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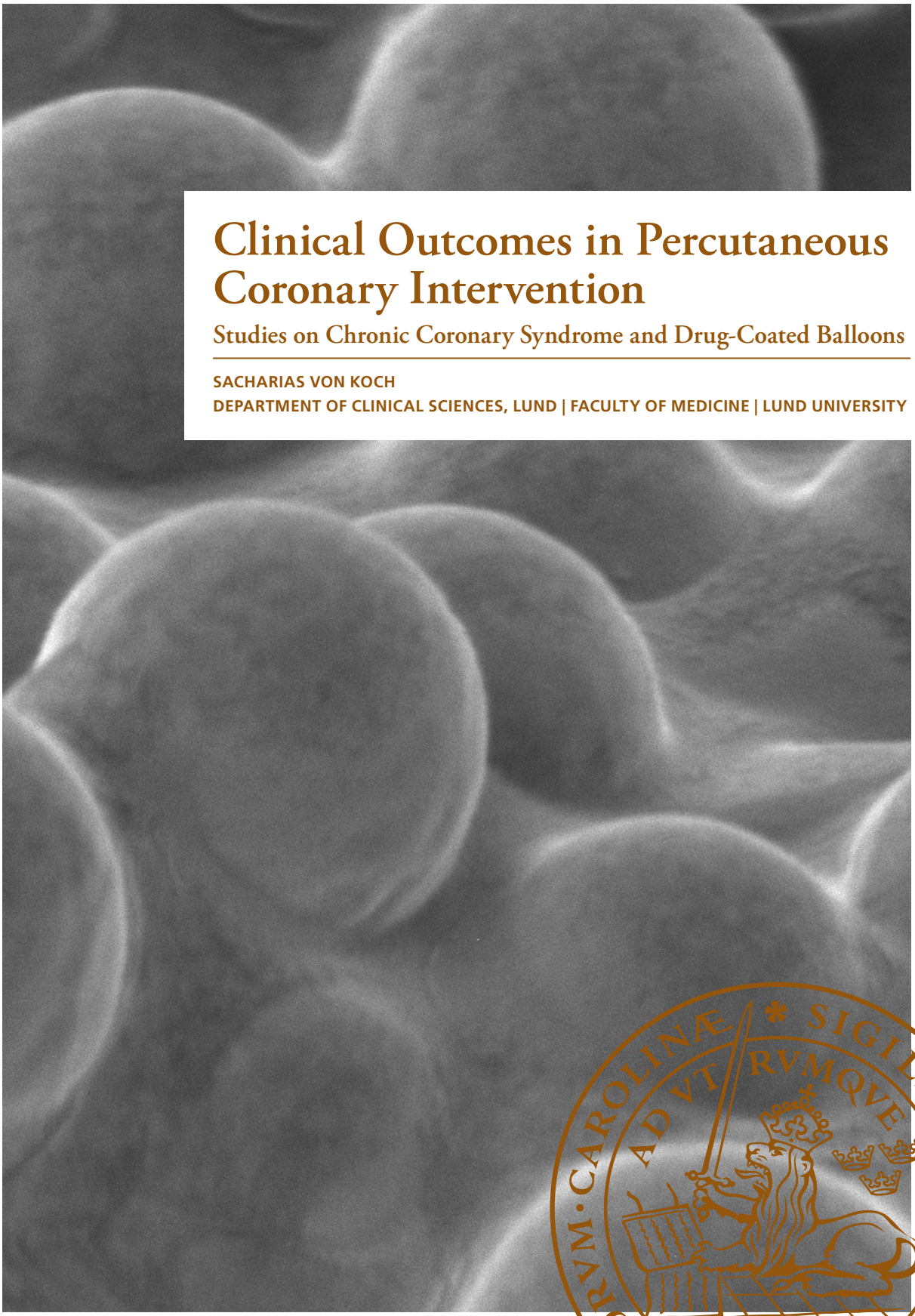

Clinical Outcomes in Percutaneous Coronary Intervention

Studies on Chronic Coronary Syndrome and Drug-Coated Balloons

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Sacharias von Koch

LUND UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended 13 May 2026, at 9:00 in Segerfalksalen, BMC, Lund university, Lund, Sweden.

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Abstract:

Background: Percutaneous coronary intervention (PCI) is frequently used in the treatment of chronic coronary syndrome (CCS), although its impact on long-term prognosis and symptom relief remains debated. Among patients undergoing revascularisation with PCI, data on clinical outcomes following drug-coated balloon (DCB) based PCI in unselected patient populations is limited, and the comparative effectiveness of DCB- versus drug-eluting stents (DES) has not been fully established.

Methods: This thesis utilised data from Swedish national registries including the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Exclusion criteria, propensity score matching, and multivariable adjustment models were applied to mitigate confounding.

Results: In paper I, PCI was associated with lower rates of 10-year all-cause mortality among patients with CCS. In paper II, revascularisation in patients with CCS with PCI or coronary artery bypass graft surgery was associated with a lower use of long-acting nitrates. In paper III, a DCB inflation time of ≥30 seconds was associated with lower 1-year rate of target segment revascularisation compared to <30 seconds. No difference was observed in Paper IV when paclitaxel-coated balloons were compared with sirolimus-coated balloons. In paper V, DES was associated with a lower rate of target vessel revascularisation compared to DCB in small non-complex de novo lesions. The use of DCB for in-stent restenosis was investigated in paper VI, DCB was associated lower rates of 5-year target lesion revascularisation compared to plain old balloon angioplasty, but an increased rate compared to DES.

Conclusions: In this thesis, which investigated outcome following PCI of CCS and PCI with DCB, PCI was associated with prognostic and symptomatic relief in CCS. A sufficient inflation time seems to be a prerequisite of DCB effectiveness, while specific drug type was not associated with any difference in outcome. The results support the continued role of DES as the standard of care in small-vessel disease and in-stent restenosis.

Key words: Drug-coated balloons, chronic coronary syndrome, percutaneous coronary intervention, Swedish Coronary Angiography and Angioplasty Registry

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MADE IN SWEDEN

Dedicated to my family

Table of contents

List of papers

This thesis is a compilation thesis comprising six papers. A list of included papers is presented below, referred to in the text by their respective Roman numerals. In addition to the papers included for the thesis, the author has published or had accepted for publication nine additional articles and one letter in peer-reviewed journals as of 31 March 2026.

Paper I

von Koch S, Koul S, Grimfjärd P, Andersson J, Jernberg T, Omerovic E, Fröbert O, Erlinge D, Mohammad MA. Percutaneous coronary intervention plus medical therapy versus medical therapy alone in chronic coronary syndrome: a propensity score-matched analysis from the Swedish Coronary Angiography and Angioplasty Registry. Heart. 2024 Oct 28;110(22):1307-1315.

Paper II

von Koch S, Sharma T, Khamis R, Jernberg T, James S, Omerovic E, Zwackman S, Sjögren J, Erlinge D, Mohammad MA. Long-acting nitrate use before and after revascularization to evaluate angina in chronic coronary syndrome: a case-crossover study from SCAAR. Lancet Reg Health Eur. 2025 Oct 28;60:101507.

Paper III

von Koch S, Zhou M, Håkansson A, Råmunddal T, Omerovic E, Zwackman S, Erlinge D, Rissanen TT, Mohammad MA. Impact of drug-coated balloon inflation time on outcome after percutaneous coronary intervention: An observational study from SCAAR. (Manuscript in press, accepted for publication in JAHA).

Paper IV

von Koch S, Yndigegn T, Koul S, Zwackman S, Desta L, Angerås O, Omerovic E, Böhm F, Fröbert O, Grimfjärd P, James S, Erlinge D, Mohammad MA. Paclitaxel-Coated Balloons Versus Sirolimus-Coated Balloons for Coronary Artery Lesions: A Nationwide Cohort Study from the Swedish Coronary Angiography and Angioplasty Registry. (Manuscript in press, accepted for publication in JSCAI).

Paper V

von Koch S, Tödt J, Zhou M, Pétursson P, Persson J, Jurga J, Zwackman S, Sarno G, Koul S, Erlinge D, Mohammad MA. Drug-coated balloons versus drug-eluting stents for small non-complex de novo coronary artery lesions: A segment-level propensity score matched analysis from SCAAR. Cardiovasc Revasc Med. 2025 Nov;80:88-95.

Paper VI

von Koch S, Zhou M, Rosén HC, Zwackman S, Jurga J, Grimfjärd P, Götberg M, Mohammad MA, Erlinge D. Drug-Coated Balloons Versus Drug-Eluting Stents or Plain Old Balloon Angioplasty: A Long-Term in-Stent Restenosis Study. J Am Heart Assoc. 2024 Dec 3;13(23):e036839.

Populärvetenskaplig sammanfattning

För att återställa blodflödet i hjärtats kärl under en hjärtinfarkt utgör ballongvidgning, så kallad perkutan koronarintervention, en viktig del av behandlingen. När det kommer till kronisk kranskärlssjukdom, som har en stabilare sjukdomsbild, är evidensen för perkutan koronarintervention däremot osäker. Perkutan koronarintervention har under de senaste två decennierna utvecklats i hög takt, inte minst genom införandet av nya tekniker så som läkemedelsavgivande stentar och läkemedelsbelagda ballonger. Syftet med föreliggande avhandling är att undersöka den roll som perkutan koronarintervention spelar i behandlingen av kronisk kranskärlssjukdom samt studera användningen av läkemedelsbelagda ballonger vid perkutan koronarintervention. Läkemedelsbelagda ballonger har utvecklats för att, till skillnad från läkemedelsavgivande stentar, behandla kärlet utan att lämna kvar ett permanent metallimplantat. Man kan tänka sig att detta kan vara fördelaktigt i vissa situationer, exempelvis vid mycket små kärl eller när det uppstått en förträngning inuti en tidigare insatt stent. Samtidigt finns det ett flertal obesvarade frågor kring hur ballongerna bäst bör användas i praktiken. Frågorna gäller hur länge ballongen bör hållas uppblåst, vilken typ av läkemedel som är mest effektivt för ballongen och hur behandlingsresultatet ser ut jämfört med andra tekniker så som läkemedelsavgivande stentar.

Den här avhandlingen utgår ifrån dessa frågor och har två övergripande mål: dels att förbättra behandlingen av kronisk kranskärlssjukdom, dels att optimera behandlingen med läkemedelsbelagda ballonger. Avhandlingen bygger på data från svenska nationella kvalitetsregister vilka i praktiken omfattar alla patienter som genomgått perkutan koronarintervention i Sverige. En stor fördel med undersökningsmaterialet är att studieresultaten speglar en reell klinisk vardag snarare än en selekterade studiepopulation.

I avhandlingens första delarbete, **delarbete I,** undersöktes den prognostiska rollen av perkutan koronarintervention hos patienter som var optimalt medicinskt behandlade. I studien fann vi att patienter som blivit behandlade med perkutan koronarintervention hade ett bättre långtidsutfall med större överlevnad efter 10 år. I **delarbete II** undersöktes patienternas symptom efter perkutan koronarintervention och kranskärlskirurgi. I detta delarbete var både perkutan koronarintervention och kranskärlskirurgi associerat med en minskad användning av långverkande nitrater, vilket är ett läkemedel som patienter tar vid kärlkramp. Resultaten av denna studie antydde att patienter som genomgått behandlingarna hade förbättrade symptom.

I **delarbete III** undersöktes betydelsen av uppblåsningstiden av en läkemedelsbelagd ballong för behandlingsresultatet. I studien jämfördes patienter som behandlats med kortare uppblåsningstider på <30 sekunder med patienter som behandlats med ≥30 sekunder. Resultaten visade att längre uppblåsningstider på ≥30 sekunder gav ett bättre utfall jämfört med kortare uppblåsningar. Därutöver visade analysen att uppblåsningstider >30 sekunder inte medförde någon ytterligare förbättring jämfört med 30 sekunder, vilket talar för att det finns en minimitid för optimal läkemedelsöverföring. I **delarbete IV** jämfördes två typer av läkemedelsballonger – de som är belagda med Sirolimus och de som är belagda med Paklitaxel. Dessa läkemedel skiljer sig åt i hur de tas upp i kärlväggen och hur länge de verkar. I studien sågs dock inga tydliga skillnader i kliniska utfall mellan de två ballongtyperna.

Slutligen, i **delarbete V** och **delarbete VI**, undersöktes läkemedelsbelagda ballonger vid behandling av små kärl respektive förträngningar i tidigare stentbehandlade kärl. Flertalet tidigare studier har fokuserat på resultat inom det första året. I delarbete V och delarbete VI utökades därför den kliniska uppföljningsperioden till att omfatta 5 år efter genomförd behandling. Resultaten visade att läkemedelsbelagda ballonger och läkemedelsavgivande stentar hade likvärdiga resultat sex månader efter ingreppet, men att därefter började resultatet skilja sig åt, med ett lägre behov av ny behandling hos patienter som fått läkemedelsavgivande stentar. Detta tyder på att läkemedelsbelagda ballonger ger god och likvärdig korttidskontroll av förträngningen medan läkemedelsavgivande stentar kan erbjuda en mer långsiktig stabilitet vid behandling av små kärl och förträngningar i ett tidigare stentbehandlat kärl. Därutöver visade resultaten att läkemedelsbelagda ballonger hade ett bättre behandlingsresultat jämfört med vanliga ballonger utan läkemedel i behandlingen av förträngningar i tidigare stentbehandlade kärl.

Sammanfattningsvis betonar resultaten av denna avhandling att perkutan koronarintervention har en viktig roll i behandlingen av kronisk kranskärlssjukdom, den understryker vikten av att använda en tillräckligt lång uppblåsningstid för läkemedelsbelagda ballonger och konstaterar inga skillnader mellan olika typer av läkemedelsbelagda ballonger. I jämförelsen mellan läkemedelsbelagda ballonger och läkemedelsavgivande stentar bidrar avhandlingen med viktig kunskap från den kliniska vardagen och styrker användandet av läkemedelsavgivande stentar.

Abstract

Background: Percutaneous coronary intervention (PCI) is frequently used in the treatment of chronic coronary syndrome (CCS), although its impact on long-term prognosis and symptom relief remains debated. Among patients undergoing revascularisation with PCI, data on clinical outcomes following drug-coated balloon (DCB) based PCI in unselected patient populations is limited, and the comparative effectiveness of DCB- versus drug-eluting stents (DES) has not been fully established.

