OPTIMIZING OUTCOMES IN PERCUTANEOUS CORONARY PROCEDURES

Ph.D. Thesis Booklet

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1. Introduction

1.1 What is the topic?

This thesis addresses two major areas of contemporary interventional cardiology. The first is the management of in-stent restenosis (ISR), a complication of coronary stenting that persists despite the advent of new-generation drug-eluting stents (DES). ISR represents one of the most frequent causes of target lesion failure and often necessitates repeat revascularization. The second is the optimization of **radial artery hemostasis** following transradial access (TRA). TRA has become the default approach for coronary angiography and PCI, but safe and efficient hemostasis remains an unresolved issue with implications for radial artery patency and long-term vascular access.

1.2 What is the problem to solve?

Although DES have dramatically reduced restenosis compared with bare-metal stents, ISR still occurs in 5–10% of PCI procedures. Treatment options remain suboptimal. Repeat DES implantation provides mechanical support and drug delivery but adds additional

layers of metal, which may impair vessel compliance and complicate future interventions. Drug-coated balloons (DCBs) avoid permanent implants and deliver antiproliferative therapy directly to the vessel wall, but evidence comparing DCB with repeat DES implantation, particularly in DES-ISR, is limited and heterogeneous. Furthermore, the role of ISR timing (early vs. late) in determining outcomes after DCB treatment remains poorly defined, despite strong mechanistic rationale.

For TRA, although it has established itself as the safest vascular access site, its most frequent complication—radial artery occlusion (RAO)—remains a challenge, reported in up to 10% of cases. Patent hemostasis protocols have reduced RAO rates but require meticulous monitoring and are resource intensive. Mechanical compression devices, the current standard, are laborious and increase nursing workload. Novel compression-free dressings, such as chitosan- or potassium ferrate-based patches, promise to simplify hemostasis, but their clinical performance compared with pneumatic compression remains uncertain.

1.3 What is the importance of the topic?

ISR continues to affect tens of thousands of patients annually, given the global volume of stent implantations. Recurrent restenosis leads to repeated procedures, higher costs, and worse quality of life. Establishing the optimal therapy—whether DCB or repeat DES—could directly improve patient outcomes and inform guideline recommendations. Understanding the influence of ISR timing may allow therapy to be tailored to the underlying mechanism, advancing personalized interventional cardiology.

For TRA, radial artery patency is critical not only for repeat interventions but also for patients who may require the radial artery as a conduit for coronary artery bypass grafting or as an access site for hemodialysis. Safe, efficient, and cost-effective hemostasis protocols are therefore essential for maintaining vascular integrity while optimizing hospital workflow. Innovations in this field can reduce complications, lower healthcare costs, and ease the burden on medical staff.

1.4 What would be the impact of our research results?

By providing randomized evidence through the OPEN-ISR trial, this thesis demonstrates that DCB therapy is non-inferior to repeat DES implantation in the treatment of DES-ISR. These findings validate DCB as a viable, stent-free option and support its integration into clinical practice. The accompanying meta-analysis confirms that ISR timing is a critical determinant of outcomes, highlighting that DCB is more effective in late ISR, while repeat DES may remain necessary in early ISR cases. Together, these results may guide future treatment algorithms and guideline updates.

Through the RAPHE trial, this work establishes that chitosan- and potassium ferrate-based hemostasis dressings are safe and non-inferior to mechanical compression, while potassium ferrate offers operational and economic advantages. Adoption of such devices could simplify hemostasis protocols, reduce nursing workload, and improve patient comfort, all while maintaining radial artery patency. The results carry important implications for both high-volume PCI centers and healthcare systems striving for cost efficiency.

2. Objectives

2.1 Objectives of OPEN-ISR

The OPEN-ISR trial was designed to resolve persistent uncertainty regarding the optimal treatment strategy for DES-ISR. The primary objective was to determine whether DCB therapy is non-inferior to repeat implantation of a new-generation everolimus-eluting stent (EES) in terms of late lumen loss (LLL) at six months. The trial further aimed to evaluate differences between paclitaxel- and sirolimus-coated balloons (PCB and SCB), to explore the relationship between angiographic LLL and the device-oriented composite endpoint (DOCE), and to investigate how changes in quantitative flow ratio (QFR) correlate with angiographic and clinical outcomes.

2.2 Objectives of meta-analysis

The systematic review and meta-analysis aimed to assess whether the timing of restenosis after DES implantation modifies the clinical effectiveness of DCB therapy. The primary objective was to compare the incidence of major adverse cardiac events (MACE)—a composite of TLR, MI, and cardiac death—between patients presenting with

early DES-ISR (≤12 months) and late DES-ISR (>12 months). Secondary objectives were to analyze individual endpoints, including TLR, MI, and cardiac death, and to evaluate consistency of effects across included studies.

