University of Szeged

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# Refining Diagnostic and Revascularisation Decisions and Outcomes Using Coronary Functional Assessments

PhD Thesis

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**Q ranking:** Q1.

II. Toth GG, Brodmann M, **Kanoun Schnur SS**, Bartus S, Vrsalovic M, Krestianinov O, Kala P, Bil J, Gil R, Kanovsky J, Di Serafino L, Paolucci L, Barbato E, Mangiacapra F, Ruzsa Z. Intentional coronary revascularization versus conservative therapy in patients after peripheral artery revascularization due to critical limb ischemia: the INCORPORATE trial. *Clinical Research in Cardiology*. 2024
**Q ranking;** Q1.

**Not Directly Related to the Thesis**

I. Elamin A, Eissa H, Abubakr MOA, Moran R, Toth GG, **Kanoun Schnur SS**. AI for Lesion Assessment and Multivessel PCI Strategy. *Cardiac Interventions Today*. 2025
**Q ranking:** Not indexed.

II. Prunea DM, Geissler R, Achim A, Stark C, **Kanoun Schnur SS**, Strobl B, Bugger H, Luha O, Zirngast B, Schmidt A, Zirlik A, Toth GG. Long-Term Follow-Up After Direct-Flow Transcatheter Aortic Valve Implantation: A Single-Center Experience. *Catheter Cardiovasc Interv.* 2025
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IV. Prunea DM, Bachl E, Herold L, **Kanoun Schnur SS**, Pätzold S, Altmanninger-Sock S, Sommer GA, Glantschnig T, Kolesnik E, Wallner M, Ablasser K, Bugger H, Buschmann E, Praschk A, Fruhwald FM, Schmidt A, von Lewinski D, Toth GG. Impact of the Timing of Mechanical Circulatory Support on the Outcomes in Myocardial Infarction-Related Cardiogenic Shock: Subanalysis of the PREPARE CS Registry. *J Clin Med*. 2024
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V. **Kanoun Schnur SS**, Pranevičius R, Prunea D, Harb S, Zweiker R, Zirlik A, Toth GG. Pseudo-Underexpansion of a Magnesium Scaffold at 6-Month Follow-Up. *JACC Cardiovasc Interv*. 2023
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**Q ranking:** Q3.

VII. **Kanoun Schnur SS**, Achim A, Toth GG. Clinical application of results of the ISCHEMIA trial. Trends Cardiovasc Med. 2023
**Q ranking:** Q1.

## Abbreviations

| Abbreviation | Meaning | Abbreviation | Meaning |
|---|---|---|---|
| ACEI | angiotensin-converting enzyme inhibitor | HR | hazard ratio |
| AI | artificial intelligence | IEA | image-based evaluation and analysis |
| APT | antiplatelet therapy | ITT | intention-to-treat (analysis) |
| ARB | angiotensin II receptor blocker | IVUS | intravascular ultrasound |
| ASA | aspirin | LAD | left anterior descending artery |
| AT | as-treated (analysis) | LM | left main |
| BB | beta blocker | LLMs | large language models |
| BN | Bayesian network | MACE | major adverse cardiac events |
| CABG | coronary artery bypass grafting | MACCE | major adverse cardiac and cerebrovascular events |
| CA | coronary angiography | MI | myocardial infarction |
| CAD | coronary artery disease | MVD | multi-vessel disease |
| CCB | calcium channel blocker | NPV | negative predictive value |
| CCS | chronic coronary syndromes | NYHA | New York Heart Association (functional classification) |
| CCSc | Canadian Cardiovascular Society (angina class) | OCT | optical coherence tomography |
| CCTA | coronary computed tomography angiography | OMT | optimal medical therapy |
| CI | confidence interval | PAD | peripheral artery disease |
| CLI | critical limb ischemia | PCI | percutaneous coronary intervention |
| CNN | convolutional neural network | PP | per-protocol (analysis) |
| CT-FFR | computed tomography-derived fractional flow reserve | PPV | positive predictive value |
| CTO | chronic total occlusion | PTA | percutaneous transluminal angioplasty |
| LCx | left circumflex artery | QFR | quantitative flow ratio |
| DAPT | dual antiplatelet therapy | RCA | right coronary artery |
| DEB | drug-eluting balloon | SD | standard deviation |
| DL | deep learning | SENS | sensitivity |
| DS | diameter stenosis | SPEC | specificity |
| DT | decision tree | SVD | single-vessel disease |
| ESC | European Society of Cardiology | SVM | support vector machine |
| FFR | fractional flow reserve | SYNTAX | Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery |
| GFR | glomerular filtration rate | | |

# 1. INTRODUCTION

## 1.1 Overview

Percutaneous coronary intervention (PCI) for coronary revascularisation has made substantial progress, yielding increasingly favourable outcomes for high-risk patients, such as those with multivessel disease and notable comorbidities. Nevertheless, avoiding unnecessary interventions is critical, especially in stable coronary artery disease (sCAD) or chronic coronary syndromes (CCS). Precise lesion evaluation and verification of functional significance are vital for achieving optimal outcomes. Historically, coronary angiography has relied on visual assessment of coronary stenosis to decide the need for physiologic evaluation of a lesion's functional significance. However, this approach is prone to interobserver and intraobserver variability, resulting in inconsistent determinations of lesion severity.

While these challenges in lesion assessment are well-recognized within the context of CCS, they are further magnified in patients with advanced peripheral artery disease (PAD), particularly those presenting with critical limb ischemia (CLI). Peripheral artery disease is associated with heightened cardiovascular risk. Moreover, non-invasive diagnostic methods to detect coronary artery disease (CAD) often lack accuracy in CLI patients due to limitations in exercise testing, frequent balanced ischemia, and extensive coronary calcification.

## 1.2 Historical Aspects

The advantages of coronary revascularisation in acute coronary syndromes are well-established. However, its role alongside optimal medical therapy (OMT) for chronic coronary syndromes, compared to OMT alone, remains controversial and has encountered significant challenges. [1,2] Historically, addressing myocardial ischemia has been deemed critical due to its substantial influence on patient outcomes, underscoring the importance of its accurate detection.[3]

Fractional flow reserve (FFR) was developed to enhance diagnostic precision as a surrogate for identifying the physiological significance of coronary lesions, specifically those causing substantial ischemia in a myocardial territory sufficient to carry potential prognostic implications.

Following the validation of FFR in the 1990s [4] its clinical utility in guiding PCI for CCS were firmly established through three landmark studies, demonstrating improved outcomes when revascularisation is based on the physiologic significance of lesions.[5–7] Despite varying viewpoints in the debate, there is broad consensus that if PCI is being considered in CCS, it should be restricted to lesions with confirmed physiologic significance. Historical data from

Hachamovitch et al indicate that patients with >10% to 12.5% ischemic myocardium may experience a survival advantage from revascularisation compared to medical therapy alone. [3] Figure 1 presents the timeline of key myocardial ischemia studies and their clinical relevance in informing revascularisation decisions for CCS.

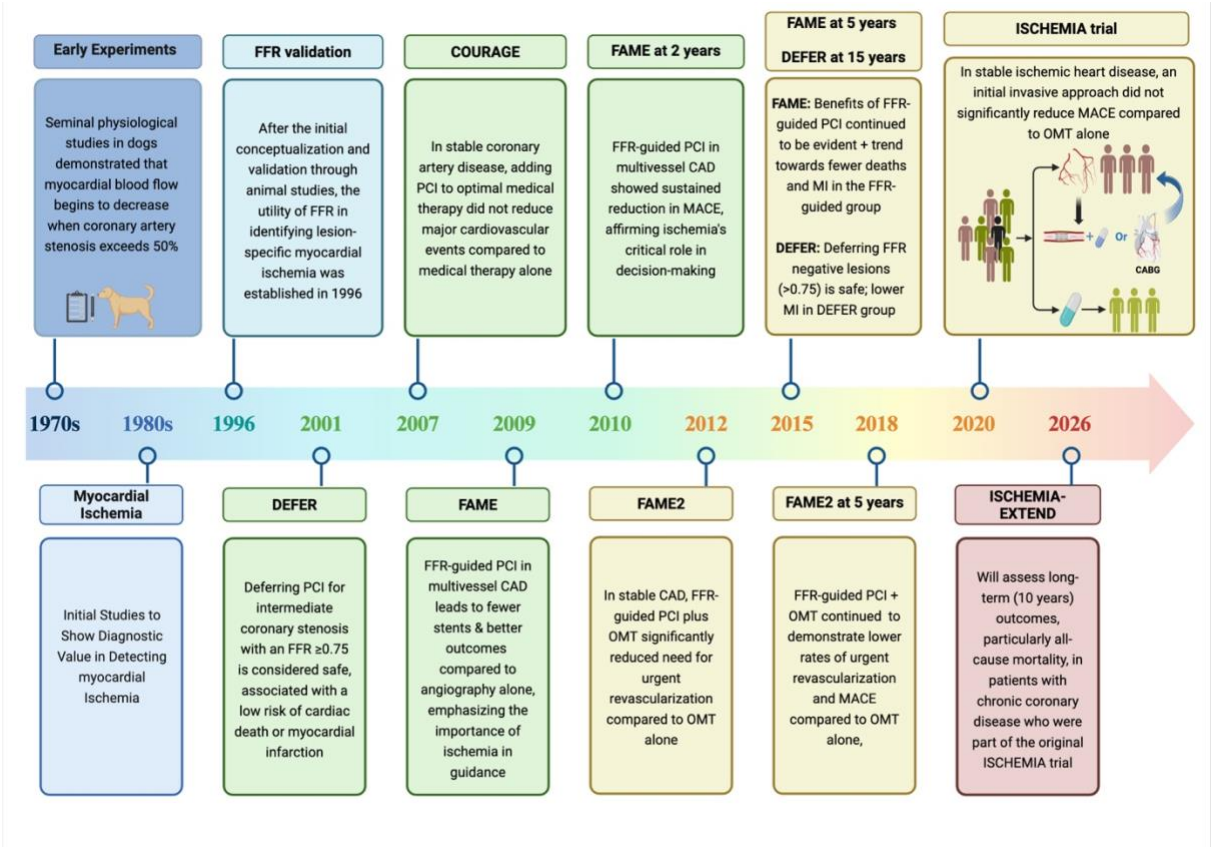


**Figure 1**. **Chronology of landmark myocardial ischemia trials**. Including their clinical impact on guiding revascularisation in stable CAD. Trials depicted include: COURAGE (Clinical Outcomes Utilizing Revascularisation and Aggressive Drug Evaluation); DEFER (Deferral versus Performance of Percutaneous Coronary Intervention of Functionally Non-significant Coronary Stenosis); FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation); FAME 2 (Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease); ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches).
Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction. *Created with BioRender.com. Kanoun Schnur S. (2025), Cardiac Interventions Today, 2025*. [8]

In the context of PAD, these issues become even more complex. Patients with CLI face mortality rates of up to 20% within 6 months of diagnosis, escalating to over 40% at 2 years, primarily due to cardiovascular and cerebrovascular events. [9–11] The mortality risk in CLI surpasses that of other occlusive cardiovascular diseases, such as CAD, owing to the systemic atherosclerotic burden. Patients with PAD exhibit poorer short- and long-term outcomes following coronary revascularisation compared to the general population, likely due to the high prevalence of complex CAD in this group. [12,13] However, when angiography reveals complex

coronary pathology without clear functional confirmation, relying solely on angiographic assessment may lead to multiple interventions without targeting definitive ischemic lesions. Up to 39% of angiographically obstructive coronary lesions may lack functional significance, a rate potentially higher in patients with severe micro- and macrovascular atherosclerosis, rendering revascularisation of non-ischemic myocardium potentially ineffective. Furthermore, unnecessary interventions may introduce adverse effects, complicating clinical outcomes. [14]

### 1.3 Current Landscape

Overtreatment via unnecessary revascularisation and undertreatment by missing significant lesions both pose short- and long-term risks. [5–7,15] Furthermore, the limitations of coronary angiography in identifying functionally significant stenoses [16,17] have highlighted the superiority of function-guided strategies over angiography alone. However, functional guidance use remains low, varying by country, centre, and operator. Adenosine-free methods have somewhat simplified the process, but functional guidance still only accounts for 15% to 20% of cases, even in high-use centres. [16] Recent advancements have introduced non–wire-based functional assessments, such as quantitative flow ratio (QFR), which are increasingly integrated into clinical practice. These methods enable both immediate and retrospective evaluations of coronary stenosis functional relevance using three-dimensional angiogram based calculations. [18] Nevertheless, the linkage between visual stenosis assessment and physiologic evaluation remains reliant on operator discretion, with only intermediate lesions typically warranting physiologic interrogation, as reflected in European and American guidelines.