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Abbreviations

CABG	Coronary artery bypass graft
CCS	Chronic coronary syndrome
CI	Confidence interval
DCB	Drug-coated balloon
DES	Drug-eluting stent
HR	Hazard ratio
NSTEMI	Non-ST-segment elevation myocardial infarction
PCB	Paclitaxel-coated balloon
PCI	Percutaneous coronary intervention
POBA	Plan old balloon angioplasty
PS	Propensity score
RR	Risk ratio
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCB	Sirolimus-coated balloon
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TLR	Target lesion revascularisation
TSR	Target segment revascularisation

Introduction

Coronary artery disease

Pathophysiology

The coronary arteries supply the myocardium with oxygenated blood and nutrients. The coronary arteries consist of a left and right vessel that both originate from the aortic root. Atherosclerosis is the underlying pathological process responsible for most cases of coronary artery disease. Atherosclerosis is initiated by endothelial injury, which increases the permeability of low-density lipoprotein particles, causing oxidation within the vessel wall. [1,2] This promotes recruitment of inflammatory cells such as monocytes that differentiate into macrophages and ultimately form lipid-laden foam cells. Over time, lipid accumulation and inflammation lead to the development of plaques composed of a necrotic lipid core and a fibrous cap. Progression of atherosclerotic plaques can result in luminal narrowing and impair coronary blood flow, causing symptoms of angina. The PROSPECT II study, which combined intravascular ultrasound and near-infrared spectroscopy, showed that coronary lesions with a high lipid content and thin fibrous caps are prone to future adverse events, highlighting the importance of recognising plaque vulnerability rather than stenosis obstructing the lumen alone. [3] Acute coronary syndrome occur when plaque disruption exposes thrombogenic material to circulating blood, leading to platelet activation, thrombus formation, and coronary occlusion. [4] Acute coronary syndrome encompasses a wide spectrum of clinical entities, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Previous studies have shown that revascularisation is paramount in the treatment of acute coronary syndrome to improve outcome. [5-7]

Chronic coronary syndrome

While evidence have shown that revascularisation play a pivotal role in acute coronary syndrome, its role in chronic coronary syndrome (CCS) remains more uncertain. The syndrome arises from atherosclerotic plaque progression in the epicardial coronary arteries and commonly precede or follow acute coronary

syndrome. In contrast to acute coronary syndromes, CCS is characterised by a stable balance between myocardial oxygen supply and demand. [8] A typical presentation of CCS is exertional angina, or dyspnoea, that are relieved by rest or antianginal therapy. CCS is of a dynamic nature and may evolve over time with progressive symptoms. The management of CCS therefore includes therapies aimed at improving prognosis as well as treatments intended to relieve angina and improve quality of life. A cornerstone in the management of CCS is lifestyle modifications and pharmacological therapies. [9,10] In addition to this, patients with CCS often undergo invasive assessment and remain a significant number of all coronary angiographies as of today (**Figure 1**). [11]

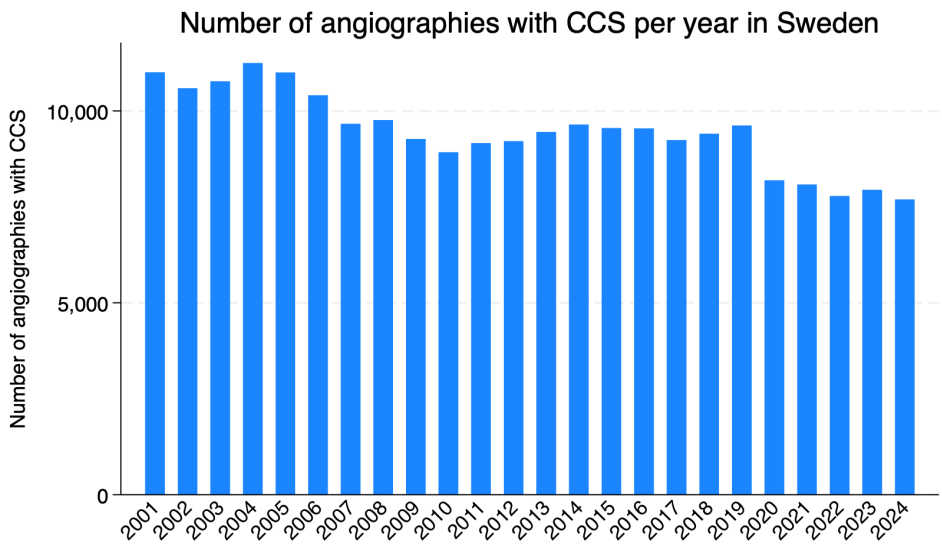

Figure 1. Number of angiographies with CCS per year.
Graph illustrating total number of angiographies with CCS per year in Sweden between 2001 and 2024.

In the COURAGE trial, patients with CCS were randomised to percutaneous coronary intervention (PCI) plus optimal medical therapy or optimal medical therapy alone. [12] In this study, PCI did not reduce the risk of death or myocardial infarction compared with medical therapy alone. More recently, the ISCHEMIA trial evaluated an invasive strategy of coronary angiography and revascularisation compared with a conservative strategy in patients with moderate to severe ischemia. [13] The study demonstrated no statistically significant reduction in ischemic cardiovascular events or death. In patients with ischemic cardiomyopathy, coronary artery bypass graft (CABG) surgery has shown prognostic benefit. The STICH trial evaluated CABG in patients with severe left ventricular systolic dysfunction and coronary artery disease. [14] While the initial results did not demonstrate a significant reduction in terms of mortality, the 10-year follow-up of the STICH Extension

Study (STICHES) revealed a significant benefit in terms of cardiovascular death (hazard ratio (HR) 0.79 [95% confidence interval (CI) 0.66–0.93], p=0.006 by log-rank test). [15] The REVIVED trail investigated the role of PCI in patients with severe ischemic left ventricular dysfunction and viable myocardium and found that PCI did not improve survival or reduce hospitalisation for heart failure compared with optimal medical therapy. [16] The BARI 2D trial evaluated patients with type 2 diabetes mellitus and CCS, and compared revascularisation with intensive medical therapy alone. [17] The trial demonstrated no significant difference in survival between the two strategies. The FAME 2 trial compared fractional flow guided PCI with medical therapy alone in patients with haemodynamically significant coronary stenoses. [18] The PCI group was associated with a significant reduction in the composite endpoint of death, myocardial infarction, or urgent revascularisation (13.9% vs 27.0%; HR 0.46 [95% CI 0.34–0.63], p<0.001), driven by a reduction in urgent revascularisation.

Beyond these trials, angina symptom relief and quality of life have also been investigated. Antianginal medications such as beta-blockers, calcium channel blockers, and long-acting nitrates, remain of essence in symptom management. However, the magnitude of symptomatic benefit from PCI has been challenged in placebo-controlled trials. The first ORBITA trial was a blinded, placebo-controlled trial of PCI in patients with CCS and single-vessel coronary disease. [19] Following an intensive medical optimisation period, patients in this trial were randomly assigned to PCI or a sham procedure. After six weeks of follow-up, PCI did not improve exercise time as compared with the sham procedure. The subsequent ORBITA-2 trial expanded upon this in a randomised placebo-controlled design with patients withdrawn from antianginal medications prior to randomisation. [20] When antianginal therapy was withdrawn, PCI was associated with a significant reduction in angina symptom score compared with the placebo group.

Percutaneous coronary intervention

Historical overview

The conceptualisation of coronary artery disease and myocardial infarction as a clinical syndrome began in the early 20th century. In 1912, James B. Herrick, a physician from Chicago, Illinois, published a landmark paper establishing acute myocardial infarction as a clinical diagnosis, a major advance at the time. [21] Since Herrick's publication, the treatment of coronary artery disease have continued to evolve. In the early decades of the 20th century, the treatment consisted of bed rest and symptom relief, yielding a poor prognosis with in-hospital mortality rates exceeding 30%.[22] In the 1950s, arrythmia was recognised as a major cause of death,

leading to the establishment of coronary care units with electrocardiography monitoring. [23] During the following decades the prognosis continued to improve with lower rates of myocardial infarctions complicated with cardiogenic shock. [24] As understanding of the underlying pathophysiology improved, coronary revascularisation emerged as a new treatment strategy. In 1960, surgeon Robert H. Goetz performed the world's first CABG, using the left internal mammary artery. [25] Simultaneously, pharmacological therapies – such as aspirin, beta-blockers and fibrinolytics – were introduced, leading to improvements of outcome. [26,27] Beside CABG, PCI has evolved as an alternative revascularisation strategy.

The first PCI was performed in Zürich, Switzerland, on 16 September 1977, by German cardiologist named Andreas R. Grüntzig. Using a balloon-tipped catheter, Grüntzig navigated the coronary arteries and, by inflating the balloon, opened a narrow segment of the proximal left anterior descending artery. [17,28] Following this procedure, no immediate complications were observed, and the patient was quickly relived from their angina as the blood flow to the myocardium was restored. Despite this advancement, elastic recoil and acute vessel closure represented a severe and common complication following the early years of PCI. To provide a structural support for the coronary arteries, the first stent was developed in the mid-1980s. [29] This first stent was a bare-metal stent, which was prone to cause inflammation and subsequently smooth muscle cell proliferation with neointimal hyperplasia. [30] Recurrent cardiovascular event were common, in one study 20.1% of patients required a new procedure within the first year after PCI with bare-metal stents. [31] The drug-eluting stent (DES) was developed in the early 2000s, aimed at reducing the risk of neointimal hyperplasia by using antiproliferative drugs. [32,33] The DES utilises a polymer to elute the antiproliferative drug over time to the coronary artery. One study, comparing a bare-metal stent with a first-generation DES using paclitaxel as the antiproliferative drug, found a significant reduction in the 9-month rate of target lesion revascularisation (TLR) (15.7% vs 8.6%, p-value<0.001). [34] The first-generation of DES was limited by thick stent struts and polymers that caused inflammation. Later generations of DES further improved the concept of coronary stenting by using thinner stent struts, refined antiproliferative agents, and biocompatible/biodegradable polymers. Subsequent comparative trials have demonstrated improved outcome with the newer generations of DES. [35] Sirolimus-eluting stents represent an advancement in stent technology and are associated with lower rates of major adverse cardiac events and reduced late lumen loss compared with paclitaxel-eluting stents. [36]

Contemporary challenges

Despite the improved properties among the newer generation of DES, stents have inherent limitations. First, thrombosis formation on the stent, remains a severe complication following stent implantation. Stent thrombosis occur most frequently

within the first 30 days after stent implantation and is associated with a high risk of mortality. [37,38] One previous study from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) found that DES was associated with lower rates of early/late stent thrombosis (up to 1 year) compared with bare-metal stents, although no difference in very late stent thrombosis (after 1 year) was observed between newer generations of DES and bare-metal stents. [39]

Second, in-stent restenosis is a narrowing of the luminal diameter within the stented segment. Similar to stent thrombosis, the advancement in stent technology has reduced the rate of in-stent restenosis. [32,40,41] Despite these advancements, in-stent restenosis remains a significant challenge and comprise approximately 10% of all PCI today, and is associated with worse outcome following the PCI as compared to de novo lesions. [42,43] Beyond the first year after DES implantation, the yearly rate of in-stent restenosis continues to be of clinical concern. One study found an incidence of stent related major adverse cardiovascular events of 8.3% between year 1 and 5 following PCI with second-generation DES. [44] In the same study, the incidence within 1 year was 5.1%. In-stent restenosis has a diverse etiology. Early in-stent restenosis is typically caused by an undersized or misplaced stent, elastic recoil or stent fractures meanwhile late in-stent restenosis is typically caused by intimal hyperplasia or neo-atherosclerosis. [45]

Third, compared to the bare-metal stents which required only a short dual antiplatelet therapy regime, DES requires a prolonged dual antiplatelet regime due to slower endothelisation. For acute coronary syndrome, the European Society of Cardiology guidelines recommend 12 months of dual antiplatelet therapy unless there are specific contraindications. [46] This increases the bleeding risk over time, which may be a problem in certain patient populations.

Fourth, for complex lesions, DES implantation may be technically not achievable. In small vessel, DES may result in a high proportion of lumen loss following the implantation. This has been observed in several studies showing an increased rate of TLR following PCI in small vessels as compared with larger vessels. [47] Other complicated lesions include in-stent restenosis where repeat stenting result in a high degree of metal and luminal narrowing.

In light of these inherent limitations of stents, new PCI techniques have been developed. Some of these techniques aim to *leave nothing behind*, potentially addressing the shortcomings of DES by overcoming the risk of long-term complications. Biodegradable vascular scaffolds, designed to fully resorb after drug deliver, held promise by providing early structural support while gradually dissolving to restore normal vessel physiology. Despite a promising concept, early studies investigating biodegradable vascular scaffolds demonstrated higher rates of stent thrombosis and TLR compared with DES. [48-50] Although inferior results were initially observed, the biodegradable scaffolds appear to have a long-term "catch-up" once complete scaffold resorption is expected. [49,51] Building on the "leave

nothing behind" concept, drug-coated balloons (DCB) have been developed as an alternative strategy for PCI.

Drug-coated balloons

Mechanism of action

DCB are designed to deliver an antiproliferative drug during a single inflation to the coronary vessel wall to the coronary vessel wall, without leaving a permanent implant. [52] DCB aims to achieve luminal gain through balloon angioplasty while mitigating late events linked to metallic scaffolds, such as those related to chronic inflammation, impaired vasomotion, and in-stent restenosis or thrombosis. The concept of DCB is therefore best understood as (1) optimised lesion preparation to achieve an acceptable acute result, followed by (2) homogeneous drug transfer to suppress neointimal hyperplasia during the healing phase. A defining technical requirement for DCB is therefore an effective antiproliferative drug, sufficient transfer within the balloon-vessel contact, and adequate tissue retention throughout the healing phase. [53] Effective drug transfer to the vessel wall is facilitated by a carrier excipient. Contemporary DCB coatings are engineered to preserve the drug on the surface of the balloon during delivery through blood and guiding catheters, and release it upon inflation and contact pressure. As no scaffold is left behind, DCB require specific procedural strategies that are different from stent-based PCI. The 2020 DCB Consensus Document underscore the importance of a maximum transit time (in order to avoid excessive drug loss before delivery) and a minimum DCB inflation time. The inflation time is of particular importance, since insufficient inflation time can result in inadequate drug-transfer, while an excessively long inflation time may cause patient discomfort and is unsuitable for patients that are hemodynamically affected. There is currently limited data supporting the optimal inflation time. Another key procedural aspect for DCB-based PCI is the lesion preparation. One study found significantly higher rates of TLR in DCB-based PCI for in-stent restenosis with inadequate lesion preparation (HR 1.99 [95% CI: 1.02-3.87]). [54] Another study found that when a scoring balloon was used for lesion preparation before DCB therapy in DES in-stent restenosis, in-segment percent diameter stenosis on a 6- to 8-month follow-up angiography was significantly lower ($35.0 \pm 16.8\%$ vs $40.4 \pm 21.4\%$; $p = 0.047$). [55] The aim of the lesion preparation is to ensure full balloon expansion, low residual stenosis and no major dissection. The DCB Consensus Group highlights four key factors to ensure a successful DCB delivery: "1) a fully inflated balloon of the correct size for the vessel; 2) ≤30% residual stenosis; 3) Thrombolysis In Myocardial Infarction flow grade 3 or better; and 4) the absence of a flow-limiting dissection." [56] Considering these recommendations, type A/B dissections and up to 30% recoil are acceptable. Bailout

stenting should be used for recoil >30% and flow limiting dissection. [57] Any dissection of type C or greater should be treated with stent implantation.