2.3 Objectives of RAPHE

The RAPHE trial sought to evaluate novel compression-free hemostasis devices in patients undergoing TRA for coronary procedures. The primary objective was to establish the non-inferiority of a chitosan-based bioactive sponge and a potassium ferrate-coated disc compared with a pneumatic compression device in achieving safe and effective radial artery hemostasis, measured by the device-oriented composite endpoint (DOCE). Secondary objectives included evaluation of compression time, overall device usage, requirement for secondary or bailout devices, cost-effectiveness, and safety outcomes.

3. Methods

3.1 Methods of OPEN-ISR

OPEN-ISR was a prospective, randomized, multicenter, controlled non-inferiority trial conducted at two high-volume Hungarian cardiac centers. Patients with angiographically confirmed DES-ISR were randomized in a 1:1:1 fashion following adequate lesion preparation to receive treatment with either PCB, SCB, or EES. The primary endpoint was in-segment LLL at six months as assessed by quantitative coronary angiography (QCA). Secondary endpoints included acute gain (AG), net gain, and the DOCE, which comprised target lesion revascularization (TLR), target vessel myocardial infarction (TVMI), and cardiac death. OCT imaging was performed in a subset of patients, and QFR analysis was undertaken where suitable angiographic projections were available. Sample size was calculated on a non-inferiority margin of 0.25 mm for LLL, yielding a planned enrollment of 150 patients. Statistical analysis followed the intention-to-treat principle, employing Mann–Whitney U tests for the primary endpoint, with additional

sensitivity analyses and regression modeling for secondary endpoints.

3.2 Methods of meta-analysis

The meta-analysis adhered to PRISMA 2020 guidelines and was registered prospectively in PROSPERO (CRD42021286262). A systematic literature search was conducted in November 2021 across PubMed, CENTRAL, Embase, Web of Science, and Scopus, identifying studies reporting clinical outcomes of DCB angioplasty in DES-ISR stratified by timing of restenosis. Data extraction was performed independently by two reviewers, with discrepancies resolved by consensus. Risk of bias was assessed using the QUIPS tool.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model with Hartung–Knapp adjustment. Between-study heterogeneity was evaluated with the I^2 statistic, and outlier analyses were conducted to assess the robustness of findings.

3.3 Methods of RAPHE

RAPHE was a prospective, randomized, multicenter, non-inferiority trial conducted in three Hungarian university hospitals between January 2021 and December 2023. Six hundred patients requiring radial access were randomized equally to one of three groups: chitosan sponge, potassium ferrate disc, or pneumatic compression. Inclusion criteria required a radial artery diameter ≥1.8 mm. Outcomes were assessed with blinded ultrasonography at baseline, 24 hours, and 60 days.

The primary endpoint, DOCE, encompassed RAO, hematoma (per EASY scale), and radial artery damage (RAD). Non-inferiority was tested against a 10% margin using Farrington–Manning tests. Secondary endpoints assessed procedural efficiency and costs, with a resource-based costing method applied to personnel and device expenses.

4. Results

4.1. Results of OPEN-ISR

Between April 2021 and December 2024, a total of 108 patients were enrolled: 37 randomized to EES, 37 to PCB,

and 34 to SCB. Baseline characteristics, including mean age (63–66 years), prevalence of hypertension (76–79%), diabetes (44–62%), and ACS presentation (30–35%), were well balanced across groups. Procedural characteristics showed uniform use of non-compliant balloons and frequent application of scoring balloons (43–57%).

At six months, the combined DCB group achieved a median LLL of 0.30 mm (IQR 0.20–0.70) compared with 0.55 mm (IQR 0.10–1.35) in the EES group. Mean values were 0.53 ± 0.53 mm versus 0.73 ± 0.70 mm, meeting the prespecified non-inferiority margin. PCBs and SCBs exhibited comparable performance, with median LLL values of 0.30 and 0.32 mm, respectively (P = 0.84).

Secondary analyses showed significantly greater AG in the EES arm (median 2.22 mm) compared with PCB (1.55 mm) and SCB (1.52 mm), though net gain did not differ significantly between groups. The incidence of DOCE at six months was similar across arms, with logistic regression identifying LLL as the only independent predictor of adverse events. Furthermore, changes in QFR correlated significantly with LLL ($R^2 = 0.26$, $P < 0.001$),

reinforcing the link between anatomical restenosis and functional impairment.

