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Drug Eluting Stents versus Bare Metal Stents for the Treatment of Coronary Artery Disease: A review of the Benefits and Harms

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Drug Eluting Stents versus Bare Metal Stents for the Treatment of Coronary Artery Disease: A Review of the Benefits and Harms

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Thesis submitted to the School of Graduate Studies and Research
in partial fulfillment of the requirements for the
MSc degree in Epidemiology

University of Ottawa

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July 2009

Your file Votre référence
ISBN: 978-0-494-58177-3
Our file Notre référence
ISBN: 978-0-494-58177-3

Abstract

Drug eluting stents (DES) have been found to reduce restenosis and the rate of repeat angiographic procedures related to restenosis. However, an increase in harms with their use has been suspected. Therefore, there may be an important trade-off of efficacy for harms with the use of DES, especially over the long term.

We conducted a systematic review and meta-analysis of RCT, examining the efficacy of DES versus bare metal stents (BMS). A separate review was then conducted which included non randomized studies, as well as RCT to evaluate long term harms of DES when compared to BMS. Analysis demonstrated that there was significant efficacy noted for DES over BMS, especially for the sirolimus coated stents. The long-term data demonstrated preserved efficacy of DES with no significant increase in the harms of death, myocardial infarction, stent thrombosis or revascularization for a follow-up extending out to four years.

Acknowledgements

I would like to thank my mentor and supervisor, Dr. George A. Wells, for the guidance and the support he provided throughout my Masters. I am grateful for the time that he spent with me and endless effort that he also put into the completion of this project. I am especially grateful to have found a supervisor that enjoys spending time "outside of the box". This allowed not only the completion of this very large project, but also made it extremely enjoyable.

I also would like to thank Dr. Terry Ruddy for encouraging me throughout the process of completing this final project and my Masters. I mostly thank him for his belief in me. I also must thank Dr. Michel Le May who, in spite of a demanding schedule, was always able to make time to provide content expertise to this project.

I would also like to recognize the technical assistance and friendship provided by Margaret Sampson, Raymond Daniels, Kasey Parker and Joan Pederson. Clerical support was kindly and tirelessly provided by Carol Marleau.

Fay Draper and Anne Gray kindly steered me through the of jungle processes from the time that I applied for my Masters until I finished my thesis. Without them, this journey would not have been possible.

The completion of this thesis would also have not been possible without the encouragement and support of my partner, Scott.

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Table of Abbreviations and Acronyms

ACS	Acute Coronary Syndrome
ARC	Academic Research Consortium
AMI	Acute Myocardial Infarction
BMS	Bare Metal Stent
CI	Confidence Interval
CONSORT	Consolodated Standards of Reporting Trials
DES	Drug Eluting Stent
ECG	ElectroCardioGram
FDA	Food and Drug Administration
HR	Hazard Ratio
ITT	Intention To Treat
IPD	Individual Patient Data
LLL	Late Luminal Loss
RVD	Reference Vessel Diameter
MACE	Multiple Adverse Cardiac Events
MI	Myocardial Infarct(ion)
NOS	Newcastle Ottawa Scale
NRS	Non Randomized Studies
PES	Paclitaxel Eluting Stent
RR	Relative Risk
SE	Standard Error
STEMI	ST Elevation Myocardial Infarction
SVG	Saphenous Vein Graft
SES	Sirolimus Eluting Stents
TLR	Target Lesion Revascularization

CHAPTER 1: Introduction

1.1 Rationale

Drug eluting stents (DES) have emerged as a treatment for coronary disease. Several categories of drugs have been applied to these stents. The two drugs that are approved in Canada since 2002 are sirolimus and paclitaxel. A third drug, zotarolimus, received approval in March 2008. Many more drug types are available in Europe, owing to differences in how stents become approved for market. The field has, however, evolved rapidly and many stent platforms and drug coatings have been evaluated for use in humans. As stent types have been disseminated for use, a number of short-term and long-terms harms have been observed. There has been concern that adverse events are linked more often to these later generation stents.

Stent trials often compare the drug eluting stent to a bare metal stent (BMS); these stents are usually identical, except for the coating. With the many DES being developed, one wonders how much better they are than BMS and how their performances may differ from each other.

Stents, once placed, are not removable from the coronary artery, and patients may, over the course of their lives, have several percutaneous interventions (PCI) or stent procedures. This can leave many stents deployed in an individual. Given the long-term nature of the procedure, potential for harm is a worry, both for patients and their physicians. There is evidence suggesting that stents are safe in the medium term. Some systematic reviews suggest that when RCTs are compiled, DES are safe in the short and medium term.(1-5) There is, however, a paucity of evidence available about the long-term safety of DES.

It is important and responsible to evaluate the efficacy of the various stent types that are developed and assess the potential that they have for producing long term harms.

Although there are other systematic reviews on the efficacy and the harms of stenting, this review provides unique features. Firstly it is formulated in the Cochrane style, which incorporates a specific style to a review. To date there is no Cochrane review on this topic. There has been a protocol in

place for 2 years, but it is not yet complete. Our efficacy review uses a similar line of thought, but has a more expansive review of harms.

This review; allows the efficacy findings of the previous reviews to be replicated; adds to the harms data that already exists in other reviews; and adds the outcome of LLL which has not yet been well studied in existing reviews. Completing a full review rather than updating an existing review was also appealing. Creating the review from the ground up allows us to be in control of the search; as well as include non-English studies and varied stent types into the review. From this data base we could formulate focused questions, especially about the efficacy and harms of stents.

1.2 Thesis objectives

The overall goals of this thesis from a methodological point of view were to:

1) to conduct a systematic review of the efficacy of DES compared with BMS for the treatment of patients with coronary artery disease;
2) to conduct a systematic review of the harms of DES and BMS for the treatment of patients with coronary disease

Specific clinical questions were to be answered:

1) "What is the incremental benefit of drug eluting stents over bare metal stents for patients presenting for treatment of native coronary disease?"
2) "What are the relative harms that occur at least one year after drug eluting stent implantation compared with bare metal stent implantation?"

These questions were addressed by designing and implementing two systematic reviews. The second question became more focused as the thesis progressed based on the large amount of harms data that was identified and comments received by the Graduate Studies committee.

1.3 Chapter description

The overall goal of this thesis was to perform a systematic review on a question in a contemporary area of cardiology and to design, implement, conduct and complete the review. The relative efficacy of different drug eluting stents and their effects in differing patients was of primary interest. The

cardiology literature is unique in that the clinical endpoints of all trials are essentially harms. The discussion of the proper method of assessing harms then dovetailed into a separate harms review. Because of the overwhelming volume of literature in this area it was necessary to focus our question and excluded some of the reports of harms from the review.

Chapter 2 provides background material on the use of stents in coronary disease. We have briefly discussed concepts that are necessary in the establishment of the methods of the review and the epidemiology of coronary disease. A review of the known methods for the assessment of harms is included. Lastly, there is a discussion about the general features of a review in the stenting field. Features specific to this literature and to the choice of outcomes are discussed.

The methods used to conduct both the efficacy and the harms review are described in Chapter 3. In this chapter, the PICO statements are presented, as well as the search methodology and the performance of the review. The PICO statement is the formalization of the plan for the review. It involves defining the population of interest, the intervention of interest, the comparator and the outcomes of interest. Once these components are precisely defined, the search strategy and the methodology follow from them. The design is based on the Cochrane format, with input from CONSORT (Consolidated Standards of Reporting Trials) when required.

The Consort Group is a collaboration including medical journal editors, clinical trialists, epidemiologists and methodologists, whose purpose is to alleviate the problems arising from the inadequate reporting of randomized controlled trials (RCT). The guidelines produced set a minimum number of recommendations for the reporting of various aspects of RCT, cohort studies and systematic reviews of these trial types.

The results of both the efficacy and the harms review are presented in Chapter 4. The search results are outlined and discussed. The overall outcomes, and the subgroups explored, are also presented. Outcomes of death, myocardial infarction, stent thrombosis, as well as angiographic outcomes, are presented.

The results of the two reviews are contrasted in Chapter 5. Potential sources of bias and pitfalls, especially with the use of non randomized trial in the evaluation of harms, are also discussed here.

CHAPTER 2: Background of Coronary Disease, Adverse Effects and Methods

This chapter consists of three sections of background material. The first section provides an overview of coronary disease, including the issues of treatment and the history of the appearance of adverse effects. The second describes the issues in the determination of adverse effects from the literature. The third provides an overview of the specific methodological issues in the design, implementation and conduct of a systematic review in the area of interventional cardiology.

2.1 Coronary disease

2.1.1 Definition

Coronary artery disease (CAD) is a long-term process that results in the build-up of plaque in the coronary arteries such that it may limit blood flow to the heart muscle. The process is heterogeneous, leading to differences in the amount of plaque, the number of involved arteries, the length of the build-up or lesions, as well as the amount of calcification and thrombus or blot clot. Each lesion can have a unique composition of these components.

2.1.2 Epidemiology

Coronary disease accounts for 45.6 % of all deaths in developed countries and 24.5 % of all deaths in developing countries.(6) A number of societal factors are responsible for rates of coronary disease seen in individual countries. The level of economic development in each country is only one factor linked to the rates of coronary disease. Within any layer of economic development, cultural factors such as diet play a major role. For instance, the rate of coronary disease in Japan has remained very low as the diet remains fish-based, keeping the caloric intake and the content of saturated fats low.

Investigation of the rate of coronary disease has identified some of the specific factors linked to the occurrence of coronary disease in various regions. The Framingham Heart Study was the first large-scale epidemiological study to describe etiologic factors linked to the occurrence of coronary disease. The etiologic connection was significant enough to have been subsequently called risk factors. The first Framingham report occurred after six years of follow-up and identified smoking, hypertension and hypercholesterolemia as important risk factors for the development of coronary disease. The risk

factors determined in Framingham have been confirmed in other studies.(7) Since this time, a number of factors, such as homocysteine, have been linked to cardiovascular disease, but there is not enough evidence to classify them as risk factors. A recent publication suggests that 80 to 90 % of patients with coronary disease still exhibit active traditional risk factors.(8)

It was thought that the control of traditional risk factors in the developed world would curb the incidence of coronary disease. However, the increasing rates of diabetes and obesity have lowered this optimism.(9) The recent increases in obesity in the United States (U.S.) and Canada are significant with at least 50 % of U.S. adults qualifying as overweight or obese.(10) Obesity is defined as having a body weight greater than 20 % of ideal body weight. Obesity also increases the rates of other risk factors, such as hypercholesterolemia, high triglycerides, hypertension and diabetes, thus also indirectly affecting the occurrence of coronary artery disease.(11)

It is projected that in North America, the rate of diabetes will increase to include 10 % of all adults and 15 to 20 % of adults over the age of 64..(6) It is projected that the countries with the largest number of new diabetes cases in 2030 will be be China, India, and the U.S. Diabetes not only has an adverse effect on vascular tissue, but is also associated with increased rates of other risk factors.(12) The projections for the developing world are for a rapid increase of coronary disease, based partly on the increasing prevalence of associated risk factors. By itself, the rapid increase in the prevalence of smoking will lead to the future occurrence of a significant burden of coronary disease.(13)

2.1.3 Diagnosis

Manifestations of CAD are varied and can include acute or chronic presentations; in some cases, there is no symptomatology. Acute presentations involve plaque rupture (usually with thrombus), which leads to a degree of occlusion of the involved segment of artery. This syndrome is now referred to as acute coronary syndrome (ACS) and encompasses a number of clinical variants, which are usually diagnosed with the help of an electrocardiogram (ECG) and sensitive markers of heart muscle damage. The range of clinical presentations includes acute myocardial infarction (AMI) or ST segment elevation myocardial infarction (STEMI). It also includes non-ST segment elevation infarction (NSTEMI). The treatment of these two syndromes is different as the STEMI have a high likelihood of coronary thrombus occluding the infarct-related artery; therapy involves attempts to open this artery. NSTEMI

have a variety of pathologic variants whereby the involved thrombus does not lead to complete arterial closure. There is a greater component of rupture or erosion in this type of infarction and the clot is believed to be of a different composition than that in STEMI. An alternate presentation is the destabilization or new presentation of symptoms which occur usually nocturnally or with exertion.(14)

Chronic symptoms can be related to activity only and may involve symptoms such as shortness of breath, chest pain, fatigue or dizziness. The patient in these cases usually has a non-invasive test to confirm the etiology on the symptoms and is treated with medication. In the setting where symptoms become limiting, or the non-invasive testing suggests severe or multi-vessel disease, revascularization of the coronary vessel is also considered.(15)

2.1.4 Treatment

2.1.4.1 Medical

The mainstay of the management of coronary disease involves the treatment and control of risk factors and the treatment of plaque growth. The latter is carried out with ASA (or aspirin), aggressive cholesterol lowering, and potentially ACE inhibitors, a class of drugs also used to treat hypertension. Weight loss and exercise also play a role in the improvement of cardiovascular outcomes. The control of risk factors, the use of ASA, cholesterol lowering, exercise and weight reduction have been shown to reduce the mortality associated with coronary disease.(13;15)

Medical therapy has progressed over the last few years, with both innovative new drugs and new methods of use for drugs already known for their effectiveness. For example, recent guideline changes suggest that more aggressive lowering of cholesterol levels leads to a further reduction of cardiac events. The addition of a rehabilitation program has also been shown to reduce deaths from coronary disease.(15)

Beyond medical therapy, there are three indications for further therapy with revascularization. The first is to alleviate symptoms and improve quality of life, the second is to prolong life and the third is to prevent non-fatal events.

2.1.4.2 Revascularization

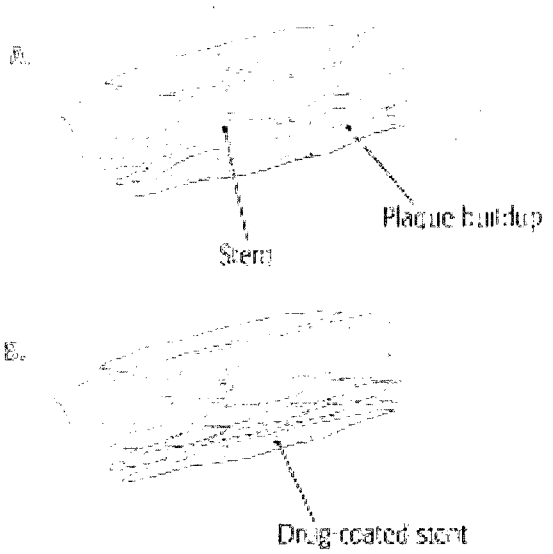
Revascularization involves coronary artery bypass surgery (CABG) and angioplasty, or what is now known as percutaneous intervention (PCI). CABG is a surgical procedure where the chest in opened and the blockage is bypassed with either a segment of vein from the leg or a dispensable artery from the wrist or chest wall. This procedure has a recovery time of two to three months and involves long-term issues with graft patency. Some complications of CABG have received negative press, such as possible cognitive dysfunction, and long wound healing at the site of the chest wound. This has lead to modifications of the procedure in order to minimize these risks.(16)

The benefits of CABG were first described in randomized trials of CABG against medical therapy. These studies were conducted in the 1970s when CABG consisted of only venous conduits. This data demonstrated a benefit over mortality for only two groups of patients. The first group of patients consisted of those with disease of the left main stem, which then bifurcates into the circumflex and left anterior descending arteries (LAD); this artery supplies the largest area of the heart. The second group of patients that benefited had triple vessel disease and some degree of heart muscle weakness or left ventricular dysfunction. Patients with disease in one, two or three vessels, and no left ventricular dysfunction, did not benefit from surgery, except for the improvement of symptoms. There is a possible benefit in prognosis in the case of one-vessel disease in the LAD if the lesion is proximal enough in the vessel. Essentially, the greater the severity of the coronary disease, the greater the benefit of revascularization from CABG.(17;18)

PCI evolved from angioplasty techniques where a balloon was used to open an artery containing a discrete plaque.(19) The procedure involves threading a balloon from the femoral artery into one of the coronary arteries where the balloon is then inflated. (Figure 2.1) The procedure has a 48-hour recovery time and frequently achieves the same results as CABG. PCI involves the addition of a small metal tube, called a stent, at the time of angioplasty. A stent is used in almost all cases. PCI involves other techniques, such as: atherectomy (with a device that removes some of the plaque burden); aspiration of thrombus (with a device that aspirates thrombus); and the use of a number of intravenous medications during the procedure, such as heparin or the class of drugs referred to as GIIb IIIa inhibitors in order reduce potential complications at the time of the procedure.(20)

Figure 2.1: Coronary Artery and Stent

The image in A represents a stent placed across a coronary lesion. The image in B represents the expanded stent across the lesion with the plaque pushed between the stent and the coronary artery wall.



Source: Harvard Health Publications (with permission)

The convenience and comfort of PCI from the patient's perspective has led to its rapid acceptance. Furthermore, neither of these procedures is usually performed for prolongation of life. The majority of patients coming to revascularization does so for the relief of symptoms and improved quality of life. (21) COURAGE is a study comparing patients with angina treated with optimum medical therapy to PCI and optimum medical therapy. There was an excellent prognosis in both groups with no superiority of the group receiving the added PCI intervention.(22) The use of revascularization between 1980 and 2000 accounts for only a 7% drop in fatalities from coronary disease in this time period.(13)

The decision about which revascularization strategy to use depends on a number of factors, including: the number of lesions, total stent length, the characteristics of the individual lesions, coronary anatomy, symptoms, as well as patient preference. The advantages of CABG over PCI for a patient with multi-vessel disease are a subject of debate. Clinical trials suggest that CABG has an impact on mortality in

patients with high risk features, but PCI has not yet been shown to reduce mortality in these circumstances.(23;24) The PCI technique, as well as surgical strategies, has evolved significantly since these trials were published.

The subgroup of patients with diabetes provides additional issues with regards to revascularization. The lesions tend to be longer and more complex in the setting of smaller coronary arteries and the patient more often has significant medical problems. The choice between PCI and CABG is often not straightforward in these types of patients.(25)

2.1.5 Issues with PCI

Angioplasty was initially limited by short-term complications involving acute closure of the artery at the time of the intervention, as well as the long-term growth of scar tissue at the site of the procedure (restenosis). Morbidity associated with restenosis includes severe angina, myocardial infarctions, the need for repeat PCI and even CABG in the most severe cases. Adding a metal coil, or stent, which was expanded and left at the site of the angioplasty, decreased the incidence of both complications. Clinical trials and reviews have demonstrated the efficacy and the safety of stenting when piggy-backed with angioplasty.(26) These early stent types consisted only of the metal coil and are now referred to as bare metal stents (BMS).

Early generation stents eliminated two of the factors leading to restenosis. Elastic recoil of the vessel wall, as well as negative remodeling of the vessel (early shrinking of the vessel post angioplasty), were improved by stenting. However, there continued to be rapid proliferation of cells (27) and tissue into and around the stent, causing recurring chronic and acute presentation with symptoms, which occurred at a rate of 10 to 40 %.(28) The need for repeat angiography and further interventional methods to treat the restenosis was not eliminated. Systemic immunosuppressants, radiation, and stent design modification have been used to reduce restenosis at the stent site. Gains were continually made in the treatment of lesions, but the issue of restenosis remained, which clinically became the "Achilles' Heel" of stents.(29)

The stents were then impregnated with drugs of various classes in an attempt to deliver the drugs locally to the coronary lesion. This local delivery of drugs had the effect of reducing the degree of

restenosis of the stent. The theory behind the addition of these agents to the stents was that local drug delivery would act directly on the area of the artery responsible for the rapid cellular proliferation.

The feature and timeframe of restenosis has been established both from autopsy and animal data.(27) The arterial wall consists of three layers, each contributing differently to the process of restenosis. The outer wall is called the adventitia, the middle layer is the media, and the inner layer has two components, the intima and its inner layer in contact with the blood components is the endothelium. The adventitia consists of a support structure and blood vessels to the artery itself. The media consists largely of smooth muscle cells. The pathology of restenosis occurs as an uncontrolled growth from the intimal layer. The process is different from the one causing coronary disease.(30) It involves the invasion of the area by inflammatory cells, rapid proliferation of smooth muscle cells and connective tissue components. The cells infiltrate the stent and cause stenosis in the stent (in-stent restenosis) itself and at its edges.(31) The addition of drugs onto the stent locally destroys the individual cells that cause restenosis. Most agents now used work by arresting smooth-muscle cell proliferation at the level of cellular division. Some agents are directed at destroying the anti-inflammatory cells which begin the restenosis process. This has been an extremely effective strategy, with the rate of in-stent restenosis falling from between 35-60 % to as low as 5 %, with the addition of these agents to the stent surface or onto a coating that was first placed on the cell surface.

2.1.6 DES and their components

Stent components include the stent structure or platform – which can vary in metal type, thickness and strut design – stent coatings, and finally, the addition of a drug, either directly to the stent or to the coating.

The coatings of stents are either biocompatible or drug eluting.(32) Biocompatible coatings are generally inert and include agents such as gold, carbon or silicon. These agents were thought to be less thrombogenic, less inflammatory and to produce less intimal proliferation. A coating of interest is phosphocholine, not only because of its potential inertness – it is a normal component of human cell membranes – but also because it serves as a platform for drugs to be delivered.(33)

Many drugs have been used in the war against restenosis; the drugs used are of different classes which target different components of the process of restenosis. Agents directed towards reducing thrombus (e.g. heparin), inflammation (e.g. dexamethasone) and cellular proliferation (e.g. paclitaxel and sirolimus) have been tried. These drugs are used, respectively, as immunosuppressants to prevent organ rejection post transplantation, and as chemotherapeutic agents, especially in the treatment of breast cancer. Other agents such as estrogen, bamastat, and actinomycin have also been mounted on stents, based solely on their anticipated effects on restenosis. Analogues of successful antiproliferative agents, such as analogues of sirolimus (tacrolimus, temsiolimus, biolimus-9 and zotarolimus) have recently dominated the literature.(32) Most stents mount drugs on to a polymer which has already been mounted onto a stent. This allows variations in drug dosing, delivery speed and timing, as well as the ability to vary the concentration on the location of drug on the stent.(34)

The two DES available for use in Canada, and accounting for most published reports are paclitaxel and sirolimus. Recently, DES stents with everolimus coatings have been approved.(34-36) These stents have also been compared in head-to-head trials. Given the effectiveness of these agents, a large trial would be required to determine which agent performs better. As one author stated: "It may be that the champion of champions may never emerge".(37) Recent reviews of the literature suggest that there is a significant reduction in reintervention with both drugs, when coated onto stents, without a significant change in adverse outcomes.(38)

Since their release, DES stents have seen an expansion in the indications for their use. The patients that were not well served by BMS stents had to either continue with medical treatment or opt for CABG. The patients at particular risk have lesions in arteries that are small (<2.5mm), large (>4.0mm), long lesions (>26mm)(39), or multiple lesions. Lesion characteristics, such as an overly calcified lesion, a lesion on an angulation or bifurcation, or one containing thrombus, precluded a consistent and excellent result with BMS. In addition, patients with diabetes, renal dysfunction or acute infarctions precluded a good result in the long term with PCI and BMS.

Both diabetics and patients with renal failure have a larger plaque burden, which is diffuse and can render the artery smaller. Results with BMS, likely multifactorial in etiology, were poorer in this group of patients. Not only does the potential for an exaggerated intimal response at the stent site exist, but

there is greater disease progression in non-target vessels.(40) Thus, these lesions require longer stents of a smaller diameter in more locations. An increased risk of restenosis was recognized as so substantial that these patients were not routinely offered PCI until DES stents became available.

2.1.7 Market penetration of stenting

The rate of adoption of DES was rapid in Canada and the United States after their introduction. DES were introduced in the United States in October 2003. Six months after approval, the average use of DES approached 80 %. Similar adoption rates were seen in Canada after DES were approved in 2002.(41) In Alberta, DES stents were adopted almost overnight. A major factor leading to this widespread adoption is likely the cardiologists' long history in dealing with the complication of restenosis with BMS use. The rate of restenosis decreased to 4 %.(42)

The excellent early results with DES rapidly led to many patients receiving more than one stent during any given procedure for the treatment of a severe, or multiple lesions. The average number implanted at the Ottawa Heart Institute (OHI) is 2.1 stents per procedure in 2007. DES use rates reached 90 % in the US and in some European countries. In most of Canada, their higher cost limited their use, but they still represented 40 % of all stents used in 2005.

2.1.8 Risks of stenting

In spite of their low rate of restenosis, DES stents have been associated with stent thrombosis (ST). This complication involves the sudden development of thrombus in the stent itself. ST is a serious complication that presents as an ACS, MI or death.

ST caused by DES stents has been linked to delayed vessel healing due to lack of endothelialization of the stent with persistence of clot or its components, such as fibrin. Poor healing exposes the stent to the blood contained within the blood vessel. Clots can then form on the stent and the bare intima of the coronary artery. Potent antiplatelet agents, in combination with life-long use of ASA, are typically used to reduce the chance of thrombosis while the stent is being endothelialized.(28;43;44)

Initially, this risk was seen only as an acute complication of stenting, usually occurring within the first four weeks of the procedure and usually related to procedural factors.(44) Angioscopy, a procedure

using a camera to directly visualize coronary arteries, can quantify the degree of endothelial coverage in vivo on stents. When compared to BMS stents, DES stents have less intimal coverage and the stent itself contains more thrombus even six months after implantation.(28) In animal models, there are fundamental differences in the healing of endothelium of a DES versus that of a BMS. In animals, there is uniform healing of a BMS stent site in 28 days. In the DES, there is delay in healing which is dependent on the dose of medication applied to the stent. The healing can be delayed as long as 180 days. Initial investigations prior to human studies involved only 28-day stent animal models, so that the knowledge of delayed healing was not available. This process of stent assessment was problematic for DES as ST could occur much later than this. This longer time line was not anticipated by investigators and sponsors. The identification of late concerns led to the early stopping of two trials where adverse events were found to be high.(45;46) Once a trial is stopped, it essentially prevents that particular stent type from reaching market.

There continue to be reports of stent thrombosis occurring as late as 40 months after stent implantation.(47) There does not appear to be a safe period after which it does not occur. The occurrence of late ST has caused some antagonists of stent use to advocate a decrease in use of stents in patients with chronic coronary disease, while maintaining their use in situations of potential myocardial salvage, such as myocardial infarction. In September 2004, Dr. S. Yusef suggested that there was a late and important risk associated with the use of DES which had yet to be quantified. There have since been several systematic reviews and databases that have demonstrated no significant increase in ST.(48)

2.1.9 Risk factors for stent thrombosis

The predisposition to ST is related to various factors, including procedural, patient-related and stent factors.(49) Technical factors, such as malapposition of the stent to the arterial wall, overlapping of stents, excessive stent length, bifurcation stenting, and the use of brachytherapy, have been associated with poor healing and an increased risk of thrombosis development at the stent site.(50)

Stent features linked to increased thrombogenicity include stent design, type metal platform, the presence of a coating, and the type of drug used. A polymer coating is found on most clinically available stents, and may be partly responsible for the late inflammation of the arterial wall.

Phosphocholine, a component of cell membranes, may have less thrombogenic qualities and has been used in newer stent types.(51) The drug choice and its elution characteristics may also influence the rate of non procedural ST.

Patient-related factors can lead to stent thrombosis. The most important factor is compliance with antiplatelet medication. Premature discontinuation of antiplatelet agents (by patients or their physicians) before the endothelium has fully lined the stent is known to produce this complication. For longer and more complex lesions, patients may require a longer course of antiplatelet medication. Resistance to the newest antiplatelet medication, clopidogrel, has also been described.(44) There has been evidence in some studies that the discontinuation of antiplatelet therapy precedes ST(52) where there may be an increase in thrombogenicity accounting for thrombosis.(53)

Patient-related factors also increase the rate of this complication, so that patients presenting with an AMI are prescribed a one-year course of therapy. Patients with diabetes, renal failure and reduced ejection fraction may also have an increase in ST risk.

The optimal timing of clopidogrel is unknown.(44) The current recommendations vary, based on the clinical presentation, degree of stenting, vessel size, and number and location of vessels stented.(54) In the future, it is hoped that the length recommendation for post-procedure medication will be individually tailored to a patient's needs.

2.1.10 Rate of stent thrombosis

The rate of stent thrombosis is unclear. In spite of the Food and Drug Administration's (FDA) recent interest in this event, the rate of late thrombosis is likely less than 0.5 % per year. This may be two to three times higher than with BMS at 0.1 % per year.(50) The increased use of stents in non-RCT patient types may have increased this rate to as high as 1.1 %.(55) Because of the increased risk of this complication, FDA organizations, such as the Cardiac Care Network of Ontario, have formulated statements suggesting the use of drug eluting stents only for situations where BMS are known to perform poorly. This includes situations where the vessels are small (<2.5mm), the lesions are long (>26mm), or the patient has diabetes.

Determining the exact rate of ST is difficult. One of the issues in determining the rate of the outcome of ST is the variance in the definition used by the individual trialists. The FDA requested that the data be reformatted using a standardized definition for stent thrombosis. The Academic Research Consortium (ARC) had already been formed in order to implement consensus definitions for implementation in clinical trials. This body included representatives from the academic research organizations, the FDA and from the stent manufacturers.(56) This led to the proposal of a standardized definition for this outcome and others. The proposed definition matrix features the outcome, based on the timing of the outcome, and the certainty that ST had actually occurred. The time periods were defined as early (0-30 days), late (31-360 days) and very late (>360 days). The probabilistic definitions are definite ST which requires the presence of an ACS with angiographic or autopsy evidence of thrombus. Probable stent thrombosis includes unexplained deaths within 30 days after the procedure or AMI of the target vessel territory without angiographic confirmation. Possible stent thrombosis included all unexplained deaths occurring at lest 30 days after the procedure.

A meta-analysis demonstrated that, with this definition, there is an increase in ST outcomes if the definition for possible ST is used. If the more restrictive definition (definite ST) is used, the authors felt that true cases of ST could be missed. The protocol definition itself provided the lowest number of events. Depending on the definition that is used, the yearly event rate ranged from 1.2 to 3.6 % ST, with 0.6 to 2.0 % of the events occurring after 360 days. These rates are higher than those measured in BMS by any definition, although not statistically significant.(57)

2.2 Assessment of adverse effects

2.2.1 Evaluation of adverse effects

Reporting bias makes the evaluation of adverse effects of a particular drug or intervention difficult through the literature. A negative trial, or one which demonstrates an excess of harm associated with an intervention, is less likely to reach publication as noted in section 10.2 of the Cochrane Handbook (58) Historically, case reports have been used to evaluate adverse effects, but this type of report does not provide the denominator required to ascertain the relative frequency of the event of interest. The use of only RCT (Randomized Controlled Trials) or systematic reviews including only RCT to determine adverse effects may not be inclusive enough to determine harm, especially if the harm is unexpected.

Even though the RCT is set up to monitor the safety of study patients and to include such unforeseen events, they also may occur infrequently and therefore be missed by this monitoring process.

The detection of adverse events became of prime interest to the Cochrane Group. Thus, the Adverse Effects Methods Group (AEMG) was registered in 2007. The purpose of this group was to provide methodological expertise to determine the degree to which adverse effects are associated with effective interventions. In this way, a balanced decision can be made about the intervention, as noted in Chapter 14 of the Cochrane Handbook.(58)

2.2.2 RCT to assess adverse events

Although RCT are the least biased type of information regarding harms, the particular design of the RCT will influence the quality of the data. Potential harms are often not identified at the outset of an RCT, which does not foster proper definition of the endpoint and its collection. If there is information about the potential harm and its time frame, its pre-specification and prospective collection allows for the least biased method of collecting harm data.

RCT may not be the best study design to collect harm data in particular instances. If the harm in question has a long latency, or occurs infrequently after the exposure, even a high quality RCT may fail to document the relationship between the exposure and the event. An example of this problem occurred with the association of an increase in MI rate from the arthritis drug, rofecoxib (Vioxx). The increase in MI was small and did not present itself until six months of follow-up.(59)

Infrequent events may also be difficult to document. For example, if clinically apparent GI bleed occurs with NSAIDS at a rate of 1/1,000 person-years, and occurs at a similar rate of 1/1,000 person-years in those taking a placebo, the RCT needed to study this effect would require 6,000 patient-years of exposure to achieve a 95 % probability of observing at least one additional serious gastrointestinal hemorrhage.(60)

In a review of the adequacy of harms reporting in RCT, it was demonstrated that reporting of harms was "inadequate and neglectful".(58) Adequate reporting of adverse events occurred only in 39 % of a series of trials using drug interventions across seven medical subject areas.(61)

2.2.3 Non-randomized studies to assess adverse events

Observational studies are considered by some investigators to be the standard for identifying serious and uncommon adverse effects of a medical intervention.(62) Observational studies refer to a range of study designs, including database analyses, longitudinal cohort studies, and uncontrolled series. Cohort studies can be used to identify the frequency of adverse effects. This study type can be larger and can run over a longer time period. Cohorts can capture data on naturally occurring events, and can catalogue the timing and the severity of these events

The major drawback of these studies is that the intervention in cohort studies is not randomly assigned. As such, the two patient populations may be different. No amount of adjusting for known and unknown factors is able to fully equalize the two groups. In addition, confounding by indication may be an issue in cohort trials. This refers to the issue that the patient's diagnosis can drive the choice of intervention. It is believed by some that cohort trials exhibit this bias when examining efficacy, but not for unexpected harms. It is unlikely that assignment of intervention to treatment groups would be determined by characteristics that would predict unexpected harms outcomes.(62) This has been shown for the occurrence of adverse drug events such as rashes. This, however, is not true in instances where harms could be related to characteristics of the patient population, or initial diagnosis.

2.2.4 Systematic review to assess adverse events

Systematic reviews of adverse effects have often been carried out through the inclusion and analysis of adverse effects data that is collected in an RCT. Collecting and combining adverse effects in this way may allow enough cases to be collected for an overall assessment of harm to be made. This is especially true for rare adverse events. Alternatively, systematic reviews that include only RCT data for the assessment of adverse effects may not achieve a complete picture of all adverse effects associated with an intervention. Many reviews include only RCT to assess the harm of the intervention with the thought that this type of data should be non-biased and a denominator be obtained.

Non randomized studies, when included in a review, may add more information about the adverse effects of an intervention. In reviews of adverse effects, there is no consistency as to which study types are best included for the evaluation of adverse effects. The choice is based on the scope of the

question and the resources available.(63) In a survey of methods used in adverse effects reviews, it was found that 28 % of reviews limited themselves to RCT, one third included case reports and cohorts, and 10 % included case reports and case series.(64)

The methodology of adding non randomized data to a systematic review is not as well developed as for RCT. The addition of the required search may not make a significant contribution to the overall results of the search. The evaluation of adverse effects through a systematic review requires different methods than an RCT efficacy review in order to identify and select eligible studies, as these documents have no reliable indexing. In addition, there is no optimal search strategy to identify reports of adverse events. Currently, a search (including a free text search for the title and abstract) is suggested to maximize finding reports of harms. This is especially the case when rare or long-term adverse effects in particular are the item of interest.(63)

A review comparing the adverse effects rates found in RCT versus cohort trials did not find a significant difference in the reporting of adverse effects in 15 medical interventions.(65) In these comparisons, neither the cohort trials nor the RCT consistently produced greater relative risks of the adverse effects of medical intervention. Other reviewers have also found that the extra effort of conducting an adverse effects review did not yield any incremental data on adverse effects over that found in reviews including only RCT.(58;66)

For reviews containing NRS, it is important to pay particular attention to issues of study quality. The lack of quality of NRS has been shown to bias studies to have either greater or smaller effect sizes. Even though many tools exist for evaluating the quality of NRS, there is no data that supports the use of these scales when evaluatiing the included studies for the collection of harms.(63) Other specific concerns that have not been quantified include NRS that have a fluctuating rate of disease; blinding of the assessors to the outcomes need to be carefully considered. Organizations such as Cochrane are attempting to publish methodology so that reviewers interested in harms may have guidance on how to best include NRS for added assessment of harms.(58;67)

2.2.5 Additional issues faced when adding non- randomized trials

There may be significant time delays before studies reporting adverse events are reported and confirmed. This may lead to different study types being added to a review in which patients received different medical or surgical therapy over the follow-up period. This is an important issue in a rapidly evolving field, as the time lag may be as long as three to five years to properly identify a new harm with an NRS.(68)

2.3 Review of methods of stent trials

In any body of trials, some issues relate to the conduct of the trials and the subsequent incorporation of these trials into a meta-analysis. The following is an outline of issues that required consideration prior to the incorporation of stent trials into a meta-analysis;

2.3.1 Populations

The patient populations used in these trials are as varied as the stent types. In the early trials, patients with simple discrete lesions and low-risk medical conditions were enrolled. Later trials included patients who were excluded in early trials. Patients having AMI, lesions in the most proximal segment called the left mainstem coronary artery, and lesions in bypass grafts, have now been included as part of trials, as well as trials specifically designed for these types of patients.

2.3.2 Interventions

There are many different BMS and DES stent types in use, mostly outside of North America. In Europe, the adoption of stent types is more liberal than in the U.S. and Canada. It is easy to ignore the existence of other stent types because they have not received approval for use in North America. In addition, some stent types fail to produce satisfactory results when initially introduced to man, or in their first clinical trial. The determination of stent types of interest requires consideration for any review of stents.

2.3.3 Quality

Many scores and checklists exist to determine the quality of a clinical trial. These lists emphasize the quality of reporting, rather than the quality of conduct of the trial. These lists feature the quality of the

allocation concealment, the presence of blinding, and the retention of the trial population for proper ascertainment of the outcomes. In device studies, these practices are even more important as the patient has the stent implanted for life. There are also markers of stent type that can unblind the patient or operators, and thus could produce different outcomes. Not only can the stents differ visually, but they also can differ radiographically. Since there is often a perception among patients, operators and paramedical personnel as to which stent is superior, this issue becomes problematic in a trial which is not concealed or blinded properly.

The overall morbidity rates in stent trials are very low. In order to prove the superiority of one stent type over another, surrogate measures of restenosis are used. Most often, a measure of stent patency is taken after the intervention, and then compared with the same measure at a follow-up angiogram. In these cases, follow-up angiography is necessary for achieving the study endpoint. The trialists' ability to have patients comply with the follow-up procedure – which is somewhat uncomfortable and has a small degree of morbidity – is pivotal to the completion and the success of the trial. If the follow-up angiogram is not completed, the data for the endpoint of the trial is missing.

2.3.4 Outcome measures

2.3.4.1 Clinical outcomes in stent trials

Stent trials usually present a number of clinical outcomes. As is the case with issues surrounding the outcome of ST, other outcome definitions can differ between trials. The definition of death can be problematic, as many trials do not report total death. This is based on the belief that many of the low-risk patients included in these trials are more likely to die of a non-cardiac, rather than a cardiac cause.(69) It is proposed that for the outcome of death, both cardiac and non-cardiac death be reported. It is also suggested that death be attributed to a cardiac cause unless a non-cardiac cause of death is clearly identified.(70)

Myocardial infarction in stent trials is usually defined by the World Health Organization criteria. This definition has not yet been amended to include the advancements achieved with more sensitive biomarkers for the detection of myocardial necrosis that occurs with AMI.(70) The timing of the outcome of myocardial infarction is also crucial, since after revascularization, it is not uncommon for

myocardial necrosis to occur. In these cases, the study may or may not actively monitor patients for post-procedural infarctions. This would provide a different rate of myocardial infarction among studies, but likely not a different relative risk. In some trials, it is considered important to collect this data and to ensure that there was no evidence of an infarction prior to the procedure. Post-procedure infarctions are thought to be related to distal embolization of thrombotic and other material of plaque down the coronary artery into the microvasculature at the time of the PCI. The use of blood work to determine myocardial damage is used in studies monitoring for infarctions in combination with ECG.

Composite endpoints used by stent trials include various combinations of death, myocardial infarction, stent thrombosis and definitions of revascularization. The definitions for revascularization are plentiful. The most simple is target lesion revascularization (TLR); TLR refers to any revascularization either as CABG or PCI at the site of the stent or within 5mm on either side of the stent. The ARC generally feels that these composites of multiple adverse cardiac events (MACE) have been used so frequently with so little consistency between trials, that this term should be abandoned.(71) There was concern in their analysis that different hazard ratios were obtained using different endpoint combinations in various trials. They provide an example between the TAXUS I trial and the TAXUS V trial. In these trials, only Q wave MI was included in the 30-day outcome measures of the former trial, and non-Q waves were included in the latter. The outcome at 30 days for TAXUS I demonstrated no significant infarcts, compared with MI rates of 4.4 % in the treatment group and 3.3 % in the control group of TAXUS V. The authors felt that safety outcomes (such as death and myocardial infarction) should not be combined with effectiveness outcomes such as TLR in PCI trials. They have suggested the use of a composite outcome that reflects patient or stent-related outcomes, but these have not been adopted by stent trialists as of yet.

2.3.4.2 Repeat revascularization

The treatment of restenosis has evolved substantially over the last few years. This event is commonly treated with the following: a repeat percutaneous procedure with a stronger balloon used to break up the scar tissue (possibly adding a DES inside of a BMS); or with a device which removes the scar tissue from the inside of the stent. Occasionally, because of the position of the stent or the degree of restenosis, a surgical procedure is required. As this event is used as an outcome event, a clear definition of revascularization is essential to the understanding of any new DES.

Restenosis, and the subsequent repeat revascularization rate, are an expected outcome of stenting and a direct indicator of the antiproliferative properties of the drug and stent which is being tested. Many stent trials mandate a follow-up angiogram and analyze the pre- and post-angiographic images at a core laboratory. This provides an exact measure of restenosis. The difficulty with this approach is that patients with greater restenosis are at risk of reintervention with a follow-up angiogram, even if they have no clinical symptoms.

