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Determinants of Clinical Outcomes Following Drug-Eluting Stent Implantation: Temporal Course, Mechanisms and Optical Characteristics of Stent Failure

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Parts of the work included in this dissertation have been previously published in the following publications:

1. 04.2022 **Ten-year patterns of stent thrombosis after percutaneous coronary intervention with new- versus early-generation drug-eluting stents: insights from the DECADE cooperation**

Coughlan JJ, Maeng M, Raber L, Brugaletta S, **Aytekin A**, Jensen LO, Bar S, Ortega-Paz L, Laugwitz KL, Madsen M, Heg D, Sabaté M, Kufner S, Warnakula Olesen KK, Kastrati A, Windecker S, Cassese S. **Rev Esp Cardiol (Engl Ed).** 2022 Apr 15. https://doi.org/10.1016/j.rec.2022.02.003.

2. 02.2023 **Sex Differences in 10-Year Outcomes After Percutaneous Coronary Intervention With Drug-Eluting Stents: Insights From the DECADE Cooperation**

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3. 02.2022 **Ten-Year Clinical Outcomes in Patients With Acute Coronary Syndrome Treated With Biodegradable, Permanent-Polymer or Polymer-Free Drug-Eluting Stents**

Coughlan JJ*, **Aytekin A***, Lenz T, Koch T, Wiebe J, Cassese S, Joner M, Koppara T, Xhepa E, Kessler T, Rheude T, Ibrahim T, Laugwitz KL, Schunkert H, Kastrati A, Kufner S. **Clin Res Cardiol.** 2022 Feb 11. Doi: 10.1007/s00392-022-01986-4. **J Invasive Cardiol 2022 Mar 25;** JIC20220325-1.

4. 09.2021 **Long-term clinical outcomes after drug eluting stent implantation with and without stent overlap**

Coughlan JJ, **Aytekin A**, Koch T, Wiebe J, Lenz T, Cassese S, Joner M, Koppara T, Xhepa E, Ibrahim T, Fusaro M, Laugwitz KL, Schunkert H, Kastrati A, Kufner S. **Catheter Cardiovasc Interv.** 2021 Sep 6. Doi: 10.1002/ccd.29944.

5. 02.2022 **Target vessel and non-target vessel related events at 10 years post percutaneous coronary intervention**

Coughlan JJ, **Aytekin A**, Xhepa E, Cassese S, Joner M, Koch T, Wiebe J, Lenz T, Rheude T, Pellegrini C, Gewalt S, Ibrahim T, Laugwitz KL, Schunkert H, Kastrati A, Kufner S. **Clin Res Cardiol.** 2022 Feb 11. Doi: 10.1007/s00392-022-01986-4.

6. 02.2023 **Derivation and validation of the ISAR score to predict the risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent restenosis**

Coughlan JJ, **Aytekin A**, Lahu S, Scalamogna M, Wiebe J, Pinieck S, Kufner S, Xhepa E, Joner M, Kuna C, Voll F, Laugwitz KL, Schunkert H, Kastrati A, Cassese S. **EuroIntervention,** 2023 Feb 8; EIJ-D-22-00860. Doi: 10.4244/EIJ-D-22-00860.

7. 09.2020 **Clinical outcomes by optical characteristics of neointima and treatment modality in patients with coronary in-stent restenosis**

Xhepa E, Bresha J, Joner M, Hapfelmeier A, Rivero F, Ndrepepa G, Nano N, Cuesta J, Kufner S, Cassese S, Bastante T, **Aytekin A**, Rroku A, García-Guimaraes M, Lahmann AL, Pinieck S, Rai H, Fusaro M, Schunkert H, Pérez-Vizcayno MJ, Gonzalo N, Alfonso F, Kastrati

A. **EuroIntervention.** 2020 Sep 8: EIJ-D-20-00662. Doi: 10.4244/EIJ-D-20-00662. PMID: 32894230

8. 04.2022 **Periprocedural myocardial injury according to optical characteristics of neointima and treatment modality of in-stent restenosis**

Nano N, **Aytekin A**, Ndrepepa G, Seguchi M, Bresha J, Alvarez Covarrubias HA, Nicol P, Lenz T, Lahu S, Gewalt S, Voll F, Rheude T, Wiebe J, Schunkert H, Kufner S, Cassese S, Joner M, Kastrati A, Xhepa E. **Clin Res in C.** 2022 Apr 27. Doi: 10.1007/s00392-022-02024-z

9. 12.2020 **Ticagrelor or Prasugrel in Patients With ST-Segment-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention**

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LIST OF ABBREVIATIONS

- **ACS=** acute coronary syndromes
- **ARC=** academic research consortium
- **BAR=** binary angiographic restenosis
- **BARC=** Bleeding Academic Research Consortium
- **BMI=** body mass index
- **BMS=** bare metal stent
- **BP=** biodegradable polymer
- **CABG=** coronary artery bypass grafting
- **CAD=** coronary artery disease
- **CART=** classification and regression tree
- **CCS=** chronic coronary syndrome
- **CI=** confidence interval
- **CK-MB=** creatine kinase myocardial band
- **CK=** creatine kinase
- **CTO=** chronic total occlusion
- **DCB=** drug-coated balloon
- **DES=** drug-eluting stent
- **DOCE=** device oriented composite endpoint
- **EACTS=** European Association for Cardio-Thoracic Surgery
- **EAPCI=** European Association of Percutaneous Cardiovascular Interventions
- **ECG=** electrocardiogram
- **EES=** everolimus-eluting stent
- **ESC=** European Society of Cardiology
- **HR=** hazard ratio

- **hs-cTnT=** high-sensitivity cardiac troponin T
- **IDI=** integrated discrimination improvements
- **ISR=** in-stent restenosis
- **LASSO=** least absolute shrinkage and selection operator
- **LCx=** left circumflex coronary artery
- **MACE=** major adverse cardiovascular events
- **MI=** myocardial infarction
- **MS=** multiple stents without stent overlap
- **mTOR=** mammalian target of rapamycin
- **NSTE-ACS=** non-ST elevation acute coronary syndromes
- **NSTEMI=** non-ST elevation myocardial infarction
- **NTVR=** non-target vessel revascularization
- **NTVRE=** non-target vessel related events
- **OCT=** optical coherence tomography
- **PCI=** percutaneous coronary intervention
- **PES=** paclitaxel-eluting stent
- **PF=** polymer-free
- $\mathbf{p_{interaction}}$**=** p value for interaction
- **PMBA=** poly n-butyl methacrylate
- **PMI=** periprocedural myocardial injury
- **POCE=** patient oriented composite endpoint
- **PP=** permanent polymer
- **QCA=** quantitative coronary angiography
- **SES=** sirolimus-eluting stent
- **SS=** single stent
- **ST=** stent thrombosis

- **STEMI=** ST elevation myocardial infarction
- **TLR=** target-lesion revascularization
- **TVR=** target vessel revascularization
- **TVRE=** target vessel related events
- **UA=** unstable angina
- **UDMI=** universal definition of myocardial infarction
- **URL=** upper range limit
- **VLST=** very late stent thrombosis
- **VVLST=** very very late stent thrombosis
- **ZES=** zotarolimus-eluting stent

LIST OF CLINICAL STUDY ACRONYMS

- **BIO-RESORT=** Comparison of Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All-Comers Population
- **BIOSCIENCE=** Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents
- **BIOSTEMI=** A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention
- **DECADE=** Adverse Events and Coronary Artery Disease Progression
- **EXAMINATION=** Clinical Evaluation of the Xience-V stent in Acute Myocardial Infarction
- **ISAR-REACT 5=** Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment
- **ISAR TEST 4=** The Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents
- **ISAR TEST 5=** The Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol- and Zotarolimus- Eluting Stents
- **LEADERS=** Limus Eluted From A Durable Versus Erodable Stent Coating
- **PLATO=** Platelet Inhibition and Clinical Outcomes
- **PRAGUE 18=** Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction
- **PROTECT=** Patient Related Out- comes With Endeavor Versus Cypher Stenting Trial
- **RESOLUTE=** A Clinical Evaluation of the Medtronic Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries
- **SIRTAX=** Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization

- **SORT OUT III=** The Scandinavian Organization for Randomized Trials with Clinical Outcome: Randomized Clinical Comparison of the Endeavor and the Cypher Coronary Stents in Non-selected Angina Pectoris Patients
- **SORT-OUT IV=** The Scandinavian Organization for Randomized Trials with Clinical Outcome: Randomized Clinical Comparison of the Xience V and the Cypher Coronary Stents in Non-selected Patients With Coronary Heart Disease
- **TRITON-TIMI 38=** Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel– Thrombolysis in Myocardial Infarction

*The study acronyms are not expanded in the text

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ABSTRACT

The advancements made in drug-eluting stent (DES) technology has reformed the standards of treatment of coronary artery disease. However, despite these improvements, stent failure in form of stent thrombosis (ST) or in-stent restenosis (ISR) persists. The undoubtedly multifactorial nature and the complex interplay between the elements underlying stent failure makes it harder to single out one central causative factor. In this regard, longer-term clinical data along with insights from intravascular imaging modalities and pharmacotherapy may allow the identification of predisposing factors more clearly.

Our study demonstrated a better efficacy and safety of newer stent platforms over a 10-year follow-up. In the analysis of patient-level data from 5 randomized clinical trial, we demonstrated a particularly reduced risk of definite ST beyond 1 year and 5 years following treatment with new generation DES compared to early generation DES. Sex related outcomes were highly relevant in this regard, as data beyond 5 years in large patient populations are lacking. In this study, female sex was associated with an increased risk of myocardial infarction (MI) in the first 30 days after percutaneous coronary intervention (PCI), but a comparable risk to men after this time point. Of note, female patients received less repeat revascularization and have similar risk of cardiovascular mortality compared to male patients. Reduced risk of repeat revascularization despite the increased risk of MI in female patients warrants further investigation. Adverse events persisted up to 10 years irrespective of sex, and the efforts should be made to improve the long-term outcomes.

With respect to mechanistic aspects of stent failure, not only patient- but also device-related and procedural factors are important. The studies included in this thesis provide an extended follow-up duration of 10 years on this topic. We showed that biodegradable polymer (BP) based DES were associated with better patient-oriented outcomes in comparison to permanent polymer-based DES in patients with acute coronary syndromes. Moreover, in a study with one of the largest numbers of DES overlap reported so far, we found that the influence of DES overlap on adverse clinical events up to 10-years after PCI was significant, with increased frequency of MI and target lesion revascularization

(TLR). This finding suggests that stent overlap should be avoided where possible, and an adequate lesion preparation beforehand may prove useful. We also investigated the frequency of events associated with target, stented lesions and non-target-vessel related remote disease progression at 10 years. A higher proportion of events were attributable to non-target vessel in patients treated with newer generation DES. These events become predominant in the follow-up period from 1 year up to 10 years.

The treatment of ISR is challenging because of high rates of recurrence after the initial treatment. Accordingly, we developed a 4-variable risk prediction model based on the following independent predictors of repeat PCI for recurrent DES-ISR at 1 year: (i) ISR morphology and (ii) restenosis interval, (iii) coronary vessel calcification, (iv) involvement of the left circumflex artery. While the model provides a modest discrimination in absolute terms, it offers a significant improvement compared with the current benchmark model for ISR classification. The subsequently developed ISAR score may serve as a standardized tool to estimate the risk of repeat PCI for recurrent DES-ISR up to 1-year.

The neointimal tissue observed in ISR is characterized according to the level of inhomogeneity assessed by intravascular optical coherence tomography imaging. However, data are lacking regarding the influence of these differences on the outcome. In a multi-centric registry study, we showed that the rate of major adverse cardiovascular events and clinically driven TLR was comparable between patients with low and high neointimal inhomogeneity at 2 years. Interestingly, there was a significant interaction between neointimal pattern and the type of treatment modality, with DES showing a significant advantage over drug-coated balloon in the high inhomogeneity group. In a similar patient population undergoing treatment for ISR lesions, the incidence of periprocedural myocardial injury (PMI) was high, and the risk was generally comparable to the PCI of the native coronary vessel. There was no association between the degree of neointimal inhomogeneity, neoatherosclerosis and occurrence of PMI.

In patients presenting with ST-elevation MI (STEMI) and undergoing primary PCI, the early procedural success depends to a greater degree on the effective antiplatelet therapy. In a prespecified

analysis of a large, randomized trial, we showed comparable efficacy and bleeding risk between the novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor at 1 year in patients with STEMI. Of note, ticagrelor was associated with a significantly higher risk of recurrent MI compared to prasugrel. This finding suggests that prasugrel may be considered in the treatment of STEMI patients at high thrombotic/ischemic risk.

ZUSAMMENFASSUNG

Die Fortschritte in der Technologie der medikamentenfreisetzenden Stents (DES) haben die Grundsätze für die Behandlung der koronaren Herzkrankheit reformiert. Trotz dieser Verbesserungen kommt es jedoch immer wieder zum Stentversagen in Form von einer Stentthrombose (ST) oder In-Stent-Restenose (ISR). Die zweifellos multifaktorielle Natur und das komplexe Zusammenspiel der Elemente, die dem Stentversagen zugrunde liegen, erschweren es, einen einzigen zentralen ursächlichen Faktor auszumachen. In dieser Hinsicht könnten längerfristige klinische Daten zusammen mit den Erkenntnissen aus der intravaskulären Bildgebung und der Pharmakotherapie eine eindeutigere Identifizierung der prädisponierenden Faktoren ermöglichen.

Unsere Studie zeigte eine bessere Wirksamkeit und Sicherheit der neueren Stent-Plattformen über eine 10-jährige Nachbeobachtungszeit. Im Vergleich zu DES der frühen Generation, konnten wir bei der Analyse von Patientendaten aus den fünf randomisierten klinischen Studien nach einem Jahr und fünf Jahren nach der Behandlung mit DES der neuen Generation ein besonders niedriges Risiko für eine definitive ST nachweisen. Die geschlechtsspezifischen Ergebnisse waren in diesem Zusammenhang von großer Bedeutung, da die Daten über fünf Jahre hinaus in großen Patientenpopulationen fehlen. In dieser Studie war das weibliche Geschlecht mit einem erhöhten Risiko für einen Myokardinfarkt (MI) in den ersten dreißig Tagen nach der perkutanen Koronarintervention (PCI) assoziiert, aber mit einem vergleichbaren Risiko wie bei den Männern nach diesem Zeitpunkt. Bemerkenswert ist, dass die weiblichen Patienten seltener revaskularisiert wurden und ein ähnliches Risiko für kardiovaskuläre Mortalität aufwiesen wie die männlichen Patienten. Das geringere Risiko einer erneuten Revaskularisierung trotz des erhöhten MI-Risikos bei den weiblichen Patienten sollte weiter untersucht werden. Unerwünschte Ereignisse blieben unabhängig vom Geschlecht bis zu 10 Jahren bestehen, und es sollten Anstrengungen unternommen werden, um die Langzeitergebnisse zu verbessern.

Was die mechanischen Aspekte des Stentversagens betrifft, so sind nicht nur patienten-, sondern auch geräte- und verfahrensbezogene Faktoren von Bedeutung. Die in diese Arbeit einbezogenen

Studien bieten eine längere Nachbeobachtungszeit von 10 Jahren zu diesem Thema. Wir konnten zeigen, dass biologisch abbaubare polymerbasierte DES im Vergleich zu permanenten polymerbasierten DES bei Patienten mit akuten Koronarsyndromen mit besseren patientenorientierten Ergebnissen verbunden sind. Darüber hinaus fanden wir in einer Studie mit einer der größten bisher berichteten Anzahl von DES-Überlappungen heraus, dass der Einfluss der DES-Überlappung auf unerwünschte klinische Ereignisse bis zu 10 Jahre nach der PCI signifikant war, mit einer erhöhten Häufigkeit von MI und Revaskularisation der Zielläsion (TLR). Dieser Befund legt nahe, dass eine Stentüberlappung nach Möglichkeit vermieden werden sollte und dass eine adäquate Läsionsvorbereitung im Vorfeld sinnvoll sein kann. Wir untersuchten auch die Häufigkeit von Ereignissen im Zusammenhang mit Zielläsionen, gestenteten Läsionen und nicht zielgefäßbedingter Fernprogression der Erkrankung nach 10 Jahren. Bei den Patienten, die mit DES der neueren Generation behandelt wurden, war ein höherer Anteil der Ereignisse auf die nicht-Zielgefäße zurückzuführen. Diese Ereignisse überwiegen in der Nachbeobachtungszeit von 1 Jahr bis zu 10 Jahren.

Die Behandlung der ISR ist aufgrund der hohen Rezidivrate nach der Erstbehandlung eine Herausforderung. Dementsprechend haben wir ein viervariables Risikovorhersagemodell entwickelt, das auf den folgenden Prädiktoren für eine erneute PCI bei rezidivierender DES-ISR nach 1 Jahr basiert: (i) ISR-Morphologie und (ii) Restenose-Intervall, (iii) Koronargefäßverkalkung, (iv) Beteiligung der linken Zirkumflexarterie. Obwohl das Modell in absoluten Zahlen nur eine bescheidene Unterscheidung bietet, stellt es im Vergleich zum derzeitigen Referenzmodell für die ISR-Klassifizierung eine erhebliche Verbesserung dar. Der anschließend entwickelte ISAR-Score kann als ein standardisiertes Instrument zur Abschätzung des Risikos einer erneuten PCI bei rezidivierender DES-ISR bis zu einem Jahr dienen.

Das bei ISR beobachtete neointimale Gewebe wird anhand des Grades der Inhomogenität charakterisiert, der mit Hilfe der intravaskulären optischen Kohärenztomographie ermittelt wird. Es fehlen jedoch Daten über den Einfluss dieser Unterschiede auf das Ergebnis. In einer multizentrischen Registerstudie konnten wir zeigen, dass die Rate an schwerwiegenden unerwünschten

kardiovaskulären Ereignissen und klinisch bedingten TLR nach 2 Jahren bei Patienten mit geringer und hoher neointimaler Inhomogenität vergleichbar war. Interessanterweise gab es eine signifikante Wechselwirkung zwischen dem neointimalen Muster und der Art der Behandlungsmodalität, wobei DES in der Gruppe mit hoher Inhomogenität einen signifikanten Vorteil gegenüber dem medikamentenbeschichteten Ballon zeigte. In einer ähnlichen Patientenpopulation, die sich einer Behandlung von ISR-Läsionen unterzog, war die Inzidenz periprozeduraler Myokardschäden (PMI) hoch, und das Risiko war im Allgemeinen mit dem der PCI des nativen Koronargefäßes vergleichbar. Es bestand kein Zusammenhang zwischen dem Grad der neointimalen Inhomogenität, der Neoatherosklerose und dem Auftreten von PMI.

Bei Patienten mit ST-Hebungsinfarkt (STEMI), die sich einer primären PCI unterziehen, hängt der frühe Erfolg des Verfahrens in stärkerem Maße von einer wirksamen Thrombozytenaggregationshemmung ab. In einer vordefinierten Analyse einer großen, randomisierten Studie konnten wir bei Patienten mit STEMI eine vergleichbare Wirksamkeit und ein vergleichbares Blutungsrisiko zwischen den neuen $P2Y_{12}$-Rezeptor-Inhibitoren Prasugrel und Ticagrelor nach einem Jahr nachweisen. Bemerkenswert ist, dass Ticagrelor im Vergleich zu Prasugrel mit einem signifikant höheren Risiko für einen erneuten MI verbunden war. Dieses Ergebnis legt nahe, dass Prasugrel bei der Behandlung von STEMI-Patienten mit hohem thrombotischem/ischämischem Risiko in Betracht gezogen werden kann.

1. INTRODUCTION

1.1. Evolution of percutaneous coronary intervention

Everyone knew that a catheter could not be inserted directly into a human coronary artery because it might completely obstruct the small vessel, depriving the heart of blood and causing sudden death. Even if the catheter allowed some blood to flow past, the non oxygenated angiographic dye would fill the coronary arteries, obstruct oxygen delivery, and end in fatal ventricular fibrillation. There was no solution. Cardiologists were stumped.

-The Heart Healers, James S. Forrester (1)

1.1.1. Cardiac catheterization

The foundation of what we know today as percutaneous coronary intervention (PCI) was first laid down shortly before World War 2 in a small-town northeast of Berlin, Germany called Eberswalde. In 1929, a young medical resident named Dr. Werner Forssmann inserted himself with a catheter designed to empty urine from the bladder (2). The idea was that the concentration and efficacy of the drug therapy would be much higher if delivered to heart directly rather than through the peripheral vasculature. With a urinary catheter projecting from his arm, he went on to document this with an X-ray image, which would later be considered as the first cardiac catheterization. Although he could show that the cardiac catheterization was possible and could be used to visualize chambers of the heart, he was criticized by the medical community due to the high-risk nature of the procedure. His method subsequently paved the way for innovators such as Dr. Dickenson Richards, Dr. André Cournand and helped to monitor and treat wounded soldiers. This was an important step forward at a time when preoperative misdiagnosis before therapy was the cause of mortality. In 1956, Dr. Forssmann received a Nobel prize in Medicine along with Drs. Richard and Cournand (1).

1.1.2. Coronary angiography

Coronary artery disease (CAD) is a major cause of mortality globally. Back in 1958, although a glimpse into the structure of the heart was possible, visualization of coronary arteries and the diagnosis of CAD was still out of reach. Dr. Charles Dotter was a radiologist living in Portland Oregon at the time. He challenged this common notion with a technique called "occlusion aortography" using a special soft double-lumen balloon catheter (3). The catheter was positioned right above the aortic valve and inflated until the aorta was occluded. At the same time, a contrast medium that could be seen through X-ray images was injected and the balloon was subsequently deflated. He confirmed these findings in canines and produced series of coronary artery images (3). This was followed by Dr. F. Mason Sones on October 30,1958, who - by serendipity - performed the first selective coronary angiogram when the tip of the catheter whiplashed into the ostium of the right coronary artery (4, 5). Against the common belief back then, the hypoxia resulting from the contrast injection directly into the coronary artery did not cause fatal ventricular arrhythmia. These events ushered in the era of invasive coronary angiography and its use for cardiovascular diagnosis. Today, European Society of Cardiology (ESC) recommend the usage of invasive coronary angiography for the diagnosis of suspected obstructive CAD in: (i) patients with a high clinical probability and severe symptoms that are unresponsive to medications, (ii) patients with the presence of typical angina at a low level of exercise and clinical assessment that suggests high event risk, (iii) left ventricular dysfunction suggestive of CAD (6).

1.1.3. Plain balloon angioplasty

Another one of Dr. Dotter's contributions to the field of cardiology (which made him dubbed by some as the father of interventional radiology) was a percutaneous technique later referred to as "Dottering". In 1963, he inadvertently performed the first arterial catheterization in a patient with right iliac artery occlusion (7, 8). It was however Dr. Andreas Grüntzig, another young radiology resident in Zurich Switzerland at the time, who improved and applied this technique to CAD in the subsequent years. He created the first functional coronary balloon catheter and in 1977, and accomplished a successful non-operative dilatation of a coronary vessel in a human (9). This was the first transluminal

balloon angioplasty, and the start of a subspecialty that would eventually be known as interventional cardiology. Balloon angioplasty consequently became a widely used alternative to open surgery to treat obstructive coronary artery disease. Still, as innovative as it was back then, the procedure was associated with certain key limitations. First of all, there were reports regarding high rate of abrupt vessel closure within hours or days often requiring emergency repeat balloon angioplasty or surgery (10). This complication was secondary to dissection of the vessel and subsequent exposure of thrombogenic material to circulating bloodstream causing thrombosis and obstruction (11). Furthermore, restenosis developed in approximately 1/3 of patients due to acute vessel recoil, chronic constrictive remodeling, and neointimal hyperplasia (11, 12).

1.1.4. Bare metal stents

The use of an expandable metal mesh, that would later be referred to as coronary stent, was the potential answer to the aforementioned abrupt closure of the vessel, with the rationale that it would provide enough radial force and stability against vessel recoil to maintain vessel patency compared to plain balloon angioplasty. The coronary stents are mainly classified as either balloon expandable or self-expanding, based on the mechanism of deployment. Balloon expandable stents were the first to be made commercially available, placed in the segment of interest by inflating a balloon. In contrast, self-expanding stents are constrained by a sheath that is removed after delivery (13). Due to technical difficulties and limitations of the latter, balloon-expandable stents are currently used in nearly all stent related procedures (11).

In 1986, Dr. Jacques Puel in Toulouse, France and Dr. Ulrich Sigwart in Lausanne, Switzerland performed the first bare metal stent (BMS) implantation in human (14, 15). The BMS was used initially in patients with abrupt and threatened vessel closure following balloon angioplasty to seal dissection flaps and improve acute procedural success (16). The transition of BMS from a bail-out strategy to a standard therapy was enabled by evidence provided by 2 randomized clinical trials in 1994. In patients with CAD, BMS was associated with better outcomes in terms of angiographic and clinical restenosis (17, 18). However, the stability of a permanent scaffold came at the price of early stent thrombosis

(ST) leading to vessel occlusion, caused by the exposure of metallic stent to circulating blood. At the time, the aggressive anticoagulant therapy given to avoid this complication resulted in bleeding and vascular complications. Subsequent investigations showed that dual antiplatelet therapy was superior and better tolerated than anticoagulant therapy following stent implantation (19, 20). These findings led to the widespread use of the coronary stents in clinical practice.

Although BMS was effective in reducing the rate of restenosis, vessel trauma caused by stent implantation resulted in neointimal hyperplasia, necessitating repeat intervention in nearly one in four cases. A potential solution to this issue was the modification of stent design.

1.1.5. Drug-eluting stents

Drug-eluting stents (DES) were developed with the purpose of targeting neointimal hyperplasia locally through release of cytotoxic or immunosuppressive drugs without instigating systemic toxicity. DES incorporates the stent backbone with an anti-restenotic drug and a carrier polymer to mediate controlled release of the selected agents.

Stent Backbone

The early generation BMS and DES were made of stainless steel, but advancements in the technology and the use of cobalt and platinum chromium alloys made it possible to manufacture thinner iterations of coronary stents in the contemporary era (11). The benefit of a thin strut design in similar devices was shown in randomized trials in early 2000s, which showed reduced rates of restenosis possibly by minimizing vessel trauma and allowing faster re-endothelization (21, 22).

Bioresorbable scaffold (BRS) was another approach to address the issues that are associated with the use of metal as stent backbone. The rationale behind developing a fully bioresorbable stent was to overcome the absence of vasomotion due to permanent caging of the coronary artery and the associated chronic inflammation against a foreign body (23). The technology was initially based on a poly-L-lactic acid backbone with poly-D-lactic acid coating that would eventually undergo degradation to produce lactic acid and finally carbon dioxide and water through oxidation in the Krebs cycle (24). Although the longer-term outcomes with poly-L-lactic acid based BRS in comparison to metallic stents

were disappointing, third generation of magnesium alloys represents a promising option for the future of BRS (23, 25-27).

The anti-restenotic drug

The mechanical injury that occurs following the stent implantation triggers the start of an instantaneous healing process in the vessel wall of the coronary arteries. This is characterized by activation of platelets facilitating thrombus formation and recruitment of inflammatory cells such as monocytes, neutrophils and lymphocytes, which would later trigger smooth muscle cell proliferation and finally in-stent restenosis (ISR) (28). Accordingly, the goal of using an immunosuppressive and anti-proliferative agent is to ultimately achieve anti-restenotic efficacy while not hindering the ongoing vessel healing process.

Sirolimus, zotarolimus and everolimus belong to “limus” family of potent immunosuppressive agents. Sirolimus delays the smooth muscle cell proliferation through binding of the cytosolic FK binding protein 12 (FKBP12), which in turn prevents the activation of the mammalian target of rapamycin (mTOR) and causes G1 cell-cycle arrest (28). The derivatives of sirolimus used in newer generation DES (zotarolimus, everolimus) differ in the chemical composition of the rapamycin ring and lipophilicity without changes in mTOR-related binding sites (11). Another anti-proliferative agent used in the early generation of DES was paclitaxel. It suppresses neointimal overgrowth by binding to β-tubulin subunit of the spindle-cell microtubules stabilizing them. Consequently, the prevention of microtubuli disassembly causes them to be non-functional leading to the arrest of cell-cycle at G2/M-phase (11). Today, paclitaxel is used only on drug-coated balloons (DCB).

Carrier stent polymer

Polymer is a high molecular weight organic macromolecule built by repeating monomer subunits joined by covalent chemical bonds. These compounds have proven to be effective for both drug loading and controlled release of the anti-restenotic agents in DES (29, 30). Key components for polymers selected to be used as drug carriers are as follows: (i) biocompatibility, (ii) mechanical stability at long-term, (iii) lack of interaction with the anti-restenotic agent, (iv) provision of a platform

for controlled drug-release kinetics and (v) property of remaining biologically inert following complete drug release (31).

With regard to stent technology, polymers are classified broadly as permanent (non-biodegradable, bio-stable) or biodegradable (bio-erodible, eventually degraded in vivo through the hydrolysis of the chemical bonds keeping the polymer intact). Initially, early generation permanent polymer (PP) sirolimus- (SES) and paclitaxel-eluting stents (PES) showed consistent reduction in the rates of ISR compared to BMS, which appeared to indicate the end of complications related to neointimal hyperplasia (32, 33). However, this initial success was compromised by the concerns raised regarding late ST burden (34, 35). This appeared to be a consequence of a healing delay in the arterial wall following DES implantation, which is certainly multifactorial in nature. The inflammatory reaction from the exposure to the PP seems to be an important contributory factor (36).

The biodegradable polymer (BP) based DES were developed to address this limitation. The earliest BP were polyesters, including polylactide, polyglycolide and polyglycolic-co-lactic acid. Subsequent findings demonstrated good biocompatibility of either polylactic or polylactic-co-glycolic acid (in addition to several others) as a polymer matrix to be used with a metallic stent backbone (37). The complete degradation of this type of polymer coating allows the stent to display the efficacy and benefits of PP-DES until the complete release of the drug, and the stent essentially becomes a BMS once this process is finished. Although in theory, this was thought to be a good solution so as to lowering the risk of late adverse events associated with the use of a PP, the evidence in this regard has been mixed. BP-DES demonstrated favorable outcomes compared to early generation PP-DES; however, it failed to show superiority to new generation PP-DES (38, 39). In line with previous findings, the 10-year follow-up data from ISAR TEST 4 trial showed comparable outcomes between BP-DES and new generation PP-DES, with higher incidence of major adverse cardiac events (MACE) and definite ST in patients treated with early generation SES (40).

Polymer-free (PF) DES were introduced as a second alternative to BP-DES in order to avoid the PP-related inflammation. The polymer allows easier adherence of the anti-restenotic drug to metallic

stent surface and helps to control drug release. As such, the biggest challenge of a PF based DES technology was to avoid rapid drug release and provide an acceptable safety profile (41-43). Thus far, several methods have been employed to achieve optimal release kinetics in DES without polymer coating. The stent included in this thesis is a PF-dual-DES, eluting both sirolimus and probucol as active drug. The mixture of these 2 components increases the lipophilicity and therefore slowing down the elution of the drug at vessel surface (41). The ISAR-TEST 5 trial showed the non-inferiority of sirolimus- and probucol-eluting PF-DES in comparison to new generation PP zotarolimus-eluting stent (ZES) at 1 year (44). Moreover, the extended follow-up duration of 10 years demonstrated comparable outcomes between these stent platforms (**Figure 1**) (45).

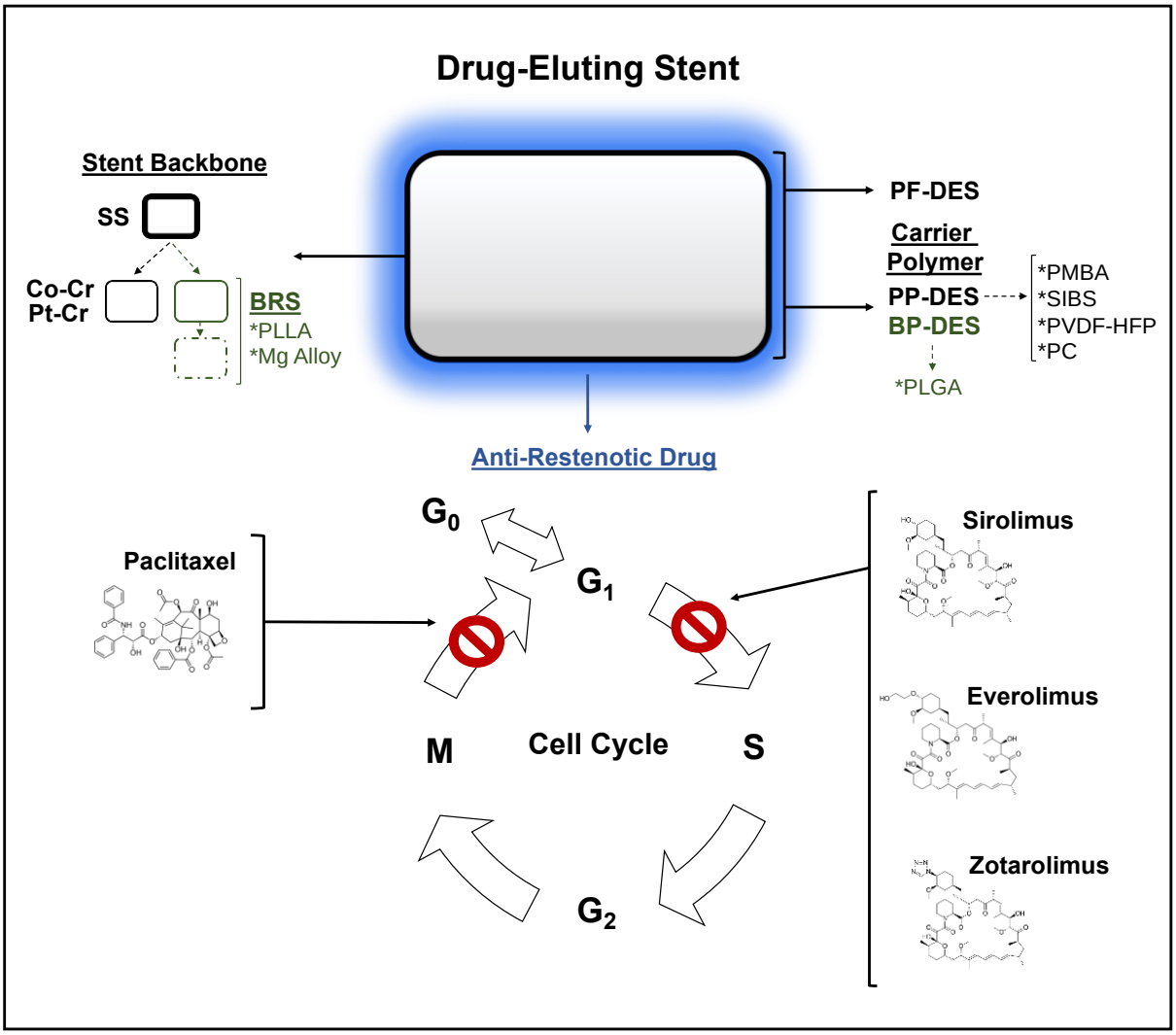

Figure 1. Principal characteristics of DES platforms.

BP=biodegradable polymer; BRS=bioresorbable scaffold; Co-Cr=cobalt-chromium; DES=drug-eluting stent; SS=stainless steel; Mg=magnesium; PC=phosphorylcholine; PF=polymer-free; PLGA= polylactic-co-glycolic acid;

PLLA= poly-L-lactic acid; PMBA= poly n-butyl methacrylate; PP=permanent polymer; Pt-Cr=platinum-chromium; PVDF-HFP= polyvinylidene fluoride-hexafluoropropylene; SIBS= poly styrene-b-isobutylene-b-styrene.

1.1.6. Drug-coated balloon angioplasty

DCB combines the conventional balloon catheter with a coating matrix that includes an anti-restenotic drug and a spacer or excipient, an inert compound that helps preventing the drug from clumping and facilitating transfer to vessel wall. It provides local drug delivery with less therapeutical footprint and hence provides potential improvement for delayed arterial healing that is associated with DES use. Paclitaxel is currently the most commonly used active drug owing to its high lipophilicity, as it offers effective tissue transfer and persistent anti-restenotic efficacy after a brief contact time compared to other alternatives like sirolimus or its analogues (46, 47). The use of an anti-restenotic drug and an excipient together was based on the initial observations that iopromide based contrast media attached to vessel surface for a few seconds following injection and before wash-out (48). The lower efficacy of paclitaxel coating alone was shown later in preclinical studies, further supporting the important role of an excipient as both carrier and solvent (49). Additionally, the type of excipient also seems to have an influence on the tissue drug levels following DCB angioplasty (50). At present, there are several commercially available DCB.

It is important to note that DCB carry the limitations of standard plain balloon angioplasty in the early period following the procedure, particularly lower acute gain and unstable acute results due to lack of a durable scaffold (46). As such, current ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines advise the use of DCB angioplasty in patients with ISR rather than "*de novo*" lesions (51). Of note, another concern associated with the use of DCB is the potential for distal particle embolization of the coating material reported in preclinical studies (46). Although this issue is not limited only to DCB, it poses a safety concern and could result in an increased risk of microvascular injury (52, 53).

1.2. Stent failure – temporal course and manifestation in the contemporary era

Regardless of the advancements made in DES technology that led to current standards of clinical practice, contemporary new-generation DES show a lesser but persistent degree of late stent failure risk caused by ISR or ST.

1.2.1. In-stent restenosis

ISR represents the most frequent form of stent failure in the contemporary DES era, accounting for 5-10% of all interventional procedures (54, 55). Moreover, previous findings indicate a prognostic relevance of ISR as a correlate of 4-year mortality (56). ISR is commonly characterized as a significant luminal narrowing (≥50% as per coronary angiography or ≥75% as per intravascular imaging) of a previously stented segment (57, 58). There are several, and possibly coexisting, causative factors that are associated with ISR formation. These include both the device-related, procedure-related factors (e.g., stent underexpansion/undersizing/fracture/type or neointimal hyperplasia, neoatherosclerosis) and lesion-related (e.g., vessel calcification, multiple stent layers) mechanisms that lead to suboptimal stent implantation (59).

The present evidence suggests that BMS-ISR and DES-ISR are 2 distinct entities, not only with respect to angiographic pattern but also the time course (60). A traditionally used ISR classification that is based on the angiographic appearance was first introduced in the BMS era (61). However, the relevance of this classification system is less clear with regard to DES-ISR, considering the differences in disease process compared to BMS-ISR. While BMS related ISR exhibits a more diffuse pattern and tends to peak at 6 months, DES-ISR appears more focal (often at stent edges) and the incidence continue to raise progressively for several years following stent implantation due to differing underlying factors (62-64).

DES-ISR is recognized to be challenging to treat with a high rate of recurrence necessitating repeat PCI following the initial treatment with a new generation DES or DCB angioplasty (65). A number of small studies have investigated the predictive factors leading to recurrent DES-ISR (66-75). Accordingly,

analyses investigating these risk factors in studies of adequate size and duration are of paramount clinical importance.

1.2.2. Stent thrombosis

Although ST is not common, it is linked with a major risk of morbidity and mortality (76). Recent clinical reports have demonstrated that the rates of definite ST are up to around 1% at 1 year and less than 2% at 5 years follow-up (77). ST is characterized by a freshly formed thrombus in a stented segment shown either by angiographic or post-mortem evidence. The underlying mechanism of ST is multifactorial and similar to ISR, resulting from an interplay between patient-related (e.g., poor response or noncompliance to antithrombotic therapy, diabetes), lesion-related (e.g., left main or left anterior descending coronary artery lesions, bifurcation lesions, severe calcification) and device-related (e.g., stent undersizing, long stent length, stent overlap) factors.

In practice, timing of ST is categorized generally in relation to index stent implantation as: (i) early ST (ST occurring in the first 30 days); (ii) late ST (ST occurring from 30 days to 1 year); (iii) very late ST (VLST) (ST occurring beyond 1 year) and (iv) very very late ST (VVLST) (ST occurring beyond 5 years) (78). Since DES superseded BMS in clinical practice, the incidence of early ST became relatively infrequent in current clinical practice (79). Nevertheless, the early-generation DES was consequently associated with an increased VLST risk compared to BMS (80, 81). While this risk appears to have been lowered with new generation DES, the clinical consequences of ST still remain significant (82-84). ST beyond 5 years has also been previously reported, but the associated risk of VVLST with regard to early and new generation DES use is less certain (85). The majority of studies lack adequate statistical power to assess this endpoint and only a few of them have a follow-up duration up to 10 years following PCI.

1.3. Factors that influence drug-eluting stent failure and adverse clinical outcomes

1.3.1. Neoatherosclerosis

Neoatherosclerosis refers to the atherosclerotic changes that develop in the new tissue growing over the scaffold (neointimal tissue) after stent implantation. The transition in the DES era caused a temporal shift, decreasing the rate of ISR in exchange for the earlier manifestation of this disease

process compared to BMS (86). It is histologically characterized through the identification of lipid-laden foamy macrophage accumulation (with/without presence of a necrotic core) and/or calcification in the neointima (87). It is thought to be an important causative factor for both forms of late stent failure, observed from months to years following DES implantation. This is in stark contrast with the atherosclerotic process that develops in native coronary arteries over decades (88). The mechanism behind the accelerated disease progression remains poorly understood. It is thought to be related to the quality of the regenerated endothelium following treatment with DES, characterized by incomplete maturation, poor connection between cells and a reduced expression of molecules that contribute to the functionality as well as stability of the endothelial lining (89-91). Paired with the vascular injury inflicted on the vessel during stent implantation, the inadequate barrier function of the newly formed endothelium allows the easier entry of lipoproteins and consequently the faster development of neoatherosclerosis (92). This eventually leads to advanced atherosclerotic lesions composed of a fibrous cap and a necrotic core followed by plaque rupture and thrombotic events, although the exact morphological features and the process remain to be elucidated. Interestingly, the necrotic core found in neoatherosclerosis is speculated to occur through macrophage apoptosis without lipid pool seen in native CAD, which could conceivably facilitate the earlier disease progression that results in in-stent plaque rupture (93).

1.3.2. Stent Overlap

Stent overlap is defined as the use of at least 2 stents with the aim of treating a single coronary lesion and an overlapping zone of at least 1 mm between these stents, as determined by quantitative coronary angiography (QCA) (94). This technique is utilized commonly in clinical setting to treat long lesions and in presence of edge dissection or incomplete coverage as a bail-out strategy, reported in up to 30% of patients undergoing PCI procedures (95, 96). The use of stent overlapping is based on the evidence of increased proliferation of the neointima and ISR when space is left between neighboring stents (97).

Earlier reports signal an increased risk of MACE in patients with BMS and DES overlap (94, 98-101). Still, the previous studies investigating an association between DES overlap and adverse outcomes following PCI have shown conflicting results (94, 96, 102, 103). The delayed neointimal healing associated with DES platforms may be particularly relevant in this regard, as the presence of two stent layers results in an increase of local drug and polymer concentration. Moreover, overlapping stents may cause hemodynamic disturbances that further effect the healing process. Imaging studies show a heterogenous healing pattern of these overlapping stent zones, demonstrating both incomplete neointimal coverage and thickening in comparison to non-overlapped segments (104). This, in turn, could have increased the risk of subsequent thrombotic and restenotic events. The data on DES overlap at longer term follow-up duration are lacking.

1.3.3. Target versus remote vessel related disease progression

Patients treated with stent implantation are at risk of later cardiac events following PCI, such as myocardial infarction (MI) and repeat revascularization (105, 106). The main focus of coronary stent trials has traditionally been on the adverse outcomes related to target vessel or target lesion up to 12-months after PCI (107). However, patients who are treated with PCI also experience a higher prevalence of events related to remote, non-treated vessels, accounting for almost half of all events (106). A previous imaging study showed that these non-culprit lesions may appear angiographically mild yet in reality are critical lesions characterized by large plaque burden (105). While there are published data on the incidence of target vessel- (TVRE) and non-target vessel related events (NTVRE) up to 5-years following PCI, the frequency of these events at an extended follow-up duration is not clear (105, 106, 108-111).

