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Coronary artery disease and myocardial revascularisation failure: diagnosis, mechanisms, prevention and management

Róisín Colleran

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Vorsitzende(r): Prof. Dr. Maximilian Reichert

Prüfer der Dissertation:

1. Prof. Dr. Adnan Kastrati
2. Prof. Dr. Michael Joner
3. Prof. Dr. Karl-Ludwig Laugwitz
4. Prof. Dr. Willibald Hochholzer

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LIST OF ABBREVIATIONS

CABG = coronary artery bypass graft

CAD = coronary artery disease

CI = confidence interval

COR = class of recommendation

CTA = computed tomography angiography

DES = drug-eluting stent(s)

DIVA = Drug-Eluting Stents vs Bare Metal Stents In Saphenous Vein Graft Angioplasty

ICA = invasive coronary angiography

ISR = in-stent restenosis

FFR = fractional flow reserve

FFR_{CT} = computed tomography-derived fractional flow reserve

HR = hazard ratio

LOE = level of evidence

LMCA = left main coronary artery

MACE = major adverse cardiac events

PCI = percutaneous coronary intervention

PCB = paclitaxel-coated balloon

PES = paclitaxel-eluting stent

QOL = quality of life

RRISC = Reduction of Restenosis In Saphenous vein grafts with Cypher SES

SES = sirolimus-eluting stent

SPES = sirolimus- and probucol-eluting stent

SVG = saphenous vein graft

TLR = target lesion revascularisation

ZES = zotarolimus-eluting stent

GLOSSARY OF CLINICAL TRIAL ACRONYMS*

BEST = Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease

EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation

FREEDOM = Future Revascularisation Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease

ISAR-CABG = Is Drug-Eluting-Stenting Associated with Improved Results in Coronary Artery Bypass Grafts?

ISAR-DESIRE 3 and 4 = Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 1, 2 and 3

ISAR-TEST 5 = The Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus- Eluting Stents (ISAR-TEST 5)

NOBLE = Nordic-Baltic-British Left Main Revascularisation

PLATFORM = Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource IMpacts

PRECOMBAT = Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease

SOS = Stenting of Saphenous Vein Grafts

SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery

*trial acronyms are not expanded in the text

ABSTRACT

Coronary artery disease (CAD) is one of the leading causes of death and disability worldwide. Significant advances have been made in the diagnosis of CAD in recent years. In an observational study, we showed that in patients with suspected obstructive CAD treated in the German healthcare system, a novel strategy of initial computed tomography angiography (CTA) +/- CTA-derived fractional flow reserve compared favourably with usual initial invasive coronary angiography (ICA) and reduced the rate of angiography showing no obstructive CAD, cumulative radiation exposure, and cost and improved quality of life, with no increase in adverse clinical events at 1 year.

Myocardial revascularisation is an important component of management for patients with coronary artery disease. Revascularisation failure – both percutaneous and surgical – is associated with significant morbidity and mortality. It has been hypothesized that the polymer coatings used on drug-eluting stents (DES) may play a role in revascularisation failure. In two patient subgroups at high risk of stent failure (diabetic patients and patients with STEMI), we showed that a polymer-free sirolimus- and probucol-eluting stent (SPES) was as safe and effective as a conventional durable polymer zotarolimus-eluting stent (ZES) at 5 years. In the largest randomized trial investigating polymer free DES, we showed comparable clinical safety and efficacy with polymer-free SPES and conventional durable polymer ZES in all-comer patients at 10-year follow-up, confirming durability of the results observed at 1 year. The incidence of stent thrombosis was low and comparable in both groups. However, cumulative adverse event rates were high, highlighting an unmet need for improving secondary prevention measures in patients undergoing PCI. In a dedicated

mechanistic study of DES-restenosis, we showed that the presence or absence of polymer coating on the restenosed DES did not impact angiographic or clinical outcomes after repeat PCI. This speaks against a role of polymer coating on the restenosed stent in the poorer outcomes after treatment of restenosis in DES versus bare metal stents. In-stent neoatherosclerosis is an important final common pathway for stent failure. We established a large animal model of neoatherosclerosis. We showed that a pro-healing stent improved vascular endothelium integrity compared with a conventional DES. In adjunctive cell culture experiments, incomplete endothelial integrity was confirmed as a key factor in neointimal foam cell formation after DES implantation. A pro-healing stent might reduce neoatherosclerosis formation and stent failure compared with conventional DES.

In patients with stent failure, angioplasty with drug-coated balloon is a recommended treatment option according to clinical practice guidelines. Paclitaxel-coated balloons (PCB) are the most frequently used in routine practice. The efficacy of PCB for treatment of in-stent restenosis is dependent on the excipient used in its coating. There is concern that the fragile composition of DCB coatings may result in distal particulate embolization, which might have adverse clinical impacts. In a non-randomized comparison, we showed that treatment of DES-restenosis with a PCB with a BTHC excipient was associated with similar angiographic outcomes at 6-8 months and clinical outcomes at 1 year to an iopromide-excipient PCB. In the setting of a randomized trial investigating treatment of DES-restenosis, we showed DCB angioplasty was not associated with a greater rise in high sensitivity troponin compared to repeat DES implantation or balloon angioplasty. This speaks against clinically relevant distal particulate embolization of DCB coating during DCB angioplasty.

The high efficacy of contemporary DES has facilitated expansion of stenting to high-risk patient subsets. In patients with significant LMCA stenosis, in a comprehensive meta-analysis of clinical trials, we showed that PCI with newer generation DES has a comparable risk of all-cause death, myocardial infarction, or stroke compared to CABG at long-term follow-up. However, the risk of repeat revascularisation is higher with PCI. The lack of difference in hard clinical endpoints suggests that either revascularisation strategy is acceptable, depending on patient preference and local expertise. A proportion of patients treated with CABG suffer clinically important graft failure at follow-up and usually require percutaneous revascularisation due to the risks associated with repeat surgery. In patients with bypass graft failure undergoing PCI of vein graft lesions, we showed that the efficacy advantage of DES over bare metal stents demonstrated at 1 year was lost at 5 years because of late catch-up in TLR in the DES group. This is likely caused by delayed arterial healing. In addition, neoatherosclerosis, which is more common with DES than bare metal stents might be more pronounced in vein grafts compared with native coronary arteries.

1. INTRODUCTION

1.1 Diagnosis of coronary artery disease requiring myocardial revascularisation

Coronary artery disease (CAD) is one of the leading causes of death and disability worldwide. European clinical practice guidelines recommend invasive coronary angiography (ICA) as the initial test for diagnosis of obstructive coronary artery disease (CAD) in patients with a high clinical likelihood, severe symptoms refractory to medical therapy or typical angina at a low level of exercise, and clinical evaluation that indicates high event risk.[1] Non-invasive functional imaging for myocardial ischaemia or coronary computed tomography angiography (CTA) is recommended as the initial test in all other patients in whom obstructive CAD cannot be excluded by clinical assessment alone (COR I, LOE B).[1]

While CTA provides anatomical assessment of the coronary vasculature, it is limited by the lack of functional assessment of stenoses, which may result in increased rates of ICA compared with non-invasive functional testing.[2] CT-derived FFR (FFR_{CT}) is a novel diagnostic tool that may address this limitation by providing functional information obtained by non-invasive means.[3] A number of trials have validated its use against invasive FFR.[4-6] The PLATFORM study showed that coronary CTA/FFR_{CT}, as an alternative initial diagnostic strategy in patients planned for ICA, was associated with a significantly lower rate of ICA showing no obstructive CAD at 90 days,[7] with no adverse impact on clinical events or quality of life (QOL) at 1 year.[8] The FFR_{CT} strategy was also associated with reduced resource use and lower cost.[8,9]

In patients with suspected CAD, diagnostic evaluation practices differ from country to

country. In the German healthcare system, specifically, a higher rate of ICA is observed in comparison with other European countries or the USA.[10-12] We investigated the comparative efficacy of a novel CTA/FFR_{CT} diagnostic strategy in patients being evaluated for CAD in collaborating hospitals in Germany.

1.2 Myocardial revascularisation failure

Myocardial revascularisation – either by PCI or coronary artery bypass graft (CABG) surgery – is one of the most frequently performed medical intervention worldwide.[13,14] Current revascularisation techniques provide excellent clinical outcomes [13,15] though depending on baseline risk and duration of follow-up, up to 20% of patients experience myocardial revascularisation failure, requiring a repeat revascularisation procedure. Understanding the mechanisms of myocardial revascularisation failure as well as its prevention and management is, therefore, an important endeavour in our research and daily clinical practice and forms the basis of this thesis.

1.3 The evolution of surgical and percutaneous myocardial revascularisation

1.3.1 Coronary artery bypass graft surgery

The first successful coronary artery bypass graft (CABG) surgery was done on May 2, 1960 by Robert Goetz at the Albert Einstein College of Medicine-Bronx Municipal Hospital Center, New York, who performed an IMA-right coronary artery anastomosis using a nonsuture technique with a tantalum ring as a connector device.[16] The first sutured anastomosis of an IMA to the LAD – which remains the gold standard of the CABG surgery – is believed to have been done by Vasilii Kolesov on February 25th, 1964.[17] Rene Favaloro at the Cleveland Clinic, now considered the father of CABG, was the first surgeon to systematically perform CABG

with reproducible results and is credited with establishing the benefits of saphenous vein grafting.[18] CABG was adopted into widespread clinical practice throughout the 1970s, becoming standard of care for treatment of care for treatment of obstructive CAD and offering the only means of myocardial revascularisation for almost a decade.

1.3.2 Balloon angioplasty

A German physician, Andreas Grünzig, developed the first functional coronary balloon catheter and performed the first successful non-operative balloon angioplasty in a human at the University Hospital in Zurich, Switzerland on 16th September 1977. Balloon angioplasty for the treatment of CAD became widely adopted as an alternative to CABG for myocardial revascularisation, facilitated by continuous refinements in devices and techniques over the ensuing years. However, despite the success of balloon angioplasty, there were some important limitations. First, acute results were unpredictable, with high rates of abrupt vessel closure occurring in the first few hours or days, resulting from dissection and thrombosis and often necessitating emergency repeat balloon angioplasty or CABG.[19] Second, restenosis developed in up to 40% of lesions in the months after PCI due to a combination of plaque prolapse, elastic recoil, constrictive remodeling and neointimal hyperplasia– an iatrogenic problem related to acute vessel wall injury.[20]

1.3.3 Bare metal stents

The first coronary stent was developed to overcome the mechanical limitations of balloon angioplasty by providing a scaffold to the vessel. The first human coronary stent

implantations were performed by Jacques Puel in Toulouse, France and by Sigwart in Lausanne weeks apart in March and April 1986, respectively.[21]

Initially used for bail-out in cases of abrupt vessel closure with balloon angioplasty, stent implantation succeeded in providing more stable acute results by covering dissection flaps and disrupted plaques, and by providing radial strength to the vessel, which prevented elastic recoil (resulting in higher acute gain) and reduced late constrictive remodeling (reducing restenosis). Randomized trials subsequently confirmed the superior efficacy of stent implantation over balloon angioplasty with respect to angiographic and clinical restenosis in patients with stable CAD.[22,23]

However, rates of acute and subacute vessel closure remained high. The reduced rates of acute vessel closure caused by dissection were offset by high rates of early stent thrombosis (ST) caused by exposure of metal stent struts to circulating blood. Use of intense anticoagulation regimens to prevent this complication after stenting led to high bleeding rates. [22,23] The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial showed that dual antiplatelet therapy (DAPT) compared with oral anticoagulation after stenting reduced both early ST and bleeding complications,[24] establishing DAPT as standard of care after PCI to this day.

The major unsolved limitation with bare metal stents was in-stent restenosis (ISR) caused by neointimal hyperplasia – a healing response to the vessel wall trauma caused by stent implantation – necessitating repeat intervention in approximately 25% of cases. The ISAR STEREO trials investigated the importance of stent design in reducing restenosis and showed

that thinner struts reduced restenosis rates compared with thicker struts,[25,26] a finding that continues to have important implications, with thin struts being the standard of current stent technology.[27]

1.3.4 Drug-eluting stents

Drug-eluting stents (DES) were developed to suppress neointimal hyperplasia, by incorporating anti-mitotic or immunosuppressive agents to inhibit smooth muscle cell proliferation, the key component of neointimal overgrowth. Early DES had 3 key components: the stent backbone (composed of stainless steel), the active drug (sirolimus or paclitaxel), and the carrier polymer (to control release of the active drug). DES succeeded in halving restenosis rates compared with bare metal stents.[28,29]

However, the observation of increased rates of very late ST with early generation DES led to the need for further refinement. Late ST was attributed to delayed healing of the stented arterial segment, which predisposed to thrombus formation on uncovered struts.[30] Delayed arterial healing was partly caused by an inflammatory response to durable polymer stent coatings.[31] To tackle the limitations of early generation DES, newer generation DES employ (i) metal alloys to allow thinner struts, while maintaining radial strength; (ii) an antiproliferative agent based on sirolimus or one of its analogues, based its superior efficacy over paclitaxel in early DES,[32] and (iii) more biocompatible polymers (either durable or biodegradable) or no polymer, to reduce the risk of polymer-associated inflammation. Newer generation DES have proven safer than earlier devices and clinical practice guidelines recommend their use across the spectrum of patients undergoing stent implantation.[33]

1.4 Limitations of DES: stent failure, delayed arterial healing, neoatherosclerosis and polymer coating

Despite these measures, newer generation DES have low but persistent rates of late stent failure caused by in-stent restenosis or stent thrombosis, particularly in certain high-risk patient and lesions subsets. In-stent restenosis is the most common mechanism of late stent failure and the most common reason for target lesion revascularisation (TLR). Recent large-scale randomized trials investigating newer generation DES generally report rates of clinical restenosis (clinically-indicated TLR) of 2-3% at one year, and up to 10% at 5 years, representing a significant clinical problem.[34] Moreover, in-stent restenosis is an independent predictor of mortality at 4 years.[35] Stent thrombosis is a less common, but potentially fatal cause of stent failure. Reported rates of definite stent thrombosis are up to 1% at 1 year and <2% at 5 years in recent large-scale randomized trials.[34]

Delayed arterial healing is the principal substrate underlying late stent failure. Delayed arterial healing causes endothelial cell dysfunction, which seems to predispose to neoatherosclerosis,[36,37] which is the process of accelerated *de novo* atherosclerosis within the stented segment and a common underlying mechanism of in-stent restenosis and stent thrombosis.[389,15,16] Neoatherosclerosis occurs more frequently and earlier in DES compared with bare metal stents, with a similar frequency in early and newer generation DES.[49] Preclinical studies represent an important means to investigate the pathophysiology and key etiological factors facilitating neoatherosclerosis formation.

1.4.1 Polymer-free DES

The efficacy of DES in suppressing neointimal hyperplasia is dependent on the controlled release of the antiproliferative drug from the stent backbone.[39,40] Drug release kinetics are controlled by polymer coatings on most DES.[19] Polymer-free DES were developed with the aim of avoiding polymer-associated inflammation. However, early polymer-free DES showed inferior clinical efficacy to durable polymer DES,[39,41] because the antiproliferative drug was released too rapidly. To address this, the polymer-free sirolimus- and probucol-eluting stent (SPES) employs an alternative method to control release of the active drug, by incorporating probucol, an active drug targeted at another element of the restenotic response cascade. The primary analysis of the ISAR-TEST 5 trial showed that the antirestenotic efficacy of the polymer free SPES was comparable to that of high performance newer generation durable polymer DES at 1 year.[42,43] Subsequently, we investigated long-term outcomes in high-risk subgroups, including patients with diabetes, patients presenting with acute myocardial infarction and patients undergoing repeat stenting for stent failure and very long-term outcomes in all-comer patients at extended 10-year follow-up.

1.5 Patient subgroups at high-risk of stent failure

1.5.1 Patients with diabetes mellitus

Approximately one quarter of patients undergoing myocardial revascularisation are diabetic.[44] Accelerated atherosclerosis in diabetic patients results in more complex coronary anatomy with small and diffusely diseased vessels, accounting for higher rates of stent failure, with the requirement for repeat revascularisation compared with non-diabetic patients.[45-48] Although second-generation durable polymer DES have demonstrated good

efficacy and safety in the treatment of CAD in diabetic patients,[49,50] the issue of persistent inflammatory response to durable polymer DES coatings is particularly relevant in diabetic patients because of their higher risk of restenosis and atherothrombosis compared with non-diabetic patients.[51,52] Indeed, higher incidences of in-stent neoatherosclerosis and very late stent thrombosis are observed in diabetic patients compared with non-diabetic patients.[53,54]

1.5.2 Patients presenting with ST-segment elevation myocardial infarction (STEMI)

DES are more efficacious than bare metal stents in the setting of STEMI.[55] However, this may be at the expense of safety: higher rates of late stent thrombosis have been shown in DES compared with bare metal stents implanted in STEMI patients.[56,57] This is partly explained by exaggerated delayed arterial healing and polymer-associated inflammation in STEMI patients: autopsy studies of stented arterial segments in DES demonstrate more inflammation and less healing at acute myocardial infarction culprit sites compared with culprit sites in stable angina patients.[58] In STEMI patients, the long-term performance of polymer-free DES technology has not been investigated.

1.5.3 Patients with DES-restenosis

Percutaneous treatment of in-stent restenosis is associated with higher rates of recurrent restenosis than *de novo* lesions.[59] Moreover, treatment of DES-restenosis compared with bare metal stent-restenosis is associated with a higher risk of recurrent restenosis, requirement for repeat revascularisation and subsequent adverse events.[60-64] This may be attributable to differences in pathophysiology: neoatherosclerosis, which is a more frequent cause of DES-restenosis, might be associated with poorer outcomes.[36] Alternatively, patients who develop

DES-restenosis may have higher rates of resistance or hyporesponsiveness to antirestenotic drugs.[62] Another possibility is that inflammatory reactions to the polymer coating on the restenosed stent may play a role. It is, therefore, conceivable that outcomes after treatment of DES-restenosis may differ in polymer-free and polymer-coated DES.

1.6 Durability of results in coronary device trials

Because of the permanent nature of implanted coronary stents and the fact that most patients enrolled in clinical trials are middle aged – a significant proportion of whom will have a long life expectancy with the implanted device – [65-69] systematic long-term follow-up of randomized trials investigating coronary devices is an important element of their evaluation. Both device approval and clinical practice guidelines are informed by the primary results of randomized trials, frequently assessed at 1 year post-PCI. In historical trials with bare metal stents, stent failure was expected to occur within the first year and due to logistical and funding challenges, few trials incorporated longer follow-up to 3, or occasionally, 5 years, with a scarcity of follow-up data beyond this time.[19] However, DES failure tends to occur later, with late catch-up in restenosis sometimes seen beyond 1 year.

While treatment effects of coronary devices at long-term follow-up are often consistent with primary results, in some instances, important differences are seen. For example, long-term follow-up of two DES trials in recent years showed that the efficacy advantage demonstrated for one DES over another with respect to TLR was lost at longer-term follow-up.[70-73] Moreover, safety concerns or advantages related to DES sometimes only become apparent during long-term follow-up, long after the primary results have been reported.[74-76] This is particularly relevant with respect to infrequently occurring late events such as stent

thrombosis, where long-term follow-up may be required to yield enough events to show a statistical difference between devices.

1.7 Treatment of stent failure: drug-coated balloon technology for in-stent restenosis

Drug-coated balloons (DCB) for treatment of in-stent restenosis were an important development by Bruno Scheller and colleagues at the University of Saarland. A DCB is a balloon catheter coated with a layer of antirestenotic drug mixed with an inert compound called an excipient. Paclitaxel is the antirestenotic drug used on most commercially because of its high lipophilicity, which facilitates effective drug transfer to the vessel wall with sustained biologic efficacy after a single, brief contact. As paclitaxel is hydrophobic and highly crystalline, it is dissolved in a hydrophilic non-polymeric excipient to prevent clumping and adhesion of particles on the balloon surface and to facilitate its transfer to the vessel wall. All clinically successful paclitaxel-coated balloons (PCB) employ an excipient. Iopromide was the first excipient used. Preclinical clinical testing shows that catheters coated with paclitaxel without excipient show poor drug transfer from the balloon surface to the target tissue and high levels of drug retention on the balloon catheter after angioplasty.[77,78] In addition, tissue levels of drug following DCB angioplasty are dependent not only on the presence or absence of excipient, but also on the excipient used.[77,78] In this respect, there is no basis to assume that there is a class effect for clinical performance of DCB.

DCB angioplasty is recommended for the treatment of coronary in-stent restenosis in European clinical practice guidelines.[79] These recommendations are primarily based on randomized trials investigating an iopromide-based PCB (SeQuent Please, B. Braun, Melsungen, Germany).[80-85] There are a number of alternative commercially available PCB.

One such device is a butyryl-tri-hexyl citrate (BTHC)-based PCB (Pantera Lux, Biotronik, Bülach, Switzerland). Comparative efficacy data for BTHC- versus iopromide-based PCB is scarce.

1.7.1 DCB and the risk of distal embolization of crystalline particles

Despite the use of hydrophilic excipient, PCB coatings are more fragile in composition than DES coatings. There is concern about the potential for distal particulate embolisation of PCB coatings. Preclinical studies of PCB in porcine coronary artery models showed that only small proportions of the coating are taken up by the vessel wall or remain on the balloon surface, with much of the drug coating being unaccounted for.[86,87] Moreover, examination of downstream microvascular beds in preclinical studies occasionally reveals distal embolization of microparticles of matrix coating.[88] In clinical settings, this could conceivably translate into an increased risk of microvascular injury. One clinical study showed a transient reduction in coronary flow reserve (CFR) of unclear etiology immediately after DCB-angioplasty, [89] which may be explained by distal particulate embolisation. This provides a rationale for investigation of evidence of myocardial injury after PCB angioplasty compared with DES implantation or plain balloon angioplasty.

1.8 Percutaneous versus surgical treatment of left main coronary artery (LMCA) disease

The high efficacy of contemporary DES has facilitated expansion of stenting to high-risk patient subsets. Compared with other sites, LMCA disease is associated with a higher risk of mortality and myocardial injury owing to the larger amount of subtended myocardium.[90,91] CABG has long been standard of care for LMCA revascularisation. However, CABG is limited by high rates of saphenous vein graft failure: reported vein graft occlusion rates are up to 27% within one

year after CABG and up to 50% of saphenous vein grafts fail within 10 years.[92-94] Moreover, due to significant advances in stent technology, PCI technique, and antithrombotic therapies, PCI has emerged as a valid alternative revascularisation strategy in certain patients,[90,91,95,96] with European and American guidelines recommending both CABG and PCI for the treatment of LMCA stenosis in patients with overall low- to intermediate complexity coronary artery disease (CAD).[97,98] The first two large-scale randomized trials comparing PCI using newer generation DES versus CABG for LMCA disease were recently reported and showed conflicting results.[99,100] We did a systematic review and meta-analysis of randomized trials comparing PCI to CABG for treatment of LMCA disease.

1.9 Treatment of bypass graft failure after coronary artery bypass graft surgery

Rates of vein graft failure after CABG are considerable. In view of the risks associated with repeat surgery, percutaneous intervention is usually preferred.[79,101] In fact, PCI of vein graft lesions accounts for up to 5-10% of all PCI procedures in some experiences.[102]

In keeping with findings in native CAD, all but one randomized trial comparing DES and bare metal stents in SVG lesions have shown favourable results for DES with respect to angiographic and clinical restenosis at short- to medium-term follow-up.[103-107] The primary analysis of ISAR-CABG showed superior clinical efficacy of DES compared with bare metal stents at one year, with respect to target lesion revascularisation (TLR). However, findings of these trials at longer term follow-up have been conflicting. Moreover, other trials have been limited by their small sample size and/or limited duration of follow-up. This provides a rationale for investigating the comparative efficacy of DES and bare metal stents at long-term follow-up.

2. THESIS AIMS

The aims of this thesis are as follows:

(i) to investigate whether a novel strategy of initial CTA combined with CT-derived FFR compared with ICA reduces rates of ICA showing no obstructive CAD in the setting of the German healthcare system;

(ii) to compare the long-term clinical safety and efficacy of polymer-free versus durable polymer coated DES technology in two patient subgroups at high risk of restenosis: patients with diabetes and patients presenting with STEMI;

(iii) to investigate the durability of the comparative efficacy and safety of polymer-free versus durable polymer coated DES technology in all-comer patients at 10-year follow-up of a randomized trial;

(iv) to investigate whether the presence or absence of polymer coating on restenosed DES impacts angiographic and clinical outcomes in patients who undergo repeat PCI;

(v) to develop a large animal model of neoatherosclerosis and investigate the role of delayed arterial healing with increased endothelial permeability in the development of neoatherosclerosis after DES implantation in a hypercholesterolaemic animal model;

(vi) to investigate the comparative angiographic and clinical efficacy of 2 PCBs with different excipient coatings for the treatment of DES-restenosis in a non-randomized comparison;

(vii) to investigate whether differences in myocardial injury, as measured by high sensitivity biomarkers, are detectable after coronary DCB-angioplasty compared with plain balloon angioplasty or DES in the treatment of DES-restenosisin the setting of a randomized trial;

(viii) to compare long-term clinical outcomes after PCI with DES or CABG for treatment of LMCA disease; and

(ix) to compare the efficacy and safety of DES and bare metal stents in vein graft lesions at 5-year follow-up of a randomized trial.

3. METHODS AND MATERIALS

3.1 Protocol for the German substudy of the PLATFORM trial

3.1.1 Study population, protocol and follow-up

PLATFORM is an observational, prospective, consecutive cohort, comparative effectiveness study (ClinicalTrials.gov number NCT01943903). Full details of the protocol were previously reported.[7] Symptomatic outpatients ≥ 18 years with an intermediate likelihood of obstructive CAD, whose physician had planned either non-invasive tests or ICA were enrolled between September 2013 and November 2014. Country of enrolment was a pre-specified subgroup. In the current study, we report the results in the group planned for ICA at German sites. Exclusion criteria were acute coronary syndrome or clinical instability, documented CAD, contraindication for CTA or FFR_{CT}, need for urgent or emergent procedure, or ICA ≤ 90 days before enrolment.

In patients with planned ICA, there were two prospective cohorts with consecutive enrolment. Patients in the first cohort received ICA as planned by the treating physician. In the second cohort, patients received an initial CTA in lieu of ICA, followed by FFR_{CT} analysis when requested by the treating site (advised if the CTA revealed ≥30% coronary stenosis). Non-invasive and invasive diagnostic testing (including CTA) was performed and interpreted on-site. All CTAs used a ≥64-slice multi-detector, single-or dual-source CT scanner and followed scanning protocols satisfying quality standards of the Society of Cardiac Computed Tomography.[108] QCA and FFR_{CT} measurements were performed by independent core laboratories. FFR_{CT} analysis was performed centrally by HeartFlow, Inc. (Redwood City, CA, USA).[4-6,109] Three-dimensional blood flow simulations in the coronary arteries were

performed using proprietary software with quantitative image quality analysis, image segmentation, and physiological modelling using computational fluid dynamics. Coronary blood flow was simulated under conditions that modelled intravenous adenosine to mirror pressure and flow data and the FFR numeric values obtained during ICA.[7] The lowest FFR_{CT} numeric value in each coronary artery and colour-scale representations of the coronary vasculature showing FFR_{CT} values in vessels >1.8 mm in diameter were provided to clinical sites. Local clinicians made all subsequent decisions regarding clinical management, following standard practice, including whether to alter management based on FFR_{CT} results. Patients were followed up by clinic visit at 90 days, 6 months and 1 year after enrolment.

3.1.2 End Points and Definitions

The primary end-point was the rate of ICA at ≤ 90 days showing no obstructive CAD. Obstructive CAD was defined as stenosis of ≥50% in any coronary artery in a vessel ≥ 2.0 mm in diameter by core laboratory QCA or invasive FFR <0.80, in the absence of this degree of stenosis. Secondary end-points included clinical, economic and QOL outcomes at 1 year. The clinical secondary endpoints were 1) a composite of major cardiovascular events (MACE) at 1 year including all-cause mortality, myocardial infarction, and unplanned hospitalisation for chest pain leading to urgent revascularisation and 2) MACE plus vascular events within 14 days of procedures. MACE events were adjudicated by an event adjudication committee blinded to the treatment groups, based on standard, prospectively determined definitions.[110] Cumulative radiation exposure from all cardiovascular tests and procedures was determined over 1 year after enrolment.[7]

Medical resource use including non-invasive tests, CTA, invasive tests, coronary

revascularisation procedures, and clinical events from enrolment through 1 year was shown. Cumulative medical costs (in euro, using German cost weights) over 1 year were calculated on a per-patient basis. Cost data were obtained using reimbursement rates for privately insured patients from the 2016 German doctor's fee schedule (GOÄ) for outpatient examinations and the 2016 German Diagnosis-Related Groups (G-DRG) system for inpatient investigations. The G-DRG system operates on a flat-fee principle based on the final documented diagnosis on discharge, taking into account factors such as co-morbidities and length of stay. GOÄ reimbursement, on the other hand, operates on a fee-for-service basis for privately insured patients. FFR_{CT} cost weight was set at zero as there is currently no G-DRG or GOÄ cost-weight at this time. QOL was assessed at baseline and 1 year using the Seattle Angina Questionnaire (SAQ), the EuroQOL scale (EQ-5D) and the EuroQOL visual analogue scale and the change from baseline was compared between the patient cohorts.

3.1.3 Statistical analysis

Continuous data are presented as mean ± SD and were compared using Student's t-test or the Wilcoxon rank-sum test. Categorical variables are presented as counts (percentages) and were compared using the Pearson chi-square test or Fisher's Exact Test where the expected cell value was < 5. The level of statistical significance was set to 0.0025 using the Bonferroni correction to adjust for multiple comparisons. The risk difference and 95% confidence interval (CI) were determined, and a one-sided Wald test (α error=0.025) for a risk difference < 0 evaluated whether CTA/FFR_{CT} was superior compared to usual testing. Cumulative radiation exposure was compared between groups using Student's t-test and the Wilcoxon rank sum test and is presented as mean ± SD and median (interquartile range). For economic analyses, unadjusted costs were compared between strategies using the non-parametric

Wilcoxon rank sum test on all patients and in the propensity-matched cohorts. A 95% CI for the difference in mean per-patient cost between usual care and FFR_{CT}-guided care cohorts was determined using empirical bootstrap resampling with 100,000 replicates. The Wilcoxon signed-rank test was used to analyse changes in QOL scores from baseline to one year of follow-up for the entire cohort, and the Wilcoxon rank sum test to compare QOL changes between groups. Changes in medication use from baseline to 1 year follow-up were compared between groups using logistic regression fit using generalized estimating equations. Statistical analyses were done using SAS version 9.3 (Cary, North Carolina, USA). A p-value < 0.05 was considered statistically significant, unless otherwise specified.