DCB differ with respect to the antiproliferative agent, surface dose, coating morphology, and excipient technology. In coronary applications, paclitaxel has historically been the predominant antiproliferative agent used for DCB. Paclitaxel is an antimitotic agent that binds to β-tubulin, stabilises microtubules, and induces irreversible cell-cycle arrest, and thereby inhibiting smooth muscle cell proliferation. [58] Its high lipophilicity enables rapid tissue uptake and sustained retention in the vessel wall. In Swedish clinical practice, the paclitaxel surface dose ranges from 2.0 to 3.5 μg/mm².[56] Preclinical studies in porcine coronary models demonstrated that paclitaxel-coated balloons (PCB) effectively inhibit neointimal hyperplasia, with safety and efficacy comparable to DES. [59] Moreover, the use of contrast medium as an excipient has been shown to produce a dose-dependent reduction in neointimal formation. [60] Sirolimus has emerged as a new alternative to DCB. Sirolimus and its analogues are the predominant drugs used in contemporary DES. Sirolimus is a mammalian target of rapamycin inhibitor that blocks cell cycle at G1-S, inhibiting smooth muscle proliferation and a reversible cell cycle inhibition. [61] Compared to paclitaxel, sirolimus has lower lipophilicity. [62] Consequently, tissue uptake and vessel retention are reduced, resulting in lower tissue levels in the adventitia over time. [63,64] Thus, translating stent technology to DCB technology presents pharmacokinetic challenges, as the short balloon-vessel contact allows only limited drug-delivery time. A previous preclinical study investigating DCB use in a rabbit model found a greater medial smooth muscle cell loss score regarding depth for PCB compared with sirolimus-coated balloons (SCB). [65] To overcome this limitation of sirolimus, novel formulation strategies have been developed to enhance uptake and prolong retention despite the lower intrinsic lipophilicity of sirolimus.

Coating morphology also differs between DCB. Paclitaxel is commonly applied in crystalline form, which provides prolonged tissue retention but may result in particulate shedding during delivery and inflation. A substantial proportion of the drug can be lost during catheter advancement, inflation, and balloon withdrawal. [66] Previous studies have shown that embolising particulates released from DCB with crystalline paclitaxel vary in size. [67] In a clinical scenario, this could potentially result in slow-flow, ischaemia, or myocardial infarction. In contrast, sirolimus-based technologies often rely on micro-, or nanoparticle encapsulation systems designed to reduce drug loss and improve targeted delivery.

Beyond the antiproliferative agent, the excipient also plays a decisive role in facilitating drug transfer and retention. Accordingly, there is no established “class effect” among DCB, as outcomes depend on the interplay between drug, dose density, coating technology, and excipient. This position is reflected in the European Society of Cardiology Guidelines and consensus documents from dedicated DCB working groups. [56,68]

Comparative clinical data on PCB and SCB remain limited, particularly in coronary artery disease. Available studies as of today is listed in **Table 1**. The SIRONA trial, a head-to-head comparison in femoropopliteal artery disease, demonstrated comparable patency between SCB and PCB. [69] In peripheral artery disease, slow-flow has been shown to reduce healing and increase the risk of amputation. [70]

Table 1. Previous randomised and observational studies investigating coronary PCB vs SCB.
Adapted from von Koch S, et al. Paclitaxel-Coated Balloons Versus Sirolimus-Coated Balloons for Coronary Artery Lesions: A Nationwide Cohort Study from the Swedish Coronary Angiography and Angiolasty Registry. Unpublished manuscript.

Previous randomized controlled trials				
Title	**Publication year**	**Nr. patients**	**PCB type (manufacturer)**	**SCB type (manufacturer)**
Treatment of Coronary De Novo Lesions by a Sirolimus- or Paclitaxel-Coated Balloon[71]	2022	70	SeQuent Please (B. Braun Melsungen)	SeQuent SCB (B. Braun Melsungen)
A Prospective Randomized Trial Comparing Sirolimus-Coated Balloon With Paclitaxel-Coated Balloon in De Novo Small Vessels[72]	2023	121	SeQuent Please NEO (B. Braun Melsungen)	MagicTouch (Concept Medical)
A randomised trial of sirolimus-versus paclitaxel-coated balloons for de novo coronary lesions[73]	2024	70	SeQuent Please NEO (B. Braun Melsungen)	SeQuent SCB (B. Braun Melsungen)
Sirolimus- vs Paclitaxel-Coated Balloon for the Treatment of Coronary In-Stent Restenosis: The SIBLINT-ISR Randomized Trial[74]	2025	258	SeQuent Please NEO (B. Braun Melsungen)	SeQuent SCB (B. Braun Melsungen)
Comparing the Efficacy of Sirolimus and Paclitaxel-Eluting Balloon Catheters in the Treatment of Coronary In-Stent Restenosis: A Prospective Randomized Study (TIS 2 Study) [75]	2025	145	SeQuent Please (B. Braun Melsungen)	MagicTouch (Concept Medical)
Sirolimus-coated versus paclitaxel-coated balloons for bifurcated coronary lesions in the side branch: the SPACIOUS trial[76]	2025	230	Not publicly available	Not publicly available
Previous observational studies				
Title	**Publication year**	**Nr. patients**	**PCB type (manufacturer)**	**SCB type (manufacturer)**
Paclitaxel-coated versus sirolimus-coated balloon angioplasty for revascularization of coronary arteries: the SIRPAC study[77]	2021	1090	Elutax SV (AR Baltic)	MagicTouch (Concept Medical)

Comparison of Sirolimus-Versus Paclitaxel-Coated Balloons in Coronary Artery Disease: One-Year Results of Two Real-World Prospective Registries[78]	2025	2596	Protégé (Translumina)	MagicTouch (Concept Medical)
Sirolimus- Versus Paclitaxel-Coated Balloons for Treatment of Coronary Artery Disease[79]	2025	1320	Multiple real-world DCB	Multiple real-world DCB

Historical overview

Early experimental work in the late 1990s and early 2000s focused on whether a short, high-concentration drug transfer during balloon inflation could achieve inhibition of neointimal hyperplasia. [80] Paclitaxel became the dominant early candidate due to its lipophilicity and rapid tissue uptake. [52] A key milestone in the development of DCB therapy was the PACCOCATH study, which provided the first robust clinical signal that local drug delivery could reduce recurrent restenosis in coronary in-stent restenosis. [81] This first-in-man study by Scheller et al reported that after a 12 month follow-up period, the rate of major adverse cardiac events was significantly reduced in the PCB group when compared with plain old balloon angioplasty (POBA) (4% vs 31%; p=0.01). Following this proof-of-concept study, the evidence base expanded through a series of randomised studies comparing DCB to POBA, as well as first-generation DES. In PEPCAD II ISR, a PCB was compared to a paclitaxel-eluting stent for bare-metal stent in-stent restenosis. In this study, the DCB group experienced numerically lower 3-year rates of lesion-related major adverse cardiac events (7.6% vs 16.9%, p=0.11). [82]

In parallel, attention shifted to other lesion subsets, including DES in-stent restenosis. In the PEPCAD-DES trial, PCB angioplasty was superior to POBA for DES in-stent restenosis with respect to 3-year TLR rates (19.4% vs 36.8%, p=0.046). [83] The internationalisation of the clinical programme was illustrated by studies such as the PEPCAD China ISR trial, which demonstrated the noninferiority of PCB angioplasty compared with paclitaxel-eluting stent implantation for DES in-stent restenosis in an Asian population. [84] In the RIBS IV randomised trial of DES in-stent restenosis, everolimus-eluting stents achieved better angiographic outcomes than DCB, with long-term results supporting the superiority of second-generation DES. [85] RIBS IV contributed to a more nuanced view of DCB for in-stent restenosis. With in-stent restenosis as the initial indication of DCB, the next phase of DCB development focused on the treatment of de novo coronary disease.

The most influential modern data on de novo disease have focused on small-vessel disease. The PICCOLETO trial compared a first-generation PCB with a first-generation DES in small coronary arteries. The DCB arm exhibited significantly greater percent diameter stenosis and angiographic restenosis at 6 months, leading to early termination of the trial. [86] In the BASKET-SMALL 2 trial, DCB angioplasty

was noninferior to DES for clinical outcomes in patients with de novo lesions in small coronary vessels. [87] More contemporary randomised comparisons, such as the PICCOLETO II trial, further supported the finding that newer-generation DCB can achieve favourable angiographic results. [88] In parallel with the expansion of clinical trials, the DCB literature evolved towards greater standardisation of definitions and endpoints, reflecting the need to compare heterogeneous devices and procedural strategies across studies and registries. Efforts, such as the Drug-Coated Balloon Academic Research Consortium consensus on definitions and standardised endpoints, represent this maturation of the field and facilitate clearer interpretation of the expanding evidence base. [89] Expert consensus documents have summarised practical aspects of patient and lesion selection, procedural technique, and antiplatelet therapy considerations, reflecting the evolution of DCB from a niche technology into an established component of contemporary PCI practice in many regions. [90,91]

Adaptation

As research on DCB has evolved, the European Society of Cardiology guidelines have progressively updated their recommendations on the use of DCB. The 2010 European Society of Cardiology Guidelines on myocardial revascularisation included the first recommendation for DCB, assigning it a Class 2, Level B recommendation for the treatment of bare-metal stent in-stent restenosis. [92] In the 2014 European Society of Cardiology guidelines on myocardial revascularisation, the recommendation was expanded to include both bare-metal stent and DES in-stent restenosis, with a Class 1, Level A. [93] Similarly, the 2018 European Society of Cardiology guideline on myocardial revascularisation recommended DCB for bare-metal stent and DES in-stent restenosis (Class 1, Level A). [68] In contrast, the 2024 European Society of Cardiology Guideline on CCS, recommend DES as the first-line treatment for DES in-stent restenosis. [8] As of today, the European Society of Cardiology has no current recommendation for DCB for de novo disease.

Reflecting these evolving guideline recommendations, the use of DCB in Sweden has increased rapidly over the past decade (**Figure 2**). DCB was introduced into Swedish clinical practice in 2009. Since this introduction in 2009, multiple DCB platforms have been used in clinical practice up to 2023, differing in drug type, dose density, and excipient technology. Examples include SeQuent Please (B. Braun), Ivatec In-Pace Falcon (Medtronic), Resonance Elutax (Aachen), Pantera Lux (Biotronik), Agent (Boston Scientific), Magictouch (Concept Medical), Selution (Cordis), Prevail (Medtronic), and SeQuent SCB (B. Braun). [11] DCB are now used for several indications, predominantly in-stent restenosis but also for selected de novo lesions. In Sweden, DCB are used in 11.6% of all PCI between 1st of January 2020 and 1st of May 2024. The proportion of DCB-based PCI varies significantly among centres and operators (**Figure 3**), with similar trends observed in other

countries. In Japan, for example, the adoption of DCB has been rapid, accounting for 20.8% of patients and 17.2% of all lesions treated in 2021. [90] In Great Britain, the use of DCB accounted for 8.1% of PCI procedures in 2021–2022. [94] In China, DCB-only PCI is used in approximately 20–25% of PCI cases as of 2022. [94] In the United States, the Food and Drug Administration approved the use of DCB for the treatment of in-stent restenosis in 2024.

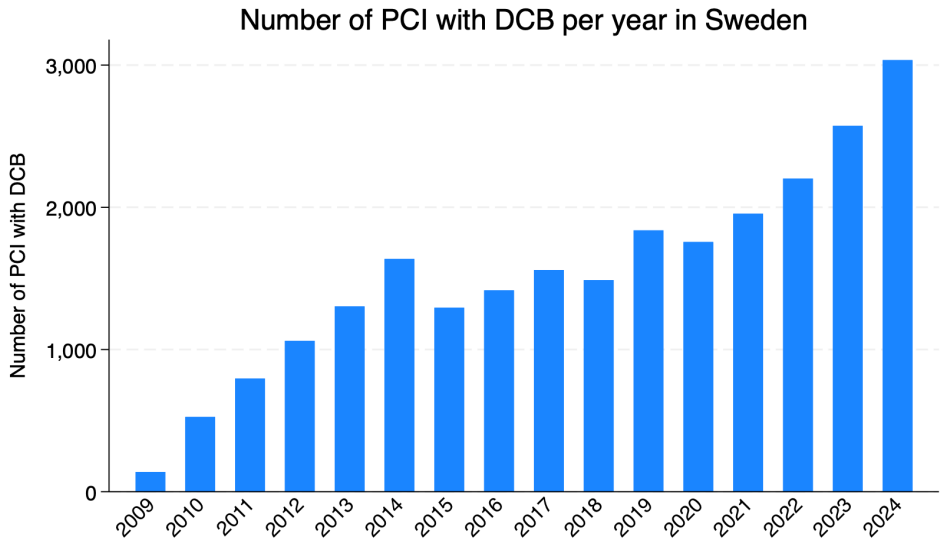

Figure 2. Number of PCI with DCB per year.
Graph illustrating total number of PCI with DCB per year in Sweden between 2009 and 2024.

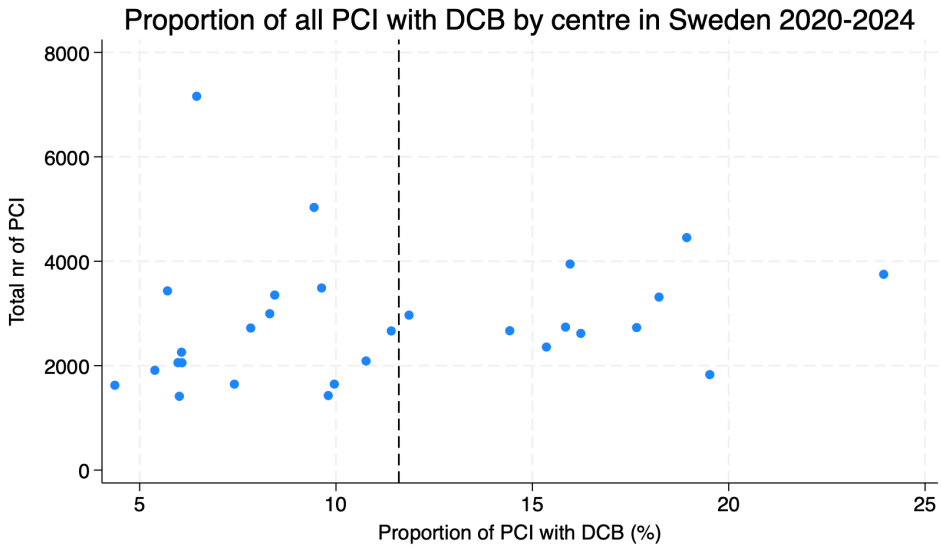

Figure 3. Proportion of PCI with DCB.
Proportion of all PCI with DCB in Sweden between 1 January 2020 and 16 May 2025. Each blue circle represents a Swedish PCI-centre. The verticle dotted line represents the mean proportion of PCI with DCB in Sweden (11.6%).

