SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3327.

KULYASSA PÉTER MÁRTON

Szív- és érrendszeri betegségek élettana és klinikuma

című program

Programvezető: Dr. Merkely Béla, egyetemi tanár

Témavezető: Dr. Édes István Ferenc, klinikai főorvos

OPTIMIZING OUTCOMES IN PERCUTANEOUS CORONARY PROCEDURES

Ph.D. Thesis

Peter Marton Kulyassa M.D.

Translational Medicine Program

Cardiovascular Medicine and Research Division

SEMMELWEIS UNIVERSITY

Supervisor:	István Ferenc Édes M.D., Ph.D.
Official reviewers:	Péter Kanizsai M.D., Ph.D.
	Octavian Andronic M.D., Ph.D.
Head of the Complex Examination Committee:	Professor Tivadar Tulassay M.D., Ph.D.
Members of the Complex Examination Committee:	Henriette Farkas M.D., Ph.D.
	Charaf Hassan M.D., Ph.D.

Budapest, 2025

“People who know little are great talkers, while men who know much say little.”

Jean-Jacques Rousseau

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1 LIST OF ABBREVIATIONS

ACS – acute coronary syndrome

AG – acute gain

ANOVA – analysis of variance

ASA – acetyl-salicylic acid

BMI – body mass index

BMS – bare-metal stent

CABG – coronary artery bypass graft surgery

CAD – coronary artery disease

CCS – chronic coronary syndrome

CENTRAL – Cochrane Central Register of Controlled Trials

CI – confidence interval

DCB – drug-coated balloon

DES – drug-eluting stent

DES-ISR – drug-eluting stent in-stent restenosis

DM – diabetes mellitus

EES – everolimus-eluting stent

eGFR – estimated glomerular filtration rate

ESC – European Society of Cardiology

F – French

GCP – Good Clinical Practice

HUF – Hungarian Forint

IDDM – insulin-dependent diabetes mellitus

IM – intermediate coronary artery

IQR – interquartile range

ISR – in-stent restenosis

IU – international unit

IVI – intravascular imaging

IVUS – intravascular ultrasound

LAD – left anterior descending artery

LCX – left circumflex coronary artery

LLL – late lumen loss

LVEF – left ventricular ejection fraction

MACE – major adverse cardiac events

MCD – mechanical compression device

MLD – minimal lumen diameter

MRA – mineralocorticoid receptor antagonist

NC balloon – non-compliant balloon

NIDDM – non-insulin-dependent diabetes mellitus

NOAC – non-K vitamin oral anticoagulant

NSTEMI – non-ST-segment elevation myocardial infarction

OAC – oral anticoagulant

OCT – optical coherence tomography

OPEN-ISR – OPtimal trEatment for coroNary In-Stent Restenosis

OR – odds ratio

PCI – percutaneous coronary intervention

PCB – paclitaxel-coated balloon

PH – patent hemostasis

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO – International Prospective Register of Systematic Reviews

QCA – quantitative coronary angiography

QFR – quantitative flow ratio

ΔQFR – change in quantitative flow ratio

RAAS – renin angiotensin aldosterone system

RAD – radial artery damage

RAO – radial artery occlusion

RAPHE – Radial Artery Patency and Hemostasis Evaluation

RCA – right coronary artery

SCB – sirolimus-coated balloon

SD – standard deviation

TLR – target lesion revascularization

TRA – transradial approach

TVMI – target vessel myocardial infarction

TVR – target vessel revascularization

UA – unstable angina

US – ultrasound

VKA – vitamin K antagonist

2 STUDENT PROFILE

2.1 Vision and mission statement, specific goals

My vision is to reduce the burden of heart disease with improved coronary interventions. My mission is to lower the need for repeat revascularization and complications by coronary interventions through scientific research. My specific goals are to conduct two randomized controlled trials: Radial Artery Puncture Hemostasis Evaluation and OPtimal trEatment for coroNary In-Stent Restenosis and a meta-analysis: Drug-coated balloon effectivity in the treatment of early and late drug-eluting stent in-stent restenosis.

2.2 Scientometrics

Number of all publications:	6
Cumulative IF:	13.6
Av IF/publication:	2.27
Ranking (SCImago):	Q1: 3, Q2: 2, Q3: 1
Number of publications related to the subject of the thesis:	3
Cumulative IF:	6,4
Av IF/publication:	2.13
Ranking (Sci Mago):	Q1:2, Q2:1
Number of citations on Google Scholar:	26
Number of citations on MTMT (independent):	16
H-index:	3

The detailed bibliography of the student can be found on pages 94-95.

2.3 Future plans

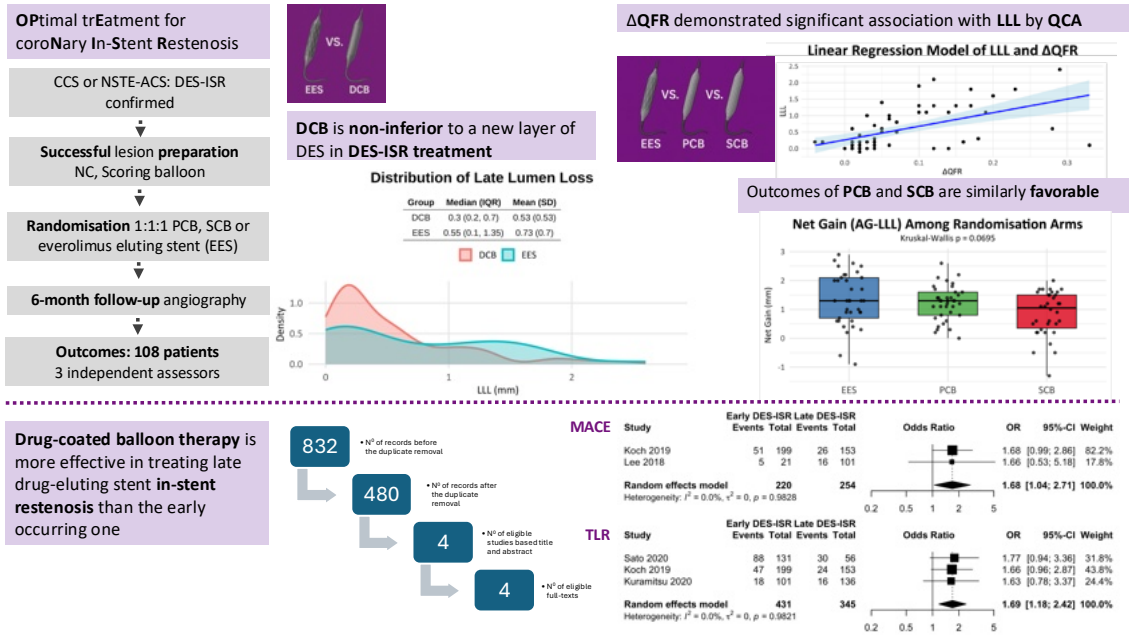
Continuing my work and research as a cardiologist, with a focus on interventional cardiology

3 SUMMARY OF THE THESIS

This thesis presents an integrated investigation into two major challenges in interventional cardiology: drug-eluting stent in-stent restenosis (DES-ISR) and radial artery hemostasis following transradial access (TRA). The OPtimal trEatment for coroNary In-Stent Restenosis (OPEN-ISR) randomized controlled trial demonstrated that drug-coated balloons (DCBs), including paclitaxel-coated (PCB) and sirolimus-coated balloons (SCB), are non-inferior to repeat everolimus-eluting stent (EES) implantation in treating DES-ISR, based on six-month late lumen loss (LLL). Secondary outcomes, including acute gain (AG), net gain, and device-oriented composite endpoints (DOCE), were also comparable between DCB and EES arms, supporting the use of DCBs for ISR. Change in quantitative flow ratio (ΔQFR) significantly associates with LLL, providing a potential functional surrogate marker for restenosis progression. A meta-analysis further revealed that early DES-ISR (≤12 months**)** was associated with significantly higher rates of major adverse cardiac events (MACE) and target lesion revascularization (TLR) following DCB treatment compared to late DES-ISR, emphasizing the importance of ISR timing. These findings suggest early ISR may involve mechanical failures, requiring tailored therapy and lesion preparation, whereas late ISR may be more biologically driven, favoring DCB use. In terms of radial artery hemostasis, the Radial Artery Patency and Hemostasis Evaluation (RAPHE) trial showed that two bioactive dressings-a chitosan sponge and a potassium ferrate disc – were non-inferior to pneumatic mechanical compression devices (MCDs) in preventing complications such as radial artery occlusion (RAO), bleeding, and vascular damage. The potassium ferrate disc demonstrated operational advantages, including shorter application time, fewer reapplications, and no bailout device use, suggesting workflow efficiency benefits. The simplified application protocol without patent hemostasis (PH) monitoring reduced nursing workload and may enable same-day discharge programs. Findings advocate for precision-based ISR treatment, incorporating intravascular imaging (IVI) to guide therapy. For radial hemostasis, bioactive dressings offer a promising alternative, especially in resource-limited settings or high-volume centers. Together, this work contributes to a more individualized**,** efficient**,** and patient-centered approach in interventional cardiology.

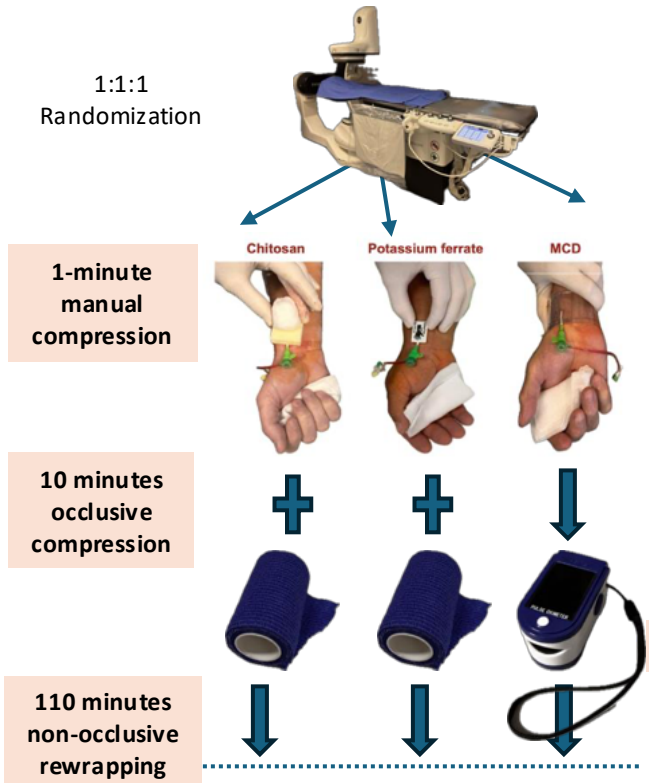
4 GRAPHICAL ABSTRACT

4.1 In-stent restenosis



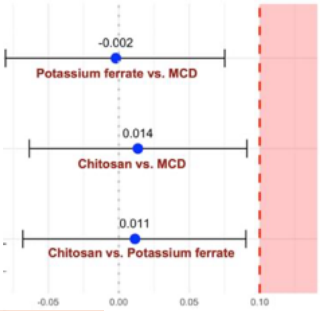
4.2 Radial artery hemostasis

Radial Artery Puncture Hemostasis Evaluation trial



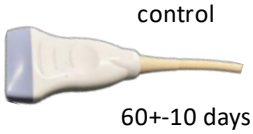
Screening

Non-inferiority for the **Device Oriented Composite Endpoint** in the three arms with similar compression times and number of extra devices used

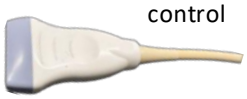


Decompression

Periprocedural control



60+-10 days control



Novel techniques ease the patent hemostasis protocol associated burden

DOCE component		Chitosan (203) n (%)	Potassium ferrate (207) n (%)	MCD (189) n (%)	Total (599) n (%)
RAO	Periprocedural	1 (0.5)	0 (0)	0 (0)	1 (0.02)
	At follow-up	4 (2)	7 (3.4)	3 (1.6)	14 (2.3)
RAD	Dissection	0 (0)	0 (0)	0 (0)	0(0)
	Fistula	3 (1.5)	0 (0)	1 (0.5)	4 (0.7)
	Pseudoaneurysm	6 (3)	5 (2.4)	9 (4.3)	20 (3.3)
Haematoma	EASY I/II	24 (11.8)	26 (12.6)	21 (11.1)	73 (12.2)
	EASY MIV	3 (1.5)	1 (0.5)	2 (1)	6 (1)
Total		41 (20.2)	39 (18.8)	36 (19)	117 (19.5)

5 INTRODUCTION

5.1 What is the topic?

5.1.1 In-stent restenosis

Cardiovascular disease remains the leading cause of mortality globally, with ischemic heart disease representing its largest subset. (1,2) Over the past three decades, percutaneous coronary intervention (PCI) has significantly improved patient prognosis and quality of life. The advent of coronary stents marked a pivotal breakthrough in managing coronary artery disease (CAD), effectively addressing acute vessel recoil and negative remodeling associated with balloon angioplasty. Despite these advancements, in-stent restenosis (ISR), a condition characterized by recurrent narrowing within previously implanted stents, remains a prominent limitation of coronary stenting procedures. (3)

ISR is generally understood as a luminal diameter reduction of at least 50% within the stented vessel segment, or up to 5 mm beyond the stent margins, as determined by coronary angiography. (4) When assessed with intravascular imaging (IVI), which provides data in three dimensions, ISR is usually defined more stringently as a reduction of at least 75% in reference vessel cross-sectional area. (3) This threshold is also consistent with observations from autopsy studies, where narrowing of ≥75% is typically regarded as pathological restenosis. (5) Beyond categorical definitions, ISR can also be described along a continuous spectrum of pathophysiological changes. The term clinical restenosis is applied when ISR produces ischemic symptoms or signs, but since not every restenotic lesion becomes symptomatic, the incidence of clinical restenosis is lower than the overall ISR rate. (6) In practice, the therapeutic approach parallels that of de novo CAD, and revascularization may be indicated in patients presenting with either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS). (7)

Historically, ISR emerged as a significant clinical challenge shortly after the widespread adoption of bare-metal stents (BMS) in the early 1990s. (8) Initially, BMS significantly reduced acute vessel closure compared to balloon angioplasty alone, but were associated with high ISR rates, particularly among diabetic patients or those with small-vessel

disease. The introduction of drug-eluting stents (DES) in the early 2000s, coated with antiproliferative agents like sirolimus and paclitaxel, dramatically reduced ISR by inhibiting neointimal hyperplasia. However, ISR continues to persist even with contemporary DES technologies. (7,9)

Biologically, ISR predominantly involves two distinct mechanisms: neointimal hyperplasia and neoatherosclerosis. Neointimal hyperplasia, driven by vascular smooth muscle cell proliferation following endothelial injury, is common in early ISR (<1 year post-implantation). Neoatherosclerosis, characterized by lipid-laden macrophages and necrotic core formation within the stented segment, dominates late ISR (>1 year post-implantation). (9) From a mechanistic standpoint, ISR represents a heterogeneous condition with several potential underlying causes that may coexist within the same lesion. Careful identification of the predominant mechanism is therefore a crucial step in determining the optimal therapeutic approach. Mechanical or technical contributors include undersizing of the stent, incomplete expansion, vessel calcification, stent fracture, and geographic miss. (10)

For ISR treatment, drug-coated balloons (DCBs) have become an established alternative alongside repeat DES implantation, delivering antiproliferative drugs without additional permanent implants and preserving vasomotor function. (11,12) Optimal outcomes with DCB therapy rely heavily on appropriate device selection and meticulous lesion preparation, underscoring the necessity of tailored treatment approaches based on ISR timing and lesion characteristics. (13)

5.1.2 Radial artery hemostasis

Parallel to advances in coronary intervention, significant progress has been made in optimizing vascular access for PCI. Introduced by Lucien Campeau in 1989, the transradial approach (TRA) has become the preferred route for coronary procedures due to its demonstrated advantages, including reduced bleeding complications, shorter hospital stays, and enhanced patient comfort. (14) TRA has been widely adopted not only for routine coronary angiography but also for complex interventions such as chronic total occlusions and rotational atherectomy. (15)

Despite these notable advantages, radial artery occlusion (RAO) and radial artery damage (RAD) – encompassing vessel dissection, pseudoaneurysm, and arteriovenous fistula formation – remain important procedural challenges. RAO remains the most common, reported in 1–10% of cases, depending on sheath size and post-procedural patency testing. Risk factors include small radial artery diameter, prolonged hemostasis, subtherapeutic anticoagulation, and multiple puncture attempts. (16–18) Access site hematoma and bleeding occur in up to 5–7%, often related to sheath size, inadequate compression, or excessive periprocedural anticoagulation. (19) Radial artery spasm is also common, particularly in younger patients, females, and those with smaller vessels, and is exacerbated by pain, anxiety, or a large sheath-to-artery ratio. (20) Rare vascular complications, as pseudoaneurysm, arteriovenous fistula, perforation, or dissection, are mostly linked to repeated puncture or high-pressure inflation. (21)

Management is largely preventive: patent hemostasis (PH) with non-occlusive compression and adequate anticoagulation significantly reduces RAO, ultrasound guidance lowers access-site failure and vascular injury, and vasodilators together with adequate sedation reduce spasm incidence. (22–24) Established RAO is frequently asymptomatic, and when symptomatic, short-course anticoagulation achieves high recanalization rates. Current expert guidance also supports the use of ipsilateral ulnar artery compression and, in selected cases, endovascular recanalization as reasonable therapeutic strategies. (18) For pseudoaneurysm and radial arteriovenous fistul**a** after TRA, most cases can be handled conservatively or with ultrasound-guided thrombin injection for pseudoaneurysm; surgery or covered stenting is generally reserved for persistent, symptomatic, or complicated lesions. (25)

Traditional hemostasis protocols following TRA rely on mechanical compression devices (MCDs), predominantly pneumatic bands, utilized with PH. PH refers to the application of compression sufficient to prevent bleeding at the puncture site while maintaining antegrade radial artery flow, thereby minimizing the risk of RAO. (22) The search for more effective solutions has led to the development of biologically and chemically active dressings designed to accelerate hemostasis without reliance on prolonged mechanical compression, borrowed from devices that were first developed in the defense industry and utilized in combat field operations. (26) Chitosan, a positively charged polysaccharide derived from crustacean shells, promotes platelet aggregation and clot formation through

electrostatic interactions with negatively charged cell membranes. (27,28) Similarly, potassium ferrate-based dressings induce rapid desiccation and protein denaturation at the puncture site, leading to effective clot stabilization. (29) These devices, applied with MCDs while maintaining PH, offer simplified hemostasis by rapidly inducing localized coagulation and stable clot formation without prolonged external pressure. (30–34)

5.2 What is the problem to solve?

5.2.1 In-stent restenosis

Despite continuous refinements in stent technology, ISR persists as a significant complication affecting 5–10% of PCI procedures in developed countries, particularly in high-risk patient groups. (35,36) Initially, BMS exhibited ISR rates as high as 30–40% among diabetic patients or those with small-vessel disease. (37) The subsequent introduction of DES, initially releasing antiproliferative agents like sirolimus or paclitaxel through durable polymer coatings, substantially reduced neointimal hyperplasia. Although subsequent generations of DES have since been widely implemented in clinical practice, ISR remains prevalent even with contemporary DES technologies. (38) ISR lesions can even appear simple to treat with balloon dilation, and angiographic success is frequently achieved; however, their management is complicated by the high likelihood of recurrence. (39)

As DCBs demonstrated mixed results in drug-eluting stent in-stent restenosis (DES-ISR) treatment in a limited number of analyses, current ESC guidelines recommend repeat DES over DCB for DES-ISR (Class I, Level A). (12,40,41) Detailed stratification by different DCB platforms, early vs late ISR, or lesion-specific scenarios remains limited, contributing to a large variability in clinical practice. (42) Consequently, therapeutic decision-making often lacks uniformity, underscoring the need for refined guidelines supported by robust clinical data. This thesis aims to address these critical knowledge gaps by presenting findings from the Optimal Treatment for Coronary Drug-Eluting Stent In-Stent Restenosis (OPEN-ISR) randomized trial, directly comparing DCB and repeat DES therapies, alongside a meta-analysis examining how ISR timing affects clinical outcomes when utilizing DCBs.