The ARC group suggests that a clinical assessment precede a protocol mandated angiogram. In this way, objective symptoms or functional testing could be secured prior to angiography. Following these suggestions could ensure that all revascularization procedures at the time of the follow-up angiogram be clinically driven. This issue is more complex if the study has not followed proper allocation concealment and blinding procedures, and in theory, could lead to differential treatment of the same problem. For example, if a patient presents at their endpoint angiogram with the same degree of restenosis, there would be a risk that treatment would be received in the BMS stent, but not in the DES stent; the argument used would be that restenosis will not likely progress any further in the DES, because "after all they have the good stent". The complex problem of treating a patient presenting with asymptomatic significant restenosis is not yet solved. It is thought that these lesions should be treated by PCI as they will become symptomatic.(72)

It can be determined that bias is introduced into outcomes from this practice. Reanalysis of study data has demonstrated a small degree of investigator-driven revascularization or TLR, but probably not accounting for more that 10 % of the events. As well, stenosis graded as severe by the operator is often not as severe when reanalyzed in the core laboratory (see next); however, these are still included as TLR events in the final trial analysis.(72)

2.3.5 Core laboratory measurements

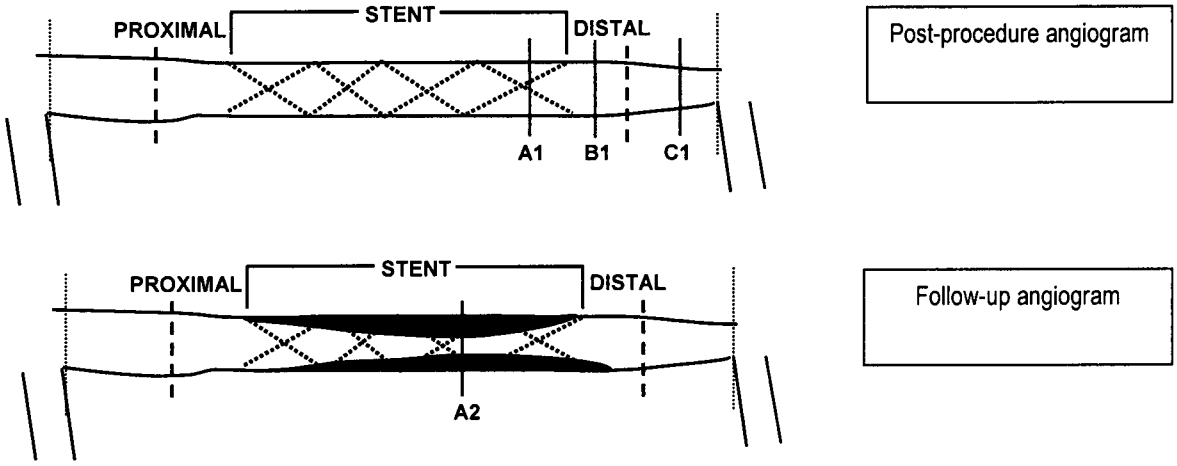
Analysis of angiograms in core laboratories is a standard practice in stent trials.(73) Typically, the entire stent length is analyzed in addition to the 5 mm of artery on either stent edge. The combination of the stent and both edges is referred to as the segment. With the development of analytic software packages, a quantitative measurement of the stented area and the segments proximal and distal to the

stent can be made. A number of outcomes obtained from these analyses can be used to understand stent success or failure. Two of the more common measurements are the percentage of stenosis at the tightest point, and the presence of binary restenosis, which is a stenosis of greater than 50 % anywhere in the lesion. In both these cases, the tightest area in the stent is compared to an adjacent area of normal artery. Often, the site of the restenosis is further quantified so that the stenosis in the stented segment (or either edge) is identified as a separate entity.

The above stent measurements, although commonly used, do not give a sense of the degree of restenosis if the process within the stent is diffuse. In this case, minimal luminal diameter (MLD) can be used. The MLD is the minimum measure of the diameter from the area of restenosis that is obtained from the stent itself or the stented segment. If a measure of change is required, then late loss (also referred to as late luminal loss) or the difference between the post-procedure MLD and the follow-up MLD, can give a surrogate of hyperplasia or the degree of overall restenosis. (Figure 2.2)

Binary restenosis occurs too infrequently to be used as an important endpoint of the new generations of DES stents. In addition, this particular endpoint varies across studies for any given stent, dependent on the individual patient populations. It has been demonstrated that late loss and binary restenosis have a strong and positive correlation, and that both are related to the clinical endpoint of TLR. Even a small degree of in-stent late loss can translate into important differences in binary restenosis and subsequently create the need for further revascularization. % diameter stenosis is not generally used in stent trials, given that it has been shown to have a wide range for any given late luminal loss. It may, however, predict TLR at least as well as late luminal loss.(74)

Figure 2.2: Calculation of late luminal loss



The upper image is a post-procedure angiogram. The MLD (C1) is located outside the stent as defied by the computer algorithm. MLD (A2) is located in within the stented segment at the follow-up angiogram. Despite the mismatch in MLD location between post-procedure on followup, LL measurements are calculated as follows:

Instent LLL=A1-A2

In-lesion conventional LLL=B1-A2

In-segment LLL=C1- A2

The decision as to which angiographic parameter is the best surrogate for stent function is important, since the stent trialists commonly use them to power the clinical trial.(75) It is possible that these surrogate parameters do not behave similarly in all stent types. The Deliver trial (76), which used paclitaxel, did not achieve its primary endpoint in spite of significant reduction in LLL.(77) This suggests that the surrogate chosen by the trialists may not reflect the overall change in the stent and its scar tissue development over time. It is known that the MLD of a BMS changes over time, with a

progressive increase in restenosis. It is important that the time frame of these changes be incorporated, not only in the choice of clinical endpoint, but in the timing of the repeat evaluation of this endpoint.

There are numerous sources of potential error in the of stent measurements. The image of the artery must be the same in both the post-PCI and the follow-up angiogram. The software must be validated and the operators need to be fully trained in the required methods. If proper techniques are used, even core labs at different sites will have reproducible results.(78)

2.3.6 Covert complications

Once the endpoints of the trial are chosen, one must determine what adverse effects are important to detect, from a patient and clinical perspective. During the early BMS use, the restenosis quoted to patients was between 15 and 40 %.(79) This meant that many patients returned for repeat angiograms and a repeat PCI. With each of these procedures, the patients have a risk of periprocedural complications such as stroke, myocardial infarction, major bleeding and death. The additional morbidity of these procedures in the Canadian health care system involves potentially long wait times during which the patients may be symptomatic and even unable to work.

The addition of antiplatelet agents is required until the inside of the stent becomes endothelialized. The time frame of this occurrence for any patient is uncertain. There is a range of required antiplatelet therapy, from three months for BMS to 12 months for DES. These medications are expensive, with clopidogrel costing $766 per year.(80) Also, when stacked on other antiplatelet and required anticoagulants, they may cause bleeding and issues if other injuries occur. Should the patient require dental work or other surgical procedures, morbidity may be an added factor (usually in the form of excessive bleeding) to the non-cardiac procedure if the antiplatelet medication cannot be reversed or stopped. The potential morbidities of these events are likely not to be captured in an RCT, but may be seen in longer-term cohort trials.

The final covert complication of DES is their substantial incremental cost over BMS. At the Ottawa Heart Institute, the cost for DES is approximately $1,150-$1,900; for BMS, it is approximately $595-$650. In spite of this, a recent Canadian cost-effective meta-analysis concluded that most studies

assessing cost effectiveness found a financial benefit to their use. This may be a more complex issue when examining the issue in countries where there is either partial or no individual medical coverage.(81)

CHAPTER 3: Methods of the Reviews

3.1 Methods for the systematic review of efficacy

3.1.1 Criteria For considering studies for this review

For inclusion in the review, studies were selected if the PICO criteria outlined below were met.

3.1.1.1 Types of studies

Only RCT published in peer review journals were included in this review. Drug eluting stents can be evaluated solely by longitudinal studies, and the decision to release them to the market can be based on these studies. The incremental effect of DES over BMS was, however, the primary focus of this review.

3.1.1.2 Types of participants

Studies that enrolled patients who required PCI for *de novo*, and who had clinically significant lesions in a native coronary artery or a bypass graft, were included in the review. There were no exclusion criteria based on the patient population or clinical presentation. Drug eluting stents are increasingly used for expanded indications beyond the initial FDA indications which were in place at the time of DES approval, or "off-label indications". Subpopulations of patients, such as those presenting during acute infarction, as well as in clinical subpopulations, patients with diabetes, or with complex anatomy, are now being considered for PCI. It was deemed important to include these varied patient populations into the review. Patients were allowed to receive concomitant therapy, during the intervention and during the follow-up period. There were no exclusion criteria based on angiographic parameters such as lesion length or reference vessel diameter. As the treatment for in-stent restenosis (ISR) has changed rapidly over the last few years, these patients were not included into the review. Restenosis in BMS and DES stents are not driven by the same etiology as native coronary lesions; therefore we felt that introducing this group of patients would lead to significant clinical heterogeneity.

3.1.1.3 Types of interventions

Studies randomizing patients to DES versus BMS were included in this review. There are a number of stent types available outside the U.S. and Canada, particularly in Europe, owing to regulatory

differences in the acceptance in the approval processes for devices in these countries. We felt that limiting the review to stent types used exclusively on this continent would subject the review to publication bias, as we are not certain of the criteria used for stent acceptance and how these stents would differ from the stents not accepted in North America. The inclusion of all stent types would allow examination of efficacy by drug type, as well as a comparison of the stent types to each other. The classes of coatings that were allowed into the review are anticoagulants, anti-inflammatory drugs and the antimitotics agents - paclitaxel, sirolimus and their analogues. The biocompatible agents – gold, carbon, and silicon – were not included into the review. We based our decision on the fact that these chemicals are inert, non-inflammatory and have no other a priori actions known to affect restenosis.(32)

We excluded studies that prespecified additional intervention, such as rotoblation, radiation, or aspiration devices. These techniques are applied to chronic lesions which are often heavily calcified. We felt that inclusion of these studies into the review would lead to significant clinical heterogeneity. Studies that allowed or specified direct stenting are included. With this technique, the stent is deployed across the lesion with the first balloon dilatation, not following an initial balloon dilatation. This decision was made on evidence that suggests that there is no increase in vascular reaction to injury by this technique, when carried out in an experienced centre.(82)

Studies comparing stents with variable release kinetics or doses of drugs were included in the review. In studies that used multiple stent types, one arm was required to use a BMS.

3.1.1.4 Types of comparators

The following comparisons were included: DES versus BMS (any type) stents; coated or uncoated BMS stent; and polymer or bare metal coating. If additional therapy (such as heparin or GIIb IIIa inhibitors) was used during the intervention or follow-up in the DES group, this treatment would need to be applied to the BMS group as well.

3.1.1.5 Types of outcome measures

The primary clinical outcomes of importance to this review are all cause mortality, myocardial infarction, stent thrombosis and target lesion revascularization. Total myocardial infarction and stent thrombosis were collected as defined in the study. The only planned angiographic outcome was in-stent late

luminal loss as this is thought to be the best angiographic measure of restenosis. Significant late luminal loss is thought to be a marker of clinical restenosis. The additional harms of angina, stroke and bleeding were also of interest to the reviewers and were to be collected, as they are thought to directly relate to the harms of stent reintervention.

We required the studies to have at least 30 days of follow-up, as the efficacy of the various stents was of primary interest in this review. The occurrence of stent complications up to this point is related more often to procedural and periprocedural complications, and not necessarily to whether the stent is bare metal or drug-coated. Although these complications can be stent dependent, we did not include studies which would have outcomes weighted towards the procedural outcomes. Having the follow-up time at least 30 days after implantation would rule out studies whose primary intentions were to compare periprocedural events.

3.1.2 Search methods for identification of studies

A computerized search strategy was created with the help of an information scientist for both the efficacy and the harms portion of the study simultaneously. An OVID interface was used to search the following electronic databases for published literature from:

- CDSR (Cochrane Database of Systematic Reviews), The Cochrane Library, Issue 2, 2008
- CENTRAL (Cochrane Register of Controlled Trials), same period
- DARE (Database of Abstracts of Reviews and Effectiveness), same period
- EMBASE (1980-2008, Week 20)
- MEDLINE (1950, May, Week 2, 2008)

In addition, bibliographies of included articles and relevant systematic and non-systematic reviews were searched for any potentially missing citations. Sources on non-indexed or non-peer review studies were not searched. Another content expert was contacted (Dr. M. Le May) to determine if they had knowledge of any further studies that our search may have missed.

Tagging of RCT was carried out using the Pub Med "Study Type" as they were brought into Reference Manager. This allowed the screening for each portion of the review to be carried out separately.

Additional efforts to locate relevant studies included internet-based sources of information on the results of clinical trials in cardiology (www.cardiosource.com/clinicaltrials). We found not-yet published studies at www.theheart.org, www.clinicaltrialresults.com and www.tctmd.com. Clinical trial registries (www.clinicaltrials.gov) and www.controlled-trials.com/mrct) were searched for completed studies.

No language or methodological limits were imposed. Non-English studies were included in the search. There is no evidence that including non-English studies into a review increases the precision of, or biases, the summary estimate. It has been demonstrated that a study with a positive endpoint is more likely to be published in an English journal. Alternatively, if the findings are negative, the study may be more likely to be published in a local non-English journal. Moher et al (83) did not find a significant effect of excluding non-English studies on systematic reviews. To date, there has been no further data suggesting that non-English studies should be included into systematic reviews, but a trend toward their inclusion has been noted in Cochrane reviews.(84)

The bibliographies of identified sources were also searched once a decision was made about all studies to be included from the search strategy. The full search is presented in the methods section of the harms review; the search strategy itself is presented in Appendix 1.

3.1.3 Methods of the review

3.1.3.1 Selection of studies

The titles and abstracts of potentially eligible RCT were screened by two independent reviewers (RH and JP) for identification of full text studies. These studies met the inclusion criteria using a pretested screening form (Appendix 2). At this stage, assessments were made independently, so that an RCT of potential interest to either reviewer was obtained in full text format. The full text studies were obtained and screened by the same reviewers. The inclusion criteria were applied and a final decision was made for inclusion. Disagreements were solved by consensus and when this was not possible, by GW. For the non-English citations, the titles and abstracts were reviewed by RH and JP. After the study was obtained in full text form, it was assessed by the same reviewers if it included an English abstract. If it did not, a translator was found who was able to apply the inclusion and exclusion criteria.

In the case of the inclusion of multiple published reports or outcomes from one study, the outcome coincident with the primary endpoint, or the follow-up angiogram, was chosen, as long as it was not within 30 days. The eligibility criteria were applied to each report and then the multiple publications were linked together and referred to by the included study.

3.1.3.2 Data extraction

Two independent reviewers, RH and KP, abstracted all information and data using a standardized data abstraction created in Excel. The form was piloted by the two abstracters, and then all abstraction was carried out independently, in duplicate. All discrepancies were discussed and resolved. GW mediated any discrepancies. Abstraction included information on pertinent aspects of study design, patient characteristics, the type of DES and BMS stent and the outcomes. If outcome information of interest was missing, the corresponding author was contacted via e-mail. All data was collated by RH prior to entry into the final spreadsheet.

The study time point for the clinical data used was coincident with the primary endpoint. If there was additional data at other time frames, it was also collected. No data was collected past the specified primary outcome.

3.1.3.3 Quality assessment

Two reviewers (RH and KP) assessed each included RCT, using the individual components of the Jadad scale (Appendix 3) with an additional assessment of allocation concealment. A total score was not tabulated, as this has recently been discouraged in the literature.(85;86) The trials were not blinded prior to their assessment of quality features, as this has not been proven to reduce bias in the assessment of quality and increased needed resources.(58)

The Jadad Score evaluates three important domains of an RCT. The first is the randomization, the second is blinding and the third is the domain of incomplete outcome data. After allocation concealment, these are considered the most important factors in trials in the producing bias.

The quality assessment tool provided in the recently developed Rev Man 5.0 by Cochrane was not used, as it could not be successfully piloted by the two reviewers. The tool involves a two-part process.

The first is an assessment of six domains. The above three domains are included, in addition to selective outcome reporting, allocation concealment and others. The second portion then involves the judgment of whether the presence of an inadequate performance in one of the domains would lead to bias in that particular study.

We found that the assessment of the effect of each item on potential bias could not be agreed on consistently by a content expert and a methodologist. An example is the performance of an open label study which has complete outcome reporting of an angiographic endpoint. One can interpret this as being "unclear" in producing bias, or as "yes", depending on the belief of the objectivity of the Core Lab analyzing the endpoint. We then piloted the SIGN 50, and for the additional factors requiring collection, there was no obvious benefit over the Jadad.

In the Jadad score, a study describing itself as randomized is given a point. An additional point is given if the generation of the scheme is appropriate. For the domain of blinding, a point is given if the study is described as double blind. An extra point was given if the methods of the study described the stents as visually equal. A point was not substracted if this description was absent, as suggested by Jadad. This is a deviation from the scoring system, but this allows us, at first glance, to determine the studies that have no double blinding at all, as a number of studies were open label.

For the domain of follow-up, the study received a point if there was a description of the follow-ups, irrespective of whether the dropout numbers were provided or not. This domain was difficult to implement, as many of the studies had a primary outcome which was angiographic, but they gathered clinical events which would necessitate collection of dropouts for both outcomes. As such, we agreed that the point would only be given to a description based on the clinical outcome.(87)

The assessment of the number of dropouts and withdrawals is not part of the Jadad scale. The percentage dropout was collected, as there is concern when the number of dropouts exceeds 80 %. A sensitivity analysis was carried out for the presence of studies having greater that 80 % dropouts.

A Jadad score was not calculated. Instead, the quality components with be used for a sensitivity analysis. The analysis will be based on the presence or absence of the four components described.

Allocation concealment, although not part of the Jadad scale, was also assessed. A point was given only if a description assuring the lack of potential bias was provided. The description of the Cochrane manual was rigorously applied. A point was given only if the description of allocation was clearly centrally allocated, or if sequentially numbered, opaque, sealed envelopes were used. Other than in these cases, a point was not given. We felt that this assessment was particularly important, as many of the studies are open label, potentially leading to post-randomization biases. A sensitivity analysis was carried out comparing those studies having proper allocation concealment versus those that did not.

3.1.3.4 Dichotomous data

For the outcomes of death, myocardial infarction, stent thrombosis and TLR, the relative risk was calculated when comparing DES to BMS. The data was collected by outcome group as presented in the study, irrespective of whether the data was presented as available case data or not.

3.1.3.5 Continuous data

For the continuous outcome of late luminal loss, the weighted mean difference (WMD) will be used for the outcome of late luminal loss between the DES and the BMS stent. Late luminal loss is the difference between the mean luminal diameter at the end of the study and that at follow-up. This will often be a negative number, as the late luminal loss in the DES stent is low and the late luminal loss for the BMS stent is greater. More explicitly, WMD late luminal loss (DES-BMS)=LLL (DES)-LLL(BMS)=(MLD (DES pre=procedure)-MLD (DES follow-up angiogram)-(MLD (BMS pre-procedure)-MLD(BMS follow-up angiogram)).

The outcome of interest was in-stent segment late luminal loss. Studies often report both in-stent and in-segment data; however if the study did not clearly report which portion of the artery the outcomes were from, then we assumed that the data referred to the in-stent portion of the artery. This may have introduced a small error into the analysis. For most studies, the number of patients undergoing repeat angiography was presented. For those where it was not, it was assumed that that the patients undergoing angiography were the same as those that were followed for clinical events. If neither denominator was presented, the number of patients entering the trial was used.

3.1.3.6 Unit of analysis issues

For studies that treated more than one coronary lesion during the study intervention, efforts were made to identify adjustment for clustering of lesions within a vessel or patient. In all cases, this data was absent. The lack of such data presents a unit of analysis error. It is clear that a second lesion treated in one patient will behave more like the first lesion than like a new lesion in another patient.

For these studies, the data was collected as reported. In general, the clinical data is presented per patient, and the angiographic data is presented per lesion. For the studies making such an error, the influence on the outcomes were believed to be small.

The correction used to avoid a unit of analysis error is the design effect and is given by the formula $1+(m-1)r$, where m is the average cluster size and r is the intracluster correlation coefficient (ICC). The design effect is used to adjust the variance of the outcome to accommodate the clustering effect in the data. There is no cluster size in our trials greater than 2, representing two lesions treated per patient. Taking a conservative ICC of 0.2, the design effect would only then be 1.02, which would not alter the results appreciably. Only if the cluster size increases, or the ICC is very large, it will it have a significant effect.(58) .

3.1.3.7 Studies with multiple treatment groups

Data from studies with multiple treatment groups needed to be modified at the extraction level. For dichotomous outcomes, if there was a shared intervention or control group, this group was then divided equally by the number of comparisons. This allowed a number of independent pair wise comparisons. For continuous outcomes, the common group was not altered, as this does not completely correct for the multiple comparisons.

3.1.3.8 Missing data

Authors were contacted to obtain any missing data, in particular for the clinical outcomes. If no response was received, this data was left out of the analysis.

3.1.3.9 Assessment of heterogeneity

The outcome data was combined only when the population characteristics of the studies and the intervention were sufficiently homogenous. Otherwise, meta-analysis was not conducted.

Statistical heterogeneity was assessed using a multi-step process whereby the Forest plots were initially examined for the presence or absence of overlap in the confidence intervals. Lack of overlap suggests heterogeneity. The heterogeneity was more formally assessed with the chi squared and the I^2 test. A $p<0.10$ suggests the presence of heterogeneity when using the Chi squared test. However this test is of low power, there may be heterogeneity in spite of the finding of a non significant p value. The I^2 statistic which quantifies the variability across studies is due to heterogeneity between studies and not to random error. A value of 25 % suggests mild, greater than 50 % suggests moderate and greater than 75 % high heterogeneity.(88) For values of I^2 greater than 50 %, heterogeneity was explored using a sensitivity analysis and influence analysis. If heterogeneity was greater than 50 % and it could not be explained, the results were presented using both fixed and random effects model, the latter using the methods of DerSimonian and Laird. In this model, the assumption is made that the studies included in a meta-analysis are estimating different treatment effects. The summary effect refers to the centre of the point estimate. The random effects point estimate is often similar to the fixed effects model, but the associated confidence intervals are usually are wider when heterogeneity is present.

For the continuous outcome of late luminal loss, the heterogeneity was very high, reaching close to 100 %. As such, an influence analysis as described by Rothman was carried out.(89) In this setting, each study was removed in order of decreasing weight and the effect on the summary point and I^2 was examined.

3.1.3.10 Assessment of reporting biases

Publication bias was assessed with funnel plots for each outcome with an asymmetric plot implying publication bias. In the absence of bias, the plot should resemble an inverted funnel. Although asymmetric funnel plots are not always related to publication bias, it is nevertheless an exploratory strategy.

3.1.3.11 Data synthesis

All statistical analyses were carried out using Rev Man 5.0 software from the Cochrane Collaboration.

Meta-analysis was undertaken for the dichotomous data with a fixed effects model using the Mantel Hanzel methods. This method of analysis has better statistical properties when the event rates are low. For each outcome the weighted RRs and corresponding 95 % confidence interval (CI) were calculated for the overall treatment effect. If one of the treatment groups has zero events, a 0.5 adjustment is automatically made to the numerator which allows the calculation of a RR. No adjustments were made to the cells for studies containing zero event rates in both the treatment and the placebo group. Unfortunately, these studies will not be included in the calculation of the weighed RR and thus will not contribute to the overall treatment effect.

The summary measure used for the continuous outcome of late luminal loss was the weighted mean difference. This was calculated with the 95 % confidence intervals. The estimate of the treatment effect was obtained using a fixed effects model and the inverse variance method. This measure reflects the fact that some of the variation of the outcome measures may be related to the patient population and not just the differences in the outcome. The data was also assumed to have a normal distribution in each arm of the studies.(58)

3.1.3.11 Subgroup Analysis and Investigation of Heterogeneity

Where data was available, subgroup analysis was preplanned for a number of variables. The first subgroup analysis was by stent type. There is increasing suggestion that all drug eluting stents may not be equivalent. The stent types were classified based on the antimitotics drug type and the presence of a polymer coating. The presence of a polymer coating may increase the inflammatory response of the arterial wall. There is porcine data that supports this, but it is not clearly an issue in humans.(34;35;90) Other meta-analyses do not handle this issue in a uniform manner. Given the large scope of this analysis, the decision was made to consider the stents that have drug eluting coatings as a separate group. The drug eluting stents of interest were initially sirolimus, sirolimus analogues (including biolimus and evolimus), paclitaxel without a polymer coating, paclitaxel with a polymer coating, and others (which included all other stents). The latter category included any studies

of agents with a primary mode of action that was anti-inflammatory, or pro-endothelialization and not antimitotic, such as heparin and dexamethasone.

The second analysis was of patient populations of similar nature initially grouped together as "on or off label" indication, then more specifically; AMI; diabetes; clopidogrel; and use of complex anatomy. Stent characteristics such as stent length per patient, reference vessel diameter and lesion length were also included.

3.1.3.12 Sensitivity analysis

In addition, a sensitivity analysis was carried for those studies that treated one lesion versus more than one lesion, and for the follow-up period. Sensitivity analysis was also carried out for methodological features such as the presence of blinding, allocation concealment and adequacy of follow-up.

3.2 Methods of systematic review of harms

3.2.1 Criteria for considering studies for this review

For inclusion into the review, studies were selected if the PICO criteria outlined below were met;

3.2.1.1 Types of studies

Any RCTs, cohorts and case reports reporting harms of DES stents at greater than one year after implantation were eligible for inclusion into the review. As many more reports than originally anticipated fulfilled these criteria, only RCT studies and cohorts with an internal control comparison group were eligible for data extraction and quantative synthesis. We required that the RCT have a mean follow-up of greater than one year. Both RCT and RCT extension studies were eligible for inclusion. Meta-analysis reports with IPD were considered eligible for inclusion into the review.

The time period of one year was chosen based on several factors. The RCT have used follow-up times of six to twelve months. Meta analyses of these studies exist that suggest that the safety of within this time period.(91) The time period beyond this is of interest, as patients receive their stents permanently and may have an ongoing need for additional therapies. Even though the literature tends to report revascularization episodes as an event in and of themselves, they represent an event in the

management of a chronic condition. The long-term risk of stenting is thus clinically relevant to both the patient and the clinician.

The cohort trials required not only the presence of a comparison group, but it needed to be an internal control group. The rationale behind this was to ensure that the patients were as similar as possible except for the type of stent used.(92;93) Although this criterion does not guarantee similarity of the groups in non-randomized studies, it improves the similarity. When examining the control group, the major factor to consider in these studies was whether or not the control group was drawn contemporaneously, either contiguously or overlapping. We felt that the groups should be exposed to the same potential medical therapy and PCI techniques, so that they should be drawn from the same time period. If the DES stents were compared to BMS stents implanted for many years prior to DES stenting medical therapy and angioplasty techniques would have changed the counterfactual ideal would not be met.

In order to ensure that known and unknown features of medical therapy were as similar as possible between the two groups, we also insisted that the study enrolled the patients within a five-year window. This was especially important for the studies that did not have overlapping enrolment periods.

Only studies satisfying the above four criteria were included in the harms analysis. In addition, studies that provide data after one year of follow-up, which do not have an internal comparator or do not satisfy the time criteria, will be collected and counted for background information.

3.2.1.2 Types of participants

The population of interest included patients who have received a coronary artery stent for the treatment of a significant, *de novo* coronary artery or coronary bypass lesion. Studies including patients with in-stent restenosis were not of interest; neither were patients who had both DES and BMS stents implanted at the index setting. Patients who had prior stents could be included in the study, as we felt that this represented a realistic situation, which is faced clinically.

3.2.1.3 Types of intervention

Drug eluting stents were the intervention of interest. If the studies divided the results by stent type, this was, although of interest, not essential for inclusion into the review. If the intervention specified other PCI techniques, such as atherectomy and rotablation, the study was excluded. If the study protocol specified any other interventions, such as intravenous or oral therapy, the interventions needed to be applied equally to each group. Unlike the efficacy portion of the review, the stent type did not need to be specified. Mixed stent types (either of DES or BMS) were allowed.

3.2.1.4 Types of comparators

The only comparator of interest was a BMS. The study could contain another treatment arm, such as medical therapy, another stent, or CABG, as long as these were present.

3.2.1.5 Types of outcome measures

Harms of interest were similar to those in the efficacy outcomes, which occur at least one year after stent placement or PCI. That is, the primary harm outcomes of interest for this review were: total death, myocardial infarction, stent thrombosis, and MACE (multiple adverse cardiac events - usually a composite of death, myocardial infarction, and target lesion revascularization). The latter was chosen, as the seed articles that we used for preparing this review contained this composite outcome. We realized that this was directly against the ARC recommendations discussed in the introduction. Soft endpoints of angina, stroke, and bleeding were also of interest, even if they were not pre-specified harms in the individual study protocols. Although we knew a priori that few studies were likely to contain these outcomes, we feel that they are clinically important and that a comment should be made, at least related to the frequency of their reporting.

3.2.2 Search methods for identification of studies

The search strategy for the harms portion of the review is stacked upon the efficacy portion of the review. This allowed the ability to screen the RCT that were identified by the search to be screened twice, for consideration of inclusion into each portion of the review. The following describes the additional modifications that were made to find studies more specifically addressing harms.

The harms search did not use a filter since filters for harms are not yet reliable. The strategy was designed for high recall of potentially relevant studies of drug eluting stents compared to bare metal stents in cardiac applications. It was developed in MEDLINE and adapted for other databases. The search was validated by confirming that it retrieved 31 relevant studies known to the investigator or identified as a study included in a relevant systematic review.(94-96) The seed articles are listed in Appendix 1. In addition, there are few MeSH terms that refer particularly to harms or adverse events, especially when related to technical procedures. The use of subheadings allows tagging of index terms so that harms may be identified. In addition, we used a combination of text words to identify harms. The full search strategy appears in Appendix 1.

There is no optimal search strategy to retrieve publications on harms. We searched using the index terms that were available in each database. The use of text words allows a highly sensitive search, at the expense of a reduction of precision. The use of free text terms was required, as there is no consistency in the range of terms for harms used to index each study. Even the use of free text terms was limited, as they apply only if the term appears in the title or the abstract of the publication.
If there were multiple publications from the same study, the study with the longest follow-up was chosen as the included study. If other outcome data of interest was found in earlier publications, it was included, with the longest study served as the source.

The bibliographies of included studies were also searched for any potential citations of interest to this review.

3.2.3 Data collection and analysis

3.2.3.1 Selection of studies

Once the database of citations was established, it was deduped and stored in Reference Manager, again with the help of an information technologist and deduping filters.

The selection of studies was carried out in two parts. For the RCT portion of the review, the RCT were selected out of the remainder of the database and screened. For the harms portion, the entire

database was screened. Essentially, the RCT were screened twice, but with different inclusion criteria for the harms and efficacy portions.

Two reviewers evaluated all citations for both the efficacy and the harms portions of the review. One was a content expert (RH) and the other was an experienced methodological expert (JP). The efficacy portion of the review was screened independently after the following training was completed for the harms portion of the review. For the harms portion of the review, the first 500 citations were reviewed independently and then together. We reviewed our choices and streamlined the study eligibility form. We reviewed the articles that each one of us selected and compared the inclusion criteria of the full text study to the abstracts. It became apparent that many abstracts qualified for inclusion, as they did not have the time frame of the outcomes reported in the Title or Abstract. This training was an important step, since the determination of the contained data about long-term harms involved a combination of content and methodological expertise.

Once the training was completed, the titles and abstracts of the citations were then reviewed independently by both RH and JP for consideration of inclusion into the review. Full text articles of potentially relevant titles and abstracts were then obtained for full text screening. The inclusion and exclusion criteria were then applied and recorded on the study eligibility sheet. In this form, the reasons for exclusion were organized hierarchically, so that they could be documented in order of importance. The form used is presented in Appendix 4. Disagreements were solved by consensus, or by GW if necessary.

The reviewers were not blinded to the authors or centres of publication, since the evidence is weak that this process would be of value, and it increases resources.(58) There was no limitation of language or year of publication.

The inclusion criteria were applied to each published report of a study. Multiple reports of a particular study were linked together. In the case of multiple publications from one study, the study which was designated as the included study was the report with the longest follow-up. All published reports of an included study were then kept on hand for abstraction of the outcomes of interest.

Once the included studies were identified, their references were scanned and evaluated for potentially includable studies. If the titles were not sufficient to make a decision about inclusion, the abstract was then obtained by PubMed search for further evaluation. If the study could not be excluded based on the abstract, the full text of the study was obtained

3.2.3.2 Data extraction

Studies that met inclusion criteria for the harms portion of the review were extracted in duplicate by RH and KP. Features of population and design characteristics were extracted to a pre-designed abstraction form in an Excel spreadsheet. Extraction was carried out independently and was collated by RH. All disagreements were solved by consensus. As previously mentioned, all publications of a study were reviewed for all of the outcomes of interest. The publications containing outcomes not included in the parent study, or containing outcomes at a different time point, were abstracted. The outcome and the year of follow-up were carefully documented. Publications of studies containing a particular subgroup of the parent study were not abstracted for data.

3.2.3.3 Assessment of methodological quality of included studies

All included studies were assessed for quality using the Newcastle Ottawa Scale (NOS). This assessment was carried out independently by RH and JP, with all conflicts resolved by consensus, and for those that could not be, by GW. The components of this scale were applied to the RCT, with extended follow-up, the cohort studies and the IPD meta-analysis. For an RCT that was selected for harms but was not eligible for inclusion in the efficacy review, the Jadad components were also assessed, as described in the methods for the efficacy review. An additional item was added to the NOS scale to determine if the study was blinded during the extended follow-up. The criteria for blinding from the Jadad score was used, and the presence of the term double blind, were required for a point in this domain.

The NOS scale components and scoring system is presented in Appendix 5. There are essentially three domains in this quality scale which primarily relate to the potential sources of bias in a cohort study. There are domains describing the selection and comparability of the intervention group and control group, and the remainders of the fields describe the quality of follow-up and ascertainment of outcomes.

Although the scale is structured for cohorts that start with a risk factor and continue follow-up until an outcome occurs, we adjusted it to apply it to extended RCT and IPD meta-analyses. We treated the initial stenting as the risk factor, and the efficacy or harms as the outcomes. The item of ensuring that the outcome of interest was not present at the beginning of the study then becomes self-fulfilling. We expected that all cohorts would score equally on this feature. Also, since internal controls were mandatory for the selection of the study, the study would score well on the selection of the cohort to be compared since they are selected from the same base population. This item was largely taken care of by the selection criteria.

The follow-up was specified by the inclusion criteria (i.e. greater than one year), so the studies also scored well on this item. A total score was not presented. There was a pre-planned analysis on the individual features of the NOS and the total score.

3.2.3.4 Measures of treatment effect

All the outcomes of interest were either dichotomous or time to event.

Dichotomous data

Where possible, the relative risk and associated confidence interval for comparing DES and BMS harms outcomes was directly extracted from the study report. If the adjusted RR (i.e. adjusted for potential confounding variables) were reported, the RR and standard deviation or confidence limits were extracted. If not reported, frequencies to calculate RR were determined wherever possible. If no denominators were given, the calculation was based on the number of patients enrolled. All count data was entered into REVMAN 5.0 where relative risks and confidence intervals were calculated.

For the collection of harms, the studies were often not clear about whether an event could occur more than once in one individual. It is unlikely that we will have events whose totals are greater that the number of patients involved in the study, given the infrequency of harms with stenting in general. The data will be collected as presented in the study, and the methods used in each study were noted.

Time to event outcomes

For time to event data, the outcome as count, dichotomous data or HR was extracted. If the data was provided only in the form of a Kaplan Meier survival curve, it was converted to relative risks using the methods of Parmar.(97) For this data, we made the assumption that the event rates were constant over time, that the censoring rate was constant over time, and that follow-up was fairly complete. The studies that did not meet these criteria were noted.

Estimates of effects

Some studies provided only a hazard ratio, which is an overall effect and not a separate measure for the intervention and the control group. These measures were derived from logistic regression in the form of HR or adjusted HR (i.e. adjusted for potential confounding variables). If studies provided this type of outcome, it was collected as well as the adjustment variables. The confidence intervals were also collected. In the absence of the presentation of these intervals, the P value or standard deviation was extracted and both converted to a standard error based on the methods of the Cochrane Handbook (58)

3.2.3.5 Unit of analysis issues

The harms portion of the review includes NRS in the form of controlled cohort studies. For patients followed for a long period of time, they could contribute more than one event to each outcome or more than one type of outcome to a composite outcome. This would represent an error. The data was collected as presented and the method used in the handling of this potential error was noted. If there was censoring of the patient to prevent them from providing another event, this was also noted. The number of patients contributing more than one event to an outcome would likely be small. Particular attention was paid to the outcome of death, as patients could only contribute to this event once.

As in the efficacy review, more than one stent may be implanted in an individual patient. This also would constitute a unit of analysis error if the outcomes are not collected at the stent level. This is similar to the issues in cluster randomization, with each patient acting as the "cluster". As with the efficacy portion, the study methods of dealing with this will be noted.

Since the time frames of harms are of interest in this review, multiple events were collected from different publications of the same study. These multiple outcomes for each study will only be presented in the analysis involving follow-up time. The outcome with the longest follow-up was presented for each study in all other analyses in order to eliminate a unit of analysis error.

3.2.3.6 Studies with multiple treatment groups

Studies with multiple treatment groups needed to be modified at the extraction level. For methods used, see 3.1.3.7.

3.2.3.7 Missing data

Authors were contacted to obtain missing data, in particular for the clinical outcomes. If no response was received, this data was left out of the analysis.

3.2.3.8 Assessment of heterogeneity

The included studies were grouped by type and the heterogeneity in each group was explored. The NRS were expected to be more heterogeneous than the RCT, owing to increased methodological diversity. Statistical heterogeneity was examined after a creating a Forest plot. The same systematic approach to exploring heterogeneity as described in the efficacy review was used.

Statistical heterogeneity was assessed using a multi-step process. Initially, the Forest Plots were examined for the lack of scatter of the confidence intervals, which suggests heterogeneity. The Chi squared test for heterogeneity was performed. Then the I^2, which describes the degree of variability which is attributable to heterogeneity statistic, was obtained. If the I^2 statistic is greater than 50 %, heterogeneity is considered moderate and it will be explored. If assessment does not yield an explanation for the increased heterogeneity, then the data will be presented using the random effects model in addition to a fixed effects model.

3.2.3.9 Assessment of publication bias

Funnel plots were used for each outcome to assess possible reporting bias.

3.2.3.10 Data synthesis

As some studies provided only relative risks based on the assumption that the data is dichotomous, and others provided data as hazard ratios without count data, the decision was made to analyze the outcome data using the inverse variance method in REVMAN 5.0. The study data was entered into the program after conversion of the risk ratio on a log scale, and calculation of a standard error from the 95 % confidence intervals. This is carried out by determining the interval between the upper and lower confidence value and dividing by 3.92, after log conversion.

Several assumptions were made in combining these data types. Hazard ratios approximate a relative risk as the follow-up period becomes more homogeneous between the intervention and the control groups. We thus made the assumption that follow-up was largely complete in the cohort studies and that censoring for reasons other than the specific outcome of interest was not a big factor. This allowed us to be able to compare the RR from the RCT to the HR, especially of the adjusted cohort studies.

There was no pooling of data of the different study types. The studies were grouped in the meta-analysis plots according to study type which included RCT, cohorts and IPD analyses. This was prespecified as the study type was anticipated to provide significant heterogeneity. The decision not to pool the data from RCT and cohort sources is supported in addition by the NRS group of the Cochrane Collaboration.(58) The cohort adjusted data and unadjusted data estimates were analyzed separately. This relates to the fact that, although biased, the unadjusted cohort data reflects the population average effect. The adjusted cohort data are described as conditional estimates and refer to an effect in observed groups with a similar covariate mix.

Data were analyzed using the fixed effects model with risk ratio and 95 % confidence intervals. Time points for analysis were combined at study end. An additional analysis was carried out at the time points of one and a half years, two years and yearly thereafter. Multiple periods of follow-up were used as it was felt that late harms may occur well after stenting.

For analysis of all other characteristics of the included studies, careful attention was paid to the inclusion of data into the analysis. Many pieces of data were retrieved from each study, sometimes at

varying time points. Where there was a choice, the data at the longest follow-up point was used. It was important to ensure that no study data was duplicated in the analysis.

3.2.3.11 Subgroup analysis and investigation of heterogeneity

The proposed subgroups for analysis, if there was adequate data, were stent length, lesion length, lesion number per patient, presence of diabetes, RVD, lesion type and the presence of single vessel disease.

3.2.3.12 Sensitivity analysis

Sensitivity analysis will be carried out using individual components of the NOS scale, the presence of blinding, as well as the year of publication, and stent type. In addition, an analysis will be carried out for length of follow-up, as we have identified this as a potential issue of heterogeneity and of particular interest to this review.

CHAPTER 4: Results of the Reviews

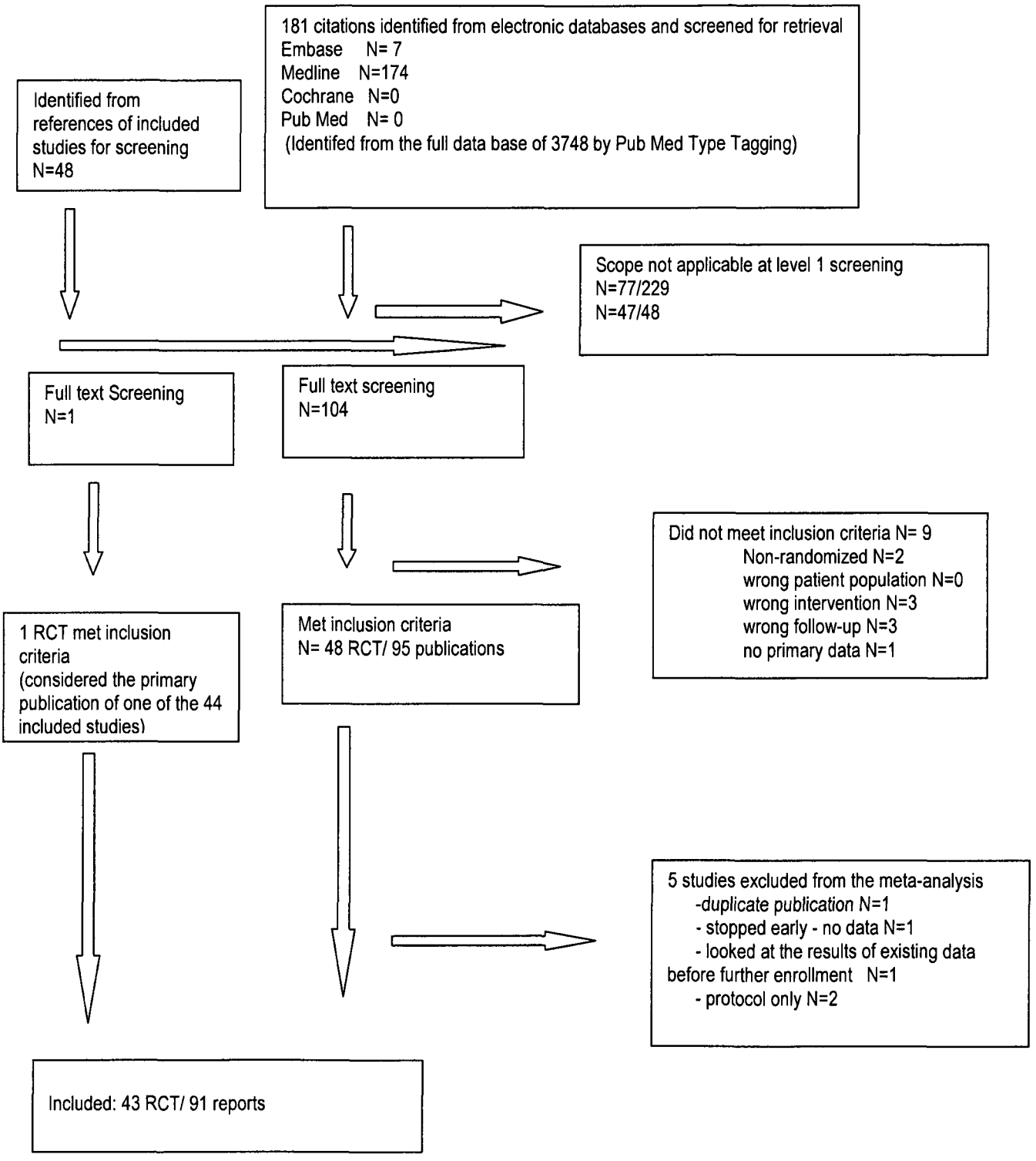
4.1 Results of efficacy review

4.1.1 Results of the search

Our search identified 181 RCT of potential relevance to our review. From the citations and abstracts, 104 studies were retrieved in full text format. Of these, 43 RCT in 91 publications of randomized trials comparing DES to BMS were included into the review. There was one duplicate publication.(98;99) The reasons for full text exclusion can be found in Figure 4.1.1.

