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Coronary Restenosis and Arterial Healing Following Drug-Eluting Stent Implantation – Time Course, Angiographic Metrics and Impact of Modifications in Polymer and Drug Coatings

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LIST OF ABBREVIATIONS

ACE = angiotensin converting enzyme

ARC = Academic Research Consortium

BMS = bare metal stent

BP = biodegradable polymer

CI = confidence interval

CK, CK-MB = creatine kinase, creatine kinase MB isoform

DES = drug-eluting stent

DP = durable polymer

Dual-DES = dual-drug sirolimus- and probucol-eluting stents

EES = everolimus-eluting stent

LLL = late luminal loss

MI = myocardial infarction

MLD = minimal lumen diameter

NSTE-ACS = Non ST-elevation acute coronary syndrome

PBMA/PEVA = polybutylmethacrylate/polyethylene-vinyl acetate

PC = phosphorylcholine

PCI = percutaneous coronary intervention

PDLLA = poly-D,L-lacic acid

PES = paclitaxel-eluting stent

PF = polymer-free

PVDF-HFP = polyvinylidene fluoride/ hexafluoropropylene

QCA = quantitative coronary angiography

SES = sirolimus-eluting stent

SIBS = stryene-isobutylene-stryene

TLF = target lesion failure

TLR = target lesion revascularization

ULN = upper limit of normal

ZES = zotarolimus-eluting stent

%DS = percentage diameter stenosis

GLOSSARY OF CLINICAL TRIAL ACRONYMS*

BENESTENT = Belgium and Netherlands Stent study

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

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

ISAR-LEFT-MAIN 1 and 2 = Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions 1 and 2

ISAR-TEST 2 = Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-2)

ISAR-TEST 3 = Intracoronary Stenting and Angiographic Restenosis – Test Efficacy of Rapamycin-Eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3)

ISAR-TEST 4 = The Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4)

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

ISAR stent project = Intracoronary Stent to Abrogate Restenosis stent project

LEADERS = Limus Eluted from A Durable versus ERodable Stent coating

RAVEL = Randomized study with the sirolimus coated BX™ Velocity balloon expandable stent in the treatment of patients with *de novo* native coronary artery lesions

STRESS = Stent Restenosis Study

*in the interests of conciseness trial acronyms are not expanded in the text

ABSTRACT

Drug-eluting stent (DES) therapy has revolutionized the treatment of coronary artery disease. However, the high antirestenotic efficacy of DES is delivered at the cost of a delay in healing of the stented arterial segment. In serial angiographic surveillance studies we documented for the first time that in a broadly inclusive patient population, systematic late erosion of anti-restenotic efficacy is a characteristic feature of DES therapy. Such "late luminal creep" is part of a spectrum of clinicopathological conditions associated with delayed arterial healing, which includes late stent thrombosis, persistent vasomotor dysfunction and accelerated *de novo* in-stent atherosclerosis. In an analysis of the metrics of restenosis at angiographic follow-up post DES implantation we also demonstrated that the distribution of late loss and percentage diameter stenosis has a complex mixed distribution pattern that may be accurately represented by a bimodal distribution model. The identification of subpopulations at increased risk may provide targets for further improvements in DES therapy particularly in an emerging era of personalized medicine. The randomized comparative efficacy studies reported in this thesis also provide clear evidence for the important role of drug-release kinetics in determining the antirestenotic efficacy of a DES device, with lowest mean late loss closely tied to the achieved drug release profile, particularly in the first 10 days after stenting. In addition these studies showed for the first time that it was possible to achieve optimal antirestenotic efficacy utilizing a dual-drug sirolimus- and probucol-eluting stent completely devoid of polymer coating, as well as with a novel biodegradable polymer-based sirolimus-eluting stent system. Whether the absence of durable polymer from the coronary milieu over the mid- to long-term translates into

significant improvement in clinical outcomes remains under study. Of note however, using meta-analysis of pooled individual patient data from the three largest trials comparing biodegradable polymer DES against durable polymer Cypher stents, we show for the first time a reduction in late safety events with biodegradable polymer stent technology at 3 years.

ZUSAMMENFASSUNG

Medikamenten-beschichtete Koronarstents haben die Behandlung der koronaren Herzerkrankung revolutioniert. Die hohe antirestenotische Effektivität der Medikamenten-beschichteten Stents erfolgt jedoch auf Kosten einer verzögerten Heilung des gestenteten Segments. In seriellen angiografischen Beobachtungsstudien mit breiten Einschlusskriterien konnten wir das erste Mal dokumentieren, dass der systematische späte Verlust der anti-restenotischen Effektivität ein charakteristisches Merkmal der Therapie mit Medikamenten-beschichteten Stents ist. Dieser sogenannte „Late Luminal Creep“ ist Teil eines Spektrums von klinisch-pathologischen Erscheinungen, die mit der verzögerten arteriellen Heilung assoziiert sind. Dazu gehören auch die späte Stentthrombose, die persistierende vasomotorische Dysfunktion und die akzelerierte de-novo Arteriosklerose im Stentbereich. In einer quantitativen Analyse der Restenose bei der angiografischen Nachbeobachtung nach Implantation von Medikamenten-beschichteten Stents konnten wir weiterhin zeigen, dass die Verteilung des späten Lumenverlustes („Late Luminal Loss“) und der Diameterstenose ein komplexes gemischtes Verteilungsmuster aufweisen, welches durch ein bimodales Verteilungsmodell akkurat widergespiegelt werden könnte. Die Identifizierung von Subpopulationen mit erhöhtem Risiko könnte ein Ziel für die weitere Verbesserung der

Therapie mit Medikamenten-beschichteten Stents darstellen, insbesondere in dem sich entwickelnden Bereich der personalisierten Medizin. Die randomisierten vergleichenden Effektivitätsstudien in dieser Arbeit belegen die wichtige Rolle der Medikamentenfreisetzungskinetik bei der Festlegung der antirestenotischen Effektivität von Medikamenten-beschichteten Stents. Der mittlere späte Lumenverlust ist eng mit dem erreichten Freisetzungsprofil der Medikamente verknüpft, insbesondere in den ersten 10 Tagen nach der Stentimplantation. Die Studien zeigen weiterhin zum ersten Mal, dass eine optimale antirestenotische Effektivität mittels dualer Medikamentenfreisetzung (Sirolimus und Probucol-freisetzende Stents) ohne Verwendung einer Polymerbeschichtung sowie mittels eines neuen biodegradablen Polymer-basierten Sirolimus-freisetzenden Stentsystems möglich ist. Ob die Vermeidung von permanenten Polymeren im koronaren Milieu sich im mittel- und langfristigen Verlauf in einer signifikanten Verbesserung des klinischen Ergebnisses äußert bleibt zu untersuchen. In einer Metaanalyse gepoolter individueller Patientendaten der 3 größten Vergleichsstudien von biodegradablen Polymerstents mit permanenten Polymer-basierten Cypherstents konnten wir zum ersten Mal eine Reduktion von späten Ereignissen durch biodegradable Polymer-basierte Stenttechnologie nach 3 Jahren zeigen.

1. INTRODUCTION

1.1 Percutaneous coronary intervention – a brief historical perspective

The human heart has always been an object of mysticism and awe…Inviolate behind a cage of ribs, and almost never glimpsed until after death, the heart's machinery was shrouded in darkness and taboo…Less than a century ago, no doctor would dare to touch a human heart. Only five decades ago, the basic therapy for a heart attack was to lie down and bear it.

– Journey into the Heart, David Monagan(1)

The history of percutaneous coronary intervention (PCI) is one of serial innovation and technological and pharmacological refinement – developments that have revolutionized the treatment of occlusive coronary artery disease. The most important foundation stones for catheter-based therapy were arguably laid by three pioneers. Firstly, Werner Forssmann a 25-year old German medical resident, who performed the first cardiac catheterization on himself at a small clinic in Eberswalde Germany in 1929.(2) Although this daring act ultimately precipitated his own academic downfall, he subsequently shared the 1956 Nobel Prize for Medicine with fellow catheterization innovators Dickenson Richards and Andre Cournand. Secondly, Mason Sones, a radiologist at the Cleveland Clinic in Ohio, who performed the first selective coronary cineangiography – albeit inadvertently – on 30th October 1958.(3) Thirdly, Charles Dotter, an eccentric vascular radiologist in Portland Oregon who developed a percutaneous technique – sometimes termed Dottering – for dilating peripheral arteries using sequential dilatation with rigid catheters.(4) Ultimately, however, its was Andreas Grüntzig, a German radiologist, who developed a functioning balloon

catheter and performed the first successful non-operative dilatation of a coronary stenosis in the left anterior descending artery of a 38-year old Swiss man called Adolf Bachmann on 16th September 1977 at the University Hospital in Zürich, Switzerland.(5) This procedure came to be known as balloon angioplasty.

Balloon angioplasty, it transpired, was limited in effectiveness both by a high-incidence of abrupt vessel closure after balloon dilatation and a requirement for later re-intervention due to restenosis in up to 40% of cases. A potential solution to this first problem was the implantation of an expandable metal mesh, on a bail-out basis, in order to maintain vessel patency following balloon dilatation. Jacques Puel and Ulrich Sigwart are credited with performing the first stent implantation in human coronary arteries in Toulouse, France and Lausanne, Switzerland respectively in the spring of 1986.(6,7) The first commercially successful stent was developed by Julio Palmaz and Richard Schatz.(8) Initially conceived as a "bail-out" strategy for abrupt vessel closure in the immediate aftermath of balloon angioplasty, availability of data from the European BENESTENT(9) and the United States STRESS(10) randomized clinical trials in 1994 provided an evidence-base for extension of the use of stents to an elective basis – a development that would significantly attenuate the problem of late luminal re-narrowing (or coronary restenosis). However the inherent thrombogenicity consequent on the exposure of metal stent struts to circulating blood resulted in a restrictive rate of thrombotic stent occlusion in the immediate aftermath of PCI despite aggressive anti-coagulant therapy with a high rate of local complications. Subsequent investigation demonstrated that a strategy based on dual antiplatelet therapy with aspirin and a thienopyridine was significantly more efficacious and better tolerated,(11-13) thereby facilitating more widespread adoption of stenting into clinical practice.

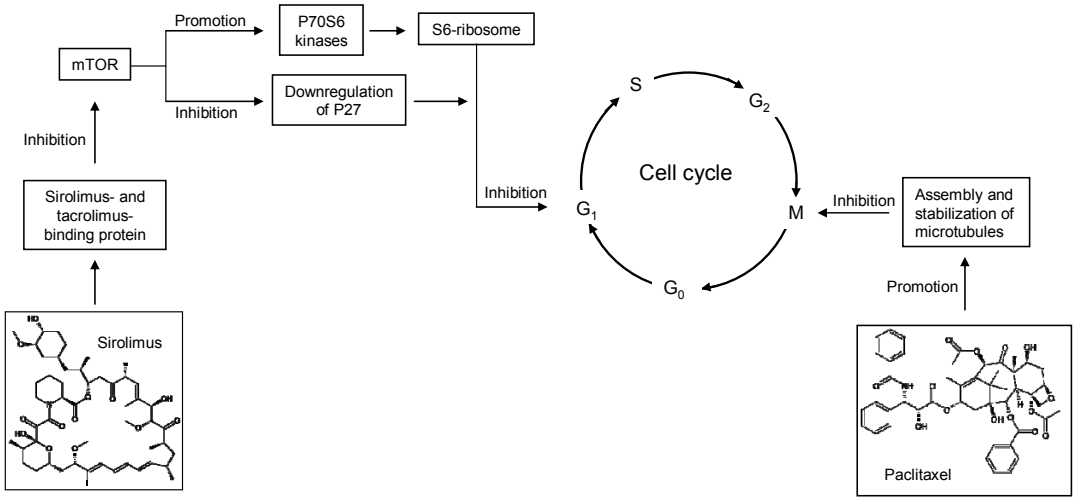
This left neo-intimal hyperplasia – a process of scar tissue formation at the site of the stented segment resulting in need for repeat intervention in approximately 25% of cases – as the remaining Achilles' heel of catheter-based intervention with uncoated or bare metal stents (BMS). Developed with the specific aim of targeting this pathophysiological process, drug-eluting stent (DES) therapy involves the incorporation into a supporting stent platform of anti-mitotic or immunosuppressive agents – with facilitated delayed elution – targeted at inhibition of smooth muscle cell proliferation, the key component of neointimal overgrowth. The performance of a DES is related to each of these 3 components: namely the stent backbone, the carrier polymer (to control drug release kinetics) and the active drug. The European Society of Cardiology congress in 2001 saw the presentation of initial successful results from the RAVEL trial with the sirolimus-eluting stent Cypher stent* (Cordis, Miami Lakes, FL. USA), data which appeared to herald the eradication of neo-intimal hyperplasia and the culmination of PCI technological development.(14) Five years later, proceedings from the annual congress of the same society provoked widespread concern with the presentation of a series of reports and debates on a potential increased risk of death and myocardial infarction associated with DES therapy.(15) The underlying pathophysiological substrate for these concerns appeared to be a delay in vascular healing of the stented arterial segment and although this process is undoubtedly multifactorial in aetiology, it seems that inflammatory response to durable polymer coatings played a central role.(16) It is against this background, that the hypothesis for the current thesis was framed.

*Footnote: The performance of a DES is related to each of 3 components: namely stent backbone, carrier polymer (to control drug release kinetics) and active drug. Proprietary stent types combine these components in a specific manner which affects drug-elution kinetics and performance. As such, in this thesis proprietary stent names are often presented alongside the generic names of the eluted drug.

1.2 Drug-eluting stents in coronary artery disease

Drug-eluting stents are a technological innovation based around the controlled release of a chemotherapeutic agent from a structurally-supportive metallic or organic stent backbone.(17) The advantage of this technology lies in the ability to achieve local drug effects without systemic toxicity. The choice of drug and the control of its release kinetics are the key determinants of antirestenotic efficacy. To date, two different classes of drugs – both with high lipophilicity – have been successfully employed on DES platforms in order to inhibit smooth muscle cell proliferation: (i) 'limus' family immunosuppressive drugs – such as sirolimus, zoratolimus and everolimus – which halt cell cycle progression in G1 phase; and (ii) paclitaxel, a microtubule stabilising drug which interrupts mitotic division in late metaphase, resulting in M phase cell cycle arrest. (**Figure 1**).

Figure 1. DES drug classes and mechanisms of action



mTOR = mammalian target of sirolimus; Adapted from Byrne et al.(17)

While significant differences exist between these drug families with regard to both pharmacological targets and clinical effects,(18) a vital determinant of their antirestenotic

efficacy relates to their *in vivo* drug-release kinetics and subsequent local tissue effects. Polymer compounds have been central to the control of drug release in stents eluting drugs from both classes.

1.3 Polymer technology

The term polymer refers to a heterogeneous group of macromolecules comprised of repeating monomer subunits joined by covalent chemical bonds. A co-polymer is a macromolecule comprised of more than one type of monomer subunit. Polymer may be either natural or synthetic and have a wide variety of medical and non-medical applications:

- natural polymers include cellulose (paper manufacturing), shellac (medical tablet coating) and latex rubber (examination gloves)
- synthetic polymers include polyacrylates (methacrylate in dentistry), polyesters and polystyrenes (textiles/packaging), polylactides (surgical sutures) and polyethylene (shopping bags)

In cardiovascular applications, it is synthetic polymers that have proven most useful and they are typically employed either to provide mechanical support or to serve as a vehicle for bioactive agents. In medical technology, polymers are often classified as durable (or non-erodable) – resistant to degradation in the human body – or biodegradable – slowly degraded *in vivo* by hydrolysis of the covalent bonds that link their repeating monomer subunits. In the field of DES therapy, polymer coating has proven the most successful vehicle both for drug-loading and control of release kinetics.(19,20) Indeed, all four of the systems currently approved by the United States Food and Drug Administration use a durable

polymer-based drug release system. In addition, polymers have occasionally been used as a lone component of a stent backbone,(21) though to date this use has been limited due to issues relating to radial strength as compared with metal alloy stents.

Polymers may also be broadly classified as hydrophilic or hydrophobic. Hydrophobic polymers readily facilitate loading and elution of the lipophilic active drugs. On the other hand, hydrophilic polymers exhibit less interfacial tension *in vivo* and confer a higher degree of biocompatibility. Marrying the need for lipophilicity with the superior biocompatibility of hydrophilicity is one of the key challenges of polymer technology.(22) First generation carrier polymers such as polybutylmethacrylate and ethylene-vinyl acetate (PBMA/PEVA; sirolimus-eluting stent; SES, Cypher; Cordis Corp., Miami Lakes, FL, USA)(14) and stryene-isobutylene-stryene (SIBS, TransLute polymer; paclitaxel-eluting stent, PES, Taxus; Boston Scientific, Natick, MA, USA)(23) were highly lipophilic, a property which facilitated drug-loading but may have been contributory to reduced biocompatibility. On the other hand the second generation phosphorylcholine polymer on the zotarolimus-eluting stent (PC polymer; zotarolimus-eluting stent, ZES, Endeavor; Medtronic, Minneapolis, MN, USA)(24) contains substantial amounts of water soluble monomers, though the trade-off for enhanced biocompatibility was a more rapid drug dissociation and lower antirestenotic efficacy. In contrast, the new generation ZES (Resolute; Medtronic, Minneapolis, MN. USA) contains a polybutyl methacrylate/hexylmethacylate/vjnyl acetate/vinyl pyrrolidinone co-polymer mix (Biolinx polymer),(25) which contains both hydrophobic and hydrophilic elements and purports to combine higher biocompatibility with effective drug-release kinetics. In a similar vein the second generation everolimus-eluting stent (EES, Xience; Abbott Vascular, Santa Clara, CA, USA)(26) is a co-polymer composed of a mix of polybutyl methacrylate (PBMA)

and polyvinylidene fluoride/ hexafluoropropylene (PDVF-HFP) polymer and also combines high efficacy with some evidence suggestive of enhanced vascular healing.

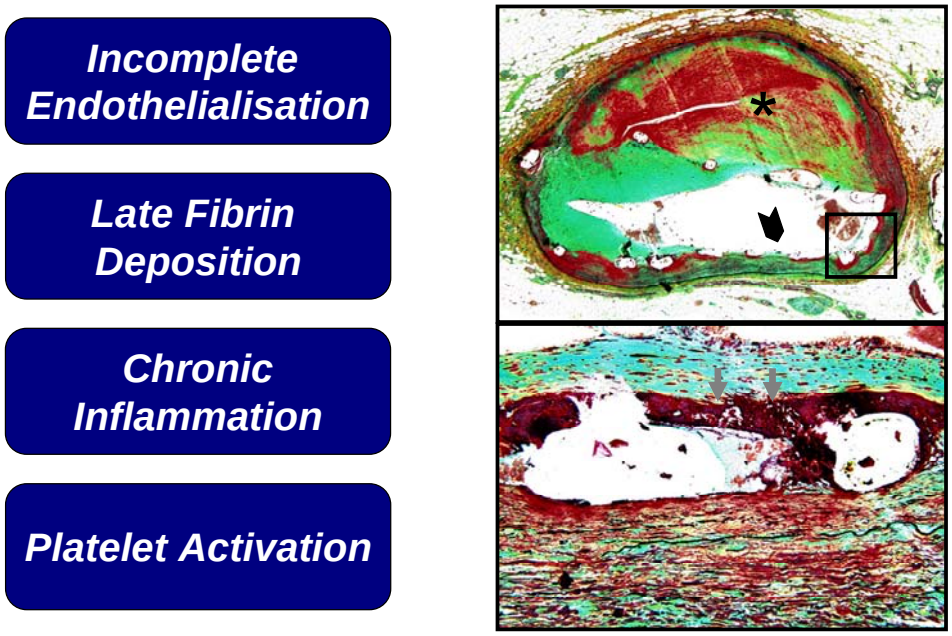
1.4 Delayed arterial healing and the role of polymer coatings

Since inception of DES therapy, it was recognised that the inhibition of neointimal overgrowth by this technology, could give rise to delayed arterial healing, late thrombotic events and late "catch-up restenosis" – problems foreshadowed to some extent by experiences with vascular brachytherapy,(27) although of smaller magnitude. Nevertheless, initial success in early clinical trials and the absence of adverse safety events out to 9-12 months prompted widespread enthusiasm for DES technology.(28) However, as clinical experience with DES usage grew rapidly, concerns emerged regarding late adverse events, in particular thrombotic stent occlusion.(15,29-32) An explanation for these concerns was hypothesized to be the existence of delayed healing processes at the arterial wall level following DES implantation. (16,22)

Delayed arterial healing after DES implantation is a pathophysiological process characterized by late fibrin deposition, delay or absence in re-endothelialization, chronic arterial wall inflammation and persistent platelet activation (**Figure 2**). Within segment heterogeneity in the degree of healing is a typical feature. While the pathophysiology of delayed arterial healing is complex, inflammatory response to polymer plays a significant role. Polymer biocompatibility in body compartments subject to direct interaction with circulating blood has long been recognised as an important limitation to their utilization in local drug delivery systems. A measure of the difficulties encountered is the report of van der Giessen after implantation of a panel of eight biostable or biodegradable polymers using a metal stent

carrier in a porcine coronary model.(33) Histomorphic analysis at 28 days showed severe inflammatory reaction and proliferative response to all polymers tested both biostable and biodegradable.

Figure 2. Hallmarks of delayed arterial healing



Low- (upper right panel) and high-power (lower right panel) magnification sections stained with Movat pentachrome from the left circumflex artery of a 75-year old patient who died following stent thrombosis 132 days following drug-eluting stent implantation. The stented plaque was predominantly fibrotic (*), which may be regarded as low-risk for delayed healing. Nevertheless the arterial wall shows evidence of impaired endothelialisation (black arrow head) and persistent fibrin deposition (grey arrows). Adapted from Byrne et al.(22)

Although the pathogenesis of delayed healing of the stented arterial segment after DES implantation is not fully understood, persistent inflammatory response to residue from nonerodable polymer coatings seems to play an important role.(16,22) In recent years, many

efforts have been made to avoid the use of polymers in DES. However, the control of release kinetics of the eluted drug appears to be the crucial step in determination of the antirestenotic efficacy of DES platforms. (22,34) In this respect, the elimination or modification of durable polymer coatings has proved difficult to achieve without compromising antirestenotic efficacy.

The type and degree of the inflammatory response to biostable (durable) polymers is determined by various factors, including the stability of the polymer *in vivo*, the inertness at relevant biological conditions, and the capability of allowing regenerative tissue growth. In the main two types of inflammatory response are observed:(35)

(1) The typical inflammatory response to biostable polymers is a non-specific process dominated by leukocytes of the monocyte-macrophage lineage. Early after stent implantation, neutrophils are deposited at the polymer sites, a process that ultimately amplifies the pro-inflammatory response in the surrounding tissue. Monocytes and macrophages are recruited later, mostly limited to areas immediately adjacent to the polymer coating itself. This process may subsequently evolve into a giant cell foreign body response aimed at reducing the burden of polymer fragments. This latter process is may be particularly important with biodegradable polymer coatings.

(2) In certain cases a more specific delayed type IV hypersensitivity reaction is observed, characterised by T-lymphocyte and eosinophil infiltration. (36) Autopsy studies with first generation DES suggest that hypersensitivity reactions are exclusively observed with the Cypher SES.(37) For example, an early pathological case report concerned a 58-year old

patient who died of acute circumflex vessel stent thrombosis 18 months following Cypher implantation.(39) Sectioning of the coronary arteries revealed absence of neointimal re-growth and signs of significant arterial wall toxicity at the stented segment: malapposition and aneurismal dilatation of the vessel wall; and diffuse T-lymphocyte and eosinophil infiltration. Collectively these changes were consistent with a specific subtype of delayed arterial healing related to delayed (type IV) hypersensitivity reaction. To date, the detailed factors resulting in a hypersensitivity response remain to be elucidated.