With the increasing use of DCB therapy, health economic considerations have gained increasing importance. In a prespecified cost-effectiveness sub-study of the BASKET-SMALL 2 trial, DCB were compared with second-generation DES. [95] Treatment with DCB in small-vessel disease was associated with slightly lower quality-adjusted life expectancy at 3 years, but also with slightly lower costs, resulting in DES being overall more cost-effective. Another cost-effectiveness analysis observed no difference between DCB and DES. [96] In selected patients, DCB treatment may allow for shorter durations of dual antiplatelet therapy. Reduced dual antiplatelet therapy duration translates into lower pharmaceutical expenditures and fewer bleeding complications, which are associated with substantial healthcare costs and morbidity. [97] In Sweden, healthcare is publicly funded and strongly guided by principles of cost-effectiveness and equitable resource allocation.

De novo small-vessel disease

One of the first randomised studies examining DCB in small de novo coronary arteries was the PICCOLETO trial, published in 2010. [86] PICCOLETO was a small trial (n=57) that compared a PCB with a first-generation DES in patients undergoing PCI for small-vessel disease (≤2.75 mm diameter). At 6 months, angiographic efficacy was inferior with DCB, including a higher residual diameter stenosis

(43.6% vs 24.3%, p=0.029) and a greater binary restenosis rate (32.1% vs 10.3%, p=0.043). Subsequent early studies showed more promising results for DCB. The BELLO trial was a multicentre randomised controlled trial in patients with small coronary vessels (<2.8 mm diameter). [98] BELLO compared a PCB versus a paclitaxel-eluting stent. In contrast to PICCOLETO, BELLO demonstrated superior angiographic results for the DCB. At a 6-month angiography follow-up, the DCB showed significantly lower late lumen loss (0.08 mm vs 0.29 mm; p(superiority)=0.001). Moreover, at 3-year follow-up, the DCB group experienced significantly fewer major adverse cardiac events: 14.4% major adverse cardiac events with DCB versus 30.4% with the paclitaxel-eluting stent (p=0.015). [99] The BASKET-SMALL 2 trial, which randomised 758 patients with small vessel disease (<3 mm in diameter) to PCI with a PCB (SeQuent Please) or a DES (everolimus-eluting Xience stent [72%] or the paclitaxel-eluting Taxus stent [28%]) is the largest study to date on this topic. [87] At 12 months, BASKET-SMALL 2 met its primary endpoint, demonstrating that the DCB strategy was non-inferior to DES in preventing major adverse cardiac events. The composite rate of cardiac death, non-fatal myocardial infarction, or target-vessel revascularisation was 7.5% with DCB versus 7.3% with DES, p(non-inferiority) =0.0217. Long-term follow-up data from BASKET-SMALL 2 found a continued similar clinical efficacy between the two treatment groups at 3 years. [91] Following the BASKET-SMALL 2 trial, several other trials proceeded to investigate the use of DCB for small coronary artery lesions. The RESTORE SVD China trial, a randomised study of 230 patients with de novo small-vessel disease (≥2.25 and ≤2.5 mm diameter), compared a PCB (Restore DCB) to a zotarolimus-eluting stent. [100] In this trial, in-segment percent diameter stenosis at 9 months and 1 year was found to be non-inferior (29.6% stenosis with DCB vs 24.1% with DES, p(non-inferiority) <0.001). At 12 and 24 months, RESTORE SVD reported no significant difference in rates of TLR between DCB- and DES-treated patients. [101] Another important study was PICCOLETO II, an Italian trial published in 2020. [88] PICCOLETO II enrolled 232 patients with lesions between 2.00 and 2.75 mm and compared a PCB (Elutax SV) with a contemporary everolimus-eluting stent (Xience DES). In this study, DCB showed significantly less late lumen loss than DES (0.04 mm vs 0.17 mm, p(superiority) =0.03). Clinical outcomes at 1 year in PICCOLETO II were similar between groups, 5.6% major adverse cardiac events in the DCB arm vs 7.5% with DES. A previous SCAAR study showed increased rates of restenosis and myocardial infarction following DCB compared with DES for small-vessel disease. [102] The Andromeda study was a metanalysis including data from randomised trials of 1154 patients with 1360 lesions. [103] It found that in patients undergoing PCI with de novo small vessel disease, DCB were associated with a reduction in 3-year major adverse cardiac events (HR 0.67 [95% CI: 0.58–0.96]) compared with DES implantation. In the recently published REC-CAGEFREE I trial, that was an open-label, randomised, non-inferiority trial, DCB with rescue stenting was compared with a strategy of DES for de novo lesions, regardless of vessel diameter. [104] At 2-year follow-up, DCB did not achieve non-inferiority as

compared with DES. Although non-inferiority was not met, the subgroup analysis revealed a significant treatment-by-subgroup interaction according to vessel size, with similar outcome observed between the two treatment arms for small-vessel disease (DCB diameter <3.0 mm).

In-stent restenosis

DES have demonstrated improved outcomes following PCI for in-stent restenosis compared with POBA. [105] DCB have emerged as an alternative to DES. The PACCOCATH ISR trial was a small first-in-human study (n=52) investigating DCB treatment for bare-metal stent in-stent restenosis, published in 2006. [81] The study found that PCB were associated with lower rates of TLR compared with POBA. Following the PACCOCATH ISR trial, several smaller randomised trials comparing PCB with DES for bare-metal stent in-stent restenosis were conducted. One randomised trial compared PCB with a paclitaxel-eluting stent. [106] After 6-month follow up, lower late lumen loss was observed in the DCB arm (0.38±0.61 mm vs 0.17±0.42 mm, p=0.03). These results persisted throughout a 3-year clinical follow-up. [82] Subsequent trials compared DCB with everolimus-eluting stents. [107] In the RIBS V trial, the everolimus-eluting stent group had a significantly larger minimal lumen diameter compared with a PCB (2.36 ± 0.6 mm vs 2.01 ± 0.6 mm, p <0.001). [108] In contrast, the TIS trial found significantly less 12-month late lumen loss in DCB compared with everolimus-eluting stents (0.02 mm vs 0.19 mm, p=0.0004). [109]

DES in-stent restenosis poses a distinct clinical challenge, with prior studies reporting higher rates of recurrent cardiovascular events compared with bare-metal stent in-stent restenosis. [110] This is also illustrated by the RIBS IV trial, which included DES in-stent restenosis, and the RIBS V trial, which included bare-metal in-stent restenosis. [85,108] After PCI with DCB, , the 3-year event rate of TLR was 15.6% in the RIBS IV trial and 8% in RIBS V.

For DES in-stent restenosis, PCB were associated with lower rates of late lumen loss after 6 months compared with POBA in the randomised PEPCAD-DES study (0.43 ± 0.61 mm vs 1.03 ± 0.77 mm, p <0.001). [111] A similar finding was observed in the AGENT IDE trial, which compared the safety and efficacy of a PCB with POBA for in-stent restenosis. [112] At 1-year follow-up, lower rates of recurrent restenosis and TLR in the DCB arm were demonstrated. In the PEPCAD China ISR trial, non-inferiority was met at 9 months in terms of in-segment late lumen loss when PCB was compared with a paclitaxel-eluting stent (0.46 ± 0.51 mm vs 0.55 ± 0.61 mm, p for non-inferiority =0.0005). [84] The three armed ISAR-DESIRE 3 trial, compared PCB with a paclitaxel-eluting stent and POBA. In the trial, non-inferiority was met when the DCB was compared with the DES in terms of diameter stenosis (38.0% [SD 21.5] vs 37.4% [21.8]; p for non-inferiority=0·007). Compared with POBA, both DCB and DES were superior (p for superiority≤0.0001 for both

comparisons). [113] The DAEDALUS meta-analysis pooled data from 10 randomised controlled trials, including more than 1,900 patients presenting with both bare-metal stent in-stent restenosis and DES in-stent restenosis. Overall, this study demonstrated that DCB was associated with a higher rate of TLR compared with repeat DES implantation. [114] The first-in-human trial investigating a SCB for in-stent restenosis was the SABRE trial. [115] The single arm trial included 50 patients presenting with bare-metal in-stent restenosis or DES in-stent restenosis. At 12-month follow-up, the target lesion failure rate was 12.2% and the major adverse cardiac event rate was 14.3%.

Aims

The overall aim of this thesis is to assess the prognostic and symptomatic role of PCI in patients with CCS and the role of DCB in PCI. The specific aims of the individual studies are outlined below.

Paper I. The study aimed to evaluate the potential benefit of PCI in patients with CCS receiving guideline-recommended medical therapy.

Paper II. The study aimed to evaluate the impact of revascularisation with CABG and PCI on angina in patients with CCS, using dispensed prescriptions of long-acting nitrates as a proxy for symptom burden.

Paper III. The study aimed to investigate the association between DCB inflation time and clinical outcomes.

Paper IV. The study aimed to assess the clinical efficacy of contemporary DCB, comparing PCB and SCB.

Paper V. The study aimed to investigate the long-term efficacy of DCB for non-complex small de novo lesions compared with DES.

Paper VI. The study aimed to compare the long-term outcomes of DCB, DES and POBA for in-stent restenosis.

Methods

Setting

The studies included in this thesis were conducted in a Swedish healthcare system. Sweden has a population of approximately 10.5 million inhabitants and a publicly funded, tax-based healthcare system, accounting for approximately 9.9% of the country's gross domestic product (2009). [116] According to a 2022 report by the Organisation for Economic Co-operation and Development, Sweden has the fifth highest life expectancy in Europe, at 84.8 years for women and 81.4 for men, surpassed only by Spain, Italy, Luxembourg and Malta. [117] Although Sweden has an ageing population, the prevalence of other cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and obesity) is moderate in an international context. The Swedish population is characterised by a low proportion of smokers (approximately 5% of the population) and a relatively widespread use of preventive pharmacotherapy, such as statins and antihypertensive agents. [118,119]

All citizens in Sweden are assigned a unique personal identification ten-digit number at birth or immigration. [120] The personal identification number enables deterministic linkage between registries. The use of anonymised personal identification numbers allows comprehensive longitudinal follow-up with minimal loss to follow-up.

Data sources

A distinctive feature of the Swedish setting is the availability of nationwide quality registries with mandatory reporting. Of particular relevance to this thesis is the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). SWEDEHEART comprise of several sub-registries, including SCAAR and the Registry for Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). [121] In quality assessment studies, the SWEDEHEART registry has continued to show high completeness and accuracy. In the 2017–2018 audit, the completeness of PCI data was 99.2% when compared with medical records, and the accuracy was 98.4%.[122] SCAAR was established 1999

and includes data on all patients in Sweden that undergo coronary angiography in any of Sweden's 30 hospitals with a catheterisation laboratory. [11,121] The reporting in SCAAR results in a nationwide coverage of all angiographies and PCI, for both elective and acute procedures. The SCAAR prospectively collect extensive information on patient demographics, comorbidities, procedural aspects and lesion characteristics. This is captured in SCAAR in more than 200 variables. RIKS-HIA was established 1995 and includes all patients admitted to coronary care units in Sweden with suspected or confirmed acute coronary syndrome. The participation in RIKS-HIA is mandatory for all 72 hospitals in Sweden. Like SCAAR, RIKS-HIA prospectively collects extensive information on demographics, cardiovascular risk factors, discharge medications, in-hospital managements, electrocardiography findings with a high accuracy and completeness. In the following passages, other registries included for this research are discussed briefly.

The Swedish Population Registry is a nationwide registry maintained by Statistics Sweden and includes all residents in Sweden. It contains information on vital status with complete coverage of the Swedish population. Registration in the Swedish Population Register is mandatory at birth or immigration. Essentially, 100% of births, 95% of immigrations and 91% of emigrations are reported to the Swedish Population Register within 30 days. [123]

The Swedish National Patient Registry, or the Swedish National Inpatient Registry, is maintained by the National Board of Health and Welfare and includes nationwide coverage on International Classification of Diseases codes from all inpatient hospital care since 1987. The positive predictive values of the Swedish National Patient Registry were 85-95% for most diagnoses in an external validation from 2011. [124]

The Swedish Prescribed Drug Registry was established in 2005 and contains detailed information on all dispensed prescriptions at Swedish pharmacies, providing longitudinal data on drug use across the Swedish population. [125] It captures complete information including date of dispensation and Anatomical Therapeutic Chemical code. The register is maintained by the Swedish National Board of Health and Welfare.

The National Cause of Death Registry is maintained by the Swedish National Board of Health and Welfare and has nationwide coverage since 1952. It includes data on underlying cause of death determined by the treating physician, coded according to successive versions of the International Classification of Diseases. [126]

Outcome definition

All outcome measures assessed in this research project are clinically driven and derived from either SCAAR, RIKS-HIA, the Swedish Population Registry, the National Patient Registry, the National Cause of Death Registry, or the Swedish Prescribed Drugs Registry. Outcome definitions are presented in **Table 2**.

Table 2. Outcome definition

Paper	Outcome	Source	Definition
Paper I	Net adverse clinical events	National Patient Registry, National Population Registry, and SCAAR	All-cause death, myocardial infarction, bleeding or urgent revascularisation.
Paper I	Major adverse cardiovascular events	National Patient Registry, National Population Registry, and SCAAR	All-cause death, myocardial infarction or urgent revascularisation.
Paper I Paper II Paper III Paper IV Paper V Paper VI	All-cause mortality/death	National Population Registry	All-cause death
Paper I Paper VI	Myocardial infarction	RIKS-HIA	New registration for myocardial infarction in the SCAAR registry with a discharge diagnosis of myocardial infarction according to the fourth universal definition of myocardial infarction ICD-10: I21–I22.
Paper III Paper IV Paper V	Myocardial infarction	SCAAR	Patient undergoing angiography or PCI with NSTEMI or STEMI.
Paper I	Bleeding	National Patient Registry	Haemorrhagic stroke: ICD-10: I60-I62. Gastrointestinal bleeding: ICD-10: K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, I850. Anaemia-related bleeding: ICD-10: D629, D500. Other bleeding: ICD-10: N421, N938, N939, N950, R041, R042, R048, R049, R210, R319, R210, T810, N501A
Paper I	Urgent revascularisation	SCAAR	Revascularisation with PCI due to acute coronary syndrome or revascularisation with CABG.

Paper I	Stroke	National Patient Registry	ICD-10: I63.0–I63.6.
Paper I Paper VI	Cardiovascular death/mortality	National Population Registry, and National Patient Registry	Death due to ICD-10: I00-I99
Paper II	Long-acting nitrate use	Swedish National Prescribed Drugs Registry	Dispensed prescription of long-acting nitrates (Anatomical Therapeutic Chemical code C01DA14)
Paper III Paper IV Paper V	Target lesion/segment revascularisation	SCAAR	Revascularisation with PCI in the same segment. (In Paper VI TLR was defined as repeat revascularisation with PCI and/or CABG)
Paper III Paper IV Paper V	Target vessel revascularisation	SCAAR	Non-staged repeat revascularisation with PCI in the previously treated vessel (LAD, RCA, Cx or IM).
Paper III Paper V	Target vessel myocardial infarction	SCAAR	Repeat revascularisation with PCI in the previously treated vessel in a patient presenting with NSTEMI or STEMI.
Paper III Paper IV Paper V Paper VI	Any/Repeat PCI	SCAAR	Any non-staged revascularisation with PCI.
Paper IV	Restenosis	SCAAR	Significant restenosis (≥50% luminal obstruction) of the previously treated lesion for a patient admitted to coronary angiograph based on a clinical diagnosis.