1.3.4. Sex differences

Assessment of sex-related clinical outcomes post-PCI has garnered not only great scientific curiosity but also clinical interest in recent years (112, 113). Nevertheless, the previous studies on this topic have given conflicting results (113, 114). The inherent limitation of sex-based comparative analyses is related to the inherent differences in the baseline characteristics between men and women

that remain partially unaccounted for. The residual confounding inserted by these differences is difficult to adjust for and pose a problem with respect to analyses using registries or insurance data. Accordingly, individual patient-level data acquired from randomized studies may help minimize this heterogeneity and may allow a more accurate comparison of sex-related differences with respect to clinical outcomes (115). Sex-related outcomes have been assessed through to 5 years following PCI in several previous studies (113). However, analyses at longer follow-up duration in large study groups treated solely with DES are lacking. This may be of clinical relevance as it has been reported that outcomes have significantly improved for women who underwent PCI and were treated with DES (116).

1.4. Modern-day antiplatelet therapy for patients presenting with acute ST-elevation myocardial infarction

Dual antiplatelet therapy consisting of an antiplatelet agent combined with aspirin is recommended in the current 2018 ESC guidelines as treatment for patients presenting with ST-segment–elevation myocardial infarction (STEMI) undergoing primary PCI (117). This therapy reduced the risk of later ischemic events in patients with STEMI including ST. Still, high on-aspirin or clopidogrel platelet reactivity observed in these patients increases the risk of later atherothrombotic events (118, 119). In this regard, potent antiplatelet therapy is of paramount importance.

The third generation $P2Y_{12}$ receptor inhibitors ticagrelor and prasugrel are currently the preferred antiplatelet agents in daily clinical practice. Ticagrelor is a non-thienopyridine (cyclopentyltriazolopyrimidine) that acts directly without biotransformation and binds to platelet $P2Y_{12}$ receptor reversibly at a different binding site than adenosine diphosphate. On the contrary, prasugrel is a thienopyridine that is metabolized to an active compound before irreversibly binding to platelet $P2Y_{12}$ receptor (120). TRITON-TIMI 38 and PLATO trials showed the superiority of these novel antiplatelet agents over clopidogrel in the treatment of patients with acute coronary syndromes (ACS) predominantly undergoing invasive therapy (121, 122). The subgroup analyses of patients with STEMI in these trials showed a consistent reduction in the ischemic risk with prasugrel or ticagrelor compared

with clopidogrel (123, 124). Nevertheless, a direct comparison of the efficacy and safety of prasugrel and ticagrelor in these trials is unreliable owing to important differences in study design, patient baseline data and interventions. Additionally, the results from the observational studies and registries are inconsistent with regard to comparative efficacy and safety of prasugrel and ticagrelor in patients presenting with STEMI (125-129). To date, there are only 2 randomized head-to-head comparison of novel $P2Y_{12}$ receptor inhibitors in patients with ACS (130, 131). The ISAR-REACT 5 trial demonstrated the superiority of prasugrel over ticagrelor in reducing the rate of ischemic events without significant difference in bleeding risk up to 1 year (131). However, data on the comparative efficacy and safety of ticagrelor and prasugrel in patients presenting with STEMI undergoing primary PCI are limited (130).

1.5. Optical coherence tomography imaging

Intravascular optical coherence tomography (OCT) is a light-based (near-infrared wavelength of ~1.3µm) cross-sectional imaging modality that provides approximately 10-20µm axial resolution (132). It allows in-depth characterization of the diseased vessel wall in vivo compared to the most widely used coronary angiography, which can only help to assess lesions through planar projections of the contrast filled vessel lumen. OCT was first developed nearly four decades ago as optical coherence domain reflectometry in order to detect the location of breaks in fibre-optic cables. The technology thereafter quickly evolved first to measure distances in the eye owing to easier light penetration in transparent tissues, and then was used to visualize the retina in ophthalmology (133, 134). Using light sources with longer wavelengths later permitted light penetration at a higher degree and its use in opaque tissues (135). Accordingly in 2000, OCT was used in vivo for the first time (136). This was followed by the first-in-human applications in 2002 (137, 138). The 2018 ESC/EACTS guidelines stated that OCT should be considered to optimize the stent implantation in selected patients and to detect the stent related mechanistic issues leading to restenosis (51).

Strength of OCT lies in its exceptional spatial resolution to visualize the surface structures typically up to ~2-3mm depth. However, the inability to increase the visual depth while maintaining the same resolution represents the inherent limitation of this imaging modality. This is challenging due to the

high-scattering nature of non-transparent tissues. Another issue is the presence of red blood cells that causes significant light attenuation (139). Consequently, intravascular OCT imaging requires flushing of the blood to attain optimal imaging quality.

The identification of the arterial wall characteristics through OCT imaging has been demonstrated in multiple correlation studies with histology. These findings helped to establish a basis with respect to development of certain standards for identifying characteristics that corresponds to tissue microstructures. The identified atherosclerotic features include: (i) macrophages, (ii) cholesterol crystals, (iii) red and white thrombus, (iv) calcium deposits, (v) fibrous- and lipid-rich plaques (137, 140-142).

Based on its optical characteristics as per OCT imaging, neointimal tissue observed in ISR has been divided into several subtypes according to level of the inhomogeneity (homogenous, heterogenous, layered), tissue backscatter (low or high) and other features in correlation with different underlying histological substrates (143, 144). These differences may influence the adverse clinical outcomes in patients undergoing PCI for ISR, depending on whether DES implantation or DCB angioplasty is employed as treatment. Still, the current data are very limited with regard to such topic and the existing literature do not allow a comparison of the contemporary treatment standards (145).

2. THESIS AIMS

Despite the improvements in clinical outcomes paralleling the advancements in stent technology, the risk of stent failure in the form of ST and ISR persists. The undoubtedly multifactorial nature of this phenomenon makes it harder to single out a central causative factor. Considering the temporal shift in the occurrence of these events following the transition from the BMS to DES era, longer term clinical data may provide invaluable information with regard to the underlying mechanism, trends of stent failure and subsets of patients at risk for these adverse clinical events. Likewise, intravascular OCT provides a unique opportunity to investigate the vessel wall structure and evaluate neointimal patterns in relation to coronary DES implantation owing to its high spatial resolution. An intravascular OCT imaging-based analysis may thus further help elucidate the effects of DES implantation on vascular surface at a detailed level not easily attainable with other imaging modalities in clinical setting. Finally, effective pharmacotherapy plays an important role in the procedural success rate following PCI. This is particularly relevant for patients presenting acutely with ACS, and the data are limited with respect to comparative safety and efficacy of novel $P2Y_{12}$ receptor inhibitor agents in these patients.

Accordingly, the principal aims of this thesis were as follows: (i) to assess the risk of definite ST up to 10 years in patients treated with early- and new-generation DES; (ii) to investigate whether sex-related differences in clinical outcomes persist at long-term (10 years) following DES implantation; (iii) to investigate the influence of stent polymer in patients with ACS over a 10 year follow-up; (iv) to investigate the impact of DES overlap on clinical outcomes over a 10 year follow-up; (v) to investigate the clinical events related to the DES implanted segments and events related to remote, non-stented segments at 10 years follow-up; (vi) to develop and validate a risk-prediction model for recurrent DES-ISR; (vii) to investigate the relation between OCT-based neointimal pattern, treatment modality and clinical events in patients with ISR; (viii) to investigate the relation between OCT-based neointimal pattern, treatment modality and occurrence of periprocedural myocardial injury in patients with ISR; (ix) to compare the safety and efficacy of novel antiplatelet agents ticagrelor and prasugrel in patients with STEMI up to 1 year.

3. METHODS AND MATERIALS

3.1. Study protocol for the DECADE co-operation series

DECADE co-operation is a pooled analysis of patient-level clinical data from DES trials with a follow-up up to 10 years (78). A search across electronic scientific databases for relevant randomized studies investigating clinical outcomes up to 10-years following DES implantation led to a selection of 6 clinical trials for this analysis (final search date was October 2020) (40, 45, 146-149). The reference lists of these publications were further inspected to identify other relevant citations, and none were identified. The principal investigators were then contacted to provide the individual patient-level data. The principal investigator of one trial did not agree to share patient-level data. As a result, one randomized study was excluded from the final analysis (147).

The principal investigator of each participating center agreed to transfer the data from the remaining studies without patient identifiers and to combine these in a single database. Following the check for completeness, the final dataset included the following trials: (i) ISAR-TEST 4 (150); (ii) ISAR-TEST 5 (44); (iii) SORT OUT III (151); (iv) SIRTAX (152) and (v) EXAMINATION (153). Participating centers were directly contacted if there were inconsistencies with the original publications or in case further data were required. Data were analyzed according to the intention-to-treat principle. Each study included in the present analysis was approved by the institutional review board or ethics committee at each participating center. All patients signed informed, written consent before undergoing the allocated treatment strategy. Key inclusion/exclusion criteria and the primary endpoints of each included clinical trial are described in supplementary **Table A1**.

3.*1.1. Study population*

The main characteristics of each included trial and the details of used antiplatelet regimen following DES implantation are shown in **Table 1**. The study population and the assigned treatment strategy for each study were as follows:

- **SIRTAX trial**: 1,012 patients randomized to receive either early-generation, permanent-polymer (PP) SES (N=503) or slow-release PES (N=509) (152).

- **ISAR-TEST 4 trial**: 2,603 patients randomized to new generation BP-SES (N=1,299), new-generation, PP everolimus-eluting stent (EES) (N=652) or early-generation, PP-SES (N=652) (150).
- **ISAR-TEST 5 trial**: 3,002 patients randomized to new-generation, PF sirolimus and probucol-eluting stents (N=2,002) or new-generation, PP-ZES (N=1,000) (44).
- **SORT OUT III trial**: 2,332 patients randomized to new-generation, PP-ZES (N=1,162) or early-generation, PP-SES (N=1,170) (151).
- **EXAMINATION trial**: 1,498 patients randomized to receive either a new-generation, permanent-polymer EES (N=751) or BMS (N=747). BMS group was excluded from the current analysis, given that the focus of the studies included in this work was clinical events following DES implantation (153).

Table 1. Characteristics of the trials included in the DECADE co-operation (78)**.**

Trial Name (Enrolment Period)	**DES Type; Brand Name** (Manufacturer)	**Patients/ Treatment Arm** (N)	**Patients with ACS at Admission** (N, %)	**Patients with Diabetes Mellitus** (N, %)	**DAPT Regimen According to Trial Protocol**	**Complete 10-year Follow-up** (N, %)
SIRTAX (2003-2004)	Early-generation, permanent polymer **SES**	503	520/1,012 (51.4)	201/1,012 (19.9)	Aspirin 100 mg once daily indefinitely; clopidogrel 75 mg once daily for 12 months	895/1,012 (88.4)
	Early-generation **PES**	509				
ISAR-TEST 4 (2007-2008)	New-generation, biodegradable-polymer **SES**	1,299	1,060/2,603 (40.7)	753/2,603 (28.9)	Aspirin 200 mg once daily indefinitely; clopidogrel 150 mg for the first 3 days (or until discharge), clopidogrel 75 mg once daily for ≥ 6 months	2,153/2,603 (82.7)
	Early-generation, permanent polymer **SES**	652				
	New-generation, permanent-polymer **EES**	652				
SORT OUT III (2006-2007)	New-generation, permanent-polymer **ZES**	1,162	1,052/2,332 (45.1)	337/2,332 (14.5)	Aspirin 75 mg once daily indefinitely; clopidogrel 75 mg once daily for 12 months	2,312/2,332 (99.1)
	Early-generation, permanent polymer **SES**	1, 170				
ISAR-TEST 5 (2008-2009)	New-generation, polymer-free sirolimus- and probucol-eluting stent	2,002	1,232/3,002 (41.0)	870/3,002 (29.0)	Aspirin 200 mg once daily indefinitely; clopidogrel 150 mg for the first 3 days (or until discharge), clopidogrel 75 mg once daily for ≥ 6 months	2,553/3,002 (85.0)
	New-generation, permanent-polymer **ZES**	1,000				
EXAMINATION (2008-2010)	New-generation, permanent-polymer **EES**	751	751/751 (100)	137/751 (18.2)	Aspirin 100 mg once daily indefinitely; clopidogrel 75 mg once daily for 12 months	710/751 (94.5)

The numbers are shown as absolute numbers or counts (%).

ACS= acute coronary syndromes; DAPT=dual antiplatelet therapy; DES=drug-eluting stents; EES=Everolimus-eluting stents; PES=Paclitaxel-eluting stents; SES=Sirolimus-eluting stents; ZES=Zotarolimus-eluting stent.

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3.1.2. Study devices

The characteristics of stent platforms included in the present analysis are as follows:

- **Early generation sirolimus-eluting stent** consists of a 316L stainless-steel backbone with a strut thickness of 140 µm. It contains a polyethylene-co-vinyl acetate and poly n-butyl methacrylate (PMBA) based PP (13 µm layer) coating. The drug polymer coating is applied to the entire stent surface (140 µg of sirolimus per cm^2 surface area) and releases nearly 80% of the drug over 30 days (28, 154).
- **Early generation paclitaxel-eluting stent** consists of a 316L stainless-steel backbone with a strut thickness of 132 µm. It is coated with a poly styrene-b-isobutylene-b-styrene based PP (22 µm layer). The drug polymer coating is applied to the entire stent surface in single layer (100 µg of paclitaxel per cm^2 surface area). The release of the drug is biphasic with an earlier burst in the first 48 hours followed by a slow release in the following days. Less than 10% of the drug is released over 10 days (28, 154).
- **New generation sirolimus-eluting stent** consists of a 316L stainless steel microporous stent backbone with a thickness 87 µm. It is coated with a mixture of sirolimus, poly-D-L-lactic acid (BP) and shellac resin (a biocompatible resin used in the coating of medical tablets). Drug polymer coating contains 180 µg of sirolimus per cm^2 surface area and releases 40% of the drug over 10 days. The BP matrix is resorbed within 6-9 weeks (150, 155, 156).
- **New generation everolimus-eluting stent** is a new generation DES that consists of a cobalt-chromium backbone with a strut thickness of 81 µm, and PMBA, polyvinylidene fluoride-hexafluoropropylene (PVDF-HFP) based PP (8 µm) coating. It releases everolimus at 100 µg/cm^2 surface area (approximately 80% is released over 30 days) (28, 154).
- **New generation sirolimus- and probucol-eluting stent** consists of a 316L stainless steel microporous stent backbone with a thickness 87 µm. It is coated on site with a mixture of sirolimus (0.7%), probucol (0.7%), and shellac resin (0.07%); no polymer was used. It releases sirolimus and

probucol at 120 µg/cm2 and 100 µg/cm^2 surface area, respectively. No traces of sirolimus, probucol, or resin are observable after 6 to 8 weeks (45, 155, 157, 158).

- **New generation zotarolimus-eluting stent** is a new generation DES that consists of a cobalt-chromium backbone with a strut thickness of 91 µm and a PP coating of a hydrophobic C10 polymer, hydrophilic C19 polymer, and polyvinylpyrrolidone (6 µm). It releases zotarolimus at 160 µg/cm^2 surface area (80% is released over 60 days) (28, 45, 154). The earlier iteration of this stent platform had phosphorylcholine based PP and released 95% of the drug (160 µg/cm^2 surface area) over 14 days (151, 154). As seen with the drug release profile, the newer polymer coating helped extend drug elution and improved biocompatibility and durability.

3.1.3. Study 1: Investigation of the 10-year patterns of stent thrombosis with new- versus early-generation drug-eluting stents

For the purposes of this study, patients were divided based on the generation of the implanted coronary stent during index PCI: patients treated with early- or new-generation DES (78). Stents included in the early-generation DES group were PP-SES and PP-PES. Stents included in the new-generation DES group were PP-ZES, BP-SES, PP-EES and PF-sirolimus/probucol-eluting stents.

Study endpoints

The primary endpoint of interest in this first analysis was definite ST up to 10 years following PCI. Information with respect to probable ST was not reported in all trials. We therefore excluded the probable ST as an endpoint. In the SORT OUT III trial, ST data were limited to 5-year follow-up (148). Data with regard to death and MI for early- and new-generation DES groups were included as additional endpoints to provide more insight to the reported definite ST results. The endpoints considered for this analysis were assessed as per the definitions given in the original trial protocols (44, 150-153). The definition of ST for each study was as follows:

- **SIRTAX trial**: Definite ST was defined as ACS with coronary angiographic documentation of target lesion occlusion or thrombus presence within the previously stented segment (152).

- **ISAR-TEST 4, ISAR-TEST 5, SORT OUT III and EXAMINATION trials:** According to the Academic Research Consortium (ARC) criteria, definite ST was confirmed by coronary angiography or pathology and defined as the presence of a coronary thrombus that is located either intra-stent or within 5 mm proximal or distal to the stent and presence of at least 1 of the following within 48-hour time-interval: (i) acute onset of ischemic symptoms at rest, (ii) new ischemic changes seen on the electrocardiogram (ECG) that indicate acute ischemia, (iii) rise/fall in cardiac biomarkers and (iv) non-occlusive or (v) occlusive coronary thrombus. In the SORT OUT III trial, definite ST was recorded through to 30-day and 12-month follow-up to report late (30 days–1 year) and very late (beyond 1 year) ST (44, 107, 150, 151, 153).

3.1.4. Study 2: Investigation of the sex related differences in 10-year outcomes with drug-eluting stents

In this second analysis, patients were divided into two groups based on sex: female and male.

Study endpoints

The main endpoints of interest were cardiovascular death, death, MI, target-lesion revascularization (TLR), target vessel revascularization (TVR), non-target vessel revascularization (NTVR) and definite ST through to 10 years following PCI. All endpoints were evaluated according to the definitions in the original trials (44, 150-153). All outcomes were evaluated according to the definitions in the original trials (supplementary **Table A2).**

3.2. Study protocol for the ISAR-TEST 4, ISAR-TEST 5 randomized trials and the subsequent pooled subgroup analyses

3.2.1. Study population

ISAR-TEST 4 trial was a non-inferiority study that randomized 2,603 patients in a 2:1:1 fashion to 3 different limus-eluting DES treatment arm: new generation BP-SES, new-generation PP-EES or early-generation, PP-SES (ClinicalTrials.gov identifier: NCT00598676) (40, 150). Similarly, ISAR-TEST 5 trial was also a non-inferiority study that randomized 3,002 patients in a 2:1 fashion to receive new-

generation, PF sirolimus and probucol-eluting stents and new-generation, PP-ZES (ClinicalTrials.gov identifier: NCT00598533) (44, 45). In each participating center (Deutsches Herzzentrum München and 1. Medizinische Klinik, Klinikum Rechts der Isar, both in Munich, Germany), assignment to study treatment was made through sealed opaque envelopes which contains a computer-generated sequence, and randomization was performed immediately after the decision of PCI/ after crossing the lesion with a guide wire. The patients were randomized in the order that they qualified, and the randomization was stratified as per the participating center. Time zero was defined as the time of randomization and hence considered as the time of enrolment for patients. In case a patient had multiple lesions, the same assigned stent type was implanted in all lesions. The trial protocols were approved by the ethics committee of each participating center. The main characteristics of these trials and details regarding study devices are summarized in **Table 1** and **section 3.1.2.** of the "study protocol for the DECADE co-operation series"**.**

The 10-year clinical outcomes were recently published for both studies (40, 45). Patients had clinical follow-up at 1 month, 1 year and then annually thereafter up to 10 years either by office visit or phone contact. Repeat coronary angiography was scheduled for all patients at 6-8 months. In ISAR-TEST 4 and ISAR-TEST 5 trials, 10-year clinical follow-up was not available in 450 patients (17.3%) and 449 patients (14.9%), respectively (40, 45).

Analysis of this extended follow-up data was not pre-specified in the trial protocols. This was approved by the institutional ethics committee of the participating centers. Additional written informed consent form was waived due to routine availability of the follow-up data. All events were adjudicated and classified by an event adjudication committee blinded to treatment allocation. Each study conforms to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices.

3.2.2. Inclusion and exclusion criteria

In both ISAR-TEST 4 and ISAR-TEST 5 trials, patients older than 18 years of age with ischemic symptoms or evidence of inducible or spontaneous myocardial ischemia in the presence of at least

50% de novo stenosis located in native coronary vessels were considered eligible for the study. Patients with a left main stem target lesion, cardiogenic shock, malignancies, or other co-morbidities with less than 12 months life expectancy, conditions that may lead to protocol non-compliance such as allergy to the study medications (clopidogrel, everolimus, sirolimus, probucol, zotarolimus, stainless steel or cobalt-chrome), or present/suspected/planned pregnancy were considered ineligible for these studies. Written informed consent was obtained from each patient or his/her legal representative for participation (44, 150). Key inclusion/exclusion criteria of each trial are also listed in supplementary **Table A1**.

3.2.3. Study Procedures

All patients received an oral loading dose of 600 mg clopidogrel ≥ 2 hours before the intervention, regardless of whether the patient was taking clopidogrel preceding the hospital admission. In the course of the procedure, patients received intravenous aspirin, heparin or bivalirudin. Glycoprotein IIb/IIIa inhibitor usage was allowed according to the judgment of the operators. Following PCI, all patients were prescribed 200 mg/day aspirin indefinitely, clopidogrel 150 mg for the first 3 days (or until discharge) and then 75 mg/day for at least 6 months. The use of other cardiac medications (e.g., beta-blockers, angiotensin-converting enzyme inhibitors, statins etc.) was at the discretion of the primary treating physician. After enrolment, patients remained in hospital for ≥ 48 hours. After randomization, cardiac biomarkers (creatine kinase (CK), creatine kinase myocardial band (CK-MB), Troponin T, or I) were measured every 8 hours for the first 24 hours and then daily thereafter. ECG was recorded in all patients every 24 hours until discharge.

3.2.4. Study endpoints and definitions

In both trials, the primary endpoint was device oriented composite endpoint (DOCE), a composite of cardiac death, target vessel related MI or TLR at 12 months following index PCI. Additional secondary endpoints were all-cause death, in-segment binary restenosis at follow-up angiography, in-stent late lumen loss, and incidence of definite/probable ST (44, 150). At 10-year follow-up, the primary endpoint of ISAR-TEST 4 trial was MACE, a composite of all-cause death, MI, or TLR. The main secondary

endpoint was definite/probable ST (40). For ISAR-TEST 5 trial, the primary endpoint was DOCE at 10 years. Further endpoints of interest included patient oriented composite endpoint (POCE), composed of all-cause death, any MI, or any revascularization, and the individual components of the composite endpoints and the incidence of definite/probable ST through to 10 years (45). The definitions of these clinical endpoints are as follows (44, 107, 150):

- **Cardiac death:** Defined as death due to (i) acute MI, (ii) cardiac perforation/pericardial tamponade, (iii) cardiac arrhythmia or conduction abnormality, (iv) stroke within 30 days of the index procedure or stroke with suspicion of being related to the index procedure, (v) death due to complication of the procedure (including bleeding, vascular repair, transfusion reaction, bypass surgery), or (vi) any death in which a cardiac cause cannot be excluded.
- **Myocardial infarction related to procedure:** Defined as either (i) an elevation in CK or CK-MB ≥ 3 upper range limit (URL) and levels ≥ 50% compared to the most recent pre-PCI measurements, or (ii) new ECG changes consistent with MI and CK-MB (or CK) elevation higher than the URL at two measurements for patients with stable angina pectoris undergoing PCI or (iii) patients with non-ST elevation acute coronary syndromes (NSTE-ACS) undergoing PCI and falling or normal CK-MB (CK) levels. For patients with NSTE-ACS and elevated CK or CK-MB level prior to PCI, a recurrent chest pain lasting more than 30 minutes with either new ECG changes (consistent with second MI) or the next CK or CK-MB biomarker level elevated ≥ 50% above the previous measurements at least 8 to 12 hours following PCI, MI was considered as “procedure-related”.
- **Bypass surgery-related myocardial infarction:** Defined either as an elevation of CK-MB ≥ 10 URL and levels ≥50% compared to the most recent pre-surgery measurements or CK-MB elevation ≥ 5 URL and levels ≥ 50% compared to the most recent pre-surgery measurements along with new abnormal Q-waves on the ECG.
- **Spontaneous myocardial infarction:** Defined as any increase in CK-MB level with or without the development of Q-waves on the ECG.

- **Target lesion revascularization:** Defined as any ischemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. “Ischemia-driven” was defined by (i) the presence of an in-segment diameter stenosis of at least 50% in QCA analysis at follow-up angiography and positive functional test corresponding to the territory supplied by the target lesion or presence of ischemic symptoms and ECG-changes at rest referable to the target lesion, (ii) diameter stenosis of less than 50% at follow-up coronary angiography with a markedly positive functional test or ECG-changes corresponding to the territory supplied by target vessel, or (iii) diameter stenosis of at least 70% at follow-up coronary angiography without documented clinical or functional ischemia. In patients undergoing PCI for multiple lesions, TLR was defined as a reintervention in ≥ 1 of the lesions treated during the index procedure (44).
- **Target vessel revascularization:** Defined as any ischemia-driven repeat PCI or bypass surgery revascularization of any segment in the same vessel proximal or distal to the previously treated coronary lesion, including upstream or downstream side branch vessels (150).
- **Stent thrombosis:** Definition of definite ST is previously described in **section 3.1.3.** of the “study protocol for the DECADE co-operation series”. A probable ST is considered to have occurred in case of any unexplained death within the first 30 days, or any MI that is related to documented acute ischemia in the area of the stent without coronary angiographic confirmation of ST and any other obvious cause, regardless of the time after the procedure. A possible ST is considered to have occurred in case of any unexplained death within the first 30 days following stent implantation until the end of study follow-up (107).

3.2.5. Quantitative coronary angiography analysis

Pre- and post-procedural, and follow-up coronary angiograms were assessed offline in a centralized imaging core laboratory (ISAResearch Center, Munich, Germany) with an automated edge-detection software (CMS version 7.1, Medis Medical Imaging Systems) by two independent operators blinded to treatment allocation. Offline measurements were performed on cine-angiograms recorded after administration of nitroglycerin in the corresponding coronary vessel. The same single worst-view

projections were used at all times. The contrast filled non-tapered catheter tip was used for calibration purposes. Quantitative analysis was performed for both in-stent and in-segment area including 5 mm margins proximal and distal to the stent. In the ISAR TEST 5 trial, intra- and interobserver variability for the vessel size measurement was calculated at 0.09±0.07 mm and 0.08±0.06 mm, respectively (44). Morphological lesion characteristics and coronary restenosis were characterized as per standard criteria (61, 159). The definitions of the angiographic parameters are as follows (44, 150):

- **In-segment binary angiographic restenosis:** Defined as diameter stenosis of at least 50% in the in-segment area at follow-up coronary angiography.
- **In-segment percentage diameter stenosis:** Defined as the maximum percentage of diameter stenosis in the in-segment area at follow-up coronary angiography.
- **In-stent late luminal loss:** Defined as the difference between the minimal luminal diameter at the end of the index procedure and at follow-up coronary angiography.

3.2.6. Study 1: Investigation of the influence of drug-eluting stent polymer on clinical outcomes at 10-years

Patients from ISAR-TEST 4 and ISAR-TEST 5 trials who presented with ACS (defined as STEMI, non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA)) were pooled for the present study (160). Patients treated with early-generation PP-SES from ISAR-TEST 4 trial were excluded from this analysis. Consequently, we compared the following 3 DES groups: (i) new-generation PP-EES and PP-ZES (the PP-DES group, N=690); (ii) BP-SES (the BP-DES group, N=541); and (iii) PF sirolimus and probucol-eluting stents (the PF-DES group, N=811). The ACS patients were further subclassified as either acute MI (STEMI/NSTEMI) or UA. This study conforms to the Declaration of Helsinki and the study protocol was approved by the ethics committee of the participating centers in Munich, Germany.

Study endpoints

The main endpoints of interest included DOCE and POCE. Additional endpoints included were the individual components of the composite endpoints and definite/probable ST. Detailed definition of each endpoint is previously shown in **section 3.2.4**. The study flow is shown in **Figure 2**.

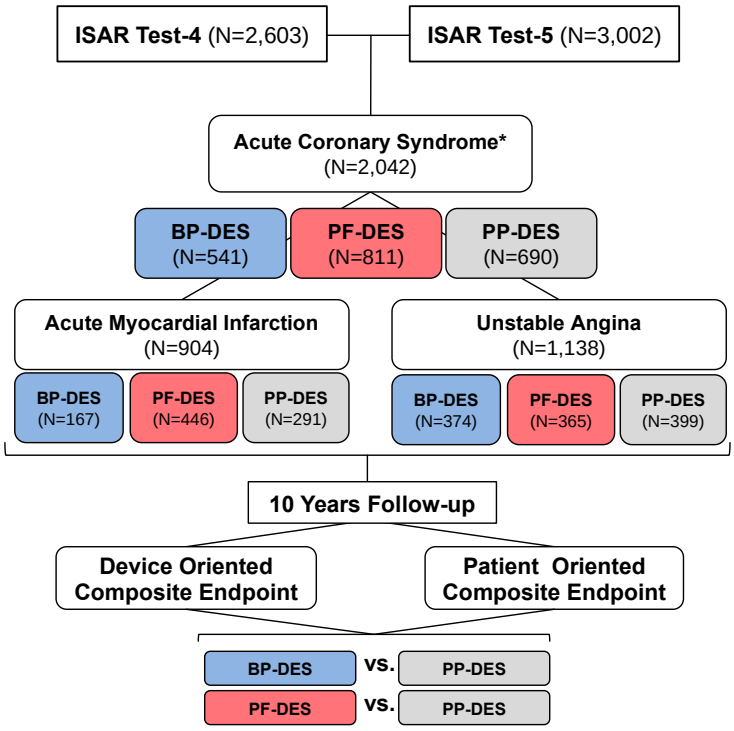


Figure 2. Study flowchart for the investigation of the influence of DES polymer on 10-year clinical outcomes.
*A multivariate approach was adopted for the purpose of adjusted analysis. Results for both acute myocardial infarction and unstable angina groups were computed using unadjusted analysis (160).
BP=biodegradable polymer; DES=drug-eluting stents; PF=polymer-free; PP= permanent polymer.

3.2.7. Study 2: Investigation of the influence of drug-eluting stent overlap on the risk of major adverse cardiovascular events at 10-years

In the present study, patient-level data from ISAR-TEST 4 and ISAR-TEST 5 trials were pooled and divided into two groups, based on the presence (1,824 patients, 2,524 lesions) or absence (3,781 patients, 5,239 lesions) of stent overlap as per QCA analysis (161). Stent overlap was defined as the use of ≥ 2 stents to treat a single lesion with an overlapping zone of ≥ 1 mm (94). This study conforms to the Declaration of Helsinki and the study protocol was approved by the ethics committee of the 2 participating centers in Munich, Germany.

Study endpoints

The main clinical endpoints were the 10-year incidence of all-cause death, MI, TLR and definite/probable ST. An additional angiographic endpoint was binary angiographic restenosis (BAR) at

6–8-month follow-up coronary angiography. The clinical and angiographic outcomes were also investigated for specific subsets, including stent generation (first vs. second generation) and polymer type (PP vs. BP vs. PF). Detailed definition of each endpoint is previously explained in **section 3.2.4**.

3.2.8. Study 3: Investigation of the 10-year comparative frequency of events attributable to target- and remote-vessel related disease progression following drug-eluting stent implantation

In this study, all patient-level data were pooled from ISAR-TEST 4 and ISAR-TEST 5 randomized trials (162). For the purposes of this analysis, patients treated with early-generation PP-SES from the ISAR-TEST 4 trial were excluded (163). Our aim was to define the 10-year risk of events attributable to the stented and non-stented vessels in patients implanted with newer generation DES. The study conforms to the Declaration of Helsinki and the study protocol was approved by the ethics committee of the 2 participating centers in Munich, Germany.

Study endpoints

The primary endpoints were TVRE, a composite of first target vessel MI or TVR, and NTVRE, a composite of first non-target vessel MI or NTVR. The "target vessel" was defined as the vessel or vessels treated at the time of the index procedure. All other vessels were defined as "non-target vessels". Accordingly, either no events, or TVRE, NTVRE or both could have occurred at 10-year follow-up. Secondary endpoints were the individual components of the primary endpoints, TVRE and NTVRE. We also assessed the median time to event for patients experiencing a specific endpoint during the follow-up and the time interval between events for patients who experienced both a TVRE and NTVRE over 10 years. Detailed definition for MI and TVR was explained in **section 3.2.4**.

3.3. Study protocol for the derivation and validation of a risk prediction model to predict recurrence following percutaneous coronary intervention for drug eluting stent restenosis

3.3.1. Study population

The current study included consecutive patients undergoing PCI for DES-ISR from two centers (Klinikum Rechts der Isar and Deutsches Herzzentrum München, both in Munich, Germany) between

September 2005 and December 2013. Clinical, procedural, and angiographic characteristics were analyzed for each patient undergoing PCI and the relevant data were collected and entered into a computer database by the Clinical Data Management Centers. The primary aim of this analysis was to develop and validate a risk prediction model to predict recurrent DES-ISR following PCI up to 1-year follow-up. Accordingly, the whole patient group was randomly divided into training and validation populations in a 3:1 ratio. The statistical methodology is described in detail in **section 3.7**.

3.3.2. Angiographic data analysis

Pre- and post-procedural and the follow-up coronary angiograms were digitally recorded and assessed offline in a centralized core laboratory (ISAResearch Center, Munich, Germany). The angiographic ISR pattern was classified as per Mehran classification (61). Herein, restenosis is characterized according to (i) ISR length (≤10 mm: focal, >10 mm: diffuse), (ii) ISR location (within or beyond stent margins) and (iii) presence of occlusion. Application of the Mehran classification hence results in four groups (61):

- **Type I:** Focal
- **Type II:** Diffuse, within stent
- **Type III:** Diffuse, within and beyond stent
- **Type IV:** Occlusive

The presence or absence of coronary artery calcification was adjudicated based on the following angiographic classification system (moderate or severe calcification were classified as coronary artery calcification for this study) (164):

- **None:** no radiopacity.
- **Mild:** faint radiopacities noted during the cardiac cycles.
- **Moderate:** dense radiopacities noted only during the cardiac cycle.
- **Severe:** dense radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen.

3.3.3. Study endpoints

The primary endpoint of the current study was the rate of repeat PCI for recurrent DES-ISR, defined as any repeat PCI of the initially treated target ISR lesion. Additional endpoints included all-cause death, MI, definite ST, and CABG following repeat PCI for recurrent DES-ISR. MI was defined based on the Universal Definition of Myocardial Infarction (UDMI) including clinical symptoms, electrocardiographic changes, and changes of cardiac biomarkers (107, 165). ST was defined as per the ARC criteria (see **section 3.1.3.** and **section 3.2.4**.).

3.4. Study protocol for the investigation of the impact of optical neointimal characteristics and treatment modality on major adverse cardiovascular events in patients with in-stent restenosis

3.4.1. Study population

This study was a multi-centric registry that collected patient-level data from the following 3 European centers: (i) Hospital Universitario de La Princesa, Madrid, Spain (from 2010 to 2017); (ii) Hospital Universitario Clínico San Carlos (from year 2010 through to 2011); (iii) Deutsches Herzzentrum München, Germany (from 2012 to 2017) (166). Patients were considered eligible if they presented with ischemic symptoms and/or evidence of myocardial ischemia and underwent intravascular OCT imaging acquisition and subsequent PCI treatment for ISR. Informed consent was obtained prior to each PCI procedure. As all procedures were required on a clinical basis, ethical approval was waived. Treatment modality (DES implantation or DCB angioplasty) was at the discretion of the operator. All patients had clinical follow-up either by office visit, phone contact or structured follow-up letter. The aim of this analysis was to evaluate the relationship between the neointimal pattern and clinical outcomes following ISR treatment; and to investigate a potential interaction between neointimal pattern and treatment modality in relation to clinical outcomes.

3.4.2. Study endpoints and definitions

The primary endpoint was the cumulative incidence of MACE, a composite of all-cause death, MI, or clinically driven TLR. The secondary endpoint was clinically driven TLR. In addition, individual components of MACE were assessed separately. The study endpoint definitions are as follows:

- **Myocardial infarction:** Defined as a rise and/or fall in cardiac biomarkers (preferably cardiac troponin) with at least one value >99th percentile URL and with at least one of the following: (i) ischemic symptoms; (ii) development of pathological Q waves in the ECG; (iii) new or presumedly new ST-segment-T wave changes or new left bundle branch block; (iv) imaging evidence of new loss of viable myocardium or abnormality of regional wall motion. MI was defined according to the Third UDMI (167). In this study, cardiac troponin was the preferred cardiac biomarker and CK or its myocardial band isoform were used only in the case cardiac troponin values were not available.
- **Clinically driven target lesion revascularization:** TLR was defined as any repeat PCI of the target lesion or coronary artery bypass surgery of the target vessel for the treatment of restenosis or other complication(s) of the target lesion in case the treated segment includes the 5 mm margin proximal and distal to the stent. A revascularization procedure was considered as "clinically driven" with the condition that a ≥50% percent diameter stenosis at coronary angiography was documented together with any of the following: (i) history of recurrent angina pectoris seemingly related to the target vessel, (ii) objective ischemic signs at rest (ECG changes) or (iii) positive non-invasive functional test seemingly related to the target vessel. TLR was defined according to the ARC-2 consensus document (168).

3.4.3. Angiographic data acquisition and analysis

Pre- and post-PCI coronary angiograms were recorded and assessed in a centralized imaging core laboratory (ISAResearch Center, Munich, Germany) with an automated edge-detection system (Medis Medical Imaging Systems, Leiden, The Netherlands). Offline measurements were performed on cine-angiograms recorded after administration of nitroglycerin in the corresponding coronary vessel. The contrast filled, non-tapered catheter tip was used for calibration purposes. Quantitative analysis was

performed for both in-stent and in-segment area including 5 mm margins proximal and distal to the stent. The Mehran classification was used to classify the angiographic pattern of ISR (61).

3.4.4. Optical coherence tomography data acquisition

Intravascular OCT was performed with non-occlusive technique using commercially available OCT imaging systems (C7XR, Ilumien or Ilumien Optis, St. Jude Medical, St. Paul, MN, USA) following the administration of intracoronary nitrates. An OCT pullback of the entire stented segment (including both distal and proximal references) was acquired with a rapid exchange imaging catheter (Dragonfly™ or Dragonfly Duo™, St. Jude Medical, St. Paul, MN, USA) and 3-5 ml/sec contrast injection through the guiding catheter. In case the segment of interest was too long, an additional pullback was obtained using angiographic landmarks. Small balloon dilatation (≤ 2.0 mm in diameter) at low pressure was allowed to achieve sufficient blood clearance and overall pullback quality in the event of sub-occlusive or occlusive ISR lesions.

3.4.5. Quantitative analysis as per optical coherence tomography

Raw OCT data were sent to an imaging core laboratory (ISAResearch Center, Munich, Germany) for offline analysis. Quantitative analysis was performed for every 1 mm along the entire segment of interest with measurements of both stent and luminal cross-sectional area using dedicated software (St. Jude Medical, St. Paul, MN, USA). The start and end frames of the stented segment were determined based on the extent of strut presence and a ¾ minimum of the perimeter was required for analysis. The number of stent struts was recorded for each analyzed frame, and the extent of tissue coverage was measured at the midpoint of each strut.

- **Covered stent strut:** The cut-off for strut coverage was established as per minimal axial resolution of OCT (20µm) and struts were accepted as “covered” if the tissue thickness was equal to, or more than 20µm.
- **Uncovered stent strut:** Struts were considered uncovered if any part was visibly exposed to the lumen. Incomplete stent strut apposition was considered present if the axial distance between the

strut's surface to the luminal surface > (strut thickness) + (polymer thickness) + 20µm (the minimal axial resolution of OCT).

- **Reference area:** None or minimally diseased distal and proximal reference segments within 10 mm from the stent edges were chosen for morphometric analysis. The reference area was calculated as (proximal + distal reference lumen area) / 2. If there were no analyzable proximal and/or distal non-stented reference segments present, the reference area was calculated from the most proximal and/or distal stented segments.
- **Stent under-expansion:** Stent under-expansion was defined by a stent expansion index (the minimal stent area divided by the reference area) lower than 0.8.

3.4.6. Qualitative analysis as per optical coherence tomography

With regard to qualitative analysis, a quadrant-based approach was adopted for neointimal characterization at the frame displaying the maximal percentage area stenosis and the 5 proximal and distal analyzed frames (169). Each frame was subdivided into 4 quadrants of 90° degree and the neointimal characteristics were individually assessed for each of them. The neointimal tissue (according to intravascular OCT imaging) has been traditionally classified as either homogeneous, heterogeneous, or layered (143, 170). Nevertheless, previous histopathological validation studies against OCT have shown homogeneous patterns to consistently correlate with abundance of smooth muscle cells and collagen/proteoglycan rich tissue, whereas the remaining neointimal patterns revealed numerous other matching histological components (171). With this in mind, we categorized the neointimal tissue as homogenous or inhomogeneous/non-homogenous in order to apply a histopathology-based and treatment-oriented classification. The latter category included heterogeneous, layered quadrants, or quadrants with neoatherosclerosis. Based on the median of distribution of non-homogeneous quadrants, the study group was divided into low and high neointimal inhomogeneity groups in order to further investigate the influence of an increase in inhomogeneous quadrants on clinical outcomes of interest. In addition, the high inhomogeneity group was classified according to level of neointimal atherosclerotic changes (low and high neoatherosclerosis subgroups).

Neoatherosclerosis was defined by the presence of one or more of the following (**Figure 3**) (92, 132, 137, 172):

- **Foam cell/macrophage infiltration**: A signal-rich band with significant attenuation within the neointimal tissue.
- **Lipid-laden tissue within stent***:* Signal-poor region with high attenuation and diffuse borders.
- **Neointimal calcification***:* Low-signal-intensity area with poor attenuation and sharp demarcation of its borders.

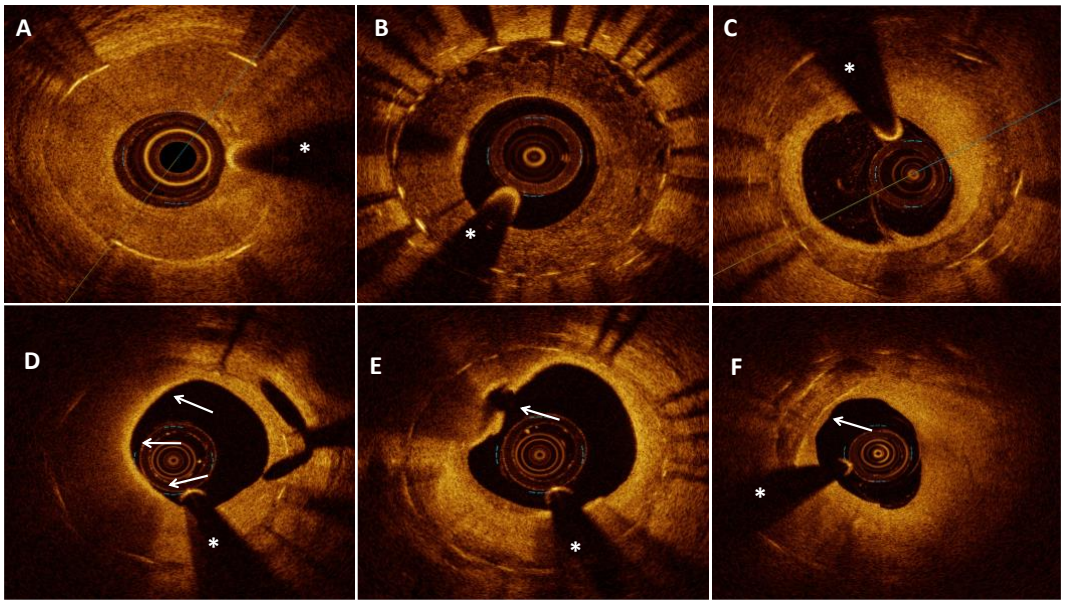


Figure 3. Representative images of optical coherence tomography findings in patients presenting with in-stent restenosis (166)**.**
(Panel A) Homogeneous neointimal pattern, **(Panel B)** Heterogeneous neointimal pattern, **(Panel C)** Layered neointimal pattern, **(Panel D)** Neoatherosclerosis with foam cell infiltration (arrows), **(Panel E)** Neoatherosclerosis and ruptured thin-cap fibroatheroma (arrow), **(Panel F)** Neointimal calcification (arrow).
*=guidewire artifact.