5.2.2 Radial artery hemostasis

Regardless of widespread TRA adoption, achieving effective radial artery hemostasis continues to impose substantial clinical and operational challenges. Standard mechanical compression methods, though effective at preventing bleeding, require meticulous titration and intensive nursing resources to maintain PH, particularly in high-volume catheterization laboratories.

Emerging hemostatic devices, specifically chitosan-based sponges and potassium ferrate-coated discs, promise streamlined hemostasis management through rapid local coagulation without extended mechanical compression. However, the currently available protocols are resource-intensive, requiring frequent adjustments, substantial nursing oversight, and extended immobilization periods. (43,44) The RAPHE trial addresses this problem by comparing a new hemostasis technique with these innovative devices against a PH protocol with traditional MCDs in a randomized setting.

5.3 What is the importance of the topic?

5.3.1 In-stent restenosis

As the global utilization of PCI continues to escalate, even a relatively low incidence of ISR translates into a considerable absolute number of patients requiring repeat revascularization procedures. It is associated not only with the recurrence of ischemic symptoms but also with impaired health-related quality of life and, in many cases, the need for further invasive interventions. The clinical manifestations of ISR are diverse, spanning from silent ischemia detected incidentally during routine follow-up to stable angina and ACS, including unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). (3,45)

From a healthcare systems perspective, ISR imposes substantial economic and organizational burdens. Repeat revascularization procedures escalate direct healthcare expenditures due to additional catheterizations, device costs, and resources required to manage complex re-interventions. These repeated procedures often necessitate prolonged hospital stays, compounding institutional costs and straining bed availability. Extended

use of dual antiplatelet therapy increases medication costs and elevates the risk of bleeding complications, potentially requiring closer monitoring and additional hospital readmissions. (13)

Scientifically and technologically, ISR embodies the intricate biological interplay between foreign implanted materials, the vascular endothelium, and systemic patient-specific factors like diabetes mellitus and dyslipidemia. The different causative mechanisms may and usually do coexist in the same lesion. (46) Hence, identification of the underlying pathology is a key aspect of adequate treatment with lasting outcomes. (10) The recognition of this multifactorial process has driven continuous innovation in stent technology. Advanced DES now features ultrathin struts, biocompatible alloys, and bioresorbable polymer coatings designed to reduce vascular irritation and promote physiological healing. (47) These innovations seek to modulate neointimal hyperplasia and minimize late adverse events such as stent thrombosis and neoatherosclerosis. Insights derived from ISR research have also influenced vascular medicine broadly, informing drug delivery methods and vascular healing in peripheral arterial and structural heart interventions. (48)

Patient-centered care considerations further highlight ISR's importance. Repeat procedures disrupt patients' lives, heighten anxiety, and compromise long-term quality of life. The cumulative metallic burden from multiple stent implantations may limit future therapeutic options, whereas the use of DCBs offers a stent-free approach, controlling the risk of recurrent ISR in the treated segment. Thus, strategies to prevent ISR and to optimize its management remain a central concern in interventional cardiology.

5.3.2 Radial artery hemostasis

Optimizing radial artery hemostasis is essential for maintaining the TRA as the preferred vascular access strategy in coronary interventions. TRA significantly reduces bleeding complications, enhances patient comfort, and facilitates earlier mobilization compared to transfemoral access. Preservation of radial artery patency is also crucial for subsequent interventions, potential coronary artery bypass graft surgery (CABG), and creation of arteriovenous fistulas for hemodialysis. (15) However, achieving effective hemostasis without compromising radial artery patency remains a clinical challenge. RAO, the

principal limiting complication, can be mitigated through the use of PH. (22) To achieve PH, conventional MCDs, with or without the concomitant use of novel hemostatic agents, require meticulous pressure titration and extensive monitoring. This increases nursing workloads and prolongs patient immobilization. A compression-free hemostatic technique combined with the novel hemostatic agents may simplify these protocols by reducing workload without compromising antegrade radial artery flow. (22,44)

5.4 What would be the importance of our research results?

5.4.1 In-stent restenosis

The studies presented in this thesis address critical gaps in managing ISR, exploring whether DCBs can deliver durable treatment outcomes without necessitating additional stent implantation. By differentiating the efficacy of treatments based on device platforms in OPEN-ISR and ISR timing (early versus late) in the meta-analysis, the thesis also aims to refine clinical decision-making and inform personalized management algorithms.

The following findings may guide clinicians in selecting therapies that optimize outcomes, reducing the likelihood of recurrent interventions. Clinically, results could influence procedural strategies and may provide additional evidence for updating future guidelines. At the healthcare system level, refined ISR management strategies could decrease procedural burdens, improve catheterization laboratory efficiency, and reduce healthcare expenditures.

5.4.2 Radial artery hemostasis

The RAPHE trial evaluates novel compression-free hemostatic devices, specifically chitosan-based sponges and potassium ferrate-coated discs, compared with standard pneumatic compression. Demonstrating non-inferiority or superiority in preventing access-site complications with a simplified technique would justify incorporating the new hemostatic agents into routine clinical practice.

Operationally, the adoption of compression-free hemostasis methods could substantially reduce nursing workloads, enable earlier patient mobilization, and yield significant cost

savings, particularly beneficial in high-volume catheterization laboratories. Streamlined approaches reduce observation times, nursing demands, and bed occupancy, thereby enhancing patient throughput. Patient-centered benefits include reduced discomfort, prevention of pressure-related injuries, and earlier mobilization, contributing to improved patient satisfaction and procedural efficiency. Additionally, the RAPHE findings complement other presented procedural innovations, such as DCB applications for ISR management, synergistically improving procedural outcomes and patient satisfaction.

6 OBJECTIVES

6.1 Objectives of OPEN-ISR

The OPEN-ISR trial was designed to address persistent uncertainties in the treatment of DES-ISR, a major clinical challenge despite advances in stent technology and pharmacotherapy. The primary objective was to compare the efficacy of DCBs with everolimus-eluting stents (EES) in treating DES-ISR. The trial hypothesized that DCBs could achieve non-inferiority to repeat stenting in DES-ISR when both therapies are appropriate. Secondary objectives were to assess the relation of our primary surrogate outcome, late lumen loss (LLL), to a device-oriented composite endpoint (DOCE), and to investigate sirolimus-coated balloon (SCB) efficacy compared to paclitaxel-coated balloon (PCB) and EES in this setting. Furthermore, to collect data on how quantitative flow ratio (QFR) – an angiography-based method that estimates fractional flow reserve by applying computational fluid dynamics to standard coronary angiograms – is associated with LLL in DES-ISR.

6.2 Objectives of meta-analysis

Recognizing the heterogeneity in study designs and patient populations, this analysis aimed to clarify whether the timing of restenosis – categorized as early (≤12 months) or late (>12 months) after stent implantation – modifies the therapeutic effectiveness of DCBs. The primary objective was to compare clinical outcomes of DCB treatment in early versus late DES-ISR, with a focus on major adverse cardiac events (MACE), including TLR, MI, and cardiac death at 12-month follow-up. It was hypothesized that DCBs demonstrate greater effectiveness in early DES-ISR compared with late DES-ISR. Secondary objectives included evaluating individual components of MACE.

6.3 Objectives of RAPHE

The RAPHE trial was designed to address radial artery hemostasis following TRA for coronary procedures. RAPHE evaluates a novel compression technique with two

compression-free hemostasis devices, a chitosan-based sponge and a potassium ferrate disc. The protocol aims to simplify post-TRA care, preserve radial artery patency, and improve both patient and system-level outcomes. The primary objective is to compare these devices with standard MCDs in achieving safe and effective hemostasis. It was hypothesized that with the simplified protocol, the use of chitosan and potassium ferrate would result in non-inferiority compared to the traditional PH technique with an MCD at similar costs. Secondary objectives included evaluating the extension of initial compression time, overall device usage time, use of a second study device, and use of a bailout device.

7 METHODS

7.1 Methods of OPEN-ISR

7.1.1 Study design

The OPEN-ISR trial was designed as a prospective, randomized, multicenter, controlled, non-inferiority clinical study to address the persistent clinical uncertainty surrounding the optimal therapeutic approach for DES-ISR. The trial sought to compare two contemporary DCB technologies (PCBs and SCBs) with repeat stent implantation using a new-generation EES.

The trial was conducted at two tertiary referral cardiac centers in Hungary: the Heart and Vascular Centre, Semmelweis University, Budapest, and the Invasive Cardiology Division, Department of Internal Medicine, University of Szeged. Both centers perform high annual procedural volumes (>2000 PCIs) and have advanced expertise in coronary imaging techniques and clinical trial conduct.

The study protocol was developed in accordance with the ethical principles outlined in the Declaration of Helsinki and adhered to Good Clinical Practice (GCP) guidelines. Ethical approval was granted by the Hungarian National Institute of Pharmacy and Nutrition (approval code OGYÉI/13134/2021), and the trial was prospectively registered on ClinicalTrials.gov (identifier NCT04862052).

7.1.2 Study population

Patients aged 18 to 85 years were eligible for inclusion if they presented with angiographically confirmed DES-ISR requiring revascularization. The ISR lesion could be identified in the context of either CCS or ACS, including NSTEMI and UA. Patients were required to provide written informed consent prior to enrolment, and a decision by the interventional cardiologist that revascularization of the DES-ISR lesion was clinically indicated was mandatory for inclusion.

Exclusion criteria were designed to eliminate confounding variables. These included the presence of flow-limiting or edge dissections identified after lesion pre-treatment, severe

calcification in the target segment resistant to plaque modification (as such lesions might require adjunctive techniques like rotational atherectomy, which could bias outcomes), stenting in a coronary bifurcation involving a side branch ≥2 mm in diameter, and any previous target segment intervention for ISR. Additional exclusion criteria comprised hemodynamic instability (to avoid enrolling patients at higher procedural risk), coronary angiography performed following sudden cardiac death, left ventricular ejection fraction <30% (due to the potential for poor prognosis unrelated to ISR treatment), a history of stroke within the preceding six months, pregnancy or breastfeeding, planned surgical intervention within six months, the presence of more than one critical lesion on the coronary angiogram (to ensure the index lesion could be most likely attributed to the assigned treatment strategy), and any inability or unwillingness to comply with study procedures or follow-up.

7.1.3 Randomization and interventions

Patients meeting eligibility criteria underwent lesion preparation prior to randomization. Lesion preparation was performed according to the operator's discretion, but was required to achieve adequate lesion expansion with a DES:balloon ratio of 1:1 to ensure uniform application of the study interventions.

Randomization was carried out in a 1:1:1 ratio to one of three study arms: (1) SCB, (2) PCB, or (3) EES. The allocation sequence was generated by an independent statistician using computerized random number generation and was concealed via a secure, web-based randomization system specifically developed for the trial. Randomization was stratified by center to balance recruitment across sites and minimize center-related biases. Due to the inherent differences between the study interventions, blinding of participants and interventional cardiologists was not feasible. However, to mitigate detection and performance bias, all outcome assessments – including quantitative coronary angiography (QCA), optical coherence tomography (OCT), and QFR analyses – were performed by independent, blinded core laboratory evaluators. In cases where inter-observer variability exceeded 20%, adjudication was performed by a third blinded evaluator, and the final measurement was calculated as the mean of all three assessments.

In the EES arm, treatment consisted of implantation of a new-generation EES followed by post-dilatation to ensure optimal stent apposition and expansion, with final angiographic confirmation of procedural success. In the DCB arms, lesion preparation was followed by balloon inflation with either SCB or PCB for a duration of 60 seconds to facilitate effective drug transfer to the vessel wall. Angiography was performed following DCB treatment to confirm the absence of flow-limiting dissections or other complications. Patients who developed complications necessitating further intervention (e.g., stent implantation for flow-limiting dissection) were withdrawn from the study and treated in accordance with current European Society of Cardiology (ESC) guidelines. (11) The flow diagram of the protocol is displayed in Figure 1.

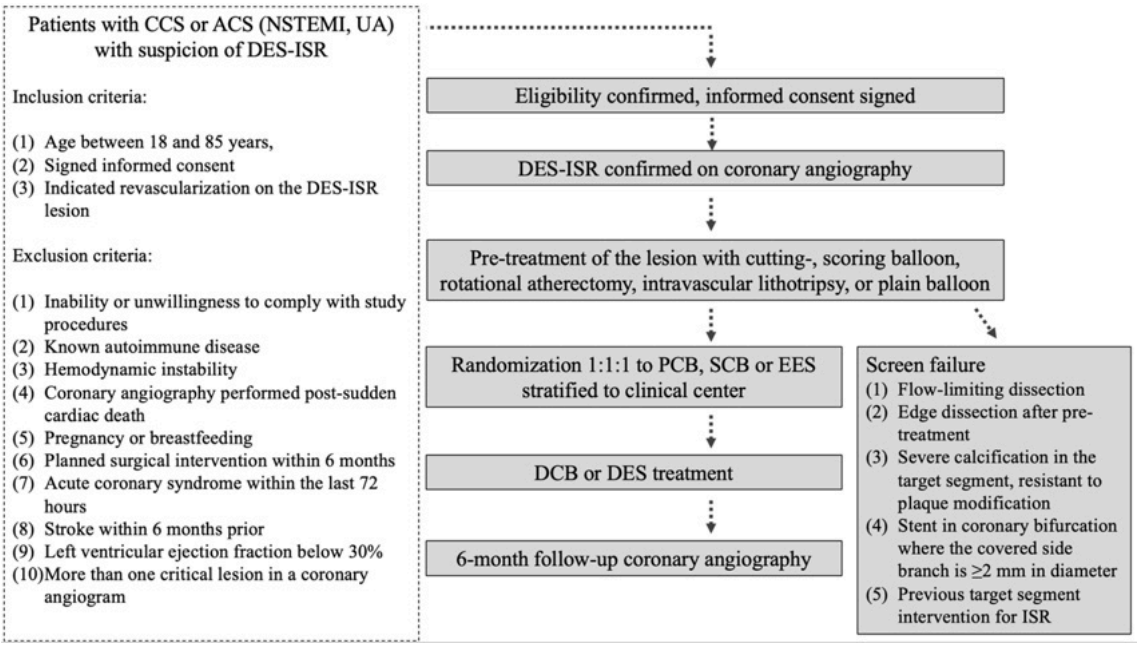


Figure 1. Flowchart of the OPEN-ISR trial

This figure displays the flowchart, main inclusion- and exclusion criteria of the trial. ACS – acute coronary syndrome, CCS – chronic coronary syndrome, DCB – drug-coated balloon, DES – drug-eluting stent, EES – everolimus-eluting stent, ISR – in-stent restenosis, NSTEMI – non-ST-segment elevation myocardial infarction, PCB – paclitaxel-coated balloon, SCB – sirolimus-coated balloon, UA – unstable angina

7.1.4 Outcomes and follow-up

The primary endpoint of the study was LLL in the treated segment at six months post-treatment, as assessed by QCA. LLL was selected as the primary endpoint because of its established role in previous randomized controlled trials as a surrogate marker for clinically meaningful outcomes, such as TLR. (49)

Secondary endpoints included a DOCE comprising target vessel myocardial infarction (TVMI), target vessel revascularization (TVR), and SCD during follow-up. Additional secondary endpoints involved assessment of acute intraluminal gain (AG) post-intervention, net gain, and LLL measured by OCT in a predefined subset of patients, and changes in QFR between the index procedure and follow-up angiography.

Angiographic follow-up was performed at six months (±30 days) post-treatment. OCT imaging was planned to be conducted in approximately 10–20% of patients based on operator discretion and technical feasibility. This subgroup analysis was planned to enable high-resolution evaluation of ISR plaque characteristics and treatment effects. QFR analyses were performed for lesions with at least two angiographic projections ≥25° apart and sufficient data for calibration; lesions failing to meet these criteria were excluded from QFR analysis.

7.1.5 Sample size calculation

The available data on the treatment of first- and second-generation DES-ISR are limited; however, given the presence of comparable trials in the literature, minor assumptions were made for the sample size estimation. In the EES arm of the RESTORE trial, an in-segment LLL, defined as including 5 mm proximal and distal to the stented segment, of 0.15 mm (SD 0.49 mm; median follow-up time: 289 days) was reported. (50) Based on these findings, we assumed a mean LLL of 0.15 mm in the EES arm with an SD of 0.45. A meta-analysis of DES-ISR treatments reported an LLL of 0.25 mm (SD 0.52 mm; mean follow-up time: 189 days) for PCB and an in-stent LLL of 0.26 mm (SD 0.61; mean follow-up time: 185 days) for SCB. (42) Furthermore, in the PCB arm of the RESTORE trial, an in-segment LLL of 0.19 mm (SD 0.41; median follow-up time: 312 days) was published. (50) We combined these two devices into a single DCB arm for analysis of the primary outcome and assumed an LLL of 0.18 mm with an SD of 0.45.

A patient-level meta-analysis including 2,426 patients treated with first- and second-generation DES identified 0.50 mm as the optimal LLL threshold for predicting a 2-year TLR event and reported that LLL exceeding this threshold was associated with a hazard ratio of 6.62 for TLR, independent of target vessel diameter. (51) Based on these findings and the expected LLLs, we prespecified a non-inferiority margin of 0.25 mm. Using the above parameters, a one-tailed test with an alpha level of 0.05, power of 80%, and a 2:1 randomization scheme, the required sample size was calculated to be 144 patients: 96 in the experimental arm and 48 in the control arm. Accounting for potential dropouts, a total enrollment of 150 patients was planned.

7.1.6 Statistical analysis

All statistical analyses were performed on an intention-to-treat basis. Continuous variables were summarized as mean ± SD or median (interquartile range (IQR)) depending on distribution, while categorical variables were presented as frequencies and percentages. The primary endpoint analyzed a combined DCB arm (PCB and SCB) using a one-tailed Mann–Whitney U test with a significance level of 5%. Additionally, the absolute difference with the upper confidence interval (CI) was calculated with the Hodges-Lehmann method, and sensitivity analysis was performed with the Miettinen-Nurminen method. Secondary endpoints were evaluated separately for the three trial arms (PCB, SCB, and EES) using analysis of variance (ANOVA), Kruskal–Wallis tests, logistic regression, or Fisher's exact test, as appropriate. An interim analysis was planned after enrollment of 50% of participants, overseen by an independent Data Safety Monitoring Board authorized to recommend early termination in the event of clear superiority, inferiority, or safety concerns. All analyses were performed using the R Studio software.

7.2 Methods of meta-analysis

7.2.1 Study design

This systematic review and meta-analysis was designed to investigate whether the timing of DES-ISR – specifically, early versus late presentation – affects the clinical efficacy of DCB therapy. The protocol was developed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021286262). (52)

7.2.2 Search strategy and study selection

To identify all relevant studies, a comprehensive and systematic literature search was performed across five major databases: Medline (via PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, and Embase. The search was executed on November 11, 2021, without restrictions on language or publication year to maximize sensitivity. Search terms were developed through iterative discussion with a medical librarian and included both controlled vocabulary (e.g., MeSH terms) and free-text terms. The final search strategy combined the following key concepts: (early OR late) AND (in-stent restenosis OR ISR) AND (drug-coated balloon OR DCB OR paclitaxel-coated balloon OR PCB OR sirolimus-coated balloon OR SCB). In Embase, the syntax was adapted appropriately for its indexing system.