As the resolution of clinically practicable invasive and non-invasive imaging techniques has until now been insufficient to characterize the extent of vascular healing *in vivo*, most of our understanding of impaired vascular healing post-DES implantation comes from autopsy studies of patients who succumbed for cardiac or non-cardiac reasons at a time point following coronary stenting. Initial reports of delayed healing and adverse clinical events following DES therapy were anecdotal in nature.(38,39) The seminal study of Joner et al.(40) however compared autopsy specimens from 23 patients with prior DES implantation (at > 30 days) to 25 matched controls with a previously implanted BMS.(40) All cases came from a registry of 484 stent specimens submitted to the institute for pathological consultation. DES specimens (Cypher and Taxus) showed greater delayed healing compared to BMS: fibrin deposition score (2.3±1.1 vs. 0.9±0.8, $p<0.001$); endothelial coverage (55.8±26.5 vs. 89.8±20.9, $p<0.001$). In addition, DES specimens were more likely to have evidence of late stent thrombosis (14/23 patients vs. 2/25 patients). Inflammatory cell infiltrate (including eosinophils) was more frequent after Cypher stenting; fibrin deposition was more pronounced with Taxus. In all 14 DES patients with late thrombosis, delayed healing appeared to be a principal contributing factor. Interestingly however, 11 of 14 patients had

evidence of a second pathological risk factor for late stent thrombosis – e.g. penetration of necrotic core, ostial/bifurcation stenting, malapposition or restenosis. This suggests that a "dual-hit" is often necessary to provoke a thrombotic clinical event. It must be acknowledged that the relative contribution of drug and polymer to these cases of delayed healing is difficult to definitively define. In 3 of 11 cases there was evidence of a full-blown chronic hypersensitivity reaction which may have been a direct immunological response to residual polymer. In the remainder of cases the relative contribution of drug effects and response to non-erodable polymer are unclear.

Evidence has continued to accrue suggesting a clinicopathological spectrum of conditions consequent on delay in healing of the DES-stented arterial segment. These conditions range from late thrombotic stent occlusion,(29,40,41) through persistent vasomotor dysfunction(42-44) and late neointimal overgrowth (see Results section 4.1 of current manuscript) to a recently identified excess of accelerated *de novo* in-stent atherosclerosis(45). These concerns provide continued stimulus for the ongoing refinement of DES, a technology which remains very much a work-in-progress.(46)

2. THESIS AIMS

Early generation drug-eluting stent systems delivered high efficacy suppression of neointimal overgrowth but did so at the collateral cost of delayed healing of the stented arterial segment. Although such delayed vascular healing is undoubtedly multifactorial, inflammatory response to the durable polymer coatings used to control drug-release has a central causative role. A key focus of the current investigations is evaluation of the effects of modification in polymer coatings on the balance between *device efficacy* in preventing restenosis and *device safety* in reducing vessel wall toxicity. The two principal aims of the thesis were (i) to examine shifts in the longitudinal time course and angiographic metrics of restenosis resultant on the altered balance between vessel healing and restenosis after drug-eluting stent implantation; and (ii) to study the translation of next generation drug-eluting stents with modified polymer or polymer-free drug-release systems from preclinical investigations into randomized clinical trials powered for either angiographic surrogate endpoints or hard clinical outcomes. These studies aimed to enroll broadly inclusive patient populations with real world clinical disease patterns and are comprised of comparative efficacy trials involving three classes of drug-eluting stent devices: (i) polymer-free single- or dual-drug stents (ii) biodegradable polymer stents and (iii) durable polymer stents, based on modified polymer coating systems. In addition, recognizing the relative paucity of data examining the specific effects of the active drug itself in isolation from the other device components, a further objective was to examine the preclinical effects of devices with identical stent backbone and polymer composition but different active drug

Table 1. Design characteristics of drug-eluting stents investigated in the current thesis

Stent name	Stent backbone	Proprietary backbone	Strut thickness	Polymer coating	Active drug	Drug load (per 3.0 x 18mm stent)	% drug-release at 10 days
Cypher stent	Stainless steel	Select	0.140 mm	Polybutylmethacrylate/ethylene-vinyl acetate (PBMA/PEVA)	Sirolimus	150 mcg	50%
Taxus stent	Stainless steel	Express Liberte	0.132 mm 0.097 mm	stryene-isobutylene-stryene (SIBS)(TransLute)	Paclitaxel	124 mcg	5-10%
Endeavor stent	Cobalt chromium	Driver	0.090 mm	phosphorylcholine	Zotarolimus	180 mcg	90-95%
Polymer-free Yukon PC Choice	Stainless steel	Yukon PC Choice	0.087 mm	stryene-isobutylene-stryene (SIBS)(TransLute)	Sirolimus	480 mcg	75%
Biodegradable polymer Yukon PC Choice				Poly-D-L-lactic acid	Sirolimus	180 mcg	40%
Dual-drug Yukon PC Choice				none	Sirolimus and Probucol	120 mcg	50%
Biomatrix Flex	Stainless steel	0.120	0.112 mm	Poly-L-lactic acid	Biolimus A9	280 mcg	30%
Xience stent	Cobalt chromium	Vision	0.081 mm	vinylidene fluoride/ hexafluoropropylene (PDVF-HFP)	Everolimus	88 mcg	50%
Resolute stent	Cobalt chromium	Driver	0.090 mm	Butyl methacrylate/ hexylmethacylate/vjnyl acetate/ vinyl pyrrolidinone (Biolinx)	Zotarolimus	180 mcg	50%

3. METHODS AND MATERIALS

3.1 Study devices

The key device characteristics for each of the stents included in clinical studies that comprise components of this thesis are shown in **Table 1**. The devices may be considered in two main groups. The polymer-free sirolimus-eluting stent, the biodegradable polymer sirolimus-eluting stent and the polymer-free sirolimus- and probucol-eluting stent are devices based on a commercially available bare metal stent backbone which is coated on-site with drug and/or polymer mixtures developed in the setting of the ISAR stent project. The remainder of the devices listed in **Table 1** are commercially available products combining proprietary stent backbones, drugs and polymer coatings.

The Yukon PC Choice stent platform consists of a pre-mounted, sand-blasted, 316L stainless steel microporous stent (produced by Translumina, Hechingen, Germany). The technology employed allows for on-site drug coating. The study medications are applied to the stent surface in a single coating process. The coating process is fully sterile and takes between 3-8 minutes depending on stent length. A detailed description for creating the micropores and its rationale, the specifics of the coating process, and the sirolimus release profile of the platform have been reported previously.(47,48) Determination of drug coating dosages is performed by drug elution in 1.5 ml ethanol 100% overnight at 4°C. Sirolimus and probucol amounts are then quantified by UV-range spectroscopy at 280 nm and 254 nm respectively. The integrity of the distribution of drug coating is verified by light microscopic examination. The reproducibility of drug loading dosages, distribution and elution kinetics is verified by

repeated examination of multiple stent samples selected at random. Details of drug concentrations in vascular tissue following stent implantation in an animal model are reported elsewhere.(48-50)

The **polymer-free sirolimus-eluting stent** is coated on site with sirolimus 2% solution without employing synthetic polymers. The total coated drug dose is 480 µg sirolimus/cm^2. The sirolimus release profile of this device is shown in **Figure 3A**.

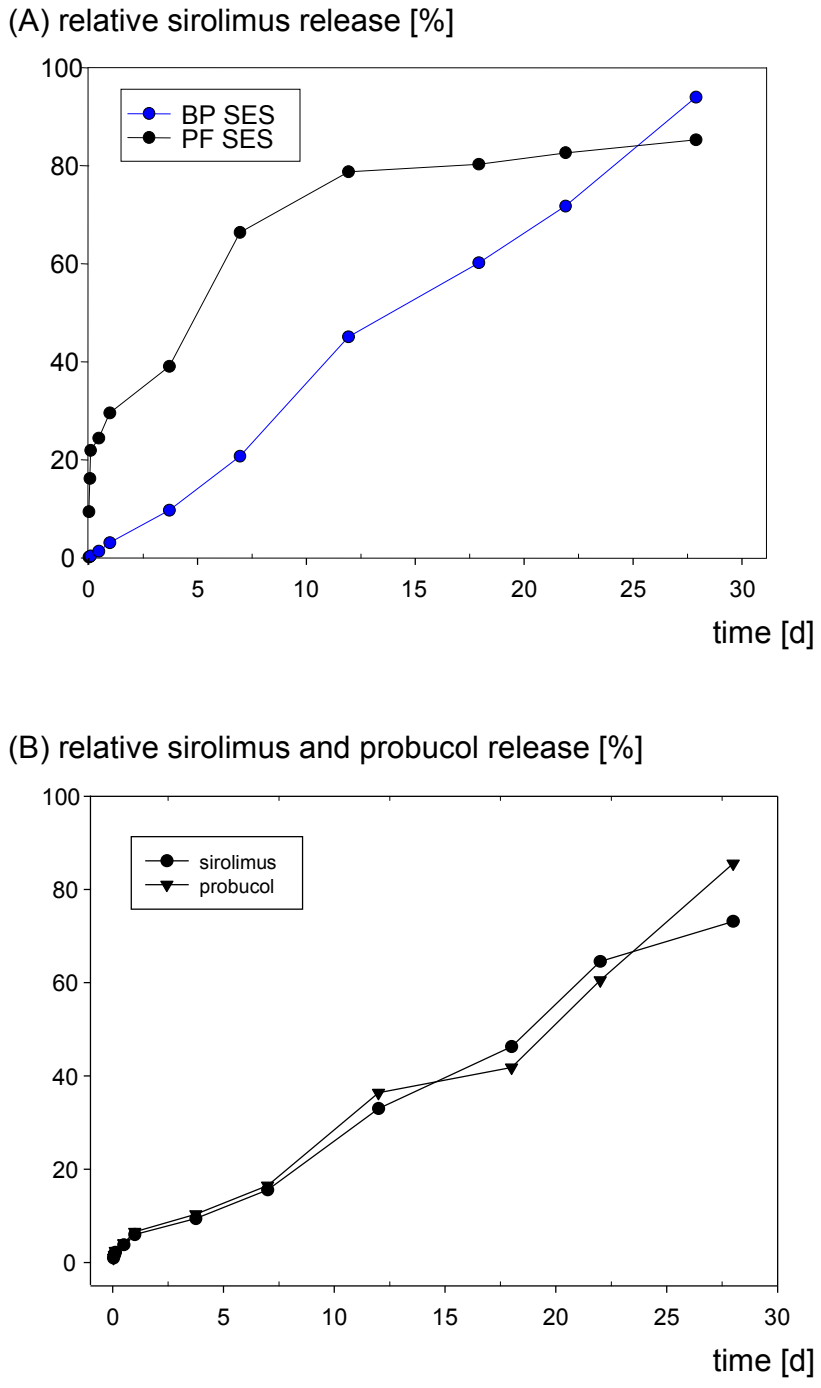
The **biodegradable polymer sirolimus-eluting stent** platform is coated on site with a mixture of sirolimus, low molecular weight PDLLA biodegradable polymer, and shellac resin (a biocompatible resin widely used in the coating of medical tablets). The total drug dosage is 180 µg sirolimus/cm^2. The biodegradable polymer matrix used is completely resorbed within 6 to 9 weeks. The sirolimus release profile of this device is shown in **Figure 3A**.

The **polymer-free sirolimus- and probucol-eluting stent (Dual-DES)** is coated on site with a mixture of sirolimus (0.7%) and probucol (0.7%) which are dissolved in solution in a 1:1 ratio, combined with a shellac resin (0.07%), and applied to the stent surface in a single coating process; no polymer is employed. The distribution of sirolimus is 120µg/cm^2 stent and of probucol is 100µg/cm^2. The sirolimus release profile of this device is shown in **Figure 3B**.

The shellac resin utilized in these platforms is a biocompatible resin widely used in the coating of medical tablets; its release kinetics are similar to those of both active drugs. The inclusion of resin allows for improved adherence of the drug mixture to the stent surface and enhances the structural integrity of the coating.

Detailed specifications of the remaining devices are reported elsewhere.(14,23-26,51)

Figure 3. Drug release profile for (A) polymer-free sirolimus-eluting stent and biodegradable polymer sirolimus-eluting stent and (B) sirolimus- and probucol-eluting (dual-drug) stent



BP SES = and biodegradable polymer sirolimus-eluting stent; PF SES = polymer-free sirolimus-eluting stent

3.2 Core study protocol for the ISAR TEST trial series

3.2.1 Inclusion and exclusion criteria

Patients older than age 18 with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥50% *de novo* stenosis located in native coronary vessels were considered eligible, provided that written, informed consent by the patient or her/his legally-authorized representative for participation in the study was obtained.

The key common lesion exclusion criteria were target lesion located in the left main stem, in-stent restenosis or location in a coronary bypass graft as these patients were triaged to enrolment in the concurrently running ISAR LEFT MAIN 1 and 2, ISAR-DESIRE 1, 2 and 3 and ISAR-CABG respectively. The key patient exclusion criteria were cardiogenic shock, malignancies or other co-morbid conditions with life expectancy less than 12 months or that may result in protocol non-compliance, known allergy to the study medications (everolimus, sirolimus, paclitaxel, zotarolimus) or pregnancy (present, suspected or planned). Each of the clinical trials was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practices. The trial protocols were approved by the institutional ethics committee responsible for the participating centres, Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum rechts der Isar, in Munich, Germany.

3.2.2 Treatment allocation

In each participating centre, allocation to treatment was made by means of sealed, opaque envelopes containing a computer-generated sequence. Randomization was performed immediately after crossing the lesion with a coronary guidewire. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order that they qualified. Randomization was stratified according to participating centre. Time zero was defined as the time of randomization and patients were considered enrolled in the study at this time point. The same randomly assigned stent had to be implanted in all lesions in those patients who required stenting in multiple lesions and the use of more than one stent per lesion was also allowed. Treatment groups were studied concurrently.

Treatment allocation of individual included clinical trials:

Byrne et al.(52) serial angiographic surveillance registry: Durable polymer SES (Cypher) or polymer-free SES or durable polymer PES (Taxus); non-randomized allocation

Byrne et al.(53) metrics of restenosis registry: Durable polymer SES (Cypher) or durable polymer PES (Taxus); non-randomized allocation

ISAR-TEST 2 trial:(54,55) Durable polymer SES (Cypher) or polymer-free sirolimus- and probucol-eluting stents (Dual-DES) or durable polymer ZES (Endeavor); randomized in 1:1:1 allocation

ISAR-TEST 3 trial:(56,57) Biodegradable polymer SES or durable polymer SES (Cypher) or polymer-free SES; randomized in 1:1:1 allocation

ISAR-TEST 4 trial:(58,59) Biodegradable polymer SES or durable polymer DES (either SES, [Cypher] or EES [Xience]); randomized in a 2:1:1 allocation

ISAR-TEST 5 trial:(60) Polymer-free sirolimus- and probucol-eluting stents (Dual-DES) or durable polymer ZES (Resolute); randomized in a 2:1 allocation

3.2.3 Interventional procedures

An oral loading dose of 600 mg clopidogrel was administered to all patients at least 2 hours prior to the intervention, regardless of whether the patient was taking clopidogrel prior to admission. During the procedure, patients were given intravenous aspirin, heparin or bivalirudin; glycoprotein IIb/IIIa inhibitor usage was at the discretion of the operators. After the intervention all patients, irrespective of treatment allocation, were prescribed 200 mg/day aspirin indefinitely, clopidogrel 150 mg for the first 3 days (or until discharge) followed by 75 mg/day for at least 6 months and other cardiac medications according to the judgment of patient's physician (e.g. ß-blockers, ACE-inhibitors, statins etc.). After enrolment patients remained in hospital for at least 48 hours. Blood samples were drawn every 8 hours for the first 24 hours after randomization and daily afterwards for the determination of cardiac markers (CK, CK-MB, Troponin T or I). Daily recording of ECG was also performed until discharge. All patients were evaluated at 1 and 12 months by phone or office visit for the evaluation of the primary clinical endpoints. Extended follow-up is performed annually thereafter out to 5 years. Repeat coronary angiography was scheduled for all patients at 6-8 months.

3.2.4 Quantitative coronary angiography analysis

Baseline, post procedural, and follow-up angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISAR Centre, Deutsches

Herzzentrum Munich). Details relating to the measurement protocol are presented in section 3.3.

The ISAR-TEST 2 and ISAR-TEST 3 trials used primary angiographic end points of interest:

- in-segment binary angiographic restenosis (defined as diameter stenosis ≥50% in the in-segment area) at follow-up angiography (ISAR-TEST 2)
- in-stent late luminal loss, defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up angiography (ISAR-TEST 3)

3.2.4 Data Management, End Points, and Definitions

Relevant data were collected and entered into a computer database by specialised personnel of the Clinical Data Management Centre. All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.

Clinical endpoint definitions

The ISAR-TEST 4 and ISAR-TEST 5 trials used primary clinical endpoints. In both cases the primary endpoint of the study was a device-oriented composite of cardiac death, myocardial infarction (MI) related to the target vessel, or revascularisation related to the target lesion (TLR) at 12 months post index intervention. This endpoint has been recommended by both regulatory and academic authorities(61) and has also been termed target lesion failure (TLF).

Definition of individual endpoint components:

- Cardiac death is defined as death due to any of the following: acute myocardial infarction; cardiac perforation/pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or stroke suspected of being related to the procedure; death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery; or any death in which a cardiac cause cannot be excluded.

- Myocardial infarction: in the serial angiographic surveillance registry, the metrics of restenosis registry and ISAR-TEST 2 and ISAR-TEST 3, MI was defined as the presence of new Q-waves on the ECG and/or elevation of creatine kinase (CK) or its MB isoform (CK-MB) to at least three times the upper limit of normal in no fewer than two blood samples. In ISAR-TEST 4 and 5 MI related to procedure was defined as either an increase in CK-MB (or CK) ≥3 upper limit of normal (ULN) and at least 50% over the most recent pre-PCI levels, or the development of new ECG changes consistent with myocardial infarction and CK-MB (or CK) elevation higher than the ULN at two measurements for patients undergoing DES implantation in setting of stable angina pectoris or non-ST-segment elevation acute coronary syndrome and falling or normal CK-MB (or CK) levels. Recurrent chest pain lasting more than 30 minutes with either new ECG changes consistent with second MI or next CK-MB (CK) level at least 8 to 12 hours after PCI elevated at least 50% above the previous level was considered procedure-related MI for patients presenting with Non-ST-elevation acute coronary syndrome (NSTE-ACS) and elevated CK-MB (CK) level prior to PCI. Bypass surgery related MI was considered either CK-MB elevation ≥10 ULN and at least 50% over the most recent pre-surgery levels or CK-MB elevation ≥5 ULN and at

least 50% over the most recent pre-surgery levels in addition to new abnormal Q-waves on the ECG. Myocardial infarction in the ISAR-TEST 4 and ISAR-TEST 5 trials refers to target-vessel MI; in the other studies any MI was included.

- TLR was defined as any ischemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. Ischemia-driven was defined by: diameter stenosis ≥50% ("in-segment" QCA-analysis) at follow-up angiography and positive functional study corresponding to the area served by the target lesion or ischemic symptoms and ECG-changes at rest referable to the target lesion; diameter stenosis <50% at follow-up angiography but a markedly positive functional study or ECG-changes corresponding to the territory supplied by target vessel; or diameter stenosis ≥70% at follow-up angiography in absence of documented clinical or functional ischemia.

- Target vessel revascularisation was defined as any ischemia-driven repeat PCI or bypass surgery revascularisation of any segment of the treated coronary vessel proximal or distal to the treated segment and including upstream and downstream side branch vessels.

- Stent thrombosis was classified according to Academic Research Consortium (ARC) criteria.(61)

3.2.5 Statistical Analysis

Sample size calculations

Byrne et al.(52) serial angiographic surveillance registry: no sample size calculation

Byrne et al.(53) metrics of restenosis registry: no sample size calculation

ISAR-TEST 2 trial:(54,55) The objective of the study was to compare the anti-restenotic efficacies of the three limus agent stents. To calculate sample size, we followed the method for detection of differences in proportions appropriate for two or more groups as described by Lachlin.(62) For a power of 80% and α-level of 0.05, for each group 245 patients were estimated to be needed to detect a difference in proportions characterized by a variance of proportions of 0.14% and an average proportion of 11.7%; the latter two parameters were generated by assuming restenosis rates of 7%, 12% and 16% for SES,(63) ZES(64) and sirolimus- and probucol-eluting stents(47,56) respectively. Expecting that up to 20-25% of the patients would not attend for follow-up angiography, 1002 patients were planned to be enrolled (334 patients per group). In the event of a significant difference in the primary analysis, two pre-specified superiority analyses were planned to be performed, comparing the performance of Dual-DES with that of the SES and ZES. To account for multiple testing a p-value of <0.025 was considered statistically significant according to the Bonferroni method.(65)

ISAR-TEST 3 trial:(56,57) The objective of the study was to assess the non-inferiority of both biodegradable and polymer-free stents to durable polymer stents. Sample size calculation was based on a margin of non-inferiority for in-stent late luminal loss set at 0.16 mm for both comparisons.(66) The assumed common standard deviation was 0.5 mm. This threshold allowed for the preservation of 80% of reduction in late lumen loss observed previously with SES compared with bare-metal stent.(67) With a power of 80% and a one-

sided α-level of 0.025 due to 2 pre-specified comparisons, we estimated that 155 patients in each of the 3 groups were needed to show the non-inferiority of biodegradable and polymer-free stents. Expecting that up to 20% of patients would not return for follow-up angiography, we aimed to enrol a total of 600 patients (200 in each treatment arm).

ISAR-TEST 4 trial:(58,59) The objective of the study was to assess the non-inferiority of biodegradable polymer DES compared with durable polymer DES. The null hypothesis regarding the primary endpoint was that the biodegradable polymer DES was inferior to the durable polymer DES. The alternative hypothesis was that the biodegradable polymer DES was non-inferior to the durable polymer DES. We estimated that with a sample size in each group of 1237, a two-group large-sample normal approximation test of proportions with a one-sided 0.05 significance level and a margin of non-inferiority (Δ) of 3% would have 80% power to reject the null hypothesis in favor of the alternative hypothesis, assuming that the incidence of the primary endpoint in both groups was 10%. In order to account for possible loss to follow-up, we planned to enrol 1300 patients in each group

ISAR-TEST 5 trial:(60) The objective of the study was to assess the non-inferiority of the sirolimus- and probucol-eluting stent (Dual-DES) compared with the polymer-based zotarolimus-eluting stent. The null hypothesis was that the sirolimus- and probucol-eluting stent was inferior to the polymer-based zotarolimus-eluting stent. Sample size calculation was based on an assumed incidence of the primary composite endpoint of 10% in both groups. The chosen margin of noninferiority was 3%, which was based on the assumption that any absolute difference in the primary endpoint less than 3% was considered of no clinical relevance. This threshold is in keeping with that used in recent drug-eluting stent comparative efficacy studies(51,68,69) and allows for preservation of 80% of the reduction in the incidence of the primary endpoint observed previously with current available drug-

eluting stents compared to bare-metal stents.(67,70) With a power of 80%, a one-sided α-level of 0.05, and a randomization sequence 2:1 it was estimated that 2783 patients (1855 receiving sirolimus- and probucol-eluting stents and 928 receiving zotarolimus-eluting stents) were needed to show the non-inferiority of the sirolimus- and probucol-eluting stent. To account for possible losses to follow-up, it was planned to enrol a total of 3000 patients.

