Systematic review and cost-effectiveness analysis of drug eluting stents compared to bare metal stents for percutaneous coronary interventions in Ontario

Interim report

Prepared for the Ontario Ministry of Health & Long-term Care

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Disclaimer

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The results and conclusions outlined in this interim report may change following the completion of the ongoing field evaluation study. Additionally, future published scientific findings may influence the final report. The final HTA report is anticipated to be available in the fall/winter of 2006.

PATH takes sole responsibility for the final form and content of this report. The statements and conclusions in this interim report are those of PATH and not of the MOHLTC, OHTAC, McMaster University or St. Joseph's Healthcare, Hamilton. Please contact PATH at www.path-hta.ca if you are aware of new research findings that should inform the report or would like further information.

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Executive Summary

In 2002, the Ontario Ministry of Health and Long-term Care (MOHLTC) completed a review of the evidence regarding drug eluting stents (DES). The systematic review of the literature identified only one published clinical trial describing the use of sirolimus. Other ongoing studies regarding both paclitaxel and sirolimus were available as published abstracts only.

In the report a preliminary economic analysis of the potential costs of DES using different hypothetical scenarios of the incremental effectiveness of DES relative to bare metal stents (BMS) revealed that, accounting for 'down-stream' cost avoidance, the additional costs of implanting a DES during all PCI procedures (both high risk and low risk patients) requiring stenting would require an additional $7.5 - $28.6 million. However, these estimates were not based on any empirical evidence of real world effectiveness of DES.

The MOHLTC felt that further Ontario-specific evaluation of the technology was warranted. Therefore, in collaboration with the MOHLTC and 12 Ontario Regional Interventional Cardiac Care Centres, the Program for Assessment and Technology in Health (PATH) at McMaster University designed and conducted an observational study or "field evaluation" to support the evaluation of the effectiveness and cost-effectiveness DES compared to BMS in Ontario.

The objectives of the study are twofold (1) To estimate the reduction in the risk of repeat revascularization associated with the use of DES, relative to BMS, among patients at high risk of restenosis; and (2) Combining the data from the registry study with costs and other published evidence, to estimate the net cost and cost-effectiveness of percutaneous coronary interventions (PCI) with DES, relative to BMS.

The purpose of this interim report is to provide an analysis of revascularization rates in patients for which 9 months of follow-up are available. The ongoing

observational study is continuing to prospectively collect data at 12 Regional Cardiac Care Centres in Ontario in order to evaluate future revascularization procedures within 1 year following the initial procedure. This interim report consists of 3 primary sections: a systematic review of the literature, the results of the field evaluation and finally presents a cost-effectiveness analysis of DES compared to BMS

Background

Coronary artery disease (CAD) manifests as a build-up of atherosclerotic plaques in the coronary arteries, and the narrowed blood vessels increase the risk of a patient sustaining a myocardial infarction (MI). Common treatment interventions for CAD include coronary artery bypass graft (CABG) surgery and PCI. During a PCI, a balloon catheter is inflated to unblock the narrowed artery (angioplasty) and most commonly a small stainless steel mesh tube known as a stent is inserted to help keep the artery open.

Coronary artery stent usage at its current rate of > 95% of procedures has been due to several factors, though two in particular stand out. First, stents reduce the restenosis rates and thus represent an improvement on balloon angioplasty. Second, by their scaffolding effect on the arterial wall, they have dramatically reduced the acute closure rates and need for emergency coronary artery bypass surgery. Stents reduce elastic recoil of the arterial wall as well as tack up dissections. Emergency bypass surgical rates have decreased from 2-3% prior to the advent of stents to about 0.3% in most high volume centres, thus making PCI a safer and more predictable procedure. These two factors as well as further improvements in stent design and technology have led to a PCI: CABG rate of almost 2:1 in Ontario.

Drug Eluting Stents (DES)

Health Canada approved the first of a new class of stents known as DES in 2002. These stents are coated with a polymer matrix containing drugs that have been shown to interrupt cellular replication and reduce neo-intimal hyperplasia (migration and growth of smooth muscle cells into the luminal space of a previously treated lesion). Two products are currently available on the Canadian market: Cypher™ Sirolimus-eluting stent (Cordis) and Taxus® Express Paclitaxel-eluting coronary stent (Boston Scientific).

Both the Cypher and Taxus stents have been shown to reduce restenosis to less than 10-15% in almost all patients: large vessels, small vessels, diabetes and non diabetes patients, short and long lesions, total occlusions. DES reduce the rates of target lesion revascularization (TLR) as well as target vessel revascularization (TVR). The long term results have added to the growth of PCI for single and multivessel angioplasty. They explain in part the PCI:CABG ratio of > 2:1 in Ontario.

Systematic Literature Review

Objectives

A systematic literature review was conducted to identify comparative studies that describe the clinical efficacy of DES versus BMS.

Methods

A search strategy was developed to identify publications discussing the use of DES in PCI, formerly known as percutaneous transluminal angioplasty (PTCA), with specific focus on those stents using either paclitaxel or sirolimus (rapamycin) as the anti-proliferative agent. Specific search strategies for the following literature databases were developed and each database was searched

individually via OVID Web Gateway (OVID Technologies, Inc. New York, NY): MEDLINE, EMBASE, Cumulative index to nursing and allied health literature (CINAHL), Evidence Based Medicine (EBM) Reviews (Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CCTR)).

No restriction on language was employed and the year of publication was restricted to 1990 – 2004 within MEDLINE and EMBASE. Identification of duplicate citations was completed using Reference Manager v.10 (ISI Researchsoft, Thomson Scientific, USA). Titles and abstracts of the unique citations were screened to identify articles where primary data was presented comparing DES to BMS. Only randomized controlled trials were included.

The clinical outcomes outlined in this report are: death, acute myocardial infarction (Q-wave and non-Q-wave), target lesion revascularizations (TLR) (PTCA or coronary artery bypass surgery), target vessel revascularization (TVR), target vessel failure (TVF) and stent thrombosis. For each outcome, the odds ratio of the effect of DES relative to BMS was estimated by meta-analytic techniques.

Results

The systematic literature review identified 11 primary publications from 9 clinical trials comparing DES to BMS. All were multi-centre trials of either 6 months, 9 months or 12 months in duration with scheduled angiographic follow-up at between 4 – 9 months following the initial PTCA procedure. These studies were conducted in patients with single de-novo lesions in native coronary arteries and follow-up evaluation ranged from 6 months to 1 year. The patients evaluated in the 9 randomized controlled trials were predominately males of approximately 60

years of age. Of the patients randomized, 2137 patients were assigned to receive a DES and 1948 patients randomized to receive a comparator BMS.

All cause mortality rates were reported in 8 of the 9 identified studies. Pooling the results from the 8 studies found no mortality difference between the two treatment groups as indicated by the OR 1.50 (95%CI 0.65, 3.46). The pooled mortality rate is dominated by the results from the SIRIUS study and several studies had treatment arms with no events. The cardiac mortality from the TAXUS IV study was not different between the DES and BMS groups, RR 1.27 (95%CI 0.47 – 3.38, p=0.80); RR 1.11 (95%CI 0.43 – 2.87, p=0.83) at both 9 months and 12 months, respectively.

Total Acute MI rates were reported in 7 of the 9 identified studies. Pooling the results from the 7 studies found no difference between the two treatment groups with respect to the rate of total acute MI as indicated by the OR 0.88 (95%CI 0.61, 1.28). TAXUS I and TAXUS II trials did not report total MI but provided Q-wave MI only (TAXUS I) and Q-wave MI and non Q-wave MI (TAXUS II) only.

TLR was reported in all of the 9 clinical studies identified. There was a statistically significant difference in the pooled TLR rates between DES compared to BMS OR 0.22 (95%CI 0.17, 0.29). The two larger randomized controlled trials, SIRIUS and TAXUS IV, have the highest weighting towards the estimate of TLR, 34.6% and 36.3%, respectively.

The endpoint of TVR was reported only in the TAXUS studies. There was a statistically significant difference in TVR between DES and BMS stents OR 0.36 (95%CI 0.26, 0.53). As with TLR, the pooled TVR result is primarily influenced by the large randomized controlled trial with a weight of 81.1.

Stent thrombosis was reported in all of the 9 clinical trials. There was no apparent difference between DES and BMS with respect to thrombosis, OR 1.08

(95%CI 0.49, 2.37). Several studies reported zero events in one or more treatment arms.

In conclusion, there was no apparent difference between DES as compared to BMS with respect to mortality, acute MI or stent thrombosis. The pooled estimates of TLR and TVR from the clinical studies indicate that DES provides a reduced rate of restenosis as compared to BMS.

Field Evaluation

Purpose

The main objective of this field evaluation was to compare the rate of all revascularization procedures in patients receiving a PCI intervention in Ontario with either a DES or a BMS.

Methods

This was a prospective, non-randomized, observational study. The prospective collection of the data was initiated at the 12 Ontario Regional Interventional Cardiac Care Centres in December 2003 using a standardized form. The use of DES and BMS was collected with an existing cardiac care registry, CCN CARDIACCESS database, in which additional fields related to the placement of coronary artery stents were added.

The study population for this interim analysis included all patients undergoing an elective or adhoc procedure and received a PCI with stent between December 1, 2003 - June 30, 2004 (for which at least 9 months of follow-up information was available) for the management of stable angina, unstable angina or silent ischemia or within 7 days following an acute myocardial infarction. In addition,

patients included in this analysis had to receive only one stent type (either DES or BMS) during the PCI procedure but not a combination of both types.

For the purpose of analysis, the patients were first stratified into four primary cohorts to allow for the comparison of patients based on their recent history of an acute myocardial infarction and whether or not they have diabetes. The resulting four primary cohorts are: Non-Post MI without diabetes, Non-Post MI with diabetes, Post-MI without diabetes and Post-MI with diabetes. As a second step, each of the four populations was further divided according to the lesion characteristics such as narrow or long lesions. In total, the outcomes were evaluated in 22 cohorts.

The primary clinical endpoint for the field evaluation was an adjusted rate of target vessel revascularization (TVRa) at 365 days. TVRa, was constructed from data in the CCN dataset and is a composite of target vessel revascularizations (TVR) (i.e. PCI with stent), all repeat PCI without stent and all CABG procedures performed in patients following their initial procedure. Secondary endpoints included: target lesion revascularization (TLR), target vessel revascularization (TVR), all PCI without stent and total revascularization (TR) procedures. As direct measurement of lesion dimensions were not available, stent size was used as a proxy for the lesion diameter and the total stent length(s) were used as a proxy for lesion length.

Statistical methods used to analyze the data included an unadjusted event rate analysis, a time to event analysis, and unadjusted KM survival analysis and a multivariate Weibull Regression analysis to adjust the event rates by potential different baseline characteristics between DES and BMS patients. Only the results of the multivariate Weibull regression models are described in this executive summary.

Results

From December 1, 2003 to March 31, 2005 a total of 20,431 PCI procedures with the placement of a stent were completed in Ontario. From this patient population, 9,103 cases had at least 9-months of follow-up data available for this interim analysis.

The use of DES only occurred in 39.13% of the 9,103 cases; BMS alone was used in 48.24% and in 9.70% of the procedures both DES and BMS were used. DES were used more commonly in patients with diabetes both in patients with a recent MI (42.09% DES in diabetes group versus 28.37% DES in non-diabetes), and in the non Post MI group (52.97% DES in diabetes group versus 37.92% DES in non-diabetes group).

Baseline differences amongst the 4 primary cohorts were apparent, as may be expected due to the observational nature of the study. The mean age is lower in the patients that received a DES in non Post MI patients (non-diabetes and diabetes) but not in Post MI patients and the patients that received a DES had a greater rate of previous PCI. In some of the groups there are differences in the use of DES by gender. For example, in the non Post MI non-diabetes and Post MI diabetes more women than men received DES.

After adjusting for differences in pre-existing comorbidities, DES had a positive treatment effect compared to BMS in extending time to repeat events, or equivalently in reducing event rates as shown by the Multivariate Weibull regressions.

Overall for the non Post MI non diabetes group, the rate of TVRa for the non Post MI non-diabetes group (n = 4188) was not statistically different at the 5% level between patients treated with DES (5.4%) compared to BMS (7.2%). When examining the predicted rates of TVRa by lesion characteristic however there

were statistically significant differences, after controlling for baseline characteristics, between DES and BMS treated patients depending on the lesion characteristics. Patients treated with DES and with long lesions had a lower rate of revascularization than BMS treated patients respectively (4.7% vs. 9.0%, $p<0.05$). The reduced rate of revascularization for DES treated patients relative to BMS treated patients was also found in patients with narrow lesions (6.4% vs. 10.7%, $p<0.05$) and in patients with longer or narrower lesions (5.4% vs. 9.5%, $p<0.05$).

Similarly for Non-Post MI patients with diabetes, the observed differences between DES and BMS were statistically significant for long and narrow (DES 6.0%, BMS 20.6%), long (DES 18.6%, BMS 7.9%), narrow (DES 5.7%, BMS 11.9%), and long or narrow lesions (DES 6.9%, BMS 14.3%). In general, the overall rate of revascularization was higher for patients with diabetes and long and/or narrow lesions as compared to the patients without diabetes.

For the post MI non-diabetes population, there were no statistically significant differences, at the 5% level, in the rates of revascularization between DES and BMS. At the 10% level, differences in TVRa were observed for patients for the overall cohort (BMS 6.1% vs. 3.8%), after adjusting for baseline characteristics, patients with long lesions (BMS 8.1%, DES 3.0%), and wide lesions (BMS 5.5%, DES 2.8%). Similarly, for Post MI diabetes patients, the rate of TVRa is higher for BMS than DES at the 10% level (BMS 12.1%, DES 5.8%) but not at the 5% level.

Discussion

This interim analysis of the Ontario “real-world” use of DES as compared to BMS presents observational data from approximately 8000 cases with at least 9 months of follow-up information. Based on a an analysis of the raw event rates, KM survival analysis and Multivariate Weibull regression, the revascularization

rates for patients treated with DES are lower than that found in the BMS treated patients but only in selected lesions (long and/or narrow lesions).

The DES revascularization rates observed in this study appear to be similar to those reported within the clinical literature (see systematic literature review), however, the revascularization rates for BMS are significantly lower than those reported from randomized controlled trials. Potential reasons for the difference may include differences in practice patterns in Ontario (utilization of HMGCoA reductase inhibitors, antiplatelet agent duration of use), the observational nature of the study as compared to randomized controlled trials, an elevated target lesion revascularization rate in the clinical trials due to protocol driven-revascularizations and the wider range/diversity of lesions treated in the "real-world" as compared to the selected lesions included in the RCT's.

Economic Analysis

Objective

The objective of the economic evaluation was to compare the one year costs and outcomes for patients undergoing a PCI that included the insertion of either a DES or a BMS.

Methods

Clinical pathways related to revascularizations following the use of DES and BMS during PCI were modeled using a decision tree model. Costs incorporated in the model included the cost of the initial PCI, including stent costs, along with costs associated with revascularizations occurring within 1 year post initial PCI. Outcomes include the expected number of revascularizations and the expected Quality Adjusted Years (QALY's) one year post initial PCI. QALYs incorporated

the quality of life impacts of anginal symptoms and recovery time associated with revascularization procedures.

Two cost effectiveness outcomes were evaluated and expressed as incremental cost-effectiveness ratios (ICER's). The primary cost-effectiveness outcome was the incremental cost per QALY gained (DES vs. BMS). The secondary cost-effectiveness outcome was the incremental cost per revascularization avoided. ICER's were not calculated if one treatment strategy dominated the other (i.e. lower costs, better outcomes). The analysis was taken from the perspective of the Ontario Ministry of Health and the time horizon was 1 year.

Various sources of data were used in the model. These include results observed from the field evaluation along with data from other sources. The results from the field evaluation were used to derive the probabilities of revascularization, the type of revascularizations (e.g. PCI stent, PCI without stent, CABG) and the number of stents (initial and follow-up stents). The average unit cost of DES and BMS were derived from the manufacturers while the costs of health care resource utilization (e.g. hospital costs) were derived from various sources including the Ontario Case Costing Project data (e.g. CABG) and the Ontario Physician Schedule of Benefits. Results from the field evaluation (i.e. average waiting time for revascularization procedures as a proxy for duration of anginal symptoms) and the literature (i.e. ARTS trial) was used to calculate QALYs. To account for uncertainty around model input parameter values, a probabilistic sensitivity analysis was conducted.

All analyses were carried out separately for Non-Post MI and Post-MI patients. In order to account for patient groups at higher risk of revascularization, groups were further stratified according to diabetes status, lesion length and lesion diameter. Due to the small sample of the Post–MI group with diabetes, from the field evaluation, it was not possible to stratify this group according to lesion

length and diameter. In total, the cost-effectiveness of DES versus BMS was determined for 22 different cohorts of patients.

Results

Results indicate that the incremental cost effectiveness of DES versus BMS is high for all 22 cohorts. In terms of incremental costs per QALY gained, the most favourable incremental cost-effectiveness ratios were $223,580 per QALY gained for the non-post MI diabetes, long and narrow lesions cohort. The cohorts with the next most favourable cost-effectiveness results were: non-post MI, diabetes, long lesions ($292,133/QALY); post MI, non-diabetes, long and narrow lesions ($393,923/QALY); post MI, diabetes, all patients ($438,415/QALY); and non-post MI, diabetes, long or narrow lesions ($477,736/QALY).

In terms of incremental cost per revascularization avoided, the most cost effective result was $9,689/revacularization procedure averted for the non-post MI diabetes, long and narrow lesions, with least favourable showing BMS being dominant over DES (non-post MI, non diabetes, short and wide).

In general the cost-effectiveness of DES was found to be more favourable in patients with diabetes, long lesions and/or narrow lesions. The mean probabilistic cost-effectiveness results are very similar to the deterministic results and the general conclusions on cost-effectiveness results do not change using the probabilistic results (i.e. when uncertainty is accounted for).

Discussion

Based upon our primary cost-effectiveness outcome (cost/QALY) the incremental cost-effectiveness of DES versus BMS is high for all cohorts investigated (i.e. the most favourable incremental cost effectiveness being $223,580 per QALY gained).

The primary strength of the current economic analysis is that revascularization rates and other key model input variables are based upon a large sample of Ontario specific “real world” data. Other published economic analyses of drug eluting and bare metal stents are mostly based upon clinical trial data which may not reflect the situation observed in the real world.

Conclusion

The studies identified in the systematic literature review demonstrate that DES reduces revascularization rates compared to BMS in patients with single-de novo lesions. No apparent differences in mortality, acute MI rate or stent thrombosis rates between DES and BMS were found in the meta-analysis of the trials.

The results from the field evaluation indicate that DES reduces predicted revascularization rates at 1 year compared to BMS in some but not all patient cohorts. In non Post MI patients, DES appears to be most effective in reducing the need for revascularization in patients with long or narrow lesions. This benefit was magnified in patients with diabetes. DES also appears to be effective in Post MI patients. However, further data collection is required in order to confirm the benefit of DES by lesion type in this patient cohort. DES as compared to BMS does not appear to provide a reduction in revascularization rates in patients with short and wide lesions, in patients with and without diabetes.

The economic analysis incorporating “real-world” data from over 9,000 patients in Ontario found that the most favourable cost-effectiveness ratio for DES compared to BMS was $223,580/QALY in patients in non Post MI, diabetes patients with long and narrow lesions. The absolute difference of approximately 15% was found in revascularization rates between the two interventions in this patient population.

Table of Contents

Tables

Figures

Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AETMIS	Agence d'évaluation des technologies et des modes d'intervention en santé
AHA	American Heart Association
ARTS	Arterial Revascularization Therapies Study
ASA	Acetylsalicylic Acid
BMS	Bare metal stent
BRR	Binary restenosis rate
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCN	Cardiac Care Network of Ontario
CCS	Canadian Cardiovascular Society
CINAHL	Cumulative index to nursing and allied health literature
CIRC or LCx	Circumflex coronary artery
CCOHTA	Canadian Coordinating Office of Health Technology Assessment
CCTR	Cochrane central register of controlled trials
CDSR	Cochrane database of systematic reviews
CEACs	Cost-effectiveness acceptability curves
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
DARE	Database of Abstracts of Reviews of Effects
DES	Drug eluting stent
DM	Diabetes mellitus
EBM	Evidence-based medicine
EMBASE	Excerpta Medica database
EQ-5D	EuroQoL 5 Dimensions
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical and Evaluative Sciences
IVUS	Intravascular ultrasound
HMGCoA	3-hydroxy-3-methylglutaryl coenzyme A
HTA	Health Technology Assessment
KM	Kaplan Meier
LAD	Left anterior descending coronary artery
LIMA	Left interior mammary artery bypass
LM	Left main coronary artery

LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MAS	Medical Advisory Secretariat
MI	Myocardial infarction
MOHLTC	Ontario Ministry of Health and Long-term Care
NYHA	New York Heart Association
OHTAC	Ontario Health Technology Assessment Committee
OR	Odds ratio
PATH	Program for Assessment of Technology in Health
PCI	Percutaneous coronary intervention
POBA	Plain old balloon angioplasty
PSA	Probabilistic sensitivity analysis
PTCA	Percutaneous transluminal coronary angioplasty
PVD	Peripheral vascular disease
QALYs	Quality adjusted life years
QCA	Quantitative coronary angiography
RCA	Right coronary artery
RVD	Reference vessel diameter
SVG	Saphenous vein graft
THR	Stent thrombosis
TIA	Transient ischemic attacks
TLR	Target lesion revascularization
TR	Total revascularizations
TVF	Target vessel failure
TVR	Target vessel revascularization
TVRa	Target vessel revascularization adjusted

1. Introduction

1.1. Rationale

Coronary artery disease (CAD) manifests as a build-up of atherosclerotic plaques in the coronary arteries, and the narrowed blood vessels increase the risk of a patient sustaining a myocardial infarction (MI). Common treatment interventions for CAD include coronary artery bypass graft (CABG) surgery and percutaneous coronary interventions (PCI). During a PCI, a balloon catheter is inflated to unblock the narrowed artery (angioplasty) and most commonly a small stainless steel mesh tube known as a stent is inserted to help keep the artery open.

Coronary artery stent usage at its current rate of > 95% of procedures has been due to several factors, though two in particular stand out. First, stents reduce the restenosis rates and thus represent an improvement on balloon angioplasty. Second, by their scaffolding effect on the arterial wall, they have dramatically reduced the acute closure rate and need for emergency coronary artery bypass surgery. Stents reduce elastic recoil of the arterial wall as well as tack up dissections. Emergency bypass surgical rates have decreased from 2-3% prior to the advent of stents to about 0.3% in most high volume centres, thus making PCI a safer and more predictable procedure. These two factors as well as further improvements in stent design and technology have led to a PCI:CABG rate of almost 2:1 in Ontario.

Although BMS clearly constitute an improvement on plain old balloon angioplasty (POBA), the angiographic restenosis rates in randomized controlled trials have been disappointing and remain high at 20-35%. Cobalt-Chromium alloys have been a significant improvement in BMS technology. The currently available alloy stents (Medtronic Driver, Guidant Vision) have thinner struts, greater radial strength, and are more flexible thus making them superior to other stainless steel bare metal stents. However there are no randomized controlled trials showing these to have significantly reduced rates of restenosis. Biodegradable stents are still being investigated but likely will not impact significantly on restenosis.

Restenosis occurs when there is intimal regrowth and smooth muscle cell proliferation at the site of angioplasty or stent. Typically restenosis occurs rapidly after PCI, usually within 1-6 months of the procedure. Most though not all restenosis manifests itself clinically. Some patients (approximately 15 – 20% will require a revascularization procedure within one year following the implantation of a bare metal stent (BMS).[1-3] There have been many attempts to modify the rates of restenosis, mostly with pharmaceutical interventions. ACE inhibitors, calcium channel blockers, antiplatelet agents, and others have been studied extensively with little success. IIb/IIIa inhibitors also do not affect the restenosis rates but do have other beneficial effects.

Since myointimal proliferation is the cause of restenosis it was hypothesized that antiproliferative or anti-inflammatory agents may be able to prevent restenosis. Different agents added to the surface of various stents (with and without polymers) have been studied in the last decade. Some agents have proven to not be effective (e.g. dexamethasone) clinically while others never got out of the laboratory. Still others continue to be investigated (e.g. everolimus).[4-6] However two agents have shown promise experimentally and clinically: sirolimus and paclitaxel.

Health Canada approved the first of a new class of stents known as Drug Eluting Stents (DES) in 2002. These stents are coated with a polymer matrix containing drugs that have been shown to interrupt cellular replication and reduce neo-intimal hyperplasia (migration and growth of smooth muscle cells into the luminal space of a previously treated lesion). Two products are currently available on the Canadian market: Cypher™ Sirolimus-eluting stent (Cordis) and Taxus® Express Paclitaxel-eluting coronary stent (Boston Scientific). Sirolimus is a macrolide antibiotic that has been applied to the surface of a stainless steel BMS (Cypher-Cordis). It is slowly released over the course of three months, thus being available at the time of greatest myointimal proliferation. It has been shown to be extremely effective in reducing myointimal proliferation in many studies and was the first clinically available drug eluting stent (DES) in Canada and world-wide. Initial studies suggested restenosis rates of 0% leading to the belief that

restenosis had been beaten.[7] Subsequent randomized trials have shown restenosis rates of less than 10% in the DES arm as compared to >30% in the BMS arm.[8-11]

Paclitaxel is an antiproliferative medication applied to the surface of a stainless steel BMS (TAXUS- Boston Scientific) and slowly released over three months. It too has been shown to reduce restenosis rates to less than 10% as compared to the BMS arm (restenosis rates of >25%) in a series of trials.[3,12-14] The TAXUS was the second DES available in Canada and world-wide.

Both the Cypher and Taxus stents have been shown to reduce restenosis to less than 10-15% in almost all patients: large vessels, small vessels, diabetics and non diabetic, short and long lesions, total occlusions. DES reduces the rates of target lesion revascularization (TLR) as well as target vessel revascularization (TVR). The long term results have added to the growth of PCI for single and multivessel angioplasty. They explain in part the PCI:CABG ratio of > 2:1 in Ontario.

Although, randomized trials comparing DES with standard BMS have shown relative risk reductions for restenosis of 90% - 100% in patients with selected lesions and 60-75% in patients with a broader range of lesions, the benefit to patients of reduced risk of repeated PCIs comes at an additional cost.[9,14-16]

The cost-effectiveness of using DES needs to account for the averted 'downstream' costs associated with a reduction in the number of 're-do' PCIs and recurrent hospital admissions for unstable angina or MI that occur secondary to restenosis. An economic evaluation of sirolimus-eluting coronary stents, based on data from a multi-centre randomized controlled trial of patients with single native de novo coronary lesions, found that the additional 'up-front' costs of the DES are almost completely offset by 'downsteam' cost avoidance of PCI and CABG procedures.[17] Other cost-effectiveness studies have, however, found that DES compared to BMS may not be as cost-effective compared to BMS when used in a real-world setting.[18,19]

One further consideration is the transferability and generalizability of these

studies findings to Ontario are dependent on the differences in re-do rates between this study and that observed here in Ontario, as well as potential differences in resource utilization and unit costs. If DES proves to be as effective in real-world usage as in the clinical trials, they may be both clinically and economically attractive, with 'down-stream' cost savings from repeated PCIs and hospital admissions averted compensating for the 'up-front' additional cost of implanting a DES.

1.1.1. Review of Drug-Eluting Coronary Stents by MOHLTC

In 2002, the Ontario Ministry of Health and Long-term Care (MOHLTC) completed a review of the evidence regarding DES.[20] The report identified and evaluated the information, available at the time, regarding coronary artery stents that were coated with various pharmacological agents (e.g. heparin, sirolimus, paclitaxel and QP2). The systematic review of the literature identified only one published clinical trial describing the use of sirolimus.[7] Other ongoing studies regarding both paclitaxel and sirolimus were available as published abstracts only.

In the report a preliminary economic analysis of the potential costs of DES using different hypothetical scenarios of the incremental effectiveness of DES relative to BMS revealed that, accounting for 'down-stream' cost avoidance, the additional costs of implanting a DES during all PCI procedures (both high risk and low risk patients) requiring stenting would require an additional $7.5 - $28.6 million.[20] The evaluation also stated that based on 2002/03 stent prices and average number of stents used per PCI, the additional cost per PCI in Ontario with DES would result in $2,500 to $3,840 in additional costs.[20] However, these estimates were not based on any empirical evidence of real world effectiveness of DES. The potential for substantial additional costs in conjunction with little evidence of effectiveness data illustrated the need for a formal, real-world cost-effectiveness analysis of drug eluting stent technology in Ontario.

1.1.2. CCN Working Group on Drug Eluting Stents

Following the completion of the initial evaluation of DES by the Medical Advisory Secretariat, the MOHLTC requested that the Cardiac Care Network of Ontario (CCN) coordinate a brief report from the interventional cardiac centres of the province to discuss the anticipated scope and target population for the targeted use of DES.[20,21] In order to create this advisory report for the MOHLTC, the CCN convened a Drug Eluting Stent Working Group consisting of the Cath Lab Director (or designate) and a program administrator or manager from each of the interventional centres in Ontario. The group considered the use of DES in four hypothetical "roll-out strategies" as the starting point of their discussions. These strategies ranged from the universal use of DES in all patients, to a more restricted utilization of DES for patients considered to be at a very high risk of restenosis.[21]

The working group recommended that the initial utilization of DES should be funded, at a minimum for use in:

a) Patients or lesions with a high risk of restenosis with conventional stenting.

b) Patients in whom restenosis may have severe clinical consequences.

At the time, definition (a) was comprised of (i) treated diabetic patients and (ii) non-diabetic patients with long lesion (> 18 mm) in a small vessel (< 2.75 mm).

Definition (b) included patients with an unprotected left main lesion or a lesion in a survival dependant vessel. It was estimated that based on these criteria that approximately 40% of BMS would be replaced by DES.[21]

The widespread use of DES in Ontario commenced in September 2003 following the annual funding approval by the Ministry of Health and Long-Term Care. (see Section 6). The total annual funding for DES initially was $12 million divided between the 12 Cardiac Care Centres in Ontario based on case volume. The condition of this funding was that the Cardiac Care Centres assist in the collection of data to allow for a Ministry of Health and Long-Term Care sponsored Health Technology Assessment (HTA) of DES to be conducted by the Program

for Assessment of Technology in Health (PATH). The project was initiated to address issues of generalizability and to help inform where Canadian specific data is required to assess the cost-effectiveness of DES.

1.2. Project Purpose

The objectives of the study are twofold (1) To estimate the reduction in the risk of repeat revascularization associated with the use of drug eluting stents, relative to bare metal stents, among patients at high risk of restenosis; and (2) Combining the data from the registry study with costs and other published evidence, to estimate the net cost and cost-effectiveness of PCI with DES, relative to BMS.

1.3. Report Purpose

This interim report provides an analysis of revascularization rates in patients for which 9 months of follow-up are available. The ongoing observational study is continuing to prospectively collect data at 12 Regional Cardiac Care Centres in Ontario in order to evaluate future revascularization procedures within 1 year following the initial procedure. This interim report consists of 3 primary sections: a systematic review of the literature, the results of the field evaluation and finally presents a cost-effectiveness analysis of DES compared to BMS

2. SYSTEMATIC REVIEW OF LITERATURE COMPARING DES TO BMS

2.1. Methods

2.1.1. Literature Search

A search strategy was developed to identify publications discussing the use of DES in PCI, formerly known as percutaneous transluminal angioplasty (PTCA), with specific focus on those stents using either paclitaxel or sirolimus (rapamycin) as the anti-proliferative agent (Appendix I). Specific search strategies for the following literature databases were developed and each database was searched individually via OVID Web Gateway (OVID Technologies, Inc. New York, NY): MEDLINE, EMBASE, Cumulative index to nursing and allied health literature (CINAHL), Evidence Based Medicine (EBM) Reviews (Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CCTR)). No restriction on language was employed and the year of publication was restricted to 1990 – 2004 within MEDLINE and EMBASE. Identification of duplicate citations was completed using Reference Manager v.10 (ISI Researchsoft, Thomson Scientific, USA)

The titles and abstracts of the unique citations were then screened to identify articles where primary data was presented comparing DES to BMS. The following publication types were excluded from further evaluation and screening: review articles, comments or letters. Publications providing clinical evaluation of DES were then identified, based on a review of the titles and abstracts and the trial design was determined. The clinical evaluation studies were categorized into case series, cohort analyses, registry studies and randomized-controlled trials. If the primary focus of the paper could not be clearly identified by reviewing the title or abstract, the article was obtained for further review. Randomized controlled trials comparing DES and BMS were selected for further full text evaluation. Full text screening of the identified publications was completed using predefined criteria (Appendix II) to identify the outcomes

analyzed in the trial and to determine if the publication was the primary study report or a sub-analysis of a clinical trial dataset. Publications were selected and the data abstracted, from articles that presented any of the following clinical outcome endpoints: death, acute myocardial infarction (Q-wave and non-Q-wave), target lesion revascularizations (TLR) (PTCA or coronary artery bypass surgery), target vessel revascularization (TVR), target vessel failure (TVF) or stent thrombosis (Appendix II). Papers that reported other outcomes (e.g. intravascular ultrasound (IVUS) or quantitative coronary angiography (QCA) only without clinical outcome measures), reported results using anti-proliferative agents other than paclitaxel or sirolimus, did not have abstractable data or were not the primary publication of the trial results were excluded.

Data was abstracted from the identified primary randomized clinical trials using a predefined data abstraction form. Information pertaining to the trial characteristics, inclusion & exclusion criteria, patient demographics and comorbidities, vessel and lesion characteristics and clinical outcomes were abstracted.

2.1.2. Statistical Analysis

2.1.2.1. Descriptive statistics

The data abstracted from the publications, where possible, were expressed as the number and proportion of the patients with a given characteristic or event. If only the percentage of a given variable was expressed in the publication the number of patients with the characteristic or event was calculated.

2.1.2.2. Meta-analysis

For each outcome, the odds ratio of the effect of DES relative to BMS was estimated by pooling individual trial results using inverse variance weighting methods [22]. A test of heterogeneity was performed for each meta-analysis. If the

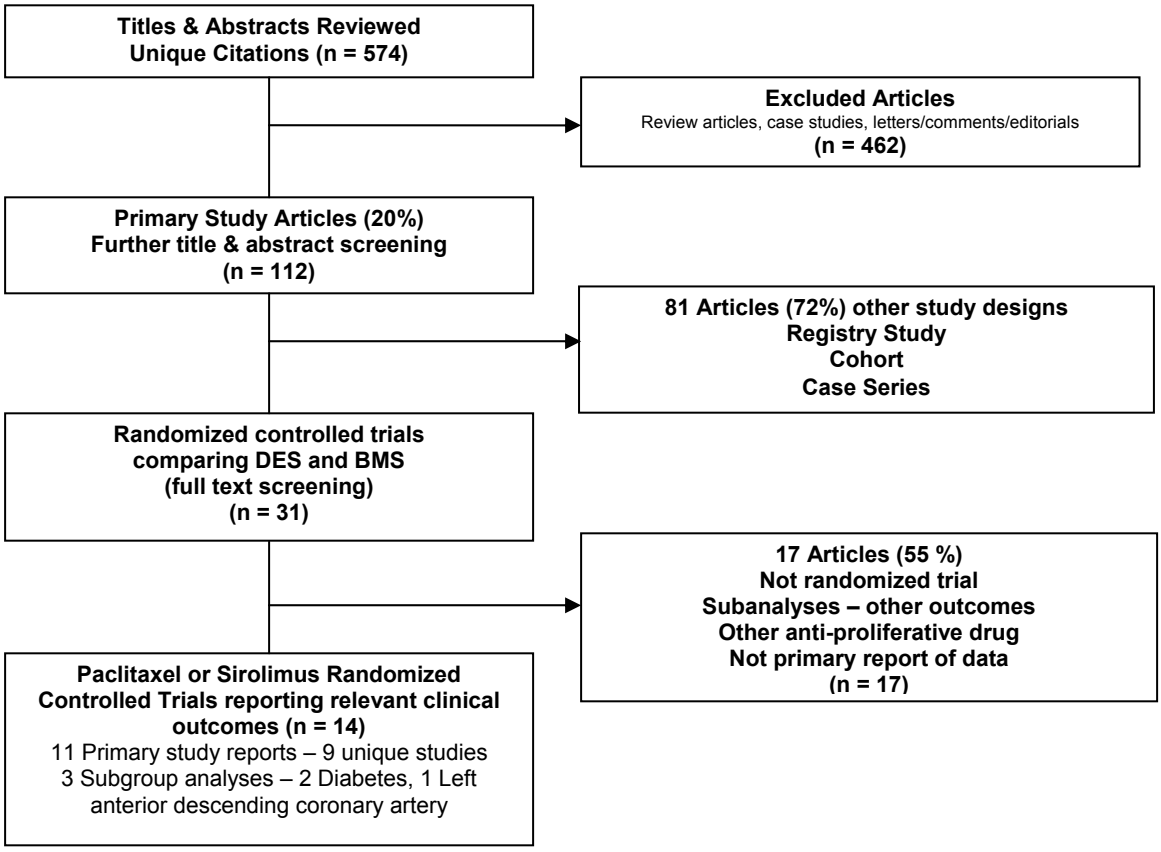
test was found to be statistically significant, a random effects model was used to estimate the odds ratio, otherwise a fixed effects model was used.