All disagreements were solved by consensus. One additional study was included which was not found using the search strategy. This study was retrieved from the references of its companion publication.(100) It was published in a non-indexed, but peer-reviewed journal.

Figure 4.1.1 Study flow diagram for retrieval of RCT for efficacy review



4.1.2 Included studies

The 43 RCT (45;76;98-139) included 14,196 randomized patients (7,409 BMS+ 6,787 DES). All studies were reported in English. Thirty-five studies were carried out primarily in North America or Europe. Eight studies were carried out in Asia. There were four studies that randomized patients to stents with different doses of drug, and one study randomized patients to two different stent types.(118) This provided a total of 52 comparisons against bare metal stents. A table of comparisons of the characteristics (i.e. patients, intervention, and outcome) of the included studies can be found in Table 4.1.1 (Appendix 6).

4.1.2.1 Characteristics of the intervention

Of the 50 identified comparisons, there were 20 comparisons using sirolimus stents. (103;104;108;110;118;123-127;129-133;136-140) Four studies used sirolimus analogues: one with zotarolimus (98), two with biolimus (100;113) and one with tacrolimus.(116) Nineteen comparisons used paclitaxel coated stents: 12 with a coated preparation (105;107;109;112;114;118;122;134;135),one which used the paclitaxel analogue QP2:7-hexanoyltaxol coated sleeves (45) and seven with an uncoated format.(76;111;128) Two used dexamethasone in three comparisons (115;121), three used B estradiol (101;102), and two used abxicimab.(117;120)

All but one study enrolled patients with only *de novo* lesions. One study (114) included 3 % with restenotic lesions but was included because of the small percentage. One study included only *de novo* lesions occurring in saphenous vein grafts.(139)

4.1.2.2 Characteristics of the outcomes

The timing of the primary endpoints of the trials varied between three and 12 months. Twenty-six of the primary endpoints were angiographic and included the core lab measurements of late luminal loss(11), percentage of stenosis (1), mean luminal diameter (3), percent stent volume(3), restenosis (2), binary restenosis (6), and one used each of cost, IVUS, and molecular levels. Fourteen of the endpoints were clinical. Thirty-six studies had protocols that pre-specified angiographic follow-up.

Five studies allowed the treatment of more than one lesion. None of these studies provided an analysis based on this cluster design. All reported results with unit of analysis errors, by providing only patient based results for the clinical data. Data was provided for lesions for the angiographic data.

4.1.2.3 Characteristics of patients

In all the studies, there was a high rate of procedural success, usually being estimated at greater than 95 %. Almost all patients received the intervention stent. The studies included a range of reference vessel diameters ranging from 2.79-3.25 mm. The lesion length that was reported ranged from 9.58 mm in the RAVEL study (124) to 33 mm in Han 2007 (116). The stent length per patient also varied from 15mm in Park (128) to 35.15mm in Taxus IV and RRISC (134;139) studies. Not all studies reported the stent length or lesion length.

There was also clinical diversity found among the included studies, as can be seen in Table 4.1.1 (Appendix 6). The studies ranged from including patients with stable symptoms to those that had evolving STEMI. Some studies allowed the inclusion of patients with AMI and stable angina combined. Studies mostly included patients with only one lesion. Several allowed the inclusion of patients who had a non-study stent placed in a non-study artery at the index intervention.

Initially, studies allowed only patients with straightforward lesions to be enrolled. The later studies allowed patients with longer, more complex lesions requiring multiple stents. The more complex lesions were more likely to contain calcium, bifurcation lesions, and osteal lesions, and were likely to be longer. Diabetics were included in all studies with two studies including only patients with diabetes.

Co-intervention was specified in all studies. Some studies specified the use of intravenous heparin and GIIb IIIa inhibitors. All studies specified the use of ASA after the PCI. The additional use of clopidogrel or ticlopidine was also specified. The length of specified therapy lasted from two months to one year.

4.1.3 Quality assessment

The quality scores of the studies are provided in Table 4.1.1. For the domain of allocation concealment, the studies scored uniformly poorly. This is related to the strict application of the Cochrane guidelines. A point was frequently not given in two instances. The report of the use of

sealed envelopes did not receive a point, unless it was specified that they were serially numbered. A point was also not given when telephone or computer randomization was used, unless it was clearly specified that there was a central component associated with this method.

Many studies were reported as open label. When blinding was carried out, there were not enough details to assure the reader that it was appropriately carried out, so few studies achieved the additional point from the Jadad Scale. Follow-up was carried out uniformly well.

All studies except one (120) reported follow-up had losses during follow-up of >20 %. Although this is not a criterion of the Jadad scale, it is generally accepted that the retention of greater than 80 % of the randomized patients assures the reader of the absence of bias related to differential losses or attrition in general. The losses often were not described, but in most of those studies the losses were usually low.

An overall score was not assigned to the studies as this is highly discouraged by Cochrane and in the literature. However, no study achieved all possible points in the four domains.

4.1.4 Unit of analysis error

Uniformly all studies that included patients who had more than one study artery, were analyzed with a unit of analysis error.

4.1.5 Publication bias

There is an issue in the stent literature of publication bias. The funnel plots for the outcomes of death (Figure 4.1.2), MI (Figure 4.1.3), and TLR (Figure 4.1.5) are suggestive of publication bias, whereas they are less suggestive for stent thrombosis (Figure 4.1.4) and LLL (Figure 4.16). The left-hand side of the funnel plot for death and MI is truncated in all figures, which suggests that there are unpublished negative results for DES stents. For the outcome of TLR, we felt that the data was so overwhelmingly in favour of the efficacy of stents that this should not be an issue. Overall, this literature has very few reports of negative studies. There are only three RCT that report non significant findings or harms that are significant and that have led to early termination.

Figure 4.1.2: Funnel plot for the outcome of death

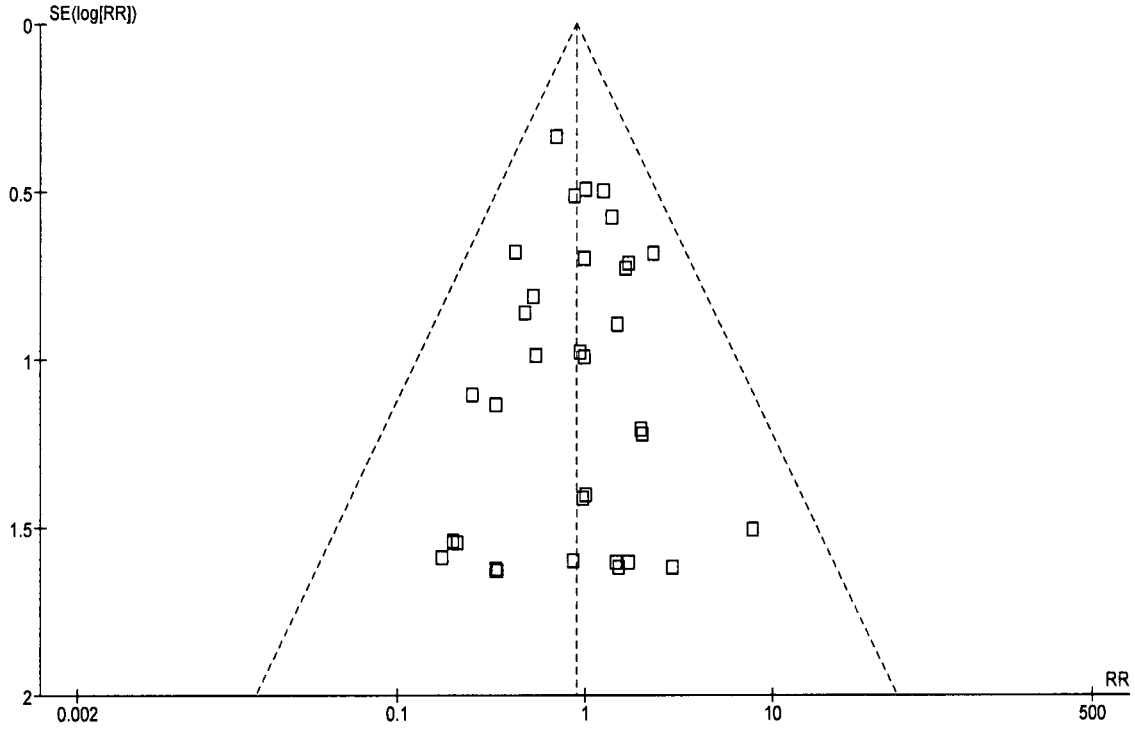


Figure 4.1.3: Funnel plot for the outcome of myocardial infarction

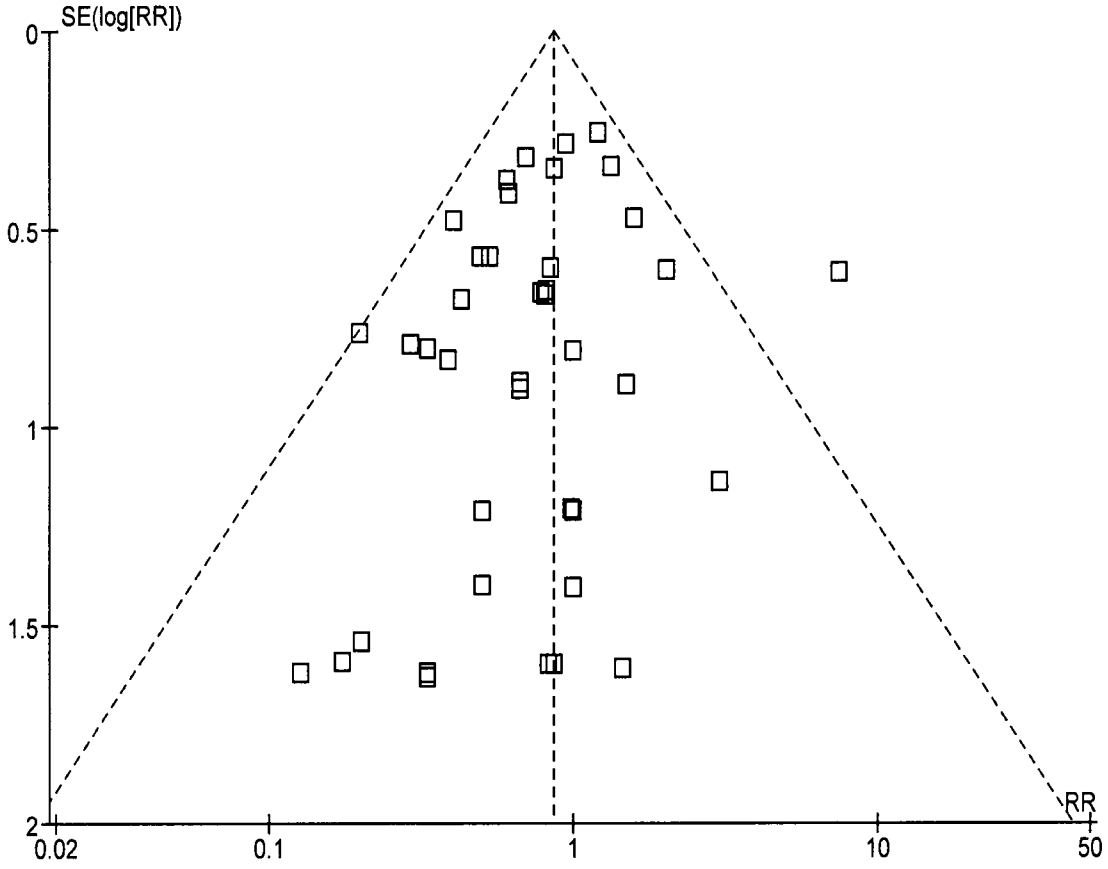


Figure 4.1.4: Funnel plot for the outcome of stent thrombosis

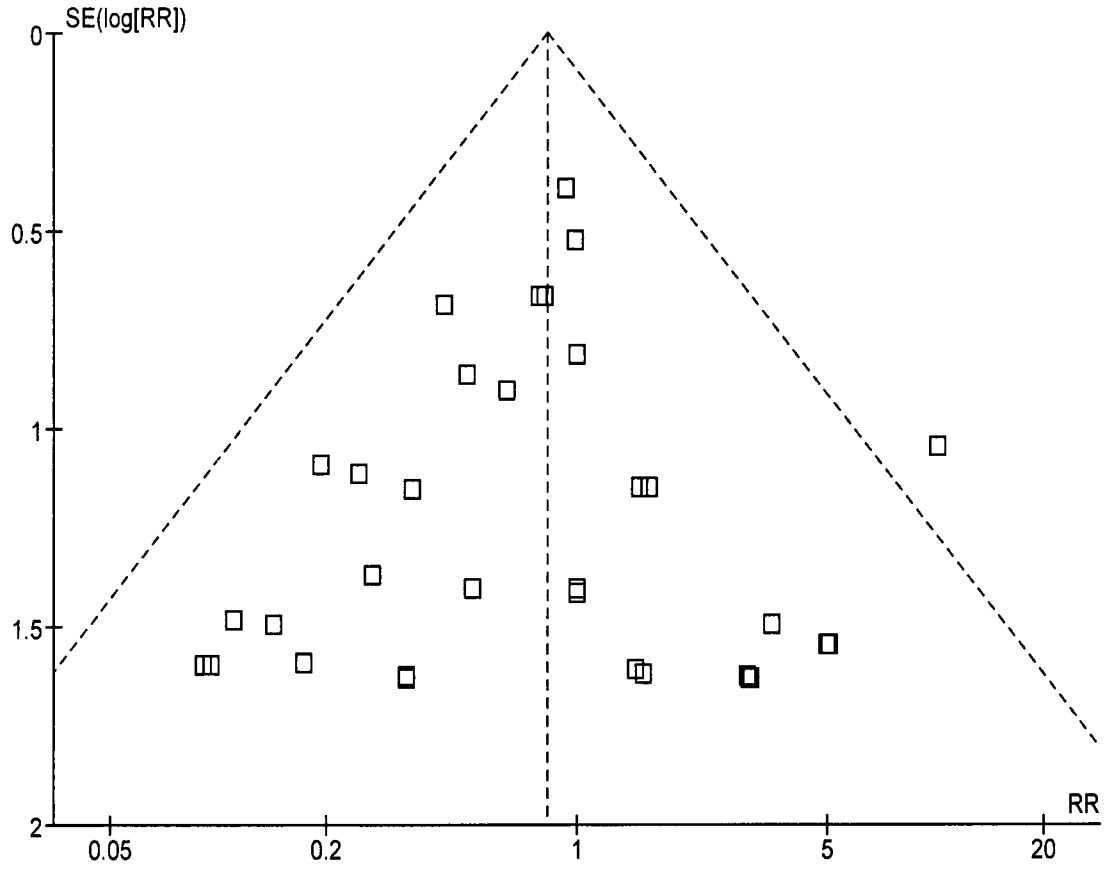


Figure 4.1.5: Funnel plot for the outcome of target lesion revascularization

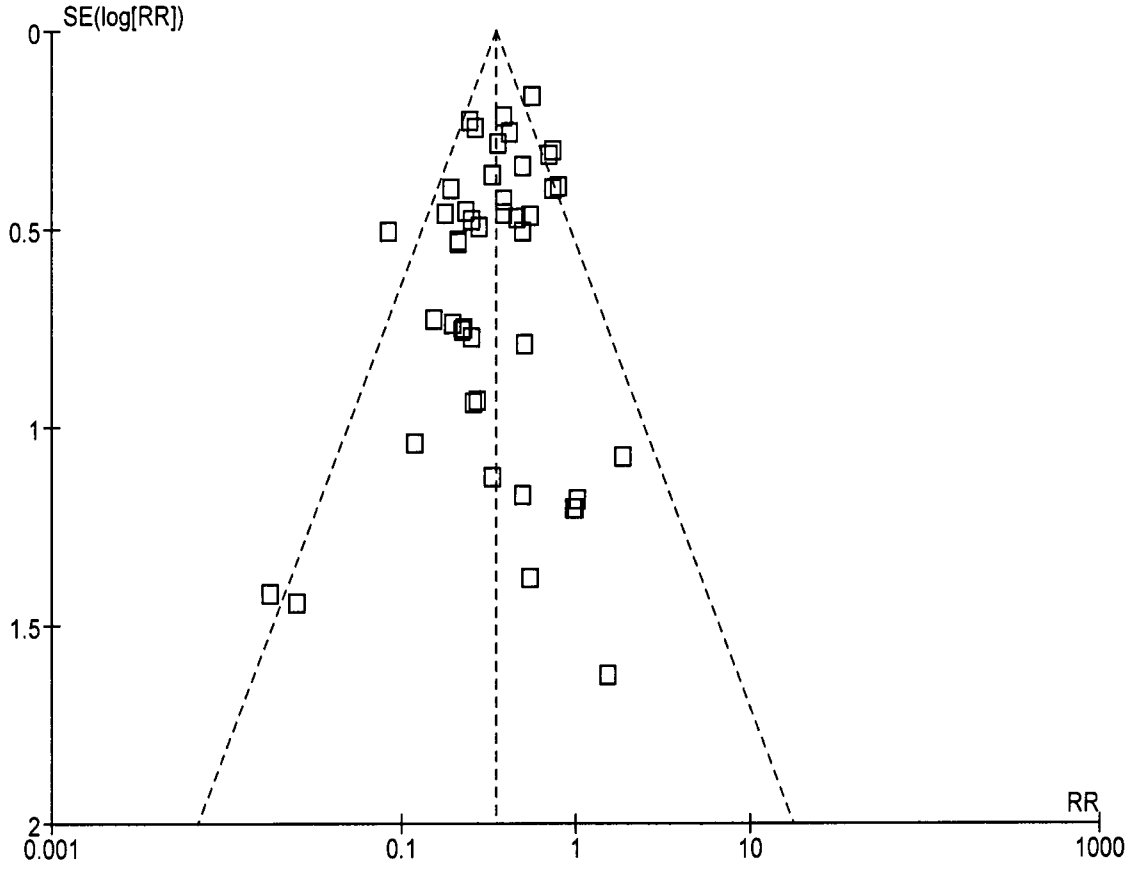
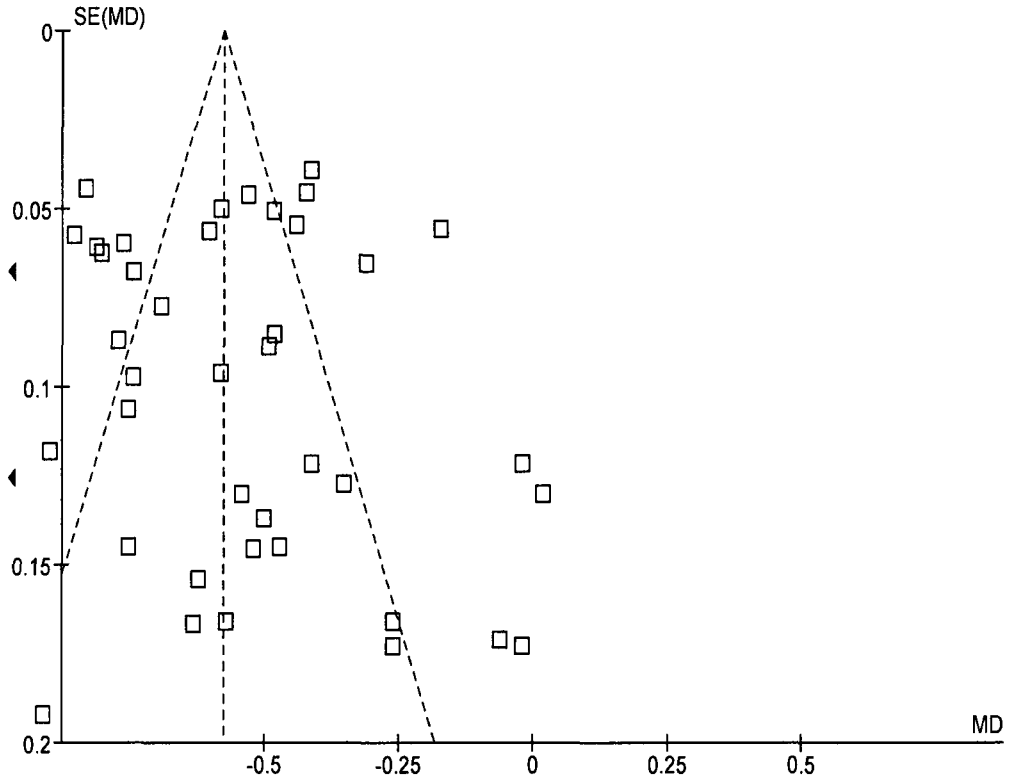


Figure 4.1.6: Funnel plot for the outcome of late luminal loss



4.1.6 Results

The following syntheses report relative risks using fixed effects comparison, unless otherwise indicated.

4.1.6.1 Death

All but one study provided information on death at the end of the study. The overall numbers of death were quite low, with 101 deaths in 6,885 patients for those receiving DES stents and 103 deaths in 6,268 patients receiving BMS. For the end of study deaths, the relative risk of death was not significant with RR=0.90 (95% CI 0.69-1.17). Figure 4.1.7

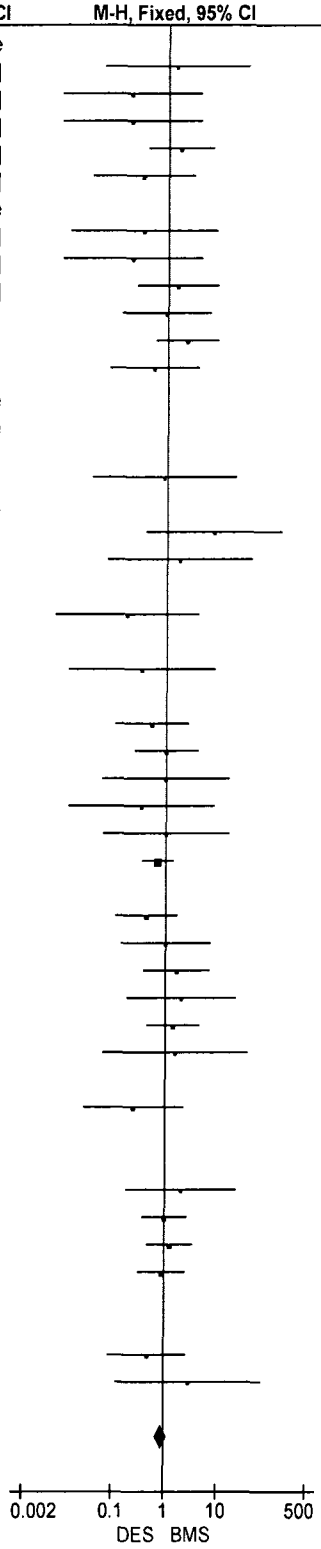
The heterogeneity was low with the I^2 =0%. The low heterogeneity is reassuring, but in this case, it is likely related to the low event rate. There was no significant trend seen for death with varying endpoints for studies of different lengths from in hospital, at 30 days, up to six months, up to nine months and at 12 months.

Figure 4.1.7: Forest plot for efficacy review outcome of death – DES vs BMS

Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
abizaid 2007 (MR)	0	29	0	15		Not estimable
abizaid 2007 (SR)	1	32	0	15	0.6%	1.45 [0.06, 33.75]
Airoldi 2005	0	54	2	54	2.2%	0.20 [0.01, 4.07]
Ardissino 2004	0	129	2	128	2.2%	0.20 [0.01, 4.09]
Baumgart 2007	5	94	3	96	2.6%	1.70 [0.42, 6.92]
Chechi 2007	1	40	3	40	2.6%	0.33 [0.04, 3.07]
Colombo 2003 (MR)	0	129	0	130		Not estimable
Colombo 2003(SR)	0	130	1	133	1.3%	0.34 [0.01, 8.29]
Dawkins 2005	0	219	2	227	2.2%	0.21 [0.01, 4.29]
Diaz 2007	3	60	2	60	1.8%	1.50 [0.26, 8.66]
Erglis 2007	2	53	2	50	1.8%	0.94 [0.14, 6.44]
Fajadet 2006	7	592	3	591	2.7%	2.33 [0.61, 8.96]
Gao 2007	2	101	2	55	2.3%	0.54 [0.08, 3.76]
Gershlick 2004 0.2µg/mm3	0	37	0	10		Not estimable
Gershlick 2004 0.7µg/mm3	0	39	0	10		Not estimable
Gershlick 2004 1.4µg/mm3	0	39	0	10		Not estimable
Gershlick 2004 2.7µg/mm3	1	37	0	10	0.7%	0.87 [0.04, 19.85]
Grube 2003 taxus I	0	31	0	30		Not estimable
Grube 2004 Score	3	126	0	140	0.4%	7.77 [0.41, 149.00]
Grube 2004b future 1	1	27	0	15	0.6%	1.71 [0.07, 39.65]
Grube 2005 Stealth	0	80	0	40		Not estimable
Grube 2006applause	0	20	1	10	1.7%	0.17 [0.01, 3.94]
Han 2006	0	67	0	25		Not estimable
Han 2007	0	100	1	100	1.3%	0.33 [0.01, 8.09]
Hong 2004	0	43	0	42		Not estimable
Kaiser Cypher 2005	3	264	3	140	3.5%	0.53 [0.11, 2.59]
Kaiser Taxus 2005	6	281	3	140	3.5%	1.00 [0.25, 3.93]
Kelbaek 2006	1	162	1	157	0.9%	0.97 [0.06, 15.36]
Kim 2006	0	48	1	48	1.3%	0.33 [0.01, 7.98]
Konig 2007	1	60	1	60	0.9%	1.00 [0.06, 15.62]
Laarman 2006	14	302	20	303	17.6%	0.70 [0.36, 1.36]
Lansky 2004	0	0	0	0		Not estimable
Menichelli 2007	3	154	7	153	6.2%	0.43 [0.11, 1.62]
Morice 2002	2	120	2	118	1.8%	0.98 [0.14, 6.87]
Moses 2003	5	533	3	525	2.7%	1.64 [0.39, 6.83]
Ortolani 2007	2	52	1	52	0.9%	2.00 [0.19, 21.38]
Pache 2005	7	250	5	250	4.4%	1.40 [0.45, 4.35]
Park 2003 1.3µg	1	58	0	29	0.6%	1.53 [0.06, 36.33]
Park 2003 3.1µg	0	59	0	29		Not estimable
Sabate 2005	1	80	4	80	3.5%	0.25 [0.03, 2.19]
Sako 2008	0	16	0	16		Not estimable
Schampaert 2004	0	50	0	50		Not estimable
Schofer 2003	2	175	1	177	0.9%	2.02 [0.19, 22.11]
Spaulding 2006	8	355	8	357	7.0%	1.01 [0.38, 2.65]
Stone 2004	9	662	7	652	6.2%	1.27 [0.47, 3.38]
Stone 2005	7	560	8	567	7.0%	0.89 [0.32, 2.43]
Strozzi 2007	0	40	0	40		Not estimable
Suttorp 2006	0	100	0	100		Not estimable
van der Hoeven 2008	2	158	4	152	3.6%	0.48 [0.09, 2.59]
Vermeersch 2006	1	38	0	37	0.4%	2.92 [0.12, 69.54]
Total (95% CI)		**6885**		**6268**	**100.0%**	**0.90 [0.69, 1.17]**
Total events	101		103			

Heterogeneity: Chi² = 18.72, df = 34 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)



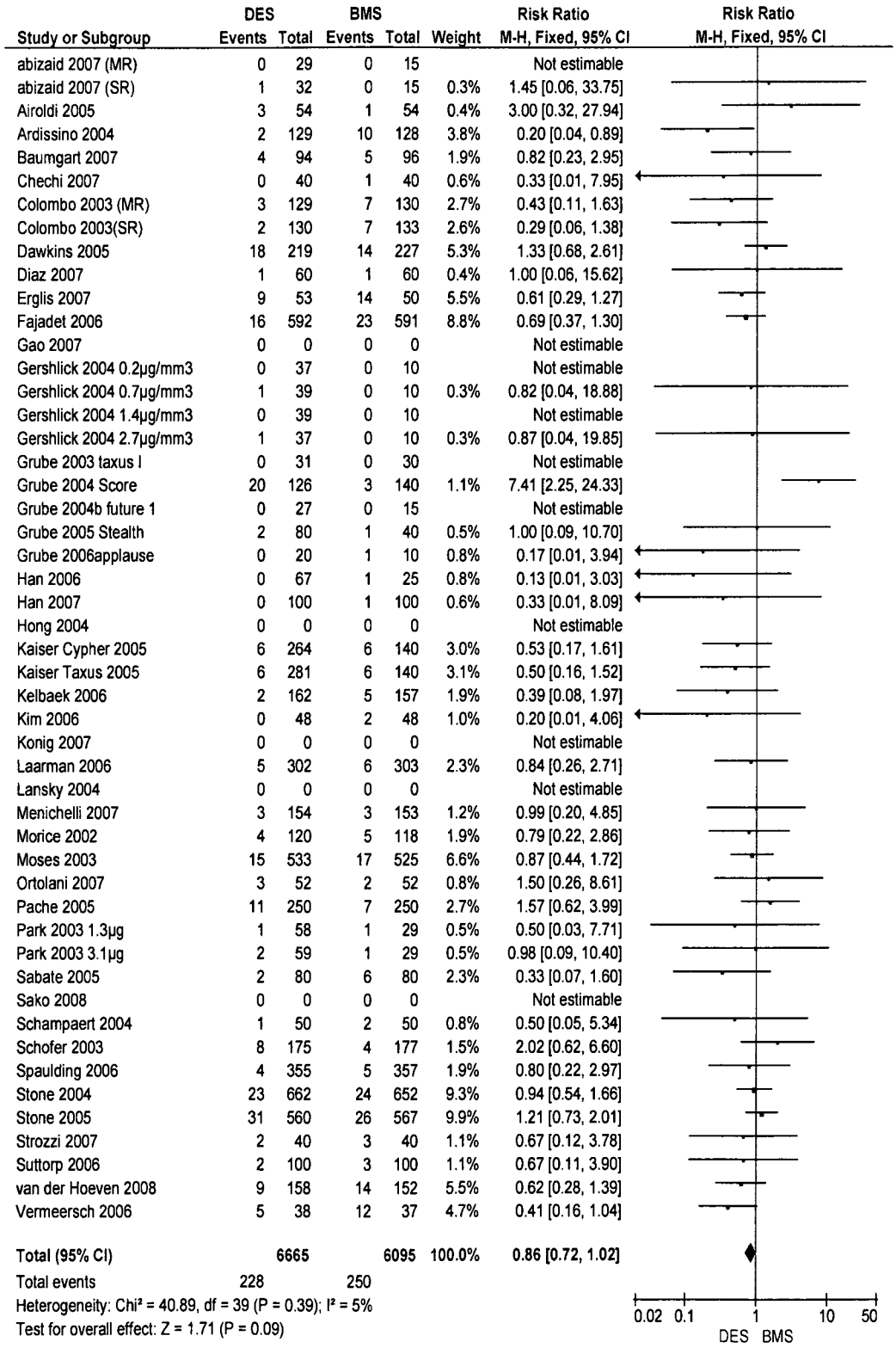
There were no effects seen for the subgroup analysis of stent type, lesion length, stent length, reference vessel diameter, inclusion of only AMI, or >30% with diabetes. Sensitivity analysis of number of lesions and quality components did not yield significant results. In addition, there is no difference seen between dosing levels of drugs for the studies that provided these. Sequential exclusion of each trial when ordered by publication date did not alter the relative risk. A summary of subgroup and sensitivity analyses in results are presented in Table 4.1.2. (Appendix 7)

4.1.6.2 Myocardial infarction

There were 45 comparisons for the endpoint of myocardial infarction. The overall rate of infarction of any type, based on the individual study definition, was less than 1 %. There were 228 events among the 6,665 patients in the DES group and 250 of 6,095 patients in the BMS group. The relative risk was not significant at 0.86 (95 % CI 0.72-1.02). (Figure 4.1.8)

There is low associated heterogeneity, represented by an I^2 of 5 %, but as reported for death, the event rate is low. There was no difference in MI when measured at different time points of in hospital, at 30 days, six months, nine months and one year.

Figure 4.1.8: Forest plot for efficacy review outcome of myocardial infarction – DES vs BMS

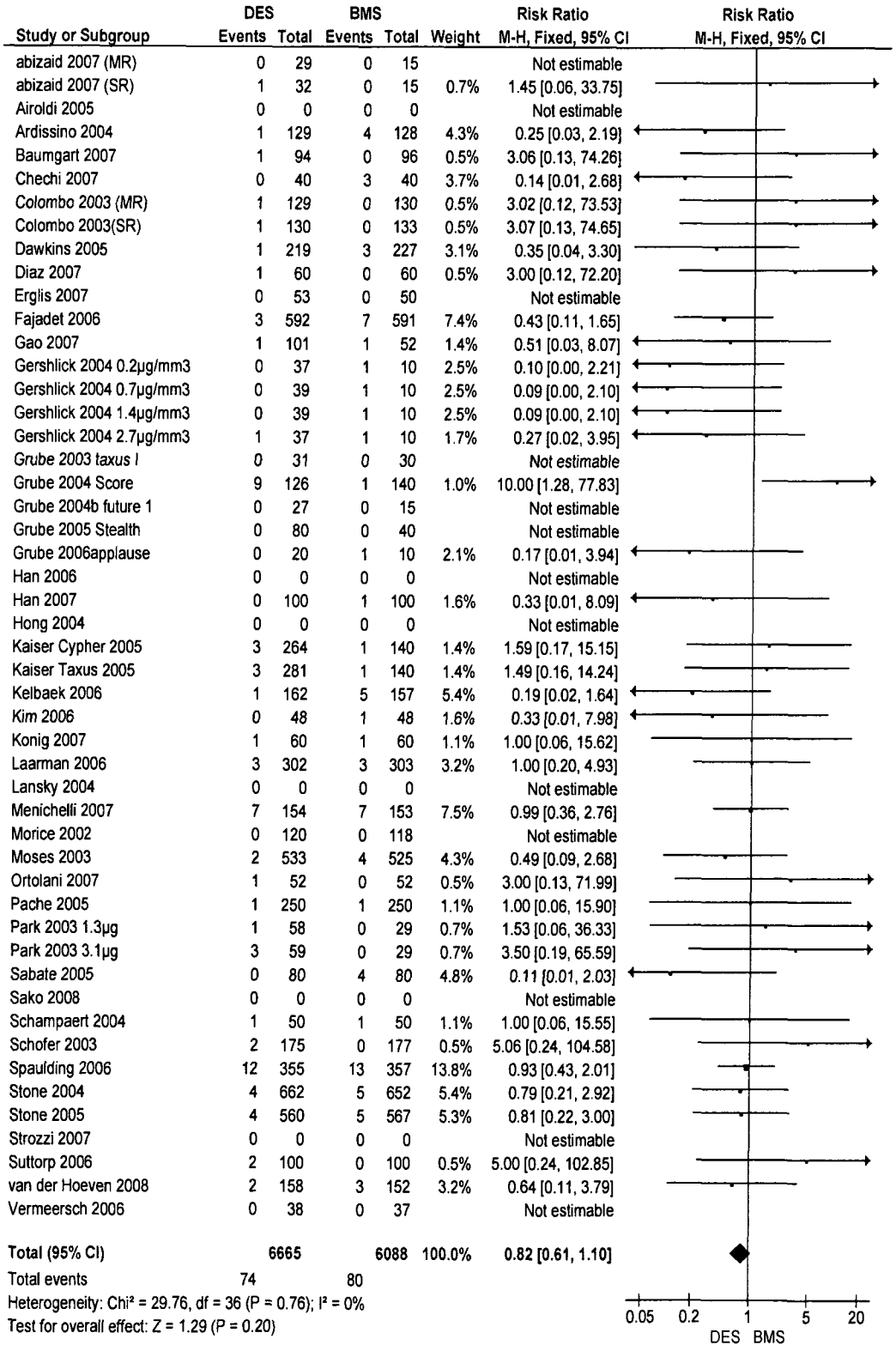


There were no effects seen for the subgroup analysis of stent type, lesion length, stent length, reference vessel diameter, inclusion of only AMI, or >30% diabetics. Sensitivity analysis of number of lesions and quality components did not yield significant results. In addition, there was no difference seen between dosing levels of drugs for the studies that provided these. Some studies had an active surveillance for post-procedural infarctions. The absolute numbers of detected infarctions was greater in these studies, but the relative risks remained consistent with those that did not have such a detection system. Sensitivity analysis for the presence of active surveillance did not demonstrate a significant effect. Subgroup and sensitivity analyses are given in Table 4.1.3. (Appendix 7)

4.1.6.3 Stent thrombosis

There were 44 comparisons of the studies that provided information on this endpoint. The overall rate of stent thrombosis pooled at study end, using the on-study definitions, was exceeding low, with only 74 events of 6,665 in the DES stent group and 80 events of 6,088 in the BMS stent group. The relative risk of events in the DES versus BMS was non significant 0.82 (95% CI 0.61-0.1.10). The heterogeneity was low with an I^2 of 0 %. (Figure 4.1.9)

Figure 4.1.9: Forest plot for efficacy review outcome of stent thrombosis – DES vs BMS



There were no effects seen for the sub-group analysis of lesion length, reference vessel diameter, inclusion of only AMI, or >30% diabetics. Sensitivity analysis of number of lesions and quality components did not yield significant results. In addition, there is no difference seen between dosing levels of drugs for the studies that provided these. Analysis of stent type demonstrated an increase in stent thrombosis for the dexamethasone stent, and a trend towards greater stent thrombosis for the paclitaxel stent without coating. Stent length >18 mm and number of stents > 1 demonstrated a trend that these factors were important for stent thrombosis.

The definition of stent thrombosis varied between studies. The primary analysis was based on the trial reported definition. The listings of comparisons that were carried out and the results are presented in Table 4.1.4. (Appendix 7)

4.1.6.4 Target lesion revascularization

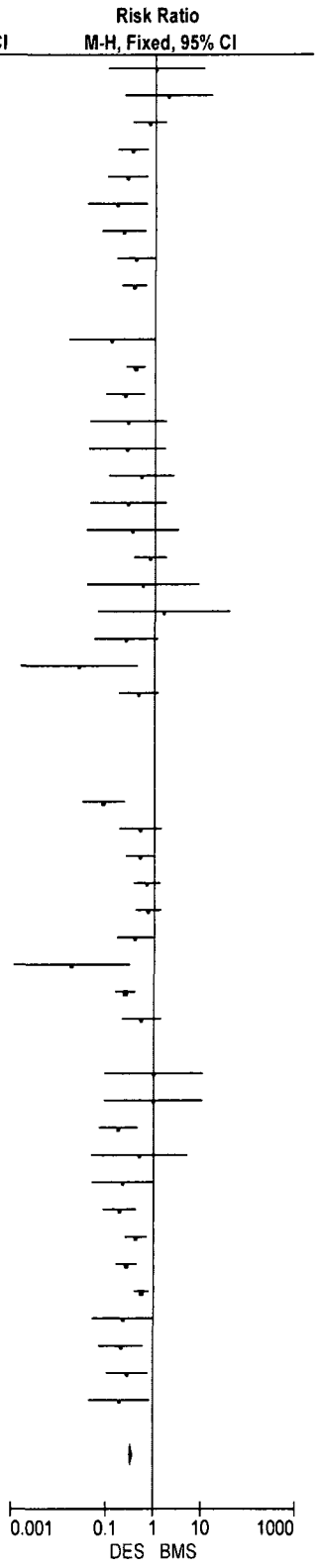
The overall rate of TLR is reported for all but four studies. TLR is the "clinical tip of the iceberg" for the process of restenosis in the stent.(72) In spite of the attention that the additional events of revascularization receive (5;27;141), the number of revascularizations is low, occurring in 330 of 6,509 DES patients and at 904 of 6,153 BMS patients. The relative rate of revascularization overwhelmingly favors drug eluting stents with pooled RR =0.35 (CI 95% 0.31, 0.39). There is mild to mild heterogeneity with an I^2 of 34 %. (Figure 4.1.10)

Figure 4.1.10: Forest plot for efficacy review outcome of target lesion revascularization

Study or Subgroup	DES Events	DES Total	BMS Events	BMS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
abizaid 2007 (MR)	2	29	1	15	0.1%	1.03 [0.10, 10.51]
abizaid 2007 (SR)	4	32	1	15	0.1%	1.88 [0.23, 15.37]
Airoldi 2005	9	54	12	54	1.3%	0.75 [0.34, 1.63]
Ardissino 2004	9	129	27	128	2.9%	0.33 [0.16, 0.68]
Baumgart 2007	5	94	20	96	2.1%	0.26 [0.10, 0.65]
Chechi 2007	2	40	13	40	1.4%	0.15 [0.04, 0.64]
Colombo 2003 (MR)	4	129	19	130	2.1%	0.21 [0.07, 0.61]
Colombo 2003(SR)	6	130	16	133	1.7%	0.38 [0.15, 0.95]
Dawkins 2005	15	219	43	227	4.6%	0.36 [0.21, 0.63]
Diaz 2007	0	0	0	0		Not estimable
Erglis 2007	1	53	8	51	0.9%	0.12 [0.02, 0.93]
Fajadet 2006	27	592	70	591	7.6%	0.39 [0.25, 0.59]
Gao 2007	6	101	14	55	2.0%	0.23 [0.10, 0.57]
Gershlick 2004 0.2µg/mm3	2	37	2	10	0.3%	0.27 [0.04, 1.69]
Gershlick 2004 0.7µg/mm3	2	39	2	10	0.3%	0.26 [0.04, 1.60]
Gershlick 2004 1.4µg/mm3	4	39	2	10	0.3%	0.51 [0.11, 2.41]
Gershlick 2004 2.7µg/mm3	2	37	2	10	0.3%	0.27 [0.04, 1.69]
Grube 2003 taxus I	1	30	3	30	0.3%	0.33 [0.04, 3.03]
Grube 2004 Score	10	126	14	140	1.4%	0.79 [0.37, 1.72]
Grube 2004b future 1	1	27	1	15	0.1%	0.56 [0.04, 8.26]
Grube 2005 Stealth	1	80	0	40	0.1%	1.52 [0.06, 36.46]
Grube 2006applause	2	20	4	10	0.6%	0.25 [0.05, 1.14]
Han 2006	0	67	7	25	1.2%	0.03 [0.00, 0.43]
Han 2007	6	100	13	100	1.4%	0.46 [0.18, 1.17]
Hong 2004	0	0	0	0		Not estimable
Kaiser Cypher 2005	0	0	0	0		Not estimable
Kaiser Taxus 2005	0	0	0	0		Not estimable
Kelbaek 2006	4	162	46	157	5.1%	0.08 [0.03, 0.23]
Kim 2006	5	48	10	48	1.1%	0.50 [0.18, 1.35]
Konig 2007	10	60	20	60	2.2%	0.50 [0.26, 0.98]
Laarman 2006	16	302	23	303	2.5%	0.70 [0.38, 1.29]
Lansky 2004	18	524	24	516	2.6%	0.74 [0.41, 1.34]
Menichelli 2007	7	154	18	153	2.0%	0.39 [0.17, 0.90]
Morice 2002	0	120	27	118	3.0%	0.02 [0.00, 0.29]
Moses 2003	22	533	87	525	9.5%	0.25 [0.16, 0.39]
Ortolani 2007	6	52	11	52	1.2%	0.55 [0.22, 1.37]
Pache 2005	0	0	0	0		Not estimable
Park 2003 1.3µg	2	58	1	29	0.1%	1.00 [0.09, 10.58]
Park 2003 3.1µg	2	59	1	29	0.1%	0.98 [0.09, 10.40]
Sabate 2005	5	80	28	80	3.0%	0.18 [0.07, 0.44]
Sako 2008	1	16	2	16	0.2%	0.50 [0.05, 4.98]
Schampaert 2004	2	50	9	50	1.0%	0.22 [0.05, 0.98]
Schofer 2003	7	175	37	177	4.0%	0.19 [0.09, 0.42]
Spaulding 2006	20	355	48	357	5.2%	0.42 [0.25, 0.69]
Stone 2004	20	662	74	652	8.1%	0.27 [0.16, 0.43]
Stone 2005	49	560	89	567	9.6%	0.56 [0.40, 0.77]
Strozzi 2007	2	39	9	40	1.0%	0.23 [0.05, 0.99]
Suttorp 2006	4	100	19	100	2.1%	0.21 [0.07, 0.60]
van der Hoeven 2008	5	158	17	152	1.9%	0.28 [0.11, 0.75]
Vermeersch 2006	2	38	10	37	1.1%	0.19 [0.05, 0.83]
Total (95% CI)		**6509**		**6153**	**100.0%**	**0.35 [0.31, 0.39]**
Total events	330		904			

Heterogeneity: Chi² = 67.17, df = 44 (P = 0.01); I² = 34%

Test for overall effect: Z = 17.13 (P < 0.00001)



When the stent subgroups are analyzed, there is a variation in effect size by the stent type associated with a reduction in this low heterogeneity and there was a greater reduction in TLR in the SES stents. The SES analogue stents and paclitaxel stents with coating had the next greatest reduction, followed by those with paclitaxel and no coating, the dexamethasone stents, and abxicimab stents.