With respect to inter-observer variability in neointimal characterization, there was an exceptional agreement between the 2 experienced cardiologists independently analyzing the data (Cohen's κ=0.931 for a subgroup of 50 randomly chosen OCT pullback).

3.5 Study protocol for the investigation of the impact of optical neointimal characteristics and treatment modality on periprocedural myocardial injury in patients with in-stent restenosis

3.5.1. Patient population

Patients with intravascular OCT undergoing PCI for treatment of ISR at our center were considered eligible for inclusion (German Heart Center Munich, Department of Cardiology) (173). For the purposes of this study, only patients with normal baseline cardiac troponin (high-sensitivity cardiac troponin T (hs-cTnT) ≤ 99th percentile of URL) or above baseline but stable/falling values (hs-cTnT ≥ 99th percentile of URL) were deemed eligible. The use of such criteria was in order to ascertain the relation between the PCI procedure and increases in cardiac biomarker values. Cardiac biomarker-based inclusion criteria were defined according to the fourth UDMI (174). Periprocedural myocardial injury (PMI) was defined according to 4th UDMI and the ESC/ European Association of percutaneous cardiovascular interventions (EAPCI) consensus document (175):

- **Minor periprocedural myocardial injury:** An increase of hs-cTnT > 99th percentile URL in patients with normal baseline troponin values.
- **Major periprocedural myocardial injury:** An increase of hs-cTnT > 5 x 99th percentile URL in patients with normal values of cardiac troponin.

For the diagnosis of PMI, a rise of hs-cTnT above 20% of the baseline value was required in patients with above baseline but stable/falling hs-cTnT values. Informed consent was obtained prior to each PCI procedure. All patients had clinical follow-up up to 2 years either by office visit, phone contact or structured follow-up letter. The aim of this analysis was to assess the influence of 2 factors on the occurrence of PMI: (i) extent of neointimal inhomogeneity and neoatherosclerosis, (ii) the type of PCI treatment for ISR.

3.5.2. Angiographic and optical coherence tomography data acquisition and analysis

Pre- and post-procedural coronary angiograms and raw intravascular OCT imaging data were assessed offline in an imaging core laboratory (ISAResearch Center, Munich, Germany). With regard to OCT imaging analysis, a quadrant-based approach was adopted for neointimal characterization at the

frame displaying the maximal percentage area stenosis and the 5 preceding and following analyzed frames (166, 169).

Neointimal tissue was categorized as homogeneous or inhomogeneous according to intravascular OCT imaging. Inhomogeneous neointimal tissue included either heterogeneous, layered or neointimal atherosclerotic quadrants. Atherosclerotic changes of the neointima were defined by the presence of one or more of the following: foam cell/macrophage infiltration, lipid-laden tissue within the neointima and/or neointimal calcification.

To further assess the influence of an increase in inhomogeneous quadrants on PMI, patients were divided into low and high neointimal inhomogeneity based on the median distribution of non-homogeneous quadrants. In addition, the high inhomogeneity group was categorized according to level of neointimal atherosclerotic changes (low and high neoatherosclerosis subgroups). In-depth description and definitions concerning angiographic, intravascular OCT data acquisition and analysis are previously explained in **section 3.4.3.** up to **section 3.4.6.**

3.5.3. Biochemical parameters

"Blood samples for hs-cTnT measurements were collected in tubes containing lithium-heparin anticoagulant at the time of admission, 3–6 h after PCI, at 6 h intervals in case of rising values, and on a daily basis thereafter. The plasma concentration of hs-cTnT was measured using a high-sensitivity assay on a Cobas e411 immunoanalyser based on electrochemiluminescence technology (Roche Diagnostics, Rotkreuz, Switzerland). The limit of blank for this assay—the concentration below which analyte-free samples are found with a probability of 95%—is ≤ 3 ng/L. The functional sensitivity— the lowest analyte concentration that can be reproducibly measured with a coefficient of variation ≤ 10%—is ≤ 13 ng/L. The 99th URL is 14 ng/L. Baseline and peak post-procedural hs-cTnT were used for the current analysis. Other biochemical parameters were measured using standard laboratory methods." (173)

3.6. Study protocol for the investigation of the comparative efficacy and safety of novel $P2Y_{12}$ receptor inhibitor agents in patients presenting with ST-elevation myocardial infarction.

3.6.1. Study population

The ISAR-REACT 5 study (ClinicalTrials.gov identifier: NCT00598533) was an investigator-initiated, phase 4, multicenter, randomized, open-label trial that investigated whether ticagrelor is superior to prasugrel in patients with ACS planned for an invasive management strategy (131). This was a prespecified analysis of this clinical trial, which was conducted between September 2013 and February 2018. All patients who presented with STEMI (N=1,653), defined as the presence of chest pain lasting ≥20 minutes at rest within 24 hours before randomization associated with electrocardiographic changes (ST-segment elevation of ≥1 mm in ≥ 2 extremity electrocardiographic leads or ≥2 mm in ≥ 2 contiguous precordial leads or left bundle-branch block of new onset), were included (176). The study conforms to the Declaration of Helsinki, and the study protocol was approved by the local ethics committee at each participating center. Written informed consent was obtained from all patients.

The clinical follow-up was scheduled at 30 (±10) days, 6 (±1) months, and 12 (±1) months. Source data were solicited in case of potential endpoint–related adverse events. All serious adverse events, primary and secondary endpoints were monitored on site. Patients were either monitored at the hospital, or by outpatient visits, through telephone, or by structured follow-up letters (176). The study flow is shown in **Figure 4**.

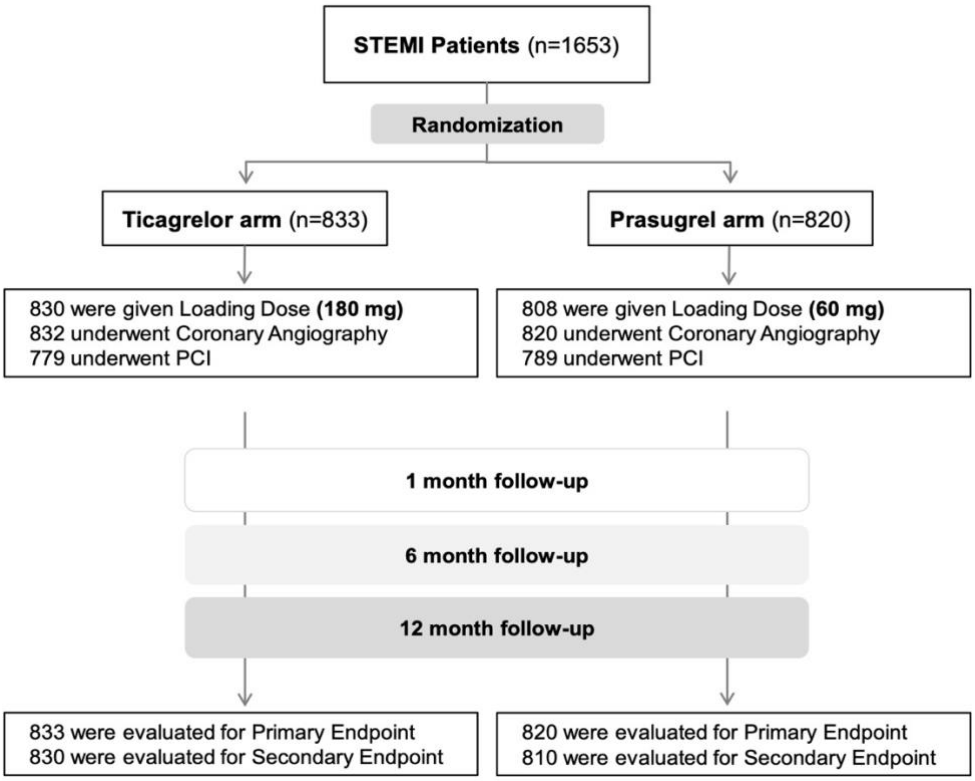


Figure 4. Study flowchart for the investigation of the comparative safety and efficacy of novel $P2Y_{12}$ receptor inhibitor agents in patients presenting with ST-elevation myocardial infarction (176).

PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.

3.6.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria of ISAR-REACT 5 trial has been previously reported:

- **Inclusion Criteria:** Patients older than 18 years of age presenting with ACS (STEMI, NSTEMI or UA) and planned to undergo an invasive management strategy were considered eligible for the study (131).
- **Exclusion Criteria:** Patients with [1] intolerance or allergy to the study medications (ticagrelor, prasugrel), [2] history of any stroke, transient ischemic attack, or intracranial bleeding, [3] known intracranial neoplasm, intracranial arteriovenous malformation, or intracranial aneurysm, [4] active bleeding or clinical findings, that are associated with an increased risk of bleeding, [5] fibrin-specific fibrinolytic therapy < 24 hours before randomization, non-fibrin-specific fibrinolytic therapy < 48 hours before randomization, [6] known platelet count of less than 100.000/µL at the time of screening, [7] known anemia (hemoglobin < 10 g/dL) at the time of screening, [8] oral anticoagulation that cannot be safely discontinued for the duration of the study, [9] INR known to

be > 1.5 at the time of screening, [10] chronic renal insufficiency requiring dialysis, [11] moderate or severe hepatic dysfunction (Child Pugh B or C), [12] increased risk of bradycardia events (Sick Sinus, atrioventricular block grade II or III, bradycardia-induced syncope), [13] index event is an acute complication (<30 days) of PCI, [14] concomitant medical illness that in the opinion of the investigator is associated with a life expectancy < 1 year, [15] concomitant oral or intravenous therapy with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, grapefruit juice >1 L/d), CYP3A substrates with narrow therapeutic indices (e.g., cyclosporine, quinidine), or strong CYP3A inducers (e.g., rifampin/rifampicin, phenytoin, carbamazepine, dexamethasone, phenobarbital) that cannot be safely discontinued, [16] ≥ 1 doses of ticagrelor or prasugrel within 5 days before randomization, [17] no written informed consent, [18] participation in another investigational drug study, [19] previous enrolment in this study, [20] women who were of childbearing potential with no negative pregnancy test and don't agree to use a reliable method of birth control during the study, [21] pregnancy, giving birth within the last 90 days, or lactation, [22] patients who are unable to cooperate with protocol requirements were considered ineligible for the study (131).

For detailed list of inclusion/exclusion criteria and definitions, please see the main publication by Schüpke et al. "Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes" (ClinicalTrials.gov identifier: NCT00598533) in New England Journal of Medicine (131).

3.6.3. Antiplatelet therapy

Patients were randomly assigned to study drug (ticagrelor or prasugrel) as soon as possible after hospital admission prior to coronary angiography and PCI. Time 0 was defined as the time of randomization. The time of study drug initiation was the same for ticagrelor and prasugrel (as soon as possible after stratified randomization). Patients in the ticagrelor group received a loading dose of 180 mg and a maintenance dose of 90 mg twice daily thereafter. Patients in the prasugrel group received

a loading dose of 60 mg and continued with a maintenance dose of 10 mg once daily. In the prasugrel group, a reduced maintenance dose of 5 mg daily was recommended in patients with a body weight of less than 60 kg and in patients ≥75 years of age (177). All patients received aspirin therapy consisted of a loading dose of 150 to 300 mg of intravenous or chewed aspirin and a maintenance dose of 75 to 100 mg daily.

3.6.4. Study endpoints and definitions

The primary efficacy endpoint was a composite of all-cause death, MI, or stroke at 1 year following randomization. The secondary safety endpoint was the incidence of bleeding, defined as type 3 to 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria at 1 year after randomization (178). Other endpoints analyzed were the components of the primary endpoint, cardiovascular death, and ST (definite or probable). Definition of each endpoint are as follows (107, 131, 167, 178):

- **Myocardial infarction:** The definition of MI was based on the Third UDMI (167). Cardiac troponin was the preferred cardiac biomarker and CK or CK-MB were used only in the case cardiac troponin values were not available. Based on this definition, MI was subclassified into following types (131):

➢ **Type 1**	Spontaneous MI	Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.
➢ **Type 2**	MI secondary to ischemic imbalance	In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand.
➢ **Type 3**	MI resulting in death when biomarker values are unavailable	Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
➢ **Type 4a**	MI related to PCI	MI related to PCI is defined by elevation of cardiac troponin values 5 x 99th percentile URL in patients with normal baseline values (< 99th percentile URL) or a 20% rise of cardiac troponin values if the baseline values are elevated and are stable or falling. In addition, either (i)

		symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new left bundle branch block, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
➢ **Type 4b**	MI related to ST	MI associated with ST is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.
➢ **Type 5**	MI related to coronary artery bypass grafting (CABG)	MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values 10 x 99th percentile URL in patients with normal baseline cardiac troponin values (99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- **Stroke:** The diagnosis of stroke involves confirmation by CT, MRI or autopsy and it is defined as the new onset of focal or widespread neurological deficit caused by ischemia or hemorrhage within or around the brain and lasting for >24 hours or leading to death (131).
- **Stent Thrombosis:** ST was defined as per the ARC criteria (see **section 3.1.3.** and **section 3.2.4**.) (107).
- **Bleeding:** Bleeding was defined as type 3 to 5 bleeding events according to BARC criteria (178). The definition as per the type of bleeding is as follows (131):

➢ **Type 0**	No bleeding.
➢ **Type 1**	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
➢ **Type 2**	Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (i) requiring nonsurgical, medical intervention by a healthcare professional, (ii) leading to hospitalization or increased level of care, or (iii) prompting evaluation.
➢ **Type 3a**	Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed); any transfusion with overt bleeding.

➢ **Type 3b**	Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin or hemorrhoid); bleeding requiring intravenous vasoactive agents.
➢ **Type 3c**	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture; intraocular bleed compromising vision.
➢ **Type 4**	CABG-related bleeding: perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period**; chest tube output ≥2L within a 24-hour period.
➢ **Type 5a**	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
➢ **Type 5b**	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).

** Cell saver products are not counted.

3.7. Statistical analysis

In all studies previously mentioned and included in this thesis, continuous data are presented as means ± standard deviation or medians and interquartile ranges (with 25^{th} to 75^{th} percentiles). Categorical data are presented as counts and proportions (%). Data distribution was tested for normality by using the Kolmogorov-Smirnov test for goodness-of-fit. Differences between groups were checked for significance using either a Student's t test, Wilcoxon rank sum test, Kruskal-Wallis test or an analysis of variance test depending on the distribution and the number of groups. The chi-squared test or Fisher exact test (for expected cell values of less than 5) was used to check for differences between categorical variables.

Adverse events were analyzed with the use of the Kaplan Meier method (for all-cause death) or cumulative incidence after accounting for the competing risk of death (for all outcomes other than all-cause death). The cumulative incidence functions were computed for outcomes other than death to account for competing risks using the *cuminc* function in the *cmprsk* package in R and compared using a Cox proportional hazards model (78, 179, 180). Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using a Cox proportional hazards model after checking for fulfilment of the proportional hazards assumption as per the method of Grambsch and Therneau (181). Statistical analysis was performed using the R ≥ 3.6.0 Statistical Package (The R Foundation for Statistical Computing, Vienna, Austria). A two tailed p value of <0.05 was taken to confer statistical significance. Additional details with regards the statistical methodology for each individual study are as follows:

3.7.1. Investigation of the 10-year patterns of stent thrombosis with new- versus early-generation drug-eluting stents

Individual participant data were analyzed using a 1-stage approach. Log-rank test was used to test the differences between 2 groups.

"Adjusted hazard ratios ($HR_{adjusted}$) with pertinent 95%CI were reported. These were derived from a conventional multivariable analysis with adjustment for the following variables: age, sex, diabetes mellitus, hypertension, smoking, hypercholesterolemia, history of myocardial infarction, acute

coronary syndrome, and vessel treated. We also performed a multivariate sensitivity analysis, which accounted for several angiographic and procedural variables in addition to patient characteristics with < 5% missing values in the pooled dataset, including age, sex, diabetes, hypertension, smoking status, hypercholesterolaemia, previous myocardial infarction, acute coronary syndrome presentation, treated vessel, lesion complexity, balloon diameter and total stented length. We performed a landmark analysis for ST for the following time periods: 0 to 30 days (accounting for acute and subacute ST), 30 days to 1 year (accounting for late ST), 1 to 5 years (accounting for VLST) and 5 to 10 years (accounting for VVLST). ST event rates were also calculated for these time periods, compared using the exact 2-sided Poisson test and expressed as a rate ratio (RR) and 95%CI. For ST from 0 to 30 days after PCI, rates of ST were expressed as the number of events per 1000 patient days of follow-up. From 30 days to 1 year, 1 to 5 years and 5 to 10 years after PCI, the ST rate was expressed as the number of events per 1000 patient years of follow-up." (78)

3.7.2. Investigation of the sex related differences in 10-year outcomes with drug-eluting stents

"Analysis of individual participant data was performed using a 1-stage approach by entering a clustering effect by parent study in all univariable and multivariable models focusing on sex. […] *Survival was analyzed by the Kaplan-Meier method, and differences between the 2 groups were tested with the log-rank test.* […] *Fulfillment of the proportional hazards assumption was assessed according to weighted residuals and by checking the graph of the scaled Schoenfeld residuals* [(181)]. […] *Adjusted HRs (HR_{adj}) and 95% CIs served as summary estimates. Conventional multivariable analyses were performed with adjustment for the following variables: age (represented as a continuous variable without any transformation), DES generation, diabetes, hypertension, smoking, hypercholesterolemia, MI history, acute coronary syndrome, and vessel treated. The selection of these variables was based on prior knowledge of their association with clinical outcomes* [(182)]. *Landmark analyses were also performed with a landmark at 1 year for death and TLR and at 30 days for MI. In addition, we investigated a potential statistical interaction between sex and age (≥75 years versus <75 years),* [(183)] *clinical presentation (acute coronary syndrome versus chronic coronary syndrome), and DES generation*

(early- versus new-generation DES) for the risk of cardiovascular death, MI, TLR, TVR, nTVR, and definite ST by entering an interaction term in the unadjusted Cox proportional hazards model and calculating a P value for interaction (P_{int}). For the subgroup analysis of cardiovascular death, adjustment for age was performed in all subgroups. For the subgroup analyses of the other outcomes (MI, TLR, TVR, nTVR, and definite ST), no adjustment for age was performed because the specific effect of age was observed only for cardiovascular and all-cause death. We also checked for a possible effect of between-study heterogeneity on sex-related outcomes by adding an interaction term between trial and sex and between trial arm and sex in the multivariable models for the outcomes of interest." (184)

3.7.3. Investigation of the influence of drug-eluting stent polymer on clinical outcomes at 10-years

"The analysis of the outcomes of interest was performed on an intention-to-treat basis with adjustment for the following variables: multivessel disease, number of lesions, clinical presentation (acute MI), vessel stented, lesion length, preprocedure percentage stenosis, and total stented length." *(160)*

3.7.4. Investigation of the influence of drug-eluting stent overlap on the risk of major adverse cardiovascular events at 10-years

"Conventional multivariable analysis was performed with adjustment for the following variables; DES type, age, gender, diabetes, hypertension, smoking, hypercholesterolaemia, multivessel disease, clinical presentation, prior MI, Prior CABG, [body mass index (BMI)] *BMI, ejection fraction, target vessel, chronic total occlusion, lesion complexity, lesion length, total stented length, and number of stents. The results of the adjusted analysis are reported as adjusted hazard ratios ($HR_{adjusted}$) and p values ($p_{adjusted}$). Sensitivity analysis was also performed, comparing outcomes amongst three groups; patients with a single stent, patients with multiple stents without stent overlap and patients with stent overlap."* (161)

3.7.5. Investigation of the 10-year comparative frequency of events attributable to target- and remote-vessel related disease progression following drug-eluting stent implantation

"In addition to the primary analysis, the cumulative incidences of TVRE and NTVRE were analysed as per stent polymer type, dividing patients into three groups; BP-DES, PP-DES and PF-DES." (162)

3.7.6. Investigation on the derivation and validation of a risk prediction model to predict recurrence following percutaneous coronary intervention for drug eluting stent restenosis

"The cumulative incidences of repeat PCI for recurrent DES-ISR and definite ST were calculated at the lesion level, and the incidences of the remaining endpoints were calculated at the patient level.

Firstly, the least absolute shrinkage and selection operator (LASSO) method was used to select clinical, angiographic and procedural variables for the logistic regression analysis. Missing data were imputed using the multiple imputation by chained equations (R package mice) method. The use of LASSO regression was deemed appropriate in order to improve the prediction accuracy and interpretability of the regression model and to prevent overfitting [(185)]*."* (186)

The variables considered by the LASSO regression model were: age, BMI, sex, diabetes mellitus, hypertension, hypercholesterolemia, smoking status, ACS presentation, multi-vessel disease, previous MI, previous CABG, restenosis morphology (focal or non-focal), left circumflex coronary artery (LCx), ostial LCx coronary artery, distal vessel, vessel calcification, ostial lesion, bifurcation lesion, CTO lesion, restenosis severity ≥90%, maximum device diameter (stent or balloon) and short restenosis interval (<6 months between the initial DES implantation and the initial treatment of the DES-ISR).

"Secondly, a logistic regression analysis was performed using the variables selected by LASSO to examine factors associated with repeat PCI for recurrent DES-ISR at 1-year follow-up [(187)]. *Regression coefficients were corrected for intracluster correlation in patients with multiple ISR lesions (R package bootcov)* [(188)]. *An exploratory analysis was also performed to predict repeat PCI for recurrent DES-ISR at longer-term follow-up (namely, from 1 to 5 years after the first reintervention for DES-ISR). The overall performance of the risk prediction model was assessed using the C-statistic. The training cohort was used to create the model with all LASSO variables, whilst the validation cohort was used to qualify*

the performance of the model. Using 400 cycles of bootstrap resampling, we performed an internal validation of the model (including only the significant variables) and repeated this analysis for a model based on the Mehran classification, after dichotomisation of the original four Mehran classification ISR categories into focal or non-focal (this latter group included diffuse intrastent, diffuse proliferative and total occlusion ISR lesions) [(61)]. *This analysis allowed empirical bootstrap distributions of sample means and bootstrap confidence intervals of the C-statistics and integrated discrimination improvements (IDI) to be calculated. The C statistic is a measure of the predictive accuracy of a model, and the IDI is a measure to quantify risk discrimination improvement* [(189, 190)]. *We calculated the delta C-statistic and delta IDI to determine whether any differences in the predictive accuracy and the risk discrimination improvement between the two models were statistically significant.*

A classification and regression tree (CART) analysis was performed with regression trees constructed using only the independent predictors of repeat PCI for recurrent DES-ISR. In addition, a numerical scoring system based on the four significant predictors served to help determine the risk of repeat PCI for recurrent DES-ISR at 1-year follow-up according to the number of predictor variables present. The risk of repeat PCI for recurrent DES-ISR was calculated as a cumulative incidence after accounting for the competing risk of death and compared using a Cox proportional hazards model with correction for intracluster correlation for lesions with increasing numbers of predictor variables compared to those without any predictor variables. These results are presented as hazard ratios (HR) and 95% confidence intervals (CI). Rates of repeat PCI for recurrent DES-ISR for patients as per the identified predictor variables were also calculated as cumulative incidences after accounting for the competing risk of death and compared using a Cox proportional hazards model with correction for intracluster correlation during two time periods (namely from 0 to 1 year and from 1 to 5 years after PCI). The results are presented as cumulative incidences, HRs and 95% CIs for both time periods." (186)

All analyses were in accordance with the TRIPOD statement (191).

3.7.7. Investigation of the impact of optical neointimal characteristics and treatment modality on major adverse cardiovascular events in patients with in-stent restenosis

"To account for the clustered nature of the data, a linear mixed model was used for the analysis of OCT data. The model contained a fixed-effects term (neointimal pattern) and a random intercept as random-effects term for patient in case of frame-level analysis and as nested random-effects term for patient and frame for strut-level analysis. […] *The 2 objectives of the study were addressed in a statistical two-step approach. First, we compared 2 patient groups defined by the OCT neointimal pattern (high and low inhomogeneity groups) regarding their clinical outcomes after PCI for ISR. The risk for the primary and secondary endpoints of the study was assessed by the use of a) a univariable Cox proportional hazards model including only the OCT pattern of neointima as an independent variable; and b) a multivariable model including baseline clinical and angiographic characteristics in addition to the OCT pattern of neointima. Second, we assessed whether the relation between the OCT pattern of neointima and clinical outcomes is influenced by the type of PCI performed for treatment of ISR (DCB or DES). For this purpose, we entered the interaction term of OCT-pattern of neointima * PCI type into the multivariable model described above. In the case of a significant adjusted interaction between these 2 variables, we proceeded with an illustrative comparison of the outcomes for the 2 PCI types (DCB or DES) in each group of OCT pattern of neointima."* (166)

3.7.8. Investigation of the impact of optical neointimal characteristics and treatment modality on periprocedural myocardial injury in patients with in-stent restenosis

"To account for the clustered nature of the data, a linear mixed model was used for the analysis of OCT data. The model contained a fixed-effects term (neointimal pattern) and a random intercept as random-effects term for patient in case of frame-level analysis and as nested random-effects term for patient and frame for strut-level analysis. A multivariable model including baseline clinical, angiographic and procedural characteristics in addition to the optical pattern of neointima was performed to evaluate the potential independent impact of neointimal pattern of ISR on changes in hs-

cTnT. An interaction test was conducted in order to assess whether the relation between optical characteristics of neointima and PMI occurrence is influenced by the treatment modality of ISR." (173)

3.7.9. Investigation of the comparative safety and efficacy of novel $P2Y_{12}$ receptor inhibitor agents in patients presenting with acute myocardial infarction

"The analysis of outcomes according to clinical presentation was prespecified [(131)]. […] *The participating center was entered into the Cox proportional hazard model as a covariate, along with the study treatment group. […] The efficacy end point was analyzed according to the intention-to-treat principle (ie, including all patients as initially assigned regardless of the actual treatment received). The safety end point (BARC type 3–5 bleeding) was analyzed in a modified intention-to-treat population (ie, including all patients with at least 1 application of the study drug with bleeding assessed for up to 7 days after discontinuation of the study drug). The outcomes were graphically displayed with the use of Kaplan-Meier estimates or cumulative incidences accounting for competing risk along with 95% CIs* [(192)]. *Landmark analysis with a prespecified landmark at 1 month was performed to assess the early and late risk of the primary and secondary end points in the ticagrelor and prasugrel groups."* (176)

4. RESULTS

4.1. The 10-year incidence of definite stent thrombosis with newer- versus early-generation drug-eluting stents

In this analysis, we included 9,700 patients by pooling individual clinical trial data. Of them, 6,866 and 2,834 were treated with new DES and early DES, respectively. The main characteristics of the specific study devices and the individual antiplatelet regimens for each trial are previously shown (see ***section 3.1.1. and 3.1.2.*** of the "study protocol for the DECADE co-operation series"). The median follow-up (25th–75th percentiles) among patients who survived was 10.0 (9.9-10.9) years. Only 7.2% the patients (N=698) had a follow-up time shorter than 9 years. Patients implanted with new DES were older (66.1±11.3 vs. 64.1±11.1; p<0.001) and were more frequently diabetic (25.3% vs. 19.8%; p<0.001) and hypertensive (62.9% vs. 58.5%; p<0.001). A higher proportion of early DES group were current smokers. More than half of patients in both groups (53.6%) presented with stable angina at the time of PCI (supplementary **Table A3**). With regard to baseline angiographic and procedural characteristics, a higher proportion of lesions in the new DES group had complex morphology (69.0% vs. 50.3%; p<0.001) and involved bifurcation lesions (26.4% vs. 14.0%; p<0.001). Moreover, longer total stented length and a higher total number of implanted stents was observed in new DES group compared with the early DES group (supplementary **Table A4**).

4.1.1. Ten-year clinical outcomes: definite stent thrombosis

Overall, definite ST occurred in 160 of 9,700 patients (1.6%): 69 of 6,866 patients (1.0%) in the new DES group and in 91 of 2,834 patients (3.5%) in the early DES group. The cumulative incidence of definite ST was lower in patients treated with new DES compared with patients treated with early DES, both in unadjusted (HR=0.30 [0.22-0.41] and adjusted ($HR_{adjusted}$=0.32 [0.23-0.45]) (**Figure 5**) analyses.

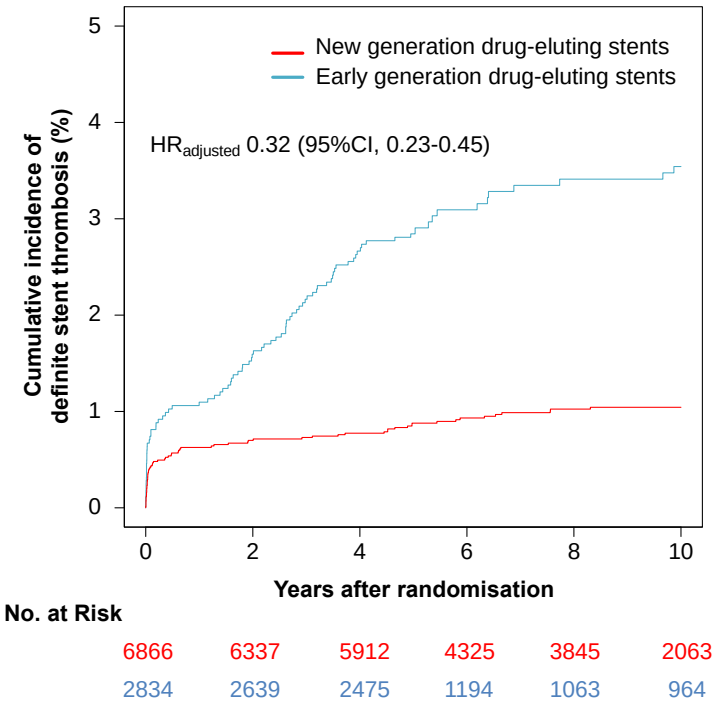


Figure 5. Ten-year cumulative incidence of definite stent thrombosis as per DES generation (78)**.**

The hazard ratio reported here was derived from a conventional multivariable analysis adjusting for the following variables: age, sex, diabetes mellitus, hypertension, smoking, hypercholesterolemia, history of myocardial infarction, acute coronary syndromes, and vessel treated.

CI=confidence interval; HR=hazard ratio.

4.1.2. Additional endpoints: death and myocardial infarction

Regarding additional endpoints, death occurred in 2,004 of 6,866 patients (30.4%) in the new DES group and in 765 of 2,834 patients (28.3%) in the early DES group at 10-year follow-up ($HR_{adjusted}$=0.97 [0.89-1.06]). MI occurred in 461 of 6,866 patients (6.9%) in the new DES group and in 291 of 2,834 patients (10.7%) in the early DES group ($HR_{adjusted}$=0.66 [0.57-0.77]). At 10 years, 31 of 74 patients who had experienced a definite ST event at 1 year died compared with 2,738 of 9,626 patients who did not experience definite ST at 1 year (41.9% vs 28.4%; p=0.01).

4.1.3. Landmark analysis

A landmark analysis was performed to demonstrate the incidence of definite ST within 4 time-periods following PCI: 0 to 30 days, 30 days to 1 year, 1 to 5 years, and 5 to 10 years **(Figure 6)**.

- From **0 days to 30 days** after PCI, the definite ST occurred in 29 of 6,866 patients (0.4%) in the new DES group and 21 of 2,834 patients (0.7%) in the early DES group (HR=0.57 [0.32-0.99] and $HR_{adjusted}$=0.58 [0.32- 1.03] in unadjusted and adjusted analysis, respectively).

- From **30 days to 1 year** after PCI, the definite ST occurred in 14 of 6,866 patients (0.2%) in the new DES group and 10 of 2,834 patients (0.4%) in the early DES group (HR=0.58 [0.26-1.30] and $HR_{adjusted}$=0.67 [0.28-1.60] in unadjusted and adjusted analysis, respectively).
- From **1 to 5 years**, the definite ST occurred in 17 of 6,866 patients (0.3%) in the new DES group and 49 of 2,834 patients (1.8%) in the early DES group (HR=0.14 [0.08-0.25] and $HR_{adjusted}$=0.16 [0.09- 0.28] in unadjusted and adjusted analysis, respectively).
- From **5 to 10 years**, the definite ST occurred in 9 of 6,866 patients (0.2%) in the new DES group and 11 of 2,834 patients (0.9%) in the early DES group (HR=0.23 [0.10-0.56] and $HR_{adjusted}$=0.25 [0.10- 0.60] in unadjusted and adjusted analysis, respectively).

Rates of definite ST per 1,000 patient days for these individual time periods is shown in **Table 2**.

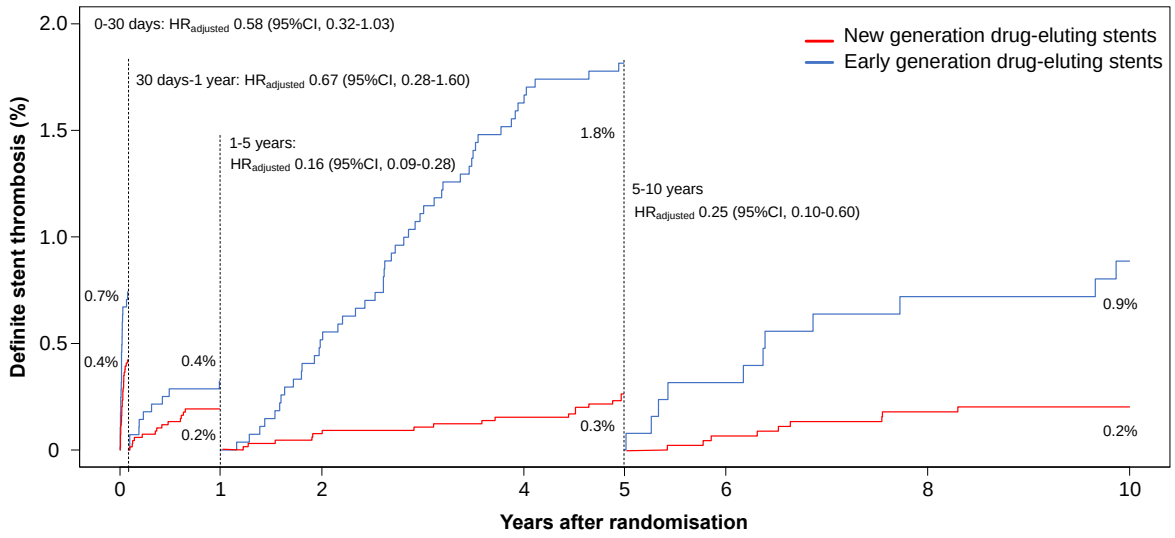


Figure 6. Landmark analysis of definite stent thrombosis up to 10 years after PCI as per DES generation (78)**.**
CI= confidence interval; HR= hazard ratio.

Table 2. Definite stent thrombosis rate as per DES generation and time after PCI (78)**.**

Time Period (Unit of rate)	Definite Stent Thrombosis Event Rate [95% CI]		Rate Ratio [95% CI]
	New-DES (N=6866)	Early-DES (N=2834)	
0 to 30 days (per 1,000 patient days)	0.14 [0.10-0.20]	0.25 [0.15-0.38]	0.57 [0.31-1.05]
30 days to 1 year (per 1,000 patient years)	2.30 [1.26-3.85]	3.97 [1.90-7.29]	0.58 [0.24-1.46]
1 to 5 years (per 1,000 patient years)	0.69 [0.40-1.11]	4.80 [3.55-6.34]	0.14 [0.08-0.26]
5 to 10 years (per 1,000 patient years)	0.46 [0.21-0.87]	1.99 [0.99-3.57]	0.23 [0.08-0.61]

Definite stent thrombosis event rates compared using the exact 2-sided Poisson test and expressed as a rate ratio and 95% confidence interval.

CI= confidence interval; DES= drug-eluting stent.

4.1.4. Multivariate sensitivity analysis

A sensitivity analysis was additionally performed, accounting for patient characteristics and several angiographic and procedural variables (see ***section 3.7.1.***). Herein, new DES were associated with a reduced risk of definite ST at 10 years (HR=0.27 [0.19-0.39]). The reduced risk of definite ST was similarly confirmed from 0 to 1 years (HR=0.57 [0.34-0.94]) and from 1 to 10 years (HR=0.11 [0.06-0.21]) in favor of new DES.

4.2. Sex-related differences in 10-year outcomes with drug-eluting stents

Of 9,700 patients included in this analysis, 2,296 were women and 7,404 were men, respectively. The main characteristics of the specific study devices and the individual antiplatelet regimens for each trial are previously shown (see ***section 3.1.1. and 3.1.2.*** of the "study protocol for the DECADE co-operation series"). The median follow-up among patients who survived was 10.0 (9.9-10.9) years with 698 patients (7.2%) having a follow-up time shorter than 9 years. Female patients tended to be older (69.6±11.1 years vs. 64.3±11.0 years; p<0.001) and had more frequently diabetes mellitus and arterial hypertension. Additionally, male patients had more three-vessel disease (38.9% vs. 46.5%; p<0.001) and a lower mean ejection fraction (54.3% ± 11.8% vs. 53.0% ± 11.7% years; p<0.001) compared to the

female patients. Male patients were more frequently current smokers and had more frequently experienced a prior MI. Approximately half of the patients (47.0%) in both groups presented with ACS at the time of PCI (supplementary **Table A5**). As shown in supplementary **Table A6,** female patients had a smaller vessel reference diameter (2.7mm (2.4mm-3.0mm) vs. 2.8mm (2.5mm-3.1mm); p<0.001) before PCI and a smaller minimal luminal diameter (2.5mm (2.2mm-2.8mm) vs. 2.6mm (2.2mm-2.9mm); p<0.001) after PCI. Male patients had a higher proportion of treated bifurcation lesions (21.3% vs. 24.0%; p=0.011) and a longer total stented length (18.0mm (15.0mm-28.0mm) vs. 20.0mm (16.0mm-28.0mm); p<0.001).

4.2.1. Ten-year clinical outcomes: death, cardiovascular death, myocardial infarction, repeat revascularization, and definite stent thrombosis

The comparison of 10-year clinical outcomes for female patients and male patients are shown in **Table 3**, with the results of both unadjusted and adjusted analyses. Multivariable adjusted analysis was additionally performed without including age as a factor variable in order to assess its impact on the statistical adjustment.

Table 3. Ten-year clinical outcomes in male and female patients (184)**.**

Clinical Outcomes	Female Patients (N=2296)	Male Patients (N=7404)	Unadjusted Hazard Ratio [95% CI]	Unadjusted p value	Adjusted Hazard Ratio [95% CI]	Adjusted p value
Cardiovascular death	407 (18.5)	1012 (14.3)	1.35 [1.08-1.68]	0.008	0.94 [0.80-1.11]	0.47
Death	767 (34.7)	2002 (28.3)	1.28 [1.12-1.47]	<0.001	0.92 [0.87-0.97]	0.003
Myocardial infarction*	198 (8.8)	554 (7.7)	-	-	-	-
0 to 30 days	81 (3.5)	146 (2.0)	1.81 [1.36-2.40]	<0.001	1.65 [1.24-2.19]	<0.001
>30 days to 10 years	117/2182 (5.6)	408/7190 (5.9)	0.98 [0.92-1.04]	0.46	0.96 [0.77-1.19]	0.69
Target lesion revascularization	273 (12.0)	1128 (15.5)	0.78 [0.72-0.85]	<0.001	0.80 [0.74-0.87]	<0.001
Target vessel revascularization	363 (16.0)	1462 (20.0)	0.80 [0.75-0.86]	<0.001	0.81 [0.76-0.87]	<0.001
Non-target vessel revascularization	325 (14.4)	1475 (20.3)	0.70 [0.63-0.78]	<0.001	0.69 [0.62-0.77]	<0.001
Definite stent thrombosis	37 (1.7)	123 (1.8)	1.00 [0.76-1.30]	0.97	1.14 [0.89-1.47]	0.30

Data are shown as number of events with Kaplan-Meier estimates (%) for endpoints. All endpoints apart from death are shown after accounting for the competing risk for death. The adjusted hazard ratios, 95% confidence intervals and p values reported here are derived from a conventional multivariable analysis with adjustment for the following variables: age, diabetes mellitus, hypertension, smoking, hypercholesterolemia, history of myocardial infarction, acute coronary syndromes and vessel treated, with clustering for trial.

* Because of the non-fulfilment of the proportional hazards assumption for myocardial infarction over 10 years of follow-up, we refrained from showing overall statistical testing results, for this outcome. Instead, we show the incidences and risk estimates for 0 to 30 days and >30 days to 10 years, separately. Note that the cumulative incidences from the 2 separate periods (with landmark at 30 days) may not sum up to the overall incidence.

CI=confidence interval.

Cardiovascular death occurred in 407 of 2,296 female patients (18.5%) and in 1,012 of 7,404 male patients (14.3%) through to 10-years. The risk of cardiovascular death was higher and statistically significant in female patients through to 10 years on unadjusted analysis (HR=1.35 [1.08-1.68]; p=0.008). Following adjustment, the risk was not statistically different ($HR_{adjusted}$=0.94 [0.80-1.11]; p=0.47) (**Figure 7)**.

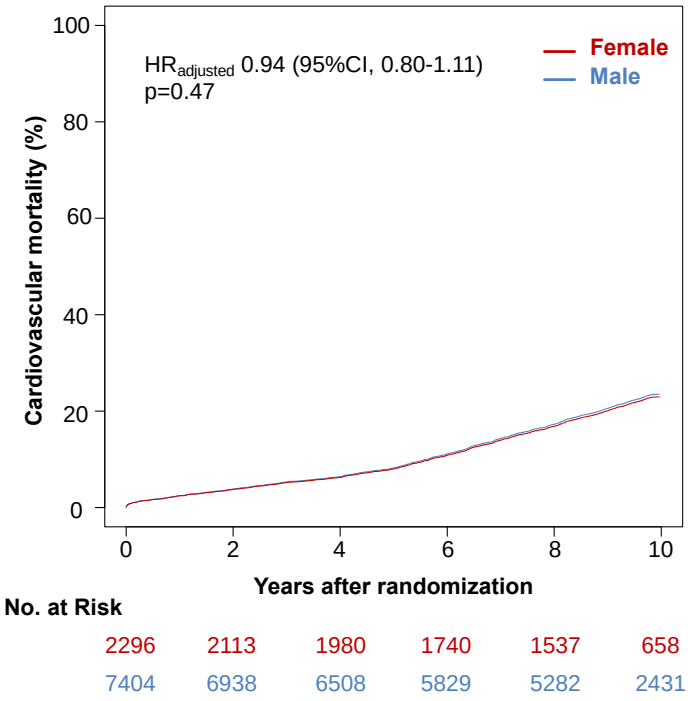


Figure 7. Ten-year cumulative incidence of cardiovascular death according to sex (184)**.**

This figure demonstrates the adjusted cumulative incidence function curves and adjusted hazard ratio with accompanying 95% confidence interval. The adjusted hazard ratios, 95% confidence intervals and p values reported here are derived from a conventional multivariable analysis with adjustment for the following variables: age, diabetes mellitus, hypertension, smoking, hypercholesterolemia, history of myocardial infarction, acute coronary syndromes and vessel treated, with clustering for trial.

CI=confidence interval; HR=hazard ratio.

Death occurred in 767 of 2,296 female patients (34.7%) and in 2,002 of 7,404 male patients (28.3%) through to 10-years. The risk of death was significantly higher in female patients on unadjusted analysis (HR= 1.28 [1.12-1.47]; p<0.001). This risk remained significantly different between groups after adjustment ($HR_{adjusted}$=0.92 [0.87-0.97]; p=0.003). In the adjusted model without the factor variable age, female sex was associated with an increased risk of cardiovascular death (p=0.006) and death (p<0.001), similar to the unadjusted model.

MI occurred in 198 of 2,296 female patients (8.8%) and 554 of 7,404 male patients (7.7%) through to 10 years. As the proportional hazards assumption for MI over 10 years of follow-up was non-fulfilled (**Table 4**), the overall statistical testing results for this outcome up to 10 years follow-up are not shown.