2.2. Results

2.2.1. Literature Search

The literature search was conducted on November 24, 2004 (Appendix III) and identified 899 citations and following de-duplication resulted in 574 unique citations for screening. The database source for the citations is outlined in Appendix III. An initial screening of the titles and abstracts identified 112 articles that contained primary clinical data describing the use of DES compared to BMS. Excluded from further review were 462 citations. The reason for exclusion is outlined in Figure 1. The trial design of the remaining 112 citations was identified based on the information contained in title and abstracts. This screening identified 31 citations that potentially contained data from randomized controlled trials comparing DES and BMS. These studies were obtained for further full text review. Excluded from further evaluation were 17 articles. Of these studies, 7 articles that reported outcomes from the randomized trials but did not provide further details regarding the clinical outcomes of the patients in the trials, 4 studies involved the use of other anti-proliferative agents, 5 articles were not the primary clinical report of the clinical trials and 1 article was not a randomized trial based on full text review. The full-text review identified 14 primary publications of randomized controlled trials using either paclitaxel or sirolimus as the anti-proliferative agent in the DES and reporting clinical outcomes. These studies consisted of 11 primary studies and 3 sub-group analyses. Data from the 3 sub-group analyses were extracted or included in further analysis as these patients were included in the primary clinical trial datasets.[23-25]

Figure 1. Flow diagram outlining the reasons for study identification for inclusion in meta-analyses



2.2.2. Studies Overview & Description

The 9 unique clinical trials described in 14 publications were identified. All were multi-centre trials of 6 months, 9 months or 12 months in duration with scheduled angiographic follow-up at between 4 – 9 months following the initial PCI procedure. Patients were enrolled in these trials from January 2000 to August 2002. The inclusion criteria for the studies primarily consisted of patients of at least 18 years of age with stable or unstable angina or silent ischemia. The inclusion for the lesion characteristics consisted of single lesions (usually de-novo) occurring in a native vessel and were of varying diameter and length as outlined in Appendix V. In general, the lesion lengths were greater than 10 mm

and when reported no longer than 32 mm in length. The lesion diameter ranged from 2.5 mm as the smallest diameter studied to a maximum diameter of 3.75 mm in one study.[3,14] The stents used in the trials consisted of 4 studies evaluating sirolimus drug eluting stents and 5 studies evaluating paclitaxel eluting stents (3 polymer based and 2 non-polymer based stents). The type and duration of post-procedure antiplatelet medication varied between studies. Post-procedure all studies required the use of acetylsalicylic acid (ASA) at doses ranging from 80 mg to 325 mg daily to be used indefinitely, when specified. The use of other antiplatelet agents varied between studies with most trials using post-procedure clopidogrel 75 mg daily. Some studies also used ticlopidine 250 mg twice daily and in one trial cilostazol were used. [13] The duration of the additional antiplatelet therapy varied from 1 month to 6 months post-procedure.

2.2.3. Patient Demographics

The patients evaluated in the 9 randomized controlled trials were predominately males of approximately 60 years of age. Of the patients randomized, 2137 patients were assigned to receive a DES and 1948 patients randomized to receive a comparator BMS. The patient demographics, baseline comorbidities and presenting condition for the patients enrolled in the clinical trials are outlined in Appendix VI.

2.2.4. Mortality

All cause mortality rates were reported in 8 of the 9 identified studies.[7-13,26,27] Pooling the results from the 8 studies found no mortality difference between the two treatment groups as indicated by the OR 1.50 (95%CI 0.65, 3.46) (Figure 2). The pooled mortality rate is dominated by the results from the SIRIUS study and several studies had treatment arms with no events.[8,9] Cardiac mortality was reported in the remaining trial.[3,14]. The cardiac mortality from the TAXUS IV study was not different between the DES and BMS groups, RR 1.27 (95%CI 0.47

– 3.38, p=0.80); RR 1.11 (95%CI 0.43 – 2.87, p=0.83) at both 9 months or 12 months, respectively.[3,14]

Figure 2: Meta-analysis of mortality comparing DES vs. BMS

	DES	BMS		
Study	**n / N**	**n / N**	**weight**	**O.R. (95%C.I.'s)**
ASPECT	0 / 59	0 / 58	4.5%	0.98 (0.02 , 50.38)
CSIRIUS	0 / 50	0 / 50	4.5%	1.00 (0.02 , 51.39)
ELUTES	1 / 37	0 / 38	6.7%	3.16 (0.12 , 80.20)
ESIRIUS	2 / 175	1 / 177	12.0%	2.03 (0.18 , 22.65)
RAVEL	2 / 120	2 / 118	17.8%	0.98 (0.14 , 7.10)
SIRIUS	7 / 533	4 / 525	45.6%	1.73 (0.50 , 5.96)
TAXUS I	0 / 31	0 / 30	4.5%	0.97 (0.02 , 50.36)
TAXUS II	0 / 131	0 / 131	4.5%	1.00 (0.02 , 50.78)
Total (95% CI)	**12 / 1136**	**7 / 1127**	**100.0%**	**1.50 (0.65 , 3.46)**

Test for heterogeneity X^2=0.67 df=7,p=0.99

Test for overall effect z=0.96,p=0.81

2.2.5. Acute MI

Total Acute MI rates were reported in 7 of the 9 identified studies. Pooling the results from the 7 studies found no difference between the two treatment groups with respect to the rate of total acute MI as indicated by the OR 0.88 (95%CI 0.61, 1.28) (Figure 3). TAXUS I and TAXUS II trials did not report total MI but provided Q-wave MI only (TAXUS I) and Q-wave MI and non Q-wave MI (TAXUS II) only (see Appendix VII).[12,27]

Figure 3: Meta-analysis of acute MI comparing DES vs BMS

	DES	BMS			
Study	**n / N**	**n / N**	**weight**	**O.R. (95%C.I.'s)**	
ASPECT	2 / 59	1 / 58	2.4%	2.00 (0.18 ,	22.68)
CSIRIUS	1 / 50	2 / 50	2.4%	0.49 (0.04 ,	5.58)
ELUTES	1 / 37	0 / 38	1.3%	3.16 (0.12 ,	80.20)
ESIRIUS	8 / 175	4 / 177	9.5%	2.07 (0.61 ,	7.01)
RAVEL	4 / 120	5 / 118	7.9%	0.78 (0.20 ,	2.98)
SIRIUS	16 / 533	18 / 525	30.1%	0.87 (0.44 ,	1.73)
TAXUS IV	23 / 639	31 / 633	46.4%	0.73 (0.42 ,	1.26)
Total (95% CI)			**100.0%**	**0.88 (0.61 ,**	**1.28)**

Test for heterogeneity X^2=3.67,df=1,p=0.72

Test for overall effect z=0.65,p=0.27

2.2.6. Target lesion revascularization

TLR was reported in all of the 9 clinical studies identified. There was a statistically significant difference in the pooled TLR rates between DES compared to BMS OR 0.22 (95%CI 0.17, 0.29) (Figure 4). The two larger randomized controlled trials, SIRIUS and TAXUS IV, have the highest weighting towards the estimate of TLR, 34.6% and 36.3%, respectively.[3,7,8,14]

Figure 4: Meta-analysis of TLR comparing DES vs BMS

	DES	BMS			
Study	**n / N**	**n / N**	**weight**	**O.R.**	**(95%C.I.'s)**
ASPECT	2 / 59	2 / 58	2.0%	0.98	(0.13 , 7.27)
CSIRIUS	3 / 50	9 / 50	4.1%	0.29	(0.07 , 1.16)
ELUTES	2 / 37	6 / 38	2.8%	0.30	(0.06 , 1.63)
ESIRIUS	7 / 175	40 / 177	10.9%	0.14	(0.06 , 0.33)
RAVEL	0 / 120	28 / 118	1.0%	0.01	(0.00 , 0.22)
SIRIUS	26 / 533	105 / 525	34.6%	0.21	(0.13 , 0.33)
TAXUS I	0 31	4 / 30	0.9%	0.09	(0.00 , 1.82)
TAXUS II	5 / 131	21 / 131	7.5%	0.21	(0.07 , 0.58)
TAXUS IV	28 / 639	96 / 633	36.3%	0.26	(0.16 , 0.41)
Total (95% CI)	**73 / 1775**	**311 / 1760**	**100.0%**	**0.22**	**(0.17 , 0.29)**

Test for heterogeneity X^2=8.3,df=8,p=0.41
Test for overall effect z=10.63,p<0.01

2.2.7. Target vessel revascularization

The endpoint of TVR was reported only in the TAXUS studies.[3,12,14,27]. The pooled estimates from these studies are outlined below in Figure 5. There was a statistically significant difference in TVR between DES and BMS stents OR 0.36 (95%CI 0.26, 0.53). As with TLR, the pooled TVR result is primarily influenced by the large randomized controlled trial with a weight of 81.1%.[3,14]

Figure 5: Meta-analysis of TVR comparing DES vs BMS

	DES	BMS			
Study	**n / N**	**n / N**	**weight**	**O.R.**	**(95%C.I.'s)**
TAXUS I	1 / 31	3 / 30	2.0%	0.30	(0.03 , 3.06)
TAXUS II	9 / 131	25 / 131	16.9%	0.31	(0.14 , 0.70)
TAXUS IV	45 / 639	108 / 633	81.1%	0.37	(0.26 , 0.53)
Total (95% CI)			**100.0%**	**0.36**	**(0.26 , 0.50**

Test for heterogeneity X^2=0.15,df=2,p=0.93

Test for overall effect z=6.11,p=0.01

2.2.8. Thrombosis

Stent thrombosis was reported in all of the 9 clinical trials. There was no apparent difference between DES and BMS with respect to thrombosis, OR 1.08 (95%CI 0.49, 2.37). Several studies reported zero events in one or more treatment arms.[7,11-13,27]

Figure 6: Meta-analysis of stent thrombosis comparing DES vs BMS

	DES	BMS			
Study	**n / N**	**n / N**	**weight**	**O.R.**	**(95%C.I.'s)**
ASPECT	3 / 58	0 / 57	6.9%	7.25	(0.37 , 143.51)
CSIRIUS	1 / 50	1 / 50	7.9%	1.00	(0.06 , 16.44)
ELUTES	1 / 37	1 / 38	7.8%	1.03	(0.06 , 17.06)
ESIRIUS	2 / 174	0 / 176	6.7%	5.12	(0.24 , 107.32)
RAVEL	0 / 120	0 / 118	4.0%	0.98	(0.02 , 49.97)
SIRIUS	2 / 533	4 / 525	21.3%	0.49	(0.09 , 2.69)
TAXUS I	0 / 31	0 / 30	4.0%	0.97	(0.02 , 50.36)
TAXUS II	1 / 131	0 / 131	6.0%	3.02	(0.12 , 74.89)
TAXUS IV	4 / 639	5 / 633	35.5%	0.79	(0.21 , 2.96)
Total (95% CI)	**14 / 1773**	**11 / 1758**	**100.0%**	**1.08**	**(0.49 , 2.37)**

Test for heterogeneity X^2=4.0,df=8,p=0.85

Test for overall effect z=0.19,p<0.57

2.3. Discussion

The systematic literature review identified 11 primary publications from 9 clinical trials comparing DES to BMS. These studies were conducted in patients with single de-novo lesions in native coronary arteries and follow-up evaluation ranged from 6 months to 1 year. The lesions characteristics included in some of the randomized controlled trials were not as diverse as what may me seen in clinical practice.

There was no apparent difference between DES as compared to BMS with respect to mortality, acute MI or stent thrombosis. The pooled estimates of TLR and TVR from the clinical studies indicate that DES provides a reduced rate of restenosis as compared to BMS. The differences between DES and BMS with respect to the TLR and TVR results may be influenced by protocol driven coronary angiograms and subsequent revascularization procedures. The influence of protocol driven revascularizations is illustrated in some of the identified clinical trials and previous studies involving only BMS.[3,7]

Since the completion of this systematic review for this interim report, several studies comparing DES to BMS and other trials comparing TAXUS to CYPHER stents have been published.[28-33] An updated systematic review will be included in the final report.

3. FIELD EVALUATION

3.1. Background

3.1.1. Cardiac Care Network of Ontario

The CCN was established in 1990 to help address problems in the delivery of adult cardiac surgery in the province. Since then, CCN and the cardiac centres have worked together to help patients receive timely, equitable and appropriate access to advanced cardiac services. The CCN's patient registry, CARDIACCESS, was established to facilitate and monitor access to cardiac surgery. Expansion of the registry began in 2000 to include cath-lab procedures (cardiac cath and angioplasty/stents) and public reporting on access to cath-lab procedures began in May 2002.[34]

3.2. Study Objectives

The objective of this field evaluation was to compare the rate of all revascularization procedures in patients receiving a PCI intervention with either a DES or a BMS.

3.3. Methods

3.3.1. Study design

This is a prospective, non-randomized observational study. All patients receiving a stent were followed-up for up to 402 days and stratified by type of stent, MI and diabetes status. Information was collected through CCN, a cardiac center registry in Ontario. Patients included in this analysis are those for who at least 9 months of follow-up were available for analysis. This time frame was deemed to be long enough to see a separation of the revascularization rates between DES and BMS.

3.3.2. CCN Database

The use of DES and BMS in the Province of Ontario was collected with an existing cardiac care registry, CCN CARDIACCESS database in which additional fields related to the placement of coronary artery stents were added. In collaboration with CCN, a limited number of new data fields (outlined below) were added to capture the following characteristics: lesion location (35 locations), lesion type (ACC-AHA classification)[35,36], survival dependant vessel (Yes/No), stent type (DES or BMS), DES type (CYPHER or TAXUS), stent size (mm), stent length (mm), and a field indicating whether the procedure was related to restenosis. A detailed description of the added data elements and field properties are outlined in Appendix X. The modification to the database allowed for the collection of information regarding the placement of up to a total of 9 stents (both DES and BMS) per procedure for a given patient.

In addition to the data elements described above, other selected information regarding patient characteristics were obtained from the CCN CARDIACCESS database: age, gender, smoking history, and the presence of the following comorbid or previous medical conditions: diabetes, hyperlipidemia, hypertension, patient receiving dialysis, chronic obstructive pulmonary disease (COPD), history of cerebrovascular accident (CVA) or transient ischemic attacks (TIA) combined as a variable CVA-TIA being the presence of either, peripheral vascular disease (PVD), and previous cardiovascular interventions including history of previous PCI, CABG or Left (internal) mammary artery bypass (LIMA). The degree of angina severity as classified by a modified Canadian Cardiovascular Society grading of angina pectoris (CCS rating) [37] and the number of diseased vessels was also obtained from the dataset. (Appendix X) The angioplasty procedures are classified within the database according to whether the angioplasty was conducted at the same time as the diagnostic angiogram to either “elective” or “adhoc” (diagnostic angiogram and angioplasty done during the same procedure). Furthermore, patients that have had an acute myocardial infarction within the previous 7 days prior to their angioplasty procedure are also identified.

Other clinical information that was obtained or calculated from the CCN dataset were waiting times for revascularization, number of stents used in the revascularization procedure, types of stents used in the revascularization procedure, and percentage of revascularization that were CABG, PCI without stent, or PCI with stent.

3.3.3. Data Collection

The prospective collection of the data was initiated at the 12 Ontario Regional Interventional Cardiac Care Centres in December 2003 using a standardized form (Appendix VII). The data was collected by the Cardiac Care Nurses and Data Clerks and entered into the CARDIACCESS database. The CCN, CARDIACCESS registry is coordinated by the CCN and is maintained and analyzed by the Institute for Clinical and Evaluative Sciences (ICES) at Sunnybrook & Women's College Health Sciences Centre. All existing CCN data collection procedures and data processing were maintained.

Data was also collected retrospectively for patients receiving a DES from April 1, 2003 to November 30, 2003. In order to examine the uptake of DES in the Province of Ontario, Where a BMS was used during the procedure along with a DES the information pertaining to the stent characteristics and placement were also obtained retrospectively. The prospective collection of information pertaining to the use of coronary artery stents (DES and BMS) is continuing at the time of this report.

The CCN dataset was also linked to the Ontario Registered Persons Database in order to obtain information pertaining to patient mortality during the study period.

3.3.4. Patient Population

The study population for this interim analysis included all patients undergoing an elective or adhoc procedure for the management of stable angina, unstable angina or silent ischemia or within 7 days following an acute myocardial infarction

and received a PCI with stent between December 1, 2003 and June 30, 2004 and for which at least 9 months of follow-up information was available.

Patients included in this analysis had to receive only one stent type (either DES or BMS) during the PCI procedure but not a combination of both types. Information was however collected regarding patients receiving both stent types but is not included in the analysis.

For the purpose of analysis, the patients were first stratified into four primary cohorts to allow for the comparison of patients based on their recent history of an acute myocardial infarction and whether or not they have diabetes. The resulting four primary cohorts are: Non-Post MI without diabetes, Non-Post MI with diabetes, Post-MI without diabetes and Post-MI with diabetes. As a second step, each of the four populations was further divided according to the lesion characteristics as described below. In total, the outcomes were evaluated in 22 cohorts.

3.3.5. Lesion Characteristics

As direct measurement of lesion dimensions were not available, stent size was used as a proxy for the lesion diameter and the total stent length(s) were used as a proxy for lesion length. Where more than one stent was placed at one lesion location during the procedure, the sum of the stent lengths were used as an estimate of the total lesion length. Further variables that were calculated included the number of lesions repaired per procedure and the number of procedural vessels.

Evaluation of the primary and secondary outcomes within each of the primary cohorts was conducted to examine the influence of baseline lesion characteristics on revascularization events and mortality. Several subgroups were constructed by separating the data by stent diameter and stent length. Long lesions were defined dichotomously as being greater than 20 mm in length.

Narrow lesions were defined dichotomously as being less than 2.75 mm in diameter. The choice of these cohorts were supported by early clinical guidelines and these variables being statistically significant in most regressions of the major cohorts. The minor cohorts included: long and narrow lesions, long lesions, narrow lesions. The complements of these minor cohorts were also investigated: short and wide lesions, short lesions, wide lesions, and another measure, long or narrow lesions.

3.3.6. Stent Utilization

For stent utilization and characteristics, the variables calculated include the average number of stents per lesion or procedure, and the total number of stents used per procedure (from 1 to 9).

3.3.7. Clinical Endpoints

The clinical literature reports target lesion revascularization (TLR) and/or target vessel revascularization (TVR). In clinical trials, TLR was initially the primary revascularization endpoint reported in earlier studies. However in later studies TVR became the predominate measure for reporting revascularization rates as it captures not only the need to revascularize the lesion but also the potential impact of the intervention to the entire vessel. As information pertaining to the lesion location for PCI procedures without the placement of a coronary artery stent (balloon angioplasty) and the vessels involved in CABG procedures were not specified in the CCN dataset, it was necessary to derive from the available data an adjusted rate of target vessel revascularization.

The primary endpoint, TVRa, was constructed from data in the CCN dataset and is a composite of target vessel revascularizations (TVR) PCI with stent, all repeat PCI without stent and all CABG procedures performed in patients following their initial procedure. The primary clinical endpoint for the field evaluation was an adjusted rate of target vessel revascularization (TVRa) at 365 days.

Secondary endpoints evaluating the rate of subsequent coronary interventions following the index PCI with stent placement included: target lesion revascularization (TLR) representing all revascularizations that occurred in the same lesion and was performed by PCI with a stent and target vessel revascularization (TVR), representing revascularizations that occurred in the same vessel and was performed by PCI with a stent. Further secondary endpoints included all PCI without stent (target lesion and non-target lesion, any CABG and total revascularization (TR) procedures which includes all revascularization procedures in any vessel (target and non-target): CABG, PCI with stent (both elective and adhoc), PCI without stent and all cause mortality. A summary of the clinical endpoints are outlined in Table 1.

In addition, all cause mortality defined as any death including death being the first event after the initial stent procedure, and death occurring after one or more subsequent revascularization procedures was determined.

Table 1: Primary and Secondary Endpoints

Endpoint	Description
Primary Endpoint: Target Vessel Revascularization adjusted (TVRa)	Composite of target vessel revascularization (TVR), (PCI with stent), all repeat PCI without stent and all CABG procedures
Target Lesion Revascularization (TLR)	All revascularizations that occurred in the same lesion and was performed by PCI with a stent,
Target Vessel Revascularization (TVR)	All revascularizations that occurred in the same vessel and was performed by PCI with a stent
Percutaneous coronary intervention without stent placement (PCI without stent)	All balloon angioplasty revascularization procedures in any vessel without the placement of a stent (target lesion or non-target lesion).
Coronary artery bypass graft (CABG)	Any bypass surgery occurring following initial intervention.
Total Revascularization (TR)	All revascularization procedures in any vessel (target or non-target): CABG, PCI with stent (both elective and adhoc), PCI without stent.
Mortality	All cause

The revascularization procedures were determined as follows: when a patient had their first stent procedure, patient characteristics, the lesion location (one of 35 possible locations), the type of stent (DES versus BMS) and other lesion characteristics, and stent utilization variables were recorded. After patients were identified by their first stent procedure, the next revascularization procedure was determined as being the follow-up event. The follow-up events occurring at the same lesion location were considered as TLR and any revascularization event occurring in the same vessel was considered to be a TVR.

3.3.8. Statistical analysis

For each of the 4 primary cohorts, patient comorbidities, lesion characteristics, stent utilization and stent characteristics are described. Categorical variables are presented as counts and percents and continuous variables as means and standard deviation, medians and interquartile ranges.

Statistical comparisons of patient comorbidities, lesion characteristics, stent utilization and description were performed with chi-squared tests for categorical variables, and 2 sided t-tests for continuous variables. The following statistical methods were used in this study.

3.3.8.1. Unadjusted Event Rates

For each of the 4 primary cohorts, the statistical analysis starts with the initial evaluation of raw event rates for the primary clinical endpoint (TVRa) and the following secondary endpoints: TLR, TVR, PCI without stent, CABG, total revascularizations (target lesion and non-target lesion). No statistical tests were performed on these crude event rates. The event rates are presented along with the proportion of patients with an event in each of the four primary cohorts.

3.3.8.2. Time to Event analysis

The time between the initial procedure and the time when the revascularization occurred was determined. This time to event crudely allows the comparison of non-restenotic short term events and long term restenotic events. TVRa and mortality were summarized for 30 day intervals for the full follow-up period and were separated by type of stent. For example, for the first 30 days all TVRa that occurred in DES in all of the four primary cohorts were added together and divided by the total population to get a percent.

3.3.8.3. Unadjusted Kaplan Meier Survival Analysis

Kaplan Meier (KM) survival analysis estimates at 365 days were determined for the following endpoints: TVRa, TLR, TVR, total revascularization and mortality. Log rank tests were used to compare DES versus BMS KM survival curves.

3.3.8.4. Weibull Regression Analysis

Weibull survival analysis was performed to adjust the event rates considering baseline differences in the patients receiving each intervention. A Weibull analysis is a parametric method, assuming a non-constant hazard, which allows for the prediction of events.

In a first step, a univariate Weibull analysis, was performed to match the non-parametric KM analysis to test for consistency of results between the two types of analysis, non-parametric and parametric. The univariate Weibull survival model was used to investigate whether or not BMS increases the likelihood of revascularization over time. The univariate model includes only the exposure variable and event rates were predicted at 365 days to match KM estimates.

To account for potential differences in baseline characteristics a multivariate Weibull regression analysis was conducted.[38] The Weibull regression included

only variables that were significant in at least one of the regressions of the primary cohorts (by cohort and endpoint). In addition to DES status, the revascularization rates were controlled for differences in age, gender, lesion and stent characteristics and angina status (Table 2).

Lesion severity was dichotomized according to angiographic lesion type. B2 or C are considered severe lesions and A or B1 being non-severe lesions. CCS class was dichotomized as 0-3 CCS or to CCS class 4A-D. Lesion length included the sum of the lengths of all stents when the lesions occurred in the same or adjacent lesion locations. Multivessel disease includes all patients with more than one diseased vessel, regardless of number of procedural vessels that received stents. The procedural vessel was dichotomized to the use of LAD or not (RCA, CIRC, LM, SVG, or Other). The variables used in the reduced Weibull model are presented in Table 2.

Table 2: Definitions of variables used for multivariate Weibull regression

Variable	Description
DES	= 1 if stent was DES = 0 if stent was BMS
Age	Age at the time of the initial procedure (years)
Male	% male
LAD	= 1 if target vessel was LAD = 0 otherwise
stent diameter	= 1 if diameter < 2.75mm = 0 if diameter >= 2.75mm
stent length	= 1 if stent length > 20mm = 0 if stent length <= 20mm
Lesion complexity	= 1 if angiographic lesion type = B2 or C = 0 if lesion type = A or B1
multi vessel disease	=1 if number of diseased vessels > 1 = 0 if number of diseased vessels = 1
unstable angina	=1 if CCS class = 4A-D =0 if CCS class = 0 – 3

Baseline characteristics not included in the model (e.g., COPD, smoking, CVA or TIA, PVD, previous CABG, LIMA, previous PTCA, renal failure or dialysis) were due to inconsistency of reporting, or because they were not statistically different at the 10% level between DES and BMS. As hypertension and hyperlipidemia were recorded only for the patients receiving adhoc procedures, these baseline characteristics were not considered for use in the model as inclusion of these variables would have resulted in the elimination of a significant amount of information from the analysis. For the univariate and multivariate analysis the p-value of the DES coefficient is presented. Log likelihood ratio tests were used to compare univariate and multivariate models. When the multivariate model was problematic (large standard errors) and the log likelihood ratio did not detect a difference in the models, only the univariate results were reported. The original dataset was maintained at ICES and all analyses were completed using SAS for UNIX version 8.2 (SAS Institute, Cary, NC). Level of statistical significance was set at 5%.

3.3.9. Data Management Policies and Ethics Approval

All data management was undertaken in accordance with current CCN and ICES privacy and confidentiality policies and personal health information or personal identifiers are not made available to the primary investigators and research team.

The CCN data was transferred to ICES using previously established procedures.

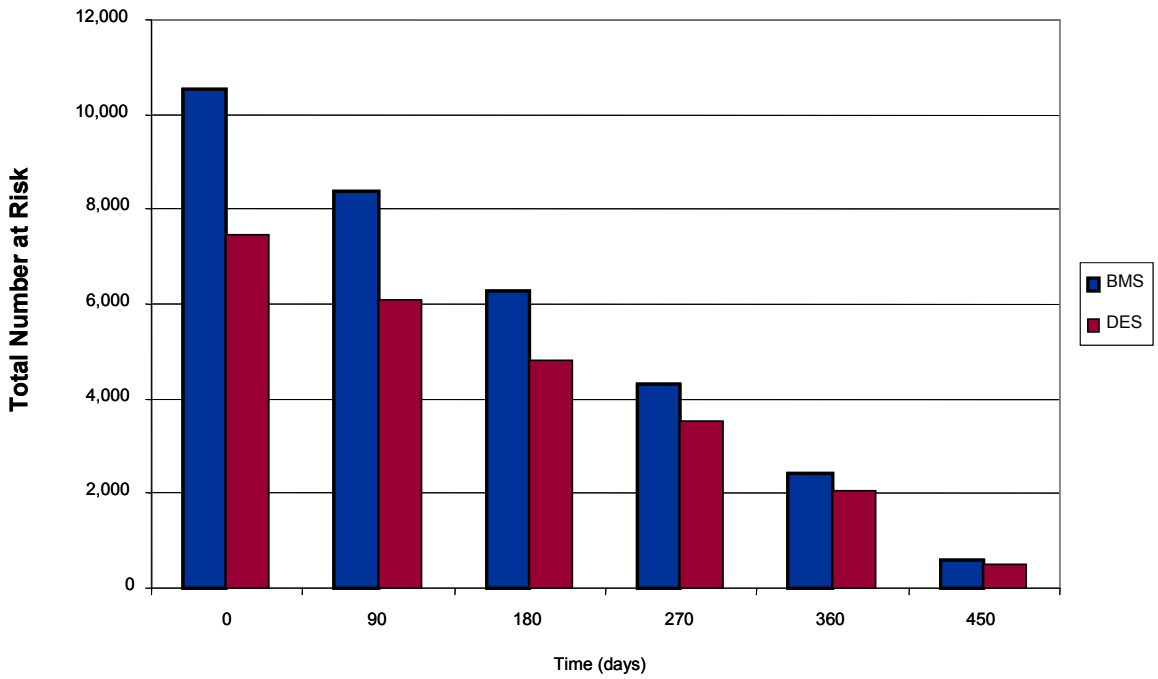
Ethics approval for the study was obtained from the Sunnybrook & Women's College Health Sciences Centre Research Ethics Board on November 13, 2003.

3.4. Results

3.4.1. Patient Population

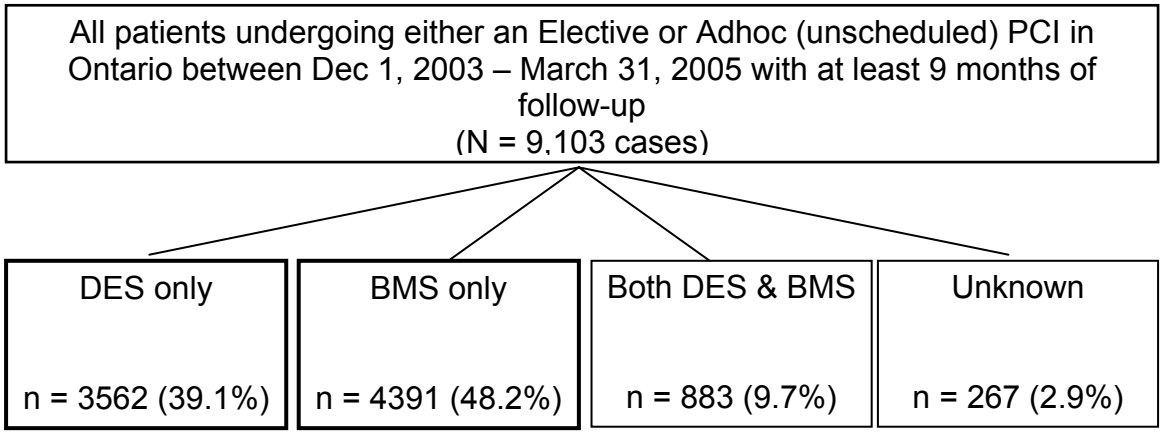
From December 1, 2003 to March 31, 2005 a total of 20,431 PCI procedures with the placement of a stent were completed in Ontario. From this patient population, 9,103 cases had at least 9-months of follow-up data available for this interim analysis. The follow-up times of the entire cohort are outlined in Figure 1 for those patients receiving only one type of coronary artery stent.

Figure 7: Follow-up times for Ontario patients receiving only DES or BMS stent(s) between December 1, 2003 and March 31, 2005



For those patients with at least 9 months of follow-up, the use of DES only occurred in 39.13% of the 9,103 cases; BMS alone was used in 48.24% and in 9.70% of the procedures both DES and BMS were used. In 267 cases (2.9%) the stent type used was unknown (Figure X).

Figure 8: Utilization of coronary artery stents by type



As shown in Table 3, DES were used more commonly in patients with diabetes both in patients with a recent MI (42.1% DES in diabetes group versus 28.4% DES in non-diabetes), and in the non Post MI group (53.0% DES in diabetes group versus 37.9% DES in non-diabetes group).

Further analysis in this report involves those cases where a comparison between DES and BMS can be made. Patients that received both stent types and where the stent type is unknown are not evaluated.

Table 3: Stent utilization by baseline patient characteristics

	N (%)	% DES	% BMS	Unknown	% DES & BMS
Post MI –non diabetes	1,579 (17.3%)	28.4%	62.2%	2.2%	7.2%
Post MI - diabetes	392 (4.3%)	42.1%	46.7%	2.3%	8.9%
Non Post MI – non diabetes	5,514 (60.6%)	37.9%	49.1%	3.2%	9.8%
Non Post MI - diabetes	1,618 (17.8%)	53.0%	32.1%	2.8%	12.1%
Total	9,103 (100.00%)	39.1%	48.3%	2.9%	9.7%

3.4.2. Patient Baseline Characteristics

Baseline differences amongst the 4 primary cohorts were apparent, as may be expected due to the observational nature of the study. The mean age is lower in the patients that received a DES in non Post MI patients (non-diabetes and diabetes) but not in Post MI patients and the patients that received a DES had a greater rate of previous PCI. In some of the groups there are differences in the use of DES by gender. For example, in the non Post MI non-diabetes and Post MI diabetes more women than men received DES.

To illustrate these differences, the baseline characteristics are presented in Table 2 for patients that did not have a MI within the previous 7 days (non-Post MI) and in Table 3 for patients with a recent history of MI within 7 days (Post MI). Both sets of patients are separated by baseline diabetes status. Only statistical differences between DES and BMS are discussed below for each of the four cohorts.

3.4.3. Patient Baseline Characteristics – Non Post-MI Cohort

For the non-diabetes, non-post MI group (Table 2), the mean age in years was higher in the BMS group than in DES (DES mean age 62.0 years, compared to BMS mean age 63.7 years, $p<0.01$). For the non post MI patients with diabetes (Table 2), the mean age was also higher in BMS than in DES (DES mean 62.5 years; BMS mean 64.8 years, $p<0.01$).

DES was less commonly used in males in the non post-MI non-diabetes group (DES 69.7% males, BMS 75.9% males, $p<0.01$), however, no significant differences were found with respect to gender in the patients with diabetes (DES 67.2% males, BMS 70.0% males, $p=0.27$).

Furthermore, a greater number of patients receiving a DES had a previous PCI in patients with and without diabetes (non-diabetes: DES 26.1% vs. BMS 13.6% $p<0.01$; diabetes: DES 34.3% vs. BMS 18.0%, $p<0.01$). Patients without

diabetes receiving a DES were also more likely to have had a previous LIMA than in BMS treated patients (DES 5.2% vs. BMS 3.5%, p=0.05). The pattern of use of the different stent types based on baseline angina severity, as determined by a modified CCS grading of angina, was also different in patients without diabetes between DES and BMS (p<0.01) with BMS being used in more patients with higher grades of angina.

Table 4: Patient characteristics at baseline for Non Post MI, by diabetes status and type of stent

	Non-diabetes			Diabetes		
	DES	**BMS**	**p-value**	**DES**	**BMS**	**p-value**
Age in years mean(SD) (N)	62.0 (11.7) (2088)	63.7 (11.5) (2700)	<0.01	62.5 (10.9) (857)	64.8 (10.3) (520)	<0.01
Age in years median (Q-range)	62 (53-72)	64(55-73)		62(55-71)	65(57-72)	
Gender (Male %)	1457 (69.7%)	2053 (75.9%)	<0.01	576 (67.2%)	364 (70.0%)	0.27
History of Smoking	932 (46.7%)	1286 (49.6%)	0.08	411 (48.4%)	247 (47.9%)	0.45
Hyperlipidemia	458 (57.8%)	496 (53.8%)	0.13	230 (79.6%)	130 (75.6%)	0.32
Hypertension	384 (48.4%)	401 (43.5%)	0.07	201 (69.6%)	114 (66.3%)	0.34
Dialysis	10 (0.5%)	16 (0.6%)	0.33	22 (2.6%)	9 (1.7%)	0.14
COPD	47 (2.4%)	78 (3%)	0.11	22 (2.6%)	15 (2.9%)	0.37
CVA or TIA	24 (2.1%)	29 (1.8%)	0.29	25 (4.6%)	22 (6.7%)	0.10
PVD	97 (4.9%)	116 (4.5%)	0.27	91 (10.7%)	62 (12%)	0.24
Previous CABG	203 (11.4%)	264 (11.2%)	0.42	149 (19.4%)	102 (21.5%)	0.21
LIMA	41 (5.2%)	32 (3.5%)	0.05	33 (11.4%)	13 (7.6%)	0.11
Previous PTCA	207 (26.1%)	125 (13.6%)	<0.01	99 (34.3%)	31 (18.0%)	<0.01
CCS Rating	n = 1993	N = 2604		n = 855	n = 518	
0	113 (5.7%)	180 (6.9%)		60 (7%)	40 (7.7%)	
1	98 (4.9%)	134 (5.1%)		52 (6.1%)	25 (4.8%)	
2	376 (18.9%)	450 (17.3%)		162 (18.9%)	93 (18%)	
3	555 (27.8%)	645 (24.8%)	<0.01	253 (29.6%)	154 (29.7%)	0.69
4A	433 (21.7%)	686 (26.3%)		206 (24.1%)	131 (25.3%)	
4B	149 (7.5%)	208 (8%)		66 (7.7%)	49 (9.5%)	
4C	65 (3.3%)	90 (3.5%)		28 (3.3%)	17 (3.3%)	
4D	<=5	11 (0.4%)		<=5	<=5	
Diseased Vessels	n = 1844	n = 2360		n = 802	n = 485	
1	1128 (61.2%)	1383 (58.6%)		416 (51.9%)	225 (46.4%)	
2	431 (23.4%)	613 (26.0%)	1.00	231 (28.8%)	149 (30.7%)	1.00
3	155 (8.4%)	206 (8.7%)		106 (13.2%)	70 (14.4%)	
4	16 (0.9%)	25 (1.1%)		8 (1.0%)	12 (2.5%)	

- differences in means were tested using student t-test
- the relationship between the categorical variables and stent type were tested with chi-squared test, where cell contents >5

3.4.4. Patient Baseline Characteristics – Post-MI Cohort

In patients with a recent history of myocardial infarction, there was no difference in age between the two groups receiving DES or BMS as seen in the non Post MI group (Table 3). In the patients with diabetes, DES was less commonly used in males (DES 60.0% males, BMS 79.2% males, p=0.02).

There was also a statistical difference in the proportion of Post MI patients receiving a DES in the non-diabetes group that had a previous PTCA (8.3%), compared to those that received a BMS 4.8% (p=0.01), and a greater proportion of patients with diabetes and that received a DES that had a previous PTCA (DES 12.7% vs. BMS 6.0%, p=0.02).

In the non-diabetes, Post MI group, more patients had peripheral vascular disease in the DES group than the BMS group (DES 4.0%, BMS 2.4%, p=0.05). In addition, in the Post-MI diabetes group there was a greater history of smoking in BMS patients (DES 47.9%, BMS 61.2%, p=0.05).