There was no significant influence of the subgroups with lesion length, stent length, studies that included >30% diabetics, RVD, study length; the sensitivity analysis for quality components demonstrated no difference. There was a non significant trend for a benefit in the outcome of TLR for the studies where more than one lesion was stented.

A pre-specified analysis of whether there was a specified follow-up angiogram was carried out. We felt that it was possible that there would be a greater rate of TLR in studies that pre-specified a follow-up angiogram versus those that used only clinical endpoints. This was not the case however, as there was no significant difference between these endpoints during analysis. The subgroup analyses carried out and the results are found in Table 4.1.5. (Appendix 7)

4.1.6.5 Late luminal loss

For this outcome, seven of the 43 studies did not provide follow-up angiographic data. All stent dosing subgroups were included within the analysis. The overall reduction of late luminal loss was given by the WMD of -0.58mm (CI 95% -0.61, -0.56) in the DES compared with the BMS group. This indicates that there was a significant reduction in the mean difference between the late luminal loss of the DES stent when compared to the BMS stent. DES stents are thus more effective in reducing restenosis. However, there is significant heterogeneity with an I^2 of 88 %.

Subgroup analysis did not demonstrate significant changes in the WMD and the heterogeneity remained high in all analyses. Heterogeneity was further explored by influence analysis.(89) There was no significant effect of removing each study by publication date. However, when the studies were ordered by weight prior to the influence analysis, it was apparent that the four studies with the largest weight were important in producing significant heterogeneity. When these four studies – Stone 2005, Stone 2004, Moses 2003 and Fajadet 2006 – were then examined, an important trend was seen. The study of greatest weight was Stone 2005. In comparing the two studies of Stone 2004 and Stone 2005,

there was a significant difference in the outcomes. These studies were essentially the same, apart from a variation in the patient population, with Stone 2005 enrolling patients who were slightly more complex. Although Stone set out to enroll more complex patients, the final result was that there were slightly more patients with type C lesions and the lesions were longer by 3 mm. There were also more patients with a presentation of unstable angina. In addition the I^2 is moderate to high at 75 %.

Moses 2003 had the second largest weight. The heterogeneity between Moses 2003 and Stone 2005 studies is 98 %. Interestingly, the studies are fairly similar in patient population and lesion characteristic. Moses 2003 used a SES stent with three months of clopidogrel and Stone 2005 used a coated Paclitaxel stent with six months of clopidogrel. We felt that the most significant difference between these studies was the stent type used, as the clinical differences were small.

During the influence analysis, we also noted that the effect size seen in Fajadet 2006 which used an SES analogue was not as significant as Moses 2003 an SES study. This suggested that the analysis of the SES stent type and its analogues was better carried out by separating these stent types.

In spite of remaining heterogeneity in some stent categories, no other manoeuver altered the overall heterogeneity at all. After the influence analysis, the subgroup analysis was then carried out re-categorizing the studies by exact stent type. This rendered the category of "other" obsolete.

When the studies were more grouped strictly by type, a significant effect of the stent type was observed in Figure 4.11. When pooled, the abxicimab, B-estradiol, and dexamethasone stents had an I^2 of 0 %. There was a significant reduction of heterogeneity in the remaining stent types. The heterogeneity for the stent types of paclitaxel with coating, paclitaxel without coating and sirolimus were, however, still high and need to be further explored.

There were also important and highly statistically significant effect differences observed between subgroups of stent types. The SES stent were more effective at reducing late luminal loss than both the SES analogue and PES with coating. The PES with coating was also more effective than the PES without coating. There was a significant difference for subgroup differences between stents using the

new classification, with a $p < 0.00001$. This can be appreciated by the lack of overlap of the confidence intervals of summary WMD between the stents.

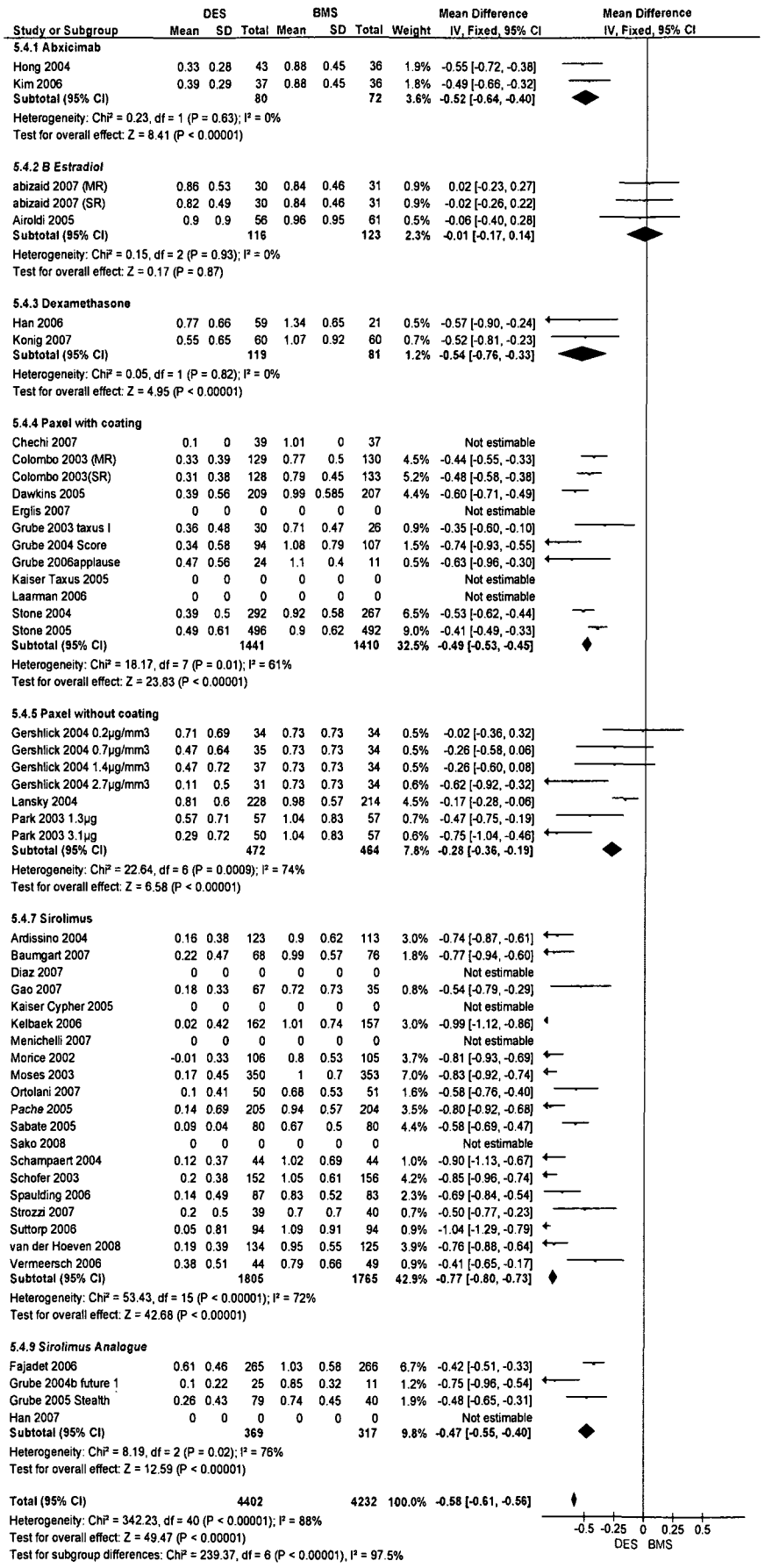


Figure 4.1.11: Forest plot for efficacy review outcome of late luminal loss

Given the differences in stent types, the subgroup analysis and exploration of any residual heterogeneity were reported by stent type and are presented in the following sections.

4.1.6.5.1 Abxicimab stent

There were two studies that used an abxicimab coated stent. Both studies demonstrated significant reduction in late luminal loss, with a pooled LLL of -0.52mm (95% CI -0.64 to -0.40). The heterogeneity was low with an I^2 of 0. Investigation by preplanned subgroups and sensitivity analysis did not yield any significant findings, partly related to the lack of heterogeneity and partly related to the small number of studies.

4.1.6.5.2 B-Estradiol stent

Two studies, one with two different doses of estradiol, provided information on late luminal loss. Overall, there was no significant reduction on late luminal loss for any of the comparisons. The WMD of LLL is -0.01mm (95 % CI -0.17 to 0.14) with an I^2 of 0 %. Investigation by preplanned subgroups and sensitivity analysis did not yield any significant findings, partly related to the lack of heterogeneity and partly related to the small number of studies.

4.1.6.5.3 Dexamethasone stent

Two studies provide information on late luminal loss. There is a significant reduction on late luminal loss in both studies. The WMD was -0.54mm (95 % CI -0.76, -0.33) with an I^2 of 0 %. Investigation by preplanned subgroups and sensitivity analysis did not yield any significant findings, again, partly related to the lack of heterogeneity and partly related to the small number of studies.

4.1.6.5.4 Paclitaxel stent with coating

Of the 12 comparisons of patients receiving stents where paclitaxel is coated onto a polymer, three studies did not report results on a follow-up angiogram, and one did not present sufficient data to calculate a standard error. The overall WMD of late luminal loss is -0.49mm (95 % CI -0.53, -0.45), using the fixed effects analysis and -0.51mm (95 % CI -0.58, -0.44) with the random effects analysis. As previously described, this was significantly less than the results obtained for the SES stents. The heterogeneity was moderate with an I^2 of 61 %. The heterogeneity is generated largely by Grube 2004

SCORE, which contributes 14 % to the overall heterogeneity. This stent uses a unique coating system where the drug is impregnated into a band around the stent. It gives the greatest reduction in LLL in this group. This finding suggests that the type of coating used, as well as the drug type, will affect overall stent performance. Additional heterogeneity is provided by Stone 2005, which is the only study reporting data that enrolled patients with complex lesions.

Exploration of subgroups demonstrated methodological diversity, with a larger effect estimate for those studies with adequate allocation concealment and a smaller effect estimate for those with adequate blinding. (Table 4.1.6 in Appendix 7) There is no significant difference in outcome for studies enrolling >30% diabetics, lesion length, stent length, or study length. There were no studies in this stent type that enrolled patients with RVD <2.5. There was no reported data for those studies that enrolled patients with AMI or left mainstem lesions. Stone 2005 represents complex anatomy of the studies analyzed. This study has already been discussed, as the benefit on WMD on the outcome of late luminal loss is not as great as when patients were enrolled with more straightforward lesions. For the study that randomized patients to either slow release or moderate release stents, there was no significant difference in the effect on late luminal loss.

4.1.6.5.5 Paclitaxel stent without coating

Studies grouped in the stent type that have paclitaxel applied directly to the stent present a number of features that suggest significant clinical heterogeneity. Two of these studies dosing studies. Park (128) used two doses of paclitaxel and Gershlick (111) used four doses. When similar doses were compared, there is a similarity in effect on late luminal loss. There was also less of an effect as the dosing of paclitaxel decreases. The smallest dose, or 0.2 µg/mm3, had no significant effect on late luminal loss.

When compared as a group, the stents that were coated with paclitaxel do not reduce LLL to the same extent as the stents that are coated and then mounted with paclitaxel. This difference is highly statistically significant with $p<0.00001$. When (128) compared to studies of paclitaxel which has been loaded on a coating, the higher drug doses perform as well as the coated stents, suggesting that the dosing studies should not be combined together in one analysis.

There were two sources of significant heterogeneity in this group of studies. There was significant heterogeneity generated by the stents with the highest dose of paclitaxel applied to the stent. If these studies were removed the remainders of the studies were homogeneous, and the I^2 falls.

Lansky 2004 used the stainless steel Multi Link PENTA stent, a different stent platform than the other studies in this group. Although the dose density of paclitaxel used on this stent is thought to be similar to other doses in this group, the performance on LLL is much poorer. The complexity of stenting was demonstrated in this subgroup, as the effect of the drug on restenosis was substantially different, even though the drug density on the stent is fairly similar. This suggests that the dose of paclitaxel used on the stent of Lansky 2004 does not have the same availability or effect as the stents with the other types of coating. Subgroup and sensitivity analysis and a list of the analyses performed are presented in Table 4.1.7 (Appendix 7).

4.1.6.5.6 Sirolimus

Data was provided on late luminal loss for 16 of the 20 comparisons involving sirolimus stents. The WMD was dramatic at -0.77 mm (95 % CI -0.80 to -0.73), suggesting a significant efficacy benefit to SES. The heterogeneity was moderate reflected by an I^2 of 72 %. Using the random effects analysis, the WMD is still dramatic at -0.75 mm (95 % CI -0.82 to -0.68) with an I^2 of 72 %.

Exploration of this heterogeneity yielded several observations. The benefit of SES stents does not change with the length of time after the procedure. For the studies that allowed stenting of only one study vessel, there was a sustained significant benefit on late luminal loss at WMD =-0.79mm (95 % CI -0.83 to -0.74), with a low I^2 of 24 %. For the three studies allowing more than one study vessel, the benefit is lost with WMD -0.65 (95 % CI -0.73 to 0.57), but with a high I^2. These later studies included patients with only SVG lesions, and diabetics with a small RVD. The studies allowing more than one lesion likely represent a surrogate for patients with more advanced disease.

Studies that contained more than 30 % diabetics also did worse than those with fewer diabetics. In two studies within the SES group, the RVD was less than 2.5 mm. Within this group, there is a significant reduction in overall late luminal loss compared with the remaining studies where the RVD

was greater than 2.5 mm. Both of these results are significant. There was no difference in any of the stent groups for the subgroups of stent length. Lesion length or the methodological parameters of allocation concealment and of the presence of blinding did not demonstrate significant findings. This is likely related to the absence of proper reporting of these study features and not to their absence in the study conduct.

When the SES studies are grouped on clinical similarity based on the FDA definitions of "on label" versus "off label" use, a significant pattern emerged. The "on label" definition had a WMD in late luminal loss of -0.81 mm (95 % CI-0.86 to -0.76) compared with - 0.73 mm (95 % CI -0.77 to -0.68) for the "off label" indications. Further exploration of effect by clinical group demonstrated that studies which enrolled only patients with AMI had less late luminal loss, as well as studies enrolling patients with only SVG and those enrolling only people with diabetes.

The patients grouped as "off label" patients consisted of a variety of clinical types. The study that included only total occlusions versus stents, including all comers (which represents real world practice), demonstrated the greatest LLL. In these two groups, the effect size was great, which was related not only to the dramatic benefit of the DES stents at preventing restenosis, but also to the poor performance of the BMS stent. The LLL at study end in the DES group was 0.05 mm (SD .81); however, the LLL for the BMS group was 1.01 mm (SD 0.74), which is much worse than that achieved in many of the control groups of other studies.

Keelbaek (119) performed its follow up angiogram at six months, which confirms the poor performance of the BMS stents in this patient population even early on. Sabate (129) also performed poorly, but this study combined diabetic patients and patients with a small RVD and the presence of multi-vessel disease. These factors are all known to be related to restenosis. For presentation of the subgroup and sensitivity analysis performed and the results see Table 4.1.8. (Appendix 7).

In summary, the heterogeneity observed in the sirolimus group is related to the diversity of clinical populations. There is a gradient of benefit in these studies based on the relative complexity of the lesion stented and risk factors of the patient. In addition, as we are using a difference score as our

overall effect measure, the overall benefit is related to the performance of the DES stent relative the BMS stent in any given population.

4.1.6.5.7 Sirolimus analogues

Of the four studies using sirolimus analogues, three provided data on LLL. The WMD of the late luminal loss is -0.47 mm (95 % CI -0.55 to -0.40). This benefit on LLL was significantly less than that seen with the sirolimus stent. There was significant heterogeneity with an I^2 76 % between these studies. The heterogeneity is accounted for by the Future 1 study, with it falling to 0 % with its removal. In this group, Grube Stealth used Biolimus analogue, and Fajadet (98) and Grube Future 1 (113) used Everolimus analogue. However, the follow-up angiogram was at six months in Grube Future 1 and at nine months in Fajadet. This by itself is a possible explanation of the remarkable reduction in late luminal loss, not only in the DES group but also in the BMS group in Grube Future 1.

The domains of quality were equally poor for all three studies. There were no significant findings for the clinical parameters of stent length, lesion length, and number of amount of patients with diabetes, RVD, and patient characteristics.

4.1.6.6 Specialized subgroups

Stent performance was examined based on the baseline characteristics of the patient. The specialized subgroups were diabetes, STEMI, renal failure and heart failure.

There was no significant effect of diabetes on the endpoints of death, myocardial infarction, or stent thrombosis. There was also no evidence that TLR or LLL was worsened by diabetes. There were, however, only seven trials that included a significant number of diabetics. The analysis was made more difficult by one study that, although it included only diabetics, the average RVD was <2.5 mm. In Baumgart 2007 (104), the inclusion of diabetics with higher RVD did not suggest greater restenosis.

For the studies that enrolled only patients presenting with STEMI, there was no increase in the harms of death, myocardial infarction and stent thrombosis. For the SES stent type, there was a significant reduction in the efficacy of stenting on the outcome of TLR and LLL. This suggests that this group of

patients have an increase in neointimal formation within the stent itself. There was still significant efficacy of the SES stent in this clinical situation.

Most studies had active exclusion criteria for patients with advanced renal failure and heart failure, and as such, there were not enough studies enrolling patient with renal failure or heart failure to be able to discern the benefits or harms of stenting. In addition, there were no included studies of patients with significant triple vessel disease.

There were few studies on the specialized group of patients of interest. One study included only patients with SVG lesions and one included patients with left mainstem lesions. Both these studies have short follow-ups at six months. There is significant efficacy in these clinical situations, but the reduction of LLL and TLR were not as great as for the baseline population. There was, however, no increase in death, MI or ST in these subpopulations.

4.1.6.7 Other outcomes

Other outcomes of interest included anginal status, stroke and bleeding complications. Few studies reported such outcomes. In total, there were no strokes reported in one study, three bleeding complications (one leading to death), and three studies reporting on anginal symptoms at study end. There was no reporting in this literature of the existence of greater harms associated with greater intervention in the BMS group.

4.2 Results of harms review

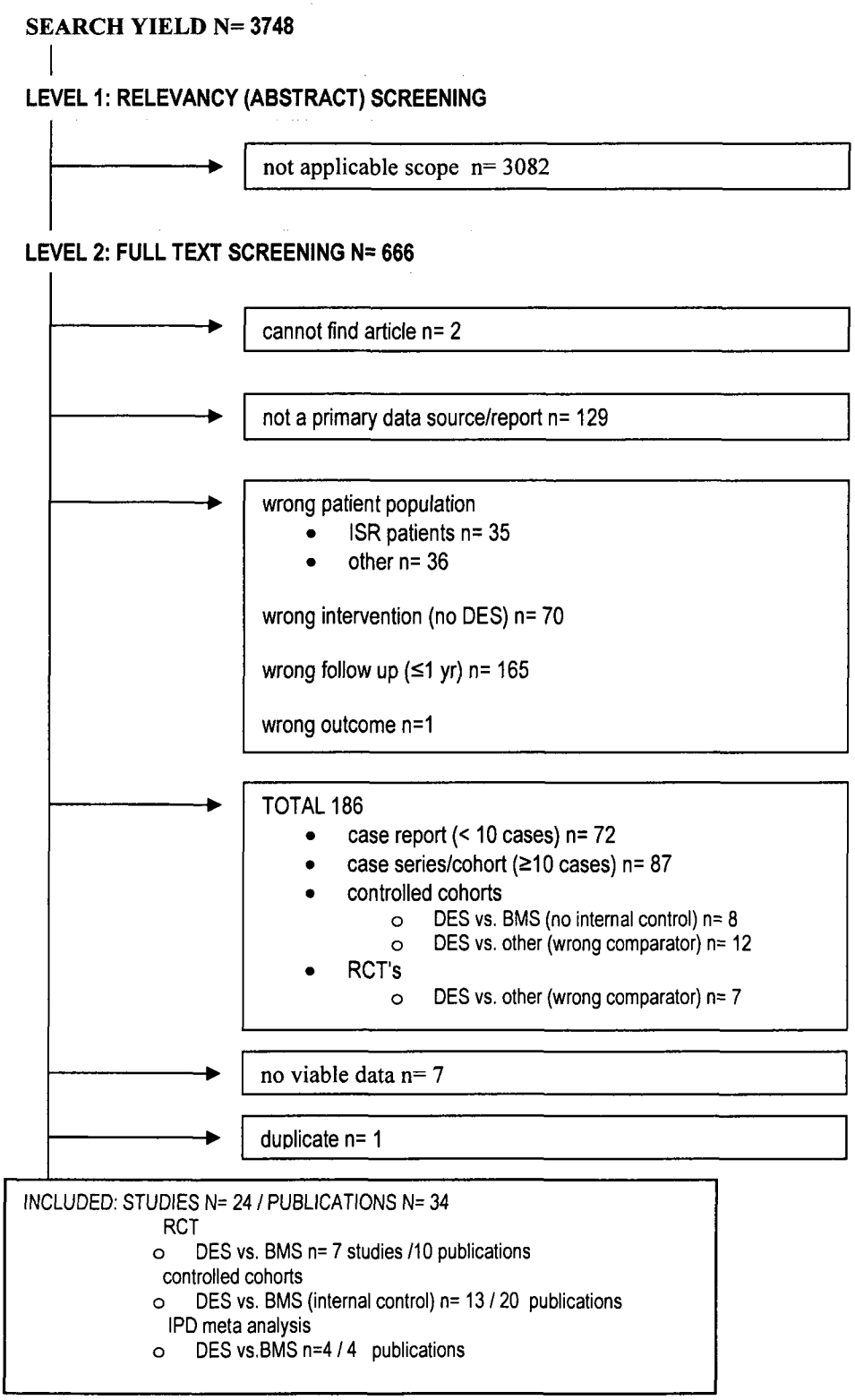
4.2.1 Results of the search

Our search yielded 3748 citations. Of these, 666 were chosen for full text review. After full text review, 24 studies (52;53;57;96;98;99;133;142-159) which were published in 34 reports met our final inclusion criteria and were included into the review. The reasons for exclusion are given in the flow diagram in Figure 4.2.1. The most common reason for exclusion was the absence of a description of the time of the reported results in the abstract.

A large number of studies did not meet the study type criteria required for analysis, but did meet the clinical inclusion criteria. There were 72 case reports, 87 case series, 12 controlled cohorts, eight cohorts without internal controls and seven RCT which described late harms of DES stenting. Of the included trials, one study was referred to by two citations which described the same results in English. This was considered a duplicate publication, and the first publication was considered in the review.

The 24 included studies consisted of seven RCT, 13 cohort trials and four individual patient meta-analyses. Our search identified all these studies.

Figure 4.2.1: Flow diagram of excluded studies for harms review



4.2.2 Characteristics of included studies

The characteristics of the included studies can be found in Table 4.2.1. (Appendix 8)

4.2.2.1 Randomized controlled trials

Seven RCT published in ten reports were included into our analysis. These studies were all extensions of RCT that were initially identified in the efficacy section of our review. All the RCT had a prespecified angiogram at the primary endpoint, with continued clinical follow-up.

Some of the studies had pre-specified follow-up in the study protocol with associated follow-up procedures, whereas others did not. These studies randomized patients form multiple centres in Europe, Asia, and North America. Overall, 2,312 patients were randomized in the DES group and 2,040 patients wee randomized in the BMS group.

Five of the studies enrolled patients with usual indications, whereas one enrolled patients with lesions only in SVGs; one selectively enrolled patients with diabetes. The characteristics of the patients were universally well reported and were similar among studies. All but one study reported the number of lesions intervened upon. Of the remainder, three studies intervened on one lesion and three intervened on more than one.

All RCT had comparisons of one DES type versus BMS. Four studies used SES stents; one used paclitaxel stents with polymer coating, one used zotarolimus, and one used SES and paclitaxel in separate groups against BMS. All studies specified the use of clopidogrel and ASA for time periods varying from one month to one year. Routine PCI practices were used, and the use of heparin and GIIa IIIb inhibitors were mostly left to the discretion of the operator.

Outcomes of interest were identified at the end of follow-up, although some studies reported outcomes at several time points. The follow-up varied from one and a half to five years.

4.2.2.2 Cohort trials

Thirteen cohorts with control groups published in 20 reports were identified in our review. DES stents were used in 26,855 patients and BMS were used in 47,418 patients.

The cohort studies included a general population (i.e. all comer population) in nine studies. Two of the cohorts involved patients whose lesions were in SVG, one was carried out in patients with renal failure, and one contained patients post-STEMI. Population registries were reported from Ontario, Denmark, Rotterdam, Germany, Duke University and Italy. The remainder of the studies was conducted in North America, China and France.

Frequently, the data on patient and lesion characteristics was missing from the report. Data on concomitant medical therapy was more often present. Clopidogrel was used in all studies except for one, and was given for a range of times from as short as one month for BMS, three months for DES and as long as one year for either stent.

The patients enrolled in the cohorts were in a 1:1 ratio except for two studies that included DES to BMS patients in a ratio of 1:2. In three studies, only SES stents were used; the remainder were mixed or not specified. Most studies excluded patients from follow-up where two types of stents were implanted at the index procedure. In only one study, they were assigned to the DES group. The follow-up in the cohorts varied from one and a half year to three years.

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Two of the cohorts reported multiple outcomes. One reported multiple data endpoints for the time period of 12-15 months. These data were kept for sensitivity analysis where appropriate, but were not included in the main analysis. A second study reported outcomes at six months and then "restarted the clock" at six months in order to report early and late events.

4.2.2.3 Individual patient data meta-analysis

Four IPD reports were included into our review. The IPD were based on the long-term follow of studies sponsored by manufacturers of paclitaxel (Boston Scientific) or SES (Cordis). Six SES or Cypher trials were included which were all published and reported in the efficacy portion of the review. There were four paclitaxel or PES studies which are also included in the efficacy portion of the review. These studies were all sponsored by their stent manufacturer. The IPD reports were published based on the

individual manufacturer's permission and are duplicated through the IPD reports. The duplication occurs for the following reasons: not all the reports include all the available studies from each manufacturer, they are analyzed at different follow-up times and they use different outcomes. One of the IPD reports, which is the most comprehensive, has a 48-month follow-up. Two reported on the SES data at 24 and 48 months, and one reported on the PES data at 36 months of follow-up.

The data on patient characteristics are well reported in these reports, but the lesion-specific data were not. We have already identified that there are specific differences between these trials in the efficacy review.

The follow-up for these patients was carried out by the manufacturer in a blinded fashion as per the original protocol.

4.2.3 Methodological quality

4.2.3.1 Randomized control trials

The quality of the RCT was previously assessed using the Jadad components. All the RCT included in the harms portion were continued past the timing of the primary endpoint. Since there is the possibility of less rigorous control in the follow-up period, the RCT follow-up at this point was thought to behave more like a cohort than an RCT. The NOS scale was applied to the follow-up period and is summarized in Table 4.2.2. (Appendix 9) The RCT extensions provided good quality follow-up, but the component of outcome ascertainment was weak with only two studies clearly describing the process of identifying the outcome of interest. All but three studies were representative of the general population.

4.2.3.2 Cohort

The included cohort studies scored well on the features of the NOS scale, as seen in Table 4.2.2. (Appendix 9) The selection of the control group for nine of the studies was contemporaneous and was as representative of the DES group, other than the stent type. For the remaining five studies, the time period of recruitment was not identical. The follow-up of the patients was uniformly excellent with all but one of the studies having follow-up of greater than 95 %. Three of the cohorts used databased record linkage to ascertain outcomes. All but one study identified and analyzed baseline

characteristics of the entry groups. Methods used to correct for baseline differences were carried out in 6 studies; one of which used propensity score matching, which eliminated a large part of the collected data from analysis. The factors used for correction vary with each study; further underscoring the difference in the entry populations and assignment of the treatment.

The absence of assessment of blinding has been identified as one of the weaknesses of the NOS scale. This data was collected and uniformly was poorly provided in all of the cohorts. Even the studies where linkage of records was used to ascertain outcomes were not clear on how the data were collected for further analysis.

4.2.3.3 Individual patient meta-analysis

There is no quality scale available for the assessment of reports of IPD. However, the assumption was made that the follow-up is carefully done and recorded at the company level. This is thought to be one of the advantages of this type of data. There were no discrepancies in the reports that duplicated the data. The NOS scale was applied to these studies. The study patient approximated that from the RCT. The patients with complex medical problems and complex lesions were excluded from these trials and thus from the IPD meta-analysis. The patients were followed with pre-specified outcomes and on the whole were blinded. Where necessary, HR were used for analysis. The follow-up was complete except in one study.

4.2.4 Assessment of publication bias

Funnel plots for outcomes of the four major outcomes were complete. As seen in Figure 4.2.2 to 4.2.5, there is no evidence of publication bias. The potential of the use of the same data more than once existed with this review. Careful steps were taken to ensure that the publication with the greatest follow- up and the greatest breadth of patients was included into the final analysis, as there was duplication of data in the collected published reports.

Figure 4.2.2: Funnel plot for the outcome of death for harms review

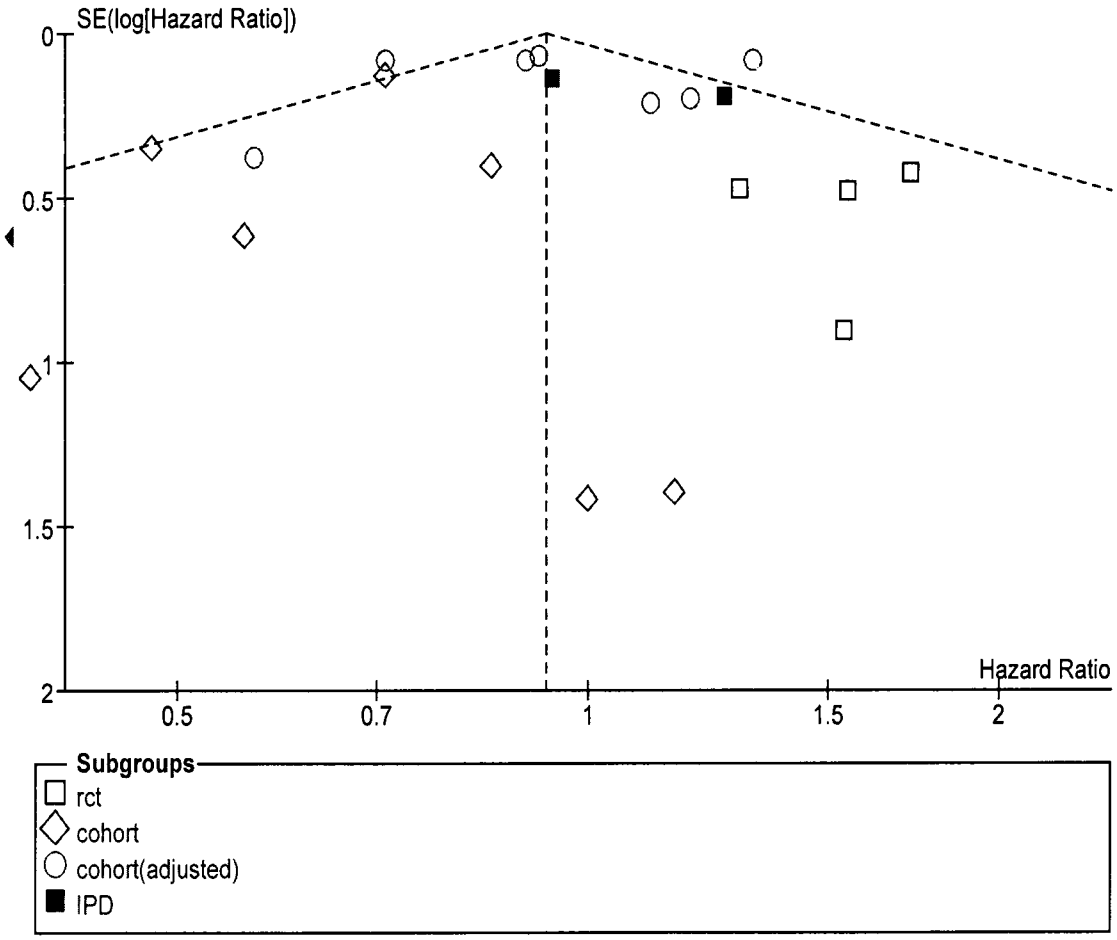


Figure 4.2.3: Funnel plot for the outcome of myocardial infarction for harms review

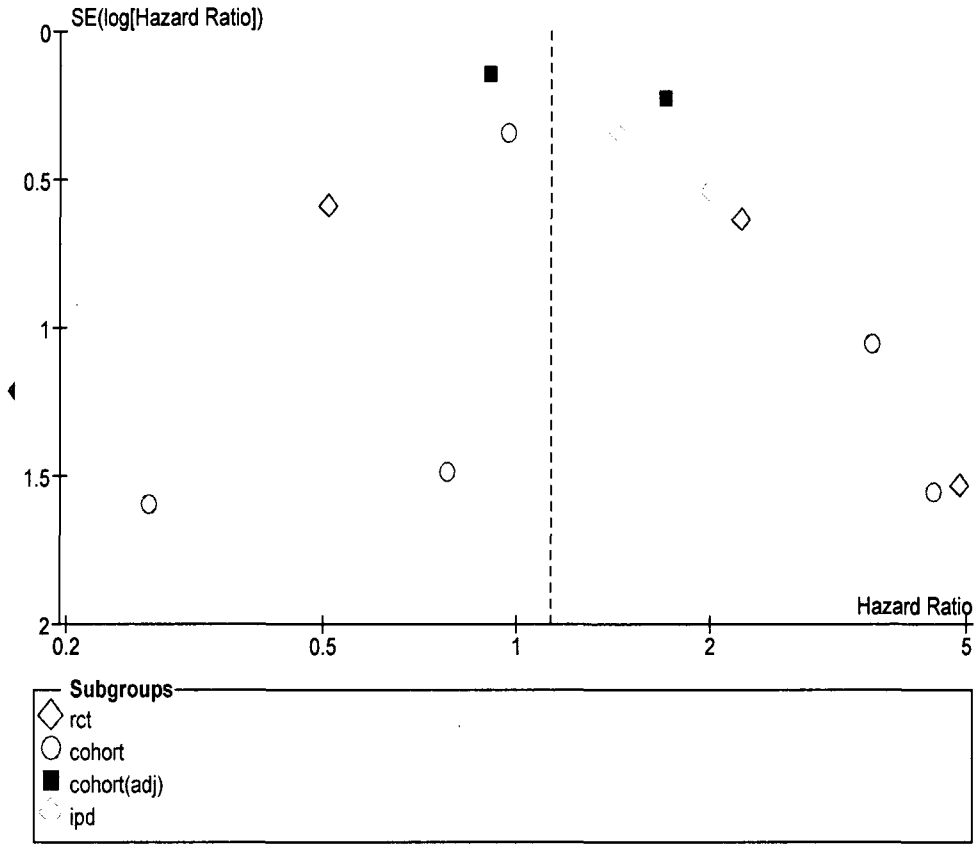


Figure 4.2.4: Funnel plot for the outcome of stent thrombosis for harms review

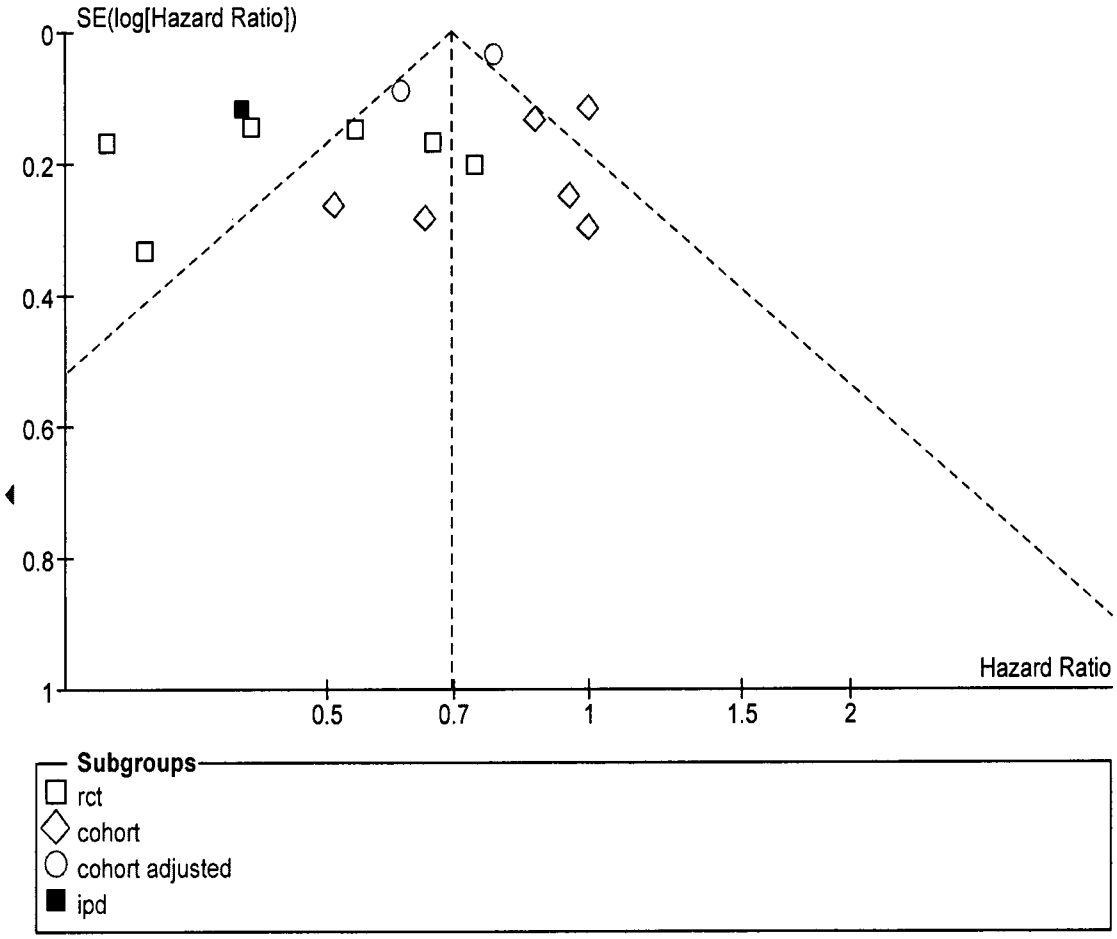
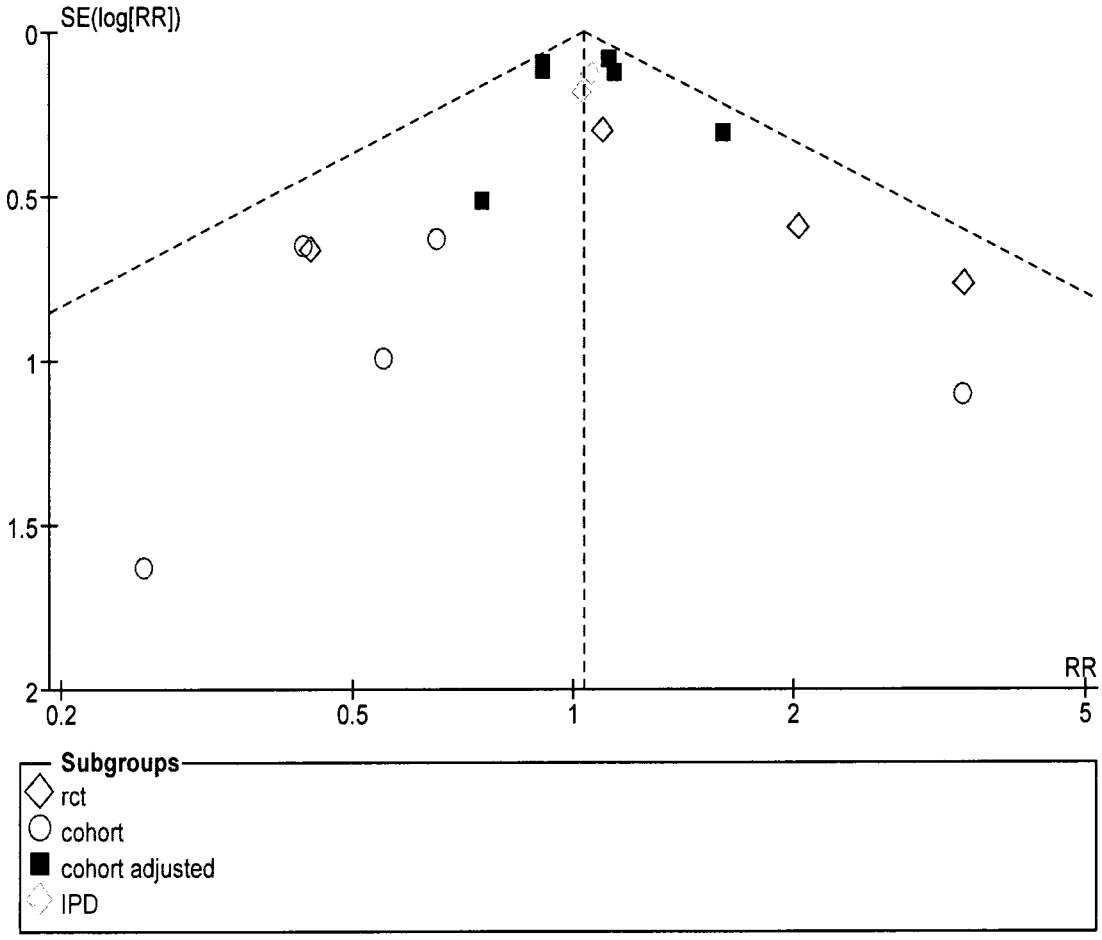


Figure 4.2.5: Funnel plot for the outcome of MACE for harms review



4.2.5.1 Death

4.2.5.1.1 Randomized control trials

Five RCT reported on the outcome of death. Total mortality was presented in all but two studies. There are 2,312 patients followed in the DES group and 2,040 patients in the BMS group. The results are presented in Figure 4.2.6. Sufficient data was obtained for the outcome of death to allow an HR for overall survival to be calculated. There was a statistically significant difference in survival, favoring the BMS group with an overall HR of 1.66 (95 % CI 1.02, 2.70). There was no heterogeneity with an I^2 of 0 %. If the study which included patients with CABG is removed, then this result becomes non significant, suggesting overall no significant risk of death for the group of patients with *de novo* coronary lesions.

In the RCT, there was no evidence of effect of follow-up time of the prespecified clinical characteristics of stent length, length of clopidogrel treatment, diabetes, lesion type, or stent type. The components of the NOS score did not apply, as all of the RCT report equally well on each component.

4.2.5.1.2 Cohort studies

In the six cohort trials that presented unadjusted data for death, six of these studies presented data that enabled a pooled HR to be calculated. In these cohort studies the HR favored the DES with a HR of 0.66 (95 % CI 0.53, 0.83). Since these studies have complete follow-up, this suggests that receiving a DES stent reduced the risk of overall death by 34 %. The I^2 is 0 %. There are no significant findings when the subgroup and sensitivity analysis are completed.

There were also six cohort studies presenting adjusted risks of death which correct for covariate imbalances between the populations receiving each stent type: Two of the studies present data in a format with which the relative risk could be calculated: one study presents the data as a relative risk; and three studies only present data as a hazard ratio. These outcomes were pooled using an inverse variance analysis for calculation of a pooled HR. The HR non significantly favors the DES at 0.94 (95 % CI 0.87, 1.02). The I^2 for heterogeneity is 80 %, which indicate high heterogeneity.

Influence analysis and sensitivity analysis of the adjusted cohorts demonstrated that Tu (156) significantly affects the pooled HR. This study is problematic on two fronts. First, is demonstrates a significant reduction in death rate with DES stent use, with a HR of 0.71 (CI 95 % 0.71, 0.84). It is difficult to imagine a mechanism by which a DES stent might have such a dramatic effect on death rate, especially in light of the very similar patient population that exists in this trial when compared to the other trials in this group. Second, there were several methodological issues which make this study very different from the others in this group. The follow-up was less complete than the other studies with only 50 % of the patients followed at one and a half year. This study was analyzed by matching propensity scores. This analysis is different from the other studies in this group, and also discards a large amount of available data. Data was reported on 3,751 pairs, with data discarded on 4,496 patients with BMS stents and 1,355 patients with DES stents. We felt that Tu likely should not be included into the analysis. The overall HR without this study is 1.02 (CI 95 % 0.93, 1.11) τ =0.05, p=0.0001 suggesting no significant difference between the stents. If this study is not removed and a random effects model is used to report the overall HR, it is 0.96 (95 % CI 0.79, 1.16), again suggesting no significant difference in death between DES and BMS stents. This is very similar to both the results obtained in the RCT follow-up and as we will see shortly in the IPD follow-up.

The studies were further examined without Tu. Eisenstein (145) provided data on patients based on their clopidogrel use at six months. There was a non significant benefit seen on this outcome for patients whose took clopidogrel for up to six months, compared to those who did not. The studies of Jensen and Marzocchi both provided a trend towards a beneficial effect of DES, which was consistent in magnitude and direction.

The remaining heterogeneity is provided by the study of Lagerqvist.(150) Lagerqvist demonstrates a benefit of BMS stenting which is statistically significant during follow up of six to 36 months. Clopidogrel use for Lagerqvist was six months. This late reporting may account for the difference in magnitude of benefit, as the patients had to be completely event-free prior to be reenrolled in the follow- up.

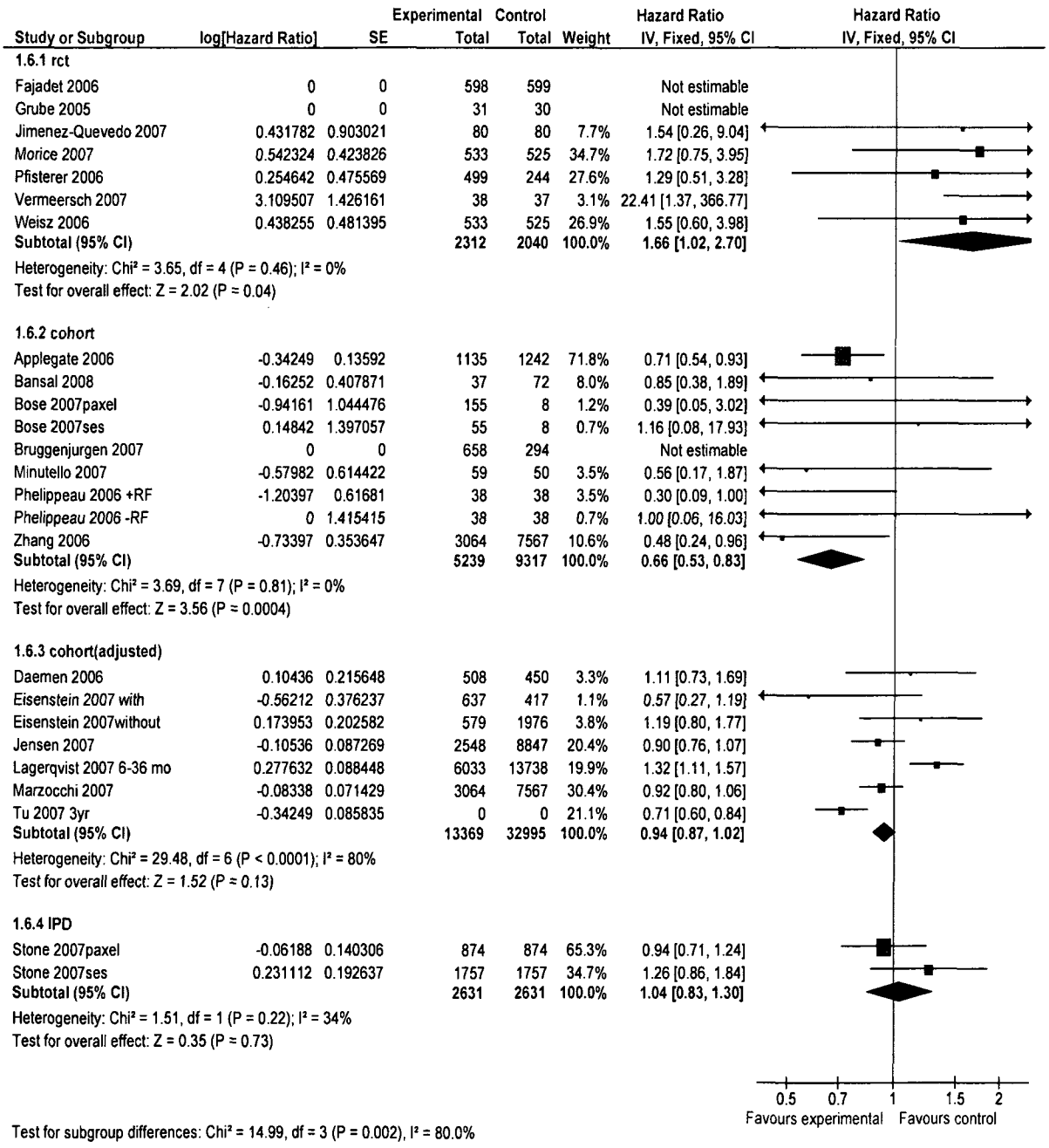
4.2.5.1.3 Individual patient meta-analysis

The data from Stone was the only data presented in this analysis, as it was the most comprehensive of the IPD analyses. In this case, there was a non significant benefit of the PES and SES stent on death with a pooled HR of 1.04 (95 % CI 0.83, 1.30). The I^2 was low at 34 %. There were no significant findings in the subgroup analysis. This summary point was consistent with findings from the RCT and cohorts.

4.2.5.1.4 Overall

Most of the included studies reported on the outcome of death. RCT follow-up demonstrated a benefit of BMS in the long term; however this only is the case when the study including patients with SVG as the PCI target are included. There were only a few RCT, but this study type is the least prone to bias. These patients also would have been the most ideal for stenting, and thus demonstrated the most ideal relative effect of DES stenting. The uncorrected cohorts have methodological issues which were difficult to identify and quantify related to the small event numbers. The adjusted cohorts demonstrated a more neutral effect of DES stenting, which is expected, when compared to the finding of clinical trials. These studies have enrolled more complex patients than the patients in the clinical trials and based on this difference alone would lead to a less significant effect size. The IPD meta-analyses also provide a more neutral effect of DES stenting in the long term, possibly related to the longer follow-up. Overall, we have found no significant findings on the outcome of death in the long term.

Figure 4.2.6: Forest plot of Death of DES vs BMS stents



4.2.5.2 Myocardial infarction

4.2.5.2.1 Randomized controlled trials

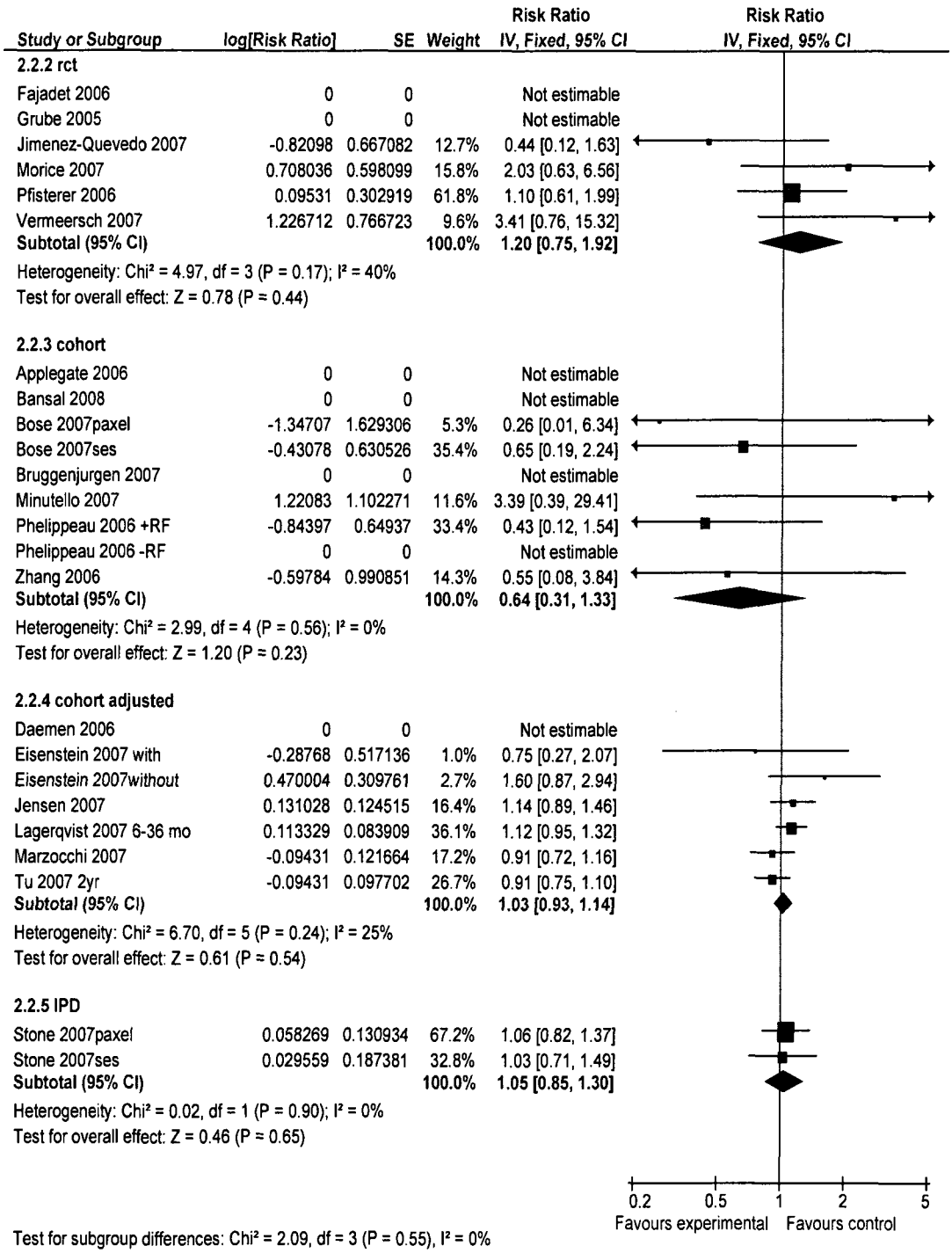
Four RCT reported data on the outcome of MI post stenting (Figure 4.2.7). There was sufficient data to calculate an overall HR, and no significant difference on the outcome of MI was found with a HR of 1.20 (95 % CI 0.75, 1.92). There was mild to moderate heterogeneity with an I^2 of 40 %. No significant findings on subgroup and sensitivity analysis were found.

4.2.5.2.2 Cohort trials

For the four studies that provided data for unadjusted cohort studies, the summary risk is 0.64 (95 % CI 0.31, 1.33). There is no heterogeneity with an I^2 of 0 %.

There were also five cohort studies that presented adjusted data on the outcome of MI. The HR is 1.03 (95 % CI 0.93, 1.14) with an I^2 of 25 %. This heterogeneity was due to the study by Tu. Removal of this study slightly shifted the summary point estimate and reduced the heterogeneity. When the MI data were assessed for different lengths of follow-up, no differences were found. Further exploration of subgroups and sensitivity yielded no significant findings.

Figure 4.2.7: Forest plot of outcome of myocardial infarction, by study type



4.2.5.2.3 Individual patient meta-analysis

Again, the IPD of Stone is presented, which demonstrates no significant effect on MI of either the PES or the SES portion of the study.

4.2.5.2.3 Overall

Again, for all study subtypes, there is consistent and no significant effect of stent type on late outcomes of MI.

4.2.5.3 Stent thrombosis

4.2.5.3.1 Randomized controlled trials

Four RCT reported data on the outcome of stent thrombosis. The pooled HR was 1.30 (95 % CI 0.59, 2.86). The I^2 for this analysis is moderate at 43 %. There were no findings on subgroup or sensitivity analysis (Figure 4.2.8).

4.2.5.3.2 Cohort trials

Four of the studies provided, in the unadjusted cohort, data which suggests that a stent thrombosis is as likely to occur in a DES stent as in a BMS stent with a HR of 0.87 (95 % CI 0.48, 1.59). The heterogeneity was low to moderate with an I^2 of 37 %.

There were three adjusted studies providing data for this outcome. Jensen (148) describes no significant increase in the occurrence of stent thrombosis when all the covariates are considered. The overall HR is 1.10 (95 % CI 0.86, 1.39). The heterogeneity was significant at 67 %. Marzocchi (160) described a significant event rate of ST in the BMS group. These two studies are very important in our analysis. They were both large population-based studies that followed patients for two to three years post-stent implantation. If cohorts are an appropriate study design to identify long-terms harms, then the data contained in these studies is very important. Comparing these studies, however, demonstrates an important difference between them. In Marzocchi, the antiplatelet agent of choice is Ticlopidine, which was only given for one monthto the patients receiving a BMS stent. In addition, this study included the greatest number of patients with Type C lesions and had an average stent length

greater than 18 mm. Both these are known to increase the risk of ST. This may account for the increase in ST seen in this BMS group.

As there were only two studies in the adjusted group and low heterogeneity in the unadjusted group, further analysis of subgroups and sensitivity are not presented.

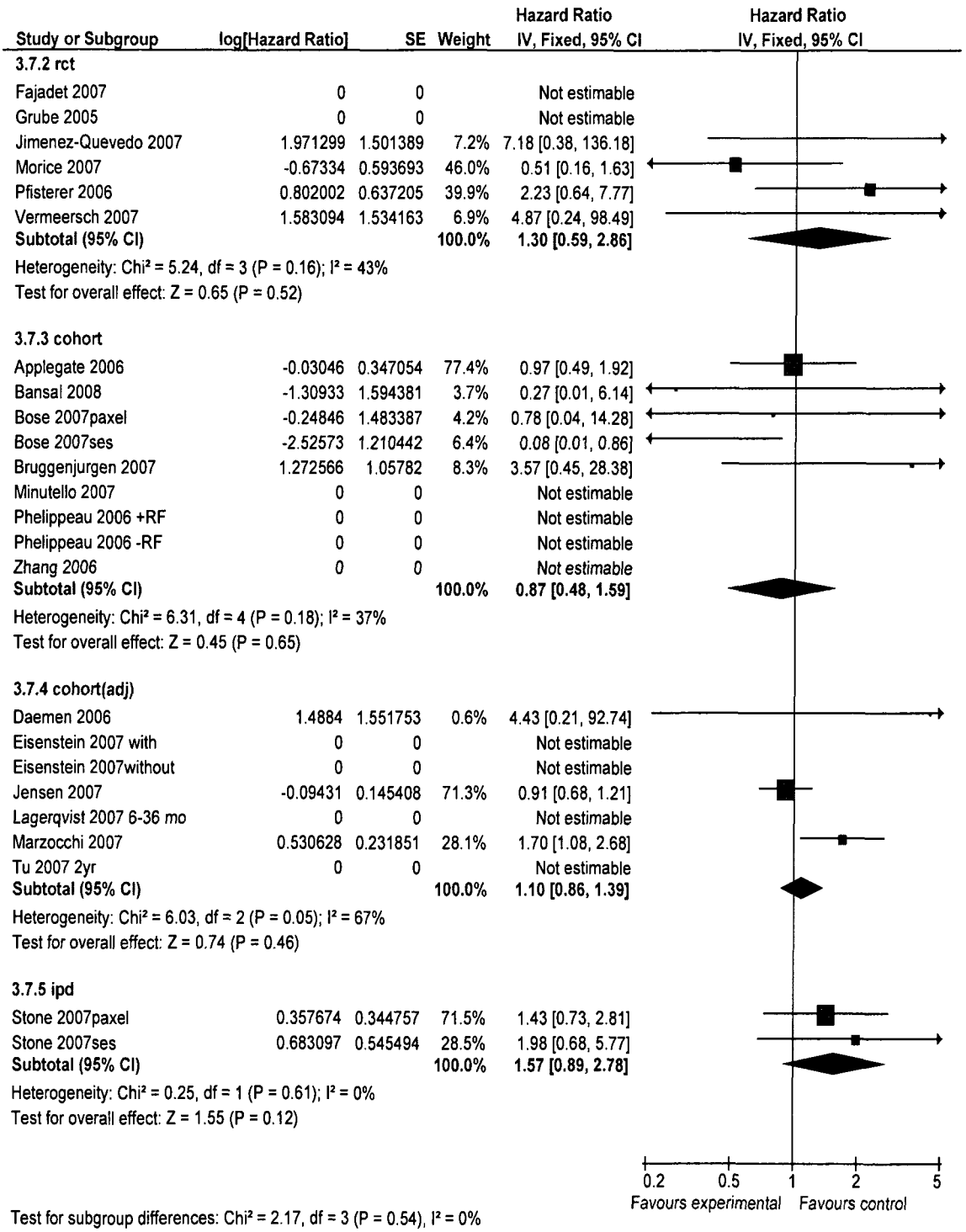
4.2.5.3.3 Individual patient meta-analysis

Again, the Stone study was used to provide data on the occurrence of the outcome of ST. There was no significant difference between the patients receiving an SES versus a PES stent. The overall HR was 1.57 (95 % CI 0.89, 2.78) with an I^2 of 0 %. This suggests that an ST is 57 % more likely to occur in a BMS stent that in a DES stent, but the result did not reach significance. Interestingly, there was no significant difference between the findings of ST for the RCT studies and the IPD studies. This was likely related to the large weight of Morice 2007 (161) which is reported at five years.

4.2.5.3.4 Overall

There are consistent overall results across study types which suggest that there is no significant increase in ST in DES. In addition, there is no increase in ST over the five years of follow-up. This suggests either that the ST occur early in followup and do not increase over time, or that the later ST occur equally in both stent groups. Examination of individual studies yields a consistent and null effect on the outcome of ST. The finding of Marzocchi suggests that antiplatelet therapy be given for longer that one month in the BMS group. It must be remembered that this outcome is relatively rare and difficult to document in large studies.

Figure 4.2.8: Forest plot of outcome of stent thrombosis, by study type



4.2.5.4 MACE (Multiple adverse cardiac events)

4.2.5.4.1 Randomized controlled trials

The seven RCT reporting this outcome demonstrated significant and consistent benefit on this combined endpoint in favour of DES. The overall HR was 0.47 (95 % CI 0.41, 0.54) with moderate heterogeneity given by an I^2 of 75 % (Figure 4.2.9). This suggested that there was almost a 50 % reduction in the composite of death, myocardial infarction and revascularization in the DES group. The benefit on MACE was driven by the significant reduction in TLR, as we have just seen that there was no significant reduction in death or infarction. This benefit does not appear to persist to five years, as Morice reported a reduction in effect at this time point. Also, the long term effect also is not as great in Vermeersch who only enrolled patient having had PCI to their SVG.

The effect was not related to the length of clopidogrel use, the number of patients with diabetes enrolled, stent length, and lesion length. This may in part be related to the small number of patients in this portion of the review.

4.2.5.4.2 Cohort trials

The six unadjusted cohort studies demonstrated a non significant benefit on this outcome with an overall HR of 0.88 (95 % CI 0.76, 1.02). The heterogeneity was low at 26 %. In this group, the individual studies did not demonstrate as large of a significant effect as expected after reviewing the RCT follow-ups. Each of the individual endpoints were non significant.

The two adjusted studies reporting this outcome both demonstrated a significant effect individually and when pooled together with a hazard ratio or 0.75 (0.71, 0.80). The effect was greater in Daeman (52) that in Marzocchi (151). This may be related to the finding that the average stent length in Daeman is 38.7 mm and 28.3 mm in Marzocchi, with the lesion type being more severe in Daeman. The BMS stent performed much worse in this environment, allowing the DES benefits to "shine through". In addition, the only stent used in Daeman was the SES stent, which had the best profile on restenosis as demonstrated in the prior review.

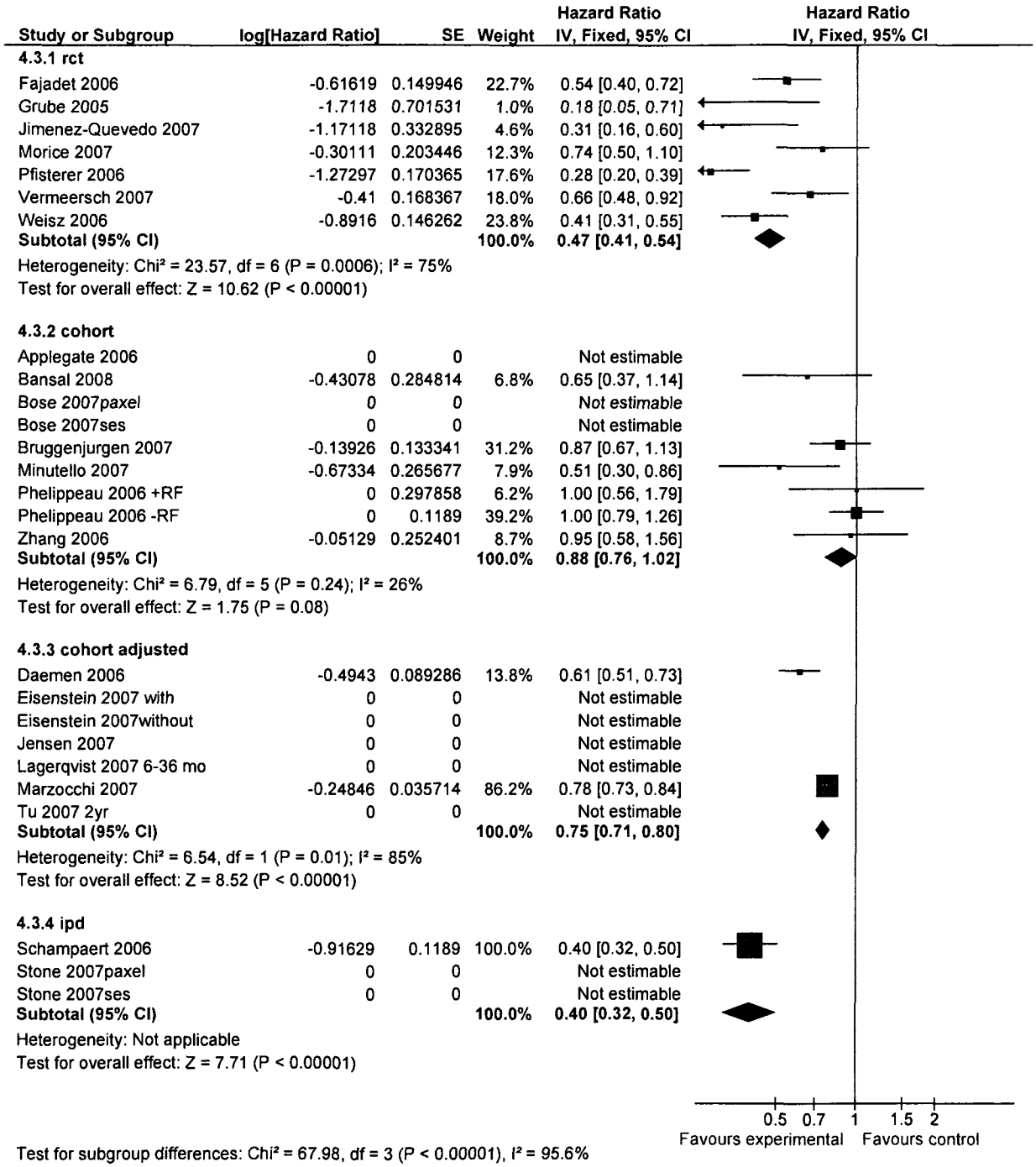
4.2.5.4.3 Individual patient meta-analysis

There was only one IPD reporting data on MACE. This study reported at two years. The benefit at this time point was impressive with an HR of 0.40 (95 % 0.32, 0.50). This is in line with the degree of benefit seen in the RCT evidence.

4.2.5.4.4 Overall

There is again a consistent effect seen on the outcome of MACE when the RCT and the IPD is compared. The cohort trials, however, did not demonstrate as large of a significant effect. As stents are incorporated into real world applications, the overall benefit is less that in the controlled trials. In addition, the cohort trials demonstrated an improvement on outcome when the baseline inconsistencies were adjusted for. There was a suggestion that the SES stent performs particularly well in lesions that are complex and long when compared to the BMS stent.

Figure 4.2.9: Forest plot of outcome of MACE, by study type



4.2.5.5 Other outcomes

Among the included studies there were only a few reports of other harms. Even the cohort trials did not collect other harms that were of interest at the beginning of this review. (i.e. bleeding, stroke and anginal class). We found this remarkable, given the risk that the patients are known to have in the long term. This is however consistent with the knowledge of the paucity of harms reporting.

CHAPTER 5: Discussion

5.1 Overall results

The benefits and harms have been debated about DES over BMS stents since their introduction. Continued references to the safety of DES have been made. We examined 43 randomized controlled trials and 24 long-term follow-up studies, and found no evidence of harms and evidence of incremental efficacy of DES over BMS. More specifically, for DES, there was significant benefit of efficacy given by TLR and LLL, but no significant increase in death, MI or ST.

For the outcome of death, which is the most important outcome and the least likely to be affected by methodological issues such as blinding and ascertainment bias, there was no significant detriment in the use of DES over BMS in the medium term. In the harms review, there was a slight benefit on this outcome seen in the RCT follow up studies, which was not duplicated in the longer term IPD meta-analysis or the cohort studies. This endpoint, however, was driven by the long-term follow-up of a study that enrolled patients only who had SVG. The lack of findings on the outcome of death is important, as the outcomes of myocardial infarction and stent thrombosis may be more difficult to ascertain, but the most severe of these outcomes can eventually lead to death.

The outcome of myocardial infarction in the medium and the long-term was not increased in the DES group. The outcome of ST was infrequent in both the DES and the BMS group. It did not increase in any particular subgroup, indicating that we found no measurable factors from a patient or methodological point of view that predict for this outcome. This may be related to the poor collection of this difficult endpoint. If the occurrence of ST was more frequent and not ascertained, however, then there would be a spillover into the events of MI and death with greater events in these outcomes in either the efficacy or the late analysis, which we do not see.

The outcome of TLR for the RCT and MACE for the long-term studies demonstrates a dramatic benefit in favour of DES. This was sustained across all the examined subgroups. This benefit was less significant over time, as seen in the longer term trials. From our review, it is not possible to determine whether this reduction in benefit is related to longer follow-up of the studies chosen for the harms

review, or the reduction of an effect as the DES are used in a "real world" population. We found that the additional treatment of TLR events in the BMS stent did not seem to lead to an increase in death, myocardial infarction or stent thrombosis either in the moderate term or the long term. In theory, the patient will incur more adverse outcomes with an increasing number of PCI procedures, such as stroke, bleeding complications and vascular access complications; however, our review demonstrated that there was no translation into an increase in major harm suffered by the patient during these additional procedures. Unfortunately, there was not enough reported data on these outcomes to allow them to be directly evaluated. This is likely related to the reduction in risks of PCI that occur in high volume centres, and the fact that there are effective treatments for restenosis events. Surprisingly, we found that the absolute overall rate of restenosis in the BMS measured by TLR was not as great a problem as anticipated. Even though LLL, the surrogate outcome for TLR demonstrated a significant effect on restenosis, it does not completely translate into an effect in clinical TLR events.

Seven stent types evaluated by the RCT review, and for each stent type, an overall judgment can be made. From this review, we suggest that evaluation of benefit of stent type was made on the basis of four criteria: the clinical efficacy of the stent; the harms of the stent and all associated therapy, the ease of use for the initial operator, and the knowledge of stent performance based on surrogate outcome measures.

Within the DES stent group, comments can be made about the overall effectiveness and harms of stent types. The DES type with the superior performance is the SES. This stent has the best performance based on the surrogate outcome of LLL. This reduction should, in theory and in our review, translate into a clinical effect on reduction of symptomatic TLR. It may then have a further impact on the outcomes of death, myocardial infarction, possibly stroke and patient inconvenience of repeat procedures.

The stent types of sirolimus analogues, paclitaxel (with and without coating), dexamethasone and abciximab demonstrate a significant effect on the reduction of LLL when compared with BMS, but significantly less so than the sirolimus stent. This is not balanced by a reduction in harms such as myocardial infarction or stent thrombosis. The stent type of estradiol demonstrates no reduction in late

luminal loss or of TLR, without an impact on the outcomes of death, myocardial infarction or stent thrombosis. This stent offers no benefit over the use of a BMS.

There was no increase in overall harms in the DES stent group in the one- to five-year time period after implantation, but a determination of long-term harms by stent type was not possible from this review. This is because of the lumping together of stent type into one group and the large penetration of SES as the stent type evaluated into most of the studies.

When reviewing this literature for harms, there are several features that mitigate against the potential findings of significant adverse events in these trials. First, the patient population that is chosen for the efficacy portion of the review is at extremely low long-term risk. On the whole, these patients have single-vessel disease, and a straightforward lesion for percutaneous intervention. These patients would only be at risk of death in cases of adverse circumstances of the PCI procedure itself, and if there is a truly adverse event rate in the short or the long term related to the stent type itself. These patients would have very little residual disease and would not be at future risk related to residual disease.

Second, there are no studies that have enrolled patients that truly had multi-vessel stenting. Equipoise for comparative studies would likely not be met in this circumstance. Even if we do not know the potential long-term risk and performance of DES in severe coronary disease, we do have experience of how BMS perform in these circumstances. The situations where BMS perform poorly, which are confirmed in this review, are in situation of long lesions, small diameter arteries and significant patient co-morbidity such as diabetes. Unfortunately, these are exactly the conditions associated with multi-vessel disease. The frontier of multi-vessel stenting will be how to judge its performance related to other procedures, such as CABG and medical therapy alone, and not to BMS. This remains an important deficit in our knowledge base, as this very situation is where the cardiac surgeons feel that their procedure excels.

Third, there are no long term studies that allow the assessment of patients and stenting procedures at higher risk alone. The cohort studies' population included patients at high and low risk. In the RCT that included these patients, there is a reduction of efficacy of the DES, but at this point, we cannot

ascertain the long term effect of this finding. Thus, there is no systematic method of determining which patients are susceptible to long-term harms from stenting. The final issue is the use of concomitant medication. The use of antiplatelet medications has changed significantly over the time span of the examined literature. In the first RCT, antiplatelet agents were given for one to three months. As the events of ST started to occur, the trials thes agents have been used for progressively longer periods. The study by Tu (156), which was carried out in Ontario where antiplatelet agents are paid largely by the health care system, found that most patients were taking such medication for a year. This may be part of the reason that we did not find increasing complications with the longer term cohorts, which included enrolled patients with increasing lesion and clinical complexity.

As in other reviews, the magnitude and direction of findings from the RCT portion are not always consistent with those obtained from cohort studies. In the evaluation of stent efficacy, the RCT evidence is abundant. Not all topic areas have the same extent of published literature that we have identified. The cohort trials confirmed this efficacy when stents were incorporated into day-to-day real world use. The addition of the cohort trials in the evaluation of efficacy did not alter the direction of our findings, but it did alter the magnitude. Nonetheless, DES remains a very effective therapy. For the purpose of evaluating efficacy, the addition of cohort trials did add interesting information about the penetration and expansion of use of stents in real life settings.

In the evaluation of the harms of death, myocardial infarction, and stent thrombosis, we obtained very consistent information from the two types of studies. The addition of this safety information over long-term follow-up is very important. Critics of RCT for the evaluation of harms feel that these study types have failings that do not allow the proper evaluation of harms. As in the case with this body of literature, the potential of the increase in harm of death, MI and ST occurred after many of the efficacy trials were completed and while others were in progress. This did not allow the ability to ascertain the ST outcome in all trials. In addition, the efficacy trials were shorter than the time frame over which these complications were being reported. The additional criticism of RCT studies to evaluate harms is that the patient population is too focused and does not completely represent the patient population that the therapy will be used in. This is the case in this area, as issues about safety only became apparent after DES were approved and their use expanded. The final issue with using RCT for the evaluation of harms is the infrequency of some harms. This also is an issue with the DES trials and explains some

of the earlier discrepant results about the frequency of ST and other adverse events. Cohort trials can overcome some of these shortcomings with a larger included population, which represents the group to which the intervention is generally applied. They also run over a longer term and are better set up to naturally identify harms that occur during the follow-up period. The downside of including these studies into a review is the greater resources required to identify and analyze them, and evaluating the bias that is inherent in the baseline populations. Miettinen (162) is convinced that baseline group selection should not be related to harms outcome as the reasons that the patient is selected for a particular therapy; this may predict for an efficacy outcome, but should not predict for a harms outcome. We do not have enough data to comment on this theory from this review. The collection of similar harms from the review that is composed mostly of cohorts suggests that there is no increase in harms from DES up to at least four years after implantation. This complements and adds further confidence to the RCT data.

A remaining concern after this harms review is whether the data, which clusters around the two- to four-year mark, has a long enough follow-up period to be certain that DES stents are safe. For this answer, we look to the physiology of the stenting process. The deployed stent is placed in a local area of a coronary artery, likely without any effect on the surrounding coronary artery or tree. The potential for cadiac risk after this is either at the stent site or in the remaining coronary tree, where there is residual disease. The stent is at risk for thrombosis until it becomes endothelialized, and for restenosis after it does. The remaining coronary disease continues to progress related to patient-related factors such as age, genetics, diabetes, cholesterol, and renal status. As the residual disease progresses, the patient is at risk of outcomes such as angina and plaque rupture, resulting in the clinical sequela of ACS, including NSTEMI. Until investigations are carried out, it is not possible to distinguish the event mechanism of stent harm from native coronary tree harm. The timing of the complication lends a clue. If an event occurs to a patient shortly after stent placement, the likelihood is greater that it is stent-related rather than related to residual coronary disease. As time passes, the event is less likely related to the stent, and more likely related to progression of residual coronary disease outside of the stent. Drawing on clinical experience, no increase in harms at two to four years post-stent implantation is a reassurance that DES stent treatment of a coronary lesion is a safe procedure.

5.2 Contrast with published reviews

There have been over a dozen published reviews – which included largely published RCT – on the efficacy and harms of stenting. Some of the reviews evaluated all stent types and patient types at once, and others evaluated specific patient populations or stent types only. In all cases, our results are consistent with the published reviews for the endpoint of death, MI, TLR and MACE.

For the outcome of ST, a variety of results were found. The most controversial was the systematic review published by Kastrati in 2007 (94). This review was published based on the increasing concern about ST. There was no significant increase in ST of the SES stent that was studied, but there was a suggestion of a trend towards an increase late in the follow-up period.

In the reviews which incorporated several stent types (2-5;56;91;163;164), only one found a non significant increase in the occurrence of ST.(163) This review included only 10 of the studies that we did, and did find a suggestive but non significant result in favour of BMS. The odds ratio is no more suggestive of harm for ST in DES than the odds ratio for their outcomes of death, non q wave or q wave MI, but it was emphasized in their reporting anyway. As it was published in 2005, this review likely rode the hype of the potential of DES harms. These reviews all reported low rates of ST in general. One review specifically looked at the definition of ST and its effect on the outcome. In this review, study level data was examined from four RCT and the outcome of ST reclassified by the ARC definitions. The outcome was then compared using study level definitions and the ARC definitions. Reclassification of the outcome using the ARC criteria increases the number of endpoints, as the more liberal definitions were used over the study defined outcomes for ST. However, the relative risk remained the same using any of the definitions.

Four reviews analyzed the stent specific efficacy outcome of restenosis, TLR or MACE.(2;5;91;164) The stent types included in these reviews were sirolimus, paclitaxel (with and without coating) and one study included a sirolimus analogue in the analysis. Three of the reviews a priori decided to analyze their data by stent type and obtained similar results to ours. Only one review (164) included a stent type with a sirolimus analogue. In this review, there was no exploration of the difference between stents with sirolimus and its analogues, in spite of differences seen on their presented plots. Our

finding of this difference is credited to the inclusion of all stent coating types, which allowed enough studies to analyze the differences between stent types.

One review examined the late consequences of DES stents and suggested an increase in late ST events.(165) This study excluded trials which used a non polymeric stent platform, and those with experimental agents, such as everolimus. At the time of publication of their results, RAVEL and SIRIUS trials had two to four years of follow-up, and TAXUS I, II, IV had two years of follow-up. The details of the late data are not published in this report. The data are not analyzed with the benefit of a Forest plot, and the confidence intervals and rate calculation data are not presented. As such, we feel that the finding of an increase in risk of ST after one year is weak and poorly defended. We did not find late harms in our review, but these methodological differences may only partially explain the contrasting results. We had the benefit in our review of further follow-up data of the studies on which they base their results, as well as additional studies.

5.3 Methodological issues

The quality of the included studies in both portions of our review was generally moderate to high. Many of the RCT did not provide full information on allocation concealment and blinding. Details of follow-up were much better provided. The sensitivity analysis for the presence and absence of these features was not significant, so we feel that the studies likely followed more rigorous processes than they reported. This is a problem in general for the evaluation of quality of study reports. The issue of the post-study angiogram haunted us at the protocol stage of this review. We felt that it was likely that the studies performing a post-study evaluation angiographically would unfairly bias the results against BMS. During the angiogram and evaluation of the stent, there were generally pre-specified conditions, such as clinical symptoms or an abnormal non-invasive study that allowed for repeat intervention on the stent. The association of the potential of such an intention with the lack of blinding, which existed in most of the trials, concerned us. We felt that it was possible that the BMS would be preferentially treated the final angiogram identified restenosis. We felt that any associated harms of TLR events would then cause an increase in all event rates. However, this concern was not supported by the findings of our review. There was clearly no major events in the BMS group and the sensitivity analysis carried out by whether the trial had a prespecified angiogram demonstrated no effect of "looking then fixing", or as we call it in the cardiology world, the "oculo-stenotic reflex".

Assessment of quality of the two types of included studies was not possible. The RCT studies with extended follow-up and the IPD meta-analysis were evaluated with the NOS, as it seemed to be the most applicable to the features of these studies for assessing bias. The use of the NOS in this area or the use of a new scale developed primarily for this study type needs to be developed and validated. For our purposes, we felt that the NOS was able to identify the issues that we were concerned with. However, a scale specifically targeted to these study types would likely be more appropriate.

Of interest in this review was the risk of ST in the medium and long-term follow up periods. This risk may be problematic, based on the determination of the ST event in the primary trials. The classification of this endpoint is difficult in general, and the ARC criteria were not universally followed in the trials. Wherever possible, the ARC criteria were used in our analysis, but they were not often presented. The use of these criteria is known to be very sensitive to ST events, and we used the definition that was most inclusive for this endpoint. We felt that it was important so that we could present the worst case scenario for this endpoint. The endpoint of myocardial infarction or death can be used somewhat as surrogate for the outcome of ST, as patients with ST present with unstable angina, myocardial infarction or death. As the rigorousness of the RCT features of trials are lost, there may be a component of error introduced into the ascertainment of this outcome, and surrogate evaluation is even more important.

For the cohort trials, we limited our review to studies where the control group was considered an internal control. Thus, we biased our NOS scores upward, by biasing our review towards high quality trials, given that several of the NOS criteria were prespecified in the inclusion criteria. In spite of having high quality data, we needed to make assumptions in the collection of data. Most frequently, we converted data from Kaplan Meyer curves and assumed that the follow-up was complete. This was an incorrect assumption in one of the cohorts that we suggested excluding from the analysis. We also were not able to evaluate the studies based on methods of analysis, as the studies analyzed their data differently, and all studies presented only one method of analysis. One of the cohorts used a matched propensity score method, which rendered a very different result from the other trials. None of the cohorts offered more that one method of analysis and justified the one that they finally settled on. The

variety in methodology to correct baseline differences may be a factor in preventing us from achieving an unbiased conclusion that DES stenting and BMS stenting are equally safe.

The cohort studies also did not practice censoring in the same way. In some studies, there was no discussion about censoring; in others, censoring was outcome-specific, so that a particular outcome could be experienced only once, and in other cases, the patient could experience the same outcome more than once. For the outcome of MACE, this may be an issue, as TLR or a similar revascularization outcome is contained in the composite MACE outcome and is relatively frequent. However, we were not given enough data on censoring of TLR in all studies to determine if it might have some effect on our harms rate.