All retrieved records were imported into EndNote X9 (Clarivate Analytics) for reference management, and duplicates were removed using first automated and then manual deduplication procedures. The selection process involved two independent reviewers who screened titles and abstracts in a blinded fashion to reduce selection bias. Articles deemed potentially eligible at this stage underwent full-text review against predefined inclusion and exclusion criteria. Studies were eligible if they reported clinical outcomes of DCB therapy in patients with DES-ISR and provided data on the interval between DES implantation and ISR occurrence. When studies did not explicitly report timing data, corresponding authors were contacted via email to request individual patient-level

information. Studies were excluded if they assessed ISR of BMS, used treatment modalities other than DCB without reporting a separate analysis of DCB-treated patients, or failed to provide extractable outcome data.

Disagreements at any stage were resolved by consensus or consultation with a third reviewer. To evaluate the consistency of study selection between reviewers, Cohen's kappa coefficient (κ) was calculated after both the title/abstract screening and full-text review phases. The study selection flow diagram is displayed in Figure 2.

7.2.3 Data extraction and outcomes

Data were extracted independently by two reviewers using structured data extraction forms developed in consultation with the study's statistical team. Extraction tables included fields for study design, sample size, patient demographics (e.g., mean age, sex distribution), baseline clinical characteristics (e.g., hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, smoking status), and procedural details where it was available.

The primary outcome of interest was the incidence of MACE at 12 months following DCB treatment. MACE was defined as a composite endpoint including TLR, MI, and cardiac death. Secondary endpoints included the individual components of MACE, as well as target lesion thrombosis, TVR, and LLL, where reported. When relevant data were missing from publications, attempts were made to obtain supplementary information through contacting study authors. No assumptions were made for missing data, and studies with insufficient information were excluded from quantitative synthesis.

7.2.4 Risk of bias assessment

The risk of bias in included studies was assessed using the Quality in Prognosis Studies (QUIPS) tool, which is specifically designed for the appraisal of prognostic factor studies. This tool evaluates six key domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis/reporting. Two reviewers performed independent assessments, and disagreements were resolved through discussion and consensus. The QUIPS tool was

selected for its ability to account for the unique methodological challenges of prognostic studies, such as potential confounding and selection bias. (53)

7.2.5 Statistical analysis

For each study, odds ratios (ORs) with 95% CIs were calculated for dichotomous outcomes using the total number of patients and events in the early and late DES-ISR groups. To account for heterogeneity in study populations and methodologies, random-effects meta-analysis models were employed. The Mantel-Haenszel method with Hartung-Knapp adjustment was applied to provide more robust estimates in the presence of small numbers of included studies. Between-study heterogeneity was assessed using the Cochrane Q test and quantified with the I^2 statistic. The τ^2 statistic, representing between-study variance, was estimated using the Paule-Mandel method, and its CIs were calculated with the Q-profile method. (54–56)

Influence and outlier analyses were conducted following recommendations from Harrer et al. and Viechtbauer and Cheung, to identify studies exerting disproportionate influence on pooled effect estimates. (57) Potential publication bias was evaluated visually using funnel plots of the log OR against its standard error. However, formal statistical testing for funnel plot asymmetry was not performed due to the limited number of included studies, in keeping with current methodological recommendations for meta-analyses involving fewer than 10 studies. (57)

All statistical analyses were performed using the R Studio software, employing relevant packages for meta-analysis and visualization. A two-tailed p-value of <0.05 was considered statistically significant for all analyses unless otherwise specified.

7.3 Methods of RAPHE

7.3.1 Study design

The RAPHE study was conceived as a prospective, randomized, multicenter clinical trial designed to evaluate the safety and efficacy of two innovative, non-compression-based hemostasis devices for radial artery access site hemostasis with a widely used pneumatic

compression device. The study was conducted at three high-volume university cardiac catheterization centers in Hungary, each with extensive experience in transradial coronary procedures and hemostasis management. Ethical approval for the trial was obtained from the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI/13123/2021), and the study adhered to the principles of the Declaration of Helsinki and GCP guidelines. All participants provided written informed consent prior to enrollment.

7.3.2 Patient population

Eligible participants included adults between 18 and 85 years of age with an indication for radial artery access for diagnostic coronary angiography or PCI. A pre-procedural ultrasound examination was performed to confirm a radial artery diameter of at least 1.8 mm; patients with smaller vessel diameters were excluded to minimize procedural risk and limit confounding. Additional exclusion criteria included unstable hemodynamics or resuscitation prior to angiography, pregnancy or lactation, systemic autoimmune disease, and significant peripheral vasculitis, as these conditions are associated with an increased risk of puncture site complications.

7.3.3 Randomization and interventions

Following sheath removal at the conclusion of the procedure, patients were randomized in a 1:1:1 ratio to receive hemostasis with either a chitosan bioactive sponge dressing, a potassium-ferrate-based topical hemostasis disc, or a pneumatic airbladder compression device serving as the control. Randomization was performed using a site-stratified, computer-generated algorithm.

The standalone potassium ferrate disc and chitosan sponge devices were both used similarly. They were placed onto the junction of the intact skin and the introducer and manually compressed. To aid better initial compression and prevent device adhesion to bloody surgical gloves, a ball gauze was placed on the chitosan device. The potassium-ferrate disc was compressed alone. During compression, the introducer was removed, allowing for a visible amount of blood to appear, which activated the hemostatic properties in both devices. Strong manual compression was held for 1 min. Devices were

then banded and held in place using self-adherent wraps with seven wraps. Strong, occlusive fixation of the devices was upheld for a total of 10 min, after which the self-adherent bond was fully unwrapped until the hemostasis device was visible. By this time, both devices were activated and initiated the coagulation cascade, and were firmly attached to the puncture site. If acute bleeding occurred, an additional minimum of 5 minutes of compression was applied. If initial devices were no longer fit for use, a new similar one was used. Rewrapping then occurred without the application of relevant pressure, in a nonocclusive way. During this time, the wrapping only protected the hemostasis device from external influence (e.g., accidental dislodgement, slipping, etc.). If the second randomized study device also failed to contain puncture site bleeding, a bail-out device of choice was applied as per protocol, the choice of which is left to the discretion of the attending physician. After a period of 120 minutes, the self-adherent wrapping was removed. The chitosan sponge device was also removed using sterile saline irrigation. The potassium-ferrate disc remained in place and was removed by the patient after 24 hours post-procedure.

In contrast, the pneumatic balloon-based MCD required incremental deflation guided by pulse oximetry in accordance with PH protocols, a process necessitating repeated nurse interventions over a similar observation period. (22) It was placed on the introducer sheath, inflated with the provided syringe to 12 mL, with simultaneous removal of the introducer. An additional 2 mL of air was inflated in case of acute bleeding and repeated if needed. It will be removed via a simplified PH protocol, in which, after achieving primary hemostasis, exact titration to true PH was achieved by removing 2–3 mL of air every 10–15 min using a pulse oximeter to verify patency. At 0 mL of remaining air, the device was removed. Study physicians were contacted by the conducting nurses in case of any potential adverse events, especially those in conjunction with radial hemostasis. The Flowchart of the RAPHE trial is displayed in Figure 2.

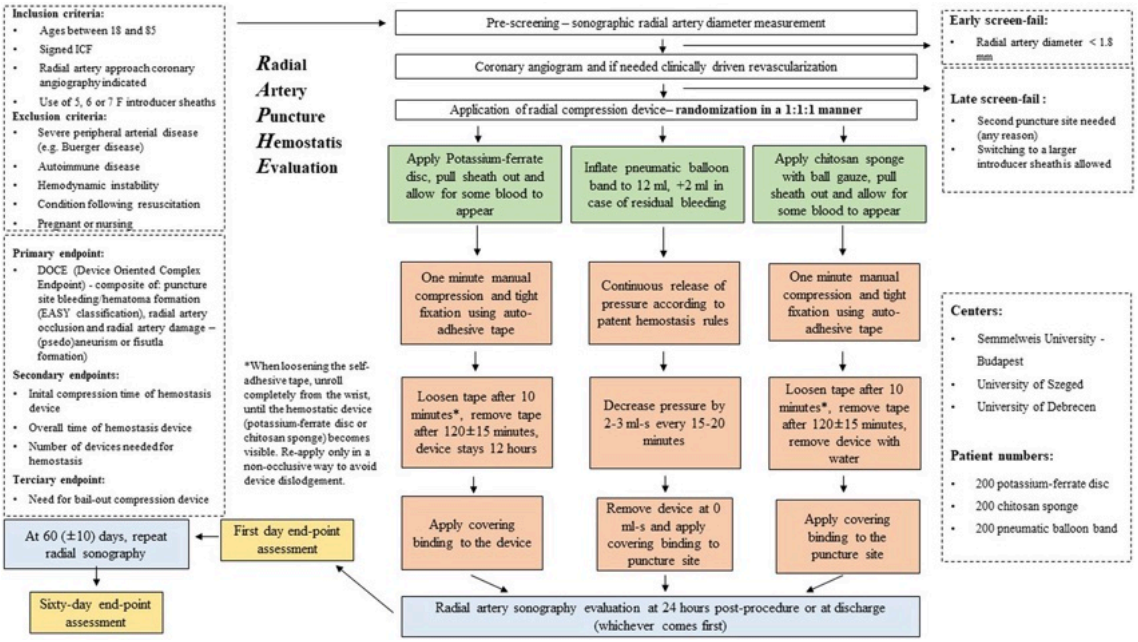


Figure 2. Flowchart of the RAPHE study

The figure details the RAPHE trial algorithm of subject inclusion/exclusion, allocation, randomization, and clinical procedures. Specifics of all three trial arms are displayed along with the required post-operative and follow-up measures. DOCE – device-oriented composite endpoint, EASY – EArly Discharge after Transradial Stenting of CoronarY Arteries, ICF – informed consent form

7.3.4 Outcome measures

The primary study outcome was a DOCE, reflecting both safety and efficacy dimensions of radial artery hemostasis. This composite endpoint encompassed three elements: (1) RAO (2) access site hematoma formation, classified according to the EASY bleeding scale; and (3) RAD, including vessel dissection, pseudoaneurysm, or arteriovenous fistula formation; determined by color duplex ultrasonography. All patients underwent blinded ultrasound assessments at three time points: pre-procedure (to establish baseline anatomy), 24 hours post-procedure or at hospital discharge (whichever occurred first), and at 60-day follow-up to capture delayed complications.

Secondary endpoints included extension of initial compression time, total time required to achieve hemostasis, need for a secondary device, and the need for a bailout device of choice. These outcomes were chosen to reflect not only patient safety but also procedural

efficiency and resource utilization, which are critical in high-volume interventional cardiology units.

7.3.5 Sample size calculation

Sample size estimation was based on a non-inferiority framework, informed by both published data and prior institutional experience. While reported RAO rates vary widely in the literature (0.5–33%), analyses of local registry data suggested a 15% incidence of the composite endpoint across groups was a conservative and realistic assumption. (58,59) The trial was powered to detect a 10% relative non-inferiority margin for the experimental devices compared to the control, with a one-sided alpha level of 0.05 and 80% power. This yielded a minimum sample size of 158 patients per group. To account for potential attrition, including loss to follow-up or protocol deviations, the target enrollment was increased to a final sample size of 200 patients per arm and an overall study population of 600 participants.

7.3.6 Statistical analysis

Statistical analysis followed an intention-to-treat principle. Hypothesis testing for non-inferiority of the primary outcome, analyzed as a categorical variable, was conducted using risk differences and 95% CI-s calculated with the Farrington-Manning test among all three trial arms, and these were assessed against the 10% non-inferiority margin. Secondary outcomes were assessed using one-way ANOVA or Kruskal-Wallis tests for continuous variables and logistic regression models for categorical outcomes. To address potential confounding factors and account for center-level differences, logistic regression was performed, including study center as a fixed effect. An interim analysis was planned after enrollment of 50% of participants, overseen by an independent Data Safety Monitoring Board authorized to recommend early termination in the event of clear superiority, inferiority, or safety concerns. All analyses were performed using the R Studio software.

7.3.7 Cost analysis

In the following chapter, we are detailing the methods of our cost analysis for the three different devices utilized in the trial. The valuation of costs is based on the resource costing method.(60) This analysis involves the costs of the hemostasis devices and the personnel time costs through approximated time burdens for applying them, calculated from publicly available Hungarian healthcare worker salary sheets. The costs of devices are the actual opportunity costs in the three participating centers of the trial and are given in Hungarian Forint (HUF). The device costs remained the same during the conduct of the clinical trial. Factors that did not differ between treatment arms were not included in the cost analysis. Personnel time costs were calculated based on the publicly available actual pre-tax salaries of Hungarian healthcare workers, including medical orderlies, nurses, and doctors participating in the application of control of all the used hemostasis devices. For generalizability, the average of the minimal and maximal basic salaries of the different caretakers was taken and divided by the average monthly working hours and minutes to get the exact numbers. The minutes demanded for the application were rounded up to eliminate uncertainty.

8 RESULTS

8.1 Results of OPEN-ISR

8.1.1 Study population

A total of 108 patients with DES-ISR were enrolled in the OPEN-ISR trial between April 2021 and December 2024 across two high-volume tertiary cardiac centers in Hungary. Following successful lesion preparation, patients were randomized in a 1:1:1 ratio to receive either a PCB (n=37), a SCB (n=34), or a new-generation EES (n=37). The trial population comprised patients presenting with either CCS or non-ST-segment elevation ACS.

Baseline demographic and clinical characteristics were similar across all three treatment arms. The time from index stent implantation to restenosis diagnosis did not differ significantly between groups. Baseline characteristics are displayed in Table 1.

Table 1. Baseline characteristics of the OPEN-ISR trial

Arm	EES (n = 37)	PCB (n = 37)	SCB (n = 34)
Age (years)	63 ± 11.2	66 ± 9.9	66 ± 8.3
BMI (kg/m²)	27.9 ± 4.2	26.8 ± 4.5	28.4 ± 5
eGFR (ml/min)	74.5 ± 18	76.2 ± 19.7	75 ± 15.6
Platelet (10^9/L)	247.4 ± 61.6	255.8 ± 66.1	250.9 ± 64.1
LVEF (%)	53.3 ± 9.6	52.6 ± 7.1	51 ± 8.4
Male	26 (70.3%)	24 (64.9%)	24 (70.6%)
Hypertension	29 (78.4%)	28 (75.7%)	27 (79.4%)
Smoking	14 (37.8%)	10 (27%)	10 (29.4%)
Dyslipidemia	31 (83.8%)	32 (86.5%)	30 (88.2%)
DM	23 (62.2%)	23 (62.2%)	15 (44.1%)
Prior ACS	15 (40.5%)	16 (43.2%)	19 (55.9%)
ASA	32 (86.5%)	33 (89.2%)	29 (85.3%)
Clopidogrel	22 (59.5%)	25 (67.6%)	21 (61.8%)
Prasugrel	5 (13.5%)	6 (16.2%)	4 (11.8%)
Ticagrelor	5 (13.5%)	3 (8.1%)	3 (8.8%)
OAC/NOAC	6 (16.2%)	6 (16.2%)	5 (14.7%)
Beta blocker	31 (83.8%)	27 (73%)	26 (76.5%)
RAAS inhibitor	32 (86.5%)	30 (81.1%)	28 (82.4%)
Statin	31 (83.8%)	31 (83.8%)	30 (88.2%)
MRA	7 (18.9%)	8 (21.6%)	7 (20.6%)

The table displays that baseline characteristics were well balanced between the treatment arms, consistent with successful randomization. ACS – acute coronary syndrome, ASA – acetyl-salicylic acid, BMI – body mass index, DM – diabetes mellitus, eGFR – estimated glomerular filtration rate, LVEF – left ventricular ejection fraction, MRA – mineralocorticoid receptor antagonist, OAC – oral anticoagulant, NOAC – non-K vitamin oral anticoagulant, RAAS – renin angiotensin aldosterone system

8.1.2 Procedural characteristics

Lesion preparation was performed using non-compliant balloons in all cases and also scoring balloons in 51% of cases, adhering to the protocol-defined DES: balloon ratio of 1:1. Procedural success was achieved in all patients without any instances of flow-limiting dissection necessitating bail-out stenting in the DCB arms. Procedural characteristics are displayed in Table 2.

Table 2. Procedural characteristics of OPEN-ISR

Arm	EES (n = 37)	PCB (n = 37)	SCB (n = 34)
1st gen. DES (%)	2 (5.4%)	4 (10.8%)	1 (2.9%)
2nd gen. DES (%)	13 (35.1%)	8 (21.6%)	8 (23.5%)
3rd gen. DES (%)	22 (59.5%)	25 (67.6%)	25 (73.5%)
Years since implant.	5.8 ± 3.8	5.5 ± 3.9	5.1 ± 3.6
Study device diam. (mm)	3.2 ± 0.5	3.1 ± 0.5	3 ± 0.5
Study device length (mm)	20.4 ± 6.5	21.1 ± 5.4	20.9 ± 5.3
Reference diameter (mm)	3.2 ± 0.5	2.8 ± 0.5	2.9 ± 0.5
MLD (mm)	0.9 ± 0.5	0.9 ± 0.5	1 ± 0.4
Diameter stenosis (%)	70 ± 15.3	65.9 ± 17.1	66.2 ± 16.1
ACS (%)	11 (29.7%)	13 (35.1%)	11 (32.4%)
Underexpansion (%)	13 (35.1%)	12 (32.4%)	14 (41.2%)
ISR type: Focal	29 (78.4%)	31 (83.8%)	27 (79.4%)
ISR type: Diffuse	8 (21.6%)	6 (16.2%)	7 (20.6%)
LAD	16 (43.2%)	12 (32.4%)	11 (32.4%)
IM	1 (2.7%)	NA	2 (5.9%)
LCX	7 (18.9%)	5 (13.5%)	8 (23.5%)
RCA	13 (35.1%)	20 (54.1%)	13 (38.2%)
NC balloon (%)	37 (100%)	37 (100%)	34 (100%)
Scoring balloon (%)	21 (56.8%)	16 (43.2%)	18 (52.9%)

The table displays that procedural characteristics were well balanced between the treatment arms, consistent with successful randomization. ACS – acute coronary syndrome, DES – drug-eluting stent, ISR – in-stent restenosis, LAD – left anterior descending artery, LCX – left circumflex coronary artery, IM – intermediate coronary artery, MLD – minimal lumen diameter, NC balloon – non-compliant balloon RCA – right coronary artery

8.1.3 Primary outcome

At six months, LLL, the primary endpoint, was comparable between the combined DCB group (PCB and SCB) and the EES group. Median LLL measured by QCA was 0.30 mm (IQR: 0.20–0.70 mm) in the combined DCB group versus 0.55 mm (IQR: 0.10–1.35 mm) in the EES group, with mean values of 0.53 ± 0.53 mm and 0.73 ± 0.70 mm. This result met the pre-specified non-inferiority margin of 0.25 mm, demonstrating that DCB therapy was non-inferior to repeat DES implantation in the treatment of DES-ISR.

When analyzed separately, PCBs and SCBs exhibited similar LLL distributions (PCB median 0.30 mm (IQR: 0.18–0.70 mm) vs. SCB median 0.32 mm (IQR: 0.22–0.68 mm); P = 0.84). The results of the primary outcome are visualized in Figures 3 and 4.