Study design and study population

Paper I

All patients with CCS undergoing angiography in Sweden between 2010 and 2020 were included. Patients with no significant stenosis, patients referred to CABG and patients not on guideline-recommended medical therapy were excluded. The remaining patients were stratified into two groups according to treatment strategy: medical therapy alone versus PCI and medical therapy. Propensity score (PS) matching was carried out based on clinically relevant baseline variables. The primary outcome was net adverse clinical events within 5 years, defined as the composite of all-cause mortality, myocardial infarction, bleeding, and urgent revascularisation.

Paper II

All patients with CCS undergoing angiography in Sweden between 1 January 2014 and 16 January 2020 were included. Patients with previous revascularisation, age

≥80 years, patients with no significant stenosis and patients that died within 2 years were excluded. The remaining patients were stratified into four groups according to treatment strategy: no revascularisation, incomplete PCI, complete PCI, and CABG. The study was designed as a case crossover study where each patient was served as their own control. The control period was defined as 1-year preceding angiography, and the case period as 1–2 years after angiography. The primary outcome was the use of long-acting nitrates, defined as a dispensed prescription during the case or control period.

Paper III

All segments treated with a DCB in Sweden between 13 June 2013 and 16 May, 2023 were included. Patients presenting with cardiogenic shock, cardiac arrest and left main disease were excluded, as well as lesions treated with DES implantation in the same segment, unsuccessful procedures, use of multiple DCB in the same segment, and PCI procedures with multiple varying DCB inflation times. Two groups were defined according to DCB inflation time, <30 seconds or and ≥30 seconds. Multivariable Cox regression was applied to reduce the risk of confounding. The primary outcome was target segment revascularisation (TSR) within 1 year, defined as a repeat revascularisation in the same segment.

Paper IV

All patients treated with DCB therapy between 1 January 2022 and 16 May 2025 were included. Exclusion criteria included cardiogenic shock, cardiac arrest, stent implantation in the same segment as the DCB, and use of both PCB and SCB within the same procedure. Two groups were defined according to DCB type: PCB and SCB. PS-matching and multivariable Cox regression were applied to reduce the risk of confounding. The primary outcome was TSR within 1 year, defined as a repeat revascularisation in the same segment.

Paper V

All segments with small (device diameter <3.0 mm), non-complex de novo coronary artery lesions treated with DCB or DES in Sweden between 1 January 2016, and 16 May 2024 were included. Non-complex lesions were defined as American College of Cardiology and American Heart Association Type A or B1 lesion. [127] Cardiogenic shock, cardiac arrest, bifurcations or left main lesions, graft lesions, chronic total occlusions, in-stent restenosis, lesion length >30 mm, or mixed DCB/DES treatment were excluded. PS-matching was performed to reduce confounding. The primary outcome was a composite of TLR, target vessel myocardial infarction and all-cause mortality, at 5-year follow-up.

Paper VI

All segments with in-stent restenosis in Sweden between 11 June 2013 and 14 January 2022 were included. Three groups were defined according to treatment strategy: DCB, DES, and POBA. Lesions treated with bare-metal stents, first-generation DES, degradable scaffolds, rare stent types, CABG, or medical therapy alone were excluded. To reduce confounding, multivariable Cox regression analyses were applied. The primary outcome was TLR within a 5-year follow-up.

Statistical analysis

Statistical comparison of baseline characteristics

In all studies of this thesis, baseline characteristics were summarised using descriptive statistics. Categorical variables were presented as frequencies and percentages, while continuous variables were summarised as means with standard deviations or medians with interquartile ranges, depending on their underlying distribution. For comparisons of categorical variables between groups, the Chi-squared test was used. [128] Continuous variables were compared using Students t-test when two groups were analysed and the assumptions of normality and homogeneity of variances were deemed acceptable. For comparisons involving more than two groups, analysis of variance (ANOVA) was employed.

Kaplan-Meier estimates and log-rank test

In all studies included for this thesis, Kaplan-Meier estimates and log-rank test were used. Kaplan-Meier is used to estimate the cumulative incidence of an outcome over the follow-up period in a time-to-event analysis. The Kaplan-Meier estimator is a non-parametric approach that provides an estimate of the survival function, while accounting for right-censored observations that arise when a patient has no remaining follow-up or remain without an event at the end of the study period. This method is particularly suitable for clinical and registry-based studies with heterogeneous follow-up times. [129] Kaplan-Meier curves were constructed to display the estimates graphically, with numbers at risk reported at predefined time intervals to aid interpretation and transparency of the estimates. Group comparisons of survival distributions were performed using the log-rank test. The log-rank test is non-parametric and evaluates whether there are significant differences between groups in the hazard of experiencing an event over time. [130] The log-rank test relies on the assumptions of proportional hazards and non-informative censoring. While the test provides a global comparison across the entire follow-up period, it does not quantify effect size or allow for adjustment for confounding variables. Therefore, Kaplan-Meier estimates and log-rank tests were mainly used for unadjusted comparisons. [131]

Propensity score

PS-matching was used in **Paper I**, **Paper II**, **Paper IV**, and **Paper V**. PS-matching is a widely used statistical technique in observational research to reduce confounding. In registry-based studies, treatment allocation is often influenced by patient characteristics, disease severity, and physician preference, leading to systematic differences between treatment groups. PS-matching addresses this issue by balancing observed baseline covariates between groups, reducing bias due to measured confounders. The PS is defined as the conditional probability of receiving a given treatment, given a set of observed covariates. This concept was formally introduced by Paul R. Rosenbaum and Donald B. Rubin, who demonstrated that, conditional on the PS, the distribution of observed baseline covariates is independent of treatment assignment. [132] In this thesis, PS were calculated using logistic regression, where treatment assignment is modelled as a function of baseline covariates. These covariates were selected based on prior evidence. Importantly, only upstream variables should be included in the model, as inclusion of post-treatment variables may introduce bias. Variables related to the exposure but not the outcome should further not be included. [133] The goal of the PS model is to achieve adequate covariate balance between groups. [134] Once estimated, PS can be applied using several approaches, including matching, stratification, inverse probability of treatment weighting, or covariate adjustment. [135] Matching involves pairing treated and untreated individuals with similar PS. For this thesis, a one-to-one nearest-neighbour matching using a calliper method was employed. A calliper defines the maximum allowable difference in PS between matched individuals. Several methodological considerations are critical when implementing PS-matching. First, assessment of covariate balance after matching is essential, for example using standardised mean differences. A standardised mean difference below 0.1 is commonly considered indicative of acceptable balance. Visual tools such as Love plots can further aid in evaluating balance across covariates before and after matching. Second, PS-matching relies on sufficient overlap in PS-distributions between groups. Individuals with extreme PS, for whom no suitable match exists, may be excluded from the matched cohort. While this improves internal validity, it may limit external validity. Third, PS matching addresses confounding due to measured variables only.

Cox regression

Univariable and/or multivariable Cox regression was used in **Paper I**, **Paper III**, **Paper IV**, **Paper V**, and **Paper VI**. Time-to-event outcomes were analysed using Cox regression, which estimates HR and corresponding CI. [136] Cox regression relates the hazard of the event of interest to a set of covariates without requiring specification of the underlying baseline hazard function, making it well suited for clinical and registry-based survival data. Multivariable Cox regression models were constructed to adjust for clinically relevant baseline covariates selected a priori based on prior evidence. Covariates were entered simultaneously into the model,

and results were reported as adjusted HR with 95% CI. The proportional hazards assumption was assessed using standard diagnostic approaches, including examination of Schoenfeld residuals and inspection of log-log survival plots. In cases where violations of the proportional hazards assumption were detected, appropriate model adaptations were considered. [137]

Subgroup analysis

Subgroup analyses were performed in all studies included in this thesis. These analyses were conducted to explore whether the association between treatment and outcome differs across predefined patient, lesion, or procedural characteristics. Subgroups were specified a priori based on clinical relevance. In addition to being hypothesis-generating, subgroup analyses can be used to investigate potential confounding by assessing the consistency of effect estimates across clinically relevant strata. Concordant results across subgroups may support the robustness of the primary analysis, whereas marked heterogeneity may suggest residual confounding or effect modification. Formal interaction terms were used to test for heterogeneity between subgroups. Given the reduced statistical power and increased risk of type I error associated with multiple testing, results from subgroup analyses are interpreted cautiously and in the context of the overall findings.

Instrumental variable analysis

Instrumental variable analysis was used in **Paper III**. Instrumental variable analysis was used to address potential unmeasured confounding in the association between exposure and outcome. Instrumental variable methods allow for consistent estimation of causal effects in the presence of unobserved confounders. A valid instrument must be associated with the exposure of interest, must not be associated with unmeasured confounders, and must influence the outcome solely through its effect on the exposure. [138] The instrumental variable analysis was conducted using a two-stage estimation approach, in which the exposure was first modelled of the instrument and relevant covariates, followed by estimation of the outcome as a function of the predicted exposure from the first stage. This approach yields an estimate of the causal effect among individuals whose exposure status is influenced by the instrument (the local average treatment effect). Instrument strength was evaluated using standard diagnostic measures from the first-stage model.

Win ratio

Win ratio was used in **Paper I**. Win ratio is a method primarily used to analyse composite outcomes. [139] The method allows the components of the outcome to be ordered according to clinical importance. Outcome is then assessed in a hierarchical structure, prioritising the most clinically meaningful event first, for example mortality. Each comparison results in either a win, loss or tie. The total number of wins in the treatment group is then divided by the number of wins in the control

group to calculate the win ratio. Thus, a win ratio >1 favour the treatment group, assuming the events are not beneficial for the patient. There are two main approaches used for win ratio: matched- and unmatched win ratio. For matched win ratio, each patient in the treatment group is paired with a patient in the control group, which can be applied for example following one-to-one PS-matching. This approach reduces confounding by ensuring that comparisons are made between clinically comparable patients. In contrast, the unmatched win ratio compares each patient in the treatment group with all patients in the control group. This method is best applied when the groups are of uneven size or when overall baseline characteristics are similar between the two groups.

E-values

E-values was used in **Paper II**, **Paper III**, and **Paper IV**. E-values are used to evaluate the robustness of the observed associations to potential unmeasured confounding. [140] The E-value represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away the observed association. E-values were calculated for both the point estimate and the CI. Larger E-values indicate greater robustness to unmeasured confounding, whereas smaller values suggest that relatively weak confounding could potentially account for the observed findings. E-values were used as a complementary sensitivity analysis alongside conventional confounding control methods.

Ethical considerations

This research was conducted in accordance with the principles of the Declaration of Helsinki and were approved by the Swedish Ethical Review Authority. [141] All studies included in this thesis are based on observational data derived from nationwide Swedish quality registries. These registries are established for quality assurance and research purposes within the Swedish healthcare system and are governed by strict legal and ethical regulations. Due to the registry-based and non-interventional nature of the studies, individual informed consent was waived in accordance with Swedish law. All data were pseudonymised prior to analysis, and no access to directly identifiable personal information were available to the researchers. The use of nationwide registry data enables large-scale evaluation of real-world clinical practice, while minimising risk of harm to individual patients. No additional interventions, examinations, or changes to standard clinical care were introduced as part of this research. Consequently, participation in the registries and inclusion in the present studies did not entail any direct risks or burdens for the individual patients. Data handling and storage were performed in accordance with the General Data Protection Regulation and Swedish data protection legislation.

Precaution was taken to protect the privacy of the patients included in the registries, access to the data was restricted to the individuals involved in the research. Results are presented exclusively at an aggregated level, ensuring that no individual patient can be identified. An important ethical consideration in registry-based research is the balance between patient privacy and the societal value of large-scale observational studies. By enabling the evaluation of treatment strategies in unselected patient populations, registry-based studies provide essential knowledge that may improve future patient care, inform clinical guidelines, and identify areas where randomised trials are lacking.

Results

Paper I

Baseline characteristics

After PS-matching, two groups of 7220 patients with CCS were formed. Baseline characteristics were similar between the two groups. The mean age was 68.3 years, 77.8% of the patients were males, 77.0% had symptoms corresponding to Canadian Cardiovascular Society scores I–II, and 62.7% had one or two-vessel disease.

Main outcome

After 5 years, PCI was associated with lower rates of net adverse clinical events compared with medical therapy alone (matched win ratio 1.28 [95% CI 1.20–1.36], p<0.001) (**Figure 4**), myocardial infarction (matched win ratio 1.15 [95% CI 1.04–1.28], p=0.008), urgent revascularisation (matched win ratio 1.85 [95% CI 1.69–2.03], p<0.001) and cardiovascular mortality (matched win ratio 1.15 [95% CI 1.00–1.34], p=0.044). No difference was observed for all-cause mortality (matched win ratio 1.10 [95% CI 0.99–1.21], p=0.073), bleeding (matched win ratio 0.96 [95% CI 0.85–1.08], p=0.502) and stroke (matched win ratio 1.01 [95% CI 0.86–1.20], p=0.867). At 10-year follow-up, PCI was also associated with lower rates of all-cause mortality (matched win ratio 1.10 [95% CI 1.01–1.20], p=0.032).

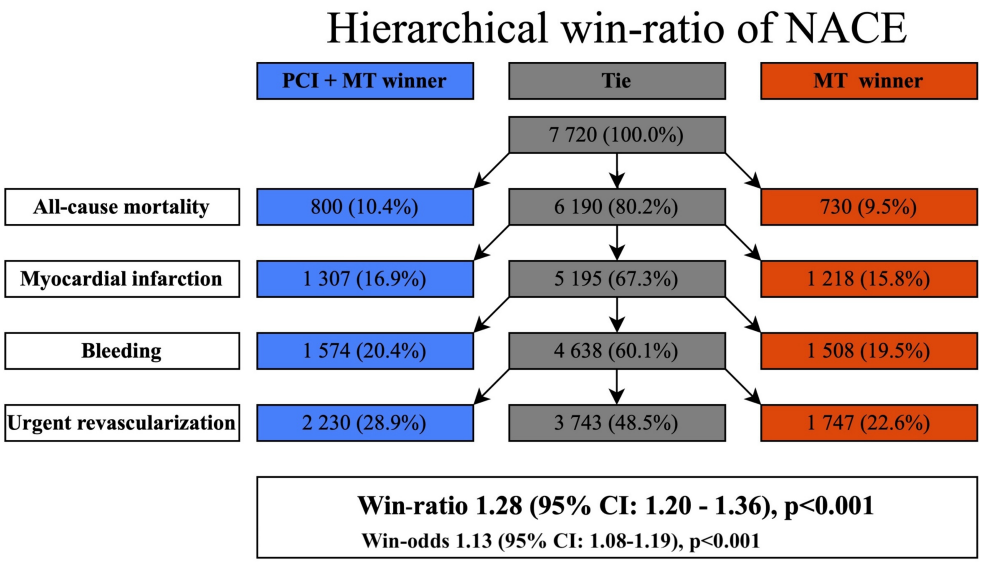

Figure 4. Hierarchical win ratio analysis of NACE.
NACE was defined as a composite of (1) all-cause mortality, (2) myocardial infarction, (3) bleeding, and (4) urgent revascularisation. MT=medical therapy; NACE=net adverse clinical events; PCI=percutaneous coronary intervention. Reproduced from von Koch S, et al. Percutaneous coronary intervention plus medical therapy versus medical therapy alone in chronic coronary syndrome: a propensity score-matched analysis from the Swedish Coronary Angiography and Angioplasty Registry. Heart. 2024 Oct 28;110(22):1307-1315. Re-use permitted under CC BY-NC.