Statistical methods

Sample size calculation was performed with nQuery Advisor (Statistical Solutions, Cork, Ireland) according to the method described by O'Brien and Muller.(71) In the trials with non-inferiority design, the non-inferiority hypothesis was tested with EquivTest (Statistical Solutions, Cork, Ireland) according to the methods described by Hauck and Anderson.(72) Non-inferiority was considered to be demonstrated if the upper one-sided 95% confidence interval surrounding the difference between the test treatment and the standard treatment was lower than the pre-specified threshold. After the determination of non-inferiority, we performed standard superiority testing. 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. The proportional hazards assumption was checked by the method of Grambsch and Therneau(73) and was fulfilled in all cases in which we used Cox proportional hazards models. Relative risk was calculated using time-to-event analyses and compared using the log-rank test based on the Mantel-Haenszel method. The analysis of primary and secondary endpoints was performed on an intention-to-treat basis. Although there are alternative opinions preferring a per protocol analysis in trials with a non-inferiority design,(74) in view of the absence of cross-over, this issue is of no relevance to the current studies. In ISAR-TEST 4 and ISAR-TEST 5 analysis of the primary endpoint was

also performed for pre-specified subgroups: old and young patients, men and women, diabetic and nondiabetic patients, small and large vessels. To identify whether there was an interaction between treatment effect and these covariates we used a Cox proportional hazards model.

Continuous data are presented as mean (standard deviation) or median [25^{th}-75^{th} percentiles]. Categorical data are presented as counts or proportions (%). Data distribution was tested for normality using the Kolmogorov-Smirnov test for goodness of fit. For 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 intrapatient correlation in patients who underwent multilesion intervention.(75) Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, Wa, USA) was used for analysis.

Additional methods for metrics of restenosis registry

The frequency distribution of the angiographic variables was tested for normality by means of the Kolmogorov-Smirnov goodness-of-fit test. For graphical presentation histograms, hanging histograms and density curves are used. For distributions with bimodal appearance and a marked deviation from the theoretical normal curve, deconvolution in two best-fitted normally distributed curves was performed with the EM-algorithm(76) using the S-Plus statistical package (S-Plus Version 2000, StaSci Division, MathSoft). As a result, the mean, SD, and proportion of the population belonging to each of the estimated component normal

distributions were obtained and used to construct the combined mixture distribution. The mixture distribution was tested against the respective observed frequency distribution by means of the Kolmogorov-Smirnov test. The improve in the fit of the distribution was performed in using the likelihood-ratio test R comparing the likelihood function under the assumption of one normal distribution or the mixture of two normal distributions. The hypothesis of a mixture of two distributions was accepted if the value of R exceeded the 95 % percentile of a χ^2-distribution with 3 degrees of freedom. The intersection point to separate between both normal distributions was obtained by the crossing between both density functions. The stability of the findings presented was ensured through the use of bootstrapping with 1000 replications of the original data.(77) The bootstrapping technique also allowed the calculation of the 95 % confidence interval for the intersection point. Statistical significance was accepted for all values of $p < 0.05$.

3.3 Quantitative coronary angiography analysis protocol

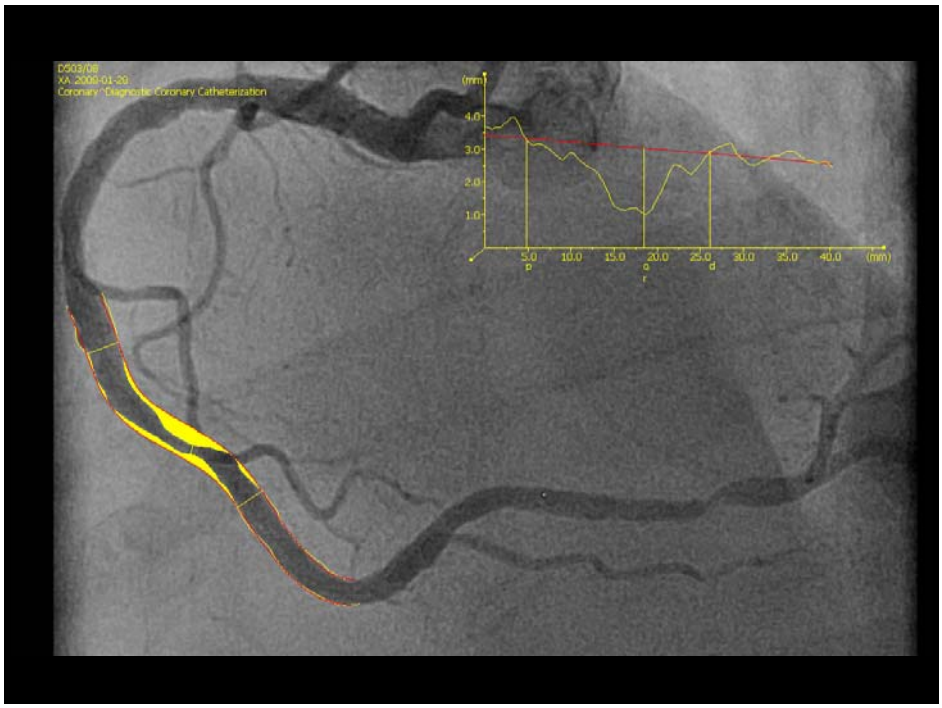
Baseline, post procedural, and follow-up angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISAR Centre, Deutsches Herzzentrum Munich) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems; **Figure 4**) by two independent experienced operators unaware of treatment allocation. Analysis was performed on cineangiograms recorded after the administration of intracoronary nitroglycerin using the same single worst-view projection at all times. The contrast-filled non-tapered catheter tip was used for calibration. Quantitative analysis was performed on both the “in-stent” and “in-segment” area (including the stented segment, as well as both 5-mm margins proximal and distal to the stent). Intra- and interobserver variability was calculated at 0.09±0.07 mm and 0.08±0.06 mm respectively for

the measurement of vessel size. (60) Qualitative morphological lesion characteristics were characterised by standard criteria.(78) Restenosis was classified as per Mehran et al.(79)

The primary angiographic end points of interest were:

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

Figure 4. Quantitative coronary angiographic analysis with CMS version 7.1



In studies with serial angiographic surveillance the additional endpoints were:

- *delayed* (or interval) in-stent late luminal loss , defined as the difference between the minimal luminal diameter at 6-8-month follow-up and the minimal luminal diameter at 2-year re-angiography, in those patients with paired follow-up data
- *final* 2-year in-stent LLL for the sub-group with paired angiographic follow-up films
- *composite* in-stent LLL for the entire cohort (defined as late loss of all study patients analysed on the basis of the latest valid angiographic follow-up whether at 6-8 months or 2 years)
- *delayed* in-segment binary angiographic restenosis, defined as diameter stenosis ≥50% in the in-segment area at 2 years in patients not undergoing initial revascularization at 6-8 months
- *composite* 2-year in-segment binary angiographic restenosis (defined as binary restenosis of all study patients analysed on the basis of the latest valid angiographic follow-up whether at 6-8 months or 2 years)

3.4 Analysis protocol for meta-analysis of individual patient data comparing biodegradable polymer stents with durable polymer sirolimus-eluting stents

3.4.1 Included patients

We performed a patient-level pooled analysis of the three largest multicenter, randomized clinical trials comparing biodegradable polymer DES with durable polymer SES for coronary revascularization: the ISAR-TEST 3 trial (ClinicalTrials.gov identifier: NCT00350454)(56,57), the ISAR-TEST 4 trial (ClinicalTrials.gov identifier: NCT00598676)(54,59) and the LEADERS trial (ClinicalTrials.gov identifier: NCT00389220).(51) A total of 4,052 patients were included in the present analysis, 2,358 of these were randomly allocated to treatment with biodegradable polymer DES (N=1,501 - sirolimus-eluting [Yukon PC Choice, stent backbone

produced by Translumina, Hechingen, Germany]; N=857 - biolimus-eluting [BioMatrix Flex, Biosensors Inc, Newport Beach, CA, USA]) and 1,704 patients to durable polymer SES (Cypher). Patients were followed up clinically out to three years after enrollment by the investigating sites.

3.4.2 Endpoints and definitions

The primary endpoint of the present analysis was the composite of cardiac death, myocardial infarction and target lesion revascularization. Stent thrombosis was defined according to the Academic Research Consortium criteria.(61)

3.4.3 Meta-analytic methods

Meta-analysis was performed on individual patient data according to intention to treat. We performed survival analyses using the Mantel-Cox method stratified by trial. Trials in which the event of interest was not observed in either treatment group were omitted from the analysis of that event. In case only one of the groups of an individual trial had no event of interest, the estimate of treatment effect estimate and its standard error were calculated after adding 0.5 to each cell of the 2x2 table for that trial.(80) We used the Cochran-test to assess heterogeneity across trials. Also, we calculated the I^2 statistic to measure the consistency between trials with values of 25%, 50%, and 75% showing respectively, low, moderate and high inconsistency.(81) Hazard ratios from individual trials were pooled using the DerSimonian and Laird method for random effects.(82) Results were considered statistically significant at two-sided $P<0.05$. Statistical analysis was performed using the Stata software, version 9.2 (Stata Corp, College Station, TX, USA). Survival curves are presented as

simple, non-stratified Kaplan-Meier curves across all trials and constructed with the use of S-Plus software version 4.5 (Insightful Corporation, Seattle, WA, USA).

3.5 Study protocol for investigation of comparative effects of sirolimus, everolimus and zotarolimus on vascular healing in a rabbit iliac model of stent implantation

3.5.1 Development of experimental DES constructs

The experimentally designed limus-DES were based on the Xience-V-EES stent system. Vinylidine fluoride and hexafluoropropylene copolymer served as the drug matrix layer for each of the three limus-drugs: everolimus, sirolimus and zotarolimus. The acquired carrier/drug solutions were coated onto the ML VISION^{TM} ASTM F-90 cobalt chromium stent system (3.0mm x 12 mm, Abbott Vascular, Santa Clara, CA, USA) at a total drug load of 40µg and a polymer thickness of 4.6 µm. The *in vitro* release kinetics for all DES constructs showed 60% elution of the drug within 30 days. The following stent constructs were obtained: everolimus-eluting stent, EES; sirolimus-eluting stent, SES, and zotarolimus-eluting stent, ZES.

3.5.2 Animal study design

The study protocol was approved by the responsible authority (Regierung von Oberbayern, AZ 55.2-1-54-2531-109-07) implementing the German Animal Welfare Act. Animal housing and care were in agreement with the EU directive 86/609/EWG, compliant with the US National Institutes of Health Guide for the Care and Use of Laboratory Animals.

A total of 34 healthy male New Zealand White rabbits (Charles River, Sulzfeld, Germany), weighing 3.5 – 3.8 kg, were included in this study. Animals were randomized to four different treatment groups: EES, SES, ZES and the BMS backbone as control.

- 12 animals were assigned for the assessment of re-endothelialization at 14 days (n=6 stents for each group: EES, SES, ZES and BMS)
- 22 animals were assigned for histopathologic analysis by light microscopy at 28 days (n=11 stents for each group: EES, SES, ZES and BMS)

For surgical procedures animals were anesthetized with propofol (Fresenius Kabi, Bad Homburg, Germany) and fentanyl (Fentanyl, DeltaSelect, Dreieich, Germany). i.v. Analgesia was secured by administration of buprenorphin (Temgesic, Essex Chemie AG, Luzern, Switzerland) pre- and post surgery. To achieve appropriate anticoagulation, 40 mg aspirin (Aspirin i.v., BayerVital, Leverkusen, Germany) and 150 IU/kg heparin were administered i.v. at the time of catheterization, continued on a daily oral dose of 40 mg aspirin until the time of study termination. Following arterial denudation, utilizing a standard angioplasty balloon catheter (Voyager RX, 3.0 mm x 8.0 mm, Abbott Vascular, Santa Clara, USA) at 6 and 8 atm, stents were deployed at nominal pressure (9 atm) in each external iliac artery. Post-procedural angiography was performed to verify vessel patency. At study termination, animals were anaesthetized to conduct a follow-up angiogram followed by euthanasia with pentobarbital overdose i.v. Subsequently, arteries were flushed with 500 ml of heparinized Ringer lactate to remove blood. Stented arteries were fixed *in situ* with 10 % neutral buffered formalin before harvest and kept in 4 % neutral buffered formalin until further histological preparation.

3.5.3 Data analysis

Assessment of endothelial surface coverage by SEM and immunostaining

Formalin-fixed arterial segments of the 14-day animal group were cut longitudinally, opened and subjected to *en face* SEM and *en face* immunostaining for CD31/PECAM-1, as previously described.(83)

For SEM evaluation, serial images were recorded at x10 magnification using a Hitachi Model 3600N scanning electron microscope and digitally assembled to provide an overview of the entire luminal stent surface. Higher magnification (x200) allowed for visualizing the strut surface with regard to composition of the adhering cells. Endothelial cells, inflammatory cells and platelets were reliably identified by their characteristic morphology. Endothelial surface coverage was assessed above and between struts by measuring the respective areas of endothelialization relative to the total strut area and the area between struts, respectively (IPLab for Mac OS X, Scanalytics, Rockville, Maryland) and expressed as percent endothelial cell coverage above and between struts.

Sequential images of the immunostained specimen were taken at x100 magnification utilizing confocal microscopy (Zeiss Pascal, Jena, Germany). The extent of endothelial cell coverage was based on a positive CD31/PECAM-1 signal and was visually semi-quantified as a percentage of the total in-stent vessel area above and between struts. Adjacent non stented segments served as positive controls for immunostaining.

Histopathological assessment by light microscopy

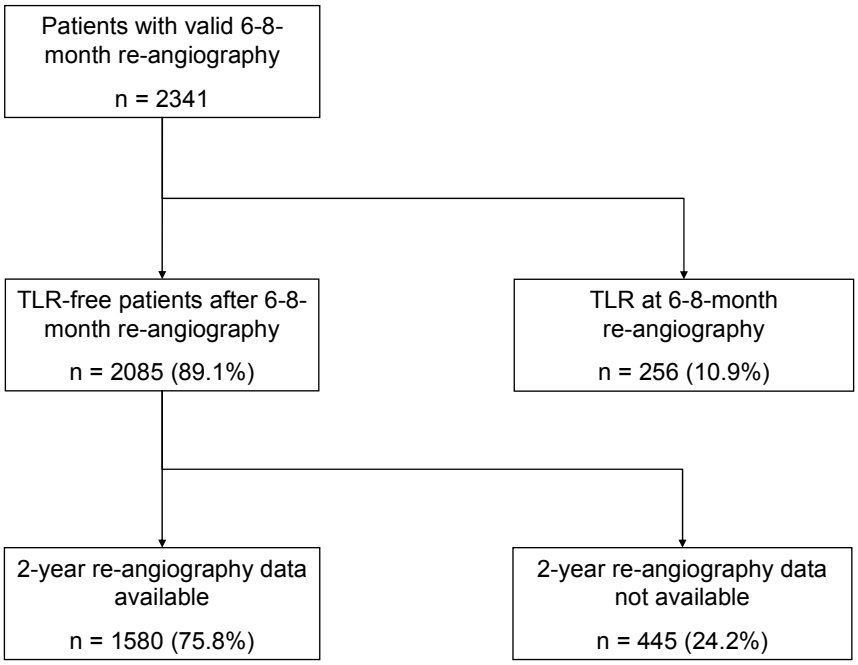
Twenty-eight days after implantation, the formalin-fixed stented vessel segments were dehydrated and embedded in methylmethacrylate polymerization mixture. Each specimen was divided into its proximal, mid and distal segment. Sections were obtained from each segment (3 sections per stent) and stained by hematoxylin and eosin (H&E) and Movat's pentachrome stains. Computerized planimetry was performed on all stented sections using Cell^F Software (Olympus, Hamburg, Germany). Vascular injury, fibrin deposition and inflammatory responses were evaluated in accordance with established scoring systems.(84) Endothelialization was assessed as percentage of endothelium occupying the luminal circumference of the artery.

4. RESULTS

4.1 Drug-eluting stents are associated with delayed late erosion of angiographic antirestenotic efficacy; absence of durable polymer attenuates this phenomenon

We studied the outcomes of 2588 patients undergoing percutaneous intervention in a *de novo* coronary vessel. Patient flow is shown in **Figure 5**. A total of 2030 patients (78.4%) returned for angiographic follow-up 6-8 months post index stenting, had valid angiographic data and were therefore considered eligible for enrolment in this study. The number of treated lesions was 2341 (1036 durable polymer SES treated lesions, 565 polymer-free SES stented lesions and 740 durable polymer PES treated lesions). Baseline clinical and procedural characteristics were similar between treatment groups (**Appendix Table A1**).

Figure 5. Patient study flow in the DES serial angiographic surveillance registry



TLR = target lesion revascularization

6-8 month Angiographic Outcomes

Angiographic outcomes are summarized in **Table 2**. Overall late luminal loss at 6-8-months was 0.37±0.56mm – comprising a LLL of 0.25±0.50 mm, 0.46±0.57 mm and 0.46±0.59 mm for durable polymer SES, polymer-free SES and durable polymer PES respectively (p<0.001). Binary angiographic restenosis was also significantly different across the 3 treatment groups: 125 (12.1%), 97 (17.2%) and 127 (17.2%) for durable polymer SES, polymer-free SES and durable polymer SES respectively (p=0.003). Restricting 6-8 month analysis to the subgroup of lesions that subsequently had available 2-year angiographic data (n=1580), LLL for the group was 0.26±0.42 mm – 0.16±0.37 mm in the patients treated with durable polymer SES (Cypher), 0.35±0.46 mm in the polymer-free SES stent group and 0.34±0.44 mm in the durable polymer PES (Taxus) group (p<0.001).

Two-year Angiographic Outcomes

Target lesion revascularisation was required in 259 patients (12.8%) at the time of 6-8-month re-angiography and accordingly these patients were not considered for 2-year angiographic recall (p=0.07 for differences across groups). Of 1771 remaining patients (with 2080 lesions), valid 2-year angiographic follow-up data, and therefore paired angiographic follow-up films, were available for 1331 (75.2%) patients (with 1580 [76.0%] treated lesions); this rate of follow-up was similar across all 3 groups (p=0.58).

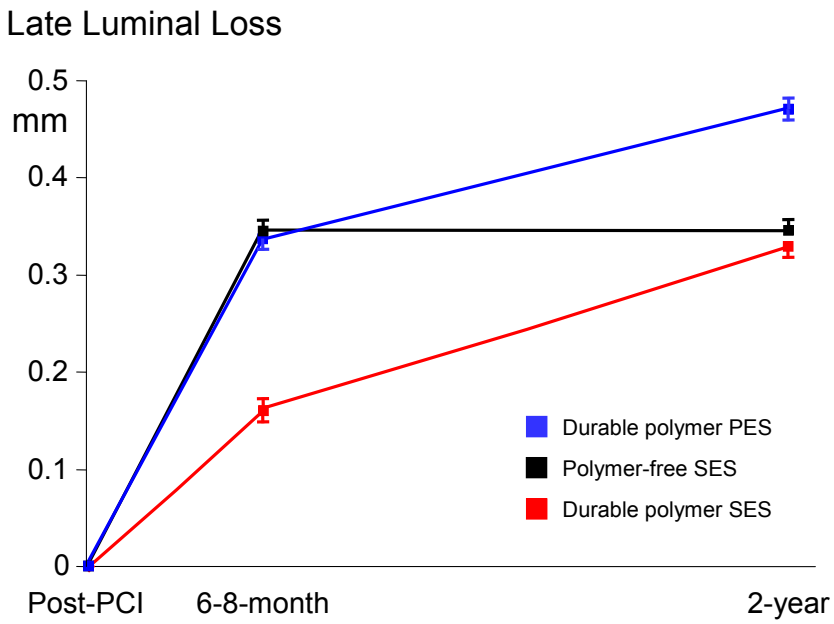
*Table 2. Results of 6-8-month and 2-year Re-angiography by Stent Type**

	Durable polymer SES	Polymer-free SES	Durable polymer PES	p-value
6-8 month re-angiography				
Re-angiography interval – days	203 ± 88	197 ± 74	199 ± 88	0.14
Lesions analyzed	1036	565	740	
MLD, in-stent – mm	2.31± 0.65	2.09 ± 0.72	2.15 ± 0.72	< 0.001
Late loss, in-stent – mm	0.25 ± 0.50	0.46 ± 0.57	0.46 ± 0.59	< 0.001
MLD, in-segment – mm	2.01 ± 0.63	1.86 ±0.66	1.91 ± 0.67	< 0.001
Stenosis, in-segment – %	30.2 ± 17.0	33.4 ±18.9	33.4 ± 18.7	< 0.001
Binary restenosis, in-segment	125 (12.1)	97 (17.2)	127 (17.2)	0.003
2-year re-angiography				
Re-angiography interval – days	701 ± 251	695 ± 237	700 ± 222	0.77
Lesions analyzed	704	375	501	
MLD, in-stent – mm	2.24 ± 0.67	2.21 ± 0.64	2.15 ± 0.69	0.015
Delayed late loss, in-stent – mm	0.17 ± 0.50	0.01 ± 0.42	0.13 ± 0.50	< 0.001
Composite late loss, in-stent – mm	0.37 ± 0.60	0.47 ± 0.59	0.55 ± 0.66	< 0.001
MLD, in-segment – mm	1.95 ± 0.63	1.96 ± 0.60	1.90 ± 0.65	0.19
Stenosis, in-segment – %	32.3 ± 17.1	29.7 ± 16.4	33.5 ± 18.1	0.004
Delayed binary restenosis, in-segment	92 (13.1)	27 (7.2)	75 (15.0)	0.002
Composite binary restenosis, in-segment	179 (17.3)	94 (16.6)	161 (21.8)	0.02

* Plus-minus values are means±SD; otherwise data are shown as number (%); MLD = minimal luminal diameter; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent

Two-year angiographic surveillance data are summarised in **Table 2**. With respect to the primary end-point, overall *delayed* LLL was 0.12±0.49 mm at 2-year angiographic follow up– 0.17±0.50 mm in the cohort treated with durable polymer SES, 0.01±0.42 mm in the polymer-free SES stent group and 0.13±0.50 mm in the durable polymer PES group (p<0.001; **Figure 6**). With regard to secondary end-points, *final* 2-year LLL in the group with paired angiographic follow-up lesions (n=1580) was 0.38±0.56 mm – 0.33±0.33 mm for durable polymer SES, 0.35±0.49 mm for polymer-free SES and 0.47±0.59 mm for durable polymer PES; p<0.001).

Figure 6. Time course of late lumen loss for patients with paired angiographic follow-up at 6-8 months and 2 years



SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent

In terms of *composite* 2-year LLL, the figure for the overall group (n=2341 lesions) was 0.45±0.62 mm – representing 0.37±0.60 mm for durable polymer SES, 0.47±0.59 mm for polymer-free SES and 0.55±0.66 mm for durable polymer PES; p<0.001. There were also

significant differences between the stent groups in the incidence of *delayed* binary angiographic restenosis, (92 [13.1%] for durable polymer SES, 27 [7.2%] for polymer-free SES and 75 [15.0%] for durable polymer PES; p=0.002), and overall 2-year *composite* binary angiographic restenosis (179 [17.3%] for durable polymer SES, 94 [16.6%] for polymer-free SES, and 161 [21.8%] for durable polymer PES; p=0.02).

Multivariate Analysis

Predictors of late luminal loss at 6-8-month re-angiography were stent group (favouring durable polymer SES), patient age, complex lesion morphology, chronic occlusion, ostial lesion location and lesion length). Only stent type (in favour of polymer-free SES) remained a predictor of *delayed* LLL between 6-8 months and 2 years.