3.2 Study protocol for the ISAR TEST 5 randomized trial and subgroup analyses

3.2.1 Study population, device description and study protocol

Inclusion criteria were age > 18 years and ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥ 50% *de novo* stenosis located in native coronary arteries. Exclusion criteria were target lesion located in the LMCA; cardiogenic shock; and malignancy or other co-morbid condition with life expectancy less than 12 months or that may result in protocol non-compliance.

Patients were assigned in a 2:1 allocation to receive polymer-free SPES or permanent polymer zotarolimus-eluting stents (ZES). The polymer-free stent platform consists of a pre-mounted, sand-blasted, 316L stainless steel microporous thin-strut (87 μm) stent coated with a mixture of sirolimus, probucol, and shellac resin (a biocompatible resin used widely in the coating of medical tablets). The control stent, the second-generation permanent polymer zotarolimus-eluting stent (ZES) consists of a thin strut stent with a polymer coating

system consisting of three different polymers: a hydrophobic C10 polymer, a hydrophilic C19 polymer and polyvinylpyrrolidinone.

3.2.2 Subgroup analyses

All patients enrolled in the trial who had diabetes mellitus were included in the diabetes subgroup analysis of clinical outcomes at 5 years. Diabetes patients were a pre-specified subgroup of interest according to the trial protocol. All enrolled patients who presented with STEMI were included in the STEMI subgroup analysis of clinical outcomes at 5 years. Analysis of data from extended follow-up was approved by the institutional ethics committee responsible for the participating centres.

3.2.3 End Points and Definitions, Follow-Up

The primary endpoint of this study was the device-oriented composite endpoint (DOCE) of cardiac death, myocardial infarction related to the target vessel, or TLR. Additional endpoints included the patient-oriented composite endpoint (POCE) of all-cause death, any myocardial infarction or any revascularisation, the individual components of the composite endpoints and the incidence of definite/probable stent thrombosis (according to Academic Research Consortium criteria). Patients were followed up at 1 and 12 months and annually to 10 years in the setting of routine care by telephone call or office visit. All events were adjudicated and classified by an event adjudication committee blinded to the treatment group.

3.2.4 Statistical analysis

Patient-level data differences between groups were checked for significance using Student's t-test or Wilcoxon rank sum test (continuous data) or the chi-squared or Fisher's exact test where the expected cell value was < 5 (categorical variables). For lesion-level data, differences between groups were checked for significance using generalized estimating equations for non-normally distributed data in order to address intra-patient correlation in patients who underwent multi-lesion intervention.[111]

Event-free survival was assessed using the methods of Kaplan-Meier. Hazard ratios, confidence intervals and p-values were calculated from univariate Cox proportional hazards models. Analysis of the primary outcome was also performed for pre-specified subsets of interest: old and young patients (> and ≤ the median age), men and women, diabetic and non-diabetic patients, small and large vessels (< and ≥ the median value). Interaction between treatment effect and these covariates was assessed with Cox proportional hazards models. The analysis of primary and secondary endpoints was performed on an intention-to-treat basis.[112] Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, Wa, USA) was used and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses.

3.3 Study protocol for investigation of the influence of polymer coating in drug-eluting stent restenosis treated by repeat percutaneous intervention

3.3.1 Study population and study protocol

Patients enrolled in the ISAR-TEST 5 trial who underwent repeat PCI for DES-restenosis within two years after their index PCI were included in this study. We excluded patients who

underwent PCI for stent thrombosis. During the repeat PCI procedure, patients were treated with repeat stenting with early or newer generation DES, balloon angioplasty, or drug-coated balloon angioplasty.

3.3.2 Follow-up, End Points and Definitions

Follow-up angiography was scheduled 6 to 8 months after the repeat intervention, as part of routine practice in patients treated for ISR at the two participating institutions. The QCA analysis protocol is described in section 3.9. Clinical follow-up was performed either by telephone, letter, or office visit at 1 month, 1, and 2 years after the repeat intervention. All clinical events were adjudicated and classified by independent adjudicators. The primary endpoint of interest was the composite of all-cause death, myocardial infarction, or TLR 2 years after the repeat intervention. Secondary endpoints were binary restenosis and late luminal loss at angiographic follow-up (defined in section 3.9); and all-cause death, myocardial infarction, TLR, and definite/probable stent thrombosis at 2 years.

3.3.3 Statistical analysis

Statistical analysis is described in section 3.2.4. Multivariate analysis was performed for the primary endpoint and for TLR to adjust for differences in baseline characteristics and treatments for ISR between groups. Cox proportional hazards models were used for clinical outcomes based on survival analysis; logistic regression analysis was used for binary restenosis. In view of the number of patients included in the study we restricted inclusion to all variables with a p-value <0.1 in the univariate analysis.

3.4 Study protocol for investigation of the effect of endothelial integrity on the development of neoatherosclerosis in a hypercholesterolaemic rabbit iliac model

3.4.1 Study 1: Establishment of a rabbit model of neointimal foam cell formation

Male New Zealand White Rabbits were fed an atherogenic diet (1% cholesterol and 6% peanut oil, F4366-CHL, Bio-Serv Inc) for 5 weeks to induce hyperlipidemia. After 5 weeks (day 35), animals were switched to reduced cholesterol chow (containing 0.025% cholesterol) for 13 weeks. Balloon injury, followed by stenting of both iliac arteries (BMS, n=14, ProKinetic Energy, 3.0 x15 mm, strut thickness 80µm) was done at 1 week. Repeat denudation of the stented segments was done 8 weeks after stent implantation (day 63) using a 3F Fogarty catheter. OCT of stented segments was done at 13 weeks (day 91). Euthanasia was induced afterwards by pentobarbital overdose. Stented vessels underwent methyl methacrylate (MMA) embedding and standard histopathology. Serum cholesterol was measured at 0, 7, 35, 63, and 91 days.

3.4.2 Study 2: Proof of principle study comparing endothelialisation between 2 stents

Everolimus eluting stents (EES, n=5, Xience, 3.0x15mm, strut thickness 81µm) and customized integrin αvβ3 ligand coated stents (ICS, n=5, 3.0 x 15mm, strut thickness 80µm) were randomly allocated to iliac arteries of male hypercholesterolemic New Zealand White Rabbits (n=5) after 7 days for a duration of 12 weeks, as per study 1. As coating ligand, the cyclic RGD (Arg-Gly-Asp) peptide, c(RGDfK), a highly selective ligand for the αvβ3 integrin was functionalized by the incorporation of a spacer-linker unit at the lysine residue. After plasma treatment of the stents, they were immersion coated with the functionalized peptide, c(RGDfK) Ahx Ahx 1 (4 isothiocyanatophenyl)thioureidyl, facilitating anchorage via the isothiocyanate group to the amine groups of chitosan forming a thiourea link. Prior to

that BMS were spray-coated with chitosan-polylactide copolymer. Endothelial permeability was assessed by FITC-dextran (250/500 kDa) injected 1 hour prior to euthanasia at day 91 (after 13 weeks). After euthanasia and tissue harvest, stented vessels (n=10; 5 EES and 5 ICS) were bisected longitudinally and analysed using confocal, scanning and transmission electron microscopy (CM; SEM; TEM).

3.4.3 Light and immunofluorescence microscopy

MMA embedded sections were cut at 5µm thickness and stained with hematoxylin-eosin (H&E) and Movat Pentachrome. Immunoflourescent staining of endothelial cells was performed by labelling against CD31 (Dako Corp., Via Real - USA). Samples were incubated in 0.1% Triton X for 20 minutes and rinsed with PBS. The stent half was exposed overnight at 4°C to anti-CD31 (Dako Corp., Via Real – USA; dilution 1:20). The antibody reaction was visualized with an Alexa Fluor 555 donkey anti-mouse secondary antibody (Life Technologies, Carlsbad, CA dilution 1:150). DAPI (Life Technologies, Carlsbad - USA) was used as the nuclear counter stain. Selected cross-sections from rabbit iliac arteries were also stained with antibodies against RAM-11 (Dako Corp., Via Real – USA) to identify macrophages and foam cells.

3.4.4 Histopathological assessment of stented arteries

Stented vessels from study 1 were examined for neointimal foam cell infiltration and additional features of atherosclerotic plaque formation in rabbits. From each vessel, 3 histological sections (proximal, middle and distal) were examined. Histological sections were screened for neointimal foamy macrophages and assigned an ordinal score from 0 to 4 based on the quantity of foam cells along the vascular circumference (0= absent, 1=

occupying <25% of circumference, 2= 25-50% of circumference, 3= 50-75% of circumference, 4= occupying >75% of circumference) and the depth of foam cell accumulation relative to the endoluminal surface (0=absent, 1= <25% foam cells penetrating into the deeper neointimal layer, 2= 25-50% foam cells, 3= 50-75% foam cells, 4= >75% of foam cells penetrating into the deeper neointimal layer). Strut-based inflammation was graded as previously described [8]. Presence of distinct neointimal features such as microcalcification, hemorrhage, cholesterol clefts and neovascularization was assessed nominally and expressed as percentage of all scored quadrants [4,9]. For morphometry, the lumen and stent area and areas within the external and internal elastic lamina (EEL/IEL), were measured by computerized morphometry.

3.4.5 Confocal, scanning, and transmission electron microscopy

CM, SEM and TEM were done as previously described.[7,11,12113] Ultrastructural examination done to assess the morphology of endothelial cells at the luminal surface, the presence of inflammatory cells, the number of SMC layers and the presence of endothelial cell-cell contacts. Quantification of endothelial coverage was achieved with the help of a customized software algorithm (ImageJ 1.5, NIH, USA). Strut endothelialization was derived from the total area of endothelialization minus the area between stent struts.

3.4.6 Cell culture experiments

All cell culture experiments were performed three times. Human umbilical vein endothelial cells (HUVECs) were thawed by standard technique and grown in endothelial cell growth medium with endothelial cell growth supplement containing 5% fetal calf serum, 4 µL/mL

heparin, 10 ng/mL epidermal growth factor, 1 µg/mL hydrocortisone, 50 µg/mL gentamycin sulfate, and 50 ng/mL amphotericin B, at humidified 5% CO_2 atmosphere. Human coronary artery endothelial cells (HCAECs) were also thawed and grown in endothelial cell growth medium. In all experiments, HUVECs or HCAECs at passage 2-5 were used. HUVECs or HCAECs were seeded at a concentration of 200,000/mL on semipermeable membranes and incubated at 37°C and 5% CO_2. Monocytes (20,000/ml) were thawed in a 37°C water bath and transferred to a 15 mL conical tube containing DMEM (+ high glucose, + 4mM L-glutamine) supplemented with 10% heat inactivated human AB serum and 20% heat inactivated fetal bovine serum. After centrifugation for 10 minutes (150 G) monocytes were seeded in 12.5 ml^2 cell culture flasks. The cells were then maintained at 37°C with 5% CO_2 for 5-8 days before they were transferred in 12-well culture plates at 10^5 cells per well using standard detachment technique.

3.4.7 In Vitro Permeability Assay (Transwell Model)

In vitro surfaces were coated with a commercially available linear peptide RGD, known to promote cell attachment [14]. Negative control coatings using a non-specific peptide sequence were used to confirm the integrin-dependent anchorage of cells. Endothelial integrity was assessed by culturing HUVECs or HCAECs on semipermeable membranes (permeability assay) with a pore size of 0.4 µm. Confluent HUVECs and HCAECs were seeded on Transwell inserts and cultured with 500 µl medium in the upper chamber and 1500 µl medium in the lower chamber. After cells were arranged in a confluent monolayer, cell culture medium was replaced with medium supplemented with everolimus (ERL) in different concentrations (10nM, 100nM, 1µM, 10µM and 100µM) for 24h. Following this treatment, 10 µg/ml of

fluorescently labelled was added to fresh medium (upper chamber) supplying the HUVEC or HCAEC monolayer after rinsing with PBS. Finally, LDL concentrations in the upper and the lower chamber were measured after six hours of incubation at 37°C and 5% CO_2 using a spectrophotometer calibrated by standard curve with reference samples in fluorescent light mode. For CM, cells were then fixed and stained within the intact transwell chambers before membranes were carefully cut out of the inserts and transferred to glass slides.

3.4.8 Immunofluorescent staining

To assess the attachment of HUVECs/HCAECs on RGD coated surfaces a nuclear staining using DAPI (4',6-Diamidino-2-Phenylindole, Dihydrochloride) was applied. VE-Cadherin staining was done to visualise endothelial cell shape and junctions. After fixation (1:1 acetone-methanol), Triton X (1% in PBS) was used to permeabilize cells. Following a 10 min blocking step with 1% bovine serum albumin (BSA, diluted in PBS), a goat anti-human VE-cadherin primary antibody was used at a dilution of 1:200 in PBS with 1% BSA and incubated overnight at 2-8°C. A polyclonal donkey anti-goat secondary antibody was then applied to visualize cell shape and junctions. Phalloidin coupled to Alexa 488 (Dilution 1:30) incubated at 1:30 dilution for 30 minutes was used to stain the actin-cytoskeleton of cells.

3.4.9 Lipid Loading of Macrophages

To further investigate passage of lipoproteins through leaky endothelial cell junctions and their potential to transform macrophages into foam cells, co-cultures with human monocytes were done. Transwell inserts with endothelial cells pre-incubated with everolimus (10nM, 100nM, 1µM, 10µM and 100µM) for 24 hours were transferred to 12-

well plates in which monocytes had been cultured for 5-8 days. To avoid everolimus toxicity, endothelial cells were rinsed with PBS and supplied with fresh media before transferring them to monocyte cultures. Prior to lipid loading, cell culture media was switched to serum free RPMI (including 1% Nutridoma-SP and 1% penicillin-streptomycin). Endothelial cells were incubated with medium containing Alexa Fluor® 488 AcLDL at 10 µg/ml concentration for 24 hours to allow trans-endothelial passage of AcLDL particles. Both supernatants (upper and lower chamber) were collected and the cells were fixed in 10% formalin for oil-red-O staining. Four independent experiments with different monocyte donors were done.

3.4.10 Oil red O staining of lipid in macrophages

Lipid deposition was determined by Oil red O (ORO) staining. Monocytes were rinsed with PBS and fixed in 10% formalin for 10 minutes before adding 100% propylene glycol for 10 minutes. Propylene glycol was then removed and cells were stained in filtered ORO solution for 1.5 hours at room temperature. Finally, cells were differentiated in 85% propylene glycol for 5 minutes and rinsed in distilled water before being photographed.

3.4.11 Statistical analysis

Statistical analysis was done as previously described.[113]

3.5 Study protocol for investigation of the comparative efficacy of two paclitaxel-coated balloons with different excipient coatings in patients with drug-eluting stent restenosis

3.5.1 Study population, devices, and intervention protocol

Patients enrolled in two consecutive, multicentre randomized trials were included. Patients treated with iopromide-PCB were enrolled in the ISAR-DESIRE 3 trial; patients treated with BTHC-PCB were enrolled in the ISAR-DESIRE 4. Inclusion and exclusion criteria were identical in both studies. Inclusion criteria were restenosis occurring in a DES eluting sirolimus or an analogue of sirolimus and symptoms or objective evidence of myocardial ischemia in the presence of a restenosis ≥50% located in a native vessel DES. Exclusion criteria included target lesion located in the LMCA or a bypass graft, STEMI within the preceding 48 hours, cardiogenic shock, and severe renal insufficiency (glomerular filtration rate ≤ 30 ml/min). In ISAR DESIRE 3, intervention in more than one lesion (with the same randomly assigned treatment) was allowed, whereas in ISAR DESIRE 4, treatment of only 1 lesion was allowed. Therefore, only the first treated lesion per patient enrolled in ISAR DESIRE 3 was included in this analysis. In ISAR DESIRE 3, patients were allocated (1:1:1) to open-label PCB (SeQuent Please, PES (Taxus Liberté) or balloon angioplasty. Lesion preparation with plain balloon angioplasty was strongly recommended in the PCB group. Stenting was permitted in the case of large dissections with flow limitation or residual stenosis > 50% after multiple balloon dilatations. In ISAR-DESIRE 4, patients in both treatment groups were treated with angioplasty with the BTHC-PCB, but were randomly allocated to lesion preparation with scoring balloon versus conventional balloon angioplasty; only patients allocated to conventional balloon angioplasty were included in this analysis. The iopromide-based PCB is coated with 3 μg of paclitaxel per square millimeter of balloon surface with iopromide as an excipient (length 10 to 30 mm, diameter 2.5 to 4.0 mm). The BTHC-based DCB is also coated

with 3 μg of paclitaxel per square millimeter of balloon surface with BTHC as an excipient (length 10 to 30 mm, diameter 2.0 to 4.0 mm). All patients were evaluated at 1 and 12 months by phone or office visit. All patients were scheduled for repeat coronary angiography at 6-8 months (see QCA analysis protocol in section 3.9).

3.5.2 Study endpoints

The primary endpoint of both trials was in-segment percent diameter stenosis at 6-8 month angiography. The secondary endpoint of interest for the present analysis was the combined incidence of death, MI or target-lesion revascularisation at 1 year. Additional secondary endpoints included in-segment binary angiographic restenosis; death; MI; TLR (defined as any revascularisation procedure involving the target lesion due to luminal re-narrowing in the presence of symptoms or objective signs of ischemia at one year); and target lesion thrombosis at 1 year. Angiographic endpoints are defined in section 3.9.

3.5.3 Statistical analysis

Statistical analysis is described in section 3.2.4. To adjust for statistically significant differences in baseline characteristics between groups ($p<0.05$), multivariate analysis was performed using a cox proportional hazards regression model for time-to-event outcomes and a logistic regression model or analysis of variance for binary or continuous angiographic outcome measures, respectively. Variables included in the multivariate analyses were sex, hypertension, prior myocardial infarction, vessel size, balloon predilatation, and % diameter stenosis post-procedure.

3.6 Study protocol for investigation of changes in high-sensitivity troponin after drug-coated balloon angioplasty for drug-eluting stent restenosis

3.6.1 Patients, biochemistry measurements, follow-up and endpoints

Patients enrolled in the ISAR-DESIRE 3 trial (described in section 3.5) who had available baseline (pre-procedural) and post-procedural high sensitivity troponin T (hs-TnT) measurements were included. Troponin T was measured using a high-sensitivity assay in a cobas e 411 immunoanalyzer based on electrochemiluminescence technology (Roche Diagnostics). The limit of blank for this assay - the concentration below which analyte-free samples are found with a probability of 95% - is ≤3 ng/L. The functional sensitivity - the lowest analyte concentration that can be reproducibly measured with a coefficient of variation ≤10% - is ≤13 ng/L. The 99th upper reference limit is 14 ng/L. Patients underwent clinical follow-up at 1, 12 and 36 months by phone or office visit.

The primary endpoint was delta troponin, calculated by subtracting baseline from peak hs-TnT values (according to treatment arm). The secondary endpoint was 3-year all cause-mortality according to delta troponin by tertile (irrespective of the treatment arm).

3.6.2 Statistical analysis

Statistical analysis is described in section 3.2.4. To assess the association between magnitude of delta troponin and mortality, the study population was also divided into tertiles according to delta troponin level, irrespective of the treatment received. Differences across groups at baseline were checked for significance using analysis of variance (ANOVA) for continuous data and chi-squared test (or Fisher's exact test where the expected cell value was < 5) for categorical variables. Categorical variables were tested across groups with pairwise testing

only in cases of significant differences across groups using Student's t-test for continuous data and chi-squared test (or Fisher's exact test where the expected cell value was < 5) for categorical variables to check for significance.

3.7 Protocol for meta-analysis of randomized trials comparing percutaneous coronary intervention with newer generation DES to coronary artery bypass grafting in patients with left main coronary artery disease

3.7.1 Eligibility criteria

In a frequentist pair-wise meta-analysis in accordance with PRISMA and Cochrane Collaboration recommendations,[114,115] we included reports fulfilling the following criteria: (i) randomized clinical trial; (ii) LMCA disease; (iii) PCI versus CABG; (iv) exclusive use of DES; and (v) follow-up ≥3 years. Trials reporting follow-up <3 years were excluded to focus on long-term outcomes and to limit the influence of early non-significant differences.[116]

3.7.2 Literature search

Three authors (R.C., A.H.F., J.W.) independently searched PubMed, Scopus, EMBASE, Web of Knowledge and ScienceDirect electronic databases from December 18th, 2001 (first-in-man with DES) to February 1st, 2017. No language restrictions or specific clinical subsets were imposed. Scientific websites of interest and bibliographies of relevant reviews and book chapters on the topic were screened to minimize the risk of missing reports. Results of search process at level of title and abstract were merged in a single dataset. After removal of duplicates, full-text screening was performed with resolution of divergences by consensus.

3.7.3 Data extraction and feasibility assessment

Data from intention-to-treat analyses were used. For each analysis, trial-level risk estimates were extracted or calculated from log-rank test p-value and observed events in the two groups.[115,117] Trial-level clinical and angiographic characteristics were extracted. Data were collected in specific electronic spreadsheets. Meta-analysis feasibility and qualitative assessment of the included trials was done before statistical analyses.

3.7.4 Endpoints

The primary endpoint was a composite of all-cause death, myocardial infarction, or stroke at the longest available follow-up. The secondary endpoints were repeat revascularisation, individual components of the primary endpoint, cardiac death, stent/graft occlusion and a composite of all-cause death, myocardial infarction, stroke, or repeat revascularisation at longest available follow-up.

3.7.5 Bias assessment

Trial-level qualitative assessment was performed using the seven-domain Cochrane Collaboration tool.[115] The risk of bias was classified as “high”, “unclear”, or “low”.[115] We assessed reliability of our results for each outcome according to GRADE.[118]

3.7.6 Statistical analysis

Fixed-effect and random-effects models with inverse variance weighting using trial-level log hazard ratio (HR) and corresponding standard errors were applied.[119,120] Trial-level and pooled estimates were reported as HR and 95% CI; risk distribution was presented by forest plots with weighting according to random-effects models.[121] We assessed heterogeneity across trials

using between-study variance τ^2 and I^2 statistics.[115,119,122] Formal testing for uniform effect size across trials with significance set at 0.10 was performed.[119] Patients with SYNTAX scores 1-22 and 23-32[123] in the PRECOMBAT and EXCEL trials were synthesized by fixed-effect models.[99,124] Testing for difference between the subgroups with significance set at 0.05 was performed.[119] Individual patient data reconstruction was performed by extreme-magnification digitization of high-quality Kaplan-Meier curves. Retrieved spatial information, numbers at risk and events for each time interval were used to run a validated algorithm.[125] Reconstructed individual patient data were used for time-to-first-event Kaplan-Meier analyses to describe distribution of events over time and define cumulative incidence at 5-year follow-up. In a one-stage individual patient data meta-analysis, a shared frailty model accounting for clustering of patients across the original trials with semi-parametric penalized likelihood estimation of the hazard function was fitted to obtain the combined HR.[126] All analyses were performed with R 3.3.1.

With respect to the primary endpoint, several sensitivity and subgroups analyses were done: (i) inspection of the influence of individual trials by omitting each trial one at a time using random-effects model;[127] (ii) selection of patients with low-to-intermediate CAD complexity (SYNTAX score 1-32);[124] (iii) comparison according to DES generation;[15] (iv) reconstruction of individual patient data, Kaplan-Meier analysis and estimation of HR by shared frailty model.[118,128] We assessed influence of individual trials for the secondary endpoints and the impact of DES generation on repeat revascularisation and secondary composite endpoint.

3.8 Study protocol for the ISAR-CABG randomized trial

3.8.1 Patients and study design

ISAR-CABG is a randomized, multicentre, assessor-blinded, open-label, superiority trial. Primary results were previously reported.[105] Patients aged >18 years, with symptoms or objective evidence of myocardial ischemia in the presence of ≥50% *de novo* stenosis of a SVG were eligible for inclusion. Exclusion criteria included cardiogenic shock and malignancies or other co-morbid conditions with life expectancy <12 months. Patients were enrolled at four centres in Germany. Follow-up to 5 years was done as part of clinical routine and ethics committee approval was received for the study of long-term follow-up data.

3.8.2 Randomization, Study Procedures and Outcomes

Patients who met all inclusion criteria and no exclusion criteria were randomized in the order that they qualified. Immediately after the lesion was crossed with a guidewire, patients were randomly allocated patients undergoing SVG stenting were (1:1:1:3) to receive either DES (one of three types: permanent-polymer paclitaxel-eluting stents [Taxus], permanent-polymer sirolimus-eluting stents [Cypher], or biodegradable-polymer sirolimus-eluting stents [Yukon] or bare metal stents. Details of the study procedure and peri-procedural antithrombotic therapy were reported previously.[105]. All patients were followed up yearly by phone or office visit.

The primary endpoint was the combined incidence of death, myocardial infarction, or TLR at 5 years. Secondary endpoints in the present analysis were the combined incidence of death or myocardial infarction, TLR, and definite stent thrombosis. TLR was defined as any repeat

percutaneous intervention of the target lesion or bypass surgery involving the vessel supplied by the target venous graft in the presence of angiographic restenosis (defined in section 3.7) and either symptoms of ischaemia or a positive functional study corresponding to the area served by the target graft, or diameter stenosis of ≥70% at follow-up angiography in the absence of documented clinical or functional ischemia.

3.8.3 Statistical analysis

Statistical analysis is described in section 3.2.4. Additional pre-specified subsets for analysis of the primary outcome were in ISAR CABG were: SVG age (> and ≤ the median age), and SVG degeneration score >1 or ≤1).

3.9 Quantitative coronary angiography (QCA) analysis protocol

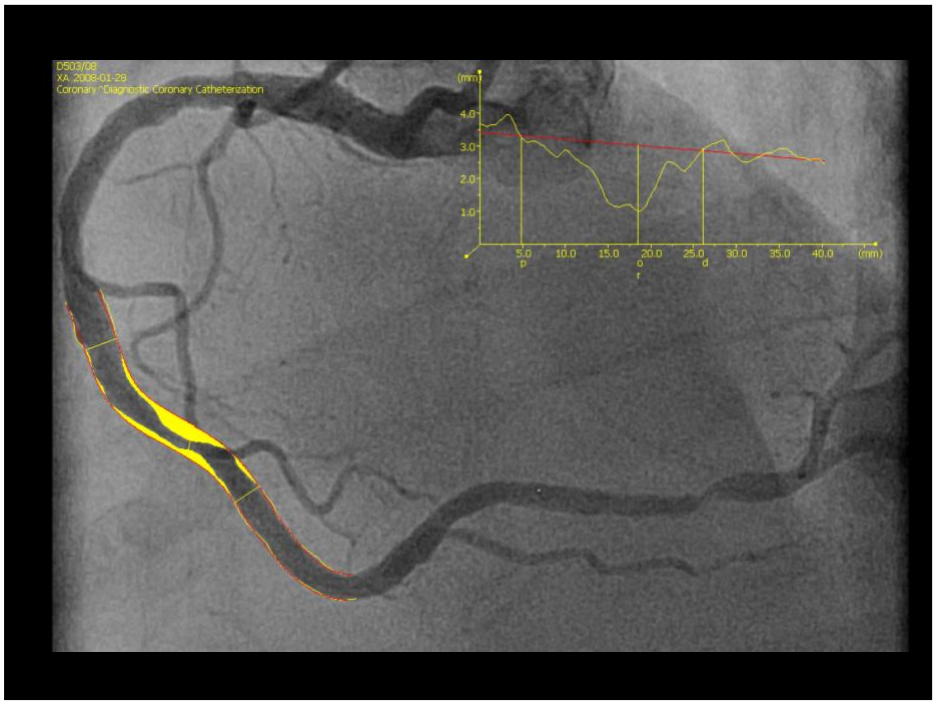
Baseline, post-procedure, and follow-up angiograms were digitally recorded and assessed offline in the QCA core laboratory (ISAR Centre, Deutsches Herzzentrum Munich) using an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems; **Figure 1**) by 2 independent operators unaware of treatment allocation. Qualitative morphological lesion characteristics and restenosis were characterised by standard criteria.[129,130]

Angiographic end points were:

- In-segment percentage diameter stenosis (%DS), defined as maximum diameter stenosis in the in-segment area at follow-up angiography
- In-segment binary angiographic restenosis, defined as diameter stenosis ≥50% in the in-segment area) at follow-up angiography

- In-stent late luminal loss (LLL), defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up angiography

***Figure 1**. QCA analysis with CMS version 7.1*

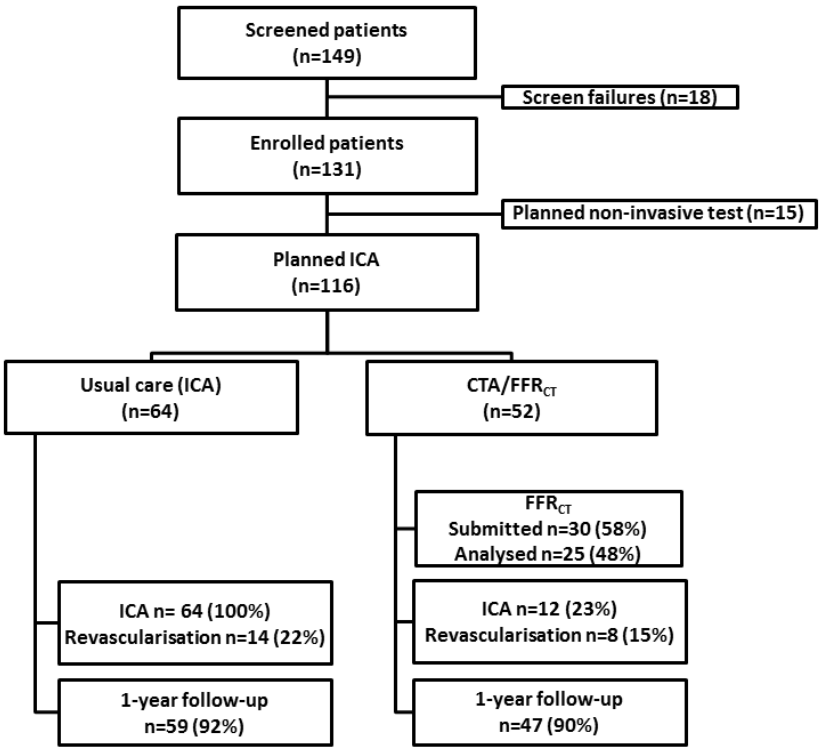


4. RESULTS

4.1 In patients with planned ICA for investigation of suspected CAD in Germany, initial CTA/FFR_{CT} was associated with a significantly lower rate of ICA showing no obstructive CAD compared with usual care

116 patients who were planned for ICA were enrolled at the three participating German sites between September 2013 and November 2014: 64 allocated to usual care and 52 allocated to CTA/FFR_{CT} (**Figure 2**). Pre-enrollment non-invasive testing had been done in 41 (64.1%) patients in the usual care group and 16 (30.8%) patients in the CTA/FFR_{CT} group (p<0.001). Complete follow-up data at one year was available for all but 5 patients in each group.