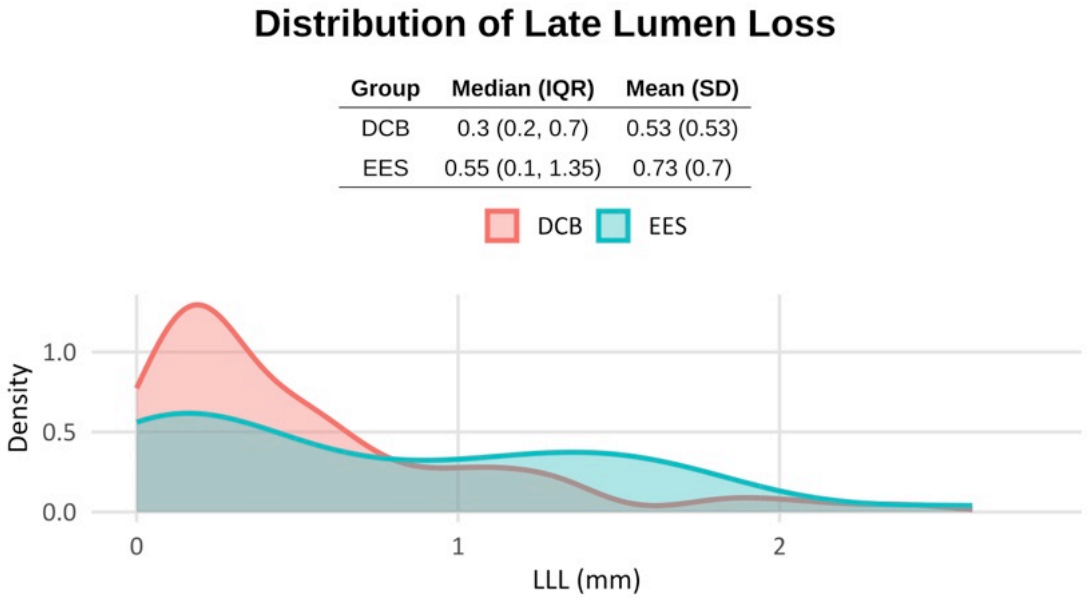


Figure 3. Distribution of late lumen loss among the primary outcome analysis arms
The distribution curves show that late lumen loss was overall lower in the DCB group compared with the EES group, with a sharper peak at lower values and less spread. In contrast, the EES group demonstrated a broader distribution shifted toward higher late lumen loss, indicating greater variability. DCB – drug-coated balloon, EES – everolimus-eluting stent, IQR – interquartile range between 25 and 75 percent of distribution, LLL – late lumen loss, SD – standard deviation

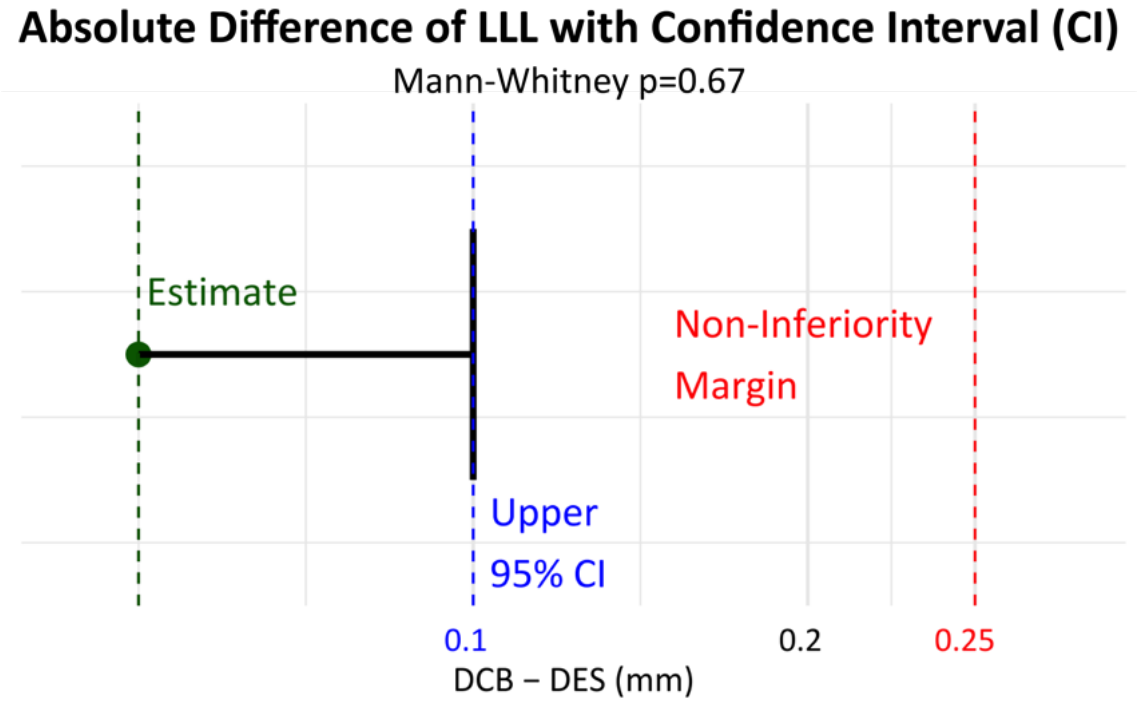


Figure 4. Absolute difference point estimate of late lumen loss with one-sided Hodges-Lehmann Confidence interval, displayed with the predetermined non-inferiority margin The figure illustrates the absolute difference in late lumen loss (LLL) between drug-coated balloon (DCB) and drug-eluting stent (DES) with the corresponding 95% confidence interval. The point estimate shows minimal difference, and the upper bound of the confidence interval (0.1 mm) remains well below the predefined non-inferiority margin of 0.25 mm, thereby establishing non-inferiority of DCB compared with DES. The Mann–Whitney test yielded a p-value of 0.67, indicating no statistically significant difference between the two groups. LLL – late lumen loss, DCB – drug-coated balloon, DES – drug-eluting stent, Upper 95% CI – upper margin of 95 percent confidence interval

8.1.4 Secondary outcomes

8.1.4.1 Acute gain

AG, calculated as the change in minimal lumen diameter (MLD) between pre-procedural and post-procedural QCA, was significantly different among treatment groups (Kruskal–Wallis P = 0.00024). The EES group demonstrated the highest AG, with a median of 2.22 mm (IQR: 1.94–2.51 mm), compared to 1.55 mm (IQR: 1.36–1.72 mm) in the PCB group and 1.52 mm (IQR: 1.37–1.72 mm) in the SCB group. Pairwise comparisons revealed significantly greater AG in the EES group relative to both DCB groups (P < 0.001 for EES vs. PCB; P < 0.001 for EES vs. SCB), whereas no significant difference was observed between PCB and SCB (P = 0.78). The results of AG are displayed in Figure 5. and Table 3.

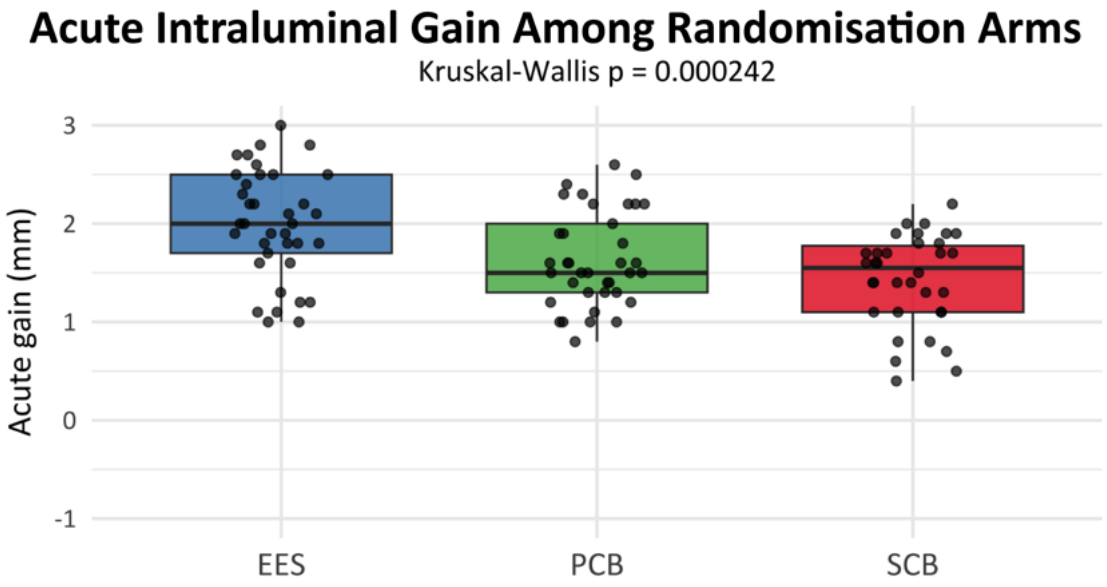


Figure 5. Distribution of Acute Intraluminal Gain Among Randomization Arms
This figure displays the distribution of index procedural acute intraluminal gain among randomization arms. Acute intraluminal gain differed significantly among the three randomization arms as indicated by the Kruskal–Wallis test (p = 0.000242). Kruskal-EES – everolimus-eluting stent; PCB – paclitaxel-coated balloon; SCB – sirolimus-coated balloon

Table 3. Comparison of Acute Intraluminal Gain Among Randomization Arms with Dunn Post-Hoc Test

Group Comparison	Z value	Raw p-value	Bonferroni-adjusted p
EES - PCB	2.8448	0.0044	0.0133
EES - SCB	3.9377	0.0001	0.0002
PCB - SCB	1.1536	0.2486	0.7459

After the Kruskal–Wallis test indicated a significant difference among the three arms, Dunn's post hoc analysis showed that EES had significantly different outcomes compared with both PCB and SCB, whereas no significant difference was observed between PCB and SCB. EES – everolimus-eluting stent, PCB – paclitaxel-coated balloon, SCB – sirolimus-coated ballon

8.1.4.2 Net gain

Net gain, which displays AG minus LLL, and is a suitable comparator if DCB and DES, was statistically nondifferent in the EES arm compared to both DCB arms. Median (IQR) net gain was 1.4 (0.9–2.1) mm in the EES group, 1.2 (0.7–1.6) mm in the PCB group, and 1.1 (0.6–1.5) mm in the SCB group. While EES showed a tendency towards greater net gain, the difference among the three groups did not reach statistical significance (Kruskal-Wallis p = 0.0695). The results of net gain are displayed in Figure 6.

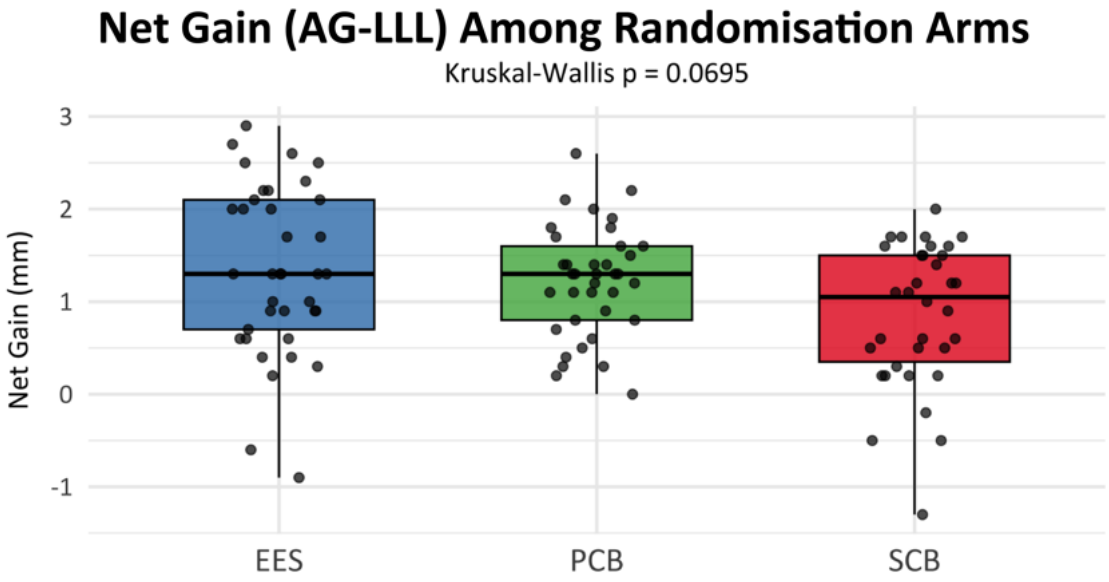


Figure 6. Distribution of net gain among randomization arms

This figure displays the achieved net gain (acute gain at index procedure reduced by late lumen loss) at follow-up among randomization arms. There was no statistical difference between the results of the three arms. AG – acute gain, EES – everolimus-eluting stent, LLL – late lumen loss, PCB – paclitaxel-coated balloon, SCB – sirolimus-coated balloon

8.1.4.3 Device-oriented composite endpoint

The DOCE, defined as the composite of TLR, TVMI, and cardiac death, was observed in 18 patients at six months. Event counts for DOCE components were as follows: TLR occurred in 16 patients in the EES group, 13 patients in the PCB group, and 12 patients in the SCB group; TVMI occurred in 3, 3, and 2 patients, respectively; and cardiac death occurred in 1 patient each in the EES and SCB groups but was not observed in the PCB group.

Logistic regression analysis identified LLL as the only variable significantly associated with DOCE ($p<0.05$). No significant differences in DOCE incidence were detected between treatment groups (SCB vs. EES and PCB vs. EES, $p>0.05$ for both comparisons). The results of DOCE are displayed in Figure 7.

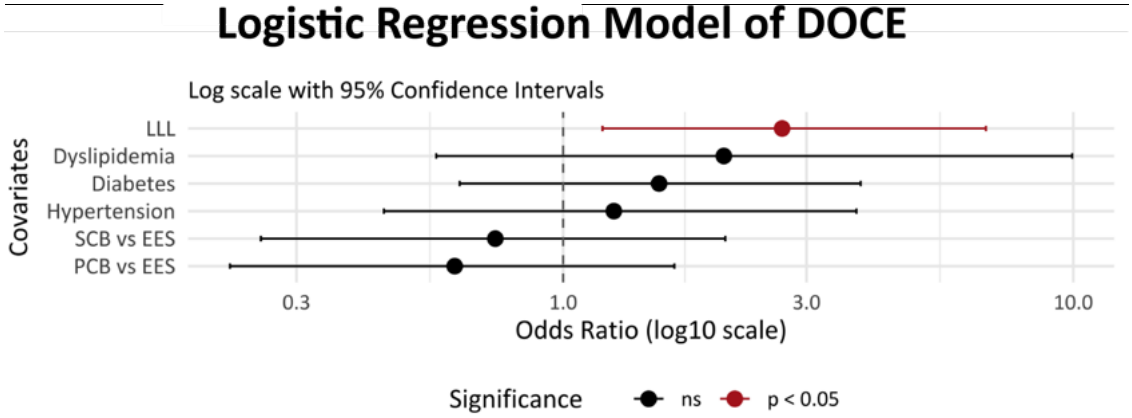


Figure 7. Logistic regression model of DOCE

In the logistic regression model of DOCE, late lumen loss emerged as a significant predictor, with greater values associated with increased risk. In contrast, dyslipidemia, diabetes, hypertension, and treatment arm (SCB vs EES, PCB vs EES) were not independently associated with DOCE. DOCE – device-oriented composite endpoint, LLL – late lumen loss, EES – everolimus-eluting stent, PCB – paclitaxel-coated balloon, SCB – sirolimus-coated balloon

8.1.4.4 QFR shift to LLL

Change in quantitative flow ratio (ΔQFR) from baseline to six-month follow-up demonstrated a significant positive correlation with LLL. Linear regression analysis yielded the equation $y = 4.01x + 0.34$, with an R^2 of 0.262, indicating that approximately 26% of the variability in LLL was explained by changes in QFR ($P = 2.47 \times 10^{-5}$). The mean ΔQFR was 0.08 ± 0.08, and the median was 0.04 (IQR: 0.02–0.12). Mean LLL was 0.64 ± 0.63 mm, and the median was 0.40 mm (IQR: 0.20–1.10 mm). OCT-based LLL measurements were performed in 24% of patients, but the limited sample size precluded formal statistical analysis of these data. Results of QFR shift compared to LLL are displayed in Figure 8. and Table 4.

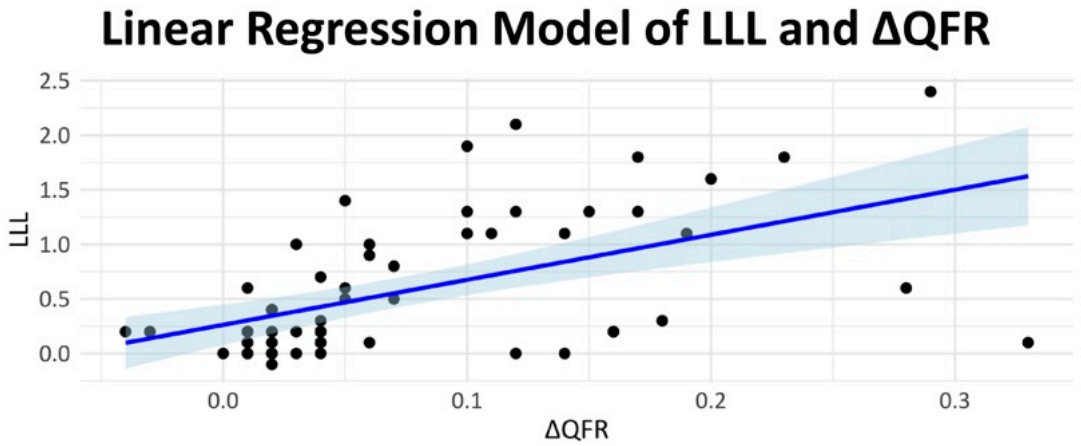


Figure 8. Linear regression model of LLL and ΔQFR

This figure displays a positive association of late lumen loss and change in quantitative flow ratio (ΔQFR) from the index procedure to follow-up. The fitted regression line with confidence band confirms an upward trend, suggesting that physiological decline is linked to angiographic restenosis severity. ΔQFR – change in quantitative flow ratio, LLL – late lumen loss

Table 4. Summary Statistics for ΔQFR and LLL

Regression: y = 4.01x + 0.34 | R^2 = 0.262 | p = 2.47e−05		
Variable	**Mean (SD)**	**Median (IQR)**
ΔQFR	0.08 (0.08)	0.04 (0.02–0.12)
LLL	0.64 (0.63)	0.40 (0.20–1.10)

The table shows a statistically significant positive linear relationship between the change in quantitative flow ratio (ΔQFR) and late lumen loss. This indicates that greater physiological deterioration is associated with increased angiographic restenosis. ΔQFR – change in quantitative flow ratio, LLL – late lumen loss

8.2 Results of Meta-analysis

8.2.1 Study Selection and Characteristics

A total of 832 records were identified through the systematic search of five major databases. After removal of duplicates and title/abstract screening, 46 articles underwent full-text review for eligibility. Of these, four studies met the inclusion criteria and were included in the meta-analysis. These studies collectively enrolled 882 patients with DES-ISR treated with DCB angioplasty. Patients were stratified into two groups based on the interval between index stent implantation and restenosis occurrence: early DES-ISR (≤12 months) and late DES-ISR (>12 months). A PRISMA flow diagram illustrating the selection process is presented in Figure 9.

