrow	1.78 / 1.84
Wide	1.36 / 1.35
Long or Narrow	1.70 / 1.77
Short and Wide	1.27 / 1.25
Post MI - Non diabetes	
All	1.39
Long & Narrow Lesions	1.92
Long	1.57
Short	1.31
Narrow	1.67
Wide	1.30
Long or Narrow	1.57
Short and Wide	1.23
Post MI - Diabetes	
All	1.42

Mean number of follow-up stents according to lesion characteristics.

Non-Post MI	Non-diabetes and diabetes
All	1.56 / 1.47
Long & Narrow Lesions	1.80 / 1.83
Long	1.60 / 1.60
Short	1.53 / 1.35
Narrow	1.60 / 1.64
Wide	1.52 / 1.32
Long or Narrow	1.56 / 1.47
Short and Wide	1.55 / 1.28
Post MI - Non diabetes	
All	1.60
Long & Narrow Lesions	1.42
Long	1.55
Short	1.64
Narrow	1.52
Wide	1.65
Long or Narrow	1.60
Short and Wide	1.66
Post MI - Diabetes	
All	1.69

Mean restenosis rate / Relative risk reduction with DES / Type of repeat procedure

Revascularization rates (in %) and type of revascularization (in %) (A: PCI-stent; B: PCI-no stent; C) CABG) according to lesion characteristics.

Non-Post MI – Non-Diabetes	BMS	DES	A	B	C
All	7.2	5.4	70.0	14.7	15.3
Long and Narrow	10.9	5.8	62.5	10.4	27.1
Long	9.0	4.7	69.2	14.1	16.7
Short	6.4	5.3	70.1	14.9	14.9
Narrow	10.7	6.4	65.8	16.8	17.4
Wide	5.9	4.8	71.8	13.6	14.6
Long or Narrow	9.5	5.4	68.4	16.4	15.2
Short and Wide	5.1	5.4	71.6	12.6	15.8

Non-Post MI - Diabetes	BMS	DES	A	B	C
All	10.0	6.7	64.2	17.0	18.8
Long and Narrow	20.6	6.0	62.1	20.7	17.2
Long	18.6	7.9	63.2	19.1	17.6
Short	6.7	5.2	63.3	16.7	20.0
Narrow	11.9	5.7	62.5	18.8	18.8
Wide	7.9	5.7	63.8	17.0	19.1
Long or Narrow	14.3	6.9	63.1	18.4	18.4
Short and Wide	5.5	5.1	63.6	16.4	20.0

Post MI - Non-Diabetes	BMS	DES	A	B	C
All	6.1	3.8	77.0	9.8	13.2
Long and Narrow	15.9	5.8	70.6	23.5	5.9
Long	8.1	3.0	71.7	11.7	16.7
Short	4.9	4.2	79.8	8.8	11.4
Narrow	6.1	6.0	68.3	22.0	9.8
Wide	5.5	2.8	79.7	6.0	14.3
Long or Narrow	7.5	4.8	70.2	14.3	15.5
Short and Wide	4.5	2.8	83.3	5.6	11.1

Post MI - Diabetes	BMS	DES	A	B	C
All	12.1	5.8	72.5	5.9	21.6

Probability of receiving a DES by initial stent type

	initial stent type: BMS vs DES
Non-Post MI - Diabetes	62 vs 66%
Non-Post MI - Non Diabetes	54 vs 68%
Post MI - Non-Diabetes	52 vs 66%
Post MI - Diabetes	67 vs 58%

Cost-effectiveness / Subgroup analysis

ICERs of the deterministic (top result) and probabilistic (bottom result) analysis:

	$/Revasc	$/QALY
Non-Post MI – Non-Diabetes		
All	95 383	2 221 692
	97 832	2 275 668
Long & Narrow	44 015	975 496
	40 384	893 610
Long	42 672	988 036
	42 616	982 469
Short	155 123	3 618 632
	159 533	3 731 167
Narrow	43 746	1 009 784
	43 448	1 004 577
Wide	161 287	3 768 758
	172 933	4 020 399
Long or Narrow	43 834	1 021 211
	42 797	995 367
Short and Wide	dominated	dominated
	dominated	dominated
Non-Post MI - Diabetes		
All	49 333	1 132 426
	51 214	1 170 050
Long & Narrow	9 689	223 580
	8 405	194 276
Long	12 677	292 133
	11 943	274 002
Short	111 650	2 552 321
	105 641	2 421 431
Narrow	28 235	648 210
	25 891	593 503
Wide	66 560	1 525 981
	65 174	1 500 389
Long or Narrow	20 788	477 736
	20 232	465 438
Short and Wide	353 944	8 091 138
	323 016	7 163 108
Post MI - Non-Diabetes		
All	69 696	1 688 786
	71 189	1 720 737
Long & Narrow	15 640	393 923
	10 904	273 498
Long	29 625	705 250
	29 896	708 163
Short	259 855	6 356 201
	320 322	7 857 601
Narrow	4 306 204	106 246 636
	dominated	dominated
Wide	52 026	1 253 708
	54 184	1 309 047
Long or Narrow	66 230	1 586 259
	65 632	1 569 126
Short and Wide	85 228	2 087 910
	83 457	2 045 644
Post MI - Diabetes		
All	17 711	438 415
	17 243	429 035

Conclusion / Sensitivity analysis / Threshold analysis

The economic analysis incorporating “real-world” data from over 9000 patients in Ontario found that the most favourable cost-effectiveness ratio for DES compared to BMS was $223 580/QALY (deterministic analysis) in patients in non Post MI, diabetes patients with long and narrow lesions. The absolute difference of approximately 15% was found in revascularization rates between the two interventions in this patient population.

Table A4.11: Brophy et al.[140, 141]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Brophy J, Erickson L, Report prepared for AETMIS. Canada 2004 None declared **Perspective** **Analytic technique** **Time window** **Discount rate** the Québec Ministry of Health and Social Services. CEA and CUA 9 months no discounting	Incident cases, i.e. patients with no previous angioplasties in the 6 or 9 months preceding the initial stent procedure. DES versus BMS meta-analysis Babapulle et al, 2004 patients utilities Yock et al, 2003 QALYs lost Return of anginal symptoms: -0.013 Traditional balloon angioplasty: -0.04 Primary stenting: -0.02 CABG: -0.07	2003, in Canadian dollar (CAD) Cost of uncoated stent: CAD700 (600-800) Cost of drug eluting stent (base model): CAD2 600 (2 000-2 800) Average cost of angioplasty, including CAD707 in medical professional fees (stent costs are excluded): CAD4 507 (4 000-5 000) Cost of CABG (including CAD1,025 in medical professional fees): CAD15 025 (9 825-17 025) Average number of stents per procedure 1.7 (1.2-2.2)	Current repeat revascularization rates in Québec following the use of BMS have been determined from examination of medico-administrative databases (Med-Écho and RAMQ) from 1995 to 2000. Repeat revascularization rate, bare stents (following 1st intervention): 12.8% (9.7 -20%). Repeat revascularization rate, bare stents (following 2nd intervention): 13.9% (12-16%). Repeat revascularization rate, bare stents (following 3rd intervention): 15% (10-20%). RR for restenosis of high-risk patients selected to receive DES: 2.67 (1-6). Repeat revascularization risk reduction, DES (following 1st intervention): 0.74 (0.48-0.89). Ratio of restenosis rates DES/BMS post PCI # 2 and post PCI #3: 0.5 (0.2-0.8). % of patients going to PCI vs. CABG after 1st PCI: 83% (78-88%) after 2nd PCI: 74% (69-79%) after 3rd PCI: 69% (64-74%)	The average cost per avoided repeat revascularizations is CAD23 067 (100% substitution of BMS). At a level of 20% DES penetration (allowing for selection of high-risk patients, RR=2.67), the average cost is CAD7 200 per avoided procedure. The cost per QALY gained is estimated at CAD96 523 in the base scenario with 20% of DES (i.e. for high-risk patients) and a RR of selected patients of 2.67.	The universal introduction of DES would greatly increase expenditures with relatively limited benefits. … At the present stent costs, there appears to be little cost-effectiveness justification for high rates of DES implementation, due to low baseline restenosis rates with BMS and diminishing returns with increased use of DES. Univariate sensitivity analysis: Most important variables: the capacity to select high-risk patients for DES use, the cost of DES, the number of stents per procedure, the baseline revascularization rate with BMS, and the effectiveness of DES. Multivariate sensitivity analysis: Results confirm the results of the univariate sensitivity analyses. Threshold analysis: scenario of 20% penetration (RR = 2.67): the breakeven cost occurs at CAD1 663. For 100% DES implementation: the purchase cost must be CAD1 161.