Paper II

Baseline characteristics

A total of 15955 patents with CCS were included. Among these patients, 3207 (20.1%) underwent CABG, 7525 (47.2%) had complete revascularisations with PCI, 2180 (13.7%) had incomplete revascularisation with PCI, and 3043 (19.1%) had no revascularisation. The mean age was 66.2 years, and 77.7% of the patients were male. The CABG group had the largest proportion of patients with three-vessel disease and/or left main disease (84.3%). Patients in the complete revascularisation with PCI group had the lowest mean age at 65.4 years. The incomplete revascularisation with PCI group had the largest proportion of patients with symptoms corresponding to Canadian Cardiovascular Society scores III-IV at baseline (34.6%). The no-revascularisation group had the largest proportion of females (25.6%).

Main outcome

Revascularisation was associated with a decreased use of long-acting nitrates for CABG (from 30.8% to 4.9%; risk-ratio (RR) 0.16 [95% CI 0.13–0.19], p-value<0.0001), complete revascularisation with PCI (from 22.3% to 12.8%; RR 0.58 [95% CI 0.53–0.62], p-value<0.0001) and incomplete revascularisation with PCI (from 27.6% to 22.7%; RR 0.82 [95% CI 0.73–0.93], p-value=0.0014). No difference in long-acting nitrates use was observed for no revascularisation (from 28.4% to 28.1%; RR 0.99 [95% CI 0.90–1.09], p-value=0.85) (**Figure 5**).

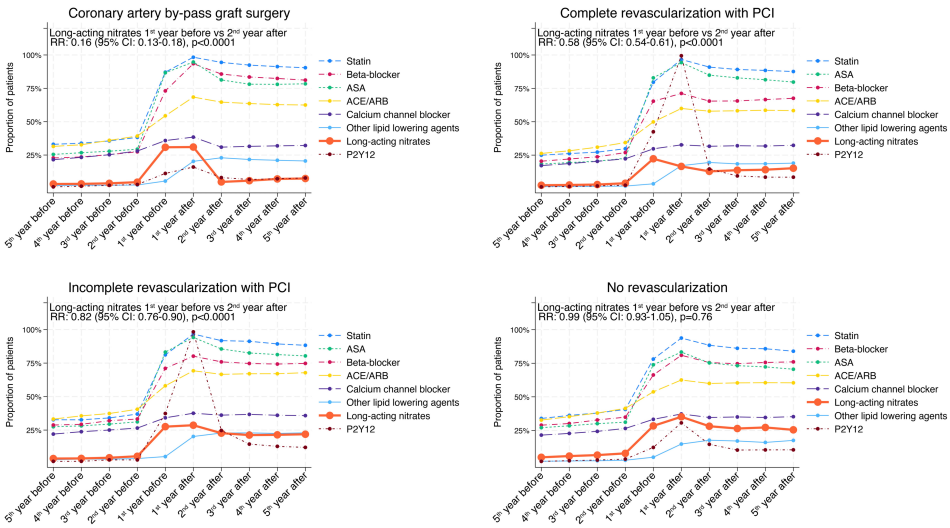

Figure 5. Change in medical therapies before and after angiography.
Use of long-acting nitrates was compared between the periods 1 year to angiography and 1–2 years after angiography and was assessed using univariable conditional Poisson regression. Reproduced from von Koch S, et al. Long-acting nitrate use before and after revascularization to evaluate angina in chronic coronary syndrome: a case-crossover study from SCAAR. Lancet Reg Health Eur. 2025 Oct 28;60:101507. Re-use permitted under CC BY.

Paper III

Baseline characteristics

For this study, 11238 patients with 12429 DCB-treated segments were eligible. The mean age was 68.5 years and 76.4% were male. The <30 seconds group (mean time 22.8 seconds) comprised 412 patients and 446 segments, while the ≥30 second group comprised of 10826 patients and 11983 segments (mean time 31.8 seconds). Age, indication, angiographic findings, and choice of P2Y12 inhibitor were similar between the two groups. For the <30 seconds group and the ≥30 seconds group, respectively, the proportions of previous myocardial infarction were 53.7% and 46.9%, and the proportion of previous PCI was 62.9% and 57.3%. The <30 seconds

group more often had lesions located in proximal segments (30.9% and 18.3%) and were more often treated with a DCB with a diameter of >3 mm (22.2% and 15.3%).

Main outcome

After a 1-year follow-up period, a ≥30 seconds inflation time was associated with lower rates of TSR compared with an inflation time of <30 seconds (3.2% vs 6.4%; adjusted HR 0.47 [95% CI 0.32–0.69], p≤0.001), target vessel myocardial infarction (1.8% vs 5.3%; adjusted HR 0.32 [95% CI 0.21–0.50], p≤0.001), target vessel revascularisation (5.2% vs 9.9%; adjusted HR 0.50 [95% CI 0.36–0.69], p≤0.001), myocardial infarction (4.2% vs 8.4%; adjusted HR 0.48 [95% CI 0.33–0.70], p≤0.001) and repeat PCI (8.8% vs 13.9%; adjusted HR 0.60 [95% CI 0.45–0.80], p≤0.001). No difference was observed for all-cause mortality (3.7% vs 4.9%; adjusted HR 0.98 [95% CI 0.60–1.60], p=0.93). In the sensitivity using a Cox regression with restricted cubic splines, as shown in **Figure 6**, the HR of TSR was elevated for inflation times below 30 seconds, followed by a plateau (p for non-linearity 0.040).

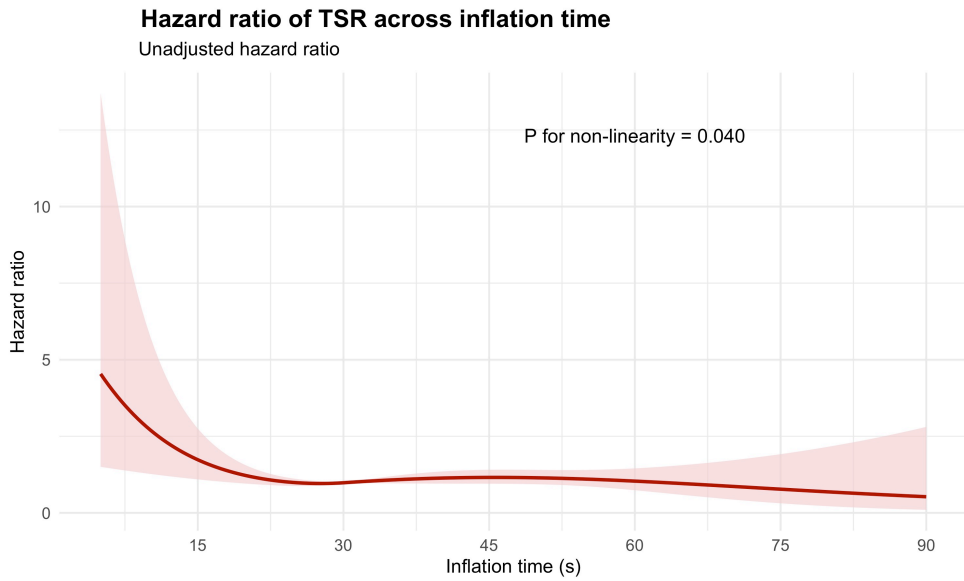

Figure 6. Spline analysis.
Analysis exploring 1-year HR of TSR across inflation time (5–90 s). Reproduced from von Koch S, et al. Impact of drug-coated balloon inflation time on outcome after percutaneous coronary intervention: An observational study from the Swedish Coronary Angiography and Angioplasty Registry. Unpublished manuscript.

Paper IV

Baseline characteristics

For this study, 7244 patients with 8357 DCB-treated segments were included. The PCB group included 6804 patients and 7855 segments, while the SCB group included 440 patients and 502 segments. Patients in the PCB group were more likely to undergo stent implantation during the same procedure (58.6% vs 50.9%) while the SCB group were more likely to have had undergone a previous PCI (60.0% vs 54.1%). Segments treated with SCB more often presented with in-stent restenosis (34.3% vs 28.8%) and intracoronary imaging was more frequently used (28.7% vs 22.3%). Following PS-matching, two groups of 501 treated segments each were formed. Baseline characteristics were well balanced between groups following the PS-matching.

Main outcome

After a 1-year follow-up period, no difference was observed between PCB and SCB in terms of TSR (3.3% vs 5.8%; adjusted HR 1.37 [95% CI 0.83–2.25], p=0.22), target vessel revascularisation (5.2% vs 8.1%; adjusted HR 1.24 [95% CI 0.78–1.97], p=0.37), restenosis (2.8% vs 4.4%; adjusted HR 1.44 [95% CI 0.85–2.44], p=0.17), myocardial infarction (3.1% vs 4.9%; adjusted HR 0.74 [95% CI 0.41–1.32], p=0.31), repeat PCI (8.8% vs 10.8%; adjusted HR 1.04 [95% CI 0.72–1.51], p=0.82) and all-cause mortality (4.4% vs 3.2%; adjusted HR 1.37 [95% CI 0.34–1.15], p=0.13) (**Figure 7**).

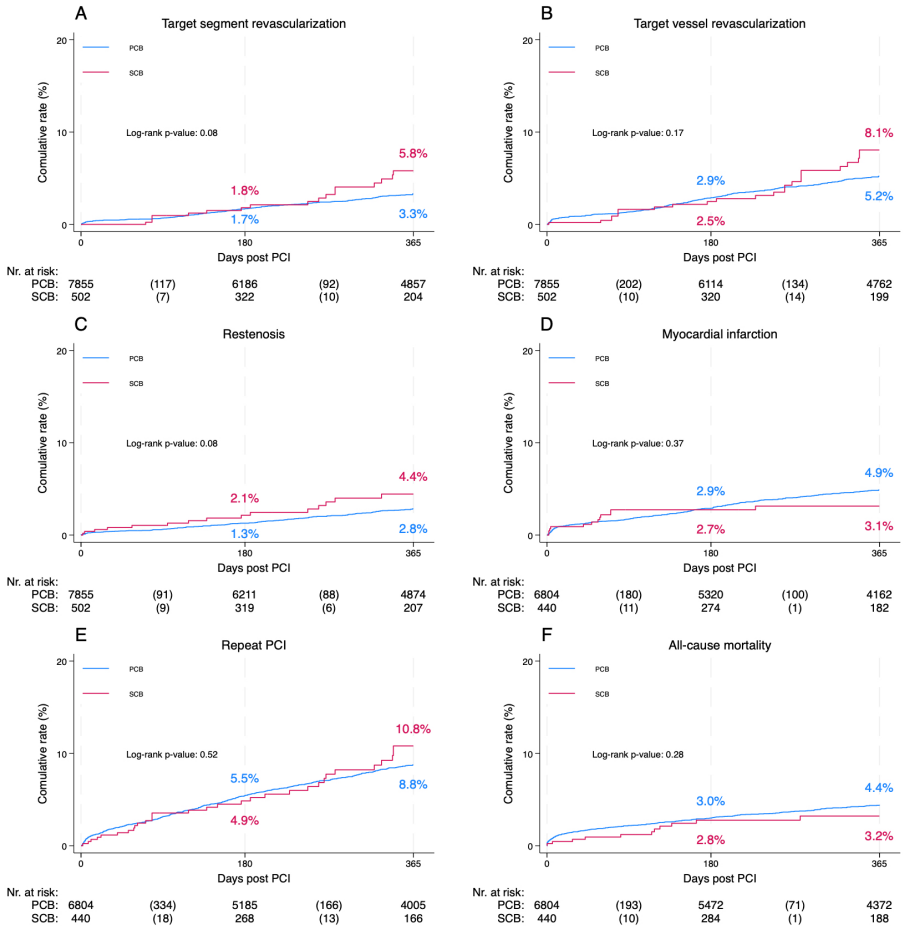

Figure 7. Kaplan-Meier curves.
Illustrating unadjusted event rates of SCB and PCB. Reproduced from von Koch S, et al. Paclitaxel-Coated Balloons Versus Sirolimus-Coated Balloons for Coronary Artery Lesions: A Nationwide Cohort Study from SCAAR. Unpublished manuscript.

Paper V

Baseline characteristics

Two groups of 1439 segments <3.0 mm treated with DCB and DES were formed after PS-matching. The baseline characteristics were similar across the two groups. The mean age was 68.8 years, 73.0% of the patients were males, and 47.3% had multivessel disease. Frequently treated segments, for DCB and DES respectively, included first diagonal (25.7% vs 27.5%), first marginal branch (13.4% vs 13.8%),

distal left anterior descending artery (11.1% vs 11.5%) and right posterior descending artery (8.3% vs 7.6%).

Main outcome

After 5 years, the use of DES was associated with lower rates of the primary composite outcome of TLR, target vessel myocardial infarction and all-cause mortality compared to DCB (19.2% vs 14.7%; HR 0.76 [95% CI 0.61–0.95], p=0.016) (**Figure 8**). DES was also associated with lower rates of target vessel revascularisation (7.7% vs 5.1%; HR 0.71 [95% CI 0.50–0.99], p=0.046), target vessel myocardial infarction (3.4% vs 1.3%; HR 0.52 [95% CI 0.29–0.94], p=0.029) and myocardial infarction (9.5% vs 7.0%; HR 0.72 [95% CI 0.53–0.98], p=0.038). No significant difference was observed between the two groups for TLR (3.4% vs 2.0%; HR 0.67 [95% CI 0.40–1.13], p=0.13), all-cause mortality (15.7% vs 13.1%; HR 0.82 [95% CI 0.64–1.05], p=0.11), and repeat PCI (13.5% vs 11.8%; HR 0.84 [95% CI 0.66–1.08], p=0.18).