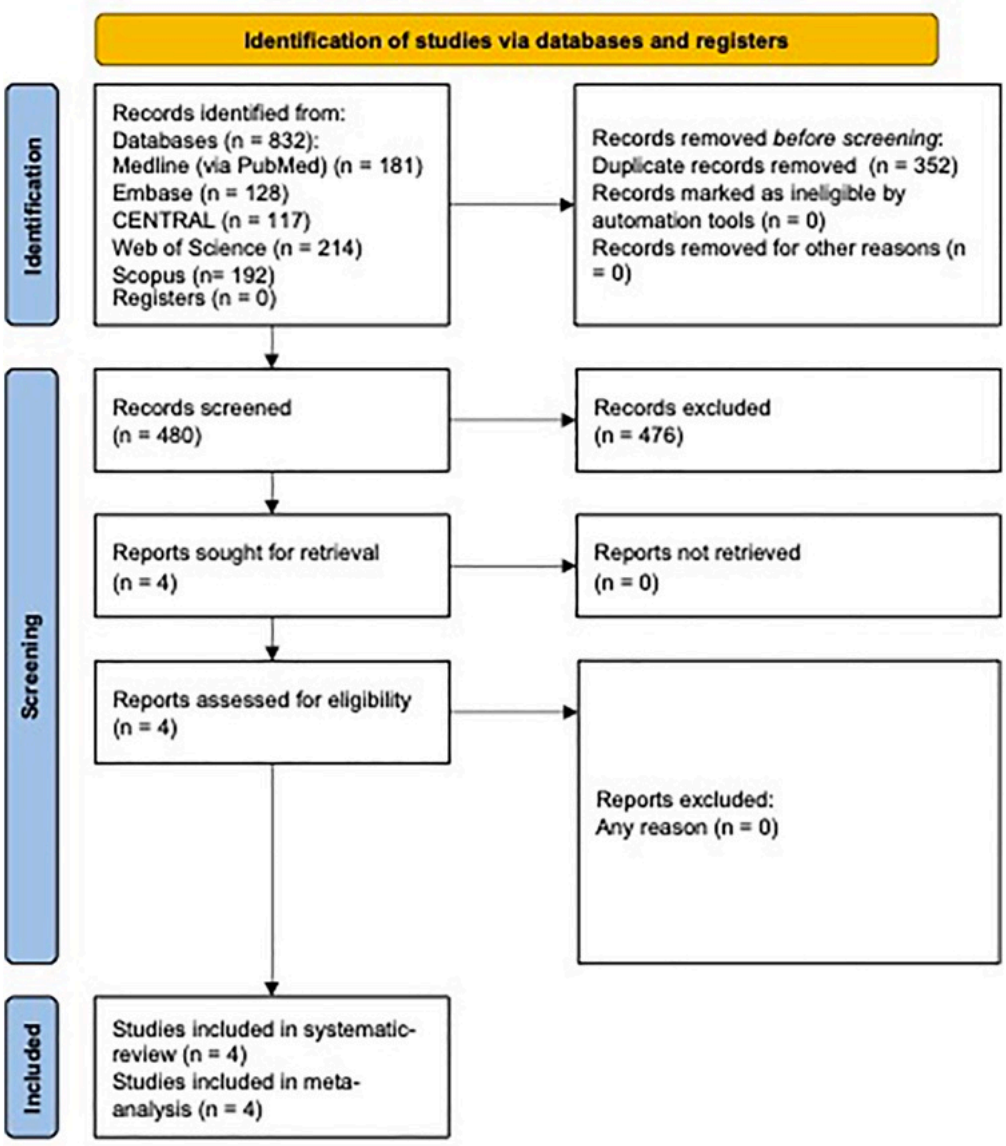


Figure 9. Flow diagram of systematic search and article selection

A total of 832 records were identified, 352 duplicates removed, and 480 screened. After exclusions, 4 studies remained and were included in the meta-analysis.

The included studies varied in design, patient population, and procedural details. All reported outcomes at 12 months following DCB treatment. Baseline demographics and clinical characteristics were broadly comparable between early and late DES-ISR groups. Across the pooled population, the mean age was 66.1 ± 9.4 years, and 73.4% were male. Diabetes mellitus was present in 31.7% of patients, and hypertension in 68.9%. One study reported a significantly higher prevalence of hemodialysis in the early ISR cohort (33.0% vs. 15.4%, p=0.002). The included study characteristics are displayed in Table 5. (61–64)

Table 5. Characteristics of included trials.

Study	Early/ late definition	Early DES-ISR	Late DES-ISR	Outcome assessment time	MACE Intervention arm	MACE Control arm	TLR Intervention arm	TLR Control arm	Inclusion criteria
Sato	average 19 months	131	56	median 1 y or at symptoms	not published	not published	88	30	DCB treatment
Koch	12 months	199	153	1 y or at symptoms	51	26	47	24	DCB treatment
Lee	12 months	21	101	5 y or at symptoms	5	16	not published	not published	DCB treatment
Kuramitsu	12 months	101	136	2 y or at symptoms	not published	not published	18	16	DCB treatment

The table displays the characteristics of the included trials. (61–64) DCB – drug-coated ballon, DES-ISR – drug-eluting stent in-stent restenosis, MACE – major adverse cardiac events, TLR – target lesion revascularization

8.2.2. Primary outcome: major adverse cardiac events

The primary outcome, MACE, a composite of TLR, MI, and cardiac death, was reported in all four studies at 12 months. Patients with early DES-ISR demonstrated a significantly higher risk of MACE following DCB therapy compared to those with late DES-ISR.
The pooled OR for MACE was 1.68 (95% CI: 1.57–1.80, $p<0.01$), indicating a 68% increased risk in the early ISR group. In Koch et al., MACE incidence was 25.9% in early ISR compared to 17.0% in late ISR ($p=0.04$), yielding an OR of 1.68 (95% CI: 0.99–2.86). Similarly, Lee et al. reported MACE rates of 23.8% and 15.8% for early and late ISR, respectively ($p<0.01$), with an OR of 1.66 (95% CI: 0.53–5.18). A forest plot summarizing these findings is shown in Figure 10.

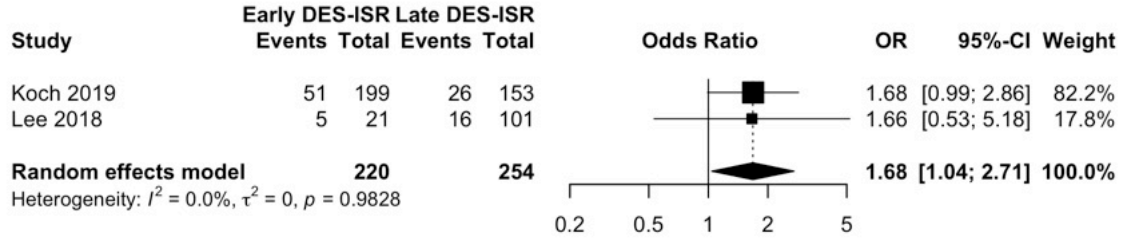


Figure 10. Forrest plot of major adverse cardiac events (MACE)

This forest plot summarizes the results of two studies (Koch 2019 and Lee 2018) comparing the early DES-ISR arm versus the late DES-ISR. In Koch 2019, 51 of 199 patients in the early DES-ISR arm and 26 of 153 in the late DES-ISR arm experienced events, yielding an odds ratio (OR) of 1.68 (95% CI 0.99–2.86) favoring late DES-ISR. In Lee 2018, 5 of 21 versus 16 of 101 patients had events, with an OR of 1.66 (95% CI 0.53–5.18) favoring late DES-ISR. The pooled analysis under a random-effects model shows a combined OR of 1.68 (95% CI 1.57–1.80), indicating a significantly higher risk of events in the early-DES ISR group compared to the late DES-ISR. Heterogeneity was negligible (I^2 = 0%, p = 0.98), suggesting consistency across studies. The overall effect test was highly significant (p < 0.01). 95%-CI – 95 percent confidence interval, DES-ISR – drug-eluting stent in-stent restenosis, OR – odds ratio

8.2.3 Secondary outcomes

8.2.3.1 Target lesion revascularization

TLR was the primary driver of the increased MACE risk in early ISR patients. The pooled OR for TLR was 1.69 (95% CI: 1.18–2.42, p<0.01). In Sato et al., TLR occurred in 40% of early ISR patients versus 16% in late ISR. Kuramitsu et al. observed TLR rates of 30.0% in early ISR compared to 18.3% in late ISR (p=0.035). These findings are depicted in Figure 11.

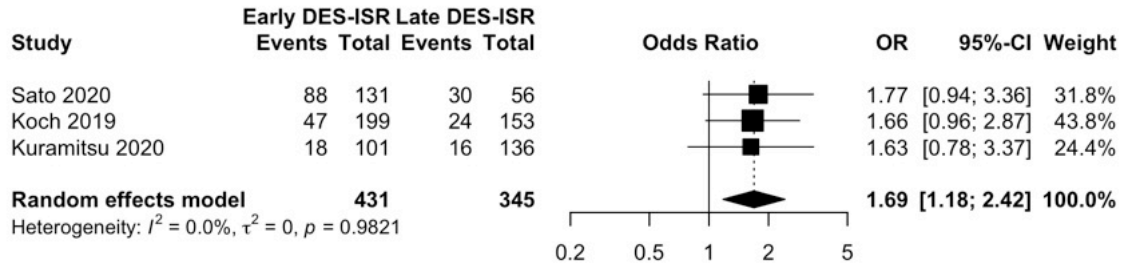


Figure 11. Forrest plot of target lesion revascularization (TLR)

This forest plot summarizes the results of three studies (Sato 2020, Koch 2019, and Kuramitsu 2020) comparing target lesion revascularization in early versus late DES-ISR. In Sato 2020, 88 of 131 patients in the early DES-ISR group and 30 of 56 in the late DES-ISR group experienced events, yielding an odds ratio (OR) of 1.77 (95% CI 0.94–3.36), suggesting a numerically higher event rate in early DES-ISR. In Koch 2019, 47 of 199 versus 24 of 153 patients had events, with an OR of 1.66 (95% CI 0.96–2.87). In Kuramitsu 2020, 18 of 101 versus 16 of 136 patients experienced events, corresponding to an OR of 1.63 (95% CI 0.78–3.37). The pooled analysis under a random-effects model shows a combined OR of 1.69 (95% CI 1.18–2.42), indicating a statistically significant higher risk of TLR in the early DES-ISR group compared with late DES-ISR. Heterogeneity was negligible (I^2 = 0%, p = 0.98), supporting consistency across studies.
95%-CI – 95% confidence interval; DES-ISR – drug-eluting stent in-stent restenosis;
OR – odds ratio.

8.2.3.2 Target vessel myocardial infarction

The incidence of TVMI was low. One study reported MI in six patients (3.0%) with early DES-ISR and in two patients (1.3%) with late DES-ISR (p=0.29).

8.2.3.3 Cardiac death

Cardiac death occurred infrequently. Only Koch et al. reported three deaths (1.5%) in the early ISR group and none in the late ISR group (p=0.82).

8.2.3.4 Target lesion thrombosis

Target lesion thrombosis was reported in one study, with a single event (0.5%) in the early ISR group and none in the late ISR group (p=0.90).

8.2.4 Risk of bias and sensitivity analyses

Risk of bias assessment using the Quality in Prognosis Studies (QUIPS) tool identified two studies at low risk and two at moderate risk of bias. Funnel plot inspection did not suggest substantial publication bias, but the small number of studies limits the robustness of this analysis. The risk of bias assessment is displayed in Figure 12.

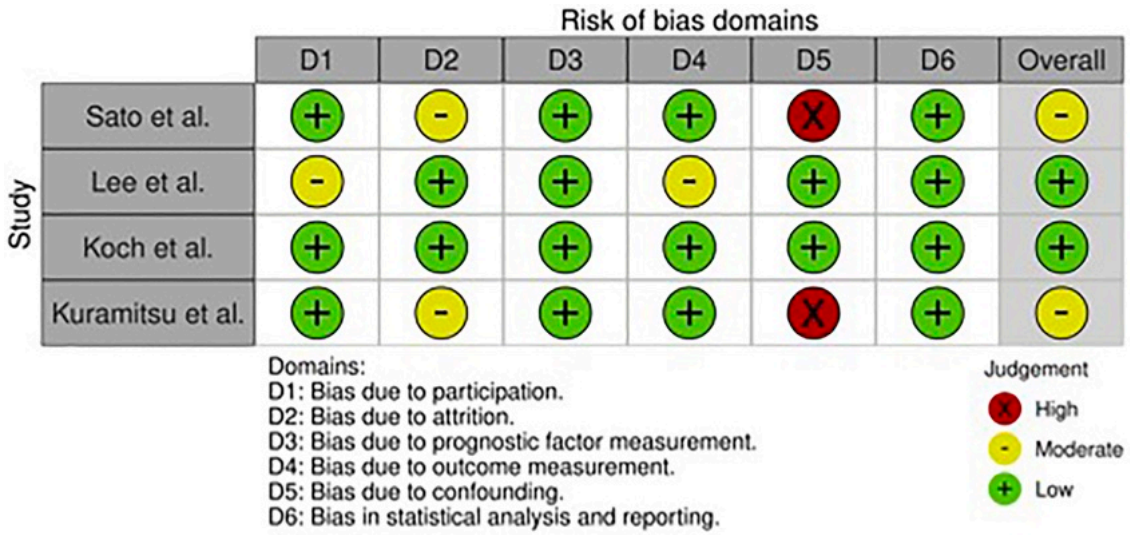


Figure 12. Risk of bias assessment among the included studies

The figure shows that most studies were judged to have a low to moderate risk of bias across domains, except for Sato et al. and Kuramitsu et al., which had an overall moderate risk of bias driven by a high risk of bias due to confounding.

8.3 Results of RAPHE

Between January 2021 and December 2023, a total of 600 patients were enrolled across three high-volume tertiary cardiac centers in Hungary for participation in the RAPHE trial. Randomization was carried out in a 1:1:1 ratio, assigning participants to one of three radial artery hemostasis strategies: the chitosan bioactive sponge dressing, the potassium

ferrate hemostatic disc, or the pneumatic compression device as control. One patient in the control group was excluded from the final analysis due to incomplete data collection, resulting in an analyzed cohort of 599 patients. Of these, 203 patients received chitosan, 207 potassium ferrate, and 189 pneumatic compression. Overall, 31 participants (5.1%) were lost to follow-up, which was well within the predefined allowance of 10% used for sample size estimation. The flowchart of screening is displayed in Figure 13.

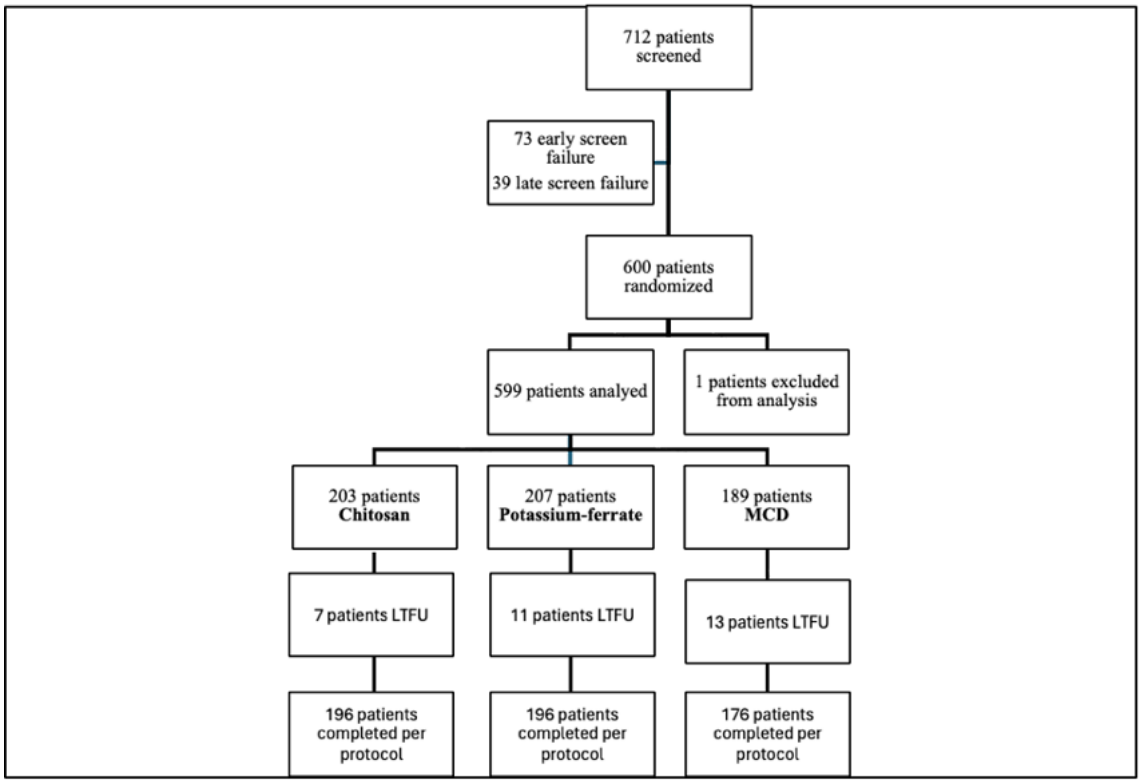


Figure 13. Flowchart of patients in the trial

This figure describes the number of all patients in the trial from screening until completion, including screen failures and lost to follow-ups. LTFU – lost to follow-up, MCD – mechanical compression device

8.3.1 Study population

Baseline demographic and clinical characteristics were well balanced between groups, suggesting successful randomization. The mean age of the study population was 66.2 ± 11.2 years, and 66.9% of participants were male. Hypertension was the most common comorbidity, present in 88.0% of patients, followed by dyslipidemia (69.3%) and diabetes

mellitus (24.7%). The prevalence of prior PCI was comparable across the three study arms. Baseline characteristics are displayed in Table 6.

Table 6. Baseline characteristics of the RAPHE trial

Arm	Total	Chitosan	Potassium ferrate	MCD
Patients	**n=599**	**n=203**	**n=207**	**n=189**
Male	401 (66.9%)	143 (70.4%)	142 (68.6%)	116 (61.4%)
Age (years)	66.2 (±11.2)	65.9 (±11.2)	65.7 (±11.3)	67.2 (±11.0)
BMI (kg/m2)	29.5 (±6.41)	29.4 (±4.74)	29.5 (±5.04)	29.8 (±8.87)
Hypertension	527 (88.0%)	175 (86.2%)	182 (87.9%)	170 (89.9%)
Smoking	80 (13.4%)	26 (12.8%)	32 (15.5%)	22 (11.6%)
Dyslipidemia	415 (69.3%)	140 (69.0%)	143 (69.1%)	132 (69.8%)
IDDM	27 (4.5%)	11 (5.4%)	7 (3.4%)	9 (4.8%)
NIDDM	121 (20.2%)	32 (15.8%)	50 (24.2%)	39 (20.6%)
ACS in history	100 (16.7%)	30 (14.8%)	44 (21.3%)	26 (13.8%)
Prior PCI	141 (23.5%)	35 (17.2%)	60 (29.0%)	46 (24.3%)
Prior stroke	18 (3.0%)	4 (2.0%)	5 (2.4%)	9 (4.8%)
Prior malignancy	31 (5.2%)	9 (4.4%)	14 (6.8%)	8 (4.2%)
Concomitant liver disease	7 (1.2%)	1 (0.5%)	3 (1.4%)	3 (1.6%)
Prior CABG	13 (2.2%)	5 (2.5%)	5 (2.4%)	3 (1.6%)
eGFR (ml/min)	69.6 (±22.6)	71.6 (±20.6)	69.3 (±23.4)	67.8 (±23.6)
Thrombocyte count (G/l)	216.0 (±83.5)	223.0 (±77.9)	213.0 (±84.6)	213.0 (±88.0)
Ejection fraction (%)	54.1 (±16.5)	56.2 (±13.5)	53.1 (±17.7)	53.0 (±17.7)

The table displays that baseline characteristics were well balanced between the treatment arms, consistent with successful randomization. ACS – acute coronary syndrome, BMI – body mass index, CABG – coronary artery bypass graft surgery, eGFR – estimated glomerular filtration rate, IDDM – insulin-dependent diabetes mellitus, NIDDM – non-insulin-dependent diabetes mellitus, PCI – percutaneous coronary intervention,

8.3.2 Procedural and follow-up characteristics

Procedural variables, as well as follow-up characteristics, demonstrated no significant differences between groups. The radial artery diameter averaged 2.46 ± 0.59 mm across

the cohort. Ad-hoc PCI following diagnostic angiography was performed in 187 cases (31.2%), evenly distributed among the three study arms. Procedural and follow-up characteristics are displayed in Table 7. and 8.