Table A4.12: Cohen et al.[142]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Cohen DJ, Bakhai A, Shi C, Githiora L, Lavelle T, Berezin RH, Leon MB, Moses JW, Carrozza JP, Zidar JP, Kuntz RE, on behalf of the SIRIUS investigators. US 2004 Study funding was provided in part by a grant from Cordis, Inc. **Perspective** **Analytic technique** **Time window** **Discount rate** societal perspective CEA and CUA 12 months no discounting	1 058 patients with complex coronary stenoses were enrolled in the SIRIUS trial and randomized to either a SES (n=533) or BMS (n=525). Patients eligible if: PCI to a de novo lesion 15 to 30 mm in length located in a native coronary artery with a reference vessel diameter between 2.5 and 3.5 mm (by visual estimate). Diabetes mellitus: 24.6% and 28.2% in resp. the sirolimus and control group. Multivessel disease: 40.7% and 42.5% in resp. the sirolimus and control group. DES versus BMS sirolimus (Cypher) SIRIUS trial patient utilities: Stent-PAMI trial No details mentioned	2002, in $ cost BMS $900 cost SES $2 900 SES (n = 533) vs BMS (n = 522) Initial procedure (p<0.001) $7 251 vs 4 395 Room/overhead (p=0.77) $1 222 vs 1 237 Supplies/drugs (p=0.14) $1 026 vs 975 Devices (p<0.001) $4 865 vs 2 052 Personnel (only nonphysician personnel) (p=0.77) $131 vs 131 Repeat procedures (p=0.32) $13 vs 3 Hospital room/ancillary (p=0.98) $2 701 vs 2704 Professional fees (p=0.34) $1 379 vs 1362 follow-up costs (p<0.001) $5 468 vs 8 040 Repeat procedures (p<0.001) $789 vs 1 788 Hospital room/ancillary (p=0.003) $1 936 vs 3 149 Inpatient physician fees (p<0.001) $1 280 vs 1 759 Outpatient services/physician fees (p=0.57) $1 463 vs 1 343 Aggregate 1-yr costs $16 813 vs 16 504 (difference: $309 (-976 to 1 594), p=0.64) Stents (p=0.59) 1.4 ± 0.8 vs 1.4 ± 0.6	The need for ≥1 repeat revascularization procedures was reduced by 52% in the sirolimus group compared with the control group (13.3% versus 28.4%; p<0.001). Repeat revascularization (%): (13.3 vs 28.4 (-15.1 (-19.9 to -10.2), p<0.001)). CABG (1.3 vs 3.0 (-1.7 (-3.5 to 0.0), p=0.059)) PCI (12.4 vs 26.9 (-14.5 (-19.2 to -9.8), p<0.001)) These benefits were driven primarily by a 15% absolute reduction in the need for clinically driven TLR (4.9% versus 20.0%; P<0.001).	The incremental cost-effectiveness ratio for SES was $1 650 per repeat revascularization event avoided or $27 540 per QALY gained. Subgroup analysis Subgroups defined by diabetic status, reference vessel diameter, and lesion length. SES were economically dominant in patients with reference vessel diameters <2.5 mm, lesion lengths >20 mm (by operator assessment) and predicted TLR 25-30%.	Although use of SES was not cost-saving compared with BMS implantation, for patients undergoing PCI of complex coronary stenoses, their use appears to be reasonably cost-effective within the context of the US healthcare system. Scenario analysis: Impact of longer stents available: Under several assumptions, the mean number of stents per patient decreased from 1.4 to 1.3 (in both treatment groups), and the cost-effectiveness ratio for SES fell to $727 per repeat revascularization avoided. Impact of duration clopidogrel treatment: If the authors assumed that patients in both the sirolimus and control groups would be treated with 1 year of postprocedure clopidogrel, use of SES was projected to be cost-saving over the 1-year follow-up period. Under updated treatment assumptions regarding available stent lengths and duration of antiplatelet therapy, use of SESs was projected to reduce total 1-year costs compared with BMSs.

Table A4.13: Ekman et al.[143]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Ekman M, Sjogren I, James S. Sweden 2006 The study was supported by an unrestricted grant from Boston Scientific Corporation. **Perspective** **Analytic technique** **Time window** **Discount rate** Health care payer perspective CEA and CUA 12 and 24 months no discounting	Patients with coronary artery disease. In order to appropriately account for patient heterogeneity and associated implications, a subgroup analysis is performed for patients known to be at high risk of restenosis. DES vs BMS paclitaxel (Taxus) TAXUS IV patient utilities: ARTS trial It is assumed that patients live with restenosis for 1 month before undergoing a repeat procedure. Utility weight post repeat procedure: 0,86 Utility weight with restenosis: 0,69 Post Revascularization: (1 x 0.86) = 0.86 QALYs Restenosis & repeat revascularization: ((1/12)x0.69+ (11/12)x0.86)= 0.846 QALYs Utility loss due to PCI repeat procedure: 0.0035 QALYs CABG repeat procedure: 0.012 QALYs	2004, in Swedish krona (SEK) PCI with BMS SEK52.300 PCI with TAXUS DES SEK66.020 Price difference DES-BMS SEK9.600 CABG SEK134.507 Coronary angiography SEK14.177 Cardiology outpatient visit SEK2.735 Cardiology nurse visit SEK1.045 Clopidogrel (per month) SEK498 An average of 1.4 stents is assumed.	TLR rates at 12 and 24 months Total Population 12 Months BMS: 15,10% 12 Months TAXUS: 4,40% 24 Months BMS: 17,40% 24 Months TAXUS: 5,60% Diabetes Patients 12 Months BMS: 19,60% 12 Months TAXUS: 7,10% 24 Months BMS: 22,00% 24 Months TAXUS: 8,00% Small vessel 12 Months BMS: 20,60% 12 Months TAXUS: 5,60% 24 Months BMS: 25,40% 24 Months TAXUS: 6,10% Long Lesion 12 Months BMS: 22,10% 12 Months TAXUS: 5,50% 24 Months BMS: 22,40% 24 Months TAXUS: 8,90% Proportion CABG or PCI for repeat procedure not mentioned.	Total population one-year follow-up: The cost per revascularization avoided is SEK46 801 (€5 126). The ICER is SEK2 350 844 (€257 486) per QALY. two-year follow-up: The cost per revascularization avoided is SEK35 607 (€3 900). The ICER is SEK1 806 164 SEK (€197 827) per QALY. High-risk group one-year follow-up: The cost per revascularization avoided is SEK7 648 SEK (€838). The ICER is SEK381 554 (€41 791) per QALY. two-year follow-up: Taxus is dominant. The savings from a lower probability of repeat revascularization is greater than the initial cost increase compared to BMS. The total average cost per patient is 73 570 SEK (€8 058) for BMS and 73 479 SEK (€8 048) for Taxus.	The Taxus stent is cost-effective in high risk patients, particularly at 24 months. Although it may be less cost-effective for the general population, there is still a substantial offset of initial procedure costs through lower rate of repeat revascularizations. One-way sensitivity analysis The analysis is particularly sensitive to changes in clopidogrel usage patterns, TLR rates, price difference between the stents, and the disutility and waiting time with restenosis. From the clinical outcome side, a greater difference in TLR rates between BMS and Taxus may lead to a cost-effective result for patients of average risk. On the cost input side, a smaller difference in stent price may result in a cost-effective outcome.