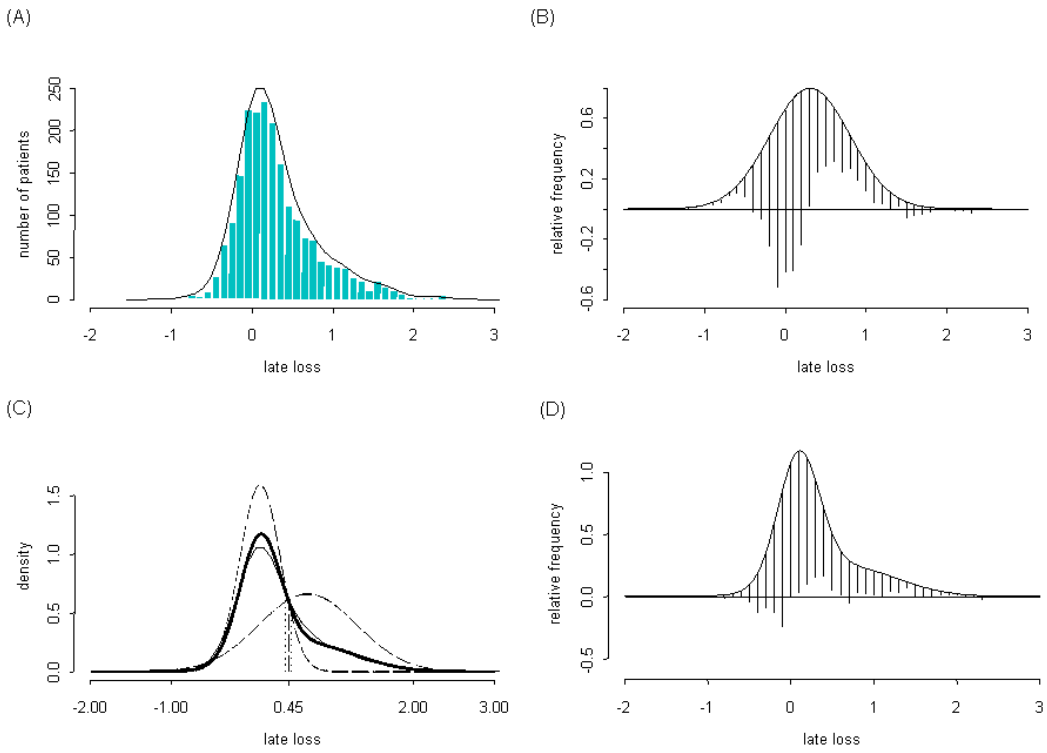
4.2 Drug-eluting stent therapy has not resulted in elimination of variable propensity to restenosis among subpopulations of stented lesions

We studied the angiographic surveillance data of 2092 patients treated with either SES or PES stents at two clinics in Munich. Thirty-five (1.7%) had a totally re-occluded artery at follow-up and were excluded from analysis. The remaining study population consisted of 2057 patients. Overall mean late luminal loss for the study cohort was 0.31±0.50 mm and mean percentage diameter stenosis was 30.3±15.7%. Binary angiographic restenosis was observed in 255 (12.4%) lesions.

Distribution of LLL differed significantly from normal (Kolmogorov-Smirnov test; p<0.001). This can be clearly seen from a frequency distribution histogram (**Figure 7A**) and a hanging histogram (**Figure 7B**). A mixed distribution model better described the data. The

Kolmogorov-Smirnov test comparing the observed frequency distribution with the mixed distribution model revealed no significant differences (p= 0.51). The likelihood ratio test confirmed this superior goodness-of-fit (with 3 degrees of freedom, p<0.001). This consisted of two deconvoluted populations with normal distribution (**Figure 7C**), the first with a mean late loss of 0.10mm and a standard deviation of 0.25mm; the second with a mean of 0.69 mm and a standard deviation of 0.60 mm. From analysis of the raw data, the weights of the populations were 64.5% and 35.5% respectively.

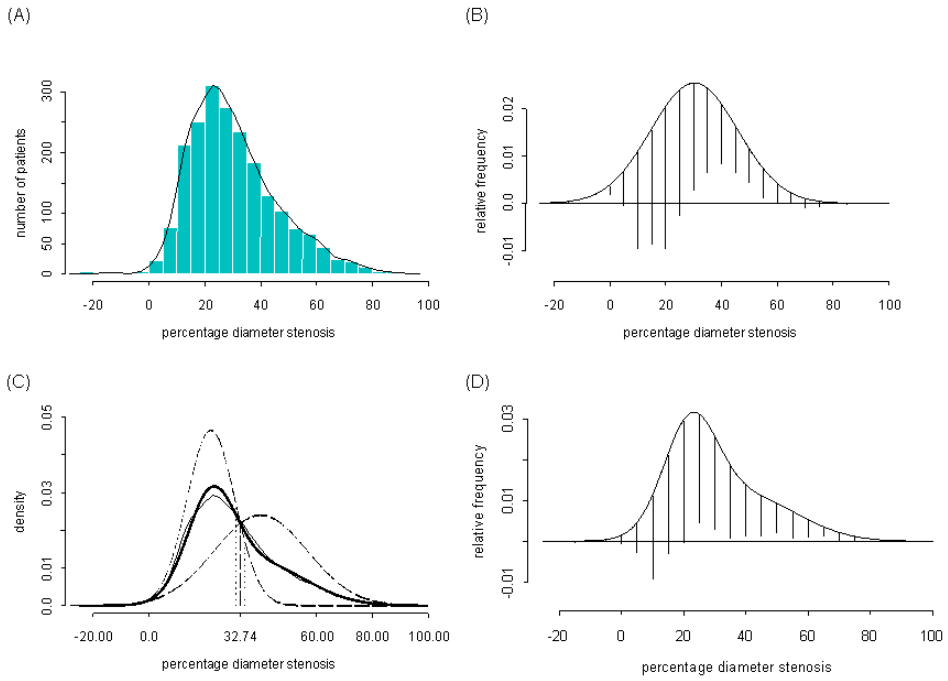
Figure 7. Distribution of late luminal loss for 2057 treated lesions



(A) Frequency distribution histogram with superimposed kernel density estimate; (B) Hanging histogram highlighting lack of goodness-of-fit with normal distribution; (C) Deconvolution of the observed frequency-distribution curves (thin solid line) yields two sub-populations with normal distribution (dashed lines). The weighted sum of these two components yields the composite distribution curve (thick solid line); (D) Hanging histograms applied to composite mixed distribution curves for late luminal loss

Similarly, distribution of %DS differed from normal (Kolmogorov-Smirnov test; p<0.001; **Figure 8A and 8B**). In this case a mixed distribution model also better described the data (Kolmogorov-Smirnov test comparing observed data with mixed model, p=0.99; likelihood ratio test with 3 degrees of freedom, p<0.001).This consisted of two deconvoluted populations with normal distribution (**Figure 8C**), the first with a mean %DS of 22.2±8.6; the second with a mean of 40.1±16.6. From the data, the weights of the populations were 54.4% and 45.6% respectively.

Figure 8. Distribution of percentage diameters stenosis for 2057 treated lesions



(A) Frequency distribution histogram with superimposed kernel density estimate; (B) Hanging histogram highlighting lack of goodness-of-fit with normal distribution; (C) Deconvolution of the observed frequency-distribution curves (thin solid line) yields two sub-populations with normal distribution (dashed lines). The weighted sum of these two components yields the composite distribution curve (thick solid line); (D) Hanging histograms applied to composite mixed distribution curves for late luminal loss

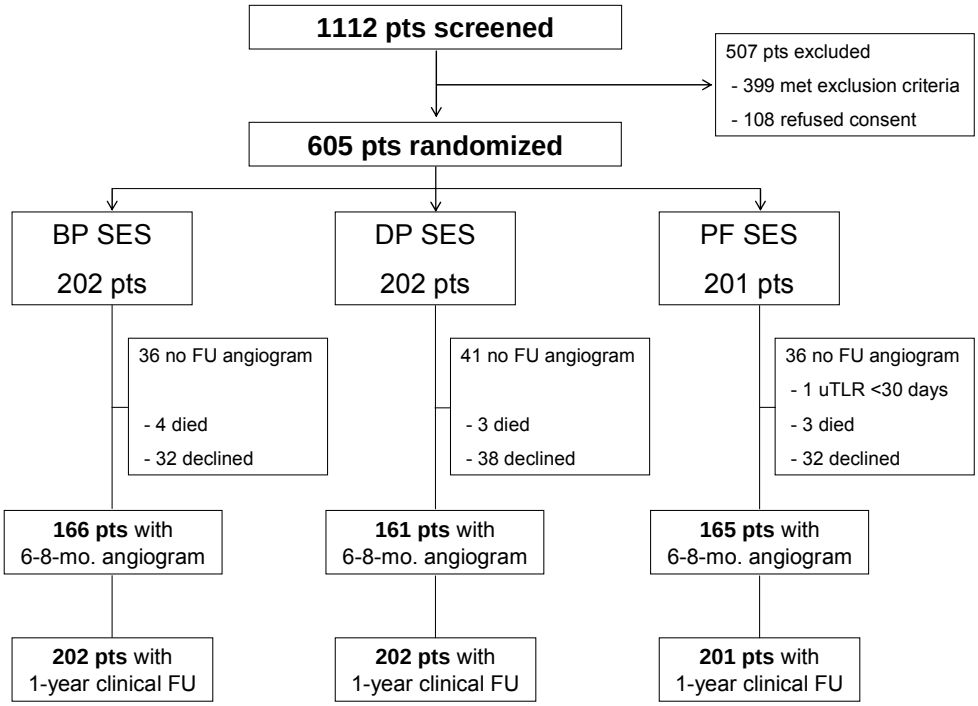
Comparison of hanging histograms fitted to a normal distribution and to the composite mixed distribution curves graphically illustrates the superior goodness-of-fit of the latter models for both parameters under investigation (**Figure 7A and 7D**; **Figure 8A and 8D**).

Exploratory subgroup analyses for LLL and %DS distributions were also performed for the two types of DES utilized in this study (Cypher versus Taxus), on-label versus off-label implantation, and in patients with diabetes versus those without. Overall, a composite mixed distribution model continued to better represent LLL and %DS across all the subgroups.

4.3 Biodegradable polymer but not single-drug polymer-free sirolimus-eluting stents are non-inferior to durable polymer sirolimus-eluting stents in terms of angiographic efficacy; this discrepancy is due to differences in drug-release kinetics

In the ISAR-TEST 3 study we randomized a total of 605 patients undergoing PCI for stable or unstable coronary disease in a trial powered for angiographic endpoints: 202 patients received the SES with biodegradable polymer (BP), 202 were treated with SES with durable polymer and 201 received a polymer-free SES. The study patient flow chart is shown in **Figure 9**. Baseline clinical and lesion characteristics are shown in **Appendix Table A2** and were well matched across.

Figure 9. Study flow chart for the ISAR-TEST 3 randomized trial

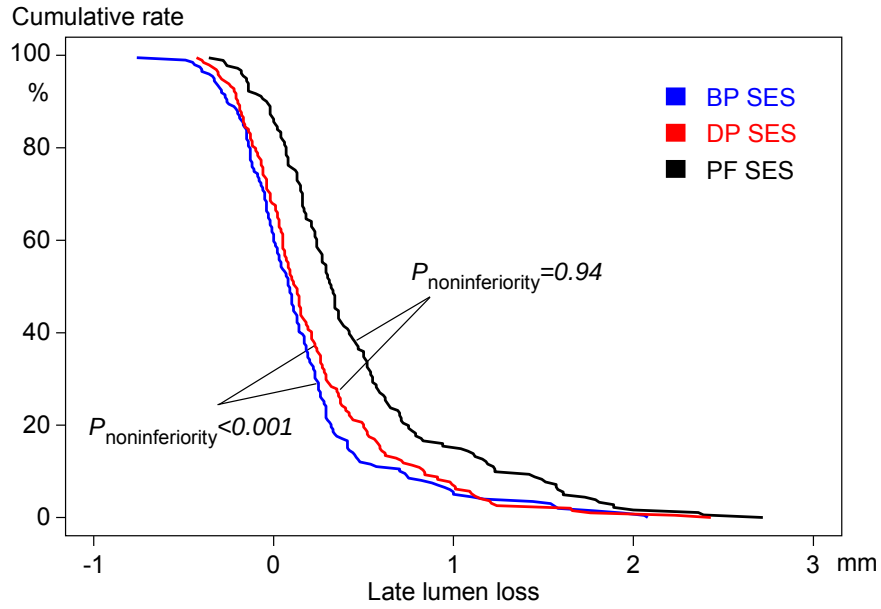


BP = biodegradable polymer; DP = durable polymer; FU = follow up; PF = polymer-free; SES = sirolimus-eluting stents

Angiographic Outcomes

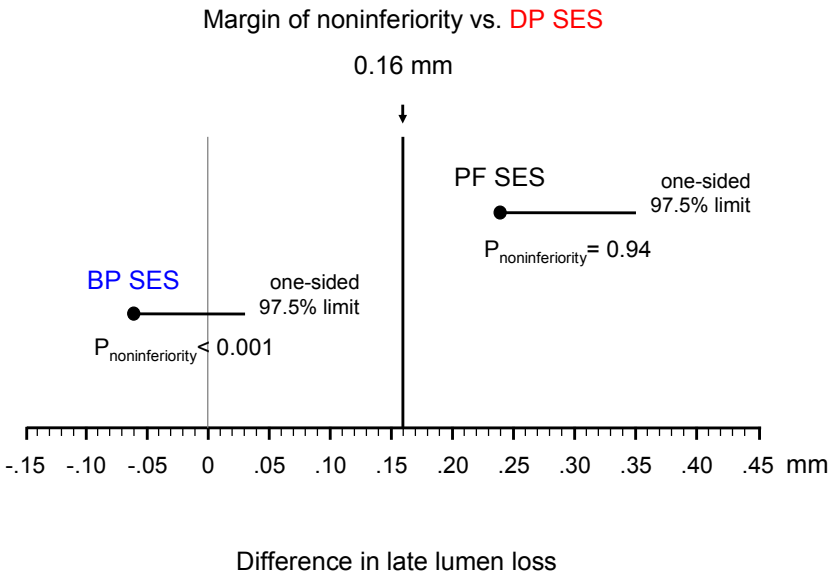
Of 605 patients, 492 re-attended (81.3%) for follow-up angiography. With respect to the primary end-point, mean LLL at 6-8-month angiographic follow up was 0.17 ± 0.45 mm in the cohort who received a BP stent, 0.23 ± 0.46 mm in those receiving a DP stent and 0.47 ± 0.56 mm in patients treated using a PF stent (**Figure 10A**). As a consequence, the BP stent met criteria for non-inferiority ($p<0.001$) whereas the PF stent did not ($p=0.94$) (**Figure 10B**).

Figure 10A. Cumulative distribution of late lumen loss with sirolimus-eluting stents with different polymer coatings



BP = biodegradable polymer; DP = durable polymer; PF = polymer-free; SES = sirolimus-eluting stents

Figure 10B. Results of on-inferiority testing for biodegradable polymer and polymer-free stents against durable polymer stents

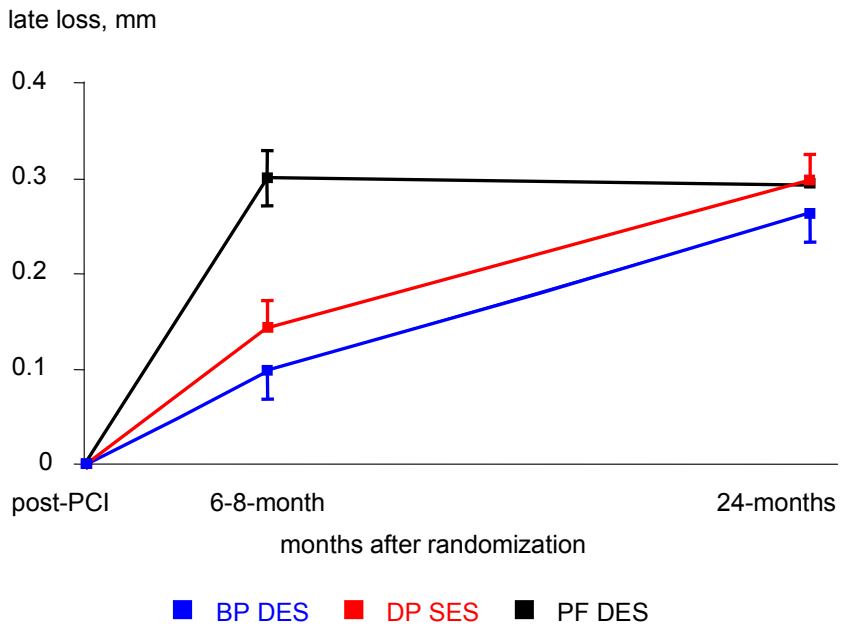


BP = biodegradable polymer; DP = durable polymer; PF = polymer-free; SES = sirolimus-eluting stents

Angiographic Follow-Up at 2 Years

In patients with 6-8 month follow-up angiography not requiring re-intervention, a second angiographic surveillance was scheduled at 2 years. Paired angiographic follow-up at 6-8 months and 2 years was available for 302 of 438 eligible patients (69.0%; 113 excluded due to no initial 6-8 months angiogram; 54 excluded due to TLR at ≤ 12 months; no significant differences in angiographic surveillance rates across the three groups, p=0.60). Restricting analysis to this group only, initial mean late loss at 6-8 months was 0.10±0.29 mm in the BP stent group, 0.14±0.32 mm in the PP group and 0.30±0.31 mm in the PF stent group (p<0.001). At second angiographic follow-up delayed late loss was also significantly different across the treatment groups: 0.17±0.42 mm in the BP stent group, 0.16±0.41 mm in the PP group and -0.01±0.36 mm in the PF stent group (p<0.001) (**Figure 11**).

Figure 11. Time course of late lumen loss for patients with paired angiographic follow-up at 6-8 months and 2 years



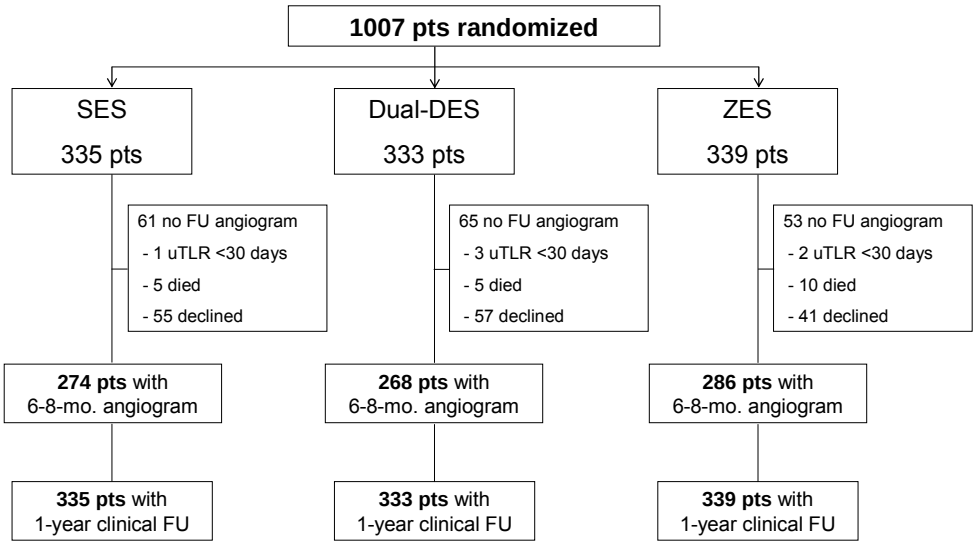
BP = biodegradable polymer; DP = durable polymer; PF = polymer-free; SES = sirolimus-eluting stents .

Overall, late luminal loss at 2 years (based on latest angiographic follow-up available for the entire study population) was 0.27±0.52 mm in the BP stent group, 0.35±0.55 mm in the PP group and 0.46±0.58 mm in the PF stent group (p=0.003).

4.4 Dual-drug polymer-free probucol- and sirolimus-eluting stents have an angiographic efficacy comparable to that of durable polymer sirolimus-eluting stents and superior to that of phosphorylcholine polymer zotarolimus-eluting stents

In the ISAR-TEST 2 randomized trail a total of 1007 patients were enrolled in a study powered for angiographic endpoints: 335 patients received the durable polymer SES, 333 were treated with the dual-drug sirolimus- and probucol-eluting stents (Dual-DES) and 339 received a durable-polymer ZES. Study patient flow chart is shown in **Figure 12**.

Figure 12. Study flow chart for the ISAR-TEST 2 randomized trial



Dual-DES = sirolimus- and probucol-eluting stent; FU = follow-up; SES = sirolimus-eluting stent; uTLR= urgent target lesion revascularization; ZES = zotarolimus-eluting stent

Baseline clinical and lesion characteristics are shown in **Appendix Table 3** and were well matched across all three treatment groups.

Angiographic outcomes at 6-8 months; Clinical outcomes at 1 year

In terms of binary angiographic restenosis – the primary endpoint of the study – there was a significant difference across the treatment groups (p=0.003). The incidence of angiographic restenosis in the Dual-DES group (11.0%) was significantly lower than that in the ZES group (19.3%; p=0.002) but similar to that in the SES group (12.0%; p=0.68). In-stent late luminal loss was significantly different across the treatment groups (p<0.001). The rate of late loss observed with the Dual-DES (0.23±0.50mm) was significantly lower that observed with the ZES (0.58±0.55mm; p<0.001), and similar to that of the SES (0.24±0.51mm; p=0.78).

There was also a significant difference in clinical restenosis across the treatment groups (p<0.001). In the Dual-DES group, target lesion revascularization occurred in 29 of 427 (6.8%) lesions treated; this was significantly lower than in the ZES group (57 of 420 [13.6%]; p=0.001) but comparable to that in the SES group (30 of 419 [7.2%]; p=0.83). No differences were observed between stent groups in terms of death, myocardial infarction or stent thrombosis out to one year.

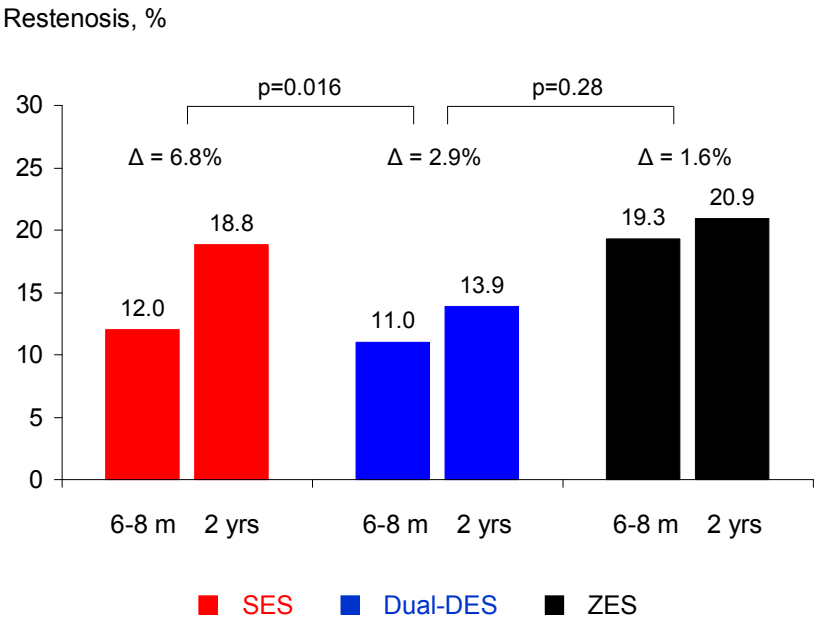
Angiographic and Clinical outcomes at 2 year

Of the 828 patients with first angiographic follow-up, 80 patients underwent a reintervention procedure during the same angiographic session and 15 died prior to

scheduled second angiographic follow-up. Of the remaining 733 eligible patients, 493 patients (67.3%) had re-angiography at 2 years.