Table 7. Procedural characteristics of the RAPHE trial

Arm	Total	Chitosan	Potassium ferrate	MCD
Patients	**n=599**	**n=203**	**n=207**	**n=189**
Proc. time (min)	16.6 (±17.1)	14.2 (±12.6)	20.1 (±20.7)	15.4 (±16.4)
Left puncture	21 (3.5%)	3 (1.5%)	9 (4.3%)	9 (4.8%)
Right puncture	578 (96.5%)	200 (98.5%)	198 (95.7%)	180 (95.2%)
Artery diameter (millimetres)	2.46 (±0.585)	2.45 (±0.583)	2.48 (±0.603)	2.45 (±0.568)
Calcification	69 (11.5%)	24 (11.8%)	22 (10.6%)	23 (12.2%)
Earlier puncture	8 (3.9%)	13 (6.3%)	9 (4.6%)	30 (5%)
5F Sheath	19 (3.2%)	5 (2.5%)	6 (2.9%)	8 (4.2%)
6F Sheath	551 (92.0%)	194 (95.6%)	189 (91.3%)	168 (88.9%)
7F Sheath	29 (4.8%)	4 (2.0%)	12 (5.8%)	13 (6.9%)
Nitrate	464 (77.5%)	159 (78.3%)	163 (78.7%)	142 (75.1%)
5000 IU heparin	439 (73.3%)	156 (76.8%)	135 (65.2%)	148 (78.3%)
10000 IU heparin	123 (20.5%)	40 (19.7%)	55 (26.6%)	28 (14.8%)
Aspirin	423 (70.6%)	139 (68.5%)	158 (76.3%)	126 (66.7%)
Clopidogrel	215 (35.9%)	69 (34.0%)	86 (41.5%)	60 (31.7%)
Prasugrel	21 (3.5%)	8 (3.9%)	11 (5.3%)	2 (1.1%)
Ticagrelor	6 (1.0%)	1 (0.5%)	3 (1.4%)	2 (1.1%)
VKA	16 (2.7%)	7 (3.4%)	7 (3.4%)	2 (1.1%)
Apixaban	39 (6.5%)	15 (7.4%)	7 (3.4%)	17 (9.0%)
Dabigatran	7 (1.2%)	2 (1.0%)	0 (0%)	5 (2.6%)
Edoxaban	8 (1.3%)	1 (0.5%)	5 (2.4%)	2 (1.1%)
Rivaroxaban	16 (2.7%)	8 (3.9%)	2 (1.0%)	6 (3.2%)

The table displays that procedural characteristics were well balanced between the treatment arms, consistent with successful randomization. F – French (1 French 0.33 mm), IU – international unit, VKA – vitamin K antagonist

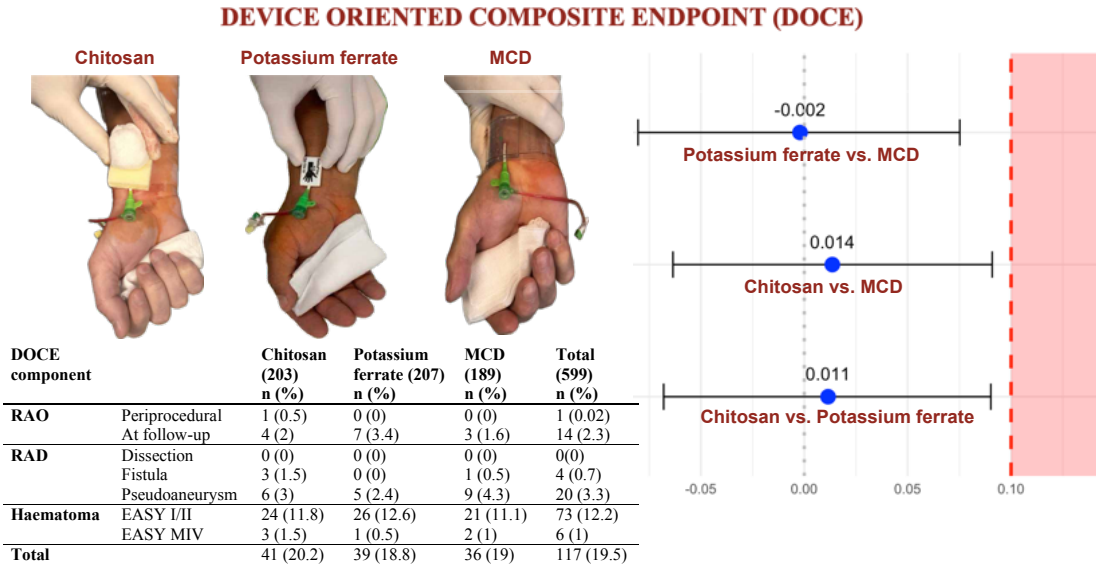
Table 8. Follow-up characteristics of the RAPHE trial

Arm	Total	Chitosan	Potassium ferrate	MCD
Patients	n=599	n=203	n=207	n=189
Follow-up time	79 (63, 132)	76 (63, 123)	79 (63, 135)	77 (63, 130)
Lost to follow-up	7 (3.4%)	11 (5.3%)	13 (6.6%)	31 (5.2%)
Follow-up by US	151 (74.4%)	149 (72%)	138 (70%)	438 (73.1%)
Follow-up by phone	45 (22.2%)	47 (22.7%)	38 (19.4%)	130 (21.7%)

The table displays that follow-up characteristics were well balanced between the treatment arms, consistent with successful randomization. US – ultrasound

8.3.3 Primary outcome

The DOCE, defined as the occurrence of RAO, access-site hematoma, or RAD, was the primary efficacy and safety outcome of the trial. DOCE events occurred in 20.2% of patients in the chitosan group, 18.8% in the potassium ferrate group, and 19.0% in the pneumatic compression group (Figure 14). These results demonstrated no significant differences between groups and confirmed the non-inferiority of both investigational devices compared with the standard pneumatic compression device.



DOCE component		Chitosan (203) n (%)	Potassium ferrate (207) n (%)	MCD (189) n (%)	Total (599) n (%)
RAO	Periprocedural	1 (0.5)	0 (0)	0 (0)	1 (0.02)
	At follow-up	4 (2)	7 (3.4)	3 (1.6)	14 (2.3)
RAD	Dissection	0 (0)	0 (0)	0 (0)	0(0)
	Fistula	3 (1.5)	0 (0)	1 (0.5)	4 (0.7)
	Pseudoaneurysm	6 (3)	5 (2.4)	9 (4.3)	20 (3.3)
Haematoma	EASY I/II	24 (11.8)	26 (12.6)	21 (11.1)	73 (12.2)
	EASY MIV	3 (1.5)	1 (0.5)	2 (1)	6 (1)
Total		41 (20.2)	39 (18.8)	36 (19)	117 (19.5)

Figure 14. Device-oriented composite endpoint (DOCE)

This figure displays the results of comparisons of the three randomization arms with risk differences, confidence intervals calculated with Farrington-Manning tests against the 10% non-inferiority margin, and the subcomponents of DOCE. The rates of DOCE and its components were comparable among chitosan, potassium ferrate, and MCD, with minimal risk differences and all comparisons remaining well within the non-inferiority margin. CI – 95% confidence interval; EASY I/II and III/IV – as per EArly Discharge after Transradial Stenting of CoronarY Arteries (EASY) Study classification, MCD – mechanical compression device, RAD – radial artery damage, RAO – radial artery occlusion, RD – risk difference.

Risk differences with 95% CIs were calculated using the Farrington-Manning test. The upper bounds of the CIs remained below the predefined non-inferiority margin of 10% for all pairwise comparisons: chitosan vs. control (0.011; 95% CI: -0.068 to 0.090), potassium ferrate vs. control (-0.002; 95% CI: -0.080 to 0.075), and chitosan vs. potassium ferrate (0.014; 95% CI: -0.064 to 0.091). Sensitivity analyses using the Miettinen-Nurminen test corroborated these findings (Figure 15.).

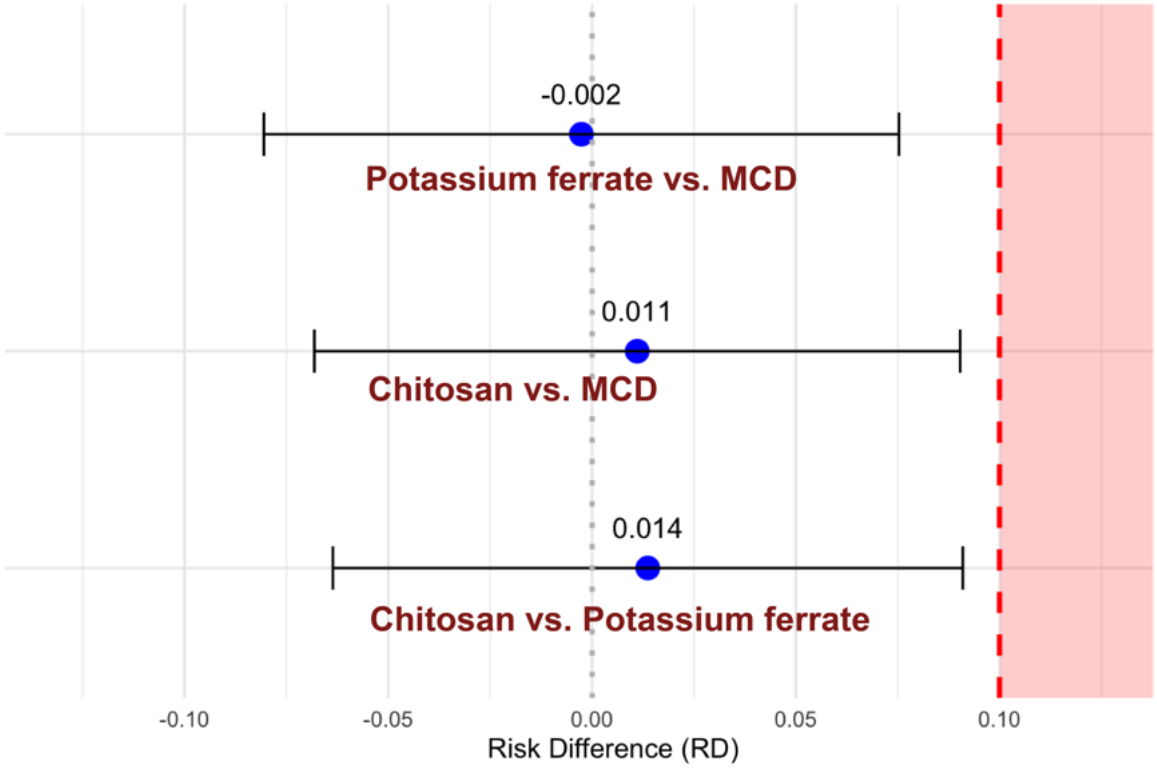


Figure 15. Sensitivity analysis of the device-oriented composite endpoint (DOCE)

In this figure, the sensitivity analysis of the DOCE is presented with the Miettinen-Nurminen method. Risk differences with 95% confidence intervals remained entirely below the predefined non-inferiority margin of 10% difference in all three comparisons. MCD – mechanical compression device

The individual components of the primary outcome revealed low rates of serious access site complications. No dissections were reported, while arteriovenous fistula occurred in 0.7% and pseudoaneurysm in 3.3% of participants. Most pseudoaneurysms were identified during follow-up ultrasound, with only a small number detected during hospitalization. Logistic regression analysis stratified by study center confirmed the robustness of the findings, with no significant center-level variability affecting primary outcome rates (Figure 16).

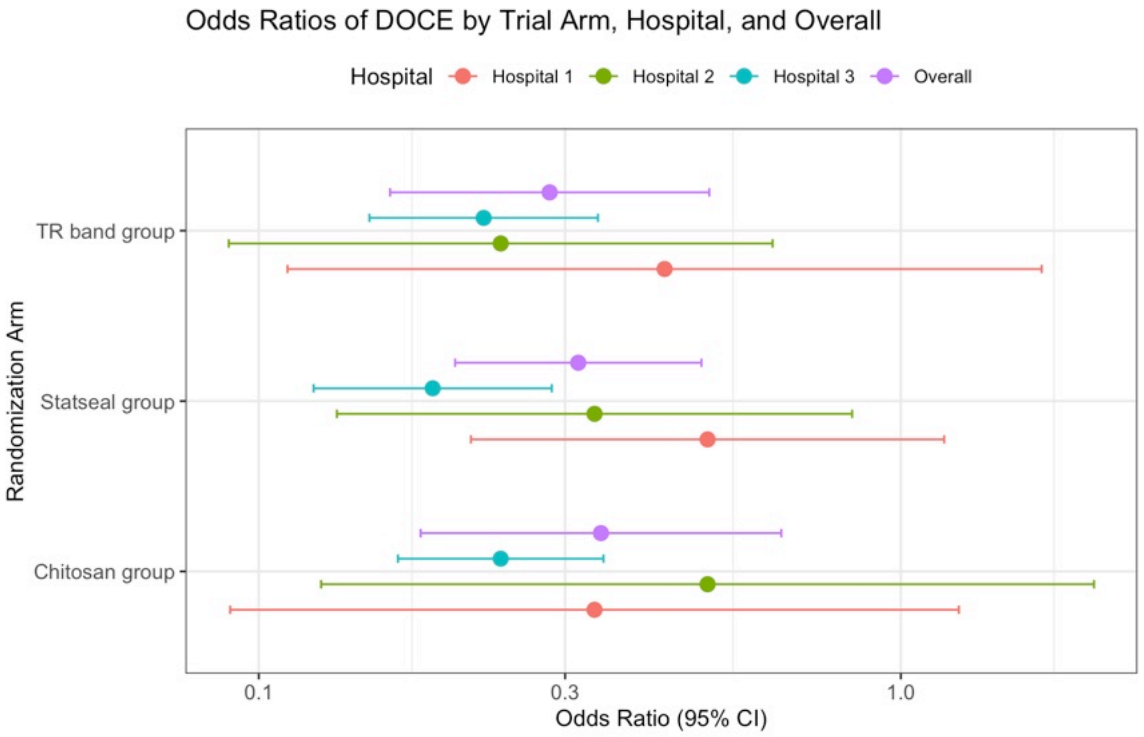


Figure 16. Logistic regression analysis of DOCE stratified by randomizing center with fixed effects model

Across all hospitals, the odds ratios of DOCE were consistently below 1 for the TR band (chitosan), Statseal (potassium ferrate), and Chitosan groups, indicating lower event rates compared with the control. While individual hospital estimates varied and confidence intervals were wide, the overall pooled effects for each randomization arm were similar and suggested a protective effect. DOCE – device-oriented composite endpoint

8.3.4 Secondary outcomes

8.3.4.1 Extension of initial compression time

The need for prolonged occlusive compression beyond the planned 10 minutes was observed in 10 patients (5.3%) in the pneumatic compression group, 10 patients (4.9%) in the chitosan group, and only 3 patients (1.4%) in the potassium ferrate group. Fisher's exact test revealed no significant difference between the chitosan and pneumatic compression groups. However, a marginally significant reduction in prolonged compression was noted in the potassium ferrate group compared with the control (p=0.048) (Figure 17).

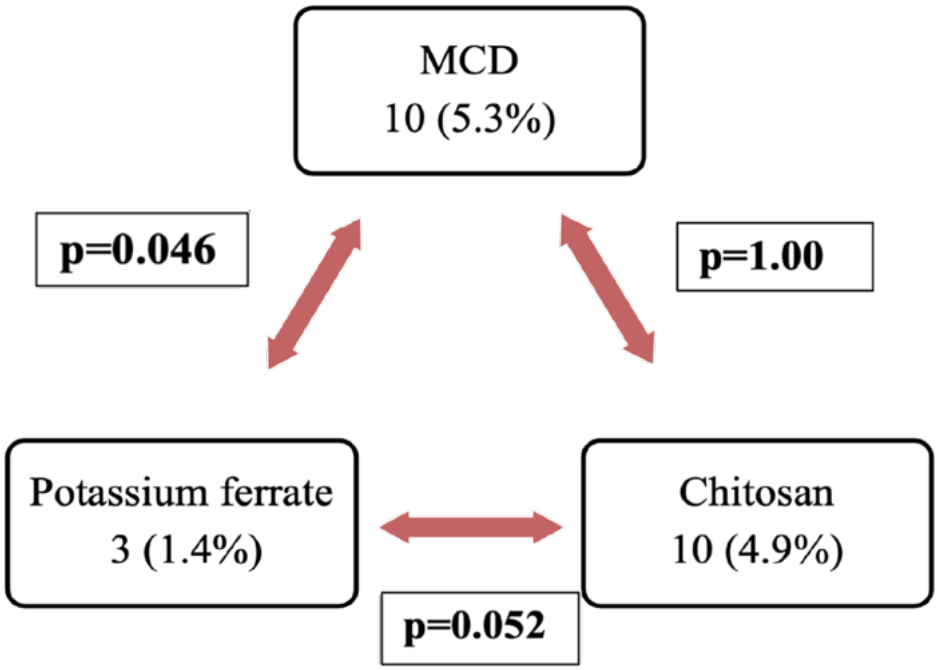


Figure 17. Patients requiring extension of initial compression time

The three treatment arms are displayed with the outcome numbers, percentages and resulting p-values of Fisher's exact tests. MCD was significantly higher than potassium ferrate, comparable with chitosan, and the difference between potassium ferrate and chitosan was borderline significant. MCD – mechanical compression device.

8.3.4.2 Overall device usage time

The median duration of overall device application was slightly shorter in the potassium ferrate group (120 minutes; (IQR): 116–124 minutes) compared with the chitosan (122 minutes; IQR: 116–128 minutes) and pneumatic compression groups (125 minutes; IQR: 118–127 minutes). The Kruskal-Wallis test indicated a statistically significant difference across groups ($p<0.05$), and pairwise comparisons showed significantly shorter times for potassium ferrate compared with both chitosan and control ($p<0.05$) (Figure 18).