Table 4. Results of Schoenfelds global goodness-of-fit test for outcomes of interest (184)**.**

Clinical Outcomes	p value
Cardiovascular death	0.96
Death	0.86
Myocardial infarction	<0.001
Target lesion revascularization	0.25
Target vessel revascularization	0.19
Non-target vessel revascularization	0.36
Definite stent thrombosis	0.17

Repeat revascularization occurred in 3,625 patients during the follow-up. A TLR event occurred in 273 of 2,296 female patients (12.0%) and in 1,128 of 7,404 male patients (15.5%). At 10-years of follow-up, female sex was associated with lower cumulative incidence of TLR on both the unadjusted (HR= 0.78 [0.72-0.85]; p<0.001) and the adjusted analyses ($HR_{adjusted}$= 0.80 [0.74-0.87]; p<0.001) (**Figure 8**). Similarly, risk of both TVR (16.0% vs 20.0%, $HR_{adjusted}$= 0.81 [0.76-0.87]; p<0.001) and NTVR (14.4% vs 20.3%, $HR_{adjusted}$= 0.69 [0.62-0.77], p<0.001) events were lower in female patients compared with male patients. Female sex was similarly associated with lower risk of revascularization (p<0.001 for TVR, TLR and NTVR individually) in the adjusted model without the factor variable age.

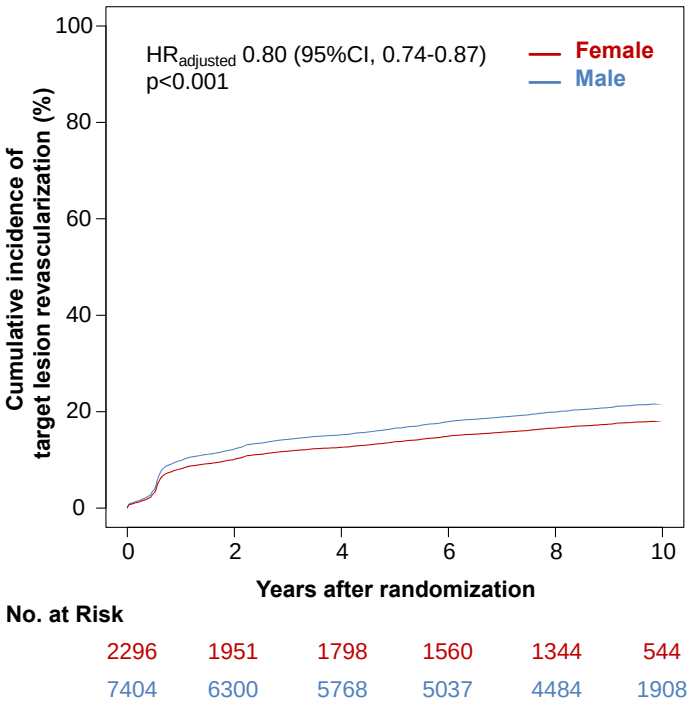


Figure 8. Ten-year cumulative incidence of target lesion revascularization according to sex (184)**.**

This figure demonstrates the adjusted cumulative incidence function curves and adjusted hazard ratio with accompanying 95% confidence interval. The adjusted hazard ratios, 95% confidence intervals and p values reported here are derived from a conventional multivariable analysis with adjustment for the following variables: age, diabetes mellitus, hypertension, smoking, hypercholesterolemia, history of myocardial infarction, acute coronary syndromes and vessel treated, with clustering for trial.

CI=confidence interval; HR=hazard ratio.

Definite ST occurred in 37 of 2,296 female patients (1.7%) and in 123 of 7,404 male patients (1.8%). The cumulative incidence of definite ST was comparable for female and male patients on the unadjusted (HR= 1.00 [0.76-1.30]; p=0.97), adjusted analyses ($HR_{adjusted}$= 1.14 [0.89-1.47]; p=0.30) and the adjusted analysis without age as a factor variable (p=0.51).

4.2.2. Landmark analysis

Cardiovascular Death

- From **0 days to 1 year** after PCI, cardiovascular death occurred in 66 of 2,296 female patients (2.9%) and in 132 of 7,404 male patients (1.8%). The risk of cardiovascular death was comparable between groups ($HR_{adjusted}$= 1.19 [0.87-1.62]).

- From **1 to 10 years** after PCI, death occurred in 341 of 2,176 female patients (4.7%) and in 880 of 7,130 male patients (4.3%). Female and male patients had a comparable risk of cardiovascular death ($HR_{adjusted}$= 0.94 [0.83-1.07]).

Death

- From **0 days to 1 year** after PCI, death occurred in 111 of 2,296 female patients (4.8%) and in 240 of 7,404 male patients (3.3%). The risk of death was comparable between groups ($HR_{adjusted}$= 1.08 [0.85-1.37]).
- From **1 to 10 years** after PCI, death occurred in 656 of 2,176 female patients (31.4%) and in 1,762 of 7,130 male patients (25.9%). The risk of death was lower for female sex ($HR_{adjusted}$= 0.89 [0.82-0.98]).

Myocardial infarction

- From **0 to 30 days** after PCI, MI occurred in 81 of 2,296 female patients (3.5%) and in 146 of 7,404 male patients (2.0%). Female sex was associated with an increased risk of MI ($HR_{adjusted}$= 1.65 [1.24-2.19]).
- From **30 days to 10 years** after PCI, MI occurred in 117 of 2,182 female patients (5.6%) and in 408 of 7,190 male patients (5.9%). Female and male patients had a comparable risk of MI ($HR_{adjusted}$= 0.96 [0.77-1.19]) (**Figure 9**).

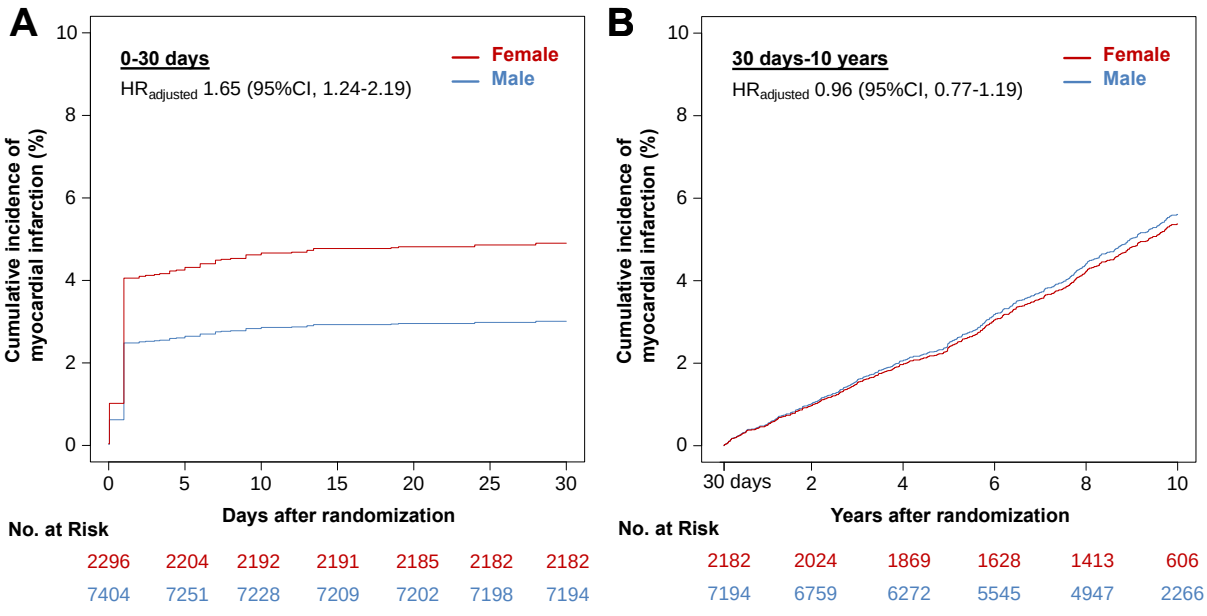


Figure 9. Landmark analysis of myocardial infarction according to sex (184)**.**

The adjusted cumulative incidence function curves display the landmark analysis of myocardial infarction from 0 to 30 days (**Panel A**) and from 30 days to 10 years (**Panel B**) according to sex.

The adjusted hazard ratios, 95% confidence intervals and p values reported here are derived from a conventional multivariable analysis with adjustment for the following variables: age, diabetes mellitus, hypertension, smoking, hypercholesterolemia, history of myocardial infarction, acute coronary syndromes and vessel treated, with clustering for trial.

CI=confidence interval; HR=hazard ratio.

Target lesion revascularization

- From **0 days to 1 year** after PCI, TLR occurred in 142 of 2,296 female patients (6.2%) and in 551 of 7,404 male patients (7.5%). The risk of TLR was comparable between female and male patients ($HR_{adjusted}$= 0.84 [0.70-1.02]).
- From **1 to 10 years** after PCI, TLR occurred in 131 of 2,042 female patients (4.4%) and in 577 of 6,598 male patients (5.4%). The risk of TLR was lower for female sex ($HR_{adjusted}$= 0.79 [0.65-0.96]).

4.2.3. Impact of age, clinical presentation, and stent-generation

An additional subgroup analysis of the clinical outcomes (cardiovascular death, MI, TLR, TVR, NTVR and ST) was carried out for the subgroups based on age (≥75 years vs. <75 years), clinical presentation (ACS vs. CCS) and DES-generation (early- vs. new-generation DES) up to 10 years after PCI (see ***section 3.7.2.***).

Risk of MI: There was a significant sex-by-stent-generation interaction (HR=0.82 [0.62-1.08] vs. HR=1.47 [1.21-1.80] for early- DES vs. new-generation DES; $p_{interaction}$<0.001). There was no sex-by-age ($p_{interaction}$=0.07) or sex-by-clinical presentation ($p_{interaction}$=0.85) interaction with respect to the risk for MI.

Risk of ST: There was a significant sex-by-age interaction (HR=0.36 [0.12-1.06] vs. HR=1.31 [0.88-1.93] for age ≥75 years vs age <75 years; $p_{interaction}$=0.03). There was no sex-by-stent generation ($p_{interaction}$=0.61) or sex-by-clinical presentation ($p_{interaction}$=0.31) interaction with respect to the risk for ST.

Risk of cardiovascular death: There was no significant interaction with respect to sex and age ($p_{interaction}$=0.84), clinical presentation ($p_{interaction}$=0.34) or stent generation ($p_{interaction}$ =0.41) up to 10 years following PCI.

Risk of TLR, TVR and NTVR: There was no statistically significant sex by age, clinical presentation, or stent-generation interaction with regard to these endpoints.

An exploratory analysis for subgroups based on age ≥55 and <55 years was also performed. However, no significant statistical interactions were observed between sex and age with regard to the clinical outcomes, including cardiovascular death ($p_{interaction}$=0.67), death ($p_{interaction}$=0.42), MI ($p_{interaction}$=0.88), TLR ($p_{interaction}$=0.17), TVR ($p_{interaction}$=0.58) and ST ($p_{interaction}$=0.64).

All sex related effect estimates were calculated after accounting for trial clustering influence. Additionally, no significant interaction between trial and sex or trial arm and sex was found with regard to endpoints of interest.

4.3. Differences in 10-year device- and patient-oriented outcomes according to drug-eluting stent polymer in patients with acute coronary syndromes

In this analysis, we included 2,042 patients presenting with ACS comprising 36.4% of the patients enrolled in the ISAR-TEST 4 and ISAR-TEST 5 trials. Of these, 690 patients (33.8%) were treated with PP-DES, 541 patients (26.5%) were treated with BP-DES, and 811 patients (39.7%) were treated with PF-DES. The groups were balanced with respect to past medical history and comorbidities but they differed in clinical presentation. There were significant differences with respect to the frequency of acute MI (BP-DES vs. PF-DES vs. PP-DES, 30.9% vs. 55.0% vs. 42.2%) and UA (BP-DES vs. PF-DES vs. PP-DES, 69.1% vs. 45.0% vs. 57.8%) (p<0.001). Baseline, angiographic and procedural characteristics are shown in supplementary **Table A7** and **Table A8**.

4.3.1. Ten-year clinical outcomes: device- and patient-oriented composite endpoint

Ten-year clinical outcomes according to stent type are shown in **Table 5**.

Table 5. Clinical outcomes at 10 years as per stent type (160)**.**

	Biodegradable Polymer Stent (N=541)	Polymer Free Stent (N=811)	Permanent Polymer Stent (N=690)	BP-DES vs. PP-DES		PF-DES vs. PP-DES	
				Hazard Ratio [95% CI]	P value	Hazard Ratio [95% CI]	p value
Device oriented composite endpoint	178 (35.4)	313 (41.4)	268 (41.5)	0.83 [0.68-1.00]	0.05	0.97 [0.83-1.15]	0.76
Cardiac death	101 (21.0)	181 (24.8)	148 (23.7)	0.89 [0.69-1.15]	0.38	1.00 [0.80-1.24]	0.98
Target vessel myocardial infarction	28 (5.4)	32 (4.0)	32 (4.8)	1.17 [0.69-1.96]	0.56	0.89 [0.54-1.47]	0.66
Target lesion revascularization	81 (15.7)	154 (19.9)	129 (19.5)	0.81 [0.61-1.08]	0.15	1.03 [0.81-1.31]	0.80
Patient oriented composite endpoint	337 (65.3)	518 (66.8)	457 (69.0)	0.86 [0.75-0.99]	0.04	0.99 [0.87-1.12]	0.82
All-cause death	182 (37.2)	260 (34.8)	229 (36.1)	1.02 [0.84-1.25]	0.83	0.95 [0.79-1.14]	0.57
Any myocardial infarction	39 (7.6)	49 (6.2)	46 (7.0)	1.11 [0.72-1.71]	0.65	0.95 [0.63-1.43]	0.79
Any revascularization	206 (39.3)	352 (44.5)	292 (43.5)	0.84 [0.70-1.00]	0.06	1.06 [0.91-1.25]	0.45
Stent Thrombosis							
Definite or probable	8 (1.5)	16 (2.0)	15 (2.3)	0.77 [0.32-1.85]	0.56	0.86 [0.42-1.77]	0.69
Definite	3 (0.6)	9 (1.2)	4 (0.6)	1.22 [0.27-5.58]	0.80	1.94 [0.59-6.40]	0.28

Data are shown as number of events with Kaplan-Meier estimates (%) for primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints. The risk estimated represent adjusted HR with 95% CI.

BP=biodegradable polymer; CI=confidence interval; DES=drug-eluting stent; PF=polymer-free; PP=permanent polymer.

Device-oriented composite endpoint

The DOCE is a composite of cardiac death, target vessel MI, or TLR. The DOCE occurred in 268 of 690 patients (41.5%) treated with PP-DES, 178 of 541 patients (35.4%) treated with BP-DES, and 313 of 811 patients (41.4%) treated with PF-DES at 10 years. Overall, there was trend toward a lower frequency of DOCE in BP-DES group compared with PP-DES group, although without statistical significance (HR=0.83 [0.68-1.00]; p=0.05). The relative frequency of the DOCE was comparable between the PF-DES group and PP-DES groups (41.4% vs. 41.5%; HR=0.97 [0.83-1.15]; p=0.76) (**Figure 10)**. There were no statistically significant differences in the relative frequency of individual components of the DOCE.

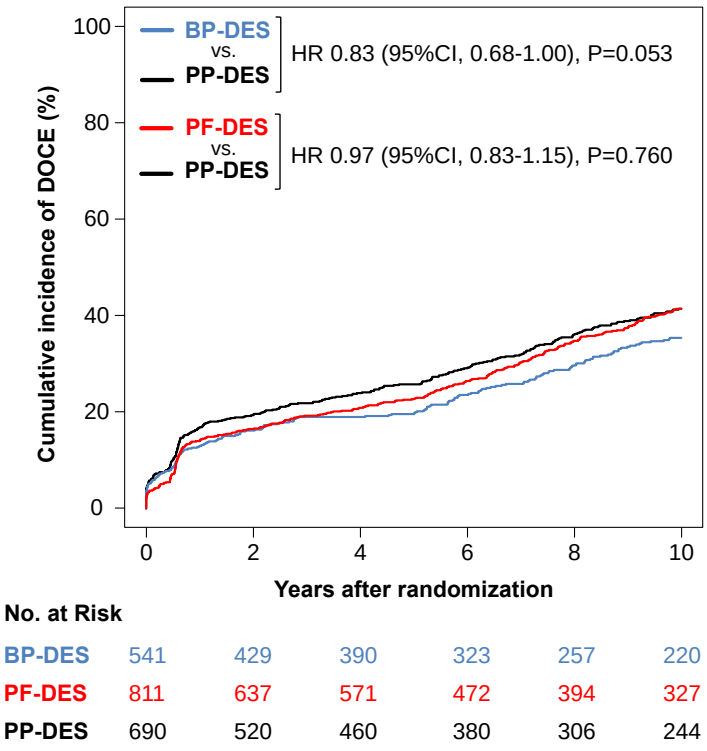


Figure 10. Ten-year cumulative incidence of the device-oriented composite endpoint according to stent type (160)**.**

BP=biodegradable polymer; CI=confidence interval; DES=drug-eluting stent; DOCE=device-oriented composite endpoint; HR=hazard ratio; PF=polymer free; PP=permanent polymer.

Patient-oriented composite endpoint

The POCE is a composite of all-cause death, any MI, or any revascularization. The POCE occurred in 457 of 690 patients (69%) treated with PP-DES, 337 of 541 patients (65.3%) treated with BP-DES, and 518 of 811 patients (66.8%) treated with PF-DES at 10 years. BP-DES compared with PP-DES was associated with a lower frequency of the POCE in patients with ACS (HR=0.86 [0.75-0.99]; p=0.04). There were no statistically significant differences between the PF-DES and PP-DES groups with respect to the frequency of the POCE (HR, 0.99; [0.87-1.12]; p=0.82) (**Figure 11**). Overall, the individual components of the POCE were comparable for both the BP-DES vs. PP-DES and PF-DES vs. PP-DES comparisons. The occurrence of any revascularization event was numerically lower in the BP-DES group compared with the PP-DES group, although this did not meet the statistical significance (39.3% vs. 43.5%; HR=0.84 [0.70-1.00]; p=0.06).

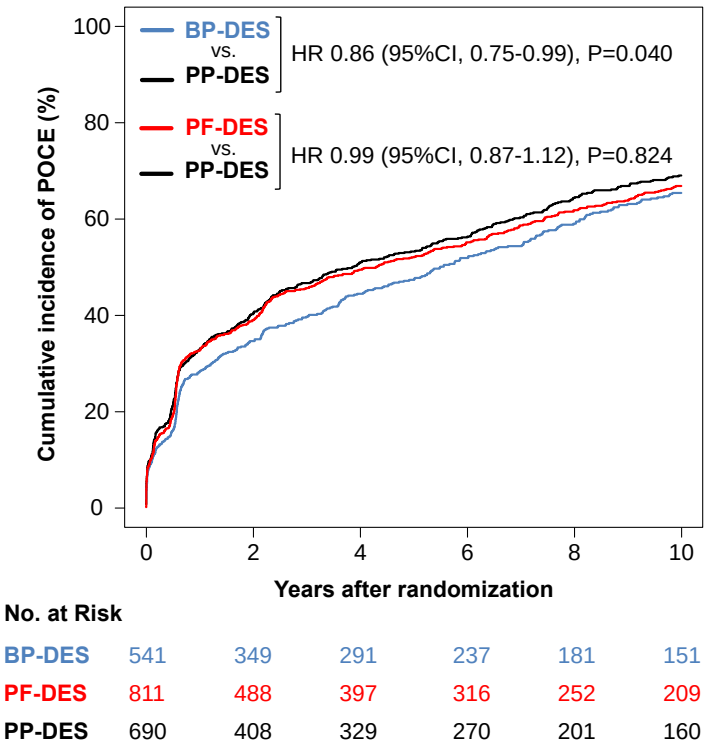


Figure 11. Ten-year cumulative incidence of the patient-oriented composite endpoint according to stent type (160)**.**

BP=biodegradable polymer; CI=confidence interval; DES=drug-eluting stent; POCE=patient-oriented composite endpoint; HR=hazard ratio; PF=polymer free; PP=permanent polymer.

4.3.2. Additional endpoint: stent thrombosis

The definite or probable ST occurred in 15 of 690 patients (2.3%) treated with PP-DES, 8 of 541 patients (1.5%) treated with BP-DES, and 16 of 811 patients (2.0%) treated with PF-DES at 10 years. There were no statistically significant differences regarding this endpoint for the BP-DES vs. PP-DES (HR=0.77 [0.32-1.85]; p=0.56) or PF-DES vs. PP-DES (HR=0.86 [0.42-1.77]; p=0.69) comparisons.

Overall, definite ST occurred in 16 of 2,042 patients at 10 years. There were no significant differences with respect to the incidence of this endpoint for either the BP-DES vs. PP-DES (0.6% vs 0.6%; HR=1.22 [0.27-5.58]; p=0.80) or PF-DES vs. PP-DES (1.2% vs. 0.6%; HR=1.94 [0.59-6.40]; p=0.28).

4.3.3. Analysis of outcomes according to clinical presentation

An unadjusted analysis was performed to investigate the clinical outcomes in patients presenting with acute MI or UA and treated with different stent types.

BP-DES vs PP-DES

The occurrence of DOCE for the BP-DES vs. PP-DES was similar in patients presenting with both acute MI (HR=0.80 [0.58-1.10]; p=0.17) or UA (HR=0.82 [0.65-1.05]; p=0.11). There was a statistically significant reduction in the frequency of the POCE in patients presenting with acute MI for the BP-DES vs. PP-DES (HR=0.78 [0.61-0.99]; P<0.05). The occurrence of POCE was comparable between the BP-DES and PP-DES groups (HR=0.93 [0.78-1.11]; p=0.41) in patients with UA.

PF-DES vs PP-DES

There were no statistically significant differences between the PF-DES and PP-DES groups in patients with acute MI (HR=0.81 [0.64-1.03]; p=0.09) and UA (HR=1.11 [0.89-1.38]; p=0.38) with respect to the occurrence of DOCE. POCE was also comparable for both the PF-DES and PP-DES groups in patients presenting with AMI and UA.

4.4. The impact of drug-eluting stent overlap on the risk of major adverse cardiovascular events at 10 years and binary angiographic restenosis at 6-8 months following percutaneous coronary intervention

This analysis included 5,605 patients collected by pooling patient level data from both ISAR-TEST 4 and ISAR-TEST 5 trials. For the purposes of this study, patients were divided into “no stent overlap” (N=3,781) and “stent overlap” (N=1,824) groups. The median follow-up was 10.0 (9.8–10.0) years. The 10-year follow-up was incomplete in 15% of the patients, amongst whom the median follow-up was 5.6 (3.9–6.8) years. Lower proportion of patients in the stent overlap group had early generation PP-DES implanted (8.5% vs. 13.1%; p < 0.001). A higher proportion of patients in the stent overlap group had multivessel disease (89.2% vs. 83%, p<0.001) and a greater number of lesions per patient (1.7±0.8 vs. 1.2±0.5; p<0.001). Less than a half of the patients (>40%) presented with ACS at the time of PCI. The group with stent overlap more frequently had lesions with complex morphology (83.4% vs. 68.5%, p<0.001) and longer stented length (31.4±14.4 mm vs. 22.5±8.96 mm, p<0.001). Stent types, baseline and procedural characteristics are shown in supplementary **Table A9** and **Table A10.**

4.4.1. Ten-year clinical outcomes: all-cause death, myocardial infarction, target lesion revascularization, and definite or probable stent thrombosis

The comparison of 10-year clinical and 6-8 months angiographic outcomes for the groups with stent overlap and no stent overlap are summarized in **Table 6**.

Table 6. Stent overlap versus no stent overlap: overall effect (161)**.**

	Stent Overlap	No Stent Overlap	Hazard Ratio [95% CI]	p value	$p_{adjusted}$
Patients	N=1824	N=3781			
All-cause death	584/1824 (35.5)	1172/3781 (33.9)	1.05 [0.95-1.16]	0.348	0.764
Myocardial infarction	148/1824 (8.4)	189/3781 (5.2)	1.67 [1.35-2.07]	<0.001	0.036
Target lesion revascularization	413/1824 (23.7)	590/3781 (16.3)	1.54 [1.36-1.74]	<0.001	<0.001
Definite or probable stent thrombosis	41/1824 (2.3)	59/3781 (1.6)	1.46 [0.98-2.17]	0.065	0.781
Lesions	N=2524	N=5239			
Binary Angiographic restenosis	394/2468 (16)	367/3546 (10.3)	1.65 [1.41-1.92]	<0.001	0.015

Data are number of events with Kaplan-Meier estimates (%) or cumulative incidence (%) after accounting for competing risk. Hazard ratios and P values are obtained from the Cox proportional hazard model. The adjusted p value ($p_{adjusted}$) is obtained from the multivariable analysis.
CI=confidence interval

At 10-year follow-up, there were no statistically significant differences with regard to **all-cause death** (35.5% vs. 33.9%, HR=1.05 [0.95–1.16]; p=0.348 and $HR_{adjusted}$=1.02 [0.89–1.17]; $p_{adjusted}$=0.764, **Figure 12**) or **definite or probable ST** (2.3% vs. 1.6%, HR=1.46 [0.98–2.17]; p=0.065 and $HR_{adjusted}$=0.93 [0.57–1.53]; $p_{adjusted}$=0.781) between the stent overlap and the no stent overlap groups on either the unadjusted or adjusted analyses.

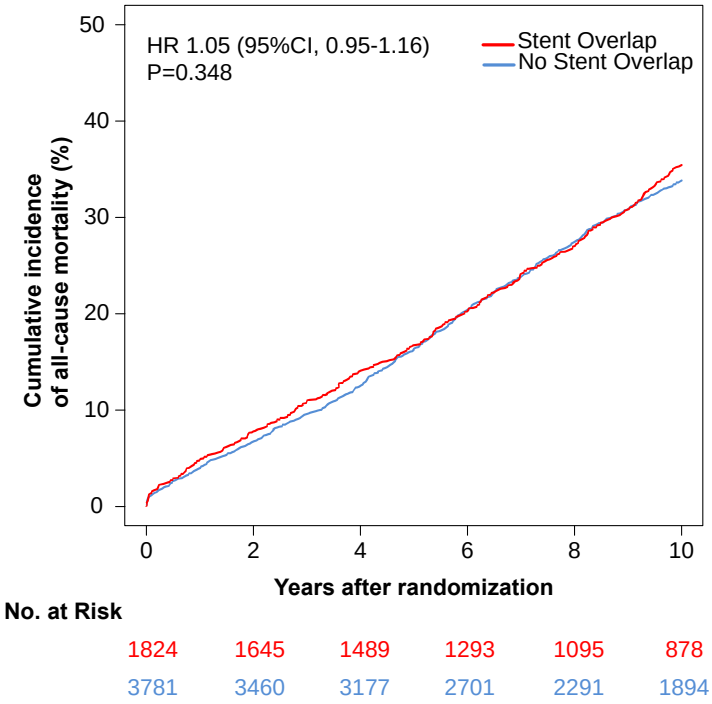


Figure 12. Cumulative incidence of all-cause death at 10 years (161)**.**

CI=confidence interval; HR=hazard ratio.

MI occurred more frequently in the stent overlap group on both the unadjusted and adjusted analyses (8.4% vs. 5.2%, HR=1.67 [1.35–2.07]; p<0.001 and $HR_{adjusted}$=1.33 [1.02–1.73]; $p_{adjusted}$=0.036) (**Figure 13**). Similarly, **TLR** (23.7% vs. 16.3%, HR=1.54 [1.36–1.74]; p<0.001) occurred more in presence of stent overlap and it remained significant after multivariate adjustment ($HR_{adjusted}$=1.43 [1.22–1.68]; $p_{adjusted}$<0.001) at 10 years (**Figure 14**).

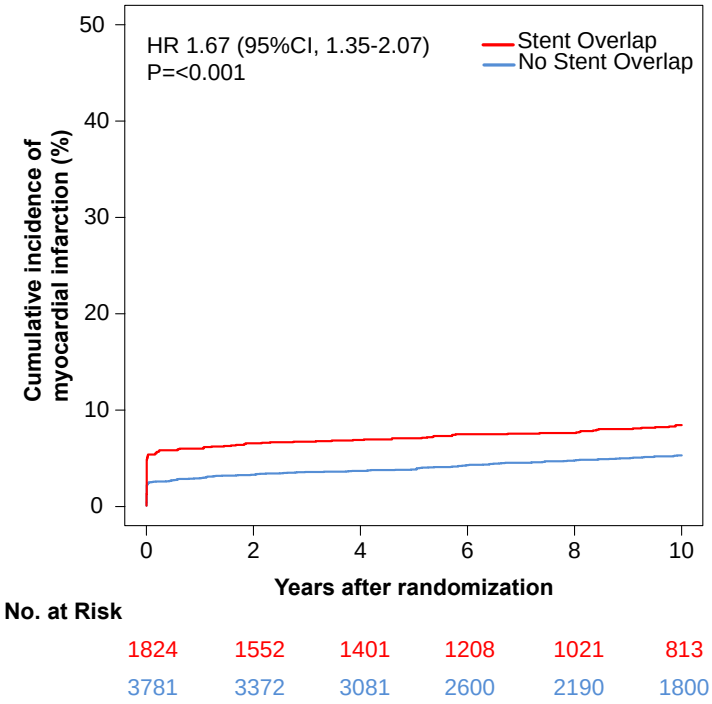


Figure 13. Cumulative incidence of myocardial infarction at 10 years (161)**.**

CI=confidence interval; HR=hazard ratio.

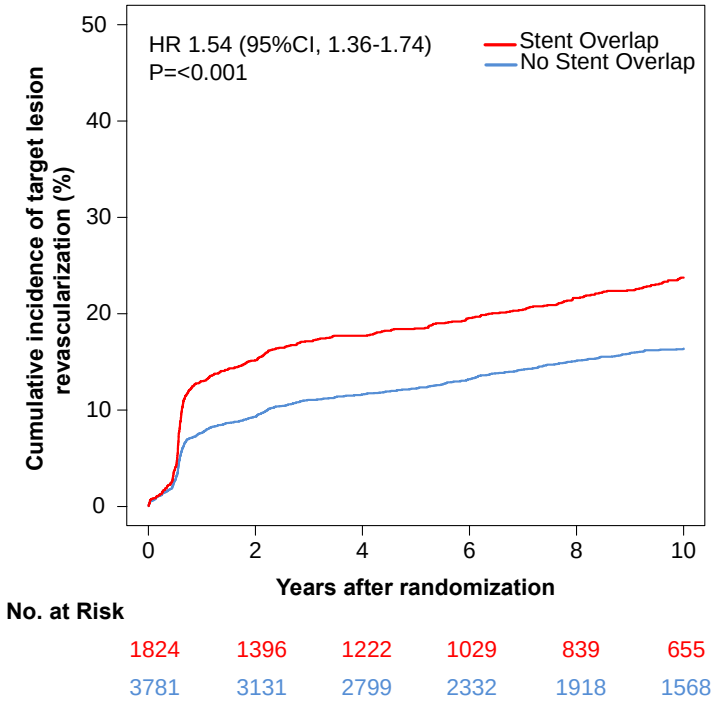


Figure 14. Cumulative incidence of target lesion revascularization at 10 years (161)**.**

CI=confidence interval; HR=hazard ratio.

In a model in which the p value was adjusted for other confounders that may be associated with stent overlap, there was no significant independent association between MI and the number of

stents (HR=1.21 [0.97-1.51]; p=0.09), total stented length (HR=1.01 [1.00-1.02]; p=0.15) or lesion length (HR=0.99 [0.98-1.01]; p=0.28). Likewise, there was no significant independent association between TLR and the number of stents (HR=1.05 [0.92-1.21]; p=0.44), total stented length (HR=1.00 [0.99-1.01]; p=0.58), or lesion length (HR=1.00 [0.99-1.01]; p=0.72).

4.4.2. Binary angiographic restenosis at 6-8 months follow-up angiography

At 6–8 months, follow-up angiography was performed in 76.2% and 78.8% of patients in the no stent overlap and stent overlap group, respectively. BAR was more frequent in the stent overlap group compared with no stent overlap group (16.0% vs. 10.3%, HR=1.65 [1.41–1.92]; p<0.001) and it remained significant after adjustment ($p_{adjusted}$=0.015). There was no interaction between stent generation and polymer type concerning this outcome.

4.4.3. Landmark analysis

Myocardial infarction

- From **0 to 30 days**, stent overlap was associated with an increased risk of MI compared to the no stent overlap group (5.3% vs. 2.4%, HR=2.22 [1.67–2.95]; p <0.001).
- From **30 days to 10 years**, there was a comparable risk of MI between the two groups (3.3% vs. 2.9%, HR=1.14 [0.81–1.60]; p=0.45).

Target lesion revascularization

- From **0 days to 1 year** after PCI, stent overlap was associated with an increased incidence of TLR in comparison to no stent overlap (13.0% vs. 7.6%, HR=1.75 [1.47–2.08]; p<0.001).
- From **1 to 10 years**, there was a higher risk of TLR in presence of stent overlap (13.0% vs. 9.8%, HR=1.33 [1.10–1.60]; p=0.003).

4.4.4. Sensitivity analysis: Single stent versus stent overlap versus multiple stents without overlap

A sensitivity analysis was performed for the main endpoints of interest, by comparing clinical and angiographic outcomes in the three groups: patients with a single stent (SS), patients with multiple stents without stent overlap (MS) and patients with stent overlap (**Table 7**).

Table 7. Sensitivity Analysis: Single Stent vs Stent Overlap vs Multiple Stents without Overlap (161)**.**

	Single Stent	Multiple Stents without Overlap	Stent Overlap	Stent Overlap vs. Single Stent		Stent Overlap vs. Multiple Stents w/o Overlap		Multiple Stents w/o Overlap vs. Single Stent	
				Hazard Ratio [95% CI)	p value	Hazard Ratio [95% CI)	p value	Hazard Ratio [95% CI]	p value
All-cause death	34.0%	33.6%	35.5%	1.05 [0.94-1.17]	0.368	1.05 [0.92-1.19]	0.493	1.01 [0.89-1.13]	0.923
Myocardial infarction	4.8%	6.0%	8.4%	1.84 [1.44-2.35]	**<0.001**	1.43 [1.09-1.88]	**0.011**	1.28 [0.96-1.71]	0.092
Target lesion revascularization	15.6%	17.7%	23.7%	1.63 [1.41-1.87]	**<0.001**	1.39 [1.19-1.64]	**<0.001**	1.17 [0.99-1.38]	0.067
Definite or probable stent thrombosis	1.5%	1.9%	2.3%	1.58 [1.01-2.49]	**0.046**	1.27 [0.77-2.10]	0.353	1.25 [0.74-2.10]	0.406
Binary angiographic restenosis	8.8%	13.1%	16.0%	1.97 [1.64-2.36]	**<0.001**	1.26 [1.04-1.54]	**0.018**	1.56 [1.25-1.94]	**<0.001**

For all-cause death, myocardial infarction, target lesion revascularization and definite/probable stent thrombosis, data are cumulative incidence at ten years (%). For binary angiographic restenosis, data are incidence on control angiography at 6-8 months (%), analyzed at a lesion level. Hazard ratios and p values are obtained from the Cox proportional hazard model.
CI=confidence interval.

The stent overlap group had a comparable risk to the SS (35.5% vs. 34.0%, HR=1.05 [0.94–1.17]; p=0.368) and the MS groups (35.5% vs. 33.6%, HR=1.05 [0.92–1.19]; p=0.493) with respect to the **all-cause death**. The risk for this endpoint was also comparable between the MS and the SS group (33.6% vs. 34.0%, HR=1.01 [0.89–1.13]; p=0.923).

The stent overlap group was associated with increased risk of **MI** compared to both the SS (8.4% vs. 4.8%, HR=1.84 [1.44–2.35]; p<0.001) and MS (8.4% vs. 6.0%, HR=1.43 [1.09–1.88]; p=0.011) groups. The MS group had a higher cumulative incidence of MI compared to the SS group, but this did not reach the statistical significance (6.0% vs. 4.8%, HR=1.28 [0.96–1.71]; p=0.092).

The stent overlap group had an increased risk of **TLR** compared to both the SS (23.7% vs. 15.6%, HR=1.63 [1.41–1.87]; p<0.001) and the MS (23.7% vs. 17.7%, HR=1.39 [1.19–1.64]; p<0.001) groups. The risk of TLR was not statistically different between the MS group the SS group (17.7% vs. 15.6%, HR=1.17 [0.99–1.38]; p=0.067).

Definite or probable ST occurred more frequently in the stent overlap group compared with the SS group (2.3% vs. 1.5%, HR=1.58 [1.01–2.49]; p=0.046). The risk for this endpoint was comparable between the stent overlap and the MS group (2.3% vs. 1.9%, HR=1.27 [0.77–2.10]; p=0.353). The MS

group also had a comparable risk of definite or probable ST to the SS group (1.9% vs. 1.5%, HR=1.25 [0.74–2.10]; p=0.406).

At 6–8 months follow-up angiography, the stent overlap group was associated with an increased risk of **BAR** compared with both the SS (16.0% vs. 8.8%, HR=1.97 [1.64–2.36]; p<0.001) and the MS (16.0% vs. 13.1%, HR=1.26 [1.04–1.54]; p=0.018) groups. Additionally, the MS group had an increased risk of BAR compared with the SS group (13.1% vs. 8.8%, HR=1.56 [1.25–1.94]; p<0.001).

4.4.5. Effect of stent generation, stent polymer and degree of stent overlap

Stent generation: early and new-generation drug-eluting stents

Early generation DES were used in 155 patients with stent overlap and 497 patients without stent overlap. New generation DES was used in 1,669 patients and 3,284 patients with and without stent overlap, respectively. The effect of stent overlap on all-cause death ($p_{interaction}$=0.686), MI ($p_{interaction}$=0.386) and TLR ($p_{interaction}$=0.909) was comparable between early and new generation stents. With regard to the effect of stent overlap on the relative frequency of definite or probable ST, there was a statistically significant interaction between early (1.3% vs. 3.8%, HR=0.35 [0.08–1.51]) and new generation DES (2.4% vs. 1.3%, HR=1.90 [1.22–2.94]) ($p_{interaction}$=0.030).

Stent polymer type: permanent polymer, biodegradable polymer, and polymer-free stents

PP-DES were used in 2,304 patients (717 and 1,587 patients with and without stent overlap, respectively), BP-DES in 1,299 patients (410 and 889 patients with and without stent overlap, respectively), and PF-DES in 2,002 patients (697 and 1,305 patients with and without DES overlap, respectively). There was no interaction between the stent polymer types with regard to all-cause death ($p_{interaction}$=0.317), MI ($p_{interaction}$=0.490), TLR ($p_{interaction}$=0.204) and definite or probable ST ($p_{interaction}$=0.281) associated with stent overlap.

Degree of stent overlap: > 5 mm and ≤ 5 mm

We also assessed whether the degree of overlap (> 5 mm and ≤ 5 mm) plays a pertinent role on clinical outcomes. The relative frequency of all-cause death, MI, TLR, and definite or probable ST were comparable between these two groups.

4.5. The 10-year event rates associated with treated target vessel and non-target vessel related remote disease

This analysis included 4,953 patients obtained by pooling patient level data from 88.4% of the patients enrolled in ISAR-TEST 4 and ISAR-TEST 5 trials. At 10 years, 2,098 (42%) patients experienced a TVRE and/or NTVRE. Amongst patients with an event, 656 (31.3%) experienced a TVRE, 860 (41%) a NTVRE and 582 (27.7%) both events following PCI. Death occurred in 1,533 of 4,953 patients (31.0%) at 10 years of follow-up. In patients who experienced no events, female sex tended to be more common compared with patients who had TVRE, NTVRE or both events. They were also more frequently older, less diabetic and had a lower frequency of triple vessel CAD. Recommended follow-up angiography at 6-8 months was performed less commonly in patients with no event. With regard to angiographic and procedural characteristics, patients who experienced no events had a lower frequency of complex lesions, shorter lesion length and a shorter total stented length. The left anterior descending artery was more commonly treated in the no event group. Baseline, angiographic and procedural characteristics according to the event type experienced are shown in supplementary **Table A11** and **Table A12**.

4.5.1. Ten-year clinical outcomes: target and non-target vessel related events

The 10-year cumulative incidence of TVRE and NTVRE and the individual components of these endpoints following PCI are shown in **Table 8.** The median time to first event was 205 (132-468) days for patients with a TVRE, 684 (193-1369) days for patients with a NTVRE and 222 (148-773) for patients with both events (p<0.001).

Table 8. Target vessel and non-target vessel related events through to 10 years follow-up post PCI (162)**.**

Total patients (N)	4,953	
Endpoint	**Number of events**	**Cumulative incidence (%)**
Primary endpoint		
Target vessel related events	1,238	25.8
Non-target vessel related events	1,442	30.3
Secondary endpoint: myocardial infarction		

Target vessel myocardial infarction	210	4.4
Non-target vessel myocardial infarction	78	1.7
Secondary endpoint: revascularization		
Target vessel revascularization	1,123	23.4
Non-target vessel revascularization	1,403	29.5

Data are cumulative incidence at ten years (%).

The TVRE (first target vessel MI or TVR) occurred in 1,238 of 4,953 patients (25.8%). The NTVRE (first non-target vessel MI or NTVR) occurred in 1,442 of 4,953 patients (30.3%). These data are shown in **Figure 15.** With respect to individual components of the primary endpoint, target vessel and non-target vessel MI occurred in 210 of 4,953 patients (4.4%) and in 78 of 4,953 patients (1.7%), respectively. TVR occurred in 1,123 of 4,953 patients (23.4%) and NTVR occurred in 1,403 of 4,953 patients (29.5%) during follow-up. Finally, cardiac death occurred in 138 of 656 patients (21.1.%) with isolated TVRE, in 129 of 860 patients (15%) with isolated NTVRE and 102 of 582 patients (17.5%) with both events.

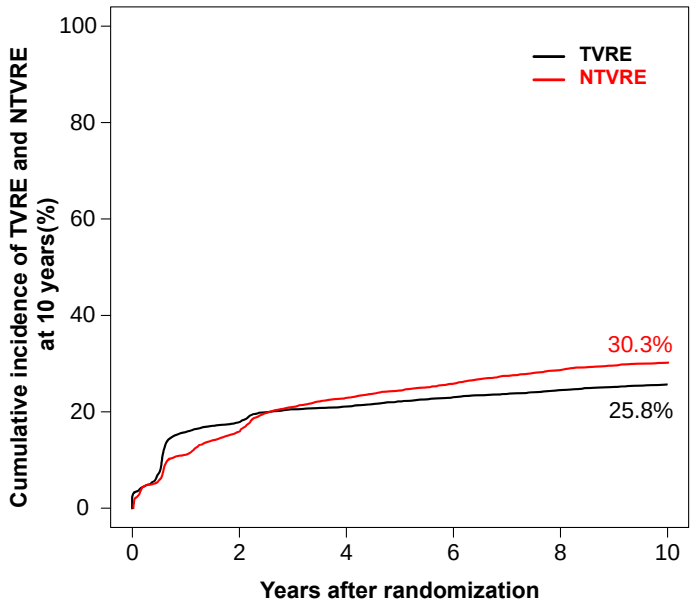
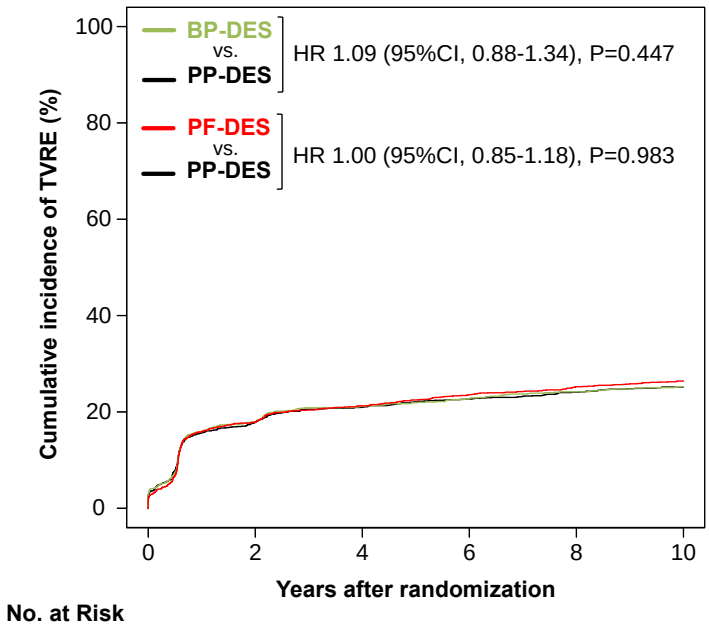


Figure 15. Ten-year cumulative incidence of target vessel and non-target vessel related events (162)**.**
TVRE=target vessel events; NTVRE=non-target vessel events.