5.4 Limitations of our review

The assessment of harms in this review is limited. The RCT portion reported harms that related to major morbidity, most often by intervention group, but not infrequently, they were combined. There was no reporting in general of anginal outcomes or of outcomes related to angiography such as stroke, bleeding or vascular injury. This is important information for the clinician, especially if the initial stent selection for a patient is a BMS. Given that the rate of reintervention is higher for a patient with BMS, the potential complication rate should be reported. This would be of help in the initial decision of stent type choice. It would also ensure that the BMS harms are not being underestimated.

Establishing the harms attributable to reintervention to a BMS is also difficult in the longer term cohort trials. In practice with these trials, the BMS patient often became censored at the point where additional therapy is required. The censoring outcome is then for TLR and not for the possible stroke that the patient suffered with reintervention. In both the RCT and the cohort trials, it is possible that the harms of the BMS are actually underestimated related to censoring of this patient at this time point. In all the cohorts, it is not clear if the harms reported inclusive of reintervention harms. In RCT and the cohort studies , the details of the treatment of the BMS patient requiring further intervention are not well reported.

CONSORT (166) has suggested guidelines for the reporting of harms that hopefully will encourage future trialists to improve the reporting of harms. The suggestions in this document are directed

towards the reporting of harms in trials evaluating a drug therapy. It does not contain the required guidelines for the assessment of harms when applied to a device trial which would allow an informed decision about the balance between harms and efficacy to be made. Only features applicable to device trials would allow trial benefits and shortcomings be noted. Items specifically missing include a statement of how to attribute reintervention harms, such as in a stent trial when crossover from one stent group to another occurs. In trials where the crossover is high, the methods used for this reporting are important. When data is collected from the manufacturers with regard to rare events, and compared to the published literature, inconsistent reporting practices are found.(167) There were different reporting strategies between the major stent manufacturers. For the reports from the Cypher program, a protocol analysis was not performed; only an intention to treat the analysis was. In contrast, the Taxus program performed a per protocol analysis. This is important as the difference between these two denominators is of the same magnitude, as the events rates that are occuring in these programs. In addition, the definition of all cause mortality rates differed for both programs. Part of the reason for this is that the published death rate was for adjudicated cardiac mortality in one program and all cause mortality in the other.

The determination of late harms was also difficult from this literature. The occurrence of harms attributable to an index stent at the end of a follow-up period in a stent study can occur in three ways: harms may occur early in the study, based on technical features of stents at the index procedure; they may occur at the time period that the antiplatelet agents are discontinued (in which case the event would be carried forward through the follow-up period with no new late events); or they may continue at a relatively constant rate or even non constant rate throughout the follow-up period. From the literature that we reviewed, it is not possible to distinguish between these patterns of harms. Concurrent to the harms related to the stent, the same events are occurring to the patient outside of the stented portion of the artery. In theory, as time progresses, the harms will shift from being stent specific to patient or coronary tree specific. The time frame of this shift cannot be determined from the existing literature in this review.

5.6 Publication bias

There is evidence of publication bias in the outcomes for the RCT review. The funnel plots for the included trial are not completely symmetrical, suggesting the possibility of publication bias for the

harms outcomes. This is unlikely to alter the outcome seen with the outcome of late luminal loss. There is, however, concern that unpublished studies may contain harm outcomes which may alter our results. It is reassuring that our RCT results are consistent with the findings from the cohort studies. Although a comprehensive search was undertaken, we included only studies published in peer review journals.

A more subtle form of publication bias likely exists in this review. As DES were used, the perception was of increased efficacy over BMS as reflected in earlier published trials. It is possible that physician or patient preference may have limited enrollment into later clinical trials. The patients that would be perceived to receive benefit from DES may have been sent directly for this procedure and not enrolled in a clinical trial. We see no evidence of a change in effect of later clinical trials, suggesting that this possible practice altered the results of later trials. The perception that certain types of patients would have better outcomes with DES would determine stent type in the cohort trials, but even with the attempts made to correct for baseline group differences, the effect of patient and physician differences cannot be completely predicted.

5.6 Policy implications

Given the growth of coronary disease and the future anticipated needs for stents of both DES and BMS types, it is important that the outcomes of such procedures be documented and analyzed. As patient and physician preference of stenting expands, a central body needs to be identified to monitor outcomes. Patients are now in the position of receiving many stents at several event times. The optimum type and number of stents should be determined, as well as the role of medical therapy and alternative revascularization strategies. The best documentation is likely to occur at a local level. This should be set up with appropriate resources with the integration with the collection of adjunctive medical therapy. There will always be unanticipated effects of a new drug or procedure. If such a surveillance system were set up, future scares, such as the recent fear of the late stent thrombosis, could perhaps be avoided.

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Appendix 1 Search Strategy for Review of Efficacy and Harms

MEDLINE search:
Ovid MEDLINE 1950- May week 2, 2007
1. Stents/
2. exp Drug Delivery Systems/
3. Drug Implants/
4. (des or drug elut$).tw.
5. 33069-62-4.rn.
6. /
7. 53123-88-9.rn.
8. Sirolimus/
9. zotarolimus.mp.
10. elut$ stent$.tw.
11. 1 and (or/2-9)
12. 10 or 11
13. exp myocardial ischemia/ or exp coronary disease/
14. (cardiac or coronary).tw.
15. 13 or 14
16. 12 and 15
17. 16 and randomized controlled trial.pt.
18. (clinical trial.pt. or randomized.ti,ab. or placebo.ti,ab. or dt.fs. or randomly.ti,ab. or trial.ti,ab. or groups.ti,ab.) not (animals/ not humans/)
19. 16 and (18 not 17)
20. exp Cerebrovascular Accident/
21. exp Myocardial Infarction/
22. (thrombo$ adj3 stent$).tw.
23. (ae or po or to or mo or ci or de or et or co or sc).fs.
24. exp survival analysis/
25. exp death/
26. exp drug interactions/
27. critical illness/
28. exp mortality/
29. abnormalities, drug-induced/
30. cohort studies/
31. harm$.mp.
32. (adverse event$ or (adverse adj2 reaction$)).mp.
33. ((side or unwanted adverse) adj effects$).tw.
34. (ADR or SAE).tw.
35. safety.mp.
36. (bleed$ or haemorrhag$ or hemorrhag$).tw.
37. (gastrotoxic$ or toxic$).tw.
38. (tolerability or tolerance or well tolerated).tw.
39. (relative risk or risks).mp.
40. (cohort and stud$).ti,ab.
41. (malignan$ or rare or surviv$ or risk#).tw.
42. (death or fatal$ or grave or die or lethal$ or mortal$).tw.
43. (adverse or serious or severe or poison$ or patholog$ or toxic$).tw.
44. (threaten$ or abnormal$ or failure event# or hazard$).tw.
45. or/20-44
46. 45 and (16 not (17 or 19))
47. 16 not (17 or 19 or 45)
48. (bare metal or bms).mp.
49. 47 and 48
50. 19 or 46 or 49
51. remove duplicates from 17

52. remove duplicates from 50

Embase search:
Ovid 1980 to 2007 Week 20
1. exp Stent/
2. exp Drug Delivery System/
3. Drug Implant/
4. (des or drug elut$).tw.
5. Rapamycin/
6. /
7. zotarolimus.mp.
8. sirolimus.mp.
9. elut$ stent$.tw.
10. 1 and (or/2-8)
11. 9 or 10
12. exp Ischemic Heart Disease/ or Coronary Artery Disease/
13. (cardiac or coronary).tw.
14. 12 or 13
15. 11 and 14
16. Cerebrovascular Accident/ or Stroke/
17. exp Heart Infarction/
18. (thrombo$ adj3 stent$).tw.
19. Survival/ or Disease Free Survival/ or Overall Survival/ or Survival Rate/ or Survival Time/
20. Death/
21. exp Drug Interaction/
22. exp Complication/
23. Critical Illness/
24. Mortality/
25. Adverse Drug Reaction/
26. Cohort Analysis/
27. harm$.mp.
28. (adverse event$ or (adverse adj2 reaction$)).mp.
29. ((side or unwanted adverse) adj effects$).tw.
30. (ADR or SAE).tw.
31. safety.mp.
32. (bleed$ or haemorrhag$ or hemorrhag$).tw.
33. (gastrotoxic$ or toxic$).tw.
34. (tolerability or tolerance or well tolerated).tw.
35. (relative risk or risks).mp.
36. (cohort and stud$).ti,ab.
37. (malignan$ or rare or surviv$ or risk#).tw.
38. (death or fatal$ or grave or die or lethal$ or mortal$).tw.
39. (adverse or serious or severe or poison$ or patholog$ or toxic$).tw.
40. (threaten$ or abnormal$ or failure event# or hazard$).tw.
41. or/16-40
42. (bare metal or bms).mp.
43. limit 15 to "treatment (2 or more terms min difference)"
44. limit 15 to "causation-etiology (optimized)"
45. 15 and 41
46. or/43-45
47. 15 not 46
48. 47 and 42
49. 46 or 48

CENTRAL search:
Ovid interface, The Cochrane Library, Issue 2, 2007
1. Stents/
2. exp Stent/
3. exp Drug Delivery Systems/
4. exp Drug Delivery System/
5. Drug Implants/
6. Drug Implant/
7. (des or drug elut$).tw.
8. Paclitaxel/
9. Sirolimus/
10. zotarolimus.mp.
11. elut$ stent$.tw.
12. (1 or 2) and (or/3-10)
13. 11 or 12

Articles used as seeds for the related articles search:

(1) Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349(14):1315-1323.

(2) Spaulding C, Henry P, Teiger E, Beatt K, Bramucci E, Carrie D et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006; 355(11):1093-1104.

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(4) Kelbaek H, Thuesen L, Helqvist S, Klovgaard L, Jorgensen E, Aljabbari S et al. The Stenting Coronary Arteries in Non-stress/benestent Disease (SCANDSTENT) trial. J Am Coll Cardiol 2006; 47(2):449-455.

(5) Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation 2004; 109(16):1942-1947.

(6) Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005; 294(10):1215-1223.

Related articles search history:

#1 Related Articles for PubMed (Search 16412876, 16971716, 16908768, 16160130, 15078803, 14523139[uid])
#2 Search Limits: published in the last 5 years, Clinical Trial
Search #1 and #2

Reference List

(1) Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007; 356(10):989-997.

(2) Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007; 356(10):1030-1039.

(3) Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J 2006; 27(23):2784-2814.

Appendix 2 Screening Form for Efficacy Review

Efficacy of DES vs BMS Study eligibility form

Study Name:
Study ID:

Type of study

Q1. Is the study described as randomized/cohort appropriate comparison group/cohort without comparison /case series/case report?

Yes Unclear - Go to next question
No **Exclude**

Participants in the study

Q2. Did the participants receive a DES?

N.B. Answer *'no' if participants had BMS alone*

Yes Unclear - Go to next question
No **Exclude**

Q3. Did another group receive the same care, with BMS?

Yes Unclear - Go to next question
No **Exclude**

Outcomes in the study

Q4. Did the study report death/myocardial infarct/stent thrombosis/target lesion revascularization/late luminal loss?

Yes Unclear **Include**

No **Exclude**

Final decision

Include

Unclear

Exclude

Appendix 3 Jadad Scale

Scoring the items:

Either give a score of 1 point for each "yes" or 0 points for each "no." There are no in-between marks.

Give 1 additional point if:	For question 1, the method to generate the sequence of randomization was described **and** it was **appropriate** (table of random numbers, computer generated, etc.)
and/or:	If for question 2 the method of double blinding was described **and** it was **appropriate** (identical placebo, active placebo, dummy, etc.)
Deduct 1 point if:	For question 1, the method to generate the sequence of randomization was described **and** it was **inappropriate** (patients were allocated alternately, or according to date of birth, hospital number, etc.)
and/or:	For question 2, the study was described as double blind but the method of blinding was **inappropriate** (e.g., comparison of tablet vs. injection with no double dummy)

Guidelines for Assessment

1. Randomization

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should be not regarded as appropriate.

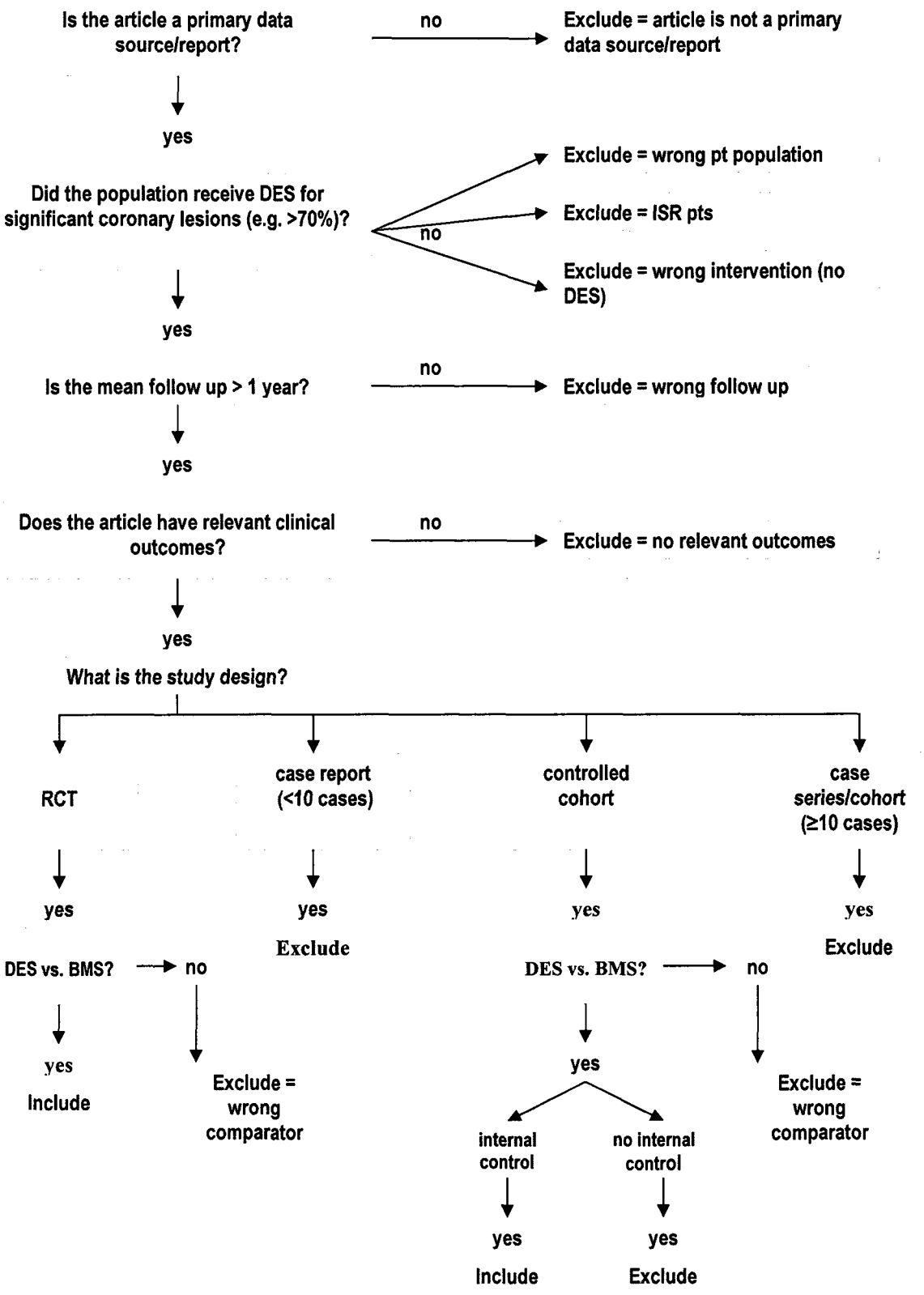
2. Double blinding

A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Appendix 4 Screening Tool for Harms Review



Appendix 5 Newcastle – Ottawa Quality Assessment Scale Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ▯
   b) somewhat representative of the average _____ *in the community* ▯
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ▯
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ▯
   b) structured interview ▯
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ▯
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ▯
   b) study controls for any additional factor ▯ *(This criteria could be modified to indicate specific control for a second important factor.)*

Outcome

1) Assessment of outcome
   a) independent blind assessment ▯
   b) record linkage ▯
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (*select an adequate follow up period for outcome of interest*) ▯
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ▯
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ▯
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

APPENDIX 6 Table of Characteristics for Included Studies for Efficacy Review

Table 4.1.1

Description of Included Trials: Sirolimus

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Ardissino 2004 (SES-SMART)	129/128	ACS/stable angina/silent ischemia by ETT with RVD<2.75 mm covered by one stent. Excluded STEMI, EF < 30%, calcification, thrombus.	Age: 63 Men: 72 Diabetes: 25 Cholesterol↑: 63 Hypertension: 65 Smoker: 42	MI: 29 PCI: 22 CABG: 8 EF: nr	SVD: nr Lesion Number: 1 Lesion Length: 11.84 Stent Length: 15.87 Type C Lesions: 4.3 RVD: 2.2	Cypher SES *vs* Uncoated Bx Sonic	Clopidogrel (2 months) ASA Ticlopidine Cilostazol	Clinical: 8 months - Death - MI - Stent thrombosis - TLR -Stroke Angio: 8 months - Late luminal loss Primary: 8 months - Angiographic re-stenosis	2, 0, 1, 1 DES/BMS<20%
Baumgart 2007 (SCORPIUS)	94/96	History of stable/unstable angina and signs of ischemia and diabetes currently treated with oral meds/insulin. Single target lesion RD 2.5-3.5 and length 42 mm. Excluded recent MI, EF <30 %, ostia ,calcified, thrombus, calcification.	Age: 66 Men: 66 Diabetes:100 Cholesterol↑: 77 Hypertension: 86 Smoker: 18	MI: 33 PCI: nr CABG: 4 EF: nr	SVD: nr Lesion Number: 1 Lesion Length: 11.84 Stent Length: 15.87 Type C Lesions: B2/c 91 RVD: 2.6	Cypher SES *vs* BMS	Clopidogrel (6 months) ASA Abciximab	Clinical: 9 months - Death - MI - Stent thrombosis - TLR Angio: 8 months - Late luminal loss Primary: 8 months - Late luminal Loss	1, 0, 1, 0 DES/BMS<20%
Diaz 2007	60/60	STEMI, CP > 30 min with ST segment elevation of 1mm on 2 or more contiguous leads, or recent onset LBBB, admitted within 12 hours, RVD 2.25-4.0 mm.	Age: 65 Men: 79 Diabetes: 28 Cholesterol↑: nr Hypertension: nr Smoker: 68	MI: 75 PCI: nr CABG: 1 EF: 53	SVD: nr Lesion Number: nr Lesion Length: Stent Length: 29.6 Type C Lesions: nr RVD: nr		Clopidogrel (1-9 months) ASA Abciximab	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angio: none Primary: 12 months - Death due to cardiac causes/MI/TLR	1, 1, 1, 0 NR

Author Year	Treatmen t/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Gao 2007	101/55	STEMI with onset of chest pain within 12 hours and STE or new LBBB. Exclusion if lesion severely calcified, low ef, renal dysfunction	Age: 59 Men: 40 Diabetes: 12 Cholesterol↑: 18 Hypertension: 36 Smoker: 36	MI: nr PCI: nr CABG: nr EF: nr	SVD: 17.9 Lesion Number: 1 Lesion Length: nr Stent Length: 31.1 Type C Lesions: nr RVD: 2.93	Firebird SES *vs* BMS Driver	Clopidogrel (9-12 months) ASA Heparin IV	Clinical: 6 months - Death - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6 months - Late Luminal Loss	1, 0, 0, 0 NR
Kaiser 2005 (BASKET)	264/281/ 281	All patients treated with PCI at a single centre irrespective of indication. Excluded RVD > 4mm, restenosis, physician preference of DES.	Age: 64 Men: 79 Diabetes: 19 Cholesterol↑: 75 Hypertension: 67 Smoker: 28	MI: 27 PCI: 16 CABG: 13 EF: nr	SVD: nr Lesion Number: 1.5 Lesion Length: nr Stent Length: 34 Type C Lesions: 24 RVD: nr	Cypher SES *vs* Taxus *vs* Vision stent BMS	Clopidogrel (6 months) ASA Heparin IV	Clinical: 8 months - Death - MI Stent Thrombosis Angio: none Primary: 8 months - Cost Effectiveness(Major Cardiac Death/Non Fatal MI/ TVR)	1, 0, 1, 0 DES/BMS<20%
Kelbaek 2006 (SCANDESTENT)	163/159	Stable / unstable angina / recent non STEMI and one or more lesions with RVD 2.25-4.50 and one of: occlusion with length >15mm, bifurcation, ostial lesion, angulation. Excluded thrombotic lesions and lesions in left main artery or bypass grafts.	Age: 63 Men: 77 Diabetes: 18 Cholesterol↑: 83 Hypertension: 42 Smoker: 35	MI: 52 PCI: nr CABG: nr EF: 54	SVD: nr Lesion Number: nr Lesion Length: 18 Stent Length: 24.35 Type C Lesions: 100 RVD: 2.87	Cypher SES *vs* BMS Bx Velocity s	Clopidogrel (12 months) ASA Heparin IV IIaIIIb ininbitor IV	Clinical: 7 months - Death -MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6 months - Mean Luminal Diameter	2, 0, 0, 0 DES/BMS<20%

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic *Primary Study Endpoint*	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Menichelli 2007 (SESAMI)	160/160	Patients with suspected acute MI having chest pain onset > 30 *min with* > 1*mm* STE in 2 leads or LBBB . Exclusion cardiogenic shock.	Age: 63 Men: 80 Diabetes: 21 Cholesterol↑: nr *Hypertension*: 57 Smoker: 54	MI: 9 PCI: 10 CABG: 6 EF: 51	SVD: 58 Lesion Number: 1 Lesion Length: 9.61 Stent Length: 18.15 *Type C Lesions: nr* RVD: nr	Cypher SES *vs* BMS Bx Velocity stent	Clopidigrel (12 months) ASA B blocker Abxicimab Heparin	Clinical: 12 months - Death - Stent thrombosis - TLR Angio: 12 months (subgroup of 50%) Late Luminal Loss Primary: 12 months - Binary Restenosis	2, 0, 0, 1 DES/BMS<20%
Morice 2002 (RAVEL)	120/118	Stable / unstable angina or silent ischemia with primary target lesion diameter 2.5-3.5 mm that could be covered by a single 18 mm stent. Excluded evolving MI / unprotected left main / osteal lesion, calcified lesion / thrombus / EF <30%.	Age: 61 Men: 76 Diabetes: 19 Cholesterol↑: 40 Hypertension: 61 Smoker: 30	MI: 36 PCI: 18 CABG: 2 EF: nr	SVD: 100 Lesion Number: 1 Lesion Length: 9.58 Stent Length: 18.00 Type C Lesions: 0 RVD: 2.62	Cypher SES *vs* BMS Bx Velocity stent	Clopidogrel (2 months) ASA Heparin Ticlopidine	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6 months - Late Luminal Loss	2, 2, 0, 0 DES/BMS<20%
Moses 2003 (SIRIUS)	533/525	History of stable / unstable angina and signs duplicate / single de novo lesion	Age: 62 Men: 71 Diabetes: 26 Cholesterol↑: 74 Hypertension: 68 Smoker: 20	MI: 31 PCI: excluded CABG: nr EF: nr	SVD: 58 Lesions number: 1 Lesion length: 14.4 Stent length: 21.2 Type C: 26 RVD: 2.8	Cypher SES *vs* BMS Bx Velocity	Clopidogrel (3months) ASA Heparin	Clinical: 9 months - Death - MI - Stent thrombosis - TLR Angio: 8 months substudy *Late Luminal Loss* Primary: 9 months - TVR	1, 2, 1, 1 DES/BMS<20%

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - *Reference Vessel* Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Ortolani 2007	52/52	Symptomatic coronary disease. Single lesion <28 mm in native vessel with RVD <3 mm. Excluded STEMI, EF < 30%, renal failure.	Age: 66 Men: 76 Diabetes: 16 Cholesterol↑: 80 Hypertension: 66 Smoker: 56	MI: 29 PCI: 16 CABG: 2 EF: 58	SVD: 24 Lesion Number: nr Lesion Length: 14.6 Stent Length: 18.4 Type C Lesions: 24 RVD: 2.93	Cypher SES *vs* Thin strut BMS	Clopidogrel (3 months) ASA	Clinical: 1 2 months - Death - MI - Stent thrombosis - TLR Angio: 9 months Late Luminal Loss Primary: 9 months - Late Luminal Loss(in segment)	1, 0, 1, 0 NR
Pache 2005	250/250	Symptomatic coronary disease in native coronary vessel. Excluded acute MI, left main lesion, ISR.	Age: 67 Men: 78 Diabetes: 31 Cholesterol↑: 59 Hypertension: 59 Smoker: 18	MI: 31 PCI: nr CABG: 8 EF: nr	SVD: nr Lesion Number: 1 Lesion Length: nr Stent Length: 18 Type C Lesions: 13.5 RVD: 2.7	Cypher SES *vs* BMS Be	Clopidogrel (6 months) ASA Heparin	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6 months - Restenosis	2, 0, 0, 0 DES/BMS<20%
Sabate 2005 (DIABETES)	80/80 (111/110)	Diabetes according to WHO, lesion in 1/2/3 vessels, with symptoms or objective evidence, RVD <4.0 mm. Excluded untreated diabetes, CABG, ACS with persistent STE, EF < 25%, ISR, non STEMI.	Age: 67 Men: 63 Diabetes: 100 Cholesterol↑: 61 Hypertension: 66 Smoker: 48	MI: 37 PCI: nr CABG: nr EF: 65	SVD: <35 Lesion Number: 1.4 Lesion Length: 15 Stent Length: 23 Type B2/C Lesions: 80.1 RVD: 2.34	Cypher SES *vs* BMS Bx Velocity stent	Clopidogrel 12 months ASA Heparin GIIaIIIb inhibitor	Clinical: 9 months - Death - MI - Stent thrombosis - TLR Angio: 9 months Late Luminal Loss Primary: 9 months - Late Luminal Loss(in segment)	2, 0, 0, 1 DES/BMS<20%

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Sako 2008	16/16	Patients with stable angina who had lesions greater than 50% on coronary angiogram. Stent diameter >2.5mm.	Age: 63 Men: 91 Diabetes: 56.3 Cholesterol↑: 56 Hypertension: 69 Smoker: 62	MI: nr PCI: nr CABG: nr EF:	SVD: 59.3 Lesion number: nr Lesion length: nr Stent length: 20.5 Type B2/C: 59.5 RVD: 3.1	Cypher SES *vs* BMS	Ticlopidine (Length of treatment not defined.) ASA Heparin	Clinical: 8 months - Death(Cardiac only) - TLR Angio: 199 days Late Luminal Loss Primary: 8 months - expression of molecules (CCR2,MCP-1)	1, 0, 0, 0 NR
Schampart 2004 (C-SIRIUS)	51/51	Angina / unstable angina / silent ischemia. Single de novo lesion 15-32mm, RVD 2.5-3.0 mm. Excluded MI, ostial calcified, thrombus, side branch, EF < 25%.	Age: 61 Men: 69 Diabetes: 24 Cholesterol↑: 85 Hypertension: 52 Smoker: 37	MI: 45 PCI: 8 CABG: 4 EF:	SVD: nr Lesion number: 1 Lesion length: 13.55 Stent length: 23.8 Type B2/C: 59 RVD: 2.63	Cypher SES *vs* BMS Bx Velocity stent	Clopidogrel (2 months) ASA Heparin GIIaIIIb inhibitor	Clinical: 8 months - Death - MI - Stent thrombosis - TLR Angio: 8 months Late Luminal Loss Primary: 8 months - Mean Luminal Diameterlin stent)	1, 2, 0, 0 DES/BMS<20%
Schofer 2003 (E SIRIUS)	175/177	Angina/unstable angina/silent ischemia. One lesion RVD 2.5-3.0 15-32 mm. Excluded MI, lesion/ostial,/calcified,/thrombus/ side branch, EF < 25%.	Age: 62 Men: 71 Diabetes: 23 Cholesterol↑: 74 Hypertension: 64 Smoker: 33	MI: 42 PCI: 21 CABG: 6 EF: nr	SVD: 64 Lesion Number: 1 Lesion Length: 15 Stent Length: 22.6 Type C Lesions: nr RVD: 2.55	Cypher SES *vs* Uncoated Bx Velocity	Clopidogrel (2 months) ASA Heparin IV	Clinical: 8 months - Death - MI - Stent thrombosis - TLR Angio: 8 months Late Luminal Loss Primary: 8 months - Mean Luminal Diameter	1, 2, 1, 0 DES/BMS<20%

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Spaulding 2006 (TYPHOON)	356/359	STEMI with symptoms less than 12 hours from onset and STE. Excluded fibrinolytic agents, CHF, EF < 30%, torotulsity ??, calcification, thrombus, severe 3VD, lesion < 30 mm and RVD 2.25 - 3.50.	Age: 58 Men: 78 Diabetes: 16 Cholesterol↑: 41 Hypertension: 39 Smoker: 46	MI: nr PCI: 3 CABG: nr EF: 52	SVD: 56 Lesion Number: 1 Lesion Length: nr Stent Length: 22.1 Type C Lesions: na RVD: 2.87	Cypher SES *vs* Any commercially available BMS stent	Clopidogrel/Ticlipidine (6 months) ASA GIIbIIIA	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angio: 8 months Late Luminal Loss Primary: 12 months - Target Vessel Failure	1 ,0 ,1, 0 DES/BMS<20%
Strozzi 2007	40/39/40	Stent implantation in the setting of ACS defined as STEMI or recurrent episodes of chest pain with enzyme elevation and ST segment deviation. Excluded previous PCI, CABG, multivessel, diffuse disease, tortuous arteries, left main and bifurcation lesions.	Age: 64 Men: 72 Diabetes: 25 Cholesterol↑: 63 Hypertension: 56 Smoker: 42	MI: nr PCI: excluded CABG: excluded	SVD: nr Lesion number: nr Lesion length: 12 Stent length: nr Type C: nr RVD: 3.4	Stent graft *vs* SES *vs* BMS	Ticlopidine (1.5 months) ASA Heparin Eptifibatide	Clinical: 188 months - Death - MI - Stent thrombosis - TLR Angio: 188 months Late Luminal Loss Primary: 188 months - In Stent Restenosis	2, 0, 0, 0 DES/BMS<20%
Suttorp 2006 (PRISON)	100/100	Coronary occlusion less than 2 weeks, with evidence of ischemia on stress testing.	Age: 60 Men: 80 Diabetes: 13 Cholesterol↑: 90 Hypertension: 46 Smoker: 37	MI: 49 PCI: 17 CABG: 2.5 EF:	SVD: 49 Lesion Number: 1 Lesion length: 16.2 Stent length: 30.4 Type C: 100 RVD: 2.57	Cypher SES *vs* BMS Bx Velocity stent	Clopidogrel (at least 6 months) ASA Heparin	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6 months - In Segment Restenosis	1, 0, 0, 1 DES/BMS<20%

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria with single de novo lesion. Single target lesion in .	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Vermeersch 2006 (RRISC)	38/37 47/49	History of prior CABG, stable/unstable angina and had one or more de novo lesion in one or more disease SVG with RVD 2.5-4.0mm. Excluded MI within 7 days, EF < 25%, distal anastamotic lesion, prior brachytherapy in the reference vessel.	Age: 73 Men: 86 Diabetes: 15 Cholesterol↑: 86 Hypertension: 57 Smoker: 54	MI: 43 PCI: 36.05 CABG: 100 EF:54	SVD: 73.30 Lesion number: 1.28 Lesion length: 17.40 Stent length: 35.15 Type C: RVD: 3.31	Cypher SES *vs* BMS Bx Velocity stent	Clopidogrel (2 months) AS Heparin GIIbIIIa	Clinical: 8 months - Death - MI - Stent thrombosis - TLR Angio: 8 months Late Luminal Loss Primary: 8 months - In Stent Late Loss	2, 2, 1, 0 DES/BMS<20%
Van der Hoven 2006 (MISSION)	158/152	STEMI with ECG evidence of ≥.2mv in 2 leads V1-V3 or new LBBB.	Age: 59 Men: 78 Diabetes: 10 Cholesterol↑: 20 Hypertension: 28 Smoker: 55	MI: 3.9 PCI: 1.6 CABG: 0.65 EF: nr	SVD: 66 Lesion number: NR Lesion length: 14.45 Stent length: 26.5 Type C: nr RVD: 2.84	Cypher SES *Vs* BMS	Clopidogrel(12 months) ASA Heparin (peri)	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angio: 9 months Late Luminal Loss Primary: 9 months - Late Luminal Loss	1, 0, 1, 0 DES/BMS<20%

Description of Included Trials: Abciximab

Author Year	Treatment Control (Number of Lesions)	Population	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Kim 2006	48/48	AMI, age 18-80 years. Target vessel diameter 2.5-4.0mm, lesion length <25mm and lesion >50%.	Age: 58 Men: 83 Diabetes: 20 Cholesterol↑: 23 Hypertension: 46 Smoker: 58	MI: 1 PCI: nr CABG: 2 EF: 58	SVD: 79 Lesion Number: 1 Lesion Length: 11.3 Stent Length: 18.1 Type C Lesions: 0 RVD: 2.99	Abciximab *vs* BMS	Clopidogrel (2 months) ASA Heparin	Clinical: 6 months - Death - MI - Stent thrombosis - TLR -Stroke -Bleeding -Angina Angio: 6 months Late Luminal Loss Primary: 6 months - Late Luminal Loss (In Stent)	1, 0, 0, 0 DES/BMS>20%
Hong 2004	43/42	Elective PCI for single short de novo lesions.	Age: 57 Men: 81 Diabetes: 20 Cholesterol↑: 35 Hypertension: 52 Smoker: 56	MI: 4 PCI: 0 CABG: 0 EF: 63	SVD: 89 Lesion Number: 1 Lesion Length: nr Stent Length: 18 Type C Lesions: 2 RVD: 3.28	Abciximab 90ug Stent *vs* BMS	Clopidogrel or Ticlopidine (30 days) ASA	Clinical: 6 months - Death - Stent thrombosis Angio: 6 months Late Luminal Loss Primary: 6 months - Angiographic/IVUS(no power calculation)	1, 0, 0, 0 NR

Description of Included Trials: Dexamethasone

Author Year	Treatment/ Control (Number of Lesions)	Population: - Inclusion / Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Han 2006	67/25	native coronary lesions which could be covered by a 15 or 18mm stent	Age: 60 Men: 62 Diabetes: 38 Cholesterol↑: 29 Hypertension: 55 Smoker: 35	MI: 3.5 PCI: 17 CABG: nr EF: 64	SVD: 38 Lesion Number: 1.05 Lesion Length: 16.71 Stent Length: nr Type B2/C Lesions: 72 RVD: 3.12	Dexamethasone eluting 0.5µg/mm2 stent biodivsio drug *vs* BMS	Clopidogrel or Ticlopidine (1 month) ASA Heparin	Clinical: 12months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 12 months - MACE(Death, non fatal q wave/nonq wav mi/TLR)	1, 0, 0, 0 DES/BMS<20%
Konig 2007	60/60	ACS with STE or enzyme elevation with de novo lesions	Age: 63 Men: 69 Diabetes: 48 Cholesterol↑: 62 Hypertension: 89 Smoker: 63	MI: 17 PCI: nr CABG: nr EF: 58	SVD: 32 Lesion Number: nr Lesion Length: 9.74 Stent Length: 15.03 Type C Lesions: 49 RVD: 2.98	Dexamethasone *vs* BMS	Clopidogrel (12 months) ASA	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6 months - Late Luminal Loss (In Stent)	1, 1, 1, 0 DES/BMS<20%

Description of Included Trials: Paclitaxel

Author Year	Treatment Control (Number of Lesions)	Population: - Inclusion/ Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Chechi 2007 (SELECTION)	40/40	Chest pain persisting more than 30 min associated with STE >0.1mV in 2 or more contiguous leads. Excluded cardiogenic shock, RVD <2.25 mm	Age: 61 Men: 83 Diabetes: 13 Cholesterol↑: 33 Hypertension: 47 Smoker: 54	MI: 3.8 PCI: nr CABG: nr EF: 53.3	SVD: 55 Lesion number: nr Lesion length: nr Stent length: 19.6 Type C: nr RVD: nr	Taxus Express *vs* Express stent	Clopidogrel (9 months) ASA, *Abciximab (pre/peri)*, Unfractioned Heparin (during)	Clinical: 7 months - Death - MI - Stent thrombosis - TLR Angio: 7 months Late Luminal Loss Primary Endpoint:: 7 months % stent volume obstructed by neointimal proliferation	1, 0, 1, 0 DES/BMS<20%
Columbo 2003 (TAXUS II)	131/136 SR 135/139 MR	Stable/unstable angina and silent ischemia; de novo single/multiple lesions. Lesion length less than 12 mm, RVD 3.0-3.5mm. Excluded: unprotected left main, AMI, necessity to implant more than 1 15mm stent for full coverage.	Age: 60 Men: 76 Diabetes: 15 Cholesterol↑: nr Hypertension: 62 Smoker: 25	MI: 40 PCI: nr CABG: nr EF: nr	SVD: nr Lesion number: 1 Lesion length: 10.55 Stent length: 15 Type C: nr RVD: 2.8	Taxus NIRx Slow release *vs* uncoated NIR Taxus NIRx Moderate release *vs* uncoated NIR	Clopidogrel or ticlopidine (at least 6 mos) ASA (alternate to x2/day, Heparin	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary Endpoint:: 6 months % stent volume by IVUS	1, 2, 0, 0 DES/BMS<20%

Author Year	Treatment Control (Number of Lesions)	Population: - Inclusion/ Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Dawkins 2005 (TAXUS VI)	219/227	Evidence of myocardial ischemia, de novo lesion in a single coronary artery, RVD 2.5-3.75 mm., lesion length 18-40mm. Lesions needed to be covered with 2 stents up to 48mm. Randomization post treatment of non study lesion in non target vessel was allowed. Excluded AMI, side branch, total occlusion ,osteal lesion.	Age: 76? Men: 63? Diabetes: 22 Cholesterol↑: 73 Hypertension: 58 Smoker: 24	MI: nr PCI: 21 CABG: nr EF: nr	SVD: nr Lesion number: 1 Lesion length: 20.31 Stent length: 33.2 Type C: 55 RVD: 2.77	Taxus Express moderate release *vs* Express stent BMS	Clopidogrel or Ticlodipine (6 mos) ASA Heparin	Clinical: 9 months - Death - MI - Stent thrombosis - TLR Angio: 9 months Late Luminal Loss Primary: 9 months -TVR	1, 2, 0, 1 DES/BMS<20%
Erglis 2007	53/50	Clinically symptomatic LM lesion with angiographic evidence of greater than 50% diameter stenosis suitable for stent implantation.	Age: 83.5??? Men: ??? Diabetes: 6? Cholesterol↑: 11.5? Hypertension: 74.5 Smoker: 54.5?	MI: 61.8 PCI: 48.5 CABG: 39 EF: nr	SVD: 54.9 Lesion number: 1 Lesion length: 11.57 Stent length: 17.5 Type C: nr RVD: 3.255	Taxus Express *vs* Express BMS/ Liberte BMS	Clopidogrel (75 mg/day/6 months) Heparin (during), GIIbIIIa (operators discretion) Cutting ballloon	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: unclear	1, 0 ,1, 0 DES/BMS<20%

Author Year	Treatment Control (Number of Lesions)	Population: - Inclusion/ Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Gershlick 2004 (ELUTES 2)	37 40 39 37 Vs 40 Controls	De novo single lesion type A/B1 < 15mm native artery in patients candidates for .CABG. Exclusion ef<35%, total occlusions, unprotected left main	Age: 60 Men: 82 Diabetes: 16 Cholesterol↑: 50 Hypertension: 46 Smoker: 35	MI: 34 PCI: 0 CABG: 2.2 EF: nr	SVD: 57 Lesion Number: 1 Lesion Length: 11.7 Stent Length: 16 Type C Lesions: 0 RVD: 2.99	V Flex Plus stent with Paxel directly on stent at different doses (0.2/0.7/ 1.4/2.7ug/mm3) *Vs* BMS	Clopidogrel (3 mos) ASA Heparin	Clinical: 6 months - Death - MI - Acute thrombosis - TLR Angiographic: 6 months Late Luminal Loss Primary Endpoint:: 6 months In stent % diameter	1 , 1 , 0 , 0 DES/BMS<20%
Grube 2004 (SCORE)	126/140	Stable/ unstable angina or silent ischemia with single de novo lesion. Single 13-17mm stent with stenosis >50% and location in vessel >3.0-3.5mm diameter. Excluded excessive tortuosity, side branch, moderate calcification acute MI.	Age: 62 Men: 78 Diabetes: 21 Cholesterol↑: 75 Hypertension: 66 Smoker: 17	MI: 40 PCI: nr CABG: nr EF: nr	SVD: nr Lesion Number: 1 Lesion Length: 11.84 Stent Length: nr Type C Lesions: nr RVD: 2.96	QuaDS QP2 stent + polymer sleeve with 800ug 7-hexanoytaxol *vs* Quest(BMS)	Clopidogrel (1 mos) or ASA Heparin	Clinical: 6months - Death - MI - Stent thrombosis - TLR Angio: 6 months Late Luminal Loss Primary: 6months -Clinical TVR(no definition provided)	1 , 0 , 0 , 0 DES/BMS<20%

Author Year	Treatment Control (Number of Lesions)	Population: - Inclusion/ Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Grube 2006 (APPLAUSE)	20/10 34/10	Stable/unstable angina or silent ischemia with single de novo lesion.	Age: 68 Men: 83 Diabetes: 20 Cholesterol↑: 85 Hypertension: 75 Smoker: 25	MI: 17.5 PCI: 22.5 CABG: 5 EF: nr	SVD: nr Lesion number: 1.17 Lesion length: 11.91 Stent length: 18.44 Type C: nr RVD: 2.90	Picoelite paclitaxel-eluting 1mcg/mm2, *vs* BMS	Clopidogrel (6 mos) ASA Heparin (pre Tx)	Clinical: 6 months - Death - MI - Stent thrombosis - Angina Angio: 6months Late Luminal Loss Primary: 6 months - Rate of major adverse events	1, 0, 0, 0 DES/BMS<20%
Grube 2005 (TAXUS 1)	31/30	Single lesion, native or ISR. Lesion length <=12 mm, 50-99% stenosis and diameter 3.0mm-3.5mm. Excluded I history of AMI or target lesion requiring > 1 study stent.	Age: 65 Men: 89 Diabetes: 18 Cholesterol↑: 81 Hypertension: 64 Smoker: 51	MI: 28 PCI: nr CABG: nr EF: nr	SVD: nr Lesion number: 1 Lesion length: 11.3 Stent length: 15 Type C: 0 RVD: 2.97	TAXUS NIR x slow rate release 1ug/mm3 *vs* NIR_bms	Clopidogrel (6 mos) ASA Heparin	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angio: 6 months *Late Luminal Loss* Primary Endpoint: 12 months - Q wave MI + TVR + stent thrombosis at 30 days	1, 2, 0, 0 NR
Laarman 2006 (PASSION)	310/309	STEMI with STE of at lest 1mm in 2 contiguous leads. Reperfusion was expected within 6 hours. Excluded thrombolytics, ISR or ST. .	Age: 61 Men: 76 Diabetes: 11 Cholesterol↑: 26 Hypertension: 30 Smoker: 52	MI: 5.15 PCI: 4.2 CABG: 0.6 EF: nr	SVD: 55.05 Lesion number: 1 Lesion length: nr Stent length: 19 Type C: nr RVD: 3.22	Taxus Express 2 stent *vs* express 2 or liberte BMS	Clopidogrel (6 mos) ASA Heparin, Giibiiia	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angio: none Primary: 12 months -Serious Adverse Events *(Cardiac Death, Recurrent* MI, Ischemia driven TLR)	1, 1, 0, 0 DES/BMS<20%