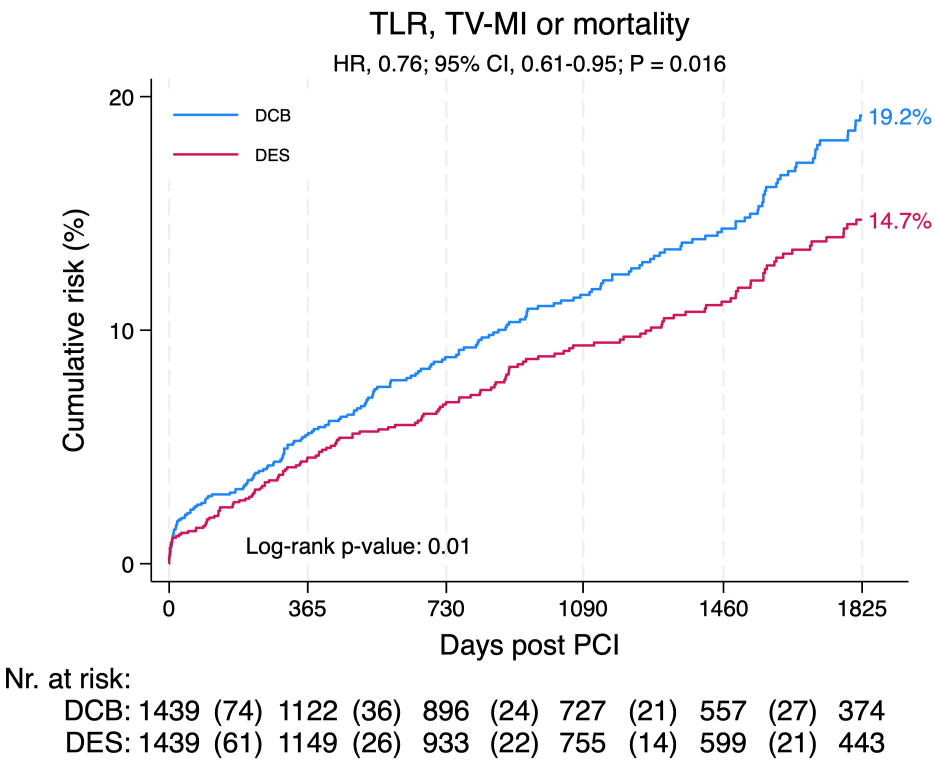

Figure 8. Kaplan-Meier curve of the primary composite outcome.
Illustrating event rate after PS-matching. TV-MI = target vessel myocardial infarction. Reproduced from von Koch S, et al. Drug-coated balloons versus drug-eluting stents for small non-complex de novo

coronary artery lesions: A segment-level propensity score matched analysis from SCAAR. Cardiovasc Revasc Med. 2025 Nov;80:88-95. Re-use permitted under CC BY.

Paper VI

Baseline characteristics

In this study, a total of 10561 lesions from 9062 patients were included. The mean age was 69.6 years, and 78.2% of the patients were men. Among the included lesions, 3322 (31.5%) were treated with DCB, 6096 (57.7%) with DES, and 1143 (10.8%) with POBA.

Main outcome

After a 5-year follow-up period, compared to POBA, DCB was associated with a lower risk of TLR (21.9% vs 21.7%; adjusted RR 0.69 [95% CI 0.57–0.82], p<0.001), all-cause death (22.0% vs 33.8%; adjusted RR 0.72 [95% CI 0.59–0.88], p=0.001), and cardiovascular death (11.5% vs 22.0%; adjusted HR 0.59 [95% CI 0.44–0.77], p<0.001). No difference was observed for myocardial infarction (26.6% vs 27.1%; adjusted RR 1.04 [95% CI 0.85–1.27], p=0.728) and any PCI (34.0% vs 33.5%; adjusted RR 0.85 [95% CI 0.72–1.01], p=0.058).

When DCB was compared with DES, DCB was associated with higher rates of TLR (21.9% vs 15.5%; adjusted HR 1.20 [95% CI 1.06–1.37], p=0.005). No difference was observed for all-cause death (22.0% vs 22.3%; adjusted HR 0.92 [95% CI 0.81–1.04], p=0.193), cardiovascular death (11.5% vs 12.3%; adjusted HR 0.84 [95% CI 0.70–1.01], p=0.062), myocardial infarction (26.6% vs 23.9%; adjusted HR 1.06 [95% CI 0.95–1.19], p=0.317), and any PCI (34.0% vs 30.9%; adjusted HR, 0.97 [95% CI, 0.88–1.07], p=0.485).

In the DCB versus POBA subgroup analysis of TLR, DCB was more advantageous when used for patients ≥80 years (p-value of interaction=0.023) and for bare-metal stent in-stent restenosis (p-value of interaction=0.003) (**Figure 9**). In the DCB versus DES subgroup analysis of TLR, DCB angioplasty was more advantageous when used for patients ≥80 years (p-value of interaction=0.001).

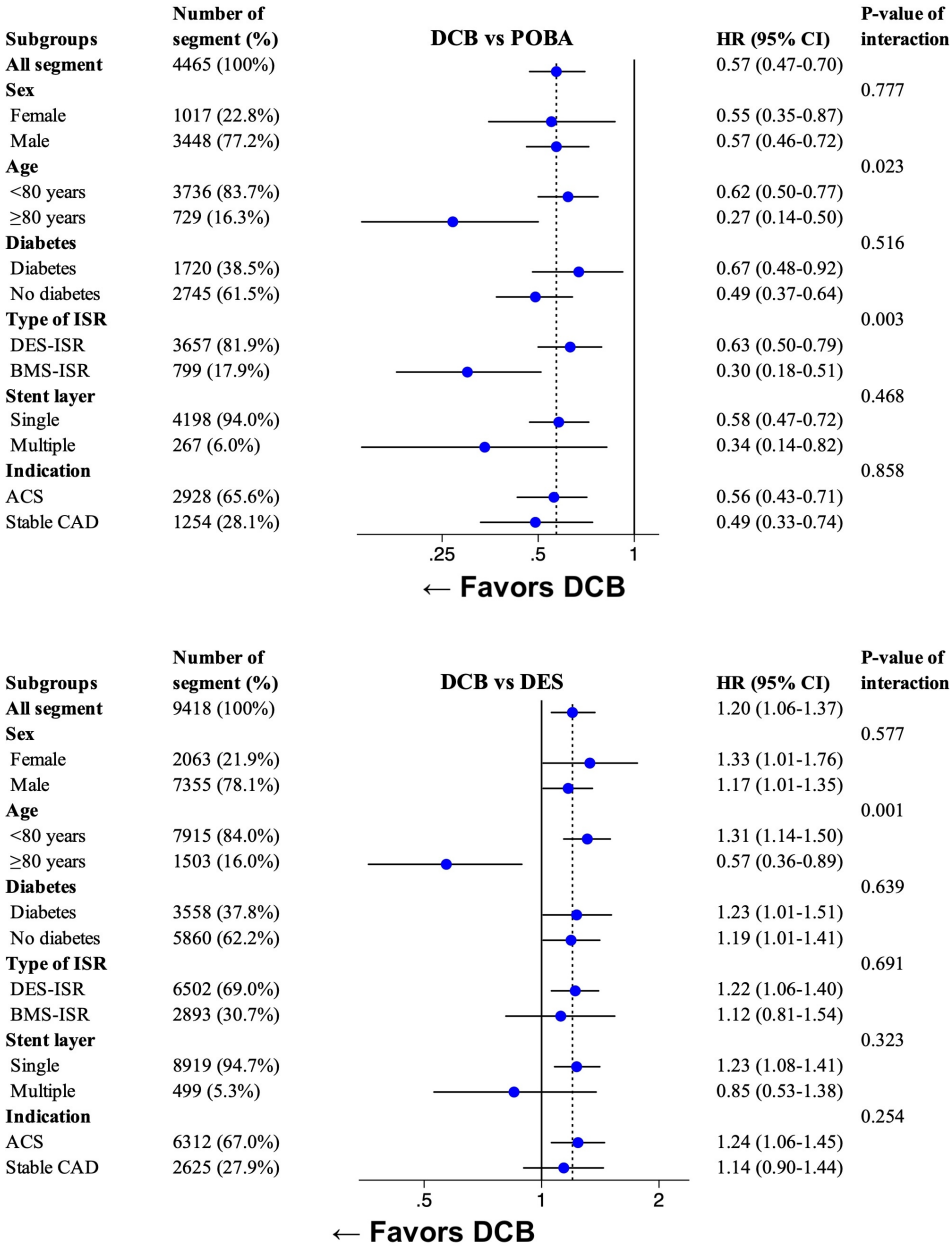

Figure 9. Subgroup analysis.

Subgroups were analysed on TLR after 5 years using an adjusted Cox regression model. Reproduced from von Koch S, et al. Drug-Coated Balloons Versus Drug-Eluting Stents or Plain Old Balloon Angioplasty: A Long-Term in-Stent Restenosis Study. J Am Heart Assoc. 2024 Dec 3;13(23):e036839. Re-use permitted under CC BY.

Discussion

This thesis evaluated several aspects in the treatment of coronary artery disease, the leading cause of mortality worldwide. For patients with CCS, the use of PCI has become a common treatment strategy, but despite this its impact remains uncertain. Moreover, despite a significant advance in interventional cardiology, adverse cardiovascular events following PCI continues to remain an important challenge. Consequently, the evaluation of novel PCI techniques, aimed at improving long-term outcomes, is a key focus of contemporary cardiovascular research. Over the past two decades, several new PCI strategies have been developed with the shared objectives of minimising the risk of stent complications and permanent presence of intravascular foreign material. While early enthusiasm for fully bioresorbable scaffolds was tempered by safety concerns highlighted in trials such as ABSORB III and AIDA, the concept of "leaving nothing behind" has continued to drive innovation. [48,142] In light of this, DCB have been rapidly adopted worldwide. The purpose of this research is to investigate the role of PCI in patients with CCS and the role of DCB in PCI in contemporary practice.

The findings of this thesis contribute to the evolving field of CCS and DCB by providing real-world evidence from nationwide Swedish registries. Overall, the results of this thesis indicate that PCI may improve long-term survival in patients with CCS and relieve angina symptoms. The results also indicate that ensuring sufficient DCB inflation time (exceeding 30 seconds) is a prerequisite for optimal DCB efficacy. Beyond this threshold, however, neither prolonged inflation nor specific drug choice was associated with superior outcomes. Furthermore, the results support the continued role of contemporary DES as the standard of care in small-vessel disease and in-stent restenosis. In the following passages, the studies will be discussed in further detail.

The role of coronary revascularisation in patients with CCS has been extensively investigated in several large randomised clinical trials, and the results of these trials has substantially shaped contemporary guidelines. Despite the valuable knowledge provided by these studies, implementation in clinical practice requires consideration of the context in which they were conducted. Many of these trials investigated revascularisation in CCS before the widespread implementation of contemporary antithrombotic therapy, lipid-lowering treatment, and modern PCI techniques. Considering this, the overall impact of revascularisation on long-term prognosis in CCS remains uncertain. In **Paper I**, PCI was associated with a lower rate of all-

cause mortality at 10-years follow-up among patients receiving optimal medical therapy. Although the results did not reach statistical significance in the ISCHEMIA trial, the direction of the effect is consistent with findings in **Paper I**. [13] Evidence supporting a benefit of revascularisation has been more clearly demonstrated for CABG. In the STICHES trial, CABG was associated with a significant reduction in all-cause mortality at 10 years among patients with left ventricular systolic dysfunction. [15] Interestingly, the magnitude of the treatment effect observed in **Paper I** was numerically smaller than that reported in the STICHES study. Although direct comparisons between studies should be made with caution, one possible explanation for the observed differences between revascularisation modalities is that CABG may provide a more complete revascularisation and protect the coronary circulation from plaque progression proximal of the anastomosis compared with PCI. However, despite the potential advantages of CABG, PCI remains an important strategy, as many patients with CCS are not eligible for surgical revascularisation because of frailty or patient preference. The findings of **Paper II** further support the clinical relevance of revascularisation in CCS. In this study, revascularisation was associated with a lower subsequent use of long-acting nitrates, suggesting symptom improvement. The largest effect was observed in the CABG group, which may reflect a more durable revascularisation. These results extend the evidence provided by the ORBITA trials. The first ORBITA trial was a placebo-controlled study evaluating PCI in patients with CCS and single-vessel disease, demonstrating that an important component of the symptomatic improvement may be derived from the placebo effect. [19] Subsequently, the ORBITA-2 trial demonstrated that PCI significantly reduced angina frequency compared with a placebo procedure when antianginal therapy was withdrawn prior to randomisation. [20] Taken together, these trials highlight the complexity of symptom assessment in CCS. On the one hand, they underscore the placebo effect and the subjective nature of angina symptoms. On the other hand, they demonstrate that PCI may provide symptomatic relief. A key limitation of the ORBITA trials, is their limited generalisability to routine clinical practice. In the first ORBITA trial, patients underwent intensive optimisation of antianginal therapy prior to randomisation. Conversely, in ORBITA-2, antianginal therapy was withdrawn prior to randomisation. In everyday clinical practice, many patients with CCS receive intermediate levels of antianginal therapy rather than the extremes represented in these trial designs. Consequently, real-world registry data, such as those presented in this thesis provide important complementary perspectives in broader patient populations.

In the evaluation of patients treated for non-complex de novo small-vessel disease (**Paper V**) and in-stent restenosis (**Paper VI**), this thesis found that DCB and DES demonstrated similar outcomes during the first 6 months of follow-up. This was reflected by overlapping Kaplan-Meier curves of TLR. These observations are consistent with the early angiographic equivalence observed in randomised trials – such as PEPCAD II, DARE, BIOLUX-RCT, BELLO and RESTORE SVD – that

have demonstrated non-inferior angiographic and clinical outcomes for DCB compared with DES at 6–9 months in selected patient populations. [98,100,106,143,144] These studies have established DCB as an effective alternative to DES based largely on early surrogate markers of efficacy. The results of these studies support the proof of concept of DCB and suggest that the antiproliferative effect of DCB is sufficient to suppress early neointimal hyperplasia and prevent short-term restenosis to a degree comparable with DES. While angiographic endpoints provide mechanistic insight into DCB effectiveness, the long-term clinical implications remain less certain, particularly beyond the first year. Notably, beyond 6–12 months follow-up, the Kaplan-Meier curves in **Paper V** and **Paper VI** began to diverge in favour of DES, with lower TLR rates during long-term follow-up. This temporal pattern highlights an important distinction between short-term angiographic efficacy and long-term clinical durability. While DCB deliver a high local drug concentration over a short period, DES provide sustained drug elution and a permanent mechanical scaffold, which may offer continued protection against late luminal narrowing and disease progression. In contrast, the absence of a scaffold following DCB angioplasty may render the treated segment more susceptible to late recoil, negative remodelling, or progression of atherosclerosis. These observations underscore the limitation of relying primarily on early angiographic endpoints, such as late lumen loss, to predict long-term clinical outcomes. The present findings complement existing randomised trial data by providing long-term follow-up data of DCB and DES. However, it is important to note that benefits in clinical outcomes such as TLR, does not always convey a survival benefits. In the REC-CAGEFREE I trial, a strategy of DCB angioplasty with rescue stenting did not achieve noninferiority when compared to an intended DES implantation strategy at 2 years for de novo lesions in terms of the device-oriented composite endpoint (cardiovascular death, clinically and physiologically indicated TLR, and target vessel myocardial infarction). [104] At the 3-year follow-up study of REC-CAGEFREE I, the strategy with DCB remained inferior to DES. [145] These results were mainly driven by lower rates of TLR in the DES arm from elective procedures, and no difference in mortality was observed. This aligns with the results of **Paper V** and **Paper VI**, which found no difference in mortality at 5-years between DCB and DES for small non-complex de novo lesions or in-stent restenosis.