***Figure 2**. Flow chart of the German subgroup of the PLATFORM study*



CTA = computed tomography angiography; ICA = invasive coronary angiography; FFR_{CT} = fractional flow reserve estimated using computed tomography

Baseline patient characteristics are shown in **Table 1.** Compared with the CTA/FFR_{CT} cohort, patients in the usual care cohort were older, with a higher incidence of diabetes and higher pre-test probability of obstructive CAD.

Table 1. *Baseline characteristics of study participants*

	Planned invasive test (n = 116)		
Variable	**Usual care (n = 64)**	**CTA/FFR_{CT} (n = 52)**	**p-value**
Demographics			
Age, years	63.6±11.6	55.3±10.2	<0.001
Female sex	25 (39.1)	24 (46.2)	0.41
Racial/ethnic minority (self-reported)	1 (1.6)	1 (1.9)	
Cardiac risk factors			
Hypertension	45 (70.3)	28 (53.8)	0.07
Diabetes	12 (18.8)	3 (5.8)	0.04
Dyslipidaemia	15 (23.4)	10 (19.2)	0.58
Current or past tobacco use	33 (51.6)	26 (50.0)	0.51
Pre-test probability of obstructive CAD*	54.5±17.1	44.6±16.1	0.002
Anginal type			0.22
Typical angina	19 (29.7)	17 (32.7)	
Atypical angina	42 (65.6)	35 (67.3)	
Non-cardiac chest pain	3 (4.7)	0 (0.0)	

Data shown as mean±SD or number (percentage). CAD=coronary artery disease. FFR_{CT}=fractional flow reserve estimated using computed tomography. *Pre-test probability of obstructive CAD±SD calculated by updated Diamond and Forrester score.[131]

By study design, all patients in the CTA/FFR_{CT} group underwent CTA. FFR_{CT} analysis was indicated in 30 cases (57.7%), 25 of which were suitable. ICA was performed in all patients in the usual care cohort, and 12 patients (23.1%) in the CTA/FFR_{CT} cohort; the remainder were cancelled by the treating physician based on the CTA/FFR_{CT} result (**Figure 2**).

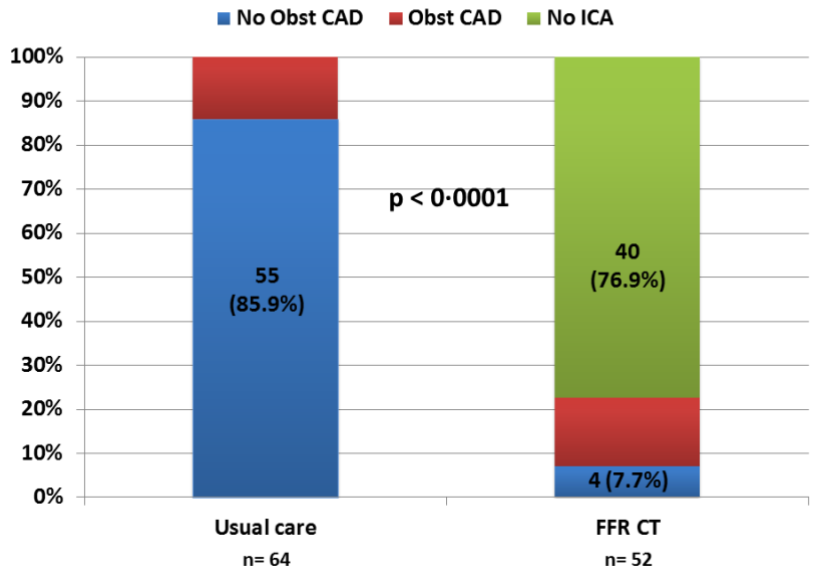
Coronary revascularisation at 90 days was performed in 14 patients (21.9%) in the usual care cohort and 8 patients (15.4%) in the FFR_{CT} cohort. Between 90 days and one year, no patient

had a new unplanned revascularisation, while one patient (1.6%) in the usual care cohort had a repeat revascularisation procedure. Medications at one year did not differ significantly between the CTA/FFR_{CT} and usual care groups: aspirin (25/47 [53%] vs. 36/59 [61%], p=0.42), clopidogrel (7/47 [15%] vs. 6/59 [10%], p=0.46), any statin (21/47 [45%] vs. 35/59 [59%], p=0.13).

4.1.1 Primary endpoint

At 90 days, 55 (85.9%) patients in the usual care group versus 4 (7.7%) patients in the CTA/FFR_{CT} group had ICA showing no obstructive CAD (risk difference 78.2%, 95% CI 67.1 – 89.4, p<0.001) (**Figure 3**).

Figure 3. *Rates of occurrence of the primary endpoint according to evaluation strategy*



The primary endpoint occurred in 85.9% and 7.7% of patients in the usual care and FFR_{CT} cohorts, respectively (risk difference of 78.2%, 95% CI 67.1-89.4, p<0.001). 76.9% of patients in the FFR_{CT} cohort had their ICA cancelled on the basis of their CTA/FFR_{CT} result. CAD = coronary artery disease; FFR_{CT} = fractional flow reserve estimated using computed tomography; ICA = invasive coronary angiography; Obst CAD = obstructive coronary artery disease.

4.1.2 Clinical efficacy and safety outcomes at one year

There were no cases of MACE at one year. No patients in the CTA/FFR_{CT} group versus two (3.1%) in the usual care group had vascular complications, both related to ICA (risk difference 3.1%, 95% CI -12.29 – 18.44).

There were no adverse clinical events at one-year follow-up in any of the 40 patients who had their ICA cancelled on the basis of their CTA/FFR_{CT} result; two (5.0%) patients required an initial ICA during one-year follow-up, both of which were performed because of a subsequent clinical presentation with chest pain. Both showed no obstructive CAD.

Cumulative radiation exposure at one year was significantly lower in the CTA/FFR_{CT} cohort compared with the usual care cohort, with mean values of 7.28 ± 9.33 versus 9.80 ± 6.73 mSv and median values of 3.68 (IQR 1.69-8.73) versus 7.00 (IQR 7.00-7.00) mSv, respectively ($p<0.001$).

4.1.3 Resource use and economic outcomes at one year

Resource use over one year is shown in **Table 2**. As there is currently no cost weight available for FFR_{CT}, we set the cost weight at the cost of CTA plus zero for the initial estimate. Mean one-year patient cost of cumulative medical care was significantly lower in the FFR_{CT} group, at €4,217 ± €9,740 compared with €6,894 ± €7,379 in the usual care group ($p<0.001$). In addition, more patients in the FFR_{CT} group had low costs than in the usual care group, with median costs of €465 (IQR €2,930) versus €5,243 (IQR €4,326), respectively ($p<0.001$). Cumulative medical costs are shown in **Figure 4**. In a sensitivity analysis, we recalculated the 1-year costs using a series of cost weights that were multiples of the cost

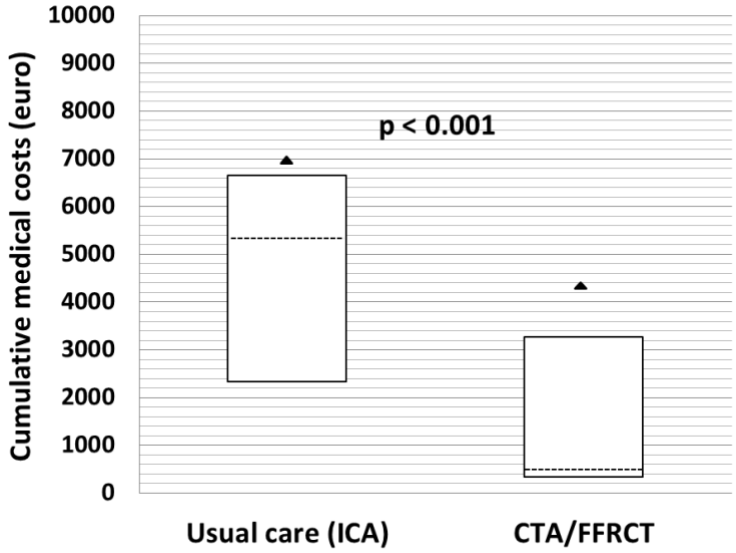
weight for CTA and compared to the costs of a usual care strategy. A cost benefit for CTA/FFR_{CT} over usual care was maintained up to the value of 14 times the cost of CTA, at €6,894 versus €6506, respectively, p=0.02.

Table 2. *Resource use over 12 months*

	Planned invasive test n =116	
	Usual care n =64	**CTA/FFR_{CT} n =52**
Non-invasive tests		
Stress ECG	6	12
Stress echo	3	2
Stress nuclear	1	0
Magnetic Resonance Imaging	2	0
CT Coronary Angiography	1	52
FFR_{CT}	0	25
Invasive Procedures		
Diagnostic ICA	61	9
ICA with PCI	11	10
FFR_{INV}	2	1
Intravascular Ultrasound	0	0
Optical Coherence Tomography	1	0
Coronary Revascularisation		
Percutaneous intervention	12	10
Stents per patient (mean)	2.1	1.6
Bypass surgery	4	1
Hospital days	122	65
Clinic visits	20	19

Data shown as number of times used. ECG=electrocardiogram; FFR_{CT}=fractional flow reserve estimated using computed tomography; FFR_{INV}=fractional flow reserve determined by invasive coronary angiography; ICA=invasive coronary angiography; MRI=magnetic resonance imaging; PCI=percutaneous coronary intervention.

Figure 4. *One-year costs by evaluation strategy*

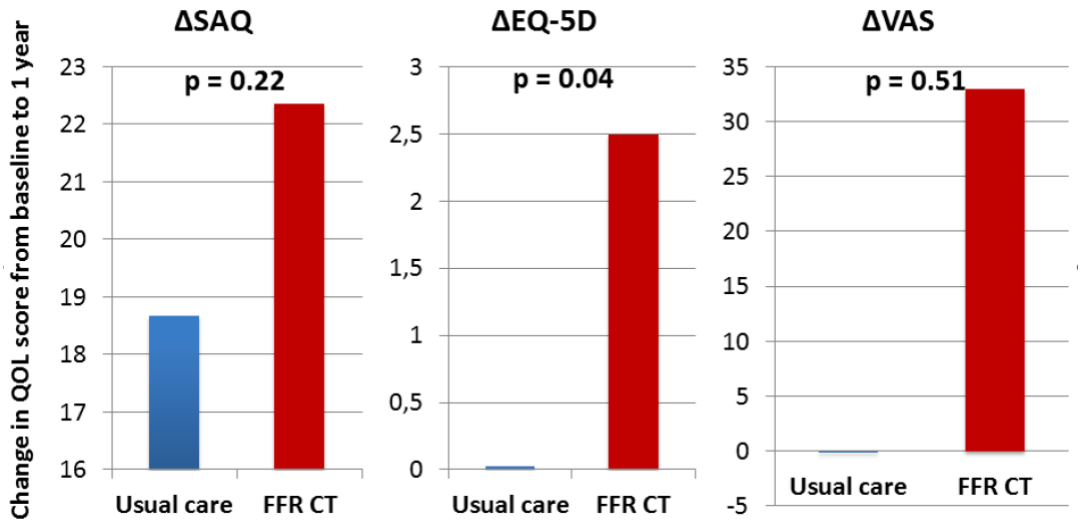


Box plot showing median (IQR) of cumulative one-year medical costs per patient. The top line of each box indicates the 75th percentile, the dashed line indicates the 50th percentile (median) and the bottom line indicates the 25th percentile. The triangles represent mean costs. Median and mean costs were significantly lower in the CTA/FFR_{CT} vs. usual care cohort. CTA = computed tomography angiography; ICA = invasive coronary angiography; FFR_{CT} = CT-derived fractional flow reserve; IQR = interquartile range.

4.1.4 Quality of life outcomes at one year

Functional status and QOL scores improved from baseline to one year follow-up to a greater degree in the CTA/FFR_{CT} cohort compared with the usual care cohort, irrespective of the score used (**Figure 5**). This difference was statistically significant when the EQ-5D score was used. Respective mean improvements using all three scores were as follows: +18.68 and +22.36 units on the SAQ (p=0.22); +0.03 versus +0.09 units on the EQ-5D (p=0.04); and -0.07 versus +5.09 units on the VAS (p=0.51).

Figure 5. *Change in quality-of-life scores from baseline to 1 year by evaluation strategy*



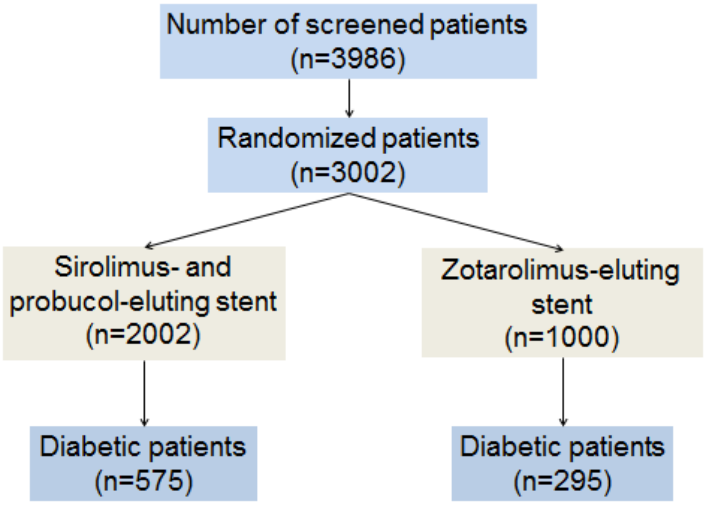
FFR_{CT} = fractional flow reserve estimated using computed tomography, SAQ = Seattle Angina Questionnaire, EQ-5D = EuroQOL, VAS = visual analogue scale for health state.

4.2 In patients with diabetes mellitus, polymer-free sirolimus- and probucol-eluting stents have comparable clinical efficacy and safety to conventional durable polymer zotarolimus-eluting stents at 5 year follow-up

4.2.1 Patient, lesion, and procedural characteristics and angiographic outcomes

Of 3002 patients enrolled in the ISAR-TEST 5 trial, 870 patients had diabetes mellitus: 575 patients assigned to treatment with polymer-free SPES and 295 assigned to durable polymer ZES (**Figure 6**).

Figure 6. *Patient flow*



The groups were well matched in terms of baseline characteristics (**Table 3**), and procedural characteristics (**Table 4**), although post-procedural minimal luminal diameter was lower and percent diameter stenosis higher in the SPES group in the in-stent but not the in-segment analysis. At 6-8 months, angiographic results were comparable in both groups (**Table 4**).

Table 3. *Baseline clinical characteristics*

Patient-level characteristics	**Polymer-free SPES (n=575)**	**Durable polymer ZES (n=295)**	***p* value**
Age (years)	69 (61-76)	70 (62-76)	0.40
Female	150 (26.1)	79 (26.8)	0.83
Diabetes mellitus therapy			
Insulin	197 (34.0)	109 (37.0)	0.43
Oral antidiabetic drugs	289 (50.0)	149 (51.0)	0.94
Hypertension	547 (95.1)	281 (95.3)	0.94
Hypercholesterolemia	389 (68.0)	188 (64.0)	0.25
Current smoker	105 (18.0)	52 (18.0)	0.82
Prior myocardial infarction	177 (30.8)	85 (28.8)	0.55
Prior bypass surgery	59 (10.3)	34 (11.5)	0.57
Clinical presentation			0.46
Silent ischemia	36 (6.3)	15 (5.1)	
Stable angina	324 (56.3)	154 (52.2)	
Unstable angina	98 (17.0)	61 (20.7)	
NSTEMI	73 (12.7)	45 (15.3)	
STEMI	44 (7.7%)	20 (6.8%)	
Multi-vessel disease	517 (89.9)	263 (89.2)	0.73

Ejection fraction (%)*	54 (44-60)	55 (41-61)	0.56
Lesion-level characteristics	**(n=849)**	**(n=439)**	
Target vessel			0.11
left anterior descending	336 (39.6)	196 (44.6)	
left circumflex	236 (27.8)	123 (28.0)	
right coronary artery	277 (32.6)	120 (27.3)	
Chronic total occlusion	56 (6.6)	22 (5.0)	0.26
Bifurcation	200 (23.6)	112 (25.5)	0.44
Ostial	152 (17.9)	80 (18.2)	0.89
Complex morphology	626 (74.0)	336 (77.0)	0.27
Lesion length (mm)	16.6±9.5	17.9±10.4	0.07
Reference vessel diameter (mm)	2.75±0.52	2.79±0.51	0.36
Minimal luminal diameter (mm)	0.91±0.50	0.92±0.47	0.83
Percent diameter stenosis (%)	67±16	67±15	0.83

Data shown as mean ± SD, median (25th-75th percentiles), or n (%). *Data available for 725 patients (86.7%). NSTEMI = Non ST- elevation myocardial infarction; STEMI = ST- elevation myocardial infarction

Table 4. *Procedural characteristics and angiographic outcomes*

Lesion-level characteristics	**Polymer-free SPES (n=849)**	**Durable polymer ZES (n=439)**	***p* value**
Balloon diameter (mm)	3.05 (2.59-3.47)	3.02 (2.60-3.45)	0.82
Stented length (mm)	25 (18-34)	24 (18-33)	0.23
In stent analysis			
Post-procedural minimal luminal diameter (mm)	2.50±0.50	2.57±0.49	0.045
Post-procedural percent diameter stenosis (%)	12±7	11±7	0.03
Minimal luminal diameter at follow-up (mm)*	2.13±0.73	2.20±0.72	0.18
Diameter stenosis at follow-up (%)*	24±22	23±21	0.68
Late lumen loss (mm)*	0.36±0.63	0.36±0.59	0.48
In segment analysis			
Post-procedural minimal luminal diameter (mm)	2.23±0.58	2.26±0.55	0.33
Post-procedural percent diameter stenosis (%)	22±12	22±12	0.83
Minimal luminal diameter at follow-up (mm)*	1.90±0.70	1.98±0.69	0.10
Diameter stenosis (%) at follow-up *	33±20	32±19	0.20
Late lumen loss (mm)*	0.31±0.61	0.26±0.57	0.34
Binary restenosis*	107 (17.0)	57 (17.2)	0.95

Shown as mean ± SD or median (25th-75th percentiles) or n (%). *Data available for 961 lesions (74.6%)

4.2.2 Outcomes at 5 years

There was no significant difference in the rate of the primary endpoint at 5 years between polymer free SPES and durable polymer ZES (32.9% versus 33.4% respectively, HR=0.88, 95% CI 0.76-1.26; P=0.88) (**Figure 7**). Rates of the individual components of the primary endpoint were similar between the two groups: cardiac death or target vessel myocardial infarction occurred in 19.1% vs. 20.1%, respectively, (HR 0.94, 95% CI 0.67-1.30; P=0.70), and TLR in 18.6% versus 18.8% respectively (HR 1.00, 95% CI 0.72-1.41; P=0.98) (**Figure 8**). There were no differences in the incidence of other secondary endpoints (**Table 5**).

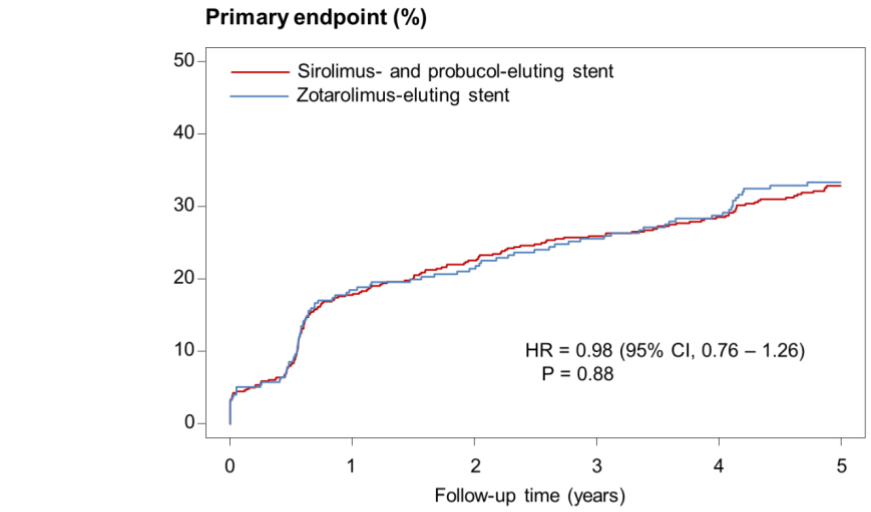
Table 5. *Clinical outcomes at 5 years*

	Polymer-free SPES (n=575)	**Durable polymer ZES (n=295)**	**Hazard ratio [95% CI]**	***p* value**
Cardiac death, TVMI or TLR	178 (32.9)	91 (33.4)	0.98 [0.76-1.26]	0.88
Cardiac death or TVMI	101 (19.1)	54 (20.1)	0.94 [0.67-1.30]	0.70
Cardiac death	81 (15.6)	44 (16.7)	0.92 [0.63-1.32]	0.64
TVMI	26 (4.6)	18 (6.6)	0.73 [0.40-1.34]	0.31
TLR	100 (18.6)	50 (18.8)	1.00 [0.72-1.41]	0.98
All-cause death	133 (24.4)	79 (27.8)	0.84 [0.63-1.11]	0.21
Any myocardial infarction	37 (6.5)	21 (7.6)	0.90 [0.53-1.54]	0.70
Any revascularisation	234 (43.4)	124 (46.9)	0.92 [0.74-1.15]	0.48
Target vessel revascularisation	144 (26.8)	70 (26.2)	0.82 [0.78-1.37]	0.82
Definite or probable stent thrombosis	14 (2.5)	7 (2.6)	1.02 [0.41-2.52]	0.97
Definite stent thrombosis	7 (1.2)	4 (1.6)	0.89 [0.26-3.04]	0.85
Probable stent thrombosis	7 (1.2)	3 (1.0)	1.19 [0.31-4.60]	0.80

Data shown as n (%) or hazard ratio [95% CI]. Rates are estimated by Kaplan-Meier method; hazard ratios

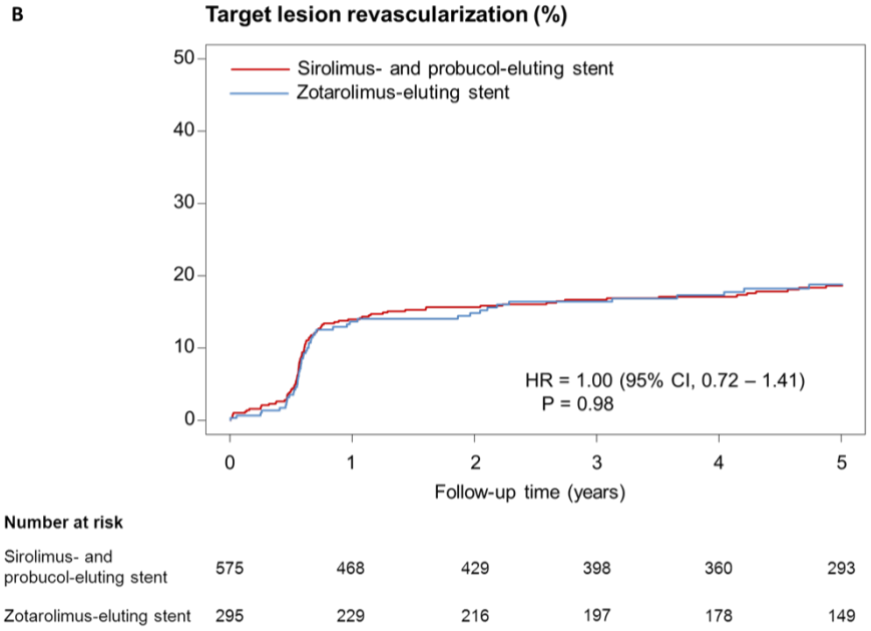
and p values were calculated by Cox's proportional hazard methods. CI = confidence intervals; TLR = target lesion; TVMI = target vessel-related myocardial infarction

Figure 7. *Time to event curve showing cumulative incidence of the primary endpoint*



Hazard ratios and P-values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio.

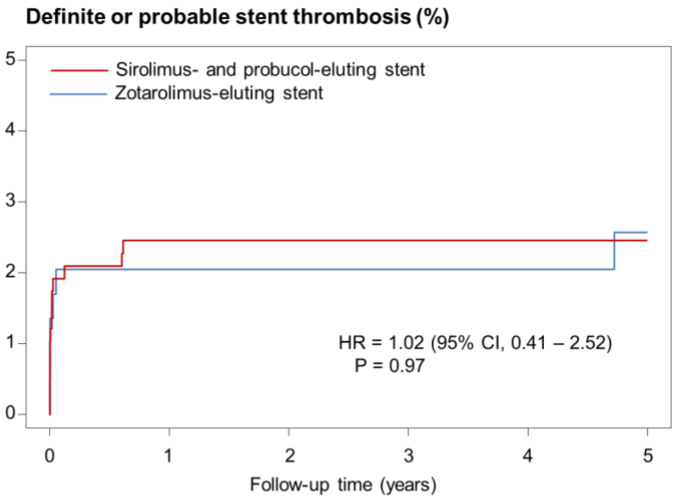
Figure 8. *Cumulative incidence of target lesion revascularisation*



CI = confidence interval; HR = hazard ratio.

The rate of definite or probable stent thrombosis was low and similar in both groups (2.5% versus 2.6% respectively, HR 1.02, 95% CI, 0.41-2.52; p=0.97), with only one case occurring in the durable polymer ZES group after 12 months (**Figure 9**).

Figure 9. *Cumulative incidence of definite or probable stent thrombosis*



Number at risk						
Sirolimus- and probucol-eluting stent	575	527	497	465	424	352
Zotarolimus-eluting stent	295	260	248	233	211	180

Hazard ratios and P-values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio

4.3 In patients presenting with STEMI, polymer-free sirolimus-and probucol-eluting stents have comparable clinical efficacy and safety to a conventional durable polymer zotarolimus-eluting stents at 5 year follow-up

A total of 311 patients presenting with STEMI were randomly allocated to the polymer-free SPES (n=215) or durable polymer ZES (n=96) groups. The groups were well matched in terms of baseline patient and lesion characteristics (**Table 6**), other than incidence of previous CABG,which was higher in the ZES group (p=0.03).

***Table 6**. Selected baseline patient, lesion and procedural characteristics*

Patient characteristics	**Polymer-free SPES (n = 215)**	**Durable polymer ZES (n = 96)**	***P*-value**
Age (years)	64.3±13.8	64.2±12.4	0.98
Female	49 (23.0)	25 (26.0)	0.53
Diabetes mellitus	44 (20.5)	20 (20.8)	0.94
insulin-dependent	12 (5.6)	7 (7.3)	0.56
Hypertension	159 (74.0)	73 (76.0)	0.70
Hyperlipidemia	89 (41.0)	45 (47.0)	0.37
Current smoker	76 (35.0)	33 (34.0)	0.87
Prior myocardial infarction	35 (16.3)	13 (13.5)	0.54
Prior bypass surgery	6 (2.8)	8 (8.3)	0.03
Multi-vessel disease	150 (69.8)	67 (69.8)	0.99
Ejection fraction (%)*	46.3±9.6	47.6±9.6	0.28
Lesions characteristics	**(n = 297)**	**(n = 125)**	
Target vessel			0.47
left anterior descending	131 (44.1)	58 (46.4)	
left circumflex	68 (22.9)	22 (17.6)	
right coronary artery	98 (33.0)	45 (36.0)	
Chronic total occlusion	3 (1.0)	3 (2.4)	0.27
Bifurcation	60 (20.2)	25 (20.0)	0.96
Ostial	51 (17.2)	30 (24.0)	0.10
Complex morphology (B2/C)	264 (88.9)	105 (84.0)	0.17
Lesion length (mm)	17.2±9.9	17.0±9.7	0.58
Vessel size (mm)	2.89±0.48	2.88±0.54	0.74
Minimal lumen diameter, pre (mm)	0.59±0.57	0.56±0.56	0.48
Stented length (mm)	27.0±13.0	28.9±12.9	0.42
% Diameter stenosis, post	12.8±9.7	12.2±10.4	0.20

Data shown as means±SD or number (percentage), *data available for 283 patients (91.0)

The total number of treated lesions was 422 (SPES, n=297; ZES, n=125). More than one lesion was treated in 30.2% of patients in the sirolimus- and probucol-eluting stent group versus 28.1% in the zotarolimus-eluting group (*P*=0.71). Five-year follow-up was complete in all but 19 patients (6.1%), without any significant difference between the groups (p= 0.11).

4.3.1 Device-oriented outcomes at 5 years

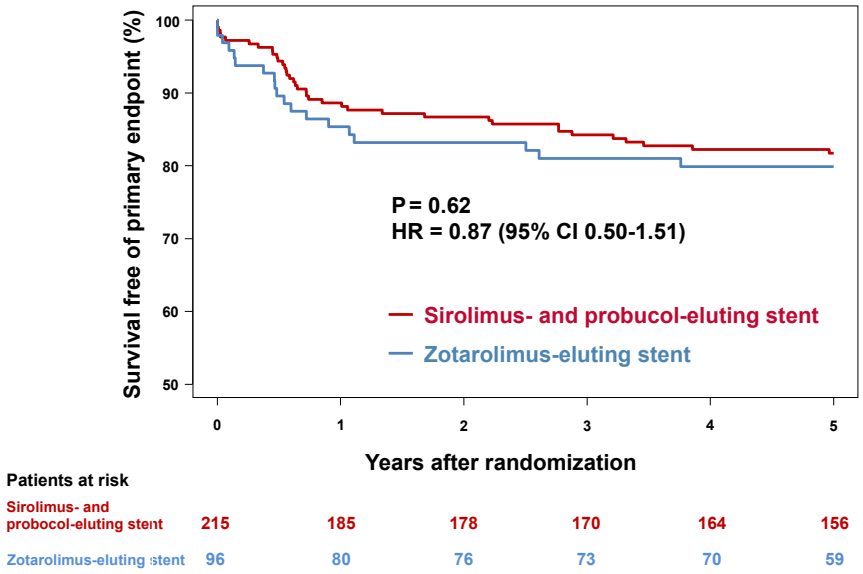
Clinical outcomes at 5-year follow-up are shown in **Table 7**. There was no difference between the polymer-free SPES and durable polymer ZES groups with respect to the primary endpoint (composite of cardiac death, myocardial infarction related to target vessel and TLR) at 5 years (18.3% versus 20.1% respectively, HR 0.87, 95% CI 0.50-1.51; *P*=0.62) (**Figure 10**).