Table 5: Patient characteristics for Post MI patients at baseline, by diabetes status and type of stent

	Non-diabetes			Diabetes		
	DES	BMS	p-value	DES	BMS	p-value
Age in years Mean (SD) (N)	58.5(13.0) (448)	59.2±12.4 (983)	0.33	60.7(11.8) (165)	61.4(12.0) (183)	0.90
Age (Median)	57(48-69)	58(50-69)		59(53-69)	62(53-70)	
Gender (M)	321 (71.7%)	760 (77.3%)	0.13	99 (60%)	145 (79.2%)	0.02
History of Smoking	250 (55.8%)	553 (56.4%)	0.44	79 (47.9%)	112 (61.2%)	0.05
Hyperlipidemia	202 (45.1%)	399 (40.7%)	0.12	103 (62.4%)	120 (65.6%)	0.35
Hypertension	191 (42.6%)	394 (40.2%)	0.26	112 (67.9%)	124 (67.8%)	0.50
Dialysis	<=5	<=5	n.a.	8 (4.8%)	<=5	n.a.
COPD	<=5	26 (2.7%)	n.a.	<=5	6 (3.3%)	n.a.
CVA or TIA	<=5	<=5	n.a.	<=5	0	n.a.
PVD	18 (4.0%)	24 (2.4%)	0.05	12 (7.3%)	18 (9.8%)	0.21
Previous CABG	11 (2.5%)	20 (2%)	0.28	17 (10.3%)	11/183 (6%)	0.08
LIMA	7 (1.6%)	9 (0.9%)	0.13	6 (3.6%)	<=5	n.a.
Previous PTCA	37 (8.3%)	47 (4.8%)	0.01	21 (12.7%)	11 (6%)	0.02
CCS Rating						
0	36 (8%)	73 (7.4%)		15 (9.1%)	15 (8.2%)	
1	9 (2%)	18 (1.8%)		<=5	11 (6%)	
2	14 (3.1%)	28 (2.8%)		6 (3.6%)	6 (3.3%)	
3	31 (6.9%)	60 (6.1%)	0.17	11 (6.7%)	11 (6%)	0.97
4A	119 (26.6%)	296 (30.1%)		48 (29.1%)	51 (27.9%)	
4B	91 (20.3%)	161 (16.4%)		27 (16.4%)	28 (15.3%)	
4C	122 (27.2%)	289 (29.4%)		42 (25.5%)	47 (25.7%)	
4D	13 (2.9%)	36 (3.7%)		9 (5.5%)	9 (4.9%)	
Diseased Vessels	N = 429	N = 934		N = 154	N = 174	
1	272 (63.4%)	602 (64.5%)		70 (45.5%)	97 (55.7%)	
2	109 (25.4%)	233 (24.9%)	0.80	53 (34.4%)	47 (27%)	0.20
3	31 (7.2%)	78 (8.4%)		26 (16.9%)	27 (15.5%)	
4	<=5	<=5		<=5	<=5	

- differences in means were tested using student t-test
- the relationship between the categorical variables and stent type were tested with chi-squared test, where cell contents >5

3.4.5. Lesion & Procedural Characteristics

The number of lesions per procedure, the number of procedural vessels and lesion complexity are outlined in Tables 4 & 5 for the non-Post MI and post MI patient groups, respectively. DES were used more commonly in lesions that were of greater complexity, as determined by the ACC-AHA classification except in the Post MI patients with diabetes. In the non Post MI patients without diabetes there was a difference in the lesion characteristics with patients that received a DES having more complex lesions ($p<0.01$) (Table 4). In the diabetes patients, there was also a difference in lesion complexity between the DES group as compared to BMS ($p<0.01$). Similarly, for those patients that had a previous MI within 7 days without diabetes, a statistical difference in lesion characteristics was a difference in lesion complexity between DES and BMS ($p<0.01$) with DES being again used in lesions with increased complexity (Table 5). The only other statistical difference between the patients receiving DES and BMS was in the number of procedural vessels for non Post-MI diabetes, with more DES patients having 2 or more procedural vessels ($p=0.02$), and a higher percentage of patients who had 2 procedural vessels in the DES cohort compared to BMS (DES 13.9%, BMS 11.3%).

Table 6: Lesion characteristics for non Post-MI patients, by diabetes status and type of stent.

	Non-diabetes			Diabetes		
	DES	**BMS**	**p-value**	**DES**	**BMS**	**p-value**
Number of Lesions per procedure						
1	1567 (75.0%)	2057 (76.0%)		626 (73.0%)	395 (76.0%)	
2	427 (20.5%)	524 (19.4%)		184 (21.5%)	99 (19%)	
3	80 (3.8%)	104 (3.8%)		40 (4.7%)	23 (4.4%)	
4	12 (0.6%)	16 (0.6%)	0.65	<=5	<=5	0.51
5	<=5	<=5		<=5	0 (0%)	
6	0 (0%)	<=5		<=5	0 (0%)	
Number of procedural vessels						
1	1839 (88.1%)	2376 (87.8%)		728 (84.9%)	457 (87.9%)	
2	233 (11.2%)	306 (11.3%)		119 (13.9%)	59 (11.3%)	
3	16 (0.8%)	25 (0.9%)	0.38	10 (1.2%)	<=5	0.02
4	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Lesion complexity	n = 2409	n = 3291		n = 1073	n = 682	
A	254 (10.5%)	528 (16%)		90 (8.4%)	80 (11.7%)	
B1	633 (26.3%)	945 (28.7%)		254 (23.7%)	234 (34.3%)	
B2	804 (33.4%)	1082 (32.9%)	<0.01	395 (36.8%)	192 (28.2%)	<0.01
C	718 (29.8%)	736 (22.4%)		334 (31.1%)	176 (25.8%)	

- the relationship between the categorical variables and stent type were tested with chi-squared test, where cell contents >5

Table 7: Lesion characteristics for post MI patients, by diabetes status and type of stent

	Non-diabetes			Diabetes		
	DES	BMS	p-value	DES	BMS	p-value
Number of lesions per procedure						
1	364 (81.3%)	798 (81.2%)		131 (79.4%)	141 (77.0%)	
2	73 (16.3%)	165 (16.8%)	0.72	27 (16.4%)	34 (18.6%)	0.81
3	10 (2.2%)	16 (1.6%)		6 (3.6%)	8 (4.4%)	
4	<=5	<=5		<=5	0 (0%)	
Number of procedural vessels						
1	406 (90.6%)	911 (92.7%)		149 (90.3%)	164 (89.6%)	
2	41 (9.2%)	69 (7%)	0.16	16 (9.7%)	18 (9.8%)	0.95
3	<=5	<=5		0 (0%)	<=5	
4	<=5	<=5		0 (0%)	0 (0%)	
Lesion complexity	n = 548	n = 1235		n = 198	n = 246	
A	20 (3.6%)	109 (8.8%)		12 (6.1%)	20 (8.1%)	
B1	138 (25.2%)	331 (26.8%)		34 (17.2%)	53 (21.5%)	
B2	207 (37.8%)	494 (40%)	<0.01	89 (44.9%)	102 (41.5%)	0.63
C	183 (33.4%)	301 (24.4%)		63 (31.8%)	71 (28.9%)	

- the relationship between the categorical variables and stent type were tested with chi-squared test, where cell contents >5

3.4.6. Stent Utilization

Presented in Tables 8 and 9 are the stent utilization and stent characteristics by diabetes status and by type of stent for all 4 primary cohorts, DES were used in narrower and longer lesions as indicated by a smaller mean diameter of stent used and longer total stent length per lesion. Only in Post MI diabetes was there a statistical difference in the number of stents per procedure, with more BMS being used. No other statistical differences were found. Stent use is described in more details below.

In the non Post-MI patients with diabetes, DES stent were used in narrower lesions (mean (s.d) stent diameter DES 2.82 (0.37) mm vs. BMS 3.11 (0.50) mm, $p<0.01$), and in longer lesions (DES 18.82 (6.50) mm vs. BMS 16.44 (5.66) mm, $p<0.01$) in the non-diabetes group. Similarly, DES were used in narrower lesions in the diabetes patients as the mean stent diameter was smaller in those patients receiving DES (DES 2.78(0.38) mm, BMS 3.09(0.51) mm, $p<0.01$) and also in longer lesions as determined by the greater mean stent length (DES 18.89 mm , BMS 16.23 mm, $p<0.01$) (Table 8). There was no significant difference in the number of stents used per procedure comparing DES and BMS (Table 8). In a small number of patients up to 9 stents were placed during one procedure with 95% of the patients receiving 3 stents or less.

DES in the Post MI patients was used more in patients without diabetes for narrower lesions as indicated by the difference in mean stent diameter, (DES 2.83(0.36) mm, BMS 3.14(0.49) mm, $p<0.01$), and also in longer lesions as the mean stent length was longer in DES (DES 19.47(6.46) mm, BMS 17.15(6.07) mm, $p<0.01$). Similarly, the mean stent diameter was smaller in the DES group (DES 2.83(0.33) mm, BMS 3.11(0.53) mm, $p<0.01$), and the mean stent length was longer in DES (DES 19.76(6.57) mm, BMS 17.96(6.07) mm, $p<0.01$) in patients with diabetes. There was also a difference in the mean number of stents per procedure used in the post MI patients with diabetes, with 1.35(0.65) DES used as compared to 1.49(0.82) BMS used as more patients received 2 or more stents (Table 9).

Table 8: Stent utilization and characteristics non post MI patients by diabetes status and type of stent

	Non-diabetes			Diabetes		
	DES	**BMS**	**p-value**	**DES**	**BMS**	**p-value**
Stents per procedure mean(SD) (N)	1.46 (0.75) (2091)	1.49(0.85) (2705)	0.20	1.54 (0.84) (857)	1.53(0.88) (520)	0.84
Median (Q-range)	1(1-2)	1(1-2)		1(1-2)	1(1-2)	
Stent utilization per procedure (N)						
1	1378 (65.9%)	1794 (66.3%)		541 (63.1%)	336 (64.6%)	
2	521 (24.9%)	625 (23.1%)		214 (25%)	125 (24%)	
3	139 (6.6%)	195 (7.2%)		68 (7.9%)	39 (7.5%)	
4	43 (2.1%)	58 (2.1%)		28 (3.3%)	12 (2.3%)	
5	9 (0.4%)	24 (0.9%)	0.67	<=5	6 (1.2%)	0.96
6	<=5	<=5		<=5	<=5	
7	0 (0%)	<=5		0 (0%)	<=5	
8	0 (0%)	<=5		0 (0%)	0 (0%)	
9	0 (0%)	<=5		0 (0%)	0 (0%)	
Stent diameter (mm) mean (SD) (N)	2.82 (0.37) (3051)	3.11 (0.5) (4048)	<0.01	2.78 (0.38) (1316)	3.09 (0.51) (794)	<0.01
Median (Q-range) (mm)	2.75 (2.5-3)	3 (2.75-3.5)		2.75(2.5-3)	3 (2.75-3.5)	
Stent length (mm) mean (SD) (N)	18.82 (6.5) (3051)	16.44 (5.66) (4048)	<0.01	18.89 (6.45) (1316)	16.23 (5.88) (794)	<0.01
Median (Q-range)	18(13-24)	15(12-18)		18(13-24)	15(12-18)	

- means were testing using student t-test
- the relationship between the categorical variables and stent type were tested with chi-squared test, where cell contents >5

Table 9: Stent utilization and characteristics for post MI patients, by diabetes status and type of stent

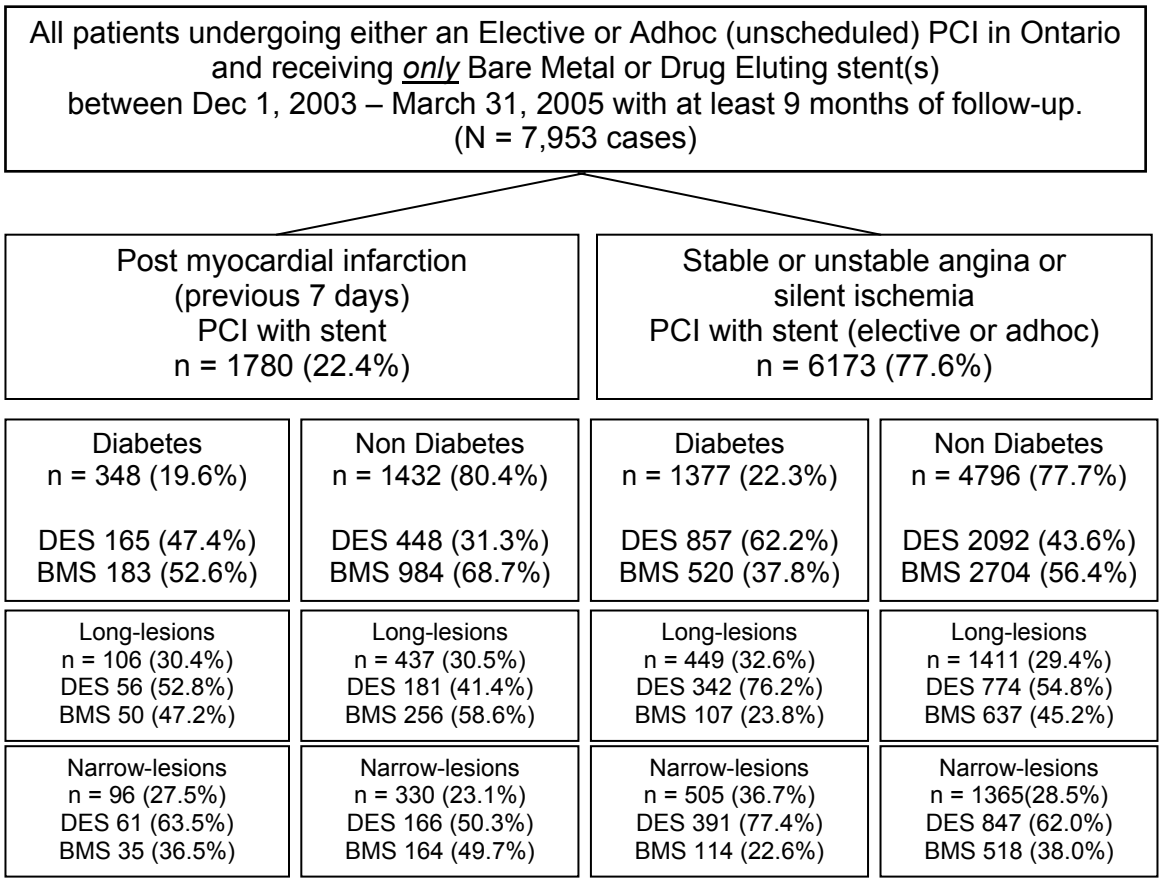
	Non-diabetes			Diabetes		
	DES	BMS	p-value	DES	BMS	p-value
Stents per procedure mean (SD) (N)	1.37(0.69) (448)	1.40(0.74) (983)	0.46	1.35(0.65) (165)	1.49(0.82) (183)	<0.01
Median (Q-range)	1(1-2)	1(1-2)		1(1-2)	1(1-2)	
Stent utilization per procedure (N)						
1	324 (72.3%)	691 (70.3%)		120 (72.7%)	120 (65.6%)	
2	96 (21.4%)	221 (22.5%)		36 (21.8%)	46 (25.1%)	
3	17 (3.8%)	53 (5.4%)		7 (4.2%)	10 (5.5%)	
4	10 (2.2%)	14 (1.4%)	0.96	<=5	6 (3.3%)	0.63
5	<=5	<=5		<=5	0 (0%)	
6	0 (0%)	0 (0%)		0 (0%)	<=5	
7	0 (0%)	<=5		0 (0%)	0 (0%)	
8	0 (0%)	<=5		0 (0%)	0 (0%)	
9	0 (0%)	<=5		0 (0%)	0 (0%)	
Stent diameter mean (SD) (N)	2.83(0.36) (612)	3.14(0.49) (1374)	<0.01	2.83 (0.33) (222)	3.11 (0.53) (272)	<0.01
Median (Q-range)	2.75(2.5-3)	3(2.75-3.5)		2.75(2.5-3)	3(2.75-3.5)	
Stent length mean (SD) (N)	19.47(6.46) (612)	17.15(5.52) (1374)	<0.01	19.76(6.57) (222)	17.96(6.07) (272)	<0.01
Median (Q-range)	20(16-24)	16(13-18)		20(16-24)	18(14-20)	

- means were testing using student t-test
- the relationship between the categorical variables and stent type were tested with chi-squared test, where cell contents >5

3.4.7. Stent utilization by lesion characteristic

The utilization of DES and BMS based on lesion characteristics are outlined in Figure 9. DES were used generally in patients with a higher risk of restenosis namely those patients with diabetes, narrow lesions and in longer lesions. The use of DES in higher risk patients was more common in patients with stable or unstable angina.

Figure 9: Utilization of DES and BMS by diabetes status and lesion characteristics



3.4.8. Clinical Results

This section presents the results of the statistical analysis of the outcomes following stent placement. The unadjusted raw event rates are presented followed by the survival analysis and finally the Weibull regression estimates.

3.4.9. Unadjusted Revascularization Event Rates

3.4.10. Unadjusted Event Rates – Primary Cohorts

The unadjusted event rates for the entire follow-up period are reported below in Table 10 for the four primary cohorts (Non Post MI – non diabetes, Non Post MI – diabetes, Post MI non-diabetes, and Post MI diabetes). The unadjusted revascularization event rates of TVRa (i.e. the primary clinical endpoint) as well as the secondary events rates of TLR and TVR are generally numerically greater for BMS than DES patients for all four primary cohorts. In patients with diabetes, the reintervention rate is higher than that of the patients without diabetes and also patients with a recent history of a MI appear to require subsequent intervention more frequently than those without an immediate history (Table 10).

Table 10: Unadjusted event rates for each of the 4 primary cohorts

	Non-diabetes				Diabetes			
	DES (n)	DES (%)	BMS (n)	BMS (%)	DES (n)	DES (%)	BMS (n)	BMS (%)
Non Post MI (n)	2092		2704		857		520	
TVRa	125	5.98%	192	7.21%	74	8.63%	49	9.42%
TLR – PCI with stent	38	1.82%	87	3.22%	28	3.27%	19	3.65%
TVR - PCI with stent	65	3.11%	122	4.51%	45	5.25%	31	5.96%
PCI without stent	33	1.58%	38	1.41%	17	1.98%	11	2.12%
CABG	35	1.67%	39	1.44%	19	2.22%	12	2.31%
Total PCI with stent	128	6.12%	211	7.80%	59	6.88%	47	9.04%
Total Revasc	196	9.37%	288	10.65%	95	11.09%	70	13.46%
Post MI (n)	448		984		165		183	
TVRa	21	4.69%	62	6.30%	10	6.06%	24	13.11%
TLR – PCI with stent	7	1.56%	21	2.13%	2	1.21%	14	7.65%
TVR- PCI with stent	16	3.57%	35	3.56%	6	3.64%	15	8.20%
PCI without stent	5	1.12%	12	1.22%	2	1.21%	1	0.55%
CABG	3	0.67%	20	2.03%	2	1.21%	9	4.92%
Total PCI with stent	37	8.26%	97	9.86%	16	9.70%	21	11.48%
Total Revasc	45	10.04%	129	13.11%	20	12.12%	31	16.94%

3.4.11. Unadjusted Event Rates – Lesion Characteristics

Further stratification was completed to evaluate the influence of baseline lesion characteristics on revascularization rates. The unadjusted raw event rates based on lesion characteristics (stent length and stent diameter) for the four primary cohorts are presented in Tables 11 – 13. In general, the rates of revascularization were higher in longer lesions and/or narrow lesions across all 4 primary cohorts.

To compare the raw event rates by type of lesions, the tables are presented in complement form, except for long and narrow lesions, long is the complement of

short, narrow is the complement of wide, and long or narrow is the complement of short and wide. The number of patients in the Post MI with diabetes cohort was insufficient to split this cohort into subgroups according to lesion characteristics for this interim analysis. Therefore the results below provide details regarding the revascularization rates for only 3 primary cohorts.

Table 11: Non post MI non-diabetes subgroups raw revascularization event rates by lesion type

Event		Long and narrow	long	short	narrow	wide	Long or narrow	Short and wide
TVR-a	DES	21/322(6.52%)	44/774(5.68%)	81/1317(6.15%)	59/847(6.97%)	66/1244(5.31%)	82/1299(6.31%)	43/792(5.43%)
	BMS	14/111(12.61%)	56/637(8.79%)	136/2068(6.58%)	57/518(11.00%)	135/2187(6.17%)	99/1044(9.48%)	93/1661(5.60%)
TLR	DES	5 (1.55%)	14 (1.81%)	24 (1.82%)	17 (2.01%)	21 (1.69%)	26 (2.00%)	12 (1.52%)
	BMS	6 (5.41%)	22 (3.45%)	65 (3.14%)	26 (5.02%)	61 (2.79%)	42 (4.02%)	45 (2.71%)
TVR	DES	10 (3.11%)	22 (2.84%)	43 (3.26%)	30 (3.54%)	35 (2.81%)	42 (3.23%)	23 (2.90%)
	BMS	9 (8.11%)	36 (5.65%)	86 (4.16%)	36 (6.95%)	86 (3.93%)	63 (6.03%)	59 (3.55%)
PCI without stent	DES	4 (1.24%)	11 (1.42%)	22 (1.67%)	15 (1.77%)	18 (1.45%)	22 (1.69%)	11 (1.39%)
	BMS	1 (0.90%)	11 (1.73%)	27 (1.31%)	12 (2.32%)	26 (1.19%)	22 (2.11%)	16 (0.96%)
CABG	DES	8 (2.48%)	15 (1.94%)	20 (1.52%)	16 (1.89%)	19 (1.53%)	23 (1.77%)	12 (1.52%)
	BMS	5 (4.50%)	11 (1.73%)	29 (1.40%)	12 (2.32%)	28 (1.28%)	18 (1.72%)	22 (1.32%)
Total Stent	DES	17 (5.28%)	46 (5.94%)	82 (6.23%)	53 (6.26%)	75 (6.03%)	82 (6.31%)	46 (5.81%)
	BMS	13 (11.71%)	62 (9.73%)	148 (7.16%)	53 (10.23%)	157 (7.18%)	102 (9.77%)	108 (6.50%)
Total Revasc	DES	29 (9.01%)	72 (9.30%)	124 (9.42%)	84 (9.92%)	112 (9.00%)	127 (9.78%)	69 (8.71%)
	BMS	19 (17.12%)	84 (13.19%)	204 (9.86%)	77 (14.86%)	211 (9.65%)	142 (13.60%)	146 (8.79%)

- The denominators listed for each group in the TVRa outcome results is the same for all subsequent endpoints for that lesion characteristic.
- Long lesions are >20mm in cumulative length, short <=20mm in cumulative length.
- Narrow lesions are <2.75mm in diameter, wide lesions are >=2.75mm in diameter.

Table 12: Non post MI diabetes subgroups raw revascularization event rates

Event		Long and narrow	long	short	narrow	wide	Long or narrow	Short and wide
TVR-a	DES	16/172 (9.30%)	32/342 (9.36%)	33/515 (6.41%)	32/391 (8.18%)	33/466 (7.08%)	48/561 (8.56%)	17/296 (5.74%)
	BMS	6/27 (22.22%)	19/107 (17.76%)	28/413 (6.78%)	14/114 (12.28%)	33/406 (8.13%)	27/191 (13.92%)	20/326 (6.13%)
TLR	DES	2 (1.16%)	8 (2.34%)	11 (2.14%)	9 (2.30%)	10 (2.15%)	15 (2.67%)	4 (1.35%)
	BMS	3 (11.11%)	7 (6.54%)	10 (2.42%)	5 (4.39%)	12 (2.96%)	9 (4.64%)	8 (2.45%)
TVR	DES	10 (5.81%)	18 (5.26%)	18 (3.50%)	19 (4.86%)	17 (3.65%)	27 (4.81%)	9 (3.04%)
	BMS	4 (14.81%)	11 (10.28%)	18 (4.36%)	10 (8.77%)	19 (4.68%)	17 (8.76%)	12 (3.68%)
PCI without stent	DES	4 (2.33%)	7 (2.05%)	10 (1.94%)	9 (2.30%)	8 (1.72%)	12 (2.14%)	5 (1.69%)
	BMS	2 (7.41%)	6 (5.61%)	5 (1.21%)	3 (2.63%)	8 (1.97%)	7 (3.61%)	4 (1.23%)
CABG	DES	4 (2.33%)	9 (2.63%)	10 (1.94%)	9 (2.30%)	10 (2.15%)	14 (2.50%)	5 (1.69%)
	BMS	1 (3.70%)	3 (2.80%)	8 (1.94%)	3 (2.63%)	8 (1.97%)	5 (2.58%)	6 (1.84%)
Total Stent	DES	14 (8.14%)	27 (7.89%)	27 (5.24%)	26 (6.65%)	28 (6.01%)	39 (6.95%)	15 (5.07%)
	BMS	4 (14.81%)	16 (14.95%)	30 (7.26%)	14 (12.28%)	32 (7.88%)	26 (13.40%)	20 (6.13%)
Total Revasc	DES	22 (12.79%)	43 (12.57%)	47 (9.13%)	44 (11.25%)	46 (9.87%)	65 (11.59%)	25 (8.45%)
	BMS	7 (25.93%)	25 (23.36%)	43 (10.41%)	20 (17.54%)	48 (11.82%)	38 (19.59%)	30 (9.20%)

- The denominators listed for each group in the TVRa outcome results is the same for all subsequent endpoints for that lesion characteristic.
- Long lesions are >20mm in cumulative length, short <=20mm in cumulative length.
- Narrow lesions are <2.75mm in diameter, wide lesions are >=2.75mm in diameter.

Table 13: Post MI non diabetes subgroups raw revascularization events

Event		Long and narrow	long	short	narrow	wide	Long or narrow	Short and wide
TVR-a	DES	4/70 (5.71%)	7/181 (3.87%)	14/267 (5.24%)	13/166 (7.83%)	8/282 (2.84%)	16/277 (5.78%)	5/171 (2.92%)
	BMS	5/32 (15.63%)	23/256 (8.98%)	39/727 (5.36%)	13/164 (7.93%)	49/819 (5.98%)	31/318 (7.99%)	31/595 (5.21%)
TLR	DES	1 (1.43%)	2 (1.10%)	5 (1.87%)	6 (3.61%)	1 (0.35%)	7 (2.53%)	0 (0.00%)
	BMS	3 (9.38%)	7 (2.73%)	14 (1.93%)	6 (3.66%)	15 (1.83%)	10 (2.58%)	11 (1.85%)
TVR	DES	4 (5.71%)	5 (2.76%)	11 (4.12%)	11 (6.63%)	5 (1.77%)	12 (4.33%)	4 (2.34%)
	BMS	4 (12.50%)	12 (4.69%)	23 (3.16%)	9 (5.49%)	26 (3.17%)	17 (4.38%)	18 (3.03%)
PCI without stent	DES	2 (2.86%)	4 (2.21%)	1 (0.37%)	3 (1.81%)	2 (0.71%)	5 (1.81%)	0 (0.00%)
	BMS	2 (6.25%)	3 (1.17%)	9 (1.24%)	6 (3.66%)	6 (0.73%)	7 (1.80%)	5 (0.84%)
CABG	DES	0 (0.00%)	0 (0.00%)	3 (1.12%)	2 (1.20%)	1 (0.35%)	2 (0.72%)	1 (0.58%)
	BMS	1 (3.13%)	10 (3.91%)	10 (1.38%)	2 (1.22%)	18 (2.20%)	11 (2.84%)	9 (1.51%)
Total Stent	DES	7 (10.00%)	16 (8.84%)	21 (7.87%)	14 (8.43%)	23 (8.16%)	23 (8.30%)	14 (8.19%)
	BMS	5 (15.63%)	27 (10.55%)	70 (9.63%)	14 (8.54%)	83 (10.13%)	36 (9.28%)	61 (10.25%)
Total Revasc	DES	9 (12.86%)	20 (11.05%)	25 (9.36%)	19 (11.45%)	26 (9.22%)	30 (10.83%)	15 (8.77%)
	BMS	8 (25.00%)	40 (15.63%)	89 (12.24%)	22 (13.41%)	107 (13.06%)	54 (13.92%)	75 (12.61%)

- The denominators listed for each group in the TVRa outcome results is the same for all subsequent endpoints for that lesion characteristic.
- Long lesions are >20mm in cumulative length, short <=20mm in cumulative length.
- Narrow lesions are <2.75mm in diameter, wide lesions are >=2.75mm in diameter.

3.4.12. Time Revascularization Event

The time to revascularization event (TVRa) is presented below for patients for both the non Post-MI and Post-MI groups. For the non Post-MI patients the mean time to event was similar between the two treatment groups (DES 160 days, BMS 151 days). The event rate however as reflected in the previous unadjusted event rates was greater for the patients receiving BMS (Figure 10).

In addition, the pattern of revascularization was different for those patients that had had a MI within the previous 7 days of their index stent placement. In both the DES and the BMS groups there were subsequent interventions occurring within the first 60 days following the initial stent placement (Figure 11). The resulting mean time to revascularization event for Post MI patients with DES was 113 days and for BMS treated patients 126 days. The initial reintervention may be attributed to staged procedures conducted in the Post MI patient group.

Figure 10: Time TVRa for non post MI patients

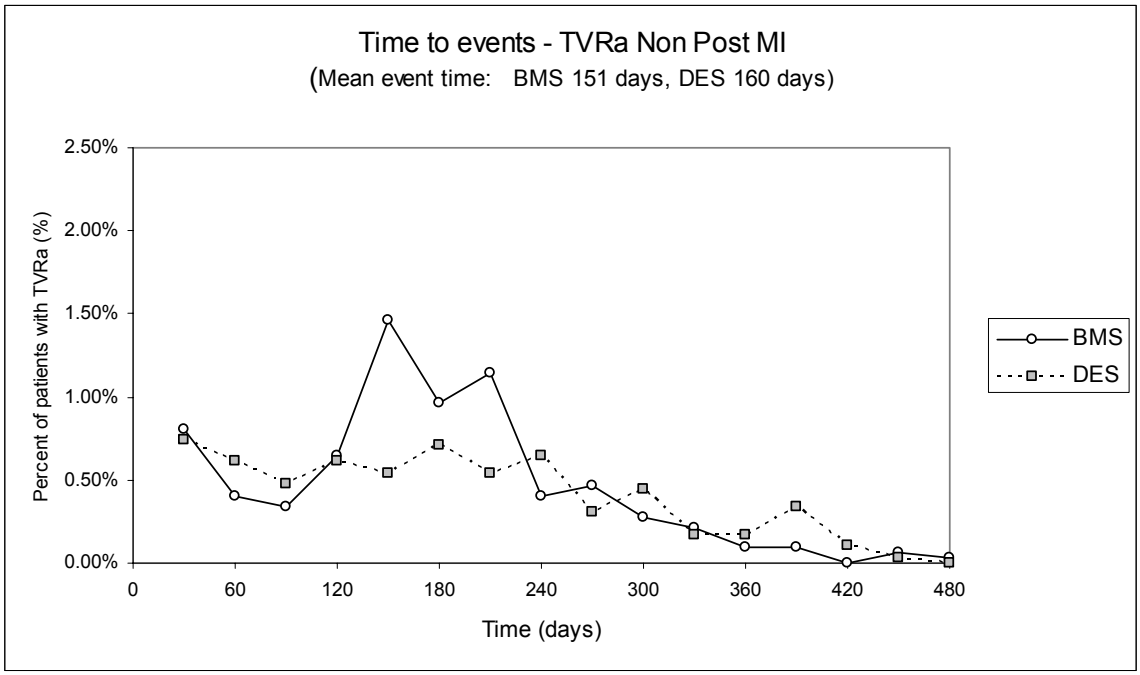
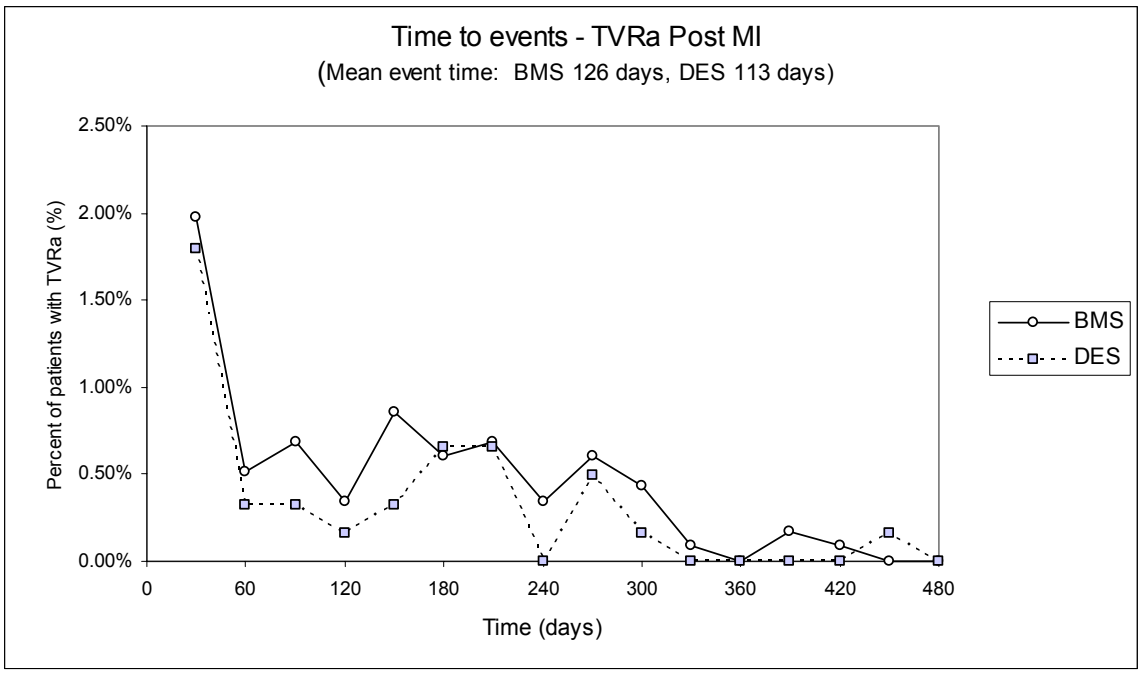


Figure 11: Time to TVRa for post MI patients



3.4.13. Kaplan Meier Estimates

Kaplan Meier (KM) estimates were derived for each of the four primary cohorts and for each lesion characteristic. The mean follow-up time for the entire cohort was 402 days, with a median follow-up of 367 days. The maximum of follow-up time within the entire cohort was 488 days or approximately 16 months.

3.4.13.1. Kaplan Meier estimates for the 4 primary cohorts

The KM curves are presented only for the 4 primary cohorts for the primary outcome variable TVRa (Figures 12 – 15) in order to illustrate the differences between the two groups (DES and BMS) within the 4 primary cohorts. The vertical scale starts at 0.8 to allow for the visual separation of the two curves. Apparent differences between the two interventions were only statistically significantly different for TVRa within the Post-MI diabetes cohort (log rank p=0.02) (Figure 15).

Figure 12: Kaplan Meier - TVRa non-post MI, non-diabetes

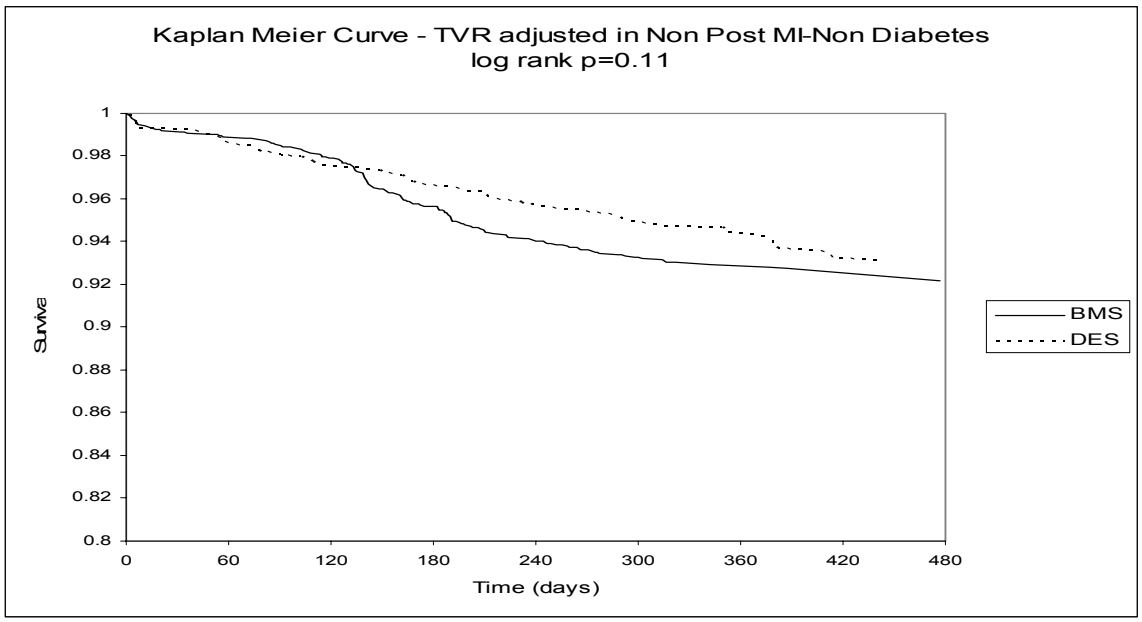


Figure 13: Kaplan Meier - TVRa non-post MI, diabetes

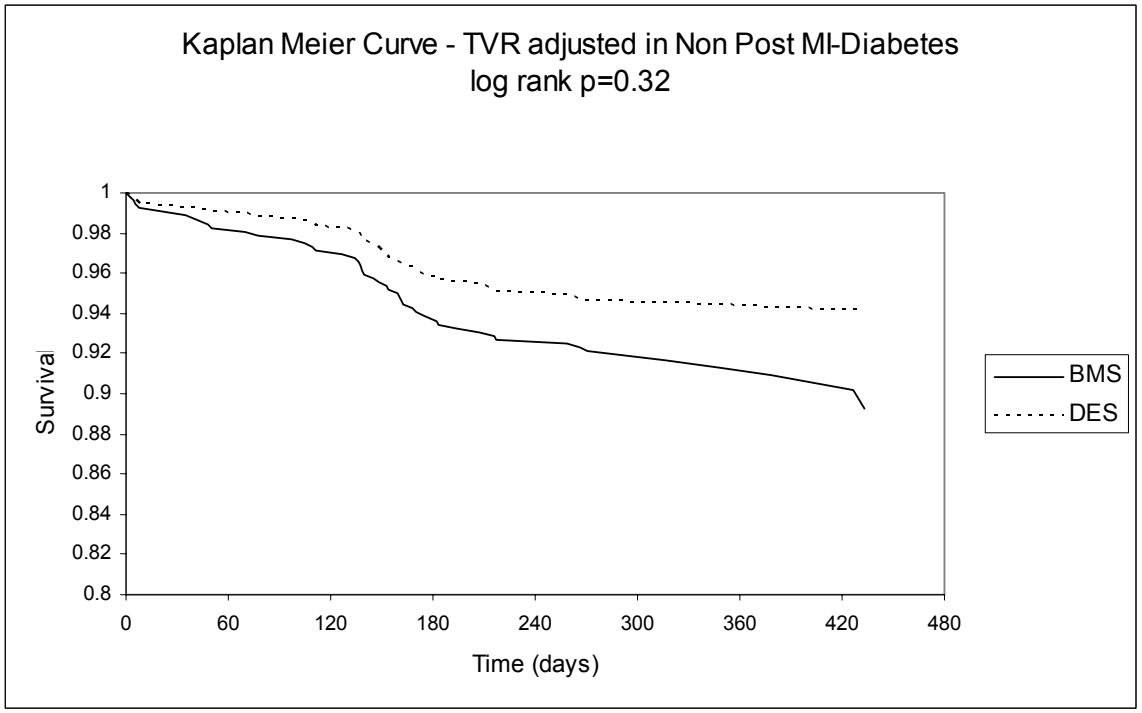


Figure 14: Kaplan Meier - TVRa post MI, non-diabetes

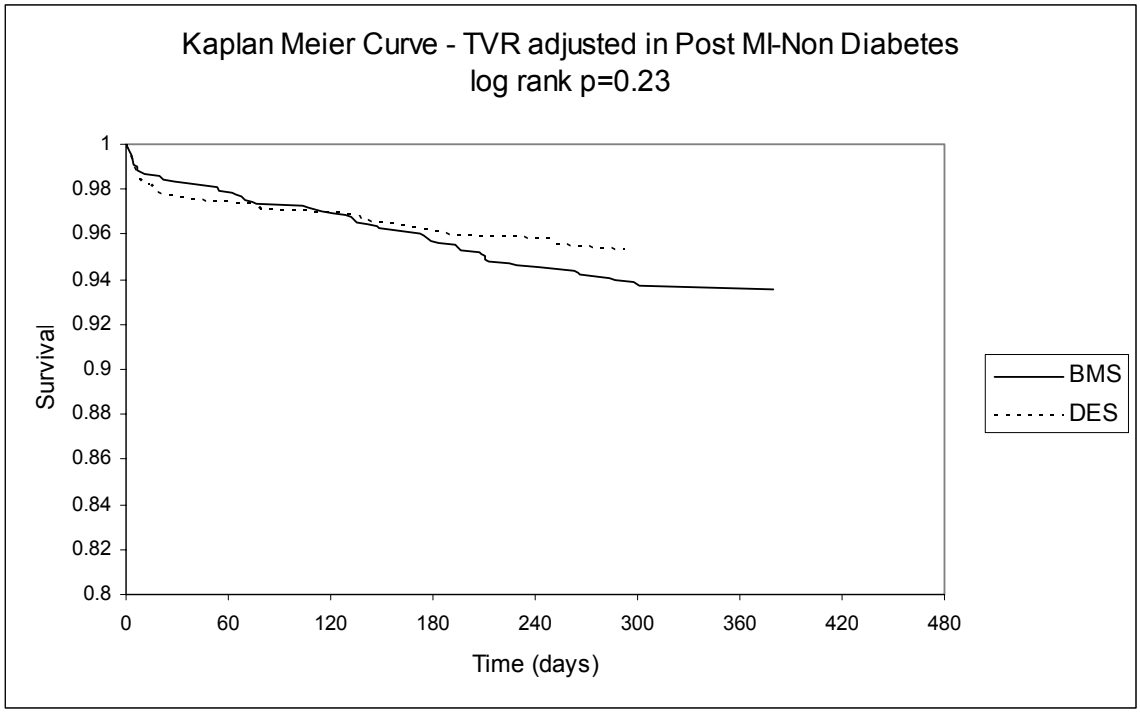
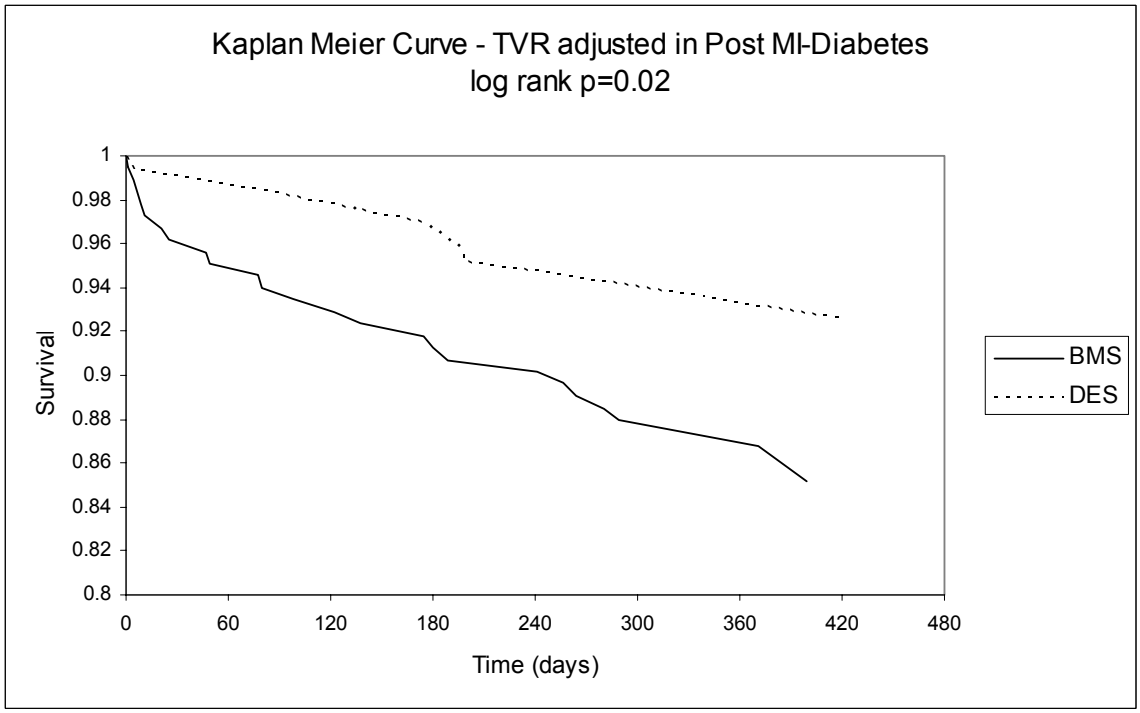


Figure 15: Kaplan Meier - TVRa post MI, diabetes



The KM estimates for TVRa, TLR, TVR and total revascularization rates are outlined in Table 14. According to the KM analysis, the rate of revascularization is higher in BMS than DES in all cohorts. However, while the TVRa revascularization rates following a DES stent are similar to those observed in the DES literature, the revascularization rates of BMS are lower that the rates reported in the literature. The only statistically significant difference observed between DES and BMS are in the Post MI patients with diabetes for whom the TVRa rates of revascularization following BMS were 12.07% versus 5.45% for DES (p=0.02).

Regarding the other secondary endpoints (i.e., TLR, TVR, total revascularization), a statistical difference between DES and BMS was observed in TLR revascularization rates for both the Non Post MI non-diabetes (DES 1.66%, BMS 3.25%, p<0.01) and Post MI diabetes (DES 0.61%, BMS 6.56%, p<0.01). The rate of TVR was also statistically significant for non-post MI diabetes patients (DES 2.93%, BMS 4.54%, p=0.01). No other statistical significance was observed in the other measures of revascularization rates at 365 days.

Table 14: KM results at 365 days

Event		Non Post MI Non-diabetes	Log-rank p-value	Non-Post MI diabetes	Log-rank p-value	Post MI non-diabetes	Log-rank p-value	Post MI diabetes	Log-rank p-value
TVR-a	DES	5.57%	0.11	7.49%	0.32	4.71%	0.23	5.45%	0.02
	BMS	7.10%		8.68%		6.25%		12.07%	
TLR	DES	1.66%	<0.01	2.11%	0.23	1.56%	0.47	0.61%	<0.01
	BMS	3.25%		3.43%		2.15%		6.56%	
TVR	DES	2.93%	0.01	4.17%	0.23	3.59%	0.98	3.03%	0.06
	BMS	4.54%		5.55%		3.36%		7.10	
Total revasc	DES	8.97%	0.13	10.41%	0.14	9.45%	0.10	11.52%	0.20
	BMS	10.56%		12.53%		12.90%		15.89%	

3.4.13.2. Kaplan Meier Estimates by lesion characteristic

The Kaplan Meier estimates at 365 days for the lesion characteristics subgroups are presented in Tables 15-17 and are summarized for each of the 4 cohorts.

For non Post MI non-diabetes, the rate of the primary endpoint, TVRa, is statistically higher for BMS than DES in long and narrow (12.03% vs. 5.32%, p=0.04) long lesions (8.79% versus 5.12%, p=0.02), narrow lesions (10.96 vs 6.6%, p=0.01) and long or narrow (9.51% versus 5.69%, p<0.01) as shown in Table 15.

In general, rates of revascularization of the other endpoints (TLR, TVR and total revascularization) are higher for BMS than DES and these differences are statistically significant in long and narrow lesions, long lesions, narrow lesions and long or narrow lesions. For short lesions, only TLR differences between BMS and DES were significant. None of the comparisons for short and wide lesions were statistically significantly different using the KM at 365 days.

Table 15: KM results at 365 days in non post MI non-diabetes lesion types

Event		Long and narrow	Log-rank p-value	long	Log-rank p-value	short	Log-rank p-value	narrow	Log-rank p-value	wide	Log-rank p-value	Long or narrow	Log-rank p-value	Short and wide	Log-rank p-value
TVRa	DES	5.32%	0.04	5.12%	0.02	5.84%	0.60	6.06%	0.01	5.24%	0.29	5.69%	<0.01	5.38%	0.86
	BMS	12.03%		8.79%		6.58%		10.96%		6.18%		9.51%		5.58%	
TLR	DES	0.62%	0.03	1.42%	0.05	1.80%	0.02	1.55%	<0.01	1.74%	0.04	1.70%	<0.01	1.59%	0.06
	BMS	5.41%		3.48%		3.18%		5.04%		2.82%		4.05%		2.75%	
TVR	DES	2.21%	0.03	2.47%	0.01	3.19%	0.17	3.01%	<0.01	2.87%	0.08	2.88%	<0.01	3.00%	0.39
	BMS	7.51%		5.60%		4.21%		6.92%		3.97%		6.04%		3.59%	
Total revasc	DES	8.07%	0.02	8.90%	0.02	9.02%	0.64	9.07%	<0.01	8.90%	0.51	9.23%	<0.01	8.55%	0.94
	BMS	15.60%		12.86%		9.85%		14.44%		9.64%		13.34%		8.81%	

For Non Post MI diabetes, the rates of revascularization are higher in BMS than DES in all subgroups and all outcomes as shown in Table 16. The event rates are higher in long than short, narrow than wide and long or narrow versus short and wide lesions.

In terms of the primary endpoint, the TVRa event rates are generally highest in long and narrow lesions (BMS 18.52% vs. DES 9.77%, p=0.04) and lowest for short and wide lesions (BMS 5.43% vs. 6.02%, p=0.82). Statistically significant differences in TVRa were observed for other lesion characteristics in long (DES 9.40%, BMS 15.89%, p=0.01), and long or narrow (DES 8.58%, BMS 131.13%, p=0.03).

With respect to the secondary endpoints, TLR is higher in long and narrow (DES 1.16%, BMS 11.11%, p<0.01), and long lesions (DES 2.08%, BMS 6.54%, p=0.03). In patients with long or narrow lesions a statistically significant difference existed in TVR (DES 4.75% vs. BMS 8.36%, p=0.04). Also, total revascularization was higher in long (DES 12.61%, BMS 20.56%, p<0.01), and long or narrow (DES 11.61%, BMS 18.46%, p<0.01).

Table 16: KM results at 365 days in non-post MI, diabetes subgroups KM results at 365 days

Event		Long and narrow	Log-rank p-value	long	Log-rank p-value	short	Log-rank p-value	narrow	Log-rank p-value	wide	Log-rank p-value	Long or narrow	Log-rank p-value	Short and wide	Log-rank p-value
TVRa	DES	9.77%	0.04	9.40%	0.01	6.23%	0.82	8.39%	0.19	6.74%	0.53	8.58%	0.03	5.43%	0.82
	BMS	18.52%		15.89%		6.82%		11.80%		7.79%		13.13%		6.02%	
TLR	DES	1.16%	<0.01	2.08%	0.03	2.14%	0.77	2.30%	0.24	1.95%	0.43	2.52%	0.18	1.35%	0.31
	BMS	11.11%		6.54%		2.63%		4.57%		3.11%		4.76%		2.65%	
TVR	DES	6.15%	0.08	5.17%	0.06	3.51%	0.50	5.00%	0.11	3.47%	0.43	4.75%	0.04	3.07%	0.65
	BMS	11.11%		9.35%		4.57%		8.09%		4.83%		8.36%		3.88%	
Total revasc	DES	13.25%	0.08	12.61%	<0.01	8.96%	0.52	11.45%	0.08	9.54%	0.33	11.61%	<0.01	8.15%	0.72
	BMS	22.22%		20.56%		10.47%		17.32%		11.14%		18.46%		8.98%	

For patients that were Post MI without diabetes the rate of TVRa is statistically higher in BMS than DES for long (DES 3.87%, BMS 8.98%, p=0.04) and wide lesions (DES 2.85%, BMS 5.89%, p=0.04) (Table 17). Furthermore concerning the secondary endpoints, only TLR demonstrated statistically significant differences between in BMS than DES for long and narrow lesions (DES 1.43%, BMS 9.37%, p=0.05). No statistical difference was found between TVR and Total revascularization.

Table 17: Kaplan Meier estimates at 365 days for post MI, non-diabetes subgroups

Event		Long and narrow	Log-rank p-value	long	Log-rank p-value	short	Log-rank p-value	narrow	Log-rank p-value	wide	Log-rank p-value	Long or narrow	Log-rank p-value	Short and wide	Log-rank p-value
TVR-a	DES	5.71%	0.10	3.87%	0.04	5.27%	0.96	7.83%	0.99	2.85%	0.04	5.78%	0.28	2.95%	0.21
	BMS	15.62%		8.98%		5.29%		8.03%		5.89%		8.04%		5.09%	
TLR	DES	1.43%	0.05	1.10%	0.24	1.87%	0.97	3.61%	0.99	0.35%	0.07	2.53%	0.97	0.00%	0.07
	BMS	9.37%		2.73%		1.94%		3.66%		1.85%		2.58%		1.87%	
TVR	DES	5.71%	0.23	2.76%	0.30	4.15%	0.45	6.63%	0.66	1.79%	0.22	4.33%	0.98	2.37%	0.62
	BMS	12.50%		4.69%		3.04%		5.49%		3.07%		4.38%		2.88%	
Total revasc	DES	10.00%	0.15	10.79%	0.17	9.10%	0.21	11.30%	0.63	8.94%	0.09	10.68%	0.25	8.31%	0.16
	BMS	21.87%		15.38%		12.03%		12.90%		12.91%		13.79%		12.32%	

3.4.14. Multivariate Weibull regression analysis

Only multivariate Weibull regressions performed to adjust for baseline imbalances and results of the regressions for TVRa are presented in Table 18 for the four primary cohorts. Results of the univariate Weibull regressions confirm that the Weibull distribution offers a good fit of the data when compared to the Kaplan Meier estimates. However, both the univariate Weibull and Kaplan Meier regressions do not adjust for potential confounders, and may offer an incomplete assessment.

The variables used to control for different baseline characteristics were DES (1 if yes; 0 if BMS), age, gender (male), stenosis of the left anterior descending coronary artery (LAD), Stent diameter (mm), Stent Length (mm), lesion severity, multivessel disease, presence of unstable angina, and whether the patient had an adhoc procedure. A positive sign associated with the DES coefficient indicates a longer time to event for repeat revascularization versus BMS, and equivalently a negative sign indicates a lower predicted time to event.

Overall, after adjusting for differences in pre-existing comorbidities, DES had a positive treatment effect compared to BMS in extending time to repeat events, or equivalently in reducing event rates. DES was only significant in the non-post MI diabetes and non-diabetes groups ($p=0.04$ and 0.02, respectively).

The statistical significance of the covariates used, to control for potential differences (e.g. age), are different between cohorts. For example, age is statistically significant in the non-Post MI diabetes group but not in the other cohorts.

Table 18: Multivariate coefficients TVR-adjusted for the four primary cohorts

	Non Post MI				Post MI			
	Non Diabetes		Diabetes		Non-Diabetes		Diabetes	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
DES	0.4001	**0.02**	0.5489	**0.04**	0.9409	0.08	1.1364	0.06
Age (yrs)	-0.0090	0.20	0.0272	**0.02**	0.0280	0.14	0.0075	0.73
Male (%)	0.0234	0.90	-0.0246	0.93	-0.6496	0.26	-0.3125	0.63
LAD	0.0014	0.99	0.0015	0.99	-0.0825	0.78	0.2186	0.58
Stent diameter	-0.2105	0.24	-0.6429	**0.01**	-1.3916	**<0.01**	0.0679	0.92
Stent Length	-0.5528	**<0.01**	-0.4684	0.07	-0.6078	0.20	-0.7824	0.17
Lesion Complexity	0.1086	0.51	-0.7675	**<0.01**	-0.5093	0.30	0.0274	0.96
Multivessel Disease	-0.0544	0.82	0.7170	0.07	1.5443	0.14	-0.0956	0.91
Unstable angina	-0.2545	0.12	0.0265	0.91	-0.5348	0.39	0.463	0.42
Adhoc	-0.3352	**0.04**	-0.5893	**0.02**	n.a.	n.a.	n.a.	n.a.
Shape	0.7500	0.75	0.7733	0.77	0.5081	0.51	0.6863	0.69

- Intercept not presented here.
- n.a. not applicable.
- Positive coefficient indicates longer survival time, and equivalently lower event rate.

3.4.15. Multivariate Weibull regression by lesion characteristic

Multivariate Weibull predictions are presented for the four cohorts stratified by lesion characteristics in Tables 19 & 20. Note that for the Post MI diabetes cohort; there were not enough patients to generate subgroup analyses.

Overall, for the non Post MI non-diabetes group (n = 4188) the rate of TVRa was not statistically different (at the 5% level) between patients treated with DES (5.4%) compared to BMS (7.2%). When examining the predicted rates of TVRa by lesion characteristic however there were statistically significant differences, after controlling for baseline characteristics, between DES and BMS treated patients depending on the lesion characteristics. Patients treated with DES and with long lesions had a lower rate of revascularization than BMS treated patients respectively (4.7% vs. 9.0%, $p<0.05$). The reduced rate of revascularization for DES treated patients relative to BMS treated patients was also found in patients

with narrow lesions (6.4% vs. 10.7%, p<0.05) and in patients with longer or narrower lesions (5.4% vs. 9.5%, p<0.05)

Similarly for Non-Post MI patients with diabetes, the observed differences between DES and BMS were statistically significant for long and narrow (DES 6.0%, BMS 20.6%), long (DES 18.6%, BMS 7.9%), narrow (DES 5.7%, BMS 11.9%), and long or narrow lesions (DES 6.9%, BMS 14.3%). In general, the overall rate of revascularization was higher for patients with diabetes and long and/or narrow lesions as compared to the patients without diabetes.

Table 19: Multivariate Weibull 1-year results for TVRa in non post-MI patients by lesion characteristic and diabetes status

	Without diabetes			With diabetes		
Lesion Cohort	n=	BMS	DES	n=	BMS	DES
All	4188	7.2%	5.4%	1342	10.0%	6.7%
Long & Narrow lesions†	388	10.9%	5.8%	197	**20.6%**	**6.0%***
Long	1234	**9.0%**	**4.7%***	440	**18.6%**	**7.9%***
Short	2954	6.4%	5.3%	902	6.7%	5.2%
Narrow	1210	**10.7%**	**6.4%***	495	**11.9%**	**5.7%***
Wide	2978	5.9%	4.8%	847	7.9%	5.7%
Long or Narrow	2056	**9.5%**	**5.4%***	738	**14.3%**	**6.9%***
Short and Wide	2132	5.1%	5.4%	604	5.5%	5.1%

* Significant at the 5% level

The predicted rates of TVRa for the post MI non-diabetes group stratified by lesion characteristics are presented in Table 20. There were no statistically significant differences, at the 5% level, in the rates of revascularization between DES and BMS. At the 10% level, differences in TVRa were observed for patients for the overall cohort (BMS 6.1% vs. 3.8%), after adjusting for baseline characteristics, patients with long lesions (BMS 8.1%, DES 3.0%), and wide lesions (BMS 5.5%, DES 2.8%).

The results of the multivariate Weibull regression in Post MI patients with diabetes results are also presented in Table 20. For Post MI diabetes, the rate of TVRa is higher for BMS than DES at the 10% level (BMS 12.1%, DES 5.8%).

Table 20: Multivariate Weibull 1-year results for TVRa in post-MI patients by lesion characteristic and diabetes status

		Without diabetes			**With diabetes**	
Lesion Cohort	n=	BMS	DES	n=	BMS	DES
All	1397	**6.1%**	**3.8%****	339	**12.1%**	**5.8%****
Long & Narrow lesions†	101	15.9	5.8%			
Long	426	8.1	**3.0%****			
Short	970	4.9	4.2%			
Narrow	325	6.1	6.0%			
Wide	1071	5.5	**2.8%****			
Long or Narrow	650	7.5	4.8%			
Short and Wide	746	4.5	2.8%			

** not significant at the 5% level, significant at the 10% level

† long lesions > 20 mm, narrow lesions < 2.75 mm

3.4.16. Mortality

The mortality rate was determined for the patients entered into the observational study by linking the CCN dataset with the registered person database. The mortality rates are for all causes and the reason for death could not be determined. As these results are not adjusted for baseline differences in comorbid conditions and there is a potential for selection bias with respect to the use of BMS in patients with higher risk of mortality, these results should be interpreted with caution and are included in this interim report for information purposes only.

3.4.17. Unadjusted Mortality

The unadjusted rate of mortality was higher following BMS in all cohorts. In addition, the mortality rate is higher for diabetes versus non-diabetes, and for Post MI versus non post MI. The unadjusted mortality rates were highest in Post MI diabetes cohort (DES 3.64%, BMS 6.56%) (see Table 21).

Table 21: Unadjusted mortality event rates for primary cohorts

	Non-diabetes				Diabetes			
	DES (n)	DES (%)	BMS (n)	BMS (%)	DES (n)	DES (%)	BMS (n)	BMS (%)
Non Post MI								
Mortality	30	1.43%	63	2.33%	24	2.80%	21	4.04%
Post MI								
Mortality	6	1.34%	36	3.66%	6	3.64%	12	6.56%

The unadjusted mortality rate by lesion characteristics are described in Table 22 below by cohort. In general, unadjusted mortality rates were higher in patients with longer lesions than short lesions and in patients with narrower lesions.

Table 22: Mortality by baseline lesion characteristics

Cohort		Long and narrow	long	short	narrow	wide	Long or narrow	Short and wide
Non-Post MI, Non-diabetes								
Mortality	DES	7 (2.17%)	10 (1.29%)	19 (1.44%)	16 (1.89%)	13 (1.05%)	19 (1.46%)	10 (1.26%)
	BMS	4 (3.60%)	16 (2.51%)	46 (2.22%)	16 (3.09%)	46 (2.10%)	28 (2.68%)	34 (2.05%)
Non-Post MI, diabetes								
Mortality	DES	2 (1.16%)	10 (2.92%)	14 (2.72%)	9 (2.30%)	15 (3.22%)	17 (3.03%)	7 (2.36%)
	BMS	3 (11.11%)	7 (6.54%)	14 (3.39%)	7 (6.14%)	14 (3.45%)	11 (5.67%)	10 (3.07%)
Post MI, diabetes								
Mortality	DES	1 (1.43%)	3 (1.66%)	3 (1.12%)	1 (0.60%)	5 (1.77%)	3 (1.08%)	3 (1.75%)
	BMS	2 (6.25%)	11 (4.30%)	25 (3.44%)	12 (7.32%)	24 (2.93%)	21 (5.41%)	15 (2.52%)

Results examining the time to death are reported in Figures 16 & 17. For the non Post MI patients that died during the study follow-up period, the mean time to death was 110 days for the BMS treated patients and 85 days for the DES treated patients. There appears to be a greater rate of mortality within the first 240 days in the patients receiving BMS after which the mortality appears to be similar between BMS and DES. There is no evidence of a late death risk in patients based on initial stent type.

In the Post MI patient group, for those patients that died during the study follow-up time, there is an apparent initial risk of death within the first 30 days, especially in patients receiving a BMS (Figure 17). The mortality rates appear to be similar between the two groups following the initial period immediately following the intervention with the BMS mortality rate being slightly higher than that of the DES treated group. The mean time to death in the Post MI patient

group was 28 days for the BMS treated patients compared to 60 days for the DES treated patients.

Figure 16: Time to events - Mortality non post MI

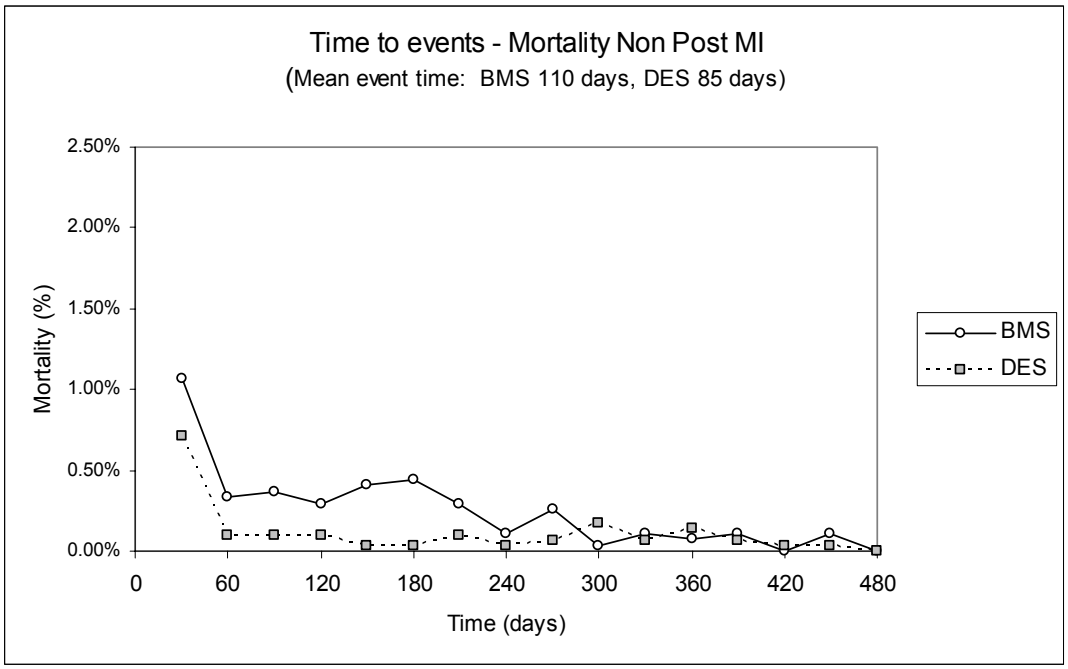
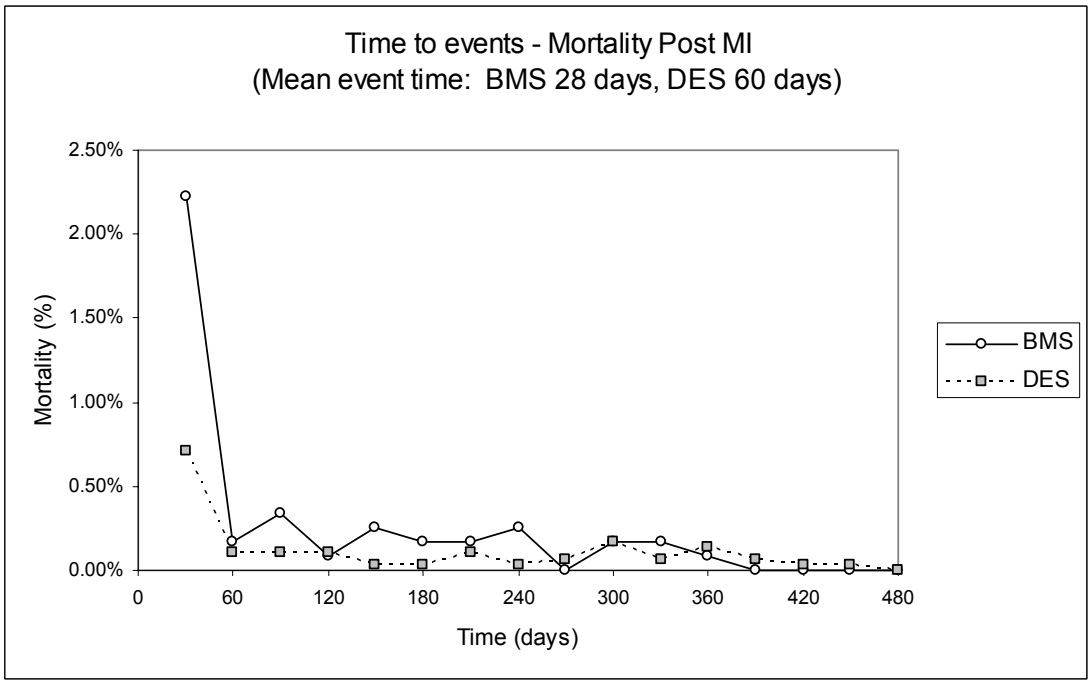


Figure 17: Time to events - Mortality post MI



3.4.18. Kaplan Meier Estimates of Mortality

The KM analyses for each of the primary 4 cohorts are displayed below in Table 23 and Figures 18 – 21. Statistically significant differences between DES and BMS were observed in the non diabetes patients, for both the non Post MI and Post MI cohorts. The rate of death is higher for BMS in non Post MI without diabetes (DES 1.38%, BMS 2.22%, p=0.02) and in Post MI without diabetes (DES 1.34%, BMS 3.69%, p=0.02).

Table 23: Kaplan Meier estimates at 365 days for mortality by primary cohorts

		Non Post MI Non-diabetes	Log-rank p-value	Non-Post MI diabetes	Log-rank p-value	Post MI non-diabetes	Log-rank p-value	Post MI diabetes	Log-rank p-value
Mortality	DES	1.38%	0.02	2.66%	0.20	1.34%	0.02	3.70%	0.22
	BMS	2.22%		3.96%		3.69%		7.10%	

Figure 18: Kaplan Meier - Death non post MI - non-diabetes

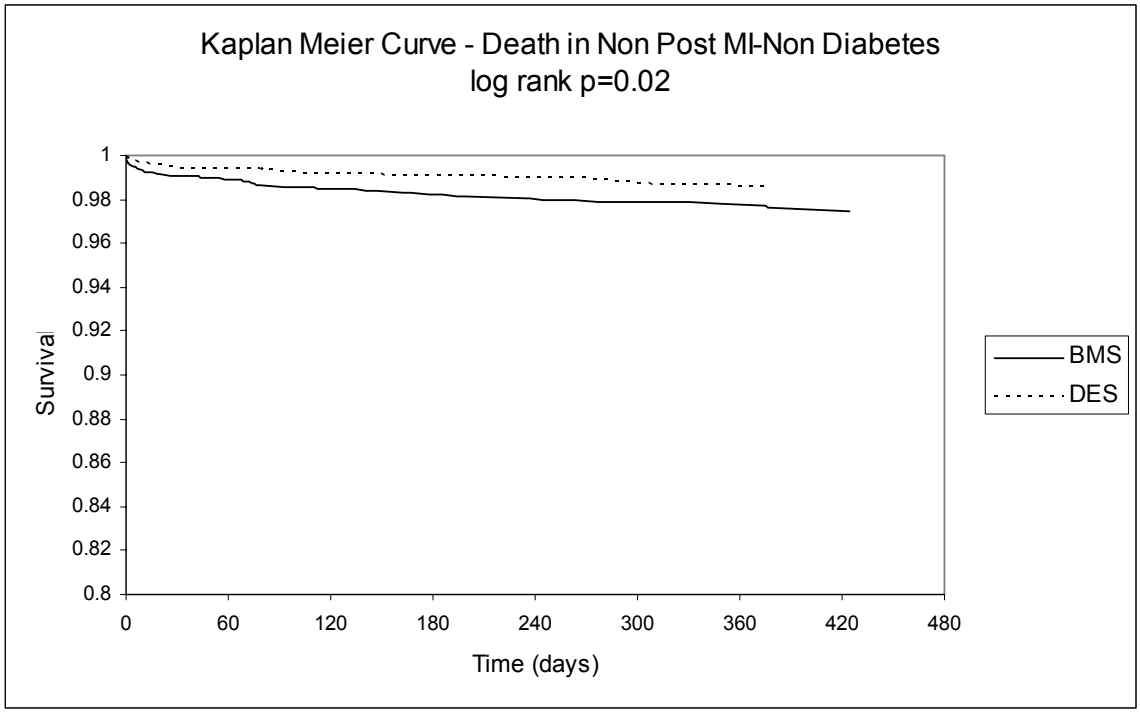


Figure 19: Kaplan Meier - Death non post MI – diabetes

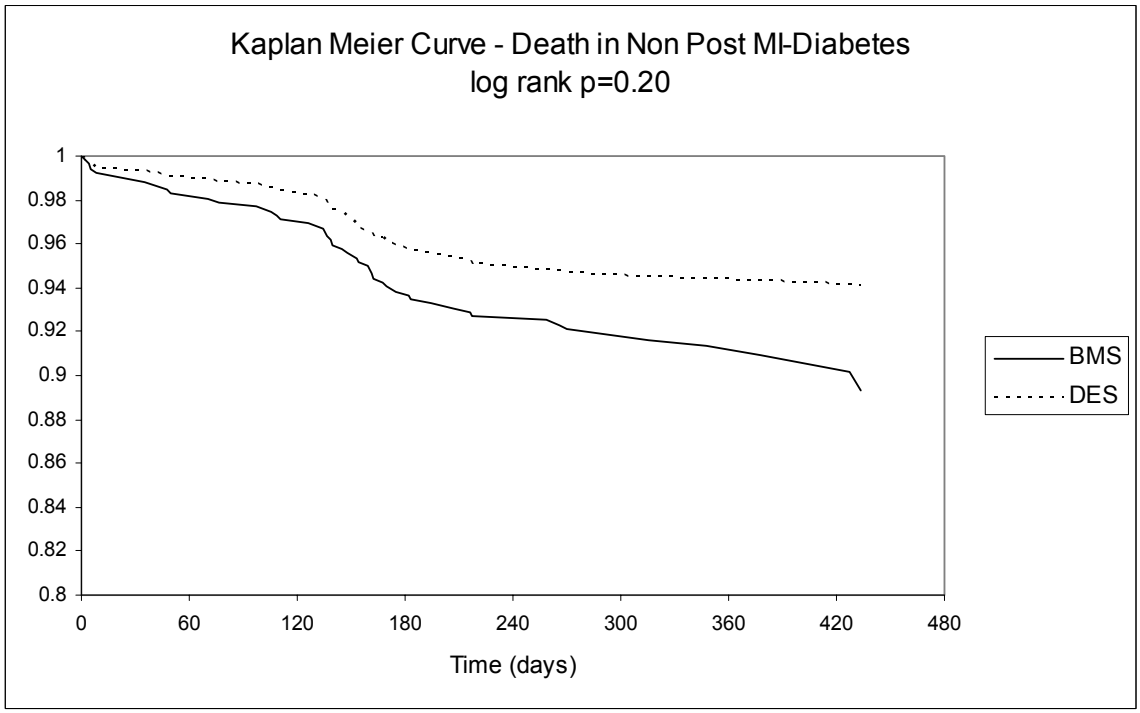


Figure 20: Kaplan Meier - Death post MI - non-diabetes

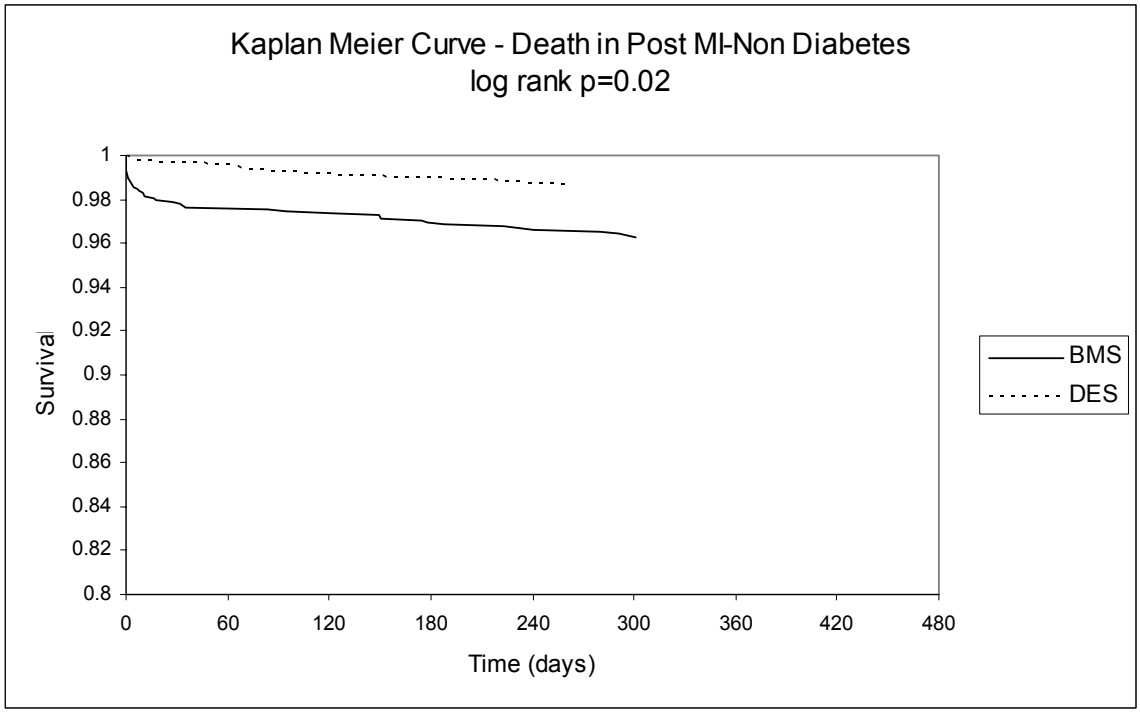
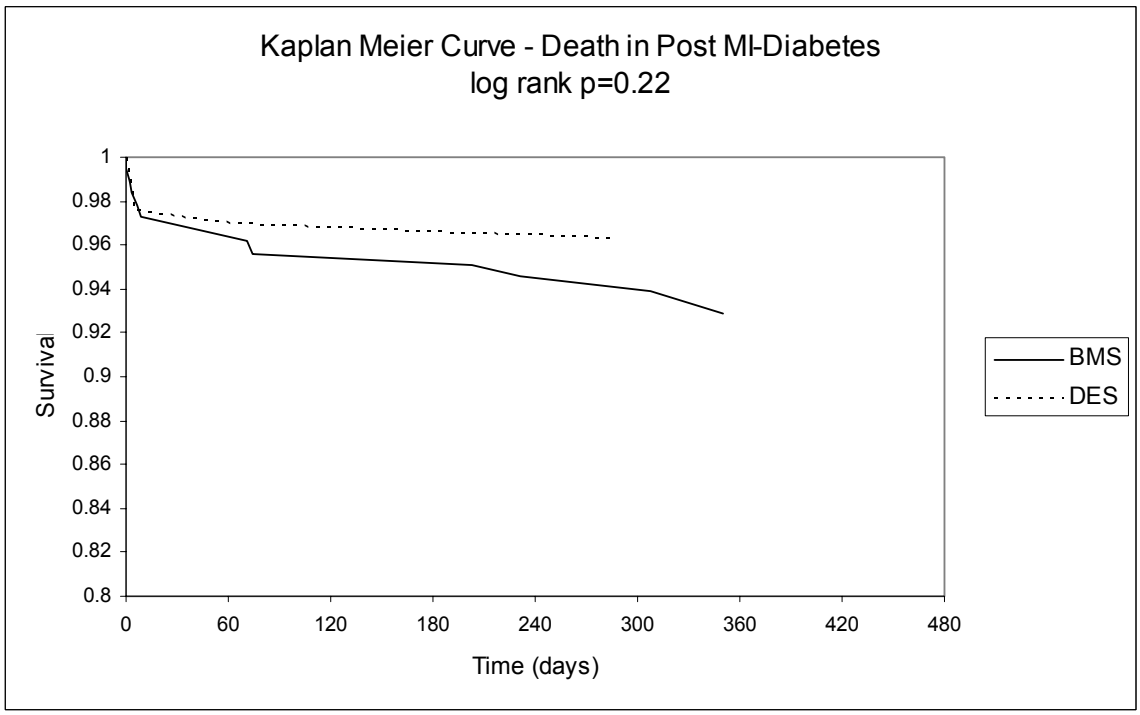


Figure 21: Kaplan Meier - Death post MI – diabetes



3.4.19. Unadjusted Mortality by Lesion Characteristic

The unadjusted mortality rates, stratified by lesion characteristic, are outlined in Table 24 below. In the non-Post MI non-diabetes patients the unadjusted rates of mortality were statistically significantly higher in patients with wide lesions (DES 1.09%, BMS 2.12%, p=0.02) and also in patients with long or narrow lesions (DES 1.41%, BMS 2.74%, p=0.02). In the non-post MI, diabetes patients mortality is statistically higher in BMS than DES for long and narrow (DES 1.16%, BMS 11.11%, p<0.01), and narrow (DES 2.62%, BMS 6.14%, p=0.04). Similarly, mortality is statistically higher in BMS than DES in short lesions (DES 1.12%, BMS 3.48%, p=0.05), narrow lesions (DES 0.60%, BMS 7.48%, p<0.01), and long or narrow lesions (DES 1.08%, BMS 5.49%, p<0.01).