With respect to the stent polymer, BP-DES were used in 1,299 (26.2%) patients, PF-DES in 2,002 (40.4%) patients and PP-DES in 1,652 (33.4%). The relative frequency of both TVRE and NTVRE during follow-up was comparable for patients treated with all 3 stent types (**Figure 16** and **Figure 17**).

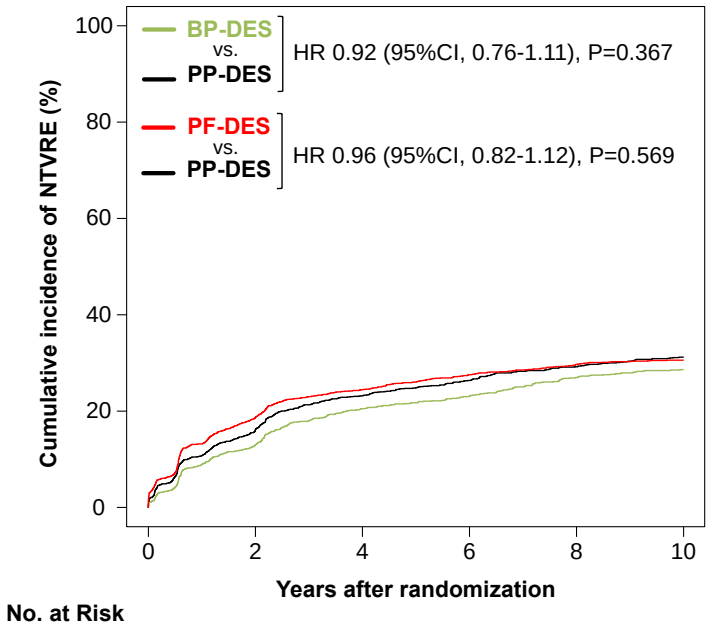


No. at Risk

BP-DES	1299	983	875	739	607	511
PF-DES	2002	1503	1308	1063	888	723
PP-DES	1652	1229	1065	889	742	571

Figure 16. Ten-year cumulative incidence of target vessel related events according to stent type (162)**.**

BP=biodegradable polymer; CI= confidence interval; DES=drug-eluting stent; HR=hazard ratio; TVRE=target vessel events; PF=polymer-free; PP=permanent polymer.



No. at Risk

BP-DES	1299	1026	858	710	557	465
PF-DES	2002	1496	1262	1023	825	661
PP-DES	1652	1256	1034	849	685	516

Figure 17. Ten-year cumulative incidence of non-target vessel related events according to stent type (162)**.**

BP=biodegradable polymer; CI= confidence interval; DES=drug-eluting stent; HR=hazard ratio; NTVRE=non-target vessel events; PF=polymer-free; PP=permanent polymer.

4.5.2. Landmark analysis

The results of the landmark analysis from 0 to 1 years and 1–10 years following PCI are shown in **Figure 18**.

- From **0 to 1 years**, the cumulative incidence of TVRE was higher compared to NTVRE (15.9% vs. 12.3%).
- From **1 to 10 years**, the cumulative incidence of NTVRE was found to be higher compared to TVRE (11.2% vs. 22.4%).

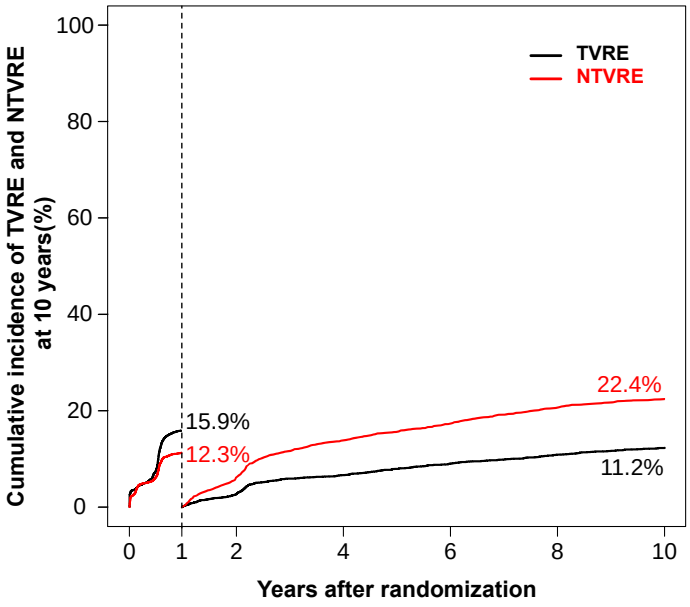


Figure 18. Landmark analysis of target vessel and non-target vessel related events from 0–1 and 1–10 years post PCI (162)**.**

TVRE=target vessel events; NTVRE=non-target vessel events.

4.5.3. Time intervals between target and non-target vessel related events

In patients who had both TVRE and NTVRE during follow-up (N=582), 205 of them had a TVRE before a NTVRE and 208 patients had a NTVRE before a TVRE. Both events occurred in the same day in the remaining patients (N=169). The time interval between the two event types was <1 year in majority of patients.

4.6. The risk prediction model and the subsequent four-item ISAR score as a tool to predict the 1-year risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent in-stent restenosis

For the purposes of this analysis, consecutive patients treated with PCI for DES-ISR were included (N=1,986). The patients were randomly divided into 2 groups in a 3:1 ratio (1,471 patients with 1,778 lesions and 515 patients with 614 lesions in training and validation groups, respectively). The median of follow-up after treatment was 7.4 (4.2-10.4) years. Notably, female sex tended to be less frequent in patients treated for DES-ISR (20% in the whole group). Approximately one quarter of the patients (25.5%) presented with ACS as indication for PCI (supplementary **Table A13**). Restenosis morphology was described according to the Mehran classification and a higher proportion of the restenosis lesions (65.3%) were identified as focal. The initial repeat PCI type was comparable in the training and validation groups (training vs. validation, 51.5% vs. 48.5% lesions treated with percutaneous transluminal coronary angioplasty and 48.5% vs. 51.5% with DES; p=219) (supplementary **Table A14**).

4.6.1. One-year clinical outcomes: all-cause death, myocardial infarction, coronary artery bypass grafting, repeat percutaneous coronary intervention and definite stent thrombosis

Clinical outcomes for the training and validation groups and the whole group of patients are shown in **Table 9**.

Table 9. Clinical Outcomes through to 1 year in the entire population, training population and validation population (186)**.**

Lesion Level Outcomes	**All lesions** (N= 2392)	**Training** (N= 1778)	**Validation** (N= 614)	**Hazard ratio [95% CI]**
Repeat PCI for recurrent DES-ISR	402 (17.7)	299 (17.7)	103 (17.7)	1.01 [0.79-1.25]
Definite stent thrombosis	3 (0.1)	2 (0.1)	1 (0.2)	1.47 [0.00-9734.2]
Patient Level Outcomes	**All patients** (N=1986)	**Training** (N=1471)	**Validation** (N=515)	**Hazard ratio [95% CI]**
All-cause death	90 (4.7)	63 (4.5)	27 (5.5)	1.23 [0.79-1.93]
Myocardial infarction	31 (1.6)	24 (1.7)	7 (1.4)	0.83 [0.36-1.94]
Coronary artery bypass grafting	18 (1.0)	15 (1.1)	3 (0.6)	0.57 [0.17-1.98]

Data are number of events with Kaplan-Meier estimates for all-cause death (%) or cumulative incidence (%) after accounting for competing risk of death for all other events. The hazard ratio and 95% confidence interval reported is for the comparison between the training and validation groups.

CI=confidence interval; DES=drug-eluting stent; ISR=in-stent restenosis; PCI=percutaneous coronary intervention.

The cumulative incidence of repeat PCI for recurrent DES-ISR up to 1-year follow-up was comparable in the training and the validation groups (17.7% vs. 17.7%, HR=1.01 [0.79-1.25]). This is demonstrated in **Figure 19**.

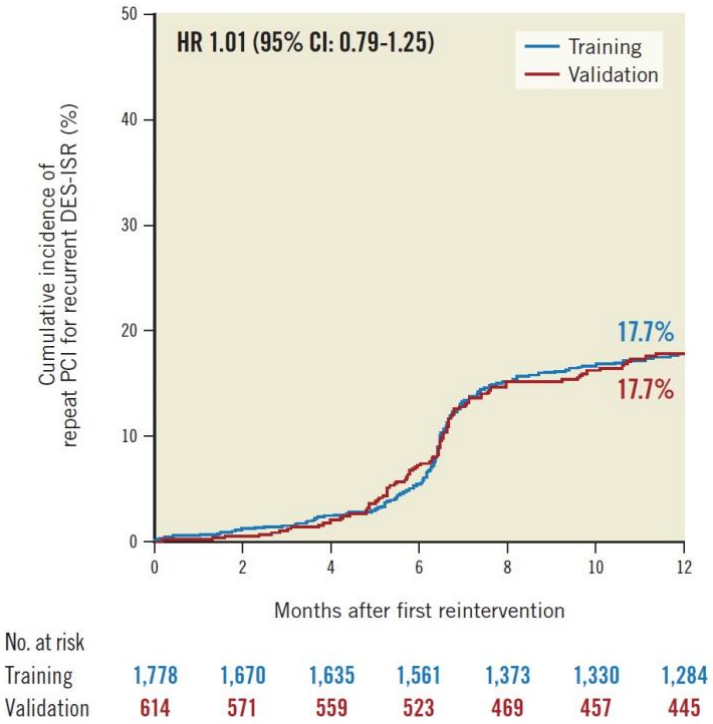


Figure 19. Repeat PCI for recurrent DES-ISR at 1 year in the training and validation populations (186)**.**
CI=confidence interval; DES=drug-eluting stent; HR=hazard ratio; ISR=in-stent restenosis; PCI=percutaneous coronary intervention.

4.6.2. Selection of predictors of repeat percutaneous coronary intervention for recurrent drug-eluting stent in-stent restenosis

0 to 1 Year

Following variables were selected by the LASSO method for the logistic regression model from 0 to 1 year: ISR type, age, hypercholesterolemia, smoking, ACS, multivessel disease, LCx coronary artery ISR, vessel calcification, ostial ISR lesion, bifurcation ISR lesion, ISR severity of >90%, maximum device (stent/balloon) diameter and ISR interval.

Of these selected variables, both the ISR type (classified as per the Mehran classification as: focal, diffuse intra-stent, diffuse proliferative, total occlusion) the ISR interval (the time interval between the initial implantation of the DES and the initial PCI of the DES-ISR lesion, classified as: <6 months, 6-12 months, 12-24 months, >24 months) were dichotomized into binary factors (non-focal/focal and <6 months/≥6 months) for the purposes of the primary analysis. This decision was based on the evaluation of the crude frequencies of repeat PCI up to 1-year follow-up for DES-ISR in the training population as per described groups.

The logistic regression model including all the variables (selected by the LASSO analysis) identified 4 independent predictors of repeat PCI for recurrent DES-ISR from 0 to 1 year: a non-focal ISR pattern, a time-interval to restenosis <6 months, ISR in the LCx coronary artery, and vessel calcification (**Table 10**). The C-statistic of the regression model including all variables was 0.62 in the training group and 0.64 in the validation group.

Table 10. Results of logistic regression analysis for repeat PCI for recurrent DES-ISR from 0 to 1 year after the first reintervention (186)**.**

Variable	Regression coefficient	p value
Non-focal ISR at index PCI	***0.346***	***0.029***
Age	-0.007	0.297
Hypercholesterolemia	0.161	0.310
Smoking	0.197	0.328
Acute coronary syndromes	0.054	0.736
Multivessel disease	0.259	0.401
Left circumflex coronary artery	***0.288***	***0.048***
Vessel calcification	***0.359***	***0.020***
Ostial lesion	0.378	0.169
Bifurcation lesion	0.143	0.333
ISR Severity > 90%	0.178	0.383
Device Diameter	-0.174	0.220
Restenosis interval < 6 months	***0.506***	***0.008***

Significant correlates are in both **bold** and *italics*.

ISR=in-stent restenosis; PCI=percutaneous coronary intervention.

1 to 5 Years

We also performed an exploratory analysis using the same methodology, searching for predictors of repeat PCI for recurrent DES-ISR from 1 to 5 years. However, the logistic regression model did not identify any independent significant predictors of repeat PCI (**Table 11**).

Table 11. Results of logistic regression analysis for repeat PCI for recurrent DES-ISR from 1 to 5 years after the first reintervention (186)**.**

Variable	Regression coefficient	p value
Age	-0.018	0.060
Diabetes	0.195	0.376
Hypertension	0.822	0.809
Hypercholesterolemia	0.256	0.308
Acute coronary syndromes	-0.056	0.801
Multivessel disease	0.258	0.512
Previous myocardial infarction	0.033	0.873
Left circumflex coronary artery	0.004	0.984
Chronic total occlusion	-0.111	0.774
Vessel calcification	0.336	0.143
Bifurcation lesion	0.273	0.136
Restenosis interval <6 months	0.263	0.322

4.6.3. Bootstrap Analysis

After the identification of 4 independent predictors by the logistic regression model from 0 to 1 year, an internal validation was performed using bootstrap method with 400 re-samples for the 4-variable model in the training and validation groups to assess how the performance of the 4-variable compares with the Mehran classification models. It should be noted that the model based on the Mehran classification included only the non-focal ISR morphology as a predictor variable.

The C-statistic of the 4-variable model was 0.61 (95% CI, 0.57-0.64) in the training group and 0.61 (95% CI, 0.55-0.67) in the validation group. There was no difference in the discriminative power of the 4-variable model in the training and validation groups (delta C-statistic=-0.003 (95% CI, -0.070-0.074); p=0.91).

In the 4-variable model developed to predict the risk of repeat PCI for recurrent DES-ISR from 0 to 1 year, the C-statistic was 0.60 (95% CI, 0.57-0.63). C-statistic for the model based on the Mehran classification was 0.54 (95% CI, 0.52-0.57). The IDI for our model and the model based on the Mehran classification was 0.021 (95% CI, 0.010-0.033) and 0.005 (95% CI, 0.001-0.011), respectively. Both the delta-C-Statistic (0.062, 95% CI, 0.035-0.094) and delta-IDI (0.016, 95% CI, 0.007-0.029) between the 4-variable model and the model based on the Mehran classification were statistically significant (p<0.001).

4.6.4. Classification and regression tree model and predictors of repeat percutaneous coronary intervention for recurrent drug-eluting stent in-stent restenosis from 0 to 1 year

The CART model in **Figure 20** shows the variables with an impact on the risk of repeat PCI for recurrent DES-ISR from 0 to 1-year follow-up. Of note, the probability of repeat PCI for recurrent DES-ISR ranged from 12.4% to 30.9% based on the presence or absence of the predictors identified in the final regression model.

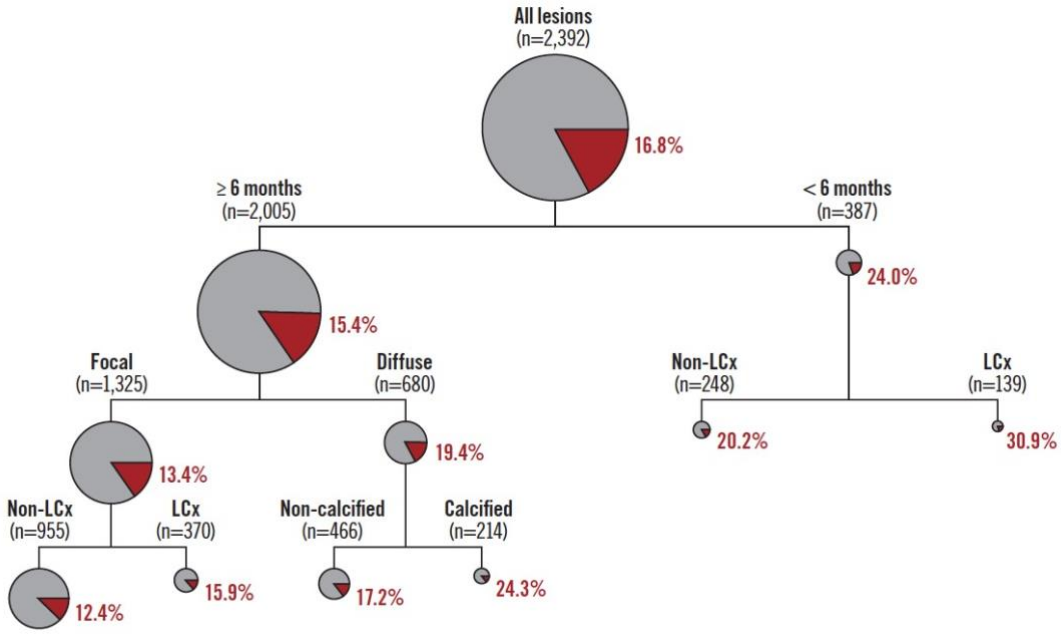


Figure 20. Classification and regression tree analysis (186)**.**

Classification and regression tree (CART) analysis demonstrating the variables which influence the likelihood of repeat PCI for recurrent DES-ISR through to 1-year follow-up. The size of the circles are proportional to the size of the subgroup. The red segments of the circles indicate the percentage of DES-ISR lesions undergoing repeat PCI through to 1 year follow-up.

LCx=left circumflex coronary artery.

We also assessed the likelihood of repeat PCI for recurrent DES-ISR according to whether the DES-ISR lesions presented one of the four significant predictors identified by the logistic regression model. These results are shown in **Table 12** and **Figure 21**. Additionally, we performed a landmark analysis (from 0 to 1 year and from 1 to 5 years) to investigate a potential time dependence in the incidence of repeat PCI for recurrent DES-ISR according to the presence of these predictors (**Figure 22**).

Table 12. Cumulative incidence of repeat PCI for recurrent DES-ISR from 0-1 years for lesions with and without the four predictor variables identified in the logistic regression model (186)**.**

	0-1 years		
Predictor	**Predictor Present (n/N, KM%)**	**Predictor not Present (n/N, KM%)**	**Hazard ratio [95% CI]**
Restenosis interval < 6 months	93/387 (24.4%)	309/2005 (16.4%)	1.62 [1.22-2.10]
Non-focal in-stent restenosis morphology	173/829 (22.4%)	229/1563 (15.3%)	1.56 [1.28-1.85]
Vessel calcification	134/680 (20.9%)	268/1707 (16.5%)	1.35 [1.09-1.63]
Left circumflex artery	147/700 (21.9%)	255/1692 (16.0%)	1.44 [1.19-1.80]

Data are number of events with cumulative incidence (%) after accounting for competing risk of death.
CI=confidence interval.

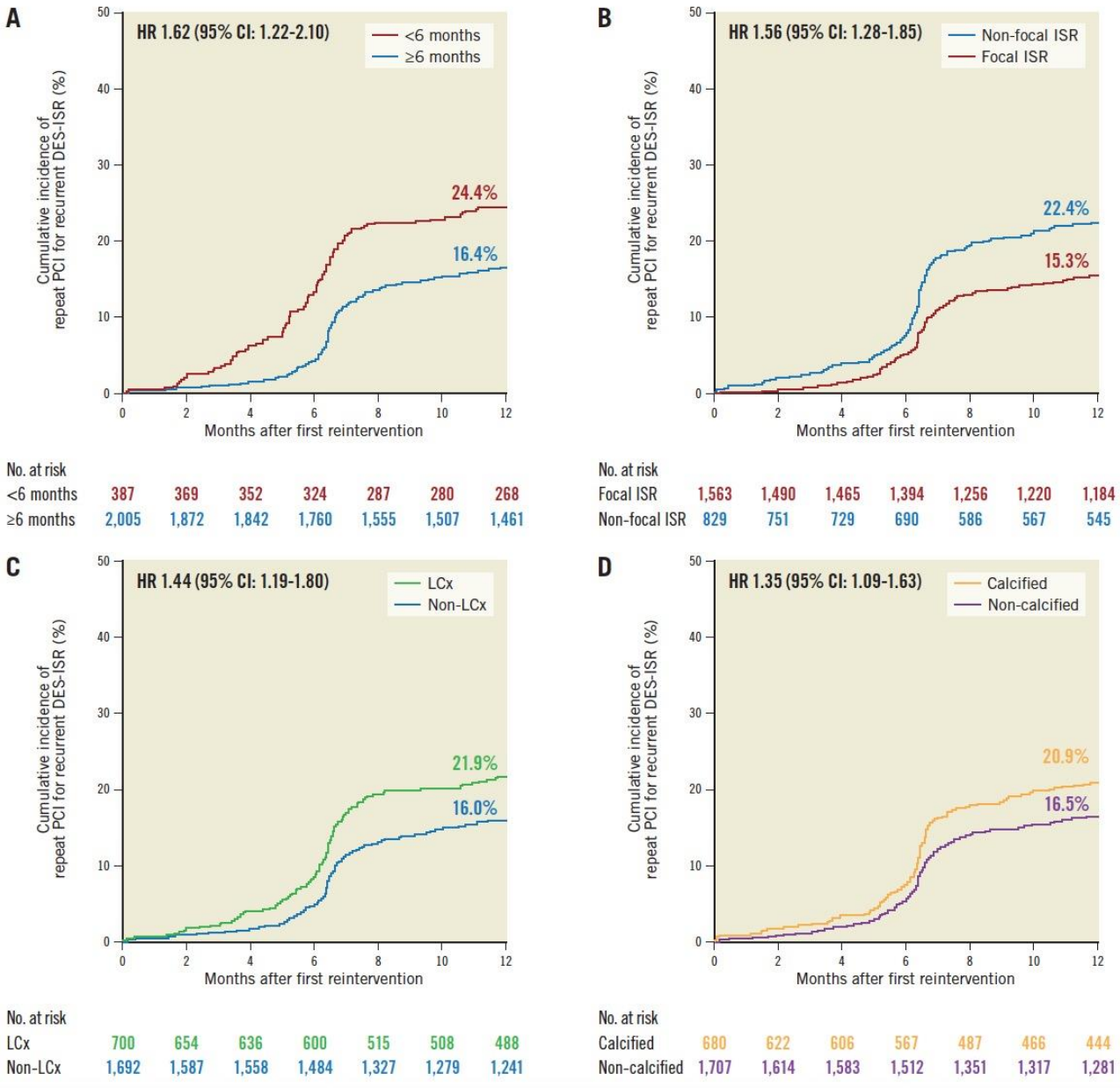


Figure 21. Cumulative incidence of repeat PCI for recurrent DES-ISR up to 1-year follow-up for lesions with and without the four predictor variables identified in the logistic regression model (186)**.**

(Panel A) Restenosis interval <6 months versus restenosis interval ≥6 months, **(Panel B)** Restenosis morphology: non-focal versus restenosis morphology: focal **(Panel C)** Artery involved: left circumflex artery versus non-left circumflex artery, **(Panel D)** Vessel calcification: calcified vessel versus non-calcified vessel.

CI=confidence interval; DES=drug-eluting stent; HR=hazard ratio; ISR=in-stent restenosis; LCx=left circumflex coronary artery; PCI=percutaneous coronary intervention.

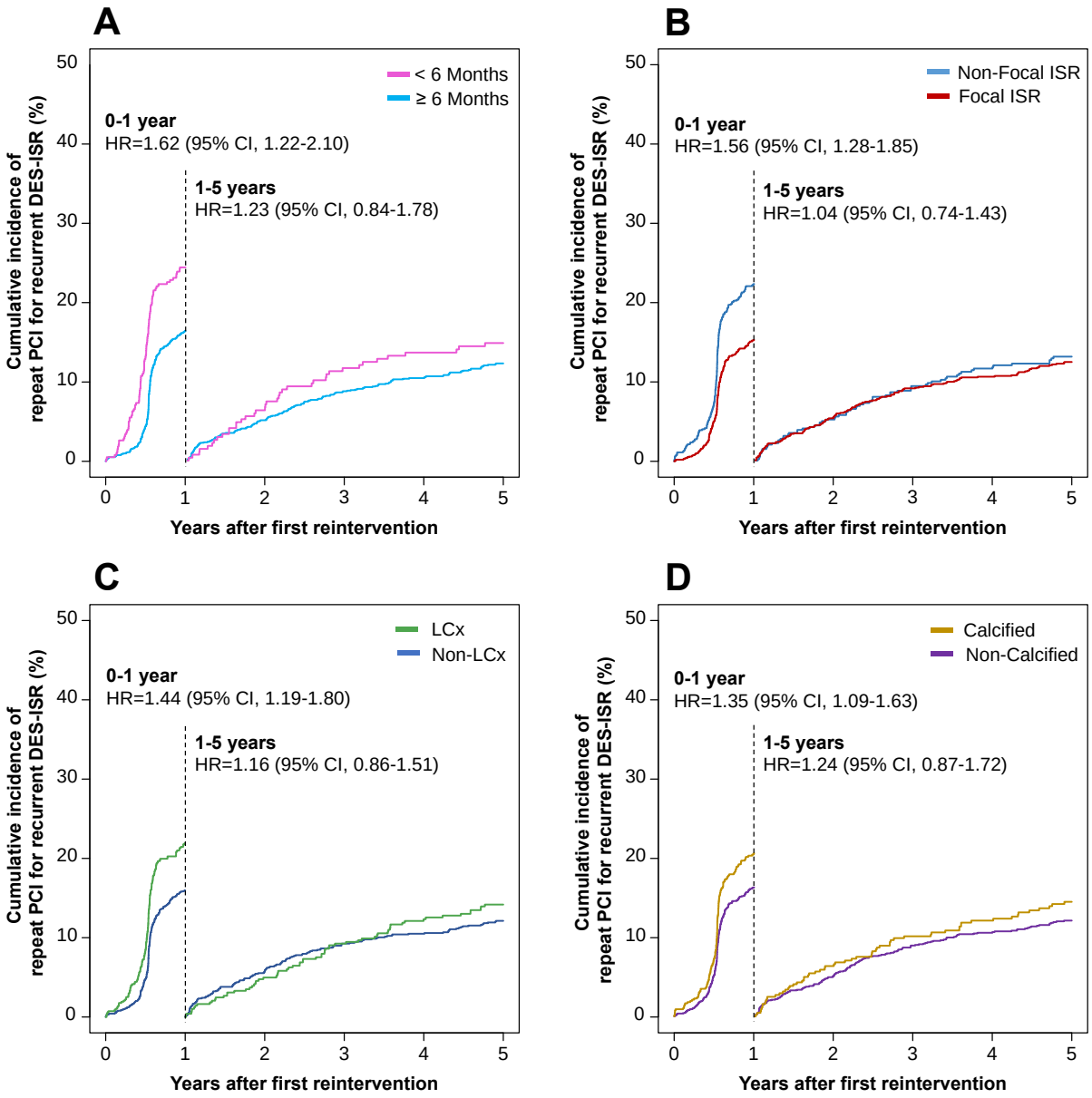


Figure 22. Landmark analysis showing the cumulative incidence of repeat PCI for recurrent DES-ISR from 0-1 years and from 1-5 years for lesions with and without the four predictor variables identified in the logistic regression model (186)**.**

(Panel A) Restenosis interval <6 months versus restenosis interval ≥6 months, **(Panel B)** Restenosis morphology: non-focal versus restenosis morphology: focal **(Panel C)** Artery involved: left circumflex artery versus non-left circumflex artery, **(Panel D)** Vessel calcification: calcified vessel versus non-calcified vessel.

CI=confidence interval; DES=drug-eluting stent; HR=hazard ratio; ISR=in-stent restenosis; LCx=left circumflex coronary artery; PCI=percutaneous coronary intervention.

4.6.5. The four-item ISAR score

Finally, we developed a four-item score ranging from 0 to 4 points to estimate the 1-year incidence of repeat PCI for recurrent DES-ISR. The score is calculated by adding 1 point to each DES-ISR lesion

according to the following criteria: (i) ISR location **I**n the LCx coronary artery; (ii) non-focal **S**tenosis morphology; (iii) presence of **A**rterial calcification of the target vessel; (iv) **R**estenosis interval of <6 months. In the present patient population, the 1-year incidences of repeat PCI for recurrent DES-ISR in lesions with ISAR scores of 0, 1, 2 and ≥3 points were 12.1%, 15.9%, 24.2% and 30.5%, respectively (p for trend <0.001) (**Figure 23**). The incidence of repeat PCI for recurrent DES-ISR was increased in lesions with an ISAR score of 1 (HR=1.37 [1.04-1.79]), 2 (HR=2.27 [1.69-3.07]) and ≥3 (HR=3.11 [2.15-4.81]) in comparison to lesions with a score of 0. Notably, the ISAR score correlated significantly with the 1-year cumulative incidence of repeat PCI for recurrent DES-ISR in both the patient populations treated with DES (p for trend=0.0016) and balloon-based (p for trend <0.001) modalities. No interaction was observed between the ISAR score and ACS presentation with respect to repeat PCI for recurrent DES-ISR. The ISAR score was significantly correlated with the incidence of repeat PCI for recurrent DES-ISR in both the patients presenting with ACS (p for trend <0.001) and CCS (p for trend <0.001) at 1-year follow-up. The ISAR score was also significantly correlated with the 5-year cumulative incidence of repeat PCI for recurrent DES-ISR (p for trend <0.001).

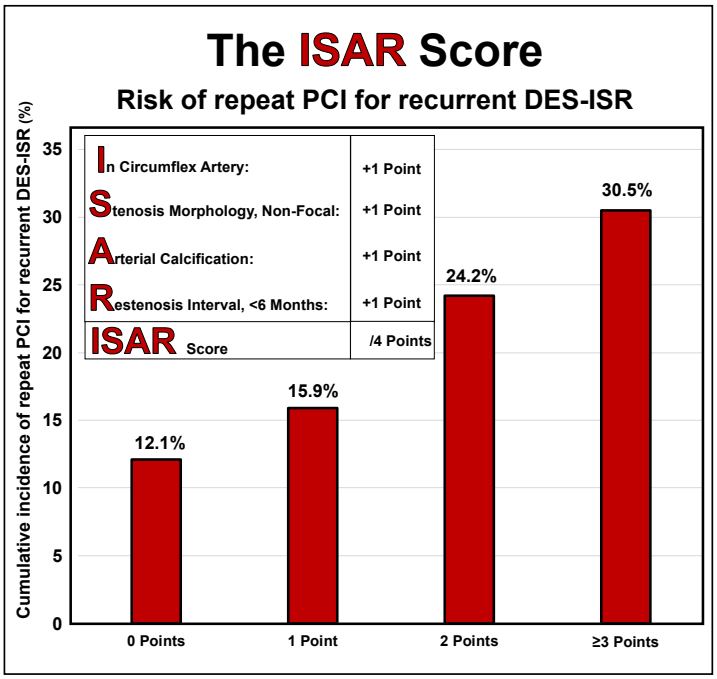


Figure 23. The cumulative incidence of repeat PCI for recurrent DES-ISR up to 1-year as per the ISAR score. Data are cumulative incidence (%). The score can range from 0 to 4 points based on the presence of 4 items. DES=drug-eluting stent; ISR=in-stent restenosis; PCI=percutaneous coronary intervention.

4.7. The impact of optical neointimal characteristics and treatment modality on 2-year risk of major adverse cardiovascular events in patients with in-stent restenosis

In this analysis, we included 197 patients with ISR who underwent PCI (one lesion imaged/treated per patient). The patients were divided into 2 groups based on the median of the distribution of non-homogeneous quadrants as per intravascular OCT imaging (100 patients in low inhomogeneity and 97 patients in high inhomogeneity group). Of these patients, 88 (44.7%) were treated with DES and 109 (55.3%) with DCB angioplasty. With respect to baseline characteristics, groups were well-matched (supplementary **Table A15**). Approximately half of the patients presented with stable angina as indication for PCI (low vs. high inhomogeneity, 49.0% vs. 50.5%). A higher proportion of restenosis morphology were identified either as focal body (41.0% vs. 39.2%) or diffuse intra-stent (29.0% vs. 38.1%) lesions (supplementary **Table A16**).

4.7.1. Morphometric analysis as per intravascular optical coherence tomography

The results of the morphometric analysis based on the degree of inhomogeneity (3,505 frames, 33,298 struts and 2,647 frames, 24,967 struts in the low inhomogeneity and high inhomogeneity groups, respectively) are shown in supplementary **Table A17**. The groups were well-balanced and there were no statistically significant differences regarding either stent diameter/area, lumen diameter/area or neointimal thickness/area. Neointimal tissue was assessed in a total of 7675 quadrants; the proportion of inhomogeneous quadrants was 2.3% (0.0-6.4) in the low inhomogeneity and 31.8% (18.2-60.7) in the high inhomogeneity group.

4.7.2. Two-year clinical outcomes: major adverse cardiac events

Table 13 shows the 2-year clinical outcomes according to the degree of neointimal inhomogeneity. Patients with low and high neointimal inhomogeneity were also assessed individually as per the treatment modality (DES or DCB). In addition, the results are shown for the high neointimal inhomogeneity group based on the extent of neoatherosclerosis. The median follow-up time was 701 (408-1087) days in the low inhomogeneity and 748 (361-1083) days in the high inhomogeneity groups (p=0.962).

Table 13. Clinical outcomes (166)**.**

All patients				
Clinical event	**Low inhomogeneity** (N=100)	**High inhomogeneity** (N=97)	**Hazard Ratio [95%CI]**	**p value**
Death	5	2	0.42 [0.09-2.08]	0.306
MI	1	1	1.04 [0.07-16.6]	0.978
Death or MI	6	3	0.53 [0.14-2.08]	0.372
CABG	2	1	0.53 [0.05-5.60]	0.603
Repeat PCI	22	24	1.18 [0.66-2.10]	0.571
TLR	24	25	1.10 [0.63-1.93]	0.732
MACE	27	26	1.02 [0.59-1.75]	0.939
Patients with high neointimal inhomogeneity				
Clinical event	**Drug-eluting stent** (N=48)	**Drug-coated balloon** (N=49)	**Hazard Ratio [95%CI]**	**p value**
Death	0	2	-	0.505*
MI	0	1	-	0.990*
Death or MI	0	3	-	0.250*
CABG	1	0	-	0.990*
Repeat PCI	5	19	0.23 [0.09-0.61]	0.003
TLR	6	19	0.28 [0.11-0.69]	0.006
MACE	6	20	0.26 [0.10-0.65]	0.004
Patients with low neointimal inhomogeneity				
Clinical event	**Drug-eluting stent** (N=40)	**Drug-coated balloon** (N=60)	**Hazard Ratio [95%CI]**	**p value**
Death	3	2	2.29 [0.38-13.70]	0.365
MI	1	0	-	0.800*
Death or MI	4	2	1.84 [0.56-16.7]	0.197
CABG	2	0	-	-
Repeat PCI	7	15	0.65 [0.27-1.60]	0.351
TLR	9	15	0.90 [0.39-2.05]	0.797
MACE	11	16	1.04 [0.48-2.25]	0.917
Patients with high neointimal inhomogeneity				
Clinical event	**High neoatherosclerosis** (N=47)	**Low neoatherosclerosis** (N=50)	**Hazard Ratio [95%CI]**	**p value**
Death	2	0	-	0.464*
MI	0	1	-	0.970*
Death or MI	3	2	1.84 [0.32-10.7]	0.503
CABG	0	1	-	0.970*
Repeat PCI	10	14	0.70 [0.31-1.57]	0.391
TLR	10	15	0.65 [0.29-1.43]	0.289
MACE	11	15	0.69 [0.32-1.51]	0.366

*Fisher's exact test.

CABG=coronary artery bypass grafting; CI=confidence interval; MACE=major adverse cardiovascular events; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLR=target lesion revascularization.

The main endpoint of interest, MACE, was a composite of all-cause death, MI, or clinically driven TLR. A MACE occurred in 27 of 100 patients in the low inhomogeneity and 26 of 97 patients in the high inhomogeneity group. There was no significant difference regarding this outcome between the groups (HR=1.02 [0.59-1.75]; p=0.939) (**Figure 24**). Of note, the treatment with DES was associated with a lower risk of MACE over DCB in the high inhomogeneity group (HR=0.26 [0.10-0.65]; p=0.004). The risk was comparable for both PCI treatments in the low inhomogeneity group (HR=1.04 [0.48-2.25]; p=0.917) (**Figure 25**).

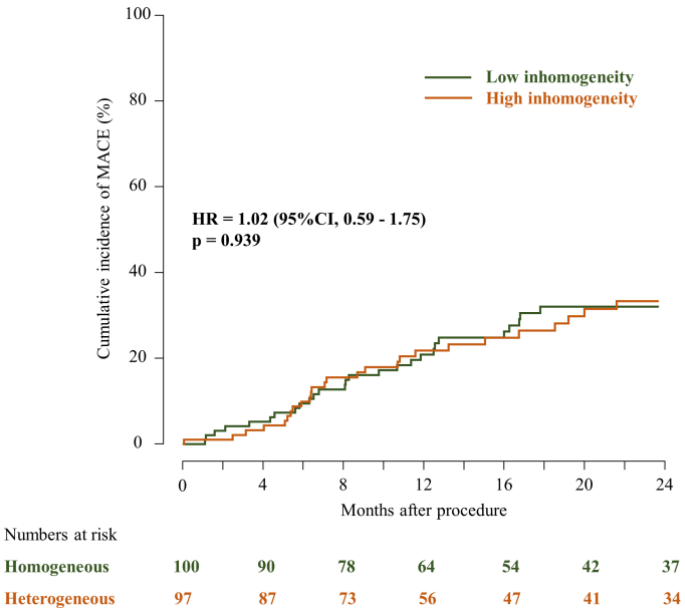


Figure 24. Cumulative incidence of major adverse cardiac events in the low and high inhomogeneity subgroups (166)**.**

CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular events.

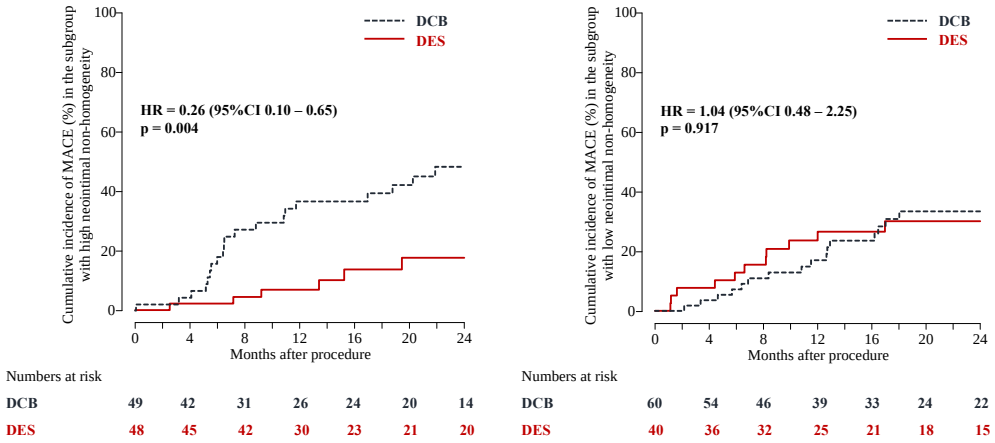


Figure 25. Cumulative incidence of major adverse cardiac events according to the treatment type in the patients with high and low neointimal inhomogeneity (166)**. ***

*There was a significant interaction between neointimal pattern and treatment modality with respect to MACE ($P_{interaction}$=0.006).

CI=confidence interval; DCB=drug-coated balloon; DES=drug-eluting stent; HR=hazard ratio; MACE=major adverse cardiovascular events.

4.7.3. Additional endpoints: target lesion revascularization and composite of all-cause death or myocardial infarction

Clinically driven TLR occurred in 24 of 100 patients in the low inhomogeneity and 25 of 97 patients in the high inhomogeneity group. The risk of a TLR event was comparable between the groups (HR=1.10 [0.63-1.93]; p=0.732) (**Figure 26**). In the high inhomogeneity group, DES compared to DCB was associated with a lower risk of clinically driven TLR (HR=0.28 [0.11-0.69]; p=0.006). The risk of TLR was comparable for both treatment modalities in the low inhomogeneity group (HR=0.90 [0.39-2.05]; p=0.797). A composite of all-cause death or MI occurred in 6 of 100 patients in the low inhomogeneity and 3 of 97 patients in the high inhomogeneity group (HR=0.53 [0.14-2.08]; p=0.372) (**Figure 27**).

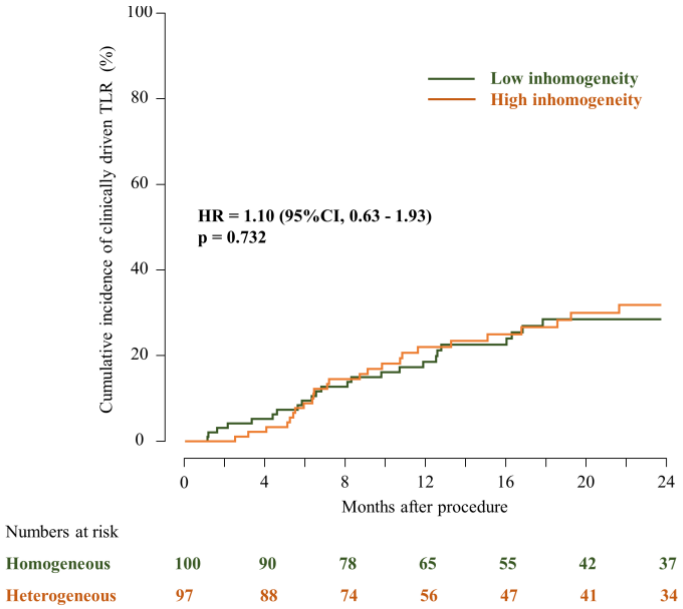


Figure 26. Cumulative incidence of clinically driven target lesion revascularization in the low and high inhomogeneity subgroups (166)**.**

CI=confidence interval; HR=hazard ratio; TLR=target lesion revascularization.

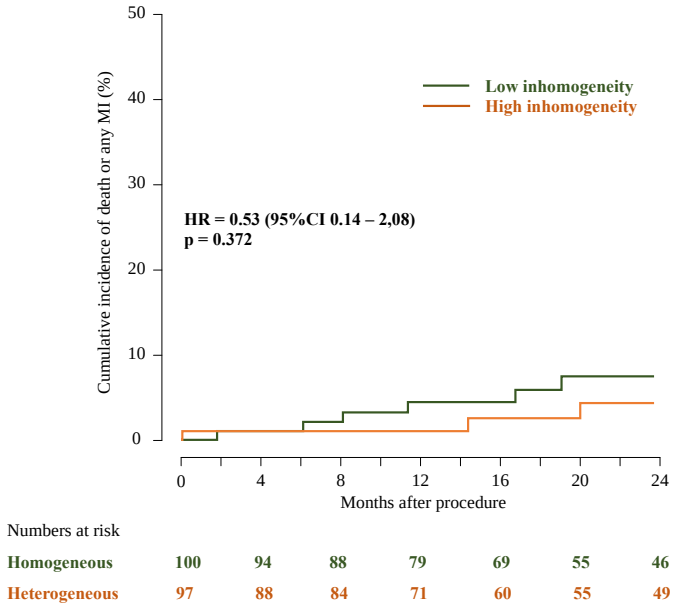


Figure 27. Cumulative incidence of all-cause death or myocardial infarction in the low and high inhomogeneity subgroups (166)**.**

CI=confidence interval; HR=hazard ratio; MI=myocardial infarction.

4.7.4. Multivariable analysis

In order to further evaluate the clinical outcomes with regard to the degree of neointimal inhomogeneity by intravascular OCT imaging and the treatment modality at the time of PCI (DES or DCB), we performed a multivariable analysis adjusting for the following baseline clinical and angiographic variables: age, gender, smoking habit, BMI, hypercholesterolemia, arterial hypertension, diabetes mellitus, history of MI, history of CABG, multivessel CAD, target vessel, ostial lesion, bifurcation lesion, completely occlusive ISR, reference diameter and diameter stenosis pre-PCI.