Two-year *composite* binary restenosis (based on latest angiographic follow-up available for an individual patient) occurred in 66/350 (18.8%) lesions with SES, 48/345 (13.9%) lesions with Dual-DES and 75/358 (20.9%) lesions with ZES (p=0.045). In terms of pair-wise comparisons only the difference between sirolimus- and probucol-eluting stents and ZES was significant (p=0.014). Incident binary restenosis between 1 and 2 years in Dual-DES group (10 lesions [delta restenosis 2.9%]) was significantly lower than with the Cypher SES (24 lesions [delta restenosis 6.8%]) (p=0.016) but comparable to that observed with the Endeavor ZES (6 lesions [delta restenosis 1.6%]) (p=0.28) (**Figure 13**).

Figure 13. Angiographic restenosis at 6-8 months and 2 years in the ISAR-TEST 2 trial



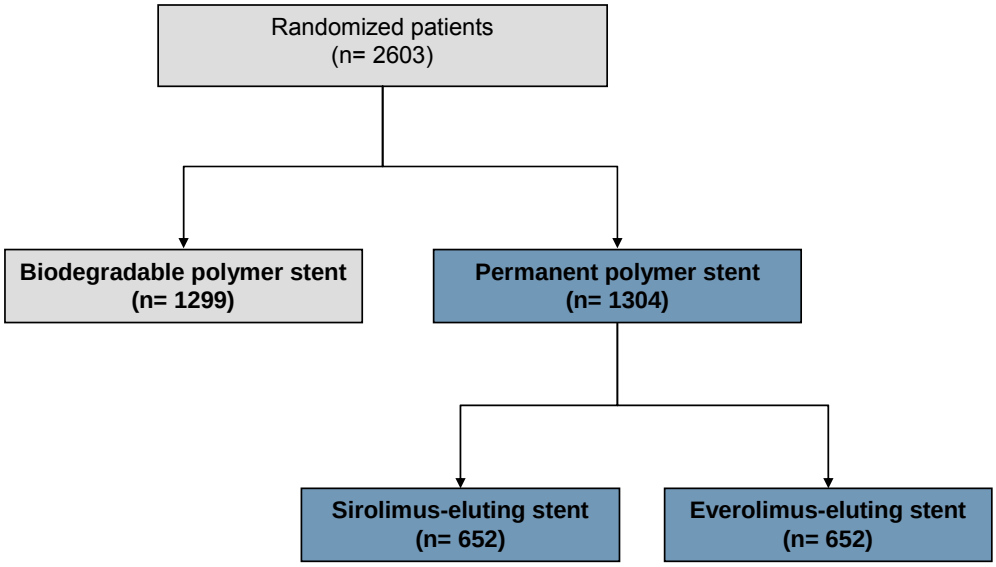
Dual-DES = sirolimus- and probucol-eluting stent; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent

Regarding clinical outcomes, the composite of death or MI at 2 years had occurred in 10.2% with SES stent, 7.8% in Dual-DES and 9.2% with ZES (p=0.61). At 2 years, target lesion revascularization had been performed in 10.7%, 7.7% and 14.3% lesions in SES, Dual-DES and ZES groups respectively (p=0.009). In terms of pair-wise comparisons only the difference between Dual-DES and ZES was significant (p=0.006). Incident TLR between 1 and 2 years in the Dual-DES group (delta TLR 0.9%) was significantly lower than with the Cypher SES (delta TLR 3.6%)(p=0.009) but comparable to that observed with the Endeavor ZES (delta TLR 0.7%)(p=0.72).

4.5 Biodegradable polymer sirolimus-eluting stents are non-inferior to durable polymer sirolimus-eluting stents and everolimus-eluting stents in terms of clinical efficacy at one year

In the large-scale ISAR-TEST 4 study 2603 patients were randomized to receive biodegradable polymer DES (n=1299) or durable polymer DES (n=1304; Cypher, n=652; Xience, n=652) in a trial powered for clinical endpoints. Patient study flow is shown in **Figure 14**. The groups were well matched in terms of baseline patient and lesion characteristics as shown in **Appendix Table 4**. The number of treated lesions was 3372 (biodegradable polymer DES, n=1689; durable polymer DES, n=1683).

Figure 14. Study flow chart for the ISAR-TEST 4 randomized trial

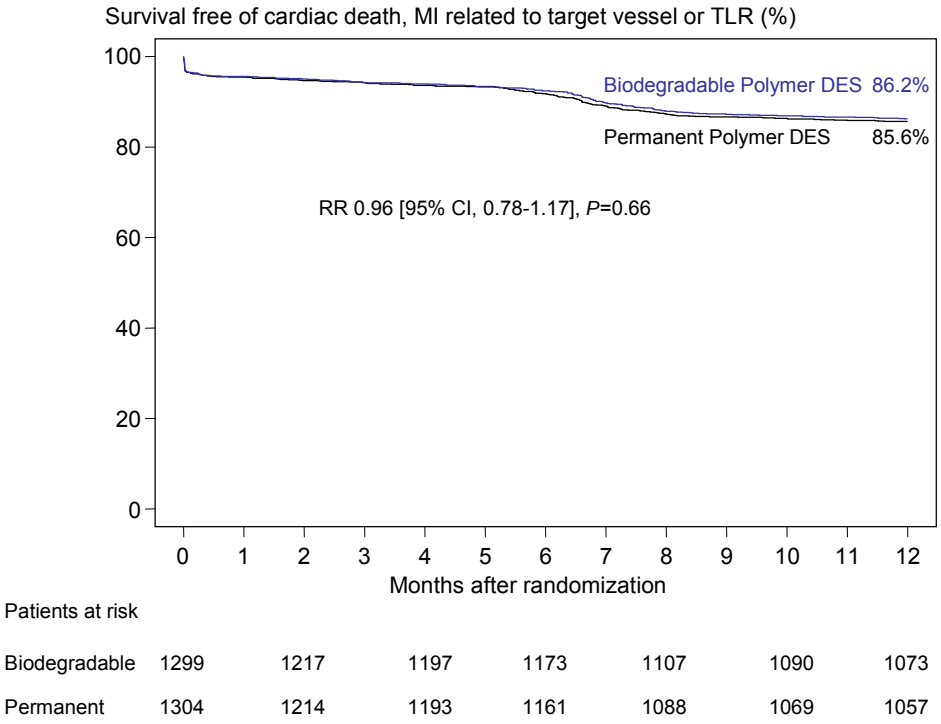


Regarding the primary endpoint of cardiac death/MI related to target vessel/TLR at 1 year, the biodegradable polymer DES was non-inferior to durable polymer DES (13.8% versus 14.4% respectively, $P_{\text{non-inferiority}}$ 0.005; relative risk = 0.96, 95% CI, 0.78-1.17; $P_{\text{superiority}}$=0.66).

Figure 15 shows survival analysis curves for freedom from occurrence of the primary endpoint.

Biodegradable polymer DES in comparison with durable polymer DES showed similar rates of cardiac death or MI related to target vessel (6.3% vs. 6.2% respectively; relative risk = 0.97 [95% CI, 0.74-1.28], *P*=0.94), and TLR (8.8% vs. 9.4% respectively; relative risk = 0.93 [95% CI, 0.72-1.21], *P*=0.58). The rate of ARC definite/probable stent thrombosis was also similar between the biodegradable polymer DES and the durable polymer DES groups (1.0% vs. 1.5% respectively; relative risk = 0.68 [95% CI, 0.34-1.38], *P*=0.29).

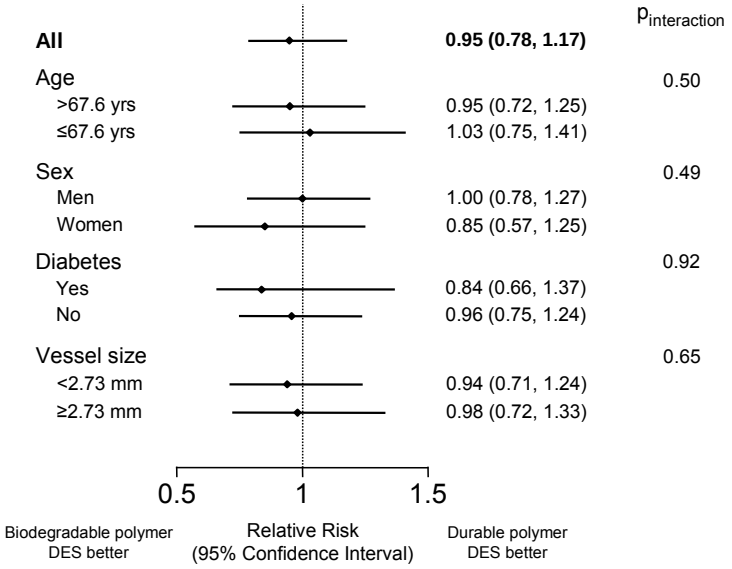
Figure 15. Survival analysis curves for the incidence of the primary composite endpoint at 1 year in patients treated with biodegradable versus durable polymer DES in ISAR-TEST 4



DES = drug-eluitng stent; MI = myocardial infarction; TLR = target lesion revascularization

In addition, comparison of outcomes for biodegradable polymer DES versus durable polymer DES in relation to the primary endpoint was not different according to analysis for each of the pre-specified subgroups of age, sex, diabetes, vessel size (**Figure 16**).

Figure 16. Analysis of outcomes for biodegradable polymer versus durable polymer stents in each of the pre-specified subgroups in ISAR-TEST 4



The demonstration of non-inferiority for biodegradable polymer DES in comparison to durable polymer DES is a prerequisite for the testing of the potential clinical advantage of biodegradable polymer DES over the medium- to long-term.

Biodegradable polymer versus durable polymer DES: Three-year clinical follow-up

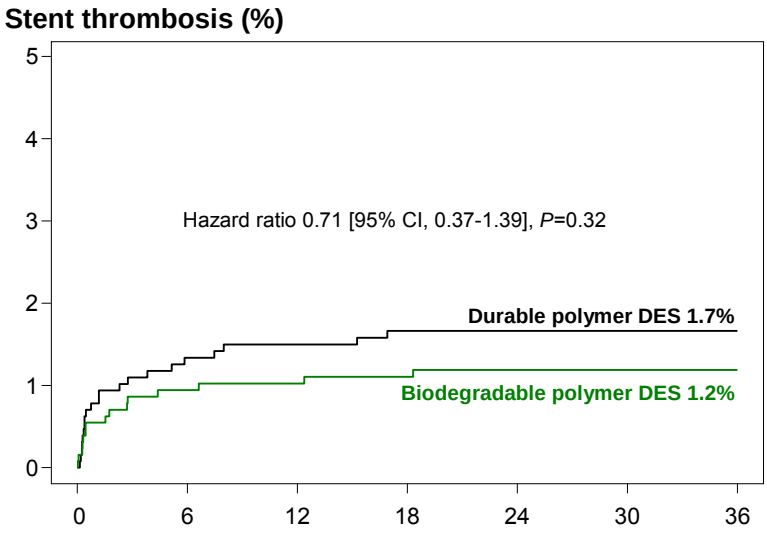
We subsequently performed additional follow-up of this study cohort out to 3 years. At this time point the incidence of the primary composite endpoint of cardiac death/MI related to target vessel/TLR was not significantly different between biodegradable polymer and durable polymer DES (20.1% versus 20.9% respectively, hazard ratio = 0.95, 95% CI, 0.80-1.13; *P*=0.59).

In terms of antirestenotic efficacy, TLR at 3 years was also similar in both groups: 13.9% with biodegradable polymer DES versus 14.2 % with durable polymer DES (hazard ratio = 0.97,

95% CI, 0.78-1.20; *P*=0.79). Incident TLR between years 1 and 3 was comparable in both groups: Δ5.1% with biodegradable polymer DES versus Δ4.8% with durable polymer DES (*P*=0.83).

Regarding safety outcomes, the incidence of adverse events between 1 and 3 years was low across the groups. At 3 years the composite of cardiac death/MI related to the target vessel was 8.5% with biodegradable polymer DES versus 8.9% with durable polymer DES (hazard ratio = 0.96, 95% CI, 0.73-1.25; *P*=0.75). The rate of definite/probable stent thrombosis at 3 years was low in both groups: 1.2% with biodegradable polymer DES versus 1.7% with durable polymer DES (hazard ratio = 0.71, 95% CI, 0.37-1.39; *P*=0.32; **Figure 17**).

Figure 17. Time to event curves for stent thrombosis out to 3 years in patients treated with biodegradable polymer versus durable polymer stents in the ISAR-TEST 4 trial



Patients at risk:							
Durable polymer DES	1304	1232	1209	1183	1154	1115	943
Biodegradable polymer DES	1299	1237	1209	1175	1149	1113	938

4.6 In meta-analysis of individual patient data biodegradable polymer stents improve clinical outcomes compared with durable polymer sirolimus-eluting stents at three years

As detection of differences in rare late adverse events requires large patient populations with extended follow-up, we performed a 3-year follow-up patient-level pooled analysis of the three largest randomized clinical trials comparing biodegradable polymer DES with durable polymer SES for coronary revascularization: the ISAR-TEST 3, ISAR-TEST 4 and LEADERS trials. A total of 4,052 patients were included in the present analysis, of whom 2,358 patients had been randomly assigned to treatment with biodegradable polymer DES – 1,501 patients with sirolimus-eluting and 857 patients with biolimus-eluting stents – and 1,704 patients to treatment with durable polymer SES. Three-year follow-up was available for 3739 (92.3%) patients; in patients with incomplete three year follow-up, median follow-up was 738 days [interquartile range 360-944 days].

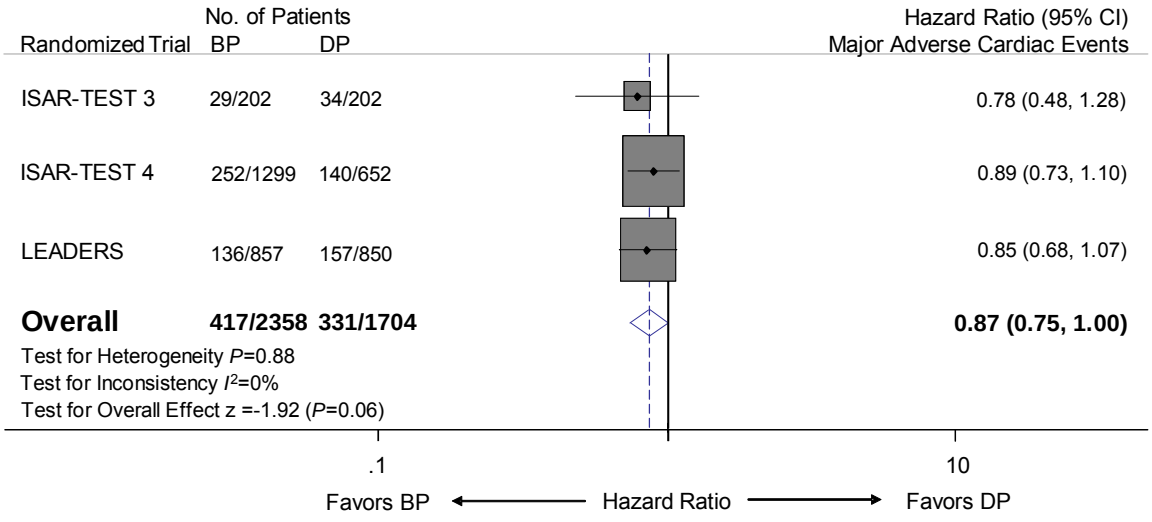
No heterogeneity across the trials was observed in the analyses of the primary and secondary endpoints. Clinical outcomes through three years are summarized in **Table 3**. The use of biodegradable polymer DES was associated with a lower risk of the primary endpoint – the composite of cardiac death, myocardial infarction, or clinically-indicated TLR – compared with durable polymer SES (18.2% vs 20.1%; hazard ratio 0.87, 95% CI 0.75-1.00, *P*=0.06; **Figure 18**) at three years. The difference was driven by numerically lower rates of both TLR (12.0% vs 13.2%; hazard ratio 0.84, 95% CI 0.70-1.01, *P*=0.07) and cardiac death or myocardial infarction (8.6% vs 9.8%; hazard ratio 0.89, 95% CI 0.73-1.11, P=0.32).

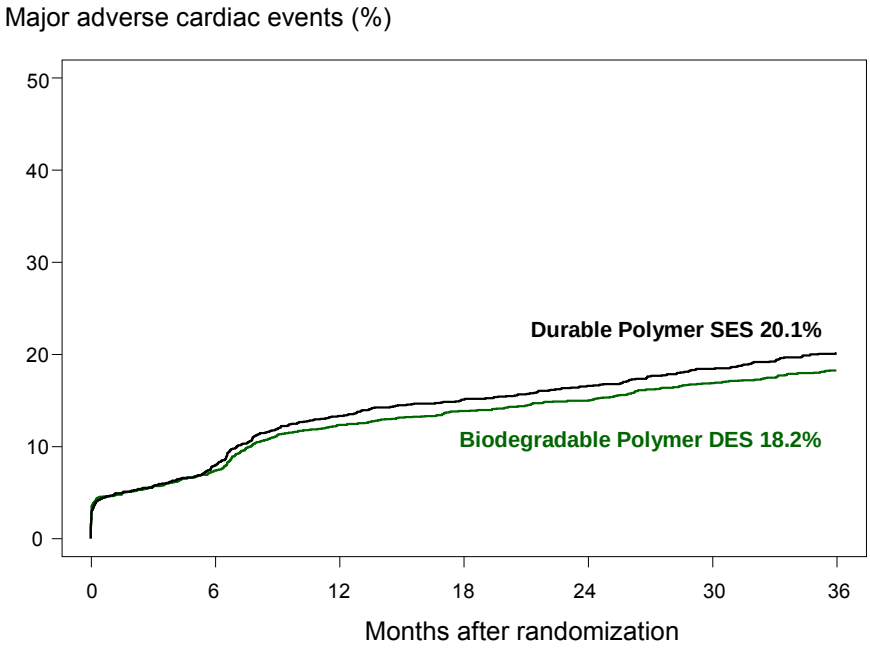
Table 3. Meta-analysis of ISAR-TEST 3, ISAR-TEST 4, LEADERS Trials: Clinical Outcomes Through 3 Years

	Biodegradable polymer DES (N=2358)	Durable polymer SES (N=1704)	Hazard Ratio (95% CI)	P-value
12 months				
Death	93 (4.0)	64 (3.8)	0.97 (0.70-1.34)	0.85
Cardiac death	55 (2.4)	47 (2.8)	0.80 (0.54-1.19)	0.26
Myocardial infarction	106 (4.5)	67 (4.4)	1.18 (0.86-1.61)	0.31
Definite stent thrombosis	26 (1.1)	26 (1.5)	0.80 (0.47-1.38)	0.43
Clinically-indicated TLR	174 (7.6)	145 (8.8)	0.82 (0.66-1.03)	0.08
Cardiac death or myocardial infarction	145 (6.2)	103 (6.1)	1.01 (0.78-1.31)	0.91
Cardiac death, myocardial infarction, or clinically-indicated TLR	287 (12.3)	223 (13.3)	0.89 (0.75-1.06)	0.20
36 months				
Death	180 (7.8)	139 (8.4)	0.87 (0.70-1.09)	0.24
Cardiac death	97 (4.3)	81 (4.9)	0.84 (0.62-1.13)	0.25
Myocardial infarction	124 (5.4)	94 (5.7)	1.00 (0.76-1.31)	0.99
Definite stent thrombosis	29 (1.2)	35 (2.1)	0.68 (0.41-1.11)	0.12
Clinically-indicated TLR	267 (12.0)	213 (13.2)	0.84 (0.70-1.01)	0.07
Cardiac death or myocardial infarction	198 (8.6)	161 (9.8)	0.90 (0.73-1.11)	0.32
Cardiac death, myocardial infarction, or clinically-indicated TLR	417 (18.2)	331 (20.1)	0.87 (0.75-1.00)	0.05

Events are reported as number (percentage from Kaplan-Meier estimate); Hazard ratios and p-values were calculated using random effects meta-analysis; CI = confidence interval; DES = drug-eluting stent; SES = sirolimus-eluting stent; TLR = target lesion revascularization

Figure 18. Major adverse cardiac events with biodegradable polymer versus durable polymer DES out to 3 years





Upper panel: Forest plot with hazard ratios for major cardiac adverse events associated with biodegradable polymer stents versus durable polymer stents for individual trials and the pooled population.Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. CI = confidence interval; BP = biodegradable polymer drug-eluting stent; DP = durable polymer sirolimus-eluting stent

Lower panel: Kaplan-Meier curves are shown for survival for the pooled population in each of the stent groups; DES = drug-eluting stent; SES = sirolimus-eluting stent

While the risk of definite stent thrombosis was numerically lower with biodegradable polymer DES as compared with durable polymer SES at three years (1.3% vs 2.1% hazard ratio 0.68, 95% CI 0.41-1.11), this difference was not statistically significant.

Landmark analyses at one year are shown in **Table 4**. Between years one and three, the risk of cardiac death or myocardial infarction was lower among patients treated with biodegradable polymer DES compared with durable polymer SES (2.6% vs 3.9%, hazard ratio 0.69, 95% CI 0.47-1.01, *P*=0.05) with a trend towards lower rates of definite stent thrombosis (0.1% vs 0.6%, hazard ratio 0.33, 95% CI 0.09-1.14, *P*=0.08).