Despite this, the results of this thesis also suggest that DCB may serve as a viable alternative in selected clinical situations when DES is clinically undesirable. This early equivalence may be particularly relevant for patients with limited life expectancy, where short-term safety and efficacy are of most importance. In **Paper VI**, a significant subgroup interaction was observed in the age subgroup analysis, with a more favourable result observed for DCB in patients ≥80 years. Elderly patients are of higher bleeding risk and competing non-cardiovascular mortality, where the potential long-term benefits of permanent stent implantation may be attenuated. [146] In addition, DCB may serve as a good alternative when DES implantation is technically challenging, such as in cases of dual layer in-stent

restenosis. An additional potential advantage of DCB-based PCI is the possibility of shorter or less intensive dual-antiplatelet therapy regimens, but the optimal duration and composition of antiplatelet therapy following DCB remains insufficiently studied, and randomised trials specifically addressing dual-antiplatelet therapy strategies warranted.

In **Paper VI**, DCB was associated with superior outcomes compared to POBA, underscoring the importance of local drug delivery in reducing restenosis and adverse events. This finding reinforces the mechanistic rationale for DCB technology and aligns with randomised trials such as the AGENT IDE trial, demonstrating the inferiority of POBA in contemporary PCI practice. [112] In the AGENT IDE trial, treatment with a DCB was associated with a favourable clinical outcome at 1 year compared with POBA, the event rate of target lesion failure was 17.9% in the PCB group and 28.6% in the POBA group (p=0.003). However, this treatment effect attenuated during longer follow-up, with a less pronounced difference observed at 2 years, with a target lesion failure rate of 27% in the DCB group and 34% in the POBA group (p=0.04) (data presented at CRT 2025). Similarly, in **Paper VI**, DCB was associated with improved short- to mid-term outcomes compared with POBA, while long-term event rates tended to converge when examining the Kaplan-Meier curve of TLR. Again, these observations suggest that the primary benefit of DCB in in-stent restenosis may be driven by early suppression of neointimal hyperplasia rather than durable prevention of late restenosis processes. The concordance between randomised evidence from AGENT IDE and real-world registry data strengthens the validity of these findings and highlights the importance of long-term follow-up when evaluating DCB efficacy. Overall, the results of this thesis support the concept that while drug delivery is crucial, mechanical support remains a cornerstone of contemporary PCI to restore and maintain coronary vessel integrity.

This thesis includes one study, **Paper III**, examining the association between DCB inflation time and clinical outcomes. Comparing a standard inflation time of ≥30 seconds with <30 seconds, ≥30 seconds was associated with a better outcome compared to shorter inflation times. These findings are consistent with the inflation durations used in major DCB trials where inflation times around 30–60 seconds were applied, including BASKET-SMALL 2 (mean 48.5 s [SD 28.2 s]) and REC CAGEFREE I (median 60 s [IQR 50–60 s]). [87,104] These findings align with the prevailing understanding that sufficient balloon inflation time is of essence for DCB efficacy and are in accordance with the comparison between DCB and POBA in **Paper VI**. The rationale behind these findings is ensuring that an effective drug transfer is paramount to suppress neointimal hyperplasia, and if a sufficient inflation time is not applied, DCB angioplasty appears to convey a similar result as compared with POBA. It is worth noting that while no randomised trial has exclusively compared different DCB inflation durations, observational evidence beyond our study supports the use of inflation times ≥30 seconds. [147] Preclinical studies have

shown that paclitaxel is absorbed into the vessel wall rapidly. [148] While this is true in controlled porcine models, it is important to recognise that clinical real-world outcomes depend on multiple factors. Although SCB are emerging in clinical practice, our studies showed that the majority of DCB used in Sweden were PCB, and thus the results of **Paper III** are most applicable to PCB.

In **Paper IV**, outcomes following SCB were compared with PCB. In this cohort, SCB and PCB were associated with similar clinical outcomes, extending evidence from randomised PCB trials such as BASKET-SMALL 2 and REC-CAGEFREE I, [87,104] while complementing emerging SCB data. This observation is notable given the substantial mechanistic differences between the two drug platforms. Paclitaxel is highly lipophilic, allowing rapid vessel wall uptake during short inflations, whereas sirolimus is less lipophilic and traditionally requires sustained tissue exposure. Early SCB development has focused on overcoming these pharmacokinetic challenges through novel excipients and encapsulation technologies. Although not published as of today (31 March 2026), SELUTION4ISR and SELUTION De Novo demonstrated non-inferiority compared with DES in both in-stent restenosis and de novo lesions (both presented at TCT 2025). At 1 year in the SELUTION De Novo trial, target vessel failure occurred in 5.3% of patients in the SCB group compared with 4.4% in the DES arm. In the SELUTION4ISR trial, the rate of target lesion failure was 15.2% compared with 13.5% in the DES/POBA arm. The present real-world analysis extends these findings by demonstrating comparable outcomes between SCB and PCB in an unselected nationwide population. This suggests that, at a population level, theoretical pharmacological differences may be less clinically relevant than anticipated, provided that modern balloon designs and procedural standards are used. Importantly, these results should not be interpreted as evidence of equivalence at the device level as individual SCB and PCB platforms differ substantially in coating technology, drug dose, and release kinetics.

The Swedish population may be regarded as neither distinctly high- nor low-risk in terms of cardiovascular risk, but rather representative of a contemporary Western population receiving guideline-directed care. While certain risk factors, such as smoking prevalence, are lower in Sweden compared with many other countries, the overall burden of coronary artery disease, diabetes, hypertension, and advanced age is comparable to that observed in other European and North American cohorts. This intermediate risk profile supports the generalisability of the findings beyond Sweden. A limitation of the present thesis is its single-country design, as differences in healthcare organisation and procedural practice may affect external validity. However, this is balanced by the major strength of nationwide coverage, including virtually all patients undergoing PCI, minimising selection bias and enabling robust analyses of real-world outcomes. Future research should focus on pragmatic registry-based randomised trials and international collaborations to confirm these

findings across different healthcare systems and to further refine patient and lesion selection for contemporary PCI strategies.

Future perspectives

Although there have been significant advances in DES technology, the long-term presence of a stent scaffold continues to pose a risk for future adverse events. [42,43] This has fuelled the "leave nothing behind" strategy, based on the hypothesis that avoiding permanent implants would improve long-term vessel health and outcomes after PCI. This concept has spurred innovations ranging from DCB to biodegradable scaffolds, all aiming to treat coronary disease without leaving permanent prostheses. Below, is a discussion on emerging PCI-technologies: SCB, dual-drug DCB, new-generation bioresorbable scaffolds, and the bioadaptor, and their anticipated roles in realising a leave-nothing-behind paradigm.

As PCI technology and techniques have advanced, the balance between procedural risk and potential clinical benefit may shift in patients with CCS. In these patients, where the indication for revascularisation is often driven by symptom relief and long-term prognostic considerations, a more favourable risk-benefit ratio could make PCI a more attractive treatment option in the future. DCB therapy has been developed to reduce the risk of stent complications and improve long-term outcome following PCI.

Research into DCB technology continues to evolve rapidly. New-generation SCB have been developed to address some of the limitations of the earlier devices, particularly with respect to drug-release kinetics and vessel uptake. Long-term outcome data for these newer devices remain limited and should be a priority for future research. Despite the emergence of sirolimus-coated devices, PCB remain the most commonly used DCB in Sweden. Looking further ahead, dual-drug DCB, combining sirolimus and paclitaxel on one platform, is an innovative offshoot in DCB technology. The rationale behind dual-drug DCB is to access the synergistic antiproliferative effects of both agents, while mitigating their individual downsides. Preclinical results with a prototype dual-drug DCB have shown that a dual-drug DCB provide a greater inhibition of intimal cell proliferation in an animal model. [149] Future clinical trials will provide further insights into the efficacy of these newer devices.

Apart from new devices, several important clinical areas also warrant further investigation. These include the use of DCB in large vessels, bifurcations, and acute coronary syndromes. In addition, the role of DCB in patients at high bleeding risk represents a particularly interesting indication, especially if supported by robust evidence for abbreviated antiplatelet regimens. In **Paper VI**, a significant subgroup-by-treatment interaction was observed for age, where DCB were associated with a

better outcome for patients ≥80 years. This might reflect a population of high bleeding risk. Similarly, DCB provided a similar outcome compared with DES during the first 6 months. This may be of importance to patients with shorter life expectancy. For these patients, DCB may allow a shorter or less intensified dual antiplatelet regime, but future studies are warranted to assess the optimal dual antiplatelet regimes for DCB based PCI. Finally, longer follow-up, and randomised comparisons against contemporary DES will be essential to better define the role of DCB in modern PCI.

Bioresorbable scaffolds are designed to completely resolve after fulfilling their scaffolding function. The first-generation of bioresorbable scaffold showed higher rates of early device thrombosis and restenosis compared to modern DES, leading to its withdrawal from the market. [51,150] The problems were largely attributed to thick struts that impaired early endothelialisation, and technical limitation (including suboptimal implantation in routine clinical practice). Redesigned devices such as magnesium-based bioresorbable scaffolds or improved polymer-based bioresorbable scaffolds are currently being investigated in clinical trials. [151] The next few years will be pivotal for bioresorbable scaffolds as ongoing randomised trials will provide insights on its efficacy.

The bioadaptor is another novel PCI technique developed to address the limitations of DES. This device function similarly to conventional DES during the first 6 months by providing a structural support for the coronary artery. However, at 6 months, the device links open, restoring pulsatility and normal vessel function. [152,153] Two randomised trials have investigated the efficacy of the bioadaptor, the BIOADAPTOR trial and the INFINITY trial. [154,155] The BIOADAPTOR trial enrolled 455 patients with de novo coronary artery lesions and randomised them to treatment with bioadaptor or DES. The bioadaptor demonstrated similar acute performance and 12-month clinical outcomes. Following the BIOADAPTOR trial, the INFINITY trial was conducted as a registry based randomised controlled trial in Sweden and enrolled 2,399 patients to receive treatment with either the bioadaptor or DES. This trial showed non-inferiority when the bioadaptor was compared with contemporary DES, with a potential to mitigate non-plateauing device-related events. Long-term results will provide further insights into the efficacy of the bioadaptor.

While the “leave nothing behind” strategy has made important progress towards pursuing stentless solutions, newer generations of DES have simultaneously made significant advances. Whereas first-generation stents had thick struts (up to 140 μm) that provoked inflammation, newer generations of DES now use refined platforms as thin as 60 μm. [156,157] Whether the future of PCI will comprise of stentless solutions or refined stents remains to be determined. Nevertheless, there is reason for optimism: technological breakthroughs aligned with rigorous clinical science will continue to improve the treatment of coronary artery disease.

Strengths and limitations

Several strengths and limitations are common to all studies included in this thesis. The study populations were derived from nationwide Swedish quality registries within SWEDEHEART, primarily SCAAR. The use of a unique, pseudonymised personal identification number for each patient allows comprehensive linkage of data across registries, enabling access to data on procedural characteristics, pharmacological treatment, and mortality. This linkage provides a robust framework for studying PCI in a real-world setting. The nationwide coverage of SWEDEHEART constitutes a major strength. Virtually all coronary angiographies and PCI performed in Sweden are registered, minimising selection bias related to geography, socioeconomic status, or hospital type. The large sample sizes increase statistical power and allow analysis of relatively uncommon treatments, such as SCB, as well as subgroup analyses. Follow-up for clinical outcomes, including mortality, is essentially complete for all patients. Another important strength is that the data reflect routine clinical practice, in contrast to randomised controlled trials which often include selected patient populations. This is particularly relevant for DCB treatment, which is frequently used in a wide range of clinical scenarios and in patients who may not be represented in randomised trials.

However, several limitations inherent to observational registry-based research must be acknowledged. First, all results reported in this thesis describe associations rather than causal relationships. Treatment is not randomised, and the choice of revascularisation technique is influenced by clinical judgment, lesion characteristics, and local practice patterns. Although multiple strategies were used to account for confounding, residual confounding due to unmeasured factors cannot be excluded. Second, while SCAAR contains detailed procedural information, certain angiographic and lesion-specific variables, particularly relevant to DCB outcomes, are not fully captured. These include detailed lesion morphology, degree of calcification, and dissections. Third, registry data rely on accurate and consistent reporting by participating centres. Although SWEDEHEART is characterised by high data quality, continuous validation, and regular audits, some degree of missing data and reporting variability is unavoidable in large national registries. [122] In addition, patient-reported outcomes, symptom burden, and quality-of-life measures are not available. Finally, unmeasured lifestyle-related factors such as physical activity, diet, and social determinants of health are not captured and may influence both treatment selection and outcomes.

Conclusions

This thesis provides new insights into the effectiveness of PCI in CCS and the use of DCB in PCI. The findings support the clinical relevance of revascularisation in CCS. Sufficient DCB inflation time appears to be a prerequisite for optimising outcomes, while no difference was observed between PCB and SCB. While DCB provide a better outcome as compared with POBA, the results of this thesis support the continued use of DES as the standard of care in in-stent restenosis and non-complex de novo lesions.

Study-specific conclusions are listed below.

Paper I. Patients treated with PCI were associated with improved outcome in terms of NACE and MACE at 5 years compared to medical therapy alone. The results were driven by lower rates of urgent revascularisation and MI. In addition, the use of PCI was associated with lower rates of cardiovascular mortality at 5 years and all-cause mortality at 10 years.

Paper II. Revascularisation with PCI or CABG were associated with a reduction in the use of long-acting nitrates among patients with CCS, suggesting angina symptom improvement. CABG appears to provide a greater benefit compared to PCI, with complete PCI associated with better effectiveness than incomplete PCI.

Paper III. A DCB inflation time of ≥30 seconds was associated with lower rates of repeat revascularisations and myocardial infarction compared to <30 seconds. When 30 seconds was compared with >30 seconds, no difference in clinical outcome was observed.

Paper IV. No statistically significant differences in clinical outcomes were observed between PCB and SCB. This was consistent across the overall cohort and when de novo lesions and in-stent restenosis were analysed separately.

Paper V. DES was associated with a lower rate of the primary composite outcome at 5-years compared with DCB for small (<3.0 mm device diameter) non-complex de novo coronary artery lesions.

Paper VI. For patients with in-stent restenosis, DCB-treated lesions were associated with lower rates of 5-year TLR compared with POBA-treated lesions, but higher rates compared with DES-treated lesions.

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