Table 7. *Clinical results at 5 year follow-up*

	Polymer-free SPES (n = 215)	**Durable polymer ZES (n = 96)**	**Hazard ratio (95% CI)**	***P*-value**
Device-oriented outcomes				
Cardiac death, TVMI or TLR	38 (18.3)	19 (20.1)	0.87 (0.50-1.51)	0.62
Cardiac death or MI related to target vessel	16 (7.7)	8 (8.6)	0.89 (0.38-2.08)	0.79
Cardiac death	14 (6.8)	8 (8.6)	0.78 (0.33-1.85)	0.57
TVMI	4 (1.9)	1 (1.0)	1.79 (0.20-16.00)	0.60
TLR	25 (12.3)	13 (14.0)	0.83 (0.43-1.63)	0.59
Patient-oriented outcomes				
All-cause death, any MI or any revascularisation	99 (46.6)	47 (49.1)	0.94 (0.66-1.33)	0.71
All-cause death or any MI	27 (12.7)	16 (16.8)	0.75 (0.41-1.40)	0.37
All-cause death	25 (11.8)	16 (16.8)	0.69 (0.37-1.30)	0.25
Any MI	4 (1.9)	1 (1.0)	1.79 (0.20-16.00)	0.60
Any revascularisation	77 (37.8)	34 (36.7)	1.00 (0.67-1.50)	0.99
Target vessel revascularisation	48 (23.6)	21 (22.7)	0.98 (0.59-1.64)	0.94

Data shown as number (percentage) by Kaplan-Meier analysis; hazard ratios and *P*-values were calculated from Cox proportional hazard methods; MI=myocardial infarction; TLR = target lesion revascularisation; TVMI = target vessel-related myocardial infarction

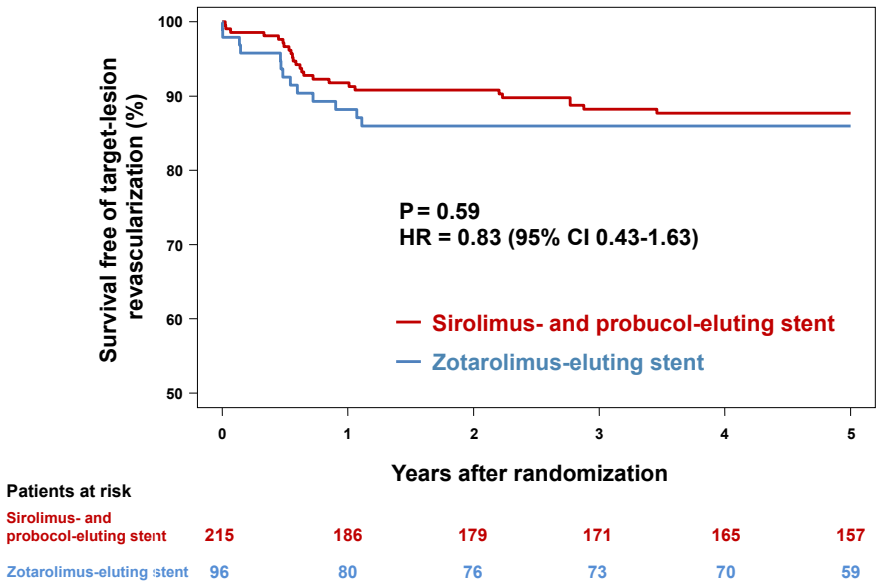
Figure 10. *Survival free from the composite of cardiac death, target-vessel myocardial infarction or TLR*



Hazard ratios and *P*-values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio

In terms of individual components of the primary endpoint, the polymer-free SPES and durable polymer ZES showed similar rates of cardiac death or myocardial infarction related to target vessel (7.7% versus 8.6%, respectively, HR 0.89, 95% CI 0.38-2.08; *P*=0.79), cardiac death (6.8% versus 8.6% respectively, HR 0.78, 95% CI 0.33-1.85; *P*=0.57), and myocardial infarction related to target vessel (1.9% versus 1.0% respectively, HR 1.79, 95% CI 0.20-16.00; *P*=0.60); rates of TLR were also similar in both groups (12.3% vs. 14.0% respectively; HR 0.83, 95% CI, 0.43-1.63, *P*=0.59, **Figure 11**).

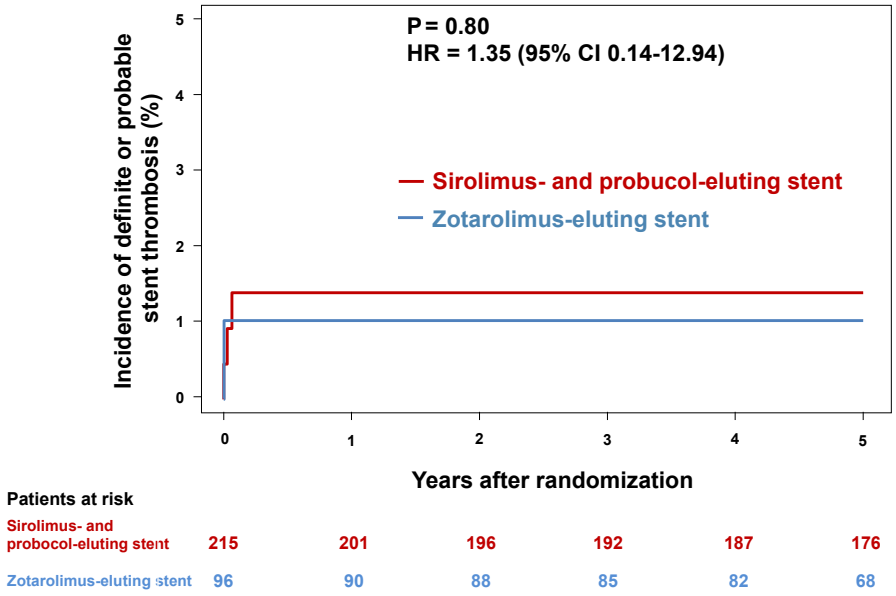
Figure 11. *Survival free from target lesion revascularisation*



Hazard ratios and *P*-values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio

In terms of safety endpoints, the SPES and ZES had similar rates of definite/probable stent thrombosis (1.4% vs. 1.0% respectively; HR 1.35, 95% CI,0.14-12.94, *P*=0.80; **Figure 12**).

Figure 12. *Cumulative incidence of definite or probable stent thrombosis*



Hazard ratios and *P*-values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio

4.3.2 Patient-oriented outcomes at five years

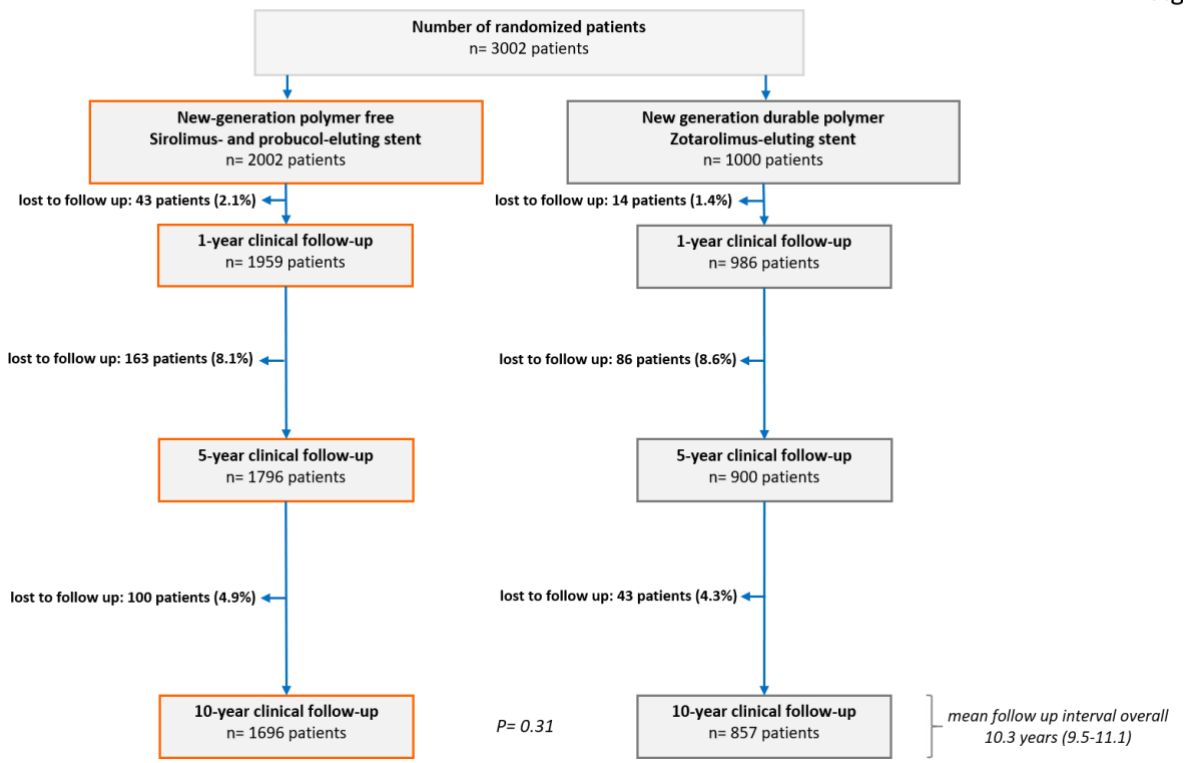
Regarding the composite endpoint of death, any myocardial infarction or any revascularisation, there was no difference between SPES and ZES (46.6% versus 49.1% respectively, HR 0.94, 95% CI 0.66-1.33; *P*=0.71). The SPES in comparison with the ZES showed similar rates of all-cause death (11.8% versus 16.8% respectively, HR 0.69, 95% CI 0.37-1.30; *P*=0.25), any myocardial infarction (1.9% versus 1.0% respectively, HR 1.79 95% CI 0.20-16.00; *P*=0.60) and any revascularisation (37.8% vs. 36.7% respectively; HR 1.00, 95% CI 0.67-1.50, *P*=0.99).

4.4 Polymer-free sirolimus- and probucol- eluting stents have comparable clinical efficacy and safety to durable polymer zotarolimus-eluting stents in all-comer patients at 10 years

Between February 2008 and August 2009, 3002 patients were randomized to treatment with polymer-free SPES (n=2002) or durable polymer ZES (n=1000) stents. Ten-year follow-up was complete on all but 449 patients (14.9%), with no significant difference between the groups: 306 (15.2%) patients in the SPES group and 143 (14.3%) patients in the ZES group (*P*=0.31) (**Figure 13**). Mean follow-up was 10.3 years (9.5-11.1).

***Figure 13**. Study flow chart and follow-up at 1, 5 and 10 years*

Fig



P-value is derived from Cox proportional hazard methods and refers to completeness of 10-year follow-up in patients treated with polymer free SPES versus durable polymer ZES. Overall follow-up interval is shown as mean ± SD.

The study enrolled a high proportion of patients with advanced age and multi-vessel disease. More than one quarter of the study population had diabetes mellitus at baseline. Over 40% of patients presented with acute coronary syndrome. The total number of treated lesions was 4391 (SPES, n=2912; ZES, n=1479). Baseline patient, lesion and procedural characteristics were well balanced (**Table 8**).

Table 8. *Selected baseline patient, lesion and procedural characteristics*

	Polymer-free SPES	**Durable polymer ZES**	***P*-value**
Patients	**(n = 2002)**	**(n = 1000)**	
Age (years)	67.7±11.2	68.1±10.8	0.30
Female	470 (23.5)	237 (23.7)	0.89
Diabetes mellitus	575 (28.7)	295 (29.5)	0.66
insulin-dependent	197 (9.8)	109 (10.9)	0.37
Hypertension	1336 (66.7)	666 (66.6)	0.94
Hyperlipidemia	1257 (62.8)	650 (65.0)	0.24
Current smoker	357 (17.8)	166 (16.6)	0.40
Prior myocardial infarction	586 (29.3)	299 (29.9)	0.72
Prior bypass surgery	188 (9.4)	96 (9.6)	0.85
Multi-vessel disease	1658 (82.3)	855 (85.5)	0.06
Clinical presentation			0.60
acute myocardial infarction	215 (10.7)	96 (9.6)	
unstable angina	596 (29.8)	325 (32.5)	
stable angina	1191 (59.5)	579 (57.9)	
Ejection fraction (%)*	52.6±11.9	52.4±11.4	0.74
Lesions	**(n = 2912)**	**(n = 1479)**	
Target vessel			0.55
left anterior descending	1315 (45.2)	666 (45.0)	
left circumflex	711 (24.4)	386 (26.1)	
right coronary artery	886 (30.4)	427 (28.9)	
Chronic total occlusion	174 (6.0)	76 (5.1)	0.28
Bifurcation	798 (27.4)	427 (28.9)	0.39
Ostial	583 (20.0)	305 (20.6)	0.66
Complex morphology (B2/C)	2164 (74.3)	1088 (73.6)	0.63
Lesion length (mm)	16.4±9.6	16.9±10.0	0.09
Vessel size (mm)	2.78±0.50	2.80±0.50	0.23
Minimal lumen diameter, pre (mm)	0.91±0.50	0.90±0.50	0.48
Stented length (mm)	25.9±12.2	26.8±12.4	0.01
% Diameter stenosis, post	12.1±7.4	11.7±8.2	0.23

Data is shown as mean ± SD or number (percentage). *Data available for 2604 patients (86.7%)

4.4.1 Device-oriented outcomes at 10 years

Clinical outcomes at 10-year follow-up are shown in **Table 9**. Regarding the primary endpoint, there was no difference between SPES and ZES (43.8% versus 43.0% respectively,

HR 1.01, 95% CI 0.89-1.14; *P*=0.90) (**Figure 14**). There was no evidence of interaction between treatment effect and any of the pre-specified subgroups (**Figure 15)**.

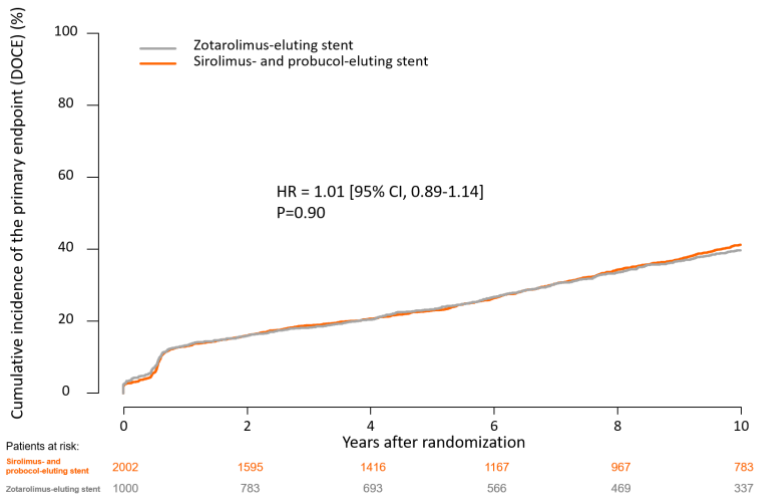
***Table 9**. Clinical results at 10 years*

	Polymer-free SPES	**Durable polymer ZES**	**Hazard ratio (95% CI)**	***P*-value**
Device-oriented outcomes				
Cardiac death, TVMI or TLR	765 (43.8)	370 (43.0)	1.01 (0.89-1.14)	0.90
Cardiac death or TVMI	488 (29.2)	242 (29.3)	0.99 (0.84-1.15)	0.85
Cardiac death	438 (26.7)	217 (26.9)	0.99 (0.84-1.16)	0.86
TVMI	69 (3.8)	41 (4.4)	0.83 (0.57-1.23)	0.35
TLR	371 (21.9)	175 (20.6)	1.04 (0.87-1.25)	0.67
Patient-oriented outcomes				
All-cause death, any MI or any revascularisation	1263 (66.2)	649 (67.7)	0.94 (0.86-1.04)	0.22
All-cause death or any MI	703 (38.3)	370 (40.0)	0.89 (0.82-1.06)	0.29
All-cause death	637 (35.0)	343 (37.3)	0.91 (0.80-1.04)	0.16
Any MI	103 (5.7)	52 (5.8)	0.98 (0.70-1.37)	0.91
Any revascularisation	826 (45.9)	415 (47.0)	0.96 (0.86-1.09)	0.56

Data is shown as number (percentage) by Kaplan-Meier analysis; hazard ratios and *P*-values were calculated from Cox proportional hazard methods; CI = confidence interval; MI=myocardial infarction; TLR = target lesion revascularisation; TVMI = target vessel-related myocardial

Figure 14. *Time to event curve showing incidence of the primary composite endpoint of cardiac death, myocardial infarction related to the target vessel or TLR*

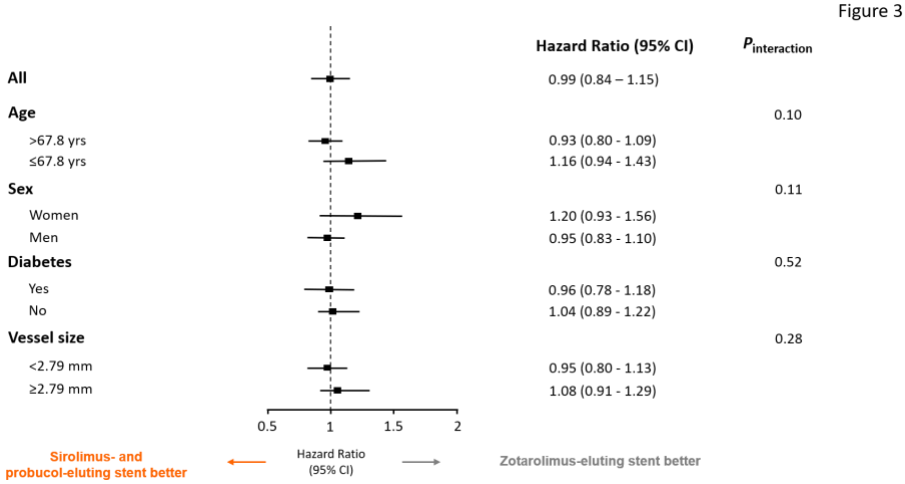
Figure 2A



Hazard ratios and *P*-values are derived from Cox proportional hazard methods. DOCE= device-oriented composite endpoint; CI = confidence interval; HR = hazard ratio

Figure 15. *Treatment effect for SPES versus ZES for the primary endpoint in the overall study population and in pre-specified subgroups*

Figure 3

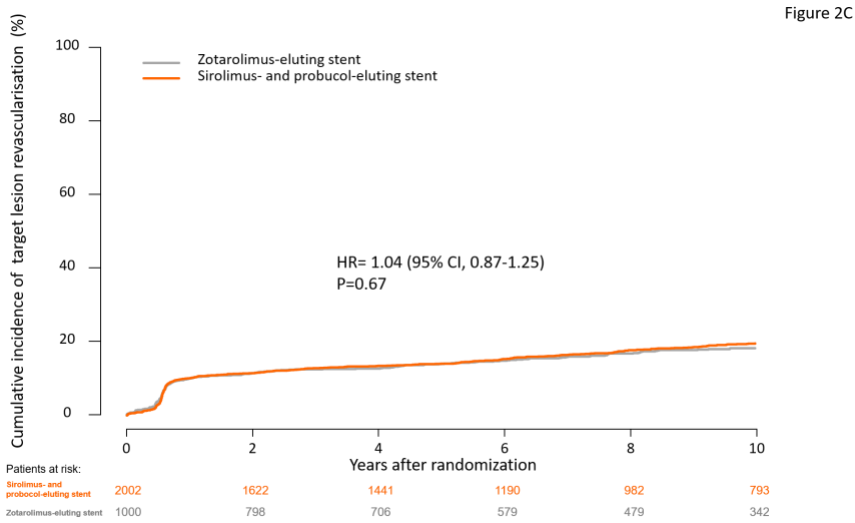


P-values for interaction are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio

In terms of individual components of the primary endpoint, the SPES and ZES showed similar rates of cardiac death or target vessel myocardial infarction (29.2% versus 29.3% HR 0.99,

95% CI 0.84-1.15; *P*=0.85), cardiac death (26.7% versus 26.9%, HR 0.99, 95% CI 0.84-1.16; *P*=0.86), target vessel myocardial infarction (3.8% versus 4.4%, HR 0.83, 95% CI 0.57-1.23; *P*=0.35); rates of TLR were also similar in both groups (21.9% vs. 20.6%, HR 1.04, 95% CI, 0.87-1.25, *P*=0.67, **Figure 16**).

Figure 16. *Time to event curve showing incidence of target lesion revascularisation*



Hazard ratios and *P*-values are derived from Cox proportional hazard methods. DOCE= device-oriented composite endpoint; CI = confidence interval; HR = hazard ratio

4.4.2 Patient-oriented outcomes at 10 years

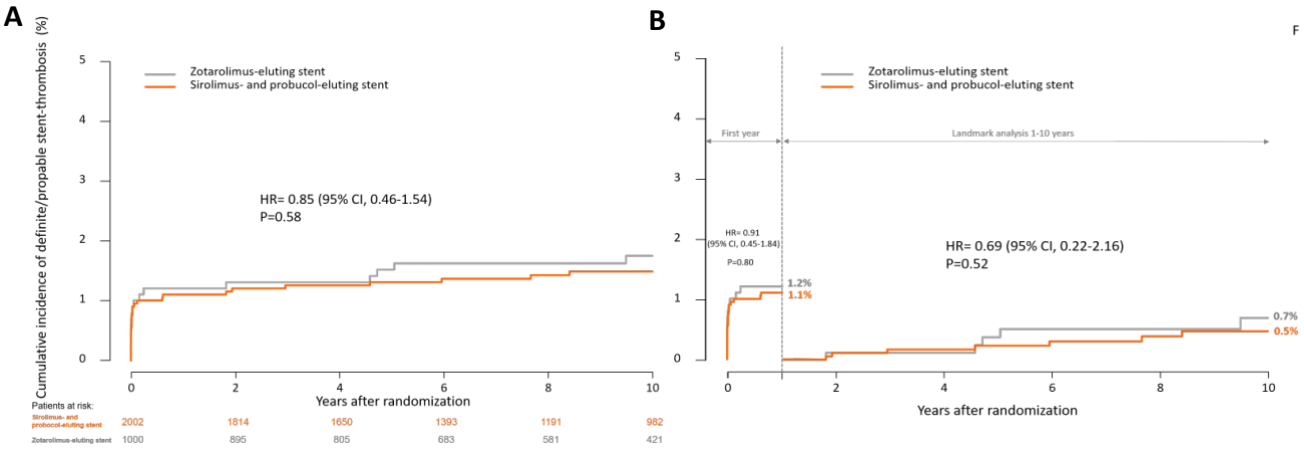
Regarding the composite endpoint of all cause death, any myocardial infarction or any revascularisation, there was no difference between the SPES and ZES (66.2% versus 67.7% respectively, HR 0.94, 95% CI 0.86-1.04; *P*=0.22). In terms of individual components of the patient-oriented composite endpoint the SPES in comparison with the ZES showed similar rates of all-cause death or any myocardial infarction (38.3% versus 40.0%, respectively, hazard ratio = 0.89, 95% CI, 0.82-1.06; *P*=0.29). At 10 years, 63.9 % of patients were alive. There was no difference between SPES and ZES concerning all-cause death (35.0% versus

37.3%, respectively, HR 0.91, 95% CI 0.80-1.04; *P*=0.16), any myocardial infarction (5.7% versus 5.8%, respectively, HR 0.98, 95% CI 0.70-1.37; *P*=0.91) any revascularisation (45.9% vs. 47.0%, respectively; HR 0.96, 95% CI, 0.86-1.09, *P*=0.56).

4.4.3 Definite or probable stent thrombosis at 10 years

In terms of safety endpoints, rates of definite or probable stent thrombosis were comparable for the SPES and ZES (1.6% vs. 1.9%; HR 0.85, 95% CI 0.46-1.54, *P*=0.58; **Figure 17A**). In a landmark analysis, between 1 and 10 years after index PCI rates of very late definite/probable stent thrombosis were comparable and low (0.5% vs. 0.7%, respectively, HR 0.69, 95% CI 0.22-2.16, *P*=0.52; **Figure 17B**).

Figure 17. Time to event curve showing cumulative incidence of definite or probable stent thrombosis **(A)** at 5 years and **(B)** between 0-1 and 1-10 years



Hazard ratios and *P*-values are derived from Cox proportional hazard methods. CI = confidence interval; HR = hazard ratio

4.5 Angiographic and clinical outcomes after re-intervention for drug-eluting stent restenosis were comparable irrespective of the absence or presence of a polymer coating

Of 3,002 patients enrolled in the ISAR-TEST 5 trial, 326 patients underwent repeat PCI for DES-restenosis within 2 years after the index intervention: 220 patients with restenosis of a polymer-free DES and 106 patients with restenosis of a durable polymer DES. Baseline characteristics of patients presenting with DES-restenosis were well-matched, except for acute coronary syndrome at presentation, which was less frequent in the polymer-free DES-restenosis group (20.0% versus 34.0%, p =0.006) (**Table 10**).

Table 10. *Baseline clinical characteristics*

	Restenosis in polymer-free DES (n = 220)	**Restenosis in polymer-coated DES (n = 106)**	***p* value**
Age (years)	69 (61 - 76)	69 (59 - 74)	0.34
Female	43 (19.5)	15 (14.2)	0.23
Body mass index (kg/m^2)	27.5 (24.9 - 30.4)	27.8 (25.3 - 29.5)	0.85
Diabetes mellitus	83 (37.7)	34 (32.1)	0.32
Insulin dependent	33 (15.0)	17 (16.0)	0.81
Hypertension	219 (99.5)	103 (97.2)	0.07
Hypercholesterolemia	148 (67.3)	72 (67.9)	0.91
Current smoker	29 (13.2)	13 (12.3)	0.82
Family history	100 (45.5)	51 (48.1)	0.65
Prior myocardial infarction	82 (37.3)	40 (37.7)	0.94
Prior coronary artery bypass surgery	34 (15.5)	14 (13.2)	0.59
Clinical presentation			0.03
Silent ischemia	38 (17.3)	12 (11.3)	
Stable angina	138 (62.7)	58 (54.7)	
Unstable angina	41 (18.6)	35 (33.0)	
Myocardial infarction	3 (1.4)	1 (1.0)	
Multivessel disease	201 (91.4)	101 (95.3)	0.20

Data shown as median [interquartile range] or n (%); CI = confidence intervals; DES = drug-eluting stents

A total of 398 lesions (polymer-free DES-restenosis, n= 265; durable polymer DES-restenosis, n= 133) underwent repeat PCI. Lesion and procedural characteristics well broadly well

matched (**Table 11**). The prevalence of bifurcation lesions was lower in the polymer-free versus durable polymer group (22.3% versus 38.2%, p < 0.001). For treatment of ISR, differences were observed between the groups in terms of the device used (p= 0.017).

Table 11. *Lesion and procedural characteristics*

	Restenosis in polymer-free DES (n = 265)	**Restenosis in polymer-coated DES (n = 133)**	***p* value**
Lesion characteristics			
Multi lesion	41 (18.6)	23 (21.7)	0.51
Target vessel			0.68
left anterior descending artery	86 (32.5)	49 (36.8)	
left circumflex artery	150 (56.6)	71 (53.4)	
right coronary artery	29 (10.9)	13 (9.8)	
Complex morphology (AHA/ACC classification B2/C)	104 (39.2)	58 (43.6)	0.40
Chronic total occlusion	25 (9.4)	6 (4.5)	0.08
Bifurcation lesion	59 (22.3)	50 (38.2)	< 0.001
Lesion length (mm)	11.5 ± 8.0	10.4 ± 5.9	0.81
Reference vessel diameter (mm)	2.78 ± 0.49	2.83 ± 0.51	0.39
Pre-procedural minimal luminal diameter (mm)	1.03 ± 0.67	1.05 ± 0.61	0.90
Pre-procedural percent diameter stenosis (%)	63 ± 22	63 ± 20	0.97
Procedural characteristics			
Intervention type			0.017
Bare-metal stent	2 (0.6)	0 (0.0)	
DES 1 generation	120 (45.3)	49 (36.8)	
DES 2 generation	36 (13.6)	25 (18.8)	
Plain balloon	79 (29.8)	54 (40.6)	
Drug-coated balloon	28 (10.6)	5 (3.8)	
Balloon diameter (mm)	3.1±0.6	3.1±0.6	0.39
Maximal balloon pressure (atm)	16 ± 4	16 ± 3	0.88
Stent diameter (mm)	3.0 ± 0.5	3.1 ± 0.5	0.34
Post-procedural minimal luminal diameter (mm)	2.43 ± 0.55	2.46 ± 0.50	0.52
Post-procedural percent diameter stenosis (%)	16 ± 11	16 ± 10	0.65

Data shown as mean ± standard deviation or n (%); DES = drug-eluting stent

4.5.1 Angiographic outcomes

A total of 272 patients (83.4%) underwent angiographic follow-up. In-stent late luminal loss was 0.58 ± 0.74 mm vs. 0.54 ± 0.67 mm in the in the polymer-free and durable polymer DES-restenosis groups (p=0.79) (**Table 12**). Binary restenosis was observed in 31.7% vs. 27.0% in the polymer-free and durable polymer groups (p =0.38)($p_{adjusted}$ =0.29).

Table 12. *Angiographic outcomes*

Angiographic outcomes	**Restenosis in polymer-free DES (n = 224)**	**Restenosis in polymer-coated DES (n = 111)**	***p* value**
In-stent minimal luminal diameter (mm)	1.84 ± 0.89	1.92 ± 0.80	0.48
In-stent percent diameter stenosis (%)	37 ± 27	34 ± 23	0.88
In-stent late luminal loss (mm)*	0.58 ± 0.74	0.54 ± 0.67	0.79
In segment minimal luminal diameter (mm)	1.67 ± 0.82	1.77 ± 0.75	0.35
In segment percent diameter stenosis (%)	43 ± 25	40 ± 21	0.55
In segment late luminal loss (mm) *	0.50 ± 0.70	0.47 ± 0.62	0.87
Binary restenosis	71 (31.7)	30 (27.0)	0.38

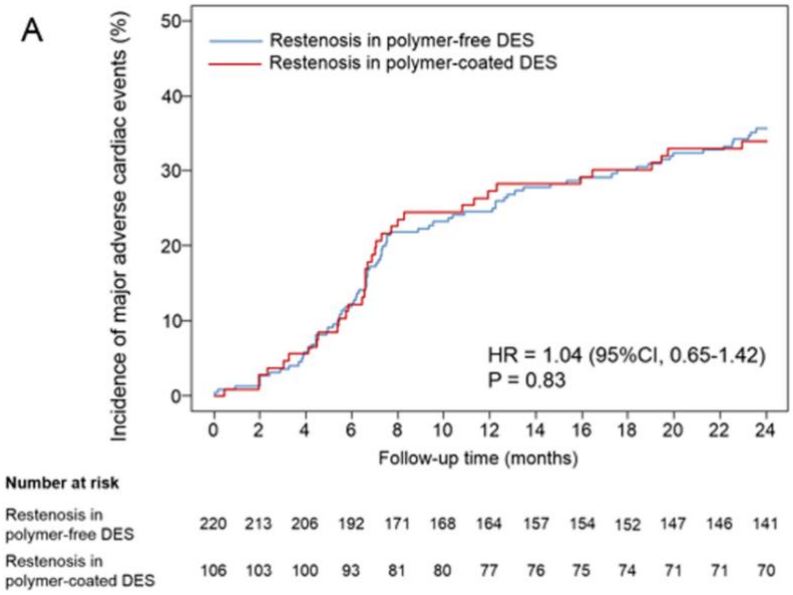
Data shown as mean ± standard deviation or n (%); DES = drug-eluting stent

4.5.2 Clinical outcomes at 2 years

There was no significant difference in the occurrence of the primary composite endpoint at 2 years between the polymer-free and the durable polymer groups (35.7% versus 34.0%, HR 1.04, 95% CI 0.70-1.55; $p_{unadjusted}$ = 0.83) (**Figure 18)**. At multivariate analysis, we found no difference in clinical outcomes after two years when adjusted for differences in baseline characteristics and ISR treatment types ($p_{adjusted}$ = 0.79). In a sensitivity analysis comparing the primary endpoint of interest in patients in both groups treated with either drug-coated

balloon or second generation DES we found no difference between the two groups (34.0% vs. 28.0%, HR 1.31, 95% CI 0.76-3.17; p =0.54).