Table 4. Clinical Outcomes in Landmark Analysis (12-36 months)

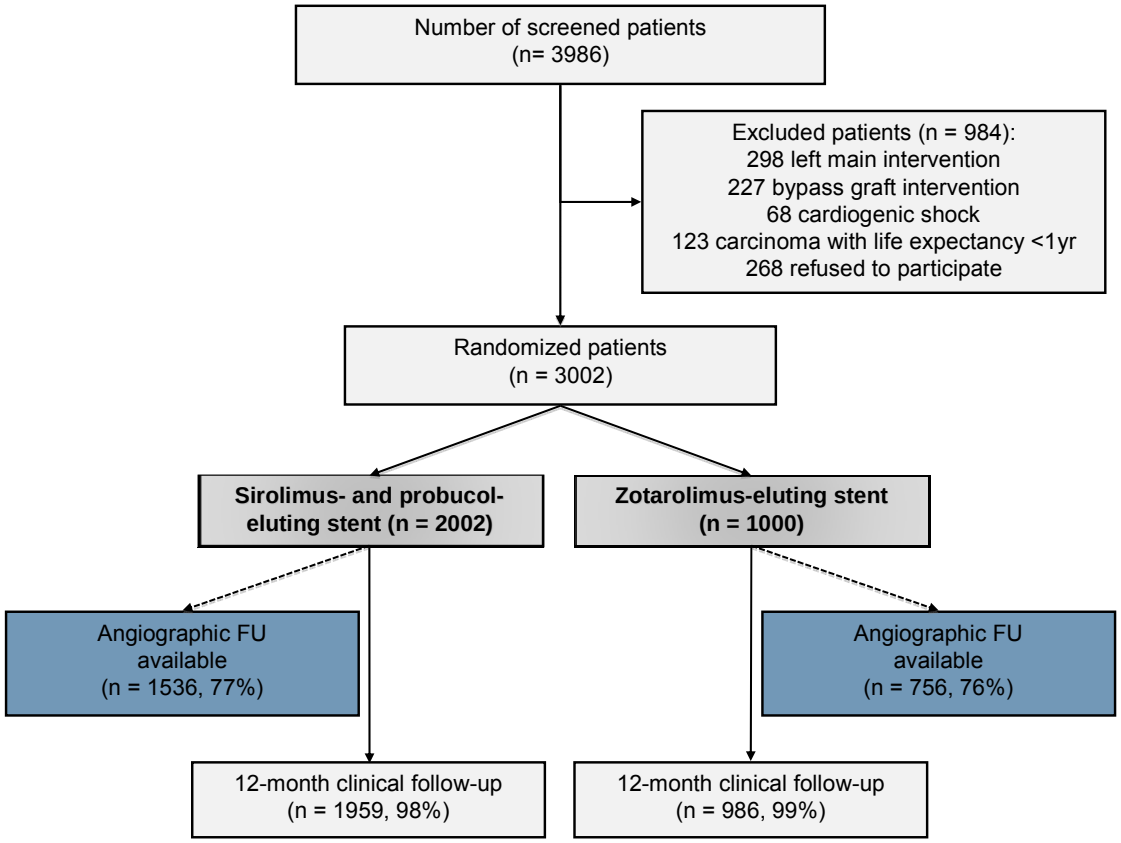
	Biodegradable polymer DES (N=2358)	Durable polymer SES (N=1704)	HR (95% CI)	P-value
12 months – 36 months				
Death	87 (4.0)	75 (4.8)	0.79 (0.58-1.08)	0.14
Cardiac death	42 (2.0)	34 (2.2)	0.89 (0.56-1.41)	0.62
Myocardial infarction	18 (0.9)	27 (1.8)	0.54 (0.29-0.99)	0.05
Clinically-indicated TLR	93 (4.7)	68 (4.9)	0.89 (0.65-1.23)	0.48
Cardiac death or MI	53 (2.6)	58 (3.9)	0.69 (0.47-1.01)	0.05
Cardiac death, MI, or clinically-indicated TLR	130 (6.7)	108 (7.9)	0.82 (0.63-1.06)	0.12

Events are reported as number (percentage from Kaplan-Meier estimate); Hazard ratios and p-values were calculated using random effects meta-analysis; CI = confidence interval; DES = drug-eluting stent; MI = myocardial infarction; TLR = target lesion revascularization; SES = sirolimus-eluting stent

4.7 Dual-drug probucol and sirolimus-eluting stents are non-inferior to new generation composite polymer zotarolimus-eluting stents in terms of clinical efficacy at one year

A total of 3002 patients were enrolled and randomized to receive either polymer-free sirolimus- and probucol-eluting (n=2002) or durable polymer zotarolimus-eluting (n=1000) stents in a trial powered for clinical endpoints (**Figure 19**). As shown in **Appendix Table 5**, the groups were well matched in terms of baseline patient and procedural, with the exception of minimal luminal diameter post procedure (*P*=0.04) and total stent length (*P*=0.01), both of which were marginally higher in the zotarolimus-eluting stent group.

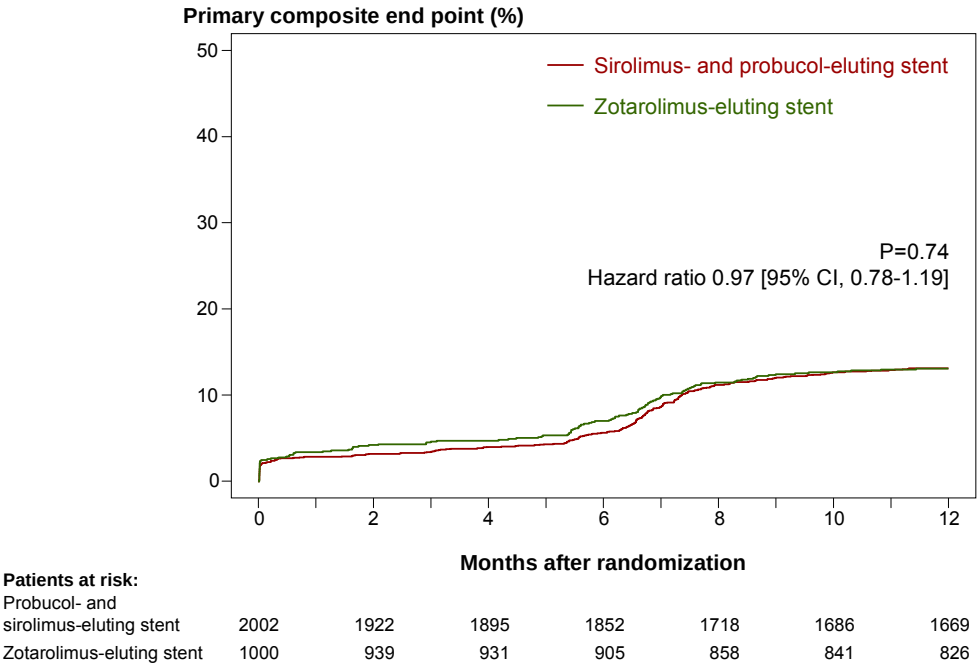
Figure 19. Study flow chart for the ISAR-TEST 5 randomized trial



Clinical outcomes

Regarding the primary endpoint of cardiac death, myocardial infarction related to target vessel and target lesion revascularization, the sirolimus- and probucol-eluting stent was non-inferior to the zotarolimus-eluting stent (13.1% versus 13.5% respectively, $P_{\text{non-inferiority}}$ 0.006; hazard ratio = 0.97, 95% CI, 0.78-1.19; $P_{\text{superiority}}$=0.74; **Figure 20**).

Figure 20. Survival analysis curves for the occurrence of the primary endpoint in ISAR-TEST 5

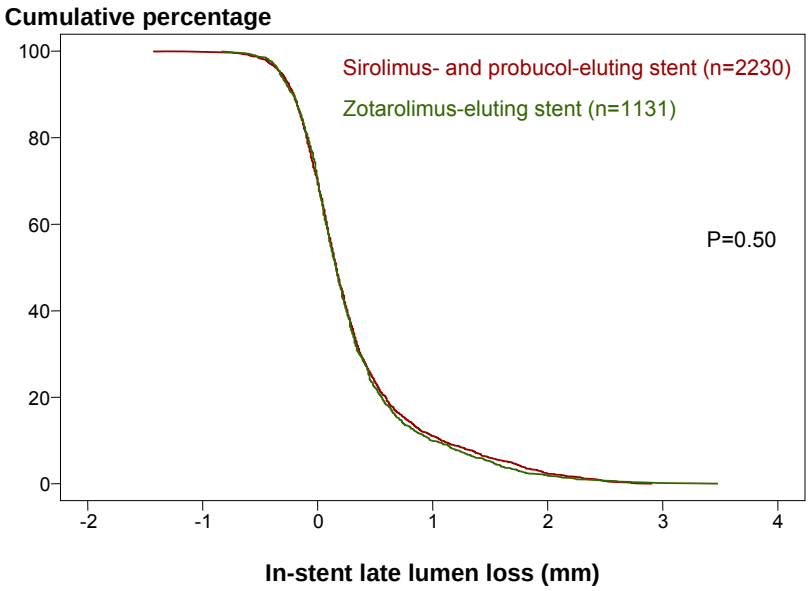


Regarding clinical antirestenotic efficacy the rate of target lesion revascularization was also similar between the sirolimus- and probucol-eluting stent and the zotarolimus-eluting stent (10.3% vs. 10.4% respectively; hazard ratio = 0.99 [95% CI, 0.78-1.26], *P*=0.94). In terms of safety endpoints, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates of all cause mortality (3.6% vs. 4.7% respectively; hazard ratio = 0.75 [95% CI, 0.52-1.08], *P*=0.13), cardiac death or myocardial infarction related to target vessel (4.1% vs. 4.3% respectively; hazard ratio = 0.94 [95% CI,

0.65-1.36], *P*=0.72), and definite/probable stent thrombosis (1.1% vs. 1.2% respectively; hazard ratio = 0.91 [95% CI, 0.45-1.84], *P*=0.80).

Follow-up angiography at 6-8 months was performed in 76.3% of patients with no difference in rates of surveillance between the two treatment groups (*P*=0.53). In terms of angiographic endpoints, there were no significant differences between the sirolimus- and probucol-eluting stent and the zotarolimus-eluting stent in terms of in-segment binary angiographic restenosis (13.3% versus 13.4% respectively**;** *P*=0.95) or in-stent late luminal loss (0.31±0.58 mm versus 0.29±0.56 mm respectively; *P*=0.50; **Figure 21**).

Figure 21. Cumulative distribution curves for late luminal loss



4.8 Durable polymer everolimus-eluting stents are comparable to durable polymer sirolimus-eluting stents in terms of clinical efficacy and safety out to 3 years

In the setting of the ISAR-TEST 4 randomized trial patients allocated to treatment with durable polymer DES were additionally randomized to either everolimus-eluting (Xience,

n=652) or sirolimus-eluting stents (Cypher, n=652) (see **Figure 14**). Baseline patient and lesion characteristics according to randomization to everolimus-eluting or sirolimus-eluting stents were well matched and are shown in **Appendix Table 6.**

Angiographic outcomes at 6-8 months and 2 years

Data from surveillance angiography is shown in **Table 5**. At 6-8 months in patients treated with everolimus-eluting compared to sirolimus-eluting stents there was a trend towards lower rates of both angiographic restenosis (10.1% versus 13.4%; *P*=0.07) and late lumen loss (0.23±0.52 mm versus 0.28±0.57 mm; *P*=0.08).

Table 5. Everolimus-Eluting Versus Sirolimus-Eluting Stents: Angiographic Characteristics of the Lesions at Follow-up

Variable	Everolimus-Eluting Stent	Sirolimus-Eluting Stents	P-Value
Number of investigated lesions	**651**	**n=663**	
6-8-month			
Minimum lumen diameter (in-segment) – mm	2.07±0.58	2.00±0.65	0.06
Percent stenosis (in-segment) – %	29.2±16.1	32.1±17.7	0.002
Late lumen loss (in-stent) – mm	0.23±0.52	0.28±0.57	0.08
Binary restenosis (in-segment) – no (%)	66 (10.1)	89 (13.4)	0.07
2-year composite			
Minimum lumen diameter (in-segment) – mm	2.04±0.63	1.97±0.70	0.05
Percent stenosis (in-segment) – %	30.1±18.3	33.2±19.9	0.004
Late lumen loss (in-stent) – mm	0.32±0.59	0.37±0.64	0.23
Binary restenosis (in-segment) – no (%)	83 (12.7)	112 (16.9)	0.03

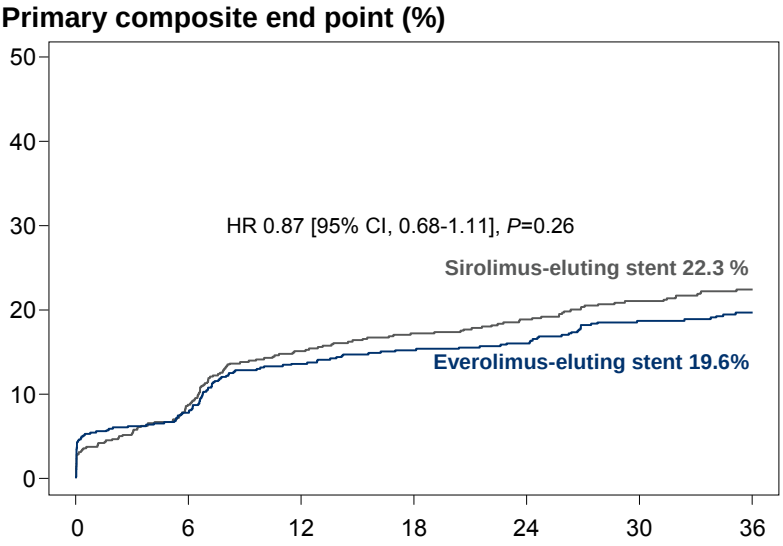
At 2 years both everolimus-eluting versus sirolimus-eluting stents were associated with similar high durability of antirestenotic efficacy; both groups showed small magnitude

additional delayed late loss. Overall there was a lower rate of angiographic restenosis with everolimus-eluting compared to sirolimus-eluting stents (12.7% versus 16.9%; *P*=0.03).

Clinical Outcomes at Three Years

The incidence of the primary composite endpoint of cardiac death/MI related to target vessel/TLR was not significantly different between everolimus-eluting and sirolimus-eluting stents (19.6% versus 22.3% respectively, hazard ratio = 0.87, 95% CI, 0.68-1.11; *P*=0.26; **Figure 22**).

Figure 22. Survival analysis curves for the incidence of the primary composite endpoint at 1 year in patients treated with everolimus- vs. sirolimus-eluting stents in ISAR-TEST 4



In terms of antirestenotic efficacy, there was a numerically lower rate of TLR at 3 years with everolimus-eluting versus sirolimus-eluting stents though this was not statistically significant (12.8 % vs. 15.5 %, hazard ratio = 0.80, 95% CI, 0.59-1.08; *P*=0.15).

Regarding safety endpoint analysis, at 3 years the composite of cardiac death/MI related to the target vessel was 8.7% with everolimus-eluting versus 9.0% with sirolimus-eluting stents (relative risk = 0.97, 95% CI, 0.67-1.41; *P*=0.88). The rate of definite/probable stent thrombosis at 3 years was 1.4% with everolimus-eluting versus 1.9% with sirolimus-eluting stents (relative risk = 0.75, 95% CI, 0.32-1.78; *P*=0.51).

The comparability between the two study devices regarding the primary endpoint was observed across all pre-specified subgroups of age, sex, diabetes status and vessel size.

4.9 In a pre-clinical model of stent implantation, sirolimus, everolimus and zotarolimus have similar effects on endothelial re-growth and neointimal thickening, though higher fibrin deposition is seen with everolimus

We included 36 New Zealand male white rabbits in the study. Two rabbits were euthanized shortly after stent implantation due to arterial dissection. All other stents were widely patent at the time of euthanasia without evidence of migration or aneurysm formation.

Endothelial surface coverage assessed by SEM

At 14 days after stent implantation the luminal surface of the DES constructs showed a similar tissue coverage profile at low power magnification (x10), with the majority of the struts being uncovered. (**Figure 23A; Table 6**). Middle DES segments in particular showed impaired endothelialization (**Figure 23B**). Endothelial cells identified at high power (x200) magnification predominantly showed an elongated morphology in the DES constructs. Bare metal control group showed significantly greater endothelial coverage of the struts with

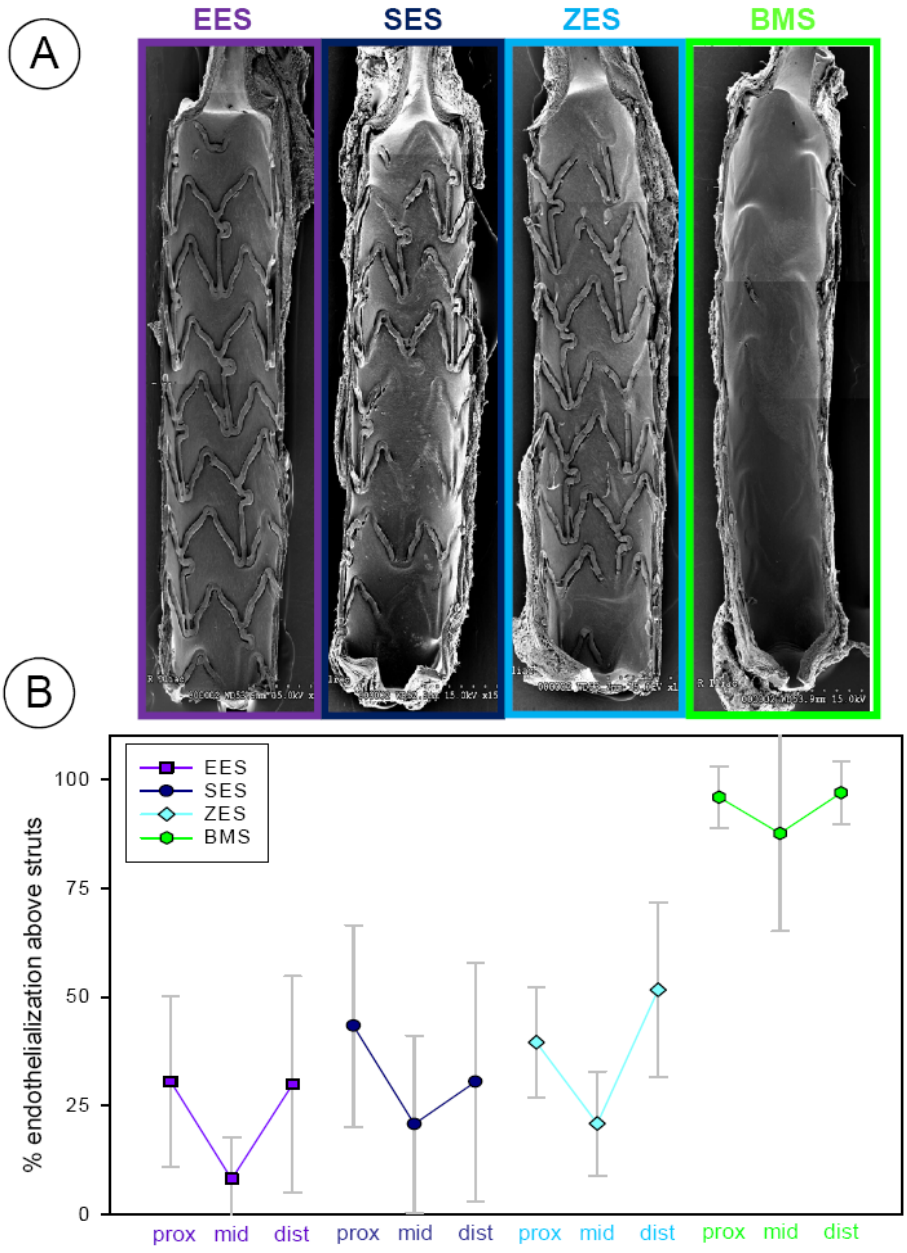
endothelial cells exhibiting cobblestone morphology. Overall there was significantly less re-endothelialization above stent struts in the DES groups as compared to control, while there was no statistical difference among the different DES groups (**Table 6**).

Table 6. Day 14 en face *scanning electron microscopy data*

	EES	**SES**	**ZES**	**BMS**	**p-value**		
Parameter as Mean±SD	n=6	n=6	n=6	n=6	ANOVA	Student's-t test	Tukey HSD
endothelialization above struts (SEM)(%)	21.2±16.5*	29.1±18.1*	32.0±11.1*	93.7±13.2	0.002*	n.s.	n.s.
endothelialization between struts (SEM) (%)	83.6±5.6	88.3±5.7	85.8±4.8	93.1±7.1	n.s.	n.s.	n.s.

BMS = bare metal stent; EES = everolimus-eluting stent; SEM = scanning electron microscopy; SES = sirolimus-eluting stent; ZES = zotarolimus-eluting stent

Figure 23. Quantitative distribution of endothelialized strut area among DES constructs and BMS control at 14 days post stenting



A. Low-power view of the entire luminal surface of each stent visualized per SEM. While the BMS shows almost complete tissue coverage of the strut surface, the DES constructs show uncovered and clearly visible stent struts, with only the very proximal and distal regions being buried under a tissue layer.

B. The distribution of relative endothelialization above struts along the longitudinal axis [proximal (prox), middle (mid) and distal (dist) segments] is shown as a line graph for each stent. The data mirrors the observation described above.

Immunostaining for CD31/PECAM-1 endothelial cell marker

Assessment of endothelialization by CD31/PECAM-1 staining using confocal microscopy demonstrated weak staining (< 30% of the visualized surface) between and above struts with no observable differences among the DES constructs at 14 days. CD31/PECAM-1 expression over the struts was limited to focal areas within the proximal and distal stented regions. In contrast, the control group showed greater CD31/PECAM-1 expression, which was more evenly distributed as compared to the DES groups.

Table 7. Day 28 healing parameters

	EES	**SES**	**ZES**	**BMS**	**p-value**		
Parameter as Mean±SD	n=11	n=11	n=11	n=11	ANOVA	Student's-t test	Tukey HSD
Fibrin score	1.23±0.3*†	0.88±0.6*†	0.97±0.3*	0.30±0.2	0.0004*	† p<0.05	n.s.
Struts with Fibrin – %	63.5±10.1*†‡	48.5±24.9*†	48.3±16.6*‡	13.1±8.2	0.0001*	‡,† p<0.05	n.s.
Inflammation score	0.82±0.3	0.93±0.3	0.88±0.3	0.74±0.3	n.s.	n.s.	n.s.
Giant cells – %	46.8±22.1	46.4±15.1	46.1±15.7	42.2±16.9	n.s.	n.s.	n.s.
Endothelia-lization – %	80.8±8.2*	80.6±14.5*	81.4±13.2*	96.0±3.5	0.009*	n.s.	n.s

* symbol marked values are significantly different from BMS control; ‡,† symbols mark values of significant difference within the DES

Histopathological assessment by light microscopy

At 28 days following stent implantation percent stenosis was significantly different across the groups (p=0.02) with lower values for all three DES (13.7±6.2% for EES, 13.7±5.3% for

SES, 13.7±6.1% for ZES) compared to BMS (20.7±6.3%). Neointimal thickness was similar among the DES and differed significantly from BMS control (**Figure 24**). Fibrin deposition was significantly greater in the DES compared to control. In terms of paired comparison, EES showed a significantly higher fibrin score than SES and differed significantly from SES and ZES in the relative number of struts with fibrin deposition (**Table 7**).

Figure 24. Representative histology sections 28 days after stenting

Movat pentachrome and HE-staining images (x40) of EES, SES, ZES and BMS. Inserts show high power images (x200) of the peri-strut areas. Fibrin deposition is marked by black arrow heads. Asterix symbol marks giant cells.

5. DISCUSSION

5.1 Drug-eluting stents are associated with delayed late erosion of angiographic antirestenotic efficacy; absence of durable polymer attenuates this phenomenon

In this large scale systematic angiographic follow-up study, we found that:

- ongoing reduction in luminal caliber beyond 6-8-months post index stenting procedure is a feature of DES therapy
- there appears to exist a device-specificity in this delayed attenuation of anti-restenotic efficacy in favor of a platform devoid of durable polymer

In those patients with paired 6-8 month and 2 -year angiographic follow up results, overall 2-year late luminal loss was 0.38 ± 0.56 mm. This comprised a *delayed* late lumen loss of 0.12 ± 0.49 mm over and above 0.26 ± 0.42 mm observed at initial re-angiography. These observations are in marked contrast to findings from studies with late angiographic follow-up in the era of bare metal stents, which revealed a peak in bare metal stent restenosis at 6 months in human subjects.(85-88) Thereafter volumes of restenotic plaque tend to remain stable or indeed regress, at least over the medium term (up to 4 years),(88) most likely due to completion of vessel wall healing and scar tissue contraction in association with a degree of positive remodeling, and consequently a stabilisation or even modest increase in luminal calibre.