Major adverse cardiovascular events

There was no significant difference with respect to MACE based on the degree of neointimal inhomogeneity through to 2 years follow-up ($p_{adjusted}$=0.567). There was a statistically significant difference for this outcome between patients treated with DES and DCB ($p_{adjusted}$=0.022).

Target lesion revascularization

Similarly, low and high neointimal inhomogeneity groups were comparable regarding clinically driven TLR events on adjusted analysis ($p_{adjusted}$=0.350). The risk of TLR was significantly different for patients treated with DES and DCB at 2 years ($p_{adjusted}$=0.013).

In addition, we investigated whether the neointimal pattern and clinical outcomes are influenced by the type of PCI treatment (DES or DCB). For the purposes of this analysis, an interaction term (OCT-pattern of neointima * PCI type) was added into the multivariable model. There was a statistically significant interaction for both MACE ($p_{interaction}$=0.006) and clinically driven TLR ($p_{interaction}$=0.022) at 2-years follow-up.

4.7.5. Neoatherosclerosis

In an effort to assess the impact of neoatherosclerosis on clinical outcomes, we separately evaluated the patients with high neointimal inhomogeneity according to the extent of atherosclerotic changes in the neointima. The groups were comparable with respect to clinical endpoints through to 2 years (**Table 13**).

4.8. The impact of optical neointimal characteristics and treatment modality on periprocedural myocardial injury in patients with in-stent restenosis

In this analysis, we included 128 patients with ISR undergoing PCI (one lesion imaged/treated per patient). The patients were then divided into following 2 groups based on the median of the distribution of non-homogeneous quadrants by intravascular OCT imaging: low (N=64) and high (N=64) neointimal inhomogeneity. The groups were well-matched with respect to baseline clinical, angiographic, and procedural characteristics, except for target vessel. Approximately three quarters of the patients in both groups presented with DES as the underlying stent type (low vs. high inhomogeneity, 75.0% vs. 79.7%). Of these patients, 45 (35.2%) were treated with DES and 83 (64.8%) with DCB angioplasty. A higher proportion of restenosis morphology were identified either as focal body (50.0% vs. 46.9%) lesions. The groups were comparable with regard to QCA parameters. These data are shown in supplementary **Table A18** and **Table A19**.

4.8.1. Morphometric analysis as per intravascular optical coherence tomography

The results of the morphometric analysis based on the extent of neointimal inhomogeneity are shown in supplementary **Table A20**. We assessed a total of 2,315 frames, 22,338 struts and 2,175 frames, 21,191 struts in the low and high inhomogeneity groups, respectively. The groups were well-balanced and there were no statistically significant differences in terms of either stent diameter/area, lumen diameter/area or neointimal thickness/area.

4.8.2. Cardiac biomarker values according to neointimal inhomogeneity, treatment modality and degree of neoatherosclerosis

Table 14 shows the changes in cardiac biomarker (hs-cTnT and CK-MB) values along with the frequency of minor and major PMI according to the degree of neointimal inhomogeneity and treatment modality. In addition, the results are shown for the high neointimal inhomogeneity group according to the extent of neoatherosclerosis.

Table 14. Biomarker values as per neointimal tissue characterization, treatment modality and extent of neoatherosclerosis (173)**.**

Cardiac biomarker values according to neointimal tissue characterization			
	Low inhomogeneity (N=64)	**High inhomogeneity** (N=64)	**p value**
Baseline hs-cTnT, ng/L	10.0 (7.0-18.2)	11.5 (8.0-18.0)	0.697
Peak post-procedural hs-cTnT, ng/L	40.5 (23.5-99.8)	40.5 (23.2-80.2)	0.728
Delta hs-cTnT, ng/L	28.0 (12.0-65.8)	25.5 (9.8-65.0)	0.355
Major PMI	20 (31.2)	20 (31.2)	1.000
Minor PMI	62 (96.9)	62 (96.9)	1.000
Baseline CK-MB, U/l	14.9 (11.2-17.4)	15.3 (12.4-18.0)	0.416
Peak post-procedural CK-MB, U/l	14.5 (11.2-20.1)	14.4 (12.3-18.7)	0.684
Delta CK-MB, U/l	-0.2 (-2.9-3.4)	-0.1 (-1.80-2.6)	0.562
Cardiac biomarker values according to treatment modality			
	Drug-coated balloon (N=83)	**Drug-eluting stent** (N=45)	**p value**
Baseline hs-cTnT, ng/L	10.0 (7.0-18.5)	12.0 (8.0-18.0)	0.288
Peak post-procedural hs-cTnT, ng/L	39.0 (22.5-79.0)	46.0 (24.0-99.0)	0.445
Delta hs-cTnT, ng/L	27.0 (10.0-64.0)	28.0 (11.0-73.0)	0.795
Major PMI	24 (28.9)	16 (35.6)	0.566
Minor PMI	80 (96.4)	44 (97.8)	1.000
Baseline CK-MB, U/l	15.2 (11.6-17.7)	14.5 (11.7-17.9)	0.853
Peak post-procedural CK-MB, U/l	14.4 (12.3-18.3)	14.5 (11.4-21.4)	0.882
Delta CK-MB, U/l	0.0 (-1.8-2.8)	-0.6 (-2.7-3.0)	0.653
Cardiac biomarker values according to neointimal tissue characterization in the subgroup treated with drug-coated balloon			
	Low inhomogeneity (N=38)	**High inhomogeneity** (N=45)	**p value**
Baseline hs-cTnT, ng/L	9.5 (7.0-23.5)	10.0 (7.0-14.0)	0.985
Peak post-procedural hs-cTnT, ng/L	44.0 (26.5-113.0)	30.0 (20.0-66.0)	0.075
Delta hs-cTnT, ng/L	31.0 (18.2-82.2)	18.0 (9.0-55.0)	0.031
Major PMI	13 (34.2)	11 (24.4)	0.462
Minor PMI	37 (97.4)	43 (95.6)	1.000
Baseline CK-MB, U/l	15.2 (11.7-17.5)	15.3 (11.9-17.8)	0.936
Peak post-procedural CK-MB, U/l	14.6 (12.1-20.6)	14.4 (12.4-17.5)	0.731
Delta CK-MB, U/l	0.0 (-2.6-3.4)	-0.10 (-1.7-2.3)	0.842
Cardiac biomarker values according to neointimal tissue characterization in the subgroup treated with drug-eluting stent			

	Low inhomogeneity (N=26)	High inhomogeneity (N=19)	p value
Baseline hs-cTnT, ng/L	11.5 (8.0-15.5)	13.0 (8.5-21.5)	0.295
Peak post-procedural hs-cTnT, ng/L	33.5 (22.0.73.0)	73.0 (33.0-130.0)	0.061
Delta hs-cTnT, ng/L	19.0 (11.0-56.2)	48.0 (17.5-96.0)	0.215
Major PMI	7 (26.9)	9 (47.4)	0.271
Minor PMI	25 (96.2)	19 (100)	1.000
Baseline CK-MB, U/l	14.5 (11.0-15.4)	15.4 (12.7-20.2)	0.278
Peak post-procedural CK-MB, U/l	13.6 (10.9-18.9)	16.2 (11.7-22.9)	0.242
Delta CK-MB, U/l	-1.0 (-4.1-2.2)	0.2 (-1.9-3.2)	0.304
Cardiac biomarker values in the subgroup with high neointimal inhomogeneity, according to the extent of neoatherosclerosis			
	Low neoatherosclerosis (N=33)	**High neoatherosclerosis (N=31)**	**p value**
Baseline hs-cTnT, ng/L	12.0 (8.0-19.0)	9.0 (6.0-14.0)	0.049
Peak post procedural hs-cTnT, ng/L	33.0 (26.0-97.0)	47.0 (22.5-75.5)	0.989
Delta hs-cTnT, ng/L	15.0 (6.0-73.0)	31.0 (14.5-57.5)	0.295
Major PMI	10 (30.3)	10 (32.3)	1.000
Minor PMI	31 (93.9)	31 (100)	0.493
Baseline CK-MB, U/l	15.3 (12.4-17.4)	15.2 (12.5-18.6)	0.697
Peak post-procedural CK-MB, U/l	14.5 (12.4-19.3)	14.4 (11.6-18.3)	0.693
Delta CK-MB, U/l	-0.1 (-1.8-3.4)	-0.0 (-1.7-1.2)	0.673

Data are median (interquartile range) or counts (%).

CK-MB= creatine kinase, myocardial band; hs-cTnT= high-sensitivity cardiac troponin T; PMI = peri-procedural myocardial injury.

The changes in cardiac biomarker values and the extent of PMI were comparable with respect to both neointimal inhomogeneity (low vs. high) and treatment modality (DES vs. DCB). Extent of neointimal inhomogeneity did not independently correlate with changes in hs-cTnT values on adjusted analysis ($p_{adjusted}$= 0.468). Of note, there was no statistically significant interaction between neointimal inhomogeneity and PCI treatment regarding changes in hs-cTnT values ($p_{interaction}$=0.432). Cumulative frequency distribution curves for hs-cTnT and CK-MB concentration in the low and high neointimal inhomogeneity groups are shown in **Figure 28** and **Figure 29.** Finally, there were no significant differences in the cardiac biomarker values according to the extent of neointimal atherosclerotic changes in patients with high neointimal inhomogeneity.

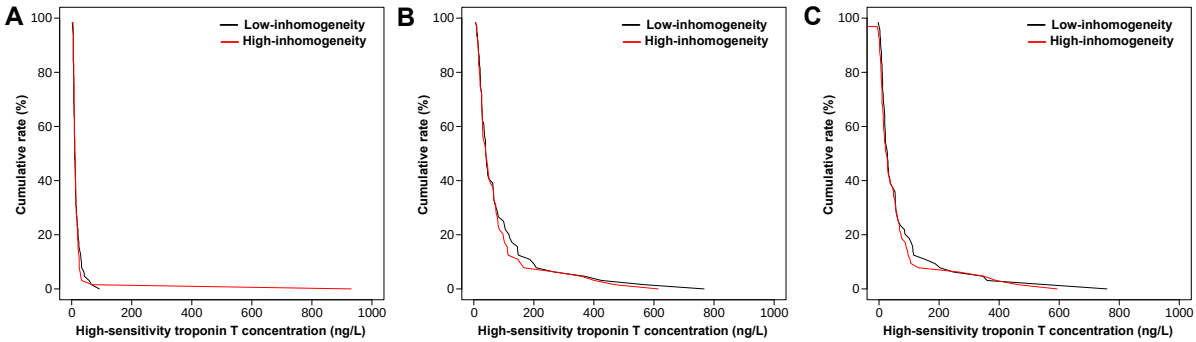


Figure 28. Cumulative frequency distribution curves for baseline (A), peak post-procedural (B) and delta (C) high-sensitivity cardiac Troponin T concentration (173)**.**

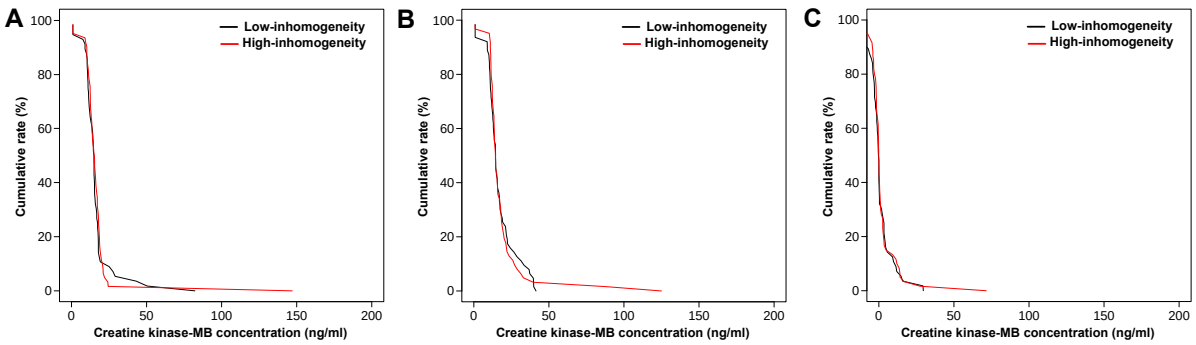


Figure 29. Cumulative frequency distribution curves for baseline (A), peak post-procedural (B) and delta (C) creatine kinase-MB concentration (173)**.**

MB= myocardial band.

4.8.3. Two-year clinical outcomes: major adverse cardiac events, death or myocardial infarction, target lesion revascularization

The risk of MACE (42.7% vs. 28.7%, HR=1.66 [0.85–3.24]; p=0.14) (**Figure 30**), composite of death or MI (7.5% vs. 4.6%, HR=1.40 [0.24–8.41]; p=0.71) (**Figure 31**), or clinically driven TLR (40.1% vs. 24.4%, HR=1.84 [0.91–3.74]; p=0.092) (**Figure 32**) was not significantly different between the low and high neointimal inhomogeneity groups.

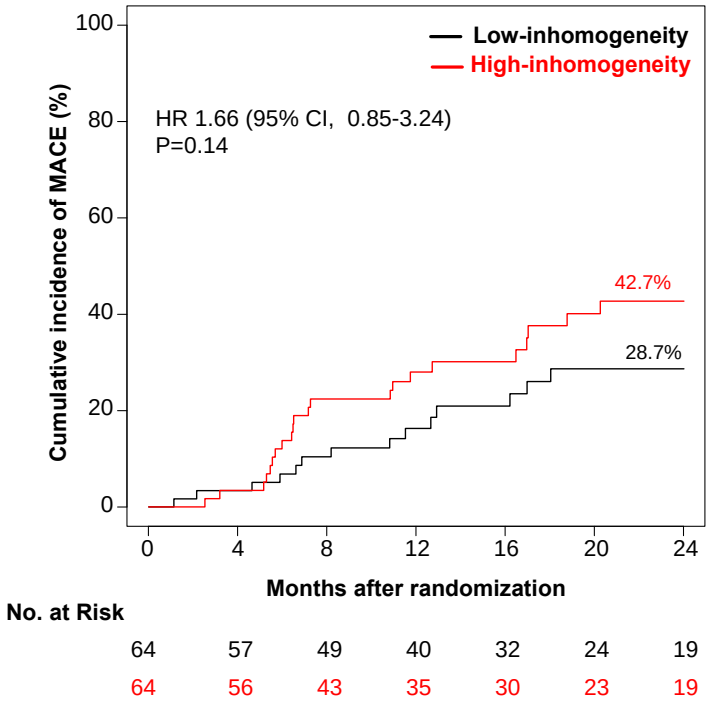


Figure 30. Two-year cumulative incidence of major adverse cardiac events according to the neointimal tissue characterization (173)**.**

CI=confidence interval; HR=hazard ratio; MACE= major adverse cardiovascular events.

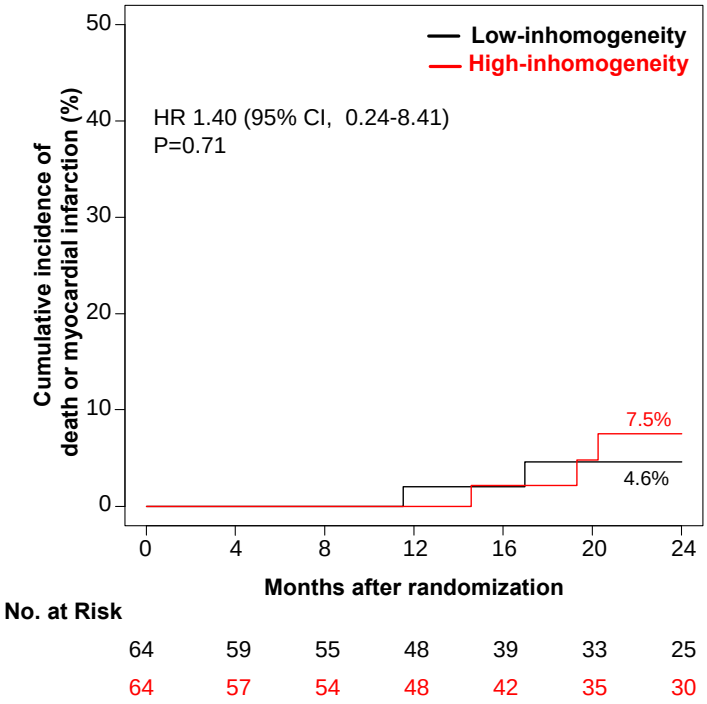


Figure 31. Two-year cumulative incidence of death or myocardial infarction according to the neointimal tissue characterization (173)**.**

CI=confidence interval; HR=hazard ratio.

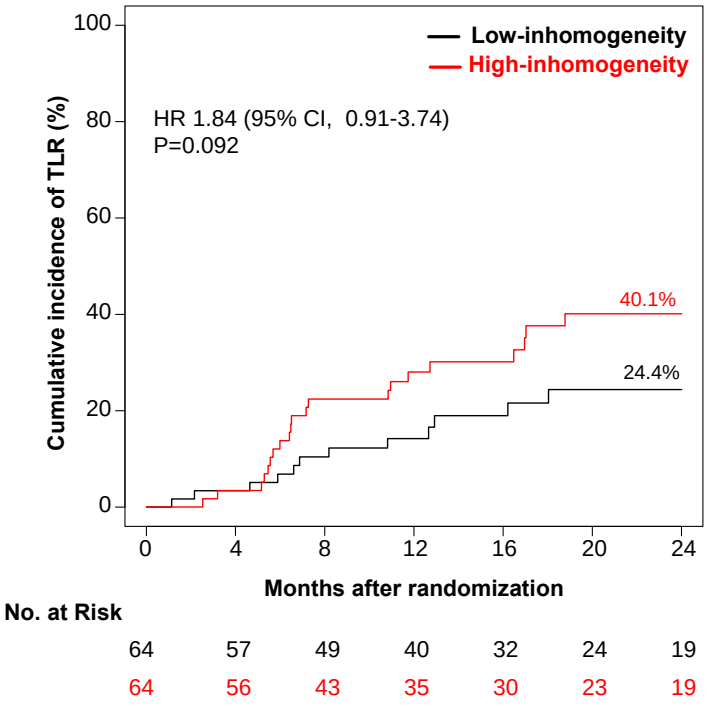


Figure 32. Two-year cumulative incidence of target-lesion revascularization according to the neointimal tissue characterization (173)**.**

CI=confidence interval; HR=hazard ratio; TLR=target-lesion revascularization.

4.9. The comparative efficacy and bleeding risk of ticagrelor and prasugrel at 1-year in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

In this prespecified analysis, we included 1,653 patients presenting with STEMI undergoing primary PCI. There was no significant interaction between diagnosis on admission (UA, NSTEMI or STEMI) and treatment effect of the study drug with respect to primary endpoint ($p_{interaction}$=0.86). The median time interval from symptom onset to randomization was 3.2 (1.8–7.7) hours in the ticagrelor group and 3.0 (1.9–8.4) hours in the prasugrel group (p=0.90). The groups were well-matched with respect to baseline characteristics, except for the treatment strategy (supplementary **Table A21**). Diagnostic angiography was performed in 1,652 patients (832 and 820 patients in the ticagrelor and prasugrel group, respectively), and PCI was performed in 1,568 patients (779 and 789 patients in the ticagrelor and prasugrel group, respectively). Although fewer patients in the ticagrelor group underwent PCI (p=0.040), the difference was reduced (97.2% vs. 98.2%; p=0.18) when the analysis was performed in patients with final diagnosis of ACS. The angiographic and procedural characteristics along with peri-procedural antithrombotic therapy appear to differ little between treatment arms (supplementary **Table A22**). Majority of the patients were implanted a DES (90.9% vs. 91.8%; p=0.60). The therapy at discharge and the assigned antithrombotic medication after study drug discontinuation is shown in supplementary **Table A23**.

4.9.1. One-year clinical outcomes

One-year follow-up was complete except for 15 patients in the ticagrelor group (1.8%) and 14 patients in the prasugrel group (1.7%). One-year clinical outcomes are shown in **Table 15**.

Table 15. Clinical outcomes (176)**.**

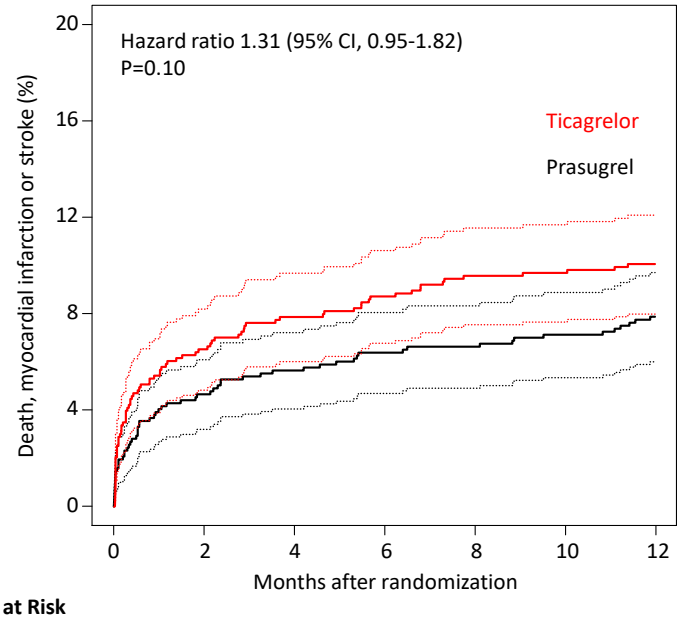
Characteristic	Ticagrelor (N=833)	Prasugrel (N=820)	Hazard Ratio [95% CI]	p value
Primary endpoint (death, myocardial infarction, or stroke)	83 (10.1)	64 (7.9)	1.31 [0.95-1.82]	0.10
All-cause death	40 (4.9)	38 (4.7)	1.05 [0.67-1.64]	0.83
Cardiovascular	29	33		
Noncardiovascular	11	5		
Myocardial Infarction	44 (5.3)	23 (2.8)	1.95 [1.18-3.23]	0.010
Type 1	24 (2.9)	12 (1.5)	2.06 [1.03-4.13]	0.041
Type 2	1	1		
Type 4	19 (2.3)	10 (1.2)	1.92 [0.89-4.14]	0.09
Type 4a	5	3		
Type 4b	14	7		
Type 5	0	0		
ST-elevation myocardial infarction	17	6		
Stroke				
Any	11 (1.3)	8 (1.0)	1.41 [0.57-3.50]	0.46
Ischemic	8	6		
Haemorrhagic	3	2		
Definite or probable stent thrombosis	17 (2.1)	11 (1.3)	1.55 [0.72-3.30]	0.26
Definite stent thrombosis	15 (1.8)	8 (1.0)	1.88 [0.80-4.44]	0.15
Secondary safety endpoint: BARC type 3 to 5 bleeding	46/830 (6.1)	39/810 (5.1)	1.22 [0.80-1.87]	0.36
BARC 3a	21	21		
BARC 3b	20	16		
BARC 3c	2	0		
BARC 4	1	0		
BARC 5a	1	0		
BARC 5b	1	2		

Data are number of events with Kaplan-Meier estimates (%) for primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints.

BARC=Bleeding Academic Research Consortium; CI=confidence interval.

Primary efficacy endpoint: composite of all-cause death, myocardial infarction, or stroke

The primary endpoint occurred in 83 of 833 patients (10.1%) in the ticagrelor group and 64 of 820 patients (7.9%) in the prasugrel group (HR=1.31 [0.95–1.82]; p=0.10) (**Figure 33)**. There was no significant difference in the incidence of all-cause death (4.9% vs. 4.7%; p=0.83) or stroke (1.3% vs. 1.0%; p=0.46) between the groups. The incidence of MI was significantly higher in the ticagrelor group (5.3% vs. 2.8%, HR=1.95 [1.18–3.23]; p=0.010) (**Figure 34**). The observed difference in the incidence of MI was driven mostly by an increase in the spontaneous and PCI-related MI. The incidence of definite ST was comparable between the groups (1.8% vs. 1.0%, HR=1.88 [0.80–4.44]; p=0.15).



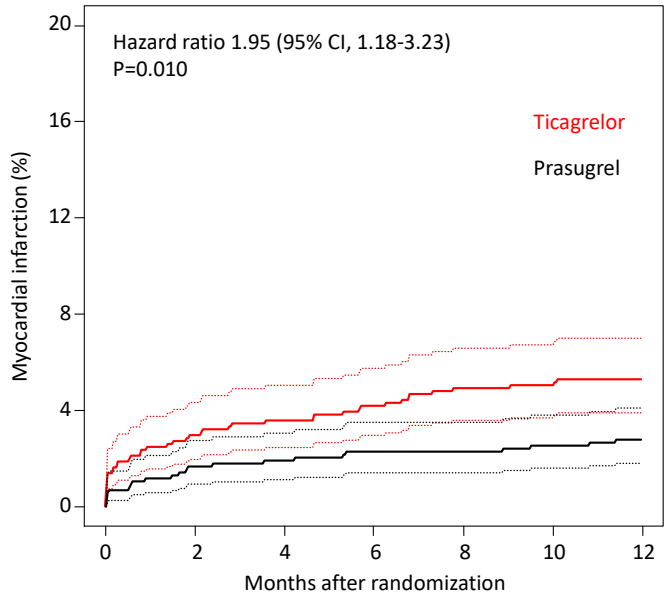
No. at Risk

Ticagrelor	833	767	756	748	740	739	730
Prasugrel	820	772	764	755	751	747	733

Figure 33. One-year cumulative incidence of the primary endpoint (death, myocardial infarction, stroke) in patients assigned to ticagrelor or prasugrel (176)**.**

Dotted lines are the 95% confidence intervals. Primary endpoint was evaluated in the intention-to-treat population.

CI=confidence interval.



No. at Risk

Ticagrelor	833	772	761	755	747	746	738
Prasugrel	820	775	769	760	756	752	742

Figure 34. One-year cumulative incidence of myocardial infarction in patients assigned to ticagrelor or prasugrel (176)**.**

Dotted lines are the 95% confidence intervals. The risk estimates (hazard ratio [HR] with 95% confidence interval [CI]) are obtained from the Cox proportional hazard model after adjustment for the participating center and accounting for computing risk.

Secondary safety endpoint: type 3 to 5 BARC bleeding

The secondary safety endpoint occurred in 46 of 830 patients (6.1%) in the ticagrelor group and 39 of 810 patients (5.1%) in the prasugrel group (HR=1.22 [0.80–1.87]; p=0.36). These data are shown in **Figure 35**.

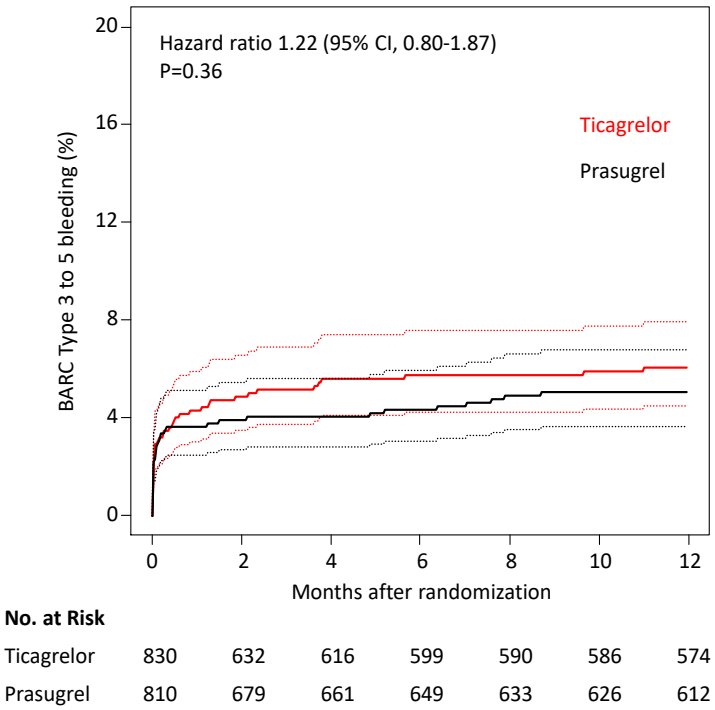


Figure 35. Cumulative incidence of the safety endpoint at 1 year (BARC type 3–5 bleeding) (176)**.**
Dotted lines are the 95% confidence intervals. Secondary endpoint was evaluated in the modified intention-to-treat population.
CI=confidence interval.

4.9.2. Landmark analysis

The results of the landmark analysis for both the primary and secondary endpoint are shown in **Figure 36**. For both early (up to 1 month) and later (1 month through to 1 year) time period, the trend observed was in line with the overall results.

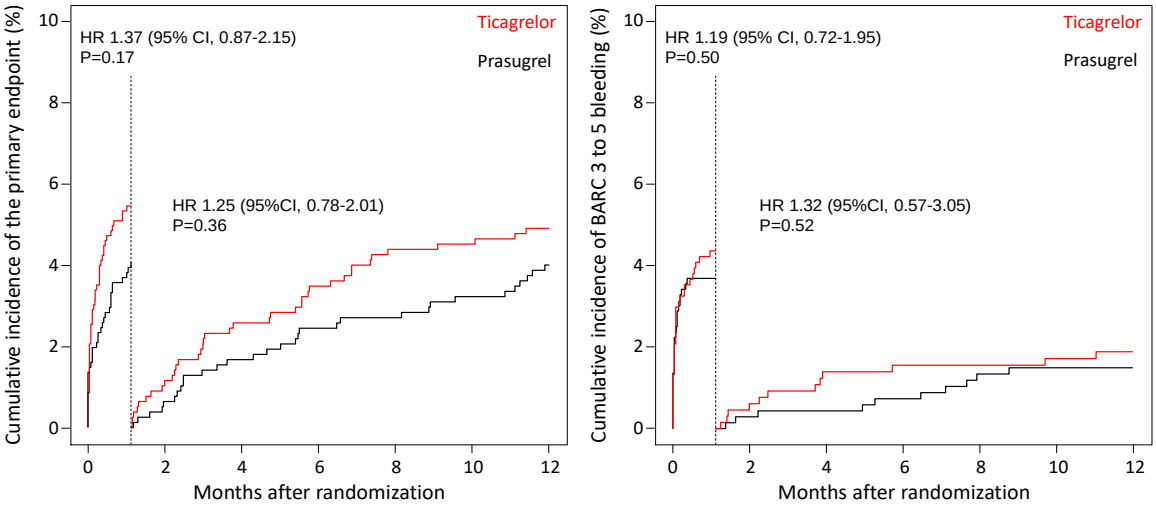


Figure 36. One-month landmark analysis for primary and secondary endpoints (176)**.**

BARC=Bleeding Academic Research Consortium; CI=confidence interval; HR=hazard ratio.

4.9.3. Per-protocol analysis

We also performed an efficacy analysis including all patients who received ≥1 dose of the randomly assigned ticagrelor or prasugrel over the period from ingestion of the first dose to the time of study drug discontinuation, death, loss to follow-up, or 1 year. These results are shown in **Table 16** and are similar to those shown for the intention-to-treat population.

Table 16. Primary endpoint, its individual components and stent thrombosis in per-protocol analysis (176)**.***

Outcome	Ticagrelor (N=830)	Prasugrel (N=810)	Hazard Ratio [95% CI]	p value
Primary endpoint (death, myocardial infarction, or stroke)	76 (9.6)	56 (7.2)	1.39 [0.98-1.96]	0.06
All-cause death	36 (4.5)	33 (4.2)	1.08 [0.68-1.74]	0.74
Myocardial infarction	41 (5.2)	21 (2.7)	2.05 [1.21-3.47]	0.008
Stroke	10 (1.2)	7 (0.9)	1.43 [0.55-3.77]	0.46
Definite or probable stent thrombosis	17 (2.1)	10 (1.2)	1.72 [0.79-3.77]	0.17
Definite stent thrombosis	15 (1.8)	7 (0.9)	2.20 [0.90-5.40]	0.08

Data are number of events with Kaplan-Meier estimates (%) for primary endpoint and death or cumulative incidence (%) after accounting for competing risk for the remaining endpoints. CI=confidence interval. The risk estimates are obtained from the Cox proportional hazard model with stratification for the participating center.

* The per-protocol analysis included all patients who received at least one dose of the randomly assigned study drug over the period from ingestion of the first dose to the time of study drug discontinuation, death, loss to follow-up or one year.

5. DISCUSSION

5.1. New-generation drug-eluting stents are associated with a lower incidence of definite stent thrombosis than early-generation drug-eluting stents at 10-years

The main findings of this analysis are as follows:

- The definite ST occurred in 69 of 6,866 patients (1.0%) with new generation DES following PCI up to 10 years of follow-up.
- Compared to early-DES, new-DES are associated with a lower 10-year incidence of definite ST.
- The rate of ST beyond 1 year (VLST) and 5 years (VVLST) was in particular attenuated with the use of new-DES in comparison to early-DES.

It should be noted that there were certain differences in baseline and procedural characteristics between early- and new-DES groups in our study, possibly due to the heterogeneity of randomization groups across the trials included in the DECADE co-operation. Patients in the new-DES group, compared with patients in the early-DES group, were more frequently diabetic, had a higher rate of treated bifurcation lesions and complex lesion morphology along with a longer stented length. As shown in previous studies, these factors are associated with an increased risk of ST (193-196). Still, the new DES group in our study was associated with a lower 10-year risk of definite ST, both in crude analysis and after adjustment for potential confounders. Considering the initial concerns with respect to the time period from 1 to 5 years following PCI in the early generation DES era, low incidence of VLST in the current analysis highlights the advancements made in DES technology (34). These include not only improvement of stent design but also reductions in strut thickness and novel polymer technologies as well. Of note, while the type and release kinetics of the anti-proliferative drugs eluted from the stent may also have played a role in these results, there were also differences in this regard between the stent technologies included within both the early and new-DES groups.

To the best of our knowledge, there are no previous reports in scientific literature comparing the incidence of ST at 10 years in patients treated with early-DES and new-DES, except for some observational analyses with shorter follow-up. In a previous study from our group, Tada et al. reported

an increased risk of ST for early-DES compared to BMS, driven by events from 1 year up to 3 years following PCI. Interestingly, risk of ST was comparable between BMS and new-DES (81). Subsequently, a meta-analysis of 33 randomized trials with short-(up to 1 year) and long-term (beyond 1 year) follow-up after PCI showed that new generation EES may reduce the risk of ST compared to early-DES (163). Similarly, several comprehensive network meta-analyses have shown significant reduction of ST at 1 year with EES compared to early generation PES (38, 197). Finally, 5-year results from the SORT OUT IV randomized trial also showed reduction in the occurrence of very late definite ST in patients treated with EES in comparison to SES (198). The overall longer duration of follow-up in this current analysis may have also allowed time for important differences to emerge between the new- and early-DES groups.

The new-DES group in this study included BP-DES, PP-DES and PF-DES platforms. In this regard, previous meta-analyses have suggested comparable safety and efficacy between new-generation, PP-DES and BP-DES, and between new-generation, PP-DES and PF-DES (39, 199). Although the data are currently limited, newer generation DES with ultra-thin strut may help further reduce the risk of ST in comparison to the current new-DES with thicker backbones (200, 201).

In patients treated with new-DES, landmark analysis showed the highest incidence of definite ST occurring within the first 30 days. This may have relevance for future studies with respect to the proposed patient-tailored pharmaco-therapeutic strategies following PCI in the contemporary DES era. Notably, the risk of definite ST was lower in new-DES group in comparison to early-DES from 1 to 5 years and from 5 to 10 years after PCI. Overall, these data suggest that the rate of VLST and VVLST has been reduced with advancements made in DES technology. Considering the 1% cumulative incidence of definite ST in patients treated with new-DES at 10 years, it will be challenging for future DES trials to have sufficient sample size to demonstrate a meaningful reduction regarding this endpoint.

5.2. Female patients are at increased risk of early myocardial infarction, undergo less repeat revascularization and have comparable risk of cardiovascular mortality as opposed to male patients following drug-eluting stent implantation at 10 years

The main findings of this analysis are as follows:

- At 10 years following PCI and treatment with DES implantation, female and male patients have comparable risk of cardiovascular death after statistical adjustment for age differences.
- The risk of MI was particularly high for female patients within 30 days of the index procedure. The MI risk was comparable between female and male patients from 30 days up to 10-years following PCI.
- The risk of repeat revascularization (TLR, TVR, NTVR) was lower for female patients than male patients after PCI.

The results of this study are valuable as it provides information on sex-related differences in clinical outcomes over a long-term follow-up. It underlines the importance of female representation in clinical trials investigating DES platforms (202). Earlier studies on sex-related outcomes reported outcomes up to 5 years and some of them also included patients treated with BMS (113, 114). We believe that the inclusion of patients who were only treated with DES may be more relevant, as it better depicts the contemporary PCI era and current clinical practice. Notably, it has been reported that outcomes in women undergoing PCI have improved with DES implantation (116).

Consistent with a previous real-world study on sex-related outcomes in 6.6 million patients undergoing PCI in the United States, the baseline characteristics of the male and female patients included in this study differed noticeably (203). This suggests that the patients included in our analysis may be largely representative of the wider patient population undergoing PCI. In addition, women tend to have smaller vessel diameters with presence of diffuse CAD involving epicardial vessels and they also have an increased incidence of microvascular disease compared to men, who are recognized to have more commonly focal stenoses in the epicardial vessels (204, 205). Accordingly, these sex-

related differences in the manifestation of CAD may have played a role in the detected differences with regard to procedural characteristics and clinical outcomes in this analysis.

In our study, the clinical outcomes in female and male patients are analyzed up to 10 years and involved crude/unadjusted and adjusted analyses. Similar to previous findings, although female patients showed a higher rate of cardiovascular death than male patients on unadjusted analysis, 10-year cardiovascular mortality overall was comparable between groups after adjustment (113). Of note, women still showed an increased risk of cardiovascular mortality up to 10-years when age was excluded as a factor variable from the multivariable adjusted analysis. Female patients included in the DECADE co-operation were on average 5 years older than men. While the increasing age is known to be a strong predictor of death and poses difficulties for analyses of this nature, our findings demonstrated that female sex was not associated with an increased risk of cardiovascular death at 10-years following statistical adjustment for age differences (206). The age difference between female and male patients observed in this study may possibly be secondary to either the time of CAD development, or later diagnosis due to decreased physician awareness of CAD in women (207, 208).

The increased risk of MI in female compared with male patients was time-dependent and only observed within the first 30 days, possibly caused by an increased risk of periprocedural MI. In contrast, the risk of MI did not differ between the two groups from 30 days to 10 years. This finding is in line with a previous report from Anderson et al. (209), which showed a higher prevalence of in-hospital-complications and worse outcomes in female patients early after PCI. The cause for the timing of the increased MI risk seen in female patients remains unclear and persisted following the statistical adjustment. This may reflect the presence of confounders that were not known and therefore accounted for, or a sex-based difference in physiological response of the coronary vessel to stent implantation. Of note, the risk of definite ST was comparable between groups on both unadjusted and adjusted analyses, expanding on the previous results from the PROTECT trial with 5 years follow-up (210).

The overall comparable risk of ischemic events and the lower frequency of repeat revascularization in female patients observed in the present analysis deserves special attention. This finding is possibly multifactorial in nature. First, compared to men, greater number of diagnosed MI and ischemia may have been caused by non-obstructive coronary arteries in female patients (211-215). Second, plaque erosion frequently present in female patients may be underrated and overlooked when assessing coronary angiography (216, 217). Third, physicians may more commonly misinterpret the symptoms of female patients with stable CAD complaining of angina, which may subsequently result in a lower number of repeat coronary angiography (218, 219). Finally, previous findings on the presence of reduced risk of ISR in female patients may have also contributed to the lower incidence of repeat revascularization observed in the current study (220). Still, the nature of our analysis unfortunately prevents drawing conclusions regarding the definitive cause of this discrepancy.

Overall, our findings highlight the persistence and the relevance of differences in outcomes between female and male patients following PCI at long-term follow-up and the necessity to prioritize research focused at improving these outcomes regardless of sex (221, 222).

5.3. Biodegradable-polymer based drug-eluting stents are associated with better patient-oriented clinical outcomes compared to permanent-polymer based drug-eluting stents at 10 years in patients with acute coronary syndromes

The main findings of this analysis are as follows:

- In ACS patients, BP-DES was associated with a lower relative frequency of POCE in comparison to PP-DES over a 10-year follow-up. The relative frequency of DOCE was numerically lower in patients treated with BP-DES than PP-DES.
- The incidence of DOCE and the POCE was comparable between PF-DES and PP-DES groups at 10-years.
- The 10-year occurrence of definite/probable ST was low and similar for BP-DES vs PP-DES or PF-DES vs PP-DES comparisons.

This analysis suggested that BP-DES are superior to PP-DES regarding the frequency of POCE with a trend toward a lower frequency of DOCE up to 10 years follow-up, mainly driven by a lower incidence of both TLR and any revascularization. It is known that delayed vessel healing following DES implantation is associated with an increased risk of late thrombotic complications and delayed loss of anti-restenotic efficacy (223). Since patients with ACS are expected to have increased levels of inflammatory markers following PCI, treatment using a DES with BP coating presents an enticing prospect with particular benefit for such patients. Accordingly, an intravascular OCT analysis of patients post STEMI has previously demonstrated superior vessel-healing status with BP-DES in comparison to PP-DES at around 1 year follow-up (224).

Our analysis is noteworthy as it provides data for ACS patients treated with BP-DES over a 10-year follow-up. At present, there are limited data from earlier studies concerning this patient group with such an extended follow-up. Although the heterogeneity between these studies makes a direct comparison difficult, overall, these data suggest improvements in adverse clinical outcomes with BP-DES compared with PP-DES. In a prespecified stratified analysis of BIOSCIENCE study, Pilgrim et al. (225) reported better outcomes with regard to target lesion failure (a composite of cardiac death, target vessel MI, and TLR) for BP-DES compared to PP-DES in patients with STEMI at 1 year. Iglesias et al. (226) subsequently reported that in patients with STEMI who underwent primary PCI in BIOSTEMI study, BP-SES is associated with a lower risk of target lesion failure (driven by reduced TLR) at 1 year. Similarly, a pooled analysis of the ISAR-TEST 3, ISAR-TEST 4, and LEADERS trials showed a significant reduction of MACE in STEMI patients treated with BP-DES in comparison with PP-DES, primarily driven by a lower incidence of TLR at 4 years follow-up (227). It should be noted, however, that in this study PP-DES was an early-generation durable-polymer SES. In this respect, the new-generation PP-EES and PP-ZES comparator in our analysis may be more relevant to current practice. Finally, the BIO-RESORT study was an all-comer non-inferiority trial in which approximately 70% of the patients presented with ACS (228). At 3 years follow-up, BP-SES, BP-EES and PP-ZES showed comparable safety and efficacy (229).

With regard to PF-DES, the current analysis demonstrated comparable outcomes to the PP-DES regarding both the DOCE and POCE over a 10-year follow-up. This finding is congruent with a previous meta-analysis comparing these 2 stent platforms in ACS patients (230). It is remarkable that the incidence of definite ST was double in the PF-DES group compared to PP-DES and BP-DES groups in this study. The overall frequency of definite/probable ST at 10 years was less than 2% and there were no significant differences between the 3 stent polymer types. Of note, no definite/probable ST events was observed in the BP-DES group from 2 to 10 years. However, the present study was not adequately powered to evaluate differences between groups with respect to this endpoint.

All in all, the relative frequency of DOCE and POCE observed in this analysis at 10 years is an important reminder that patients with ACS undergoing PCI treatment represent a high-risk group in need of aggressive secondary prevention measures to reduce the recurrence of MACE. Novel pharmacotherapeutic strategies along with progresses in stent technology will certainly help to achieve this goal.

5.4. Drug-eluting stent overlap is associated with a higher 10-year risk of myocardial infarction and target lesion revascularization and binary angiographic restenosis at 6–8 months following percutaneous coronary intervention

The main findings of this analysis are as follows:

- DES overlap was associated with a higher 10-year risk of MI and TLR and BAR at 6–8 months following PCI. The increased frequency of MI was only observed in the first 30 days, with comparable risk from 30 days to 10 years between stent overlap and no stent overlap groups.
- Risk of all-cause mortality and definite/probable ST was comparable between the 2 groups up to 10 years of follow-up.
- The effect of stent overlap on all-cause mortality, MI and TLR was comparable between early and new generation DES. There was also no interaction between stent overlap and different

polymer types (BP, PP, PF) on the relative frequency of adverse clinical events over a 10 year follow-up.