Figure 18. *Time to event curves showing cumulative incidence of the composite outcomes of all-cause death, myocardial infarction, or target lesion revascularisation*

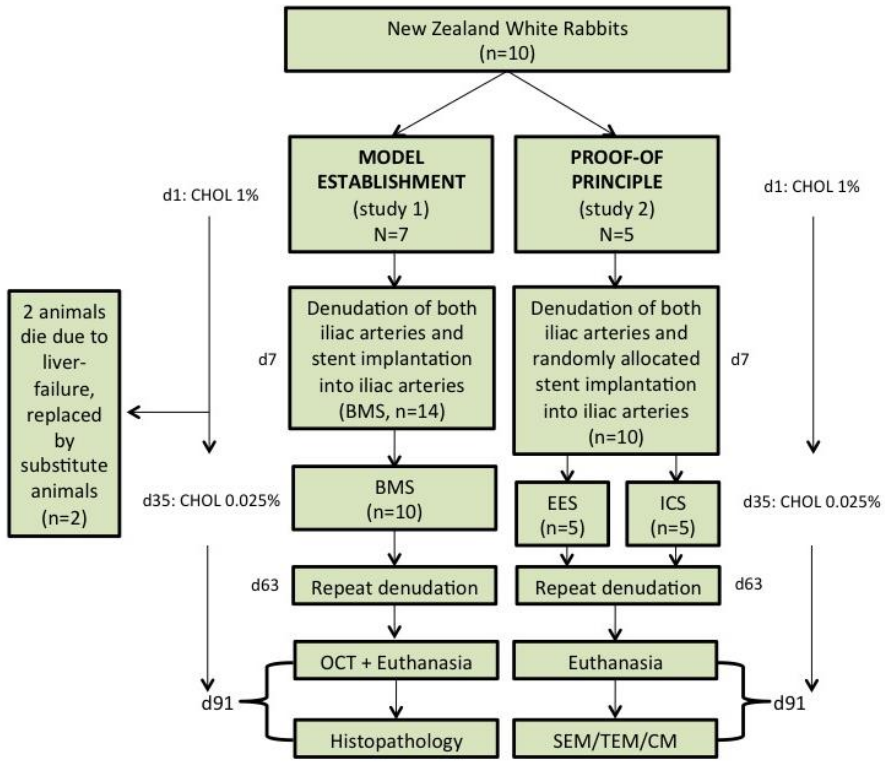


Hazard ratios and P-values are derived from Cox proportional hazard methods. CI = confidence intervals; DES = drug-eluting stents; HR = hazard ratio

Individual component rates of the primary endpoint were similar between the two groups: all-cause death, 8.3% versus 6.6% (HR 1.25, 95% CI 0.52-3.00; P =0.61) and myocardial infarction, 1.0% versus 2.9% (HR 0.33, 95% CI 0.05-1.95; P =0.22). TLR was also similar between the groups: 29.8% versus 31.5% (HR 0.91, 95% CI 0.60-1.39; p =0.68; $p_{adjusted}$ =0.62). Median time to TLR was similar in both groups: 211 [190-269] days vs. 204 [166-269] days (P=0.17). No case of stent thrombosis was observed.

4.6 In an hypercholesterolaemic rabbit iliac model of stent implantation, incomplete endothelial integrity is a key factor in neointimal foam cell formation after drug-eluting stent implantation. Pro-healing stent coatings may facilitate re-endothelialisation, thus reducing the risk of neoatherosclerosis.

Figure 19. *Study flow*

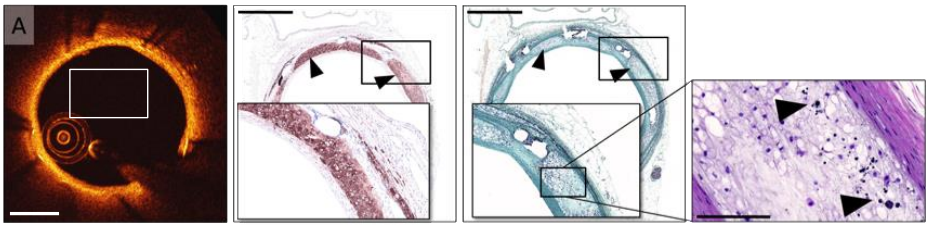


4.6.1 Histopathological features in atherosclerotic rabbits

The study flow is shown in **Figure 19**. Circumferential and depth of foam cell accumulation was significant, with foam cells being mostly observed within the peri-strut regions and the neointima above stent struts. Assessment of neointimal foam cells showed a mean score of 3 for both circumferential and depth infiltration (**Figures 20A and B**). Cholesterol clefts were the most prominent finding of atherosclerotic plaque formation, detected in 33.3% of all sections, with neovascularization detected in 29.2% (**Figure 20B**). Peri-strut inflammatory reactions were mild to moderate, with a median score of 1 (1– 2). Assessment of neointima formation

by OCT confirmed histological results (**Figure 20C**). Neointimal area following BMS implantation was moderate, with a median area of 1.6 mm^2 (1.5 – 2.2, **Figure 20C**).

Figure 20



B NEOATHEROSCLEROTIC FEATURES

Foam Cell Score Circumference	3 (1-4)
Foam Cell Score Depth	3 (1-3,75)
Microcalcification	16.7%
Hemorrhage	12.5%
Cholesterol clefts	33.3%
Inflammation Score	1 (1-2)
Neovascularisation	29.2%

C MORPHOMETRY

OCT		Histopathology	
Stent Area (mm^2)	5.9 (5.7-6.7)	EEL Area (mm^2)	7.4 (6.7-8.7)
		IEL Area (mm^2)	6.9 (6.4-8.3)
Lumen Area (mm^2)	5.0 (4.4-5.6)	Lumen Area (mm^2)	5.2 (4.3-6.6)
Neointimal Area (mm^2)	0.9 (0.7-1.5)	Neointimal Area (mm^2)	1.6 (1.5-2.2)
%Stenosis	16.4 (12.0-25.2)	%Stenosis	24.7 (18.2-32.6)
Neointimal Thickness (mm)	0.13 (0.04-0.19)	Neointimal thickness (mm^2)	0.14 (0.04-0.17)

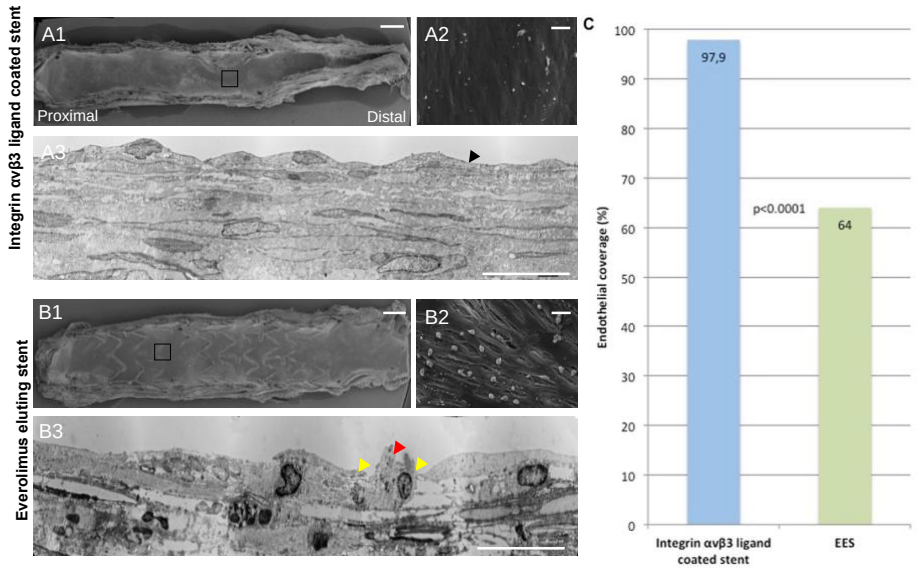
(**A**) ProKinetic Energy BMS in a rabbit iliac artery 12 weeks after implantation, assessed by histopathology and OCT. OCT shows surface with almost circumferential high backscattering intensity and attenuation. Corresponding histological cross section (Movat Pentachrome staining) shows circumferential foamy macrophage accumulation in a moderately thickened neointimal tissue (arrowheads indicate foamy macrophages; scale bar = 1000 µm). High-magnified image of Hematoxylin Eosin staining shows microcalcifications between foamy macrophages (scale bar = 100 µm). (**B**) Neointimal characteristics from study 1 and **(C)** morphometric analysis derived from OCT and histopathology (n=5 rabbits, 24 quadrants scored in total).

4.6.2 Assessment of endothelial integrity in-vivo

Mean cholesterol levels were 37.2 ± 7.3 mg/dl (baseline), 680.2 ± 150.3 mg/dl (denudation), 1872.3 ± 295.3 mg/dl (diet switch), 1110.0 ± 544.8 mg/dl (stenting) and 656.0 ± 198.8 mg/dl (termination). Evaluation of stented iliac arteries by CM revealed substantial heterogeneity in vascular healing among commercially available EES and integrin αvβ3 ligand coated stents,

where overall CD31 expression was significantly greater in integrin αvβ3 ligand coated stents compared to EES (311.5 mm2 vs. 65.7 mm2, p<0.05). SEM confirmed the greater overall endothelial coverage of stent struts in integrin αvβ3 ligand coated stents compared to EES (97.9% vs. 64.0% covered stent struts, p<0.0001) (**Figure 21; A1 and B1**). High magnifications of representative SEM images confirmed the gaps in endothelial junctions in EES relative to integrin αvβ3 ligand stents (**Figure 21; A2 and B2**), which was further confirmed by TEM (**Figure 21; A3 and B3**).

Figure 21

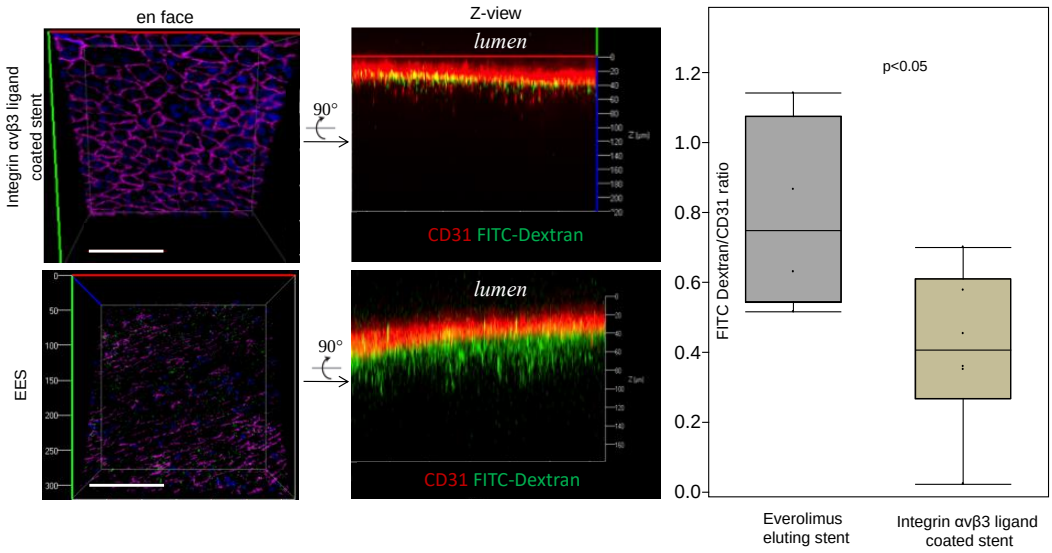


Comparison of integrin αvβ3 ligand coated stent (**A1-A3**) and EES (**B1-B3**) 12 weeks after implantation in a hypercholesterolemic rabbit model with receptive quantification of endothelia coverage (**C**). Scanning electron microscopy (SEM) of an integrin αvβ3 ligand coated stent half (**A1**) and an Everolimus eluting stent (EES) half (**B1**) shows improved strut-coverage as compared to EES. High-magnification SEM images (**A2** and **B2**) confirm a continuous monolayer of endothelial cells above integrin αvβ3 ligand coated stent struts whereas EES-struts seem to be covered by loosely arranged endothelial cells in the presence of scattered inflammatory cells and platelets (red asterisks = stent strut). Transmission electron microscopy (TEM) demonstrates a continuous endothelial monolayer with abundant intercellular junctions (arrowheads) in an integrin αvβ3 ligand coated stent (**A3**) while impaired endothelial monolayer integrity is observed in EES (**B3**, yellow arrowheads mark endothelial cells in the absence of intercellular junction, red arrowhead

indicates incidental finding of a transmigrating monocyte). Scale bar: A1/B1= 1mm. A2/A3=25 µm. A3/B3=100µm.

Co-registration of en-face confocal microscopy and SEM images revealed a predominance of FITC-dextran deposition in arterial segments where CD31-positive endothelial cells were absent. The ratio of FITC-dextran/CD31 positive area*intensity was significantly greater in EES as compared to integrin αvβ3 ligand coated stents ($p<0.05$) (**Figure 22**). More importantly, Z-stack tile imaging provided evidence that most of FITC-dextran (green channel, Figure 3) in EES was located underneath the endothelial monolayer (red channel, Figure 3), which was not the case with integrin αvβ3 ligand coated stents, where the signal of endothelial cells was almost superimposed with that of FITC-dextran confirming the integrity of endothelial monolayer.

Figure 22



Left: Confocal microscopy images of an integrin αvβ3 ligand coated stent (top) and EES (bottom) 12 weeks after implantation in a hypercholesterolemic rabbit model. En-face images (left) show strong CD31 staining of endothelial cells (cell shape, red channel, pink pseudocolor) in the integrin αvβ3 ligand coated stent and decreased CD31 staining in EES. FITC-dextran accumulation (green channel) between endothelial cells (red

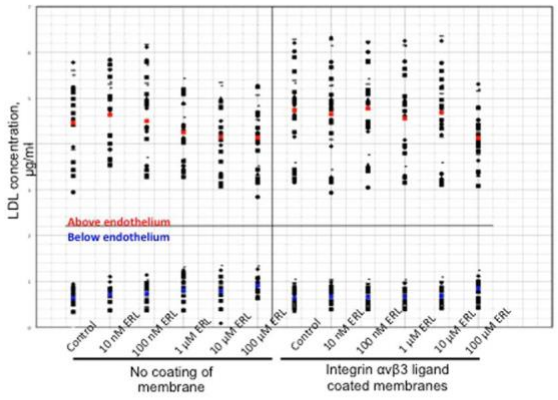
channel) is increased in EES as compared to integrin αvβ3 ligand coated stents ($p<0.05$). n=5 each and expressed as means with standard deviation calculated by ANOVA. Scale bar = 1 mm

4.6.3 Assessment of endothelial integrity in-vitro

To verify that leaky endothelial junctions result in increased lipid uptake and foam cell transformation of monocytes, cell culture experiments were performed: CM revealed a dose-dependent effect of everolimus on both HUVECs and HCAECs since organization of actin cytoskeleton (green phalloidin staining) as well as formation of adhesive cell-cell contacts (red VE-cadherin staining) were structurally modified and impaired. Everolimus concentration was inversely related to VE-cadherin expression, where highest concentrations of everolimus (100µM) resulted in obvious gaps in the endothelial monolayer, which was observed on uncoated and RGD-peptide coated surfaces (**Figure 23B).** Everolimus treatment of endothelial cells grown on uncoated and RGD-peptide coated membranes caused an increase in AcLDL-permeability. However, measurement of AcLDL concentrations above and beneath the endothelial monolayer showed a substantially decreased gradient when endothelial cells were grown on uncoated membranes (greater passage of AcLDL), while endothelial cells grown on RGD-peptide coated membranes not only showed more consistent confluence but also an increased gradient of AcLDL (decreased passage of AcLDL, **Figure 23A**). This effect was seen on both, HUVECs and HCAECs. Co-cultures of monocytes and endothelial cells incubated with media containing increasing concentrations of everolimus and a fixed concentration of AcLDL, showed a dose-dependent transformation of monocytes into foam cells. Oil-red-O staining showed greater lipid accumulation in monocytes co-cultured with endothelial cells under high concentrations of everolimus as compared to those incubated with lower everolimus concentrations (**Figure 24**). This effect was seen in HUVECs and HCAECs.

Figure 23

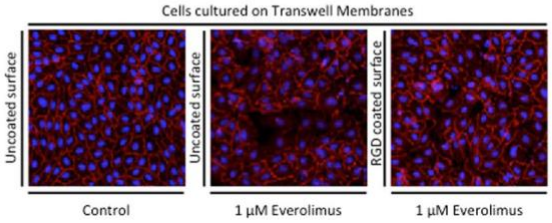
A



B

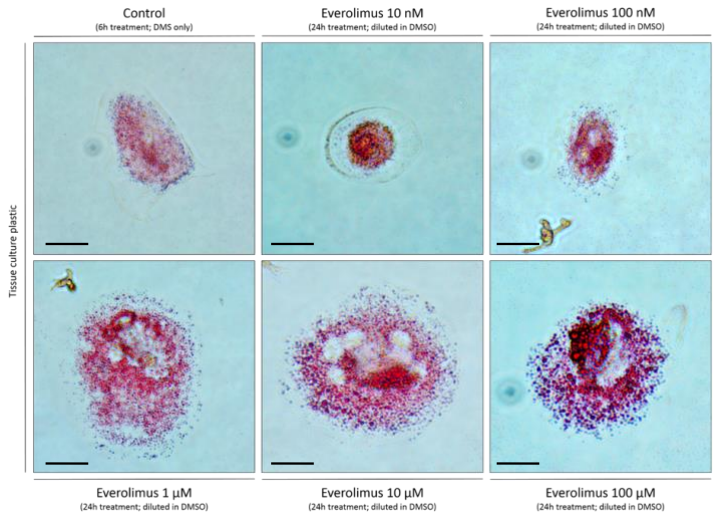
EVL (µg)	LDL upper chamber (µg/ml)		LDL lower chamber (µg/ml)		p
	No coating	RGD	No coating	RGD	
CTRL	44,632 (+7445)	47,420 (+9,336)	6,435 (±1,842)	6,439 (±1,944)	0.9
10nm	46,343 (+7216)	46,522 (+9,737)	7,093 (±1,901)	6,606 (±2,023)	0.4
100nm	44,956 (+11,724)	47,805 (+9,229)	7,287 (±1,918)	6,534 (±1,819)	0.14
1µm	42,617 (+6010)	45,5561 (+9,553)	8,143 (±25,89	6,496 (+1,865)	0.009*
10µm	41,562 (+6469)	46,801 (+9,253)	7,777 (±2,822)	6,729 (+1,849)	0.1
100µm	41,423 (+6,031)	41,360 (+5,797)	9,003 (±1,799)	8,444 (±2,129)	0.3

C



(**A**) AcLDL-concentrations in an in vitro permeability assay (transwell model) above and below endothelium which was cultured on ± integrin αvβ3 ligand coated semipermeable membranes and treated with everolimus in different concentrations (see B) for 24h. Everolimus treatment causes a dose-dependent decrease of AcLDL in the upper compartment of the semipermeable membrane and an increase of AcLDL in the lower compartment (mean LDL concentration above endothelium marked in red and below endothelium in blue; n=15). (**B**) Endothelial cells cultured on transwell membranes exposed to different concentrations of everolimus. The control group (uncoated surface) shows a confluent monolayer with intense VE-Cadherin staining (left). Incubation with everolimus at 1 µM for 24h resulted in incomplete endothelial integrity on uncoated surfaces (centre image). Endothelial cells cultured on integrin αvβ3 ligand coated surfaces (right image) show preserved VE-Cadherin expression and less intercellular gaps. (C) Endothelial cells cultured on transwell membranes exposed to different concentrations of everolimus. The control group (uncoated surface) shows a confluent monolayer with intense VE-Cadherin. staining (left). Incubation with everolimus at 1 µM for 24 h resulted in incomplete endothelial integrity on. uncoated surfaces (centre image). Endothelial cells cultured on integrin αvβ3 ligand coated surfaces (right image) show preserved VE-Cadherin expression and less intercellular gaps. Scale bar = 100 µm.

Figure 24



Everolimus (µg)	Lipid particles
CTRL (-)	393 (±15)
10nm	145 (±98)
100nm	245 (±31)
1µm	308 (±67)
10µm	1143 (±173)
100µm	1433 (±368)

Brightfield images of foamy monocytes in the presence of AcLDL (24h incubation on tissue culture plastic, n=3). Monocytes were co-cultured with endothelial cells after exposure to everolimus. Increasing concentrations of everolimus and fixed concentration of AcLDL result in dose-dependent transformation of monocytes into foam cells. (Foam cells stained with Oil-red-O, greater lipid accumulation in monocytes co-cultured with endothelial cells under high concentrations of everolimus). Scale bar = 20µm

4.7 A paclitaxel-coated balloon with a butyryl-tri-hexyl citrate excipient has similar angiographic efficacy to a paclitaxel-coated balloon with an iopromide excipient for the treatment of drug-eluting stent restenosis at 6-8 months.

A total of 264 patients underwent treatment of DES-restenosis with BTHC-PCB (n=127) or iopromide-PCB (n=137). Baseline clinical characteristics were similar for both groups, apart from a lower proportion of females, a lower incidence of hypertension and a higher incidence of prior MI in the BTHC-PCB group (**Table 13**). Treatment groups were well-matched in terms of baseline angiographic and procedural characteristics, apart from a smaller vessel size (2.78 [SD 0.48] mm vs. 2.89 [SD 0.48] mm, P=0.02), higher rate of balloon predilatation (122 (96.1) vs. 117 (85.4), P=0.01) and slightly larger post-procedure stenosis (22.3 [SD 8.2]% vs. 18.4 [SD 9.9]%, P=0.001) in the BTHC-PCB group (**Table 13**).

Table 13. *Patient, angiographic and procedural characteristics according to treatment*

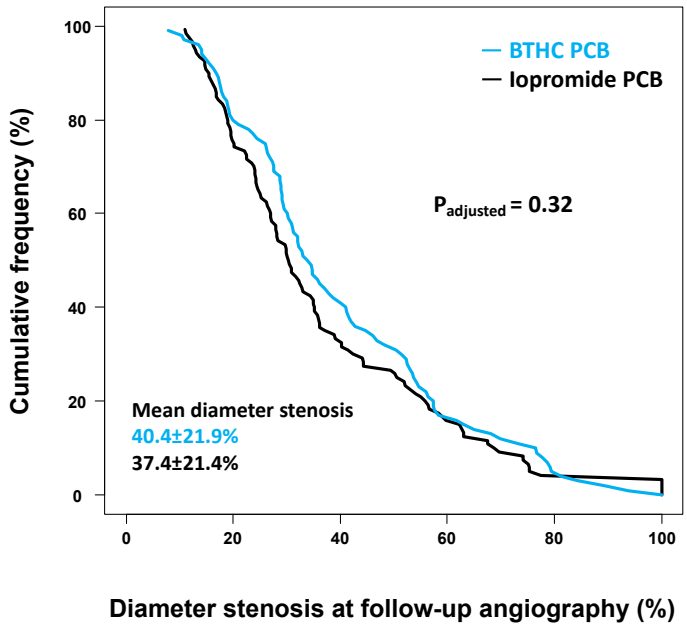
	BTHC-PCB	**Iopromide-PCB**	**P-value**
Patients	**n = 127**	**n = 137**	
Age	69.4 [SD 10.4]	67.7 [SD 10.4]	0.17
Female	16 (12.6)	32 (23.4)	0.02
Diabetes mellitus	55 (43.3)	56 (40.9)	0.69
Hypertension	81 (63.8)	105 (76.6)	0.02
Hyperlipidaemia	105 (82.7)	108 (78.8)	0.43
Current smoker	23 (18.1)	19 (13.9)	0.35
Prior myocardial infarction	68 (53.5)	53 (38.7)	0.02
Prior bypass surgery	17 (13.4)	15 (10.9)	0.54
Multivessel disease	113 (89.0)	129 (94.1)	0.13
Clinical presentation			0.44
stable angina pectoris	98 (77.2)	111 (81.0)	
unstable angina pectoris	29 (22.8)	26 (19.0)	
Ejection fraction †	52.9 [SD 11.4]	53.6 [SD 9.8]	0.87
Lesions			
Target vessel			0.55
left anterior descending	52 (41.0)	49 (35.8)	
left circumflex	38 (29.9)	40 (29.2)	
right coronary artery	37 (29.1)	48 (35.0)	
Restenosis morphology			0.32
focal	87 (68.5)	80 (58.4)	
multifocal	9 (7.1)	16 (11.7)	
diffuse	29 (22.8)	37 (27.0)	
occlusive	2 (1.6)	4 (2.9)	
Bifurcation	34 (27.0)	34 (24.8)	0.69
Vessel size (mm)	2.89 [SD 0.48]	2.78 [SD 0.48]	0.02
Diameter stenosis, pre (%)	67.2 [SD 12.2]	64.8 [SD 16.0]	0.34
Lesion length	10.45 [6.15]	10.24 [6.56]	0.53
Minimal lumen diameter, pre (mm)	0.94 [SD 0.36]	0.98 [SD 0.47]	0.92
Procedures			
Balloon predilatation	122 (96.1)	117 (85.4)	0.01
Balloon pressure, max (atm)	14.2 [SD 3.8]	13.8 [SD 4.2]	0.32
TIMI flow, post			0.28
0-I	0 (0)	0 (0)	
II	3 (2.4)	1 (0.7)	
III	124 (97.6)	136 (99.3)	
Minimal lumen diameter, post (mm)	2.28 [SD 0.40]	2.31 [SD 0.41]	0.94
Diameter stenosis, post (%)	22.3 [SD 9.9]	18.4 [SD 8.2]	0.001

Data is shown as mean [SD] or number (percentage) based on in-stent analysis. † data available for 75% of study sample (197 pts)

4.7.1 Primary endpoint - Angiographic follow-up

Angiographic follow-up data were available for 220 (83%) patients, with no significant difference between the groups (P=0.07). Regarding the primary endpoint, there was no difference between the BTHC-PCB and iopromide-PCB treated groups at follow-up angiography (40.4 [SD 21.9]% vs. 37.4 [SD 21.4]%, respectively, P=0.16; $P_{adjusted}$=0.32) (**Figure 25**). There was no difference in binary angiographic restenosis between the groups (32 patients [32.0%] versus 39 patients [32.5%], respectively, P =0.94; $P_{adjusted}$=0.97). Late-lumen-loss was comparable in both groups (0.41 [SD 0.74] mm versus 0.37 [SD 0.64] mm, respectively, P =0.91; $P_{adjusted}$=0.69). Morphology of recurrent restenosis at was similar in both groups: focal pattern ISR was the predominant morphology, occurring in 20 (62.5%) patients treated and 26 (66.7%) patients, respectively (P=0.28; $P_{adjusted}$=0.84).

Figure 25. *Cumulative frequency of percent diameter stenosis at 6-8 month angiography*

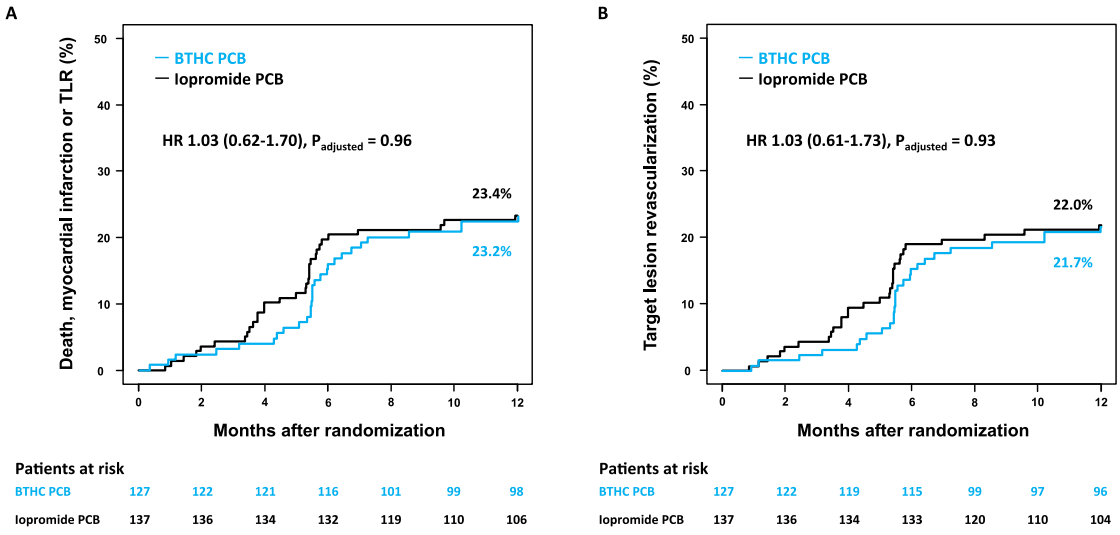


BTHC = Butyryl-tri-hexyl citrate; PCB = paclitaxel-coated balloon

4.7.2 Clinical results

Clinical follow-up at one year was complete in all but 2 patients. There was no significant difference in the composite of death, MI and TLR between the BTHC-PCB and iopromide-PCB groups (29 [23.2%] vs. 32 [23.4%] patients, respectively, HR 1.03 [95% CI 0.62-1.70], P=0.91; $P_{adjusted}$=0.96) (**Figure 26A**). There were no differences with respect to the individual components of this endpoint for the BTHC-PCB and iopromide-PCB groups: death occurred in 2 [1.6%] versus 3 [2.2%] patients, P=0.73; $P_{adjusted}$=0.81), MI occurred in 2 [1.6%] vs. 3 [2.2%] patients, P=0.73; $P_{adjusted}$=0.51), and TLR occurred in 27 [21.7%] vs. 30 [22.0%] patients, P=0.91; $P_{adjusted}$=0.93). Cumulative incidence curves for TLR are shown in **Figure 26B**. Target-lesion thrombosis rates were low and comparable at one year (0 [0%] vs. 1 [0.7%] patients, P=0.34, $P_{adjusted}$=0.93).

Figure 26 *(A) Cumulative incidence of cardiac death, myocardial infarction or target-lesion revascularisation and (B) target-lesion revascularisation at 1 year*



BTHC= butyryl-tri-hexyl citrate; TLR= target lesion revascularisation

4.8 Treatment with a paclitaxel-coated balloon was not associated with greater myocardial injury, as evidenced by high-sensitivity troponin rise, compared to treatment with a paclitaxel-eluting stent or an uncoated balloon

4.8.1 Delta troponin according to treatment group

A total of 343 patients with DES-restenosis randomized to treatment with PEB (n=112), PES (n=116) or balloon angioplasty (n=115) with available pre- and post-procedure hs-TnT measurements were included. Baseline patient, lesion and procedural characteristics were well matched (**Table 14**).

Table 14. *Baseline patient, lesion and procedural characteristics by treatment group**

	Paclitaxel-coated balloon	**Paclitaxel-eluting stent**	**Balloon angioplasty**	**p-value**
Patients	**n = 112**	**n = 116**	**n = 115**	
Age	67.1±10.3	68.6±9.8	67.2±9.1	0.43
Female	25 (22.3)	36 (31.0)	35 (30.4)	0.26
Diabetes mellitus	44 (39.3)	55 (47.4)	42 (36.5)	0.22
insulin-dependent	16 (14.3)	24 (20.7)	14 (12.2)	0.18
Prior myocardial infarction	43 (38.4)	46 (39.7)	47 (40.9)	0.93
Prior bypass surgery	14 (12.5)	29 (25.0)	22 (19.1)	0.06
Multivessel disease	105 (93.8)	107 (92.2)	108 (93.9)	0.86
Clinical presentation with ACS	22 (19.6)	19 (16.4)	26 (22.6)	0.49
Ejection fraction†	53.7±9.4	54.3±10.5	53.1±10.3	0.75
Lesions	**n = 138**	**n = 146**	**n = 136**	
Target vessel				0.61
left anterior descending	50 (36.2)	47 (32.2)	46 (33.8)	
left circumflex	40 (29.0)	55 (37.7)	45 (33.1)	
right coronary artery	48 (34.8)	43 (29.4)	45 (33.1)	
left main	0 (0.0)	1 (0.7)	0 (0.0)	
Restenosis morphology				0.78
focal	98 (71.0)	94 (64.3)	87 (64.0)	
diffuse	33 (23.9)	43 (29.5)	39 (28.7)	
proliferative	3 (2.2)	3 (2.1)	1 (0.7)	
occlusive	4 (2.9)	6 (4.1)	9 (6.6)	
Bifurcation	36 (26.1)	35 (24.0)	34 (25.0)	0.92
Vessel size (mm)	2.73±0.49	2.79±0.51	2.72±0.45	0.46
Diameter stenosis, pre (%)	63.4±17.1	66.0±16.7	67.2±16.4	0.17

Minimal lumen diameter, pre (mm)	1.00±0.48	0.95±0.50	0.90±0.52	0.29
Procedures				
Cutting balloon	2 (1.5)	2 (1.4)	0 (0.0)	0.38
Balloon pressure, max (atm)†	13.7±4.3	15.8±3.2	15.7±4.0	<0.001
Minimal lumen diameter post (mm)‡	2.28±0.43	2.50±0.49	2.07±0.49	<0.001
Diameter stenosis, post (%)∫	18.5±8.5	13.2±8.1	24.1±13.1	<0.001
TIMI flow post				0.24
0	0 (0)	0 (0)	2 (1.5)	
I	0 (0)	1 (0.7)	0 (0)	
II	2 (1.5)	6 (4.1)	4 (2.9)	
III	136 (98.5)	139 (95.2)	130 (95.6)	

Data is shown as mean ± SD or count (percentage) based on in-stent analysis. †Data was available for 250 patients (72.9%). *There were no significant differences between the groups except as indicated. †Maximal balloon pressure was significantly lower for PEB versus PES (p<0.001) and PEB versus balloon angioplasty (p=0.0001). ‡Minimal lumen diameter post procedure was significantly lower for PEB versus PES (p<0.001) and significantly higher for PEB versus balloon angioplasty (p=0.00016) and PES versus balloon angioplasty (p<0.001). ∫Diameter stenosis post procedure was significantly higher for PEB versus PES (p<0.001) and significantly lower for PEB versus balloon angioplasty (p<0.001) and PES versus balloon angioplasty (p<0.001).

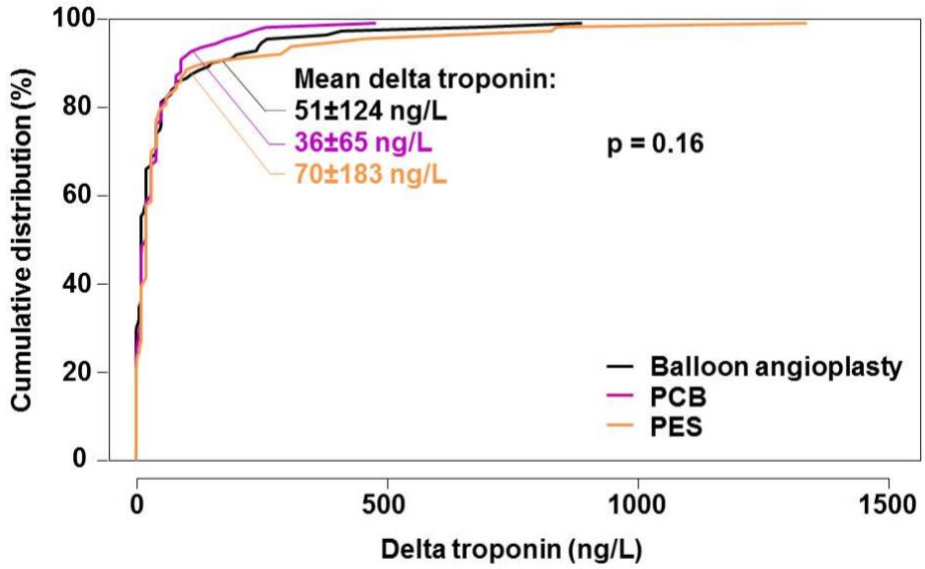
A total of 420 lesions were treated with PEB (n=138), PES (n=146) or balloon angioplasty (n=136). Focal pattern in-stent restenosis was present in 279 (66.4%) lesions. There were no differences between the groups in terms of the proportion of patients treated as per protocol. Nine lesions in the PCB group and 8 lesions in the balloon angioplasty group were treated with stent implantation; 10 lesions in the PES group were treated with balloon dilatation only (p=0.95).

4.8.2 Primary endpoint

There was no significant difference between PCB, PES and balloon angioplasty in terms of mean delta troponin (36±65, 70±183, and 51±124 ng/L, respectively, p=0.16) (**Figure 27)**.

There was no significant difference between treatment groups in terms of TIMI flow grade post-procedure or the proportion of patients with a peak hs-TnT value > 5 times the 99th percentile upper reference limit of normal: PCB:24 (30.4%); PES:29 (36.7%); and BA:26 (32.9%) patients, p=0.81. When analysed per protocol, mean delta troponin levels were: PCB=34±64; PES=67±182; and BA=42±92 ng/L, p=0.13. Clinical outcomes at 1 year are shown in **Table 15**.

***Figure 27**. Cumulative distribution curve showing delta troponin according to treatment*



PCB = paclitaxel-coated balloon; PES = paclitaxel-eluting stent

***Table 15**. Clinical results at 1 year according to treatment group**

	Paclitaxel-eluting balloon	Paclitaxel-eluting stent	Balloon angioplasty	p-value
Death	3 (2.7)	6 (5.2)	5 (4.3)	0.78
Myocardial infarction	3 (2.7)	3 (2.6)	1 (0.9)	0.32
Target lesion thrombosis	1 (0.9)	1 (0.9)	0 (0.0)	0.32
TLR	25 (22.3)	14 (12.1)	46 (40.0)	<0.001
Death or myocardial infarction	6 (5.4)	9 (7.8)	6 (5.2)	0.44
Death, myocardial infarction, TLR	27 (24.1)	22 (19.0)	50 (43.5)	<0.001

*Data shown as number (%s are Kaplan-Meier estimates). P-values are derived from log-rank tests. BA = balloon angioplasty; PEB = paclitaxel-eluting balloon; PES = paclitaxel-eluting stent; TLR = target lesion revascularisation

4.8.3 Survival analysis according to tertile of delta troponin

Mean delta troponin values in tertiles of delta troponin were 0±8, 15±5 and 132±197 ng/L, respectively, p<0.001. There were no significant differences in baseline patient, lesion, or procedural characteristics (**Table 16**), except for a higher proportion of bifurcation lesions in the third tertile and higher mean maximum balloon pressure with increasing tertile.

***Table 16**. Baseline patient, lesion and procedural characteristics according to delta troponin tertile**

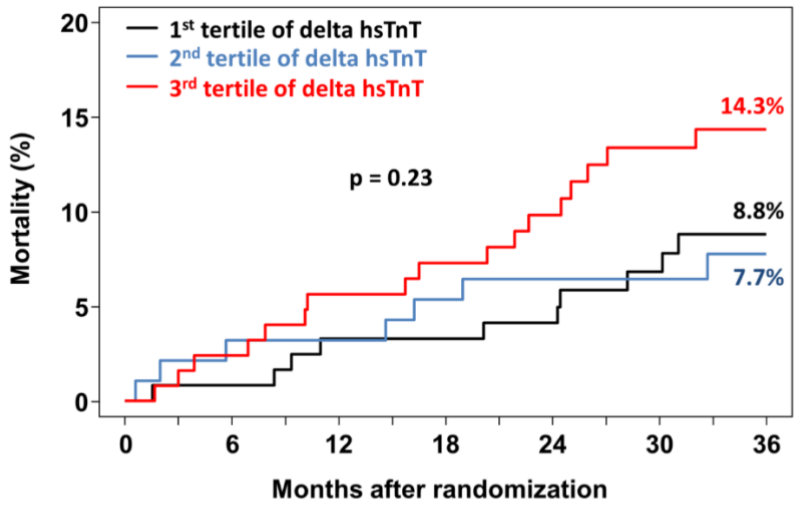
	First tertile	Second tertile	Third tertile	p-value
Patients	**n = 123**	**n = 94**	**n = 126**	
Age	67.2±8.3	67.6±10.2	68.2±10.7	0.72
Female	38 (39.6)	30 (31.2)	28 (29.2)	0.19
Diabetes mellitus	55 (39.0)	37 (26.0)	49 (35.0)	0.60
insulin-dependent	21 (38.9)	15 (27.8)	18 (33.3)	0.83
Prior myocardial infarction	47 (35.0)	40 (29.0)	49 (36.0)	0.79
Prior bypass surgery	20 (30.8)	19 (29.2)	26 (40.0)	0.63
Multivessel disease	117 (36.6)	84 (26.2)	119 (37.2)	0.20
Clinical presentation with ACS	25 (37.3)	13 (19.4)	29 (43.3)	0.22
Ejection fraction†	53.9±8.7	55.1±10.3	52.3±11.0	0.20
Lesions	**n = 140**	**n = 118**	**n = 162**	
Target vessel				0.16
left anterior descending	47 (33.6)	37 (31.4)	59 (36.4)	
left circumflex	48 (34.3)	32 (27.1)	60 (37.0)	
right coronary artery	45 (32.1)	49 (41.5)	42 (25.9)	
left main	0 (0.0)	0 (0.0)	1 (0.6)	
Restenosis morphology				0.06
focal	97 (69.3)	79 (67.0)	103 (63.6)	
diffuse	33 (23.6)	34 (28.8)	48 (29.6)	
proliferative	6 (4.3)	0 (0.0)	1 (0.6)	
occlusive	4 (2.9)	5 (4.2)	10 (6.2)	
Bifurcation§	31 (22.1)	23 (19.5)	51 (31.5)	0.046
Vessel size (mm)	2.76±0.46	2.71±0.49	2.76±0.50	0.62

Diameter stenosis, pre (%)	67.0±15.5	64.4±15.2	65.0±18.8	0.43
Minimal lumen diameter, pre (mm)	0.91±0.45	0.98±0.47	0.96±0.56	0.51
Procedures				
Cutting balloon	1 (0.7)	1 (0.9)	2 (1.2)	0.89
Balloon pressure, max (atm)†	13.9±3.6	15.4±3.8	15.8±4.2	<0.001
Minimal lumen diameter post (mm)	2.29±0.51	2.27±0.46	2.30±0.52	0.91
Diameter stenosis, post (%)	18.5±12.3	18.3±9.7	18.7±10.8	0.95

Data are shown as mean ± SD or number (percentage) based on in-stent analysis.†Data was available for 72.9% of study sample (250 pts). *There were no significant differences between the groups except where indicated. †Maximal balloon pressure was significantly lower for the first tertile compared with both the second (p=0.001) and third tertiles (p<0.001), with no difference between the second and third tertile.
ACS = acute coronary syndrome

Mean baseline hs-TnT was 22±45, 13±31, and 40±88 ng/L (p=0.005) in the first, second and third tertile of delta troponin, respectively. Respective mean peak hs-TnT was 23±39, 28±33, and 172±240 ng/L (p<0.001). Mean peak CK-MB level remained within normal limits in each tertile (15.1±8.7, 15.2±6.0, and 21.4±12.7 U/L, respectively, p<0.001). Mean C-reactive protein was 3.7±5.0, 2.5±2.8, and 5.5±9.2 mg/L, p=0.05. Mean baseline creatinine was 1.19±1.16, 1.07±0.89, and 1.18±0.83 mg/dL, respectively (p=0.62). Three-year mortality rates according to delta troponin were 7.7%, 8.8% and 14.3% for the first, second and third tertiles, respectively, p=0.23 (**Figure 28**).

Figure 28. *Cumulative incidence of mortality according to delta troponin tertile*



1st tertile	123	121	181	117	116	96	78
2nd tertile	94	91	90	88	85	77	55
3rd tertile	126	122	117	112	107	95	80

hsTnT = high sensitivity troponin T

4.9 In a meta-analysis of randomized trials, percutaneous compared with surgical revascularisation of left main coronary artery disease is associated with a comparable risk of the composite of all-cause death, myocardial infarction, or stroke at long-term follow-up but a higher risk of repeat revascularisation.

4.9.1 Characteristics of the included studies

After merging independent searches and removing duplicates, we identified 6,569 reports. We found 4 eligible randomized trials,[99,100,124,128,132-135] including the LMCA cohort of the SYNTAX trial.[128,132-134,136] All were prospective, multi-center, open-label trials, with 5-year follow-up, except the EXCEL trial,[99] which had 3-year follow-up. In total, 4,394 patients allocated to PCI (n=2,197) or CABG (n=2,197) were included. Main trial and patient characteristics are shown in **Tables 17 and 18**.

Table 17. *Main characteristics of included trials*

	Patients randomized (PCI vs. CABG)	Center (n)	Region	Enrollment period	Design	Primary endpoint	Follow-up[b] (years)	Registration[c]
Left main coronary artery disease								
SYNTAX (LMCA Cohort)	357 vs. 348	85	Netherlands, US, Germany, UK, France, Italy, Sweden, Belgium, Hungary, Poland, Austria, Denmark, Latvia, Finland, Spain, Portugal	Mar 2005-Apr 2007	Non-Inferiority	All-cause death, myocardial infarction, stroke, or repeat revascularisation	5	NCT00114972
PRECOMBAT	300 vs. 300	13	South Korea	Apr 2004-Aug 2009	Non-Inferiority	All-cause death, myocardial infarction, stroke, or ischemia-driven target-vessel revascularisation	5	NCT00422968
EXCEL	948 vs. 957	126	US, UK, Canada, France, Italy, Germany, Spain, Netherlands, Hungary, Switzerland, Poland, Latvia, Portugal, Argentina, Brazil, Australia, South Korea	Sept 2010-Mar 2014	Non-Inferiority	All-cause death, myocardial infarction, or stroke[a]	3	NCT01205776
NOBLE	598 vs. 603	36	UK, Sweden, Denmark, Latvia, Estonia, Finland, Germany	Dec 2008-Jan 2015	Non-Inferiority	All-cause death, non-procedural myocardial infarction, stroke, or repeat revascularisation	5	NCT01496651

[a]In the EXCEL trial[99] the composite of all-cause death, myocardial infarction, stroke, or repeat revascularisation was defined as secondary endpoint. [b]Longest follow-up at Kaplan-Meier analysis. [c]Registration number in www.clinicaltrial.gov database.

Table 18. *Main trial-level clinical and procedural characteristics*

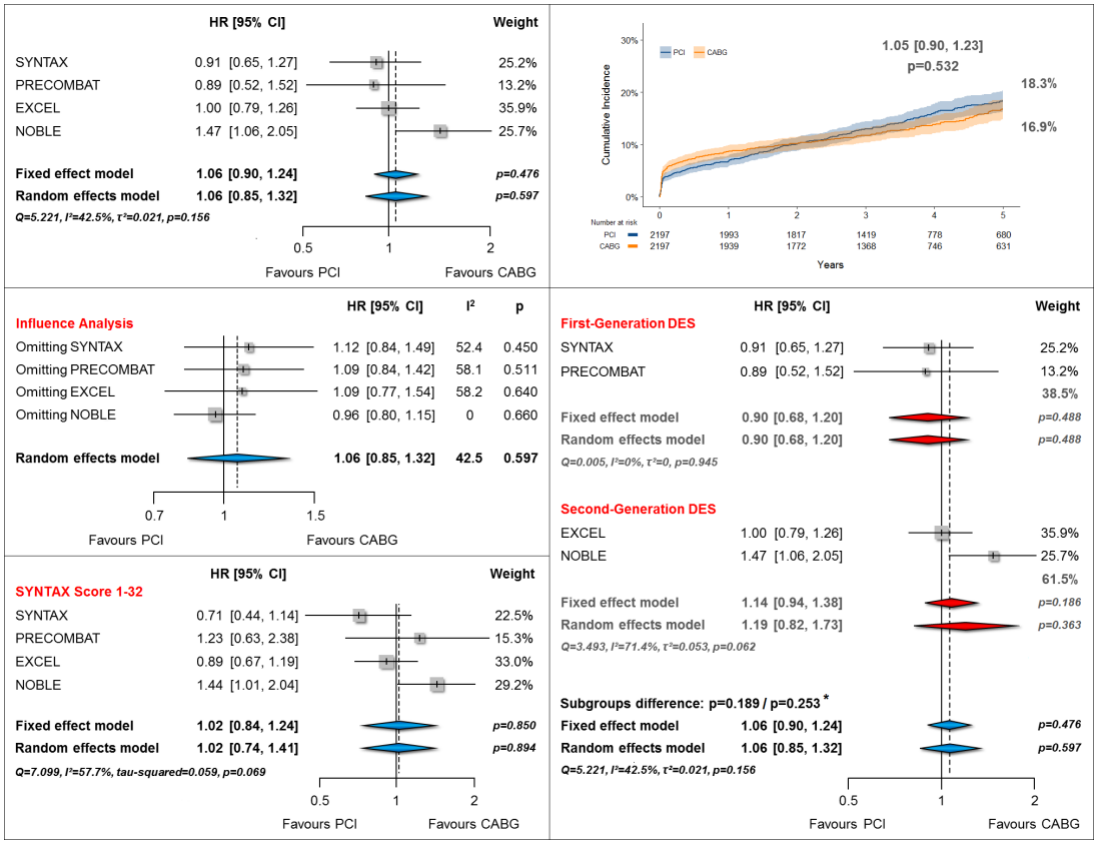
	Age (years)	Male n (%)	DM n (%)	Smoker n (%)	CKD n (%)	Prior MI n (%)	Prior PCI n (%)	LVEF % or n (%)[e]	Stable CAD n (%)	ACS n (%)	DES type	LMCA + 2-/3-Vessel Disease n (%)	Left IMA n (%)	Arterial Graft/Patient mean (SD)	Off-Pump n (%)
Left main coronary artery disease															
SYNTAX (LMCA Cohort)	62	459 (76.5)	192 (32.0)[a]	147 (20.9)	13 (1.8)[c]	190 (27.0)	0 (0)	10 (1.4)	495 (70.2)	210 (29.8)	DP-PES (G1-DES)	248 (69.5)	305 (87.6)	1.3 (0.6)	56 (16.7)
PRECOMBAT	65	520 (73.8)	174 (24.7)[a]	172 (28.7)	5 (0.8)[d]	33 (5.5)	76 (12.7)	61	297 (49.5)	303 (50.5)	DP-SES (G1-DES)	223 (74.3)	233 (93.6)	2.1 (0.9)	155 (63.8)
EXCEL	66	1464 (76.9)	554 (29.1)	415 (22.4)	308 (16.5)[c]	330 (17.5)	326 (17.1)	57	1148 (60.7)	1017 (53.8)	99.2% DP-EES (G2-DES) 0.8% Other	487 (51.7)	908 (98.8)	1.4 (0.6)	271 (29.4)
NOBLE	66	928 (78.4)	176 (14.9)	235 (19.8)	NR	NR	234 (19.8)	60	977 (82.5)	206 (17.4)	12% DP-SES (G1-DES) 88% BP-BES (G2-DES)	NR	526 (93.4)	NR	88 (15.6)

ACS = acute coronary syndrome; BES = Biolimus-eluting stent; BP = biodegradable-polymer; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; DP = durable polymer; DSL = Dyslipidemia; G1-DES = first generation drug-eluting stent; G2-DES = second generation drug-eluting stent IMA = internal mammary artery; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction, NR = not reported, PCI = percutaneous coronary intervention; PES = ; SES = Sirolimus-eluting stent. All within-trial comparisons were not significantly different. [a]Medically-treated. [b]Statin-therapy. [c]Serum creatinine >200 µmol/L (2.26 mg/dL). [d]Creatinine clearance ≤60 mL/min according to Cockcroft–Gault formula. [e]For the SYNTAX trial,[133,134] only n (%) of patients with LVEF <30% was available. For the other trials the weighted average of arm-level mean or median (NOBLE trial)[100] values is reported.

4.9.2 Primary endpoint

PCI and CABG had comparable outcomes (**Figure 29, upper left**) (random-effects HR 1.06, 95% CI 0.85-1.32, p=0.597). The EXCEL trial[7] had the highest relative weight (35.9%). Heterogeneity was moderate (I^2=42.5%, p=0.154). Kaplan-Meier analysis showed no significant difference between treatments over time **(Figure 29, upper right**), with a cumulative incidence of 18.3% (319 events) and 16.9% (292 events) in the PCI and CABG groups at 5 years. In the first 2 years, PCI had a numerical advantage over CABG; from 3 to 5 years CABG group had a numerical advantage over PCI. Risk estimation by shared frailty model showed similar safety of both techniques (HR 1.05, 95% CI 0.90-1.23, p=0.532).

Figure 29. *Major adverse cardiac and cerebrovascular events.*



CABG=Coronary Artery Bypass Grafting; CI=Confidence Interval; HR=Hazard Ratio, PCI=Percutaneous Coronary Intervention. *

Influence analysis showed heterogeneity was mainly due to the NOBLE trial (**Figure 29, middle left**)–the only trial favoring CABG (omitting NOBLE, HR 0.96, 95% CI 0.80-1.15, p=0.660; I^2=0%).[100] After including only patients with SYNTAX score 1-32, results were consistent (**Figure 29, lower left**): random-effects, HR 1.02, 95% CI 0.74-1.41, p=0.894. Grouping of trials according to DES generation showed consistent results (**Figure 29, lower right**), with comparable pooled estimates (first-generation: HR 0.90, 95% CI 0.68-1.20, p=0.488; second-generation: HR 1.19, 95% CI 0.82-1.73, p=0.363). Effect size was uniform within the first-generation DES group (I^2=0%, p=0.945), while second-generation DES group showed high heterogeneity (I^2=71.4%, p=0.061), explained by the contrasting results of EXCEL and NOBLE.[99,100]

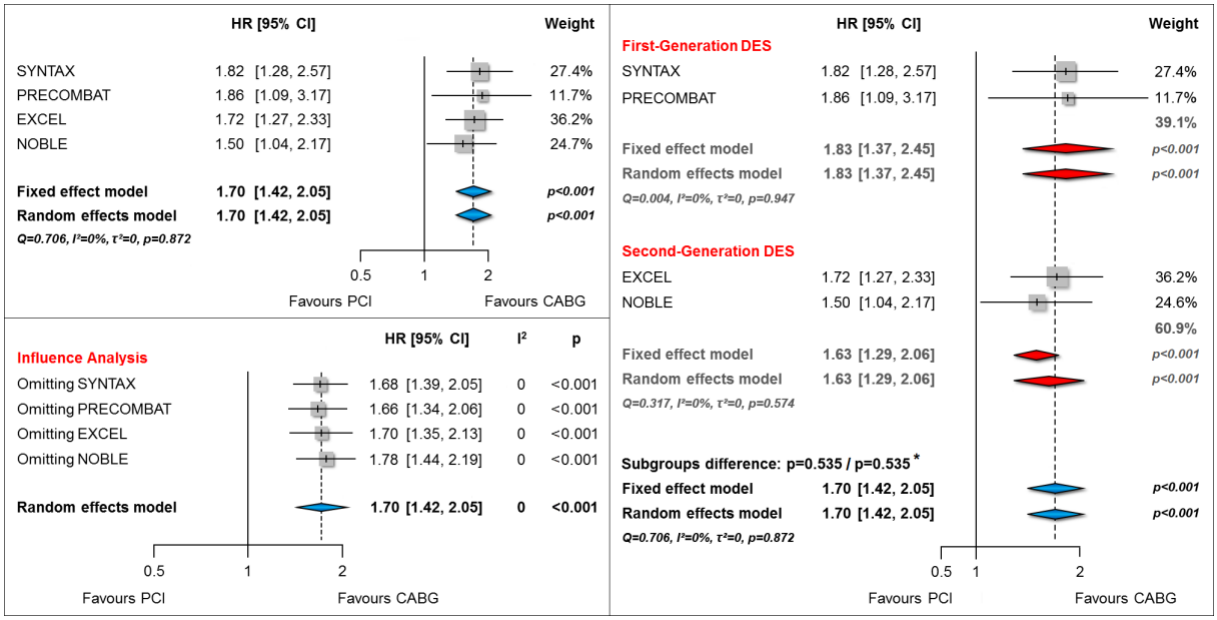
The comparison between trials of patients with LMCA stenosis with those of patients with MV-CAD without LMCA stenosis showed a significant difference (random-effects p=0.036). Descriptive data of trials with MV-CAD have been reported previously.[137] After pooling all trials irrespective of the anatomic pattern, PCI was associated with a significant risk increase at long term follow-up (random-effects, HR 1.21, 95% CI 1.02-1.45, p=0.029).

4.9.3 Secondary endpoints

PCI was associated with a significantly higher risk of repeat revascularisation compared with CABG (HR 1.70, 95% CI 1.42-2.05, p<0.001) (**Figure 30, upper left**). A total of 313 events occurred in PCI group and 184 events occurred in CABG group. Effect size was consistent across trials (I^2=0%, p=0.872). Results remained consistent at influence analysis (**Figure 30 lower left**). The grouping of trials according to DES generation did not significantly change the results (**Figure 30, right**). Second-generation DES (HR 1.63, 95% CI 1.29-2.06, p<0.001)

and first-generation DES groups (HR 1.83, 95% CI 1.37-2.45, p<0.001) had a similar risk of repeat revascularisation (p=0.535).

Figure 30. *Repeat revascularisation*



CABG=Coronary Artery Bypass Grafting; CI=Confidence Interval; HR=Hazard Ratio, PCI=Percutaneous Coronary Intervention.

PCI was associated with increased risk of the secondary composite endpoint (death, myocardial infarction, stroke or repeat revascularisation) compared to CABG (HR 1.27, 95% CI 1.11-1.44, p<0.001), without significant heterogeneity (I^2=0%, p=0.576). Influence analysis showed consistent results. The risk was similar with first- and second-generation DES.

There was a comparable risk of death for PCI and CABG, both all-cause (random-effects, HR 1.04, 95% CI 0.81-1.33, p=0.772) and cardiac (random-effects, HR 1.00, 95% CI 0.72-1.39, p=0.991), with mild heterogeneity and limited influence of individual trials. Although the risk of myocardial infarction was comparable between techniques (random-effects, HR 1.48,

95% CI 0.85-2.58, p=0.170), high heterogeneity was detected (I^2=67.4%, p=0.027) as a result of the risk increase in the PCI arm of the NOBLE trial[8] (omitting NOBLE, HR 1.13, 95% CI 0.76-1.67, p=0.543; I^2=27.3%) and the comparable incidence between treatments observed in the EXCEL trial (omitting EXCEL, HR 1.95, 95% CI 1.26-3.02, p=0.003; I^2=0.6%).[99] The risk of stroke was comparable between PCI and CABG (random-effects, HR 0.87, 95% CI 0.39-1.92, p=0.722), with a high degree of heterogeneity (I^2=62.7%, p=0.045), mainly because of the increased incidence observed after PCI in the NOBLE trial (omitting NOBLE, HR 0.63, 95% CI 0.37-1.09, p=0.097; I^2=9.1%).[100] Stent/graft occlusion was documented less frequently in patients treated with PCI as compared with CABG, with differences according to the model used and substantial heterogeneity (I^2=87.6%, p<0.001) mainly introduced by the EXCEL trial where stent occlusion was definitely less frequent than graft occlusion (omitting EXCEL, HR 0.85, 95% CI 0.45-1.64, p=0.636; I^2=31.0%).[99]

The comparison between trials of patients with LMCA stenosis with those of patients with MV-CAD without LMCA stenosis showed mixed results according to the model applied. Overall, there was a significant difference between the two groups of trials for the outcomes of all-cause death and myocardial infarction. Conversely, the two groups of trials seemed to be uniform in terms of stroke. Pooled estimates described a significant risk increase in all-cause death (random-effects, HR 1.21, 95% CI 1.01-1.46, p=0.042) and myocardial infarction (random-effects, HR 1.77, 95% CI 1.20-2.59, p=0.004) associated with PCI compared with CABG. Stroke showed numerically reduced incidence after PCI as compared with CABG (random-effects, HR 0.78, 95% CI 0.49-1.26, p=0.311).

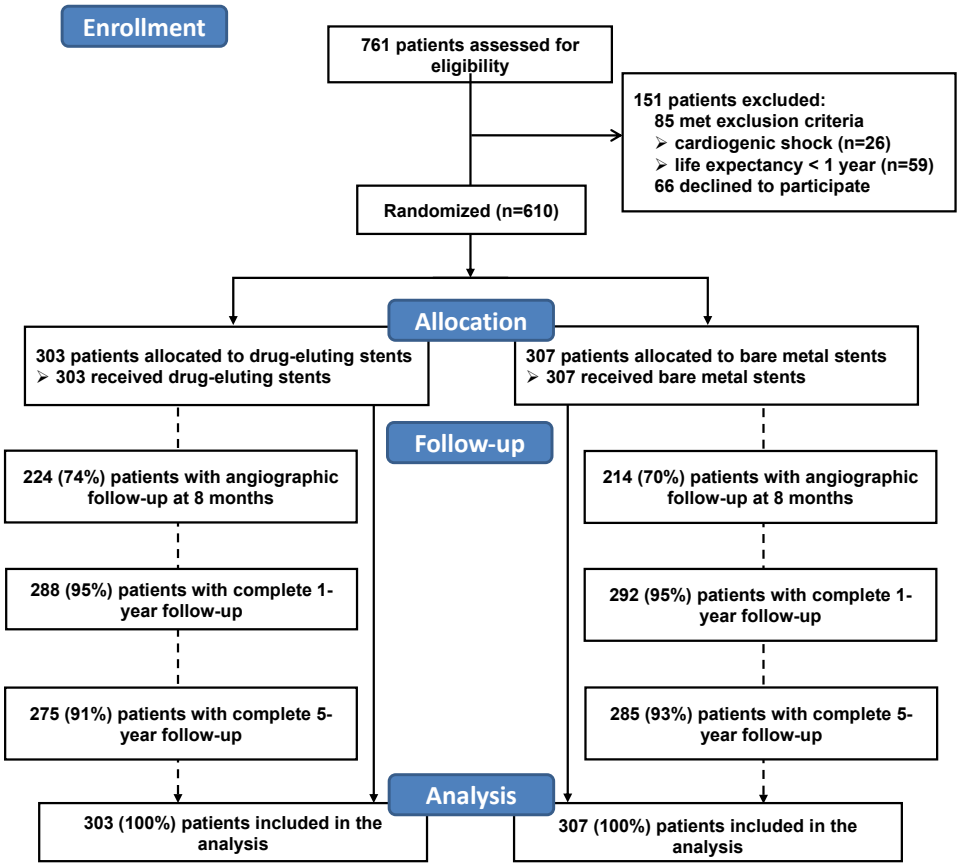
Qualitative assessment of trials showed a low risk of bias. According to GRADE, the quality

of evidence was high for the primary endpoint and repeat revascularisation, moderate for death, and low for myocardial infarction, stroke, and graft/stent occlusion.

4.10 After stenting of vein graft lesions in patients with previous coronary artery bypass surgery, the efficacy advantage for drug-eluting stents over bare metal stents observed at 1 year was lost at 5 years because of late catch-up in target lesion revascularisation with drug-eluting stents.

In total, 610 patients were enrolled in the study, 303 patients in the DES group (permanent polymer PES [n=101], permanent polymer SES [n=101] or biodegradable polymer SES [n=101]) and 307 patients in the bare metal stent group.

Figure 31. *Patient flow in the ISAR-CABG trial*



All patients received the allocated stent type. A study flow diagram is shown in **Figure 31**. Baseline clinical, lesion and procedural characteristics were similar in both treatment groups (**Tables 19 and 20**). 438 (72%) patients underwent 6-8 month angiography. Clinical follow-up at 5 years was complete in all but 50 (8.1%) patients, with no significant difference between treatment groups (P=0.28). Median follow-up in patients with incomplete follow-up was 1.1 (0.7-2.6) years. Clinical outcomes at 5 years are shown in **Table 21**.

Table 19*. Baseline patient characteristics according to treatment group*

	DES	**BMS**
Patients	**n = 303**	**n = 307**
Age	71·4±9·0	71·5±9·3
Female	40 (13%)	48 (16%)
Diabetes mellitus	111 (37%)	107 (35%)
- insulin-dependent	39 (13%)	34 (11%)
Hypertension	216 (71%)	223 (73%)
Hyperlipidaemia	268 (88%)	264 (86%)
Current smoker	25 (8%)	18 (6%)
Prior myocardial infarction	170 (56%)	168 (55%)
Clinical presentation		
- unstable angina pectoris	115 (38%)	124 (40%)
- stable angina pectoris	188 (62%)	183 (60%)
No of diseased coronary vessels		
- One vessel	3 (1%)	5 (2%)
- Two vessels	12 (4%)	18 (6%)
- Three vessels	288 (95%)	284 (92%)
Saphenous vein graft age (years)	13·4±5·6	13·7±5·2
Serum creatinine (µmol/L)	106·1±62·8	103·4±46·0
Left ventricular ejection fraction (%)*	49·2±12·2	49·5±13·8
Multiple treated lesions	69 (22·5%)	74 (24·4%)

Data shown as mean±SD or number (%). P>0.05 for all comparisons. *Data available for 83% of study sample (505 patients). BMS = bare metal stent; DES = drug-eluting stent

***Table 20**. Baseline lesion and procedural characteristics according to treatment group*

	DES	**BMS**
Lesions	**n = 386**	**n = 385**
Recipient vessel		
- Left anterior descending coronary artery	123 (32%)	118 (31%)
- Left circumflex coronary artery	134 (35%)	140 (36%)
- Right coronary artery	129 (33%)	127 (33%)
Stenosis localization		
- aortic anastomosis	60 (16%)	71 (18%)
- coronary anastomosis	47 (12%)	39 (10%)
- proximal	101 (26%)	90 (23%)
- medial	108 (28%)	98 (25%)
- distal	56 (15%)	65 (17%)
- diffuse	14 (4%)	22 (6%)
Degeneration score		
- 0	139 (36%)	130 (34%)
- 1	100 (26%)	106 (28%)
- 2	77 (20%)	76 (20%)
.- 3	70 (18%)	73 (19%)
TIMI flow prior to procedure		
- 0	20 (5%)	20 (5%)
- 1	11 (3%)	17 (4%)
- 2	65 (17%)	66 (17%)
- 3	290 (75%)	282 (73%)
TIMI flow after procedure		
- 0	1 (<1%)	6 (2%)
- 1	0 (0%)	3 (1%)
- 2	25 (6%)	27 (7%)
- 3	360 (93%)	349 (91%)
Reference vessel diameter, pre (mm)	3.36 ± 0.68	3.38 ± 0.73
Lesion length (mm)	15·1±10.2	14·3±9.8
Lesion predilatation	227 (65·0)	232 (63·2)
Diameter stenosis, pre (%)	65·3±14·8	64·6±16·1
Balloon diameter, max (mm)	3.65 ± 0.64	3.72 ± 0.76
Balloon pressure, max (mmHg)	15·0±3·6	15·3±3·8
Diameter stenosis, post (%)	11·4±7·4	10·6±13·1
Length of stented segment (mm)	26·8±15·4	27·5±13·4

Data shown as mean±SD or number (percentage) based on in-stent analysis. There were no significant differences in baseline lesion and procedural characteristics between treatment groups (P>0.05 for all comparisons). BMS = bare metal stent; DES = drug-eluting stent; TIMI = Thrombolysis in Myocardial Infarction

***Table 21**. Clinical results at 5 years according to treatment group*

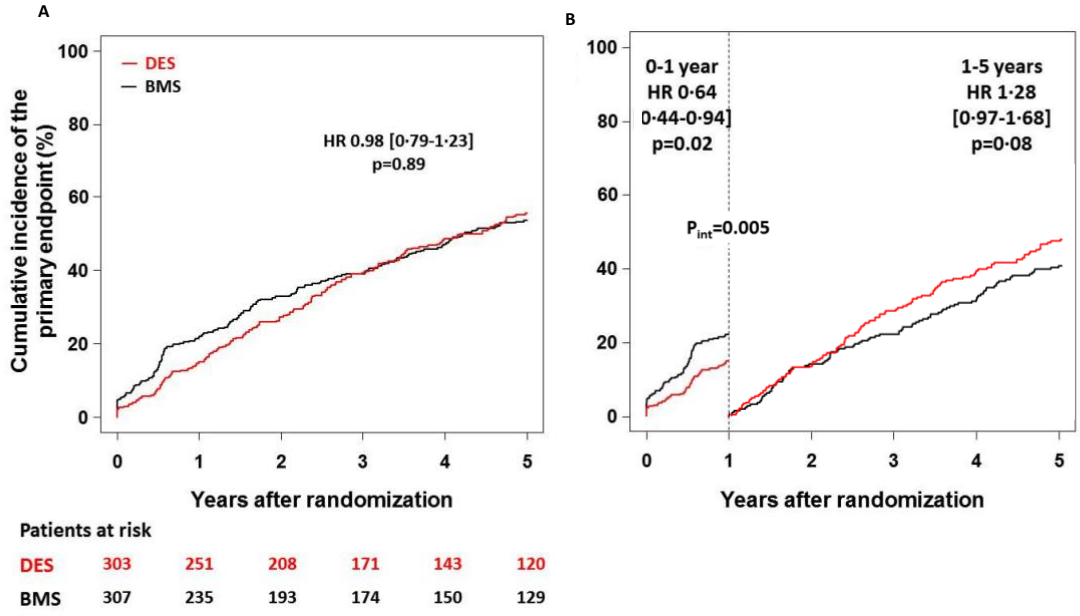
	DES	BMS	Hazard ratio (95% CI)	P-value
Patients	**n = 303**	**n = 307**		
Death	78 (27·5%)	84 (28.9%)	0·94 (0·69-1·28)	0·70
Cardiac death	48 (18·2%)	53 (20·1%)	0·92 (0·62-1·36)	0·67
Myocardial infarction	22 (8·2%)	28 (9·9%)	0·76 (0·44-1·36)	0·37
- STEMI	4 (1.5%)	6 (2.0)	0.67 (0.19-2.37)	0.53
Definite stent thrombosis	5 (2·0%)	1 (0·4%)	5·11 (0·60-44·72)	0·14
TLR	84 (33·1%)	69 (25.5%)	1·20 (0·87-1·64)	0·27
- Repeat PCI	84 (33.1%)	67 (24.8%)	1.24 (0.90-1.71)	0.19
- Repeat CABG	0 (0%)	3 (1.1%)	-	0.99
Target vessel revascularisation*	100 (39.5%)	89 (32.9%)	1.09 (0.82-1.45)	0.57
Death or myocardial infarction	93 (32·8%)	108 (36·6%)	0·85 (0·64-1·12)	0·24
Death, myocardial infarction, TLR	159 (55·5%)	157 (53·6%)	0.98 (0·79-1·23)	0·89

Percentages are Kaplan-Meier estimates. BMS = bare metal stent; CABG = coronary artery bypass surgery; CI = confidence interval; DES = drug-eluting stent; PCI = percutaneous coronary intervention; TLR = target lesion revascularisation; STEMI = ST elevation myocardial infarction

4.10.1 Primary endpoint

At 5 years, the primary endpoint occurred in 159 (55.5%) patients in the DES group and 157 (53.6%) patients in the bare metal stent group (HR 0.98, 95% CI 0·79-1·23, P=0·89) (**Figure 32A**). A significant interaction between treatment effect and time was observed ($P_{interaction}$=0·005). Landmark analysis showed a lower rate of the primary endpoint in the DES group compared with the bare metal stent group at 1 year (HR 0·64, 95% CI 0·44-0·94, P=0·02) but a numerically higher rate in the DES group between 1 and 5 years (HR 1·24, 95% CI 0·94-1·63, P=0·13) (**Figure 32B**). There was no significant difference in outcomes between patients randomized to treatment with each of the three different DES types with respect to the primary endpoint. In the prespecified patient subgroups, there was no interaction with treatment effect with respect to the primary endpoint ($P_{interaction}$>0.13 in all cases).

Figure 32. *Cumulative incidence of* ***(A)*** *the primary endpoint (composite of death, myocardial infarction or TLR) at 5 years, with* ***(B)*** *landmark analysis at 1 year*



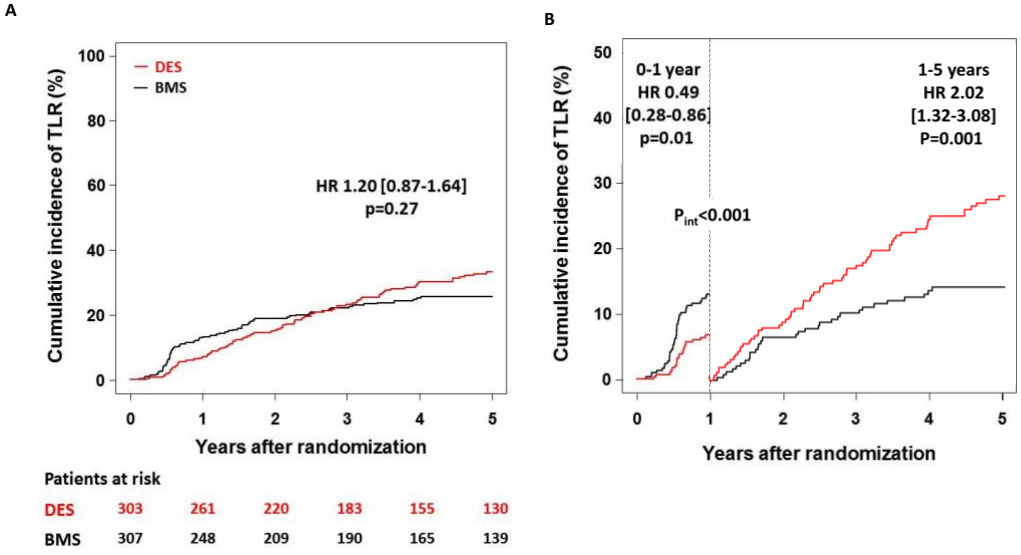
BMS = bare metal stent; DES = drug-eluting stent; MI = myocardial infarction

4.10.2 Secondary endpoints

The composite of death or myocardial infarction occurred in 93 (32·8%) vs. 108 (36·6%) patients (HR 0·85, 95% CI 0·64-1·12, P=0·24) at 5 years. There was no significant interaction between treatment effect and time (P_{int}=0·57). Landmark analysis showed comparable rates of death or myocardial infarction in the DES and bare metal stent groups at 1 year (HR 0·74, 95% CI 0·44-1·25, P=0·27) and between 1 and 5 years (HR 0·89, 95% CI 0·64-1·24, P=0·49).

At 5 years, TLR occurred in 84 (33·1%) vs. 69 (25.5%) patients in the DES and bare metal stent group (HR 1·20, 95% CI 0·87-1·64, P=0·27) (**Figure 33A**). A significant interaction between treatment effect and time was observed ($P_{interaction}$<0·001). Landmark analysis showed lower TLR rates in the DES group at one year (HR 0·49, 95% CI 0·28-0·86, P=0·01) but higher rates between one and five years (HR 2·02, 95% CI 1·32-3·08, P=0·001) (**Figure 33B**).

***Figure 33**. Kaplan Meier curves showing **(A)** cumulative incidence of TLR at 5 years and **(B)** landmark analysis showing cumulative incidence of TLR at 1 year and between 1 and 5 years*



BMS = bare metal stent; DES = drug-eluting stent; TLR = target lesion revascularisation

There was no difference between treatment groups in the clinical presentation of patients who underwent TLR: presentation was with acute coronary syndrome in 51 (33.3%) patients, with stable angina in 94 (61·4%) patients and 8 (5.2%) patients were asymptomatic (P=0·52). The angiographic morphology of restenotic lesions in patients who underwent TLR was diffuse in 84 (55.6%), within the stented area in 67 (44.4%) patients and in the 5 mm segment proximal or distal to the stent in the remainder of patients, with no difference between the groups (P=0.40 and 0.66, respectively). 49 (32.0%) patients underwent multiple TLR procedures throughout the follow-up period, with no difference between the treatment groups (P=0.47). 84 (13.8%) patients underwent TVR that did not involve the target lesion, with no difference between the treatment groups (P=0.34); of these 20 patients underwent multiple TVR procedures that did not involve the target lesion during the follow-up period, with no difference between the groups (P=0·29). SVG occlusion was

found in 63 (10·3%) patients within the follow-up period: 32 were managed conservatively, with no difference between the groups (P=0.72). Of those who underwent revascularisation, 17 were treated by TLR and 14 by PCI of the native vessel supplied by the target SVG.

Definite stent thrombosis occurred in five (2·0%) versus one (0·4%) patient in the DES and bare metal stent groups, respectively (HR 5·11, 95% CI 0·60-44·72, P=0·14).

There was no significant difference between the three DES types with respect to any secondary endpoint.

5. DISCUSSION

5.1 In patients with planned invasive coronary angiography (ICA) for investigation of suspected CAD in Germany, initial CTA/FFR_{CT} was associated with a significantly lower rate of ICA showing no obstructive CAD compared with usual care

The main findings are as follows:

- In patients with planned ICA for investigation of suspected CAD enrolled in a consecutive cohort study at German sites, an initial CTA/FFR_{CT} strategy was associated with a significantly lower rate of ICA showing no obstructive CAD compared with usual care.
- Initial CTA±FFR_{CT} was associated with a high rate of cancellation of ICA, significantly lower cumulative radiation exposure, significantly lower medical resource use and cost, and greater improvement in QOL at one-year follow-up.

Although the role of CTA in the investigation of stable chest pain is supported by randomized trial data, some trials have shown that CTA alone for the investigation of stable chest pain leads to a higher rate of ICA showing no obstructive CAD, and potentially a higher rate of revascularisation in the absence of knowledge of lesion functional severity.[138,139] One of the limitations of CTA in routine practice is that it has a low specificity for obstructive CAD and may increase the rate of referral for ICA. The PLATFORM study suggests that using a combination of CTA and FFR_{CT} might address this limitation.[6,138] In patients with chest pain and intermediate risk of obstructive CAD, considerable variation exists in relation to diagnostic practices. In Germany, the rate of ICA may be higher than in other European countries or in the USA.[10] In addition, the ratio of myocardial revascularisation to ICA is

lower in Germany than elsewhere,[10] which would imply that a higher proportion of ICA performed in Germany shows no obstructive CAD. This was the rationale for analysing outcomes of patients enrolled in the PLATFORM study at German sites.

In terms of the primary endpoint, findings are consistent with the main PLATFORM study, although the benefits of an initial CTA/FFR_{CT} strategy appeared more pronounced in the setting of the German healthcare system: the risk difference in occurrence of the primary endpoint between the CTA/FFR_{CT} group and usual care group was greater than in the main PLATFORM study (78.2% versus 61.0%, respectively). This is because of (i) a higher rate of ICA showing no obstructive CAD in the usual care cohort (86% versus 73%) – which is expected, given the higher rate of ICA in Germany – and (ii) a lower rate of ICA showing no obstructive CAD in the CTA/FFR_{CT} cohort in the German subgroup compared with the main study (8% versus 12%, respectively) – which is partly explained by a higher rate of ICA cancellation based on the CTA/FFR_{CT} result in this cohort in the German subgroup (77%) compared with in the main study (61%). It is noteworthy that a lower proportion of patients with CTA were referred for FFR_{CT} analysis in the German subgroup than in the main study (57.7% versus 69.4%, respectively). This is probably because more patients with normal coronary arteries were filtered out by CTA alone.

The absence of MACE among patients in the CTA/FFR_{CT} group who did not undergo ICA is important and consistent with findings in the overall PLATFORM population. Only two patients underwent ICA by one year, both showing no obstructive CAD. The finding of lower cumulative medical costs over one year in the CTA/FFR_{CT} cohort compared with the usual care cohort is also consistent with findings from the main PLATFORM study. The result was

unchanged when German cost weights were used.

Interestingly, cumulative radiation exposure at one year was significantly lower in the FFR_{CT} vs. usual care cohort in the German subgroup, an effect not observed in the main PLATFORM study. While radiation exposure was similar with ICA in the German and overall cohorts, radiation exposure in the FFR_{CT} cohort was markedly lower in the German vs. overall cohort (median 3.68 versus 7.94 mSv, respectively). Also in contrast with the main study, the greater improvement in QOL in the FFR_{CT} cohort was statistically significant in the German subgroup. The reasons for this is unclear and must be interpreted with caution due to the non-randomized, unblinded nature of the study. However, it is possible that the avoidance of an invasive procedure – even if no further intervention was required – and the overall lower number of hospital days may have contributed to the observed differences.

5.2 In patients with diabetes mellitus, polymer-free sirolimus- and probucol- eluting stents have comparable clinical efficacy and safety to conventional durable polymer zotarolimus-eluting stents at 5 year follow-up

The main findings of this study are as follows:

- In the high-risk subgroup of patients with diabetes mellitus enrolled in a large-scale randomized trial, the primary composite outcome measure of cardiac death, target vessel-related myocardial infarction or TLR occurred with similar frequency at 5 years in patients

randomized to treatment with a polymer-free SPES in comparison with a durable polymer ZES.

- The incidence of very late stent thrombosis was low and comparable in both treatment groups, with few events beyond 1 year.

Prior investigation in diabetic patients showed that a polymer-free sirolimus-eluting stent had similar long-term efficacy and safety compared with a first-generation paclitaxel-eluting stent.[140] However, this data was limited by the fact that the comparator stent was an early-generation DES with only moderate antirestenotic efficacy, which has subsequently fallen out of clinical use. In addition, the study stent was coated only with sirolimus, an approach that likely does not result in adequate clinical efficacy. In our study, in a large cohort of diabetic patient we showed comparable clinical efficacy at 5 years between a polymer-free sirolimus- and probucol-eluting stent compared with a high performance second-generation durable polymer zotarolimus-eluting stent. As previously reported, the improved angiographic antirestenotic efficacy with the polymer-free stent used in our study (in comparison with a similar single-drug polymer-free stent) are likely due to the incorporation of probucol in the stent coating [13, 22]. This compensates for the inherently less favorable drug-release kinetic seen with polymer-free DES. The mechanism of benefit is likely two-fold: as probucol is highly lipophilic it can retard the release of sirolimus from the stent surface and improve tissue drug levels, in addition, due to the antioxidant effects of probucol it targets a separate component of the restenotic response cascade [23, 24].

Importantly, the polymer-free sirolimus- and probucol-eluting stent also demonstrated a low incidence of stent thrombosis out to 5 years. Indeed, we observed no cases of stent thrombosis beyond one year in patients treated with the polymer-free stent in this study. On the other hand, it should be observed that no clear advantage could be seen with polymer-free stents in comparison to durable polymer stents with regard to very late stent thrombosis. This is broadly in line with results of a recent meta-analysis of both diabetic and nondiabetic patients [25], though this lack of difference must be interpreted in light of the low event rates in both groups.

With regard to angiographic antirestenotic efficacy, the late lumen loss observed in patients with diabetes in our study was 0.36 mm (in stent) both with sirolimus- and probucol-eluting and zotarolimus-eluting stents. This is somewhat higher than in other studies investigating patients with diabetes. For example, in the SPIRIT V diabetic study, late loss was 0.19 mm; in the RESORVOIR study, 0.24 mm with everolimus-eluting stent [8, 26]. Although the reasons for this are unclear, this may be related to baseline patient and lesion complexity: the inclusion criteria in our study were broader and exclusion criteria were fewer. Moreover, our results may be expected to be representative of real-world practice and therefore broadly applicable to diabetic patients in a wide variety of settings.

5.3 In patients presenting with ST-segment elevation myocardial infarction, polymer-free sirolimus- and probucol-eluting stents have comparable clinical efficacy and safety to conventional durable polymer zotarolimus-eluting stents at 5 year follow-up

The main findings of our report are as follows:

- In patients presenting with STEMI enrolled in a large-scale clinical trial, the primary composite outcome measure of cardiac death, target vessel-related myocardial infarction or TLR occurred with similar frequency at 5 years in patients randomized to treatment with a polymer-free SPES versus a durable polymer ZES.
- Late safety events, including stent thrombosis, were low and comparable in both groups beyond 1 year.

Randomized trials comparing outcomes with early generation DES versus bare metal stents implanted in the setting of AMI demonstrated superior efficacy with DES at one year.[141-143] In addition, a meta-analysis of 8 randomized trials comparing early generation DES with bare metal stents in STEMI patients showed no difference in stent thrombosis risk at 1-2 years.[55] Five-year follow-up of the PASSION trial showed comparable clinical efficacy for PES versus bare metal stents.[144] However, definite very late stent thrombosis was seen almost exclusively after DES implantation, with 9 cases (3.3%) in the DES arm versus 2 (0.7%) in the bare metal stent arm at 5 years (p=0.04). Observational studies have raised similar concerns regarding the long-term safety of DES use in this setting, also reporting increased rates of very late stent thrombosis in patients treated with DES compared with bare metal stents.[56,57] In addition, observational studies have shown that acute cornary syndrome at the time of the index stenting is an independent risk factor for late stent thrombosis.[145]

A potential explanation for the higher rate of stent thrombosis after primary angioplasty with DES is the effect of underlying plaque morphology on local healing characteristics.[58] Delayed arterial healing is the principal substrate for late DES stent thrombosis [31]. In STEMI patients, there may be a more pronounced inflammatory reaction to durable polymer DES coatings. Autopsy studies of stented arterial segments in patients treated with DES for AMI versus stable angina have demonstrated increased inflammation with delayed healing and increased rates of stent thrombosis at AMI culprit sites compared with both non-culprit sites within the same stent and culprit sites in stable angina patients[58]. An additional factor that may contribute to delayed healing in this setting is strut penetration of necrotic core underlying a ruptured fibrous cap[58]. As plaque rupture is the most frequent cause of AMI, penetration of necrotic core is frequently found at the site of culprit lesions.

An OCT substudy of HORIZONS-AMI reported decreased neointimal growth but higher rates of uncovered struts and strut malapposition at 13-month follow-up in patients who received DES compared with bare metal stent in the setting of STEMI[146]. Another OCT study also demonstrated a higher incidence of incomplete stent apposition and delayed tissue coverage in patients who underwent DES implantation in the setting of primary percutaneous intervention versus in the setting of stable or unstable angina. [147] This supports the theory that late dissolution of thrombus underlying stent struts may also contribute to late acquired malapposition and adverse clinical events. For DES implanted in the setting of AMI, rates of definite stent thrombosis in first-generation DES have been reported at 3.7% at 2 years[148].

In the setting of AMI, two randomized trials have demonstrated superior efficacy of second-generation DES over bare metal stents. The COMFORTABLE-AMI trial compared biodegradable polymer biolimus A9-eluting stents to bare metal stents implanted for AMI and showed superior efficacy of DES at one year, with no significant difference in stent thrombosis rates.[149] The EXAMINATION trial compared a durable polymer everolimus-eluting stent with a bare metal stent in the setting of STEMI and showed superior efficacy and significantly lower rates of stent thrombosis in the DES arm at one year.[150] A pooled analysis of these trials demonstrated improved efficacy with a significantly reduced risk of LST for newer generation DES versus bare metal stents at one year but it remains to be seen if these results are sustained at long-term follow-up[151].

This is the first long-term report of patients with STEMI implanted with a polymer-free DES. The data show long-term clinical efficacy which is comparable to leading durable polymer stents. Although no difference in late clinical outcomes in favour of the polymer-free DES was seen, the study was significantly underpowered to detect such a difference. Importantly, rates of stent thrombosis were low and numerically similar with both stent platforms. The low rates in the control group are consistent with findings from long-term follow-up of patients enrolled in the EXAMINATION trial who received durable polymer DES in the setting of STEMI, with rates of definite stent thrombosis of 2.0% (versus 1.0% in the current report) at 5 years. [152] Dedicated randomized trials of polymer-free versus durable-polymer DES in STEMI patients are ultimately needed to determine the comparative efficacy and safety of these devices.

5.4 Polymer-free sirolimus- and probucol- eluting stents have comparable clinical efficacy and safety to durable polymer zotarolimus-eluting stents in all-comers at 10 years

The main findings of this study are as follows:

- At 10 years, treatment with polymer-free SPES in comparison with a durable polymer ZES is associated with a similar frequency of device- and patient-oriented adverse events.
- The incidence of stent thrombosis was low and comparable in both groups.
- The very low rate of very late stent thrombosis (between 1 and 10 years; <1% in both groups) is remarkable and seems to be representative of an improvement in the safety profile of current generation DES in comparison with early generation DES.
- The steady rate of patient-related adverse events over time (>65% incidence in both study groups) remains considerable. This is broadly in line with other trials,[153-155] and highlights the need for optimization of background medical therapies targeted at retardation of disease progression as well as the unmet need for novel adjunctive therapies.

This is the first report of long-term follow-up of patients treated with durable polymer ZES – which are frequently used in clinical practice – and the first with polymer-free DES – which are hypothesized to have a possible late safety advantage in comparison with conventional DES. The benefit of polymer free DES is expected to accrue with time. However, in many respects, the failure to detect a late advantage with the polymer-free DES – despite following a large number of patients out to 10 years – calls this hypothesis into question. On the other hand, it might be observed that the rate of device-related adverse events (e.g. stent thrombosis) was low and comparable in both groups. This may reflect improvements in the technology studied in both treatment arms – with the absence of polymer in the

polymer-free stent group offset by enhanced biocompatibility of the durable polymer coating used on the device in the control group. In addition, while we cannot discount that the absence of differences was due to lack of statistical power and the impact of missing data, meaningful differences between the two studies devices in relation to stent thrombosis seems unlikely.

Our study has some important strengths. First, it is among the few reports in the literature of trials of coronary stents with greater than 5-year follow-up. Second, we used active rather than passive follow-up methods, which, in our opinion, is more likely to capture events as compared with follow-up restricted to analysis of registries of vital status or hospital admission. Third, clinical outcomes were adjudicated by dedicated study personnel.

Target vessel revascularisation rates in both groups are high in comparison with other recent clinical trials, for example the BIONICS trial, which also used ZES as a comparator. [156] There are two main reasons for this. The first relates to increased baseline risk of the enrolled patients in ISAR-TEST 5 and the second relates to the study methodology used. First, ISAR-TEST 5 was conducted at centres where the majority of eligible patients undergoing coronary stenting were enrolled in the trial. In ISAR-TEST 5, 3002 patients were enrolled at 2 centres over 18 months. In BIONICS, 1919 patients were enrolled at 76 sites over 17 months. Selection bias for inclusion into the trial was likely lower in ISAR-TEST 5 than in other trials. As evidence of this, mean age at baseline is considerably higher than in other device trials (ca. 68 years in ISAR-TEST 5 vs. ca. 63 years in BIONICS), and all cause death at 1 year is significantly higher (3.9% [118 deaths] vs. 1.1% [21 deaths], respectively). Second, the trial protocol in ISAR-TEST 5 planned angiographic follow-up at 6-8 months for

all patients in ISAR-TEST 5. This is known to inflate the rate of revascularisation in comparison with standard follow-up. In comparison, the BIONICS trial included follow-up angiography at 13 months in 8% of the overall study cohort.