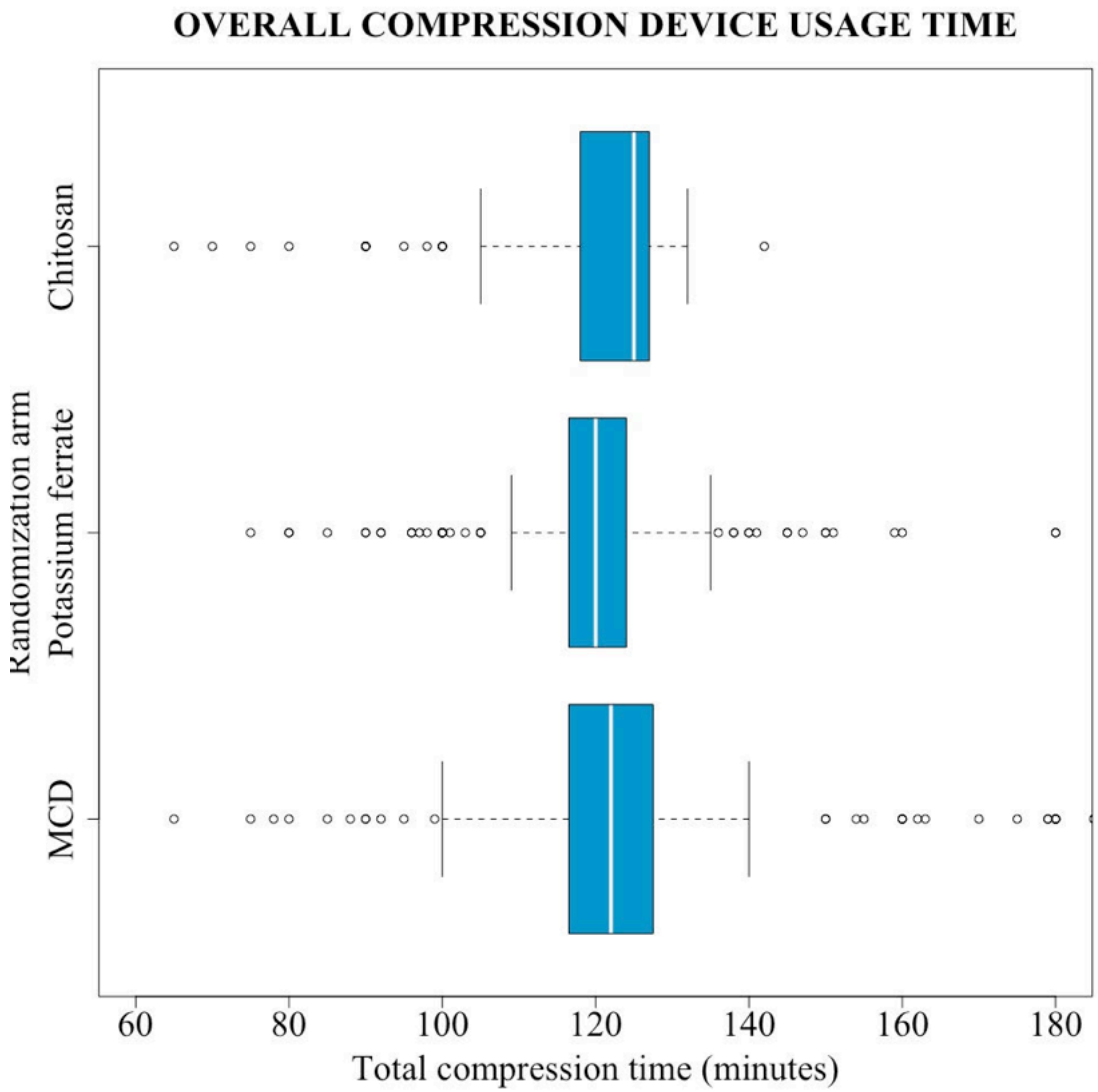


Figure 18. Overall compression device usage time

The median values (white lines), interquartile ranges at the 25th and 75th percentile (the left and right end of the boxes), minimum and maximum values (black vertical lines) plus outlier values on compression times in all three study groups are displayed. The three arms were compared with Kruskal-Wallis test. Compression device usage times were broadly similar across the three groups, with median values clustering around 120 minutes and a wide distribution of outliers in each arm. MCD – mechanical compression device.

8.3.4.3 Use of a second study device

The need for a second study device to achieve hemostasis was greatest in the chitosan group, with 22 patients (10.8%) requiring an additional device. In the pneumatic compression group, 8 patients (4.2%) required a second device, while no patients in the potassium ferrate group required reapplication. Pairwise Fisher's exact tests demonstrated statistically significant differences between all three groups ($p<0.05$) (Figure 19).

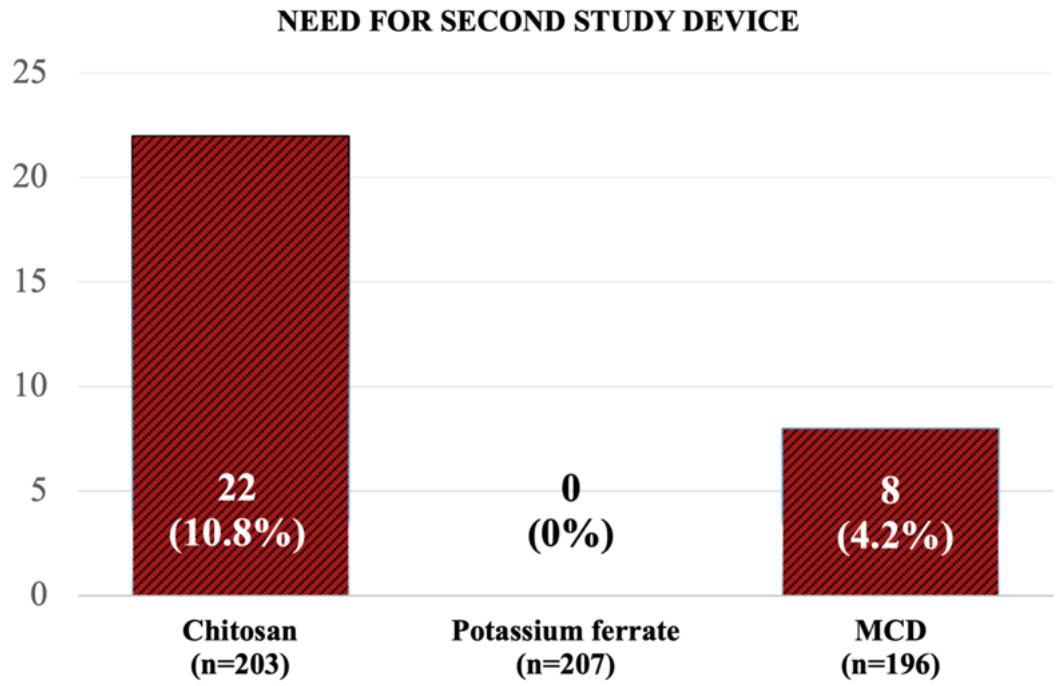


Figure 19. Secondary study devices needed during primary hemostasis
In this figure, the discrete numbers and percentages of patients are shown, where a second study device was needed. It was the highest in the chitosan group, followed by the MCD group, while no additional devices were required with potassium ferrate. MCD – mechanical compression device.

8.3.4.4 Use of bailout devices

Bailout hemostasis with an alternative device was necessary in 7 patients (3.4%) in the chitosan group and 6 patients (3.2%) in the pneumatic compression group. No bailout

device usage was required in the potassium ferrate group. Statistical comparison revealed no significant difference between chitosan and pneumatic compression groups (p=1.00), but significant differences were observed between potassium ferrate and both chitosan (p=0.007) and control (p=0.011) (Figure 20).

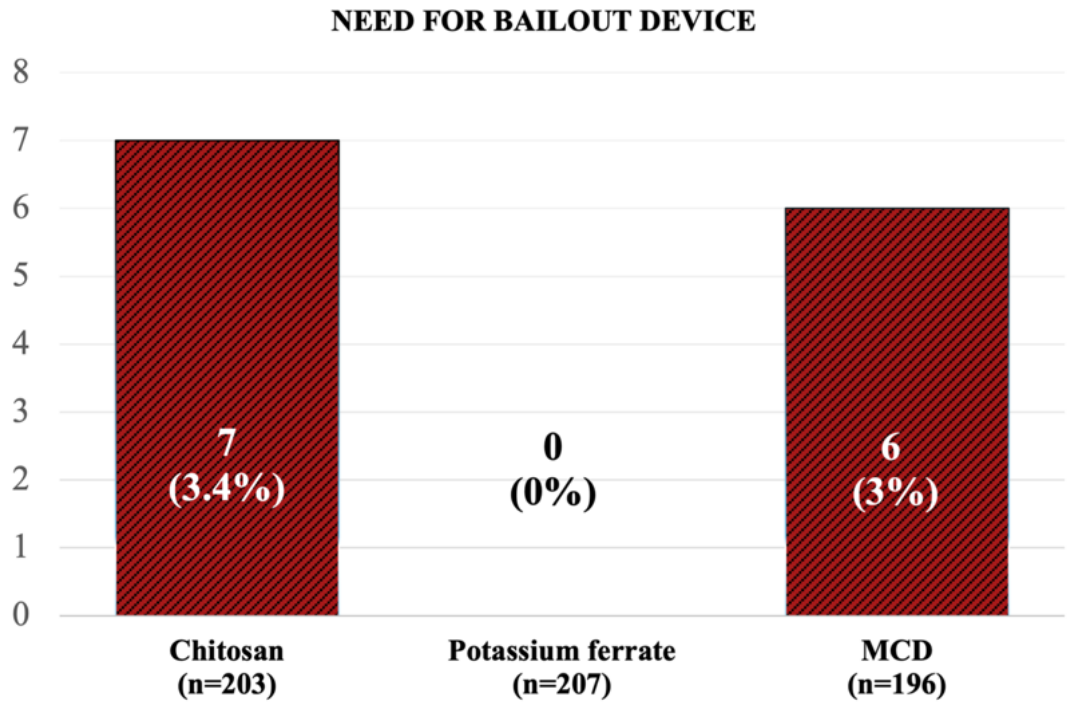


Figure 20. Bail-out device usage after failure to achieve primary hemostasis
Patients for whom a bailout device of choice was needed are displayed in this figure. The need for bailout devices occurred in both the chitosan and MCD groups, while no bailout devices were required with potassium ferrate. MCD – mechanical compression device

8.3.4.5 Safety outcomes

Throughout the trial, no allergic reactions or adverse events related to the bioactive components of the investigational devices were reported. Importantly, no infections or delayed wound healing occurred in any group.

8.3.4.6 Cost analysis

Medical orderlies lowest monthly salary (289 000 HUF) added to the highest monthly salary (770 000 HUF) and divided by two is 529 500 HUF. Nurses' lowest monthly salary (390 000 HUF) added to the highest monthly salary (1 100 000 HUF) divided by two is 745 000 HUF. Doctors lowest monthly salary (1 154 000 HUF) added to the highest monthly salary (2 025 512 HUF) and divided by two is 1 589 756 HUF. Calculating with daily 8 hours of work, with 4 weeks in a week, it represents approximately 9600 minutes a week. Dividing the mean by the calculated minutes at doctors (1589756/9600) is 165.6 HUF per minute; at medical orderlies (529000/9600) is 55.104 HUF per minute; and at nurses is (745000/9600) is 77.604 HUF per minute.

8.3.4.6.1 Chitosan

In case if the chitosan device, the personnel costs of management of the device constitutes of 2 minutes of the doctors salary for the application and the wrapping of the device (165.6x2) that is 331.2 HUF; 2 minutes of medical orderlies salary for the application and the wrapping of the device (55.1x2) that is 110.2 HUF; and 2 minutes of nurse salary for rewrapping the device after 10 minutes and checking for bleeding (77.6x2) that is 155.2 HUF. Added together (331.2+110.2+155.2) sums up to 596.2 HUF.
The personnel costs of management of the chitosan device were accordingly 596.2 HUF. The device cost for each participating center in the clinical trial was 5300 HUF/device. The self-adherent elastic band was the 3M Coban Band, which cost 595 HUF and it was enough for three bandage applications. That translates to 198 HUF/bandage/patient. Adding together, it costs 6094.2 HUF to apply the chitosan device.

8.3.4.6.2 Potassium ferrate

In case of the potassium ferrate device, the personnel costs of management of the potassium ferrate device constitute of 2 minutes of the doctor's salary for the application and the wrapping of the device (165.6x2) that is 331.2 HUF; 2 minutes of medical orderlies salary for the application and the wrapping of the device (55.1x2) that is 110.2 HUF; and 2 minutes of nurse salary for rewrapping the device after 10 minutes and

checking for bleeding (77.6x2) that is 155.2 HUF. Added together, (331.2+110.2+155.2) sums up to 596.2 HUF.

The personnel costs of management of the potassium ferrate device were accordingly 596.2 HUF. The device cost for each participating center in the clinical trial was 5000 HUF/device. The self-adherent elastic band was the 3M Coban Band, which cost 595 HUF and it was enough for three bandage applications. That translates to 198 HUF/bandage/patient. Adding together, it costs 5794.2 HUF to apply the potassium ferrate device.

8.3.4.6.3 Mechanical compression device

In case of MCD, the personnel costs of management of the device constitutes of 1 minute of doctor's salary for the application and the air filling of the device that is 165.6 HUF, 1 minute of medical orderlies salary for the application of the device that is 55.1 and 14 minutes of nurse's salary to reduce air volume simultaneously while checking radial artery patency with plethysmography and bleeding (77.6x14) that is 1086.4. Added together (165.6+55.1+1086.4) sums up to 1307.1 HUF. The personnel costs of management of the MCD were accordingly 1307.1 HUF. The device cost for each participating center in the clinical trial was 4750 HUF/device. Adding together, it costs 6057.1 HUF to apply the MCD.

9 DISCUSSION

9.1 In-stent restenosis

This work provides a perspective on the management of DES-ISR from different angles, by combining a prospective randomized controlled trial, OPEN-ISR, with findings from a systematic review and meta-analysis. Together, these analyses highlight the evolving role of DCBs in the treatment of DES-ISR and emphasize the importance of patient and lesion-specific factors in guiding therapeutic decisions.

The OPEN-ISR trial provided prospective evidence supporting the use of DCBs in DES-ISR. The trial demonstrated non-inferiority of DCB therapy, in the case of both PCBs and SCBs, compared to repeat DES implantation in terms of LLL at six months. Both PCBs and SCBs performed comparably across all measured endpoints, including DOCE and net gain. QFR shift showed a correlation with LLL, which in turn correlated with DOCE, thereby contributing insight to the limited body of literature on this topic, which should be further investigated with dedicated trials. However, when interpreting the results of the trial, there are plenty of important factors to consider, which mandate an understanding of ISR pathology.

The pathophysiology of ISR involves intricate mechanical and biological interactions, broadly categorized into extra-stent, stent-related, and intra-stent contributors, which often act synergistically to precipitate restenosis. (3)

Extra-stent factors primarily involve the characteristics of the arterial wall and lesion morphology that impede optimal stent deployment. Heavily calcified lesions, for instance, may resist balloon dilation and stent expansion, resulting in inadequate luminal gain and residual plaque burden. The presence of multiple overlapping stent layers further exacerbates these mechanical limitations by increasing vessel rigidity and reducing compliance, thereby predisposing to suboptimal expansion and neointimal proliferation. (13)

Stent-related factors encompass technical issues such as stent undersizing, underexpansion, and structural failure. Undersized stents may fail to provide adequate scaffolding of the arterial wall, leading to disturbed flow patterns and promoting neointimal hyperplasia. Similarly, stent underexpansion, often secondary to unaddressed

lesion calcification or insufficient lesion preparation, has been identified as a critical predictor of ISR recurrence. Stent fractures and geographical miss further contribute to the pathogenesis of ISR by creating foci of mechanical stress and turbulence that facilitate thrombus formation and subsequent neointimal growth. (65,66)

Intra-stent factors predominantly involve biological processes within the stent lumen. Neointimal hyperplasia, characterized by smooth muscle cell proliferation and extracellular matrix deposition, represents the hallmark mechanism of ISR in BMS. In contrast, DES have shifted the pathological paradigm towards neoatherosclerosis, which is defined by the accelerated development of lipid-laden foamy macrophages, necrotic core formation, and intra-stent calcification. Notably, neoatherosclerosis exhibits an aggressive clinical course and has been implicated in late stent failure, often presenting as ACS with thrombus generation. (67)

Additionally, the distinction between BMS-ISR and DES-ISR is of critical importance, as these entities differ significantly in their time course, angiographic appearance, histopathological features, and response to therapy. While BMS-ISR typically manifests within the first six months post-implantation due to mostly early neointimal proliferation, DES-ISR may develop later and is often driven by neoatherosclerotic changes that mimic native CAD but with a more rapid progression. These pathophysiological differences underscore the necessity of an individualized approach to ISR management. As BMS is not utilized anymore, the clinical implication of BMS-ISR is becoming sparse; consequently, we excluded BMS-ISR cases from both studies.

In the quest to manage ISR effectively, a variety of interventional strategies have been developed, each with distinct mechanistic underpinnings and clinical implications. As plain old balloon angioplasty does not provide antiproliferative drug delivery and is thus burdened by high rates of recurrent restenosis attributable to elastic recoil and neointimal hyperplasia, current guidelines recommend a new layer of DES implantation or DCB treatment. (11,68) The implantation of a second DES offers renewed drug delivery, and have been shown to attain mildly better outcomes combined with mechanical scaffolding, yet this approach inevitably increases the cumulative metallic burden within the artery. (40) This, in turn, may exacerbate risks such as late stent thrombosis, complicate future revascularization procedures, and promote the development of complex, layered stent pathology. (69)

DCBs have emerged as an alternative that permits local delivery of antiproliferative agents without the addition of further metallic scaffolds, thereby preserving native vessel anatomy and potentially facilitating subsequent interventions. Despite these theoretical advantages, each strategy carries inherent limitations, and randomized controlled trials have yielded heterogeneous results regarding their comparative efficacy in differing ISR contexts. (3,70–82)

While coronary angiography has traditionally served as the gold standard for the detection of ISR, its two-dimensional nature limits the ability to accurately characterize the underlying mechanisms responsible for restenosis. This limitation is particularly critical in the context of DES-ISR, where the pathological processes are heterogeneous and often more complex than in BMS restenosis. IVI modalities, particularly intravascular ultrasound (IVUS) and OCT, overcome these limitations by offering high-resolution, cross-sectional visualization of the stented segment and adjacent vessel wall, enabling a more detailed assessment of DES-ISR pathophysiology. (83,84)

IVUS facilitates evaluation of mechanical factors such as stent underexpansion, malapposition, undersizing, or fracture – recognized determinants of ISR recurrence. By delineating the external elastic lamina, IVUS also allows accurate vessel sizing, which is pivotal for optimal stent deployment during both initial PCI and the treatment of restenosis. Despite its relatively limited axial resolution (~150 μm), IVUS provides superior tissue penetration compared to OCT, making it particularly valuable in assessing DES-ISR lesions with multiple stent layers or extensive calcification. (85)

In contrast, OCT offers unparalleled spatial resolution (12–15 μm), which enables detailed characterization of neointimal tissue and identification of neoatherosclerosis – a key driver of late DES-ISR. Neoatherosclerosis in DES-ISR is characterized by the accelerated development of lipid-laden neointima, macrophage infiltration, and thin-cap fibroatheromas, all of which are associated with heightened risks of target lesion thrombosis and ACS. OCT-based classification systems have defined distinct neointimal patterns – homogeneous, heterogeneous, layered, and attenuated – that correlate with specific histopathological substrates and influence therapeutic strategies. For instance, homogeneous neointima, predominantly composed of smooth muscle cells, is less common in DES-ISR, whereas heterogeneous and attenuated patterns suggest lipid accumulation and inflammatory cell infiltration indicative of neoatherosclerosis. The

ability of OCT to detect such microstructural differences supports its role in precision-guided DES-ISR management, informing decisions on adjunctive therapies such as DCB or repeat stenting. (86,87)

Importantly, IVI is not merely diagnostic but also plays a pivotal role in guiding interventions for DES-ISR. Pre-treatment imaging can uncover mechanical contributors such as stent underexpansion or incomplete lesion coverage (geographic miss), which may require correction before definitive therapy. Post-treatment imaging ensures procedural optimization by confirming adequate stent expansion and apposition, mitigating the risk of recurrent restenosis. Complementary imaging techniques, such as stent enhancement fluoroscopy, may assist in rapidly identifying gross structural abnormalities during interventions, although they lack the depth and resolution of IVI modalities. (88) Despite the absence of randomized controlled trials directly demonstrating improved long-term outcomes with IVI-guided DES-ISR treatment, expert consensus guidelines recommend its use (Class IIa, Level of Evidence B). (83).