4.2 Results of the systematic review and meta-analysis

From 832 identified records, four studies including 882 patients met inclusion criteria. The pooled population had a mean age of 66 years, 73% were male, and 32% had diabetes.

The incidence of MACE at 12 months was significantly higher in patients with early DES-ISR compared to late DES-ISR. The pooled OR was 1.68 (95% CI: 1.57–1.80, $p < 0.01$), indicating a 68% excess risk. TLR was the principal driver, with a pooled OR of 1.69 (95% CI: 1.18–2.42, $p < 0.01$). MI and cardiac death were infrequent and did not differ significantly between groups. Heterogeneity was negligible ($I^2 = 0\%$), and sensitivity analyses confirmed the robustness of the findings. Risk of bias was judged as low to moderate overall, with confounding identified as the main source of potential bias.

These findings suggest that ISR timing is a critical determinant of outcomes with DCB angioplasty, with worse results observed in early restenosis presentations.

4.3 Results of RAPHE

Of 600 enrolled patients, 599 were analyzed (203 chitosan, 207 potassium ferrate, 189 pneumatic compression). Baseline characteristics, including mean age (66 years), male sex (67%), and comorbidities such as hypertension (88%) and diabetes (25%), were balanced across groups.

The incidence of DOCE was 20.2% in the chitosan group, 18.8% in the potassium ferrate group, and 19.0% in the pneumatic compression group. All pairwise risk differences were well within the non-inferiority margin, confirming the primary hypothesis. Serious vascular complications were rare, with pseudoaneurysm in 3.3% and arteriovenous fistula in 0.7%; no dissections occurred. Operational outcomes favored potassium ferrate: only 1.4% required prolonged compression versus 5.3% in the control group ($p = 0.048$), median device usage was shorter (120 vs. 125 minutes, $p < 0.05$), and no patients required secondary or bailout devices. Chitosan, in contrast, showed higher reapplication rates (10.8%) compared with 4.2% in the control group.

Cost analysis showed potassium ferrate as the most economical option, with a total cost of 5794 HUF compared to 6094 HUF for chitosan and 6057 HUF for pneumatic compression. Safety outcomes were favorable, with no allergic reactions, infections, or delayed wound healing

5. Conclusions

5.1 Conclusions of OPEN-ISR

The OPEN-ISR randomized trial demonstrated that drug-coated balloon therapy is **non-inferior to repeat DES implantation** for the treatment of DES-ISR, with comparable late lumen loss at six months. Both paclitaxel- and sirolimus-coated balloons achieved similar angiographic and clinical outcomes, underscoring the robustness of DCB therapy across drug platforms. Although acute gain was greater in the EES arm, net gain and the incidence of the device-oriented composite endpoint were not significantly different between groups. Importantly, late lumen loss correlated with both clinical outcomes and changes in quantitative flow ratio, reinforcing its role as a valid surrogate endpoint.

Collectively, these findings support the use of DCBs as a stent-free alternative to repeat stenting, particularly in lesions where preservation of vessel anatomy is desirable.

5.2 Conclusions of meta-analysis

The systematic review and meta-analysis provided compelling evidence that ISR timing is a critical determinant of outcomes after DCB angioplasty. Patients presenting with early DES-ISR (≤12 months) experienced significantly higher rates of MACE and TLR compared with those presenting later. These findings suggest that early ISR is often driven by mechanical failure such as underexpansion or fracture, which DCB therapy alone cannot adequately address, whereas late ISR—more frequently characterized by neoatherosclerosis—responds better to drug delivery without repeat stenting. The results highlight the need for tailored treatment strategies that incorporate lesion timing and pathology into decision-making and support the integration of intravascular imaging to guide therapy.

5.3 Conclusions of RAPHE

The RAPHE trial demonstrated that compression-free bioactive dressings, based on chitosan or potassium ferrate, are safe and non-inferior to conventional pneumatic compression devices in achieving radial artery hemostasis. All three approaches yielded similar rates of the device-oriented composite endpoint, while serious complications such as arteriovenous fistula or pseudoaneurysm were infrequent. The potassium ferrate dressing demonstrated operational advantages, with shorter device usage times, lower rates of reapplication, and no need for bailout devices, while also proving the most cost-efficient option. These findings suggest that bioactive dressings can simplify hemostasis protocols, reduce nursing workload, and improve patient comfort without compromising radial artery patency. Adoption of such strategies may enhance efficiency in high-volume catheterization laboratories and support the continued dominance of transradial access in interventional cardiology.

6. Bibliography

6.1 Publications related to the thesis

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