Table A4.14: Elezi et al.[144]

Authors **Country** **Year of publication** **Conflict of interest**	**Population** **Comparator** **Data from trial** **QALYs**	**Year costs, currency** **Costs details** **Number of stents**	**Mean restenosis rate** **Relative risk reduction with DES** **Type of repeat procedure**	**Cost-effectiveness** **Subgroup analysis**	**Conclusion** **Sensitivity analysis** **Threshold analysis**
Elezi S, Dibra A, Folkerts U, Mehilli J, Heigl S, Schömig A, Kastrati A. Germany 2006 Dr. Kastrati reports having received lecture fees from Bristol-Myers, Cordis, Glaxo, Lilly, Medtronic, and Sanofi-Aventis. **Perspective** **Analytic technique** **Time window** **Discount rate** The health insurance system's perspective CEA 9 to 12 months no discounting	Patients at high risk of restenosis: 450 patients with diabetes mellitus and in-stent restenosis from 2 randomized studies comparing SES with PES were included. Diabetes mellitus: 69% and 68% in resp. the SES and PES group. SES versus PES ISAR-DESIRE and ISAR-DIABETES randomized studies.	Year of costs not explicitly mentioned, in € cost (difference) of SES and PES: not mentioned Whole-study cohort — SES vs PES Initial hospital costs (p=0.53) €6 240 vs 6 377 Follow-up costs (p<0.001) €2 684 vs 4 527 Total costs (p<0.001) €8 924 vs 10 903 Diabetic patients Initial hospital costs (p=0.34) €6 498 vs 6 771 Follow-up costs (p=0.001) €2 668 vs 4 589 Total costs (p=0.002) €9 166 vs 11 360 Non-diabetic patients Initial hospital costs (p=0.69) €5 658 vs 5 557 Follow-up costs (p=0.01) €2 720 vs 4 397 Total costs (p=0.03) €8 378 vs 9 954 De novo lesions Initial hospital costs (p=0.74) €6 726 vs 6 833 Follow-up costs (p=0.004) €2 734 vs 4 708 Total costs (p=0.01) €9 461 vs 11 542 Restenotic lesions Initial hospital costs (p=0.50) €5 632 vs 5 805 Follow-up costs (p=0.003) €2 621 vs 4 300 Total costs (p=0.003) €8 254 vs 10 106 Number of stents SES vs PES 0 ± 0.36 vs 1.10 ± 0.38	SES versus PES Reintervention (p=0.01): 7.1% versus 15.1% Re-PTCA (p=0.02): 7.1% versus 14.2 Bypass (p=0.50): 0.0% versus 0.9% Major adverse cardiac events (MACE) (p=0.04): 12% versus 19% for respectively SES and PES (MACE = death + myocardial infarction + reintervention).	SES is a cost-saving (dominant) treatment strategy compared to PES, being associated with a higher effectiveness and reduced costs. For all subgroup analysis, there was a significant difference in follow-up and in total costs that favored the SES group. Higher costs associated with the use of PES almost entirely reflect the difference in the efficacy in the reduction of repeat revascularization procedures between the 2 DES.	In patients at high risk of restenosis, use of SES is associated with lower costs compared with PES. The cost savings are mainly due to the reduced need of repeat revascularization procedures with SES. Sensitivity analysis not explicitly performed.

Table A4.15: Greenberg et al.[145]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Greenberg D, Bakhai A, Cohen DJ US 2004 Dr. Cohen has received grant support from manufacturers of both drug-eluting and bare metal stents, including Cordis Corp. (Miami Lakes, Florida), Boston Scientific (Natick, Massachusetts), Guidant (Santa Clara, California), and Medtronic (Minneapolis, Minnesota). **Perspective** **Analytic technique** **Time window** **Discount rate** health care system perspective CEA 24 months no discounting	The overall PCI population Subgroups as a function of lesion length, reference vessel diameter, and diabetes. DES versus BMS data from literature	2003, in $ cost BMS $700 cost DES $2 700 Direct one-year cost of clinical restenosis $19 000 In the key assumptions, a mean utilization of 1.3 stents per single-vessel stent procedure was mentioned. In the calculations, however, 1.4 stents are taken into account.	An average TVR rate of 14% with BMS is assumed. Predicted rates of clinical restenosis after BMS as a function of lesion length, reference vessel diameter, and diabetes (based on a logistic regression model of 4 227 patients undergoing BMS implantation and clinical follow-up only (Cutlip et al, 2002)). Predicted rates of clinical restenosis after BMS. (in %) lesion length (mm) 10 15 20 25 30 35 40 vessel diameter (mm) diabetic patients 2,5 18 21 24 28 33 38 45 3 12 14 16 18 21 25 29 3,5 8 9 10 12 14 16 19 4 5 6 7 8 9 10 12 non-diabetic patients 2,5 11 13 15 18 21 24 28 3 7 8 10 11 13 15 18 3,5 5 5 6 7 9 10 12 4 3 4 4 5 6 6 7 An 80% reduction in TVR with DES is assumed.	Over a two-year follow-up period, the ICER is about $7 000 per repeat revascularization avoided. The ICER is less than $10 000 per repeat revascularization avoided for virtually all diabetic patients and for non-diabetic patients with smaller vessels (reference vessel diameter <3.0 mm) and longer lesions (lesion length >15 mm).	DES will be reasonably cost effective for the majority of patients and even cost saving for a large subgroup of patients who are at relatively high risk of clinical restenosis with conventional PCI techniques. Sensitivity analyses demonstrated that treatment with DES would be cost saving for patients with a BMS TVR rate >20%. An ICER of <$10 000 per repeat revascularization avoided is reached for patients with a BMS TVR rate >12%.

Table A4.16: Hill et al.[32]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, Mota RM, Reaney A, Roberts D, Williamson P, Walley T. UK 2004 None declared **Perspective** **Analytic technique** **Time window** **Discount rate** the NHS CUA a 5-year time horizon and 12 months for a simplified model. The headings of the tables mention that a discount rate was applied on costs and life years. However, the text does not inform us about which discount rate was applied. No discounting for the simplified model.	Elective patients with single-vessel and two-vessel disease. DES versus BMS large-scale audit database, TAXUS II, RAVEL, SIRIUS. patient utilities: ARTS trial baseline utility value (asymptomatic CHD): 0.86 Using the ARTS results for surviving post-CABG patients (EQ-5D 68 at baseline versus 86 at 6 months), we estimate a disutility of 0.012 QALY spread over 13 weeks, compared with 0.0035 QALY for surviving stented patients (based on EQ-5D 69 at baseline versus 86 at 6 months) spread over 6 weeks. Patients developing new anginal symptoms prior to a repeat revascularisation will lose 0.02 QALY over a 6-week period. For nonfatal AMI, a more speculative value of 0.1 QALY has been assigned over 13 weeks. In the case of stroke, a proportion of surviving patients will suffer from continuing loss of utility (arbitrarily set at 0.3 on the EQ-5D scale) associated with serious disability. Assumption: this proportion increases following each subsequent CVA episode (10% for 1st stroke, 15% for 2nd, 25% for 3rd and 50% for subsequent events).	2001-2002, in £ Single uncoated stent £380 Single DES £900 Initial revascularisation procedure PTCA (excluding stents) £2.156 Cardiac rehabilitation £500 Emergency CABG post-PCI failure £7.161 Early complications Acute renal failure episode £1.680 Severe bleeding episode post-PTCA £1.000 Follow-up Cardiology outpatient review post-PTCA £63 Cardiac surgery outpatient review post-CABG £111 Clopidogrel (per week) £9 Recurrence of symptoms Cardiology outpatient review £63 Angiography £278 Repeat revascularisation procedure PTCA (excluding stents) £2.156 CABG £8.368 Acute events AMI episode – fatal £814 AMI episode – non-fatal £1.017 Cardiology outpatient review post-AMI £63 CVA episode – fatal £1.600 CVA episode – non-fatal £2.124 General physician outpatient review post-CVA £87 mean number of stents single-vessel disease 1,3 two-vessel disease 2,4 in simplified model 1, 2 or 3 repeat intervention: BMS 1,3 DES 1,1	Absolute risk reduction (%) Single-vessel, non-diabetic: 6.0% Two-vessel, non-diabetic: 7.9% Simplified model Single-vessel, non-diabetic: 6.0% Two-vessel, non-diabetic: 7.9% Single-vessel, small diameter: 10.0% Single-vessel, long lesion, non-diabetic: 10.1% Single-vessel, long lesion, diabetic: 12.6% Distribution of type of subsequent revascularisation (%), for both single- and two-vessel disease: PTCA Stent DES CABG DES: 0 80 10 10 BMS: 25 55 0 20	ICER per QALY gained DES vs BMS (in function of time from initial procedure). single-vessel disease 1 year: £1 099 858 2 years: £825 512 3 years: £780 442 4 years: £771 347 5 years: £769 434 single-vessel disease Assuming 30% DES efficacy in function of relative risk / Assuming 75% DES efficacy in function of relative risk RR x1.0: £769 434 / RR x1.0: £201 364 RR x1.5: £415 864 / RR x1.5: £54 714 RR x2.0: £238 848 / RR x2.0: £-18 685 RR x2.5: £132 439 / RR x2.5: £-62 789 RR x3.0: £61 319 / RR x3.0: £-92 249 RR x4.0: £-28 034 / RR x4.0: £-129 215 RR x5.0: £-82 213 / RR x5.0: £-151 568 multi-vessel disease Assuming 30% DES efficacy in function of relative risk / Assuming 75% DES efficacy in function of relative risk RR x1.0: £1 086 356 / RR x1.0: £332 904 RR x1.5: £613 823 / RR x1.5: £136 918 RR x2.0: £376 843 / RR x2.0: £38 661 RR x2.5: £234 014 / RR x2.5: £-20 528 RR x3.0: £138 188 / RR x3.0: £-60 207 RR x4.0: £16 751 / RR x4.0: £-110 403 RR x5.0: £-58 482 / RR x5.0: £-141 357 simplified model: Incremental cost (£) per QALY gained: 1stent 2 stents 3 stents Single-vessel, non-diabetic 94.179 289.239 484.300 Single-vessel, small diameter 16.155 133.191 250.227 Single-vessel long lesion non-diabetic 9.531 119.942 230.353 Single-vessel long lesion diabetic -4 157 92.567 189.291 Two-vessel non-diabetic / 195.413 343.560	DES may not generally be considered a cost-effective alternative to BMS in single-vessel disease by policy makers as substantially higher costs are involved with a very small outcome benefit. DES might be considered cost-effective if one or more of the following options apply: a: The additional cost of DES (compared with ordinary stents) was substantially reduced. b: The outcome benefits from the use of DES are much improved. c: The use of DES is targeted on the subgroups of patients with the highest risks of requiring reintervention. one-way sensitivity analysis: The results reported were not vulnerable to uncertainty in particular model parameter values.

