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Curriculum in Fisiopatologia e Clinica delle Malattie Renali, Cardiovascolari e dell'Ipertensione Arteriosa

Tesi di Dottorato:

"Contribution of Coronary Physiology and Imaging to Clinical Decision-Making in Patients with Coronary Artery Disease"

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TABLE OF CONTENTS

Part A.

General introduction and outline of the thesis

The combined use of coronary physiology and imaging has profoundly enhanced our understanding and management of coronary artery disease (CAD). Pressure-derived physiological indices such as fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) allow the functional assessment of epicardial coronary stenoses and guide revascularization decisions with high diagnostic accuracy, while intravascular imaging modalities—including intravascular ultrasound (IVUS) and optical coherence tomography (OCT)—provide detailed characterization of plaque morphology, vessel architecture, and stent performance (1-3). Reflecting the strength of accumulated evidence, contemporary European guidelines grant both physiology and imaging a Class I, Level of Evidence A recommendation for their use in the catheterization laboratory (4). Yet, despite such robust indications, global adoption of these techniques remains low. Recent analyses have underscored the limited routine use of intracoronary imaging and the similarly modest penetration of pressure-wire physiology in catheterization laboratories worldwide, revealing a paradox whereby technologies with proven clinical benefit are infrequently implemented in daily practice (5,6). This discrepancy is clinically meaningful, as both physiology and imaging have been consistently associated with improved long-term outcomes (7,8). Their utility extends beyond lesion classification and procedural guidance, informing individualized diagnoses and therapeutic decisions that angiography alone cannot provide (9). The relevance of comprehensive coronary assessment is further emphasized by the persistent burden of angina after percutaneous coronary interventions (PCI), a multifaceted and frequently underestimated problem affecting up to half of patients following percutaneous revascularization (10). Residual ischemia, suboptimal stent deployment, CAD progression, unrecognized coronary microvascular dysfunction or vasomotor disorders are common contributors to persistent symptoms and cannot be reliably identified by angiography alone (9-11). Accordingly, physiology and imaging are indispensable tools for understanding patient-specific mechanisms of ischemia and guiding tailored treatment strategies (1-3, 11).

In this thesis, we sought to expand the contemporary applications of coronary physiology and imaging across a spectrum of clinical scenarios. In Chapter 1, we investigated the prognostic implications of pressure-wire assessment by comparing outcomes in patients for whom revascularization was deferred or performed on the basis of physiological indices, thereby clarifying the long-term safety of physiologically guided deferral and highlighting the inherently high cardiovascular risk profile of patients with obstructive CAD independently of revascularization. In Chapter 2, we examined the two major randomized clinical trials comparing iFR and FFR (12,13), pooling patient-level data with extended follow-up to refine understanding of the relative performance of these indices in both treated and deferred populations. Recognizing the barriers to the widespread adoption of physiology, a central component of this thesis was the evaluation of a comprehensive wire-free invasive diagnostic strategy capable of identifying obstructive and non-obstructive causes of myocardial ischemia at the time of coronary angiography, thereby offering a pragmatic approach to broaden access to mechanistic assessment; this was addressed in Chapter 3. Finally, in Chapter 4, we developed and validated an OCT-based bifurcation score designed to predict side-branch compromise during stepwise provisional stenting, providing an imaging-guided tool for procedural planning in bifurcation PCI and supporting a more personalized approach in this complex anatomical scenario.

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Part B.
Research chapters

Chapter 1.

Cardiovascular Outcomes in Patients with Deferred and Performed Coronary Revascularization Based on Intracoronary Physiology: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: While large studies and pooled analyses of individual patient data have demonstrated the safety of deferring coronary revascularization based on a non-ischemic intracoronary pressure index result, conflicting findings have emerged in specific patient subsets and with varying follow-up. Thus, we conducted an updated comprehensive systematic review and meta-analysis to investigate the cardiovascular outcomes associated with deferred or performed coronary revascularization based on intracoronary physiology.

Methods: Available studies were identified through a systematic search of PubMed, EMBASE and CENTRAL. Efficacy outcomes investigated were major adverse cardiovascular events (MACE), all cause death, cardiovascular death, non-cardiovascular death, myocardial infarction (MI), and unplanned revascularization.

Results: A total of 24 studies enrolling 24,285 patients were included in the meta-analysis. After a mean follow up of 2.6±1.6 years, patients undergoing physiology-guided deferred revascularization show consistently better outcomes than patients who underwent revascularization, including all cause death (incidence rate ratio (IRR) 1.14, 95% confidence interval (CI) [1.00-1.30], p=0.05), cardiovascular death (IRR 1.53 (95%CI [1.17-2.00], p=0.002), and unplanned revascularization (IRR 1.38 (95% CI [1.06-1.79, p=0.01). For MACE (IRR 1.15, 95% CI 0.99–1.34, p = 0.07) and MI (IRR 1.24, 95% CI 0.95–1.61, p = 0.11), the associations did not reach statistical significance.

Conclusions: Patients in whom revascularization was deferred based on intracoronary physiology show lower risk of adverse cardiovascular events compared to those that underwent revascularization. These findings suggest that pressure wire assessment has prognostic implications besides the indication for revascularization.

INTRODUCTION

Assessment of the functional significance of coronary stenosis using pressure-derived indices, such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR), has gained increasing importance over the past two decades because of its significant impact on clinical outcomes (1–4). Large studies and pooled analyses of individual patient data have demonstrated the safety of deferring coronary revascularization based on non-ischemic FFR or iFR values (5).

These results have been primarily consistent in selected subsets of patients, such as those with stable coronary artery disease (CAD) affecting a single coronary vessel, with a follow-up duration within 1 year. Studies with a different design (both randomized clinical trials [RCTs] and not-RCTs), including those involving patients with non-culprit acute coronary syndromes (ACS) stenoses and/or with multivessel disease, and reporting long-term data, have yielded conflicting results, highlighting the rationale for a more thorough and comprehensive assessment of the topic (6).

We conducted a systematic review and meta-analysis with the main objective to examine the impact on cardiovascular outcomes of clinical decision-making based on intracoronary physiological indices, describing the difference between deferral and performance of coronary revascularization.

METHODS

We performed a systematic review and meta-analysis in accordance with the guidelines from the Cochrane collaboration and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)(7), which was registered within the PROSPERO International Prospective Register of Systematic Reviews (CRD42023432774). Ethical approval was not obtained for this study because it consisted of a study-level systematic review and meta-analysis. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Data sources and searches

We conducted a systematic search of PubMed, EMBASE and CENTRAL. The search utilized the following terms: “fractional flow reserve", "instantaneous wave-free ratio", "percutaneous coronary intervention", "revascularization", and "deferred" (*Supplementary Table S1*).

The search of articles compatible with predefined inclusion and exclusion criteria was performed from inception through 23rd August 2024 and returned a combined total of 7,923 articles.

Study abstracts were screened for established inclusion and exclusion criteria. Studies believed to be relevant to our search were downloaded and the full manuscripts reviewed. The reference lists of the reviewed manuscripts were screened in order to identify potential studies not previously included in the initial database search. The PRISMA checklist and flow diagram are shown in the online supplementary material (*Supplementary Table S2* and *Figure S1*).

Study selection

We included the articles that satisfied the following inclusion criteria: 1) randomized clinical trials (RCTs) or observational/retrospective studies comparing pressure indices recommended versus deferred coronary revascularization; 2) reported cardiovascular outcomes; 3) enrollment of chronic and/or acute coronary syndrome; 4) follow-up period >1 year; 5) utilization of drug eluting stents (DES); and 6) English language. Exclusion criteria were: 1) absence of reported outcomes or reported per-lesion and not per-patient; 2) comparison between FFR-guided and angiography-guided revascularization which did not report clinical outcomes for treated or deferred patients; 3) revascularization decision not based on pressure indices; 4) follow-up period <1 year; 5) CABG as the only revascularization modality; 6) significant use of plain old balloon angioplasty (POBA) or bare metal stent (BMS); 7) studies including a significant number of patients with left main disease or aortic stenosis.

Outcomes and Definitions

The outcomes of interest were all cause death, cardiovascular death, non-cardiovascular death, myocardial infarction (MI), unplanned revascularization, and major adverse cardiovascular events (MACE).

Data extraction

Two investigators (ML and AT) independently reviewed study titles, abstracts, and articles. Those that satisfied the inclusion and exclusion criteria were retrieved for full text evaluation. Discrepancies regarding data incorporation to the database were resolved through consensus among the authors. We extracted the following data from each selected study: number of participants, demographics, and clinical outcomes of interest.

Internal validity and quality appraisal

Two independent reviewers (ML and AT) evaluated the quality of the studies, with divergences resolved after consensus. According to the Newcastle – Ottawa Scale (NOS) (8) and Risk of Bias Assessment Tool version 2 (Rob2) (9), we separately abstracted and appraised study design, setting, data source, as well as (following the Cochrane Collaboration recommendations) the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low-, moderate-, or high-risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias). *Supplementary Figure S1* and *Table S3* show the appraisal synthesis. The assessment of the certainty of evidence per each outcome was performed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (*Supplementary Table S4*).

Data synthesis and analysis

To take into account different follow-up times data, we adopted a patient-per-year approach and calculated incidence rate ratios (IRR) with 95% confidence intervals (95%CI). For the primary

analysis the treatment effect estimates were computed through random effects models; fixed effects models were computed as a sensitivity analysis. Exact Poisson regression was applied to address small counts and improve estimation accuracy; additionally, as a sensitivity analysis, the Knapp-Hartung method was performed to better account for uncertainty in heterogeneity estimates.

Heterogeneity across studies was assessed using Cochran's Q statistic and reported using I^2 and τ^2. The degree of heterogeneity was described as low, moderate, or high based on the magnitude and consistency of these estimates.

For hypothesis generation the presence of publication bias for small study effect appraisal was assessed by visual examination of Funnel plots and Egger's test (*Supplementary Figure S2 and Table S5*).

Through sensitivity analyses we sought to explore whether the observed trend in physiology-guided treatment applies consistently across different subsets. Two main subgroup analyses were performed according to sample size (<500 patients and ≥500 patients) and study design (RCT and not-RCT). A sensitivity analysis was performed using the leave-one-out approach for comparisons by sequentially removing each study to investigate its influence on the main results. Univariable random-effect meta-regressions were performed to explore the potential association between some variables (age, sex, acute coronary syndrome, diabetes mellitus, multivessel disease, dyslipidemia, hypertension, smoking status, CABG as revascularization strategy, prior PCI or CABG) and treatment effect for outcomes of interest, accounting for between-study heterogeneity while investigating the influence of a single covariate.

All analyses were performed with the R statistical software (R project for statistical computing 4.2.1 version, Vienna, Austria) using the R packages "meta", "metafor", and "metareg".

RESULTS

Study selection

A total of 7,923 studies were identified via electronic database research. After screening 24 studies were included providing data on a total of 24,285 patients (**Figure 1** and **Table 1**) (10–33). Detailed variations in endpoint definitions across the included studies are provided in *Supplementary Table S5*.

18 studies used FFR as the pressure index for decision-making, whereas 2 studies used iFR and 4 studies used both FFR and iFR. Most studies used 0.80 as the ischemic cut-off in FFR, while only 2 used 0.75. For iFR, all included studies used the 0.89 cut-off.

Baseline patient characteristics are shown in **Table 2**. Mean age of the overall cohort of patients was 64.9±3.8 years, 75% were men and 36% were diabetics. ACS was the clinical presentation in 47% of cases, multivessel disease was present in 56% of patients and 5% underwent revascularization with CABG. Mean follow-up was 2.6±1.6 years, and long-term follow-up data (defined as ≥ 3 years) was presented in 9 studies out of 24.

All cause death

17 studies (7 RCTs and 10 not-RCTs) involving a total of 19,263 patients, reported the incidence of death in those allocated to revascularization (n=8,494) or defer (n=10,769) groups. The overall IRR was 1.14 (95%CI [1.00-1.30], p=0.05), with negligible heterogeneity among studies (I^2=0%, τ^2=0) (**Figure 2,** Panel A).

Cardiovascular death

12 studies (4 RCTs and 8 not-RCTs) involving a total of 13,980 patients, reported the incidence of cardiovascular death in those allocated to revascularization (n=6,208) or defer (n=7,772) groups. The overall IRR was 1.53 (95%CI [1.17-2.00], p=0.002), without significant heterogeneity among studies (I^2=18%, τ^2=0) (**Figure 2**, Panel B).

Non cardiovascular death

8 studies (4 RCTs and 4 not-RCTs) involving a total of 12,760 patients, reported the incidence of non-cardiovascular death in those allocated to revascularization (n=5,763) or defer (n=6,997) groups. There was no statistically significant difference in the occurrence of cardiovascular death among the studies, with an overall IRR 0.97 (95% CI [0.78-1.20], p=0.77) with moderate-to-high degree of heterogeneity among studies (I^2=60%, τ^2=0) (**Figure 2**, Panel C).

MACE

19 studies (7 RCTs and 12 not-RCTs) involving a total of 18,105 patients, reported the incidence of MACE in those allocated to revascularization (n=7,701) or defer (n=10,404) groups. The overall IRR was 1.15 (95%CI [0.99-1.34], p=0.06) (**Figure 3**, Panel A), with a moderate degree of heterogeneity (I^2=44%, τ^2=0.03).

Myocardial Infarction

20 studies (6 RCTs and 14 not-RCTs) involving a total of 21,163 patients, reported the incidence of myocardial infarction in those allocated to revascularization (n=8,822) or defer (n=12,341) groups. The overall IRR was 1.24 (95%CI [0.95-1.61], p=0.11) (**Figure 3**, Panel B) with a mild degree heterogeneity (I^2=27%, τ^2=0.11).

Unplanned revascularization

17 studies (6 RCTs and 11 not-RCTs) involving a total of 20,434 patients, reported the incidence of unplanned revascularizations in those allocated to revascularization (n=8,498) or defer (n=11,936) groups. The overall IRR was 1.38 (95% CI [1.06-1.79, p=0.01) but with a high degree of heterogeneity (I^2=79%, τ^2=0.19) (**Figure 3**, Panel C).

Publication bias assessment and sensitivity analyses

For all endpoints, funnel plots and Egger's plots suggested no evidence of significant publication bias or small study effect (*Supplementary Figure S2 and Table S5*). Subgroup analysis showed that the pooled estimate was consistent among large sample sizes or RCT studies in all endpoints (*Supplementary Figures S3-S8*). Sensitivity analysis accounting for small counts study effect demonstrated robustness of the overall result (*Supplementary Table S6*). Meta-regression analyses showed no significant relation between all covariates and pooled estimates for cardiovascular events, except for a direct relation between MACE and diabetes mellitus (estimate -0.01, $p<0.01$) (*Supplementary Table S7*). Leave-one-out analyses demonstrated that the main findings remained consistent, with no single study disproportionately influencing the pooled effect estimates. Although minor variations in heterogeneity and statistical significance were observed when omitting certain individual studies, the overall direction and magnitude of the associations remained stable across outcomes of interest (*Supplementary Table S8*).

DISCUSSION

The main finding of this study is that, when decision making is based on intracoronary pressure guidewire interrogation, deferral of revascularization is consistently associated to better outcomes than performance of revascularization.

The aim of physiology-guided revascularization is to improve patient symptoms and outcomes by performing interventions only in vessels with demonstrated flow-limiting stenoses. It has been shown that pressure wire interrogation determines the hemodynamic significance of coronary stenoses in a more accurate fashion that angiography (34). Pivotal studies using FFR showed that avoiding revascularization in lesions with non-significant pressure drops is safe, being this one of the fundamentals of physiology-guided revascularization (35). Non-hyperaemic pressures indices such as iFR have demonstrated equivalence with FFR when used as a tool for decision-making on coronary revascularization (2,3).

This meta-analysis supports the generally favorable prognosis of patients with stable ischemic heart disease and underscores the importance of medical therapy as a cornerstone of disease management, regardless of whether revascularization was performed or deferred based on intracoronary physiology interrogation.

Current understanding on the prognostic impact on coronary vascularization in chronic coronary syndromes stems from the ISCHEMIA (36) and FAME 2 (17) trials. Yet, may be important to highlight the differences in management of patients in whom the diagnosis of myocardial ischemia is based on either non-invasive tests or intracoronary diagnostics. In the former case, the diagnosis of ischaemia can be made without knowledge of the coronary anatomy, while in the case of intracoronary indices the diagnosis and management of myocardial ischaemia is always performed with awareness of the coronary anatomy. This fact may be associated to an excess of subsequent revascularization in those patients investigated invasively. A second consideration is that, in clinical practice, a dichotomous classification of FFR/iFR values as “positive” and “negative” in terms of causing myocardial ischaemia is typically used. Despite this categorization facilitates clinical

decision making it may lead to a significant loss of information, due to the fact that FFR/iFR values depict a continuum of ischaemia and prognosis (37). Clinical decision-making made on a dichotomous index such as FFR or iFR may, therefore, differ from non-invasive tests which typically do not use binary classification.

In this regard, recent trials such as FAME 2 (17) and ISCHEMIA (36) have shown that in the presence of demonstrable myocardial ischaemia with either invasive or non-invasive tests, revascularization is not associated with better outcomes than optimal medical therapy alone, although the extended follow-up of the ISCHEMIA trial has suggested a lower cardiovascular mortality in invasively managed patients (38).

Building upon these insights, in the present meta-analysis we aimed for a nuanced understanding of cardiovascular outcomes in patients undergoing physiology guided decision-making in current clinical practice, including those with multivessel disease, non-culprit ACS stenoses, and with a long-term follow-up.

We found a significantly higher incidence of cardiovascular events in patients undergoing revascularization, compared to those not requiring revascularization on the grounds of pressure guidewire interrogation. This higher risk of events can be attributable to various causes.

First, patients undergoing coronary revascularization due to a positive intracoronary pressure index result often exhibit a higher burden of cardiovascular risk factors, which may contribute to the worse prognosis observed when compared with those in whom revascularization was deferred. From a methodological perspective, however, we cannot infer whether patients with abnormal FFR/iFR inherently have worse baseline characteristics than those whose revascularization has been deferred. Nevertheless, this hypothesis is in line with other studies that show a prognostic impact of functional evaluation in patients undergoing PCI. For example, in a sub-study of the FLAVOUR trial, patients undergoing PCI based on intravascular ultrasound criteria showed different outcomes according to a functional assessment performed with angiography-based physiology (μQFR) – being significantly better in patients undergoing PCI with negative μQFR (>0.80) than those also undergoing PCI with

positive μQFR (<0.80) (39). These findings suggest that physiological assessment reveals a higher risk of events that persist after revascularization.

The second of them can be revascularization failure, namely in-stent restenosis and stent thrombosis, leading to an excess of unplanned revascularization, myocardial infarction, and ultimately, death. However, with the adoption of modern DES platforms, the incidence of those phenomena has been steadily decreasing in the past years and are unlikely to be the unique determinants of the worse prognosis observed in treated patients (40).

And last but not least, an additional cause could be an incorrect detection of the ischemia-generating lesions. In the context of different disease patterns (focal vs. diffuse vs tandem), revascularization decision based on a single spot FFR/iFR measurements may lead to an incorrect identification of the ischaemia generating lesion, leading to significant residual disease after PCI (41). Recent studies have shown that these scenarios are relatively frequent in daily practice, and in most cases pressure pullbacks are needed to precisely depict the pattern of disease and the lesion with the more pronounced pressure drop in serial stenoses (42). While these misidentifications may be somewhat common, their impact on mortality is likely limited.

In a prior meta-analysis conducted by Nascimento et al. (43), involving 3,097 patients with an average follow-up of 21 months, comparable outcomes were observed in terms of death and MI between patients revascularized only with PCI and deferred based on FFR values. However, an increased revascularization rate was observed among patients who underwent PCI. In our updated meta-analysis, we have expanded upon these findings in a way that reflects contemporary clinical practice. Indeed, in our analysis we incorporated iFR as alternative potential tool for the clinical decision-making alongside FFR. We have also deliberately excluded studies in which a high proportion of patients was treated with bare-metal stent or plain balloon angioplasty, and included studies where CABG was considered as a potential, though not exclusive, revascularization strategy. Finally, we included patients who underwent coronary physiology assessments at non-culprit coronary stenoses within the context of ACS, encompassing a total population of approximately

11,000 ACS patients. The role of FFR in the setting of acute myocardial infarction has been a topic of ongoing debate, as it may lead to an underestimation of the true hemodynamic severity of non-culprit stenosis. As part of our study, we conducted a meta-regression analysis where the presence of ACS did not demonstrate a significant impact on the overall results for the investigated outcomes (*Supplementary Table S7*).

By conducting sensitivity and subgroup analyses that consider variations in sample size, type of study and patient characteristics, we have ensured that our findings regarding the trend in physiology-guided treatment remain highly applicable to real-world clinical practice. Indeed, the pooled estimates were consistent among studies with large sample sizes or RCT design among all clinical endpoints explored and they were not influenced by factors such as the presence of multivessel disease, revascularization modality, or clinical presentation.

Study limitations:

Our study has several limitations. Firstly, it is a study level meta-analysis data, rather than individual patient-level. Consequently, we were unable to perform in depth sub-group analyses.

To address this limitation, we conducted classical sensitivity analyses exploring any potential cofounder through metaregression, subgroup and leave-one-out analyses.

Second, the study comprises patients with known CAD that underwent invasive physiological evaluation. For this reason, our conclusions cannot be directly extrapolated to studies comparing invasive vs. non-invasive strategies for the management of CAD, such as the ISCHEMIA trial (36,38).

Third, we could not differentiate between unplanned revascularizations occurring in previously FFR-deferred lesions and new de novo stenoses. Additionally, as our analysis was performed on a per-patient basis rather than a per-lesion basis, patients who received treatment in one coronary artery and deferred in another were categorized within the revascularization group, introducing the potential occurrence of events related to the deferred lesion.

Fourth, there is a potential limitation related to the utilization of a different FFR cut-off for detecting myocardial ischemia in the DEFER DES[14] and de la Torre Hernandez et al. (13) studies (0.75 instead of 0.80). However, upon exclusion of these studies in leave-one-out analyses, the overall results mainly remained unaffected.

Fifth, most of the studies did not have pressure pullbacks as part of the standard evaluation to guide treatment, so detailed information about the coronary disease phenotype (focal vs. diffuse) is not available and we can assume that it was not used to decide the treatment strategy. Moreover, post-PCI physiology measurements are also not available and prevent from drawing conclusions regarding the successfulness of revascularization. Another important limitation that likely contributed to the high degree of heterogeneity and the trend toward significance in the random-effects model analysis for MACE, MI, and unplanned revascularization (which reached significance in the sensitivity analysis using fixed-effects model) is the variability in endpoint definitions (see *Supplementary Table S9*). Finally, symptom-related outcomes such as angina burden were not assessed in this meta-analysis. It is important to highlight that revascularization of ischemic lesions may offer patient-level benefits beyond the reduction of hard clinical events, including improvements in angina symptoms and reduced reliance on anti-anginal medications.

CONCLUSIONS

Patients undergoing physiology-guided deferred revascularization show consistently better outcomes than patients where revascularization was performed.

These findings suggest that pressure wire assessment has deeper prognostic implications besides the indication for revascularization.

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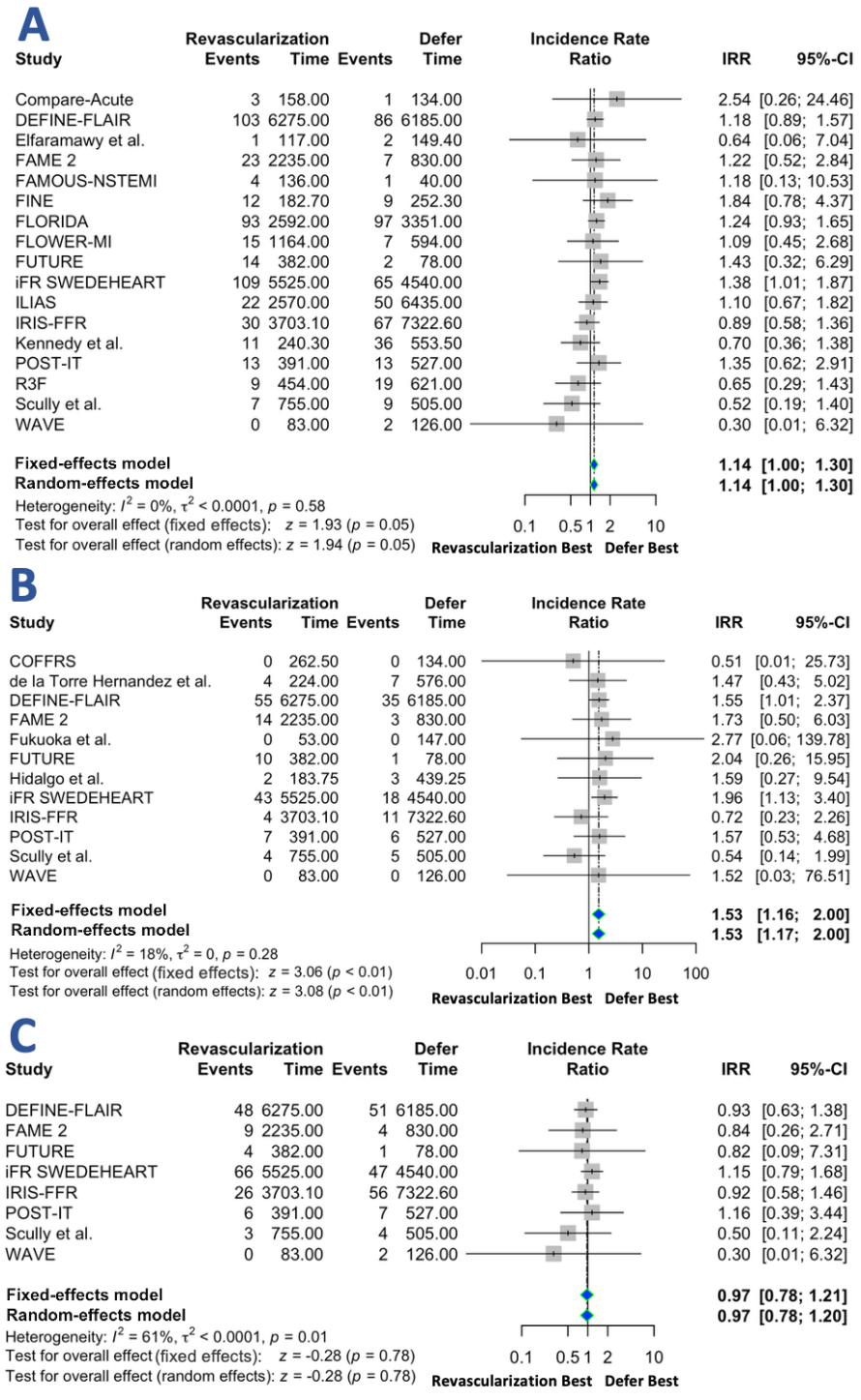
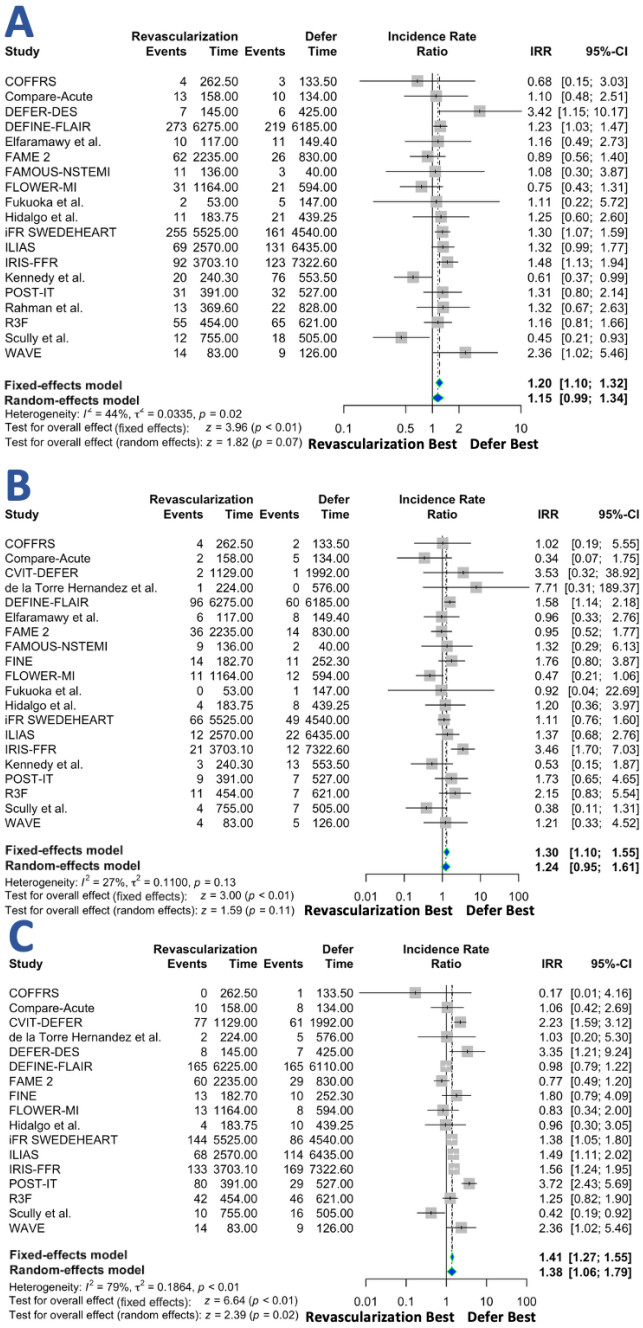
FIGURES

Figure 2. Forest plots for mortality outcomes comparing revascularization versus defer groups.
Panel A: all-cause death, Panel B: cardiovascular death, Panel C: non-cardiovascular death.



Abbreviations: CI: confidence interval; IRR, incidence rate ratio

Figure 3. Forest plots for major adverse cardiovascular events (MACE), myocardial infarction (MI), and unplanned revascularization comparing revascularization versus defer groups.
Panel A: MACE, Panel B: MI, Panel C: unplanned revascularization.



Abbreviations: CI: confidence interval; IRR, incidence rate ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

TABLES

Table 1. Characteristics of the included studies(10–33).

Study	Year	Journal	Design	Number of patients	Follow-up (years)	Intracoronary physiology index	Cut-off
COFFRS[10]	2017	*Indian heart Journal*	Retrospective	264	1,5	FFR	0,80
Compare-Acute[11]	2017	*New England Journal of Medicine*	RCT	295	3	FFR	0,80
CVIT-DEFER[12]	2017	*Circulation Journal*	Registry	3121	1	FFR	0,80
de la Torre Hernandez et al.[13]	2013	*EuroIntervention*	Prospective cohort	400	2	FFR	0,75
DEFER DES[14]	2015	*Circulation: Cardiovascular Intervention*	RCT	114	5	FFR	0,75
DEFINE-FLAIR[15]	2024	*JAMA Cardiology*	RCT	2492	5	FFR/iFR	0,80/0,89
Elfaramawy et al.[16]	2017	*The Egyptian Heart Journal*	Retrospective	148	1,8	FFR	0,80
FAME 2[17]	2018	*New England Journal of Medicine*	RCT	613	5	FFR	0,80
FAMOUS-NSTEMI[18]	2015	*European Heart Journal*	RCT	176	1	FFR	0,80
FINE[19]	2021	*Journal of Cardiovascular Medicine*	Registry	150	2,9	FFR	0,80
FLORIDA[20]	2024	*Frontiers in Cardiovascular Medicine*	All comer cohort-study	1981	3	FFR	NA
FLOWER-MI[21]	2024	*Circulation: Cardiovascular Intervention*	RCT	586	3	FFR	0,80
Fukuoka et al.[22]	2020	*IJC Heart & Vasculature*	Retrospective	200	1	FFR/iFR	0,80/0,89
FUTURE[23]	2021	*Journal of the American College of Cardiology*	RCT	460	1	FFR	0,80
Hidalgo et al.[24]	2021	*Catheterization and Cardiovascular Intervention*	Registry	356	1,75	iFR	0,89
iFR SWEDEHEART[25]	2022	*Journal of the American College of Cardiology*	RCT	2013	5	FFR/iFR	0,80/0,89
ILIAS[26]	2022	*Circulation: Cardiovascular Intervention*	Registry	1801	5	FFR	0,80
IRIS-FFR[27]	2017	*Circulation*	Registry	5846	1,9	FFR	0,80
Kennedy et al.[28]	2016	*American Journal of Cardiology*	Retrospective	294	2,7	FFR	0,80
POST-IT[29]	2016	*Circulation: Cardiovascular Intervention*	Registry	918	1	FFR	0,80
Rahman et al.[30]	2021	*Journal of College of Physicians and Surgeons Pakistan*	Retrospective	499	2,4	FFR/iFR	0,80/0,89
R3F[31]	2014	*Circulation*	Registry	1075	1	FFR	0,80
Scully et al.[32]	2021	*Heart, Lung and Circulation*	Retrospective	274	5	FFR	0,80
WAVE[33]	2022	*Catheterization and Cardiovascular Intervention*	Registry	209	1	iFR	0,89

Abbreviations: iFR: instantaneous flow ratio, FFR: fractional flow reserve, RCT: randomized controlled trial

Table 2. Clinical characteristics of the included studies(10–33).

Study	Age (mean)	Male (%)	ACS (%)	DM (%)	MVD (%)	Dyslipidemia (%)	Hypertension (%)	Current smoker (%)	CABG (%)	Prior MI (%)	Prior PCI (%)	Prior CABG (%)	CKD (%)	EF (mean)
COFFRS[10]	57,7	81	13,2	54,5	NA	27,3	40,5	55	11,7	NA	NA	NA	NA	61
Compare-Acute[11]	62	79	100	14,6	100	32,2	46,1	40,8	0	NA	8,5	NA	1	NA
CVIT-DEFER[12]	70	74	10	37	16	59	68	31	0	NA	52	3	NA	NA
de la Torre Hernandez et al.[13]	65,9	74,2	63	39,8	22,5	53,5	72,8	25,5	NA	19,5	23,3	1	NA	NA
DEFER DES[14]	62	73	51	26	63	70	64	26	0	19	19	NA	NA	62
DEFINE-FLAIR[15]	65,3	76	18,5	30,4	41,1	63,6	70,5	20,3	2,7	29,5	40,8	NA	NA	NA
Elfaramawy et al.[16]	55,9	70,9	34,4	52,3	26,5	66,9	57,6	64,9	NA	NA	35	4	NA	NA
FAME 2[17]	63,5	76,5	0	26,9	36,9	73,1	78,8	20,2	0	NA	18,6	NA	2,5	NA
FAMOUS-NSTEMI[18]	62,3	75,6	100	14,8	100	40,3	44,3	40,9	6,2	12,5	10,8	NA	12,7	NA
FINE[19]	68,3	67,3	100	30	NA	62,7	71,3	40,7	4	36,7	NA	NA	1,9	NA
FLORIDA[20]	69,3	67,5	31,8	32,5	NA	65	82,9	NA	0,5	NA	NA	6	1,9	50
FLOWER-MI[21]	62,5	85	100	18,3	100	39,6	43,2	40,1	0	7,7	10,1	NA	1,9	50
Fukuoka et al.[22]	73,2	73	NA	46,5	29,5	75	79	17	0	22	51,5	0	NA	63
FUTURE[23]	65	85	47	31	98	60	58	24	12	20	25	NA	41	55
Hidalgo et al.[24]	66	76,9	100	37,1	100	52,5	64,6	33,1	0	29,2	24,7	0,8	NA	54,9
iFR SWEDEHEART[25]	67,5	74,7	38	21,8	36	70,5	70,7	16	10,1	32,9	41,9	4,5	NA	NA
ILIAS[26]	63,3	73,4	13,3	26,7	32	67,5	58,6	22	0	17,8	22,3	0	NA	NA
IRIS-FFR[27]	63,6	71,6	23,7	30,9	46,7	60	63,1	24	NA	6,5	19,5	NA	2	NA
Kennedy et al.[28]	69,2	65,3	36	100	52	97	96	24	12,5	47	43,5	15	15	51,1
POST-IT[29]	65,1	76,3	35,4	35	37,5	75,8	80,7	24,1	NA	31,5	35,2	3,2	NA	NA
Rahman et al.[30]	62,8	71,9	44,7	50,3	70,1	52,7	76	17,2	5,6	11	17,2	2,4	7,8	NA
R3F[31]	64,7	75,3	19,5	35,8	47	64,6	65,5	53,7	10	25,2	39	3,6	NA	NA
Scully et al.[32]	65,4	75,2	5,5	34,7	22,6	67,9	69	34,7	23	NA	NA	NA	18,2	NA
WAVE[33]	67,9	NA	100	28,2	100	56	69,4	48,8	0	15,8	NA	NA	NA	50,3

Abbreviations: ACS: acute coronary syndrome, CABG: coronary artery by-pass graft, CKD: chronic kidney disease, DM: diabetes mellitus, EF: ejection fraction, MI: myocardial infarction, MVD: multivessel disease, NA: not available, PCI: percutaneous coronary intervention

SUPPLEMENTARY MATERIAL

Supplemental Table S1. Search Strategy and Terms

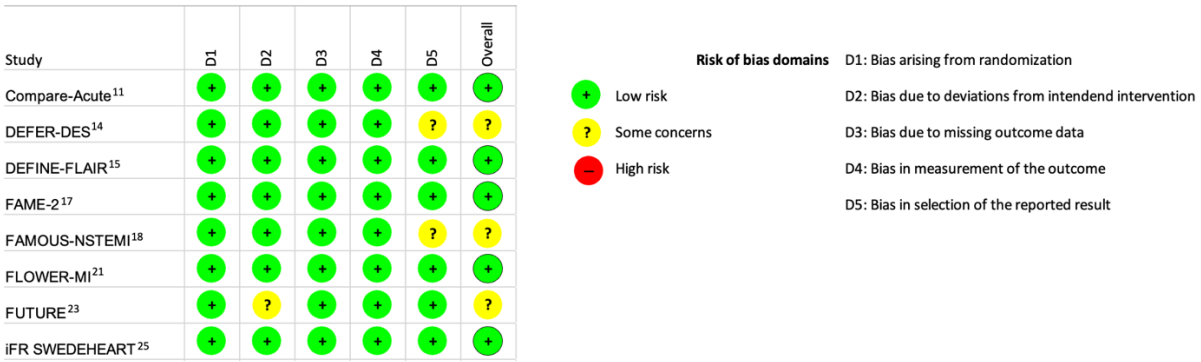
Database	Search Date	Advanced Search terms	Filter	Results
PubMed	23/8/2024	("fractional flow reserve" OR "FFR" OR "instantaneous wave-free ratio" OR "iFR") AND ("percutaneous coronary intervention" OR "PCI" OR "revascularization" OR "deferred" OR "FFR-deferred")	None	2299
Embase	23/8/2024	('fractional flow reserve'/exp OR 'ffr' OR 'instantaneous wave free ratio'/exp OR 'ifr') AND ('percutaneous coronary intervention'/exp OR 'pci' OR 'revascularization'/exp OR 'deferred' OR 'ffr deferred')	None	4987
Cochrane Library	23/8/2024	("fractional flow reserve" OR "FFR" OR "instantaneous wave-free ratio" OR "iFR") AND ("percutaneous coronary intervention" OR "PCI" OR "revascularization" OR "deferred" OR "FFR-deferred")	None	637

Supplementary Table S2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist for reporting a systematic review involving a meta-analysis(7).

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			1
Title	1	Identify the report as a systematic review.	1
ABSTRACT			2
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			4
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			4-7
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4-5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6-7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6-7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6-7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6-7, S10
RESULTS			8-10
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-10, S10
DISCUSSION			11-15
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-13
	23b	Discuss any limitations of the evidence included in the review.	14-15
	23c	Discuss any limitations of the review processes used.	14-15
	23d	Discuss implications of the results for practice, policy, and future research.	4, 11-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

Supplementary Figure S1. Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2). In this color-coded ranking, green color represents low risk of bias, yellow some concerns, and red high risk of bias(9).



Supplementary Table S3. Assessment of study quality using the Newcastle-Ottawa Scale Cohort Studies(8).

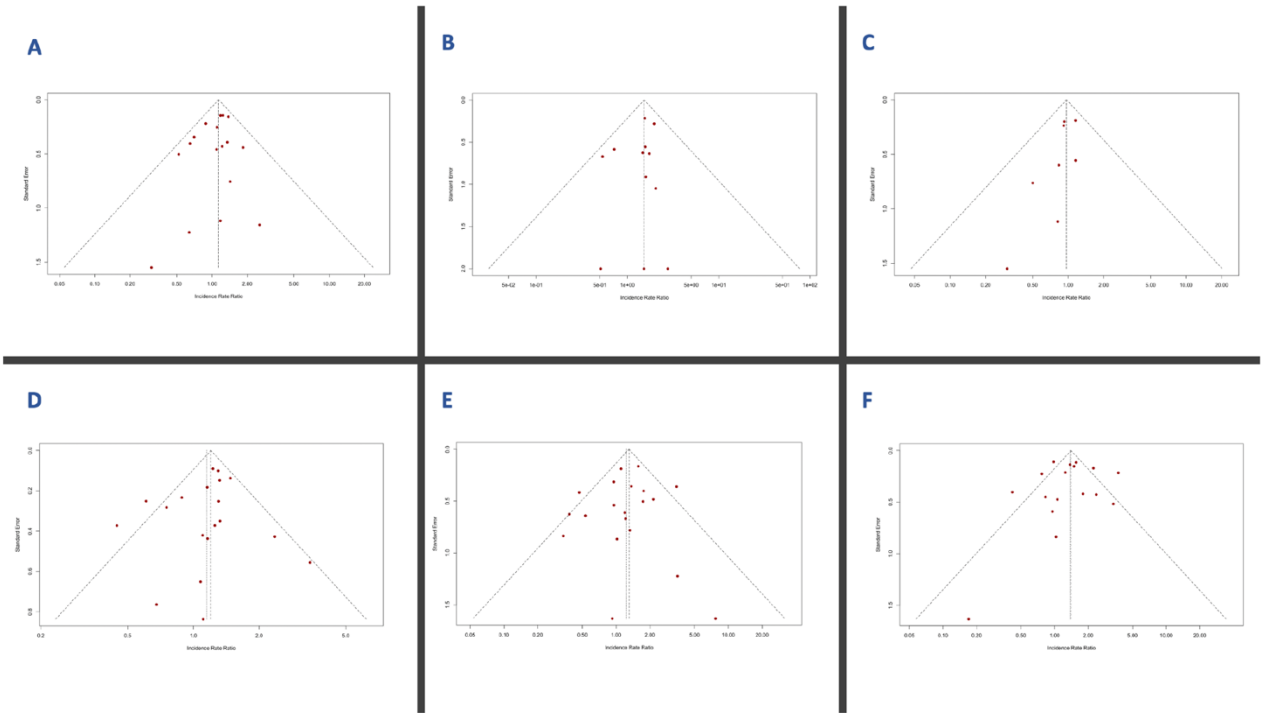
Author	Selection				Comparability of cohorts	Outcome			Total score
	Exposed cohort representativeness	Non-exposed cohort selection	Exposure ascertainment	Absence of outcome at baseline		Outcome ascertainment	Long enough follow-up	Follow-up adequacy	
COFFRS	1	1	1	1	2	1	0	1	**8**
CVIT-DEFER	1	1	1	1	1	1	1	1	**8**
de la Torre Hernandez et al.	1	1	1	1	1	1	1	1	**8**
Elfaramawy et al.	1	1	1	1	2	1	1	1	**9**
FINE	1	1	1	1	2	1	1	1	**9**
FLORIDA	1	1	1	1	2	1	1	1	**9**
Fukuoka et al.	1	1	1	1	2	1	0	1	**8**
Hidalgo et al.	1	1	1	1	2	1	0	1	**8**
ILIAS	1	1	1	1	1	1	1	1	**8**
IRIS-FFR	1	1	1	1	1	1	0	1	**7**
Kennedy et al.	1	1	1	1	1	1	0	1	**7**
POST-IT	1	1	1	1	1	1	0	1	**7**
Rahman et al.	1	1	1	1	2	1	1	1	**9**
R3F	1	1	1	1	1	1	0	1	**7**
Scully et al.	1	1	1	1	0	1	1	1	**7**
WAVE	1	1	1	1	2	1	0	1	**8**

Supplementary Table S4. Evaluation of Quality of Pooled Evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Framework.

Outcome	Subjects (n)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
All-cause death	19,263	7 RCTs / 10 not-RCTs	Serious	Not serious	Not serious	Not serious	**Moderate (⊕⊕⊕)**
Cardiovascular death	13,980	4 RCTs / 8 not-RCTs	Serious	Not serious	Not serious	Not serious	**Moderate (⊕⊕⊕)**
Non-cardiovascular death	12,760	4 RCTs / 4 not-RCTs	Serious	Very serious	Not serious	Very serious	**Very Low (⊕)**
MACE	18,105	7 RCTs / 12 not-RCTs	Serious	Serious	Not serious	Not serious	**Low (⊕⊕)**
Myocardial infarction	21,163	6 RCTs / 14 not-RCTs	Serious	Serious	Not serious	Serious	**Very Low (⊕)**
Unplanned revascularization	20,434	6 RCTs / 11 not-RCTs	Serious	Very serious	Not serious	Not serious	**Very Low (⊕)**

Abbreviations: MACE, major adverse cardiovascular events; RCT, randomized clinical trial

Supplementary Figure S2. Funnel plots for the assessed outcomes (Panel A: all cause death, Panel B: cardiovascular death, Panel C: non cardiovascular death, Panel D: major adverse cardiovascular events (MACE), Panel E: myocardial infarction (MI), Panel F: unplanned revascularization).



Supplementary Table S5. Linear regression of funnel plot asymmetry (Egger test).

Outcome	Egger test (p value)
All cause death	0.23
Cardiovascular death	0.34
Non cardiovascular death	0.10
MACE	0.36
MI	0.55
Unplanned revascularization	0.84

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction

Supplementary Table S6. Sensitivity analysis comparing exact Poisson regression and the Hartung-Knapp method random effect models.

Outcome	Exact Poisson regression	Hartung-Knapp correction
All cause death	IRR 1.14, 95%CI [1.00-1.30], p=0.0529	IRR 1.14, 95%CI [1.00-1.30], p=0.0523
Cardiovascular death	IRR 1.53, 95%CI [1.17-2.00], p=0.0021	IRR 1.51, 95%CI [1.15-1.99], p=0.0029
Non cardiovascular death	IRR 0.97 [0.78-1.20], p=0.7764	IRR 0.98, 95%CI [0.79-1.22], p=0.8590
MACE	IRR 1.15, 95%CI [0.99-1.34], p=0.0693	IRR 1.17, 95%CI [1.01-1.35], p=0.0360
MI	IRR 1.24, 95%CI [0.95-1.61], p=0.1119	IRR 1.22, 95%CI [0.94-1.58], p=0.1262
Unplanned revascularization	IRR 1.38, 95%CI [1.06-1.79], p=0.0167	IRR 1.38, 95%CI [1.07-1.78], p=0.0145

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

Supplementary Table S7. Metaregression results.

Variable	All cause death				Cardiovascular death				Non cardiovascular death			
	Coefficient	*Lower 95% CI*	*Upper 95% CI*	*p-value*	*Coefficient*	*Lower 95% CI*	*Upper 95% CI*	*p-value*	*Coefficient*	*Lower 95% CI*	*Upper 95% CI*	*p-value*
Age	0.03	-0.03	0.08	0.30	0.14	-0.09	0.37	0.23	0.06	-0.08	0.20	0.40
Male sex	0.00	-0.03	0.04	0.76	0.07	-0.09	0.22	0.42	-0.00	-0.11	0.11	0.99
ACS	0.00	-0.00	0.01	0.20	0.01	-0.01	0.02	0.48	0.01	-0.01	0.02	0.50
Diabetes Mellitus	-0.01	-0.02	0.00	0.06	-0.03	-0.09	0.02	0.26	-0.02	-0.07	0.02	0.32
MVD	-0.00	-0.01	0.01	0.90	0.00	-0.02	0.02	0.73	-0.01	-0.03	0.02	0.55
Dyslipidemia	-0.01	-0.02	0.01	0.46	0.02	-0.03	0.06	0.54	0.02	-0.03	0.06	0.39
Hypertension	0.00	-0.01	0.01	0.95	0.02	-0.04	0.09	0.49	0.01	-0.04	0.06	0.69
Current smokers	-0.01	-0.03	0.00	0.11	-0.05	-0.11	0.01	0.09	-0.04	-0.08	0.01	0.17
CABG	-0.02	-0.05	0.01	0.17	-0.03	-0.09	0.03	0.36	0.01	-0.05	0.06	0.83
Previous MI	0.01	-0.01	0.02	0.38	0.03	-0.01	0.07	0.16	0.01	-0.01	0.03	0.51
Previous PCI	0.00	-0.01	0.02	0.55	0.02	-0.02	0.05	0.39	0.01	-0.02	0.03	0.55
Previous CABG	-0.03	-0.09	0.03	0.35	0.08	-0.24	0.39	0.63	0.01	-0.02	0.03	0.55

Variable	MACE				Myocardial infarction				Unplanned revascularization			
	Coefficient	*Lower 95% CI*	*Upper 95% CI*	*p-value*	*Coefficient*	*Lower 95% CI*	*Upper 95% CI*	*p-value*	*Coefficient*	*Lower 95% CI*	*Upper 95% CI*	*p-value*
Age	-0.01	-0.07	0.05	0.67	0.03	-0.06	0.11	0.53	0.07	-0.04	0.18	0.22
Male sex	-0.00	-0.04	0.04	0.90	-0.05	-0.11	0.01	0.09	-0.06	-0.14	0.02	0.13
ACS	0.00	-0.00	0.01	0.50	-0.00	-0.01	0.00	0.41	0.00	-0.01	0.01	0.53
Diabetes Mellitus	-0.01	-0.01	-0.00	<0.01*	-0.00	-0.02	0.01	0.68	0.00	-0.04	0.05	0.87
MVD	0.00	-0.01	0.01	0.61	-0.01	-0.02	0.00	0.20	-0.00	-0.01	0.01	0.98
Dyslipidemia	-0.00	-0.02	0.01	0.40	0.00	-0.02	0.02	0.67	0.01	-0.01	0.04	0.25
Hypertension	-0.01	-0.02	0.01	0.41	0.01	-0.01	0.03	0.50	0.02	-0.01	0.05	0.28
Current smokers	-0.00	-0.01	0.01	0.72	-0.01	-0.03	0.01	0.58	-0.00	-0.03	0.02	0.74
CABG	-0.03	-0.06	-0.00	0.02	-0.02	-0.06	0.03	0.42	-0.03	-0.08	0.02	0.19
Previous MI	-0.01	-0.02	0.00	0.08	-0.01	-0.04	0.02	0.62	0.01	-0.02	0.03	0.73
Previous PCI	-0.00	-0.01	0.01	0.75	0.01	-0.01	0.04	0.35	0.01	-0.01	0.03	0.29
Previous CABG	-0.00	-0.01	0.01	0.75	-0.05	-0.14	0.03	0.22	0.04	-0.15	0.23	0.67

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery by-pass graft; CI, confidence interval; MI, myocardial infarction; MVD, multivessel disease; MACE, major cardiovascular events; PCI percutaneous coronary intervention.
*Statistically significant.

Supplementary Table S8. Leave one out models reporting random effect models (primary analysis) for sources of heterogeneity(10–33).

	All cause death	Cardiovascular death	Non cardiovascular death	MACE	Myocardial infarction	Unplanned revascularization
COFFRS[10]	-	1.5255 [1.1656; 1.9964] p=0.0021, I2=17.9%	-	1.1588 [0.9964; 1.3475] p=0.0557, I2=43%	1.2394 [0.9479; 1.6206] p=0.1166, I2=29.4%	1.4052 [1.0837; 1.8221] p=0.0103, I2=79.5%
Compare-Acute[11]	1.1342 [0.9951; 1.2929] p=0.0593, I2=0%	-	-	1.1495 [0.9827; 1.3446] p=0.0816, I2=46.6%	1.2804 [0.9911; 1.6541] p=0.0585, I2=23.6%	1.3880 [1.0579; 1.8211] p=0.0180, I2 =79.3%
CVIT-DEFER[12]	-	-	-	-	1.2206 [0.9329; 1.5970] p=0.1461, I2=29.0%	1.3173 [1.0048; 1.7269] p=0.0461, I2=76.9%
de la Torre Hernandez et al.[13]	-	1.5382 [1.1663; 2.0287] p=0.0023, I2=35.9%	-	-	1.2185 [0.9342; 1.5895] p=0.1449, I2=29.4%	1.3763 [1.0523; 1.8000] p=0.0197, I2=80.4%
DEFER-DES[14]	-	-	-	1.1320 [0.9691; 1.3222] p=0.1180, I2=43.7%	-	1.3285 [1.0200; 1.7303] p=0.0351, I2=79.3%
DEFINE-FLAIR[15]	1.1267 [0.9727; 1.3050] p=0.1116, I2=0%	1.5069 [1.0629; 2.1364] p=0.0213, I2=20.5%	0.9904 [0.7620; 1.2874] p=0.9428, I2=62.9%	1.1323 [0.9511; 1.3481] p=0.1625, I2=46.5%	1.1886 [0.8884; 1.5903] p=0.2448, I2=24.3%	1.4196 [1.0749; 1.8749] p=0.0136, I2=75%
Elfaramawy et al.[16]	1.1395 [0.9998; 1.2988] p= 0.0504, I2=0%	-	-	1.1489 [0.9824; 1.3436] p=0.0823, I2=46.5%	1.2514 [0.9517; 1.6455] p=0.1083, I2=30.3%	-
FAME 2[17]	1.1380 [0.9969; 1.2989] p=0.0555, I2=0%	1.5190 [1.1521; 2.0028] p=0.0030, I2=20.3%	0.9951 [0.7970; 1.2426] p=0.9658, I2=48.9%	1.1737 [1.0050; 1.3706] p=0.0430, I2=42.2%	1.2588 [0.9474; 1.6726] p=0.1124, I2=26.8%	1.4435 [1.1097; 1.8777] p=0.0062, I2=76.6%
FAMOUS- NSTEMI[18]	1.1368 [0.9973; 1.2958] p=0.0550, I2=0%	-	-	1.1484 [0.9839; 1.3403] p=0.0794, I2=46.3%	1.2238 [0.9327; 1.6059] p=0.1451, I2=27.6%	-
FINE[19]	1.1257 [0.9863; 1.2847] p=0.0791, I2=0%	-	-	-	1.2041 [0.9098; 1.5936] p=0.1940, I2=27%	1.3537 [1.0290; 1.7809] p=0.0304, I2=79.5%
FLORIDA[20]	1.1125 [0.9604; 1.2887] p=0.1552, I2=0%	-	-	-	-	-
FLOWER-MI[21]	1.1396 [0.9987; 1.3005] p=0.0524, I2=0%	-	-	1.1827 [1.0218; 1.3690] p=0.0245, I2=40.1%	1.3355 [1.0600; 1.6826] p=0.0141, I2=8%	1.4110 [1.0801; 1.8431] p=0.0116, I2=78.5%
Fukuoka et al.[22]	-	1.5255 [1.1656; 1.9964] p=0.0021, I2=17.9%	-	1.1502 [0.9868; 1.3407] p=0.0735, I2=46.6%	1.2409 [0.9536; 1.6148] p=0.1082, I2=30.9%	-

FUTURE[23]	1.1330 [0.9935; 1.2921] p=0.0624, I2=0%	1.4994 [1.1417; 1.9690] p=0.0036, I2=0%	0.9671 [0.7764; 1.2047] p=0.7655, I2=66%	-	-	-
Hidalgo et al.[24]	1.1717 [1.0670; 1.2866] p=0.0009, I2=0%	1.5239 [1.1604; 2.0013] p=0.0024, I2=24.4%	-	1.1457 [0.9779; 1.3423] p=0.0924, I2=46.5%	1.2370 [0.9408; 1.6264] p=0.1278, I2=29.5%	1.3915 [1.0632; 1.8210] p=0.0161, I2=79.5%
iFR SWEDEHEART[25]	1.0889 [0.9417; 1.2590] p=0.2505, I2=0%	1.3977 [1.0235; 1.9088] p=0.0352, I2=13.6%	0.8652 [0.6631; 1.1288] p=0.2860, I2=27.5%	1.1254 [0.9491; 1.3345] p=0.1740, I2=45.5%	1.2442 [0.9237; 1.6758] p=0.1505, I2=28.2%	1.3704 [1.0296; 1.8241] p=0.0308, I2=79.9%
ILIAS[26]	1.1369 [0.9929; 1.3018] p=0.0633, I2=0%	-	-	1.1276 [0.9533; 1.3337] p=0.1610, I2=46.9%	1.2200 [0.9174; 1.6226] p=0.1716, I2=30.9%	1.3607 [1.0232; 1.8096] p=0.0342, I2=80.0%
IRIS-FFR[27]	1.1664 [1.0162; 1.3387] p=0.0286, I2=0%	1.5776 [1.1922; 2.0877] p=0.0014, I2=65.8%	0.9826 [0.7658; 1.2608] p=0.8901, I2=62.5%	1.1173 [0.9541; 1.3085] p=0.1685, I2=44.5%	1.1743 [0.9334; 1.4773] p=0.1701, I2=7.3%	1.3550 [1.0182; 1.8030] p=0.0372, I2=79.4%
Kennedy et al.[28]	1.1666 [1.0205; 1.3337] p=0.0240, I2=0%	-	-	1.2407 [1.1297; 1.3626] p < 0.0001, I2=35.9%	1.2857 [0.9918; 1.6668] p=0.0577, I2=25.5%	-
POST-IT[29]	1.1324 [0.9918; 1.2930] p=0.0659, I2=0%	1.5253 [1.1553; 2.0140] p=0.0029, I2=30.8%	0.9660 [0.7735; 1.2064] p=0.7602, I2=62.4%	1.1376 [0.9661; 1.3395] p=0.1222, I2=46.2%	1.2112 [0.9179; 1.5980] p=0.1756, I2 = 28.5%	1.2784 [1.0318; 1.5840] p=0.0247, I2=68.7%
Rahman et al.[30]	-	-	-	1.1412 [0.9728; 1.3387] p=0.1049, I2=46.8%	-	-
R3F[31]	1.1578 [1.0139; 1.3221] p=0.0305, I2=0%	-	-	1.1432 [0.9647; 1.3547] p=0.1222, I2=47.3%	1.1971 [0.9102; 1.5745] p=0.1981, I2=26.3%	1.3829 [1.0419; 1.8355] p=0.0248, I2=82.2%
Scully et al.[32]	1.1543 [1.0118; 1.3168] p=0.0328, I2=0%	1.5948 [1.2106; 2.1010] p=0.0009, I2=5.3%	0.9853 [0.7905; 1.2281] p=0.8953, I2 = 62.0%	1.2122 [1.0319; 1.4240] p=0.0192, I2=27.9%	1.2995 [1.0128; 1.6674] p=0.0394, I2=16.7%	1.4720 [1.1592; 1.8693] p=0.0015, I2=75.8%
WAVE[33]	1.1415 [1.0016; 1.3010] p=0.0473, I2=0%	1.5255 [1.1656; 1.9964] p=0.0021, I2=17.9%	0.9790 [0.7867; 1.2182] p=0.8489, I2=66.2%	1.1301 [0.9661; 1.3220] p=0.1264, I2=38.1%	1.2371 [0.9425; 1.6239] p=0.1252, I2=30.4%	1.3358 [1.0195; 1.7503] p=0.0357, I2=78.8%

Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction.

Supplementary Table S9. Outcomes definition(10–33).

Study	MACE	Death definition	Myocardial Infarction	Revascularization definition
COFFRS[10]	Composite of cardiovascular death, non-fatal acute coronary syndrome, and any repeat revascularization of the vessel in which FFR was studied	NA	Myocardial infarction was defined as (two out of three criteria): prolonged chest pain >20 min; levels of serum creatine kinase (or the MB fraction) or troponin over two-fold higher than the upper normal limit; and ST-T segment changes or new Q waves on serial electrocardiogram indicative of myocardial damage	NA
Compare-Acute[11]	Composite of all-cause death, non-fatal myocardial infarction, any revascularization and cerebrovascular events	NA	Myocardial infarction was defined as one of: 1) typical rise and fall of biochemical markers of myocardial necrosis with at least one of: a) ischemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischemia; 2) pathologic findings of an acute MI. Periprocedural MI was included.	Any revascularization
CVIT-DEFER[12]	NA	NA	NA	NA
de la Torre Hernandez et al.[13]	Composite of cardiac death, target lesion MI and target lesion revascularisation	Cardiac death included any sudden death by undefined cause	Myocardial infarction, defined as a typical increase and gradual fall (troponin), or as a faster increase and fall (CK-MB) of biochemical markers for myocardial necrosis along with at least one of the following: chest pain, new ST-T changes or new left bundle branch block, development of pathological Q-waves, new regional wall motion or perfusion abnormalities and finally intracoronay thrombus detection in angiography or autopsy. Periprocedural MI was included in the target lesion MI definition.	Target lesion revascularization
DEFER-DES[14]	Composite of cardiac death, myocardial infarction, and target lesion revascularization.	All deaths were considered cardiac unless there was a clear noncardiac cause.	Myocardial infarction was defined as an elevated cardiac enzyme with ischemic symptoms or new pathological Q waves on ECG. Periprocedural MI was not included.	NA
DEFINE-FLAIR[15]	Composite of death, nonfatal myocardial infarction, or unplanned revascularization	Death was considered to be from cardiovascular causes unless an unequivocal noncardiovascular cause was established.	Myocardial infarction was classified as either spontaneous or periprocedural and as either ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI).	Revascularization was considered to be unplanned when it was not the index procedure and was not identified at the time of the index procedure as a staged procedure to occur within 60 days.
Elfaramawy et al.[16]	Composite of cardiovascular death, non-fatal acute coronary syndrome, target lesion revascularization.	NA	NA	NA
FAME 2[17]	Composite of death, myocardial infarction, or urgent revascularization.	All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Unwitnessed death and death of unknown cause were classified as cardiac death.	A myocardial infarction were considered an event whether it occurred within the first 24 hours after randomization (CK-MB increase) or more than 24 hours after randomization (CK-MB or troponin).	Every subsequent revascularization procedure.
FAMOUS-NSTEMI[18]	Composite of cardiac death, hospitalization for MI or heart failure	NA	NA	NA
FINE[19]	Composite of death from any cause, nonfatal MI, and unplanned coronary revascularization.	NA	NA	Unplanned revascularization was defined as any unscheduled clinically driven treatment that occurred during follow-up and that was not already an indication at the baseline coronary angiography
FLORIDA[20]	NA	NA	NA	NA
FLOWER-MI[21]	Composite of all cause death, nonfatal myocardial	NA	NA	NA

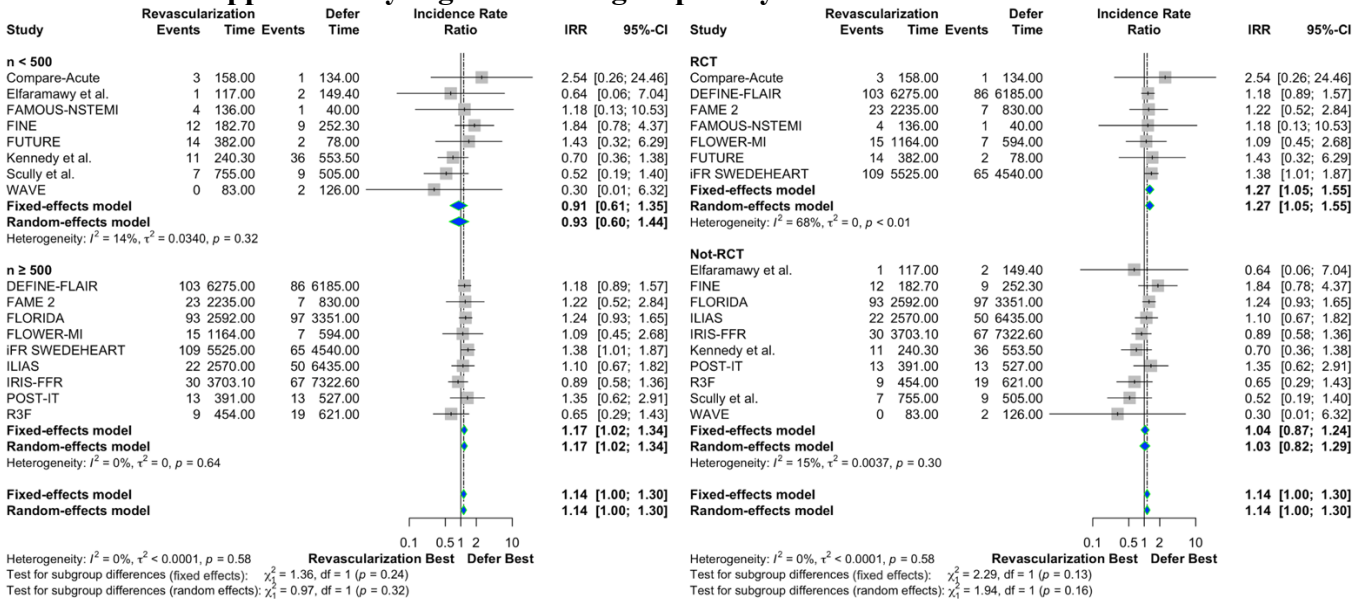
	infarction, and unplanned hospitalization leading to urgent revascularization.			
Fukuoka et al.[22]	Composite of cardiovascular death, non-fatal myocardial infarction, unstable angina pectoris, fatal arrhythmia and heart failure	NA	NA	NA
FUTURE[23]	Composite of death from any cause, nonfatal myocardial infarction, stroke, or unplanned revascularization	Deaths without witnesses or of unknown cause were considered as cardiac deaths.	Presence of symptoms of acute MI (chest pain, blockpnea) associated with significant changes in the ST segment (above or below shift) or appearance of a new left bundle branch block with elevation of cardiac biomarkers. o Presence of an increase in reference cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit. o Evolution or appearance of pathological Q wave (s) on the ECG.	Revascularization subsequent to the initial strategy that might include a staged procedure
Hidalgo et al.[24]	Defined as cardiac death, probable or definitive stent thrombosis, nonfatal myocardial infarction or repeat revascularization of a lesion physiologically evaluated during the index procedure, during the follow-up	Any death was considered of cardiac origin unless an unequivocal noncardiovascular cause was established.	Myocardial infarction included spontaneous STEMI or NSTEMI.	NA
iFR SWEDEHEART[25]	Composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization	Death was defined as all-cause mortality. Cause of death was classified as either cardiovascular or non-cardiovascular. All deaths that unobserved were assumed to be cardiovascular in nature unless a non-cardiovascular cause	Spontaneous myocardial infarction was considered an event after the first 48 hours after randomization and after 7 days following CABG which was unrelated to the procedure (CK-MB or troponin)	Revascularization by either PCI or CABG that was not anticipated when enrolled in the study.

		can be clearly provided.		
ILIAS[26]	Composite of all-cause death, any acute myocardial infarction, and clinically driven revascularization by means of coronary artery bypass graft surgery or PCI.	NA	NA	Clinically driven revascularization by means of coronary artery bypass graft surgery or PCI
IRIS-FFR[27]	Composite of cardiac death, myocardial infarction, and repeat revascularization	Cardiac death was defined as any death because of a proximate cardiac cause, including cardiac arrest, myocardial infarction, low-output failure, or fatal arrhythmia.	Myocardial infarction was defined as follows: (1) within the first 48 hours of the procedure: ischemic symptoms and signs with an elevation of the concentration of CK-MB fraction >5 times baseline; (2) ≥48 hours after the procedure: any CK-MB or troponin level increase above the upper normal limit accompanied by ischemic symptoms.	Repeat revascularization was defined as any PCI or coronary artery bypass surgery of a lesion with an index FFR measurement.
Kennedy et al.[28]	Composite of death, myocardial infarction, target lesion revascularization, or rehospitalization for acute coronary syndrome	NA	Myocardial infarction and periprocedural myocardial infarction were defined according to the established guidelines.	NA
POST-IT[29]	Composite of death from cardiovascular causes, myocardial infarction or new unplanned revascularization	NA	Myocardial infarction was defined according to the third universal definition of MI.	Revascularization was considered unplanned when it was not performed or planned at the time of the index procedure
Rahman et al.[30]	Composite of cardiac death, non-fatal myocardial infarction,	Cardiac death was defined as any death in which a cardiac cause could	Non-fatal myocardial infarction was defined according to the fourth universal definition of MI.	Target vessel revascularisation was defined as PCI or application of

	and target vessel revascularisation.	not be excluded		bypass grafts for restenosis of the previously-done FFR vessel
R3F[31]	Composite of death, myocardial infarction, or unplanned coronary revascularization.	All deaths were considered cardiovascular unless an unequivocal noncardiac cause could be established.	Periprocedural MI was defined as within 48 hours after PCI (CK >2 times ULN in the presence of a confirming cardiac specific biomarker) and within 7 days after CABG (CK-MB or troponin >5x and ECG changes or >10x) Spontaneous MI: rise and fall of cardiac biomarkers with at least one of: 1) ischemic symptoms, 2) ECG changes	Revascularization was considered unplanned when it was not performed as part of the index procedure or identified at the time of the index procedure.
Scully et al.[32]	Composite of cardiac death, target vessel revascularisation and MI	Causes of death were determined by two independent investigators, and where there was disagreement, the death was assumed to be cardiac.	MI was defined according to the current European Society of Cardiology guideline definition	Target vessel revascularization was defined as subsequent revascularisation by either PCI or coronary artery bypass graft (CABG) surgery of the vessel measured by FFR, excluding patients who underwent staged PCI to another vessel
WAVE[33]	Composite of death from any cause, nonfatal myocardial infarction or ischemia-driven revascularization of any coronary arteries	NA	NA	NA

Abbreviations: MACE, major cardiovascular events; NA, not available; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting; ECG, electrocardiogram; CK-MB, creatin kinase myocardial band; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; ULN, upper limit normal

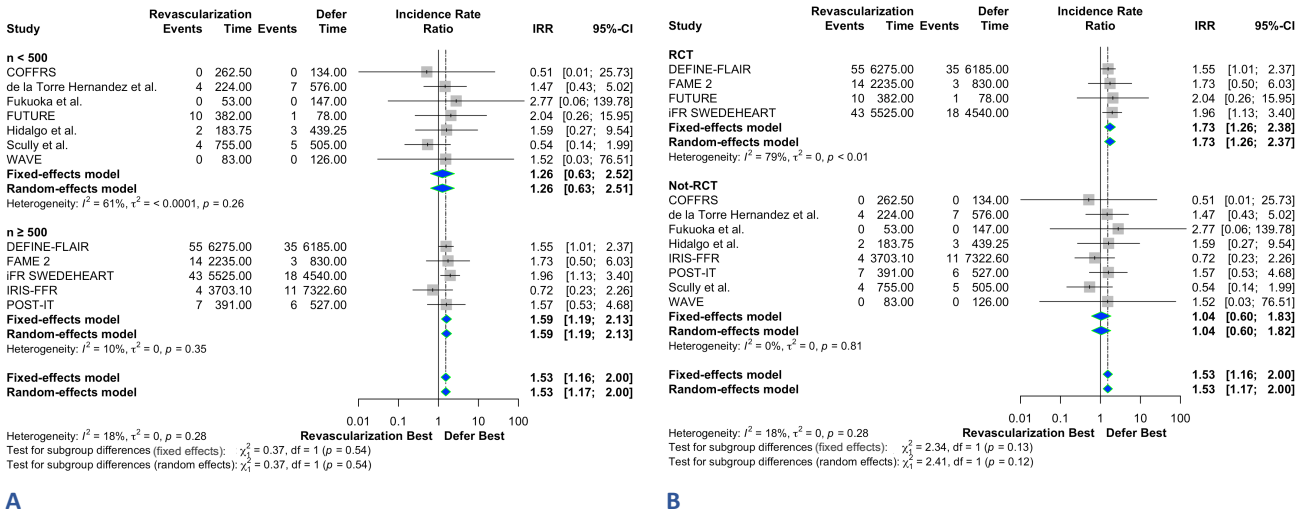
Supplementary Figure S3. Subgroup analysis for all cause death.



Panel A, subgroup analysis according to sample size (<500 patients and ≥500 patients)
Panel B, subgroup analysis according to study design (RCT and not-RCT)

Abbreviations, CI, confidence interval; IRR, incidence rate ratio; RCT, randomized clinical trial

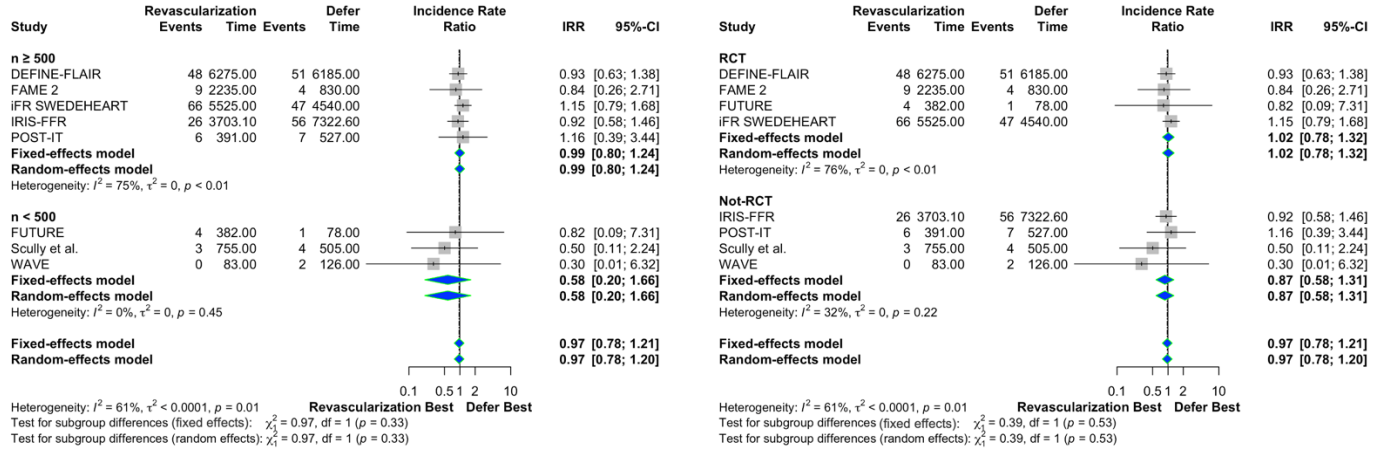
Supplementary Figure S4. Subgroup analysis for cardiovascular death.



Panel A, subgroup analysis according to sample size (<500 patients and ≥500 patients)
Panel B, subgroup analysis according to study design (RCT and not-RCT)

Abbreviations, CI, confidence interval; IRR, incidence rate ratio; RCT, randomized clinical trial

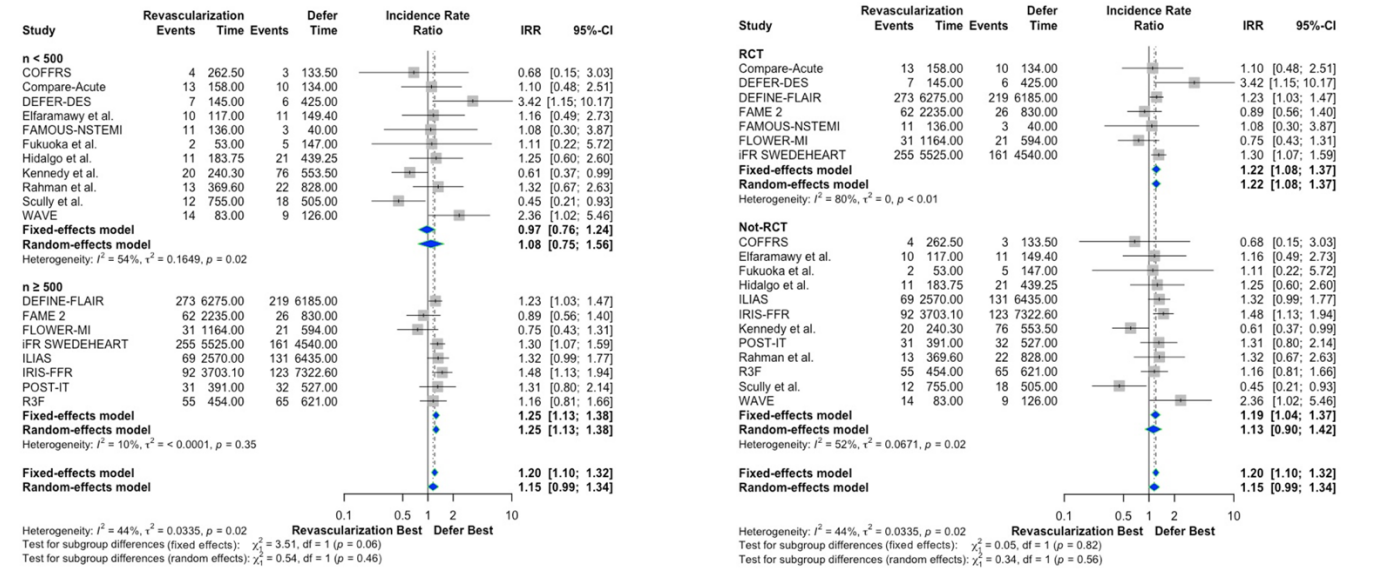
Supplementary Figure S5. Subgroup analysis for non cardiovascular death.



Panel A, subgroup analysis according to sample size (<500 patients and ≥500 patients)
Panel B, subgroup analysis according to study design (RCT and not-RCT)

Abbreviations, CI, confidence interval; IRR, incidence rate ratio; RCT, randomized clinical trial

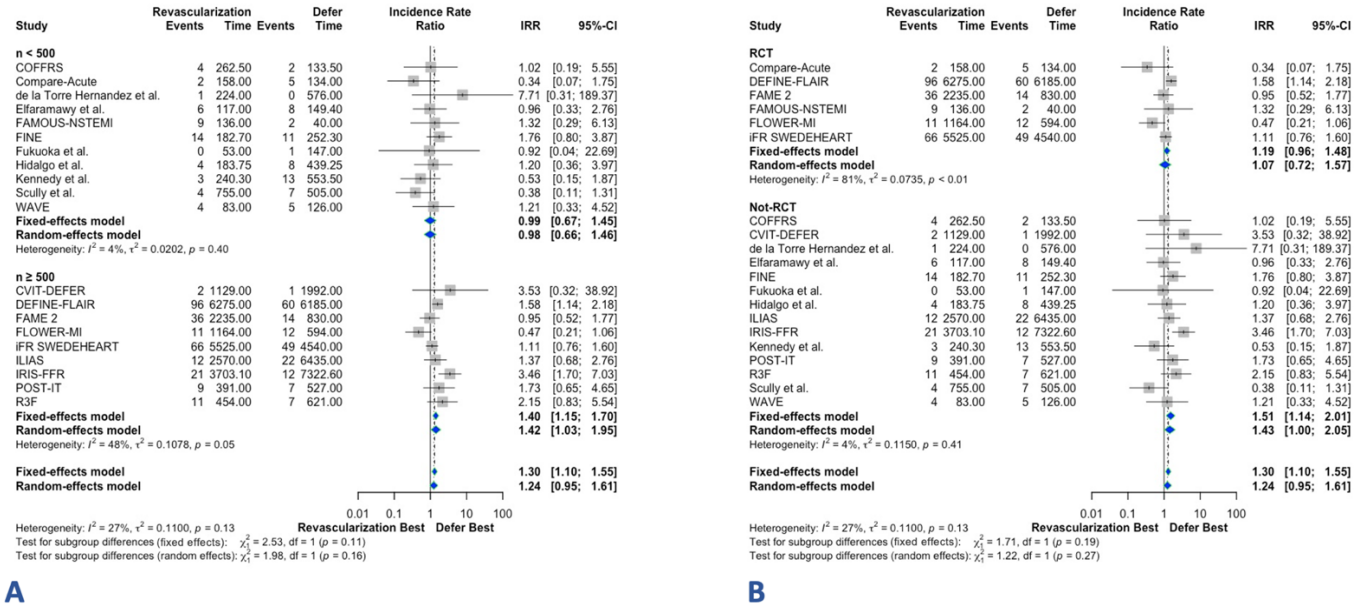
Supplementary Figure S6. Subgroup analysis for major adverse cardiovascular events (MACE).



Panel A, subgroup analysis according to sample size (<500 patients and ≥500 patients)
Panel B, subgroup analysis according to study design (RCT and not-RCT)

Abbreviations, CI, confidence interval; IRR, incidence rate ratio; RCT, randomized clinical trial

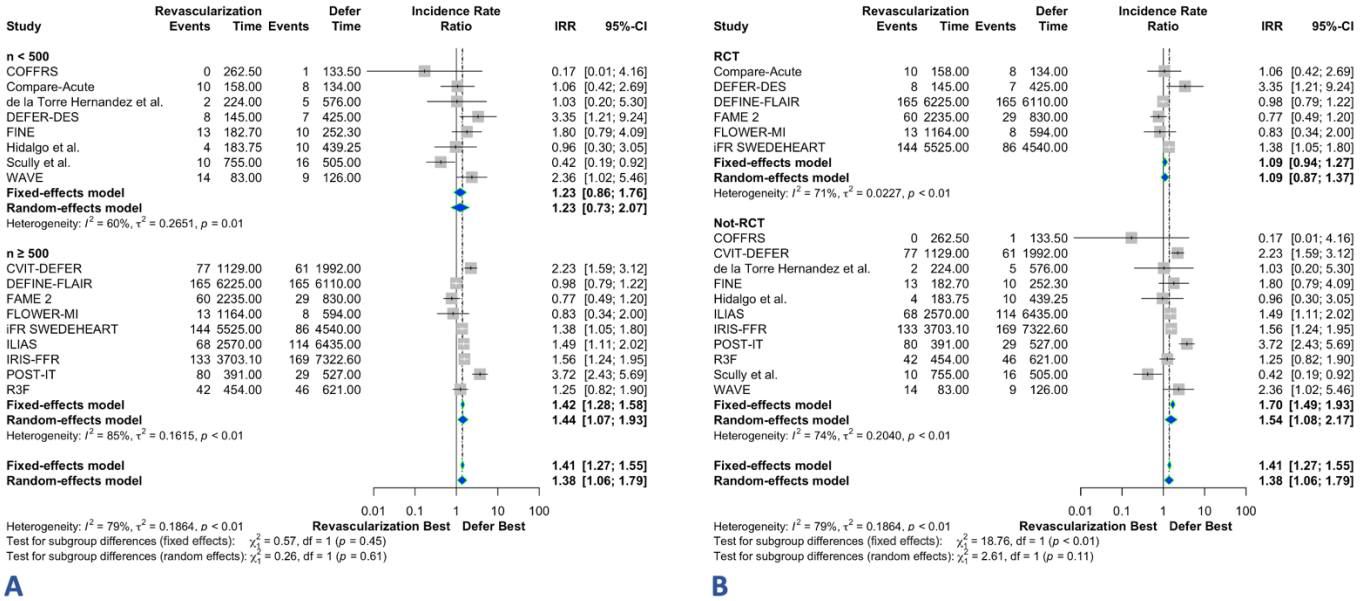
Supplementary Figure S7. Subgroup analysis for myocardial infarction (MI).



Panel A, subgroup analysis according to sample size (<500 patients and ≥500 patients)
Panel B, subgroup analysis according to study design (RCT and not-RCT)

Abbreviations, CI, confidence interval; IRR, incidence rate ratio; RCT, randomized clinical trial

Supplementary Figure S8. Subgroup analysis for unplanned revascularization.



Panel A, subgroup analysis according to sample size (<500 patients and ≥500 patients)
Panel B, subgroup analysis according to study design (RCT and not-RCT)

Abbreviations, CI, confidence interval; IRR, incidence rate ratio; RCT, randomized clinical trial

Chapter 2.

Pooled patient-level analysis of the DEFINE-FLAIR and iFR-SWEDEHEART trials: 5-year follow-up

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ABSTRACT

Background: Instantaneous wave-free ratio (iFR) is a coronary physiology index used to assess the severity of coronary artery stenosis and guide revascularisation. The DEFINE-FLAIR and iFR-SWEDEHEART randomized trials showed non-inferiority of iFR compared to fractional flow reserve (FFR) at one year follow-up. However, 5-year follow-up has shown differences between both trials.

Methods: In this pooled patient-level analysis of the DEFINE-FLAIR and iFR-SWEDEHEART trials, we assessed the 5-year cumulative incidence of major adverse cardiovascular events (MACE) and its individual components as separate events: all cause death, non-fatal myocardial infarction (MI) and unplanned revascularisation.

Results: A total of 4,511 patients were included, with 2,261 in the iFR group and 2,257 in the FFR group. At five years MACE occurred in 21.3% of the iFR group and 19.1% of the FFR group (HR 1.14, 95% CI 1.00 – 1.30). The iFR group had higher rates of all-cause death (HR 1.35, 95% CI 1.10-1.67) and non-cardiovascular death (HR 1.36, 95% CI 1.03 – 1.78). A numerically but not significant higher incidence in cardiovascular death was observed in the iFR group (HR 1.35, 95% CI 0.98 – 1.86). Non-fatal MI and unplanned revascularisation were similar in both groups.

In the prespecified subgroup analysis of patients guided for revascularisation, MACE was higher in the iFR group, driven by a higher rate of all-cause mortality. However, among patients deferred from revascularisation, MACE and its components were similar between iFR and FFR-guided groups. Subgroup analysis of the primary endpoint revealed no significant interactions across baseline characteristics, including vessel location.

Conclusion: In this pooled patient-level analysis of the DEFINE-FLAIR and iFR-SWEDEHEART trials, iFR-guided revascularisation showed higher incidence of MACE and death than FFR at 5 years of follow-up, while no differences were seen in CV death, non-fatal MI and revascularisation.

INTRODUCTION

Physiology-guided revascularisation of coronary artery disease is widely used to guide revascularisation in coronary artery disease and is supported by ample evidence (1,2). Stemming from the concept of using pressure ratios across a given coronary stenosis as a surrogate of flow, it allows functionally significant stenosis to be detected, while avoiding the treatment of functionally non-significant stenoses (3,4).

Fractional Flow Reserve (FFR), the ratio between distal and aortic pressure during maximal hyperaemia, has been used for decades as a tool to guide decision-making in coronary revascularisation (5). However, it requires administration of pharmacological agents to induce maximal hyperaemia, a manoeuvre that can be associated with increased procedural time, significant side effects and costs. More recently, instantaneous wave-Free Ratio (iFR) has gained widespread adoption as an alternative fo FFR, as it does not require the use of hyperaemic agents for the detection of a hemodynamically significant stenosis, circumventing some of the limitations of FFR (6).

DEFINE-FLAIR and iFR-SWEDEHEART were two independent randomised clinical trials that demonstrated non-inferiority of iFR when compared to FFR as a tool to guide guiding coronary revascularisation at 1 year follow-up (7,8). These pivotal trials sustained the recommendations of current clinical practice guidelines for the use of iFR and FFR for the evaluation of coronary artery disease (9).

However, despite similarities in design, long-term follow up showed substantial differences between both trials (10,11) raising interesting mechanistic questions. In this study, we present the combined results of the 5-year follow-up of the DEFINE-FLAIR and iFR SWEDEHEART randomized trials to explore commonalities and differences between the two trials.

METHODS

Study design

The DEFINE-FLAIR and iFR-SWEDEHEART trials were two multicenter, prospective, randomized trials comparing iFR versus FFR as a tool for decision-making in coronary revascularisation. While DEFINE-FLAIR was a double-blind trial where patients and follow-up teams were blinded to the randomized strategy, iFR-SWEDEHEART had an open-label design with follow-up based on the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), a part of the larger SWEDEHEART registry that provided continuous feedback on outcomes and quality-of-care measurements.

Both trials were designed to test the non-inferiority of iFR compared to FFR for Major Adverse Cardiovascular Events (MACE) at 1 year follow-up, and the two of them confirmed the primary hypothesis. 5-year follow-up was planned in the original study protocols to provide information about safety, and individual 5-year follow-up results of both trials have been published (10,11). Trials were funded by independent and unrestricted grants from Volcano Corp (Rancho Cordova, US) subsequently acquired by Philips.

Population

This study combines and analyses the merged population of both DEFINE-FLAIR and iFR-SWEDEHEART randomized clinical trials. In brief, patients included had clinical indication for intracoronary physiological evaluation of at least 1 coronary stenosis with intermediate severity (e.g. between 40% and 80% stenosis by visual assessment of the coronary angiogram). In patients with chronic coronary syndrome any lesions could be investigated. In patients with acute coronary syndrome, non-culprit lesions were investigated. In case of ST-segment elevation myocardial infarction, non-culprit stenoses were evaluated only after at least 48h after primary percutaneous coronary intervention (PCI). Full inclusion and exclusion criteria of the original trials is provided in

the supplementary material (**Table 1, suppl**). In all cases, all participants granted written informed consent before enrolment.

Patient randomization and intracoronary evaluation

Eligible patients were randomized to an iFR-based or FFR-based strategy to guide coronary revascularisation. The complete randomization process of the trials can be found in the original publications. In brief, after identifying the coronary lesion to be evaluated, the intracoronary physiological evaluation was carried out following standard practice. After the administration of nitrates to control vasomotion, pressure measurements were obtained using the same intracoronary guidewire (Verrata, Philips Volcano, San Diego, CA). Prespecified treatment thresholds of 0.80 and 0.89 for FFR and iFR, were used respectively. When any of both indices was equal or lower than these given values, the stenosis was revascularised using either PCI or by coronary artery bypass grafting (CABG). On the other hand, whenever the value of the pressure index was above the cut-off, revascularisation of the given lesion was deferred.

Follow up and event adjudication

The primary endpoint of both trials was the incidence of major adverse cardiovascular events (MACE) at 1 year follow-up. MACE was a composite of death, non-fatal myocardial infarction (MI) or unplanned revascularisation.

In the DEFINE-FLAIR study, all deaths (either unwitnessed or with an unknown cause) were considered of cardiovascular origin unless an unequivocal non-cardiovascular cause was clearly identified, whereas in the iFR-SWEDEHEART, observed deaths with unknown cause were classified as non-cardiovascular and unobserved deaths were classified as of cardiovascular origin (**Table 2, suppl.**). In this study, we assessed the 5-year cumulative incidence of MACE and its individual components as separate events: all cause death, non-fatal MI and unplanned revascularisation.

In the population enrolled in the DEFINE-FLAIR trial, 5-year follow-up was performed with clinical visits in each participant centre. In iFR-SWEDEHEART, follow-up was obtained from the national registries. In both trials, electronic monitoring of data was performed, and the adjudication of death and MI events was carried out using anonymized sources of documentation by independent expert committees. Unplanned revascularisation events and secondary angiographic outcomes were adjudicated by the clinical event adjudication committee in DEFINE-FLAIR and by an independent experienced observer in iFR-SWEDEHEART. All of them were blinded to the group assignment of each patient.

Statistical analysis

For the study endpoints, a time-to-event analysis comparing both study arms were performed using the Kaplan-Meier method. All patients from the DEFINE-FLAIR trial that were withdrawn from the study or did not complete the 5-year follow-up were included in the time-to-event analysis. Data for these patients was censored at the time of withdrawal or at the time of last medical contact. From iFR-SWEDEHEART trial, all patients with available follow-up were included in the analysis. In a complementary analysis, patients not included in the per-protocol analysis from DEFINE-FLAIR were excluded. Cox survival models were calculated to derive hazard ratios (HR), and two-sided 95% confidence intervals are reported. The validity of the proportional hazards assumption was tested using Schoenfeld residuals, and no signs of violation were observed.

As an addition to the primary analysis of the study, exploratory subgroup analysis was performed in patients that underwent revascularisation and in those who did not. Further stratification was performed using baseline clinical, angiographic and procedural variables to check for potential interactions on the primary event.

Calculations were made with STATA software, version 14 (STATACorp, Texas, United States) and R (R project for statistical computing, Vienna, Austria). A p value of less than 0.05 was considered statistically significant.

RESULTS

Study population

A combined total of 4,511 participants were enrolled; 2,254 were assigned to the iFR group and 2,257 to the FFR group. While 5-year follow-up was completed in all patients from iFR-SWEDEHEART, 351 patients (14% of the original cohort) from DEFINE-FLAIR did not complete the entire 5-year follow-up (191 from iFR arm and 160 from FFR arm) (**Figure 1, study flowchart**). A total of 25 patients from DEFINE-FLAIR had protocol violations and were not included in the per-protocol analysis.

Baseline characteristics of the merged population is shown in **Table 1**. 3,255 patients (72.2%) presented as chronic coronary syndromes. Lesion deferral was more frequent in the iFR study group (1125 patients, 50.0%) than in the FFR group (1019 patients, 45.2%).

Clinical events

At 5 year-follow up there were 480 (21.3%) MACE in the iFR group and 430 (19.1%) in the FFR group (HR 1.14, 95% CI 1.00 – 1.30, p=0.049) (**Figure 2**). Among the individual components of the composite event, all-cause death was higher in the iFR group (9.2% vs. 6.9% in FFR study group, HR 1.35, 95% CI 1.10-1.67, p=0.004), as well as non-cardiovascular death (5.4% vs. 4.0% in FFR, HR 1.36, 95% CI 1.03-1.78, p=0.028). Death due to cardiovascular causes was numerically higher in the iFR group, although not statistically significant (3.8% in the iFR group vs. 2.9% in FFR, HR 1.35, 95% CI 0.98-1.86, p=0.069).

The incidence of non-fatal MI and unplanned revascularisation was almost identical in both groups (**Table 2**) (**Figure 3**). Per-protocol analysis showed no significant differences among all study outcomes (**Supplementary Table 4**).

Revascularisation vs. deferral

When comparing outcomes between deferred and treated patients, those who underwent revascularisation showed higher rates of MACE in the iFR group compared to FFR (HR 1.21, 95% CI 1.02-1.43, p=0.030). This was mainly driven by higher rates of all-cause death in the iFR group vs. FFR (HR 1.58, 95% CI 1.20-2.08, p=0.001), while the incidence of MI and unplanned revascularisation remained similar (**Table 3**).

On the contrary, patients in which revascularisation was deferred based on iFR or FFR showed similar incidence of MACE (HR 1.08, 95% CI 0.88-1.32, p=0.458), all cause death (HR 1.12, 95% CI 0.81-1.54), MI (0.84, 95% CI 0.58-1.22, p=0.366) and unplanned revascularisation (HR 1.00, 95% CI 0.76-1.30, p=0.973) (**Table 4, Figure 4**).

Subgroup analysis

Stratification of the primary event (MACE) across various variables, including baseline characteristics, clinical presentation and lesion location, showed no significant interaction within both study groups (**Figure 5**). In addition, when comparing the incidence of events between studies, both DEFINE-FLAIR and iFR-SWEDEHEART populations showed similar event rates, except for non-cardiovascular death, that was higher in the iFR-SWEDEHEART cohort that in its twin study (4.0% in DEFINE-FLAIR vs. 5.6% in iFR-SWEDEHEART, p=0.010, **Supplementary figure 1**).

DISCUSSION

The DEFINE-FLAIR and iFR-SWEDEHEART randomized trials demonstrated the non-inferiority at 1 year of iFR against FFR in the guidance of revascularisation of stable coronary artery lesions. Since the primary endpoint of both studies were reported, iFR has been broadly used in diverse clinical scenarios, and several non-randomized studies have continued to support the initial evidence gathered from both pivotal trials.

However, and despite having similar results in the primary outcome at 1 year, the pre-specified 5-year results revealed differences between the trials, especially in observed mortality rates between iFR and FFR study cohorts.

This patient-level pooled analysis of both DEFINE-FLAIR and iFR-SWEDEHEART trials provides new insights on this topic. In the analysis, which comprised 4,511 patients, we found a 14% relative increase in the risk of MACE and 35% in the risk of death in the iFR group compared to FFR. This excess of events was mainly driven by the higher mortality rates seen in the iFR group in the DEFINE-FLAIR trial, that especially affected those patients selected for revascularisation. Conversely, the incidence of non-fatal MI and unplanned revascularisation was almost identical in patients randomized to iFR and FFR. Patients allocated to revascularisation deferral showed similar rates of all endpoints in both study arms.

In the context of stable coronary artery disease, the role of revascularisation is still today a matter of debate. While some studies have shown that revascularisation of flow-limiting coronary stenoses reduces cardiovascular events (3), other contemporary randomized trials, such as ISCHEMIA and FAME-II, have consolidated the view that, even in patients with demonstrated ischemia, deferral of revascularisation does not result in an increase of mortality (4,12). Our findings should therefore be interpreted within the context of this existing evidence.

A previous study-based meta-analysis hypothesized that the observed differences in mortality between iFR and FFR arms in the 5-year follow up of DEFINE-FLAIR was related to unproper

revascularisation deferral with iFR in flow-limiting stenoses. It was also hypothesized that the clinical consequences of this would be more noticeable in lesions with a more proximal vessel anatomical location (13).

However, those hypotheses can be refuted based on the results of the present patient-level analysis. There were no significant differences in MACE in patients in whom revascularisation deferral was based on iFR or FFR, but only in those in whom revascularisation was performed. Furthermore, the subgroup analysis also highlights that the localization of the interrogated vessel and, subsequently, the extension of the subtended myocardium at risk, did not interact with the observed differences between both indices.

A second aspect of the analysis refers to the disconnect between mortality and other cardiovascular events encompassed in MACE. Overall, the consequences of equivocal revascularisation decisions with iFR should translate in clinical terms in a continuum of events, reflected as unplanned revascularisation, MI and death, the latter questioned by the findings of the ISCHEMIA and FAME II trials. The current analysis shows that the distribution of events clashes with this vision, showing an isolated excess in mortality in the iFR arm, with virtually no differences in terms of MI and unplanned revascularisation.

Several factors may contribute to this observation. First, mortality was defined differently across the two trials. In DEFINE-FLAIR, deaths of unknown cause were classified as cardiovascular unless a clear non-cardiovascular cause was identified, leading to 50% of deaths being adjudicated as cardiovascular without clarification. By contrast, in iFR-SWEDEHEART, unknown deaths were categorized as non-cardiovascular. These divergent definitions likely influenced both the absolute mortality rates and the attribution of cardiovascular versus non-cardiovascular causes of death.

Second, despite the large overall sample size of more than 4,500 patients, the possibility of a type I error must be acknowledged. The excess of mortality observed with iFR may therefore represent a statistical artifact, particularly as it was mainly driven by DEFINE-FLAIR, which accounted for 55%

of the pooled cohort. This interpretation is reinforced by the lack of plausible clinical mechanisms explaining why mortality would diverge in the absence of corresponding increases in MI or revascularisation, and by the higher rate of non-cardiovascular deaths in the iFR group. The findings contrast with other evidence, including solid observational data from the nationwide SWEDEHEART registry, which included more than 42,000 patients undergoing iFR- or FFR-guided revascularisation, and found no significant differences in the rates of MACE or its individual components, including all-cause or cardiovascular mortality, over 5 years (14).

Finally, differences in event reporting and external factors may also have influenced outcomes. DEFINE FLAIR included centers across five continents, whereas iFR-SWEDEHEART was limited to the Nordic countries with more uniform and robust clinical reporting systems. Moreover, the impact of the COVID-19 pandemic during follow-up may have been greater in the multicontinental DEFINE-FLAIR network than in the Nordic setting, further complicating interpretation of mortality outcomes.

Limitations.

This study has several limitations. First, it comprises two studies with different designs and outcome definitions. The latter which affects primarily the definition of cardiovascular and non-cardiovascular death, must be taken into consideration before interpreting the potential causes of death. Second, although pressure wire interrogation is a lesion-specific technique, outcomes are reported in a per-patient basis and lesion-level data was not available. Third, the population of both studies are significantly different: while DEFINE-FLAIR was a multinational trial involving patients from all continents, iFR-SWEDEHEART was a more homogeneous study including patients from a specific geographical region in northern Europe. Moreover, follow-up in each trial was also different: while DEFINE-FLAIR relied on clinical visits performed at each participant centre, iFR-SWEDEHEART data was based on a robust national registry that performs continuous monitoring of the population.

CONCLUSIONS

In this large study combining data from 2 randomised clinical trials, iFR-guided revascularisation was associated at 5 years of follow-up with a higher incidence of MACE and death compared with FFR, while rates of non-cardiovascular death, non-fatal MI and unplanned revascularisation were similar between groups. These differences were predominantly driven by patients undergoing revascularisation, whereas outcomes among those in whom revascularisation was deferred were comparable between iFR and FFR.

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TABLES

Table 1: **baseline characteristics of the overall cohort.**

	FFR (n=2257)	**iFR (n=2254)**
Age (yr)	66.2 (10.1)	66.4 (10.3)
Female sex (mis=1)	569 (25.2)	538 (23.9)
Disease type (mis=28)		
Acute coronary syndrome	606 (26.9)	622 (27.6)
Stable disease	1642 (72.8)	1613 (71.6)
Diabetes (mis=9)	588 (26.1)	609 (27.0)
Smoking status (mis=25)		
Former smoker	907 (40.2)	957 (42.5)
Current smoker	425 (18.8)	402 (17.8)
Hypertension (mis=10)	1587 (70.3)	1597 (70.9)
Hypercholesterolemia (mis=9)	1488 (66.0)	1521 (67.5)
Treatment or deferral (mis=6)		
Treated	1235 (54.7)	1125 (49.9)
Deferred	1019 (45.2)	1126 (50.0)

Data is shown as mean (standard deviation) for continuous variables and as count (percentage) for categorical variables. The sums of complementary categories may not be exact due to rounding. There were some missing data for the abovementioned variables: 1 for gender, 28 for disease type (ACS vs. SA), 9 for diabetes, 25 for smoking status, 10 for hypertension, 9 for hypercholesterolemia and 6 for treatment/deferred status.

Table 2: 5-year outcomes.

Event	FFR (n=2257)	iFR (n=2254)	HR (95% CI)	p-value
MACE	430 (19.05%)	480 (21.30%)	1.14 (1.00 to 1.30)	0.049
All-cause death	156 (6.91%)	207 (9.18%)	1.35 (1.10 to 1.67)	0.004
CV death	65 (2.88%)	86 (3.82%)	1.35 (0.98 to 1.86)	0.069
Non-CV death	91 (4.03%)	121 (5.37%)	1.36 (1.03 to 1.78)	0.028
MI	136 (6.03%)	136 (6.03%)	1.02 (0.81 to 1.30)	0.854
Revascularisation	266 (11.79%)	265 (11.76%)	1.01 (0.85 to 1.20)	0.895

Table 3: Outcomes in treated patients.

	FFR (n=1235)	iFR (n=1125)	HR (95% CI)	p-value
MACE	254 (20.57%)	274 (24.36%)	1.21 (1.02 to 1.43)	0.030
All-cause death	88 (7.13%)	124 (11.02%)	1.58 (1.20 to 2.08)	0.001
CV death	44 (3.56%)	54 (4.80%)	1.38 (0.93 to 2.05)	0.114
Non-CV death	44 (3.56%)	70 (6.22%)	1.78 (1.22 to 2.60)	0.003
MI	79 (6.40%)	83 (7.38%)	1.18 (0.87 to 1.60)	0.296
Revascularisation	159 (12.87%)	150 (13.33%)	1.05 (0.84 to 1.31)	0.666

Table 4: **outcomes in deferred patients**

	FFR (n=1019)	iFR (n=1126)	HR (95% CI)	p-value
MACE	175 (17.17%)	205 (18.21%)	1.08 (0.88 to 1.32)	0.458
All-cause death	68 (6.67%)	83 (7.37%)	1.12 (0.81 to 1.54)	0.493
CV death	21 (2.06%)	32 (2.84%)	1.40 (0.81 to 2.42)	0.235
Non-CV death	47 (4.61%)	51 (4.53%)	0.99 (0.67 to 1.48)	0.978
MI	57 (5.59%)	52 (4.62%)	0.84 (0.58 to 1.22)	0.366
Revascularisation	106 (10.40%)	115 (10.21%)	1.00 (0.76 to 1.30)	0.973

FIGURES

Figure 1: study flowchart.

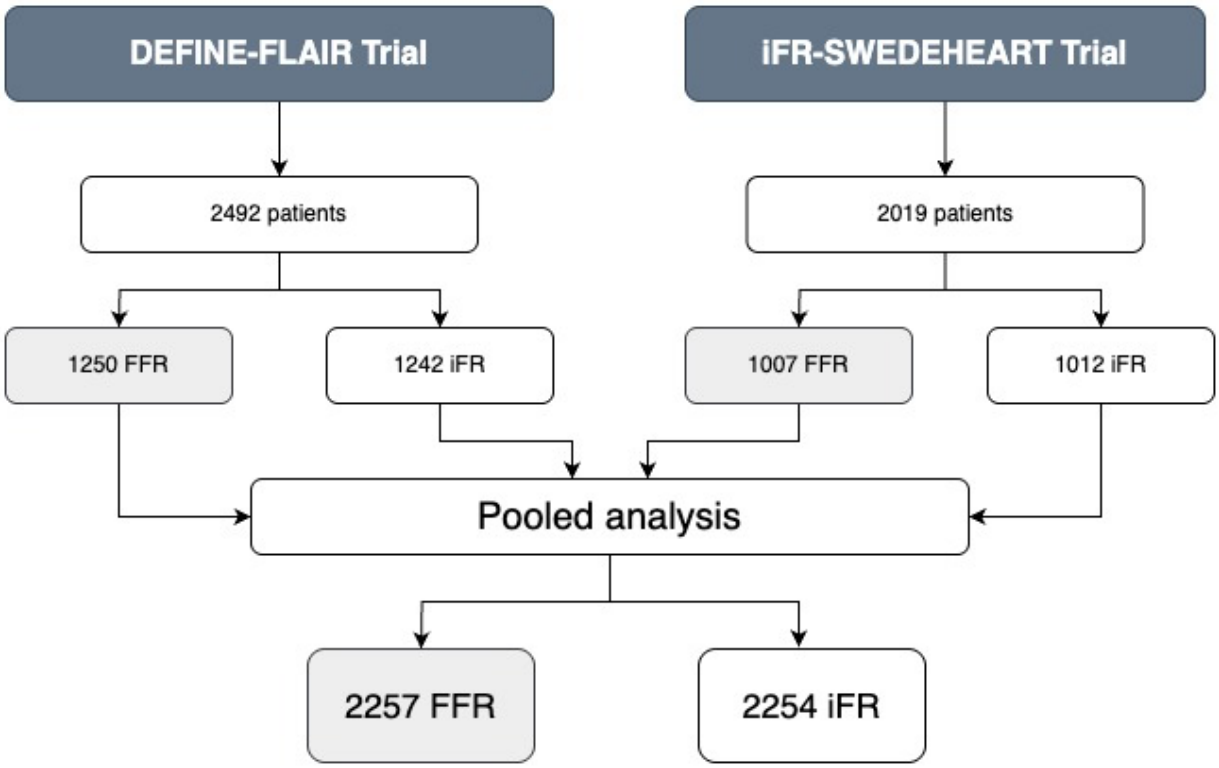


Figure 2: 5-year MACE.

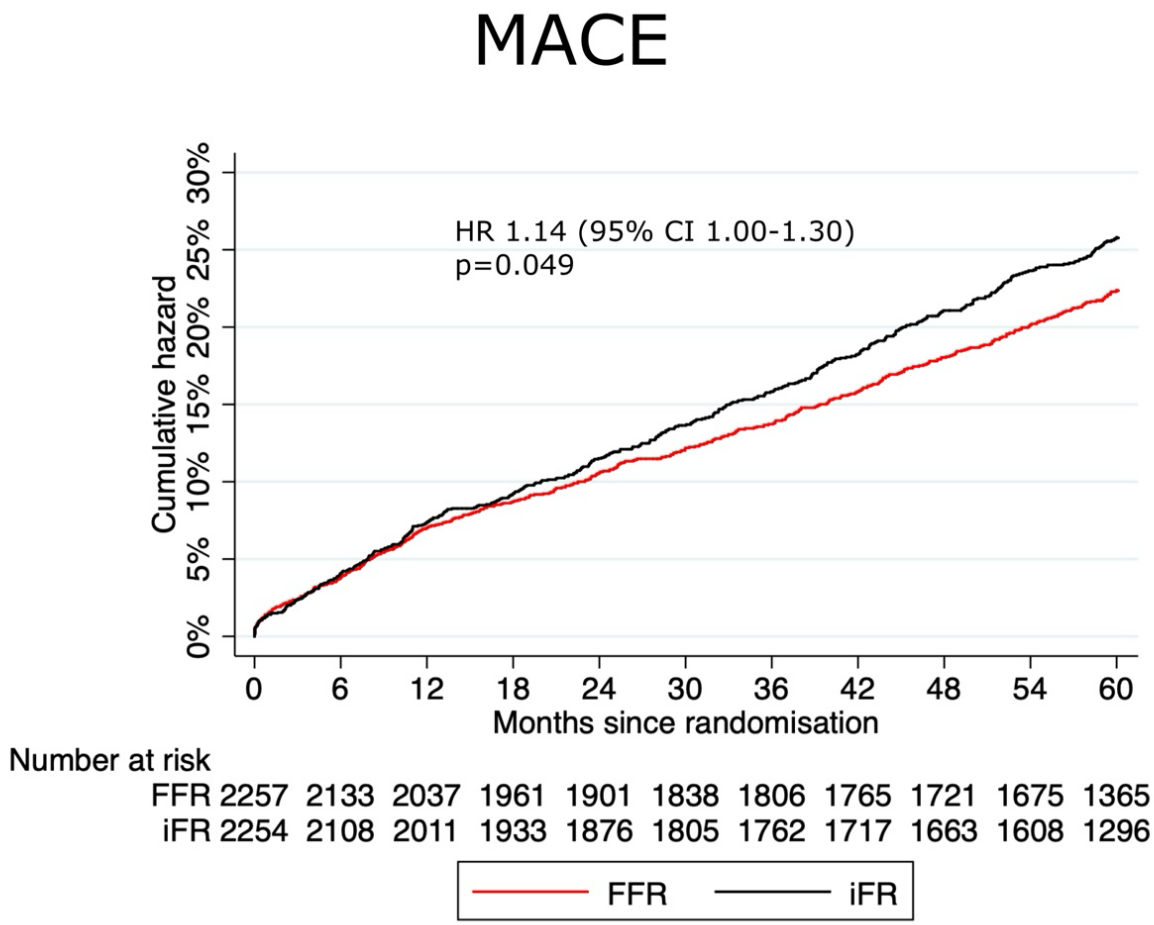


Figure 3: 5-year death, CV death, MI and revascularisation.

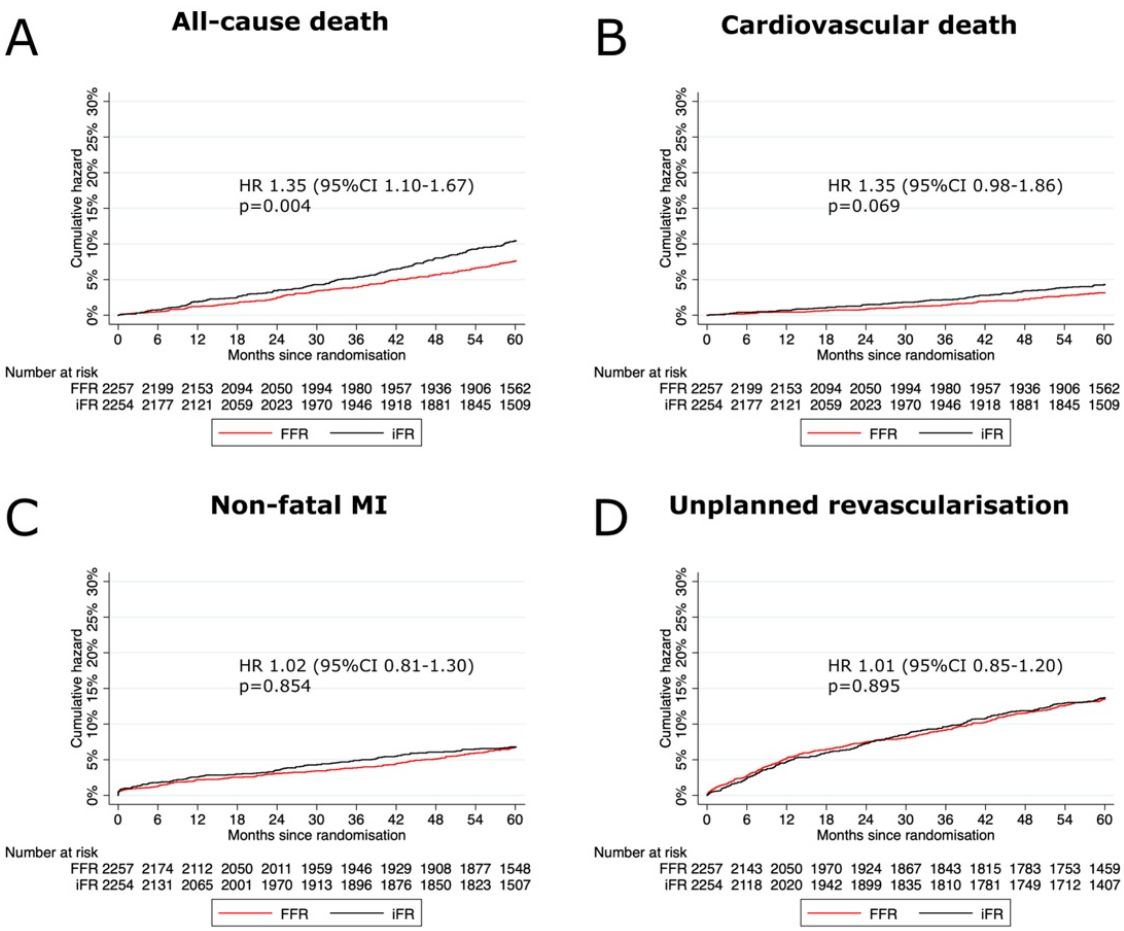


Figure 4: 5-year MACE in treated vs. deferred.

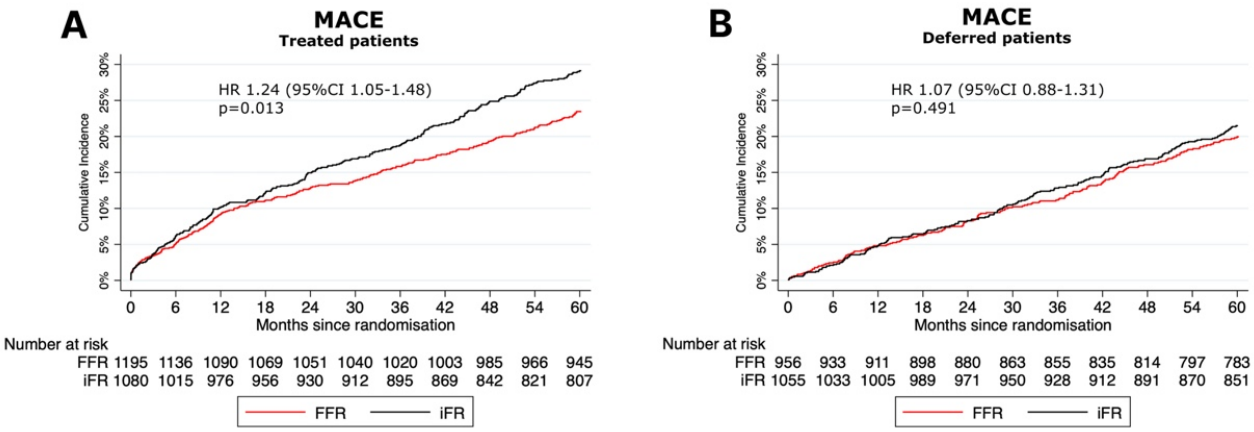
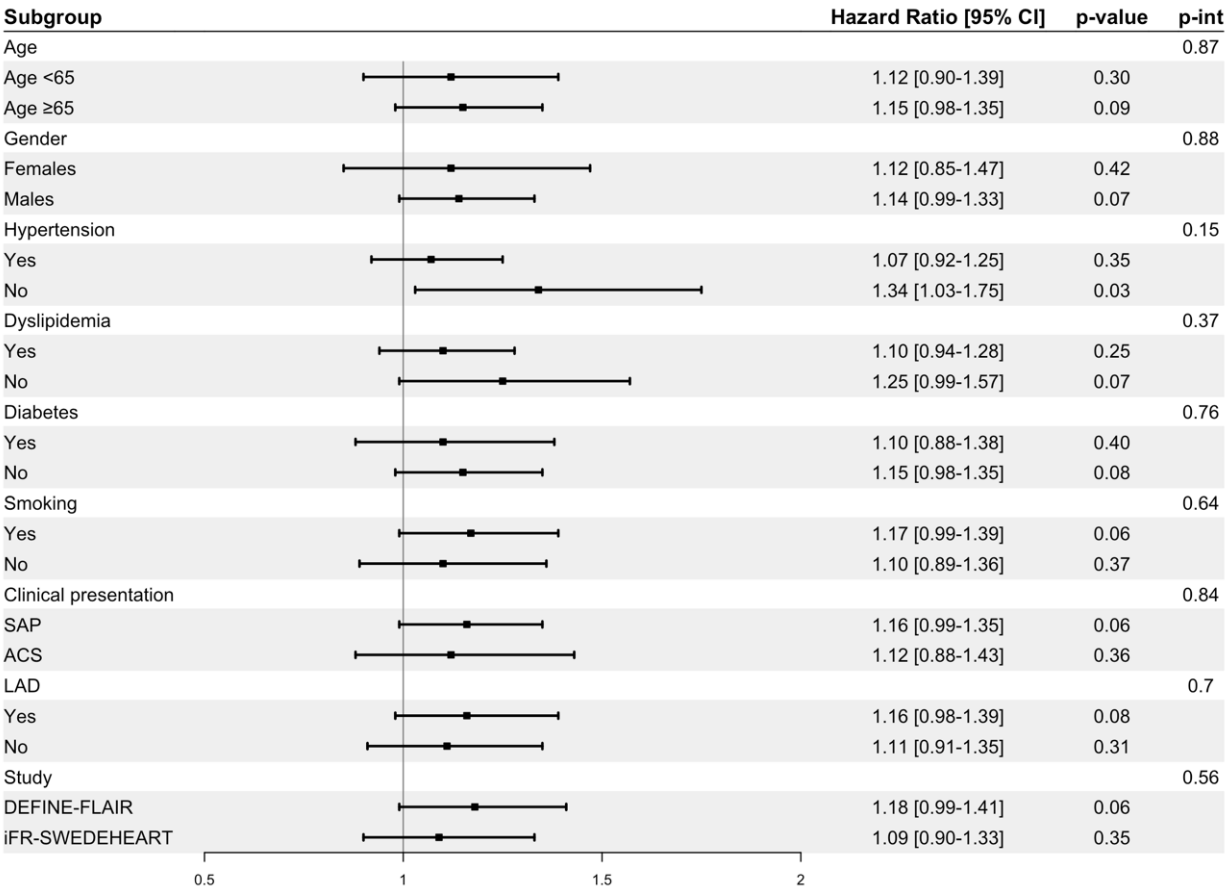


Figure 5: subgroup analysis for the primary endpoint (MACE).



SUPPLEMENTARY MATERIAL

Table 1: inclusion and exclusion criteria for both trials.

	DEFINE-FLAIR	iFR-SWEDEHEART
Inclusion criteria	Age >18 years	Age >18 years
	Willing to participate and able to understand, read and sign the informed consent document before the planned procedure	Provision of informed consent prior to any study specific procedures
	Eligible for coronary angiography and/or percutaneous coronary intervention	Patients with suspected stable angina pectoris or unstable angina pectoris/NSTEMI who are scheduled to undergo coronary angiography.
	Coronary artery disease in one or more native major epicardial vessels or their branches by coronary angiogram with visually assessed de novo coronary stenosis in which the physiological severity of the lesion is in question (typically 40-70% diameter stenosis)	Coronary lesions with an indication for physiology guided assessment (lesions with a stenosis grade of 40-80%).

	Stable angina or ACS (non-culprit vessels only and outside of primary intervention during acute STEMI)	Stable angina or Unstable Angina/ACS (in those cases only non-culprit vessels may be assessed)
Exclusion criteria	Previous CABG with patent grafts to the interrogated vessel	Previous CABG with patent grafts to the interrogated vessel
	Left main stenosis	
	Tandem stenoses separated by more than 10mm that require separate pressure guide wire interrogation or PCI (not to be interrogated or treated as a single stenosis)	
	Total coronary occlusions	
	Reestenotic lesions	
	Haemodynamic instability at the time of intervention (heart rate<50 beats per minute, systolic blood pressure <90mmHg) or balloon pump	Unstable hemodynamics (Killip class III or IV).
	Significant contraindication to adenosine administration (e.g. heart block, severe asthma)	Inability to tolerate adenosine

	Contraindications to PCI or drug-eluting stent (DES) implantation	
	Heavily calcified or tortuous vessels	Heavily calcified or tortuous vessels where inability to cross the lesion with a pressure wire is expected
	Significant hepatic or lung disease (chronic pulmonary obstructive disease), and/or malignant disease with unfavourable prognosis that may influence survival within the next 5 years	Known terminal disease with a life expectancy of less than one year.
	Pregnancy	
	STEMI within 48 hours of procedure	
	Severe valvular heart disease	
	ACS patients in whom more than one target vessel is present	In patients with multi-vessel disease and other indication than stable angina pectoris, difficulty in assessing which is the culprit lesion
		Previous randomization in the iFR-SWEDEHEART trial

Legend: ACS: acute coronary syndrome. NSTEMI: non-ST segment elevation myocardial infarction. STEMI: ST elevation myocardial infarction. PCI: percutaneous coronary intervention. CABG: coronary artery bypass grafting.

Table 2: death definitions for both trials.

Trial	**DEFINE-FLAIR**	**iFR-SWEDEHEART**
All-cause death	Mortality due to any cause	Mortality due to any cause
Cardiovascular	Cardiac: Any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia).	Death due to ischemic and hemorrhagic stroke, systemic embolism, myocardial infarction, sudden death, heart failure and other cardiovascular
	Vascular: Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause	
Unknown	Unwitnessed death and death of unknown cause will be classified as cardiac death even in patients with co-existing and potentially fatal non cardiac disease (e.g. cancer or infection).	Unobserved: will be assumed to be cardiovascular unless a non-CV cause can be clearly provided
		Observed: will be classified as non-cardiovascular
Non-cardiovascular	Any death not covered by the cardiovascular definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.	Deaths due to a clearly documented non-cardiovascular cause.

Legend: CV: cardiovascular. MI: myocardial infarction.

Table 3: outcomes in the per-protocol population.

Event	FFR (N=2246)	iFR (N=2240)	HR (95% CI)	p-value
MACE	428 (19.06%)	479 (21.38%)	1.14 (1.00 to 1.30)	0.044
All-cause death	156 (6.95%)	206 (9.20%)	1.35 (1.09 to 1.66)	0.005
CV death	65 (2.89%)	86 (3.84%)	1.35 (0.98 to 1.86)	0.069
Non-CV death	91 (4.05%)	120 (5.36%)	1.35 (1.02 to 1.77)	0.033
MI	135 (6.01%)	136 (6.07%)	1.03 (0.81 to 1.31)	0.805
Revascularisation	264 (11.75%)	265 (11.83%)	1.02 (0.86 to 1.21)	0.823

Chapter 3.

Comprehensive diagnosis of myocardial ischemia of obstructive and non-obstructive origin with a wire-free diagnostic strategy

Marco Lombardi, Adrian Jeronimo, Akram Lahrifa, Luca Paolucci, Giulia Nardi, Juan Carlos Diaz-Polanco, Alejandro Travieso, Pilar Jimenez-Quevedo, Fernando Macaya-Ten, Gabriela Tirado Conte, Luis Nombela-Franco, Pablo Salinas, Antonio I. Fernandez-Ortiz, Hernan Mejia-Renteria, Nieves Gonzalo, Javier Escaned

ABSTRACT

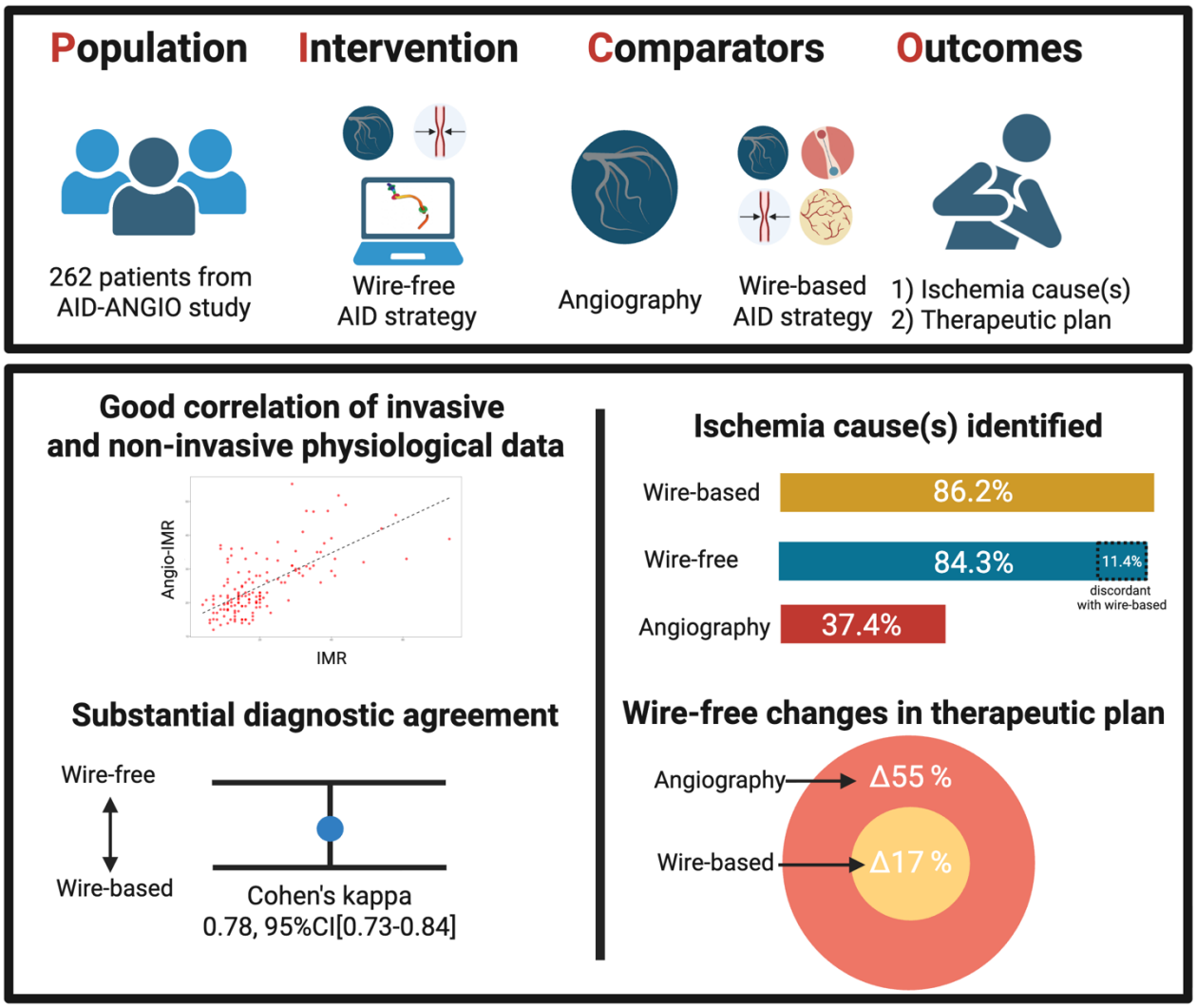
Background: Current clinical guidelines recommend considering both obstructive and non obstructive causes of myocardial ischemia in patients with chronic coronary syndrome (CCS). Wire-based physiological assessment constitutes a valid approach for this, but it remains underutilized. We evaluated the diagnostic yield and clinical impact of an alternative wire-free approach for this purpose.

Methods: This is a sub-analysis of the multicenter, prospective AID-ANGIO study, evaluating the impact of a wire-free advanced invasive diagnosis (AID) strategy in the diagnostic workflow of patients with CCS admitted to the catheterization laboratory. The wire-free AID strategy combined quantitative flow ratio for epicardial evaluation, contrast angiography-derived index of coronary microcirculatory resistance for microvascular assessment, and acetylcholine testing for the endothelial-dependent coronary function.

Results: The study included 262 patients. The wire-free AID strategy identified a cause of myocardial ischemia in 84.3% of patients, representing a twofold increase in the identification of a cause of myocardial ischemia, compared to coronary angiography alone ($p<0.0001$). Additionally, the wire-free AID strategy demonstrated substantial agreement compared to the wire-based AID strategy (Cohen's kappa 0.78). The wire-free AID strategy led to a change in the initial therapeutic plan in 55.3% compared to coronary angiography. Nevertheless, the wire-free AID strategy maintained a good concordance with the wire-based AID strategy (16.8% of therapeutic changes).

Conclusion: This study supports the clinical utility of a wire-free AID strategy in CCS patients, demonstrating its potential to improve diagnostic yield and guide clinical decision-making compared to coronary angiography alone. Additionally, it shows substantial agreement with the wire-based approach.

GRAPHIC ABSTRACT



Abbreviations: 95%CI: 95% confidence interval; AID: advanced invasive diagnosis.

INTRODUCTION

More than half a century after revolutionizing clinical practice, coronary angiography remains the mainstay for evaluating and managing coronary artery disease (CAD). However, its diagnostic yield is limited, particularly for intermediate-grade stenoses and non-obstructive coronary artery disease (INOCA) (1,2).

Current guidelines recommend assessing intermediate-grade stenoses using pressure-derived indices, such as fractional flow reserve (FFR) or non-hyperemic pressure ratios. Similarly, they advocate for invasive evaluation of microvascular function and vasomotor abnormalities in patients with persistent anginal symptoms, despite angiographically normal or functionally nonsignificant stenoses (3).

The Advanced Invasive Diagnosis for Patients with Chronic Coronary Syndromes Undergoing Coronary Angiography (AID-ANGIO) study demonstrated the clinical value of a structured, guideline-based, hierarchical approach to improve diagnostic accuracy and optimize patient management. The advanced invasive diagnostic (AID) strategy significantly enhanced diagnostic yield compared to invasive coronary angiography alone, primarily through improved identification of INOCA mechanisms (2).

Despite these promising results, the adoption of wire-based coronary physiology remains suboptimal, in part due to operators' reluctance to perform intracoronary instrumentation (4). Alternative versions of the AID algorithm not requiring the use of intracoronary guidewires might contribute to a better implementation of this strategy in patients management. In this regards, recent developments made in the field of functional coronary angiography (FCA) allow not only assessment of epicardial stenoses but also of the microcirculation (5–8).

The objective of this study was to evaluate the diagnostic yield and impact on therapeutic decision-making of a non-invasive, hierarchical algorithm — the wire-free AID strategy — for identifying both obstructive and non-obstructive mechanisms of ischemia in patients with chronic coronary syndrome (CCS).

METHODS

Study design

This is a sub-analysis of the multicenter, observational, prospective AID-ANGIO study (NCT05635994), which evaluates the impact of wire-free techniques in the diagnostic workflow of patients with CCS admitted to the catheterization laboratory.

Study population

The AID-ANGIO study enrolled consecutive patients with CCS who were referred for invasive coronary angiography by their cardiologists due to symptoms of angina and/or evidence of ischemia on non-invasive tests, or the presence of CAD on coronary computed tomography angiography (CCTA) (2).

Exclusion criteria of the AID-ANGIO study are available in the original publication (2). Additional exclusions for the present sub-analysis included patients with angiographic views unsuitable for FCA analysis or those without available DICOM files. A detailed list of exclusion criteria is provided in **Supplementary Table 1**.

Coronary angiography, QFR analysis and Angio-IMR calculation

The FCA analysis has been performed post-hoc. In the AID-ANGIO study, after routine intracoronary nitrates (200 mcg) administration, orthogonal angiographic projections were acquired to ensure optimal visualization of the epicardial vessels.

A Philips X-ray system operating at 15 frames per second was used, and contrast injections were performed using a power injector system (ACIST CVi Contrast Delivery System).

DICOM files were transferred to the quantitative flow ratio (QFR) console (Qangio XA 3D version 2.0; Medis Medical Imaging Systems). An expert analyst performed QFR calculations offline according to standard guidelines (9), and contrast angiography-derived index of coronary microcirculatory resistance (Angio-IMR) was derived from resting angiograms as previously

described (7), blinded to the intracoronary physiology data. Abnormal thresholds for QFR were set at ≤0.80, and for Angio-IMR, the threshold was ≥25.

Additional information about the FCA analysis is provided in the Supplementary Appendix (**Supplementary Appendix 1-2, Supplementary Table 1 and Supplementary Figure 1**).

The wire-free AID strategy

The wire-free AID strategy represents a hierarchical algorithm designed to evaluate both obstructive and non-obstructive causes of myocardial ischemia during invasive coronary angiography without the need for a pressure guidewire and adenosine administration.

The wire-free AID strategy uses QFR and Angio-IMR analysis for assessing the epicardial and microvascular domains, respectively, calculated post-hoc (**Figure 1**).

For severe stenosis [≥90% diameter stenosis (DS) by visual assessment], no further evaluation was required, as these were considered flow-limiting and responsible for the patient's symptoms. Intermediate-grade stenoses (<90% DS by visual assessment) were evaluated post-hoc using QFR to determine their physiological significance.

In patients with either angiographically normal coronary arteries or intermediate stenosis with non-ischemic QFR values, coronary microvascular dysfunction (CMD) was established in the presence of an increased Angio-IMR.

The assesment of the endothelial-dependent coronary function was based on data from the AID-ANGIO study, where sequential intracoronary injections of Ach were administered, as previously described (2). Epicardial coronary spasm was diagnosed if ≥90% vessel diameter reduction occurred, accompanied by reproduction of the patient's anginal symptoms and transient ischemic ECG changes. Microvascular spasm was diagnosed when anginal symptoms and ischemic ECG changes occurred without epicardial spasm (10,11).

For comparison, the physiological data obtained from the AID-ANGIO study were used. The invasive physiological evaluation was performed using the PressureWire X Guidewire (Abbott) with the

CoroFlow Cardiovascular System (Coroventis). Presence of ischemia generated by the epicardial domain was defined as FFR ≤0.80 or resting full-cycle ratio (RFR) ≤0.89. CMD was established in the presence of a reduced coronary flow reserve (CFR) and/or an increased index of microcirculatory resistance (IMR), measured by bolus thermodilution. The abnormal cutoff values for CFR and IMR were <2.0 and ≥25, respectively (10). IMR was corrected by Yong's formula to account for epicardial disease.

Impact of the wire-free AID strategy on clinical decision-making

To assess how the complementary information from the wire-free AID strategy might impact clinical decision-making, we compared the final diagnostic and therapeutic decisions based on the wire-free approach to those based on angiography alone. We also compared these decisions to the standard of reference (wire-based AID strategy). The final clinical diagnosis and therapeutic plan was elaborated by two independent interventional cardiologists, based on the information from FCA and assessment of endothelial-dependent coronary function with acetylcholine. In cases of discrepancy, the evaluations were jointly reassessed, and a consensual decision was reached.

Study Endpoints

The primary endpoint was the proportion of patients in which the wire-free AID strategy identified the cause of ischemia, compared with both the angiography and AID strategies. Additionally, a direct comparison was performed between the wire-free AID strategy, angiography alone, and the AID strategy.

The secondary endpoint included the proportion of patients in which the wire-free AID strategy led to a change in the therapeutic plan compared to those based on angiography alone or the AID strategy.

Statistics

Quantitative variables are presented as medians with interquartile ranges (IQR) or as means with standard deviations. Categorical variables are presented as frequencies and percentages and were compared using the chi-square test.

The primary and secondary endpoints were visualized using Sankey diagrams. Agreement between the wire-free and wire-based AID strategies was assessed using Cohen's kappa. Additional correlation, agreement, discriminatory power, and accuracy analyses between estimated and true invasive parameters were performed using Pearson correlation coefficient, Bland-Altman analysis, receiver operating characteristic (ROC) analysis, and dichotomic agreement (invasive IMR $\geq$25 U and RFR $\leq$0.89 or FFR $\leq$0.80 as reference standards).

All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant. All analyses were conducted using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

The study enrollment period spanned from June 2022 to December 2023 (**Supplementary Table 2**). A total of 262 patients met the inclusion criteria and comprised the final population of the wire-free AID strategy study. Reasons for exclusion are summarized in the **Supplementary Figure 2**. A comparison of baseline characteristics between included and excluded patients is provided in **Supplementary Table 3**.

Baseline characteristics

The mean age was 66 years (IQR 58-73), with a good gender balance (43.1% of female patients). Other baseline characteristics, including angina-related quality of life and the results from non-invasive ischemia tests, are summarized in **Table 1**.

Invasive and non-invasive physiological data

A total of 215 vessels in 182 patients were investigated using FFR or RFR and subsequently analyzed for QFR. Details about procedural data are available in **Table 2**.

In the 108 vessels (74 patients) with intermediate coronary stenoses, the median QFR, FFR and RFR were 0.89 (IQR: 0.78-0.96), 0.87 (IQR: 0.81-0.90), and 0.92 (IQR: 0.87-0.95), respectively (**Table 2**). Regression analysis identified a positive correlation between both QFR-FFR and QFR-RFR (r=0.78 and r=0.68, respectively. **Figure 2, Panel A1-2**). Bland-Altman plot showed a mean difference between techniques of 0.04 and –0.04, respectively (**Figure 2, Panel A3-4)**. The AUC of QFR predicting FFR$\leq$0.80 or RFR$\leq$0.89 was 0.93, whereas the sensitivity, specificity, positive predictive value, and negative predictive value of QFR were 0.81, 0.98, 0.96, 0.90, respectively **(Figure 2, Panel A5)**.

A total of 147 patients without coronary stenoses or with non-ischemic intermediate stenoses were evaluated with both Angio-IMR and IMR. Median Angio-IMR and IMR were 22 (IQR: 19-29.75)

and 16 (IQR: 12-25), respectively (**Table 2**). Regression analysis identified a positive correlation between Angio-IMR and IMR with a good agreement by the Pearson correlation coefficient (r = 0.68, (**Figure 2, Panel B1**). Bland-Altman plot showed a mean difference between the techniques of –4.8 (**Figure 2, Panel B2**). The AUC of Angio-IMR predicting IMR≥25 was 0.91, whereas the sensitivity, specificity, positive predictive value, and negative predictive value of Angio-IMR were 0.97, 0.78, 0.58, 0.98, respectively (**Figure 2, Panel B3**).

Diagnostic yield of the wire-free AID strategy – primary endpoint

Based on coronary angiography alone, obstructive CAD with angiographically severe stenoses was identified in 98 (37.4%, 95% CI 31.8%-43.4%) patients, of whom 18 (18.4%) had multivessel disease with also intermediate-grade stenoses (**Supplementary Table 4**). With the information of the wire-free AID strategy, a cause of myocardial ischemia was identified in 221 (84.3%, 95% CI: 79.5%-88.3%) patients, representing an additional 46.9% of patients with an identified cause of ischemia, compared to angiography alone (95% CI: 39.6%-54.3%, p<0.0001).