Observations in relation to patient-oriented outcomes in the current report also deserve consideration. In keeping with previous randomized trials, at 10-year follow-up in our study, patient-oriented endpoints – such all-cause mortality, any myocardial infarction and any revascularisation – predominate over device-specific endpoints.[153-155] Overall mortality rates – ca. 37% in the current study – are higher than rates reported in other trials with 10-year follow-up, with mortality rates ranging from 24-27%.[154,155] As already discussed, this may reflect higher baseline risk of the population enrolled in ISAR-TEST 5. Moreover, the majority of patients (67%) died from cardiac cause. These findings contrast with previous registry-based reports, that mortality, especially during long-term follow up after PCI, is mainly driven by non-cardiac death, with a temporal switch from predominantly cardiac to predominantly non-cardiac caused death during long term follow up.[157] In relation to repeat revascularisation, rates of any revascularisation are two-fold higher than rates of TLR. In line with previous observations, this finding suggests that disease progression in other coronary segments is a stronger prognostic factor for late and very-late patient related outcomes than recurrent events in the index lesion.[158] This underlines the importance of improved secondary prevention measures in future research and development.

5.5 Angiographic and clinical outcomes after re-intervention for in-stent restenosis of a drug-eluting stent were comparable irrespective of the presence or absence of a polymer coating

The main findings are as follows:

- After repeat PCI for DES-restenosis, there was no difference in the rate of angiographic restenosis or clinical outcomes based on whether the restenosed DES was polymer-free or polymer coated.

To the best of our knowledge, this is the first study comparing outcomes of patients treated for restenosis of polymer-free versus durable polymer stents. Patients who developed restenosis after polymer-free and polymer-coated DES implantation were well matched at the time of the index stent implantation as treatment allocation was randomized. The rate of angiographic follow-up after repeat intervention was high (83.4%), and accordingly, the findings in relation to angiographic outcomes are likely to be robust.[159] The observations should be interpreted in light of the fact that the polymer-free and permanent polymer stents studied differed in components other than the presence or absence of a polymer coating (e.g. stent backbone, type of drug eluted), although this is unavoidable when comparing commercially available stents that combine specific stent components in a single device.

There are a number of potential reasons for the absence of differences observed between the groups. First and foremost, this may be due to the fact that whether the restenotic DES is polymer-free or polymer coated, it does not exert a strong impact on outcomes subsequent to repeat PCI. Secondly, it should be acknowledged that our study is non-randomized in

nature and the existence of some differences between the groups may have obscured any true effect. Thirdly, treatment of ISR in the two groups differed somewhat. Although the proportion of patients treated with repeat DES stenting was similar, more patients with polymer-free DES underwent drug-coated balloon angioplasty. As the operators performing the repeat procedure were not blinded to the type of the underlying DES, the risk of treatment selection bias cannot be excluded. However, multivariate analysis adjusted for different treatment types including first generation DES, second generation DES, balloon angioplasty, or drug-coated balloon angioplasty, showed no differences. Finally, our study was underpowered to detect a difference in clinical outcomes.

5.6 In an hypercholesterolaemic rabbit iliac model of stent implantation, incomplete endothelial integrity is a key factor in neointimal foam cell formation after drug-eluting stent implantation. Pro-healing stent coatings may facilitate re-endothelialisation, thus reducing the risk of neoatherosclerosis.

The main findings are as follows:

(i) Pro-healing integrin αvβ3 ligand coated stents resulted in augmented endothelial integrity as compared to commercially available EES and reduced deposition of FITC-dextran as a marker of endothelial permeability

(ii) Adjunctive cell culture experiments confirmed the permeability of endothelial cells for AcLDL particles in the presence of increasing everolimus concentrations, which could partly be counterbalanced by the cell-adhesive properties of integrin αvβ3 ligand coating.

(iii) Exposure of monocyte co-cultures with endothelial cells incubated with increasing concentrations of everolimus resulted in dose-dependent foam cell transformation.

5.6.1 Establishment of an animal model

In this work we succeeded in reproducing early features of neoatherosclerosis by means of neointimal foam cell formation in a hypercholesterolemic animal model. However, our model – like many established atherosclerotic animal models – depends on supra-physiological cholesterol levels achieved by dietary intake, and repeat endothelial denudation by balloon injury, to mimic human atherosclerotic conditions. In contrast, atherosclerosis in humans often takes decades to develop and depends on additional important cofactors that cannot be reproduced in current animal models. In our study, neointimal foam cell formation was observed 13 weeks following study initiation, which represents a vastly accelerated course of neoatherosclerosis formation known from human pathology studies. However, our model is also limited in the duration of cholesterol feeding owing to diet-induced liver failure resulting in premature drop-out of animals. Furthermore, the aim of the current study was not to quantitatively compare neoatherosclerosis formation among stent types but rather to provide insights into their differential endothelial healing and barrier function, which represent important preconditions of neoatherosclerosis formation.

5.6.2 Defective endothelial barrier function

The integrity of the vascular endothelium is maintained by complex interactions of junctional proteins, which play a pivotal role in its permeability and vascular haemostasis. It is known that low concentrations of integrin αvβ3 ligands stimulate endothelial activation and stabilize endothelial cell barrier function (“vascular stabilisation”) [14,17].

While a number of junctional proteins such as occludins, claudins and junctional adhesion molecules (JAMs) contribute to the formation of tight junctions between individual endothelial cells, the same level of complexity is installed to regulate trans-endothelial exchange of nutrients, water and ions [18]. Whereas gap junctions are involved in intercellular exchange of smaller molecules, larger particles such as LDL are predominantly transported transcellular by the use of caveolae under physiologic conditions. During stent implantation, the vascular endothelium gets largely disrupted and regenerates over a variable time frame ranging from several weeks to months or even years in the presence of anti-proliferative drugs [6]. Delayed re-endothelialization has been described as a hallmark of increased thrombotic risk even late after DES implantation [11], where the absence of junctional adhesive proteins has been shown to parallel decreased expression of anti-coagulatory markers in preclinical studies. The transmembrane protein platelet/endothelial cell adhesion molecule 1 (PECAM-1, CD31) is constitutively expressed along the intercellular junctions of endothelial cells, where it was shown to inhibit platelet aggregation in genetically engineered mice [19,20]. In the current study, we could show that disrupted integrity of the endothelial monolayer as exemplified by the absence of CD31 expression is giving rise to trans-endothelial permeability of dextran molecules in the range of 250-500kDa, which resembles the size of LDL particles. In adjunct cell culture studies, we demonstrated foam cell transformation of human monocytes in the presence of high everolimus concentrations, where drug-induced endothelial toxicity was likely the key phenomenon explaining increased permeability of LDL particles. Whether the occasional absence of endothelial cells after apoptotic cell death or their unstable intercellular junctions among viable cells were paramount in this process remains to be determined in future dedicated studies.

5.6.3 The relevance of stent coating

Endothelial function is largely supported by integrins, a family of heterodimeric transmembrane receptors.[7,21] One of the abundantly expressed receptor subtypes on vascular endothelial cells is the integrin αvβ3 that stabilizes endothelial cells under stress [14,17,22] and facilitates anchorage of endothelial cells to the extracellular matrix.[23] This interaction is mediated by the RGD integrin-binding motif (Arg-Gly-Asp) which is an integral component of several extracellular matrix compounds and is leveraged to promote cellular adhesion using integrin αvβ3 ligand coating of stent surfaces.[7] In the current study a cyclic αvβ3 ligand was applied which is highly specific for integrin αvβ3; it has been reported previously that cyclic RGD peptides specific for integrin αvβ3 foster endothelialization of stent surfaces.[7,21,24] Consequently, integrin αvβ3 represents a passive pro-healing coating technology to facilitate vascular healing following stent implantation and was not only shown to increase endothelial cell attachment but rather improve its integrity. Whether improved endothelial integrity achieved by integrin αvβ3 coating results in decreased neoatherosclerosis formation needs to be determined in dedicated preclinical studies. Our findings are supported by other studies, which have shown a beneficial effect of integrin αvβ3 in sepsis through vascular stabilization, eventually preventing endothelial leakage.[25–27]

In-vitro studies focusing on immunosuppressive drug effect on endothelial barrier function showed a protein kinase C mediated destabilization of the p120-VE cadherin interaction causing internalization of VE-cadherin and, consequently, impaired endothelial integrity.[28] These findings strengthen the hypothesis that DES are especially susceptible to neoatherosclerosis because of impaired endothelial barrier function. While the precise molecular mechanisms underlying this pathophysiology remain to be determined, the current

study suggests that a prolonged delay of endothelial integrity may play a pivotal role for premature onset of neoatherosclerosis formation in current generation DES.

However, targeting endothelial healing with novel stent-based approaches has not been proven to be clinically effective in terms of cardiovascular event reduction or decrease in revascularisation procedures. In the most recent HARMONEE trial, the dual therapy COMBO DES using luminal anti-CD34 antibody coating to capture endothelial progenitor cells has proven clinical equipoise with regards to classical patient and device-oriented endpoints, however superiority with regards to these endpoints could not be achieved (30). Healthy strut coverage defined as strut coverage with thickness of greater than 40µm above stent struts was shown to be superior in COMBO vs. Xience DES. The hypothetical advantage of using DES, which fosters vascular healing, may only be proven at long-term follow up since progression of atherosclerosis within stented vascular segments takes years to manifest clinically (31). We also agree that stent failure is likely multi-factorial, where formation of neoatherosclerosis is only one factor among others to contribute to this dire phenomenon. Improvement of stent technology alone may not be sufficient to overcome the sustained increase in cardiovascular events over time observed with implantation of DES. Optimized preventive strategies focusing on individualized patient care and novel pharmacological approaches may be used in synergy with novel stent designs to tackle this significant clinical problem.

5.7 A paclitaxel-coated balloon with a butyryl-tri-hexyl citrate excipient has similar angiographic efficacy to a paclitaxel-coated balloon with an iopromide excipient for the treatment of drug-eluting stent restenosis at 6-8 months.

The main finding of our study was as follows:

- In patients treated with DCB for coronary DES-restenosis, there was no significant difference in the performance of two widely used devices – the BTHC-based Pantera Lux PCB or the iopromide-based SeQuent Please PCB – in terms of angiographic or clinical outcomes.

Iopromide and BTHC excipient are two of the most widely used excipients on PCB. Iopromide is a hydrophilic, non-ionic (low-osmolar), iodinated angiographic contrast medium capable of dissolving paclitaxel at much higher concentrations than saline. BTHC is a citric acid ester developed for use as a plasticizer for poly vinyl chloride blood bags in order to reduce hemolysis during storage. BTHC is highly biocompatible and degrades to citric acid and alcohol.

A preclinical comparative efficacy study of the BTHC-PCB and the iopromide-PCB demonstrated similar results for both devices with respect to reducing late lumen loss and neointimal growth, as demonstrated by QCA and histomorphology, respectively, in a porcine model of coronary restenosis. [78] Injury and inflammation scores were also similar with both devices. These findings suggest similar paclitaxel-release kinetics with both devices. In terms of clinical data, however, at the time of this study, there is no prospective head-to-head clinical comparison of the performance of these two devices. A single observational study reported lower rates of adverse events at 3-year follow-up in patients with ISR treated with the BTHC-PCB as compared with the iopromide-PCB, which was mainly driven by a lower rate of TLR. [160] However, this study was limited by absence of angiographic surveillance or core lab analysis, lack of independent event adjudication, and a high rate of loss to follow-up (almost one quarter of patients). Moreover, although significant differences in patient and lesion characteristics between treatment groups were

present at baseline, no adjustment was made to account for the influence of these differences on the rates of subsequent outcomes. In contrast, patients in our study had treatment and follow-up performed according to a study protocol (with high rates of follow-up), independent event adjudication, planned angiographic surveillance and core lab analysis of all angiographic films by personnel blinded to treatment allocation. In contrast to this earlier study but consistent with preclinical data, in our analysis, we found comparable efficacy between both devices. Specifically, we found no difference between the BTHC-PCB and iopromide-PCB treated groups with respect to angiographic outcomes (%diameter stenosis at follow-up angiography 40.4 [SD 21.9]% vs. 37.4 [SD 21.4]%, respectively, $P_{adjusted}$=0.32) or clinical outcomes, with a similar combined incidence of death, MI and TLR in the BTHC-PCB and iopromide-PCB groups (29 [23.2]% vs. 32 [23.4]% patients, respectively, $P_{adjusted}$=0.96).

5.8 Treatment with a paclitaxel-coated balloon was not associated with greater myocardial injury, as evidenced by high-sensitivity troponin rise, compared to treatment with a paclitaxel-eluting stent or an uncoated balloon

The main finding of this report are as follows:

- In patients with DES restenosis, treatment with a PCB was not associated with a greater troponin rise or reduction in TIMI flow grade compared to treatment with DES or balloon angioplasty.
- In patients with a troponin rise, the magnitude of rise did not appear to correlate with mortality risk at three years, irrespective of the therapy received.

This is the first dedicated study looking for evidence of myocardial necrosis due to distal embolization following DCB angioplasty using a high sensitivity troponin assay. A strength of the analysis is the use of delta hs-TnT rather than peak value as a marker of procedure-related hs-TnT rise to avoid the confounding effect of baseline hs-TnT.

Preclinical studies of paclitaxel-coated balloon catheters in porcine coronary overstretch models, using a variety of different matrix formulations, comprising urea, iopromide and acetone excipients mixed with paclitaxel at concentrations of 3.0, 3.0 and 2.5 µg/mm^2, respectively, reported that approximately 6% of the drug coating is lost during floating time, 10-30% is taken up by the vessel wall during balloon inflation, and up to 10% remains on the balloon[86,87]. The fate of the remainder of the drug coating is unknown but distal embolization has been proposed as a potential explanation. Indeed, during preliminary coating development, an early DCB-coating formulation was abandoned on account of unacceptable distal embolic findings[161]. Particulate embolization in the coronary arteries may result in impaired flow or peri-procedural myocardial infarction[88]. Slow flow or no reflow immediately after DCB-angioplasty of ISR lesions has occasionally been observed and hypothesized to be due to distal embolization of DCB coating[162,163]. Moreover, a clinical study of CFR after DCB therapy showed a transient reduction in CFR of unclear etiology immediately after DCB-angioplasty (using the In.PACT DCB, coated with 3.0 µg/mm^2 paclitaxel and a urea excipient), which resolved spontaneously within ten minutes[89]. The authors concluded that distal embolization in the microvascular bed was the most likely explanation given the major contribution of the coronary microcirculation to CFR[89].

In patients with peripheral artery disease undergoing angioplasty with DCB, there have also been some safety concerns possibly attributable to distal embolization of particulate coatings[164]. The IN.PACT DEEP randomized trial compared treatment of infrapopliteal peripheral artery disease with plain balloon angioplasty versus DCB therapy using the In.PACT Amphirion balloon for below-the-knee indications [165]. Although the trial formally met its non-inferiority hypothesis with regard to the primary safety end point, there was an unexplained trend toward more major amputation in the DCB arm (8.8% vs. 3.6%; p = 0.08), which ultimately led to market withdrawal of the study device. Results of randomized studies examining other iterations of the IN.PACT DCB technology in the femoropoliteal territory (IN.PACT PACIFIC and IN.PACT Admiral DCB devices) as well as other DCB did not raise such concerns. One potential explanation is that differences between balloon-coating processes may be responsible for these observed differences. In particular, the IN.PACT Amphirion DCB was coated after wrapping of the balloon, rather than beforehand, as for other DCB devices. This may have resulted in non-uniform drug-coating on the balloon surface, with all of the matrix coating on the outer exposed surface, rendering it vulnerable to loss during transit to and during deployment at the target lesion (2).

A prior preclinical study examined angiographic or histophological evidence of distal embolization after low pressure inflation of the Lutonix DCB (polysorbate/sorbitol excipient and 2.0 μg/mm^2 paclitaxel) against a balloon angioplasty control in a swine femoral artery model at 28, 90 and 180 days post-procedure. Although no evidence of vascular embolization or dependent tissue ischaemia downstream from the intervention was found, it is important to take into consideration the variable coating integrity reported among DCB devices. For example, less than 0.1% of the drug coating was found to be lost during

inflation and dry shaking of the DCB used in the study in question.[161] On the other hand, 20-40% paclitaxel loss has been reported for DCB with urea and iopromide excipients[86]. This would imply that the microstructure of the DCB surface coating – including presence or absence of a spacer, choice of spacer, and concentration of both paclitaxel and spacer – is also likely to be important in promoting or limiting downstream particulate embolization[88].

Interestingly, a previous clinical study comparing patients treated with PCB (also the SeQuent Please device) and DES in the setting of de novo lesions in stable CAD found significantly lower proportions of patients with peak post-procedural troponin T levels more than 5 times the 99th percentile upper reference limit of normal within 48 hours of PCI in the PCB compared with the PES group [166]. This finding contrasts with that of the current study: although mean delta troponin was numerically lower in the PCB compared with the DES group in our study, this difference was not statistically significant. Moreover, the proportion of patients in whom peak hsTnT exceeded 5 times the 99th percentile upper reference limit of normal was similar across treatment groups. The differences between the two studies should be interpreted in light of the non-randomized nature of the prior study, its consecutive cohort design and the small sample size (52 patients in each group).

We also examined the association between the delta troponin levels observed and the survival of patients at 3-year follow-up. Despite a marked difference in delta troponin between patients in the third tertile (132±197 ng/L) compared with those in the first (0±8 ng/L) and second (15±5 ng/L) tertiles, we found no significant difference in 3-year mortality rates according to delta troponin tertile. Although the power of our study to detect differences in mortality is limited by the relatively small sample size, this observation is

broadly in line with larger studies showing that while baseline elevated hs-TnT level is an independent predictor of mortality in patients undergoing PCI[167,168], delta hs-TnT adds little prognostic information beyond what is already known from the baseline hs-TnT level[169].

Our analysis offers some reassurance in relation to myocardial injury after DCB angioplasty. Although prior randomized controlled trials failed to detect differences in the rates of myocardial infarction between patients treated with DCB or repeat stenting[81,85,170,171], our analysis is the first to report on detailed analysis of hs-TnT following intervention. In this respect, the lack of difference observed across the treatment groups speaks against a relevant difference in subclinical myocardial injury and supports the safety of DCB use for this indication.

5.9 In a meta-analysis of randomized trials, percutaneous compared with surgical revascularisation of left main coronary artery disease is associated with a comparable risk of the composite of all-cause death, myocardial infarction, or stroke at long-term follow-up but a higher risk of repeat revascularisation.

The main findings of this meta-analysis are as follows:

- In patients with significant LMCA stenosis, PCI with DES and CABG are associated with a comparable risk of all-cause death, myocardial infarction, or stroke at long-term follow-up. Cumulative Kaplan-Meier curves reconstruction did not show significant difference over time and long-term safety was acceptable with both PCI and CABG.
- Risk of repeat revascularisation is the most important difference between techniques, with a

higher risk with PCI at long-term follow-up as compared with CABG.

Previous meta-analyses comparing DES and CABG for revascularisation of LMCA disease are limited by the inclusion of both observational and randomized trials[172-174] and patients treated with bare-metal stents and early generation DES,[173-175] limited duration of follow-up,[172] and failure to use hazards ratios for assessment of long-term outcomes.[172-175] The use of first-generation DES has been traditionally considered one of the explanations for the differential effectiveness between PCI and CABG in early randomized trials. However, in our analysis, neither the risk of repeat revascularisation nor the risk of the primary endpoint between techniques was influenced by DES-generation. Indeed, considering the large amount of evidence supporting the superior anti-restenotic properties of second-generation DES as compared with first-generation[25,37-39], it might be speculated that superiority of CABG in this respect is driven by protection against need for further revascularisation in lesions outside of the treated segment. Indeed, in the EXCEL and NOBLE trials[7,8] a several-fold increased risk of revascularisation outside of the target lesion was observed with PCI as compared with CABG.

We performed a sensitivity analysis for the primary endpoint including only patients with low-to-intermediate complexity of CAD (according to the SYNTAX score[40]) without detecting significant variations in treatment effects. In the SYNTAX trial[26], the stratification of LMCA patients according to SYNTAX score terciles showed significant differences in the primary outcome. However, in the PRECOMBAT and EXCEL trials[7,31] the largest number of events occurred in the tercile 23-32 and there were no significant differences across terciles, while in the NOBLE trial[8] the distribution of events was higher in the first tercile. These findings may

reflect limitations of the anatomic SYNTAX score and support the use of tools accounting also for clinical characteristics[41].

The risk of all-cause death and cardiac death between the techniques is quite similar at long-term follow-up. However, although also the risks of myocardial infarction and stroke were similar, we observed numerical variations between techniques that are both likely attributable to heterogeneity introduced by the NOBLE trial[8]. With respect to myocardial infarction, in the NOBLE trial[8] there was a substantial risk increase with PCI. On the one hand, this finding can be partially explained by the definition of myocardial infarction used in the trial:[8] this excluded periprocedural events—generally more frequent in patients undergoing CABG than PCI and sometimes large enough to be prognostically relevant over the long-term. Moreover, although the incidence of periprocedural myocardial infarction between PCI and CABG in the NOBLE trial[8] seemed comparable, data were collected in only about half of patients. On the other hand, as observed in the SYNTAX trial[30], a numerical increase in myocardial infarction may be partially explained by a possible superior protection of grafts against ischemic events due to CAD progression in non-target lesions and by a possible increase in periprocedural events in the higher number of patients requiring repeat revascularisation after PCI. Similarly, with respect to stroke, the risk between techniques was reduced or comparable in all the trials but the NOBLE[8], in which an unexpected numerical increase in events occurred after PCI.

PCI presents a higher risk of a composite endpoint of major adverse cardiac and cerebrovascular events including repeat revascularisation as compared with CABG as a consequence of the significant excess in repeat revascularisation. Indeed, trial design should

take into account the prominent impact of repeat revascularisation in driving differences in this endpoint. It is likely inadvisable in this setting to combine safety endpoints–all-cause death, myocardial infarction, or stroke–with an efficacy endpoint–repeat revascularisation. In patients with LMCA stenosis undergoing PCI or CABG, the importance of endpoint and estimator selection has been recently highlighted in the DELTA registry[42].

These findings suggest that in patients with significant stenosis of LMCA and predominantly low-to-intermediate CAD complexity both PCI and CABG are valid approaches to revascularisation. Patient preference should be taken into consideration in relation to the risks of periprocedural complication of surgery and long-term repeat revascularisation after PCI. Patients with low surgical risk may benefit from CABG due to more sustained effectiveness as evidenced by reduced incidence of repeat revascularisation. However, if a patient is not a good candidate for surgery or wishes to avoid the morbidity associated with surgical revascularisation, PCI is a safe and effective alternative.

5.10 After stenting of vein graft lesions in patients with previous coronary artery bypass graft surgery, the efficacy advantage for drug-eluting stents over bare metal stents observed at 1 year was lost at 5 years because of late catch-up in target lesion revascularisation with drug-eluting stents.

The main findings are as follows:

- In patients who underwent PCI of SVG lesions, the advantage of DES over bare metal stents with respect to clinical outcomes observed at 1 year was no longer apparent at 5 years because of late catch-up in TLR rates in the DES group: although at 1 year, the incidence of

TLR in the DES group was less than half that in the bare metal stent group, between 1 and 5 years, the rate was more than double that in the bare metal stent group.

- Findings were consistent irrespective of DES type.

This report represents the longest follow-up of a trial comparing DES and bare metal stents for the treatment of SVG lesions. Other randomized trials investigating this question are small or have limited duration of follow-up.[106,176,177] At primary analysis, the RRISC (n=75) and SOS (n=80) trials both showed lower angiographic restenosis with DES compared with bare metal stents at six and 12 months, respectively; which translated into lower rates of repeat revascularisation at six and 18 months, respectively.[103,104] More recently, the BASKET-SAVAGE trial, which was terminated early after enrolment of 173 patients, also showed improved clinical outcomes at one year with DES, mainly driven by lower rates of repeat revascularisation.[106]

However, at longer-term follow-up, some differences in comparative efficacy were seen. Although follow-up of the SOS trial demonstrated persistently lower repeat revascularisation rates in the DES group at 35 months,[177] the DELAYED RRISC trial showed some evidence of late 'catch up' in repeat revascularisation in the DES group, resulting in loss of the early efficacy advantage of DES at 32 months.[176] In addition, for reasons that are unclear, late all-cause mortality was significantly higher in the SES group in comparison with the bare metal stent group. The reason for the discordance with respect to late antirestenotic efficacy between these two trials is not known, though these results should be interpreted with caution, due to the modest number of included patients. Although

durability of the efficacy advantage for DES over bare metal stents was reported at three years in the BASKET-SAVAGE trial, follow-up at three years was complete on only two thirds of patients.[106] More recently, the DIVA trial showed no difference in clinical outcomes between newer generation DES and bare metal stents at 12 months.[107]

Late catch-up in repeat revascularisation after DES implantation has been described in native coronary vessels during long-term follow-up of a number of randomized trials. In the SIRTAX LATE study, the advantage of SES over PES with respect to major adverse cardiac events (MACE) and TLR demonstrated at one year was lost at five years on account of higher late TLR rates in the SES group between one and five years.[73] The SORT-OUT III trial reported a similar phenomenon, with the superiority of SES over zotarolimus-eluting stents (ZES) at one year in terms of MACE and TLR no longer evident at five years due to late catch-up in TLR in the SES group. [71] Likewise, in the PROTECT trial, the TLR advantage demonstrated for SES over ZES at one and three years was no longer present at four years due to differential TLR rates between treatment groups after one year.[76]

The observation of late catch-up in TLR is in keeping with findings from preclinical and human imaging studies. In animal models, late catch-up in neointimal growth has been demonstrated in DES but not in bare metal stent controls.[178,179] Angiographic surveillance studies in man have shown late catch-up in angiographic restenosis – also termed late luminal creep – in DES. Studies of patients with serial angiographic follow-up show that neointimal formation peaks six months after bare metal stenting,[180] but in the case of DES, this process is temporally right-shifted and remains a dynamic ongoing process out to two or even five years.[73,181] In addition, the formation of in-stent neoatherosclerosis is be more

accelerated in DES as compared with bare metal stents.[36] Nonetheless, randomized trials enrolling patients with predominantly native vessel disease have shown sustained clinical advantage with DES over bare metal stents out to five to six years.[182-184]

The difference in underlying pathological substrates between SVGs and native arteries may be an important consideration. First, the atherosclerotic process in SVGs is accelerated compared with native coronary arteries. Autopsy studies have shown that in the first year after implantation, the SVG wall becomes thickened by neointimal growth, likely due to exposure to arterial pressure ten-fold higher than venous pressure.[185] Second, similar to observations in native coronary arteries, delayed vessel healing is observed with greater frequency in SVGs treated with DES compared with bare metal stents. However, this seems to be exaggerated in SVGs compared with native coronary arteries.[183] This is possibly explained by the differences in the pathology of the underlying plaques: SVGs plaques are typically fibroatheromata with large necrotic cores, and stenting of such lesions generally results in strut penetration of necrotic core. In the case of DES, this contributes to delayed vessel healing, possibly due to longer retention of lipophilic drug.[185] It is possible that delayed healing in the DES group may have contributed to the late catch-up in TLR observed in the current study. Finally, the development of DES and determination of drug dosage was based on observations from implantation in arterial vessels in non-clinical and early human studies.

6. SUMMARY OF FINDINGS

- In patients with stable chest pain planned for invasive coronary angiography at German sites, an initial CTA/FFR_{CT} strategy compared with usual care was associated with a significantly lower rate of invasive coronary angiography showing no obstructive CAD. This strategy was also associated with lower cumulative radiation exposure, lower cost and improved quality of life, with no increase in adverse clinical events at 1 year.
- In patients with diabetes mellitus, polymer-free sirolimus- and probucol-eluting stents have comparable long-term clinical efficacy and safety to conventional durable polymer zotarolimus-eluting stents at 5 year follow-up. Rates of stent thrombosis were comparable and low, with few events beyond 12 months.
- In patients presenting with ST-segment elevation myocardial infarction, polymer-free sirolimus- and probucol-eluting stents have comparable long-term clinical efficacy and safety to conventional durable polymer zotarolimus-eluting stents at 5 year follow-up. Rates of late adverse events such as stent thrombosis were low and comparable in both treatment groups, with few events beyond 12 months.
- At 10-year follow-up of a large-scale randomized trial, there were no significant differences in clinical outcomes between patients treated with a polymer-free sirolimus- and probucol-eluting stent or a new generation durable polymer zotarolimus-eluting stent. The incidence of stent thrombosis was low and comparable in both groups. However, overall cumulative adverse cardiac event rates were high at 10 years, highlighting an unmet need for improved secondary prevention measures in patients undergoing coronary stenting.
- Clinical and angiographic outcomes after treatment of DES-restenosis did not differ according to the presence or absence of polymer on the restenosed DES.

- In an hypercholesterolaemic animal model, incomplete endothelial integrity is a key factor in neointimal foam cell formation after DES implantation. Pro-healing stent coatings may facilitate re-endothelialisation, thus reducing the risk of neoatherosclerosis.
- In patients undergoing intervention for DES-restenosis, angioplasty with BTHC-PCB showed comparable angiographic outcomes at 6-8 months and comparable clinical outcomes at 1 year compared with iopromide-PCB.
- Treatment of DES-restenosis with a PCB was not associated with more myocardial injury, as evidenced by a post-procedural rise in high sensitivity troponin T, compared with repeat DES implantation or balloon angioplasty. This is a reassuring finding, speaking against clinically relevant distal particulate embolization of the balloon coating during PCB angioplasty.
- Based on meta-analysis of clinical trial data, PCI with DES and CABG are associated with a comparable risk of hard clinical endpoints as measured by a composite of all-cause death, myocardial infarction, or stroke at long-term follow-up. However, patients treated with PCI have a higher risk of repeat revascularisation. These findings suggest that in patients with significant LMCA stenosis and low-to-intermediate CAD complexity, both PCI and CABG are valid approaches to revascularisation, depending on availability and patient- and operator-preference.
- In patients undergoing stenting of vein graft lesions, safety outcomes for DES and bare metal stents remained comparable at long-term follow-up. However, the efficacy advantage of DES over bare metal stents demonstrated at 1 year was lost at 5-year follow-up because of late catch-up in TLR in the DES group.

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10. LIST OF PUBLICATIONS

Publications in peer-reviewed journals

1. **Colleran R**, Joner M, Cutlip D, Urban P, Maeng M, Michel JM, Mehran R, Kirtane AJ, Maillard L, Kastrati A, Byrne RA. Design and rationale of a Randomized Trial of COBRA PzF Stenting to REDUCE Duration of Triple Therapy (COBRA-REDUCE). Cardiovascular Revascularization Medicine. Epub 2021 Jan 22. Doi: 10.1016/j.carrev.2021.01.022
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