Thus, the challenges in coronary physiology extend beyond the limited adoption of interrogative assessments for moderate lesions to potentially include the functional misclassification of unsuspected lesions. This includes visually or anatomically mild stenoses that are potentially functionally relevant but not selected for PCI, as well as visually severe stenoses that prompt stenting despite being functionally insignificant. Such misclassifications can have broader implications beyond immediate revascularisation decisions, potentially affecting SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) scoring, influencing the choice of coronary artery bypass grafting (particularly in multivessel disease), and informing predictions regarding graft patency. [19,20] Investigating such misclassifications in everyday clinical practice is the basis of our first trial: The ABNORM study (Operator decision-making in angiography-only guided revascularisation for lesions not indicated for FFR: a QFR-based functional assessment in chronic coronary syndrome).

In patients with PAD a prospective registry, demonstrated that 58% of patients treated for CLI exhibited significant CAD on coronary angiography (CA). However, the functional relevance of this CAD was not incorporated into treatment strategies, and it did not significantly impact 1-year clinical outcomes. [21] Given the limitations of non-invasive methods and recent guideline recommendations, invasive physiologic interrogation may be critical for accurate risk stratification in this population. [22–24] Investigating stable CAD or CCS in patients who have undergone successful CLI revascularisation, followed by lesion-level physiology-guided coronary intervention when indicated, forms the basis of our second study, the INCORPORATE trial (Intentional coronary revascularisation versus conservative therapy in patients after peripheral artery revascularisation due to critical limb ischemia).

## 2. **OBJECTIVES**

This thesis comprises two main studies, a prospective single-centre registry and a multicentre randomised trial that address existing gaps in the decision-making process for coronary revascularisation. The first study, The ABNORM study (Operator decision-making in angiography-only guided revascularisation for lesions not indicated for FFR: a QFR-based functional assessment in chronic coronary syndrome), examines the rate of misclassification that occurs when operators rely exclusively on angiography for decision-making in patients who were not selected for pressure wire assessment because their lesions were judged, by anatomical criteria, to fall outside the moderate stenosis range (i.e., <30% or >90% diameter stenosis). In these cases, QFR was used retrospectively to assess the functional significance of the lesions. The second study, The INCORPORATE trial (Intentional coronary revascularisation versus conservative therapy in patients after peripheral artery revascularisation due to critical limb ischemia) evaluates the outcomes of an intentional upfront invasive strategy, in which patients with critical limb ischemia undergoing peripheral artery intervention received coronary angiography and, where indicated, FFR-guided PCI. This approach is compared to conservative management. Together, these studies aim to refine the role of systematic coronary functional assessment and to inform optimal revascularisation strategies, particularly in high-risk populations.

### 2.1 Objectives of Study 1: The ABNORM Study

Discordance between coronary angiographic findings and invasive functional significance is well-established. However, the prevalence of this mismatch in an era of increasing utilization of invasive functional assessments, such as fractional flow reserve, remains uncertain. This study aims to investigate the extent of such discrepancies in contemporary clinical practice by exploring the correlation between revascularisation decisions based solely on coronary angiography and actual functional significance, particularly in settings with high FFR use and for lesions not meeting estimated anatomical thresholds for FFR interrogation.

#### *2.1.2 Endpoints*

At the vessel level, treatment decisions were classified based on offline QFR: (1) Appropriate Revascularisation (significant stenosis treated), (2) Appropriate Deferral (non-significant stenosis untreated), (3) Inappropriate Revascularisation (non-significant stenosis treated), and (4) Inappropriate Deferral (significant stenosis untreated). At the patient level, strategies were: (a) Overall Appropriate Revascularisation (all vessels aligned with QFR), (b)

Incomplete Revascularisation (untreated significant lesions), and (c) Functional Overtreatment (excess revascularisation).

## 2.2 Objectives of Study 2: The INCORPORATE Trial

Given the significant cardiovascular risks and high pre-test probability of CCS in patients with severe peripheral artery disease, the INCORPORATE trial was designed to determine whether an intentional invasive strategy, including coronary angiography and ischemia-targeted, reasonably complete coronary revascularisation alongside optimal medical therapy, is superior to a traditional conservative approach with optimal medical therapy alone in patients who have undergone successful peripheral artery revascularisation for CLI.

The trial hypothesized that, based on previous evidence, [10–13,25] an intentional invasive strategy guided by ischemia and aiming for reasonably complete revascularisation would result in improved spontaneous myocardial infarction-free survival and overall survival compared to a primarily conservative approach. Figure 2 provides an illustrative abstract of the trial design.

### *2.2.1 Endpoints*

- The primary endpoint was the composite of all-cause mortality and spontaneous myocardial infarction (MI) at 1-year follow-up.
- The secondary endpoint was the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 1 year, defined as a composite of all-cause mortality, spontaneous MI, ischemic stroke, and urgent coronary revascularisation, as well as the individual components of this composite endpoint.
- An exploratory endpoint included major adverse cardiac events (MACE) at 1 year, which was reported in the trial's results table but was not pre-specified as a formal primary or secondary endpoint. In this context, MACE is defined as the composite of all-cause death, myocardial infarction, and any repeat coronary revascularisation.

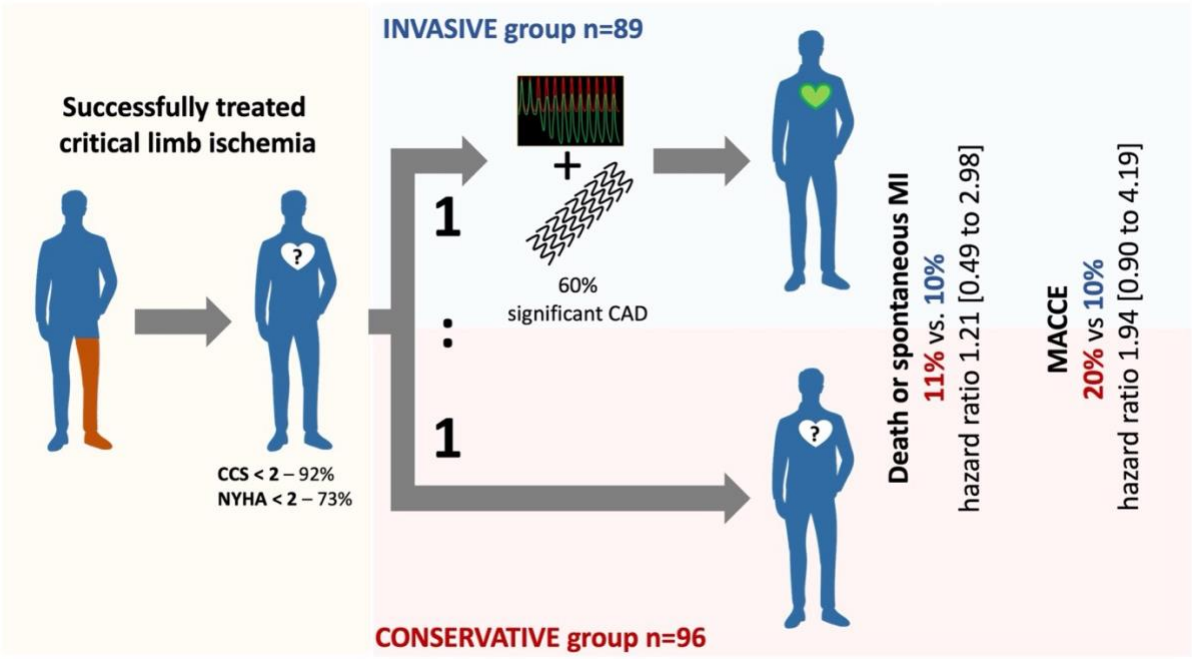


**Figure 2. Illustrative abstract of the INCORPORATE trial.** Patients with successfully revascularised CLI were randomised 1:1 to either a conservative strategy (medical therapy alone) or an invasive strategy involving coronary angiography and, if indicated, FFR-guided complete revascularisation. *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024,* [26] *CC BY 4.*

# 3. MATERIALS AND METHODS

## 3.1 Study 1: The ABNORM Study

### *3.1.1 Study Design*

This was a single-centre, prospective registry that enrolled consecutive patients over a two-month period who underwent elective coronary catheterization for suspected CCS, with or without subsequent revascularisation. The study was approved by the local ethics committee. Figure 3 illustrates the flow of patients through the study protocol.

### *3.1.2 Patient Selection: Inclusion and Exclusion Criteria*

Inclusion criteria: Patients were included if they underwent elective coronary catheterization for suspected CCS and were considered suitable for angiography-only guided assessment based on contemporary clinical guidelines and operators' discretion.

Exclusion criteria: Patients were excluded if invasive physiologic or intravascular imaging assessments were indicated, according to established parameters outlined in current guidelines for the use of invasive functional assessments, such as FFR, to evaluate lesion significance. The interpretation of these anatomical thresholds was at the operator's discretion, reflecting routine clinical practice. Additional exclusion criteria included prior coronary artery bypass grafting (CABG), significant valvular disease, and cases in which revascularisation was indicated but deferred due to overall clinical considerations. QFR assessments were also excluded for aorto-ostial lesions, chronic total occlusions, cases with inadequate projections for analysis, poor contrast opacification, or atrial fibrillation.