There are some important implications of these findings:

1. These data support a hypothesis of late "catch-up" restenosis after drug-eluting stent implantation, though sensitive imaging modalities such as surveillance angiography are required to detect this
2. The prolonged longitudinal time course of restenosis comprises further evidence for systematic delayed healing after DES implantation: the most likely reason for this late neointimal overgrowth is persistent inflammation in the stented arterial vessel wall. This delayed late loss ("late luminal creep") is part of the emerging spectrum of clinicopathological conditions consequent on delayed arterial healing (**Figure 25**)

Figure 25. Clinicopathological spectrum of delayed arterial healing

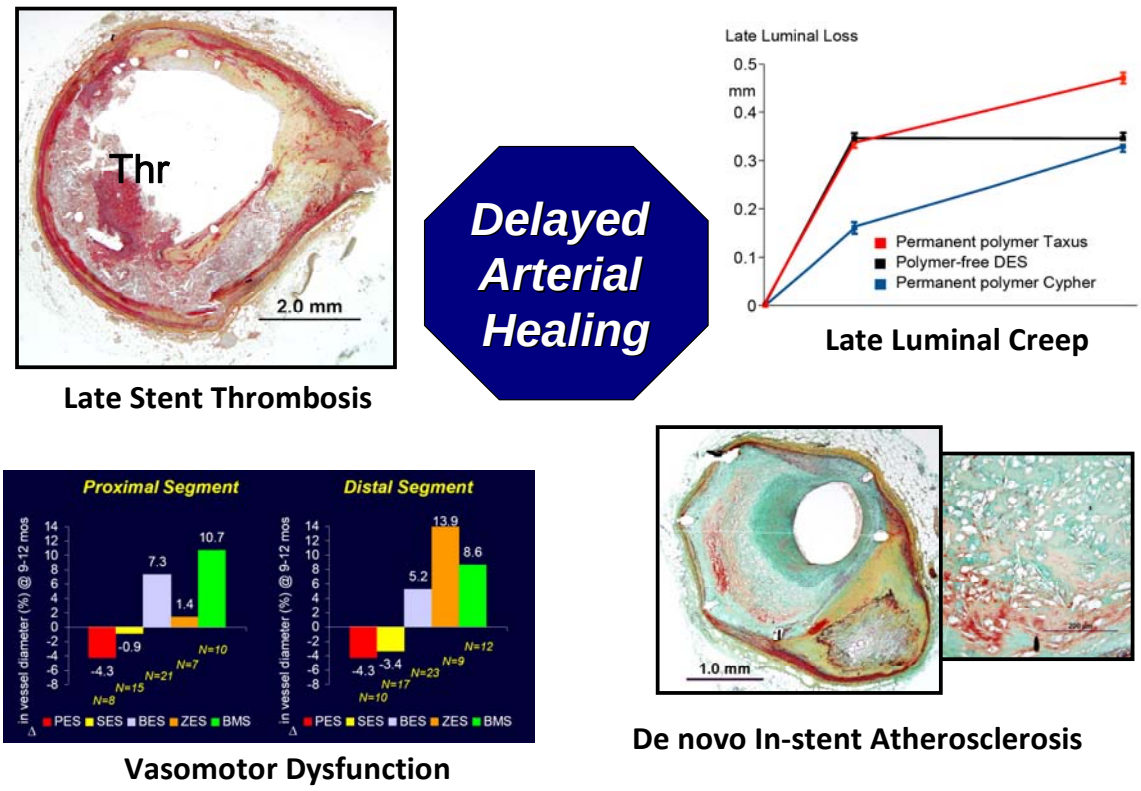


Figure based on data of Nakazawa et al.,(89) Byrne et al.,(52) Hamilos et al.,(44) and Nakazawa et al.(45)

3. The choice of most appropriate time point for protocol mandated angiographic follow-up in trials comparing different stent platforms must be carefully considered. As late loss and binary restenosis appear to be dynamic ongoing processes between 6-8 months and 2 years, caution is necessary in the interpretation of inter-device efficacy comparisons based solely on angiographic follow up in the first two years
4. As delayed late luminal loss in this current analysis was a phenomenon restricted only to durable-polymer based stents – no appreciable interval loss was seen with the polymer-free RES platform – this suggests that the absence of durable polymer from the coronary milieu over the mid- to long-term may translate into an improved late anti-restenotic efficacy, perhaps related to enhanced vessel healing

5.2 Drug-eluting stent therapy has not resulted in elimination of variable propensity to restenosis among subpopulations of stented lesions

This study is the first to report detailed statistical analysis of the metrics of restenosis at angiographic follow-up post DES implantation. We report that:

- the distribution of late loss and percentage diameter stenosis has a complex mixed distribution pattern that may accurately be represented by a bimodal distribution model. Curve deconvolution reveals two distinct theoretical normally-distributed populations for both late loss and percentage diameter stenosis
- For both parameters a composite mixed distribution curve, derived from merging these subpopulations, accurately describes the data
- These distribution patterns appear to hold when analysed according to type of DES implanted, on-label versus off-label usage, and presence or absence of diabetes

Restenosis following coronary intervention was initially perceived as the tail-end of a universal response to vessel healing following injury related to balloon dilatation and stent implantation.(90-92) As with other biological processes a Gaussian distribution of indices of restenosis would therefore be expected. Subsequent investigation however, revealed a complex dispersal pattern of such markers following both balloon angioplasty and Palmaz-Schatz stent implantation – a pattern best represented in both cases by a bimodal distribution model.(93,94) Consequently, it was hypothesized that two different subpopulations exist, comprising subsets of lesions with varying propensity to restenosis. This was in keeping with a series of studies identifying both patient and lesion characteristics portending a higher risk of restenosis at late follow-up following percutaneous coronary intervention.(95-97)

The introduction of DES therapy has resulted in a levelling of the playing field with respect to the effects of certain characteristics on likelihood of restenosis following coronary intervention. For example, the influence of diabetes mellitus on the risk of target lesion revascularization has been largely negated by DES treatment.(98-100) At the same time utilization of restenotic indices as surrogate endpoints in clinical trials of new DES platforms has assumed increasing importance in the performance of comparative efficacy studies permitting the ongoing refinement of DES technology.(101) An insight into their patterns of distribution may contribute to an improved understanding of the role of these indices in inter-DES efficacy studies.

In the current study, we found that late loss can be accurately represented by two populations – a larger population (comprising two-thirds of the patients) with a low mean (0.10 mm), perhaps defined by patient, lesion or procedural characteristics portending a more favourable antirestenotic outcome); and a second smaller group with a higher mean (0.69 mm), representative of a cohort with higher risk features. In terms of percentage diameter stenosis, our findings show two more equally divided populations – the first with a peak at about 20% diameter stenosis comprising ~55% of the patients studied; the second with a peak at around 40% stenosis containing the remainder. These findings are notably similar to the bimodal distributions observed in the bare metal stent era,(94) with the exception of a significant left-shift (from centres at ~ 0.5 mm and 1.5 mm for late loss and ~ 30% and 70% for percentage diameter stenosis). This left-shift is illustrative of the significant neointimal inhibitory effect of DES technology. The disconnect between the weights of the subpopulations in the LLL and %DS analyses may be observed due to a number of reasons, including the influence of vessel size (only a factor in the latter parameter) and the use of *in-segment* (as opposed to *in-stent*) analysis in the measurement of %DS.

These findings have at least two important implications:

1. The confirmation of subpopulations at increased risk is relevant. Perhaps these patients should be chosen to receive DES with the highest antirestenotic efficacy? Furthermore the fact that high-risk subpopulations are found even in traditionally straightforward lesion types (on-label indications) may imply the existence of additional risk factors not yet fully delineated (e.g. drug resistance; polymer hypersensitivity). This may prove a target for further improvements in DES therapy.

2. A bimodal distribution pattern may help to explain why the some time highly significant differences in indices of restenosis observed in comparative efficacy studies between certain DES platforms do not invariably translate into clear differences in target lesion revascularization.(102) The current data suggests that differences between competing DES platforms across *low mean late loss populations* (which comprise the bulk of DES-treated patients) are unlikely to have any impact on rates of restenosis and revascularization, regardless of vessel size or residual stenosis, as even patients at the extreme upper limits of the distribution pattern are unlikely to exceed the threshold late loss (e.g. 1.1-1.4mm)(101) associated with binary restenosis at an individual patient level. On the other hand, it is differences in the smaller number of patients comprising these higher late loss sub-populations which will impact significantly on the comparative number of patients spilling over the theoretical revascularization threshold and declaring themselves as cases of clinical restenosis.

5.3 Biodegradable polymer but not single-drug polymer-free sirolimus-eluting stents are non-inferior to durable polymer sirolimus-eluting stents in terms of angiographic efficacy; this discrepancy is due to differences in drug-release kinetics

The salient outcomes of the ISAR-TEST 3 randomised trial are that:

- the treatment of complex coronary lesions in native vessels with both biodegradable and polymer-free sirolimus-eluting stents is feasible and safe
- in comparison with the durable polymer SES, a biodegradable polymer SES shows equivalent anti-restenotic efficacy in terms of the primary end-point of in-stent late

luminal loss, whereas a polymer-free SES is associated with significantly higher luminal loss at follow-up angiography

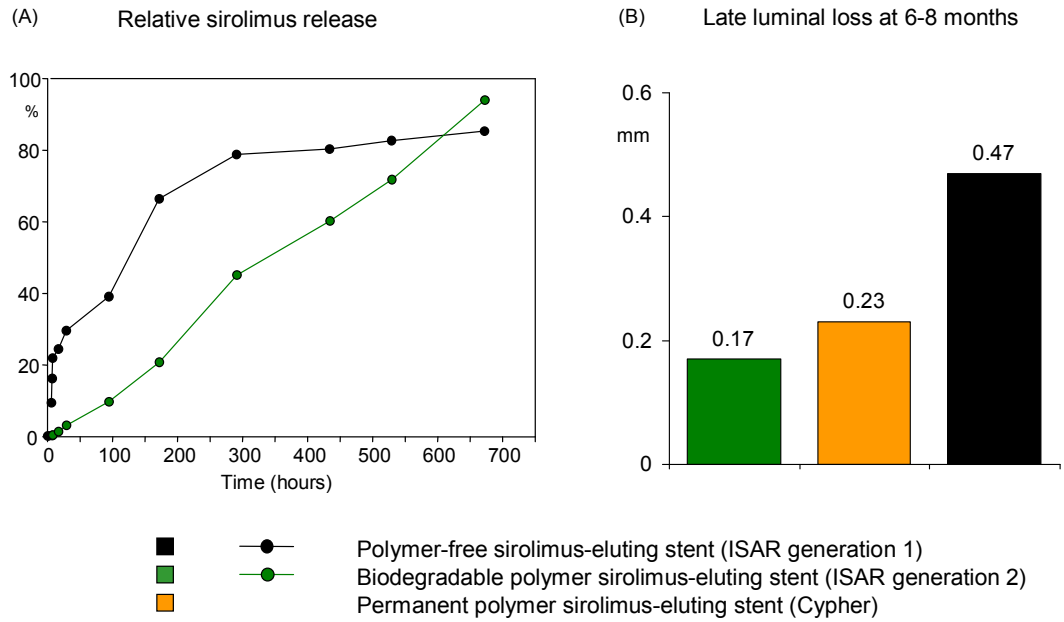
- in terms of clinical outcomes, there was a trend towards an excess of target lesion revascularisation procedures at 12-months with the polymer-free platform as compared with the durable polymer platform. This parallels the differences seen in late luminal loss

In a previous study we showed that employing a sirolimus coating on a microporous polymer-free stent platform, results in superior clinical and angiographic outcomes than BMS implantation and that a dose response exists up to 2% sirolimus.(47,48) Furthermore, when this model was compared against a commercially available paclitaxel-eluting durable polymer stent (Taxus) in a group of patients with similarly complex disease to this current cohort, outcomes were equivalent.(103) In the present study, however, this platform proved inferior in terms of anti-restenotic efficacy, when compared with the durable polymer SES Cypher stent. It seems clear that this significant inferiority is due to the use of a superior comparator (durable polymer sirolimus stent).

The significant improvement in anti-restenotic efficacy derived from the delay in sirolimus release associated with the addition of a novel biodegradable polymer is noteworthy. This study is the first to make use of a novel stent coating comprised of a biodegradable polymer combined with a natural resin. The biodegradable polymer used in this study remains *in situ* for approximately 6 to 9 weeks thereby delaying sirolimus release and enhancing primary stent efficacy. On the other hand, its absence from the vessel wall after this period removes a putative nidus for persistent inflammation and thrombosis.

The comparative antirestenotic efficacy findings in the ISAR-TEST 3 trial highlight the important role of drug-release kinetics in determining the antirestenotic efficacy of a DES device. More specifically the high late lumen loss seen with the polymer-free SES is most likely related to the rapid release of sirolimus in the first 10 days after stenting. On the other hand the retardation of sirolimus release via the incorporation of a biodegradable polymer resulted in a similar antirestenotic efficacy to Cypher (**Figure 26**).

Figure 26. Drug release kinetics and antirestenotic efficacy in the ISAR-TEST-3 study



(A) Drug-elution curve of polymer-free and biodegradable polymer sirolimus-eluting stents. (B) Antirestenotic efficacy of polymer-free and biodegradable polymer sirolimus-eluting stents compared with durable polymer sirolimus-eluting stent

5.4 Dual-drug polymer-free probucol- and sirolimus-eluting stents have an angiographic efficacy comparable to that of durable polymer sirolimus-eluting stents and superior to that of phosphorylcholine polymer zotarolimus-eluting stents

- The ISAR-TEST 2 trial represents the first report of the successful incorporation of a double active-drug system into a DES platform.
- The main finding was that the described novel sirolimus - and probucol-eluting Dual-DES demonstrated an antirestenotic efficacy comparable to that of the durable polymer SES and superior to that of the durable polymer ZES.

The importance of these results lies in the achievement of an excellent performance efficacy – in keeping with that of the high efficacy Cypher SES – utilizing a stent platform which is devoid of polymer. Whether the absence of durable polymer from the coronary milieu over the mid- to long-term translates into significant differences in clinical outcomes will require further investigation. However, the potential safety implications in terms of a reduced incidence of late adverse events and an obviation of the need for prolonged thienopyridine therapy (and its attendant bleeding risks) are inherently attractive.

In recent years, many efforts have been made to develop high efficacy polymer-free DES. However, the control of release kinetics of the eluted drug appears to be the crucial step in determination of the antirestenotic efficacy of DES platforms and in this respect, the elimination or modification of durable polymer coatings has proved difficult to achieve without compromising antirestenotic efficacy.(34) One option to further supplement the anti-restenotic performance of the experimental platform by the incorporation of a second active agent targeted at another element of the restenotic response cascade following stent-induced acute vessel trauma. Previous investigations with the addition of oestrogen or pimecrolimus as second agents have not yielded positive results.(104,105)

In the current study we studied a novel DES platform eluting both sirolimus and probucol and not employing any polymer to control drug-release kinetics. Probucol is a potent lipophilic antioxidant typically orally-administered and has proven effective in inhibiting this restenotic response to balloon injury both in animal models and clinical trials. (106-109) The mechanisms of benefit appear to involve inhibition of LDL oxidation, impairment of endothelial cell adhesion molecule expression and macrophage-derived cytokine production, as well as a direct free-radical scavenging effect.(110-112) To this point however the benefits of probucol in preventing restenosis post-balloon angioplasty have not been reliably replicated in the era of coronary stenting.(109,113-115) In the current study however, the extent of late luminal loss we observed with this novel Dual-DES platform is clearly superior to that observed with previous ISAR stent iterations. There are two possible explanations for this enhanced antirestenotic efficacy:

(i) It is conceivable that a stent-based delivery system resulted in enhanced local drug concentrations and effects. Indeed the relatively narrow therapeutic index of oral probucol – consequent perhaps on the oral administration of a slowly-accumulating liposoluble drug – has restrained its widespread use in clinical practice.(116) This issue is largely overcome by a tissue-specific stent delivery system. In support of a direct probucol-effect on the neointima, more recent evidence from experimental models suggests that probucol significantly improves re-endothelialisation following stent implantation(117) – a feature which is strongly related to lower neointimal overgrowth (as well as attractive from a DES safety viewpoint)

(ii) A second possibility is that the presence of probucol may have retarded the release of sirolimus thereby enhancing its efficacy

5.5 Biodegradable polymer sirolimus-eluting stents are non-inferior to durable polymer sirolimus-eluting stents and everolimus-eluting stents in terms of clinical efficacy at one year

In the ISAR-TEST 4 randomized trial, we found that:

- a biodegradable polymer sirolimus-eluting stent was not inferior to durable polymer DES in a large-scale study powered for a composite clinical safety and efficacy endpoint
- at 1 year there was no signal of difference between biodegradable polymer DES and durable polymer DES regarding individual efficacy (target lesion revascularization) or safety (cardiac death/myocardial infarction or stent thrombosis) endpoint components

The rationale behind the employment of biodegradable polymer coating on a metal stent backbone is intuitively attractive: loading and elution of the lipophilic active-drug is facilitated by a biocompatible polymer, which after completion of its useful function, is slowly degraded to inert organic monomers, thereby eliminating the risk associated with the long-term presence of polymer in the coronary vessel wall. (118) In addition, although fully-biodegradable stent-and-polymer platforms have shown encouraging results,(21) the presence of an underlying metal alloy backbone appears to offer superior mechanical support and enhanced antirestenotic efficacy. The promise inherent in this model has prompted a number of studies with novel biodegradable polymer platforms in the recent

past. (44,51,56,119-121) In particular, the LEADERS investigators have shown non-inferiority against the durable polymer Cypher DES with a biolimus-eluting biodegradable polymer DES in a trial which similar to the current study was powered for clinical endpoints.(51)

The present trial is the largest completed randomized trial involving patients treated with biodegradable polymer DES. As previously reported, at 12 months biodegradable polymer stents were statistically non-inferior to durable polymer stents in relation to the occurrence of hard clinical events. Such a demonstration of non-inferiority at 1-year against leading polymer-based DES is regarded as a prerequisite before a switch to biodegradable polymer coating technology might be advocated. However, the clinical advantage of biodegradable polymer stent systems is expected to first become manifest late after stent implantation, when the absence of polymer residue from the coronary vessel wall might translate into improved vascular healing, a lower rate of late safety events and perhaps also an enhanced durability of antirestenotic efficacy. In this respect the results of the current analysis at the 3-year time point are of particular interest.

We subsequently extended follow-up out to 3 years and found that in terms of clinical events there was no significant difference in outcomes between patients treated with biodegradable polymer or durable polymer DES. Notably the current analysis failed to detect a signal of differential safety between the two treatment groups out to 3 years. In particular the composite of cardiac death and MI related to the target vessel occurred at almost identical rates in both groups between years 1 and 3. Furthermore while a numerically lower rate of definite/probable stent thrombosis was observed with biodegradable polymer DES, this difference was not statistically significant and the confidence intervals surrounding the

risk reduction are broad and overlapping reflecting the overall low incidence of events. These observations are broadly similar to those seen in the 2-year follow-up of the LEADERS trial.(122) However, the failure to detect a safety advantage with biodegradable polymer coatings requires qualification by the observation that the current study was not powered to detect differences in the rates of rarely-occurring safety events. This is an ongoing issue in trials of emerging DES technology. Certainly the overall low rate of stent thrombosis beyond 6 months in DES-treated patients (123,124) makes the design of trials powered to detect benefit with comparator stents largely infeasible. In time however, aggregate long-term data from completed or ongoing biodegradable polymer trials may conceivably shed some further light on this question.

5.6 In meta-analysis of individual patient data biodegradable polymer stents improve clinical outcomes compared with durable polymer sirolimus-eluting stents at three years

The individual patient data pooled analysis from the three largest randomized clinical trials comparing biodegradable polymer DES with durable polymer SES has the following findings:

- Biodegradable polymer DES are associated with a lower risk of clinical events during long-term follow-up through three years compared with durable polymer SES
- The lower risk of clinical events is driven by numerically lower rates of both repeat revascularization and cardiac death or myocardial infarction
- Biodegradable polymer DES show a lower risk of adverse safety events (cardiac death or myocardial infarction) beyond one year after stent implantation. In addition there was a trend towards lower rates of very late definite ST compared with durable polymer SES through 3 years

These findings are important as biodegradable polymer DES have been developed with the aim of reducing the adverse long-term sequelae related to the persistence of durable polymers beyond the period necessary to control drug-release. However while several clinical trials have confirmed the safety and efficacy of biodegradable polymer DES as compared to durable polymer DES, none of the individual trials were sufficiently powered to detect differences in relatively rarely-occurring adverse events such as (very late) stent thrombosis. Furthermore, as the potential clinical benefit of biodegradable polymer DES is hypothesized to emerge only during the late post-intervention phase, once the polymer coating is completely resorbed, long-term follow-up is required to assess the potential clinical advantage of these devices.

The findings of the present analysis lend some support to the hypothesized benefit of biodegradable polymer DES. More specifically, landmark analysis showed that beyond one year the incidence of cardiac death and myocardial infarction was significantly lower in biodegradable polymer DES-treated patients. Furthermore there was a strong trend towards lower rates of definite stent thrombosis between years one and three. The observed risk reduction in terms of late adverse events associated with the use of biodegradable polymer DES represents a major potential benefit as it may overcome the principal limitation of early generation durable polymer SES and resolve the safety concerns that have surrounded these devices. Furthermore it is tempting to hypothesize that biodegradable polymer DES by means of improved biocompatibility not only provide superior endothelial coverage of stent struts but also sustain efficacy by avoiding the sequelae of a chronic inflammatory stimulus.

5.7 Dual-drug probucol and sirolimus-eluting stents are non-inferior to new generation composite polymer zotarolimus-eluting stents in terms of clinical efficacy at one year

The results of the ISAR-TEST 5 trial demonstrate that:

- in the setting of a large-scale randomized control trial with broad inclusion criteria, polymer-free sirolimus- and probucol-eluting dual-drug stents were not inferior to new generation durable polymer-based zotarolimus-eluting stents in terms of the occurrence of clinical and angiographic end points
- both stent platforms were associated with low and comparable rates of stent thrombosis out to 1 year

This is the first demonstration of clinical efficacy of a novel DES which uses a dual-drug combination and no polymer.

The zotarolimus-eluting Resolute stent is based on the same stent backbone as the Endeavor stent and is coated with zotarolimus at a similar concentration. The key difference in comparison with the earlier Endeavor stent is its polymer coating – a mixture composed of three different hydrophilic and hydrophobic polymeric elements. This platform has demonstrated high biocompatibility, superior drug-release kinetics and enhanced antirestenotic efficacy in comparison with its predecessor.(125,126) Recently, it was demonstrated to be non-inferior to the everolimus-eluting Xience stent in a large-scale randomized trial.(68) The current study provides further encouraging data supporting high clinical safety and efficacy outcomes. In particular, in comparison with Resolute All Comers study, the safety composite of cardiac death and myocardial infarction related to the target vessel was similar in both studies, while the rate of definite stent thrombosis was lower in the current study (at 0.4% after 12 months). Furthermore, in patients undergoing

angiographic surveillance, the mean late loss seen in our study of 0.30 mm in the Resolute group is comparable to that of 0.27 mm (Resolute All Comers trial(68)) and 0.30 mm (Resolute US registry(127)) recently reported with this stent in nonselected patients cohorts.

The stent backbone utilized in the polymer-free sirolimus- and probucol-eluting dual-drug stent described in this study is a commercially-available thin-strut stainless steel platform, with surface micropores which facilitate drug-loading and may promote more rapid endothelial overgrowth.(128) The current device iteration is coated with a mixture of sirolimus and probucol. Prior studies confirmed an optimal drug-release profile without recourse to polymer coating. The current report extends the encouraging results seen with this technology to the setting of a large scale clinical trial powered for clinical endpoints. The demonstration of excellent clinical outcomes in a broadly inclusive patient population without recourse to durable polymer coatings may represent an important development in DES technology. In particular the very low rate of definite stent thrombosis at 1 year may be seen as an encouraging safety signal. Nevertheless, the hypothesized benefit of high efficacy polymer-free DES platforms – particularly in relation to delayed adverse events such as very late stent thrombosis – can only be adjudicated upon following long-term follow-up of large numbers of treated patients. Likewise, potential benefits in terms of a requirement for a shorter duration of dual antiplatelet therapy remain to be proven.