Table 24: Kaplan Meier results at 365 days for mortality by lesion types

Event		Long and narrow	Log-rank p-value	long	Log-rank p-value	short	Log-rank p-value	narrow	Log-rank p-value	wide	Log-rank p-value	Long or narrow	Log-rank p-value	Short and wide	Log-rank p-value
Non-Post MI, Non-diabetes															
Mortality	DES	2.27%	0.42	1.33%	0.06	1.42%	0.10	1.82%	0.15	1.09%	0.02	1.41%	0.02	1.33%	0.17
	BMS	3.60%		2.60%		2.22%		3.09%		2.12%		2.74%		1.98%	
Non-Post MI, diabetes															
Mortality	DES	1.16%	<0.01	3.08%	0.09	2.37%	0.51	2.62%	0.04	2.71%	0.79	3.34%	0.10	1.39%	0.52
	BMS	11.11%		6.85%		3.21%		6.14%		3.36%		5.83%		2.84%	
Post MI, Non-diabetes															
Mortality	DES	1.43%	0.18	1.66%	0.12	1.12%	0.05	0.60%	<0.01	1.77%	0.29	1.08%	<0.01	1.75%	0.56
	BMS	6.25%		4.30%		3.48%		7.48%		2.93%		5.49%		2.53%	

3.4.20. Multivariate Weibull Regression Predicted Mortality Rates

Multivariate Weibull analysis of mortality is presented below in Table 25. The shape function in all 4 cohorts is less than unity (1) indicating that the risk of death falls with time. Looking at all four cohorts, DES has a positive effect in reducing mortality. However, this effect is only significant for non-diabetes patients Post MI patients (p=0.04).

Table 25: Results of multivariate Weibull analysis of mortality for the four primary cohorts

	Non Post MI				**Post MI**			
	Non-Diabetes		**Diabetes**		**Non-Diabetes**		**Diabetes**	
	Coefficient	**p-value**	**Coefficient**	**p-value**	**Coefficient**	**p-value**	**Coefficient**	**p-value**
DES	0.96	0.09	0.30	0.631	2.35	**0.04**	1.94	0.22
Age (yrs)	-0.20	**<0.01**	-0.09	**<0.01**	-0.15	**<0.01**	-0.05	0.45
Male (%)	0.17	0.75	0.66	0.28	0.25	0.77	2.45	0.14
LAD	-0.24	0.42	-0.06	0.88	-0.01	0.99	-1.31	0.14
Stent diameter	-0.47	0.41	0.001	0.99	-0.69	0.46	-1.43	0.37
Stent Length	0.27	0.64	-0.29	0.63	-0.53	0.55	-0.07	0.96
Lesion Severity	-1.08	**0.05**	-1.84	**0.01**	-0.85	0.37	-1.96	0.31
Multivessel Disease	-0.51	0.46	1.18	0.24	-1.45	0.20	-3.53	**0.05**
Unstable angina	-0.94	0.07	-1.47	**0.02**	-1.11	0.39	0.51	0.76
Adhoc	-1.01	0.06	0.66	0.31	n.a.	n.a.	n.a.	n.a.
Shape	0.49	0.49	0.55	0.55	0.43	0.43	0.36	0.36

- Intercept not presented here.
- n.a. not applicable.
- Positive coefficient indicates longer survival time, and equivalently lower event rate.

The multivariate regression prediction rates in the non Post MI patients (Table 26) for mortality at 365 days demonstrate that mortality is generally higher in the BMS than DES in almost all subgroups. The exceptions are in the wide, and short and wide subgroups where BMS and DES have identical mortality rates. The highest rate of mortality for BMS is in the long and narrow subgroup (7.6%)

and the highest mortality for DES is in the long or narrow subgroup (2.1%). In the non Post MI patients none of the differences in mortality were significant at the 5% level.

For the Post MI group, in general BMS mortality rates are higher than DES for all subgroups including the full cohort.(Table 27) However, statistical differences between DES and BMS were only observed at the 5% level for long or narrow lesions (BMS 3.0%, DES 0.7%) and at the 10% level in narrow lesions (BMS 4.2%, DES 0.4%). The highest rate of mortality for BMS was in long and narrow (5.7%) and for DES also in long and narrow (1.1%). For the full cohort, mortality is higher in BMS than DES at the 5% level (DES 0.8%, BMS 2.0%).

Table 26: Multivariate Weibull regression predicted mortality rates at 1 year for non post MI patients by diabetes status

		Non-diabetes		**Diabetes**	
Lesion Cohort	n =	BMS	DES	BMS	DES
All	1342	1.0%	0.6%	2.2%	1.8%
Long and Narrow ^	197	3.6%	2.2%	7.6%	0.0%
Long	440	1.2%	0.6%	2.1%	1.4%
Short	902	0.9%	0.6%	1.6%	1.4%
Narrow	495	1.0%	0.8%	2.9%	1.5%
Wide	847	0.9%	0.4%**	0.2%	0.2%
Long or narrow	738	1.1%	0.7%	2.6%	2.1%
Short and Wide	604	0.9%	0.5%	0.2%	0.2%

- * indicates significance at the 5% level
- ** indicates significance at the 10% level
- ^ univariate model used for TVR-a

Table 27: Multivariate Weibull regression predicted mortality rates at 1 year for post MI patients by diabetes status

		Non-diabetes		Diabetes	
Lesion Cohort	n =	BMS	DES	BMS	DES
All	1397	2.0%	0.8%*	4.2%	2.1%
Long and Narrow ^	101	5.7%	1.1%		
Long	426	2.3%	0.9%		
Short	970	1.7%	0.6%		
Narrow	325	4.2%	0.4%**		
Wide	1071	1.3%	1.0%		
Long or narrow	650	3.0%	0.7%*		
Short and Wide	746	0.4%	0.3%		

- * indicates significance at the 5% level
- ** indicates significance at the 10% level
- ^ univariate model used for TVR-a

3.5. Summary

This interim analysis of the Ontario "real-world" use of DES as compared to BMS presents observational data from approximately 8000 cases with at least 9 months of follow-up information. Based on an analysis of the raw event rates, KM survival analysis and Multivariate Weibull regression, the revascularization rates for patients treated with DES are lower than that found in the BMS treated patients but only in selected lesions (long and/or narrow lesions). The DES revascularization rates observed in this study appear to be similar to those reported within the clinical literature (see systematic literature review), however, the revascularization rates for BMS are significantly lower than those reported from randomized controlled trials. The revascularization rates observed in both the DES and BMS treated patients are however similar to analyses of other patient registry data.[15,39] Potential reasons for the difference may include differences in practice patterns in Ontario (utilization of HMGCoA reductase inhibitors, antiplatelet agent duration of use – currently for 1 year, if possible), the

observational nature of the study as compared to randomized controlled trials, an elevated target vessel revascularization rate in the clinical trials due to protocol driven-revascularizations and the wider range/diversity of lesions treated in the "real-world" as compared to the selected lesions included in the RCT's.

Differences exist in TVRa between DES and BMS. TVRa is higher in BMS than in the DES cohort in the unadjusted Kaplan Meier analysis. However, this is an observational study where differences exist in baseline comorbidities. There were differences in age, gender, history of smoking, previous PTCA, PVD and CCS ratings between treatment groups. There were also differences between DES and BMS in lesion characteristics, number of procedural vessels, and lesion severity. The utilization patterns of DES and BMS were different in the patient populations studied.

These differences in comorbidities, lesion characteristics and stent utilization and characteristics were adjusted for by using the multivariate Weibull model. Based on the multivariate Weibull results, the use of DES versus BMS as the choice of stent was a significant factor in TVRa for all major cohorts. The variables that were significant in the rate of TVRa were age, gender, LAD, stent diameter, stent length, lesion severity, number of diseased vessels, and CCS rating (severe angina). Variables not significant in affecting rate of TVRa were history of smoking, renal disease, previous PTCA and previous CABG.

After adjusting for baseline imbalances the difference in the rate of TVRa for BMS versus DES continued to be statistically significantly higher and the differences in revascularization rates were apparent in patients with long, narrow, or combinations of long and/or narrow lesions. The use of DES in patients with short and/or wide lesions did not appear, following adjustment for baseline characteristics, to provide any apparent benefit with respect to reducing revascularization rates.

Some limitations should be considered when evaluating the results of this field evaluation. TVRa is a composite variable that includes all target vessel revascularizations plus all CABG and all PCI without stents. Some of the CABG

and PCI without stents captured in TVRa may not be of the target vessel. TVRa may therefore overestimate TVR but it was felt that the adjustment was necessary in order to compare the revascularization rates to those reported in the literature that include both PCI without stent and CABG within the TVR calculation. The percent of treatments that were CABG or PCI without stent were similar to each other for DES and BMS for the non Post MI. (The number of CABG and PCI without stent are small events in Post MI and no conclusions should be drawn). As a result, TVRa does provide a consistent estimate of the difference of repeat revascularization events.

The availability of baseline characteristics and comorbidities was limited for all patients. However, baseline characteristics and comorbidities were available for approximately 90% of the patients who received a stent. In about 10% of the patients, the existence of some co-morbidities were unknown. Second, the reporting of comorbidities was different between patients that received adhoc versus an elective PCI with stent. As a final restriction on availability, in order to maintain patient confidentiality as per ICES confidentiality policies, exact counts are not provided for small cells. For example, the Post MI cohort is a smaller cohort, resulting in some cells having less than 5 patients for a given comorbidity. The mortality data presented in the field evaluation should be interpreted with some caution as it was not possible to identify with the current data linkages in the analysis the cause of death and furthermore additional information is required from other sources to be able to control for as many baseline comorbidities as possible.

One further consideration when examining the data from the Post-MI patients is that the calculated revascularization rate for these patients may be an overestimate of the TVR and TVRa as some of the revascularizations may be planned staged procedures. A staged procedure occurs when a patient (typically Post MI) has the vessel causing the MI to be corrected and the clinician plans future procedures to other vessels in the near future, typically within 2 weeks. These staged procedures that occur within two weeks are not a true revascularization of the initial target vessel. Thus, the reported primary endpoint,

TVRa, and secondary endpoints TLR, TVR are overstated by the inclusion of these staged procedures as revascularizations in the Post MI patients.

4. ECONOMIC EVALUATION

A decision analytic model was developed to estimate the one year costs and outcomes for patients undergoing a PCI that included the insertion of coronary stent(s). Two treatment strategies were compared: 1) PCI with bare metal stent(s) (BMS); 2) PCI with drug eluting stent(s) (DES).

Costs incorporated in the model included the cost of the initial PCI, including stent costs, along with costs associated with revascularizations occurring within 1 year post initial PCI. Outcomes include the expected number of revascularizations and the expected Quality Adjusted Years (QALY's) one year post initial PCI. QALYs incorporated the quality of life impacts of anginal symptoms and recovery time associated with revascularization procedures.

Two cost effectiveness outcomes were evaluated and expressed as incremental cost-effectiveness ratios (ICER's). The primary cost-effectiveness outcome was the incremental cost per QALY gained (DES vs. BMS). The secondary cost-effectiveness outcome was the incremental cost per revascularization avoided. ICER's were not calculated if one treatment strategy dominated the other (i.e. lower costs, better outcomes). The analysis was taken from the perspective of the Ontario Ministry of Health and the time horizon was 1 year.

To account for uncertainty around model input parameter values, a probabilistic sensitivity analysis was conducted, with uncertainty results expressed using cost-effectiveness acceptability curves, showing the probability DES or BMS treatment is cost-effective at various willingness-to-pay values for patient outcomes.

4.1. Patient Population

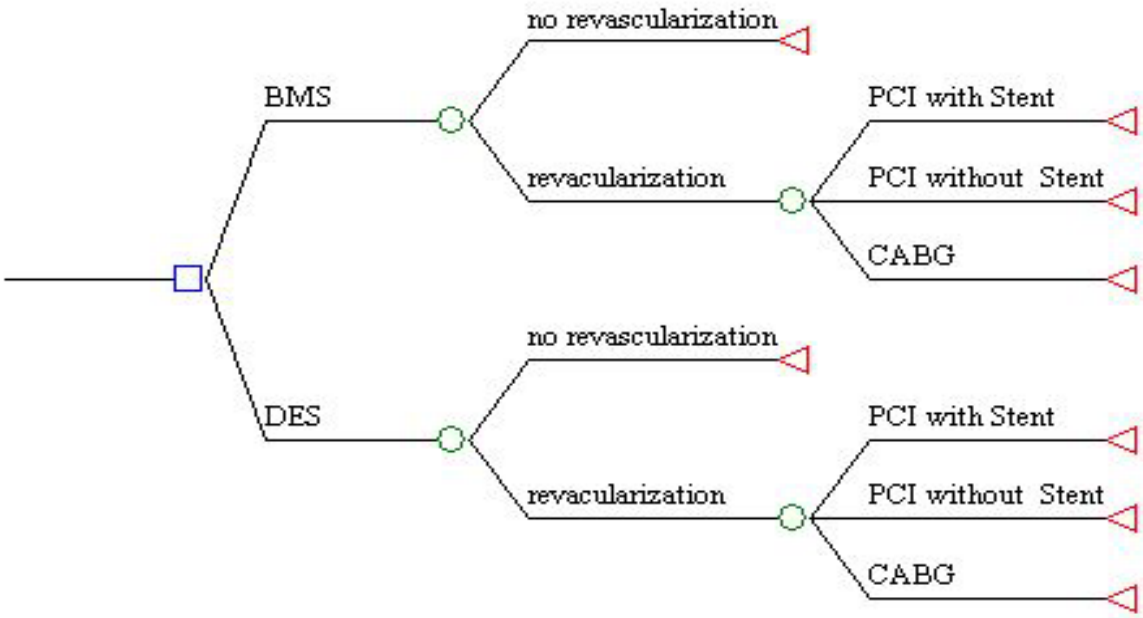
The analysis was carried out separately for Non-Post MI and Post-MI patients. In order to account for patient groups at higher risk of revascularization, groups were further stratified according to diabetes status, lesion length and lesion diameter. Due to the small sample of the Post–MI group with diabetes, from the

field evaluation, it was not possible to stratify this group according to lesion length and diameter. In total, the cost-effectiveness of DES versus BMS was determined for 22 different cohorts of patients.

4.2. Decision Analytic Model

Clinical pathways related to revascularizations following the use of DES and BMS during PCI were modeled using a decision tree model. Figure 22 illustrates the structure of the model following the initial PCI.

Figure 22: Structure of the decision analytic model for patients undergoing a stent implantation



As shown in Figure 22, there were four pathways considered in the model: 1) no revascularization: 2) revascularization by PCI with stent; 3) revascularization by PCI without stent; and 4) revascularization by CABG. Each pathway has

different cost and outcome implications. The probability of ending up in each pathway differs according to treatment group and patient cohort.

4.3. Data sources and assumptions

Various sources of data were used in the model. These include results observed from the field evaluation along with data from other sources. Input parameters into the model can be classified into the following categories: 1) revascularization probability input variables; 2) cost input variables; and 3) utility input variables. A summary of the input parameters used in the model is provided in the following three subsections.

4.3.1. Revascularization probability input variables

The revascularization probability input variables used in the model were derived from the field evaluation study. These variables include the probability of having any revascularization procedure, along with the proportion of each revascularization type (PCI with stent, PCI no stent, CABG).

The model assumes that the type of revascularization is independent of the treatment group. That is, it assumes that the proportion of each revascularization type is the same for the DES and BMS treatment groups. Table 28 presents the probability of revascularization along with the proportion of each type of revascularization by treatment group and patient cohort.

Table 28: Revascularization rates and type of revascularization

Non-Post MI – Non-Diabetes	Revascularization Rates		Type of Revascularization		
Lesion Characteristics	**BMS**	**DES**	**PCI-stent**	**PCI-no stent**	**CABG**
All	7.2%	5.4%	70.0%	14.7%	15.3%
Long & Narrow Lesions	10.9%	5.8%	62.5%	10.4%	27.1%
Long	9.0%	4.7%	69.2%	14.1%	16.7%
Short	6.4%	5.3%	70.1%	14.9%	14.9%
Narrow	10.7%	6.4%	65.8%	16.8%	17.4%
Wide	5.9%	4.8%	71.8%	13.6%	14.6%
Long or Narrow	9.5%	5.4%	68.4%	16.4%	15.2%
Short and Wide	5.1%	5.4%	71.6%	12.6%	15.8%
Non-Post MI - Diabetes	**Revascularization rates**		**Type of Revascularization**		
Lesion Characteristics	**BMS**	**DES**	**PCI-stent**	**PCI-no stent**	**CABG**
All	10.0%	6.7%	64.2%	17.0%	18.8%
Long & Narrow Lesions	20.6%	6.0%	62.1%	20.7%	17.2%
Long	18.6%	7.9%	63.2%	19.1%	17.6%
Short	6.7%	5.2%	63.3%	16.7%	20.0%
Narrow	11.9%	5.7%	62.5%	18.8%	18.8%
Wide	7.9%	5.7%	63.8%	17.0%	19.1%
Long or Narrow	14.3%	6.9%	63.1%	18.4%	18.4%
Short and Wide	5.5%	5.1%	63.6%	16.4%	20.0%
Post MI - Non-Diabetes	**Revascularization rates**		**Type of Revascularization**		
Lesion Characteristics	**BMS**	**DES**	**PCI-stent**	**PCI-no stent**	**CABG**
All	6.1%	3.8%	77.0%	9.8%	13.2%
Long & Narrow Lesions	15.9%	5.8%	70.6%	23.5%	5.9%
Long	8.1%	3.0%	71.7%	11.7%	16.7%
Short	4.9%	4.2%	79.8%	8.8%	11.4%
Narrow	6.1%	6.0%	68.3%	22.0%	9.8%
Wide	5.5%	2.8%	79.7%	6.0%	14.3%
Long or Narrow	7.5%	4.8%	70.2%	14.3%	15.5%
Short and Wide	4.5%	2.8%	83.3%	5.6%	11.1%
Post MI - Diabetes	**Revascularization rates**		**Type of Revascularization**		
Lesion Characteristics	**BMS**	**DES**	**PCI-stent**	**PCI-no stent**	**CABG**
All	12.1%	5.8%	72.5%	5.9%	21.6%

For example, 7.2% of all Non-Post MI, Non-Diabetic patients (1st row of Table 28) who initially received a BMS, will experience a revascularization within 1 year and 92.1% will not (1st branch of the decision tree). Of these 7.2% of patients, 70.0% will undergo a PCI with stent (2nd branch of the decision tree), 14.7% will undergo a PCI with no stent (3rd branch of the decision tree), and 15.3% will undergo a CABG (4th branch of the decision tree). All of these probabilities presented in Table 28 are based on the results of the field evaluation.

4.3.2. Cost of Health Resource Utilization

Various sources were used in the analysis to estimate the costs associated with the initial PCI (including stent costs) and the costs associated with revascularizations following the initial PCI.

4.3.3. Initial procedure costs

The model assumes that the costs of the initial PCI hospitalization for the two treatment groups are identical except for cost of the stent(s) implanted. Therefore only the costs of the stents are included in the initial procedure costs. The total stent costs are based on both the mean cost per individual stent and the mean number of stents used in the initial procedure.

Based on price information obtained from DES manufacturers, and the relative market shares of the different DES stents in Ontario, a weighted average cost of DES was derived. This weighted average cost of $1,899 per DES stent was used in the model. The unit cost of BMS was assumed to be $600, based on information obtained from a BMS stent manufacturer. Table 29 shows the mean cost per BMS and DES stent used in the model.[40,41]

Table 29: Cost per stent by stent type

Stent	Cost
BMS	$600
DES	$1899
Difference (DES-BMS)	$1299

The mean number of stents implanted during the initial procedure was derived from the field evaluation and was assumed to be independent of stent type. However, the initial mean number of stents differs for each cohort (i.e. MI and diabetes status, lesion characteristics). In general, the mean number of stents is lower for patients with wide or short lesions and higher for patients with long or narrow lesions.

The initial procedure costs per stent type and cohort, was derived by multiplying the unit cost of each stent by the mean number of stents used during the initial procedure. Table 30 presents the stent unit costs, the mean number of stents implanted, and the total costs of the initial procedure by treatment group and cohort.

Table 30: Mean number of stents and cost of initial procedure

Non-Post MI – Non-Diabetes	Initial Number of Stents	Cost of Initial Procedure*	
Lesion Characteristics		**BMS**	**DES**
All	1.48	$888	$2,811
Long & Narrow Lesions	2.21	$1,326	$4,197
Long	1.78	$1,068	$3,380
Short	1.35	$810	$2,564
Narrow	1.78	$1,068	$3,380
Wide	1.36	$816	$2,583
Long or Narrow	1.70	$1,020	$3,228
Short and Wide	1.27	$762	$2,412
Non-Post MI - Diabetes	**Initial Number of Stents**	**Cost of Initial Procedure***	
Lesion Characteristics		**BMS**	**DES**
All	1.54	$924	$2,924
Long & Narrow Lesions	2.26	$1,356	$4,292
Long	1.89	$1,134	$3,589
Short	1.36	$816	$2,583
Narrow	1.84	$1,104	$3,494
Wide	1.35	$810	$2,564
Long or Narrow	1.77	$1,062	$3,361
Short and Wide	1.25	$750	$2,374
Post MI - Non-Diabetes	**Initial Number of Stents**	**Cost of Initial Procedure***	
Lesion Characteristics		**BMS**	**DES**
All	1.39	$834	$2,640
Long & Narrow Lesions	1.92	$1,152	$3,646
Long	1.57	$942	$2,981
Short	1.31	$786	$2,488
Narrow	1.67	$1,002	$3,171
Wide	1.30	$780	$2,469
Long or Narrow	1.57	$942	$2,981
Short and Wide	1.23	$738	$2,336
Post MI - Diabetes	**Initial Number of Stents**	**Cost of Initial Procedure***	
Lesion Characteristics		**BMS**	**DES**
All	1.42	$852	$2,697

* BMS unit cost $600, DES unit cost $ 1,899.

4.3.4. Revascularization costs

Costs were estimated for the three types of revascularization considered in the model. These were PCI with stent, PCI without stent and CABG. These costs were comprised primarily of the inpatient costs associated with the revascularization procedures. Table 31 presents the revascularizations costs calculated for use in the model. Costs are broken down by hospital costs, physician fees and stent costs.

Table 31: Hospital Cost of Revascularizations

Revascularization	Revascularization Costs			
	Hospital costs	Physician Fees	Stent Costs (unit costs * # of stents)	Total
PCI with stent	$6,048	$1,069	varies	Varies by cohort
PCI with no stent	$6,048	$967	n/a	$7,015
CABG	$15,835	$2,965	n/a	$18,799

The hospital costs for PCI ($6,048 for both with and without stent) were estimated from 519 detailed costing records from London Health Sciences (2003/2004). These costing records were based on patient admissions for elective PCIs with stent implantation. Stent costs were subtracted from the total costs of the 519 records in order to estimate the mean cost of PCI admission net of stent costs. The mean hospital cost for CABG ($15,835) was derived from the Ontario Case Cost Project database.

Physician fees were based on the Ontario Physician Schedule of Benefits and include both inpatient and outpatient related fees. A local cardiologist provided information on the appropriate billing codes associated with CABG and PCI procedures along with outpatient care. Physician fees for both elective and non-elective PCI's were calculated. A weighted average fee based on the proportion of elective PCI's observed in the field evaluation was used. It was assumed that

outpatient care post PCI would include a general practitioner visit and a cardiologist assessment. It was assumed that post CABG care would include a general practitioner visit, assessments from a cardiologist and a vascular surgeon, along with an echocardiogram.

As shown in Table 31 the total revascularization costs related to PCI without stent and CABG was estimated to be $7,111 and, $18,799 respectively. These costs were assumed to be the same for all cohorts and for both treatment groups. The costs associated with PCI with stent(s) were assumed to vary according to cohort and treatment group. This is because the stent costs depend on the mean number of stents used per procedure along with the type of stent(s) (BMS or DES) used in the procedure. Based on data collected in the field evaluation the mean number of stents used in follow-up PCI procedures were varied according to cohort. The proportion of follow-up stents that were DES differed both by cohort and by treatment arm.

Table 32 presents for each cohort and treatment group the mean number of stents used in follow-up PCIs along with the proportion of follow-up stents that were DES by treatment group. In general, the mean number of stents used per procedure was higher for patients with longer and/or narrower lesions. The proportion of follow-up stents that were DES was generally higher in the DES treatment group.

To derive the mean total stent cost for follow-up PCI with stent, a weighted average cost was calculated based on the unit cost per stent (Table 29), the mean number of stents implanted during revascularization (Table 31) and the percentage of stents implanted that were DES and BMS (i.e. Table 32).

For example, in the Non-Post MI, Diabetes All patient cohort (Row 1 of Table 32), the stent cost for the BMS treatment group was calculated as: [0.62*$1,899 + (1-0.62)*$600]*1.56 = $2,194. In this equation, 0.62 and (1-0.62) are the proportion of patients receiving a DES and a BMS during a follow-up PCI procedure. $1,899 and $600 are the respective unit prices of BMS and DES and 1.56 is the mean number of follow-up stents. The total cost of PCI with stent(s) includes the mean

cost of stent(s) along with the hospital cost and physician fees listed in Table 31. The costs of PCI with stent by cohort and treatment group are shown in the last column of Table 32.

Table 32: Mean number of follow-up stents, probability of receiving a DES by initial stent type and cost of PCI with stent by initial stent type

Cohort	Mean Number of Follow-Up Stents	Probability of Receiving a DES During a PCI		Mean Cost of stents		Total Cost of PCI with stent	
Non-Post MI - Diabetes		**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**
Lesion Characteristics							
All	1.56	62%	66%	$2,194	$2,275	$9,311	$9,392
Long & Narrow Lesions	1.80	62%	66%	$2,529	$2,622	$9,646	$9,739
Long	1.60	62%	66%	$2,246	$2,329	$9,363	$9,446
Short	1.53	62%	66%	$2,154	$2,233	$9,271	$9,350
Narrow	1.60	62%	66%	$2,255	$2,338	$9,372	$9,455
Wide	1.52	62%	66%	$2,139	$2,218	$9,256	$9,335
Long or Narrow	1.56	62%	66%	$2,187	$2,268	$9,304	$9,385
Short and Wide	1.55	62%	66%	$2,176	$2,257	$9,293	$9,374
Non-Post MI - Non Diabetes		**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**
Lesion Characteristics							
All	1.47	54%	68%	$1,909	$2,175	$9,026	$9,292
Long & Narrow Lesions	1.83	54%	68%	$2,376	$2,708	$9,493	$9,825
Long	1.60	54%	68%	$2,083	$2,374	$9,200	$9,491
Short	1.35	54%	68%	$1,752	$1,997	$8,869	$9,114
Narrow	1.64	54%	68%	$2,136	$2,434	$9,253	$9,551
Wide	1.32	54%	68%	$1,715	$1,955	$8,832	$9,072
Long or Narrow	1.47	54%	68%	$1,918	$2,186	$9,035	$9,303
Short and Wide	1.28	54%	68%	$1,670	$1,903	$8,787	$9,020
Post MI - Non-Diabetes		**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**
Lesion Characteristics							
All	1.60	52%	66%	$2,043	$2,334	$9,160	$9,451
Long & Narrow Lesions	1.42	52%	66%	$1,813	$2,071	$8,930	$9,188
Long	1.55	52%	66%	$1,976	$2,258	$9,093	$9,375
Short	1.64	52%	66%	$2,096	$2,395	$9,213	$9,512
Narrow	1.52	52%	66%	$1,939	$2,215	$9,056	$9,332
Wide	1.65	52%	66%	$2,109	$2,409	$9,226	$9,526
Long or Narrow	1.60	52%	66%	$2,044	$2,336	$9,161	$9,453
Short and Wide	1.66	52%	66%	$2,112	$2,413	$9,229	$9,530
Post MI - Diabetes		**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**
Lesion Characteristics							
All	1.69	67%	58%	$2,486	$2,289	$9,603	$9,406

4.3.5. Quality of Life

Quality of life was quantified as the expected number of QALYs for each treatment group over the one year time horizon of the model. The expected number of QALYs differed for each clinical pathway in the decision tree.

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

The utility values used to capture these impacts were derived from Arterial Revascularization Therapies Study (ARTS)[42]. In this trial, 1,205 patients were randomly assigned to undergo stent implantation or bypass surgery and were followed for 1 year. The EQ-5D questionnaire was used to estimate mean utility values over time for the trial patients. Table 33 presents the summary EQ5D utility values from this trial following CABG and stent implantation at baseline and at months 1, 6 and 12.

Table 33: EQ-5D utility values observed in the ARTS trial

	baseline		1 month		6 month		12 month	
	Stent	**CABG**	**Stent**	**CABG**	**Stent**	**CABG**	**Stent**	**CABG**
EQ-5D utilities	0.69	0.68	0.84	0.78	0.86	0.86	0.86	0.87

Based on this data, the utility value for anginal symptoms was assumed to be 0.69 (baseline utility value) while the utility value of an otherwise healthy patient was assumed to be 0.86 (i.e. 12 month post stent value from the ARTS study).[42]

Duration of anginal symptoms was approximated by the average waiting time for revascularization procedures as observed in the field evaluation. The mean waiting time by type of revascularization and by cohort is shown in Table 34. In

addition to the waiting time for revascularizations, the model assumes an additional 30 days of anginal symptoms prior to getting on the waiting list.

Table 34: Waiting times by revascularization type and cohort

	Waiting time (days)	
	PCI	**CABG**
Non-Post MI, without diabetes	16.32	21.97
Non-Post MI, diabetes	17.76	15.53
Post MI, without diabetes	12.78	24.46
Post MI, diabetes	8.65	13.10

QALYs were calculated for 6 months post CABG and PCI based upon the utility values reported from ARTS at baseline, 1 month and 6 months for the CABG and stent patient groups respectively. Utility was plotted over time for both CABG and stent with the area under each curve used to estimate the 6 month QALY values. The total QALYs over 6 months post CABG was estimated to be 0.396 while total QALYs over 6 months post PCI was estimated to be 0.412. This compares to the 6 month utility value with no revsacularization of 0.43 (0.86 x ½ year).

Figure 23 graphically represents utility over time for CABG, PCI and no revascularization and Table 35 shows the total number of QALYs over a one-year, estimated by cohort for each clinical pathway. The difference in QALYs for PCI and CABG reflects the difference in utility values over time observed in the ARTS study.[42]

Figure 23: Utilities over time

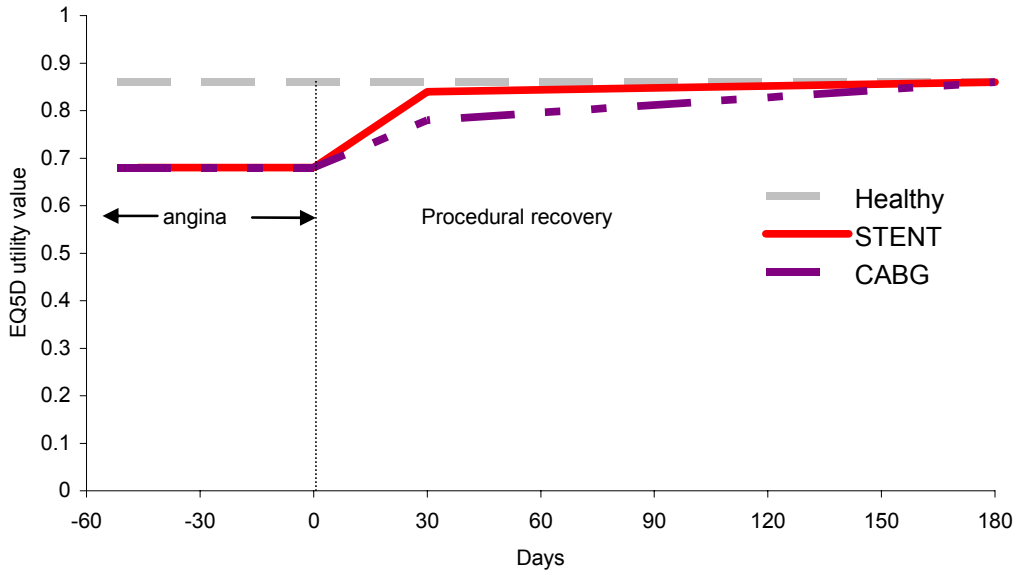


Table 35: QALYs

	One-year QALYs by clinical pathways		
	No revascularization	PCI with or without stent	CABG
Non-Post MI, diabetes	0.860	0.819	0.804
Non-Post MI, without diabetes	0.860	0.820	0.801
Post MI, diabetes	0.860	0.823	0.805
Post MI, without diabetes	0.860	0.822	0.800

4.3.6. Probabilistic Sensitivity Analysis

To reflect uncertainty in the model input parameter values, a probabilistic sensitivity analysis (PSA) was conducted. In this approach, probability distributions are assigned to parameters in the model instead of point estimates. Simulation techniques are used to make random draws from these distributions simultaneously and generate resultant cost and effect estimates for the two treatment strategies. For the PSA, 1000 simulations were conducted.