Table A4.17: Ikeda et al.[146]

Authors **Country** **Year of publication** **Conflict of interest**	**Population** **Comparator** **Data from trial** **QALYs**	**Year costs, currency** **Costs details** **Number of stents**	**Mean restenosis rate** **Relative risk reduction with DES** **Type of repeat procedure**	**Cost-effectiveness** **Subgroup analysis**	**Conclusion** **Sensitivity analysis** **Threshold analysis**
Ikeda S, Kobayashi M Japan 2006 None declared **Perspective** **Analytic technique** **Time window** **Discount rate** the payer's perspective CEA The analyses covered a 3-year period. no discounting	Based on SIRIUS trial SES versus BMS SIRIUS	2005, in ¥ cost of BMS ¥318 000 cost of SES ¥421 000 total cost of PCI using BMS 1-vessel lesion ¥1 530 496 2-vessel lesion ¥1 821 950 3-vessel lesion ¥2 650 210 average cost rehabilitation at outpatient clinics ¥9 261 total cost of PTCA 1-vessel lesion ¥1 289 193 2-vessel lesion ¥1 457 305 3-vessel lesion ¥2 234 441 average cost rehabilitation at outpatient clinics ¥18 522 (unadjusted) cost inpatient care CABG 1-vessel lesion ¥3 912 033 2-vessel lesion ¥4 989 161 3-vessel lesion ¥4 255 033 average cost rehabilitation at outpatient clinics ¥185 224 average cost treatment MI ¥570 587 number of stents: not explicitly mentioned. (3 757, 2 283, and 1 047 cases with resp. 1, 2, and 3 vessel lesions).	Probability of TLR in the BMS Group PTCA within 1 year: 28,00% 1–2 years: 1,50% 2–3 years: 1,00% CABG within 1 year: 2,10% 1–2 years: 0,50% 2–3 years: 0,50% Based on the SIRIUS study result, the authors estimated that the probability of PTCA required for revascularization would be 0.224 times in SES implantation versus BMS implantation. (PTCA (p<0.001): 19.2% in BMS group versus 4.3% in SES group).	SES was dominant in comparison with BMS	The authors concluded that the use of SES would be a cost-saving option as compared with BMS implantation within the context of the Japanese healthcare system. sensitivity and scenario analysis: Although this difference was not statistically significantin the SIRIUS trial, the percentage of patients undergoing CABG in the SES patient was assumed to be 0.547 times that of the BMS patient. Cost of inpatient care. Time preference: discount rates of 3% and 3.5%. Result: SES remained dominant in comparison with BMS.

Table A4.18: Kaiser et al.[147]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A, Bernheim A, Zutter A, Zellweger M, Grize L, Pfisterer E, for the BASKET investigators. Switzerland 2005 None declared **Perspective** **Analytic technique** **Time window** **Discount rate** Third party payer CEA and CUA 6 months no discounting	Unselected patients, as treated in everyday practice. The Basel stent cost-effectiveness trial (BASKET) included 826 consecutive patients treated with angioplasty and stenting for 1281 de-novo lesions, irrespective of indication for angioplasty. Diabetes: Overall: 19%; Cypher: 16%; Taxus: 19%; BMS: 21%. Multivessel disease: Overall: 69%; Cypher: 65%; Taxus: 71%; BMS: 69%. DES versus BMS Patients were randomised to one of two DES (Cypher, n=264; Taxus, n=281) or to a cobalt-chromium-based BMS (Vision, n=281). BASKET To assess QALYs, data for 515 patients (62%) for whom complete data were available from the self-administered EQ-5D questionnaire, including the visual analogue scale, were analysed from baseline and after 6 months. Mean EQ-5D scores increased similarly in both groups (DES from 0.84 [SD 0.21] to 0.91 [0.17], p<0.0001; BMS from 0.83 [0.22] to 0.89 [0.20], p=0.004) whereas the mean visual analogue scale increased more in the DES group (from 68 [23] to 75 [20], p<0.0001) than in the BMS group (from 68 [21] to 70 [20], p=0.21; all Mann-Whitney U test).	2003, 2004 in € Stents: (official list price per stent) Cypher (until Nov 23, 2003) €2.380 Cypher (after Nov 24, 2003) €2.145 Taxus €1.935 Vision €1.260 Pixel (Vision stents of 2·5 mm diameter were unavailable at the time of BASKET). €1.130 hospital stay (1 day) €420 intensive care (1 day) €1.935 coronary angiography €1.810 PCI €3.095 coronary bypass surgery €7.095 Costs for medications were not included since prescriptions were identical for all stent types. Cost of stents Mean BMS €2.259 Cypher €4.269 Taxus €3.617 Initial hospital treatment BMS €6.194 Cypher €5.930 Taxus €5.505 Follow-up BMS €1.185 Cypher €676 Taxus €1.058 Overall 6-month MACE costs BMS €9.639 Cypher €10.875 Taxus €10.233 Implanted stents: 1.9 (SD=1.1)	Compared with BMS, the use of DES reduced the rate of major adverse cardiac events by 44% (odds ratio [OR] 0.56; 95% CI 0.35–0.91, p=0.02) mainly due to a lower rate of target vessel revascularisation (0.57; 0.31–1.02) without significant changes in the rate of cardiac death (0.77; 0.27–2.18), myocardial infarction (0.51; 0.22–1.14) or hospital admissions for acute coronary syndrome (1.16; 0.36–3.81, all Fisher's exact test). Cardiac death (%) AMI (%) BMS 2,1 BMS 4,3 DES 1,7 DES 2,2 Cypher 1,1 Cypher 2,3 Taxus 2,1 Taxus 2,1 TVR (%) MACE (%) BMS 7,8 BMS 12,1 DES 4,6 DES 7,2 Cypher 3,0 Cypher 5,7 Taxus 6,0 Taxus 8,5 number of PCI and CABG PCI CABG (n=281) BMS 17 6 (n=545) DES 27 3 (n=264) Cypher 9 1 (n=281) Taxus 18 2	Incremental cost-effectiveness ratio of DES compared with BMS to avoid one major event was €18 311. SES: €19 264 PES: €16 694 The cost-utility ratio for DES versus BMS for each QALY gained was €73 283 when calculated from the EQ-5D index, and €54 546 when calculated from the visual analogue scale. Subgroup analyses of parameters predicting MACE regarding cost-effectiveness ratios indicate that DES might be cost-effective in high-risk patients such as: those with three-vessel disease, age older than 65 years, more than one segment treated, small stent sizes, or stent length greater than 20 mm.	In a real-world setting, use of DES in all patients is less cost effective than in studies with selected patients. Use of these stents could be restricted to patients in high-risk groups.