The present study is unique in that it allows the assessment of DES overlap associated outcomes over a long-term follow-up in patients who were treated with various polymer strategies. It represents the largest study group (5,605 patients, 1,824 of whom had stent overlap) with DES overlap reported in the scientific literature. In addition, an extended follow-up duration of 10 years might have been long enough for the detection of relevant differences between the two groups.

The results from previous reports suggested a mechanistic reasoning for the events observed in our analysis. A porcine model-based imaging and histopathology study from Lim et al. (231) showed that overlapped DES segments have poorer endothelialization and persistent inflammation in comparison to BMS, albeit with a better prevention of neointimal hyperplasia. Another intravascular OCT analysis suggested a heterogenous effect with regard to DES overlap, with an exaggerated neointimal reaction at the overlap zone occurring in some patients (apart from the usual incomplete neointimal healing and strut coverage) (104).

With regard to impact of DES overlap on clinical outcomes, our results differed from previously published studies in several respects. In a pooled analysis of 5 clinical studies comparing outcomes in overlapping early-generation SES, MACE were similar with and without DES overlap up to 1 year. Still, overlap was associated with a higher rate of late lumen loss and more frequent BAR regardless of stent type (BMS or DES) (96). Another study investigated the influence of DES overlap up to 3 years in patients from the SIRTAX trial, who were treated with SES or PES (94). In this study, patients with stent overlap had a numerically higher degree of MACE in comparison to patients with multiple stents but no overlap (25.4% vs. 21.1%) or patients who were implanted with a single stent (25.4% vs. 14%). In a subsequent analysis of 5,130 patients treated with new generation ZES, stent overlap and no stent overlap groups were compared with regard to 2-year clinical and 13-month angiographic outcomes (102). At 2 years follow-up, MACE were comparable between the groups. Finally, in an analysis of the

EXAMINATION trial (with 1,498 STEMI patient randomized to either BMS or EES treatment arm), the frequency of POCE was similar between the stent overlap and no stent overlap groups at 5 years (232).

Our study demonstrated that DES overlap is associated with an increased risk of adverse clinical events following index PCI. This includes both BAR at 6–8 months and MI and TLR at 10 years. MI occurred more frequently in the stent overlap group from 0 to 30 days, with comparable risk between the groups from 30 days to 10 years. Of note, DES overlap was not associated with an increase in all-cause mortality regardless of the increased frequency of these adverse clinical events. The 10-year incidence of definite or probable ST was low, which may reflect the efficacy of contemporary stent technologies. Still, the present analysis is not sufficiently powered to rule out potential meaningful differences between the two groups for this endpoint.

Lack of any apparent significant interaction between stent overlap and the 3 different polymer types used to treat patients in this analysis (PP, BP, and PF) suggests that stent strut thickness may play an important role in stent overlap associated adverse outcomes. Hence, newer technologies with the goal of reducing strut thickness remains an important area of future research.

5.5. Non-target-vessel related remote disease progression is associated with a higher number of events compared to treated target vessel following drug-eluting stent implantation through to 10-years

The main findings of this analysis are as follows:

- NTVRE is associated with a higher proportion of total events compared to TVRE over a 10-year follow-up.
- The timing of TVRE and NTVRE showed a divergent pattern, with a higher incidence of TVRE up to 1 year following PCI. Thereafter, higher incidence of NTVRE was observed from 1 year to 10 years of follow-up. Accordingly, median time to first TVRE was shorter compared with first NTVRE.

- For the majority of patients who experienced both events related to stented and remote vessels, the time interval in-between was <1 year.

The current study is the only analysis of the events related target and non-target vessels over 10-years following PCI with 3 new generation DES polymer. There are several other studies reporting on similar events with divergent results in patients who underwent PCI (105, 106, 108, 109, 233). In a previous study with 5-year follow-up, it was shown that stented lesions (treated with a second generation BMS) were stable up to 1 year, with outcomes beyond this time point determined by a high rate of events related to disease progression in other segments of the target vessel or non-target vessels (108). A subsequent study reported that the risk of MACE was equally attributable to both target and non-target lesions at a median follow-up duration of 3.4 years in patients who with ACS who underwent PCI (105). This study also draws attention to the inherent limitations of coronary angiography as an imaging modality, where target lesions responsible for events were frequently defined as angiographically mild. Conversely, use of grey-scale and radiofrequency intravascular ultrasonography revealed the high-risk characteristics of these lesions, including thin-cap fibroatheroma, large plaque burden and small luminal area. It should also be mentioned that compared to our current analysis, in this study early generation DES were implanted in only 589 of 891 (66.1%) lesions in this study (105). A study of patients from 7-months to 5-years follow-up post-PCI by Zellweger et al. (106) showed that non-fatal remote events accounted for 37.1% of all events and were comparable between BMS and early generation DES.

With respect to newer generation DES, an analysis of pooled patient-level data from the RESOLUTE global clinical trial demonstrated that the cumulative incidence of non-TLR was almost 3 times higher than TLR at 3-years post-PCI (111). Still, this study excluded patients who had both TLR and non-TLR events, and the analyzed patient group was not derived exclusively from randomized controlled trial data like the current analysis.

In our study, TVRE tended to occur earlier compared to NTVRE following PCI. Of note, a greater proportion of events were attributable to target vessel in the first year post-PCI. However, there was

a shift beyond first year and events related to non-target vessels began to accrue with overall higher rate of total events than TVRE at 10-year follow-up. This finding is in line with a previous study with 5-year follow-up from Cutlip et al. (108), which reported that clinical outcome beyond 1 year is determined at a higher degree by events related to disease progression in segments other than the stented lesion. In addition, over 1/4 of patients will have a further event related to treated target vessel at long term follow-up according to our analysis. It is important to note that these events could have been also related to disease progression in other regions of the same vessel and not the target lesion treated during index procedure. Nevertheless, it is clear from our findings that both TVRE and NTVRE evidently contribute to overall adverse event rates.

The paucity of data makes it difficult to comment regarding the potential influence of novel stent polymer technologies on the rate of TVRE and NTVRE at follow-up. In the current study, the relative 10-year frequencies of TVRE and NTVRE were comparable between the PP, BP and PF based coronary stents. Still, considering the previous reports on chronic vascular inflammation due to the presence of a PP, and the evidence of accelerated atherosclerosis in remote coronary segments secondary to focal vascular inflammation as shown in animal models, this may be an important point to consider when designing future studies (223, 234-236).

5.6. The risk prediction model and the subsequent four-item ISAR score may prove to be a useful tool to predict the 1-year risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent in-stent restenosis

The main findings of this analysis are as follows:

- The independent predictors of repeat PCI due to recurrent DES-ISR at 1 year were: a DES-ISR interval <6 months, a non-focal DES-ISR pattern, DES-ISR in the LCx coronary artery and a calcified coronary vessel.

- A risk prediction model was developed and validated using these four variables. Despite the modest discriminative power, it was still stronger when compared to a model based on a prior ISR classification system presented during the BMS era.
- The 4-item ISAR score was created using this four-variable model and allows for estimation of the risk of repeat PCI for recurrent DES-ISR up to 1-year.

To the best of our knowledge, this is the largest study that have assessed the predictors of repeat PCI for recurrent DES-ISR. The results presented in this study underlines the relatively high recurrence of DES-ISR, with repeat PCI occurring in 16.8% of lesions at 1-year follow-up. This follow-up duration allows the comparison of our model with a model based on the Mehran classification, which reported clinical outcomes out to the same follow-up time point (61). In addition, a large number of clinical studies with similar research interests assess the main clinical endpoints up to 1-year (237-240).

Compared to BMS-ISR, DES-ISR lesions are reportedly more challenging to treat (65). Accordingly, a prediction model for the recurrence of DES-ISR could not only help to detect patients at the highest risk of ISR recurrence, but also to stratify them for clinical follow-up. Although several risk models have been suggested for the prediction of developing ISR following DES-PCI thus far, the current analysis represents the first risk prediction model for repeat PCI for recurrent DES-ISR developed and validated in a large cohort (66-70). Overall, our model demonstrated a relatively limited discriminative power for the prediction of recurrent DES-ISR events at 1-year follow-up, still with an improvement compared to the current benchmark model for ISR classification introduced during BMS era (61). The inevitably multifactorial nature of the recurrent DES-ISR PCI may have contributed to our results, relative to the initial DES-ISR treatment along with eventual differences in patient, lesion, and index procedure (71-73). This may also explain in part the failure of our model to detect predictors of repeat PCI for recurrent DES-ISR after 1 year, and a longer time may have made this complexity even more evident.

Our analysis, including a large number of patients (with 1,986 patients and 2,392 DES-ISR lesions), shows that the restenosis interval (<6 months), DES-ISR morphology (non-focal), involved coronary artery (LCx) and the presence of vessel calcification are predictors of recurrent DES-ISR PCI up to 1-

year. Previous studies suggested that these factors may be associated with an increased risk of TLR in patients presenting with DES-ISR. Restenosis occurring within the first 12 months has been reported by our group to be associated with an increased risk of adverse clinical events in DES-ISR treated with DCB angioplasty (241). It might be logical to consider that the development of early DES-ISR may be indicative of a more aggressive ISR phenotype although there are limited data at present to support this hypothesis. It has been suggested that neointimal hyperplasia plays a central role in the development of early DES-ISR while later occurring DES-ISR tends to be caused by neoatherosclerosis (242).

The ISR morphology for DES-ISR was most commonly focal in our analysis, confirming earlier findings (243). In a moderately small study group (203 patient, 250 ISR lesions) with a median follow-up of approximately 1 year (13.7 months), Cosgrave et al. (74) previously reported that the ISR morphology was prognostically important in the early generation DES era with respect to both angiographic restenosis and repeat DES-ISR PCI. The findings from another smaller study (100 patient, 105 ISR lesions) showed that occlusive DES-ISR is similarly associated with increased risk for both angiographic restenosis and recurrent TLR (66). A study including higher number of patients (N=392) with a longer follow-up duration (approximately 3 years) demonstrated the pertinence of the initial DES-ISR morphology on extended clinical outcomes following PCI for a DES-ISR (75).

With regard to involved coronary artery, ostial ISR lesions in the LCx coronary artery were found to be associated with an increased risk of TLR compared to non-LCx coronary lesions (244). Another study reported similar findings, where an increased TLR rate was observed in patients treated with DCB for ostial DES-ISR in LCx coronary artery (245). In addition, previous reports also suggested a correlation between the coronary vessel or lesion calcification and the risk of DES-ISR (246-248).

The present data demonstrated the challenges to accurately predict the probability of a repeat PCI for recurrent DES-ISR. In this respect, the ISAR score may be a relevant and useful tool. An ISAR score of 0, 1, 2 and ≥3 was associated with 12.1%, 15.9%, 24.2% and 30.5% risk of repeat PCI for recurrent DES-ISR up to 1-year follow-up, respectively. The score can be rapidly calculated in the

cardiac catheterization laboratory using the already available angiographic and clinical information. In addition, it may be helpful for both guidance of clinical follow-up and counselling of patients concerning the risk of repeat PCI in the first year after PCI.

5.7. Drug-eluting stent is associated with better 2-year clinical outcomes compared to drug-coated balloon in patients with high inhomogeneity in-stent restenosis lesions as per intravascular optical coherence tomography

The main findings of this analysis are as follows:

- In patients with ISR undergoing PCI, the 2-year risk of MACE and clinically driven TLR was comparable between low and high neointimal inhomogeneity groups.
- In patients with high inhomogeneity, we found a significant interaction between the type of PCI treatment and neointimal ISR pattern with an advantage of DES over DCB.
- The degree of neointimal atherosclerotic changes had no impact on clinical outcomes in patients with high neointimal inhomogeneity.

Current guidelines recommend the use of either DES implantation or DCB angioplasty for the treatment of patients with ISR (51). The efficacy of DCB treatment is related to the rapid delivery and tissue retention of the antiproliferative agent, providing consistent suppression of cell proliferation without adding new stent layers (46). Such mechanism of action is of particular clinical relevance for smooth muscle cell rich ISR lesions. According to previous histopathological validation studies, neointimal homogeneous patterns by OCT imaging correlates with the abundance of smooth muscle cells along with collagen and proteoglycan rich tissue (171). With respect to repeat DES implantation, clinical outcomes appear to depend less on the underlying degree of neointimal homogeneity. Nevertheless, an additional stent layer on top of the existing ISR lesion and the accelerated development of neoatherosclerosis is not ideal (87, 92). This subsequently triggers the potential risk of late adverse events such as repeat ISR and ST (169, 249).

In line with our analysis, a previous study showed a comparable risk with respect to TLR events after treatment with DCB and repeat DES in patients with homogeneous neointima (145). The current study supports the use of DES in ISR lesions with high neointimal inhomogeneity, whereas DCB angioplasty could be the preferred treatment modality for ISR lesions with low neointimal inhomogeneity. Our analysis is therefore of relevance not only for presenting unique data up to 2 years but also for underlining the importance of personally tailored treatment strategies. Considering the overall rate of MACE in ISR patients, integrating intravascular OCT imaging into specific treatment algorithms may have positive impact on clinical outcomes following PCI. Still, the clinical implementation of such algorithm demands confirmation from specifically designed randomized clinical trials with relevant clinical and angiographic endpoints.

Finally, several factors add on the robustness of this report. First, a detailed quadrant-based multi-frame neointimal characterization for each ISR lesion help to overcome the significant intra-lesion neointimal heterogeneity encountered in single frame-based qualitative analyses (145, 169, 250). Second, the inconsistencies that might occur between the 3 participating centers are minimized by the analysis of the OCT data in a centralized imaging core laboratory following a standardized protocol. Third, the extended follow-up up to 2 years should have allowed the detection of potentially late-occurring clinically adverse events, such as those related to neointimal atherosclerotic changes.

5.8. There is no association between periprocedural myocardial injury, treatment modality or neointimal inhomogeneity of in-stent restenosis lesions as per intravascular optical coherence tomography

The main findings of this analysis are as follows:

- In patients with ISR undergoing PCI, the incidence of PMI is high, and the risk is generally comparable to the PCI of the native coronary vessel.
- There was no association between the extent of neointimal inhomogeneity and PMI occurrence.

- In patients with high neointimal inhomogeneity ISR lesion, the degree of neoatherosclerotic changes did not influence the risk of PMI.
- PMI occurrence was not influenced by the type of PCI treatment.

The current analysis is clinically relevant as the data regarding neointimal characteristics and PMI events following contemporary PCI for ISR are scarce. Previous studies in this area reported an increased prevalence of PMI in patients with stable CAD undergoing PCI. Nevertheless, the frequency of PMI events differs depending on the type of cardiac biomarker and the definitions used in these studies. The prognostic relevance of PMI is consequently subject to ongoing debate owing to conflicting study data (251-255). A recent ESC/EAPCI consensus document subdivided PMI in prognostically relevant “major” and “minor” PMI (175). This decision was based on the results of a recent patient-level pooled analysis, where a PMI event defined according to the 4th UDMI criteria occurred in 52.8% of patients (79.8% if restricted to high-sensitivity cardiac troponin) (254). Applying such definition, hs-cTnT-based major PMI occurred in approximately 30% of the patients in our study, confirming the relevance of PMI not only in native coronary vessel but also in ISR-PCI.

With regard to previous reports concerning the PMI and ISR, a retrospective study by Lee et al. (256) evaluated the potential relation between PMI (defined as CK-MB > 99th percentile URL) and neointimal characteristics by intravascular OCT imaging in 125 patients undergoing PCI for ISR. They found a significant association between the increased axial length of neoatherosclerosis and thin-cap fibroatheroma with the occurrence of PMI. Another single-center study with a relatively smaller cohort investigated the relationship between PMI (defined as hs-cTnT > 5 x 99th percentile URL) and neointimal characteristics based on OCT and coronary angioscopy in 72 patients with ISR undergoing PCI (257). Here, a thinner fibrous cap and a higher prevalence of thin-cap fibroatheroma was reported for culprit lesions with PMI. Nonetheless, only atheromatous appearance based on coronary angioscopy independently correlated with PMI at multivariate analysis.

It is important to note that in the present study, there were no statistically significant differences in PMI occurrence based on the chosen PCI treatment modality. Considering the general concern

associated with DCB angioplasty and distal embolization of the particulate balloon coating, this finding further supports the safety of DCB use for ISR treatment (46).

5.9. Ticagrelor and prasugrel have comparable efficacy and bleeding risk at 1-year in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

The main findings are as follows:

- In patients with STEMI planned to undergo invasive management, there was no significant difference with regard to the primary endpoint (a composite of death, MI, or stroke) between prasugrel and ticagrelor up to 1 year follow-up.
- Ticagrelor therapy was associated with a significant risk of MI compared to therapy with prasugrel at 1 year.
- Following primary PCI, the risk of BARC type 3–5 major bleeding was not significantly different in patients assigned to the ticagrelor or prasugrel group at 1 year.

The ISAR-REACT 5 trial assessed the comparative efficacy and safety of a ticagrelor and prasugrel based strategy in patients with ACS planned to undergo invasive treatment (131). This prespecified analysis of patients with STEMI is clinically relevant as it allows a direct head-to-head comparison of these novel $P2Y_{12}$ receptor inhibitor drug.

In patients presenting with STEMI requiring coronary stent implantation, presence of a highly thrombogenic environment related to infarct-related artery necessitates a potent antiplatelet agent to prevent ST. Previous reports from meta-analyses including trials of ACS patients have shown a greater clinical efficacy of novel $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) in comparison to clopidogrel and suggested a better protection of prasugrel over ticagrelor in reducing the risk of ST (258, 259). It is important to note, however, that ACS presents with heterogeneous pathophysiology and prognosis post-PCI, and the relative efficacy of novel antiplatelet agents may hence differ according to the ACS type (128, 260). Earlier subgroup analyses of TRITON-TIMI 38 and PLATO trials demonstrated the superiority of prasugrel and ticagrelor over clopidogrel in reducing the risk of MI and ST in patients

with STEMI following primary PCI (123, 124). This finding is in line with observational studies and registries that showed the superiority of these drugs with respect to risk of ischemic events in STEMI patients following primary PCI, which left open the question whether prasugrel or ticagrelor should be the preferred antiplatelet agent in these patients. In a large registry of patients with STEMI undergoing primary PCI, Olier et al. (127) reported better survival with prasugrel compared with clopidogrel or ticagrelor up to 1 year. In another real-world registry, Krishnamurthy et al. (125) reported lower adjusted 30-day mortality with prasugrel in comparison to ticagrelor or clopidogrel and lower adjusted mortality with prasugrel than clopidogrel at 1 year. Interestingly, both prasugrel and ticagrelor were associated with a reduced risk of MI following primary PCI. The findings from other registries were neutral with regard to efficacy or safety of novel $P2Y_{12}$ inhibitor-based dual antiplatelet therapy following primary PCI (126, 128, 129). A propensity matched-analysis of retrospective RENAMI registry (Registry of New Antiplatelets in patients with Myocardial Infarction) reported reduced incidence of net adverse clinical events and MACE with prasugrel in comparison with ticagrelor, driven mainly by a reduction in the recurrent MI and lower incidence of BARC type 3 to 5 bleeding. Of note, the benefit of prasugrel was confirmed for patients with NSTEMI but not for patients with STEMI in this study (128).

Only 2 clinical studies have so far performed a direct randomized comparison of prasugrel and ticagrelor in patients with ACS undergoing PCI (130, 131). The PRAGUE-18 trial was the first study to provide a head to-head comparison between these antiplatelet agents in ACS patients (95% with STEMI or bundle-branch block) undergoing primary PCI (130). In this study, the authors reported no significant difference between prasugrel and ticagrelor assigned groups with regard to composite endpoint (cardiovascular death, MI, or stroke) or individual endpoints including bleeding up to both 30 days and 1 year follow-up (130, 261). Still, the premature study termination with smaller sample size (1,230 patients), the high rate of study drug discontinuation and switching to clopidogrel (34.1% of the prasugrel group and 44.4% of the ticagrelor group) prevents an adequate comparison between these agents.

The current analysis included the STEMI group of the ISAR-REACT 5 trial with 95% of patients undergoing primary PCI. Our results show no significant difference regarding the primary endpoint (a composite of all-cause death, MI, or stroke) between prasugrel and ticagrelor up to 1 year. Of note, the incidence of MI was significantly higher in patients assigned to a ticagrelor based therapy, mainly driven by fewer spontaneous (Type 1) and ST–related (Type 4b) infarctions. While the mechanisms underlying this finding in patients with STEMI remain poorly understood, it might be related to a stronger anti-ischemic protection provided by prasugrel. In a recent randomized comparison of clopidogrel, ticagrelor and prasugrel in patients with ACS undergoing PCI with coronary stenting, prasugrel therapy was associated with stronger platelet inhibition, improved endothelial function, and reduced interleukin-6 levels (262). Lastly, the lack of significant difference in bleeding between ticagrelor and prasugrel groups is consistent with the results of the primary publication and several other studies, which might possibly be explained by the adjusted (reduced) prasugrel dose regimen used in patient groups characterized by a high bleeding risk (in elderly and underweight patients) (127-129, 131, 177).

SUMMARY OF FINDINGS

- In patients treated with early- and new-generation DES, the incidence of definite ST up to 10 years after treatment with new-generation DES was 1%. The risk of definite ST was particularly reduced beyond 1 year (VLST) and 5 years (VVLST) following PCI with new-DES. Considering the difficulties of conducting such head-to-head comparisons in a sizable study group, these data are clinically relevant as they reflect the improvements made in DES technology as well as the safety and efficacy of these devices in the contemporary era.
- In patients who underwent PCI and treated with DES, female sex was associated with an increased risk of early MI within the first 30 days and a comparable risk from 30 days up to 10 years. Of note, female patients received less repeat revascularization and had similar cardiovascular mortality compared with male patients at 10 years follow-up. Reduced risk of repeat revascularization despite the increased risk of MI in female patients warrants further investigation. Considering the persistence of adverse events up to 10 years regardless of sex, efforts should be focused on improving these long-term outcomes.
- In ACS patients treated with 3 different stent polymer types, BP- DES was found to be superior to newer-generation PP-DES with regard to a POCE (a composite of all-cause death, any MI, or any revascularization) at 10 years follow-up. In addition, the relative frequency of the DOCE (a composite of cardiac death, target vessel related MI or TLR) was numerically lower in patients treated with BP-DES at 10 years. The risk of both device- and patient-related outcomes was comparable in patients treated with PF- and PP-DES. These results support the hypothesis that patients with ACS may benefit from a BP-based stent platform, possibly avoiding the persistent inflammation and delayed vascular healing associated with the use of PP.
- The influence of DES overlap on adverse clinical events up to 10-years after PCI was significant and associated with increased frequency of MI and TLR. Our analysis demonstrated that the increased risk of MI occurred only during the first 30 days after PCI, while the risk of TLR was increased for both 0–1 year and 1–10 years period following the index procedure. The effect of stent overlap on

all-cause mortality, MI, TLR, and definite/probable ST was comparable between the different polymer types (PF, BP, PP). Our findings suggest that stent overlap should be avoided where possible in clinical practice. For this purpose, adequate lesion preparation with adjuvant contemporary technologies (e.g., high pressure balloons, rotational atherectomy, and intravascular lithotripsy) may prove useful. Inability to deliver a stent of desired length to cover the target lesion or lesions should alert operators to prioritize optimizing vessel preparation instead of multiple shorter length overlapping stent use.

- At 10-year follow-up post-PCI, higher proportion of total events were attributable to non-target vessel than target vessel in patients treated with newer generation DES. The temporal pattern of TVRE and NTVRE were divergent, with a higher incidence of TVRE occurring up to 1 year. Thereafter, NTVRE became predominant from 1 to 10 years of follow-up. The relative frequency of these events was overall comparable between the PF, BP and PP based coronary stents.
- ISR morphology and interval, coronary vessel calcification and involvement of the LCx are found to be independent predictors of repeat PCI for recurrent DES-ISR at 1 year follow-up. The four-variable risk prediction model for repeat PCI for recurrent DES-ISR up to 1-year follow-up showed a modest discriminative power in absolute terms, although with a significant improvement in comparison to the currently used ISR classification model. The subsequently developed ISAR score may serve as a standardized tool to assess the risk of repeat PCI for recurrent DES-ISR up to 1-year.
- In patients undergoing PCI for treatment of ISR lesions, there was no significant difference with regard to MACE or clinically driven TLR between patients with low and high inhomogeneity of the neointima up to 2 years. The exploratory analysis showed a significant interaction between neointimal pattern and the type of treatment modality, with DES showing a significant advantage over DCB in the high inhomogeneity group. These results support repeat DES implantation for coronary lesions with high neointimal inhomogeneity, while DCB angioplasty could potentially represent a safe and effective treatment for coronary lesions with low neointimal inhomogeneity.

- In a similar patient group undergoing treatment of ISR lesions, the incidence of PMI was high, and the risk was generally comparable to the PCI of the native coronary vessel. We found no association between the degree of neointimal inhomogeneity, neoatherosclerosis and occurrence of PMI. The type of PCI treatment modality (DES or DCB) did not appear to impact the occurrence of PMI in patients with ISR.
- In patients with STEMI undergoing primary PCI, there was no significant difference in the primary endpoint (a composite of all-cause death, MI, or stroke) between novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor at 1 year. The bleeding risk was comparable between the groups. Prasugrel was associated with a significant decrease in the risk for recurrent myocardial infarction, which might be a relevant finding to consider in the treatment of patients at higher risk of thrombotic events.

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1. 09.2020 **Clinical outcomes by optical characteristics of neointima and treatment modality in patients with coronary in-stent restenosis**

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23. 11.2022 **The Effect of a Prasugrel- versus a Ticagrelor-based Strategy on Total Ischemic and Bleeding Events in Patients with Acute Coronary Syndromes**

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25. 01.2023 **Iliofemoral artery predilation prior to transfemoral transcatheter aortic valve implantation in patients with aortic valve stenosis and advanced peripheral artery disease**
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26. 02.2023 **Derivation and validation of the ISAR score to predict the risk of repeat percutaneous coronary intervention for recurrent drug-eluting stent restenosis**

Coughlan JJ, **Aytekin A**, Lahu S, Scalamogna M, Wiebe J, Pinieck S, Kufner S, Xhepa E, Joner M, Kuna C, Voll F, Laugwitz KL, Schunkert H, Kastrati A, Cassese S. **EuroIntervention,** 2023 Feb 8; EIJ-D-22-00860. doi: 10.4244/EIJ-D-22-00860.

27. 02.2023 **Sex Differences in 10-Year Outcomes After Percutaneous Coronary Intervention With Drug-Eluting Stents: Insights From the DECADE Cooperation**

Coughlan JJ, Raber L, Brugaletta S, Kufner S, Maeng M, Jensen LO, Ortega-Paz L, Bar S, Laugwitz KL, Madsen M, Heg D, **Aytekin A**, Windecker S, Warnakula Olesen KK, Sabaté M, Kastrati A, Cassese S. **Circulation**, 2023 Feb 14;147(7):575-585. doi: 10.1161/CIRCULATIONAHA.122.062049.Epub 2023 Feb 13.

28. 02.2023 **High on-aspirin treatment platelet reactivity and restenosis after percutaneous coronary intervention: results of the Intracoronary Stenting and Antithrombotic Regimen-ASpirin and Platelet Inhibition (ISAR-ASPI) Registry**

Mayer K, Ndrepepa G, Schroeter M, Emmer C, Bernlochner I, Schüpke S, Gewalt S, Hilz R, Coughlan JJ, **Aytekin A**, Heyken C, Morath T, Schunkert H, Laugwitz KL,

Sibbing D, Kastrati A. **Clin Res Cardiol**, 2023 Feb 14. doi: 10.1007/s00392-023-02161-z.

29. 04.2023 **Association of De Ritis Ratio with Prognosis in Patients with Coronary Artery Disease and Aminotransferase Activity within and outside the Healthy Values of Reference Range**

Ndrepepa G, Cassese S, Scalamogna M, Lahu S, **Aytekin A**, Schunkert H, Kastrati A. **Journal of Clinical Medicine**, 2023 Apr 28. doi: 10.3390/jcm12093174.

30. 06.2023 **Near-infrared Spectroscopy-Intravascular Ultrasound to Improve Assessment of Coronary Artery Disease Severity in Patients Referred for Transcatheter Aortic Valve Implantation (The IMPACTavi registry): Design and Rationale**

Seguchi M, **Aytekin A**, Steiger L, Nicol P, Pellegrini C, Rheude T, Engel LC, Alvarez-Covarrubias H, Xhepa E, Mayr NP, Hadamitzky M, Kastrati A, Schunkert H, Joner M, Lenz T. **American Heart J**, 2023 June 12. doi: 10.1016/j.ahj.2023.06.004

SUPPLEMENTARY APPENDIX

Table A1. Key inclusion/exclusion criteria and primary endpoints for the trials included in the DECADE co-operation (78).

Trial name (Enrollment Period)	Registration Number	Key Inclusion Criteria	Key Exclusion Criteria	Primary Endpoint

SIRTAX (2003-2004)	**NCT00297661**	• Patients aged 18 years or older with either
		  • Stable angina or
		  • Acute coronary syndromes
		were eligible to participate if they had at least one lesion with stenosis of ≥ 50% in a vessel with a reference diameter between 2.25 and 4.00 mm that was suitable for stent implantation.
		• The time from the onset of symptoms to treatment was less than 24 hours in patients classified as having a myocardial infarction characterized by ST-segment elevation.
		• There were no limitations on the number of lesions or vessels or on the length of the lesions.
			• Allergy to antiplatelet drugs, Heparin, stainless steel, contrast agents, Sirolimus, or Paclitaxel.
			• Participation in another coronary-device study.
			• Terminal illness.
				Major adverse cardiac events at **9 months** (composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization).

ISAR-TEST 4 (2007-2008)	**NCT00598676**	• 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. • Written, informed consent by the patient or her/his legally-authorized representative for participation in the study. • In women with childbearing potential a negative pregnancy test was mandatory.	• Target lesion located in the left main trunk. • Target lesion located in the bypass graft. • In-stent restenosis. • Cardiogenic shock. • Malignancies or other comorbid conditions (for example severe liver, renal and pancreatic disease) with life expectancy less than 12 months or that may result in protocol non-compliance. • Known allergy to the study medications: Clopidogrel, Rapamycin, Everolimus, stainless steel or cobalt chrome. • Inability to take Clopidogrel for at least 6 months. • Pregnancy (present, suspected or planned) or positive pregnancy test. • Previous enrolment in this trial. • Patient's inability to fully cooperate with the study protocol.	A device-oriented composite endpoint of cardiac death, myocardial infarction related to the target vessel or revascularization related to the target lesion at **1 year** after index intervention.
SORT OUT III (2006-2007)	**NCT00660478**	• All patients aged 18 years or older, had chronic stable coronary artery disease or acute coronary syndromes, and had at least one target lesion, defined as a lesion needing treatment with a drug-eluting stent. • If more than one lesion needed treatment, the allocated study stent had to be used in all lesions. • No upper limits were imposed for the number of treated lesions, treated vessels, or lesion length treated with one or more drug eluting stents in the coronary arteries.	• The patient will not participate or could not provide informed consent. • The patient participates in other randomized stent studies. • Life expectancy less than 1 year. • Allergy to Aspirin, Clopidogrel or Ticlopidine. • Allergy to Sirolimus or Zotarolimus (ABT-578).	Major adverse cardiac events within **9 months** (composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization).
ISAR-TEST 5 (2008-2009)	**NCT00598533**	• 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. • Written, informed consent by the patient or her/his legally authorized	• Target lesion located in the left main trunk. • Target lesion located in the bypass graft. • In-stent restenosis. • Cardiogenic shock. • Malignancies or other comorbid conditions (for example severe liver, renal	A device-oriented composite endpoint of cardiac death, myocardial infarction related to the target vessel or target lesion

		representative for participation in the study. • In women with childbearing potential a negative pregnancy test was mandatory.	and pancreatic disease) with life expectancy less than 12 months or that may result in protocol non-compliance. • Known allergy to the study medications: Clopidogrel, Rapamycin, Probucol, Zotarolimus, stainless steel or cobalt chrome. • Inability to take Clopidogrel for at least 6 months. • Pregnancy (present, suspected or planned) or positive pregnancy test. • Previous enrolment in this trial. • Patient's inability to fully cooperate with the study protocol.	revascularization at **1 year** after index intervention.
EXAMINATION (2008-2010)	**NCT00828087**	• Patients presenting with a ST-elevation myocardial infarction who must meet at least one of the following criteria ○ Patients presenting with a ST-elevation myocardial infarction <12 hours after onset of symptoms who are treated with primary angioplasty + stent implantation ○ Cardiogenic shock. ○ Rescue PCI after failed thrombolysis. ○ PCI indicated early (<24h) after effective thrombolysis following current ESC guidelines. ○ Patients presenting late ("latecomers") with ST-elevation myocardial infarction (>12h-48h) after the onset of symptoms. • Written informed consent. • The patient or his/her family (in the event the patient cannot be clinically available) accept clinical controls. • Angiographic: Vessel size has to range between 2.25-4.0 mm by visual estimation to allow the implantation of currently available stents.	• Age < 18 years. • Pregnancy or breastfeeding. • Known intolerance to Aspirin, Clopidogrel, Heparin, stainless steel, Everolimus, contrast material. • Patients with absolute indication of being chronic treated with Acenocoumarol. • Myocardial infarction due to a previously implanted stent thrombosis. • Patients with myocardial infarction that will require elective surgical coronary revascularization within a 1-year period.	Composite endpoint of all-cause death, any myocardial infarction, and any revascularization at **1 year**.

Table A2. Definitions of and adjudication of outcomes used in trials in the DECADE co-operation as well as angiographic analysis protocols (184)**.**

Trial name (Enrollment period)	Myocardial Infarction	Stent Thrombosis	Target Lesion Revascularization	Adjudication of Outcomes	Angiographic Analysis Protocol
SIRTAX (2003-2004)	The diagnosis of myocardial infarction was based on the presence of new Q waves in at least two contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of myocardial infarction was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin I.	Acute coronary syndromes with angiographic documentation of either • Occlusion of the target lesion or • Thrombus within the previously stented segment.	Target-lesion revascularization was defined as revascularization for a stenosis within the stent or within the 5-mm borders adjacent to the stent.	An independent clinical-events committee whose members were unaware of the patients' treatment assignments adjudicated all clinical end points.	Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up and were assessed at the angiographic core laboratory of the University Hospital Bern. Angiogram readers were unaware of the type of stent implanted. The projection that best showed the stenosis was used for all analyses. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, nontapered tip of the catheter was used for calibration. Digital angiograms were analyzed with the use of an automated edge-detection system (CAAS II, Pie Medical Imaging).
ISAR TEST 4 (2007-2008)	Myocardial infarction 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 MI and CK-MB (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 syndromes (NSTE-ACS) and falling or normal CK-MB (CK) levels. Recurrent chest pain lasting >30 min with either new ECG changes consistent with second MI or next CK-MB (CK) level at least 8–12 h after PCI elevated at least 50% above the previous level was considered procedure-related MI for patients presenting with NSTE-ACS and elevated CK-MB (CK) level prior to PCI. Spontaneous MI was defined as any CK-MB increase with or without the development of Q-waves on ECG.	According to Academic Research Consortium criteria • **Definite** stent thrombosis: angiographic or pathological confirmation of stent thrombosis. • **Probable** stent thrombosis: any unexplained death within the first 30 days or any myocardial infarction (irrespective of the time after the index procedure) that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause. • **Possible** stent thrombosis: any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.	Target lesion revascularization was defined as any ischemia-driven repeat percutaneous coronary intervention of the target lesion or bypass surgery of the target vessel.	All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.	Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic (QCA) core laboratory (ISARESEARCH Center, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems) by two independent experienced operators unaware of the treatment allocation. Measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerine 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). Qualitative morphological lesion characteristics were characterized by standard criteria.
SORT OUT III (2006-2007)	Myocardial infarction was defined in accordance with the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction but procedure-related myocardial infarction was excluded as an endpoint.	According to Academic Research Consortium criteria, definite stent thrombosis was recorded at 30-day and 12-month follow-up to report late (30 days–1 year) and very late (>1 year) stent thrombosis.	Target lesion revascularization was defined as repeat revascularization caused by stenosis within the stent or	An independent endpoint committee masked to treatment assignment reviewed all events and	Independent study monitors masked to treatment assignment reviewed all repeat coronary interventions (balloon angioplasty, stent implantation, and coronary artery bypass grafting). Reinterventions were characterized as target vessel revascularization and non- target

			within a 5 mm border proximal or distal to the stent.	classified all myocardial infarctions and deaths.	vessel revascularization. All target lesion revascularizations were identified and classified as caused by in-stent restenosis or stent thrombosis, based on review of angiograms and patient files. The indication for repeat intervention was identified and classified as ST-segment elevation myocardial infarction (STEMI), non-STEMI, unstable angina pectoris, or stable angina pectoris.
ISAR TEST 5 (2008-2009)	Spontaneous myocardial infarction was defined as any creatine kinase MB or troponin increase with or without the development of Q waves on ECG.	According to Academic Research Consortium criteria **Definite** stent thrombosis: angiographic or pathological confirmation of stent thrombosis. **Probable** stent thrombosis: any unexplained death within the first 30 days or any myocardial infarction (irrespective of the time after the index procedure) that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause. **Possible** stent thrombosis: any unexplained death from 30 days after intracoronary stenting until end of trial	Target lesion revascularization was defined as any ischemia-driven repeat percutaneous coronary intervention of the target lesion or bypass surgery of the target vessel.	All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups.	Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISARESEARCH Center, Munich. Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems) by 2 independent experienced operators unaware of the treatment allocation. Measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerine using the same single worst-view projection at all times. The contrast-filled nontapered 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). Qualitative morphological lesion characteristics were characterized by standard criteria.
EXAMINATION (2008-2010)	Recurrent myocardial infarction is defined according to the WHO extended definition. Both periprocedural and spontaneous myocardial infarction were assessed. For both situations a dedicated algorithm was used in the adjudication process (also adopted from the WHO extended definition)	According to Academic Research Consortium criteria • **Definite** stent thrombosis: angiographic or pathological confirmation of stent thrombosis. • **Probable** stent thrombosis: any unexplained death within the first 30 days or any myocardial infarction (irrespective of the time after the index procedure) that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause	TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion	A clinical event committee, whose members were masked to the assigned stent independently adjudicated all deaths, potential myocardial infarctions, stent thrombosis, and revascularization procedures.	N/A

Table A3. Baseline characteristics as per DES generation (78)**. ***

Characteristic	All DES (N=9700)	New-DES (N=6866)	Early-DES (N=2834)	p value
Trials				
EXAMINATION	751 (7.7)	751 (10.9)	0 (0)	
ISAR-TEST 4	2603 (26.8)	1951 (28.4)	652 (23.0)	
ISAR-TEST 5	3002 (30.9)	3002 (43.7)	0 (0)	
SIRTAX	1012 (10.4)	0 (0)	1012 (35.7)	
SORT OUT III	2332 (24.0)	1162 (16.9)	1170 (41.3)	
Age (years)	65.5±11.3	66.1±11.3	64.1±11.1	<0.001
Female	2296 (23.7)	1600 (23.3)	696 (24.6)	0.195
Diabetes mellitus	2298/9699 (23.7)	1736/6865 (25.3)	562 (19.8)	<0.001
Insulin-dependent	638 (6.6)	536 (7.8)	102 (3.6)	<0.001
Hypertension	5923/9609 (61.6)	4293/6824 (62.9)	1630/2785 (58.5)	<0.001
Current smoker	2365/9527 (24.8)	1545/6783 (22.8)	820/2744 (29.9)	<0.001
Hypercholesterolemia	6110/9613 (63.6)	4333/6,827 (63.5)	1777/2786 (63.8)	0.789
Body mass index (kg/m²)	27.4±4.4	27.5±4.5	27.3±4.3	0.036
Prior myocardial infarction	2547/9598 (26.5)	1766/6,816 (25.9)	781/2789 (28.1)	0.031
Number of diseased coronary vessels				<0.001
One vessel	2258/7368 (30.6)	1327 (23.3)	931/1664 (55.9)	
Two vessels	1798/7368 (24.4)	1463 (25.6)	335/1664 (20.1)	
Three vessels	3297/7368 (44.7)	2914 (51.1)	383/1664 (23.0)	
Number of lesions	1.4±0.6	1.4±0.6	1.4±0.6	0.742
Clinical presentation				0.001
Acute Coronary Syndromes	4557 (47.0)	3299 (48.0)	1258 (44.4)	
Stable angina	5143 (53.6)	3567 (52.0)	1576 (55.6)	
Ejection fraction (%)	53.3±11.7	52.6±11.6	55.6±12.0	<0.001

Data are mean ± standard deviation or counts (%).

* Completeness of continuous data: ejection fraction was not available in 3,296 patients (1,274 in the early-DES group and 2,022 in the new-DES group); body-mass index was not available in 212 patients (97 in the early-DES group and 115 in the new-DES group). The remaining data are complete.

DES= drug-eluting stents.

Table A4. Angiographic and procedural characteristics as per DES generation (78)**. ***

	All DES	New-DES	Early-DES	p value
Lesion Characteristics	N=13180	N=9320	N=3860	
Target vessel				<0.001
Left main coronary artery	80 (0.6)	29 (0.3)	51 (1.3)	
Left anterior descending coronary artery	5791 (43.9)	4118 (44.2)	1673 (43.3)	
Left circumflex coronary artery	3234 (24.5)	2283 (24.5)	951 (24.6)	
Right coronary artery	4023 (30.5)	2873 (30.8)	1150 (29.8)	
Bypass graft	48 (0.4)	14 (0.2)	34 (0.9)	
Bifurcation involved and treated	2145/9172 (23.4)	1831/6924 (26.4)	314/2248 (14.0)	<0.001
Complex lesion (type B2/C)	7804/12343 (63.2)	5882/8520 (69.0)	1922/3823 (50.3)	<0.001
Pre-procedural reference vessel diameter, mm	2.8 (2.44-3.1)	2.8 (2.4-3.1)	2.8 (2.5-3.1)	0.066
Pre-procedural minimal lumen diameter, mm	0.9 (0.6-1.2)	0.9 (0.6-1.2)	0.7 (0.3-1.0)	<0.001
Balloon diameter, mm	3.0 (2.8-3.5)	3.1 (2.7-3.5)	3.0 (2.8-3.5)	<0.001
Maximal balloon pressure, atm	16.0 (12.2-18.0)	16.0 (13.0-18.0)	14.0 (12.0-16.3)	<0.001
Total stented length, mm	18.0 (16.0-28.0)	23.0 (18.0-30.0)	18.0 (13.0-23.0)	<0.001
Number of Stents	1.0 (1.0-2.0)	2.0 (1.0-2.0)	1.0 (1.0-1.0)	<0.001
Post-procedural minimal lumen diameter, mm	2.6 (2.2-2.9)	2.6 (2.2-2.9)	2.6 (2.3-2.9)	0.414
Post-procedural diameter stenosis, %	10.7 (7.3-14.9)	11.0 (7.6-15.1)	9.5 (6.0-13.5)	<0.001

Data are median (interquartile range) or counts (%).

* Completeness of continuous data: pre-procedural reference vessel and minimal lumen diameter was not available for 4,103 lesions (1,692 in the early-DES group and 2,411 in the new-DES group); balloon diameter was not available for 159 lesions (63 in the early-DES group and 96 in the new-DES group); maximal balloon pressure was not available for 4,526 lesions (2,104 in the early-DES group and 2,422 in the new-DES group); total stented length was not available for 67 lesions (21 in the early-DES group and 46 in the new-DES group); number of stents was not available for 417 lesions (216 in the early-DES group and 201 in the new-DES group); post-procedural minimal lumen diameter and diameter stenosis was not available for 4,865 lesions (2,447 in the early-DES group and 2,418 in the new-DES group). The remaining data are complete.

DES= drug-eluting stents.