Table 36 presents the distributions, parameters, and 95% confidence intervals assigned to the input variables in the model. As shown, beta distributions were

assigned to all variables which were bounded by values of 0 and 1 (i.e. utility values, proportion of follow-up stents that were DES). Dirchelet distributions were assigned to variables that were categorical and had more than two categories (e.g. type of revascularization). Other variables were assigned either gamma or normal distributions. As noted previously, the revascularization rates were derived from multivariate regression models specific to the cohort under study. In order to generate probabilistic estimates of revascularization rates, distributions were assigned to all covariates (e.g. age, angina severity) and the population estimates of the covariates in the multivariate models. Correlations between covariates were taken into account when generating the probabilistic estimates of revascularization rates from the regression models.

The probabilistic sensitivity analysis was expressed in two ways. First, cost effectiveness results for all cohorts were re-estimated based on the mean of the expected cost and effect estimates generated from the 1000 simulations. It has been argued that this type of analysis provides a more accurate estimate of expected costs and effects, particularly when models are non-linear <ref>. Secondly, uncertainty is expressed in the form of cost-effectiveness acceptability curves (CEACs). CEACs show the probability that a treatment strategy is cost-effective as a function of societies' willingness to pay for a unit of outcome. In this case the CEACs will show the probability that the DES treatment strategy is cost effective relative to BMS for different levels of willingness to pay for a QALY.

Table 36: Distribution used in the probabilistic sensitivity analysis

Summary of distributions, parameters and resultant 95% Confidence Intervals used for model variables in probabilistic analysis			
Variable	**Distribution**	**Parameters**	**95% CI**
Revascularization Rates	Multivariate Models	varies by cohort	varies by cohort
Type of Revascularization (%CABG,% PCI w stent, %PCI no stent)	Dirichlet	varies by cohort	varies by cohort
Mean number of stents used in initial PCI procedure	Normal	varies by cohort	varies by cohort
Mean number of stents used in follow-up PCI procedure	Normal	varies by cohort	varies by cohort
Proportion of follow-up stents that were DES-BMS patients	Beta	varies by cohort	varies by cohort
Proportion of follow-up stents that were DES-DES patients	Beta	varies by cohort	varies by cohort
Utility value for healthy (no revascularization)	Beta	(α=516, β=84)	(0.83,0.89)
Utility weight applied to patients with anginal symptoms	Beta	(α=481.2, β=118.8)	(0.77,0.83)
Utility weight applied to patients post PCI revascularization	Beta	(α=552, β=48)	(0.89,0.94)
Utility weight applied to patients post CABG revascularization	Beta	(α=574.2, β=25.8)	(0.94,0.97)
Waiting time for revascularization: PCI with stent	Gamma	varies by cohort	varies by cohort
Waiting time for revascularization: PCI no stent	Gamma	varies by cohort	varies by cohort
Waiting time for revascularization: CABG	Gamma	varies by cohort	varies by cohort
Hospitalization Cost for PCI-net of stent costs	Gamma	(1111,6)	(5663,6432)
Hospitalization Cost for CABG-net of stent costs	Gamma	(952,6)	(15462,16207)

4.4. Results

4.4.1. Deterministic Analysis

The results of the deterministic incremental cost-effectiveness analysis are shown in Table 37. This table presents the expected costs, number of revascularizations, and QALYs for each treatment group along with the incremental cost per revascularization avoided and incremental cost per QALY gained. This information is presented for each of the 22 cohorts analyzed.

Based on our primary outcome (cost per QALY gained), results indicate that the incremental cost effectiveness is high for all 22 cohorts. The most favourable cost-effectiveness results are $223,580/QALY (non-post MI diabetes, long and narrow lesions), with least favourable showing BMS being dominant over DES (non-post MI, non diabetes, short and wide). The cohorts with the next most favourable cost-effectiveness results are: non-post MI, diabetes, long lesions ($292,133/QALY); post MI, non-diabetes, long and narrow lesions ($393,923/QALY); post MI, diabetes, all patients ($438,415/QALY); and non-post MI, diabetes, long or narrow lesions ($477,736/QALY).

Based on our secondary outcome (cost per revascularization avoided), the most cost effectiveness result was $9,689/revacularization procedure avoided (non-post MI diabetes, long and narrow lesions), with least favourable showing BMS being dominant over DES (non-post MI, non diabetes, short and wide).

In general the cost-effectiveness of DES was found to be more favourable in patients with diabetes, long lesions and/or narrow lesions.

Table 37: Incremental cost-effectiveness analysis

Non-Post MI - Non Diabetes	Costs		Revascularization Rates		QALYS		Incremental Cost Effectiveness Ratios	
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$1,638	$3,370	0.07	0.05	0.8569	0.8577	95,383	2,221,692
Long & Narrow Lesions	$2,622	$4,882	0.11	0.06	0.8551	0.8574	44,015	975,496
Long	$2,022	$3,875	0.09	0.05	0.8561	0.8580	42,672	988,036
Short	$1,473	$3,123	0.06	0.05	0.8573	0.8577	155,123	3,618,632
Narrow	$2,200	$4,059	0.11	0.06	0.8554	0.8572	43,746	1,009,784
Wide	$1,425	$3,092	0.06	0.05	0.8575	0.8579	161,287	3,768,758
Long or Narrow	$2,009	$3,797	0.10	0.05	0.8559	0.8577	43,834	1,021,211
Short and Wide	$1,295	$2,974	0.05	0.05	0.8578	0.8577	dominated	dominated
Non-Post MI - Diabetes								
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$1,978	$3,632	0.10	0.07	0.8556	0.8571	49,333	1,132,426
Long & Narrow Lesions	$3,537	$4,949	0.21	0.06	0.8511	0.8574	9,689	223,580
Long	$3,082	$4,437	0.19	0.08	0.8519	0.8566	12,677	292,133
Short	$1,518	$3,134	0.07	0.05	0.8571	0.8577	111,650	2,552,321
Narrow	$2,374	$4,123	0.12	0.06	0.8548	0.8575	28,235	648,210
Wide	$1,639	$3,164	0.08	0.06	0.8565	0.8575	66,560	1,525,981
Long or Narrow	$2,556	$4,089	0.14	0.07	0.8538	0.8570	20,788	477,736
Short and Wide	$1,327	$2,910	0.06	0.05	0.8576	0.8578	353,944	8,091,138
Post-MI - Non Diabetes								
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$1,458	$3,041	0.06	0.04	0.8575	0.8584	69,696	1,688,786
Long & Narrow Lesions	$2,591	$4,173	0.16	0.06	0.8537	0.8577	15,640	393,923
Long	$1,787	$3,297	0.08	0.03	0.8566	0.8588	29,625	705,250
Short	$1,277	$2,923	0.05	0.04	0.8580	0.8583	259,855	6,356,201
Narrow	$1,586	$3,768	0.06	0.06	0.8575	0.8576	4,306,204	106,246,636
Wide	$1,357	$2,773	0.05	0.03	0.8577	0.8589	52,026	1,253,708
Long or Narrow	$1,719	$3,489	0.08	0.05	0.8569	0.8580	66,230	1,586,259
Short and Wide	$1,193	$2,628	0.04	0.03	0.8582	0.8589	85,228	2,087,910
Post-MI - Diabetes								
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$2,237	$3,356	0.12	0.06	0.8551	0.8577	17,711	438,415

4.4.2. Probabilistic Sensitivity Analysis (PSA)

Cost effectiveness results by cohort using PSA are presented in Table 38. As shown, the mean probabilistic cost-effectiveness results are very similar to the deterministic results previously presented. The cohorts with the most favourable cost-effectiveness are: non-post MI, diabetes, long and narrow lesions ($194,276/QALY); non-post MI, diabetes, long lesions ($274,002/QALY); post MI, non-diabetic, long and narrow lesions ($273,498/QALY); post MI, diabetes, all patients ($429,035/QALY); and non-post MI, diabetes, long or narrow lesions ($465,438/QALY). The general conclusions of mean cost-effectiveness results do not change using the probabilistic results.

The cost effectiveness acceptability curves for the 5 cohorts with the most favourable cost-effectiveness results are presented in Figures 24 and 25. As shown in Figure 24, if societies' willingness to pay for a QALY is $100,000, the probability that DES is cost-effective is 26% in the non post MI, diabetes, long and narrow lesion cohort. The probability that DES is cost-effective at this willingness to pay value is less than 15% in all other cohorts.

Table 38: Probabilistic incremental cost-effectiveness results

Non-Post MI - Non Diabetes	Costs		Revascularization Rates		QALYS		Incremental Cost Effectiveness Ratios	
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$1,638	$3,375	0.07	0.05	0.8561	0.8569	97,832	2,275,668
Long & Narrow Lesions	$2,691	$4,906	0.12	0.06	0.8541	0.8566	40,384	893,610
Long	$2,033	$3,887	0.09	0.05	0.8571	0.8590	42,616	982,469
Short	$1,473	$3,125	0.06	0.05	0.8566	0.8570	159,533	3,731,167
Narrow	$2,211	$4,067	0.11	0.07	0.8550	0.8568	43,448	1,004,577
Wide	$1,425	$3,101	0.06	0.05	0.8580	0.8584	172,933	4,020,399
Long or Narrow	$2,019	$3,800	0.10	0.05	0.8553	0.8571	42,797	995,367
Short and Wide	$1,302	$2,974	0.05	0.05	0.8576	0.8575	dominated	dominated
Non-Post MI - Diabetes								
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$1,978	$3,643	0.10	0.07	0.8556	0.8570	51,214	1,170,050
Long & Narrow Lesions	$3,672	$4,978	0.22	0.06	0.8509	0.8576	8,405	194,276
Long	$3,133	$4,449	0.19	0.08	0.8519	0.8567	11,943	274,002
Short	$1,536	$3,145	0.07	0.05	0.8569	0.8576	105,641	2,421,431
Narrow	$2,434	$4,141	0.12	0.06	0.8549	0.8577	25,891	593,503
Wide	$1,649	$3,171	0.08	0.06	0.8560	0.8570	65,174	1,500,389
Long or Narrow	$2,578	$4,097	0.14	0.07	0.8528	0.8560	20,232	465,438
Short and Wide	$1,348	$2,925	0.06	0.05	0.8576	0.8578	323,016	7,163,108
Post-MI - Non Diabetes								
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$1,464	$3,051	0.06	0.04	0.8579	0.8588	71,189	1,720,737
Long & Narrow Lesions	$2,808	$4,174	0.18	0.06	0.8524	0.8574	10,904	273,498
Long	$1,809	$3,323	0.08	0.03	0.8564	0.8585	29,896	708,163
Short	$1,282	$2,941	0.05	0.04	0.8578	0.8580	320,322	7,857,601
Narrow	$1,592	$3,787	0.06	0.06	0.8584	0.8584	dominated	dominated
Wide	$1,370	$2,796	0.06	0.03	0.8564	0.8575	54,184	1,309,047
Long or Narrow	$1,834	$3,604	0.09	0.06	0.8560	0.8571	65,632	1,569,126
Short and Wide	$1,263	$2,694	0.05	0.03	0.8580	0.8587	83,457	2,045,644
Post-MI - Diabetes								
Lesion Characteristics	**BMS**	**DES**	**BMS**	**DES**	**BMS**	**DES**	**$/Revasc**	**$/QALY**
All	$2,336	$3,441	0.13	0.07	0.8560	0.8586	17,243	429,035

Figure 24: Cost-effectiveness acceptability curves for non post MI, diabetes: Long and narrow lesions, long lesions, long or narrow lesions cohorts

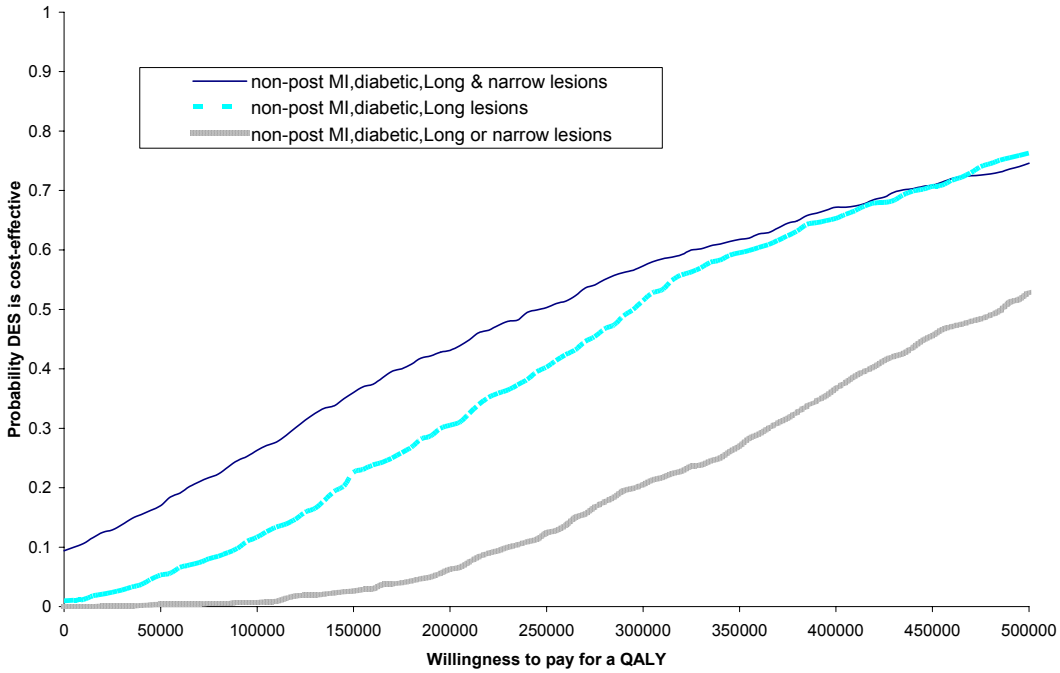
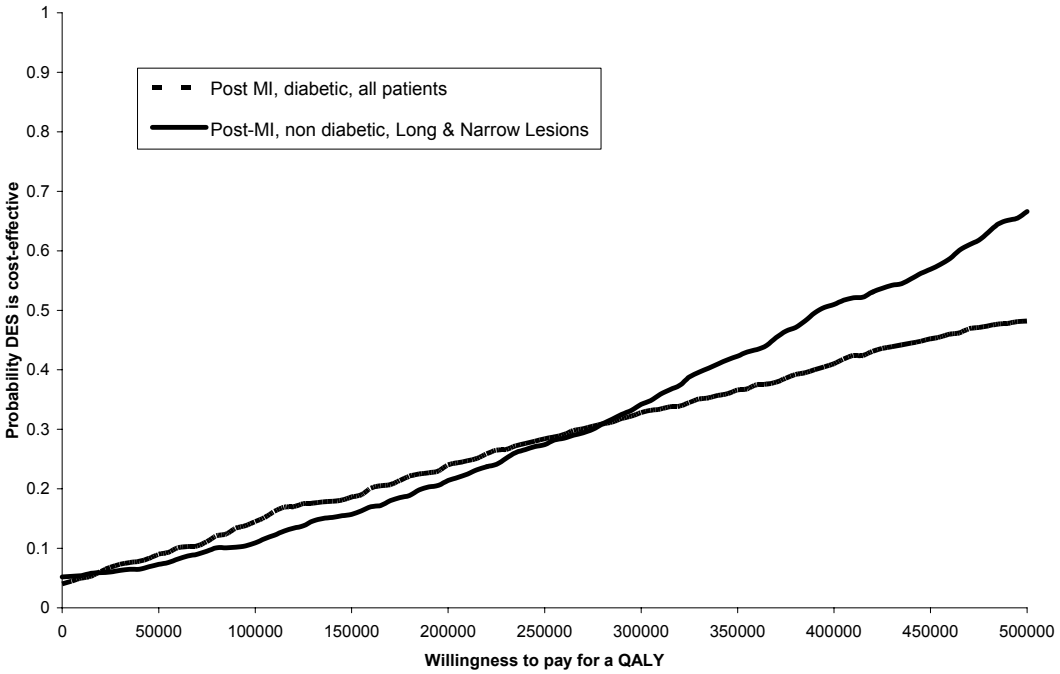


Figure 25: Cost-effectiveness acceptability curves for: post MI, diabetes, all patients and post MI, non-diabetes, long and narrow lesions cohorts



4.5. Discussion

Based upon our primary cost-effectiveness outcome (cost/QALY) the cost-effectiveness of Drug Eluting Stents is high for all cohorts investigated, the most favorable cost effectiveness being $223,580 per QALY gained. The primary strength of the current economic analysis is that revascularization rates and other key model input variables are based upon a large sample of Ontario specific "real world" data. Other published economic analyses of drug eluting and bare metal stents are mostly based upon clinical trial data which may not reflect the situation observed in the real world.

Comparisons with other economic studies are difficult as most of them have used clinical trial data. In addition, not all economic evaluations considered quality of life as an outcome measure. Finally, some of the published economic analyses present multiple cost-effectiveness results based risk factors or type of DES.

In order to facilitate comparison of our cost-effectiveness results with other studies, it is helpful to use the results from the non-post MI, diabetic, long & narrow lesion cohort as a reference point. The absolute difference in revascularization rates observed in this cohort was 15% which is similar to clinical trial findings. The incremental cost effectiveness of BMS versus DES was estimated to be $223,580 per QALY gained and $9,689 per revascularization avoided.

In another Ontario evaluation of the cost-effectiveness of DES versus BMS conducted by CCOHTA, the authors used a one-year decision tree to simulate the clinical outcomes and the use of resources associated with DES and BMS.[43] Clinical rates were derived from a meta-analysis of randomized clinical trial of sirolimus (pooled) and paclitaxel (pooled) to estimate the incremental cost-effectiveness of sirolimus versus BMS and paclitaxel versus BMS. Taking as a reference the economic analysis of sirolimus in which a 15% difference rate in TLR was assumed between DES and BMS (i.e. similar to our non-post MI, diabetic, long & narrow lesion cohort), our results are similar to this CCOHTA

report which indicated that the incremental cost per TLR avoided was $12,527. In contrast, our cost-effectiveness ratio was $9,689 per TVRa avoided. Although the CCOHTA report used TLR as primary endpoint and our study TVRa, these results showed that our study results are comparable with CCOHTA results when using a similar difference in event rates.[43]

Our study results are also comparable with the economic evaluation conducted by AETMIS.[44] In this economic report, administrative databases (RAMQ and MedEcho) were used to determine the revascularization rates following the use of BMS. The rates of revascularization following DES were derived from a meta-analysis of randomized clinical trials and the model considered a rate of revascularization of 12.8% for BMS and 3.3% for DES. Results indicated that at a 20% use of DES (i.e. DES used only for high risk patients defined as diabetes), the incremental cost was calculated at $7,200 per procedure avoided. This is again similar to the result of our reference cohort (i.e. $9,689 per revascularization avoided when using a 15% difference in rates of revascularization rates).[44]

In the United Kingdom, Bagust *et al.* in 2004 used a model similar to ours to evaluate the cost-effectiveness of DES for a number of cohorts based upon revascularization risk factors.[18] BMS revascularization rates were based upon data from a cardiac patient registry in Liverpool U.K. Relative risk of revascularization with DES was based on pooled clinical trial data. The cost effectiveness of DES in a cohort of patients in which the absolute difference in revascularization rates was 14% was £87,900/QALY. [18] This finding is very similar to the result our reference cohort after conversion to Canadian dollars ($223,580/QALY vs. $181,074/QALY).

In their economic analysis of DES, Shrive *et al*. in 2005 used data from the Alberta Provincial Project for Outcome Assessment in Coronary Heart (Approach) to estimate event rates for bare metal stents, costs associated with clinical events and utility values associated with clinical events.[45] The relative risk of revascularization with DES was derived from pooling of clinical trial data.

The absolute difference in restenosis rates used in the base case was 11%. The authors estimated the cost-effectiveness of DES to be $58,721. This is substantially lower than our findings; however there were some key differences between the assumptions made in the 2 analyses. First, Shrive et al assumed that the quality of life impact of restenosis would last for a full year in duration. We assumed that the majority of the quality of life impact of revascularizations occurs in the 1 to 2 months occurring from the start of anginal symptoms to the time of procedure (waiting time plus 30 days). In addition, Shrive et al incorporated mortality in their model by assuming patients post PCI, CABG, and catheterization without a procedure have increased mortality than similar patients without these procedures.[45]

Finally a one-year economic evaluation conducted in Australia considered a differential of 15% between the revascularization rates concluded that the incremental costs per TLR avoided was $4,233 (Canadian $).[46] However, as mentioned by the authors, resource utilization was derived from SIRIUS and TAXUS IV randomized clinical trials and may not be reflective of the real practice.[46]

This short overview of the economic evaluations of DES and BMS indicates that when we use a similar differential rate of revascularization between BMS and DES (i.e. 15%) our results are aligned with 4 out of these 5 studies. Our results differ from the study conducted in Alberta due to the assumptions inherent to this model (i.e. mortality, utility gained).[45]

One of the strengths of our study is the use of revascularization rates derived from the CCN database and not from the clinical literature. In addition, our field evaluation allowed us to stratify the patients according to MI and diabetes status, and lesion characteristics. This enabled us to conduct a very detailed economic assessment in which revascularization rates and other key parameters (e.g. types of revascularization, mean number of stents) were specific to each of the 22 cohorts evaluated in this economic study. For almost all cohorts, we found a much lower absolute difference in revascularization rates compared to those

found in clinical trials. To account for uncertainty a comprehensive probabilistic sensitivity analysis was conducted and indicated that results were robust under alternative assumptions in the model.

5. CONCLUSIONS

The studies identified in the systematic literature review demonstrate that DES reduces revascularization rates compared to BMS in patients with single-de novo lesions. No apparent differences in mortality, acute MI rate or stent thrombosis rates between DES and BMS were found in the meta-analysis of the trials.

The results from the field evaluation indicate that DES reduces predicted revascularization rates at 1 year compared to BMS in some but not all patient cohorts. In non Post MI patients, DES appears to be most effective in reducing the need for revascularization in patients with long *or* narrow lesions. This benefit was magnified in patients with diabetes. DES also appears to be effective in Post MI patients. However, further data collection is required in order to confirm the benefit of DES by lesion type in this patient cohort. DES as compared to BMS does not appear to provide a reduction in revascularization rates in patients with short and wide lesions, in patients with and without diabetes.

The economic analysis incorporating “real-world” data from over 9,000 patients in Ontario found that the most favourable cost-effectiveness ratio for DES compared to BMS was $223,580/QALY in patients in non Post MI, diabetes patients with long and narrow lesions. The absolute difference of approximately 15% was found in revascularization rates between the two interventions in this patient population.

6. REFERENCES

1. George CJ, Baim DS, Brinker JA, Fischman DL, Goldberg S, Holubkov R et al. One-year follow-up of the Stent Restenosis (STRESS I) Study. American Journal of Cardiology 1998;81(7):860-865.

2. Macaya C, Serruys PW, Ruygrok P, Suryapranata H, Mast G, Klugmann S et al. Continued benefit of coronary stenting versus balloon angioplasty: one-year clinical follow-up of Benestent trial. Benestent Study Group. Journal of the American College of Cardiology 1996;27(2):255-261.

3. 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.

4. Liu X, Huang Y, Hanet C, Vandormael M, Legrand V, Dens J et al. Study of antirestenosis with the BiodivYsio dexamethasone-eluting stent (STRIDE): a first-in-human multicenter pilot trial. Catheterization & Cardiovascular Interventions 2003;60(2):172-178.

5. Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation 2004;109(18):2168-2171.

6. Honda H, Meguro T, Takizawa K, Isoyama S. Use of everolimus-eluting stent with a bioresorbable polymer coating for treatment of recurrent in-stent restenosis. J Invasive Cardiol 2005;17(2):112-115.

7. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. New England Journal of Medicine 2002;346(23):1773-1780.

8. Holmes DR, Jr., Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109(5):634-640.

9. 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.[see comment]. New England Journal of Medicine 2003;349(14):1315-1323.

10. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). Journal of the American College of Cardiology 2004;43(6):1110-1115.

11. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362(9390):1093-1099.

12. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108(7):788-794.

13. Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. New England Journal of Medicine 2003;348(16):1537-1545.

14. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. New England Journal of Medicine 2004;350(3):221-231.

15. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109(2):190-195.

16. Regar E, Serruys PW, Bode C, Holubarsch C, Guermonprez JL, Wijns W et al. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106(15):1949-1956.

17. van Hout BA, Serruys PW, Lemos PA, van den Brand MJ, van Es GA, Lindeboom WK et al. One year cost effectiveness of sirolimus eluting stents compared with bare metal stents in the treatment of single native de

novo coronary lesions: an analysis from the RAVEL trial. Heart 2005;91(4):507-512.

18. Bagust A, Grayson AD, Palmer ND, Perry RA, Walley T. Cost-effectiveness of drug-eluting coronary artery stenting in a UK setting: cost-utility study. Heart 2006;92(1):68-74. Epub 2005 Apr 14.

19. Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). Lancet 2005;366(9489):921-929.

20. Medical advisory secretariat and Cohen E. Review of drug-eluting coronary stents. Toronto, Ontario, Canada: Ontario Ministry of Health and Long-term Care; 2003 Jan 7. pp. 23.

21. Working group on Drug Eluting Stents and Cohen E (chair). Drug eluting stents. Report on initial utilization strategy: final report and recommendations. Toronto, Ontario, Canada: Cardiac Care Network of Ontario (CCN); 2002 Dec. pp. 15. Available from: http://www.ccn.on.ca/index.cfm?fuseaction=ts&tm=23&ts=163&tsb=0

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-188.

23. Abizaid A, Costa MA, Blanchard D, Albertal M, Eltchaninoff H, Guagliumi G et al. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Insights from the RAVEL Trial. European Heart Journal 2004;25(2):107-112.

24. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 2004;109(19):2273-2278.

25. Sawhney N, Moses JW, Leon MB, Kuntz RE, Popma JJ, Bachinsky W et al. Treatment of left anterior descending coronary artery disease with sirolimus-eluting stents. Circulation 2004;110(4):374-379.

26. Gershlick A, De S, I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free

coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. Circulation 2004;109(4):487-493.

27. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107(1):38-42.

28. 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.

29. Weissman NJ, Koglin J, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT et al. Polymer-based paclitaxel-eluting stents reduce in-stent neointimal tissue proliferation: a serial volumetric intravascular ultrasound analysis from the TAXUS-IV trial. J Am Coll Cardiol 2005;45(8):1201-1205.

30. Pache J, Dibra A, Mehilli J, Dirschinger J, Schomig A, Kastrati A. Drug-eluting stents compared with thin-strut bare stents for the reduction of restenosis: a prospective, randomized trial. Eur Heart J 2005;26(13):1262-1268.

31. Fajadet J, Morice MC, Bode C, Barragan P, Serruys PW, Wijns W et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. Circulation 2005;111(8):1040-1044.

32. Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. J Am Coll Cardiol 2005;45(2):308-311.

33. Costa RA, Lansky AJ, Mintz GS, Mehran R, Tsuchiya Y, Negoita M et al. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). Am J Cardiol 2005;95(1):113-116.

34. Trypuc J. The CCN story: Ten years 1990 - 2000. Toronto, Ontario, Canada: Cardiac Care Network of Ontario; 2001 Apr. pp. 28. Available from: http://www.ccn.on.ca/index.cfm?fuseaction=tm&tm=25&ts=0&tsb=0

35. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, III, Loop FD et al. Guidelines for percutaneous transluminal coronary angioplasty. A

report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation 1988;78(2):486-502.

36. Ellis SG, Vandormael MG, Cowley MJ, DiSciascio G, Deligonul U, Topol EJ et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. Circulation 1990;82(4):1193-1202.

37. Campeau L. Letter: Grading of angina pectoris. Circulation 1976;54(3):522-523.

38. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. Control Clin Trials 2003;24(6):682-701.

39. Marzocchi A, Piovaccari G, Manari A, Aurier E, Benassi A, Saia F et al. Comparison of effectiveness of sirolimus-eluting stents versus bare metal stents for percutaneous coronary intervention in patients at high risk for coronary restenosis or clinical adverse events. Am J Cardiol 2005;95(12):1409-1414.

40. Viminitz M. Personal communication with Bowen J. Average selling price of Cypher™ stents in Canada over past year. 24 Jun 2005.

41. Spears K. Personal communication with Bowen J. Average selling price of TAXUS® and bare metal stents over the past year. 4 Jul 2005.

42. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344(15):1117-1124.

43. Mittmann N, Brown A, Seung SJ, Coyle D, Cohen E, Brophy J, and Title L. Economic evaluation of drug eluting stents. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2005. Report No. Technology Report no 53. Available from: http://www.ccohta.ca/

44. Brophy J and Erickson L. An economic analysis of drug eluting coronary stents: a Quebec perspective. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS); 2004. Report No. AETMIS 04-04. Available from: http://www.aetmis.gouv.qc.ca/

45. Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA. Economic evaluation of sirolimus-eluting stents. CMAJ 2005;172(3):345-351.

46. Medical Services Advisory Committee. Drug-eluting stents. Canberra: Medical Services Advisory Committee (MSAC); 2005. Available from: http://www.msac.gov.au/reports.htm

6. APPENDICES

APPENDIX I: LITERATURE SEARCH STRATEGY

Database: Ovid MEDLINE(R) <1966 to November Week 2 2004>
Search Strategy:
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1 Angioplasty, Transluminal, Percutaneous Coronary/ (15748)
2 exp coronary stenosis/ (2968)
3 coronary.mp. (170991)
4 stenosis.mp. (64612)
5 restenosis.mp. (9139)
6 revascularization.mp. (17663)
7 angioplasty.mp. (25331)
8 3 and 4 (13611)
9 3 and 5 (4941)
10 3 and 6 (9333)
11 3 and 7 (14598)
12 8 or 9 or 10 or 11 (32078)
13 PTCA.mp. (5437)
14 PCI.mp. (2174)
15 1 or 2 or 12 or 13 or 14 (40835)
16 stents/ (19462)
17 stent$.mp. (26269)
18 15 and 17 (7104)
19 eluting stent$.mp. (418)
20 sirolimus/ (3244)
21 sirolimus.mp. (3399)
22 rapamycin.mp. (3134)
23 cypher.mp. (39)
24 20 or 21 or 22 or 23 (4458)
25 paclitaxel/ (8949)
26 paclitaxel.mp. (10210)
27 taxus.mp. (484)
28 25 or 26 or 27 (10408)
29 19 or 24 or 28 (14928)
30 18 and 29 (440)
31 from 30 keep 1-440 (440)
32 limit 31 to yr=1990 - 2004 (440)
33 from 32 keep 1-440 (440)

Database: EMBASE <1980 to 2004 Week 47>
Search Strategy:
---

1 Angioplasty, Transluminal, Percutaneous Coronary/ (12285)
2 exp coronary stenosis/ (10359)
3 coronary.mp. (139261)
4 stenosis.mp. (49841)
5 restenosis.mp. (10578)
6 revascularization.mp. (16970)
7 angioplasty.mp. (24642)
8 3 and 4 (12056)
9 3 and 5 (5400)
10 3 and 6 (8726)
11 3 and 7 (13924)
12 8 or 9 or 10 or 11 (29663)
13 PTCA.mp. (5118)
14 PCI.mp. (2325)
15 1 or 2 or 12 or 13 or 14 (39868)
16 stents/ (13768)
17 stent$.mp. (23606)
18 15 and 17 (6055)
19 eluting stent$.mp. (458)
20 sirolimus/ (5805)
21 sirolimus.mp. (1089)
22 rapamycin.mp. (6210)
23 cypher.mp. (53)
24 20 or 21 or 22 or 23 (6252)
25 paclitaxel/ (6510)
26 paclitaxel.mp. (10602)
27 taxus.mp. (580)
28 25 or 26 or 27 (11013)
29 19 or 24 or 28 (17051)
30 18 and 29 (421)
31 [from 30 keep 1-440] (0)
32 limit 31 to yr=1990-2004 (0)
33 [from 32 keep 1-440] (0)
34 percutaneous transluminal angioplasty/ or exp percutaneous coronary intervention/ (21697)
35 34 or 2 or 12 or 13 or 14 (46569)
36 18 and 35 (6055)
37 29 and 36 (421)
38 30 not 37 (0)
39 30 (421)
40 limit 39 to yr=1990 - 2004 (420)
41 from 40 keep 1-420 (420)

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to December Week 2 2004>
Search Strategy:
---
1 Angioplasty, Transluminal, Percutaneous Coronary/ (1063)
2 exp coronary disease/ (12491)
3 ((stenosis or restenosis or angioplasty or revasculari?ation) and coronary).mp. (1090)
4 PTCA.mp. (203)
5 PCI.mp. (125)
6 1 or 2 or 3 or 4 or 5 (13206)
7 Stents/ (880)
8 stent$.mp. (1066)
9 7 or 8 (1066)
10 6 and 9 (461)
11 eluting stent$.mp. (68)
12 sirolimus.mp. (43)
13 rapamycin.mp. (12)
14 cypher.mp. (6)
15 12 or 13 or 14 (55)
16 Paclitaxel/ (232)
17 paclitaxel.mp. (268)
18 taxus.mp. (10)
19 16 or 17 or 18 (269)
20 11 or 15 or 19 (359)
21 10 and 20 (50)
22 from 21 keep 1-50 (50)

CDSR, ACP Journal Club, DARE, CCTR

Database: CDSR, ACP Journal Club, DARE, CCTR
Search Strategy:
---
1 Angioplasty, Transluminal, Percutaneous Coronary/ (1386)
2 exp coronary disease/ (7420)
3 ((stenosis or restenosis or angioplasty or revasculari?ation) and coronary).mp. (4071)
4 PTCA.mp. (962)
5 PCI.mp. (219)
6 1 or 2 or 3 or 4 or 5 (9901)
7 Stents/ (823)
8 stent$.mp. (1623)
9 7 or 8 (1623)
10 6 and 9 (904)
11 eluting stent$.mp. (32)
12 sirolimus.mp. (256)
13 rapamycin.mp. (51)
14 cypher.mp. (1)
15 12 or 13 or 14 (263)
16 Paclitaxel/ (361)
17 paclitaxel.mp. (732)
18 taxus.mp. (9)
19 16 or 17 or 18 (733)
20 11 or 15 or 19 (1000)
21 10 and 20 (32)
22 from 21 keep 1-32 (32)

APPENDIX II: LITERATURE SCREENING & DATA ABSTRACTION FORMS

DES Full Text Screening Form

Refman #:
Authors:
Title:
Citation:
Year:
Study Acronym:

Were patients randomly assigned to treatment with DES vs. BMS?

Yes (include) No (exclude)

Is the active drug in the study either sirolimus (rapamycin) or paclitaxel?

Yes (include) No (exclude) Drug Used «Drug»

Is this paper the primary report of the clinical trial data?

Yes (include) Sub-analysis (include) No (exclude)

Does the article report one or more of the following outcome measures?