Table A4.19: Lord et al.[148, 79]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Lord SJ, Howard K, Allen F, Marinovich L, Burgess DC, King R, Atherton JJ. (+report MSAC, 2005) Australia 2005 None declared	Patients with de novo single vessel lesions. DES versus BMS sirolimus and paclitaxel TAXUS I, TAXUS II, TAXUS IV (resource use), C-SIRIUS, E-SIRIUS, RAVEL, SIRIUS (resource use). patient utilities Data from study of Shrive et al (2005) (APPROACH database) Utility weights: 0.77 for patients who experienced an event and 0.85 for patients who experienced no events. Data from stent-PAMI trial in sensitivity analysis: 0.80 for patients who required a repeat revascularisation and to 0.86 for patients who required no repeat revascularisation.	2001-2002 and 2004, Australian dollars (AUD) cost DES AUD2400 cost BMS AUD850 PCI procedure (including staff costs) AUD4 571 drug costs (clopidogrel) AUD504 death AUD3 711 MI AUD5 372 CABG AUD19 550 repeat PCI AUD5 753 diagnostic catheterization AUD668 stroke AUD8 198 vascular complications requiring surgery/transfusion AUD6 420 estimated average number of stents: 1.5	Drug-eluting stents (DESs) resulted in a 71%–80% lower risk of revascularisation at 12 months. RR 0.29 (95% CI, 0.20–0.43) for paclitaxel-eluting stents (n = 1593 patients). RR 0.20 (95% CI, 0.13–0.29) for sirolimus-eluting stents (n = 1296 patients). TLR rates at 12 months PES BMS difference 34/798 116/795 10,30% SES BMS difference 26/653 132/643 16,50%	SES versus BMS The cost per revascularisation avoided by using SESs was AUD3 746, with an estimated cost per QALY gained of AUD46 829. PES versus BMS The cost per revascularisation avoided by using PESs was AUD6 117, with an estimated cost per QALY gained of AUD76 467.	Drug-eluting stents are cost-effective if a cost of AUD3 700- 6 200 is considered acceptable to avoid revascularisation of the target lesion. one-way sensitivity analysis changing: average number of stents (1 or 2), rates of TLR (50 and 75% of trial rates), rates of PCI for non-target lesions and diagnostic catheterisations (50% of trial rates), cost per DES (AUD3 700 and 2 000), utility weight TLR events (Stent-PAMI trial). Results are sensitive to changes in estimates of true effects in clinical practice, market price and number of stents used per patient. Results varied between being cost-saving to costing AUD25 150 per revascularisation avoided or AUD314 385 per QALY gained.
Perspective **Analytic technique** **Time window** **Discount rate** Health care payer perspective CEA and CUA 12 months no discounting					

Table A4.20: Mittmann et al.[149]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Mittmann N, Brown A, Seung SJ, Coyle D, Cohen E, Brophy J, Title L, Oh P. Canada 2005 Nicole Mittmann and Soo Jin Seung have done research for Janssen Ortho, which is owned by Johnson & Johnson, the manufacturers of the Cordis stent. Eric Cohen's centre has been involved in research for several stent manufacturers, including Boston Scientific and Medtronic. He has received honoraria, for speaking engagements, from Boston Scientific, Cordis and Guidant. Boston Scientific co-sponsors a conference of which he is co-director. Lawrence Title owns shares in Johnson & Johnson, Boston Scientific X and Angiotech (<$10,000 per company). He has received a speaker's fee and travel expenses from Johnson & Johnson for an international conference in Japan. He was an investigator for Johnson & Johnson on the C-SIRIUS trial (no compensation received).	General population (at high or low risk of restenosis) DES versus BMS sirolimus paclitaxel SIRIUS, TAXUS IV, pooled data Babapulle et al, 2004.	2002, 2003 Canadian dollars (CAD) cost DES (2004) CAD2 400 cost BMS (2004) CAD608 ordinary balloon CAD250 PTCA CAD9 761 CABG CAD19 618 brachytherapy CAD3 057 MI or death CAD8 851 complication CAD9 761 rehabilitation CAD1 500 clopidogrel for one year CAD807 number of stents 1,5 (1 + gamma (0.5, 1))	TLR DES: 0.048 (Beta(127, 2 520)) BMS: 0.142 (Beta(349, 2 107)) stent thrombosis DES: 0.007 (Beta(19, 2 628)) BMS: 0.005 (Beta(12, 2 444)) type of repeat procedure Ordinary balloon 0,01875 Cutting balloon 0,05625 Brachytherapy 0,25 DES implantation 0,375 CABG 0,2 Medications 0,1	ICER per TLR avoided: hospital perspective: SES: CAD12 527 - 16 600 PES: CAD26 562 - 29 048 provincial perspective: SES: CAD11 133 - 15 192 PES: CAD25 202 - 27 687	For hospitals using the paclitaxel DES, the additional cost relative to BMS per TLR avoided is estimated to be between CAD26 000 and CAD29 000. For the sirolimus DES, it is estimated to be between CAD12 000 and CAD17 000. The two DES, however, were not compared head-to-head in the clinical trials and they were each compared with different BMS. There is no consensus on an acceptable range of cost per TLR avoided that would be considered cost-effective in a Canadian context. one-way sensitivity analysis by varying the cost of DES from CAD608 (the cost of BMS) to the original DES list price of CAD3 500. probabilistic sensitivity analysis The incremental cost per TLR avoided with DES was calculated to be CAD19 640, but a large credible interval (ranging from CAD5 177 to CAD57 420) reflects a great degree of uncertainty with this figure. threshold analysis: price difference DES versus BMS to obtain an ICER of CAD5 000 per TLR avoided. SES: CAD750 PES: CAD445
Perspective **Analytic technique** **Time window** **Discount rate**					
A tertiary care hospital and a provincial ministry of health. The analysis from a hospital perspective included acquisition costs for stents and drugs, costs for hospitalization (including the costs of repeat vascularization) and costs for rehabilitation. The analysis from a provincial payer perspective included all these costs, plus physician fees and charges for laboratory and diagnostic testing. CEA 12 months no discounting					

Table A4.21: Ong et al.[150]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Ong ATL, Daemen J, van Hout BA, Lemos PA, Bosch JL, van Domburg RT, Serruys PW. the Netherlands 2006 This study was supported by an unrestricted institutional grant from Cordis, a Johnson and Johnson company. **Perspective** **Analytic technique** **Time window** **Discount rate** institutional perspective (procedural and follow-up costs directly impacting on the Rotterdam Cardiology Hospital). CEA 12 and 24 months no discounting	Unselected patients with de novo lesions. The total study population comprised 958 patients divided into two sequential cohorts. In the first 6 months of enrolment, 508 patients with de novo lesions were treated exclusively with SES and compared with a group of 450 consecutive patients treated with BMS for de novo lesions in the preceding 6 months. SES versus BMS the RESEARCH Registry, RAVEL.	2001-2002, in € price paid for BMS € 692 price paid for SES € 1.929 (April 2002) BMS vs SES total cost index procedure (p=0.000) €6887 vs 9 924 stents (p=0.000) €1 266 vs 4 192 consumables (p=0.000) €1 575 vs 1 819 medication (p=0.015) €765 vs 685 laboratory cost (p=0.000) €1 790 vs 2 078 post-procedural hospital stay (p=0.11) €1 491 vs 1 150 follow-up events First year of follow-up total follow-up cost €1 594 vs 525 clinically driven repeat revascularization re-PCI €695 vs 279 CABG €393 vs 69 total coronary angiography €506 vs 177 Second year of follow-up total follow-up cost €561 vs 461 clinically driven repeat revascularization re-PCI €331 vs 203 CABG €82 vs 73 total coronary angiography €148 vs 185 number of stents BMS vs SES 1.81 vs 2.16	Rates of TVR in the SES and BMS groups were respectively 3.65% vs. 10.4% (P<0.01) at 1 year and 6.4% vs. 14.7% (P<0.001) at 2 years (2.75% repeat revascularization in second year with SES versus 4.3% with BMS). first year of follow-up BMS: re-PCI: 8.1% CABG: 2.3% SES: re-PCI: 3.3% CABG: 0.4% second year of follow-up BMS: re-PCI: 3.8% CABG: 0.5% SES: re-PCI: 2.3% CABG: 0.4%	The ICER per TVR avoided was €29 373 (14 659; 83 884) at 1 year, and €22 267 (10 737; 65 978) at 2 years.	The use of SES, while significantly beneficial in reducing the need for repeat revascularization, was more expensive and not cost-effective in the RESEARCH registry at either 1 or 2-years when compared with BMS. threshold analysis: At a price of €692 per BMS, the calculated cost neutral price for the DES would be €1 023 with the 1-year result of the registry, while at the maximum acceptable threshold of €10 000 per repeat revascularization avoided, the highest price would be €1 336 per DES. At 2 years, this would be respectively €1 069 and €1 452. Given a not unreasonable bare stent price of €400 today, a DES would have to fall to €779 to be cost-neutral.

Table A4.22: Polanczyk et al.[151]

Authors **Country** **Year of publication** **Conflict of interest**	**Population** **Comparator** **Data from trial** **QALYs**	**Year costs, currency** **Costs details** **Number of stents**	**Mean restenosis rate** **Relative risk reduction with DES** **Type of repeat procedure**	**Cost-effectiveness** **Subgroup analysis**	**Conclusion** **Sensitivity analysis** **Threshold analysis**
Polanczyk CA, Wainstein MV, Ribeiro JP. Brazil 2007 This study was sponsored by Cordis do Brasil **Perspective** **Analytic technique** **Time window** **Discount rate** Two perspectives: the "supplementary medical system (SMS)" (health plans and private patients) and the public health (SUS) system. CEA Endpoints were one-year event-free survival and life expectancy. All future costs and health benefits were discounted at 3% per year.	Patients with symptomatic, single-vessel disease. It was assumed that the cohort would be composed of subjects whose characteristics were similar to those described in clinical trials, that is, mean lesion length of 14 mm, vessels ranging from 2.5 to 3.5 mm in diameter, and a representative number of diabetics. Compare the cost-effectiveness ratios of sirolimus-eluting stents (SES) with bare-metal stents (BMS). Three therapeutic strategies for patients with symptomatic coronary artery disease. (a) percutaneous coronary intervention (PCI) with bare-metal stent; (b) PCI with sirolimus-eluting stents; and (c) PCI with BMS followed by SES for symptomatic restenosis. Estimates were derived from the literature, by means of a systematic review of the randomized clinical trials published up to 2003 involving bare-metal stents and data from multinational registries of PCI (SIRIUS, C-SIRIUS, E-SIRIUS, Cypher-restenose).	2003, in Brazilian reals (R$) SUS or SMS perspective Index procedure BMS R$4,210 or 10,195 (stent, mean cost) R$2,707 or 4,527 Index procedure SES R$11,762 or 15,889 (stent, mean cost) R$10,320 or 10,320 Restenosis management PTCA + stent (11%) R$1,738 or 3,930 PTCA + SES (11%) R$2,577 or 4,567 PCI with SES R$10,787 or 15,247 CABG Elective R$5,967 or 21,826 Emergency R$8,950 or 26,214 Index acute MI R$5,155 or 11,812 Annual after PCI or stable CABG, without events R$1,383 or 1,465 Cardiac catheterization R$539 or 1,276 Mean PCI cost R$4,210 or 10,195 Mean cost balloon PTCA R$1,442 or 3,432 Death from CAD R$2,577 or 5,906 Mean number of stents not mentioned.	Angiographic restenosis rate de novo lesion BMS 0.30 (0.10-0.50) SES 0.06 (0.02-0.15) Relative risk reduction of 80%, compared with the expected restenosis rate with BMS. Patients with recurrent symptoms of restenosis could undergo at most three percutaneous intervention attempts before being referred for CABG.	Under the "supplementary medical system (SMS)" (health plans and private patients): The ICER of SES versus BMS is R$27,403 per event avoided in one year. The strategy of using SES only for restenosis was associated with a higher cumulative cost than that of bare-metal stent, but yielding the same clinical benefit, so that, in this short-term endpoint, it was considered dominated. Under the "public health (SUS)" perspective: The cost per event avoided in one year was R$47,529 when comparing SES with BMS. The strategy of using SES only for conventional restenosis was also considered dominated in this scenario. Estimated life expectancy was very similar for all the strategies, ranging from 18.5 to 19 years.	The cost-effectiveness ratios for SES were elevated. The use of SES was more favorable for patients with high risk of restenosis, as it is associated with elevated costs in restenosis management. In the sensitivity analysis, probability of restenosis, risk reduction expected with SES, the price of the stent and cost of treating restenosis were all important predictors.

Table A4.23: Rinfret et al.[152]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Rinfret S, Cohen DJ, Tahami Monfared AA, Lelorier J, Mireault J, Schampaert E. Canada. 2006 This study was supported by an unrestricted grant from Cordis Canada. S Rinfret has received honoraria from Cordis Canada. OJ Cohen has done consulting work for Medtronic Inc. and has received grants from Cordis Canada and Boston Scientific Inc. E Scharnpaert has received honoraria from Cordis Canada and JJMP; a research grunt from Cordis Canada for conducting the C-SIRIUS trial; and has a grant pending to conduct the coordination of COMBAT in Canada from Cordis Canada. **Perspective** **Analytic technique** **Time window** **Discount rate** The third-party payer perspective. CEA. 1-year time horizon. Neither costs nor benefits were discounted.	High-risk patients with single long (15-32mm in length) de novo lesions in small (2.5-3.0mm in diameter) coronary arteries. Sirolimus-eluting stents (SES) versus bare metal stents (BMS) Based on the clinical results and resource-utilization data of the C-SIRIUS.	Results are expressed in 2003 Canadian dollars (CAD). Cost of BMS CAD700 Cost of SES CAD2700 Balloon catheter cost CAD200 Cost of GP IIb-IIIa inhibitors CAD434 Hospital cost initial PCI, excluding stents CAD2510 Hospital cost repeat PCI following BMS, excluding stents or brachytherapy CAD2708 Brachytherapy cost (including physician fees) CAD3800 Hospital cost of CABG CAD11 927 Physician fees for CABG CAD2475 Physician fees for PCI without stenting or brachytherapy CAD599 Physician fees for PCI with stenting or brachytherapy CAD730 Number of stents per lesion 1,5	At 1-year follow-up, no patients had died in either group, and the rate of subsequent MI was 4% in both the BMS and SES groups. However, the use of SES was associated with an 82% relative reduction in the need for repeat revascularization (11 of 50 patients [22%] with BMS versus 2 of 50 patients [4%] for SES; p = 0.015). i.e. an absolute risk reduction of 18% in repeat revascularization procedure rate with SES compared with BMS, as observed in the C-SIRIUS trial. Two CABG for every 15 repeat PCI	The ICER of SES versus BMS was CAD11 275 per repeat revascularization avoided. This is borderline cost effective compared with the implicit WTP of CAD12 551 for such health benefit in Canada.	Treatment of long lesions in small vessels with SES increases net healthcare costs. However, the ICER for SES compares favorably with the currently accepted comparator, i.e. BMS, to reduce coronary restenosis - at least for higher risk patients undergoing single-vessel revascularization. 1.5 stents per lesion base-case analysis CAD11 275 SES <$1147 (BMS = $500) SES saves money 1.2 stents per lesion base-case analysis CAD7 941 SES <$1309 (BMS = $500) SES saves money SES = $2200 (BMS = $650) CAD4 941 SES >$3400 (BMS = $700) >CAD12 500 SES for in-stent restenosis CAD5 918 threshold analysis: With a stent/lesion ratio of 1.5, the cost of the SES would have to fall below CAD1 147 (with a BMS cost of CAD500) to achieve cost savings. Assuming 1.2 stents per lesion, use of SES price <CAD1 309 (still with a BMS cost of CAD500) would save money.

Table A4.24: Russell et al.[153]

Authors **Country** **Year of publication** **Conflict of interest**	**Population** **Comparator** **Data from trial** **QALYs**	**Year costs, currency** **Costs details** **Number of stents**	**Mean restenosis rate** **Relative risk reduction with DES** **Type of repeat procedure**	**Cost-effectiveness** **Subgroup analysis**	**Conclusion** **Sensitivity analysis** **Threshold analysis**
Russell S, Antonanzas F, Mainar V. Spain 2006 Stephen Russell has received funds from Boston Scientific to carry out the study. Fernando Antoñanzas has received funds from Boston Scientific for access to the Soikos Database. Vincent Mainar is a member of a Boston Scientific advisory committee. **Perspective** **Analytic technique** **Time window** **Discount rate** a Spanish hospital (costs from SOIKOS database). CEA 12 and 24 months Future costs have been discounted at an annual rate of 3%.	The analysis considers the general patient population and a high-risk subpopulation (diabetes, small vessel (<2.5 mm), long lesion (>20 mm)). DES versus BMS Taxus TAXUS IV	Year of costs not explicitly mentioned, in € Additional cost of Taxus stent versus BMS € 712 Other material (1.3 guidewires, 1.3 catheters, 1 balloon, 3 vials IIb/IIa (% use of IIb/IIa=38%)) €1.069 Procedural cost €1.847 Hospital stay Cardiac ward (2 stays) €340 General ward (1 stay) €285 Other procedures CABG €14.068 Angiography €629 number of stents: 1.54 stents (all procedures) 3 stents (multivessel)	TLR for total population at 12 months (BMS versus PES) Overall 15.1% vs 4.4% (RR: 0.27 (0.18-0.41)) Re-PCI 12.2% vs 3.7% (RR: 0.28 (0.18-0.45)) Re-CABG 3.7% vs 0.8% (RR: 0.20 (0.08-0.53)) Cumulative 15.9% vs 4.5% at 24 months (BMS versus PES) Overall 17.4% vs 5.6% (RR: 0.32) Re-PCI 14.3% vs 4.8% Re-CABG 3.9% vs 0.8% Cumulative 18.3% vs 5.6% TLR for high-risk patients at 12 months (BMS versus PES) Diabetes patients 19.6% vs 7.1% Small vessel 20.6% vs 5.6% (RR: 0.24) Long lesion 22.1% vs 5.5% (RR: 0.23) at 24 months (BMS versus PES) Diabetes patients 22.0% vs 8.0% Small vessel 25.4% vs 6.1% (RR: 0.24) Long lesion 22.4% vs 8.9% (RR: 0.40)	At 12 months, PES costs €1 568 per repeat revascularization avoided. At 24 months, PES costs €811 per repeat revascularization avoided. In the high-risk subpopulation, PES was overall cost saving as compared to BMS both at 12 months (decrease of 3.0%) and 24 months (decrease of 4.7%).	Given the decrease in the number of repeat revascularizations with PES, the cost-effectiveness relationship could be acceptable in the general patient population and is dominant in the high-risk subpopulation. The cost-effectiveness of the PES is highly sensitive to the TLR rates of both PES and BMS, as well as to the difference in cost of PES and BMS and, to a lesser extent, to the duration of clopidogrel treatment.

Table A4.25: Shrive et al.[154]

Authors **Country** **Year of publication** **Conflict of interest**	**Population** **Comparator** **Data from trial** **QALYs**	**Year costs, currency** **Costs details** **Number of stents**	**Mean restenosis rate** **Relative risk reduction with DES** **Type of repeat procedure**	**Cost-effectiveness** **Subgroup analysis**	**Conclusion** **Sensitivity analysis** **Threshold analysis**
Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA, for the APPROACH Investigators. Canada 2005 None declared **Perspective** **Analytic technique** **Time window** **Discount rate** health care payer perspective CUA lifetime Costs and outcomes were discounted by 3% per year.	Patients undergoing PCI and subgroups based on age and diabetes mellitus status. DES versus BMS sirolimus APPROACH database and meta-analysis of 4 RCTs (RAVEL, SIRIUS, C-SIRIUS, E-SIRIUS). patient utilities APPROACH database (HRQOL was estimated in 1 954 patients of the APPROACH 1998–2000 cohort from self-reported EuroQol EQ-5D utility scores obtained 1 year after catheterization). The EQ-5D utility scores were higher among event-free patients than among patients who underwent a second procedure to manage restenosis (overall cohort, 0.85 v. 0.77, p < 0.001).	2002, in Canadian dollars (CAD) cost of SES CAD2 900 cost of BMS CAD500 Reimbursement and coding guidelines for DES (Johnson & Johnson–Cordis Corporation; 2003) cost year 1 Event-free: CAD5 195 (2 079–5 733) CABG: CAD32 009 (20 750–40 072) Repeat PCI: CAD15 569 (8 870–17 343) Repeat catheterization without revascularization procedure: CAD12 591 (5 603–15 114) cost year 2: CAD3 226 (401–3 142) cost year 3: CAD2 337 (336–2 525) cost year 4: CAD1 775 (231–2 189) number of stents 1,4	The relative risk of clinical restenosis was estimated at 0.23. Baseline event rates (with BMS): Repeat catheterization for restenosis within 12 months after index PCI. With revascularization procedure 8,2% Proportion with CABG as second procedure 28,0% Without revascularization procedure 12,2% Death within 7 days after initial PCI 1,1% For patients with repeat catheterization, death within 30 days: After CABG 3,1% After repeat PCI 1,4% Without revascularization procedure 1,8% Death in first 6 months 1,4% Subsequent annual mortality rate 1,4%	Cost per QALY gained in the baseline analysis was CAD58 721. SES was more cost-effective in patients with diabetes (CAD44 135/QALY) and in those over 75 years of age (CAD40 129/QALY). subgroups: age <65: CAD72 464/QALY 65-75: CAD47 441/QALY >75: CAD40 129/QALY diabetes status no diabetes: CAD63 383/QALY diabetes: CAD44 135/QALY	The use of sirolimus-eluting stents is associated with a cost per QALY that is similar to or higher than that of other accepted medical forms of therapy and is associated with a significant incremental cost. Sirolimus-eluting stents are more economically attractive for patients who are at higher risk of restenosis or at a high risk of death if a second revascularization procedure were to be required. one-way sensitivity analysis The results were sensitive to plausible variations in the cost of stents, the estimate of the effectiveness of sirolimus-eluting stents and the assumption that sirolimus-eluting stents would prevent the need for cardiac catheterizations in the subsequent year when no revascularization procedure was performed to treat restenosis. - if such procedures were not prevented by SES: CAD108 340/QALY. - RR varied within a range of 0.01–0.55: CAD39 777/QALY to CAD119 280/QALY. - clinical restenosis rate increased by 50% (CAD33 723/QALY) and by 100% (CAD21 312/QALY). - Cost of SES decreased by 25% (CAD35 082/QALY) or 50% (CAD11 443/QALY).

Table A4.26 : Tarricone et al.[155]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Tarricone R, Marchetti M, Lamotte M, Annemans L, de Jong P. Italy 2004 The study was sponsored by Cordis Italia and Cordis Europe. **Perspective** **Analytic technique** **Time window** **Discount rate** Health care payer CEA 12 months no discounting	Patients suffering from stable or unstable angina because of a new lesion in one or more native coronary vessels. DES versus BMS sirolimus RAVEL, SIRIUS, ARTS, BENESTENT II.	2003, in € difference in acquisition costs SES versus BMS (not taken into account) €1.400 CABG €16.992 Stenting with SES €6.023 Stenting with BMS €6.023 Balloon angioplasty €6.023 Myocardial infarction €5.834 Death (cardiac) €3.511 Angiography €451 Aspirin €2,3 Ticlopidin €16,8 number of stents single-vessel disease 1,2 multi-vessel disease 2,6 remark: 1.2 stents were SES and the remaining 1.4 BMS.	Clinically driven TLR: / Proportion of TLR employing CABG: Overall population single-vessel disease Normal-length lesion, normal-size vessel BMS: 13,00% 14% SES: 0,72% 14% efficacy on TLR: 94% Normal-length lesion, small-size vessel BMS: 14,40% 7% SES: 0,83% 6% efficacy on TLR: 94% Long lesion, normal-size vessel BMS: 20,00% 7% SES: 4,90% 7% efficacy on TLR: 75% Multivessel disease BMS: 22,33% 35% SES: 5,47% 38% efficacy on TLR: 75% Diabetic population single-vessel disease Normal-length lesion, normal-size vessel BMS: 15,21% 14% SES: 0,91% 14% efficacy on TLR: 94% Normal-length lesion, small-size vessel BMS: 16,85% 0% SES: 1,01% 99% efficacy on TLR: 94% Long lesion, normal-size vessel BMS: 26,40% 7% SES: 8,40% 15% efficacy on TLR: 68% Multivessel disease BMS: 22,32% 35% SES: 5,80% 38% efficacy on TLR: 68%	The incremental costs of SES vs. BMS are all negative values. Savings range from a minimum of €768 to a maximum of €1 757 per patient in 1 year time. However, the highest savings occur in diabetic patients, ranging from a minimum of €1 145 to a maximum of €1 588 per patient.	To stimulate SES adoption a SES-specific DRG might by introduced with a reimbursement value 23% higher than the current charge. SES is thus a cost-saving strategy in the perspective of the Italian Health Care System that could therefore support the introduction of the new technology by reimbursing about 80% of its current incremental acquisition cost. Two-way sensitivity analysis: CABG proportion in TLR: 0-30% SES efficacy: 50-80% Threshold analysis: The break-even additional charge was €1 371 for overall population and €1 404 for diabetics.

Table A4.27: van Hout et al.[156]

Authors Country Year of publication Conflict of interest	Population Comparator Data from trial QALYs	Year costs, currency Costs details Number of stents	Mean restenosis rate Relative risk reduction with DES Type of repeat procedure	Cost-effectiveness Subgroup analysis	Conclusion Sensitivity analysis Threshold analysis
Van Hout BA, Serruys PW, Lemos PA, Van Den Brand MJBM, Van Es G-A, Lindeboom WK, Morice MC. the Netherlands 2005 The RAVEL trial was supported by a grant from Cordis, a Johnson & Johnson company.	Percutaneous coronary intervention for single de novo coronary lesions. 238 patients with stable or unstable angina. 120 patients were randomly assigned to sirolimus eluting stent implantation and 118 patients to bare metal stents. DES versus BMS sirolimus bare metal Bx Velocity stent RAVEL and BENESTENT II (correction angiographic follow up).	Year of costs not explicitly mentioned, in € cost of SES €2.000 cost of BMS €672 SES vs BMS Total procedure costs €5 872 vs €4 588 Total follow up costs €3 473 vs €4 683 Total direct medical cost (excluding medication) €9 345 vs €9 271 Medication €624 vs €644 Total direct medical cost (including medication) €9 969 vs €9 915 number of stents SES 1,03 BMS 1,02	Clinical events SES vs BMS With angiographic follow up Death 1.7% vs 1.7% Myocardial infarction 3.3% vs 5.1% TLRs 0.8% vs 23.6% Surgical 0.8% vs 0.8% Percutaneous 0.0% vs 22.9% MACE-free survival 94.2% vs 71.2% 95% CI (89.9 to 98.4) vs (62.9 to 79.4) Without angiographic follow up Death 1.7% vs 1.7% Myocardial infarction 3.3% vs 5.1% TLRs 0.8% vs 11.8% Surgical 0.8% vs 0.3% Percutaneous 0.0 vs 11.5% MACE-free survival 94.2% vs 83.1% 95% CI (88.9 to 97.5) vs (64.2 to 90.9)	Costs per MACE-free survivor were estimated at €234 with an upper 95% limit of €5 679.	The one year data from RAVEL suggest an attractive balance between costs and effects for SES in the treatment of single native de novo coronary lesions. The cost effectiveness of drug eluting stents in more complex lesion subsets remains to be determined. Scenario analysis: Excluding follow up angiography as a standard procedure: the costs per additional MACE-free survivor were estimated to be €1 495 with an upper 95% limit of €61 243.
Perspective **Analytic technique** **Time window** **Discount rate**					
hospital perspective CEA 12 months no discounting					

APPENDIX FOR CHAPTER ON BELGIAN COST DATA (CHAPTER 5)

COST OF RE-PCI INTERVENTIONS BY TYPE OF STENT USED DURING REPEAT PCI.

Table A5.1: Cost re-PCI intervention within one year after the initial PCI (reimbursement and co-payment) and number of stents used. New intervention without stenting.

		No correction		
		mean cost	Stents	median cost
BMS	Non-Diabetics	6564.3€	0	4486.8€
	Diabetics	6711.7€	0	5511.0€
DES	Non-Diabetics	7805.4€	0	3875.2€
	Diabetics	8109.4€	0	7234.7€
BMS		6577.0€	0	4598.8€
DES		7966.0€	0	4979.7€
ALL		6901.3€	0	4655.3€

Table A5.2: Cost re-PCI intervention within one year after the initial PCI (reimbursement and co-payment) and number of stents used. New intervention with BMS.

		No correction			
		mean cost	mean stents	median cost	median stents
BMS	Non-Diabetics	6054.8€	1.22	4704.5€	1
	Diabetics	6276.3€	1.24	4786.0€	1
DES	Non-Diabetics	6115.8€	1.19	4552.7€	1
	Diabetics	9204.5€	1.43	5286.1€	1
BMS		6062.6€	1.22	4706.4€	1
DES		7333.9€	1.28	4664.0€	1
ALL		6177.6€	1.23	4705.4€	1

Table A5.3: Cost re-PCI intervention within one year after the initial PCI (reimbursement and co-payment) and number of stents used. New intervention with DES.

		No correction			
		mean cost	mean Stents	median cost	median stents
BMS	Non-Diabetics	6521.9€	1.17	4992.6€	1
	Diabetics	7540.7€	1.10	5756.7€	1
DES	Non-Diabetics	5329.2€	1.12	4552.7€	1
	Diabetics	6711.4€	1.12	5721.0€	1
BMS		6706.8€	1.16	5133.5€	1
DES		6396.6€	1.12	5534.3€	1
ALL		6571.8€	1.14	5374.2€	1

Table A5.4: Cost re- PCI intervention within one year after the initial PCI (reimbursement and co-payment) and number of stents used. New intervention with combination BMS/DES.

		No correction			
		mean cost	mean stents	median cost	median stents
BMS	Non-Diabetics	7340.5€	2.09	5202.9€	2
	Diabetics	7184.1€	2.50	7341.2€	2
DES	Non-Diabetics	4906.5€	2.14	5108.2€	2
	Diabetics	9043.2€	2.24	7072.5€	2
BMS		7316.5€	2.15	5572.1€	2
DES		8009.0€	2.21	6263.1€	2
ALL		7605.9€	2.18	5835.8€	2

DESCRIPTION AND DEFINITIONS

Table A5.5: Description of the cost-categories during index hospitalization

Cost categories index hospitalization	description
Material PCI (1)	nomenclature codes 687875, 687886, 687890, 687901
Fees PCI (2)	nomenclature codes 589013, 589024
Additional fees PCI (3)	nomenclature codes 589035, 589046
Hart catherisation (4)	nomenclature codes 476055, 476066
Coronarography (5)	nomenclature codes 464122, 464133, 464144
Clinical biology (6)	fees or clinical biology
Other fees	fees except (2), (3), (4), (5), (6)
Other implants	implants except (1)
Delivery margin implants	delivery margin for all implants (OOP of patient)
Nursing day	nursing day reimbursement
Lump sum day-hospital	nursing day cost of day hospital
Out-of-pocket nursing day	patient contribution for nursing day
thrombocyte aggregation blockers (7)	inpatient expenditures for thrombocyte aggregation blockers
Other drugs	inpatient expenditures for drugs except (7)
Diverse costs	supplements the hospital can charge for amenities in the room such as refrigerator, safe or telephone and for non-reimbursed items (thermometer, ..)
Other costs	all other expenditures

Table A5.6: Description of the cost-categories during the one year follow-up

Cost categories one year follow-up	Description
Fees GP OP	Fees of general practitioners for outpatients
Specialist fees OP	Fees of specialists for outpatients
Drugs OP	Drugs for outpatients
Paramedical fees OP	Fees of paramedicals for outpatients
Dental care OP	Dental care for outpatients
Other OP except cllinical biology, medical imaging, dialysis	Other care for outpatients except for clinical biology, medical imaging, dialysis
Clinical biology OP&IP	Fees for clinical biology, outpatient as well as inpatient
Medical imaging OP&IP	Fees for medical imaging, outpatient as well as inpatient
Dialysis OP&IP	Fees for dialysis, outpatient as well as inpatient
Surgical fees IP	Surgical fees for inpatients
Specialist fees 'special treatments' IP(speciale verstrekkingen)	Specialist fees for special treatments for inpatients
Other fees IP	Other fees for inpatients (ofthalmology, paramedical, dental)
Implants IP	Implants inclusive delivery margin
Nursing day IP	Nursing day (including diverse cost)
Drugs IP	Drugs for inpatients
Else	All other expenditures, including nursing and rest homes, daycenter, psychiatric care, medical pedagogical centers, palliative care, parapharmaceutical products
Total	Sum of above

Table A5.7: Description of the indicators for massive bleeding

Amb	Hosp	Label_NL
470271	470282	Verstrekkingen die tot het specialisme inwendige geneeskunde (FA) behoren: Medisch toezicht op een hoog risico transfusie van volledig bloed, packed cells, bloedplaatjes-, granulocyten- of lymfocytenconcentraat
555111	555122	Verstrekkingen waarvoor de bekwaming van geneesheer, specialist voor klinische biologie (P) vereist is - 9/Immuno-Hematologie & Niet Infectueuze Serologie : Compatibiliteitstest vóór de transfusie met tenminste twee technieken waarvan een indirecte Coombsreactie
555155	555166	Verstrekkingen waarvoor de bekwaming van geneesheer, specialist voor klinische biologie (P) vereist is - 9/Immuno-Hematologie & Niet Infectueuze Serologie : Opzoeken, voor de transfusie, van onregelmatige anti-erythrocyten-antilichamen met behulp van gefenotypeerde bloedlichaampjes met een minimum van 18 antigenen in geval van bestelling van bloed, inclusief een compatibiliteitstest A, B, O op het geheel van de kolven die dezelfde bestelling van bloed vormen
555531	555542	Verstrekkingen waarvoor de bekwaming van geneesheer, specialist voor klinische biologie (P) vereist is - 9/Immuno-Hematologie & Niet Infectueuze Serologie: Compatibiliteitsproef die voorafgaat aan een, van één enkele donor afkomstige, massale transfusie van van leucocyten of thrombocyten,indien een anti-HLA antilichaam bij de receptor werd ontdekt.
752415	752426	Vol bloed en labiele bloedproducten - Bevroren vers menselijk plasma bestemd om te worden gebruikt voor geprogrammeerde autologe transfusies : per eenheid bevroren vers menselijk plasma

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