Author Year	Treatment Control (Number of Lesions)	Population: - Inclusion/ Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Lansky 2004 (DELIVER)	524/519	Angina or positive functional study with at least a single de novo lesion. RVD 2.5-4.0mm, <25mm and TIMI≥1. Two vessel treatment was allowed if lesions if one lesion per vessel	Age: 62 Men: 71 Diabetes: 29 Cholesterol↑: 60 Hypertension: 66 Smoker: 25	MI: 26 PCI: nr CABG: nr EF: nr	SVD: nr Lesion Number: 1 Lesion Length: 11 Stent Length: nr Type C Lesions: 6 RVD: 2.81	Paclitaxel coated RX Achieve *vs* stainless steel RX multi-link Penta	Clopidogrel (3 months) ASA	Clinical: 9 months TLR Angiographic: 8 months substudy Late Luminal Loss Primary Endpoint: TVF (death, qwave mi, nonqwave mi, tlr by cabg or pci)	1, 0, 1, 0 nr
Park 2003 (ASPECT)	58/59 60/69	Patients with CAD requiring stenting of a single new lesion <15mm.	Age: 60 Men: 76 Diabetes: 20 Cholesterol↑: 13 Hypertension: 47 Smoker: 44	MI: 25 PCI: nr CABG: 2 EF: nr	SVD: 60 Lesion Number: 1 Lesion Length: 11 Stent Length: 15 Type C Lesions: 1 RVD: 2.92	Supra G stent 1.3 ug/mm2 Taxus *vs* Supra stent (Cook) Supra G stent 3.1 Tax ug/mm2 *vs* Supra stent (Cook)	Clopidogrel (4-24 wks) ASA Heparin Ticlopidine	Clinical: 6 months - Death - MI - Acute thrombosis - TIR Angiographic: 6 months Late Luminal Loss Primary Endpoint::6 months % stenosis	1, 2, 0, 0 DES/BMS<20%

Author Year	Treatment Control (Number of Lesions)	Population: - Inclusion/ Exclusion Criteria	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Stone 2005 (TAXUS 5)	596/586	Angina/ unstable angina or positive functional image in more complex lesions and single de novo lesion. Excluded MI within 72 hours, left main or ostial lesion, significant calcification, tortuosity or calcification , bifurcation disease, total occlusion, RVD 2.5-4.0 mm. Successful treatment of 1-2 non study lesions in non study vessel prior to randomization was permitted.	Age: 63 Men: 69 Diabetes: 31 Cholesterol↑: 73 Hypertension: 75 Smoker: 21	MI: 29 PCI: nr CABG: nr EF: nr	SVD: nr Lesion number: 1 Lesion length: 17.3 Stent length: 28.5 Type C: 37 RVD: 2.68	Taxus Express Slow release 1ug/mm3 *vs* Express stent	Clopidogrel (6 mos) ASA Heparin	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angio: none Primary: 12 months -Serious Adverse Events (Cardiac Death, Recurrent MI, Ischemia driven TLR)	1 ,2 ,0 , 0 DES/BMS<20%
Stone 2004 (TAXUS IV)	667/659	Stable/ unstable angina or irrevocable angina and single de novo lesion. Excluded AMI, left main lesion, osteal lesion, calcification tortuosity, angulation, bifurcation, occlusion. One additional non study lesion in non study lesion was allowed.	Age: 63 Men: 72 Diabetes: 24 Cholesterol↑: 65 Hypertension: 70 Smoker: 22	MI: 30 PCI: 19 CABG: 0 EF: 55	SVD: nr Lesion number: 1 Lesion length: 21.8 Stent length: 13.4 Type C: 37.3 RVD: 2.75	Taxus NIRx slow release 1ug/mm3 *vs* Express BMS	Clopidogrel (6 mos) ASA, Heparin	Clinical: 9 months - Death - MI - Stent thrombosis - TLR Angio: 9 months Late Luminal Loss Primary: 9 months TVR(>50% + ECG changes/MPI +ve or 70% with symptoms	1, 2, 0, 0 NR

Description of Included Trials: Estradiol

Author Year	Treatment Control (Number of Lesions)	Population	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization , - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Abizaid 2007 (ETHOS 1)	32/32/31	18 years+, stable angina pectoris (CCS 1-4), unstable angina pectoris (Braunwald Class IB-C, IIB-C or IIIB-C) or silent ischemia, candidates for coronary artery bypass surgery, ≥2.5-≤3.5 RVD	Age: 62 Men: 74 Diabetes: 30 Cholesterol↑: 83 Hypertension: 80 Smoker: 22	MI: 27 PCI: 16 CABG: 1 EF: 64	SVD: 100 Lesion Number: 1.0 Lesion Length: 11.6 Stent Length: 19.9 Type C Lesions: nr RVD: 2.9	17-β Estradiol-Eluting Stent Slow Release vs 17-β Estradiol-Eluting Stent Moderate Release *vs* BMS uncoated	Clopidogrel (75mg/day) or ticlopidine 2 months ASA 325 mg po od1 month then 75 mg po od Heparin - (during)	Clinical: 6 months - Death - MI - Stent Thrombosis - TLR Angiographic: 6 months Late Luminal Loss Primary Endpoint: in-stent volume obstruction	1, 2, 0, 0 nr
Airoldi 2005	54/54	Stable /unstable angina and/or had objective evidence of ischemia. De novo single/multiple lesion	Age: 61 Men: 91 Diabetes: 25 Cholesterol↑: 48 Hypertension: 59 Smoker: 18	MI: 43 PCI: 9 CABG: 24 EF: nr	SVD: nr Lesion Number: 1.22 Lesion Length: 12.4 Stent Length: 22.8 Type C Lesions: nr RVD: 2.98	17-β Estradiol Stent 50-100 um vs BMS	Clopidogrel or Ticlopidine (12 weeks) ASA Heparin	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angiographic: 6 months Late Luminal Loss Primary Endpoint: 6 months angiographic restenosis>50%	1, 0, 0, 0 nr

Description of Included Trials: Sirolimus Analogues

Author Year	Treatment Control (Number of Lesions)	Population	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Fajadet 2006 (ENDEAVOR 2)	598/599	Ischemia/positive function study of single untreated lesion.	Age: 62 Men: 76 Diabetes: 20 Cholesterol↑: 79 Hypertension: nr Smoker: 35	MI: 41 PCI: 20 CABG: nr EF: nr	SVD: 100 Lesion Number: 1 Lesion Length: 12.72 Stent Length: 23.4 Type C Lesions: 28 RVD: 2.79	Zotarolimus *vs* Driver BMS	Clopidogrel (3 months) ASA	Clinical: 9 months - Death - MI - Stent thrombosis - TLR Angiographic 8 months subgroup Late Luminal Loss Primary: 9 months TVR	1, 2, 0, 0 DES/BMS<20%
Han 2007	100/100	Symptomatic or documented myocardial ischemia including AMI, one kind of stent, not greater than 3 stents per target vessel (total length ≤ 85mm)	Age: 58 Men: 77 Diabetes: 22 Cholesterol↑: 36 Hypertension: 56 Smoker: nr	MI: nr PCI: nr CABG: nr EF: nr	SVD: nr Lesion Number: 1.07 Lesion Length: 27 Stent Length: nr Type C Lesions: 95 RVD: 3.08	Tacrolimus *vs* BMS	Clopidogrel (4months) ASA 300mg od for 1 month then 100 mg od lefelong	Clinical: 12 months - Death - MI - Stent thrombosis - TLR Angiographic: none Primary: 12 months MACE	2, 0, 1, 0 DES/BMS<20%

Author Year	Treatment Control (Number of Lesions)	Population	Patient Characteristics: - Age (SD) - Male (%) - Diabetes (%) - Cholesterol↑ (%) - Hypertension (%) - Smoker (%)	Degree of Coronary Disease: - Prior MI (%) - Prior PCI (%) - Prior CABG (%) - Ejection Fraction (%)	Lesions: - Single Vessel Disease (%) - Lesion Number (N) - Lesion Length (mm) - Stent Length (mm) - Type C Lesions (%) - Reference Vessel Diameter (mm)	Treatment vs Comparison	Antiplatelet Therapy	Included Endpoints: - Clinical - Angiographic Primary Study Endpoint	Quality: R, B, W, AC - Randomization, - Blinding - Withdrawals - Allocation Concealment Withdrawal details:
Grube 2004 (FUTURE)	80/40	Focal non-complex de novo leisons.	Age: 65 Men: 86 Diabetes: 2 Cholesterol↑: 79 Hypertension: 76 Smoker: 30	MI: 14 PCI: 25 CABG: nr EF: nr	SVD: nr Lesion Number: 1.02 Lesion Length: 14.56 Stent Length: nr Type C Lesions: 2 RVD: 2.96	Biolimus A9 DES *vs* BMS	Clopidogrel (6 months) ASA	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angiographic: 6 months Late Luminal Loss Primary Endpoint: 1 month Freedom from major adverse events	1, 0, 0, 0 DES/BMS<20%
Grube 2005 (STEALTH)	80/40	≥18 years, angina or ischemia, candidate for coronary artery bypass surgery, RVD 2.75-4.0. Exclusion included side branch>2mm, prior stenting of the target lesion, EF<30%, indication for >1 stent, AMI or recent stroke	Age: 62 Men: 60 Diabetes: 27 Cholesterol↑: 80 Hypertension: 84 Smoker: 46	MI: 38 PCI: nr CABG: 10 EF: 62	SVD: nr Lesion Number: 1.03 Lesion Length: 14.56 Stent Length: 17.63 Type C Lesions: 21 RVD: 2.96	Biolimus A9 DES, *vs* BMS Stent ,	Clopidogrel (6 months) ASA	Clinical: 6 months - Death - MI - Stent thrombosis - TLR Angiographic: 6 months Late Luminal Loss Primary Endpoint: 6 months in lesion late loss	1, 0, 0, 0 DES/BMS<20%

Nr = not reported
Na = not available
For additional clinical short forms, see Table of abbreviations
EF = ejection fraction
ETT = exercise treadmill test
LBBB = left bundle branch block

Appendix 7-Tables 4.1.2 to 4.1.8
Table 4.1.2: Subgroup and Sensitivity Analysis for the Outcome of Death

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 total death- on treatment analysis	50	13153	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.2 total death- itt	50	14303	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.69, 1.16]
1.3 outcome of death-divided by time point	47	21044	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.74, 1.17]
1.3.1 in hospital	12	3205	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.25, 1.84]
1.3.2 30 days	19	3511	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.42, 1.49]
1.3.3 6 months	25	3173	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.60, 1.89]
1.3.7 outcomes reported 6-9 months	14	6979	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.69]
1.3.8 12months	18	4176	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.26]
1.4 Allocation Concealment?	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.4.1 +	5	2241	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.25, 1.12]
1.4.2 ?/-	45	10903	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.29]
1.5 Blinding?	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.5.1 +	14	5459	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.65, 1.85]
1.5.2 ?/-	36	7685	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.13]
1.7 Reference vessel Diameter	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.7.1 >2.5	43	11388	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.35]
1.7.2 ≤2.5	2	417	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.04, 1.34]
1.7.3 No data	5	1339	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.33, 1.28]
1.8 Lesion length	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.8.1 >12	19	7847	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.57]
1.8.2 ≤12	22	2688	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.50, 1.51]
1.8.3 No data	9	2609	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.49, 1.19]
1.9 Stent length	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.9.1 >18	27	10164	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.64, 1.15]
1.9.2 ≤18	15	2312	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.46, 1.91]
1.9.3 No data	8	668	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.47, 8.76]
1.10 Number of lesions stented	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.10.1 >1	11	2152	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.36]
1.10.2 =1	32	9902	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.35]
1.10.3 No data	7	1090	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.27, 1.51]
1.11 Diabetes	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.11.1 >30%	10	2376	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.57, 1.84]
1.11.2 ≤30%	40	10768	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.64, 1.16]
1.11.3 No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.12 total death- by stent type at study end	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.12.1 Sirolimus Analogue	4	1545	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.56, 4.98]
1.12.2 Sirolimus	20	5665	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.35]

1.12.3 Paxel with coating	12	4975	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.56, 1.24]
1.12.4 Paxel without coating	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.12.5 Abxicimab	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.12.6 Estradiol	3	199	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.28]
1.12.7 Dexamethasone	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.13 Total death - by stent type and allocation concealment	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.13.1 Dexamethasone +	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.13.2 Dexamethasone -/?	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.13.3 Sirolimus Analogue+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.13.4 Sirolimus Analogue -/?	4	1545	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.56, 4.98]
1.13.5 Abxicimab +	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.13.6 Abxicimab -/?	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.13.7 Estradiol +	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.13.8 Estradiol -/?	3	199	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.28]
1.13.9 Sirolimus +	4	1795	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.26, 1.26]
1.13.10 Sirolimus -/?	18	4896	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.66, 1.35]
1.13.11 Paxel with coating +	1	446	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.29]
1.13.12 Paxel with coating -/?	8	3423	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.60, 1.92]
1.13.13 Paxel without coating +	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.13.14 Paxel without coating -/?	8	447	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.70]
1.14 Length of Plavix treatment	50	13153	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.14.1 1 month	4	523	Risk Ratio (M-H, Fixed, 95% CI)	7.77 [0.41, 149.00]
1.14.2 2 month	8	1209	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.34, 2.44]
1.14.3 3 month	10	2845	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.63, 2.81]
1.14.4 6 month	19	6972	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.64, 1.27]
1.14.5 9 month	3	356	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.07]
1.14.6 12 month	5	1216	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.20, 1.07]
1.14.7 no data	1	32	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.15 time post Plavix treatment	50	13153	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.15.1 delta 0	19	3501	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.34, 0.96]
1.15.2 delta 1 month	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.15.3 delta 2 month	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.15.4 delta 3 month	10	3497	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.58, 1.72]
1.15.5 4 months	6	580	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.30, 3.70]
1.15.6 delta 5 month	4	643	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [0.40, 11.18]
1.15.7 delta 6 month	11	4932	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.70, 1.58]
1.16 Length of Plavix treatment on at endpoint	50	13153	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.16.1 1 month	4	523	Risk Ratio (M-H, Fixed, 95% CI)	7.77 [0.41, 149.00]
1.16.2 1 month and at endpoint	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.16.3 2 month	8	1209	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.34, 2.44]
1.16.4 2 month and at endpoint	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

1.16.5 3 month	10	2845	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.63, 2.81]
1.16.6 3 month and at endpoint	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.16.7 6 month	9	4630	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.36]
1.16.8 6 month and at endpoint	10	2342	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.47, 1.68]
1.16.9 9 month	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.16.10 9 month and at endpoint	3	356	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.07]
1.16.11 12 month	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.16.12 12 month and at endpoint	5	1216	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.20, 1.07]
1.16.13 no data	1	32	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.17 Total death - by stent type and blinding	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.17.1 Dexamethasone +	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.17.2 Dexamethasone -/?	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.17.3 Sirolimus Analogue+	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.17.4 Sirolimus Analogue -/?	2	1303	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.61, 8.96]
1.17.5 Abxicimab +	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.17.6 Abxicimab -/?	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.17.7 Estradiol +	2	91	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.06, 33.75]
1.17.8 Estradiol -/?	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.07]
1.17.9 Sirolimus +	3	1371	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.52, 4.41]
1.17.10 Sirolimus -/?	19	4536	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.27]
1.17.11 Paxel without coating +	2	175	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.06, 36.33]
1.17.12 Paxel without coating -/?	5	192	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.04, 19.85]
1.17.13 Paxel with coating +	6	3470	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.47, 1.72]
1.17.14 Paxel with coating -/?	6	1505	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.32]
1.18 total death- by stent type at study end and reference vessel diameter	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.18.1 dexamethasone >2.5	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.18.2 dexamethasone ≤2.5	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.3 dexamethasone No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.4 sirolimus analogue >2.5	4	1545	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.56, 4.98]
1.18.5 sirolimus analogue ≤2.5	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.6 sirolimus analogue No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.7 abciximab >2.5	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.18.8 abciximab ≤2.5	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.9 abciximab no data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.10 b estradiol >2.5	3	199	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.28]
1.18.11 b estradiol ≤2.5	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.12 b estradiol No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.13 Sirolimus >2.5	15	4410	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.74, 1.90]
1.18.14 Sirolimus ≤2.5	2	417	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.04, 1.34]
1.18.15 Sirolimus No data	3	838	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.44]
1.18.16 Paxel with coating >2.5	10	4474	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.55, 1.31]

1.18.17 Paxel with coating ≤2.5	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.18 Paxel with coating No data	2	501	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.21]
1.18.19 Paxel without coating >2.5	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.18.20 Paxel without coating ≤2.5	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.18.21 Paxel without coating No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19 total death- by stent type at study end and lesion length	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.19.1 dexamethasone >12	1	92	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.2 dexamethasone ≤12	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.19.3 dexamethasone No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.4 sirolimus analogue >12	3	1503	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.52, 5.33]
1.19.5 sirolimus analogue ≤12	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.07, 39.65]
1.19.6 sirolimus analogue No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.7 abciximab >12	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.8 abciximab ≤12	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.19.9 abciximab no data	1	85	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.10 b estradiol >12	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.07]
1.19.11 b estradiol ≤12	2	91	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.06, 33.75]
1.19.12 b estradiol No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.13 Sirolimus >12	11	3257	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.59, 2.00]
1.19.14 Sirolimus ≤12	4	990	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.33, 1.59]
1.19.15 Sirolimus No data	5	1418	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.43, 1.72]
1.19.16 Paxel with coating >12	3	2887	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.84]
1.19.17 Paxel with coating ≤12	6	982	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.37, 3.15]
1.19.18 Paxel with coating No data	3	1106	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.40, 1.25]
1.19.19 Paxel without coating >12	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.19.20 Paxel without coating ≤12	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.19.21 Paxel without coating No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20 total death- by stent type at study end and stent length	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.20.1 dexamethasone >18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.2 dexamethasone ≤18	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.20.3 dexamethasone No data	1	92	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.4 sirolimus analogue >18	2	1383	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.52, 5.33]
1.20.5 sirolimus analogue ≤18	1	120	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.6 sirolimus analogue No data	2	74	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.07, 39.65]
1.20.7 abciximab > 18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.8 abciximab ≤ 18	1	85	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.9 abciximab No data	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.20.10 b estradiol >18	3	199	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.28]
1.20.11 b estradiol ≤18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.12 b estradiol No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.13 Sirolimus >18	17	5059	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.60, 1.37]

1.20.14 Sirolimus ≤18	2	495	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.12, 2.55]
1.20.15 Sirolimus No data	1	500	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.45, 4.35]
1.20.16 Paxel with coating >18	5	3522	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.49, 1.24]
1.20.17 Paxel with coating ≤18	4	891	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.44, 5.26]
1.20.18 Paxel with coating No data	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.07]
1.20.19 Paxel without coating >18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20.20 Paxel without coating ≤18	6	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.20.21 Paxel without coating No data	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21 total death- by stent type at study end and number of lesions stented	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.21.1 dexamethasone >1	1	92	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.2 dexamethasone = 1	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.21.3 dexamethasone No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.4 sirolimus analogue >1	2	242	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.09, 5.86]
1.21.5 sirolimus analogue = 1	2	1303	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.61, 8.96]
1.21.6 sirolimus analogue No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.7 abciximab >1	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.8 abciximab = 1	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.21.9 abciximab no data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.10 Sirolimus > 1	4	1139	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.86]
1.21.11 Sirolimus = 1	10	3516	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.60, 1.69]
1.21.12 Sirolimus No data	6	1010	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.29, 1.88]
1.21.13 b estradiol >1	3	199	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.28]
1.21.14 b estradiol = 1	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.15 b estradiol No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.16 Paxel with coating >1	2	451	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.22, 2.38]
1.21.17 Paxel with coating = 1	10	4524	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.55, 1.30]
1.21.18 Paxel with coating No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.19 Paxel without coating >1	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.21.20 Paxel without coating =1	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.21.21 Paxel without coating No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.22 Total death - by stent type and diabetes	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.22.1 Dexamethasone > 30	1	92	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.22.2 Dexamethasone < 30	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.22.3 Sirolimus Analogue > 30	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.22.4 Sirolimus Analogue < 30	4	1545	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.56, 4.98]
1.22.5 Abxicimab > 30	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.22.6 Abxicimab < 30	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.22.7 Estradiol > 30	2	91	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.06, 33.75]
1.22.8 Estradiol < 30	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.07]
1.22.9 Sirolimus > 30	4	914	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.51, 2.37]
1.22.10 Sirolimus < 30	16	4751	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.35]

1.22.11 Paxel with coating > 30	1	1127	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.32, 2.43]
1.22.12 Paxel with coating < 30	11	3848	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.53, 1.27]
1.22.13 Paxel without coating > 30	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.22.14 Paxel without coating < 30	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.23 total death- by stent type and timepoint	50	13144	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
1.23.1 Dexamethasone	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.62]
1.23.2 Sirolimus Analogue	3	362	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.09, 5.86]
1.23.3 Sirolimus analogue 7-9 months	1	1183	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.61, 8.96]
1.23.4 Abxicimab	2	181	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]
1.23.5 Estradiol	3	199	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.07, 3.28]
1.23.6 Sirolimus	6	860	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.34, 2.14]
1.23.7 Sirolimus 7-9 months	8	2660	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.40, 1.65]
1.23.8 Sirolimus 12 months	6	2145	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.58, 1.74]
1.23.9 Paxel with coating 6 months	7	1403	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.45, 2.43]
1.23.10 Paxel with coating 7-9 months	4	2967	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.45, 1.61]
1.23.11 Paxel with coating 12 months	1	605	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.36]
1.23.12 Paxel without coating	7	367	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.13, 10.69]
1.25 Total death by stent type and patient population for sirilimus subgroup comparison	20	5665	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.35]
1.25.1 Sirolimus on label	7	2384	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.72, 3.08]
1.25.2 Sirolimus off label diabetes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.25.3 Sirolimus AMI	6	1691	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.39, 1.34]
1.25.4 Sirolimus off label complex anatomy	6	1515	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.30, 1.48]
1.25.5 Sirolimus off label CABG	1	75	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 69.54]
1.26 Total death by stent type and patient population (a)	50	13144	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.68, 1.17]
1.26.1 Sirolimus on label	7	2384	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.72, 3.14]
1.26.2 Sirolimul off label indications	13	3281	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.45, 1.19]
1.26.3 Paxel with coating on label	8	2873	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.45, 1.71]
1.26.4 Paxel with coating off label	4	2102	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.47, 1.36]
1.26.5 Paexel without coating on label	7	367	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.12, 11.70]
1.26.6 Estradiol on label	2	91	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.06, 38.37]
1.26.7 Estradiol off label	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.11]
1.26.8 Dexamethasone on label	1	92	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.26.9 Dexamethasone off label	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 16.37]
1.26.10 Sirolimus analogue on label	3	1345	Odds Ratio (M-H, Fixed, 95% CI)	2.25 [0.64, 7.87]
1.26.11 Sirolimus Analogue off label	1	200	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.20]
1.26.12 Abxicimab on label	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.26.13 Abxicimab off label	2	181	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.22]
1.27 Total death by stent type and patient population (b)	50	13144	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.68, 1.17]
1.27.1 Sirolimus on label	7	2384	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.72, 3.14]
1.27.2 Sirolimus off label diabetes	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.27.3 Sirolimus AMI	6	1691	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.35]

1.27.4 Sirolimus off label complex anatomy	6	1515	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.29, 1.51]
1.27.5 Sirolimus off label CABG	1	75	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 76.03]
1.27.6 Paxel with coating on label	8	3060	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.53, 2.00]
1.27.7 Paxel with coating off label AMI	2	685	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.33, 1.25]
1.27.8 Paxel with coating off label Left Main	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.13, 6.95]
1.27.9 Paxel with coating off label complex lesions	1	1127	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.46]
1.27.10 Paxel without coating on label	7	367	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.12, 11.70]
1.27.11 Estradiol on label	2	91	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.06, 38.37]
1.27.12 Estradiol off label	1	108	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.11]
1.27.13 Dexamethasone on label	1	92	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.27.14 Dexamethasone off label	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 16.37]
1.27.15 Sirolimus Analogue on label	3	1345	Odds Ratio (M-H, Fixed, 95% CI)	2.25 [0.64, 7.87]
1.27.16 Sirolimus Analogue off label	1	200	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.20]
1.27.17 Abxicimab on label	1	85	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.27.18 Abxicimab off label AMI	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.22]

Table 4.1.3: Subgroup and Sensitivity Analysis for the Outcome of Myocardial Infarction

Outcome or Subgroup	Studies	*Participants*	Statistical Method	Effect Estimate
2.1 total infarction/on treatment analysis	50	12760	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.02]
2.2 total MI/ITT	42	12527	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
2.4 divided by time point	40		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 in hospital infarction	12	2898	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.81, 1.93]
2.4.2 30 days	17	3758	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.93, 2.17]
2.4.3 cumulative to 6 months	16	2512	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.76, 1.81]
2.4.4 6-9 months	17	7091	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.07]
2.4.5 1 year	16	3884	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.98, 1.97]
2.5 Allocation concealment?	50	12557	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.5.1 +	4	1782	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.93]
2.5.2 ?/-	46	10775	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.15]
2.6 Blinding?	50	12557	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.6.1 +	17	5777	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.25]
2.6.2 ?/-	33	6780	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.69, 1.07]
2.8 Ascertainment bias of mi	50	12443	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.8.1 +	24	3753	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.61, 1.17]
2.8.2 -/?	26	8690	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.11]
2.9 Reference Vessel Diameter	50	12599	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.9.1 >2.5	42	10708	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.27]
2.9.2 ≤2.5	2	417	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.11, 0.65]
2.9.3 No data	7	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.92]
2.10 Lesion length	50	12557	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.10.1 >12	24	7146	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.74, 1.18]
2.10.2 ≤12	16	2266	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.64, 1.30]
2.10.3 No data	11	3145	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.51, 1.12]
2.11 Stent length	50	12557	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.11.1 >18	24	9431	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.08]
2.11.2 ≤18	14	2138	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.84, 1.89]
2.11.3 No data	12	988	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.37, 0.97]
2.12 Number of lesions stented	50	12557	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.12.1 >1	9	1808	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.47, 1.17]
2.12.2 =1	39	10388	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.13]
2.12.3 No data	2	361	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.97]
2.13 Diabetes	49	12557	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
2.13.1 >30%	8	2191	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.67, 1.41]
2.13.2 ≤30%	41	10366	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
2.13.3 No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.14 length of Plavix	50	12760	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.02]

2.14.1 1 month	4	438	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [1.36, 6.24]
2.14.2 2 month	8	1209	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.35, 0.98]
2.14.3 3 month	10	2845	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.27]
2.14.4 6 month	19	6972	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.12]
2.14.5 9 month	3	200	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.08, 4.46]
2.14.6 12 month	5	1096	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.31, 1.01]
2.14.7 no data	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.15 stent type at study end	50	12465	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
2.15.1 Dexamethasone	2	92	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 3.03]
2.15.2 Sirolimus Analogue	4	1359	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.39, 1.31]
2.15.3 Abciximab	2	96	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.06]
2.15.4 B Estradiol	3	204	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [0.40, 14.64]
2.15.5 Sirolimus	20	5340	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 1.00]
2.15.6 Paxel with coating	12	5007	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.88, 1.46]
2.15.8 Paxel without coating	7	367	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.20, 3.10]
2.18 total infarction/by stent type and patient population	49	10703	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.21]
2.18.1 Sirolimus on label	7	1846	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.67]
2.18.2 Sirolimus off label indications	13	2267	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.19]
2.18.3 Paxel with coating on label	7	2625	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.90, 1.77]
2.18.4 Paxel with coating-off label	4	1975	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
2.18.5 Paxel without coating-on label	7	367	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.20, 3.10]
2.18.6 B Estradiol on label	2	92	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.06, 33.75]
2.18.7 B Estradiol off label	1	106	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.93]
2.18.8 Dexamethasone on label	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 3.03]
2.18.9 Dexamethasone off label	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.18.10 Sirolimus Analogue on label	3	1239	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.37, 1.31]
2.18.11 Sirolimus Analogue off label	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.18.12 Abxicimab on label	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.18.13 Abxicimab off label	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.06]

Table 4.1.4: Subgroup and Sensitivity Analysis for the Outcome of Stent Thrombosis

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 at study end	50	12753	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.10]
3.2 1 year stent thrombosis	18	4146	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.93, 2.15]
3.3 Allocation concealment?	48	12313	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.59, 1.07]
3.3.1 +	4	1782	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.25, 1.12]
3.3.2 ?/-	44	10531	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.21]
3.4 Blinding?	49	12107	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.47, 0.82]
3.4.1 +	17	5733	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.22]
3.4.2 ?/-	32	6374	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.43, 0.82]
3.5 Cluster analysis	50	12099	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]
3.5.1 -	11	1994	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.21, 1.45]
3.5.2 +/?	39	10105	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.59, 1.13]
3.6 Reference Vessel Diameter	50	12009	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
3.6.1 >2.5	41	10119	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]
3.6.2 ≤2.5	2	417	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.03, 0.99]
3.6.3 No data	7	1473	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.33, 2.06]
3.7 Lesion length	49	12116	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]
3.7.1 >12	23	6818	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.32, 0.85]
3.7.2 ≤12	16	1997	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.77, 2.71]
3.7.3 No data	10	3301	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.50]
3.8 Stent Length	49	12116	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]
3.8.1 >18	23	9190	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.52, 1.09]
3.8.2 ≤18	14	2033	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.99]
3.8.3 No data	12	893	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.22, 1.90]
3.9 Number of lesions stented	50	12121	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.59, 1.09]
3.9.1 >1	9	1702	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.22, 1.61]
3.9.2 =1	39	10058	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.21]
3.9.3 No data	2	361	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.64]
3.10 Diabetes	50	12316	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.57, 1.01]
3.10.1 >30%	8	1971	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.22, 1.53]
3.10.2 ≤30%	42	10345	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.05]
3.10.3 No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.11 *at study end by time point*	50	12753	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.10]
3.11.1 1 month	4	266	Risk Ratio (M-H, Fixed, 95% CI)	10.00 [1.28, 77.83]
3.11.2 2 month	8	1209	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.27, 2.26]
3.11.3 3 month	10	2737	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.18, 0.78]
3.11.4 6 month	19	6972	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.68, 1.64]
3.11.5 9 month	3	353	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.12, 2.12]
3.11.6 12 month	5	1216	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.13]

3.11.7 no data	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.12 by stent type at study end	50	12313	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.52, 0.91]
3.12.1 Dexamethasone	2	92	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.07, 0.40]
3.12.2 Sirolimus Analogue	4	1545	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.12, 1.42]
3.12.3 Abciximab	2	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.12.4 B Estradiol	3	92	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.06, 33.75]
3.12.5 Sirolimus	20	5255	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.51, 1.20]
3.12.6 Paxel with coating	12	4962	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.62, 1.85]
3.12.7 Paxel without coating	7	367	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.17, 1.16]
3.14 lenght of Plavix	50	12753	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.10]
3.14.1 1 month	4	266	Risk Ratio (M-H, Fixed, 95% CI)	10.00 [1.28, 77.83]
3.14.2 2 month	8	1209	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.27, 2.26]
3.14.3 3 month	10	2737	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.18, 0.78]
3.14.4 6 month	19	6972	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.68, 1.64]
3.14.5 9 month	3	353	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.12, 2.12]
3.14.6 12 month	5	1216	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.13]
3.14.7 no data	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.17 Ascertainment of stent thrombosis	45	11856	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.14]
3.17.1 +	16	4795	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.43, 1.11]
3.17.2 -/?	29	7061	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.47]

Table 4.1.5: Subgroup and Sensitivity Analysis for the Outcome of Target Lesion Revascularization

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Target Lesion Revascularization at Primary endpoint	50	12662	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.39]
4.2 Allocation concealment?	44	11680	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.32, 0.40]
4.2.1 +	4	1427	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.20, 0.37]
4.2.2 ?/-	40	10253	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.33, 0.42]
4.3 Blinding?	44	11760	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.40]
4.3.1 +	17	5351	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.28, 0.41]
4.3.2 ?/-	27	6409	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.31, 0.42]
4.4 TLR	44	11544	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.32, 0.40]
4.4.1 -	38	10265	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.40]
4.4.2 +/?	6	1279	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.30, 0.62]
4.5 Reference vessel diameter	44	11576	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.32, 0.40]
4.5.1 >2.5	37	10316	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.33, 0.42]
4.5.2 ≤2.5	2	417	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.15, 0.44]
4.5.3 No data	5	843	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.16, 0.46]
4.6 Lesion length	43	10832	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.40]
4.6.1 >12	22	6746	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.28, 0.39]
4.6.2 ≤12	16	2859	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.30, 0.49]
4.6.3 No data	5	1227	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.63]
4.7 Stent length	44	11544	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.32, 0.40]
4.7.1 >18	20	8213	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.28, 0.37]
4.7.2 ≤18	14	1959	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.35, 0.61]
4.7.3 No data	10	1372	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.32, 0.65]
4.8 Number of lesions stented	43	10864	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.40]
4.8.1 >1	5	485	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.21, 0.54]
4.8.2 =1	36	9986	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.33, 0.42]
4.8.3 No data	3	393	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.10, 0.31]
4.9 Diabetes	43	10864	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.40]
4.9.1 >30%	7	1710	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.36, 0.58]
4.9.2 ≤30%	36	9154	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.29, 0.38]
4.9.3 No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.10 lenght of Plavix	50	12662	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.39]
4.10.1 1 month	4	437	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.22, 0.70]
4.10.2 2 month	8	1209	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.16, 0.35]
4.10.3 3 month	10	3885	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.32, 0.50]
4.10.4 6 month	19	5647	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.33, 0.48]
4.10.5 9 month	3	236	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.09, 0.43]
4.10.6 12 month	5	1216	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.16, 0.34]

4.10.7 no data	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 4.98]
4.11 Target Lesion Revascularization at Primary endpoint by stent type	50	11544	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.32, 0.40]
4.11.1 Dexamethasone	2	212	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.84]
4.11.2 Sirolimus Analogue	4	1545	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.28, 0.59]
4.11.3 Abciximab	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.18, 1.35]
4.11.4 B Estradiol	3	198	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.75]
4.11.5 Sirolimus	20	4087	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.20, 0.30]
4.11.6 Paxel with coating	12	4543	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.34, 0.51]
4.11.8 Paxel without coating	7	865	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 1.00]
4.14 Ascertainment bias of myocardial infarction	43	11446	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.31, 0.40]
4.14.1 +	21	2736	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.22, 0.37]
4.14.2 -/?	22	8710	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.33, 0.43]
4.15 Target Lesion Revascularization at Primary endpoint by stent type and patient population	49	10552	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.32, 0.41]
4.15.1 Sirolimus on label	7	1496	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.17, 0.32]
4.15.2 Sirolimus off label indications	13	1719	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.16, 0.32]
4.15.3 Paxel with coating on label	7	2627	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.26, 0.45]
4.15.4 Paxel with coating-off label	4	1916	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.39, 0.68]
4.15.5 Paxel without coating on label	7	865	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 1.00]
4.15.6 B Estradiol on label	2	92	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.31, 6.75]
4.15.7 B Estradiol off label	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.63]
4.15.8 Dexamethasone on label	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.17]
4.15.9 Dexamethasone off label	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.98]
4.15.10 Sirolimus Analogue on label	3	1225	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.25, 0.59]
4.15.11 Sirolimus Analogue off label	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.17, 1.07]
4.15.12 Abxicimab on label	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.15.13 Abxicimab off label	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.18, 1.35]
4.16 Target Lesion Revascularization at Primary endpoint by stent type and then stent length	43	13732	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.33, 0.41]
4.16.1 Dexamethasone >18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.16.2 Dexamethasone ≤18	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.26, 0.98]
4.16.3 Dexamethasone No data	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.16, 1.17]
4.16.4 Sirolimus >18	11	4113	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.23, 0.36]
4.16.5 Sirolimus ≤18	3	577	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.22, 0.66]
4.16.6 Sirolimus No data	5	900	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.13, 0.29]
4.16.7 B Estradiol >18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.16.8 B Estradiol ≤18	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.63]
4.16.9 B Estradiol No data	2	92	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.31, 6.75]

4.16.10 Paxel with coating >18	5	3510	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.35, 0.54]
4.16.11 Paxel with coating ≤18	3	789	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.28, 0.74]
4.16.12 Paxel with coating No data	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.07, 2.19]
4.16.13 Sirolimus Analogue >18	1	1183	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.25, 0.59]
4.16.14 Sirolimus Analogue ≤18	2	320	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.20, 1.14]
4.16.15 Sirolimus Analogue No data	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.16.16 Other >18	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.98]
4.16.17 Other ≤18	6	504	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.40, 0.88]
4.16.18 Other No data	4	278	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.11]
4.16.19 Paxel without coating >18	1	175	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.10, 0.62]
4.16.20 Paxel without coating ≤18	6	367	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.21, 0.94]
4.16.21 Paxel without coating No data	2	184	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.04, 0.45]
4.16.22 Abciximab >18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.16.23 Abciximab ≤18	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.16.24 Abciximab No data	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.18, 1.35]

Table 4.1.6: Subgroup and Sensitivity Analysis for Outcome of Late Luminal Loss for Paclitaxel Stent with Coating

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
13.1 outcome	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.2 allocation concealment	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.2.2 allocation concealment +	1	416	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-0.71, -0.49]
13.2.3 allocation concealment -/?	11	2435	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.52, -0.43]
13.3 RVD	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.3.1 >2.5mm	10	2775	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.3.2 ≤2.5mm	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.3.3 no data	2	76	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.4 blinding	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.4.3 +	6	2539	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.52, -0.44]
13.4.4 -/?	6	312	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-0.88, -0.55]
13.5 lesion lenght	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.5.1 >12mm	3	1963	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.54, -0.44]
13.5.2 ≤12mm	6	812	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.56, -0.43]
13.5.3 no data	3	76	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.6 stent lenght	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.6.1 >18mm	5	1998	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.55, -0.44]
13.6.2 ≤18mm	5	721	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.57, -0.43]
13.6.3 no data	2	132	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.60, -0.10]
13.7 number of lesions stented	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.7.1 >1lesion	2	35	Mean Difference (IV, Fixed, 95% CI)	-0.63 [-0.96, -0.30]
13.7.2 1 lesion	10	2816	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.7.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.8 diabetes	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.8.1 >30%	1	988	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.49, -0.33]
13.8.2 ≤30%	11	1863	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.57, -0.48]
13.8.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.9 patient populations	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.9.1 on label	7	2216	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.53, -0.44]
13.9.2 off label	5	635	Mean Difference (IV, Fixed,	-0.53 [-0.62, -0.44]
13.9.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.10 patient populations	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.10.1 on label	7	2216	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.53, -0.44]
13.10.2 AMI	2	76	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.10.3 off label	2	559	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.62, -0.44]
13.10.4 Left Main	1	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

13.16 Plavix use	12	2851	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.16.1 1 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.16.2 2 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.16.3 3 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.16.4 4 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.16.5 6 month	11	2775	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]
13.16.6 9 month	1	76	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.16.7 12 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.16.8 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Table 4.1.7: Subgroup and Sensitivity Analysis for Outcome of Late Luminal Loss for Paclitaxel Stent without Coating

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
12.1 outcome	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.2 allocation concealment	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.2.2 allocation concealment +	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.2.3 allocation concealment -/?	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.3 blinding	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.3.3 +	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.3.4 -/?	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.4 RVD	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.4.1 >2.5mm	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.4.2 ≤2.5mm	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.4.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.5 lesion lenght	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.5.1 >12mm	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.5.2 <12mm	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.5.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.6 stent lenght	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.6.1 >18mm	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.6.2 ≤18mm	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.6.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.7 number of lesions stented	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.7.1 >1lesion	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.7.2 1 lesion	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.7.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.8 diabetes	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.8.1 >30%	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.8.2 ≤30%	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.8.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.9 patient populations	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.9.1 on label	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.9.2 off label	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.9.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.10 patient populations	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.10.3 no data	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.16 Plavix use	7	936	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.19]
12.16.1 1 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

12.16.2 2 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.16.3 3 month	5	715	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.30, -0.12]
12.16.4 4 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.16.5 6 month	2	221	Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.81, -0.40]
12.16.6 9 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.16.7 12 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.16.8 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Table 4.1.8: Subgroup and Sensitivity Analysis for Outcome of Late Luminal Loss for Sirolimus Coating

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
14.1 outcome	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.2 allocation concealment	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.2.2 allocation concealment +	4	1099	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-0.80, -0.67]
14.2.3 allocation concealment -/?	16	2471	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-0.83, -0.74]
14.3 RVD	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.3.1 >2.5mm	15	3174	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-0.83, -0.75]
14.3.2 ≤2.5mm	2	396	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-0.73, -0.56]
14.3.3 no data	3	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.4 blinding	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.4.3 +	3	1007	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-0.86, -0.72]
14.4.4 -/?	17	2563	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-0.80, -0.72]
14.5 lesion lenght	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.5.1 >12mm	11	2707	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-0.82, -0.73]
14.5.2 ≤12mm	4	591	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-0.86, -0.70]
14.5.3 no data	5	272	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-0.78, -0.52]
14.6 stent lenght	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.6.1 >18mm	2	447	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-0.87, -0.69]
14.6.2 ≤18mm	17	2714	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-0.80, -0.72]
14.6.3 no data	1	409	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-0.92, -0.68]
14.7 number of lesions stented	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.7.1 >1lesion	4	662	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-0.73, -0.57]
14.7.2 1 lesion	10	2149	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-0.84, -0.75]
14.7.3 no data	6	759	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-0.88, -0.72]
14.8 diabetes	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.8.1 >30%	4	792	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-0.75, -0.61]
14.8.2 ≤30%	16	2778	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-0.84, -0.75]
14.8.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.9 *patient populations*	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.9.1 on label	7	1820	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-0.86, -0.76]
14.9.2 off label	13	1750	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-0.77, -0.68]
14.9.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.10 patient populations	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.10.1 on label	7	1820	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-0.86, -0.76]
14.10.2 diabetes	2	304	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-0.73, -0.54]
14.10.3 no data	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.10.4 AMI	6	610	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-0.77, -0.61]
14.10.5 CABG	1	93	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.65, -0.17]

14.10.6 off label	3	507	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.12, -0.88]
14.10.7 small arteries	1	236	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-0.87, -0.61]
14.16 Plavix use	20	3570	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.80, -0.73]
14.16.1 1 month	1	79	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.77, -0.23]
14.16.2 2 month	5	936	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-0.85, -0.72]
14.16.3 3 month	1	703	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-0.92, -0.74]
14.16.4 4 month	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.16.5 6 month	6	1012	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-0.83, -0.68]
14.16.6 9 month	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.79, -0.29]
14.16.7 12 month	4	738	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-0.82, -0.68]
14.16.8 no data	1	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Appendix 8
Table 4.2.1: Table of Characteristics of Included Studies for Harms Review

RCT and RCT Extensions for long-term harms of DES and BMS stenting for coronary disease

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Fajadet 2006 **Fajadet 2007a-duplicate publication**	**Randomized Control Trial Extension of Endeavour** DES: n=598 BMS: n= 599 **Group Selection** Multicentre Study in Europe and Asia/ Australia Patients with clinical evidence of ischemia or a positive function of study who were undergoing of a single, de novo lesion. RVD 2.25-3.50mm, lesion length >14mm and < 27mmExclusion: Ef <30%, recent MI, bifurcation lesion, calcification, left main. **Study Dates:** Nov 2002,-Oct 2003	Age : 61.6/61.9 Men: 77/75 Smoker: 35/35 Diabetes: 18/22 Prior MI: 40/42 Prior PCI: 22/18 Prior CABG: excluded	Single Vessel Disease=100 Lesion no =1.0 Lesion length=nr Stent number DES: n=1.13 BMS: n= 1.12 stent length=23.4 Type C=26 RVD=nr	Routine PCI practices of the centre DES: zotarolimus BMS: nr Clopidogrel 75 mg od 12 weeks ASA 75 mg od indefinitely Heparin and GIIbIIIa at the operators discretion	**Censoring:** no detail **Ascertainment of Outcome:** All endpoints defined. Independent research organization. Independent events committee. No follow up details given, but clinical follow up was to occur yearly after 1 year. Primary endpoint at 9 months; continued follow up yearly for 5 years **Blinding-** yes; not sure about the post primary endpoint follow up	Follow up: 24 months Death nr MI nr Stent thrombosis nr MACE n

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Grube 2005(TAXUS I) **(Bullesfield 2003)***	**RCT Extension of PES I** DES: n=31 BMS: n= 30 **Group Selection:** Single lesion, native or ISR. Lesion length <=12 mm, 50-99% stenosis and diameter 3.0mm-3.5mm. Excluded I history of AMI or target lesion requiring > 1 study stent. **Study Dates: nr**	Age: 65 Men: 89 Diabetes: 18 Cholesterol↑: 81 Hypertension: 64 Smoker: 51 MI: 28 Prior PCI: nr CABG: nr	SVD: nr Lesion number: na Lesion/patient:1 Lesion length: 11.3 Stent length: 15 Type C: 0 RVD: 2.97	PCI technique nr heparin PES NIR x slow rate release 1ug/mm3 *vs* NIR_bms Clopidogrel 6 months ASA	**Censoring:** no detail **Ascertainment of Outcome:** **After primary endpoint,** clinical follow up was conducted at 24 months by telephone contact to ascertain whether the patients had experienced ST or MACE since the 12 month visit. Similarly a follow up call was made at 36 months. Blinding: nr	Follow Up: 18 months*/24 months /36 months Death n *calculated total death MI n Stent thrombosis n MACE n

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Jimenez Quevedo 2007 (DIABETES)	**Randomized Control Trial Extension of Diabetes** DES: n=80 BMS: n= 80 **Group Selection: Multi centre trial Spain.** Diabetes, non insulin or insulin dependant, on pharmacologic treatment for at least 1 month. **Study Dates:** Feb 2003-Nov 2003	Age: 67 Men: 63 Diabetes: 100 Cholesterol↑: 61 Hypertension: 66 Smoker: 48 MI: 37 PCI: nr CABG: nr	SVD: <35 DES/BMS=111/110 Lesion Number: 1.4 Lesion Length: 15 Stent Length: 23 Type B2/C Lesions: 80.1 RVD: 2.34	Routine PCI practices Heparin/ GIIaIIIb inhibitor SES *vs* BMS Bx Velocity stent Clopidogrel 12 months ASA	Na	Follow up: 24 months Death *cadiac death n MI n Stent thrombosis n MACE n

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Morice 2007 (RAVEL) **(Fajadet 2005)***	**Randomized Control Trial Extension of RAVEL** **Participant number:** DES: n=533 BMS: n=525 **Group Selection:** Multi centre European Stable / unstable angina or silent ischemia with primary target lesion diameter 2.5-3.5 mm that could be covered by a single 18 mm stent. Excluded evolving MI / unprotected left main / osteal lesion, calcified lesion / thrombus / EF <30%.	Age: 61 Men: 76 Diabetes: 19 Cholesterol↑: 40 Hypertension: 61 Smoker: 30 MI: 36 Prior PCI: 18 CABG: 2	SVD: 100 Lesion Number: 1 Lesion length: nr Lesion Length: 9.58 Stent Length: 18.00 Type C Lesions: 0 RVD: 2.62	Routine PCI practices SES *vs* BMS Bx Velocity stent Clopidogrel/Ticlopidine for 8 weeks ASA 325mg od indefinitely	**Censoring:** no detail **Ascertainment of Outcome:** Clinical evaluation at 30 days,6,9,12,24 months. Two year follow up was supervised by the physician investigators of each enrolling centre. Patients queried by telephone interview and in the case of events, source medical documents were retrieved and adjudicated by an independent clinical Events Committee blinded to the treatment assignment Bliniding: nr	Follow Up: 24/36 */60 months Death n MI n Stent thrombosis n MACE n

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Pfisterer 2006 Basket Late **(Brunner La- Rocca)***	**Randomized Control Trial –Late Follow up** **Participant number** DES: n=499 BMS: n=244 **Group Selection:** Initially enrolled in BASKET trial. Multi centre Swiss Patients treated by PCI. Exclusion of those that with diameter>4mm or greater, restenosis. All patients surviving trial were enrolled in the Late portion of the trial and were followed for another 12 months **Study Dates:** May 2003-May 2004	Age DES:63.6 BMS;63.6 % male DES: 78.8 BMS:78.3 %smoker DES: 26.8 BMS:31.4 % diabetes DES:16.9 BMS:21.1 % prior pci DES: 16.6 BMS:14.3 % past mi DES:27.5 BMS:27 % cabg DES:13.2 BMS:10.7	SVD: nr Lesion Number: nr Lesion Number: 1.5 Lesion Length: nr Stent Length: 34 Type C Lesions: 24 RVD: nr	Standard PCI practices of the centre DES: Cyper/PES BMS: Viision ASA 100 mg po od Clopidogrel 75 mg po od For 6 months	**Censoring:** Patients who survived the first 6 months and had no recurrent event of TVR continued to be followed. No mention of censoring going forward **Followed up was not specified by the trial** After 18 months all patients received a questionnaire with questions regarding hospitalization, adverse events and drug therapy. Data of patients with repeat procedures were collected prospectively. Patients followed in an observational manner Blinding: no	Follow up: 18 months(The initial follow up of 6 months plus another 12 months) Death *cardiac death n MI n Stent thrombosis n MACE % *all calculated back to baseline data calculated with the n given in the baseline characteristics table

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Vermeersch 2007 (RRISC)	**Randomized Control Trial Extension of RRISC** **Participant number** DES: n=38 BMS: n=37 **Group Selection:** Single centre Belgium Patients with prior CABG with de novo lesions in SVGs with RVD >2.5mm and less than 4.0mm **Study Dates:** Sept2003-Nov 2004	Age DES: 73 BMS: 72 % male DES: 82 BMS: 89 %smoker DES: 5 BMS: 11 % diabetes DES: 16 BMS: 14 % prior pci DES: 32 BMS: 41 % past mi DES: 45 BMS: 41 %cabg DES: 100 BMS: 100	SVD: 73.30 Lesion Number :47/49 Lesion number: 1.28 Lesion length: 17.40 Stent length: 35.15 Type C: RVD: 3.31	Routine PCI practices SES *vs* BMS Bx Velocity stent ASA 100mg-300mg Clopidogrel 75mg/Ticlopidine 250mg bid for at least 2 months and then at the physicians discretion	**Censoring: nr** **Ascertainment of Outcome:** After the trial was completed, an extension was created and all the patients were contacted by phone and were asked questions using a prespecified questionnaire. If there were positive results to any of the morbidity questions the patients chart was requested from the hospital Survival status was obtained from the National Civil Registry. **Blinding:** maintain during the follow up period for patients and referring clinical cardiologists but not for the interventional cardiologist performing the *index procedure and* analyzing data	Follow up: 36 months Death n MI n Stent thrombosis nr MACE n

Author Year (Additional Publications of the same data, not classified as companion publications)	Study Type Study Number Population Group Selection Study Dates	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Weisz (SIRIUS)	**Randomized Control Trial Extension of SIRIUS** **Participant number:** DES: n=533 BMS: n=525 **Group Selection**: Multi centre American. History of stable / unstable angina and signs duplicate / single de novo lesion	Age: 62 Men: 71 Diabetes: 26 Cholesterol↑: 74 Hypertension: 68 Smoker: 20 Priori MI: 31 PCI: excluded CABG: nr	SVD: 58 Lesions number: na Lesion/patient: 1 Lesion length: 14.4 Stent length: 21.2 Type C: 26 RVD: 2.8	Routine PCI practices heparin SES Vs BMS Bx Velocity Clopidogrel (3months) ASA	**Censoring: nr** **Ascertainment of Outcome:** After the clinical trial, there were 12 and 24 month follow up which were supervised by the investigating physician from the enrolling sites. Patients were queried by telephone interview, and in the case of clinical events, source medical documents were retrieved and adjudicated by an independent Events Committee blinded to the treatment assignment.	Follow up: 12, 24 months Death n MI n Stent thrombosis n MACE n

Cohort trials – Adjusted and Unadjusted

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Applegate 2008	**Cohort Study** DES: n=1135 BMS: n= 1242 **Group Selection:** Patients at single Institution in North Carolina presenting for PCI. Exclusion only if patient received DES and BMS. **Study Dates**: DES April 2003- April 2005 BMS April 2002-April 2003	Age : 63/64 Men: 65/66 Smoker: 34/31 Diabetes: 32/32 Prior MI: nr/nr Prior PCI: 24/29 Prior CABG: 16/17	Single Vessel Disease DES: n=nr BMS: n=nr Lesion number DES: nr BMS: nr Lesion no per patient DES: 1.4 BMS: 1.5 Lesion length DES: nr BMS: nr Stent number DES: nr BMS: nr Stent length DES: 25 BMS: 20 Type C DES: n=nr BMS: n= nr RVD DES: n=nr BMS: n= nr	Standard PCI practices of the centre DES: N= 971 SES/ N=259 DES/ N=12 both BMS : nr Clopidogrel 1 month for BMS and 3 months for DES ASA 81mg po od	Stent length per lesion Renal failure STEMI NSTEMI Stented length per lesion Adjustment: None carried out	**Censoring:** No details **Ascertainment of Outcome:** Clinical follow up(independent chart review, scripted phone interviews and Social Security Death Index for those missing	Follow up:324months+/- 30 days Death Kaplan-Meier MI nr Stent thrombosis Kaplan-Meier MACE nr

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Bansal 2008	**Cohort Study** DES: n=37 BMS: n= 72 **Group Selection:** Subset of procedures that were performed on saphenous vein grafts in single centre Connecticut **Study Dates**: Jan 2003-Feb 2005	-Age :68/65 -Men: nr/nr -Smoker: 16/18 -Diabetes: 51/35 -Prior MI: nr/nr -Prior pci: nr/nr -Prior CABG: 100/100	Single Vessel Disease DES: n=nr BMS: n=nr Lesion number DES: nr BMS: nr Lesion no per patient DES: nr BMS: nr Lesion length DES: 17.1 BMS: 17.9 Stent number DES: nr BMS: nr Stent length DES: nr BMS: nr Type C DES: n=nr BMS: n= nr RVD DES: n=nr BMS: n= nr	Routine PCI practices of the centre DES: 95% SES BMS : nr ASA 75-150 mg po od Clopidogrel nr, but much shorter than one year	Stent diameter Hb 1a c smoking Adjustment through analysis, details not given	**Censoring:** No details **Ascertainment of Outcome:** Data collected over 3 years	Follow up:36 months Death n MI n Stent thrombosis n Person years MACE n Adjusted data

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Bose 2007	**Cohort Study** DES/Paxel: n=115 DES/Sirolimus: n=55 BMS: n= 18 **Group Selection:** Consecutive patients presenting to Baylor Medical Centre with STEMI and treated with primary or rescue angioplasty within 24 hours of onset of symptoms. Patients> 18 years old, with ≥1 mm STE elevation in ≥consecutive leads and PCI as described. **Study dates:** March 2004-July 2005	Age : 59.8 Men: 71 Smoker: 46 Diabetes: 21 Prior MI: nr Prior PCI: nr Prior CABG: nr	Single Vessel Disease nr Lesion number nr Lesion no per patient nr, but likely 1 Lesion length(mm) nr Stent number nr Stent length(mm) Paxel: 21.3 Sirolimus:22.3 BMS:24.3 All: 21.8 Type C nr RVD nr	Routine PCI practices of the centre PES: N= 971 SES/ N=259 DES/ N=12 both BMS : nr Clopidogrel 75mg for 1,3 or 6 months for the BMS/Sirolimus/ stents ASA for all patients	No analysis of individual features No adjustment of the data	**Censoring:** no mention **Ascertainment of Outcome** Using telephone interviews, in hospital and office follow up chart review	Follow up: 19.6 months Death n MI n Stent thrombosis n MACE nr

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Bruggenjurgen 2007 (GERSHWIN)	**Cohort Study** DES: n=658 BMS: n= 294 **Group Selection:** 35 centre study in Germany. Patients presenting for PCI for clinical indications. Inclusion criteria: lesions ≤n30mm or a RVD 2.5-3.0mm. Excluded patients with AMI, ISR, Left mainstem lesion, previous brachytherapy, bypass lesions, chronic stenosis **Study Dates**: April 2003-June 2005. Enrollment of the BMS started prior to the enrollment of the DES, with the time periods being contiguous	Age : 63/64 Men: 87/79 Smoker: 63/59 Diabetes: 24/20 Prior MI: 27/27 Prior PCI: 36/31 Prior CABG: 12/10	Single Vessel Disease DES: n=nr BMS: n=nr Lesion number DES: nr BMS: nr Lesion no per patient DES: nr BMS: nr Lesion length DES: 17.1 BMS: 17.9 Stent number DES: 1.3 BMS: 1.8 Stent length DES: 14.5 BMS: 18.8 Type C DES: n=17 BMS: n= 10.8 RVD DES: n=nr BMS: n= nr	Routine PCI practices of the centre DES: SES BMS : nr ASA nr Clopidogrel: BMS 1 month/SES 3 months	Age Living alone Type c lesion Stent length Number of implanted stents **Adjustment:** Through analysis, for the features of age, gender household status, three vessel disease and number of stents.	BMS patients were recruited and then the DES stent patients were recruited in a 1:2 ratio. **Censoring:** No details **Ascertainment of Outcome:** 4 Questionnaires over 18 months. Physician interviews at 6/12/18 months	Follow up:18 months Death nr MI nr Stent thrombosis Kaplan-Meier MACE Kaplan-Meier

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Daeman 2006	**Cohort Study** DES: n=508 BMS: n= 450 **Group Selection:** Single centre registry in Rotterdam, DES use started on April 16, 2002. In the first 6 months all patients treated with SES stents. all PCIs which occurred during or before the study period for de novo lesions and restricted receiving a DES or BM stent . Those treated with both DES and BMS or no stent were excluded Compared to those treated in the 6 months prior to this date with BMS. All in hospital outcomes were obtained form electronic database. Survival data from the Municipal Civil Registries **Study Dates:** April 16 2002+/- 6 months	Age : 61/61 Men: 68/72 Smoker: 31/34 Diabetes: 18/15 Prior MI: 30/40 Prior PCI: 19/18 Prior CABG: 9/8	Single Vessel Disease DES: n=46 BMS: n= 52 Lesion number DES: n=nr BMS: n= nr Lesion no per patient DES: n=nr BMS: n= nr Lesion length(mm) DES: n=nr BMS: n= nr Stent number DES: n=2.1 BMS: n= 1.9 stent length(mm) DES=38.7 BMS=30.1 Type C DES: n=43 BMS: n= 30 RVD DES: n=nr BMS: n= nr	Routine PCI practices of the centre DES: SES BMS: nr ASA 75-150 mg po od lifelong Clopidogrel for 1 month in the pre SES phase, for 3 months in the post SES unless one of ;> 3 stents, total length greater than 36mm or Chronic total occlusion or bifurcation present	Multisystem disease Type C lesions Bifurcation stenting Segment number Stent number Stent diameter Stent length GIIaI IIIa administration **Methods to deal with baseline differences** Cox proportional hazard regression models were used to control for differences between groups. Data was then adjusted using these factors BMS patients from the selection period matched for stent diameter	**Censoring:** Patients considered at risk until last day of contact and then were censored. Dynamic registry. Patient not censored but reentered into registry to contribute further person time **Ascertainment of Outcome** Patients were contacted at 0.5,1,2,3 years. Survival status obtained through civil registries. Health questionnaires were sent to all patients	Follow up: 36 months .Follow up obtained in 97.5% of patients at mean time of 1095+/- 265 days Death Hazard ratio Adjusted Hazard ratio death MI nr Stent thrombosis n MACE Hazard ratio Adjusted hazard ratio

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Eisenstein 2007	**Cohort Study** DES: n=637 with n=579 without BMS: n= 417 with N=1976 without **Group Selection** Consecutive patients from Duke who had an initial PCI with a DES or BMS who had no adverse event in the first 6 months. Excluded congenital Heart Disease, valvular disease, CABG, prior PCI and significant Left mainstem stenosis. Also excluded if intervention required other than PCI. If received both stents during procedure, were assigned to DES. Patients divided based on whether on clopidogrel at 6/12 montths.Before being assigned to 1 of 4 groups. Patients were required to complete 6 month contact and have no events **Study Dates:** DES April 2003-July 2005 BMS Jan 2000-July 2005	Age 61 DES with 60 DES without 61 BMS with 61 BMS without % male 62.5 DES with 63.6 DES without 63.8 BMS with 62.4 BMS without %smoker nr % diabetes 26.8 DES with 29.5 DES without 29 BMS with 22.7 BMS without Past mi 38.8 DES with 38.2 DES without 51.1 BMS with 46.2 BMS without % prior pci 0 0 %Cabg 0 0	Single Vessel Disease DES: 58 with DES: 62 without BMS: 66 with BMS: 667without Lesion number DES: n=nr BMS: n= nr Lesion no per patient DES: n=nr BMS: n= nr Lesion length(mm) DES: n=nr BMS: n= nr Stent number DES: n=nr BMS: n= nr stent length(mm) DES: n=nr BMS: n= nr Type C DES: nr BMS: nr RVD DES: nr BMS: nr	Routine PCI practices of the centre DES: nr BMS:nr ASA 75-150 mg po od Clopidogrel nr, but given at their physicians discretion	Diabetes History of congestive heart failure History of MI Multi vessel disease House hold incomes **Methods to deal with baseline differences** Cox proportional hazard model Classification based on whether on clopidogrel at 6/12 months	**Censoring;** No censoring information given Patient started their follow up at 6 months referred to as landmark analysis. Conditional Risk based on good initial outcome **Ascertainment of Outcome** Patients contacted at 6 and 12 months and annually. Independent committee reviewed deaths. Follow up MI based on clinical diagnosis assigned by patient's physician and was not centrally adjudicated	Follow up: 24 months 98 % complete at least 12 months Death n Hazard Ratio MI n Hazard Ratio Stent thrombosis nr MACE nr

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Jensen 2007	**Cohort Study** DES: n=2548 BMS: n= 8847 **Group Selection** Consecutive patients Danish National Health Service Western Denmark Heart Registry identified patients; All PCIs which occurred during or before the study period and restricted receiving a DES or BMS stent. Those treated with both DES and BMS or no stent were excluded **Study Dates:** Jan 2002-June 2005 consecutively	Age : 62/64 Men: 72. /72. Smoker: 34/35 Diabetes: 51/35 Prior MI: 23/27 Prior PCI: 7/6 Prior CABG: nr/nr	Single Vessel Disease DES: n=nr BMS: n=nr Lesion number DES: 5422 BMS: 11730 Lesion no per patient DES: 2.13 BMS: 1.33 Lesion length(mm) DES: 14 BMS: 12 Stent number DES: 1 BMS: 1 stent length(mm) 18.0 15.0 Type C DES: n=nr BMS: n= 29.2 RVD DES: n=3.1 BMS: n=3.3	Routine PCI practices of the centre DES: SES and PES BMS: NR ASA 75-150 mg po od Clopidogrel 3-12 months until Nov 2002 and 12 months after this time	Age Family history Diabetes Hypertension Previous MI Lipid lowering therapy Co morbidity score Procedure time Fluoroscopy time Number of lesions treated Indication for treatment Vessel location Lesion length Lesion type Restenosis lesion Stent length Stent number Max balloon pressure Max balloon diameter RVD Charlson comorbidity Index **Methods to deal with baseline differences:** Cox proportional hazard model,	**Censoring:** No censoring occurred. All patients followed for 15 months until death or individual endpoint. Rate of each event calculated **Ascertainment of Outcome:** record linkage between Heart Registry obtained endpoints and other registries(National Patient Registry/Danish Civil Registration System/National Registry of causes of death)	Follow up: 15 months For all patients Death n Person Years Adjusted HR total Adjusted death 15-18 months MI n n 12- 15 months Adjusted MI total Adjusted MI 12-15 months Stent thrombosis n Person years Detailed Adjusted HR MACE nr

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Lagerqvist 2007	**Cohort Study** DES: n=6033 BMS: n= 13738 **Group Selection:** All patients in Sweden who received stents for whom complete follow up data were available from other national registries. Analysis based on the type of stent first implanted at the first record ed procedure. patient would be assigned to DES regardless of whether had any other stent at any other time, other wise was assigned to BMS group Used SCAAR database to identify patients. Long term follow up was based on merging SCAAR with other national databases. **Study dates:** April 2003-Dec 2004	Age : 65/66 Men: 31/32 Smoker: 19/21 Diabetes: 24/16 Prior MI: 38/37 Prior PCI: 16/10 Prior CABG: 11/10	Single Vessel Disease DES: :47 BMS: :51 Lesion number DES: nr BMS: nr Lesion no per patient DES: n=nr BMS: n= nr Lesion length(mm) DES: nr BMS: nr Stent number DES: 60.1 stent BMS: 75.2 1 stent stent length(mm) DES: 48.70%<16mm BMS: 65.20%<18mm Type C DES: nr BMS: nr RVD DES: nr BMS: nr	Routine PCI practices of the centre DES: SES and PES BMS: nr ASA 75-150 mg po od lifelong Clopidogrel for 1 -3 monts in BMS and 6 months for DES	Age Sex Diabetes Hypertension Clinical presentation Presence of heart failure Clopidogrel use Number of prior pci CABG No of implanted stents **Methods to deal with baseline differences** Propensity score method defined as the conditional probability of obtaining a DES based on available comorbidities with multiple logistic regression.. Used landmark analysis and reset events to) at 6 months	**Censoring:** Death was the only censoring event **Ascertainment of Outcome** Patients were contacted at 0.5,1,2,3 years. Survival status obtained through civil registries. Health questionnaires were sent to all patients	Follow up: 36 months Follow up by definition is complete Death Total Total-adjusted 6 months-RR-adjusted 6-36 months-RR-adjusted MI total 6 months-RR-adjusted 6-36 months-RR-adjusted Stent thrombosis n MACE nr

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Marzocchi 2007	**Cohort Study** DES: n=3064 BMS: n= 7567 **Group Selection:** REAL registry is a Web based registry which collects data on all PCIs performed in Italy .PCI data collected from centres In Italy. All consecutive PCI data collected, but excluded those who received DES and BMS as well as those presenting with STEMI. **Study Dates:** July 2002-June 2005	Age : 65/68 Men: 75/75 Smoker: 25/24 Diabetes: 31/22 Prior MI: 27/28 Prior PCI: 13/10 Prior CABG: 10/10	Single Vessel Disease DES: nr BMS: nr Lesion number DES: n=4392 BMS: n= 11190 Lesion no per patient DES: n=1.43 BMS: n= 1.48 Lesion length(mm) DES: n=18.6 BMS: n= 15.3 Stent number DES: n=1.4 BMS: n= 1.5 stent length(mm)/lesion DES: 28.3 BMS: 24.5 Type B2/C DES: 59 BMS: 68 RVD DES: 2.8 BMS: 3.0	Routine PCI practices of the centre DES: nr BMS: nr ASA 75-150 mg po od Ticlopidine 1 month; for BMS and 2 months for patients with DES	Age Diabetes Prior PCI Diagnosis of ACS Location of lesion in LAD Unprotected left main CABG Angiographic profiles were less favorable Lesion type bifurcations Long lesions Small vessels Multi vessel intervention High risk patient profile **Method to deal with differences** Propensity score method used for adjustment for obtaining DES vs BMS Then matched for the outcome of stent thrombosis	**Censoring:** No censoring information given **Ascertainment of Outcome:** All endpoints defined. Mi diagnosed by local cardiologist at the time of admission. Follow up data was obtained directly and independently from the Emilia Romagna Regional Health Agency through analysis of hospital discharge records and the mortality registries	Follow up: Mean 703 days(range 182-1279)/24 months Is 100% complete Death Kaplan-Meier Adjusted MI Kaplan-Meier Adjusted Stent thrombosis Kaplan-Meier MACE Kaplan-Meier Adjusted Potential Source of Bias: not all centres had same DES rate.

Author year	Population *Treatment/Control* (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) *Male*(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel *Disease* (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention *Stent type* Antiplatelet therapy	Significantly different Characteristics between *populations* Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Minutello 2007	**Cohort Study** DES: n=59 BMS: n= 50 **Group Selection:** Consecutive patients presenting to single New York Centre who underwent SES implantation for the treatment of single lesion in SVG compared with those that underwent implantation prior to this period with BMS. All patients referred to angiography based on symptoms or positive stress test.. Patients presenting with cardiogenic shock were excluded from analysis **Study Dates:** SES April 2003-June 2005 DES Sept 2000-March 2003	-Age : 71/69 -Men: 71/80 -Smoker: 19/6 -Diabetes: 48/44 -Prior MI: 32/28 -Prior PCI: 32/38 -Prior CABG: 100/100	Single Vessel Disease DES: 100 BMS: 100 Lesion number DES: n=59 BMS: n= 50 Lesion no per patient DES: n=1 BMS: n= 1 Lesion length(mm) DES: n=8.69 BMS: n= 9.25 Stent number DES: n=1.29 BMS: n= 1.18 stent length(mm)/lesion DES: 26.09 BMS: 20.77 Type C DES: 23 BMS: 25 RVD DES: 3.26 BMS: 3.13	Routine PCI practices of the centre . Interventional strategy at the discretion of the operator DES: SES BMS: nr Clopidogrel 1 month for BMS and 3 months for DES ASA for all patients	Mean stent diameter **Method to deal with differences** **Not dealt with**	**Clincal Follow up** **Censoring:** No censoring information given. Follow up complete **Ascertainment of Outcome:** Clinical follow up available on all patients and consisted for clinical follow up and well as telephone conversation with the patient and the referring cardiologist	Follow up: Mean 20.3 +/- 11.8 months Death Kaplan-Meier MI Kaplan-Meier Stent thrombosis Kaplan-Meier MACE Kaplan-Meier

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Phellipeau 2006 Published in French	**Cohort Study** DES no RF: n=38 DES + RF: n=38 BMS no RF: n=38 BMS + RF: n= 38 **Group Selection:** Single centre French study of patients presenting for routine PCI. These patients were then matched by sex, and diabetic status to the above groups. Allowed **ISR** **Study Dates:** Sept 2002-October 2005	-Age : 63/63 -Men: 34/34 -Smoker: 13/11 -Diabetes: 39/39 -Prior MI: 28/15 -Prior PCI: 51/25 -Prior CABG: 10.5/8	Single Vessel Disease DES: 37.5 BMS: 29.5 Lesion number DES: n=nr BMS: n= nr Lesion no per patient DES: n= nr BMS: n= nr Lesion length(mm) DES: n=19.05 BMS: n= nr Stent number DES: n=1.4 BMS: n= 1.35 stent length(mm)/lesion DES: nr BMS: nr Type C DES: nr BMS: nr RVD DES: nr BMS: nr	Routine PCI practices of the centre . Preference of radial access and direct stenting DES: SES and BMS: nr ASA 75-150 mg po od Clopidogrel 75 mg po od 1 month for BMS and 9 months for DES	Creatinine clearance smoker Prior MI Prior PCI **Method to deal with differences** none	**Censoring:** No censoring information given **Ascertainment of Outcome:** Clinical and telephone follow up	Follow up: Mean of groups is 16 months Death n Kaplan-Meier MI n Kaplan-Meier Stent thrombosis n MACE Kaplan-Meier Potential Source of Bias: not all centres had same DES rate.

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Tu **2006**	**Cohort Study** DES: n=8247 BMS: n= 5106 **Group Selection:** The CCN clinical database which captures all patients undergoing PCI in Ontario at 12 PIC centre. This database was linked to other population base administrative databases in Ontario. Of the initial cohort exclusions included those with invalid health cards, those with missing important prognostic information, those receiving 2 stent types, prior PCI in the previous year, left mainstem PCI. **Study Dates: December** 2003-March 2005	After Matching Age : 62.3/62.3 Men: 71/70 Smoker: nr Diabetes: 32.6/32.6 Prior MI: nr/nr Prior PCI: nr/nr Prior CABG: 8.5/9.0	Single Vessel Disease DES: nr BMS: nr Lesion number DES: n=nr BMS: n= nr Lesion no per patient DES: n=1.1 BMS: n= 1.1 Lesion length(mm) DES: n=nr BMS: n= nr Stent number DES: n=1.5 BMS: n= 1.5 stent length(mm)/lesion DES: 26. BMS: 26.3 Type C DES: 25 BMS: 25 RVD DES: nr BMS: nr	Routine PCI practices of the centre DES: nr BMS : nr Clopidogrel: 1 year as reported in the conclusions ASA nr	STEMI NSTEMI Mean stent diameter Mean stent length **Method to deal with differences** Propensity score matched cohort predictive for outcome. Matching occurred using 'nearest neighbor' matching algorithm with a greedy heuristic. The diabetic status and propensity score based on 21 factors was used if the difference in the logit scores of the propensity score was less than 0.2 times the SD of the scores. At the end of matching there were 3751 pairs available for matching	**Censoring:** Excluded from study if endpoint data not present **Ascertainment of Outcome:** Linkage to databases	Follow up: 24 months Significant losses through follow up Death Adjusted MI Adjusted Stent thrombosis nr MACE nr

Author year	Population Treatment/Control (number of lesions) Inclusion/Exclusion	Patient Characteristics Age(DES/BMS) Male(%)(DES/BMS) Diabetes(%)(DES/BMS) Smoker(%)(DES/BMS) Prior MI%(DES/BMS) Prior PCI %(DES/BMS) Prior CABG %(DES/BMS)	Lesions Single Vessel Disease (%) Lesion number(N) Lesion/patient(N) Lesion length(mm) Stent number(N) Stent length(mm) Type C lesions (%) RVD(mm)	Intervention Stent type Antiplatelet therapy	Significantly different Characteristics between populations Methods for Correction of Group Differences	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Zhang 2006	**Cohort Study** DES: n=3064 BMS: n= 7567 **Group Selection:** All consecutive PCI data collected for patients undergoing PCI in single centre in Shanghai, but excluded those who received both DES and BMS as well as STEMI. **Study Dates:** Jan 2002,-Dec 31, 2004	Age : 65/68 Men: 75//75 Smoker: 25/24 Diabetes: 31/22 Prior MI: 27/28 Prior PCI: 13/10 Prior CABG: 10/10	Single Vessel Disease DES: nr BMS: nr Lesion number DES: n=4392 BMS: n= 11190 Lesion no per patient DES: n=1.43 BMS: n= 1.48 Lesion length(mm) DES: n=18.6 BMS: n= 15.3 Stent number DES: n=1.4 BMS: n= 1.5 stent length(mm)/lesion DES: 28.3 BMS: 24.5 Type B2/C DES: 59 BMS: 68 RVD DES: 2.8 BMS: 3.0	Routine PCI practices of the centre DES: nr BMS: nr Ticlopidine 1 month; for BMS and 2 months for patients with DES ASA 75-150 mg po od	Age Diabetes Prior PCI Diagnosis of ACS Location of lesion in LAD Unprotected left main CABG Angiographic profiles were less favorable Lesion type bifurcations Long lesions Small vessels Multi vessel intervention High risk patient profile **Method to deal with differences** Propensity score method used for adjustment	**Censoring:** No censoring information given **Ascertainment of Outcome:** Collected by interview t clinical visit, review of records or telephone conversation	Follow up: Mean 703 days(range 182- 1279)/24 months Death n MI n Stent thrombosis nr MACE n

Table Individual Patient Meta-analysis

Author year	Population -Treatment/Control (number of lesions) -Inclusion/Exclusion	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Ellis 2007	**Individual Patient Meta Analysis** **Participant number:** DES: n=533 BMS: n=525 **Group Selection:** Patient based meta analysis using the 4 PES multicentre trials (II, IV, V, VI)Enrolled increasingly comples patient and lesion populations. Patients presenting with AMI, RF, thrombus, SVG lesions excluded.	Age: 62/62 Men: 72/73 Diabetes: 23/24 Cholesterol↑: 70/71 Hypertension: 69/68 Smoker: 22/22 MI: 34/32 PCI: nr CABG: nr	SVD: nr Lesions number: na Lesion /patient:1 Lesion length: 15.2/15.1 Stent length: 24.6/24.3 Type C: nr RVD: 2.74/2.73	SES SES *vs* BMS Bx Velocity Clopidogrel 1 month: 98.7% 4-6 months : 93% 9 months: 55% ASA Heparin	Censoring: not censored **Ascertainment of Outcome:** The data was obtained from Boston Scientific. **Blinding: nr**	Follow Up: 36 months for Taus II/IV, 2 years for Taxus VI and one year for Taxus VI Death nr MI nr Stent thrombosis n Hazard ratio MACE nr

Author year	Population -Treatment/Control (number of lesions) -Inclusion/Exclusion	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Schampaert 2006	**Individual Patient Meta Analysis** DES: n=758 BMS: n=752 **Group Selection:** Pooled 3 RCTS that compared SES to BMS(SIRIUS, ESIRIUS, CSIRIUS). Theses studies enrolled patients with single de novo lesions15-32mm.	Age: 62/62 Men: 72/70 Diabetes: 23/24 Cholesterol↑: nr Hypertension: nr Smoker: 25/28 MI: 34/32 PCI: 24/22 CABG: 8/8	SVD: nr Lesion Number: nr Lesion/Patient: nr Lesion Length: 14.5 Stent Length: Type C Lesions: nr RVD: nr	SES SES *vs* BMS Bx Velocity ASA 81-325 mg Plavix 2-3 months	**Censoring**: Na **Ascertainment of Outcome:** All endpoints defined. All patients were evaluated at 270 and 720 days. Clinical follow up obtained at 720 days for 98>9 % of patients **Blinding-** continued for 5 years	Follow up: 24 months For 98% of patients Death n MI n Stent thrombosis n MACE n

Author year	Population -Treatment/Control (number of lesions) -Inclusion/Exclusion	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)	Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Spaulding 2007	**Individual Patient Meta Analysis** DES: n=758 BMS: n=752 **Group Selection:** Pooled 4 RCTs that compared SES to BMS(SIRIUS, ESIRIUS, CSIRIUS, RAVEL) All trials excluded patients with AMI	Age: 62/61 Men: 72/72 Diabetes: 22/27 Cholesterol↑: 71/72 Hypertension: 64/63 Smoker: 21/25 MI: 33/36 PCI: 23/21 CABG: 8/7	SVD: nr Lesion Number: nr Lesion/Patient: nr Lesion Length: 14.5 Stent number: nr Stent Length: nr Type C Lesions: nr RVD: nr	SES vs Bx Velocity ASA 81-325 mg indefinitely Clopidogrel 2-3 months dependant on the trial	**Censoring**: Na **Ascertainment of Outcome:** All endpoints defined. Independent events committee a ascertained **Blinding**- continued	Follow up: 48 months Death n MI n Stent thrombosis n MACE Nr

Author year	Population -Treatment/Control (number of lesions) -Inclusion/Exclusion	Patient Characteristics -Age(DES/BMS) -Male(%)(DES/BMS) -Diabetes(%)(DES/BMS) -Smoker(%)(DES/BMS) -Prior MI%(DES/BMS) -Prior PCI %(DES/BMS) -Prior CABG %(DES/BMS)
Stone **2007**	**Individual Patient Meta Analysis** Participant number SES DES:BMS n= 1748 Participant number PES DES/BMS: n=3513 Four prospective trials of SES vs BMS were obtained from Cordis(RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS). 5 data bases from 5 prospective trials of PES vs BMS were obtained from Boston Scientific (PES1, PESII, PESIII, PESIV, PES V, PESVI). Permission was obtained to perform a patient level analysis. These studies are all included in the efficacy section	Age SES/ Age PES 62 62 62 62 % male SES/PES 71.6 72.4 71.5 72.7 %smoker SES/PES 21.2 23.7 24.5 22.9 % diabetes SES/PES 22.2 23.2 26.8 23.8 % prior pci SES/PES Nr % past mi SES/PES Nr %cabg SES/PES Nr

Lesions -Single Vessel Disease (%) -Lesion number(N) -Lesion/patient(N) -Lesion length(mm) -Stent number(N) -Stent length(mm) -Type C lesions (%) -RVD(mm)	Intervention -Intervention -stent type -antiplatelet therapy	Management of Cohort	Outcomes Follow up(months) Death -data presented MI -data presented Stent Thrombosis -data presented MACE -data presented
Single Vessel Disease DES: nr BMS: nr Lesion number SES DES: n=Nr BMS: n= Nr Lesion number PES DES: n= Nr BMS: n= Nr Lesion length(mm)SES DES: n=13.8 BMS: n= 13.9 Lesion length(mm)PES DES: n=15.1 BMS: n= 15.1 Stent number SES DES: n=1.42 BMS: n= 1.39 Stent number PES DES: n=1.21 BMS: n= 1.19 stlength(mm)/lesion SES DES: n=22.9 BMS: n= 22.5 stlength(mm)/lesion PES DES: n=24.4 BMS: n= 24.1 Type C DES: nr BMS: nr RVD DES: 2.70 BMS: 2.73	Routine PCI practices of the centre Abciximab recommended DES:: BMS: nr ASA yes Clopidogrel SES/BMS: 2-3 months PES/BMS: 6 months Longer follow up not captured	**Censoring:** Na **Ascertainment of Outcome:** Data was used form the original databases, as defined and adjudicated by the clinical events committees for each study. Original source documents were not available. **Blinding-** All patient s, investigators, study personnel, and sponsors were still blinded	Follow up: 48 months at the time of the writing Death n HR MI n HR Stent thrombosis n HR MACE nr

Appendix 9
Table 4.2.2: Quality Assessment – Harms Review Assessment

(For each study, place stars under appropriate variables)

Study	SELECTION				COMPARABILITY	OUTCOME		
	Representativeness of Exposed Cohort	Selection of Non Exposed Cohort	Ascertainment of Exposure For rct star if Prespecified	Demonstration Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of Design or Analysis	Ascertainment of Outcome	Adequate Length of Follow Up	Adequacy of Follow Up
RCTS								
Fajadet 2007	+	+	+	+	na/rct	nr	+	+
Grube 2005	+	+	+	+	na/rct	nr	+	+
Jiminez Quevedo 2007	0	+	+	+	na/rct	+	+	+
Morice 2006	+	+	+	+	na/rct	0-endpoint defined; clinical	+	+ DES 91.6% BMS 92%
Pfisterer 2006	+	+	+	+	na/rct	0	+	+
Schampaert 2006	+	+	+	+	na/rct	+	+	+

Study	SELECTION				COMPARABILITY	OUTCOME		
	Representativeness of Exposed Cohort	Selection of Non Exposed Cohort	Ascertainment of Exposure For rct star if prespecified	Demonstration Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of Design or Analysis	Ascertainment of Outcome	Adequate Length of Follow Up	Adequacy of Follow Up
Vermeersch 2007	0	+	+	+	na/rct	0	+	+
Cohort Studies								
Applegate 2008	+ all patients requiring PCI	0 time period not same	+	+	0 no adjustment	0-endpoint defined; data collection	+	+ 90% DES 95%BMS
Bansai 2008	0 selected; SVG	+	+	+	0 no adjustment	0-endpoint defined; data collection	+	0 nr
Bose 2007	0 selected; STEMI	+	+	+	0 no adjustment	0-endpoint defined; clinical	+	+ 100%
Bruggenjurgen 2007	+ all patients requiring PCI	0 time period not same	+	+	0 Some adjustment of outcomes only	0-endpoint defined; data collection	+	+ 90% DES 95%BMS

Study	SELECTION				COMPARABILITY	OUTCOME		
	Representativeness of Exposed Cohort	Selection of Non Exposed Cohort	Ascertainment of Exposure For rct Star if Prespecified	Demonstration Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of Design or Analysis	Ascertainment of Outcome	Adequate Length of Follow Up	Adequacy of Follow Up
Daemen 2006	+ all patients requiring PCI	0 time period not same	+	+	+ + - analysis/matching	+	+	+ 97.5%
Einsenstein 2007	0 Patients with no events at 6 months	0 time period not same	+	+	+-analysis	0 MI diagnosed by MDS	+	+ 98%
Jensen 2007	+ all patients requiring PCI	+	+	+	+-analysis	+ Record linkage	+	+ 100%
Langerqvist 2007	+ all patients requiring PCI	+	+	+	+-analysis	+ Record linkage	+	+ 100%
Marzocchi 2007	+ all patients requiring PCI	+	+	+	+-analysis	+ Record linkage	+	+ 100%
Minutello 2007	0 selected; SVG	0 time period not same	+	+	0- no adjustment	0-endpoint defined; clinical	0 SD is large	+ 100%
Phellipeau 2006	0 Primary comparison is renal failure	+	+	+	0 No adjustment	0-endpoint defined; clinical	+	NR

Study	SELECTION				COMPARABILITY	OUTCOME		
	Representativeness of Exposed Cohort	Selection of Non Exposed Cohort	Ascertainment of Exposure For rct Star if Prespecified	Demonstration Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of Design or Analysis	Ascertainment of Outcome	Adequate Length of Follow Up	Adequacy of Follow Up
Tu 2007	+	+	+	+	+-propensity score by matching technique	+ Record Linkage	+ Full follow up for 1.5 years only	+ 50% by 1. year
Zhang 2006	+	+	+	+	0	0	+	+
IPD								
Ellis 2007	0 Patient and lesion population low risk	+	+	+	na/rct	+	+	+ Medley of follow up; 1/3 for 3 years
Schampaert 2006	0 Patient and lesion population low risk	+	+	+	na/rct	+	+	+ 98%

Study	SELECTION				COMPARABILITY	OUTCOME		
	Representativeness of Exposed Cohort	Selection of Non Exposed Cohort	Ascertainment of Exposure For rct Star if Prespecified	Demonstration Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of Design or Analysis	Ascertainment of Outcome	Adequate Length of Follow Up	Adequacy of Follow Up
Spaulding 2007	0 Patient and lesion population low risk	+	+	+	na/rct	+	+	+ 98%
Stone 2007	0 Patient and lesion population low risk	+	+	+	na/rct	+	+	+ 98%