5.8 Durable polymer everolimus-eluting stents are comparable to durable polymer sirolimus-eluting stents in terms of clinical efficacy and safety out to 3 years

There is increasing interest in the comparison between the everolimus-eluting (Xience) and sirolimus-eluting (Cypher) stents. Although the everolimus-eluting stent has proven superior

to the first generation paclitaxel-eluting (Taxus) stent in a number of randomized clinical trials (129,130) it is well recognized that this latter stent is a weak comparator.(17) Indeed, benchmark evaluation against the sirolimus-eluting Cypher stent in the setting of a randomized trial is imperative before we can fully define the role of everolimus-eluting stents in contemporary practice.

In this respect the main finding of the ISAR-TEST 4 EES vs. SES analysis was that in a broadly inclusive patient cohort everolimus-eluting stents are associated with similar clinical outcomes in comparison with sirolimus-eluting stents out to 3 years. These observations are in line with a recently-published 2-year comparative analysis of both stents in large vessels (131) and also with the 9-month results from a second randomized trial.(132) Furthermore, while there was no significant difference between the 2 stent platforms in terms of safety, the numerically lower rates of stent thrombosis observed with the everolimus-eluting stent seems to be a consistent feature of clinical trials with this stent. Moreover, the remarkably low incidence of definite stent thrombosis (0.6%) observed with everolimus-eluting stent at 3 years in the present study is in line with rates seen in other studies.(129,130) Finally, in terms of antirestenotic performance, although there was no statistically significant difference in clinical efficacy, a trend was observed in favor of the everolimus-eluting stent in terms of both angiographic and clinical outcomes.

5.9 In a pre-clinical model of stent implantation, sirolimus, everolimus and zotarolimus have similar effects on endothelial re-growth and neointimal thickening, though higher fibrin deposition is seen with everolimus

The current study aimed to investigate comparative biological vascular healing responses following implantation of DES eluting different sirolimus derivatives from otherwise identical bare metal stents with identical polymer (fluorinated copolymer) coatings. The study findings may be summarized as:

(i) DES releasing sirolimus or its derivatives everolimus and zotarolimus from a fluorinated copolymer show a substantial delay in arterial healing, documented by decreased rates of re-endothelialization and increased fibrin deposition compared to uncoated control BMS at two different time points post-stenting (14- and 28-days)

(ii) Among the different DES used, there was no difference with respect to re-endothelialization, either quantitatively or morphologically at 14- and 28-days following stent implantation

(iii) All DES studied provoke a significant reduction in in-stent neointimal growth compared to uncoated control BMS in a healthy rabbit model at 28 days following stent implantation

(iv) Everolimus-eluting stents displayed greater fibrin accumulation in the peristrut regions compared to sirolimus and zotarolimus eluting stents at 28 days

A previous comparator analysis of arterial healing following implantation of the four FDA-approved polymeric DES platforms performed in the rabbit iliac model showed evidence of differential arterial healing patterns – both in terms of structural and functional endothelial recovery after DES implantation across the stents tested.(83) Importantly however the four DES platforms tested differed in terms of each of the major stent platform components –

namely stent backbone, polymer coating and eluted drug. Consequently it remains unclear what the relevant contribution of these individual device components was to the differential healing response observed. In the current study we addressed the contribution of the eluted drug and assessed whether the sirolimus derivative used on these stents has a differential impact on quantitative and morphologic re-endothelialization and other markers of vascular healing. We found that among the different sirolimus derivatives used for drug elution there were no significant differences in quantitative re-endothelialization of the stent strut surface and the endothelial cells exhibited the same morphological characteristics indicative of an immature endothelial cell phenotype. The results demonstrate that the choice of the sirolimus derivative itself, has limited influence on either the pace of structural re-endothelialization or the functionality of the endothelial cells.

Most preclinical studies evaluating the vascular effects of limus-eluting DES were able to document a significant increase in peri-strut fibrin deposition, which was substantially prolonged compared to control BMS. (133) To date, this is the first study that showed a greater induction of fibrin deposition in everolimus-eluting stents compared to DES releasing other contemporary sirolimus analogues. The finding of increased fibrin deposition in the everolimus-eluting group may be a hallmark of increased drug potency.(16) At the same time, re-endothelialization of the strut surface was not impaired compared to other limus-DES highlighting the relevance of a rapid re-establishment of the endothelial layer to protect from coagulation. Taken together, these findings suggest an independent sequence of repair mechanisms including re-endothelialization and fibrin deposition following vascular injury. Further preclinical investigation will be necessary to confirm these observations.

6. SUMMARY OF FINDINGS

- Drug-eluting stent therapy has revolutionized the treatment of coronary artery disease facilitating percutaneous treatment of lesion and patient subsets formerly the preserve of the cardiac surgeon. However, the high antirestenotic efficacy of drug-eluting stents is delivered at the cost of a delay in healing of the stented arterial vessel and at present the focus of technological development is on DES devices which deliver high antirestenotic efficacy with a minimum of vessel wall toxicity. As such drug-eluting stent technology may be regarded most certainly as a *work-in-progress*.
- In our serial angiographic surveillance studies we documented for the first time that in a broadly inclusive patient population, systematic ongoing delayed erosion of luminal caliber is a characteristic feature of drug-eluting stents. This is in marked contrast to the case with bare metal stents where luminal caliber reaches a nadir at 6-8 months and there after remains stable or increases slightly due to completion of vessel healing. The identification of delayed late luminal loss (or "late luminal creep") adds to the evidence concerning a spectrum of clinicopathological conditions associated with delayed arterial healing, which also comprises late stent thrombosis, persistent vasomotor dysfunction and *de novo* in-stent atherosclerosis (see **Figure 25**).
- In a detailed analysis of the metrics of restenosis at angiographic follow-up post DES implantation we were the first to demonstrate that the distribution of late loss and percentage diameter stenosis has a complex mixed distribution pattern that may accurately be represented by a bimodal distribution model. Curve deconvolution

reveals two distinct theoretical normally-distributed populations for both late loss and percentage diameter stenosis. The identification of subpopulations at increased risk is relevant. In an emerging era of personalized medicine perhaps these patients should be chosen to receive DES with the higher antirestenotic efficacy. Furthermore the fact that high-risk subpopulations are found even in traditionally straightforward lesion types (on-label indications) may imply the existence of additional risk factors not yet fully delineated (e.g. drug resistance; polymer hypersensitivity). This may prove a target for further improvements in DES therapy.

- The comparative antirestenotic efficacy findings in the ISAR-TEST 3 trial highlight the important role of drug-release kinetics in determining the antirestenotic efficacy of a DES device. In a trial comparing three stents using the same drug (i.e. sirolimus) but different polymer coatings (i.e. no polymer, biodegradable polymer, durable polymer), we saw that antirestenotic efficacy was closely tied to the drug release kinetic that could be achieved by the different stent coatings. More specifically the high late lumen loss seen with the polymer-free SES is most likely related to the rapid release of sirolimus in the first 10 days after stenting. On the other hand the retardation of sirolimus release via the incorporation of a biodegradable polymer resulted in a similar antirestenotic efficacy to the durable polymer Cypher (see **Figure 26**).
- In the ISAR-TEST 2 trial we showed for the first time that it was possible to achieve excellent antirestenotic performance efficacy – in keeping with that of the high efficacy Cypher SES – utilizing a stent platform which is completely devoid of polymer. In order to compensate for the erosion in efficacy seen in polymer-free stent systems (as illustrated in ISAR-TEST 3 for example) we added a second drug, the

lipophilic antioxidant probucol, which delays the release profile of sirolimus and also targets neointimal hyperplasia via additional mechanisms including the inhibition of oxidation.

- Whether the absence of durable polymer from the coronary milieu over the mid- to long-term translates into significant differences in clinical outcomes requires study of large patient numbers in trials powered for hard clinical endpoints as well as extended clinical follow-up. This was the goal of the large scale ISAR-TEST 4 and ISAR-TEST 5 trials.
- The primary aim of the ISAR-TEST 4 trial – namely to demonstrated non-inferior clinical outcomes at 12 months with biodegradable polymer versus durable polymer DES – was met with a high statistical significance. Such a proof of non-inferiority at one year against gold standard durable polymer DES is pre-requisite before we can address the issue of whether the putative long-term advantages of biodegradable polymer DES can be delineated with longer term clinical surveillance.
- One of the key challenges facing investigators of novel DES devices is the demonstration of reduction in rarely-occurring late adverse events. In this respect, the three year follow-up of ISAR-TEST 4 was unable to show a statistically significant reduction in late adverse events. However, when we combined the data from the three largest trials comparing biodegradable polymer DES against durable polymer Cypher stents, using meta-analysis of individual patient data, we were able to show for the first time a reduction in late safety events with this novel stent technology. This may have important implications concerning the duration of dual antiplatelet therapy after stenting.

- In the ISAR-TEST 5 trial we could demonstrate for the first time a high clinical efficacy of a novel DES which uses a dual-drug combination and no polymer. In addition, the study confirmed the excellent results seen with the new generation durable polymer zotarolimus-eluting Resolute stent.
- Comparative efficacy data with the second generation durable polymer everolimus-eluting Xience stent and the first generation benchmark sirolimus-eluting stent have been lacking. In a substudy of the ISAR-TEST 4 trial we were the first to show comparative efficacy of these two platforms in a broadly inclusive patient cohort.
- Finally in a preclinical investigation using stents with identical backbones, polymer coating and drug dosages, we demonstrated that patterns of vascular healing may be different when only the eluted drug is varied. This was the first study that showed a greater induction of fibrin deposition in everolimus-eluting stents compared to DES releasing other sirolimus analogues. The finding of increased fibrin deposition in the everolimus-eluting group may be a hallmark of increased drug potency. At the same time, re-endothelialization of the strut surface was not differentially impaired. Taken together, these findings suggest an independent sequence of repair mechanisms including re-endothelialization and fibrin deposition following vascular injury. Further preclinical investigation will be necessary to confirm these observations.

7. SOURCES OF FUNDING

The ISAR stent project series of trials were investigator-initiated industry-independent studies. There was no remuneration for investigators or subjects. The microporous metal stent platform utilized in the ISAR stent project is produced by Translumina, Hechingen, Germany who had no input into the design, conduct or funding of the trials. The biodegradable polymer and polymer-free dual-drug sirolimus- and probucol-eluting coatings are not commercially available and none of the investigators receive remuneration of any sort related to the stent platform. Funding for the studies included in this thesis was provided in part by the Bavarian Research Foundation (BFS-ISAR Aktenzeichen AZ: 504/02 and BFS-DES Aktenzeichen AZ: 668/05) and by the European Union FP7 (PRESTIGE 260309). The LEADERS trial, data from which was included in the pooled analysis of biodegradable polymer versus durable polymer drug-eluting stents, was funded by Biosensors Europe SA, Switzerland.

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9. ACKNOWLEDGEMENTS

The idea to pursue a research fellowship in Munich came from reading the output of the ISAR group in numerous high quality publications particularly over the course of the first half of the last decade. What stood out was a no nonsense approach to clinical trials. The first step was always the identification of the relevant clinical question in a timely manner. There followed the capacity to rapidly formulate this question into a trial protocol, which was quickly and rigorously executed, analyzed and reported. Consequently, while many were still searching for the question, the ISAR group was already formulating the answer, or so it seemed to me at least.

That this vague idea became a reality is largely due to the interest and support of Adnan Kastrati. It is doubtful if many busy researchers would have answered a random e-mail enquiry composed in schoolboy German wondering about the possibility of employment at some point in the foreseeable future. However starting with a reply to come and talk about it in Munich, the ever good humored encouragement, guidance and support I have received has been unwavering. It is a privilege to have learned so much about interventional cardiology, clinical trial design, statistical analysis and scientific writing. If I have taken even a modicum of his insight into discerning what the important issues of clinical equipoise are it will be of even great value. I am also deeply indebted to Albert Schömig as chief and clinical leader for providing the professional environment and infrastructure in which I could learn so much, and to Julinda Mehilli for her support and friendship as well as for first proposing the idea of enrollment in the PhD programme at the Technische Universität. Particular

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10. CURRICULUM VITAE

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11. LIST OF PUBLICATIONS

Book Chapters

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12. SUPPLEMENTARY APPENDIX

Table A1. DES serial angiographic surveillance registry: Characteristics of Patients and Lesions at Baseline

	Durable polymer SES	Polymer-free SES	Durable polymer PES	p-value
Patients	909	494	627	
Age – yrs	65.7 ± 10.0	66.7 ± 9.7	65.9 ± 10.0	0.23
Male	718 (79.0)	391 (79.1)	500 (79.7)	0.94
Diabetes	269 (29.6)	136 (27.5)	176 (28.1)	0.67
Hypertension	595 (65.5)	323 (65.4)	426 (67.9)	0.54
Current smokers	124 (13.6)	68 (13.8)	84 (13.4)	0.98
Hypercholesterolaemia	688 (75.7)	361 (73.1)	478 (76.2)	0.43
Multivessel disease	769 (84.6)	408 (82.6)	528 (84.2)	0.61
Previous myocardial infarction	358 (39.4)	195 (39.5)	254 (40.5)	0.90
Prior bypass surgery	88 (9.7)	45 (9.1)	65 (10.4)	0.78
Lesions	*1036*	*565*	*740*	
Ostial	197 (19.0)	96 (17.0)	144 (19.5)	0.49
Bifurcational	270 (26.1)	148 (26.2)	207 (28.0)	0.64
Chronic occlusion	64 (6.2)	44 (7.8)	33 (4.5)	0.04
Complex lesion (B2/C)	775 (74.8)	415 (73.5)	545 (73.6)	0.79
Lesion length – mm	14.1 ± 7.8	13.6 ± 6.5	13.4 ± 7.7	0.06
Reference vessel – mm	2.70 ± 0.51	2.70 ± 0.49	2.71 ± 0.51	0.84
MLD, pre – mm	1.07 ± 0.48	1.10 ± 0.46	1.09 ± 0.48	0.15
Stenosis, pre – mm	60.6 ± 15.2	59.6 ± 14.4	59.7 ± 15.9	0.13
Max. balloon pressure – atm	14.7 ± 3.0	14.5 ± 3.0	14.8 ± 2.9	0.36
MLD, post – %	2.57 ± 0.45	2.56 ± 0.44	2.61 ± 0.46	0.13
Stenosis, post – %	8.7 ± 6.3	8.3 ± 5.8	8.4 ± 6.56	0.06

Table A2. ISAR-TEST 3 randomized trial: Characteristics of Patients and Lesions at Baseline

	Biodegradable polymer SES	Durable polymer SES	Polymer-Free SES
Patients	*202*	*202*	*201*
Age – yrs	66.5 ± 11.6	65.0 ± 10.7	66.8 ± 9.70
Male	158 (78.2)	165 (81.7)	157 (78.1)
Diabetes	58 (28.7)	53 (26.4)	55 (27.2)
Hypertension	145 (71.8)	130 (64.4)	135 (67.2)
Current smokers	33 (16.3)	30 (14.9)	36 (17.8)
Hypercholesterolaemia	144 (71.3)	129 (63.9)	143 (71.1)
Multivessel disease	167 (82.7)	175 (86.6)	158 (78.6)
Previous myocardial infarction	65 (32.2)	68 (33.7)	66 (32.9)
Prior bypass surgery	21 (10.4)	21 (10.4)	27 (13.4)
Ejection fraction – %	53.8 ± 11.6	54.9 ± 11.0	53.5 ± 13.6
Lesions	*239*	*241*	*231*
Bifurcational	55 (23.0)	73 (30.2)	58 (25.1)
Chronic occlusion	18 (7.5)	22 (9.1)	15 (6.5)
Complex lesion (type B2/C)	170 (71.1)	186 (77.2)	172 (74.2)
Lesion length – mm	13.9 ± 7.2	14.6 ± 7.0	14.3 ± 5.1
Reference vessel – mm	2.74 ± 0.52	2.75 ± 0.51	2.75 ± 0.45
MLD, pre – mm	1.06 ± 0.42	1.13 ± 0.49	1.13 ± 0.39
Stenosis, pre – %	61.5 ± 12.8	59.3 ± 14.5	58.8 ± 12.1
Balloon/vessel ratio	1.10 ± 0.08	1.11 ± 0.10	1.11 ± 0.10
MLD, post – mm	2.51 ± 0.48	2.56 ± 0.46	2.59 ± 0.42
Stenosis, post – %	10.9 ± 5.3	10.2 ± 5.9	11.0 ± 5.4

Table A3. ISAR-TEST 2 randomized trial: Characteristics of Patients and Lesions at Baseline

	SES	Dual-DES	ZES	P-Value
Patients	*335*	*333*	*339*	
Female – no. (%)	76 (22.7)	76 (22.8)	83 (24.5)	0.83
Age – years	66.6 ± 11.1	67.0 ± 11.2	67.2 ± 10.9	0.65
Diabetes – no. (%)	91 (27.2)	96 (28.8)	89 (26.3)	0.75
Hypertension – no. (%)	214 (63.9)	229 (64.9)	229 (67.6)	0.58
Current smoker – no. (%)	58 (17.3)	66 (19.8)	61 (18.0)	0.69
Hyperlipidaemia – no. (%)	231 (69.0)	209 (62.8)	222 (65.5)	0.24
Prior myocardial infarction – no. (%)	100 (29.9)	84 (25.2)	88 (26.0)	0.35
Prior coronary bypass graft – no. (%)	27 (8.1)	33 (9.9)	29 (8.6)	0.68
Multivessel disease – no. (%)	287 (85.7)	269 (80.8)	280 (82.6)	0.23
Ejection fraction – %*	52.4 ± 12.0	53.0 ± 12.0	54.5 ± 10.4	0.19
Multilesion intervention – no. (%)	1.25 ± 0.53	1.28 ± 0.51	1.24 ± 0.45	0.42
Lesions	*419*	*427*	*420*	
Ostial – no. (%)	56 (13.4)	48 (11.2)	55 (13.1)	0.60
Bifurcational – no. (%)	86 (20.5)	78 (18.3)	94 (22.4)	0.33
Chronic occlusion – no. (%)	17 (4.1)	24 (5.6)	16 (3.8)	0.39
Complex (B2/C) lesions – no. (%)	306 (73.0)	297 (69.6)	315 (75.0)	0.20
Lesion length – mm	14.8 ± 8.3	14.0 ± 8.2	14.7 ± 8.0	0.17
Vessel size – mm	2.75 ± 0.46	2.69 ± 0.52	2.71 ± 0.49	0.10
Minimal luminal diameter post procedure, in-stent – mm	2.55 ± 0.43	2.49 ± 0.48	2.51 ± 0.47	0.07
Diameter stenosis post procedure, in-segment – %	23.5 ± 11.0	23.2 ± 11.8	24.2 ± 11.7	0.18

Table A4. Biodegradable Versus Durable Polymer Stents in the ISAR-TEST 4 trial:

Characteristics of Patients and Lesions at Baseline

	Biodegradable Polymer DES	Durable Polymer DES	P-Value
Patients	*1299*	*1304*	
Age – yr	66.7±10.7	66.8±11.1	0.79
Male sex – no. (%)	978 (75.3)	1002 (76.8)	0.35
Diabetes mellitus– no. (%)	376 (29.0)	377 (28.9)	0.99
Arterial hypertension – no. (%)	897 (69.1)	881 (67.6)	0.41
Hyperlipidemia – no. (%)	868 (66.8)	846 (64.9)	0.30
Current smoker – no. (%)	202 (15.6)	215 (16.5)	0.52
Prior myocardial infarction – no. (%)	372 (28.6)	373 (28.6)	0.99
Prior coronary bypass grafting – no. (%)	129 (9.9)	129 (9.9)	0.97
Clinical presentation – no. (%)			0.24
Acute myocardial infarction	167 (12.9)	140 (10.7)	
Unstable angina	374 (28.8)	379 (29.1)	
Stable angina	758 (58.4)	785 (60.2)	
Ejection fraction – %*	53.1±11.9	53.6±11.3	0.34
Multivessel disease – no. (%)	1124 (86.5)	1126 (86.3)	0.89
Lesions	*1683*	*1689*	
Chronic total occlusion – no (%)	86 (5.1)	89 (5.3)	0.80
Bifurcation – no (%)	421 (25.0)	383 (22.7)	0.11
Ostial – no (%)	267 (15.9)	304 (18.0)	0.10
Complex morphology (B2/C) – no (%)	1225 (72.8)	1218 (72.1)	0.66
Lesion length – mm	14.8±8.6	15.0±8.8	0.53
Vessel size – mm	2.79±0.47	2.80±0.52	0.67
Minimum lumen diameter – mm			
MLD, pre procedure – mm	0.98±0.50	0.98±0.51	0.97
MLD, post procedure – mm	2.58±0.44	2.59±0.50	0.40
Post procedure stenosis, in-segment – %	23.2±11.7	23.5±11.1	0.56

Table A5. *Polymer-Free Sirolimus- and Probucol-Eluting Versus Durable Polymer Zotarolimus-Eluting Stents in the ISAR-TEST 5 trial: Characteristics of Patients and Lesions at Baseline*

	Sirolimus- and probucol DES	Zotarolimus-eluting stents	P-Value
Patients	*2002*	*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
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
Multivessel 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	*2912*	*1479*	
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
Minimal lumen diameter, post (mm)	2.54±0.48	2.58±0.49	0.04
% Diameter stenosis, post	12.1±7.4	11.7±8.2	0.23

Table A6. Everolimus-Eluting Versus Sirolimus-Eluting Stents in the ISAR-TEST 4 trial:

Characteristics of Patients and Lesions at Baseline

	Everolimus-eluting stents	Sirolimus-eluting stents	P-Value
Patients	*652*	*652*	
Age – yr	66.7±10.3	66.8±11.1	0.93
Male sex – no. (%)	507 (77.8)	495 (75.9)	0.43
Diabetes mellitus– no. (%)	184 (28.2)	193 (29.6)	0.58
Arterial hypertension – no. (%)	442 (67.8)	439 (67.3)	0.86
Hyperlipidemia – no. (%)	423 (64.9)	423 (64.6)	>0.99
Current smoker – no. (%)	101 (15.5)	114 (17.5)	0.33
Prior myocardial infarction – no. (%)	191 (29.3)	182 (27.9)	0.58
Prior coronary artery bypass grafting – no. (%)	69 (10.6)	60 (9.2)	0.40
Clinical presentation – no. (%)			0.49
Acute myocardial infarction	70 (10.7)	70 (10.7)	
Unstable angina	199 (30.6)	180 (27.6)	
Stable angina	383 (58.7)	402 (61.7)	
Ejection fraction – %*	53.4±11.7	53.8±12.1	0.64
Multivessel disease – no. (%)	557 (85.4)	569 (87.3)	0.33
Lesions	*850*	*839*	
Chronic total occlusion – no (%)	36 (4.2)	50 (6.0)	0.11
Bifurcation – no (%)	185 (21.8)	198 (23.6)	0.37
Ostial – no (%)	158 (18.6)	146 (17.4)	0.53
Complex morphology (B2/C) – no (%)	604 (71.1)	614 (73.2)	0.33
Lesion length – mm	15.2±8.9	14.8±8.2	0.37
Vessel size – mm	2.80±0.45	2.80±0.48	0.82
MLD, pre-procedure – mm	0.99±0.49	0.97±0.51	0.48
MLD, post procedure – mm	2.59±0.45	2.59±0.44	0.94
Post procedure stenosis, in-segment – %	23.2±11.7	23.5±11.1	0.56