Acute MI (include) Stroke (include) Death (include)

Major Adverse Cardiac Events (MACE) Composite (include)

Clinical Revascularization Rates

Target Lesion Revascularization (TLR)
PTCA (include)
CABG (include)

Target Vessel Revascularization (TVR)
PTCA (include)
CABG (include)

Papers reporting outcomes other than one of the above (exclude)

List other outcome measures studied

1. _____ 2. _____
3. _____ 4. _____
5. _____ 6. _____

Reviewer Initials: _____ Date: _____ dd/mmm/yyyy

DES study data abstraction form

Refman #: «Refman_ID»
Authors: «Author»
Title: «Title»
Citation: «Citation»
Year: «Pub_Year»
Study Acronym: «Trial»

Reviewer Initials: _____ Date: _____
dd/mmm/yyyy

Study Information / Methods:

Anti-proliferative drug: «Drug» Report Type:

«Report_Type»

Countries: _____

Number of Centres _____

Blinding: _____

Method of Randomization: _____

Patient Recruitment Period: Start: _____ End: _____

Patient Characteristics (inclusion criteria):

_____
_____

Lesion Characteristics (inclusion criteria):

_____
_____
_____

Stent Characteristics:
Name of Stent: _____ Polymer based: Yes No
Stent Lengths (mm): _____ Stent Diameters (mm): _____

Exclusion Criteria:

_____
_____
_____
_____

Anti coagulant/Antiplatelet Therapy

_____
_____

Primary Outcome Measure(s):

1. _____
2. _____

Primary Outcome Measure follow-up time(s) (days or months): _____

Secondary Outcome Measures (specify time intervals – days or months):

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

Target vessel failure definition:

_____

Target lesion revascularization criteria/definition:

_____
_____
_____

Criteria for revascularization:

Clinical Angiographic Both Not Specified

Methods: Other Notes:

_____

_____

_____

_____

_____

Patient Characteristics

	DES	BMS
Baseline Characteristics		
No. patients randomized		
No. patients treated		
Mean age (years) ± sd		
Males n (%)		
Current Smoker n (%)		
Previous Smoker n (%)		
Diabetes mellitus (DM) n (%)		
DM requiring oral therapy n (%)		
DM requiring insulin n (%)		
Hyperlipidemia n (%)		
Hypertension n (%)		
COPD n (%)		
Congestive Heart Failure (CHF) n (%)		
Obesity n (%)		
Previous MI n (%)		
Previous Revascularization n (%)		
Previous CABG n (%)		
Previous PCI n (%)		
Left Ventricular Ejection Fraction (LVEF) mean % ± sd		
Presenting Condition		
Angina Pectoris n (%)		
Stable Angina (CCS or NYHA or Other) n (%)		
CCS I n (%)		
CCS II n (%)		
CCS III n (%)		
CCS IV n (%)		
Unstable Angina (Braunwald) n (%)		
Class I n (%)		
Class II n (%)		
Class III n (%)		
Silent Ischemia n (%)		
Post Myocardial Infarction n (%)		
Target Artery n (%)		
LM		
LAD		
RCA		
CIRC		

	DES	BMS
SVG		
Ramus		
Diseased vessels n (%)		
Multivessel disease n (%)		
1		
2		
3		
4		
Lesion Characteristics		
Diameter of reference vessel (mm) (mean ± sd)		
Length of lesion (mm) (mean ± sd)		
Vessel lesion diameter threshold for analysis (mm)		
% above threshold		
% below threshold		
Vessel lesion length threshold for analysis (mm)		
% above threshold		
% below threshold		
ACC-AHA class n (%)		
A		
B1		
B2		
C		
Procedural information		
Number of stents used/lesion (mean ± sd)		
Length of hospital stay (days) (mean ± sd)		
Multiple vessels n (%)		

Notes:

Clinical Outcomes

	DES	BMS
Follow-up time (days or months)		
Death n (%)		
Cardiac Death n (%)		
Myocardial infarction n (%)		
Q-wave n (%)		
Non-Q wave n (%)		
Target-lesion revascularization (TLR) n (%)		
CABG n (%)		
PTCA n (%)		
Any Major Adverse Cardiac Event (MACE) n (%)		
Target-vessel failure (TVF) n (%)		
Target-vessel revascularization (TVR) n (%)		
CABG n (%)		
PTCA n (%)		
Target-vessel revascularization (TVR) n (%) (non TLR)		
Stent thrombosis n (%)		
Follow-up time (days or months)		
Death n (%)		
Cardiac Death n (%)		
Myocardial infarction n (%)		
Q-wave n (%)		
Non-Q wave n (%)		
Target-lesion revascularization (TLR) n (%)		
CABG n (%)		
PTCA n (%)		
Any Major Adverse Cardiac Event (MACE) n (%)		
Target-vessel failure (TVF) n (%)		
Target-vessel revascularization (TVR) n (%)		
CABG n (%)		
PTCA n (%)		

	DES	BMS
Target-vessel revascularization (TVR) n (%) (non TLR)		
Stent thrombosis n (%)		
Follow-up time (days or months)		
Death n (%)		
Cardiac Death n (%)		
Myocardial infarction n (%)		
Q-wave n (%)		
Non-Q wave n (%)		
Target-lesion revascularization (TLR) n (%)		
CABG n (%)		
PTCA n (%)		
Any Major Adverse Cardiac Event (MACE) n (%)		
Target-vessel failure (TVF) n (%)		
Target-vessel revascularization (TVR) n (%)		
CABG n (%)		
PTCA n (%)		
Target-vessel revascularization (TVR) n (%) (non TLR)		
Stent thrombosis n (%)		

Notes:

_____

_____

_____

_____

_____

_____

_____

APPENDIX III: SUMMARY OF DATABASE SOURCE FOR CITATIONS OBTAINED FROM LITERATURE SEARCH OF ELECTRONIC DATABASES

Initial number of references obtained from each database

MEDLINE	440
MEDLINE duplicate citations	42
MEDLINE final number of citations	398
EMBASE	420
EMBASE duplicate citations	1
MEDLINE final number of citations	419
CINAHL	50
CDSR, ACP Journal Club, DARE, CCTR	32
Total Number of References	899
Total Number of Unique References	574

Citation Source

	Subtotal	**Cumulative**
MEDLINE only	125	125
EMBASE only	148	273
CINAHL only	16	289
COCHRANE only	5	294
MEDLINE, EMBASE	229	523
MEDLINE, CINAHL	7	530
MEDLINE, COCHRANE	1	531
EMBASE, CINAHL	6	539
MEDLINE, EMBASE, CINAHL	11	550
MEDLINE, EMBASE, COCHRANE	15	565
MEDLINE, CINAHL, COCHRANE	1	566
MEDLINE, EMBASE, CINAHL, COCHRANE	9	574

APPENDIX IV: LITERATURE INCLUDED IN FULL TEXT SCREENING AND REVIEW

Full text Screening

Abizaid A, Costa MA, Blanchard D, Albertal M, Eltchaninoff H, Guagliumi G et al. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Insights from the RAVEL Trial.[see comment]. European Heart Journal 2004;25(2):107-112.

Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108(7):788-794.

Gershlick A, De S, I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. Circulation 2004;109(4):487-493.

Grube E, Lansky A, Hauptmann KE, Di Mario C, Di Sciascio G, Colombo A et al. High-dose 7-hexanoyltaxol-eluting stent with polymer sleeves for coronary revascularization: one-year results from the SCORE randomized trial. Journal of the American College of Cardiology 2004;44(7):1368-1372.

Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation 2004;109(18):2168-2171.

Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107(1):38-42.

Holmes DR, Jr., Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109(5):634-640.

Hong MK, Mintz GS, Lee CW, Song JM, Han KH, Kang DH et al. Paclitaxel coating reduces in-stent intimal hyperplasia in human coronary arteries: a serial volumetric intravascular ultrasound analysis from the Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT). Circulation 2003;107(4):517-520.

Kataoka T, Grube E, Honda Y, Morino Y, Hur SH, Bonneau HN et al. 7-hexanoyltaxol-eluting stent for prevention of neointimal growth: an intravascular ultrasound analysis from the Study to COmpare REstenosis rate between QueST and QuaDS-QP2 (SCORE). Circulation 2002;106(14):1788-1793.

Lansky AJ, Costa RA, Mintz GS, Tsuchiya Y, Midei M, Cox DA et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. Circulation 2004;109(16):1948-1954.

Mintz GS, Tinana A, Hong MK, Lee CW, Kim JJ, Fearnot NE et al. Impact of preinterventional arterial remodeling on neointimal hyperplasia after implantation of (non-polymer-encapsulated) paclitaxel-coated stents: a serial volumetric intravascular ultrasound analysis from the ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT). Circulation 2003;108(11):1295-1298.

Morice M-C, Serruys PW, Sousa JE. Erratum: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization (New England Journal of Medicine (2002) 346 (1773-1780)). N Engl J Med 2002;347(16):1285.

Morice M-C. Sirolimus-eluting stents for coronary revascularization. Cardiology Review 2003;20(5):36-39.

Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. New England Journal of Medicine 2002;346(23):1773-1780.

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. New England Journal of Medicine 2003;349(14):1315-1323.

Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. Circulation 2004;109(19):2273-2278.

Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. New England Journal of Medicine 2003;348(16):1537-1545.

Regar E, Serruys PW, Bode C, Holubarsch C, Guermonprez JL, Wijns W et al. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106(15):1949-1956.

Regar E, Sousa J, Morice MC, Fajadet J, Perin M, Ban HE et al. Sirolimus-coated coronary stents prevent restenosis in diabetics. A subgroup analysis of the randomised, multi-centre RAVEL study. Z Kardiol 2002;91(Suppl 1):I/65.

Saia F, Lemos PA, Sianos G, Degertekin M, Lee C-H, Arampatzis CA et al. Effectiveness of sirolimus-eluting stent implantation for recurrent in-stent restenosis after brachytherapy. Am J Cardiol 2003;92(2):200-203.

Sawhney N, Moses JW, Leon MB, Kuntz RE, Popma JJ, Bachinsky W et al. Treatment of left anterior descending coronary artery disease with sirolimus-eluting stents. Circulation 2004;110(4):374-379.

Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). Journal of the American College of Cardiology 2004;43(6):1110-1115.

Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362(9390):1093-1099.

Serruys PW, Ormiston JA, Sianos G, Sousa JE, Grube E, den Heijer P et al. Actinomycin-eluting stent for coronary revascularization: a randomized feasibility and safety study: the ACTION trial. Journal of the American College of Cardiology 2004;44(7):1363-1367.

Serruys PW, Degertekin M, Tanabe K, Russell ME, Guagliumi G, Webb J et al. Vascular responses at proximal and distal edges of paclitaxel-eluting stents: serial intravascular ultrasound analysis from the TAXUS II trial. Circulation 2004;109(5):627-633.

Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002;106(7):798-803.

Sousa JE, Sousa AG, Costa MA, Abizaid AC, Feres F. Use of rapamycin-impregnated stents in coronary arteries. Transplantation Proceedings 2003;35(3 Suppl):165S-170S.

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.

Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. New England Journal of Medicine 2004;350(3):221-231.

Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C et al. Chronic Arterial Responses to Polymer-Controlled Paclitaxel-Eluting Stents: Comparison with Bare Metal Stents by Serial Intravascular Ultrasound Analyses: Data from the Randomized TAXUS-II Trial. Circulation 2004;109(2):196-200.

Tanabe K, Serruys PW, Degertekin M, Regar E, van Domburg RT, Sousa JE et al. Fate of side branches after coronary arterial sirolimus-eluting stent implantation. American Journal of Cardiology 2002;90(9):937-941.

Included in analysis

Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108(7):788-794.

Gershlick A, De S, I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaLUation of pacliTaxel Eluting Stent (ELUTES) trial. Circulation 2004;109(4):487-493.

Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107(1):38-42.

Holmes DR, Jr., Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109(5):634-640.

Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. New England Journal of Medicine 2002;346(23):1773-1780.

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.[see comment]. New England Journal of Medicine 2003;349(14):1315-1323.

Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. New England Journal of Medicine 2003;348(16):1537-1545.

Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). Journal of the American College of Cardiology 2004;43(6):1110-1115.

Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362(9390):1093-1099.

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.[see comment]. Circulation 2004;109(16):1942-1947.

Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease.[see comment]. New England Journal of Medicine 2004;350(3):221-231.

APPENDIX V: CHARACTERISTICS OF STUDIES

Study	Study Design	Inclusion Criteria	Stent Characteristics	Antiplatelet pharmacotherapy
Morice, M. C. et al. 2002 RAVEL	19 European, Mexican, Brazilian Centres 12 months, double-blind, randomized trial to 1 of 2 arms randomized using 1:1 computer-generated in blocks of four and distributed to centres in sealed envelopes Enrollment from 2000 Aug to 2001 Jan Clinical follow-up: 1, 6, 12 months Angiographic follow-up: 6 months	Patient characteristics Patient age (years): 18 to 85 stable or unstable angina, silent ischemia Lesion characteristics Single de novo, native coronary artery Lesion length (mm): < 18 mm Lesion diameter (mm): 2.5 to 3.5 mm	DES Polymer Sirolimus (Bx Velocity - sirolimus polymer matrix) Drug concentration(s): 140 µg/cm² BMS Bx Velocity (J&J Cordis) Stent length(s): 18 mm Stent diameter(s): 2.5; 3.0 mm	ASA regimen: 100 mg po daily Duration of ASA therapy: Indefinitely Clopidogrel 75 mg po daily or ticlopidine 250 mg po twice daily. Duration of therapy: 2 months
Schofer, J. et al. 2003 ESIRIUS	35 European Centres 9 months, double-blind, randomized trial to 1 of 2 arms randomized using 1:1 Sealed Randomization Envelopes Enrollment from 2001 Aug to 2002 Feb Clinical follow-up: 1, 9 months Angiographic follow-up: 8 months	Patient characteristics Patient age (years): at least 18 angina pectoris, unstable angina, silent ischemia Lesion characteristics Single de novo, native coronary artery Lesion length (mm): 15 to 32 mm Lesion diameter (mm): 2.5 to 3.0 mm	DES Polymer Sirolimus (CYPHER) Drug concentration(s): 140 µg/cm² BMS Bx Velocity (J&J Cordis) Stent length(s): 8; 18 mm Stent diameter(s): 2.5; 3.0 mm	ASA regimen: 100 mg po daily Duration of ASA therapy: Indefinitely Clopidogrel 75 mg po daily or ticlopidine 250 mg po twice daily. Duration of therapy: 2 months
Schampaert, E. et al. 2004 CSIRIUS	8 Canadian Centres 9 months, double-blind, randomized trial to 1 of 2 arms randomized using 1:1 Sealed Randomization Envelopes Enrollment from 2001 Nov to 2002 Apr Clinical follow-up: 1, 3, 6, 9 months Angiographic follow-up: 8 months	Patient characteristics Patient age (years): at least 18 angina pectoris, unstable angina, silent ischemia Lesion characteristics Single de novo, native vessel Lesion length (mm): 15 to 32 mm Lesion diameter (mm): 2.5 to 3.0 mm	DES Polymer Sirolimus (CYPHER) Drug concentration(s): 140 µg/cm² BMS Bx Velocity (J&J Cordis) Stent length(s): 8; 18 mm Stent diameter(s): 2.5; 3.0 mm	ASA regimen: 81 or 325 mg po daily Duration of ASA therapy: Indefinitely Clopidogrel 75 mg po daily. Duration of therapy: 2 months
Moses, J. W. et al. 2003 Holmes, D. R., Jr. et al. 2004 SIRIUS	53 United States Centres 12 months, double-blind, randomized trial to 1 of 2 arms randomized using automated telephone randomization system, randomized in blocks by clinical centre and diabetes status Enrollment from 2001 Feb to 2001 Aug Clinical follow-up: 1, 3, 6, 9, 12 months Angiographic follow-up: 8 months	Patient characteristics Patient age (years): nr stable or unstable angina and signs of myocardial ischemia Lesion characteristics Single de novo, native coronary artery Lesion length (mm): 15 mm to 30 mm Lesion diameter (mm): 2.5 to 3.5 mm	DES Polymer Sirolimus (CYPHER) Drug concentration(s): 140 µg/cm² BMS Bx Velocity (J&J Cordis) Stent length(s): 8; 18 mm Stent diameter(s): 2.5; 3.0; 3.5 mm	ASA regimen: 325 mg po daily Duration of ASA therapy: not specified Clopidogrel 75 mg po daily. Duration of therapy: 3 months

Study	Study Design	Inclusion Criteria	Stent Characteristics	Antiplatelet pharmacotherapy
Grube, E. et al. 2003 TAXUS I	3 German Centres 12 months, double-blind, randomized trial to 1 of 2 arms randomized using nr Enrollment from 2000 Oct to 2001 Mar Clinical follow-up: 1, 6, 9, 12 months Angiographic follow-up: 6 months	Patient characteristics Patient age (years): nr not reported Lesion characteristics Single de novo or restenotic Lesion length (mm): <= 12 mm Lesion diameter (mm): 3.0 to 3.5 mm	DES Polymer Paclitaxel (TAXUS NIRx) Drug concentration(s): 1 µg/mm² BMS NIR (Boston Scientific) Stent length(s): 15 mm Stent diameter(s): 3.0; 3.5 mm	ASA regimen: > 80 mg po daily Duration of ASA therapy: 12 months Clopidogrel 75 mg po daily. Duration of therapy: 6 months
Colombo, A. et al. 2003 TAXUS II	38 International (Outside U.S) Centres 12 months, double-blind, randomized trial to 1 of 4 arms randomized using randomized into 2 consecutive and independent cohorts Enrollment from 2001 Jun to 2002 Jan Clinical follow-up: 1, 6, 12 months Angiographic follow-up: 6 months	Patient characteristics Patient age (years): at least 18 stable or unstable angina or silent ischemia and were acceptable candidates for PCI or CABG Lesion characteristics Single de novo, native coronary artery Lesion length (mm): <= 12 mm Lesion diameter (mm): 3.0 to 3.5 mm	DES Polymer Paclitaxel (TAXUS NIR (SR); TAXUS NIR (MR)) Drug concentration(s): 1 µg/mm² BMS NIR (Medinol) Stent length(s): 15 mm Stent diameter(s): 3.0; 3.5 mm	ASA regimen: 75 mg po daily Duration of ASA therapy: Indefinitely Clopidogrel 75 mg po daily or ticlopidine 250 mg po twice daily. Duration of therapy: 6 months
Stone, G. W. et al. 2004 Stone, G. W. et al. 2004 TAXUS IV	73 United States Centres 12 months, double-blind, randomized trial to 1 of 2 arms randomized using random serial numbers by telephone and stratified by diabetes mellitus and vessel size < 3.0 mm vs. 3.0 mm or more. Enrollment from 37344 to 37445 Clinical follow-up: 1, 4, 9, 12 months then yearly for 5 years Angiographic follow-up: 9 months	Patient characteristics Patient age (years): at least 18 stable or unstable angina with provokable ischemia Lesion characteristics Single de novo, native coronary artery Lesion length (mm): 10 mm to 28 mm Lesion diameter (mm): 2.5 to 3.75 mm	DES Polymer Paclitaxel (TAXUS EXPRESS) Drug concentration(s): 1 µg/mm² BMS EXPRESS (Boston Scientific) Stent length(s): 16; 24; 32 mm Stent diameter(s): 2.5; 3.0; 3.5 mm	ASA regimen: 325 mg po daily Duration of ASA therapy: Indefinitely Clopidogrel 75 mg po daily. Duration of therapy: 6 months
Park, S. J. et al. 2003 ASPECT	3 Asian Centres 6 months, triple-blind, randomized trial to 1 of 3 arms randomized using 1:1:1 Enrollment from 2000 Jan to 2001 Mar Clinical follow-up: 1, 4 to 6 months Angiographic follow-up: 4 to 6 months	Patient characteristics Patient age (years): at least 18 symptomatic Lesion characteristics Single de novo Lesion length (mm): <= 15 mm Lesion diameter (mm): nr	DES Non-polymer Paclitaxel Drug concentration(s): 1.3; 3.1 µg/mm² BMS Supra G (Cook) Stent length(s): 15 mm Stent diameter(s): 2.5; 3.0; 3.5 mm	ASA regimen: not specified Duration of ASA therapy: 1 month or 6 months Ticlopidine; clopidogrel; cilostazol. Duration of therapy: 1 month or 6 months

Study	Study Design	Inclusion Criteria	Stent Characteristics	Antiplatelet pharmacotherapy
Gershlick, A. et al. 2004 ELUTES	10 European Centres 12 months, triple-blind, randomized trial to 1 of 5 arms randomized using computer-generated tabulated random order Enrollment from 2000 Jan to 2001 Apr Clinical follow-up: 1, 6, 12 months Angiographic follow-up: 6 months	Patient characteristics Patient age (years): nr candidates for coronary surgery if required Lesion characteristics Single de novo, Type A or B1, native vessel Lesion length (mm): < 15 mm Lesion diameter (mm): nr	DES Non-polymer Paclitaxel Drug concentration(s): 0.2; 0.7; 1.4; 2.7 µg/mm² BMS V-Flex Plus (Cook) Stent length(s): 16 mm Stent diameter(s): 3.0; 3.5 mm	ASA regimen: not specified Duration of ASA therapy: 3 months Clopidogrel. Duration of therapy: 3 months

APPENDIX VI: CHARACTERISTICS OF PATIENTS

Study	Treatment Arm	Demographics & Comorbidities	Presenting Condition	Target Artery & Number of Diseased Vessels	Lesion Characteristics
Morice, M. C. et al. 2002 RAVEL	Sirolimus 140 µg/cm² Number randomized n = 120 Number treated n = 120	Mean age ± sd 61.8 ± 10.7 years Males n (%) 84 (70.0%) Current Smoker n (%) 32 (26.7%) Diabetes mellitus n (%) 19 (15.8%) Hyperlipidemia n (%) 45 (37.5%) Hypertension n (%) 74 (61.7%) Previous MI n (%) 45 (37.5%) Previous CABG n (%) nr	Stable Angina n (%) 49 (40.8%) Unstable Angina n (%) 57 (47.5%) Silent Ischemia n (%) 13 (10.8%) Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 59 (49.2%) RCA n (%) 32 (26.7%) LCx n (%) 29 (24.2%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.60 ± 0.54 mm Mean Lesion Length ± sd 9.6 ± 3.3 mm ACC-AHA class A n (%) 9 (7.5%) B1 n (%) 46 (38.3%) B2 n (%) 65 (54.2%) C n (%) 0 (0.0%)
	Bx Velocity Number randomized n = 118 Number treated n = 118	Mean age ± sd 59.7 ± 10.1 years Males n (%) 96 (81.4%) Current Smoker n (%) 39 (33.1%) Diabetes mellitus n (%) 25 (21.2%) Hyperlipidemia n (%) 51 (43.2%) Hypertension n (%) 72 (61.0%) Previous MI n (%) 40 (33.9%) Previous CABG n (%) nr	Stable Angina n (%) 44 (37.3%) Unstable Angina n (%) 61 (51.7%) Silent Ischemia n (%) 13 (11.0%) Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 60 (50.8%) RCA n (%) 32 (27.1%) LCx n (%) 26 (22.0%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.64 ± 0.52 mm Mean Lesion Length ± sd 9.6 ± 3.2 mm ACC-AHA class A n (%) 5 (4.2%) B1 n (%) 41 (34.7%) B2 n (%) 72 (61.0%) C n (%) 0 (0.0%)
Schofer, J. et al. 2003 ESIRIUS	Sirolimus 140 µg/cm² Number randomized n = 175 Number treated n = 175	Mean age ± sd 62.0 ± 11.4 years Males n (%) 123 (70.3%) Current Smoker n (%) 63 (36.4%) Diabetes mellitus n (%) 33 (18.9%) Hyperlipidemia n (%) 132 (76.7%) Hypertension n (%) 109 (63.0%) Previous MI n (%) 71 (40.8%) Previous CABG n (%) 10 (5.7%)	Stable Angina n (%) nr Unstable Angina n (%) 53 (30.3%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 97 (56.7%) RCA n (%) 38 (22.2%) LCx n (%) 36 (21.1%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 110 (63.6%) Multiple vessel n (%) 65 (37.1%) 2 35 (20.2%) 3 28 (16.2%) 4 0 (0.0%)	Mean RVD ± sd 2.60 ± 0.37 mm Mean Lesion Length ± sd 14.9 ± 5.4 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	Bx Velocity Number randomized n = 177 Number treated n = 177	Mean age ± sd 62.6 ± 10.3 years Males n (%) 126 (71.2%) Current Smoker n (%) 53 (30.1%) Diabetes mellitus n (%) 48 (27.3%) Hyperlipidemia n (%) 124 (71.3%) Hypertension n (%) 114 (64.4%) Previous MI n (%) 76 (43.4%) Previous CABG n (%) 11 (6.2%)	Stable Angina n (%) nr Unstable Angina n (%) 64 (36.2%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 97 (56.1%) RCA n (%) 33 (19.1%) LCx n (%) 42 (24.3%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 113 (64.6%) Multiple vessel n (%) 64 (36.2%) 2 42 (24.0%) 3 20 (11.4%) 4 nr	Mean RVD ± sd 2.51 ± 0.37 mm Mean Lesion Length ± sd 15.1 ± 6.5 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
Schampaert, E. et al. 2004 CSIRIUS	Sirolimus 140 µg/cm² Number randomized n = 51 Number treated n = 50	Mean age ± sd 60.3 ± 10.6 years Males n (%) 35 (70.0%) Current Smoker n (%) 18 (36.0%) Diabetes mellitus n (%) 12 (24.0%) Hyperlipidemia n (%) 42 (84.0%) Hypertension n (%) 28 (56.0%) Previous MI n (%) 24 (48.0%) Previous CABG n (%) 3 (6.0%)	Stable Angina n (%) 5 (10.0%) Unstable Angina n (%) 24 (48.0%) Silent Ischemia n (%) nr Post MI n (%) 11 (22.0%)	LM n (%) 0 (0.0%) LAD n (%) 16 (32.0%) RCA n (%) 23 (46.0%) LCx n (%) 11 (22.0%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 27 (54.0%) Multiple vessel n (%) 23 (46.0%) 2 nr 3 nr 4 nr	Mean RVD ± sd 2.65 ± 0.30 mm Mean Lesion Length ± sd 14.5 ± 6.3 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr

Study	Treatment Arm	Demographics & Comorbidities	Presenting Condition	Target Artery & Number of Diseased Vessels	Lesion Characteristics
	Bx Velocity Number randomized n = 51 Number treated n = 50	Mean age ± sd 60.7 ± 9.1 years Males n (%) 34 (68.0%) Current Smoker n (%) 19 (38.0%) Diabetes mellitus n (%) 12 (24.0%) Hyperlipidemia n (%) 43 (86.0%) Hypertension n (%) 24 (48.0%) Previous MI n (%) 21 (42.0%) Previous CABG n (%) 1 (2.0%)	Stable Angina n (%) 7 (14.0%) Unstable Angina n (%) 27 (54.0%) Silent Ischemia n (%) nr Post MI n (%) 4 (8.0%)	LM n (%) 0 (0.0%) LAD n (%) 20 (40.0%) RCA n (%) 18 (36.0%) LCx n (%) 12 (24.0%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 33 (66.0%) Multiple vessel n (%) 17 (34.0%) 2 nr 3 nr 4 nr	Mean RVD ± sd 2.62 ± 0.35 mm Mean Lesion Length ± sd 12.6 ± 5.2 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
Moses, J. W. et al. 2003 SIRIUS	Sirolimus 140 µg/cm² Number randomized n = 556 Number treated n = 533	Mean age ± sd 62.1 ± 11.2 years Males n (%) 387 (72.6%) Current Smoker n (%) 96 (18.0%) Diabetes mellitus n (%) 131 (24.6%) Hyperlipidemia n (%) 389 (73.0%) Hypertension n (%) 359 (67.4%) Previous MI n (%) 147 (27.6%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) 283 (53.1%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) nr LAD n (%) 234 (43.9%) RCA n (%) 159 (29.8%) LCx n (%) 134 (25.1%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 316 (59.3%) Multiple vessel n (%) 217 (40.7%) 2 nr 3 nr 4 nr	Mean RVD ± sd 2.79 ± 0.45 mm Mean Lesion Length ± sd 14.4 ± 5.8 mm ACC-AHA class A n (%) 39 (7.3%) B1 n (%) 180 (33.8%) B2 n (%) 173 (32.5%) C n (%) 138 (25.9%)
	Bx Velocity Number randomized n = 545 Number treated n = 525	Mean age ± sd 62.4 ± 11.0 years Males n (%) 366 (69.7%) Current Smoker n (%) 116 (22.1%) Diabetes mellitus n (%) 148 (28.2%) Hyperlipidemia n (%) 394 (75.0%) Hypertension n (%) 354 (67.4%) Previous MI n (%) 171 (32.6%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) 283 (53.9%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) nr LAD n (%) 228 (43.4%) RCA n (%) 171 (32.6%) LCx n (%) 126 (24.0%) SVG n (%) nr Ramus n (%) nr Single vessel n (%) 302 (57.5%) Multiple vessel n (%) 223 (42.5%) 2 nr 3 nr 4 nr	Mean RVD ± sd 2.81 ± 0.49 mm Mean Lesion Length ± sd 14.4 ± 5.8 mm ACC-AHA class A n (%) 41 (7.8%) B1 n (%) 201 (38.3%) B2 n (%) 177 (33.7%) C n (%) 109 (20.8%)
Holmes, D. R., Jr. et al. 2004 SIRIUS	Sirolimus 140 µg/cm² Number randomized n = 556 Number treated n = 533	Mean age ± sd 62.0 ± 11.0 years Males n (%) 387 (72.6%) Current Smoker n (%) nr Diabetes mellitus n (%) 131 (24.6%) Hyperlipidemia n (%) 389 (73.0%) Hypertension n (%) 359 (67.4%) Previous MI n (%) 147 (27.6%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) 115 (21.6%) Post MI n (%) nr	LM n (%) 3 (0.6%) LAD n (%) 234 (43.9%) RCA n (%) 159 (29.8%) LCx n (%) 134 (25.1%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 316 (59.3%) Multiple vessel n (%) 217 (40.7%) 2 135 (25.3%) 3 82 (15.4%) 4 0 (0.0%)	Mean RVD ± sd nr ± nr mm Mean Lesion Length ± sd 14.4 ± 5.7 mm ACC-AHA class A n (%) 39 (7.3%) B1 n (%) 180 (33.8%) B2 n (%) 173 (32.5%) C n (%) 138 (25.9%)
	Bx Velocity Number randomized n = 545 Number treated n = 525	Mean age ± sd 62.0 ± 11.0 years Males n (%) 366 (69.7%) Current Smoker n (%) nr Diabetes mellitus n (%) 148 (28.2%) Hyperlipidemia n (%) 394 (75.0%) Hypertension n (%) 354 (67.4%) Previous MI n (%) 171 (32.6%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) 283 (53.9%) Silent Ischemia n (%) 115 (21.9%) Post MI n (%) nr	LM n (%) 2 (0.4%) LAD n (%) 228 (43.4%) RCA n (%) 171 (32.6%) LCx n (%) 126 (24.0%) SVG n (%) 1 (0.2%) Ramus n (%) 0 (0.0%) Single vessel n (%) 302 (57.5%) Multiple vessel n (%) 223 (42.5%) 2 151 (28.8%) 3 72 (13.7%) 4 0 (0.0%)	Mean RVD ± sd nr ± nr mm Mean Lesion Length ± sd 14.4 ± 5.8 mm ACC-AHA class A n (%) 41 (7.8%) B1 n (%) 201 (38.3%) B2 n (%) 177 (33.7%) C n (%) 109 (20.8%)

Study	Treatment Arm	Demographics & Comorbidities	Presenting Condition	Target Artery & Number of Diseased Vessels	Lesion Characteristics
Grube, E. et al. 2003 TAXUS I	TAXUS-SRPaclitaxel 1 µg/mm² Number randomized n = 31 Number treated n = 31	Mean age ± sd 66.0 ± 6.8 years Males n (%) 29 (93.5%) Current Smoker n (%) nr Diabetes mellitus n (%) 7 (22.6%) Hyperlipidemia n (%) 25 (80.6%) Hypertension n (%) 20 (64.5%) Previous MI n (%) 8 (25.8%) Previous CABG n (%) nr	Stable Angina n (%) 27 (87.1%) Unstable Angina n (%) nr Silent Ischemia n (%) 7 (22.6%) Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 17 (54.8%) RCA n (%) 7 (22.6%) LCx n (%) 7 (22.6%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.99 ± 0.46 mm Mean Lesion Length ± sd 10.7 ± 3.3 mm ACC-AHA class A n (%) 10 (32.3%) B1 n (%) 12 (38.7%) B2 n (%) 9 (29.0%) C n (%) 0 (0.0%)
	NIR Number randomized n = 30 Number treated n = 30	Mean age ± sd 63.8 ± 7.8 years Males n (%) 26 (86.7%) Current Smoker n (%) nr Diabetes mellitus n (%) 4 (13.3%) Hyperlipidemia n (%) 24 (80.0%) Hypertension n (%) 19 (63.3%) Previous MI n (%) 9 (30.0%) Previous CABG n (%) nr	Stable Angina n (%) 23 (76.7%) Unstable Angina n (%) nr Silent Ischemia n (%) 11 (36.7%) Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 8 (26.7%) RCA n (%) 11 (36.7%) LCx n (%) 11 (36.7%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.94 ± 0.52 mm Mean Lesion Length ± sd 11.9 ± 4.9 mm ACC-AHA class A n (%) 4 (13.3%) B1 n (%) 13 (43.3%) B2 n (%) 13 (43.3%) C n (%) 0 (0.0%)
Colombo, A. et al. 2003 TAXUS II	TAXUS-SRPaclitaxel 1 µg/mm² Number randomized n = 131 Number treated n = 130	Mean age ± sd 61.5 ± 10.5 years Males n (%) 92 (70.2%) Current Smoker n (%) 27 (20.6%) Diabetes mellitus n (%) 14 (10.7%) Hyperlipidemia n (%) nr Hypertension n (%) 83 (63.4%) Previous MI n (%) 47 (35.9%) Previous CABG n (%) nr	Stable Angina n (%) 75 (57.3%) Unstable Angina n (%) 46 (35.1%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 52 (39.7%) RCA n (%) 50 (38.2%) LCx n (%) 29 (22.1%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.80 ± 0.40 mm Mean Lesion Length ± sd 10.6 ± 3.9 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	NIR Number randomized n = 136 Number treated n = 133	Mean age ± sd 60.4 ± 9.3 years Males n (%) 107 (78.7%) Current Smoker n (%) 34 (25.0%) Diabetes mellitus n (%) 22 (16.2%) Hyperlipidemia n (%) nr Hypertension n (%) 91 (66.9%) Previous MI n (%) 58 (42.6%) Previous CABG n (%) nr	Stable Angina n (%) 76 (55.9%) Unstable Angina n (%) 45 (33.1%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 60 (44.1%) RCA n (%) 54 (39.7%) LCx n (%) 22 (16.2%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.80 ± 0.50 mm Mean Lesion Length ± sd 10.5 ± 4.1 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
Colombo, A. et al. 2003 TAXUS II	TAXUS-MRPaclitaxel 1 µg/mm² Number randomized n = 135 Number treated n = 129	Mean age ± sd 59.3 ± 10.1 years Males n (%) 103 (76.3%) Current Smoker n (%) 32 (23.7%) Diabetes mellitus n (%) 23 (17.0%) Hyperlipidemia n (%) nr Hypertension n (%) 81 (60.0%) Previous MI n (%) 53 (39.3%) Previous CABG n (%) nr	Stable Angina n (%) 90 (66.7%) Unstable Angina n (%) 40 (29.6%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 57 (42.2%) RCA n (%) 44 (32.6%) LCx n (%) 34 (25.2%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.70 ± 0.50 mm Mean Lesion Length ± sd 10.2 ± 4.8 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr

Study	Treatment Arm	Demographics & Comorbidities	Presenting Condition	Target Artery & Number of Diseased Vessels	Lesion Characteristics
	NIR Number randomized n = 134 Number treated n = 130	Mean age ± sd 59.3 ± 10.0 years Males n (%) 103 (76.9%) Current Smoker n (%) 39 (29.1%) Diabetes mellitus n (%) 19 (14.2%) Hyperlipidemia n (%) nr Hypertension n (%) 75 (56.0%) Previous MI n (%) 56 (41.8%) Previous CABG n (%) nr	Stable Angina n (%) 78 (58.2%) Unstable Angina n (%) 53 (39.6%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 70 (52.2%) RCA n (%) 44 (32.8%) LCx n (%) 20 (14.9%) SVG n (%) nr Ramus n (%) nr Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.70 ± 0.50 mm Mean Lesion Length ± sd 10.7 ± 4.1 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
Stone, G. W. et al. 2004 TAXUS IV	TAXUS-SRPaclitaxel 1 µg/mm² Number randomized n = 667 Number treated n = 662	Mean age ± sd 62.8 ± 11.2 years Males n (%) 475 (71.8%) Current Smoker n (%) 155 (23.4%) Diabetes mellitus n (%) 0 (0.0%) Hyperlipidemia n (%) 430 (65.0%) Hypertension n (%) 467 (70.5%) Previous MI n (%) 202 (30.5%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) 237 (35.8%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 265 (40.0%) RCA n (%) 206 (31.1%) LCx n (%) 191 (28.9%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.75 ± 0.47 mm Mean Lesion Length ± sd 13.4 ± 6.3 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	EXPRESS Number randomized n = 659 Number treated n = 652	Mean age ± sd 62.1 ± 10.9 years Males n (%) 472 (72.4%) Current Smoker n (%) 131 (20.1%) Diabetes mellitus n (%) 0 (0.0%) Hyperlipidemia n (%) 428 (65.6%) Hypertension n (%) 450 (69.0%) Previous MI n (%) 195 (29.9%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) 213 (32.7%) Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 270 (41.4%) RCA n (%) 209 (32.0%) LCx n (%) 173 (26.6%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.75 ± 0.49 mm Mean Lesion Length ± sd 13.4 ± 6.2 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
Stone, G. W. et al. 2004 TAXUS IV	TAXUS-SRPaclitaxel 1 µg/mm² Number randomized n = 667 Number treated n = 662	Mean age ± sd 62.8 ± 11.2 years Males n (%) 475 (71.8%) Current Smoker n (%) nr Diabetes mellitus n (%) 0 (0.0%) Hyperlipidemia n (%) nr Hypertension n (%) 0 (0.0%) Previous MI n (%) 0 (0.0%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 265 (40.0%) RCA n (%) 206 (31.1%) LCx n (%) 191 (28.9%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.75 ± 0.47 mm Mean Lesion Length ± sd 13.4 ± 6.3 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	EXPRESS Number randomized n = 659 Number treated n = 652	Mean age ± sd 62.1 ± 10.9 years Males n (%) 472 (72.4%) Current Smoker n (%) nr Diabetes mellitus n (%) 0 (0.0%) Hyperlipidemia n (%) nr Hypertension n (%) 0 (0.0%) Previous MI n (%) 0 (0.0%) Previous CABG n (%) nr	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 270 (41.4%) RCA n (%) 209 (32.0%) LCx n (%) 173 (26.6%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) nr Multiple vessel n (%) nr 2 nr 3 nr 4 nr	Mean RVD ± sd 2.75 ± 0.49 mm Mean Lesion Length ± sd 13.4 ± 6.2 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr

Study	Treatment Arm	Demographics & Comorbidities	Presenting Condition	Target Artery & Number of Diseased Vessels	Lesion Characteristics
Park, S. J. et al. 2003 ASPECT	Paclitaxel 1.3 µg/mm² Number randomized n = 58 Number treated n = 58	Mean age ± sd 60.0 ± 9.0 years Males n (%) 42 (72.4%) Current Smoker n (%) 23 (39.7%) Diabetes mellitus n (%) 14 (24.1%) Hyperlipidemia n (%) 4 (6.9%) Hypertension n (%) 31 (53.4%) Previous MI n (%) 13 (22.4%) Previous CABG n (%) 1 (1.7%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 29 (50.0%) RCA n (%) 18 (31.0%) LCx n (%) 10 (17.2%) SVG n (%) 0 (0.0%) Ramus n (%) 1 (1.7%) Single vessel n (%) 36 (62.1%) Multiple vessel n (%) 22 (37.9%) 2 17 (29.3%) 3 4 (6.9%) 4 1 (1.7%)	Mean RVD ± sd 2.93 ± 0.38 mm Mean Lesion Length ± sd 11.2 ± 3.2 mm ACC-AHA class A n (%) 35 (60.3%) B1 n (%) 21 (36.2%) B2 n (%) 1 (1.7%) C n (%) 1 (1.7%)
	Paclitaxel 3.1 µg/mm² Number randomized n = 60 Number treated n = 59	Mean age ± sd 58.0 ± 9.0 years Males n (%) 48 (80.0%) Current Smoker n (%) 28 (46.7%) Diabetes mellitus n (%) 11 (18.3%) Hyperlipidemia n (%) 8 (13.3%) Hypertension n (%) 25 (41.7%) Previous MI n (%) 14 (23.3%) Previous CABG n (%) 2 (3.3%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 31 (52.5%) RCA n (%) 10 (16.9%) LCx n (%) 17 (28.8%) SVG n (%) 0 (0.0%) Ramus n (%) 1 (1.7%) Single vessel n (%) 32 (53.3%) Multiple vessel n (%) 28 (46.7%) 2 20 (33.3%) 3 8 (13.3%) 4 0 (0.0%)	Mean RVD ± sd 2.94 ± 0.39 mm Mean Lesion Length ± sd 10.9 ± 3.9 mm ACC-AHA class A n (%) 29 (49.2%) B1 n (%) 26 (44.1%) B2 n (%) 4 (6.8%) C n (%) 0 (0.0%)
	Supra G Number randomized n = 59 Number treated n = 59	Mean age ± sd 58.0 ± 11.0 years Males n (%) 45 (76.3%) Current Smoker n (%) 27 (45.8%) Diabetes mellitus n (%) 10 (16.9%) Hyperlipidemia n (%) 11 (18.6%) Hypertension n (%) 28 (47.5%) Previous MI n (%) 17 (28.8%) Previous CABG n (%) 0 (0.0%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 30 (50.8%) RCA n (%) 17 (28.8%) LCx n (%) 12 (20.3%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 39 (66.1%) Multiple vessel n (%) 20 (33.9%) 2 15 (25.4%) 3 5 (8.5%) 4 0 (0.0%)	Mean RVD ± sd 2.88 ± 0.36 mm Mean Lesion Length ± sd 10.5 ± 3.1 mm ACC-AHA class A n (%) 30 (50.8%) B1 n (%) 24 (40.7%) B2 n (%) 5 (8.5%) C n (%) 0 (0.0%)
Gershlick, A. et al. 2004 ELUTES	Paclitaxel 0.2 µg/mm² Number randomized n = 37 Number treated n = 37	Mean age ± sd 64.0 ± 10.0 years Males n (%) 27 (73.0%) Current Smoker n (%) 8 (21.6%) Diabetes mellitus n (%) 8 (21.6%) Hyperlipidemia n (%) 18 (48.6%) Hypertension n (%) 19 (51.4%) Previous MI n (%) 12 (32.4%) Previous CABG n (%) 0 (0.0%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 14 (37.8%) RCA n (%) 16 (43.2%) LCx n (%) 6 (16.2%) SVG n (%) 0 (0.0%) Ramus n (%) 1 (2.7%) Single vessel n (%) 24 (64.9%) Multiple vessel n (%) 13 (35.1%) 2 10 (27.0%) 3 1 (2.7%) 4 1 (2.7%)	Mean RVD ± sd 3.03 ± 0.41 mm Mean Lesion Length ± sd 11.3 ± 4.4 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	Paclitaxel 0.7 µg/mm² Number randomized n = 40 Number treated n = 39	Mean age ± sd 58.0 ± 9.0 years Males n (%) 38 (95.0%) Current Smoker n (%) 13 (32.5%) Diabetes mellitus n (%) 6 (15.0%) Hyperlipidemia n (%) 20 (50.0%) Hypertension n (%) 16 (40.0%) Previous MI n (%) 18 (45.0%) Previous CABG n (%) 0 (0.0%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 9 (22.5%) RCA n (%) 17 (42.5%) LCx n (%) 12 (30.0%) SVG n (%) 0 (0.0%) Ramus n (%) 2 (5.0%) Single vessel n (%) 22 (55.0%) Multiple vessel n (%) 18 (45.0%) 2 12 (30.0%) 3 5 (12.5%) 4 0 (0.0%)	Mean RVD ± sd 2.90 ± 0.39 mm Mean Lesion Length ± sd 10.6 ± 3.1 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr

Study	Treatment Arm	Demographics & Comorbidities	Presenting Condition	Target Artery & Number of Diseased Vessels	Lesion Characteristics
	Paclitaxel 1.4 µg/mm² Number randomized n = 39 Number treated n = 39	Mean age ± sd 61.0 ± 10.0 years Males n (%) 31 (79.5%) Current Smoker n (%) 18 (46.2%) Diabetes mellitus n (%) 8 (20.5%) Hyperlipidemia n (%) 18 (46.2%) Hypertension n (%) 14 (35.9%) Previous MI n (%) 9 (23.1%) Previous CABG n (%) 1 (2.6%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 20 (51.3%) RCA n (%) 9 (23.1%) LCx n (%) 7 (17.9%) SVG n (%) 0 (0.0%) Ramus n (%) 3 (7.7%) Single vessel n (%) 20 (51.3%) Multiple vessel n (%) 19 (48.7%) 2 11 (28.2%) 3 6 (15.4%) 4 2 (5.1%)	Mean RVD ± sd 2.93 ± 0.37 mm Mean Lesion Length ± sd 10.2 ± 3.7 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	Paclitaxel 2.7 µg/mm² Number randomized n = 37 Number treated n = 37	Mean age ± sd 56.0 ± 11.0 years Males n (%) 30 (81.1%) Current Smoker n (%) 16 (43.2%) Diabetes mellitus n (%) 4 (10.8%) Hyperlipidemia n (%) 22 (59.5%) Hypertension n (%) 18 (48.6%) Previous MI n (%) 11 (29.7%) Previous CABG n (%) 0 (0.0%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 15 (40.5%) RCA n (%) 15 (40.5%) LCx n (%) 7 (18.9%) SVG n (%) 0 (0.0%) Ramus n (%) 0 (0.0%) Single vessel n (%) 23 (62.2%) Multiple vessel n (%) 14 (37.8%) 2 9 (24.3%) 3 2 (5.4%) 4 3 (8.1%)	Mean RVD ± sd 2.95 ± 0.43 mm Mean Lesion Length ± sd 11.1 ± 3.1 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr
	V Flex Plus Number randomized n = 39 Number treated n = 38	Mean age ± sd 61.0 ± 11.0 years Males n (%) 32 (82.1%) Current Smoker n (%) 13 (33.3%) Diabetes mellitus n (%) 4 (10.3%) Hyperlipidemia n (%) 17 (43.6%) Hypertension n (%) 21 (53.8%) Previous MI n (%) 16 (41.0%) Previous CABG n (%) 3 (7.7%)	Stable Angina n (%) nr Unstable Angina n (%) nr Silent Ischemia n (%) nr Post MI n (%) nr	LM n (%) 0 (0.0%) LAD n (%) 15 (38.5%) RCA n (%) 11 (28.2%) LCx n (%) 9 (23.1%) SVG n (%) 0 (0.0%) Ramus n (%) 4 (10.3%) Single vessel n (%) 20 (51.3%) Multiple vessel n (%) 18 (47.4%) 2 10 (25.6%) 3 8 (20.5%) 4 1 (2.6%)	Mean RVD ± sd 2.99 ± 0.51 mm Mean Lesion Length ± sd 10.8 ± 3.8 mm ACC-AHA class A n (%) nr B1 n (%) nr B2 n (%) nr C n (%) nr

APPENDIX VII: SUMMARY OF CLINICAL OUTCOMES FROM CLINICAL TRIALS

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)	Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)	Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)
Morice, M. C. et al. 2002 RAVEL Before discharge days	DES Bx Velocity (sirolimus-polymer matrix) Sirolimus 140 µg/cm² n = 120	Death 0 (0.00%) Cardiac death nr MI 3 (2.50%) Qwave MI 2 (1.67%) Non-Qwave MI 1 (0.83%) MACE total nr	TLR total nr TLR CABG 0 (0.00%) TLR PTCA nr TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR nr
	BMS Bx Velocity n = 118	Death 0 (0.00%) Cardiac death nr MI 3 (2.54%) Qwave MI 1 (0.85%) Non-Qwave MI 2 (1.69%) MACE total nr	TLR total nr TLR CABG 0 (0.00%) TLR PTCA nr TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR nr
Morice, M. C. et al. 2002 RAVEL After discharge days	DES Bx Velocity (sirolimus-polymer matrix) Sirolimus 140 µg/cm² n = 120	Death 2 (1.67%) Cardiac death nr MI 1 (0.83%) Qwave MI 0 (0.00%) Non-Qwave MI 1 (0.83%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL 1 (0.83%)	TVF nr THR nr
	BMS Bx Velocity n = 118	Death 2 (1.69%) Cardiac death nr MI 2 (1.69%) Qwave MI 0 (0.00%) Non-Qwave MI 2 (1.69%) MACE total nr	TLR total 28 (23.73%) TLR CABG 1 (0.85%) TLR PTCA 27 (22.88%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL 0 (0.00%)	TVF nr THR nr

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)		Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)		Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)	
Morice, M. C. et al. 2002 RAVEL 365 days	DES Bx Velocity (sirolimus-polymer matrix) Sirolimus 140 µg/cm² n = 120	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	2 (1.67%) nr 4 (3.33%) 2 (1.67%) 2 (1.67%) 7 (5.83%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	0 (0.00%) 0 (0.00%) 0 (0.00%) nr nr nr 1 (0.83%)	TVF Angiography BRR at 6 months THR	nr nr nr (0.00%) 0 (0.00%)
	BMS Bx Velocity n = 118	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	2 (1.69%) nr 5 (4.24%) 1 (0.85%) 4 (3.39%) 34 (28.81%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	28 (23.73%) 1 (0.85%) 27 (22.88%) nr nr nr 0 (0.00%)	TVF Angiography BRR at 6 months THR	nr nr nr (26.60%) 0 (0.00%)
Schofer, J. et al. 2003 ESIRIUS 270 days	DES CYPHER Sirolimus 140 µg/cm² n = 175	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	2 (1.14%) 1 (0.57%) 8 (4.57%) 2 (1.14%) 6 (3.43%) 14 (8.00%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	7 (4.00%) 0 (0.00%) 7 (4.00%) nr nr nr nr	TVF Angiography BRR at 8 months THR	nr 152 (86.86%) 6 (3.95%) 2 (1.14%)
	BMS Bx Velocity n = 177	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	1 (0.56%) 0 (0.00%) 4 (2.26%) 0 (0.00%) 4 (2.26%) 40 (22.60%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	40 (22.60%) 3 (1.69%) 37 (20.90%) nr nr nr nr	TVF Angiography BRR at 8 months THR	nr 156 (88.10%) 65 (41.67%) 0 (0.00%)
Schampaert, E. et al. 2004 CSIRIUS 270 days	DES CYPHER Sirolimus 140 µg/cm² n = 50	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 (0.00%) nr 1 (2.00%) 0 (0.00%) 1 (2.00%) 2 (4.00%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	3 (6.00%) 1 (2.00%) 3 (4.00%) nr nr nr 0 (0.00%)	TVF Angiography BRR at 8 months THR	nr 44 (88.00%) 0 (0.00%) 1 (2.00%)
	BMS Bx Velocity	Death Cardiac death	0 (0.00%) nr	TLR total TLR CABG	9 (18.00%) 0 (0.00%)	TVF Angiography	nr 44 (88.00%)

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)			Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)			Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)		
		MI	2	(4.00%)	TLR PTCA	9	(18.00%)	BRR at 8 months	20	(45.45%)
	n = 50	Qwave MI	0	(0.00%)	TVR total	nr		THR	1	(2.00%)
		Non-Qwave MI	2	(4.00%)	TVR CABG	0	(0.00%)			
		MACE total	9	(18.00%)	TVR PTCA	nr				
					TVRNTL	2	(4.00%)			
	DES	Death	5	(0.94%)	TLR total	22	(4.13%)	TVF	46	(8.63%)
Moses, J. W. et al. 2003	CYPHER	Cardiac death	nr		TLR CABG	3	(0.56%)	Angiography	350	(65.67%)
		MI	15	(2.81%)	TLR PTCA	22	(3.75%)	BRR at 8 months	11	(3.14%)
SIRIUS	Sirolimus 140 µg/cm²	Qwave MI	4	(0.75%)	TVR total	nr		THR	2	(0.38%)
270 days		Non-Qwave MI	11	(2.06%)	TVR CABG	nr				
	n = 533	MACE total	38	(7.13%)	TVR PTCA	nr				
					TVRNTL	18	(3.38%)			
	BMS	Death	3	(0.57%)	TLR total	87	(16.57%)	TVF	110	(20.95%)
	Bx Velocity	Cardiac death	nr		TLR CABG	8	(1.52%)	Angiography	353	(67.20%)
		MI	17	(3.24%)	TLR PTCA	83	(15.81%)	BRR at 8 months	125	(35.41%)
	n = 525	Qwave MI	2	(0.38%)	TVR total	nr		THR	4	(0.76%)
		Non-Qwave MI	15	(2.86%)	TVR CABG	nr				
		MACE total	99	(18.86%)	TVR PTCA	nr				
					TVRNTL	25	(4.76%)			
	DES	Death	7	(1.31%)	TLR total	26	(4.88%)	TVF	52	(9.76%)
Holmes, D. R., Jr. et al.	CYPHER	Cardiac death	nr		TLR CABG	5	(0.94%)			
2004		MI	16	(3.00%)	TLR PTCA	26	(4.32%)	THR	2	(0.38%)
	Sirolimus 140 µg/cm²	Qwave MI	4	(0.75%)	TVR total	nr				
SIRIUS		Non-Qwave MI	12	(2.25%)	TVR CABG	nr				
360 days	n = 533	MACE total	44	(8.26%)	TVR PTCA	nr				
					TVRNTL	19	(3.56%)			
	BMS	Death	4	(0.76%)	TLR total	105	(20.00%)	TVF	130	(24.76%)
	Bx Velocity	Cardiac death	nr		TLR CABG	9	(1.71%)			
		MI	18	(3.43%)	TLR PTCA	101	(19.24%)	THR	4	(0.76%)
	n = 525	Qwave MI	2	(0.38%)	TVR total	nr				
		Non-Qwave MI	16	(3.05%)	TVR CABG	nr				
		MACE total	117	(22.29%)	TVR PTCA	nr				
					TVRNTL	35	(6.67%)			

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)		Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)		Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)	
	DES	Death	0 (0.00%)	TLR total	0 (0.00%)	TVF	nr
Grube, E. et al. 2003	TAXUS NIRx	Cardiac death	nr	TLR CABG	0 (0.00%)	Angiography	30 (96.77%)
		MI	nr	TLR PTCA	0 (0.00%)	BRR at 6 months	0 (0.00%)
TAXUS I	Paclitaxel 1 µg/mm²	Qwave MI	0 (0.00%)	TVR total	0 (0.00%)	THR	0 (0.00%)
180 days		Non-Qwave MI	nr	TVR CABG	nr		
	n = 31	MACE total	0 (0.00%)	TVR PTCA	0 (0.00%)		
				TVRNTL	1 (3.23%)		
	BMS	Death	0 (0.00%)	TLR total	2 (6.67%)	TVF	nr
	NIR	Cardiac death	nr	TLR CABG	0 (0.00%)	Angiography	29 (96.70%)
		MI	nr	TLR PTCA	2 (6.67%)	BRR at 6 months	3 (10.34%)
	n = 30	Qwave MI	0 (0.00%)	TVR total	2 (6.67%)	THR	0 (0.00%)
		Non-Qwave MI	nr	TVR CABG	nr		
		MACE total	2 (6.67%)	TVR PTCA	2 (6.67%)		
				TVRNTL	0 (0.00%)		
	DES	Death	0 (0.00%)	TLR total	0 (0.00%)	TVF	nr
Grube, E. et al. 2003	TAXUS NIRx	Cardiac death	nr	TLR CABG	0 (0.00%)		
		MI	nr	TLR PTCA	0 (0.00%)	THR	0 (0.00%)
TAXUS I	Paclitaxel 1 µg/mm²	Qwave MI	0 (0.00%)	TVR total	1 (3.23%)		
365 days		Non-Qwave MI	nr	TVR CABG	nr		
	n = 31	MACE total	1 (3.23%)	TVR PTCA	1 (3.23%)		
				TVRNTL	1 (3.23%)		
	BMS	Death	0 (0.00%)	TLR total	4 (13.33%)	TVF	nr
	NIR	Cardiac death	nr	TLR CABG	1 (3.33%)		
		MI	nr	TLR PTCA	3 (10.00%)	THR	0 (0.00%)
	n = 30	Qwave MI	0 (0.00%)	TVR total	3 (10.00%)		
		Non-Qwave MI	nr	TVR CABG	nr		
		MACE total	3 (10.00%)	TVR PTCA	3 (10.00%)		
				TVRNTL	0 (0.00%)		
	DES	Death	0 (0.00%)	TLR total	6 (4.62%)	TVF	nr
Colombo, A. et al. 2003	TAXUS-NIR (SR)	Cardiac death	nr	TLR CABG	0 (0.00%)	Angiography	nr
		MI	nr	TLR PTCA	6	BRR at 6 months	nr (2.30%)
TAXUS II	Paclitaxel 1 µg/mm²	Qwave MI	0 (0.00%)	TVR total	10 (7.69%)	THR	1 (0.77%)
180 days		Non-Qwave MI	2 (1.54%)	TVR CABG	1 (0.77%)		
	n = 130	MACE total	11 (8.46%)	TVR PTCA	nr		
				TVRNTL	4 (3.08%)		
	BMS	Death	1 (0.75%)	TLR total	16 (12.03%)	TVF	nr
	NIR	Cardiac death	nr	TLR CABG	0 (0.00%)	Angiography	nr

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)			Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)			Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)		
		MI	nr		TLR PTCA	nr		BRR at 6 months	nr	(17.90%)
	n = 133	Qwave MI	2	(1.50%)	TVR total	19	(14.29%)	THR	0	(0.00%)
		Non-Qwave MI	5	(3.76%)	TVR CABG	1	(0.75%)			
		MACE total	26	(19.55%)	TVR PTCA	nr				
					TVRNTL	3	(2.26%)			
	DES	Death	0	(0.00%)	TLR total	6	(4.65%)	TVF	nr	
Colombo, A. et al. 2003	TAXUS-NIR (SR)	Cardiac death	nr		TLR CABG	0	(0.00%)			
		MI	nr		TLR PTCA	6		THR	2	(1.55%)
TAXUS II	Paclitaxel 1 µg/mm²	Qwave MI	1	(0.78%)	TVR total	13	(10.08%)			
365 days		Non-Qwave MI	2	(1.55%)	TVR CABG	4	(3.10%)			
	n = 129	MACE total	14	(10.85%)	TVR PTCA	nr				
					TVRNTL	4	(3.10%)			
	BMS	Death	2	(1.52%)	TLR total	17	(12.88%)	TVF	nr	
	NIR	Cardiac death	nr		TLR CABG	0	(0.00%)			
		MI	nr		TLR PTCA	nr		THR	0	(0.00%)
	n = 132	Qwave MI	2	(1.52%)	TVR total	21	(15.91%)			
		Non-Qwave MI	5	(3.79%)	TVR CABG	1	(0.76%)			
		MACE total	29	(21.97%)	TVR PTCA	nr				
					TVRNTL	4	(3.03%)			
	DES	Death	0	(0.00%)	TLR total	4	(3.10%)	TVF	nr	
Colombo, A. et al. 2003	TAXUS-NIR (MR)	Cardiac death	nr		TLR CABG	0	(0.00%)	Angiography	nr	
		MI	nr		TLR PTCA	4	(3.10%)	BRR at 6 months	nr	(4.70%)
TAXUS II	Paclitaxel 1 µg/mm²	Qwave MI	0	(0.00%)	TVR total	8	(6.20%)	THR	0	(0.00%)
180 days		Non-Qwave MI	3	(2.33%)	TVR CABG	1	(0.78%)			
	n = 129	MACE total	10	(7.75%)	TVR PTCA	nr				
					TVRNTL	3	(2.33%)			
	BMS	Death	0	(0.00%)	TLR total	19	(14.62%)	TVF	nr	
	NIR	Cardiac death	nr		TLR CABG	0	(0.00%)	Angiography	nr	
		MI	nr		TLR PTCA	nr		BRR at 6 months	nr	(20.20%)
	n = 130	Qwave MI	0	(0.00%)	TVR total	23	(17.69%)	THR	0	(0.00%)
		Non-Qwave MI	7	(5.38%)	TVR CABG	1	(0.77%)			
		MACE total	26	(20.00%)	TVR PTCA	nr				
					TVRNTL	4	(3.08%)			

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)		Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)		Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)	
Colombo, A. et al. 2003 TAXUS II 365 days	DES TAXUS-NIR (MR) Paclitaxel 1 µg/mm² n = 131	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 (0.00%) nr nr 2 (1.53%) 3 (2.29%) 13 (9.92%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	5 (3.82%) 0 (0.00%) 5 (3.82%) 9 (6.87%) 2 (1.53%) nr 2 (1.53%)	TVF THR	nr 1 (0.76%)
	BMS NIR n = 131	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 (0.00%) nr nr 1 (0.76%) 6 (4.58%) 28 (21.37%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	21 (16.03%) 0 (0.00%) nr 25 (19.08%) 2 (1.53%) nr 4 (3.05%)	TVF THR	nr 0 (0.00%)
Stone, G. W. et al. 2004 TAXUS IV 30 days	DES TAXUS EXPRESS Paclitaxel 1 µg/mm² n = 662	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 (0.00%) nr nr 0 (0.00%) nr 19 (2.87%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	nr 0 (0.00%) nr 0 (0.00%) nr nr nr	TVF THR	17 (2.57%) 2 (0.30%)
	BMS EXPRESS n = 652	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 (0.00%) nr nr 0 (0.00%) nr 16 (2.45%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	nr 0 (0.00%) nr 2 (0.31%) nr nr nr	TVF THR	16 (2.45%) 2 (0.31%)
Stone, G. W. et al. 2004 TAXUS IV 270 days	DES TAXUS EXPRESS Paclitaxel 1 µg/mm² n = 662	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 (0.00%) 9 (1.36%) 23 (3.47%) 5 (0.76%) 18 (2.72%) 56 (8.46%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	20 (3.02%) 4 (0.60%) 20 (2.42%) 31 (4.68%) 7 (1.06%) 24 (3.63%) nr	TVF Angiography BRR at 9 months THR	50 (7.55%) 292 (44.11%) 16 (5.48%) 4 (0.60%)
	BMS EXPRESS	Death Cardiac death	0 (0.00%) 7 (1.07%)	TLR total TLR CABG	74 (11.35%) 20 (3.07%)	TVF Angiography	94 (14.42%) 267 (41.00%)

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)			Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)			Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)		
		MI	24	(3.68%)	TLR PTCA	57	(8.74%)	BRR at 9 months	65	(24.34%)
	n = 652	Qwave MI	2	(0.31%)	TVR total	78	(11.96%)	THR	5	(0.77%)
		Non-Qwave MI	22	(3.37%)	TVR CABG	22	(3.37%)			
		MACE total	98	(15.03%)	TVR PTCA	59	(9.05%)			
					TVRNTL	nr				
	DES	Death	0	(0.00%)	TLR total	28	(4.38%)	TVF	64	(10.02%)
Stone, G. W. et al. 2004	TAXUS EXPRESS	Cardiac death	9	(1.41%)	TLR CABG	5	(0.78%)			
		MI	23	(3.60%)	TLR PTCA	28	(3.76%)	THR	4	(0.63%)
TAXUS IV	Paclitaxel 1 µg/mm²	Qwave MI	0	(0.00%)	TVR total	45	(7.04%)			
365 days		Non-Qwave MI	nr		TVR CABG	12	(1.88%)			
	n = 639	MACE total	69	(10.80%)	TVR PTCA	35	(5.48%)			
					TVRNTL	19	(2.97%)			
	BMS	Death	0	(0.00%)	TLR total	96	(15.17%)	TVF	123	(19.43%)
	EXPRESS	Cardiac death	8	(1.26%)	TLR CABG	23	(3.63%)			
		MI	31	(4.90%)	TLR PTCA	77	(12.16%)	THR	5	(0.79%)
	n = 633	Qwave MI	0	(0.00%)	TVR total	108	(17.06%)			
		Non-Qwave MI	nr		TVR CABG	25	(3.95%)			
		MACE total	126	(19.91%)	TVR PTCA	88	(13.90%)			
					TVRNTL	20	(3.16%)			
	DES	Death	1	(1.72%)	TLR total	0	(0.00%)	TVF	nr	
Park, S. J. et al. 2003	Non-Polymer	Cardiac death	nr		TLR CABG	0	(0.00%)			
		MI	1	(1.72%)	TLR PTCA	0	(0.00%)	THR	1	(1.72%)
ASPECT	Paclitaxel 1.3 µg/mm²	Qwave MI	0	(0.00%)	TVR total	nr				
30 days		Non-Qwave MI	1	(1.72%)	TVR CABG	nr				
	n = 58	MACE total	2	(3.45%)	TVR PTCA	nr				
					TVRNTL	nr				
	DES	Death	0	(0.00%)	TLR total	0	(0.00%)	TVF	nr	
	Non-Polymer	Cardiac death	nr		TLR CABG	0	(0.00%)			
		MI	2	(3.39%)	TLR PTCA	0	(0.00%)	THR	3	(5.08%)
	Paclitaxel 3.1 µg/mm²	Qwave MI	0	(0.00%)	TVR total	nr				
		Non-Qwave MI	2	(3.39%)	TVR CABG	nr				
	n = 59	MACE total	4	(6.78%)	TVR PTCA	nr				
					TVRNTL	nr				
	BMS	Death	0	(0.00%)	TLR total	0	(0.00%)	TVF	nr	
	Supra G	Cardiac death	nr		TLR CABG	0	(0.00%)			
		MI	1	(1.72%)	TLR PTCA	0	(0.00%)	THR	0	(0.00%)
	n = 58	Qwave MI	0	(0.00%)	TVR total	nr				

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)	Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)	Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)
		Non-Qwave MI 1 (1.72%) MACE total 1 (1.72%)	TVR CABG nr TVR PTCA nr TVRNTL nr	
Park, S. J. et al. 2003 ASPECT 180 days	DES Non-Polymer Paclitaxel 1.3 µg/mm² n = 58	Death 1 (1.72%) Cardiac death nr MI 1 (1.72%) Qwave MI 0 (0.00%) Non-Qwave MI 1 (1.72%) MACE total 4 (6.90%)	TLR total 2 (3.45%) TLR CABG 0 (0.00%) TLR PTCA 2 (3.45%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography nr BRR at 6 months nr (12.00%) THR 1 (1.72%)
	DES Non-Polymer Paclitaxel 3.1 µg/mm² n = 59	Death 0 (0.00%) Cardiac death nr MI 2 (3.39%) Qwave MI 0 (0.00%) Non-Qwave MI 2 (3.39%) MACE total 6 (10.17%)	TLR total 2 (3.39%) TLR CABG 0 (0.00%) TLR PTCA 2 (3.39%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography nr BRR at 6 months nr (4.00%) THR 3 (5.08%)
	BMS Supra G n = 58	Death 0 (0.00%) Cardiac death nr MI 1 (1.72%) Qwave MI 0 (0.00%) Non-Qwave MI 1 (1.72%) MACE total 3 (5.17%)	TLR total 2 (3.45%) TLR CABG 0 (0.00%) TLR PTCA 2 (3.45%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography nr BRR at 6 months nr (27.00%) THR 0 (0.00%)
Gershlick, A. et al. 2004 ELUTES 30 days	DES Non-Polymer Paclitaxel 0.2 µg/mm² n = 37	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR 0 (0.00%)

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)	Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)	Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)
	DES Non-Polymer Paclitaxel 0.7 µg/mm² n = 39	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR 0 (0.00%)
	DES Non-Polymer Paclitaxel 1.4 µg/mm² n = 39	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR 0 (0.00%)
	DES Non-Polymer Paclitaxel 2.7 µg/mm² n = 37	Death 1 (2.70%) Cardiac death nr MI 1 (2.70%) Qwave MI 0 (0.00%) Non-Qwave MI 1 (2.70%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR 1 (2.70%)
	BMS V-Flex Plus n = 38	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR 1 (2.63%)
Gershlick, A. et al. 2004 ELUTES 180 days	DES Non-Polymer Paclitaxel 0.2 µg/mm² n = 37	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 1 (2.70%) TLR CABG 0 (0.00%) TLR PTCA 1 (2.70%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography 34 (91.89%) BRR at 6 months 7 (20.59%) THR 0 (0.00%)

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)	Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)	Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)
	DES Non-Polymer Paclitaxel 0.7 µg/mm² n = 39	Death 0 (0.00%) Cardiac death nr MI 1 (2.56%) Qwave MI 0 (0.00%) Non-Qwave MI 1 (2.56%) MACE total nr	TLR total 0 (0.00%) TLR CABG 0 (0.00%) TLR PTCA 0 (0.00%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography 35 (89.74%) BRR at 6 months 5 (14.29%) THR 0 (0.00%)
	DES Non-Polymer Paclitaxel 1.4 µg/mm² n = 39	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 3 (7.69%) TLR CABG 0 (0.00%) TLR PTCA 3 (7.69%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography 37 (94.87%) BRR at 6 months 5 (13.51%) THR 0 (0.00%)
	DES Non-Polymer Paclitaxel 2.7 µg/mm² n = 37	Death 1 (2.70%) Cardiac death nr MI 1 (2.70%) Qwave MI 0 (0.00%) Non-Qwave MI 1 (2.70%) MACE total nr	TLR total 1 (2.70%) TLR CABG 0 (0.00%) TLR PTCA 1 (2.70%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography 31 (83.78%) BRR at 6 months 1 (3.23%) THR 1 (2.70%)
	BMS V-Flex Plus n = 38	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total nr	TLR total 4 (10.53%) TLR CABG 0 (0.00%) TLR PTCA 4 (10.53%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr Angiography 34 (89.50%) BRR at 6 months 7 (20.59%) THR 1 (2.63%)
Gershlick, A. et al. 2004 ELUTES 365 days	DES Non-Polymer Paclitaxel 0.2 µg/mm² n = 37	Death 0 (0.00%) Cardiac death nr MI 0 (0.00%) Qwave MI 0 (0.00%) Non-Qwave MI 0 (0.00%) MACE total 2 (5.41%)	TLR total 2 (5.41%) TLR CABG 0 (0.00%) TLR PTCA 2 (5.41%) TVR total nr TVR CABG nr TVR PTCA nr TVRNTL nr	TVF nr THR 0 (0.00%)

Citation Study Name Follow-up Time	Stent Characteristics & Sample Size (n)	Major Adverse Cardiac Events (MACE) n (%)			Revascularizations Rates Target Lesion (TLR), Target Vessel (TVR) n (%)			Target Vessel Failure (TVF), Follow-up Angiography, In-Stent Binary Restenosis Rate (BRR) Stent Thrombosis (THR) n (%)		
	DES Non-Polymer Paclitaxel 0.7 µg/mm² n = 39	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 nr 1 0 1 3	(0.00%) (2.56%) (0.00%) (2.56%) (7.69%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	2 1 2 nr nr nr nr	(5.13%) (2.56%) (2.56%)	TVF THR	nr 0	(0.00%)
	DES Non-Polymer Paclitaxel 1.4 µg/mm² n = 39	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 nr 0 0 0 4	(0.00%) (0.00%) (0.00%) (0.00%) (10.26%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	4 0 4 nr nr nr nr	(10.26%) (0.00%) (10.26%)	TVF THR	nr 0	(0.00%)
	DES Non-Polymer Paclitaxel 2.7 µg/mm² n = 37	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	1 nr 1 0 1 5	(2.70%) (2.70%) (0.00%) (2.70%) (13.51%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	2 0 2 nr nr nr nr	(5.41%) (0.00%) (5.41%)	TVF THR	nr 1	(2.70%)
	BMS V-Flex Plus n = 38	Death Cardiac death MI Qwave MI Non-Qwave MI MACE total	0 nr 0 0 0 nr	(0.00%) (0.00%) (0.00%) (0.00%)	TLR total TLR CABG TLR PTCA TVR total TVR CABG TVR PTCA TVRNTL	6 1 5 nr nr nr nr	(15.79%) (2.63%) (13.16%)	TVF THR	nr 1	(2.63%)

APPENDIX VIII: LIST OF PARTICIPATING CARDIAC CARE CENTRES IN ONTARIO

Hamilton Health Sciences – General Site	Hamilton, Ontario
Kingston General Hospital	Kingston, Ontario
London Health Sciences Centre	London, Ontario
Ottawa Heart Institute	Ottawa, Ontario
Rouge Valley Health System	Scarborough, Ontario
Southlake Regional Health Centre	Newmarket, Ontario
St. Mary's General Hospital	Kitchener, Ontario
St. Michael's Hospital	Toronto, Ontario
Sudbury Regional Hospital	Sudbury, Ontario
Sunnybrook & Women's College Health Sciences Centre	Toronto, Ontario
Trillium Health Centre	Mississauga, Ontario
University Health Network	Toronto, Ontario

APPENDIX IX: DATA COLLECTION FORM

DES DATA COLLECTION FORM

The following information should be collected for each separate vessel where a stent is used. The columns in the table refer to multiple stents for the same vessel. Please note that a separate table should be completed for each separate vessel. If more than 6 stents are placed in one vessel please use additional sheet.

	1st Stent	2nd Stent	3rd Stent	4th Stent	5th Stent
Lesion Location 1-35					
Lesion Type A, B1, B2, C					
Survival Dependent Vessel Yes/No					
Stent Type 1 = Drug Eluting 2 = Bare Metal					
If DES, which one: 1 = Cypher® (sirolimus) 2 = Taxus® (paclitaxel)					
Stent Size (mm to 2 decimal places)					
Stent Length (mm to no decimal place)					
Due to restenosis Y = Yes N = No U - Unknown					

Coding for Lesion Type:

Type A:
- **Concentric, no calcification**
- **No ostia or branches involved**
- **No thrombus or total occlusion**

Type B1 (one of the following):
- **Eccentric, calcification**
- **Ostia or branches involved**
- **Thrombus – total occlusion**
- **10-20 mm long or 49-90 degrees**

Type B2
Two or m ore of type B1 criteria

Type C:
- **> 2cm long, very tortuous**
- **>90 degree bend, old vein graft**
- **Total occlusion > 3 months**

Lesion Location / Survival Dependency (1-35):

1. **Prox RCA**
2. **Mid RCA**
3. **Dist RCA**
4. **R. post desc**
5. **R post lat. Seg**
6. **1st R post lat.**
7. **2nd R post lat.**
8. **3rd R post lat.**
9. **inf Sept.**
10. **Acute marg**
11. **Left main**
12. **prox. LAD**
13. **Mid LAD**
14. **Dist LAD**
15. **1st Diag**
16. **2nd Diag**
17. **1st Sept**
18. **prox Circ**
19. **Mid/Distal Circ**
20. **1st OM**
21. **2nd OM**
22. **3rd OM**
23. **L. atriove**
24. **1st L post lat.**
25. **2nd L post lat.**
26. **3rd L post lat.**
27. **LP desc**
28. **SVG-LAD**
29. **SVG-CIRC**
30. **SVG-RCA**
31. **LIMA**
32. **Other**
33. **Intermediate (ramus)**
34. **Undeployed/Undelivered**
35. **RIMA**

APPENDIX X: DATA ELEMENTS FROM DRUG-ELUTING STENTS TABLE CARDIACCESS

Field Description	Values	Type	Field Name
Lesion Location *(also anatomical location)*		Numeric	Lesion_Location
Right Coronary Artery (RCA)	1. Prox RCA		
	2. Mid RCA		
	3. Dist RCA		
	4. R Post Desc		
	5. R Post lat. Seg		
	6. 1st R post lat		
	7. 2nd R post lat.		
	8. 3rd R post lat.		
	9. inf Sept.		
	10. Acute marg		
Left Main Coronary Artery	11. Left main		
Left Anterior Descending (LAD)	12. prox. LAD		
	13. Mid LAD		
	14. Dist LAD		
	15. 1st Diag		
	16. 2nd Diag		
	17. 1st Sept		
Circumflex (CIRC)	18. prox Circ		
	19. Mid/Distal Circ		
	20. 1st OM		
	21. 2nd OM		
	22. 3rd OM		
	23. L. atriove		
	24. 1st L post lat.		
	25. 2nd L post lat.		
	26. 3rd L post lat.		
	27. LP desc		
Saphenous Vein Grafts	28. SVG-SAD		
	29. SVG-CIRC		

Field Description	Values	Type	Field Name
	30. SVG-RCA		
Other Grafts	31. LIMA		
	32. Other		
	33. Intermediate (ramus)		
	35. RIMA		
	34. Undeployed/Undelivered		
Lesion Type	A	Text	Lesion_Type
	B1		
	B2		
	C		
Survival Dependent Vessel	Yes	Numeric	Survival_Dependent_Vessel
	No		
Stent Type	1 = Drug Eluting	Text	Stent_Type
	2 = Bare Metal		
DES Type	1 = Cypher (sirolimus)	Numeric	Company_Name
	2 = Taxus (paclitaxel)		
Stent Size (mm to 2 decimals)	2.00 – 5.00 (by 0.25 increments)	Numeric	Stent_Size
Stent Length (mm)	06 - 26	Numeric	Stent_Length
	28		
	30		
	32		
	33		
	38		
	40		
	45		
Due to Restenosis	Y = Yes	Text	Due_to_Restenosis
	N = No		
	U = Unknown		

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