In OPEN-ISR, the comparable LLL observed between DCB and DES groups suggests that for many DES-ISR lesions – particularly those dominated by tissue proliferation without significant neoatherosclerosis – DCB therapy provides sufficient anti-proliferative effect. AG was significantly greater in the EES arm compared to PCB and SCB, which is in line with the available literature, and is explained by the mechanical properties of the implanted stent. (3) However, the observed numerical advantage of DES in net gain, which is a more precise comparator of different modalities, may suggest superior efficacy in addressing mechanical issues such as stent underexpansion or resistant calcification. This underscores the importance of mechanistic evaluation using IVI to guide the choice of therapy in DES-ISR, ensuring that both biological and mechanical contributors to restenosis are adequately addressed. The observed association between LLL and DOCE reinforces the validity of employing LLL as a surrogate endpoint in smaller randomized trials, given its link with clinically harder outcomes. In contrast to LLL's anatomical information, QFR provides a physiological estimate of lesion-induced flow limitation based on computational modeling of angiography. The analysis suggests that greater LLL after DES-ISR treatment is associated with a corresponding decline in post-procedural QFR, indicating that anatomical luminal loss translates into functional impairment. However, it needs to be interpreted with caution,

since QFR is also influenced by lesion distribution, vessel size, and microvascular resistance. (89) The meta-analysis highlights the critical role of ISR timing in shaping clinical outcomes after DCB angioplasty. Early DES-ISR was associated with a significantly higher risk of MACE and TLR. In contrast, late DES-ISR patients experienced improved outcomes with DCB treatment. Based on OCT data, early DES-ISR is dominated by neointimal hyperplasia (traditionally considered more responsive to anti-proliferative therapy), and late DES-ISR is more often associated with fibrotic and lipid-rich neoatherosclerotic lesions and with progressive calcification, which typically translates into less favorable clinical outcomes. (87,90,91)

This apparent paradox may reflect fundamental differences in patient characteristics in the included studies. In these, early DES-ISR may have been dominantly driven by mechanical failure, such as stent underexpansion, malapposition, or fracture, that maintains continuous tissue irritation and shear stress. (92) This leads to inflammatory cell recruitment, **s**mooth muscle cell migration, and proliferation into the intimal layer. Subsequently, the fibroblasts and smooth muscle cells promote extracellular matrix deposition, further thickening the neointima. (7) These mechanical factors create a nidus for restenosis that DCB therapy alone cannot adequately address, since DCBs deliver antiproliferative agents without correcting the underlying structural issues. If lesion preparation is insufficient to rectify such mechanical problems, the effectiveness of DCB is compromised, predisposing to higher rates of TLR and MACE.

In contrast, in the included trials, the late DES-ISR population may represent dominantly biological failure, with neoatherosclerosis as the dominant process. Provided that adequate lesion preparation is performed, DCB therapy can achieve effective drug delivery and inhibit further proliferation and lipid accumulation, as observed in the trial results, but IVI and control for confounders in the observational trial would have been crucial to address these questions. Nevertheless, in the case of early DES ISR, which is based on OCT data mainly containing neointimal hyperplasia, and no DES implantation is mandated after successful lesion preparation, DCB should be used. To underscore, for the precise distinction of pathology and the development of a treatment plan, intravascular IVI is mandatory.

9.2 Radial artery hemostasis

Radial artery access has become the preferred vascular approach for diagnostic and interventional coronary procedures due to its association with lower bleeding complications, improved patient comfort, and enhanced procedural safety compared to femoral access. However, the transradial technique introduces unique challenges related to puncture site hemostasis, including the risk of RAO and local vascular complications. Over the past two decades, considerable effort has been devoted to developing hemostasis techniques and devices that minimize these risks while improving procedural efficiency. (93)

Historically, radial artery hemostasis relied on manual compression, a labor-intensive and operator-dependent technique prone to inconsistent results. As transradial interventions gained global acceptance in the early 2000s, MCDs emerged as a standardized solution to achieve hemostasis. These devices, including pneumatic airbladder systems, as the ones used here as control, with simultaneous achievement of PH, reduce the incidence of RAO by enabling gradual decompression and allowing antegrade flow through the radial artery during the hemostasis period. However, despite their clinical success, MCDs aren't without limitations: they require frequent monitoring and adjustments by nursing staff, extend post-procedural immobilization times, and carry a risk of over- or under-compression, potentially leading to RAO or prolonged bleeding. (22,44)

In recent years, novel hemostasis technologies such as bioactive chitosan-based sponges and potassium ferrate-coated discs have been introduced. (27,28) These novel hemostatic agents, concomitantly utilized with MCDs, shorten device application times and reduce complication rates compared to standalone MCD use while maintaining safety. (30–34)

However, the PH protocol remains demanding in terms of frequent monitoring and pressure release. The RAPHE trial provides evidence comparing a more simplified hemostasis protocol with chitosan and potassium ferrate dressings to PH with pneumatic MCDs in patients undergoing TRA. The primary findings of the trial demonstrated that both investigational devices were non-inferior to the pneumatic control device in achieving hemostasis, as assessed by the DOCE. The DOCE, encompassing RAO, access site hematoma, and RAD, occurred at similar rates across all three study arms. Notably,

serious access site complications such as arteriovenous fistulas and pseudoaneurysms were rare, and no cases of arterial dissection were reported.

The potassium ferrate dressing, in particular, showed promising operational advantages. It was associated with a slightly shorter median device application time and required no reapplications or bailout device usage, in contrast to the chitosan dressing, which had higher rates of second-device application. This observation may reflect the different physical properties of the two devices: the potassium ferrate patch is a thinner, stiffer tool, which may be more effectively applied in the current setting, compared to the chitosan device. Additionally, the two dressings operate with unique mechanisms of action: while chitosan achieves hemostasis through electrostatic interactions with blood components, potassium ferrate induces rapid desiccation and protein aggregation. (27–29)

Our cost analysis demonstrated small differences between the three evaluated devices. The potassium ferrate dressing emerged as the most cost-efficient strategy, primarily driven by its lower device price while requiring similar personnel time as the chitosan dressing. In contrast, the MCD incurred higher personnel costs due to the longer nursing time required for monitoring and gradual pressure reduction, although its device price was slightly lower than the others. Chitosan and MCDs ultimately yielded comparable overall costs, but with different cost structures, material versus personnel-driven. While the absolute differences appear modest on a per-patient basis, their impact could be magnified in high-volume catheterization laboratories.

The RAPHE protocol, which omitted the need for PH monitoring and incremental decompression, was shown to be safe and effective in this study population. Unlike the use of MCDs, which require frequent adjustments and active surveillance by nursing staff, the investigational dressings enable a simplified approach that may streamline workflow in busy catheterization laboratories.

9.3. Strengths

9.3.1 In-stent restenosis

A major strength of this work lies in the complementary nature of the randomized trial and the meta-analysis. The OPEN-ISR trial adds prospective, randomized evidence comparing two DCB technologies and a new-generation DES within a standardized protocol. The meta-analysis synthesizes data from studies and provides a perspective of clinical outcomes associated with DCB use in early versus late DES-ISR. Together, these approaches strengthen the validity of the findings and offer insights applicable to daily clinical practice. The trial minimized bias through concealed allocation and blinded outcome assessment, with QCA performed by independent assessors.
The meta-analysis adhered to PRISMA guidelines, employed a comprehensive search strategy, and used statistical techniques to address between-study heterogeneity.

9.3.2 Radial artery hemostasis

Comparisons to prior studies support the robustness of the RAPHE findings. Randomized control trials of chitosan- and potassium ferrate-based dressings have reported comparable hemostasis efficacy and low rates of RAO, in a facilitated dressing configuration, combined with an MCD. (27,30–34) However, data in the context of an application without an MCD has been nonexistent until now. By providing randomized evidence with blinded ultrasonographic follow-up and a prespecified non-inferiority framework, the RAPHE trial provides additional insights into the subject.

9.4 Limitations

9.4.1 In-stent restenosis

In the OPEN-ISR trial, while randomized and prospective, it had a relatively small sample size and was conducted at two centers in Hungary. The trial's six-month follow-up period, although appropriate for assessing LLL, does not capture the full natural course of DES-

ISR. Moreover, OCT data were available in only 24% of patients, precluding meaningful analyses based on imaging findings. Finally, while SCBs showed non-inferiority to PCBs in this trial, the overall evidence base for SCBs remains relatively small, and larger trials are needed to confirm these findings. Since then, accumulating clinical and animal studies suggest that the SCB used in the study is not as effective in coronary arteries as concurrent PCBs. (94,95) Additionally, there is a new promising SCB technology that is currently being investigated in large-scale de novo CAD trials, which could also be later examined in the ISR setting. (96) These factors may limit the external validity of the findings.

The meta-analysis included a limited number of studies and patients, potentially introducing selection bias and limiting the generalizability of the results. Variability in the definitions of early and late ISR, differences in DCB technologies, and heterogeneity in patient populations and procedural techniques may have influenced the pooled estimates. Additionally, the small number of events for outcomes, the retrospective design of some of the studies, and the lack of IVI in the included studies limited insights for identifying the exact pathomechanism of the ISR lesion and controlling for confounding.

9.4.2 Radial artery hemostasis

The RAPHE trial was conducted in high-volume tertiary cardiac centers with extensive experience in transradial procedures and ultrasound-based radial artery assessments, which likely contributed to the low complication rates observed across all study arms. This setting may not fully reflect outcomes in smaller centers or among less experienced operators, where adherence to simplified hemostasis protocols or the technical application of bioactive dressings could vary.

The trial population was restricted to patients with radial artery diameters ≥1.8 mm and excluded individuals at high bleeding risk, those receiving glycoprotein IIb/IIIa inhibitors, and patients undergoing complex coronary interventions with intensified antithrombotic regimens. These criteria, while necessary for procedural safety and device compatibility, limit the generalizability of findings to subgroups such as women with smaller-caliber arteries, patients with chronic kidney disease, and those requiring more complex procedural strategies.

As the trial was open-label, the potential for performance and detection bias cannot be excluded. Although outcomes at the follow-up were assessed by blinded investigators using standardized ultrasonography, concealment of treatment allocation among clinical staff at the peri-procedural assessment was not possible, which could have had influenced the outcomes. While the primary and key secondary endpoints were objective and adjudicated rigorously, bias in subjective outcomes, such as minor bleeding events or the decision to reapply a study device, remains possible.

The use of a DOCE provided a broad measure of safety and efficacy but treated all events equally, from minor hematomas to RAO. This approach may obscure differences in the relative clinical importance of individual components. RAO, for example, has implications for future radial access and vascular health, whereas minor bleeding events often resolve spontaneously without long-term sequelae. Future studies could explore hierarchical or weighted composite endpoints to better capture these distinctions.

The follow-up period of 60 days was sufficient to evaluate early access site complications, but did not allow assessment of very late RAO or delayed vascular remodeling. Some cases of RAO may spontaneously resolve beyond this period, while others could develop later, particularly with repeat radial access. Longer-term follow-up incorporating serial ultrasonography would provide additional insights into the durability of radial artery patency and the safety profiles of bioactive dressings.

10. CONCLUSIONS

This body of work provides an integrated evaluation of contemporary strategies for addressing two pivotal challenges in interventional cardiology: the treatment of DES-ISR and the optimization of radial artery hemostasis following TRA. Through the conduct of the OPEN-ISR and RAPHE trials and a meta-analysis, insights have been gained into the mechanistic underpinnings, comparative efficacy, and operational considerations of these interventions.

10.1 In-stent restenosis

The OPEN-ISR randomized trial provided prospective evidence supporting the use of DCBs in the treatment of DES-ISR. The trial demonstrated the non-inferiority of DCB therapy (encompassing both PCBs and SCBs) relative to new-generation DES implantation in terms of LLL at six months. Both DCB types achieved comparable results across key secondary endpoints, underscoring their viability as alternative treatment options. Importantly, QFR shifts correlated with LLL, offering a potential functional marker for monitoring procedural efficacy.

Complementing these findings, the meta-analysis highlighted the prognostic significance of the temporal profile of DES-ISR in shaping therapeutic outcomes with DCB angioplasty. Patients presenting with early ISR (≤12 months) experienced significantly higher rates of MACE and TLR compared to those with late ISR (>12 months), suggesting that lesion biology and mechanical factors may differentially influence treatment responsiveness. These results emphasize the critical need for lesion-specific assessment with IVI and tailored therapeutic approaches in the management of DES-ISR.

Collectively, these findings advocate for a nuanced approach to DES-ISR management. While DCB therapy appears well-suited for biologically driven late ISR, cases of early ISR characterized by mechanical failure may derive greater benefit from repeat stenting, provided meticulous lesion preparation is undertaken. The routine integration of IVUS and OCT is likely to enhance mechanistic understanding and procedural optimization, ultimately guiding precision-based ISR treatment algorithms.

10.2 Radial artery hemostasis

The RAPHE trial addressed a critical operational aspect of TRA – achieving safe and efficient hemostasis. The investigation established the non-inferiority of a novel, cost-effective protocol with a chitosan-based sponge and a potassium ferrate disc compared to PH with pneumatic MCD, in preventing access site complications. Among the three evaluated hemostasis strategies, potassium ferrate was the most cost-efficient option, whereas chitosan and MCDs entailed slightly higher but similar overall costs. Both investigational devices achieved similar rates of the DOCE, encompassing RAO, access site bleeding, and RAD.

Notably, the potassium ferrate dressing demonstrated operational advantages, including shorter device application times, lower rates of second-device application, and elimination of bailout device use. These attributes suggest potential workflow efficiencies and may allow reduced nursing workload in high-volume catheterization laboratories. Furthermore, the absence of allergic reactions or delayed wound healing reinforces the safety profile of these bioactive devices.

11. IMPLEMENTATION FOR PRACTICE

The findings of this thesis offer data for current interventional cardiology practice. In the management of DES-ISR, DCB therapy may emerge as an effective treatment strategy, particularly for lesions exhibiting late restenosis where biological mechanisms such as neoatherosclerosis are dominant. The evidence from the OPEN-ISR trial reinforces the role of both PCBs and SCBs as viable alternatives to repeat DES implantation, with the advantage of avoiding additional metallic layers and preserving vascular architecture. In contrast, early DES-ISR, often characterized by mechanical failures such as stent underexpansion or malapposition, may respond more favorably to repeat stenting, provided lesion preparation is meticulous and optimized. The integration of IVI modalities such as IVUS and OCT into routine practice is likely to improve procedural success by enabling precise lesion characterization, guiding intervention, and reducing recurrence rates.

In the context of radial artery hemostasis, the RAPHE trial provides evidence supporting the use of chitosan-based sponges and potassium ferrate discs in a novel, more cost-effective manner as effective and safe alternatives to PH with conventional pneumatic MCDs. These dressings demonstrated comparable efficacy in achieving hemostasis while offering operational advantages, including shorter application times and reduced need for reapplication or bailout interventions. Their simplicity of use and reduced requirement for nursing oversight position them as practical solutions in high-volume catheterization laboratories. The implementation of such devices may streamline post-procedural care, facilitate early patient mobilization, and support the adoption of same-day discharge protocols in selected populations.

12. IMPLEMENTATION FOR RESEARCH

This work also highlights several areas that warrant further scientific exploration. In DES-ISR treatment, the findings underscore the need for prospective randomized trials that integrate systematic use of IVI to evaluate whether imaging-guided strategies can improve clinical outcomes. The role of SCBs remains to be fully elucidated in larger trials, particularly in comparison to paclitaxel-coated technologies, given the limited evidence base currently available. Longitudinal studies focusing on the durability of DCB therapy in various lesion types, especially in complex or high-risk subsets, are necessary to inform future treatment algorithms.

In radial artery hemostasis, the promising performance of bioactive dressings merits evaluation in broader patient cohorts, including those with smaller-caliber radial arteries, individuals at high bleeding risk, and patients undergoing complex PCIs requiring intensified antithrombotic therapy. Pragmatic trials designed to assess not only safety and efficacy but also cost-effectiveness and healthcare resource utilization are crucial to determining the scalability and sustainability of these novel devices in diverse clinical environments.

13. IMPLEMENTATION FOR POLICY MAKERS

In the treatment of DES-ISR, policies supporting the wider availability and reimbursement of IVI technologies are crucial to facilitate precision-guided interventions and improve patient outcomes. The development and dissemination of updated national and institutional guidelines reflecting the evolving evidence base for DCB therapy and advanced hemostasis strategies are essential to ensure equitable access to these innovations and to support clinicians in implementing best practices across diverse healthcare systems.

At the health system level, the introduction of simplified hemostasis devices could contribute to significant operational efficiencies. By reducing the need for frequent monitoring and adjustments, these devices have the potential to decrease nursing workload and shorten recovery times, which may, in turn, reduce hospital costs and improve throughput in catheterization laboratories. In resource-constrained settings, where staffing limitations often hinder the implementation of standard PH protocols, bioactive dressings may offer a pragmatic solution for maintaining radial access site safety without compromising outcomes.

14. FUTURE PERSPECTIVES

This thesis underscores the dynamic evolution of interventional cardiology toward more patient-centered and biologically informed approaches. In DES-ISR management, future research should seek to clarify the long-term performance of sirolimus-based DCBs and to establish robust imaging-guided treatment protocols tailored to lesion morphology and restenosis timing. The growing role of IVI in identifying mechanical and biological contributors to ISR suggests a paradigm shift toward individualized therapy, which may ultimately improve procedural outcomes and reduce recurrence.

In radial artery hemostasis, bioactive dressings represent an important innovation with the potential to transform post-procedural care. However, their long-term impact on vascular health, cost-effectiveness in different healthcare settings, and utility in high-risk populations remain areas for further inquiry. The development of next-generation hemostatic technologies, including bioresorbable patches and hybrid systems, may further enhance procedural safety and efficiency.

Taken together, these findings point to an interventional landscape in which technological advancements, mechanistic insights, and procedural refinements converge to optimize patient care. The continued integration of innovative devices and imaging modalities, guided by evidence, will be pivotal in shaping future practice, research, and policy in interventional cardiology.

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16. BIBLIOGRAPHY

16.1 Publications related to this thesis

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2. **Kulyassa P** et al. - Drug-coated balloon therapy is more effective in treating late drug-eluting stent in-stent restenosis than the early occurring one - a systematic review and meta-analysis FRONTIERS IN CARDIOVASCULAR MEDICINE (2297-055X 2297-055X): Volume 10 – (2023) 10.3389/fcvm.2023.1062130
3. **Kulyassa P** et al. - The Design and Feasibility of the: Radial Artery Puncture Hemostasis Evaluation – RAPHE Study, a Prospective, Randomized, Multicenter Clinical Trial FRONTIERS IN CARDIOVASCULAR MEDICINE (2297-055X 2297-055X): 9 Paper 881266. 7 p. (2022) 10.3389/fcvm.2022.881266

16.2. Publications not related to this thesis

1. Száraz L, **Kulyassa P** et al. – Photon-counting CT for coronary stent evaluation: OCT-validated case of severe in-stent restenosis INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING (1569-5794 1875-8312): 1 1 p. 1. Paper https://doi.org/10.1007/s10554-025-03484-w. (2025)
2. Ehrenberger R, **Kulyassa P** et al. – Acute coronary syndrome associated cardiogenic shock in the catheterization laboratory: peripheral veno-arterial extracorporeal membrane oxygenator management and recommendations FRONTIERS IN MEDICINE (N/A 2296-858X): 10 Paper 1277504. 12 p. (2023)
3. **Kulyassa P** et al. – Radial artery hemostasis- earlier practice, actualities CARDIOLOGIA HUNGARICA (0133-5596) VOLUME 53, ISSUE 1 (2023) 10.26430/CHUNGARICA.2023.53.1.20
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17 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to István Ferenc Édes for his invaluable guidance, encouragement, and continuous support throughout this work and Professor Béla Merkely for providing the opportunity to conduct the research. I am deeply thankful to my colleagues and collaborators for their constructive feedback, insightful discussions, and assistance during the process. I am especially grateful to Prof. Péter Hegyi, Prof. Dávid Becker, Prof. László Gellér, Marie Anne Engh, Zoltán Ruzsa, Zoltán Jambrik, Balázs Tamás Németh, István Hizoh, Brúnó Bánk Balázs, Réka Ehrenberger, Bálint Lakatos, Bálint Szilveszter, and György Bárczi for their support throughout the course of my research.

I owe my deepest gratitude to my wife, Zsófia Király, whose love, patience, and unwavering support have been a constant source of strength and inspiration throughout this journey. I am equally indebted to my parents, Mária Joós and Endre Kulyassa, who have always encouraged me, instilled in me the value of perseverance, and supported me unconditionally in all my endeavors, as well as to my wider family, whose presence and encouragement have provided comfort and motivation along the way.