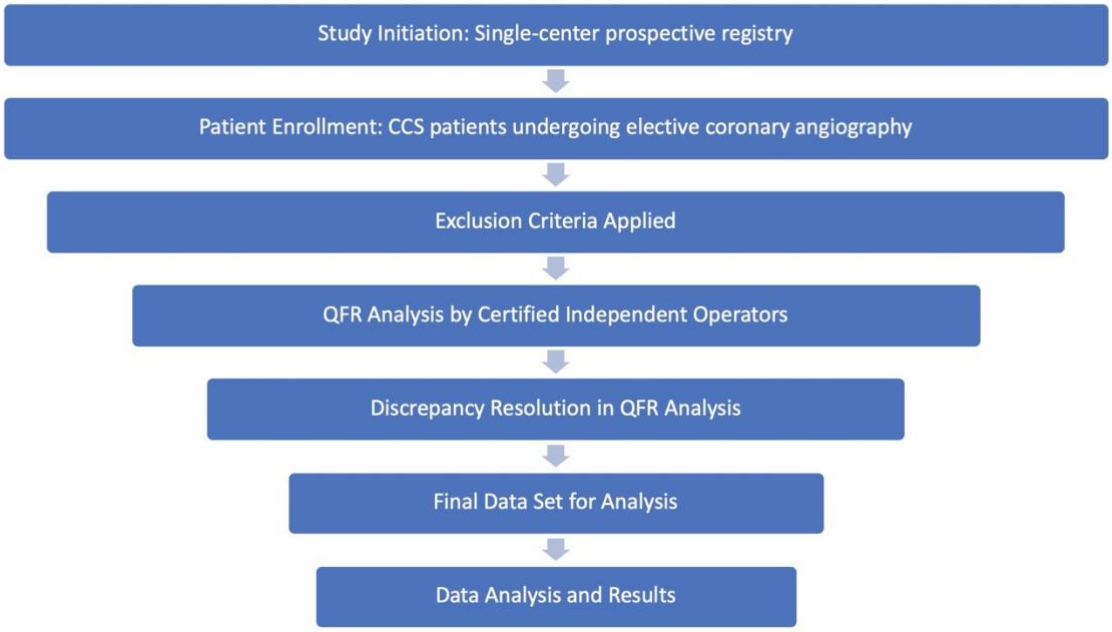


**Figure 3. Flowchart of the study protocol**. The process includes patient enrolment, application of exclusion criteria, QFR analysis by certified independent operators, resolution of any discrepancies, and final data analysis. *Reproduced from Kanoun Schnur SS et al., Frontiers in Cardiovascular Medicine, 2024, [27] CC BY 4.0.*

### *3.1.3 Coronary Angiography*

Coronary angiography was conducted per standard of care, using 6F diagnostic coronary catheters and multiple standard projections to visualize all coronary arteries in at least two orthogonal views. Quantitative coronary angiography was not performed in any cases. The decision to perform revascularisation and the use of additional lesion assessment tools, such as invasive physiology or intravascular imaging, were left to the operator's discretion. Patients undergoing invasive physiologic assessment were excluded from the analysis.

### *3.1.4 Coronary Angiography Assessment*

Analysis was conducted by three independent operators who provided visually estimated diameter stenosis severity for all three major coronary arteries (DS), ranging from 0% to 99%. Notably, assessments were performed prior to QFR analysis, ensuring operators were blinded to the functional significance of lesions. Additionally, operators were unaware of the final revascularisation decisions. In cases of significant discrepancies, a consensus was reached through case review.

### *3.1.5 Quantitative Flow Ratio*

Quantitative flow ratio, available through Medis QAngio XA 3D and Pulse AngioPlus solutions, was the first angiogram-based functional assessment tool utilized in this study. QFR

demonstrated superiority to three-dimensional quantitative coronary angiography in predicting FFR values, with 88% specificity and 84% sensitivity. [28–30] It calculates FFR using three-dimensional reconstructions from two coronary angiography (CAG) projections separated by a minimum of 25 degrees. QFR was calculated using three-dimensional angiographic data to assess the physiologic significance of coronary lesions without the need for invasive pressure wire measurements or pharmacologic hyperaemia induction. QFR analysis was performed post hoc on all three coronary arteries from the offline baseline angiogram using Medis QFR® software, developed by Medis Medical Imaging Systems. The analysis was conducted by three independent operators certified in QFR analysis, following a systematic nine-step protocol. This protocol began with the selection of appropriate angiographic frames, proceeded with delineation of vessel contours, and culminated in the computation of FFR values using the software's integrated algorithms. These operators were blinded to the operators' visual assessments and definitive revascularisation decisions, and any discrepancies were resolved through a consensus review process to ensure the accuracy and reliability of the QFR measurements. QFR values ≤0.80 were considered indicative of functionally significant lesions, aligning with established thresholds for clinical decision-making. Cases with technical limitations, such as suboptimal image quality or inadequate projections, were excluded from QFR analysis to ensure accuracy.

*3.1.6 Statistical Methods*

All statistical analyses were conducted using Prism GraphPad 9.0 (GraphPad Software Inc., California, USA). Descriptive statistics are presented as mean ± standard deviation (SD) or number (percentage, %), as appropriate. Normality of data distribution was assessed using the D'Agostino-Pearson omnibus normality test. Continuous variables were compared using the Mann-Whitney test or Kruskal-Wallis test, while categorical variables were analysed with Fisher's exact test or chi-square test, as appropriate. Sensitivity, specificity, and diagnostic accuracy were calculated. Correlations were evaluated using the Pearson correlation coefficient. A probability value of $p < 0.05$ was considered statistically significant.

*3.1.7 Analysis of Revascularisation Strategies*

The analysis evaluated discrepancies between QFR-based indications for revascularisation and the definitive revascularisation strategies employed. These strategies were assessed at two levels: vessel-level (based on independent visual decisions from three operators blinded to both the index procedure and QFR) and patient-level (based on actual

revascularisation decisions for individual patients). Two comparisons were made: (i) offline QFR results contrasted with independent visual decisions from three blinded operators; and (ii) offline QFR results contrasted with the actual clinical decision recorded for that lesion.

At the vessel level, treatment decisions were compared with offline QFR assessment results and categorised as: (1) Appropriate Revascularisation, where QFR indicated significant stenosis and revascularisation was performed; (2) Appropriate Deferral, where QFR indicated no significant stenosis and no revascularisation was performed; (3) Inappropriate Revascularisation, where QFR indicated no significant stenosis but revascularisation was performed; and (4) Inappropriate Deferral, where QFR indicated significant stenosis but no revascularisation was performed.

At the patient level, overall revascularisation strategies were analysed by aligning actual clinical revascularisation decisions with offline QFR assessment results. These strategies were classified as: (a) Overall Appropriate Revascularisation Strategy, where decisions for all three coronary vessels aligned with QFR assessments; (b) Incomplete Revascularisation, where some lesions warranting treatment based on QFR were not revascularised; and (c) Functional Overtreatment, where revascularisation exceeded QFR-based recommendations.

### 3.2 Study 2 – INCORPORATE trial.

#### *3.2.1 Study Design*

The INCORPORATE trial is a prospective, 1:1 randomised, open-label, multicentre study conducted across ten sites. The study flowchart is depicted in Figure 4. The detailed design and rationale of the study were previously published. [31] INCORPORATE is an investigator-initiated trial, partially supported by Boston Scientific (Marlborough, MA, USA) through non-financial support. The protocol was approved by the ethical committees of all participating centres, and the study was registered at clinicaltrials.gov (NCT03712644).

The trial aimed to enrol 650 patients who had undergone successful percutaneous or surgical peripheral revascularisation for CLI, defined as Rutherford-Becker classification 4 or higher. Patients in the conservative group received optimal medical therapy alone and were followed up according to the protocol, with further cardiac investigations performed only in cases of clinical suspicion of chronic or acute myocardial ischemia-related symptoms. Patients in the invasive group received optimal medical therapy and underwent elective CA, followed by FFR-guided assessment of existing CAD. Coronary revascularisation was performed only

when justified by FFR measurements. In both groups, non-invasive myocardial functional assessments were not conducted following CLI revascularisation and prior to randomization.

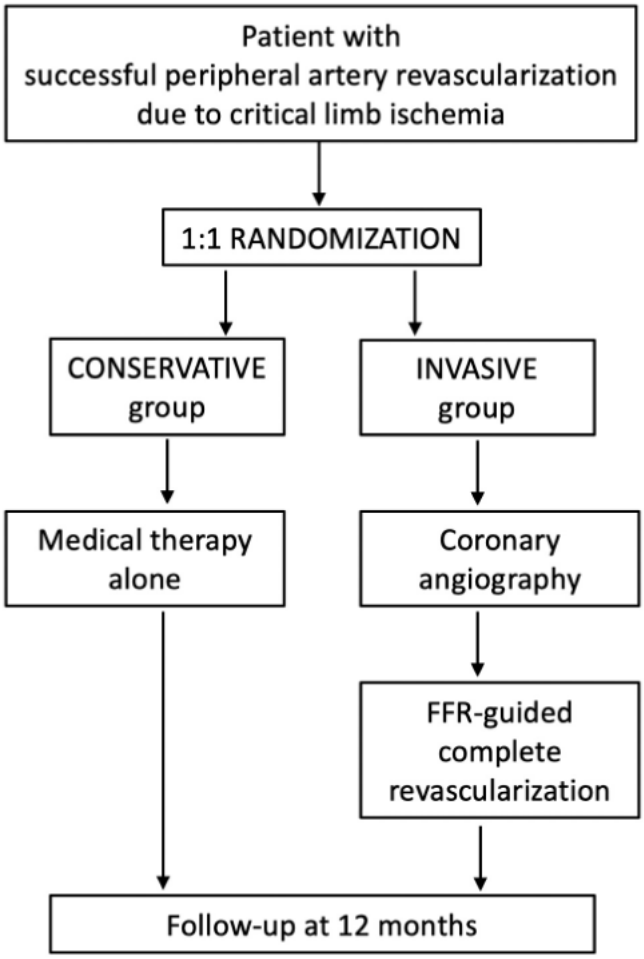


**Figure 4. Study flow diagram for the INCORPORATE trial.**
Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, [26] CC BY 4

*3.2.2 Patient selection: Inclusion and Exclusion Criteria*

Inclusion criteria: Patients were eligible if they had undergone successful percutaneous or surgical peripheral revascularisation for CLI, defined as Rutherford-Becker classification 4 or higher, and were considered stable and suitable for randomization within 14 days of revascularisation. All patients were required to provide written informed consent prior to participation.

Exclusion criteria: Patients were excluded if they had a life expectancy of less than one-year, previous CABG, acute coronary syndrome within the previous three months, severe non-

cardiac comorbidities that could interfere with study participation or follow-up, contraindications to coronary angiography or to dual antiplatelet therapy, or if optimal medical therapy could not be maintained. Further exclusion criteria included active infection, sepsis, or a requirement for amputation at the time of enrolment, as well as any other condition deemed by the investigators to pose excessive risk or interfere with protocol adherence.

*3.2.3 Coronary Catheterization and Revascularisation*

Coronary catheterization was preferably performed via radial access. The procedure was carried out irrespective of the presence or absence of prior non-invasive evidence of ischemia; therefore, routine non-invasive testing before coronary catheterization was not indicated. Lesions demonstrating 50–90% diameter stenosis by visual estimation in a major coronary artery with a vessel diameter of ≥2.5 mm were assessed using FFR, following guideline recommendations. [23] Lesions with FFR ≤0.80 were treated using standard PCI techniques, while those with FFR >0.80 were managed conservatively with medical therapy, regardless of their angiographic appearance. Lesions exhibiting ≥90% diameter stenosis in major coronary arteries of ≥2.5 mm were treated with PCI, employing contemporary drug-eluting stents. This also included efforts to recanalize chronic total occlusions (CTOs) involving large territories of viable myocardium (for example, proximal or mid segments of major coronary arteries). However, excessive or repeated revascularisation attempts were discouraged, and CTO revascularisation was performed only in the presence of documented myocardial viability.

Following PCI, dual antiplatelet therapy (DAPT) was administered in accordance with current guideline recommendations. [23]

In cases of complex or multivessel disease, complete revascularisation could be achieved through multiple staged procedures, preferably during the same hospitalization. For patients whose coronary anatomy was unsuitable for PCI, for instance, in severe and complex multivessel disease with multiple CTOs or a high SYNTAX score, CABG was considered at the discretion of the treating team. Nonetheless, PCI was recommended whenever feasible.

*3.2.3 Fractional Flow Reserve Measurement*

Fractional flow reserve measurements were performed as indicated. [32] In brief, a pressure-monitoring guide wire was advanced distal to the coronary artery stenosis. Maximal hyperaemia was achieved using intracoronary isosorbide dinitrate (200 μg) and either an intravenous continuous infusion of adenosine at 140 μg/kg/min or an intracoronary bolus of adenosine at 160–200 μg.

FFR was defined as the ratio of the mean arterial pressure measured distal to the stenosis to the mean aortic pressure at the tip of the guiding catheter during stable, steady-state hyperaemia. An FFR value of ≤0.80 was considered functionally significant, warranting revascularisation. Conversely, lesions with an FFR >0.80 were considered non-significant, and revascularisation was not indicated, irrespective of their angiographic appearance. [23,32]

*3.2.4 Follow-up*

Clinical, face-to-face follow-up visits was conducted at one year (12 months, with an allowable window of −1/+1 month). During these visits, quality of life will be assessed using the EQ-5D questionnaire, and data was collected on adverse events as defined by the study protocol, hospitalizations, current medication use, and clinical status, evaluated according to the Rutherford-Becker classification and the Canadian Cardiovascular Society (CCSc) classification. Additional follow-up contacts will be made by telephone, email, or mail at 30 days (−5/+10 days), 6 months (−1/+1 month), and 24 months (−1/+2 months).

*3.2.5 Statistical Methods*

The sample size calculation for the INCORPORATE trial, as detailed in our previously published study design and rationale, [31] was based on an expected absolute difference of 10% in the composite outcome of spontaneous myocardial infarction and all-cause mortality between treatment groups at 1-year follow-up. This was predicated on an anticipated event rate of 20% in the conservative group and 10% in the invasive group. To achieve 90% power at a 5% alpha level, while accounting for an expected crossover rate of 5%, a sample size of 650 patients was determined necessary.

All statistical analyses were performed using Prism GraphPad 9.0 (GraphPad Software Inc., CA, USA). Continuous variables are reported as mean ± standard deviation or median [interquartile range], as appropriate. Categorical variables are presented as counts (percentages). Normality of continuous variables was assessed using the D'Agostino-Pearson omnibus normality test. Continuous variables were compared between two groups using the two-sample t-test or Mann-Whitney test, while categorical variables were compared using Fisher's exact or chi-square tests, as appropriate. The Kaplan-Meier method was employed to generate time-to-first-event curves. Clinical outcomes between the two groups were compared using Cox regression. A p-value < 0.05 was considered statistically significant.

In the intention-to-treat (ITT) analysis, subjects were analysed based on their initial group assignment, regardless of the treatment received or protocol adherence. In the per-protocol (PP) analysis, only subjects whose treatment strictly adhered to the study protocol

were included. In the as-treated (AT) analysis, patients were categorised based on the treatment strategy they actually received.

# 4. RESULTS

## 4.1 Results: The ABNORM Study.

A total of 191 consecutive patients with CCS were enrolled, of whom 98 (51.3%) underwent revascularisation and 93 (48.7%) were managed without revascularisation. The cohort comprised 68.9% male patients, with a mean age of 72.3 years. Detailed patient characteristics are presented in Table 1.

**Table 1.** Baseline characteristics of the study population

| Characteristics | *N* | Percentage of patients (%) |
|---|---|---|
| **Gender** | | |
| - Male | 132 | 68.9 |
| - Female | 59 | 31.1 |
| **NYHA Classification** | | |
| - Class 1 | 139 | 72.6 |
| - Class 2 | 41 | 21.7 |
| - Class 3 | 11 | 5.7 |
| - Class 4 | 0 | 0.0 |
| **CCSc Grading** | | |
| - Class 0 | 110 | 57.5 |
| - Class 1 | 27 | 14.1 |
| - Class 2 | 49 | 25.7 |
| - Class 3 | 5 | 1.9 |
| - Class 4 | 0 | 0.0 |
| **Comorbidities and Risk Factors** | | |
| Hypertension | 146 | 76.4 |
| Hyperlipidaemia | 128 | 67.0 |
| Diabetes Mellitus | 43 | 22.6 |
| Previous PCI | 40 | 20.7 |
| **Coronary Angiographic Characteristics** | | |
| - SVD | 57 | 30 |
| - MVD | 63 | 33 |
| - LAD > 50% stenosis | 83 | 43.6 |
| - LAD > 70% stenosis | 66 | 34.6 |
| - LCx > 50% stenosis | 25 | 13.3 |
| - LCx > 70% stenosis | 15 | 8.0 |
| - RCA > 50% stenosis | 29 | 15.4 |
| - RCA > 70% stenosis | 20 | 10.6 |
| Revascularisation performed | 87 | 45.7 |

**Notes and Abbreviations.** NYHA, New York Heart Association functional classification; SVD, single-vessel disease; MVD, multi-vessel disease. CCSc Class 0 indicates no angina symptoms. *Reproduced from Kanoun Schnur SS et al., Frontiers in Cardiovascular Medicine, 2024, [27] CC BY 4.0.*

Across these patients, 488 coronary vessels were assessed: 37% left anterior descending artery (LAD), 30% left circumflex artery (LCx), and 33% right coronary artery (RCA). The mean visually estimated diameter stenosis (DS) was 37% (±34%), the median DS was 30%, and the mean QFR was 0.87 (±0.15).

A moderate correlation was observed between angiographic severity (DS) and functional significance determined by QFR (r = –0.84; 95% CI, –0.86 to –0.81; p < 0.01; see Figure 5). The strongest correlation was found in the LAD (r = –0.86), with slightly weaker correlations in the RCA (r = –0.82) and LCx (r = –0.80).

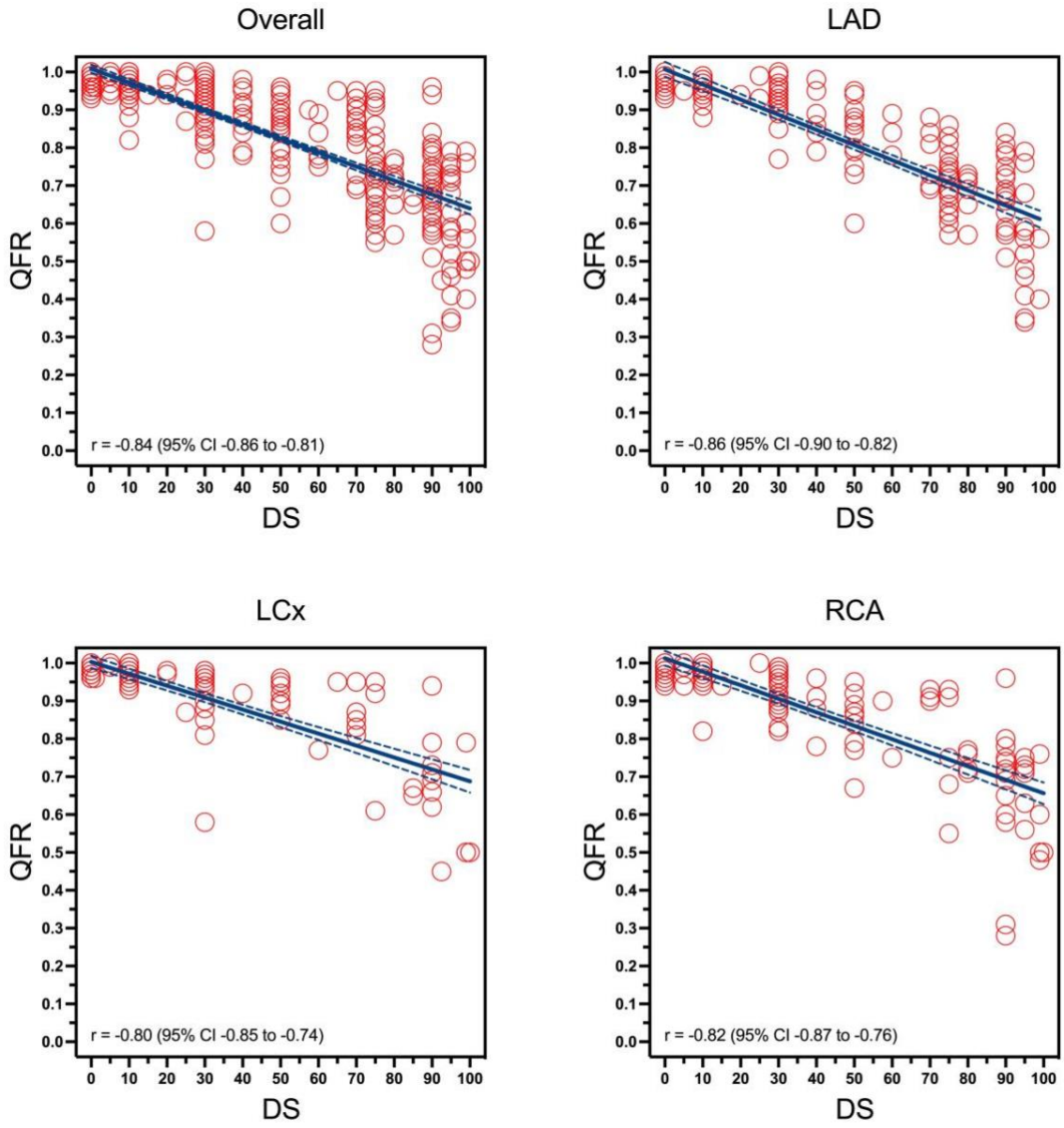


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**Figure 5. Correlation between visually estimated diameter stenosis (DS) and QFR in different coronary arteries.** Each panel displays a regression curve depicting the relationship between angiographic severity (DS, X-axis) and functional significance determined by QFR (Y-axis) for the overall cohort (top left), as well as for

the LAD (top right), LCx (bottom left), and RCA (bottom right). DS = diameter stenosis. *Reproduced from Kanoun Schnur SS et al., Frontiers in Cardiovascular Medicine, 2024, [27] CC BY 4.0*.

When comparing QFR-based functional significance with an angiographic cut-off of 50% DS, the overall agreement was 88%. The specificity for identifying significant lesions was 84%, and sensitivity was 97%. Using a 70% DS threshold, agreement improved to 91% (specificity 93%, sensitivity 88%). Diagnostic accuracy for 50% and 70% DS cut-offs by vessel type is provided in Table 2.

**Table 2.** Comparison of Diagnostic Performance for 50% and 70% DS Cutoff Values

| | **50% DS cutoff** | | | | | | **70% DS cutoff** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Agree | Disagree | SENS | SPEC | PPV | NPV | Agree | Disagree | SENS | SPEC | PPV | NPV |
| **Overall** | 87.50 | 12.50 | 96.88 | 84.17 | 68.51 | 98.70 | 91.39 | 8.61 | 87.50 | 92.78 | 81.16 | 95.43 |
| **LAD** | 86.81 | 13.19 | 97.14 | 80.36 | 75.56 | 97.83 | 90.11 | 9.89 | 87.14 | 91.96 | 87.14 | 91.96 |
| **LCX** | 85.81 | 14.19 | 95.00 | 84.38 | 48.72 | 99.08 | 91.89 | 8.11 | 90.00 | 92.19 | 64.29 | 98.33 |
| **RCA** | 89.87 | 10.13 | 97.37 | 87.50 | 71.15 | 99.06 | 92.41 | 7.59 | 86.84 | 94.17 | 82.50 | 95.76 |

**Abbreviations:** SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; DS, diameter stenosis. *Reproduced from Kanoun Schnur SS et al., Frontiers in Cardiovascular Medicine, 2024, [27] CC BY 4.0.*

Operators' angiogram-based decision led to revascularisation in 127 vessels (26%); the remaining vessels were deemed suitable for conservative treatment. In 437 vessels (90%), revascularisation decisions agreed with QFR-based indications (21% appropriate revascularisations, 69% appropriate deferrals). In 51 vessels (10%), decisions were discordant (5%inappropriate revascularisations, 5% inappropriate deferrals; see Figure 6).

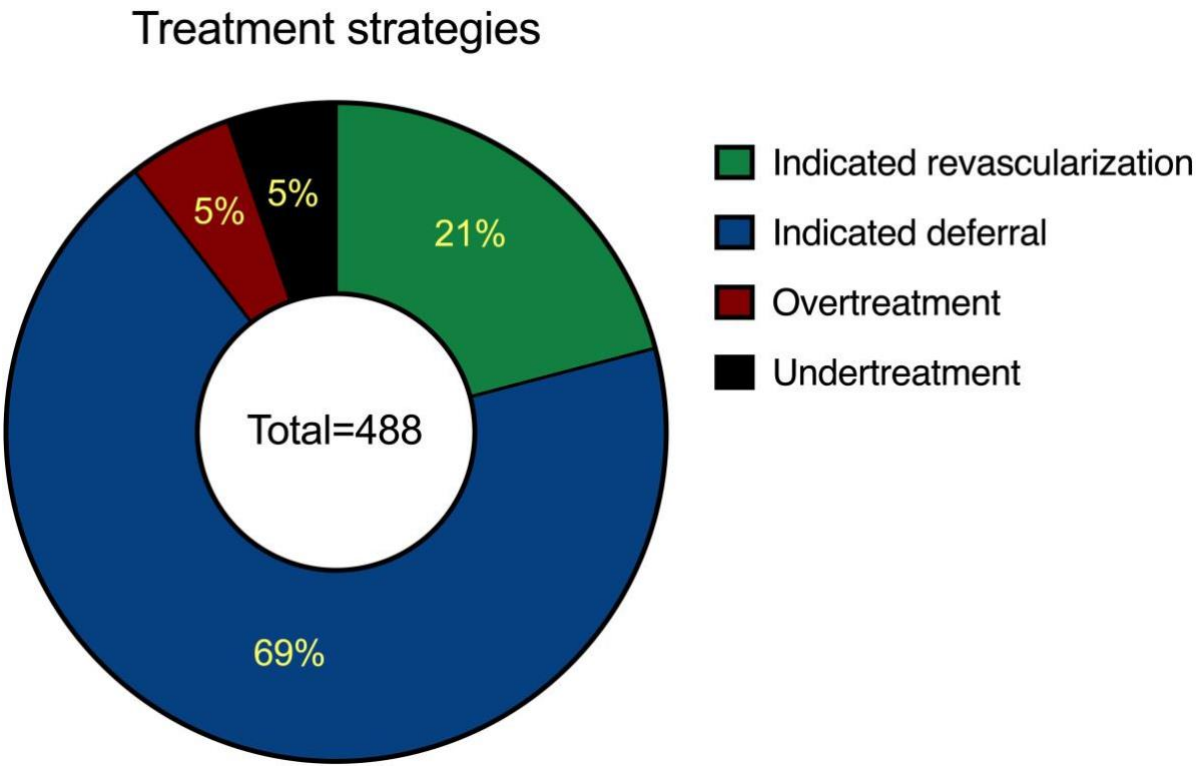


**Figure 6. Distribution of revascularisation strategies in the study cohort.** Pie chart depicting vessel-level concordance between angiography-based decisions and QFR across 488 analysed vessels. Concordant decisions (90%) are subdivided into 21% appropriate revascularisations and 69% appropriate deferrals. Discordant decisions (10%) include 5% inappropriate revascularisations and 5% inappropriate deferrals. *Reproduced from Kanoun Schnur SS et al., Frontiers in Cardiovascular Medicine, 2024, [27]CC BY 4.0.*

For vessels with inappropriate deferral, QFR was 0.67 ± 0.13, with no significant difference compared to QFR for appropriate revascularisation (0.65 ± 0.12; p = 0.18). Meanwhile, QFR for vessels with inappropriate revascularisation was 0.88 ± 0.05, markedly lower than for vessels with appropriate deferrals (0.95 ± 0.04; p < 0.01). The highest rate of decision discrepancy was most frequently observed in the LAD with 14.3% inappropriate decisions (7.7% inappropriate deferrals and 6.6% inappropriate revascularisations of all decisions), which is notably higher than in the LCx (6.8%) and RCA (9.5%) (p = 0.07; see Figure 7).

Three-vessel QFR was available in 160 patients (84%). Here, an overall appropriate revascularisation strategy was observed in 75% of cases. Incomplete revascularisation was seen in 21 patients (13%), while in 21 patients (13%), there was functional overtreatment. Both over- and undertreatment were noted in 1% of patients.

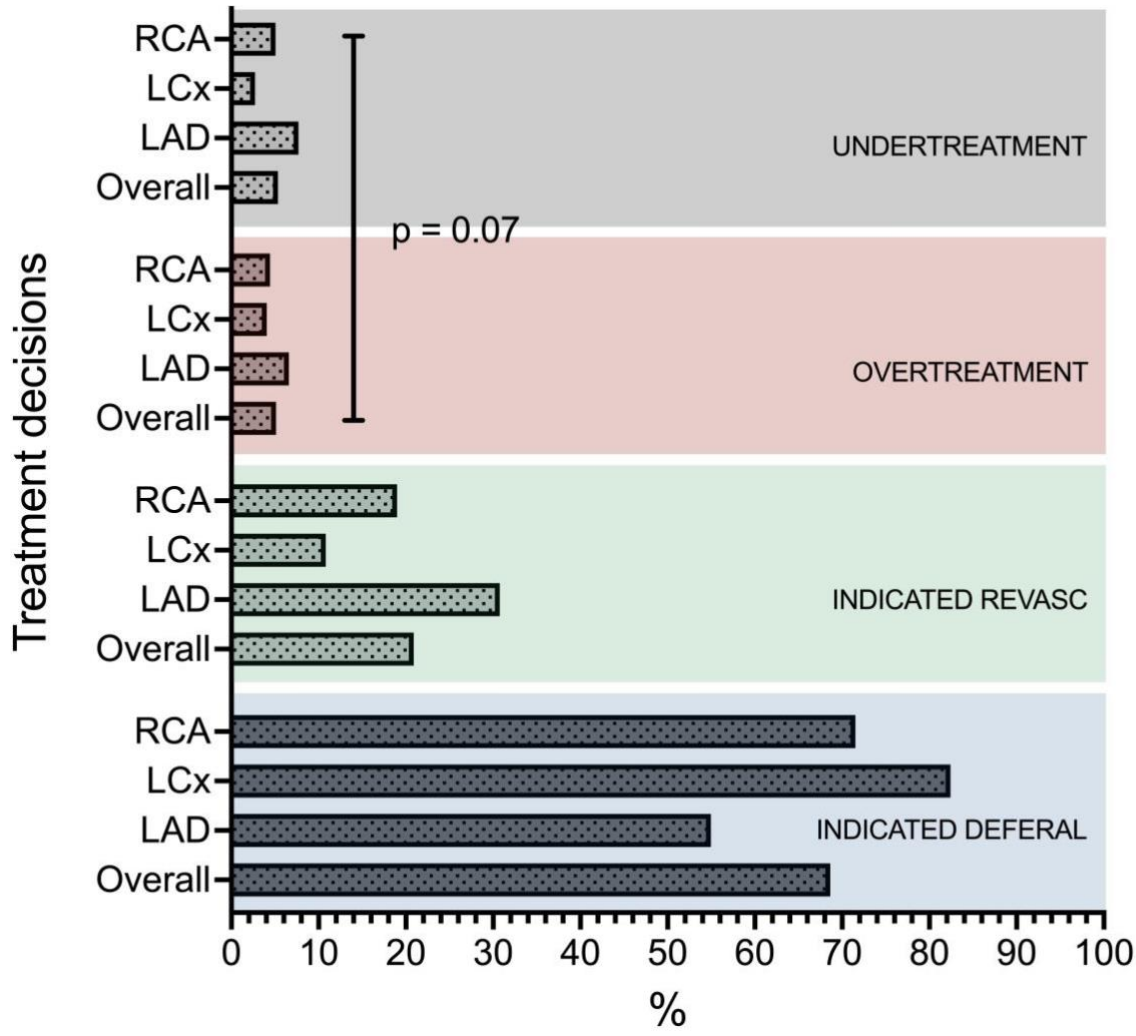


**Figure 7. Distribution of revascularisation strategies by coronary artery**. The bar chart displays the percentage of appropriate and inappropriate revascularisation decisions, as defined by QFR, for the LAD, LCx, RCA, and for all arteries combined (Overall). Decision discrepancy was most prevalent in the LAD territory. *Reproduced from Kanoun Schnur SS et al., Frontiers in Cardiovascular Medicine, 2024, [27] CC BY 4.0.*

### 4.2 Results: The INCORPORATE trial

The COVID-19 pandemic significantly impacted the conduct of this clinical trial, causing substantial challenges in patient enrolment, protocol alignment, and data collection, which ultimately led to premature termination of the study.

The overall number of patients enrolled was 185, with 96 assigned to the conservative group and 89 to the invasive group. This final enrolment was significantly below the projected sample size of 650. The observed event rate in the conservative group was 11%, lower than the anticipated 20%.

67% of patients were male, and the mean age was 69 ± 9 years. Detailed baseline characteristics are presented in Table 3. Baseline medication use in both groups is outlined in Table 4.

**Table 3.** Clinical Characteristics.

| | **Conservative group** | **n=96** | **Invasive group** | **n=89** | **p** |
|---|---|---|---|---|---|
| | n / mean | % or SD | n / mean | % or SD | |
| Male gender | 61 | 63.5 | 60 | 69.8 | 0.43 |
| Age | 70 | 8.65 | 68.4 | 9.4 | 0.23 |
| Weight (kg) | 82 | 20.7 | 84 | 19.8 | 0.62 |
| Height (cm) | 167 | 19.2 | 170 | 18.1 | 0.17 |
| Hypertension | 84 | 87.5 | 72 | 83.7 | 0.53 |
| Dyslipidemia | 66 | 68.8 | 57 | 66.3 | 0.75 |
| Diabetes mellitus | 56 | 58.3 | 45 | 52.3 | 0.46 |
| Smoking | 37 | 38.5 | 57 | 66.3 | <0.01 |
| Family history | 8 | 8.3 | 19 | 22.1 | 0.01 |
| GFR | 66 | 17 | 65 | 22 | 0.69 |
| PCI in medical history | 17 | 17.7 | 16 | 18.6 | 0.99 |
| Myocardial infarction in medical history | 14 | 14.6 | 10 | 11.6 | 0.66 |
| CABG in medical history | 4 | 4.2 | 7 | 8.1 | 0.35 |
| Atrial fibrillation | 19 | 19.8 | 12 | 14.0 | 0.33 |
| Rutherford Score | 4.7 | 0.76 | 4.5 | 0.96 | 0.13 |
| Ilio-femoral revascularisation | 30 | 31.3 | 30 | 31.3 | 0.64 |
| Femoro-popliteal revascularisation | 22 | 22.9 | 22 | 22.9 | 0.46 |
| Below-the-knee revascularisation | 39 | 40.6 | 39 | 40.6 | 0.55 |

**Notes and Abbreviations.** GFR, glomerular filtration rate; SD, standard deviation**.** *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, [26] CC BY 4.*

**Table 4.** Baseline Medications Administered in the Invasive and Conservative Treatment Groups According to Initial Randomization (Per-Protocol Population)

| Medication | Invasive Group | | Conservative Group | | P |
|---|---|---|---|---|---|
| | n / mean | % or SD | n / mean | % or SD | |
| ASA | 67 | 77.9 | 79 | 82.3 | 0.464 |
| Second APT | 54 | 62.8 | 66 | 68.8 | 0.436 |
| Anticoagulant | 21 | 24.4 | 29 | 30.2 | 0.410 |
| Statin | 65 | 75.6 | 79 | 82.3 | 0.279 |
| ACEI/ARB | 50 | 58.1 | 59 | 61.5 | 0.653 |
| BB | 44 | 51.2 | 47 | 49.0 | 0.882 |
| CCB | 17 | 19.8 | 28 | 29.2 | 0.170 |

**Abbreviations:** ASA, aspirin; BB, beta blocker; APT, antiplatelet therapy; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CCB, calcium channel blocker. *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, [26] CC BY 4.*

All patients had CLI, with 96% presenting at or above Rutherford class 4. Prior to recruitment, patients were successfully treated with various revascularisation methods: 44% underwent iliofemoral, 34% had below-the-knee, and 21% received combined revascularisation. Of these interventions, 92.5% involved angioplasty-related procedures, while 7.5% underwent surgical procedures. Specifically, among those treated with angioplasty-related procedures, 35.8% received percutaneous transluminal angioplasty, 32.4% underwent plain old balloon angioplasty, 16.9% were treated with drug-eluting balloons (DEB), and 14.8% had a combination of stent placement and DEB.

At baseline, 21.8% of all patients were on aspirin alone, and 78.1% were on dual antiplatelet therapy (DAPT). Within the invasive group, 68.2% were on DAPT and 15.1% were on aspirin alone. At baseline, cardiac symptoms were predominantly mild and infrequent: 92% of patients had a CCSc grading of angina pectoris of <2, while 73% were classified with a New York Heart Association (NYHA) score of <2.

Of the 89 patients randomised to the invasive group, 73 underwent CA as per protocol, performed either during the same hospital stay or within 14 days. In cases of complex or multivessel disease, revascularisation could be staged. There were 16 instances of crossover from the invasive group to the conservative group, primarily due to bed shortages during the COVID-19 pandemic and patient preferences.

Angiographically, 81% demonstrated significant CAD: 33% with single-vessel disease and 48% with multi-vessel disease. Following FFR, 60% had functionally significant CAD

(34% single-vessel, 26% multivessel), with a mean FFR of 0.65 ± 0.12. After the invasive strategy, 91% of patients were free of functionally relevant stenosis. Protocol deviations occurred in 9% of patients with significant CAD, often due to lesion complexity, patient risk, or physician judgement. Coronary status and methods of revascularisation are detailed in Table 5.

**Table 5.** Coronary angiographic and procedural characteristics

| **Invasive group – Coronary characteristics** | | **n** | **%** |
|---|---|---|---|
| **Angiographically significant involvement** | | | |
| Single-vessel disease | | 24 | 33% |
| Multi-vessel disease | | 35 | 48% |
| Left main | | 7 | 9% |
| Left anterior descending artery | | 44 | 60% |
| Left circumflex artery | | 28 | 38% |
| Right coronary artery | | 29 | 40% |
| **Functionally significant involvement** | | | |
| Single-vessel disease | | 25 | 34% |
| Multi-vessel disease | | 20 | 27% |
| Left main | | 3 | 5% |
| Left anterior descending artery | | 31 | 42% |
| Left circumflex artery | | 12 | 16% |
| Right coronary artery | | 21 | 29% |
| **FFR - overall** | 0.77 ± 0.15 (mean ± SD) | / | / |
| **FFR – for significant stenoses** | 0.65 ± 0.12 (mean ± SD) | / | / |
| **Strategy** | | | |
| Revascularisation performed | | 39 | 54% |
| Single-vessel revascularisation | | 21 | 29% |
| Multi-vessel revascularisation | | 18 | 25% |
| No functionally relevant stenoses left behind | | 66 | 91% |

**Notes and Abbreviations.** SD, standard deviation**.** *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, [26] CC BY 4.*

All patients completed 1-year follow-up. In the ITT analysis, the incidence of the combined primary endpoint of death and spontaneous MI at 1 year was similar between the conservative and invasive groups (11% vs 10%; hazard ratio 1.21 [0.49 to 2.98]). Nevertheless, a numerical rise in the risk of MACCE was observed with the conservative approach (20% vs 10%; hazard ratio 1.94 [0.90 to 4.19]).

In the PP analysis, the primary endpoint remained non-significant (11% vs 7%; hazard ratio 2.01 [0.72 to 5.57]), while an increased risk of MACCE was shown for the conservative approach (20% vs 7%; hazard ratio 2.88 [1.24 to 6.68]). The primary contributor to this increase in MACCE was a higher incidence of revascularisation in the conservative arm. Specifically, these events were driven by urgent revascularisations in five cases, while three cases were attributed to spontaneous myocardial infarctions. All revascularisation procedures were performed via PCI, targeting the culprit lesion and aiming for a functionally guided complete revascularisation whenever possible.

In the AT analysis, a tendency for a higher incidence of the primary endpoint was seen for conservatively treated patients (14% vs 6%; hazard ratio 2.34 [0.94 to 6.67]), along with a significant risk of MACCE as well (22% vs 7%; hazard ratio 3.01 [1.38 to 6.56]) the findings are summarized in Table 6 and illustrated in Figure 8.

**Table 6.** Primary and secondary outcomes of patients at 12 months according to Intention-To-Treat, Per-Protocol and As-treated analyses.

| Outcome | Conservative N (%) | Invasive N (%) | Hazard Ratio (90% CI) |
|---|---|---|---|
| **Intention-to-Treat Analysis** | | | |
| Death & spontaneous MI | 11 | 8 | 1.21 (0.49 to 2.98) |
| Death | 9 | 8 | 0.96 (0.37 to 2.49) |
| Spontaneous MI | 3 | 0 | 6.67 (0.69 to 64.48) |
| Revascularisation | 8 | 0 | 6.33 (1.58 to 25.47) |
| Stroke | 3 | 0 | 5.99 (0.61 to 58.47) |
| MACE | 16 | 8 | 1.74 (0.78 to 3.88) |
| MACCE | 18 | 8 | 1.94 (0.90 to 4.19) |
| **Per-Protocol Analysis** | | | |
| Death & spontaneous MI | 11 | 4 | 2.01 (0.72 to 5.57) |
| Death | 9 | 4 | 1.66 (0.55 to 4.97) |
| Spontaneous MI | 3 | 0 | 6.06 (0.61 to 58.65) |
| Revascularisation | 8 | 0 | 5.82 (1.44 to 23.56) |
| Stroke | 3 | 0 | 5.63 (0.57 to 55.70) |
| MACE | 16 | 4 | 2.66 (1.10 to 6.43) |
| MACCE | 18 | 4 | 2.88 (1.24 to 6.68) |
| **As-Treated Analysis** | | | |
| Death & spontaneous MI | 15 | 4 | 2.34 (0.94 to 6.67) |
| Death | 13 | 4 | 2.07 (0.79 to 5.43) |
| Spontaneous MI | 3 | 0 | 5.57 (0.56 to 55.29) |
| Revascularisation | 8 | 0 | 5.48 (1.34 to 22.39) |
| Stroke | 3 | 0 | 5.40 (0.54 to 54.04) |
| MACE | 20 | 4 | 2.84 (1.26 to 6.38) |
| MACCE | 22 | 4 | 3.01 (1.38 to 6.56) |

**Abbreviations.** HR, hazard ratio; CI, confidence interval. *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, [26] CC BY 4.*

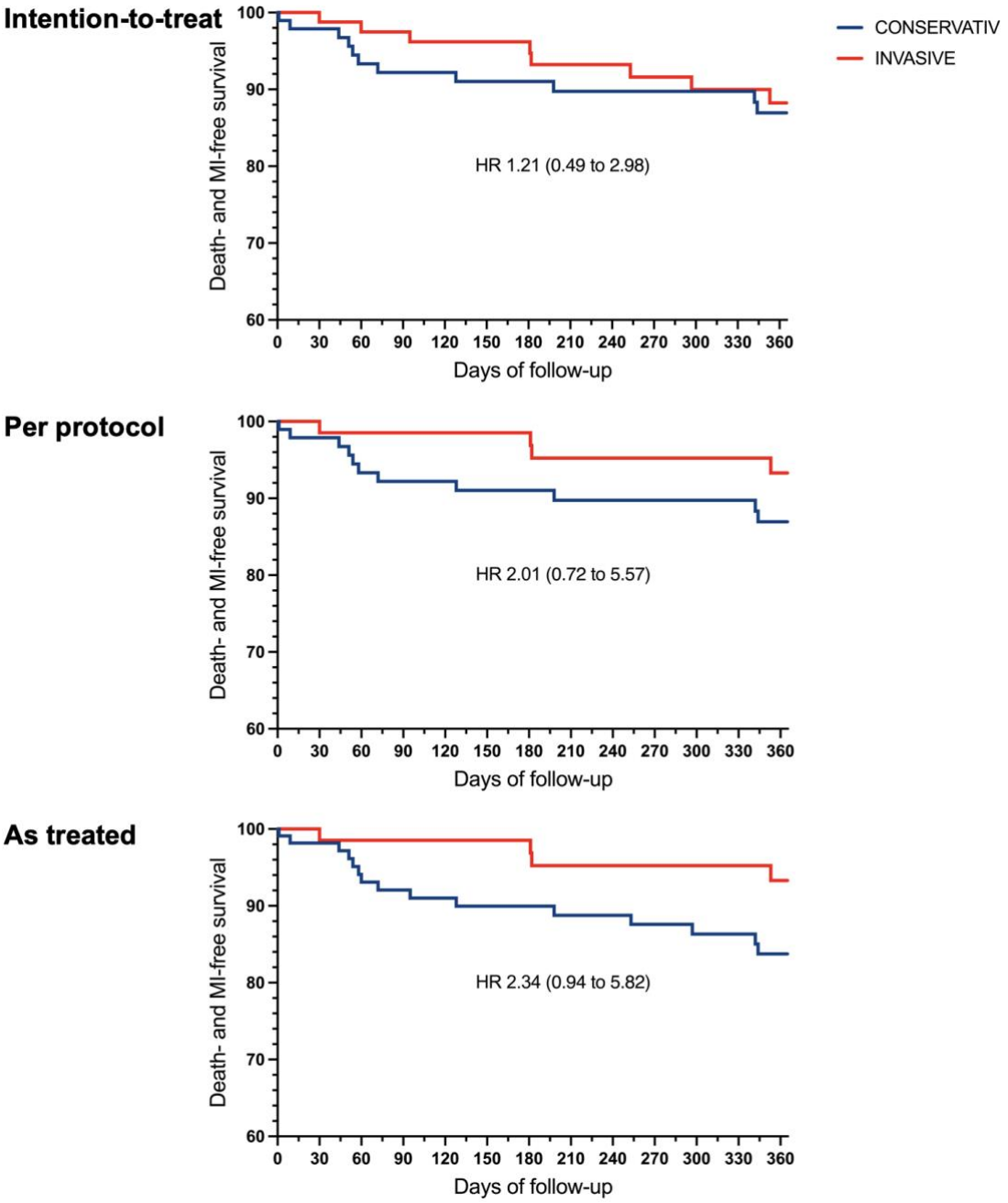


**Figure 8. Kaplan–Meier curves showing freedom from death and spontaneous MI at 12 months in patients undergoing either a conservative or invasive strategy following peripheral artery revascularisation for critical limb ischemia**. Results are presented for the intention-to-treat (top), per-protocol (middle), and as-treated (bottom) analyses.
Abbreviations: HR = hazard ratio. *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024,* [26] *CC BY*

## 5. DISCUSSION

The present thesis addresses two important and interrelated gaps in contemporary interventional cardiovascular medicine. Firstly, drawing on one of the two studies presented, we evaluated for the first time the rate of functional misclassification among unsuspected coronary lesions in routine clinical practice, and specifically lesions falling outside the conventional anatomical thresholds for functional interrogation. The second study highlights the extent of undiagnosed CAD in patients with CLI and investigates the potential benefit of an upfront invasive strategy with coronary angiography and, if indicated, FFR-guided PCI in improving outcomes for patients with CLI following peripheral revascularisation when compared to a conservative medical therapy alone.

### 5.1 Discussion of Study 1: The ABNORM Study

#### *5.1.1 Principal Findings*

This study evaluated the correlation between revascularisation decisions based solely on coronary angiography and the physiological significance determined by QFR in patients with CCS. Specifically, it focused on cases where FFR was considered unnecessary. Notably, the cohort included patients who underwent diagnostic angiography at a centre with a high prevalence of physiology-guided PCI (approximately 15%), representing lesions thought not to be ambiguous enough for physiological assessment on the initial coronary angiography.

A persistent rate of functional misclassification was observed: Of the 488 lesions assessed, 90% had a definitive revascularisation decision corroborating the true functional status as defined by QFR, while 5% of functionally significant stenoses were left untreated and 5% underwent unnecessary revascularisation. Similar rates of inaccuracy were seen regardless of the different arbitrarily selected "optimal" angiographic cut-off values.

#### *5.1.2 Comparison with Previous Studies*

Guidelines recommend FFR for intermediate stenoses when non-invasive testing is unavailable, yet visual estimation often prevails. RIPCORD demonstrated routine FFR altered management in 26% of cases across all lesions. [33] ISIS-2, a survey of 334 cardiologists, revealed 39% of angiography-based decisions were discordant with functional severity, with only 31% requesting physiologic assessment for moderate lesions, an improvement on ISIS-1 which provided earlier survey insights. [16,17] Our QFR-based single-centre registry captures daily clinical practice in CCS, uniquely assessing functional relevance of unsuspected lesions and revealing 10% misclassification.

### *5.1.3 Explanations and Mechanisms*

One main limitation of relying solely on angiography is the assumption that a two-dimensional luminogram of the epicardial coronary artery can accurately reflect the complexity of myocardial perfusion system. This includes not only evaluation of the epicardial vessels, but also the microvascular compartment and the assessment of viable myocardium. The traditional definition of significant coronary artery obstruction is based on physiological principles derived from animal experiments in the early 1970s [34]; however, the applicability of these principles to the typical patient cohort undergoing coronary angiography is far from obvious and lacks accuracy. [14] Angiogram-based lesion assessment is subject to significant intra- and interobserver variability, which limits its standardisation. [35] Additionally, due to the complexity of the coronary circulation and myocardial perfusion, anatomical assessments alone are limited in their ability to accurately determine the global relevance of a lesion, regardless of carefully selected cut-off values or improved accuracy of anatomical measurements. [36]

For those patients who do undergo invasive coronary angiography, relying solely on angiogram-based decisions is no longer sufficient in the modern era of CCS management: functional assessment of both the macrovasculature and microvasculature plays an integral role in determining the correlation between symptoms, clinical status, and angiographic findings. This approach facilitates a more integrated understanding of the patient's vascular health and supports the development of effective, personalized treatment strategies.

### *5.1.4 Implications for clinical Practice*

The findings highlight potential errors that can result from relying solely on angiographic findings in clinical decision making, even in centres with extensive experience in intravascular physiology. Our study therefore underscores the potential value of incorporating a default functional guidance as an effective approach for optimising diagnostic and treatment strategies in patients with CCS.

A promising area for future improvement in diagnostic accuracy is the integration of artificial intelligence (AI) into coronary physiology and revascularisation decision-making. AI, particularly through deep learning (DL) and machine learning (ML) algorithms, offers the potential to standardise and enhance the interpretation of coronary angiography and other diagnostic data, as illustrated in Figure 9. [37] Thereby reducing inter- and intraobserver variability in lesion assessment.

### *5.1.5 Limitations*

This study has some limitations that should be acknowledged. Firstly, although consecutive patients were enrolled, not all cases were suitable for three-vessel QFR analysis, with three-vessel QFR available in 160 patients (84%). Some angiograms lacked necessary projections or sufficient angulation between acquisitions, and in certain cases, vessel segments were obscured due to overlap, both factors are crucial for accurate QFR analysis and led to exclusion of some vessels. Secondly, some angiograms were performed without administration of intracoronary nitroglycerin, which might have influenced QFR accuracy. Thirdly, detailed characterization of coronary artery disease (i.e., diffuse disease, calcification, tandem stenoses, etc.), which could provide deeper insight into causes of discrepancies, was not available. Finally, clinical follow-up was not included, so the clinical impact of under- or overtreatment was not directly evaluated. Nevertheless, it can be speculated based on previous literature, where large, randomised trials have demonstrated negative impact of functional over- and undertreatment on long-term clinical outcome.

## 5.2 Discussion of Study 2: The INCORPORATE Trial

### *5.2.1 Principal Findings*

Considering the distinct cardiovascular risk in patients presenting with CLI, the INCORPORATE trial sought to determine whether a proactive approach with default CA and ischemia-targeted revascularisation is superior to a conventional conservative approach in reducing spontaneous MI and overall mortality at 12 months. The trial was prematurely terminated due to challenges imposed by the COVID-19 pandemic, resulting in insufficient power to detect statistically significant differences between the two groups. Nonetheless, there was a clear trend toward worse outcomes in patients managed conservatively, particularly concerning the combined secondary endpoint of MACCE, as shown in Table 6.

### *5.2.2 Comparison with Previous Studies*

Given the results of trials, including ORBITA trial (Percutaneous Coronary Intervention in Stable Angina): a double-blind, randomised controlled trial, which questioned the symptomatic benefit of PCI over placebo in stable angina; [38] the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches, [2] which found no reduction in hard outcomes with an initial invasive strategy versus medical therapy in patients with moderate-to-severe ischemia; and the REVIVED-BCIS2 trial (Randomised Evaluation of PCI versus Optimal Medical Therapy for the Treatment of Ischemic Ventricular Dysfunction), [39] there is growing debate about the necessity of coronary revascularisation in

CCS. [2,38,39] Contrarily, other studies have demonstrated that when revascularisation is selectively performed in patients with extensive ischemia and targeted specifically to functionally significant lesions, favourable outcomes can be achieved compared to optimal medical therapy alone. [7,15] Moreover, patients with significant coronary artery disease that remains untreated by revascularisation appear to face a higher long-term risk of death or myocardial infarction, even if they initially present with no or only mild symptoms. [40]

Indeed, the patient population investigated in the INCORPORATE trial shares many characteristics with this latter cohort. These patients exhibit a significant atherosclerotic burden in the peripheral vasculature; a condition inherently associated with a higher prevalence of coronary atherosclerosis and increased cardiovascular risk. [41,42] This observation is consistent with our findings, in which nearly two-thirds of patients in the invasive group were found to have one or more functionally significant coronary artery stenoses, with FFR values as low as $0.65 \pm 0.12$. Notably, the incidence of left main stem and left anterior descending artery stenosis reached as high as 45%.

A previous prospective registry investigated the strategy of routine CA and subsequent coronary revascularisation, if anatomically indicated, in patients with CLI undergoing percutaneous transluminal angioplasty (PTA). Of 286 consecutive CLI patients treated with PTA, 252 underwent CA either before or after their peripheral intervention. In that cohort, CAD was defined as an angiographic stenosis of ≥50%, and significant CAD as ≥70% stenosis. Notably, 58% of patients demonstrated anatomically significant CAD. However, the presence of CAD did not influence 1-year clinical outcomes in that study. [21] Importantly, the functional relevance of the coronary lesions was neither assessed nor integrated into treatment strategies, an essential gap that the INCORPORATE trial was designed to address as well as the randomised design, thereby offering a more robust evaluation of whether a default invasive strategy based on functional assessment could improve outcomes in this high-risk population.

*5.2.3 Explanations and Mechanisms*

Clinical symptoms such as angina or exertional dyspnoea may remain concealed in patients with CLI, largely due to their severely limited exercise capacity imposed by their primary peripheral vascular disease. In the INCORPORATE trial, patients were recruited with Rutherford class 4 symptoms or higher, indicating severe claudication or even rest pain in the lower extremities. Consequently, these individuals rarely engage in physical activity sufficient to provoke myocardial ischaemia. Consistent with this, fewer than one-tenth of patients reported CCSc class II angina or worse, and only around one-quarter exhibited a NYHA class

II or higher functional status. However, it is important to note that the applicability and interpretability of the CCS and NYHA classification systems may be limited in this specific patient population.

Crucially, while these patients may initially have minimal or no cardiac symptoms, this clinical picture can change significantly following successful peripheral revascularisation. Once the peripheral limitation to exercise capacity is relieved, the myocardium may be subjected to increased workloads, potentially exceeding coronary perfusion capacity. In the best-case scenario, this may result in stable angina. However, it could also account for the high incidence of early myocardial infarction and cardiac mortality as initial cardiac presentations in patients previously treated for CLI. [9,43–45]

*5.2.4 Implications for Clinical Practice*

These observations suggest that careful cardiological assessment for underlying CAD is prudent in patients who have undergone revascularisation for CLI. The optimal diagnostic pathway—whether to begin with non-invasive testing or proceed directly to invasive CA—remains a subject of ongoing debate, often influenced by local resources and logistical considerations.

While systematic non-invasive testing could serve as a valuable gatekeeper strategy, traditional modalities such as exercise testing, myocardial scintigraphy, and coronary computed tomography angiography (CCTA) each have notable limitations in sensitivity or specificity, particularly in this complex CAD population. [46] However, as emphasised in a recent consensus paper, advances in CCTA, especially with the latest generation of scanners, offer the potential not only to diagnose CAD but also to guide its management, including in multivessel disease. [47] Similarly, stress echocardiography or stress magnetic resonance imaging may provide more definitive assessments in experienced centres and can inform subsequent revascularisation strategies.

Conversely, one could argue for maintaining a low threshold for invasive CA in this high-risk population, given the inherently elevated pre-test probability of significant CAD. Nonetheless, the cornerstone of modern revascularisation strategy remains the functional confirmation of lesion significance. This can be achieved effectively via either angiography-based technologies, such as QFR, or wire-based measurements like fractional flow reserve.

In the INCORPORATE trial, non-invasive functional testing was deliberately avoided in this high-risk cohort for several reasons, as outlined in the trial design paper. [31] Firstly, the patients' limited physical capacity precluded exercise-based testing. Secondly, balanced

ischaemia, a phenomenon wherein diffuse and symmetrical reductions in myocardial perfusion obscure regional differences, frequently occurs in this patient group, reducing the diagnostic value of non-invasive imaging. Thirdly, extensive coronary calcification, common in CLI patients, can significantly impair the accuracy of non-invasive modalities. Given these challenges, invasive coronary angiography combined with FFR assessment was chosen as the preferred strategy for obtaining precise functional information on coronary lesions.

This approach aligns with European Society of Cardiology (ESC) guidelines, which recommend invasive functional assessment when non-invasive tests are unavailable or inconclusive, particularly in patients with lower pre-test probabilities of significant CAD. However, in high-risk patients or those with inconclusive non-invasive results, invasive coronary angiography remains the gold standard for definitive diagnosis. [22]

It is also noteworthy that since the initiation of the INCORPORATE trial, substantial technological advances have emerged in the field of high-resolution CT imaging and CT-derived fractional flow reserve (CT-FFR). These innovations may merit consideration in future studies or in clinical practice for similar patient populations.

Lastly, while the INCORPORATE trial did not specifically investigate the impact of routine coronary angiography before PAD surgery on surgical outcomes, existing evidence suggests no significant benefit in this context. [48] Previous studies indicate that routine pre-operative coronary angiography does not reduce surgical risk or improve outcomes in PAD patients. This underscores the need for careful patient selection and highlights the distinct focus of the INCORPORATE trial on FFR-guided revascularisation in patients who have already undergone successful peripheral revascularisation.

### *5.2.5 Limitations*

Several limitations of the INCORPORATE trial should be acknowledged. Firstly, despite the high-risk profile of the population, only 75% of patients in the invasive group were receiving statin therapy. Additionally, patients treated invasively were more frequently smokers compared to those in the conservative group. Given that smoking is a well-established risk factor for adverse cardiovascular events, this imbalance may have diminished the potential benefits of revascularisation observed in the invasive arm. Secondly, the COVID-19 pandemic substantially affected the conduct of the trial. Challenges included difficulties in patient recruitment and maintaining protocol adherence, particularly because rapid hospital discharge became common practice due to limited bed availability. These factors contributed to a higher-than-expected crossover rate between treatment arms. Thirdly, these logistical constraints led

to premature termination of the study, resulting in significantly lower patient enrolment than originally planned. Only 185 patients were ultimately included, representing just 28% of the intended sample size of 650.

Moreover, the observed event rate in the conservative group was considerably lower than anticipated at 11% compared with the expected 20%. This combination of reduced enrolment and lower event rates substantially compromised the statistical power of the trial. Post hoc calculations indicate that the power to detect a significant difference between the treatment groups under these conditions was only approximately 5.57%, far below the initially targeted 90%. To achieve the original statistical power given the observed event rate, an estimated sample size of around 39,476 patients would have been required, vastly exceeding the initial projection.

These limitations highlight the challenges of conducting adequately powered clinical trials in high-risk patient populations under extraordinary circumstances such as a global pandemic. While the smaller sample size raises concerns about the precision and variability of the event rates, we nonetheless believe the data generated are valuable for enhancing our understanding of this particularly vulnerable patient cohort. However, these findings should be interpreted cautiously, and further studies are warranted to validate the results and clarify the true event rates in a broader population.

### 5.3 Future directions

As highlighted in Section 5.1.4, the integration of AI offers promising advancements in diagnostic accuracy within cardiology. As with all aspects of clinical medicine, cardiology involves managing vast data sets to craft tailored management plans. Currently, it is still in its early stages of adoption in cardiology, but increasingly utilized, with several applications gaining validation and regulatory approval. [49,50] In interventional cardiology, most studies remain small and single centre, often lacking external validation. [51] The potential for AI, particularly through ML and DL is substantial. Figure 8 [8] illustrates the AI hierarchy, highlighting applications such as image interpretation and feature extraction enabled by ML, DL, and image enhancement algorithms (IEAs). Our findings underscore diagnostic gaps that could be addressed by AI integration. First, AI can help overcome operator-dependent functional–anatomical discordance, as demonstrated in our ABNORM study, which highlighted the limitations of relying on visual "eyeballing" to decide on coronary physiologic assessment, even for unsuspected lesions that do not meet anatomical thresholds for physiological interrogation. The challenges in coronary physiology extend beyond the limited

adoption of interrogative assessments for moderate lesions to include the functional misclassification of such unsuspected lesions. AI-driven tools may facilitate the identification of ischemia-producing lesions, optimize strategy selection, and even integrate vast clinical and imaging data, including patient demographics, frailty and comorbidities, reflective of our complex patient cohort in the INCORPORATE trial to support a comprehensive risk assessment and individualized care as illustrated in Figure 9. [8,52,53]

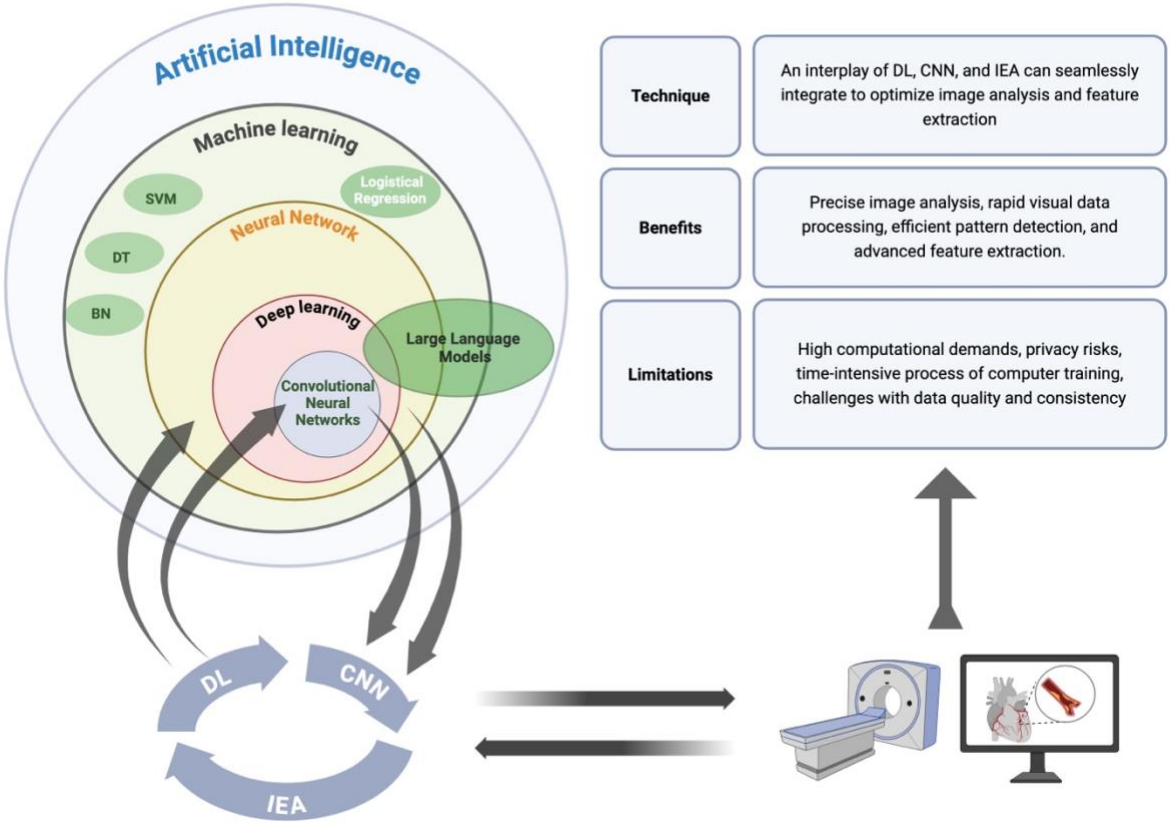


**Figure 9. Hierarchy and integration of AI methods and their application in image analysis and feature extraction.** The interplay of CNN, DL, and IEA enhances clinical imaging interpretation.
Abbreviations: DL, deep learning; CNN, convolutional neural networks; IEA, image-based evaluation and analysis; SVM, support vector machine; DT, decision tree; BN, Bayesian network; LLMs, large language models. *Created with BioRender.com. Kanoun Schnur S. (2025), Cardiac Interventions Today, 2025.* [8]

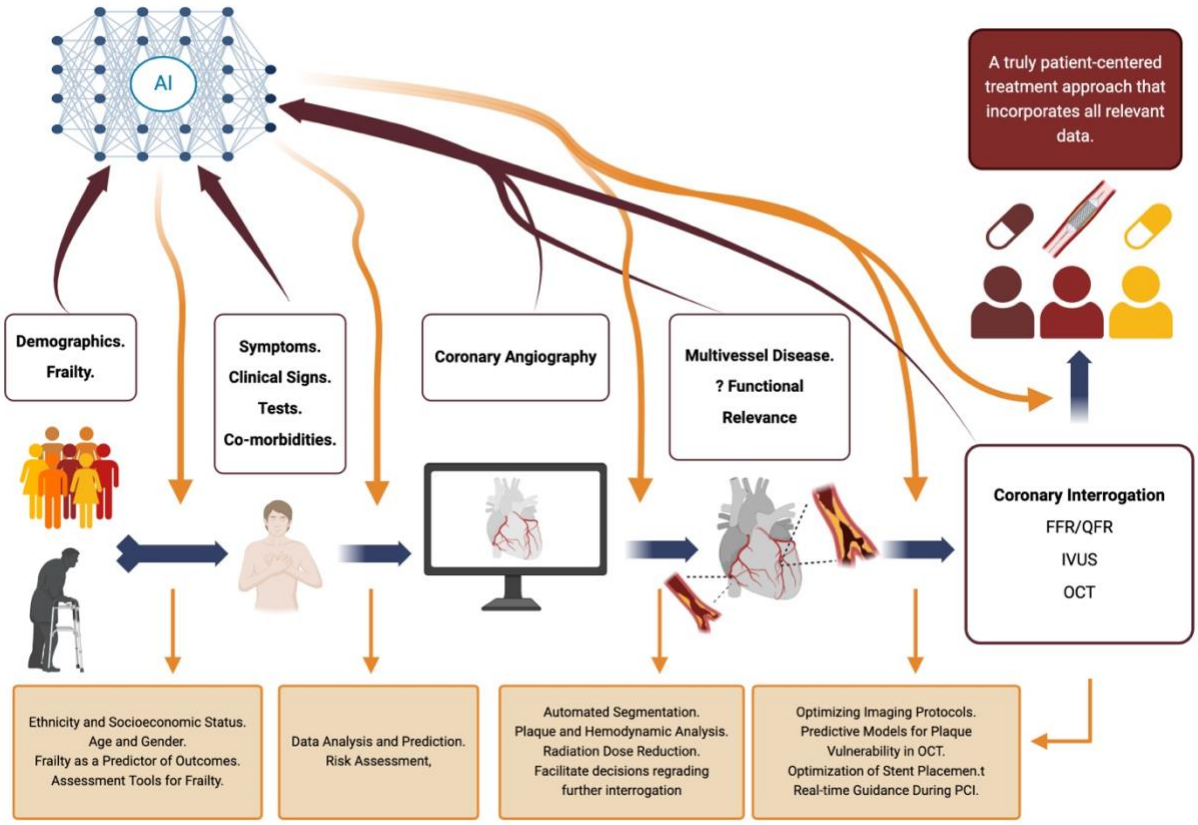


**Figure 10. Integration of AI**. Types of data and potential inputs for AI in clinical decision-making for multivessel CAD, CCS, PCI strategy selection. AI may integrate patient demographics, clinical signs, coronary angiography data, and coronary lesion assessment (e.g. FFR, QFR, IVUS, OCT) to support a patient-centred approach. *Created with BioRender.com. Kanoun Schnur S. (2024), Cardiac Interventions Today, 2025.* [8]

## 6. CONCLUSION

Both studies forming the basis of this thesis address key diagnostic gaps in patients with chronic coronary syndrome and in those with critical limb ischemia who are suspected of having chronic coronary syndrome.

First, this research demonstrates a persistent rate of discordance between angiography-guided revascularisation and true functional significance of coronary lesions, even when these lesions do not meet anatomical thresholds typically warranting functional interrogation. This finding underscores the need to integrate coronary physiology assessment as a standard component of all coronary angiograms, a strategy increasingly feasible through angiography-based calculations and advances in artificial intelligence.

Second, there is a high incidence of undiagnosed functionally severe coronary artery disease in patients with critical limb ischemia, which often remains unmasked prior to revascularisation of the critical limb ischaemia due to limited mobility. Detection and revascularisation guided by coronary physiology may reduce the risk of MACCE, as suggested by trends observed in one-year outcomes, with potential for even greater benefit during longer-term follow-up.

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