Table A5. Baseline characteristics in male and female patients (184)**. ***

Patient Characteristics	**All Patients** (N=9700)	**Female Patients** (N=2296)	**Male Patients** (N=7404)	**p value**
Trials				<0.001
EXAMINATION	751 (7.7)	117 (5.1)	634 (8.6)	
ISAR-TEST 4	2603 (26.8)	623 (27.1)	1980 (26.7)	
ISAR-TEST 5	3002 (30.9)	707 (30.8)	2295 (31.0)	
SIRTAX	1012 (10.4)	231 (10.1)	781 (10.5)	
SORT OUT III	2332 (24.0)	618 (26.9)	1714 (23.1)	
Age (years)	65.5±11.3	69.6±11.1	64.3±11.0	<0.001
Diabetes mellitus	2298/9699 (23.7)	608 (26.5)	1690/7403 (22.8)	<0.001
Insulin-dependent	638 (6.6)	190 (8.3)	448 (6.1)	<0.001
Hypertension	5923/9609 (61.6)	1591/2267 (70.2)	4332/7342 (59.0)	<0.001
Current smoker	2365/9527 (24.8)	459/2249 (20.4)	1906/7278 (26.2)	<0.001
Hypercholesterolemia	6110/9613 (63.6)	1435/2266 (63.3)	4675/7347 (63.6)	0.81
Body mass index (kg/m²)	27.4±4.4	26.9±5.2	27.6±4.2	<0.001
Prior myocardial infarction	2547/9598 (26.5)	469/2264 (20.7)	2078/7334 (28.3)	<0.001
Number of diseased coronary vessels				<0.001
One vessel	2258/7368 (30.6)	570/1678 (34.0)	1688/5690 (29.7)	
Two vessels	1798/7368 (24.4)	453/1678 (27.0)	1345/5690 (23.6)	
Three vessels	3297/7368 (44.7)	652/1678 (38.9)	2645/5690 (46.5)	
Number of lesions	1.4±0.6	1.3±0.6	1.4±0.7	0.01
Clinical presentation				0.10
…ACS	4557 (47.0)	1114 (48.5)	3443 (46.5)	
…CCS	5143 (53.0)	1182 (51.5)	3961 (53.5)	
Ejection fraction (%)	53.3±11.7	54.3±11.8	53.0±11.7	<0.001

Data are mean ± standard deviation or counts (%). Data were analyzed at a patient level.

* Completeness of data: Ejection fraction was not available in 3,296 patients (2,467 in the male group and 829 in the female group); body-mass index was not available in 212 patients (155 in the male group and 57 in the female group). The remaining data are complete.

ACS=acute coronary syndromes; CCS=chronic coronary syndrome.

Table A6. Angiographic and procedural lesion characteristics in male and female patients (184)**. ***

Angiographic Characteristics	**All Patients** (N=13180 lesions)	**Female Patients** (N=3048 lesions)	**Male Patients** (N=10132 lesions)	**p value**
Target vessel				0.001
Left main coronary artery	80 (0.6)	17 (0.6)	63 (0.6)	
Left anterior descending coronary artery	5791 (44.0)	1381 (45.4)	4410 (43.5)	
Left circumflex coronary artery	3234 (24.5)	683 (22.4)	2551 (25.2)	
Right coronary artery	4023 (30.5)	961 (31.6)	3062 (30.2)	
Bypass graft	48 (0.4)	3 (0.1)	45 (0.4)	
Bifurcation involved and treated	2145/9172 (23.4)	453/2124 (21.3)	1692/7048 (24.0)	0.01
Complex lesion (type B2/C)	7804/12343 (63.2)	1814/2905 (62.4)	5990/9438 (63.5)	0.33
Pre-procedural reference vessel diameter (mm)	2.8 (2.4-3.1)	2.7 (2.4-3.0)	2.8 (2.5-3.1)	<0.001
Pre-procedural minimal lumen diameter (mm)	0.9 (0.6-1.2)	0.9 (0.6-1.2)	0.9 (0.6-1.2)	0.33
Balloon diameter (mm)	3.0 (2.8-3.5)	3.0 (2.6-3.5)	3.1 (2.8-3.5)	<0.001
Maximal balloon pressure (atm)	16.0 (12.2-18.0)	14.3 (12.0-17.0)	16.0 (13.0-18.0)	<0.001
Total stented length (mm)	18.0 (16.0-28.0)	18.0 (15.0-28.0)	20.0 (16.0-28.0)	<0.001
Number of Stents	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.12
Post-procedural minimal lumen diameter (mm)	2.6 (2.2-2.9)	2.5 (2.2-2.8)	2.6 (2.2-2.9)	<0.001
Post-procedural diameter stenosis (%)	10.7 (7.3-14.9)	10.8 (7.3-14.7)	10.7 (7.3-14.9)	0.56

Data are median (interquartile range) or counts (%). Data were analyzed at a lesion-level.

* Completeness of continuous data: Pre-procedural reference vessel and minimal lumen diameter was not available for 4,103 lesions; (3,163 in the male group and 940 in the female group); balloon diameter was not available for 159 lesions (121 in the male group and 38 in the female group); maximal balloon pressure was not available for 4,526 lesions (3,477 in the male group and 1,049 in the female group); total stented length was not available for 67 lesions (51 in the male group and 16 in the female group); number of stents was not available for 417 lesions (285 in the male group and 132 in the female group); post-procedural minimal lumen diameter and diameter stenosis was not available for 4,865 lesions (3,732 in the male group and 1,133 in the female group). The remaining data are complete.

Table A7. Baseline characteristics as per stent type (160)**. ***

	Biodegradable Polymer Stent	Polymer Free Stent	Permanent Polymer Stent	p value
Patient Characteristics	N=541	N=811	N=690	
Age (years)	66.7±11.9	67.5±12.1	67.1±11.1	0.48
Female	161 (29.8)	217 (26.8)	171 (24.8)	0.15
Diabetes mellitus	164 (30.3)	215 (26.5)	200 (29.0)	0.28
Insulin-dependent	53 (9.8)	87 (10.7)	73 (10.6)	0.85
Hypertension	330 (61.0)	512 (63.1)	418 (60.6)	0.55
Current smoker	117 (21.6)	192 (23.7)	152 (22.0)	0.62
Hypercholesterolemia	327 (60.4)	455 (56.1)	420 (60.9)	0.12
Body mass index (kg/m²) *	27.1±4.4	27.6±4.7	27.4±4.4	0.13
Prior myocardial infarction	137 (25.3)	200 (24.7)	174 (25.2)	0.95
Prior aortocoronary bypass surgery	51 (9.4)	57 (7.0)	63 (9.1)	0.20
Number of diseased coronary vessels				0.02
One vessel	79 (14.6)	176 (21.7)	117 (17.0)	
Two vessels	153 (28.3)	205 (25.3)	192 (27.8)	
Three vessels	309 (57.1)	430 (53.0)	381 (55.2)	
Number of lesions	1.3±0.6	1.5±0.7	1.4±0.6	<0.001
Clinical presentation				<0.001
Acute myocardial infarction	167 (30.9)	446 (55.0)	291 (42.2)	
Unstable angina	374 (69.1)	365 (45.0)	399 (57.8)	
Ejection fraction (%) *	50.7±11.7	51.3±11.7	50.6±12.1	0.50
Relook Angiogram	398 (73.6)	607 (74.8)	509 (73.8)	0.84

Data are mean ± standard deviation or counts (%).

*Completeness of continuous data: Body-mass index was not available in 5 patients (1 in the permanent polymer group, 3 in the biodegradable polymer group and 1 in the polymer free group); ejection fraction was not available in 269 patients (85 in the permanent polymer group, 72 in the biodegradable polymer group and 112 in the polymer free group). The remaining continuous data were complete.

Table A8. Angiographic and procedural characteristics as per stent type (160)**.**

	Biodegradable Polymer Stent	Polymer Free Stent	Permanent Polymer Stent	p value
Lesion Characteristics	N=685	N=1214	N=969	
Target vessel				0.02
Left anterior descending artery	319 (46.6)	585 (48.2)	438 (45.2)	
Left circumflex artery	181 (26.4)	248 (20.4)	235 (24.3)	
Right coronary artery	185 (27.0)	381 (31.4)	296 (30.5)	
Chronic total occlusion	35 (5.1)	66 (5.4)	45 (4.6)	0.70
Complex morphology (B2/C)	547 (79.9)	996 (82.0)	770 (79.5)	0.26
Lesion length (mm)	15.2±8.5	16.7±9.5	17.3±9.7	<0.001
Vessel size (mm)	2.8±0.5	2.8±0.5	2.8±0.5	0.63
Total stented length (mm)	23.8±10.6	26.2±12.1	27.2±12.1	<0.001
Percent stenosis, pre-procedure (%)	69.2±17.0	71.3±17.3	70.9±16.9	0.03
Percent stenosis, post-procedure (%)	11.8±8.8	12.3±8.0	11.3±7.8	0.02
Balloon diameter (mm)	3.1±0.5	3.1±0.5	3.1±0.5	0.86

Data are mean ± standard deviation or counts (%).

Table A9. Stent types and baseline characteristics (161)**.**

	Stent Overlap	No Stent Overlap	p value
Patients	N=1824	N=3781	
Drug-eluting stent type			<0.001
Biodegradable polymer (New Generation)	410/1824 (22.5)	889/3781 (23.5)	
Polymer-free (New Generation)	697/1824 (38.2)	1305/3781 (34.5)	
Permanent polymer (Early Generation)	155/1824 (8.5)	497/3781 (13.1)	
Permanent polymer (New Generation)	562/1824 (30.8)	1090/3781 (28.8)	
Age (years)	67.6±10.7	67.1±11.1	0.114
Female	425/1824 (23.3)	905/3781 (23.9)	0.624
Diabetes mellitus	530/1824 (29.1)	1093/3781 (28.9)	0.933
Insulin-dependent	181/1824 (9.9)	355/3781 (9.4)	0.556
Hypertension	1257/1824 (68.9)	2523/3781 (66.7)	0.108
Current smoker	280/1824 (15.4)	660/3781 (17.5)	0.053
Hypercholesterolemia	1216/1824 (66.7)	2405/3781 (63.6)	0.027
Body mass index (kg/m²)	27.5±4.3	27.5±4.5	0.786
Prior myocardial infarction	522/1824 (28.6)	1108/3781 (29.3)	0.618
Prior aortocoronary bypass surgery	186/1824 (10.2)	356/3781 (9.4)	0.379
Multi-vessel disease	1627/1824 (89.2)	3136/3781 (83.0)	<0.001
Number of lesions	1.7±0.8	1.2±0.5	<0.001
Clinical presentation			0.107
Acute myocardial infarction	300/1824 (16.4)	674/3781 (17.8)	
Unstable angina	458/1824 (25.1)	860/3781 (22.7)	
Stable angina	1066/1824 (58.4)	2247/3781 (59.4)	
Ejection fraction (%)	52.9±11.4	52.9±11.8	0.852
Relook Angiogram	1437/1824 (78.8)	2882/3781 (76.2)	0.036

Data are mean ± standard deviation or counts (%). Data available for 4868 (87%) patients.

Table A10. Angiographic and procedural characteristics (161)**.**

	Stent Overlap	No Stent Overlap	p value
Lesions	N=2524	N=5239	
Target vessel			<0.001
Left anterior descending artery	1251/2524 (49.6)	2231/5239 (42.6)	
Left circumflex artery	579/2524 (22.9)	1425/5239 (27.2)	
Right coronary artery	694/2524 (27.5)	1583/5239 (30.2)	
Chronic total occlusion	185/2524 (7.3)	240/5239 (4.6)	<0.001
Complex morphology (B2/C)	2104/2524 (83.4)	3591/5239 (68.5)	<0.001
Lesion length (mm)	18.7±11.5	14.5±7.7	<0.001
Vessel size (mm)	2.8 ± 0.5	2.8 ± 0.5	0.899
Maximum balloon diameter (mm)	3.10 ± 0.50	3.07 ± 0.52	0.031
Maximum balloon pressure (mmHg)	16.1 ± 3.14	15.2 ± 3.13	<0.001
Balloon: Vessel ratio	0.44 ± 0.55	0.50 ± 0.56	<0.001
Total stented length (mm)	31.4 ± 14.4	22.5 ± 9.0	<0.001
Percent stenosis, pre-procedure (%)	66.9 ± 16.9	66.5 ± 15.6	0.289
Percent stenosis, post-procedure (%)	12.8 ± 7.9	11.2 ± 7.0	<0.001
Late luminal loss (mm)	0.4 ± 0.6	0.2 ± 0.5	<0.001

Data are mean ± standard deviation or counts (%).

Table A11. Baseline characteristics as per the event type experienced during 10-year follow-up (162)**. ***

	No Event	TVRE	NTVRE	Both Events	p value
Patients	N=2855	N=656	N=860	N=582	
Age (years)	68.0±11.3	66.4±10.4	66.4±10.3	66.5±10.4	<0.001
Female	757 (26.5)	145 (22.1)	156 (18.1)	115 (19.8)	<0.001
Diabetes mellitus	746 (26.1)	221 (33.7)	267 (31.0)	196 (33.7)	<0.001
Insulin-dependent	244 (8.6)	84 (12.8)	72 (8.4)	74 (12.7)	<0.001
Hypertension	1883 (66.0)	459 (70.0)	587 (68.3)	412 (70.8)	0.046
Current smoker	472 (16.5)	108 (16.5)	153 (17.8)	93 (16.0)	0.793
Hypercholesterolemia	1811 (63.4)	433 (66.0)	542 (63.0)	412 (70.8)	0.005
Body mass index (kg/m²) *	27.4±4.5	27.8±4.7	27.9±4.3	27.8±4.0	0.007
Prior myocardial infarction	797 (27.9)	192 (29.3)	260 (30.2)	199 (34.2)	0.021
Prior aortocoronary bypass surgery	228 (8.0)	67 (10.2)	110 (12.8)	77 (13.2)	<0.001
Number of diseased coronary vessels					<0.001
One vessel	568 (19.9)	102 (15.5)	60 (7.0)	29 (5.0)	
Two vessels	843 (29.5)	150 (22.9)	199 (23.1)	118 (20.3)	
Three vessels	1444 (50.6)	404 (61.6)	601 (69.9)	435 (74.7)	
Number of lesions	1.4±0.6	1.5±0.7	1.4±0.6	1.6±0.8	<0.001
Clinical presentation					0.022
Acute myocardial infarction	542 (19.0)	111 (16.9)	149 (17.3)	102 (17.5)	
Unstable angina	613 (21.5)	173 (26.4)	194 (22.6)	158 (27.1)	
Stable angina	1700 (59.2)	372 (56.7)	517 (60.1)	322 (55.3)	
Ejection fraction (%) *	52.8±12.0	53.3±10.7	52.5±11.5	52.5±10.8	0.651
Relook Angiography Performed (As Recommended by Trial Protocols)	1940 (68.0)	552 (84.1)	771 (89.7)	543 (93.3)	<0.001

Data are mean ± standard deviation or counts (%).

*Completeness of continuous data: Body-mass index was not available in 6 patients (5 in the no event group and 1 in the both events group); ejection fraction was not available in 650 patients (356 in the no event group, 85 in the TVRE group, 116 in the NTVRE group and 93 in the both events group). The remaining continuous data were complete.

TVRE=target vessel related events; NTVRE=non-target vessel related events.

Table A12. Angiographic and Procedural Characteristics as per the event type experienced during 10-year follow-up (162)**.**

	No Event	TVRE	NTVRE	Both Events	p value
Lesions	N=3869	N=970	N=1173	N=912	
Stent polymer type					<0.001
Permanent polymer	1290 (33.3)	309 (31.9)	411 (35.0)	319 (35.0)	
Biodegradable Polymer	964 (24.9)	276 (28.5)	295 (25.1)	148 (16.2)	
Polymer-free	1615 (41.7)	385 (39.7)	467 (39.8)	445 (48.8)	
Target vessel					<0.001
Left anterior descending artery	1855 (47.9)	398 (41.0)	483 (41.2)	370 (40.6)	
Left circumflex artery	925 (23.9)	231 (23.8)	320 (27.3)	298 (32.7)	
Right coronary artery	1089 (28.1)	341 (35.2)	370 (31.5)	244 (26.8)	
Chronic total occlusion	205 (5.3)	49 (5.1)	54 (4.6)	67 (7.4)	0.037
Complex morphology (B2/C)	2744 (70.9)	741 (76.4)	878 (74.9)	718 (78.7)	<0.001
Lesion length (mm)	15.7±9.2	16.1±10.0	16.2±9.4	16.8±10.0	0.005
Vessel size (mm)	2.8±0.5	2.8±0.5	2.8±0.5	2.7±0.5	<0.001
Total stented length (mm)	24.9±11.6	26.5±12.3	25.8±12.0	26.7±12.6	<0.001
Percent stenosis, pre-procedure (%)	66.7±16.2	66.9±16.2	66.4±15.8	67.4±15.5	0.547
Percent stenosis, post-procedure (%)	11.4±7.3	12.4±8.3	12.0±7.4	12.4±6.9	<0.001
Balloon diameter (mm)	3.1±0.5	3.0±0.5	3.1±0.5	3.0±0.5	<0.001
Balloon: Vessel Ratio	0.41 (0.54)	0.46 (0.55)	0.44 (0.55)	0.27 (0.49)	<0.001
Maximal Balloon Pressure (mmHg)	15.4 (3.1)	15.6 (3.2)	15.5 (3.1)	15.8 (3.3)	0.02

Data are mean ± standard deviation or counts (%).

TVRE=target vessel related events; NTVRE=non-target vessel related events.

Table A13. Baseline characteristics (186)**.***

Characteristic	All Patients (N=1986)	Training Population (N=1471)	Validation Population (N=515)	p value
Age, median (IQR), years	69.8 (61.6-76.2)	69.2 (60.8-76.1)	70.9 (63.5-76.7)	0.003
Sex, Female – no. (%)	398 (20.0)	295 (20.1)	103 (20.0)	>0.999
BMI, median (IQR), kg/m²	27.2 (24.7-30.0)	27.2 (24.7-30.1)	27.2 (24.7-29.7)	0.453
First re PCI interval, median (IQR), days	247 (197-840)	254 (197-886)	230 (196-744)	0.093
Restenosis interval – no. (%)				0.276
<6 months	326 (16.4)	237 (16.1)	89 (17.3)	
6-12 months	833 (41.9)	603 (41.0)	230 (44.7)	
>12-24 months	247 (12.4)	186 (12.6)	61 (11.8)	
>24 months	580 (29.2)	445 (30.3)	135 (26.2)	
Short restenosis interval – no. (%)	326 (16.4)	237 (16.1)	89 (17.3)	0.584
Diabetes – no. (%)	748/1980 (37.8)	586/1468 (39.9)	162/512 (31.6)	0.001
Insulin-treated – no. (%)	293/1980 (14.8)	229/1468 (15.6)	64/512 (12.5)	0.103
Arterial hypertension – no. (%)	1,886/1982 (95.2)	1,406/1468 (95.8)	480/512 (93.4)	0.040
Hypercholesterolemia – no. (%)	1,505/1971 (76.4)	1,115/1461 (76.3)	390/510 (76.5)	0.992
Smoker – no. (%)	302/1981 (15.2)	231/1468 (15.7)	71/513 (13.8)	0.339
ACS – no. (%)	506/1982 (25.5)	369/1467 (25.2)	137 (26.6)	0.555
NYHA Classification – no. (%)				0.159
I	732 (36.9)	553 (37.6)	179 (34.8)	
II	964 (48.5)	709 (48.2)	255 (49.5)	
III	241 (12.1)	179 (12.2)	62 (12.0)	
IV	49 (2.5)	30 (2.0)	19 (3.7)	
Coronary artery disease – no. (%)				0.929
Single-vessel	151 (7.6)	113 (7.7)	38 (7.4)	
Two-vessel	359 (18.1)	268 (18.2)	91 (17.7)	
Three-vessel	1476 (74.3)	1090 (74.1)	386 (75.0)	
Multivessel disease – no. (%)	1835 (92.4)	1358 (92.3)	477 (92.6)	0.899
Prior myocardial infarction – no. (%)	830/1979 (41.9)	608/1466 (41.5)	222/513 (43.3)	0.509
Prior CABG – no. (%)	275/1984 (13.9)	192/1469 (13.1)	83 (16.1)	0.099
Atrial fibrillation – no. (%)	97 (4.9)	76 (5.2)	21 (4.1)	0.385
LV-EF – no. (%)				0.030
<35%	64 (3.2)	51 (3.5)	13 (2.5)	
35-50%	576 (29.0)	425 (28.9)	151 (29.4)	
>50-55%	297 (15.0)	201 (13.7)	96 (18.7)	
>55%	1048 (52.8)	794 (54.0)	254 (49.4)	

Data are median (interquartile range) or counts (%).

*Completeness of continuous data: Training Population: body mass index, 2 patients, Validation Population: body mass index, 1 patient. The remaining continuous data were complete.

ACS=acute coronary syndromes; BMI=body mass index; CABG=coronary artery bypass grafting; IQR=interquartile range; LV-EF=left ventricular ejection fraction; MI=myocardial infarction; NYHA=New York Heart Association; PCI=percutaneous coronary intervention.

Table A14. Angiographic characteristics (186)**.**

Characteristic	All Lesions (N= 2392)	Training Population Lesions (N= 1778)	Validation Population Lesions (N= 614)	p value
Restenosis morphology – no. (%)				0.092
I (focal)	1563 (65.3)	1163 (65.4)	400 (65.1)	
II (diffuse intrastent)	581 (24.3)	420 (23.6)	161 (26.2)	
III (diffuse proliferative)	57 (2.4)	40 (2.3)	17 (2.8)	
IV (total occlusion)	191 (8.0)	155 (8.7)	36 (5.9)	
Vessel – no. (%)				0.067
LCA	97 (4.1)	64 (3.6)	33 (5.4)	
LAD	870 (36.4)	645 (36.3)	225 (36.6)	
LCx	700 (29.3)	540 (30.4)	160 (26.1)	
RCA	725 (30.3)	529 (29.8)	196 (31.9)	
Initially implanted DES type				0.51
BP-BES	166 (6.9)	119 (6.7)	47 (7.7)	
BP-SES	543 (22.7)	402 (22.6)	141 (23.0)	
PF-SES	465 (19.4)	355 (20.0)	110 (17.9)	
PP-EES	885 (37.0)	664 (37.3)	221 (36.0)	
PP-ZES	333 (13.9)	238 (13.4)	95 (15.5)	
Initial Repeat PCI Type				
DES	1178 (49.2)	862 (48.5)	316 (51.5)	0.219
PTCA (DCB or POBA)	1214 (50.8)	916 (51.5)	298 (48.5)	
DCB	635 (26.5)	479 (26.9)	156 (25.4)	-
POBA	579 (24.2)	437 (24.6)	142 (23.1)	-
Scoring balloon	160 (6.7)	122 (6.9)	38 (6.2)	0.630
Rotational atherectomy	2 (0.1)	2 (0.1)	0 (0.0)	0.628
IVUS	4 (0.2)	2 (0.1)	2 (0.3)	0.577
OCT	59 (2.5)	44 (2.5)	15 (2.4)	>0.999
Calcification – no. (%)	680 (28.5)	512 (28.9)	168 (27.4)	0.506
Ostial lesion – no. (%)	173 (7.3)	129 (7.3)	44 (7.2)	>0.999
Bifurcation – no. (%)	818 (34.3)	608 (34.3)	210 (34.2)	>0.999
CTO – no. (%)	169 (7.1)	135 (7.6)	34 (5.5)	0.101
Restenosis ≥ 90% – no. (%)	343/2387 (14.4)	270/1773 (15.2)	73 (11.9)	0.049
Device diameter, median (IQR) mm	3.00 (2.50-3.50)	3.00 (2.50-3.50)	3.00 (2.75-3.50)	0.054

Data are median (interquartile range) or counts (%).

BES=biolimus-eluting stent; BP=biodegradable polymer; CTO=chronic total occlusion; DCB=Drug Coated Balloon; DES=drug eluting stent; EES=everolimus-eluting stent; IQR=interquartile range; IVUS=intravascular ultrasound; LAD=left anterior descending; LCA=left coronary artery; LCx=left circumflex coronary artery; OCT=optical coherence tomography; PF=polymer-free; POBA=plain old balloon angioplasty; PTCA=percutaneous transluminal coronary angioplasty; RCA=right coronary artery; SES=sirolimus-eluting stent; ZES=zotarolimus-eluting stent.

Table A15. Baseline clinical characteristics according to the extent of inhomogeneity (166)**.**

Characteristics	**Low Inhomogeneity** (N=100)	**High Inhomogeneity** (N=97)	**p value**
Age, years	66.9±10.6	66.9±10.1	0.978
Male	82 (82.0)	77 (79.4)	0.776
Current smoker	18 (18.0)	13 (13.4)	0.49
Ex-smoker	38 (38.0)	34 (35.1)	0.778
Body mass index (kg/m^2)	28.2±3.97	28.0±4.93	0.797
Hypercholesterolemia	71 (71.0)	63 (64.9)	0.449
Arterial hypertension	93 (93.0)	84 (86.6)	0.211
Diabetes mellitus	45 (45.0)	37 (38.1)	0.406
Oral therapy	27 (27.0)	24 (24.7)	0.842
Insulin therapy	13 (13.0)	6 (6.19)	0.168
Previous myocardial infarction	56 (56.0)	52 (53.6)	0.846
Previous coronary artery bypass grafting	15 (15.0)	11 (11.3)	0.584
Clinical presentation			0.525
Silent ischemia	21 (21.0)	21 (21.6)	
Stable angina pectoris	49 (49.0)	49 (50.5)	
Unstable angina pectoris	20 (20.0)	12 (12.4)	
Non-ST-segment elevation myocardial infarction	9 (9.0)	14 (14.4)	
ST-segment elevation myocardial infarction	1 (1.0)	1 (1.0)	
Multivessel disease	84 (84.0)	71 (73.2)	0.094
Affected vessels			0.072
One vessel	16 (16.0)	26 (26.8)	
Two vessels	19 (19.0)	23 (23.7)	
Three vessels	65 (65.0)	48 (49.5)	
Ejection fraction (%)	54.0±13.3	58.8±13.2	0.079

Data are mean ± standard deviation or counts (%).

Table A16. Angiographic and procedural characteristics according to the extent of inhomogeneity (166)**.**

	Low Inhomogeneity (N=100)	**High Inhomogeneity** (N=97)	**p value**
Index stent interval, days	378 (198-1772)	416 (215-2015)	0.403
Target coronary vessel			0.266
Left main coronary artery	1 (1.0)	2 (2.1)	
Left anterior descending coronary artery	50 (50.0)	43 (44.3)	
Left circumflex coronary artery	18 (18.0)	28 (28.9)	
Right coronary artery	31 (31.0)	24 (24.7)	
Restenosis morphology			0.065
Focal margin	9 (9.0)	13 (13.4)	
Focal body	41 (41.0)	38 (39.2)	
Multifocal	12 (12.0)	2 (2.1)	
Diffuse intra-stent	29 (29.0)	37 (38.1)	
Proliferative	3 (3.0)	4 (4.1)	
Complete occlusion	6 (6.0)	3 (3.1)	
Underlying stent type			0.731
Bare-metal stent	18 (18.0)	20 (20.6)	
Drug-eluting stent	73 (73.0)	68 (70.1)	
Unknown	9 (9.0)	9 (9.3)	
Ostial lesion	18 (18.0)	19 (19.6)	0.918
Bifurcation lesion	26 (26.0)	29 (29.9)	0.652
Quantitative coronary angiography			
Reference diameter, mm	2.96±0.45	2.83±0.53	0.067
Lesion length, mm	13.3±6.79	13.8±7.66	0.633
Pre-procedural minimal lumen diameter, mm	1.09±0.45	1.02±0.45	0.267
Post-procedural minimal lumen diameter, mm	2.44±0.47	2.50±0.48	0.388
Pre-procedural diameter stenosis, %	63.5±13.6	65.3±13.7	0.358
Post-procedural diameter stenosis, %	19.4±11.5	17.5±9.1	0.196
Nominal balloon diameter, mm	3.34±0.46	3.28±0.51	0.337
Maximal balloon pressure, atm	16.9±4.4	17.3±4.9	0.552
Repeat drug-eluting stent implantation	40 (40.0)	48 (49.5)	0.232
Maximal stent diameter, mm	3.29±0.44	3.22±0.53	0.468
Total stented length, mm	30.3±15.8	29.3±12.9	0.791

Data are mean ± standard deviation, median (interquartile range) or counts (%).

Table A17. Optical coherence tomography characteristics according to the extent of inhomogeneity (166)**.**

	Low Inhomogeneity (N=100)	**High Inhomogeneity** (N=97)	**p value**
Frames analyzed	3505	2647	-
Struts analyzed	33298	24967	-
Mean stent area, mm^2	6.50 (5.04-8.49)	6.59 (5.28-7.94)	0.533
Mean stent diameter, mm	2.87 (2.53-3.28)	2.89 (2.59-3.18)	0.755
Min. stent diameter, mm	2.74 (2.38-3.10)	2.74 (2.43-3.01)	0.652
Max. stent diameter, mm	3.03 (2.67-3.47)	3.06 (2.74-3.39)	0.837
Mean lumen area, mm^2	4.35 (2.91-6.28)	4.22 (3.01-6.17)	0.774
Min. lumen area, mm^2	2.00±1.34	2.34±1.42	0.087
Mean lumen diameter, mm	2.35 (1.91-2.82)	2.31 (1.95-2.80)	0.998
Min. lumen diameter, mm	2.15 (1.74-2.58)	2.13 (1.77-2.57)	0.977
Max. lumen diameter, mm	2.55 (2.09-3.07)	2.52 (2.14-3.04)	0.995
Mean area stenosis, %	29.4 (14.7-47.1)	27.9 (14.9-46.4)	0.635
Max. area stenosis, %	64.7±18.3	59.4±20.2	0.060
Neointimal area, mm^2	1.75 (0.94-2.97)	1.76 (0.95-2.94)	0.618
Mean neointimal thickness, µm	210.0 (110.0-390.0)	220.0 (120.0-390.0)	0.461
Stent underexpansion	77 (77.0)	63 (64.9)	0.101
Strut coverage, %	93.7	93.7	0.134
Strut malapposition, %	0.89	1.19	0.392
Mean malapposition distance, µm	160.0 (130.0-260.0)	180.0 (130.0-280.0)	0.978

Data are mean ± standard deviation, median (interquartile range) or counts (%).

Table A18. Clinical characteristics according to neointimal tissue characterization (173)**.**

	Low Inhomogeneity (N=64)	**High Inhomogeneity** (N=64)	**p value**
Age, years	66.8±10.8	68.3±8.9	0.380
Sex, male	10 (15.6)	13 (20.3)	0.645
Body mass index, kg/ m^2	28.6±3.8	28.4±4.6	0.787
Current smoker	13 (20.3)	10 (15.6)	0.645
Ex-Smoker	20 (31.2)	23 (35.9)	0.708
Hypercholesterolemia	43 (67.2)	44 (68.8)	1.000
Arterial hypertension	61 (95.3)	63 (98.4)	0.619
Diabetes mellitus	29 (45.3)	28 (43.8)	1.000
Oral therapy	16 (25.0)	16 (25.0)	1.000
Insulin therapy	11 (17.2)	6 (9.4)	0.298
Previous coronary artery bypass surgery	10 (15.6)	12 (18.8)	0.815
Previous myocardial infarction	34 (53.1)	30 (46.9)	0.596
Clinical presentation			0.206
Silent Ischemia	16 (25.0)	14 (21.9)	
Stable Angina Pectoris	37 (57.8)	45 (70.3)	
Unstable Angina Pectoris	11 (17.2)	5 (7.8)	
Number of diseased coronary arteries			0.621
One vessel	6 (9.4)	8 (12.5)	
Two vessels	10 (15.6)	13 (20.3)	
Three vessels	48 (75.0)	43 (67.2)	
Multi-vessel disease	58 (90.6)	56 (87.5)	0.777
Left ventricular ejection fraction, %	52.7±10.0	51.9±10.3	0.786

Data are mean ± standard deviation or counts (%).

Table A19. Angiographic and procedural characteristics according to neointimal tissue characterization (173).

	Low Inhomogeneity (N=64)	**High Inhomogeneity** (N=64)	**p value**
Target vessel			0.033
Left main coronary artery	0 (0.0)	3 (4.7)	
Left anterior descending artery	30 (46.9)	30 (46.9)	
Left circumflex artery	11 (17.2)	19 (29.7)	
Right coronary artery	23 (35.9)	12 (18.8)	
Restenosis morphology			0.106
Focal margin	2 (3.1)	5 (7.8)	
Focal body	32 (50.0)	30 (46.9)	
Multifocal	10 (15.6)	2 (3.1)	
Diffuse intrastent	18 (28.1)	23 (35.9)	
Proliferative	1 (1.6)	1 (1.6)	
Complete occlusion	1 (1.6)	3 (4.7)	
Index Stent Interval, days	364 (197-1024)	384 (196-1663)	0.982
Underlying stent type			0.072
Bare Metal Stent	2 (3.1)	5 (7.8)	
Drug Eluting Stent	48 (75.0)	51 (79.7)	
Bioresorbable vascular scaffold	8 (12.5)	1 (1.6)	
Unknown	6 (9.4)	7 (10.9)	
Ostial lesion	12 (18.8)	17 (26.6)	0.398
Bifurcation lesion	19 (29.7)	25 (39.1)	0.352
Quantitative coronary angiography			
Lesion length, mm	12.4±5.7	14.0±7.4	0.177
Reference vessel diameter, mm	3.0±0.5	2.9±0.5	0.268
Pre-procedural minimal lumen diameter, mm	1.2±0.4	1.1±0.4	0.557
Pre-procedural diameter stenosis, %	60.9±11.5	63.4±13.1	0.256
Post-procedural minimal lumen diameter, mm	2.5±0.5	2.5±0.5	0.863
Post-procedural diameter stenosis, %	19.6±10.3	20.3±7.9	0.673
Predilatation	58 (90.6)	56 (90.3)	1.000
Nominal balloon diameter, mm	3.4±0.5	3.4±0.6	0.966
Maximal balloon pressure, atm	16.0±4.4	15.8±4.4	0.825
Treatment modality			0.267
Drug-coated balloon	38 (59.4)	45 (70.3)	
Drug-eluting stent implantation	26 (40.6)	19 (29.7)	
Maximal stent diameter, mm	3.3±0.5	3.4±0.6	0.300
Total stented length, mm	29.1±14.0	30.4±14.0	0.752
Number of Stents	1.2±0.4	1.2±0.4	0.769
Stent type			0.087
Biolimus-eluting stent	1 (1.6)	0 (0.0)	
Everolimus-eluting Stent	25 (39.1)	16 (25.0)	
Paclitaxel-eluting stent	0 (0.0)	1 (1.6)	
Sirolimus-eluting stent	0 (0.0)	2 (3.1)	

Data are mean ± standard deviation, median (interquartile range) or counts (%).

Table A20. Optical coherence tomography characteristics according to the extent of inhomogeneity (173)**.**

	Low Inhomogeneity (N=64)	**High Inhomogeneity** (N=64)	**p value**
Frames analyzed	2315	2175	-
Struts analyzed	22338	21191	-
Mean stent area, mm^2	6.38 (5.04-8.37)	6.44 (4.96-7.83)	0.273
Mean stent diameter, mm	2.85 (2.53-3.26)	2.86 (2.51-3.15)	0.342
Minimal stent diameter, mm	2.70 (2.38-3.09)	2.70 (2.37-2.98)	0.271
Maximal stent diameter, mm	2.99 (2.66-3.45)	3.01 (2.65-3.36)	0.430
Mean lumen area, mm^2	4.39 (2.93-6.25)	3.96 (2.84-5.85)	0.243
Mean lumen diameter, mm	2.36 (1.92-2.81)	2.24 (1.89-2.72)	0.308
Minimal lumen diameter, mm	2.17 (1.75-2.57)	2.06 (1.71-2.49)	0.317
Maximal lumen diameter, mm	2.56 (2.08-3.08)	2.43 (2.09-2.97)	0.322
Mean area stenosis, %	28.78 (13.97-45.92)	31.18 (15.88-49.08)	0.595
Neointimal area, mm^2	1.65 (0.90-2.86)	1.88 (1.00-3.03)	0.922
Mean neointimal thickness, µm	170.0 (80.0-320.0)	170.0 (90.0-320.0)	0.396
Strut coverage, %	93.1	93.1	0.113
Strut malapposition, %	0.7	1.3	0.279
Mean malapposition distance, µm	150.0 (130.0-200.0)	180.0 (130.0-300.0)	0.519
Proportion of inhomogeneous quadrants, %	1 (0–5)	20 (12–41)	<0.001

Data are median (interquartile range) or counts (%).

Table A21. Baseline characteristics (176)**. ***

Characteristic	Ticagrelor (N=833)	Prasugrel (N=820)	p value
Age (years)	62.4±12.1	63.2 ±12.1	0.17
Women	168 (20.2)	176 (21.5)	0.56
Diabetes	166/832 (20.0)	146 (17.8)	0.29
On insulin therapy	45/832 (5.4)	42 (5.1)	0.88
Current smoker	345/827 (41.7)	333/815 (40.9)	0.76
Arterial hypertension	518/831 (62.3)	495/818 (60.5)	0.48
Hypercholesterolemia	420/831 (50.5)	398 (48.5)	0.44
Prior myocardial infarction	99/832 (11.9)	89/819 (10.9)	0.56
Prior percutaneous coronary intervention	122/832 (14.7)	120/819 (14.7)	1.00
Prior aortocoronary bypass surgery	27/832 (3.3)	22/819 (2.7)	0.60
Cardiogenic shock	19 (2.3)	22 (2.7)	0.71
Systolic blood pressure (mmHg)	139±25.6	139 ± 24.7	0.80
Diastolic blood pressure (mmHg)	82.2 ±15	81.6 ±13.8	0.40
Heart rate (beats/min)	78.3 ±16.9	77.4 ±17	0.25
Body mass index (kg/m²)	27.6 ±4.44	27.7 ±4.32	0.82
Body weight < 60 kg	41/829 (5.0)	38/810 (4.7)	0.90
Creatinine (µmol/L)	88.2 ±28.4	87.7±32.6	0.74
Coronary angiography	832 (99.9)	820 (100.0)	1.00
Treatment strategy			0.040
Percutaneous coronary intervention	779 (93.5)	789 (96.2)	
Coronary artery bypass grafting	6 (0.7)	3 (0.4)	
Conservative	48 (5.8)	28 (3.4)	

Data are mean ± standard deviation or counts (%).

* Completeness of continuous data:

Systolic blood pressure was not available in 3 patients (1 in the ticagrelor group and 2 in the prasugrel group); diastolic blood pressure was not available in 16 patients (7 in the ticagrelor group and 9 in the prasugrel group); heart rate was not available in 2 patients (1 in each group); body-mass index was not available in 17 patients (6 in the ticagrelor group and 11 in the prasugrel group); body weight was not available in 14 patients (4 in the ticagrelor group and 10 in the prasugrel group); creatinine level was not available in 5 patients (4 in the ticagrelor group and 1 in the prasugrel group). The remaining continuous data are complete.

Table A22. Angiographic and procedural characteristics (176)**.**

Angiographic Characteristics			
	Ticagrelor (N=832)	**Prasugrel** (N=820)	**p value**
Access site			0.92
Femoral	573 (68.9)	573 (69.9)	
Radial	254 (30.5)	242 (29.5)	
Other	5 (0.6)	5 (0.6)	
Number of diseased coronary vessels			0.35
No obstructive coronary artery disease	32 (3.9)	19 (2.3)	
One vessel	304 (36.5)	302 (36.8)	
Two vessels	244 (29.3)	241 (29.4)	
Three vessels	252 (30.3)	258 (31.5)	
Left ventricular ejection fraction*	49 ± 11.2	48.8 ± 11.2	0.73
Procedural Characteristics			
	Ticagrelor (N=779)	**Prasugrel** (N=789)	**p value**
More than 1 lesion treated	249 (32.0)	241 (30.5)	0.58
Target vessel			0.10
Left main coronary artery	9 (1.2)	12 (1.5)	
Left anterior descending coronary artery	362 (46.5)	333 (42.2)	
Left circumflex coronary artery	116 (14.9)	98 (12.4)	
Right coronary artery	284 (36.5)	338 (42.8)	
Bypass graft	8 (1.0)	8 (1.0)	
Complex lesion (type B2/C)	438 (56.2)	466 (59.1)	0.28
Thrombolysis in Myocardial Infarction flow grade before the intervention			0.76
0	418 (53.7)	419 (53.1)	
1	77 (9.9)	91 (11.5)	
2	151 (19.4)	147 (18.6)	
3	133 (17.1)	132 (16.7)	
Thrombolysis in Myocardial Infarction flow grade after the intervention			0.42
0	9 (1.2)	6 (0.8)	
1	7 (0.9)	4 (0.5)	
2	33 (4.2)	25 (3.2)	
3	730 (93.7)	754 (95.6)	
Type of intervention			
Drug-eluting stent	708 (90.9)	724 (91.8)	0.60
Bare-metal stent	2 (0.3)	5 (0.6)	0.45
Bioresorbable vascular scaffold	40 (5.1)	44 (5.6)	0.78
Drug-eluting balloon	6 (0.8)	6 (0.8)	1.00
Plain balloon angioplasty	26 (3.3)	19 (2.4)	0.34
Maximal stent diameter (mm)	3.24 ± 0.48	3.25 ± 0.5	0.57
Total stented length (mm)	32 ± 16.5	32 ± 17.6	0.99
Successful percutaneous coronary intervention	757 (97.2)	770 (97.6)	0.72
Periprocedural antithrombotic medication			
Aspirin	736 (94.5)	729 (92.4)	0.12
Unfractionated heparin	701 (90.0)	699 (88.6)	0.42
Low molecular weight heparin	20 (2.6)	18 (2.3)	0.84
Bivalirudin	91 (11.7)	96 (12.2)	0.83
Glycoprotein IIb/IIIa inhibitor	158 (20.3)	132 (16.7)	0.08

Data are as counts (%) or mean ± standard deviation. Angiographic data are not available in one patient

*Left ventricular ejection fraction was not available in 122 patients.

Table A23. The therapy at discharge and the assigned antithrombotic medication after study drug discontinuation (176)**.**

Diagnosis and Drug Therapy at Discharge*			
Characteristic	**Ticagrelor** (N=833)	**Prasugrel** (N=820)	**p value**
Acute coronary syndromes as final diagnosis	799/832 (96.0)	799/819 (97.6)	0.11
Type of acute coronary syndromes			0.79
Unstable angina	7/799 (0.9)	7/799 (0.9)	
Non-ST-segment elevation myocardial infarction	19/799 (2.4)	15/799 (1.9)	
ST-segment elevation myocardial infarction	773/799 (96.7)	777/799 (97.2)	
Therapy at discharge†			
Aspirin	771/810 (95.2)	784/803 (97.6)	0.012
Ticagrelor	705/810 (87.0)	2/803 (0.3)	<0.001
Prasugrel	11/810 (1.4)	725/803 (90.3)	<0.001
Clopidogrel	43/810 (5.3)	49/803 (6.1)	0.56
Oral anticoagulant drugs	48/810 (5.9)	50/803 (6.2)	0.88
Betablocker	715/810 (88.3)	696/803 (86.7)	0.37
ACE inhibitor/ARB	685/810 (84.6)	696/803 (86.7)	0.26
Statin	759/810 (93.7)	772/803 (96.1)	0.035
Antithrombotic Medication after Discontinuation of Study Drug during the Follow-up**			
Characteristic	**Ticagrelor** (N=88)	**Prasugrel** (N=69)	**p value**
Ticagrelor	0 (0.0)	5 (7.3)	0.015
Prasugrel	16 (18.2)	0 (0.0)	0.001
Clopidogrel	45 (51.1)	38 (55.1)	0.74
Oral anticoagulation	17 (19.3)	21 (30.4)	0.15
None of the aforementioned medication	22 (25.0)	20 (29.0)	0.71

Data are shown as counts (%).

* Not available for patients who withdrew consent before discharge.

† Shown for patients discharged alive, not available for patients who withdrew consent.

** Percentages refer to patients who discontinued the study drugs during follow-up.

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker.