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

Thesis Booklet

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## Abbreviations

Abbreviation	Definition	Abbreviation	Definition
<b>ABNORM</b>	Operator angiography-only decisions vs retrospective QFR in non-intermediate lesions (Study 1)	<b>INCORPORATE</b>	CLI trial: conservative <b>OMT</b> vs invasive, physiology-guided coronary strategy after successful peripheral revascularisation (Study 2)
<b>AT</b>	As-treated	<b>ITT</b>	Intention-to-treat
<b>CABG</b>	Coronary artery bypass grafting	<b>LAD / LCx / RCA</b>	Left anterior descending / left circumflex / right coronary artery
<b>CAD</b>	Coronary artery disease	<b>MACCE</b>	Major adverse cardiovascular & cerebrovascular events
<b>CCS</b>	Chronic coronary syndromes	<b>MI</b>	Myocardial infarction
<b>CI</b>	Confidence interval	<b>OMT</b>	Optimal medical therapy
<b>CLI</b>	Critical limb ischaemia	<b>PCI</b>	Percutaneous coronary intervention
<b>DS</b>	Diameter stenosis	<b>PP</b>	Per-protocol
<b>FFR</b>	Fractional flow reserve	<b>QFR</b>	Quantitative flow ratio
<b>HR</b>	Hazard ratio	<b>SENS / SPEC</b>	Sensitivity / Specificity

## **1. INTRODUCTION**

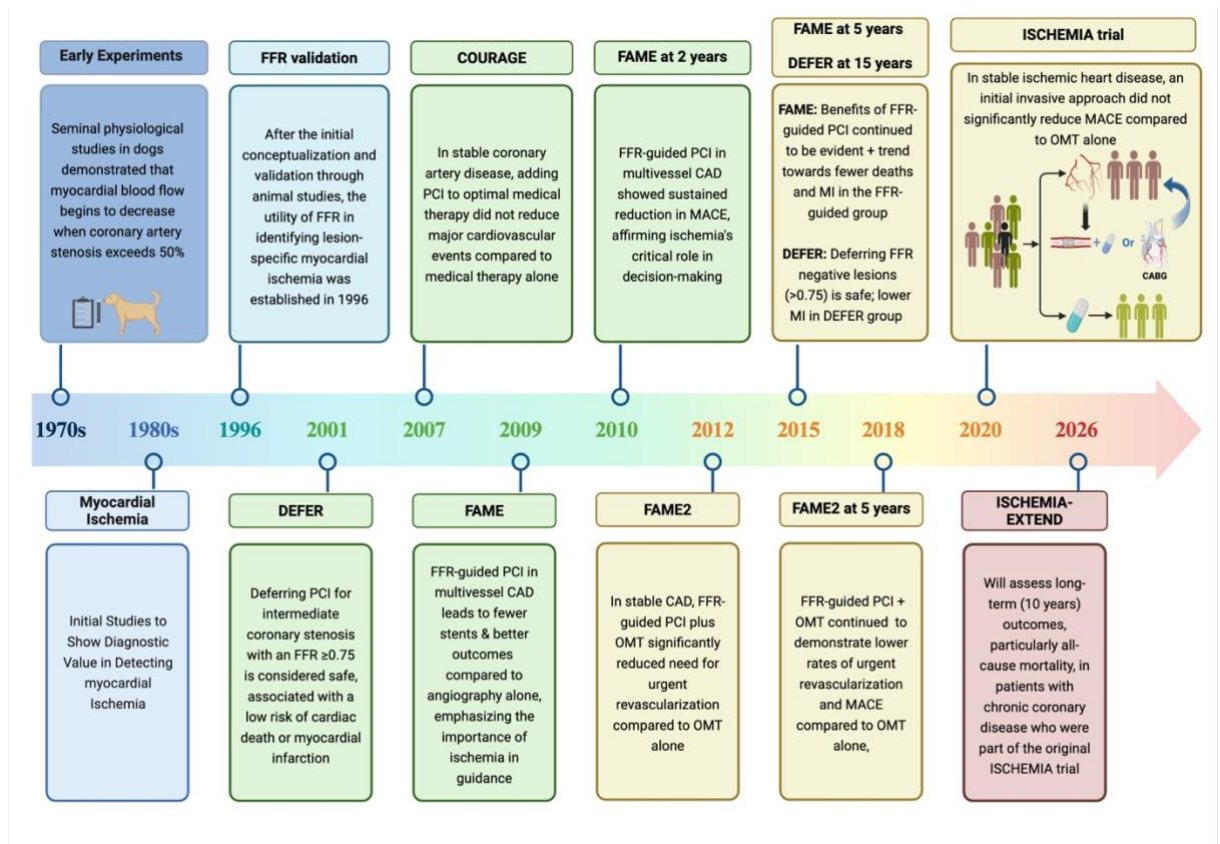
Percutaneous coronary intervention (PCI) for coronary revascularisation has made substantial progress, yielding increasingly favourable outcomes for high-risk patients, such as those with multivessel disease and notable comorbidities. Nevertheless, avoiding unnecessary interventions is critical, especially 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. Figure 1 summarises the historical studies underpinning physiology-guided revascularisation decisions.

## **2. BACKGROUND**

Decisions about coronary revascularisation in CCS still rely heavily on angiographic visual assessment, despite known discordance with functional significance. This thesis evaluates how systematic coronary functional assessment can refine diagnosis, decisions, and outcomes. It comprises: (1) ABNORM, a prospective single-centre registry assessing operator decisions made without pressure-wire testing using retrospective quantitative flow ratio (QFR); and (2) INCORPORATE, a multicentre randomised trial in patients with critical limb ischaemia (CLI) comparing a default invasive strategy (angiography with fractional flow reserve (FFR)-

guided revascularisation when indicated) versus conservative management after successful peripheral revascularisation.



**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.*

### 3. METHODS

In the ABNORM study, we enrolled consecutive patients with suspected CCS undergoing elective invasive coronary angiography. Lesions were included only when operators judged them to be clearly outside the “intermediate” zone—that is, either visually non-significant or clearly significant such that routine pressure-wire assessment would not normally be performed. Per protocol, all anatomical assessments and immediate treatment decisions (medical therapy vs percutaneous coronary intervention [PCI]/coronary artery bypass grafting [CABG]) were left entirely to operator discretion, mirroring everyday practice.

At the vessel level, we compared the quantitative flow ratio (QFR)-based appropriateness categories with independent, blinded anatomical assessments of each target lesion performed by operators not involved in the index procedure. In parallel, patient-level adjudication captured the real-world treatment strategy actually delivered (medical therapy vs PCI/CABG, target selection and staging), allowing us to separate per-lesion agreement from the appropriateness of the overall management plan.

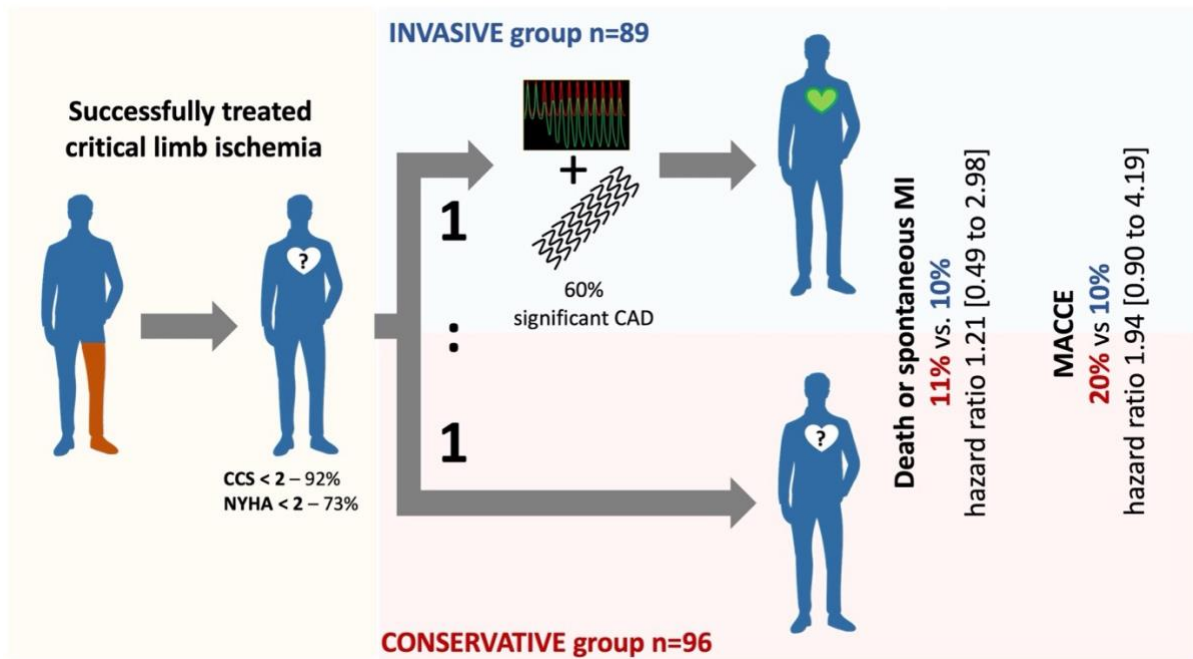
After the index procedure, offline QFR analysis was performed by trained analysts blinded to the clinical and vessel level decisions. At the vessel level, we compared the QFR-based appropriateness categories with independent, blinded anatomical assessments of each target lesion performed by operators not involved in the index procedure. In parallel, at the patient level, adjudication captured the real-world treatment strategy actually delivered (medical therapy vs PCI/CABG, target selection and staging), allowing us to separate per-lesion agreement from the appropriateness of the overall management plan. QFR results were then used to classify the appropriateness of revascularisation at both the vessel level (appropriate revascularisation, appropriate deferral, inappropriate revascularisation, inappropriate deferral) and the patient level (overall strategy appropriate, functional overtreatment, or incomplete revascularisation), enabling us to quantify how often visually “obvious” decisions align with functional significance when physiology is applied systematically in retrospect. The full ABNORM workflow, screening, exclusions, blinded offline QFR, consensus, and analysis, is summarised in Figure 2.

In INCORPORATE, patients with critical limb ischaemia (CLI) after successful peripheral revascularisation were randomised 1:1 to conservative therapy (optimal medical therapy, OMT) or to an invasive coronary strategy comprising diagnostic coronary angiography with physiology-guided revascularisation of haemodynamically significant lesions, aiming for reasonably complete revascularisation. The conservative arm received OMT with coronary

angiography reserved for clinical triggers. Follow-up visits were scheduled to 12 months, with events adjudicated blinded to treatment allocation. The primary endpoint was all-cause death or spontaneous myocardial infarction at 12 months; the key secondary endpoint was MACCE (pre-specified composite of major adverse cardiovascular and cerebrovascular events). Analyses were conducted on an intention-to-treat basis, with per-protocol and as-treated sensitivity analyses. The INCORPORATE trial design, treatment pathways and outcomes are shown in Figure 3.



**Figure 2. Flowchart of the ABNORM 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, CC BY 4.0.*



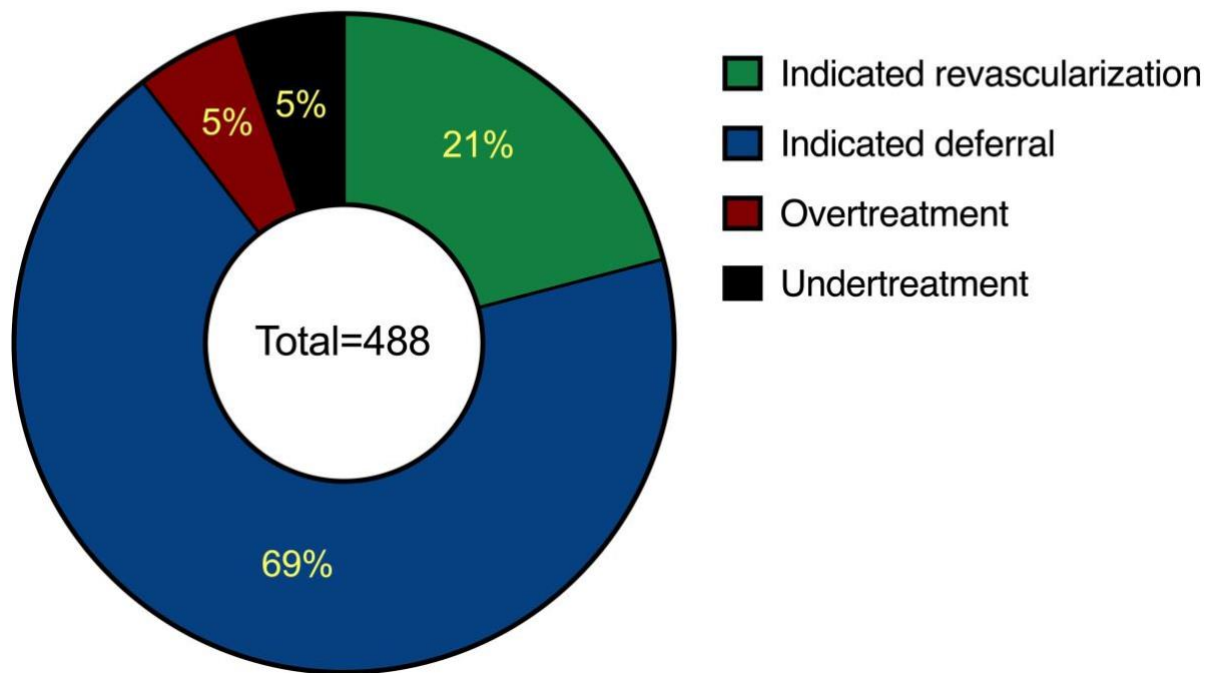
**Figure 3. Illustrative abstract of the INCORPORATE trial.** Patients with successfully revascularised CLI were randomised 1:1 to either a conservative strategy (medical therapy alone) or an invasive strategy involving coronary angiography and, if indicated, FFR-guided complete revascularisation. *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, CC BY 4.*

## 4. RESULTS

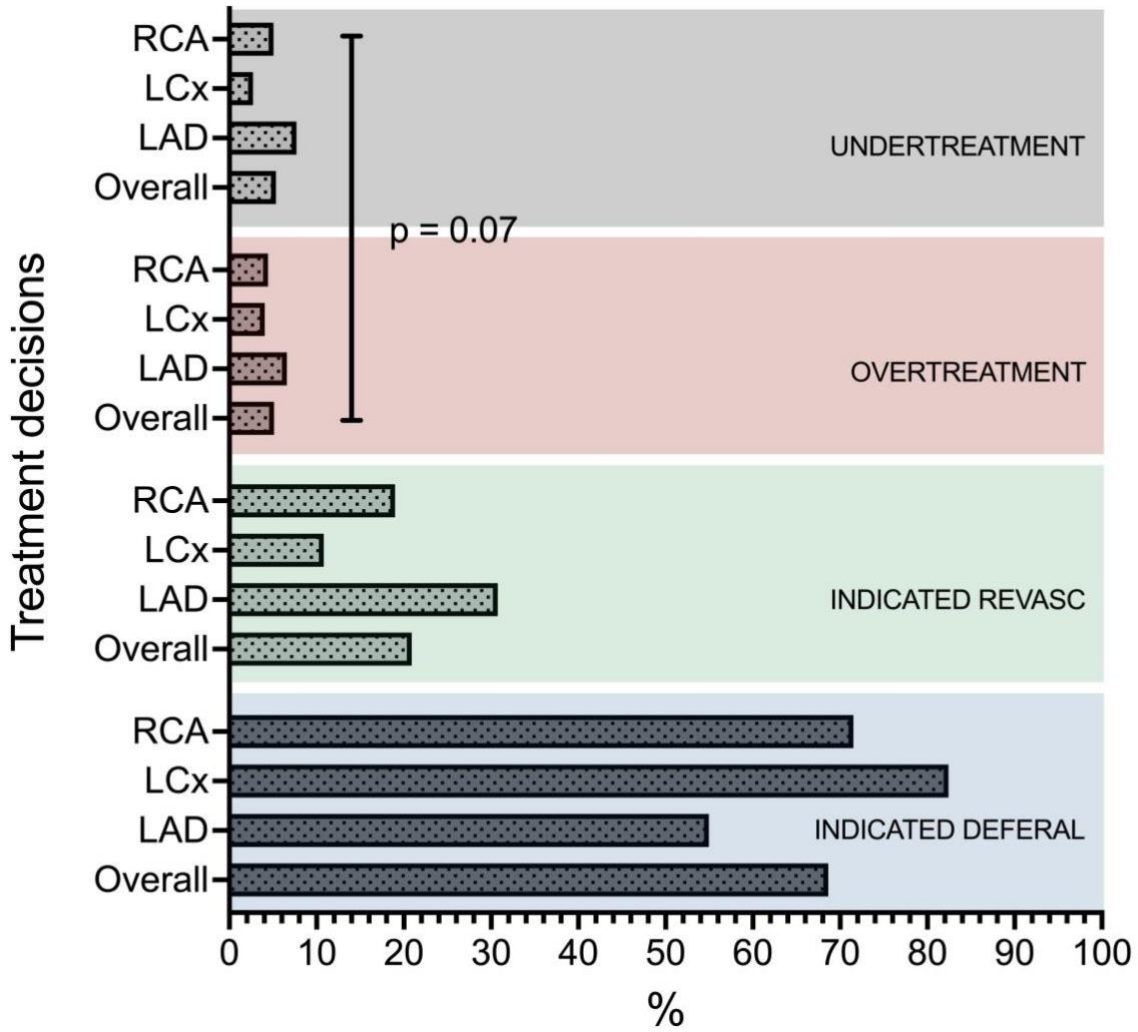
ABNORM enrolled a total of 191 patients and 488 vessels were analysed. Agreement between angiography-based decisions and QFR was 90% overall (21% appropriate revascularisations; 69% appropriate deferrals). Misclassification occurred in 10% (5% inappropriate revascularisation; 5% inappropriate deferral). By vessel, discrepancy was highest in the left anterior descending (LAD) 14.3% versus left circumflex (LCx) 6.8% and right coronary artery (RCA) 9.5% ( $p = 0.07$ ). Using angiographic cut-offs, agreement with QFR was 88% at 50% diameter stenosis (DS) (SPEC 84%, SENS 97%) and 91% at 70% DS (SPEC 93%, SENS 88%). Three-vessel QFR was available in 160 patients (84%); the overall strategy was appropriate in 75%, with 13% incomplete revascularisation and 13% functional overtreatment; both over- and undertreatment co-occurred in 1%. The overall distribution of concordant vs discordant decisions is shown in Figure 4, with the vessel-specific breakdown by artery in Figure 5

INCORPORATE enrolled 185 patients: 96 randomised to conservative care and 89 to an invasive strategy after successful peripheral revascularisation for critical limb ischaemia. In the invasive arm, 81% had angiographic CAD and 60% had functionally significant disease; after physiology-guided treatment, 91% were discharged with no residual functionally significant stenosis. The primary endpoint (all-cause death or spontaneous myocardial infarction [MI] at 12 months) was neutral (11% conservative vs 10% invasive; hazard ratio [HR] 1.21, 95% CI 0.49–2.98). MACCE rates were numerically lower in the invasive group in per-protocol (20% vs 7%; HR 2.88 [1.24–6.68]) and as-treated analyses (22% vs 7%; HR 3.01 [1.38–6.56]), with a non-significant trend in intention-to-treat (ITT) (20% vs 10%; HR 1.94 [0.90–4.19]). Given under-recruitment and limited power, these findings should be interpreted cautiously and viewed as hypothesis-generating rather than confirmatory. Kaplan–Meier curves for the intention-to-treat, per-protocol, and as-treated analyses are presented in Figure 6

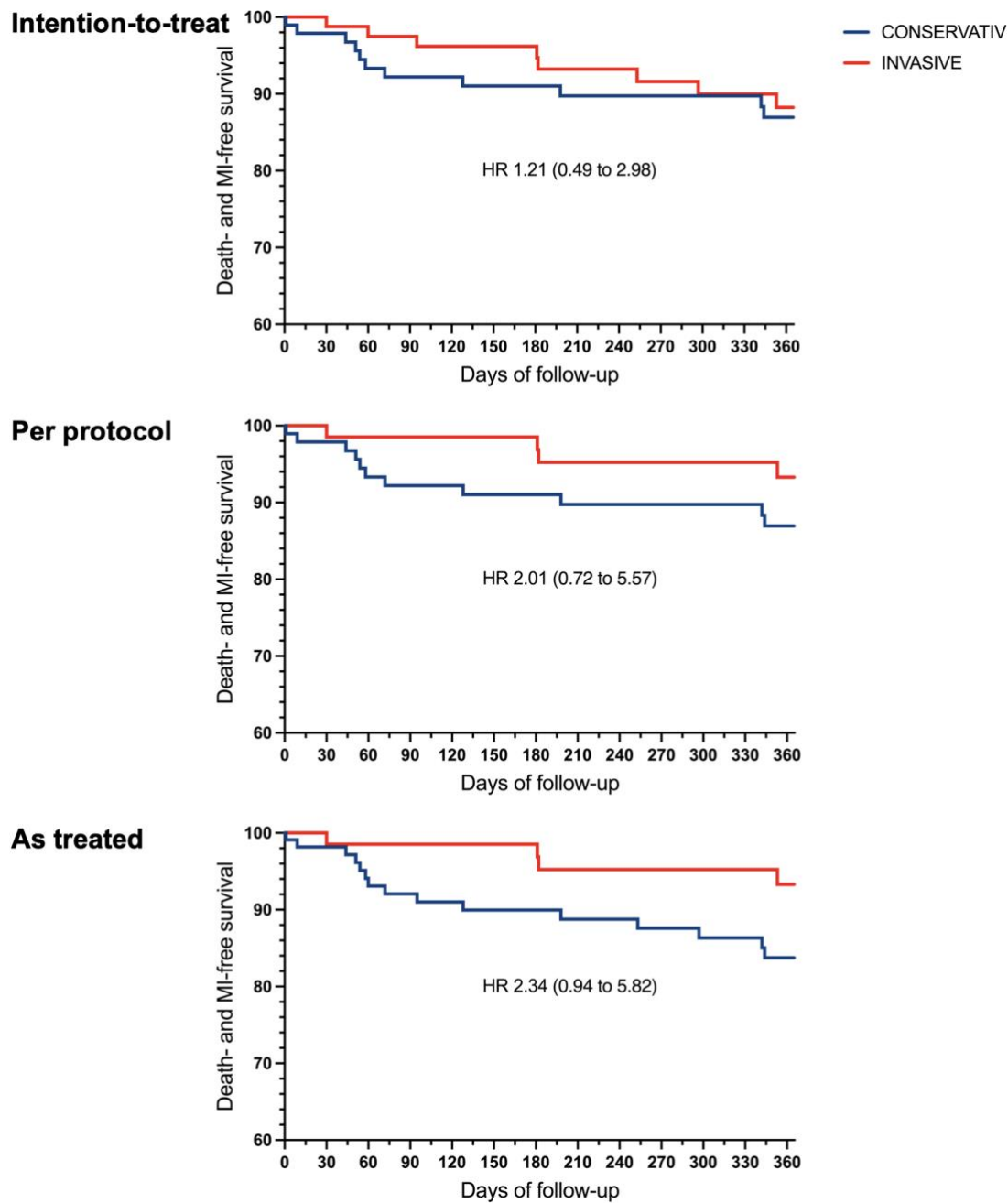
## Treatment strategies



**Figure 4. 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, CC BY 4.0.*



**Figure 5. 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, CC BY 4.0.*



**Figure 6. 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: MI = Myocardial infarction, HR = hazard ratio. *Reproduced from Toth GG et al., Clinical Research in Cardiology, 2024, CC BY*

## **5. CONCLUSION**

Both studies address diagnostic gaps in chronic coronary syndromes and critical limb ischaemia patients with suspected chronic coronary syndromes. First, persistent discordance between angiography and functional significance underscores integrating physiology in all angiograms, feasible via angiogram based functional assessments and artificial intelligence. Second, high rates of undiagnosed severe coronary artery disease in critical limb ischaemia remain unmasked pre-revascularisation due to limited mobility. An upfront invasive strategy with physiology-guided detection of functional relevance may reduce major adverse cardiac and cerebrovascular events, as per one-year trends, with greater long-term benefit.