Obstructive CAD was diagnosed in 110 (42%) patients, of whom 30 (27.3%) presented with intermediate stenoses with significant QFR values. Details about significant coronary lesions in patients with obstructive CAD, according to the wire-free AID strategy, are available in the **Supplementary Table 5**.

INOCA was diagnosed in 111 (42.4%) patients, including 25 (22.5%) with microvascular dysfunction, 55 (49.5%) with vasomotor disorder and 31 (27.9%) with a mixed endotype. Finally, in 41 (15.6%) patients a cause of ischemia has not been detected (**Figure 3**).

Regarding the agreement of the wire-free AID strategy with the standard of reference (wire-based AID strategy), Cohen's kappa was 0.78 (95% CI: 0.73-0.84) indicating a substantial agreement among the two approaches (**Figure 3**). When patients with angiographic stenosis ≥90% were excluded, the diagnostic reclassification remained consistent with the main analysis: the wire-free AID strategy changed the angiography-based diagnosis in 123 out of 182 patients (67.6%, 95% CI

60.2%–74.2%), while maintaining a good agreement with the wire-based AID strategy (Cohen's kappa = 0.71, 95% CI 0.63–0.79; **Supplementary Figure 3**).

Overall, 41 patients showed discordant final diagnoses between the wire-free and wire-based AID strategies. Among these, 30 patients (11.4% of all patients with an identified ischemic cause) had a discordant diagnosis of myocardial ischemia. In the remaining 11 discordant cases, the wire-free strategy failed to identify a cause of ischemia, in contrast to the wire-based approach (**Figure 3**). Additionally, 16 of the discordant cases (6.1% of all patients) were associated with a diagnosis of CMD due to a low CFR (**Supplementary Table 6**), occurring in patients with normal IMR values (median IMR 18.5, IQR 14–20).

Impact of wire-free AID strategy on therapeutic plan – secondary endpoint

As shown in **Figure 4**, application of the wire-free AID strategy, alongside clinical information and invasive coronary angiography, led to a change in the initial therapeutic plan in 145 out of 262 cases (55.3%, 95% CI: 49.3-61.2). This result was primarily driven by intra-group changes in the medical treatment of INOCA, due to misclassification of specific INOCA endotypes and the subsequent indication to optimize medical therapy (69/129 patients, 53.5% of INOCA cases).

Compared to the standard of reference (wire-based AID strategy), the wire-free approach resulted in changes of therapeutic plan in 44 (16.8%, 95% CI: 12.8%–21.8%) cases. Among INOCA patients an intragroup change was observed in 23 (20.5%) cases. Further details regarding these changes are summarized in **Supplementary Table 7-9**.

When restricting the analysis to patients with stenosis <90%, the wire-free AID strategy led to a change in the initial therapeutic plan in 131 out of 182 cases (72.0%, 95% CI: 64.7%–78.2%), while changes relative to the wire-based AID strategy occurred in 44 out of 182 cases (24.2%, 95% CI: 18.3%–31.2%; **Supplementary Figure 4**).

DISCUSSION

This subanalysis of the AID-ANGIO study explores the value of a novel wire-free diagnostic strategy of both obstructive- and non-obstructive causes of myocardial ischemia in patients with CCS. Overall, we found that such strategy significantly improves the diagnostic yield and modifies the therapeutic attitude compared with an angiography-based strategy supported by clinical patient information, while keeping a good agreement with the invasive, wire-based AID strategy. These aspects are discussed in the following paragraphs.

Invasive physiological coronary assessment is currently recommended in clinical practice guidelines for both the assessment of epicardial stenoses (class I recommendation, level of evidence A) and the coronary microcirculation (IB) (3). The AID strategy, which combines angiographic and intracoronary pressure-wire assessment, has shown to dramatically increase the percentage of CCS patients in whom a cause for myocardial ischemia is found in the catheterization laboratory, compared with angiography alone (2).

We evaluated a variation of the AID diagnostic algorithm that does not require intracoronary instrumentation, being compared with both diagnostic angiography and the full, wire-based AID strategy. The potential value of such algorithm is that may increase the adoption of comprehensive evaluation of patients with CCS. In fact, despite robust evidence supporting wire-based physiological assessments, global adoption of these conventional techniques in coronary catheterization laboratories remains low (4). This is likely due to the need for dedicated pressure guidewires, additional coronary instrumentation, prolonged procedural time, and the use of hyperemic agents such as adenosine, all of which increase costs and patient discomfort.

This alternative AID-algorithm leverages previous evidence supporting the feasibility of assessing both functional relevance of epicardial stenoses, based on QFR, and measurement of microvascular resistance, using the Angio-IMR index. The results of the present study are encouraging regarding

the value of this wire-free AID algorithm. As shown in the **Figure 3**, the wire-free AID strategy identified a cause of myocardial ischemia in 84.3% of patients, representing an additional twofold increase of identification of a cause of myocardial ischemia, compared to coronary angiography alone. At the same time the wire-free AID strategy demonstrated a substantial agreement compared to the standard of reference (wire-based AID strategy). We also found an excellent agreement between QFR-derived indices and invasive measurements.

Main advantages of this wire-free AID approach is the ability to perform post-hoc assessments, reducing procedural time and patient's discomfort (5,8,9). However, to enhance real-world clinical applicability, standardized angiographic acquisition protocols are essential, particularly regarding optimal image quality, projection angle selection, frame rate (at least 15 frames/s), and good contrast opacification (**Supplementary Appendix 2** and **Supplementary Table 1**). In addition, artificial intelligence-assisted frame selection and real-time angiographic feedback systems may further reduce analysis failures and improve feasibility in routine catheterization laboratory workflows. While QFR and Angio-IMR allow for comprehensive functional evaluation without the need for pressure guidewires, they do not assess vasomotor function. To complement this aspect, we retrospectively collected the Ach data from the AID-ANGIO study. In terms of simplifying the wire-free AID algorithm, a diagnostic coronary catheter could be used as an alternative to a guiding catheter for the performance of the Ach testing (12).

In clinical practice, Angio-IMR may therefore serve primarily as a rule-out tool for CMD, supported by its high sensitivity and negative predictive value. However, a caveat of the wire-free AID algorithm is that it does not provide measurement of CFR. Our study reveals that 6.1% of patients would be misclassified with the wire-free AID strategy due to abnormal CFR values despite normal IMR values. From the perspective of reaching a diagnosis, at a difference with Ach testing, CFR can be assessed with non-invasive methods (13), including cardiac magnetic resonance (CMR) (14), positron emission tomography (PET) (15), computed tomography (CT) scan (16) and pulsed-wave

Doppler measurements obtained with transthoracic echocardiography (17). Therefore, patients with persistent symptoms despite a normal wire-free assessment, or in whom diagnostic uncertainty remains, may benefit from complementary non-invasive CFR evaluation. From the therapeutic standpoint, it is important that patients with elevated IMR will generally receive similar treatment irrespective of the CFR value. The prognostic value of Angio-IMR has received new support from a recent post-hoc analysis of the Fractional Flow Reserve and Intravascular Ultrasound for Clinical Outcomes in Patients with Intermediate Stenosis (FLAVOUR) trial, which identified Angio-IMR >25 as an independent predictor of adverse events at two years, in both percutaneous coronary intervetion (PCI) and non-PCI groups (18).

Beyond improving diagnostic yield, the wire-free AID strategy demonstrated a meaningful impact on clinical decision-making. As shown in **Figure 4**, this approach led to a change in the therapeutic plan in approximately half of the patients when compared to diagnostic coronary angiography alone (145 out 262 cases), while maintaining good concordance with the wire-based AID strategy (therapeutic changes only in 44 out 262 cases). This finding reinforces the idea that coronary angiography alone is not be sufficient for guiding management in patients with CCS, and highlights the added value of a complete assessment of both obstructive and non obstructive causes of myocardial ischemia — even when performed without intracoronary instrumentation.

Limitations

This study has limitations. First, this was a post-hoc analysis of an all-comers, prospective and multicentre study, which may introduce selection bias, primarily due to the additional inclusion criteria determined by the availability of coronary angiography compatible with QFR/Angio-IMR analysis, which led to the exclusion of 17% of patients (55 out 317) from the AID ANGIO study. Nevertheless, no significant differences in baseline characteristics were observed between included and excluded patients. Second, the inability to derive CFR from coronary angiograms remains a limitation of the wire-free AID approach, particularly given that reduced CFR has been associated

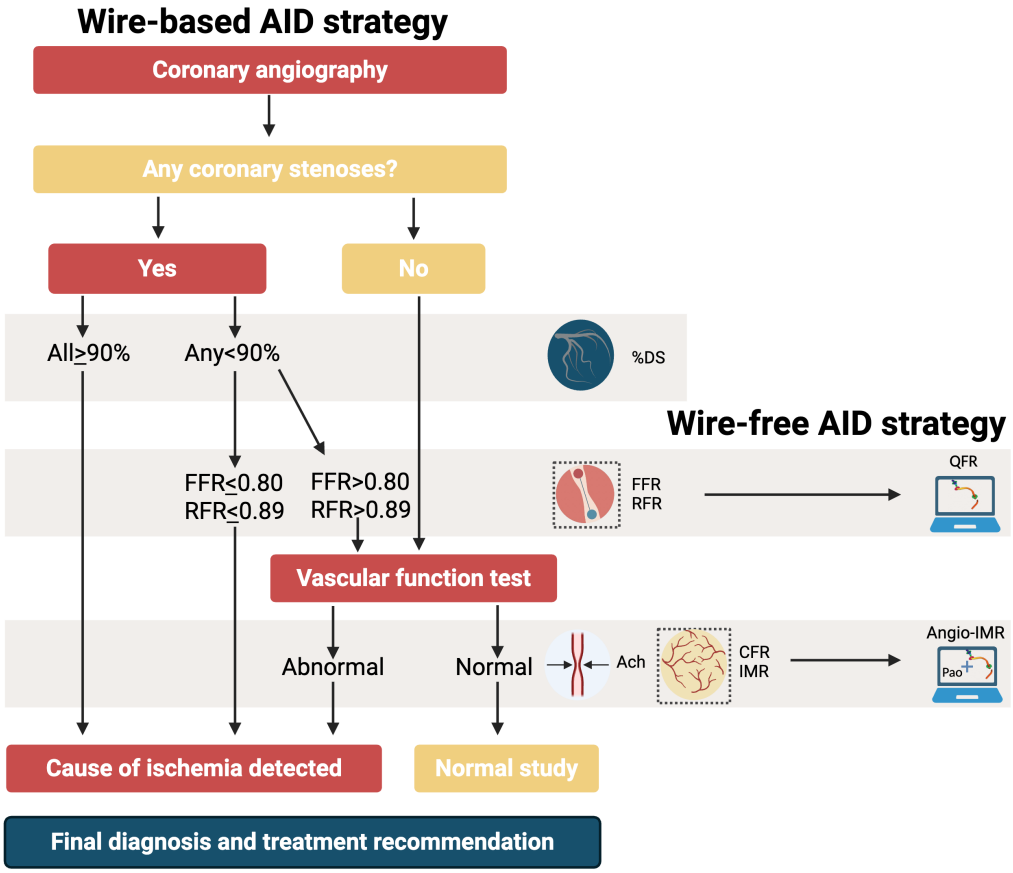
with adverse clinical outcomes (19,20), and that cases of functional CMD (low CFR despite normal IMR) cannot be detected without direct assessment of coronary flow. Future developments in FCA will provide a method for wire-free CFR assessment based on coronary angiography. For the time being, non-invasive methods to measure CFR can be considered in combination with our angiography-based strategy. Third, the diagnostic performance of the wire-free strategy may be affected by the relatively low positive predictive value and specificity of Angio-IMR compared to the invasive IMR, potentially leading to false positive diagnoses. Finally, the lack of longitudinal follow-up data precludes a comprehensive assessment of the clinical impact of the wire-free AID strategy on symptom relief, revascularization rates, and long-term clinical outcomes. Further studies with planned follow-up — including future analyses from the AID-ANGIO study — will help clarify the prognostic and therapeutic implications of this approach.

CONCLUSION

In conclusion, our results suggest that a wire-free AID strategy may contribute to an adequate assessment of both obstructive and non-obstructive causes of myocardial ischemia in CCS patients, demonstrating its potential to improve diagnostic yield and guide clinical decision-making compared to coronary angiography alone. Additionally, it shows a substantial agreement with the standard of reference (wire-based AID strategy). We believe that the wire-free approach may represent a feasible alternative for a comprehensive diagnosis of patients admitted to the cath-lab, with its adoption being facilitated by not requiring intracoronary instrumentation or the use of hyperaemic agents.

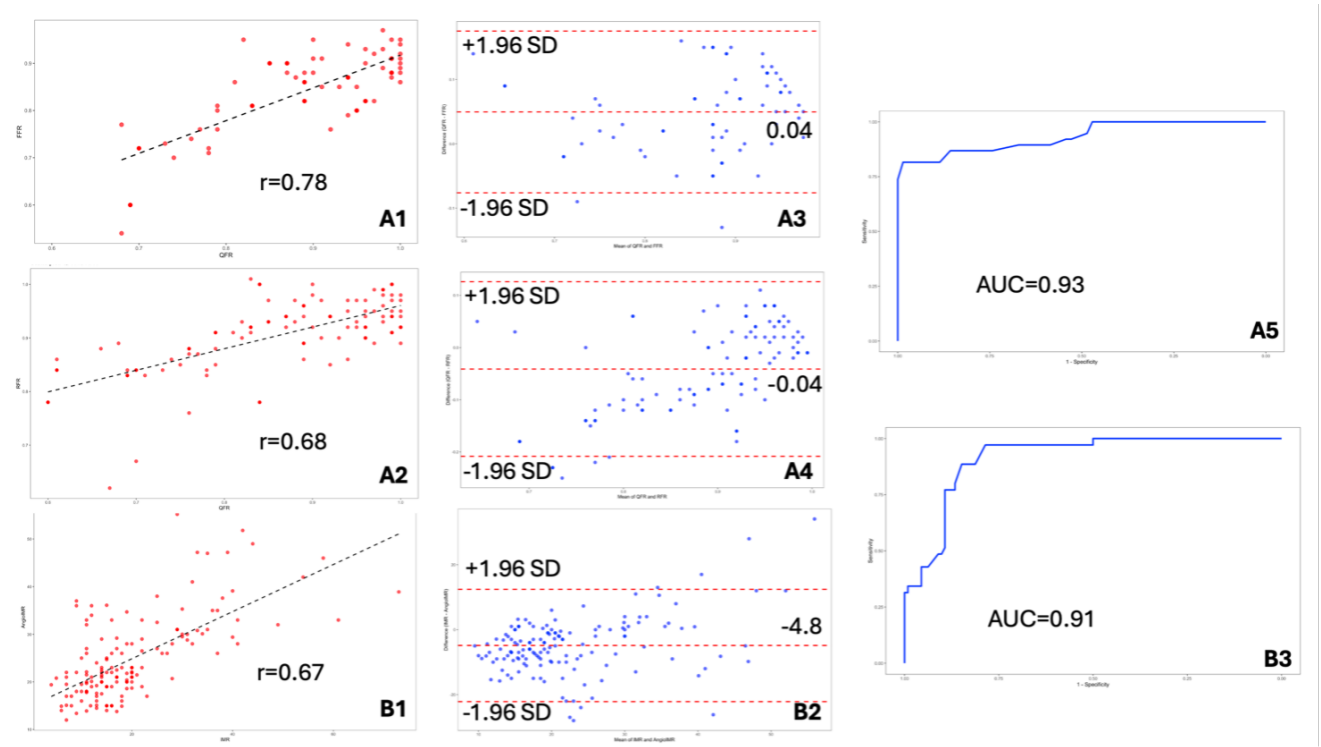
FIGURES

Figure 1. Wire-free AID strategy algorithm.



Abbreviations: %DS: percentage diameter stenosis; Ach: acetylcholine; AID: advanced invasive diagnosis; Angio-IMR: angiography-derived index of coronary microcirculatory resistance; CFR: coronary flow reserve; FCA: functional coronary angiography; FFR: fractional flow reserve; IMR: index of coronary microcirculatory resistance; QFR: quantitative flow ratio; RFR: resting full-cycle ratio

Figure 2. Diagnostic performance of QFR and Angio-IMR.

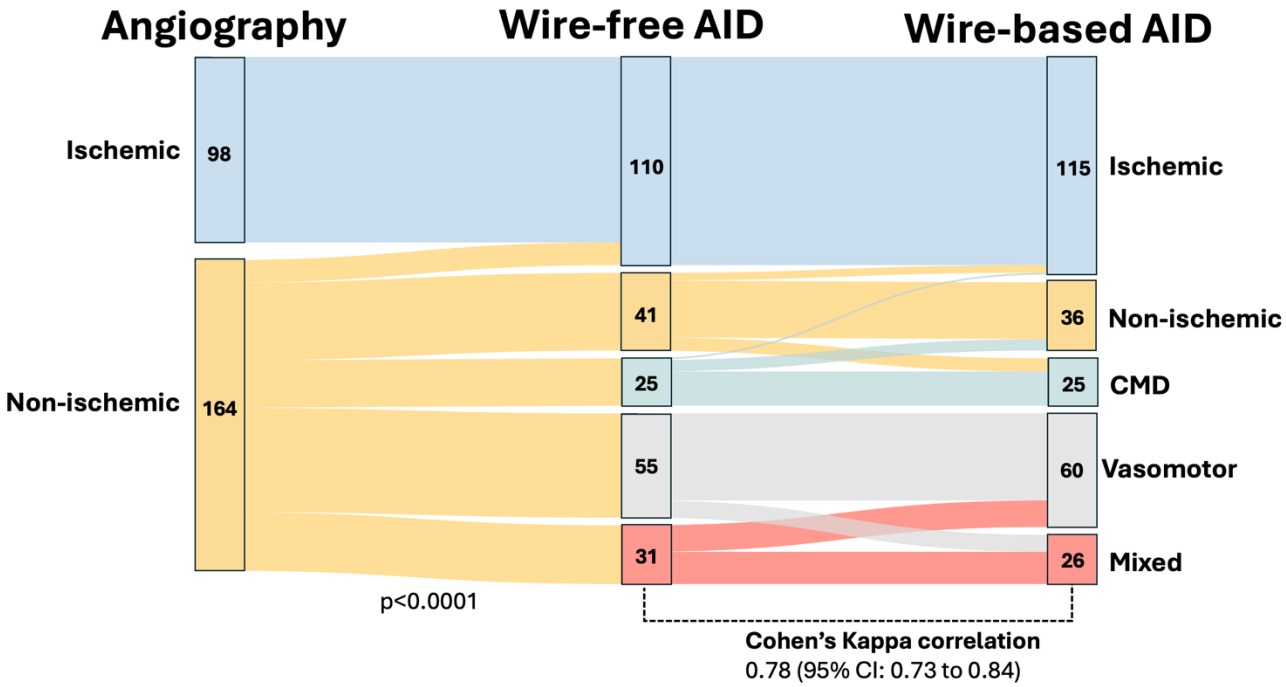


Panel A: diagnostic performance of QFR among patients with coronary stenoses. Scatter diagram with regression line and Pearson correlation coefficient (r) between QFR and invasive FFR (A1) or RFR (A2). Panel B. Agreement between QFR and FFR (A3) or RFR (A4) from Bland–Altman analysis. Panel A5. Area under the curve (AUC) for QFR to predict invasive the presence of an epicardial significant stenosis defined as RFR ≤0.89 and/or FFR≤0.80.

Panel B: diagnostic performance of Angio-IMR. Scatter diagram with regression line and Pearson correlation coefficient (r) between Angio-IMR and invasive IMR (B1). Agreement between both methods from Bland–Altman analysis (B2). Area under the curve (AUC) for angio-IMR to predict invasive IMR≥25 U (B3).

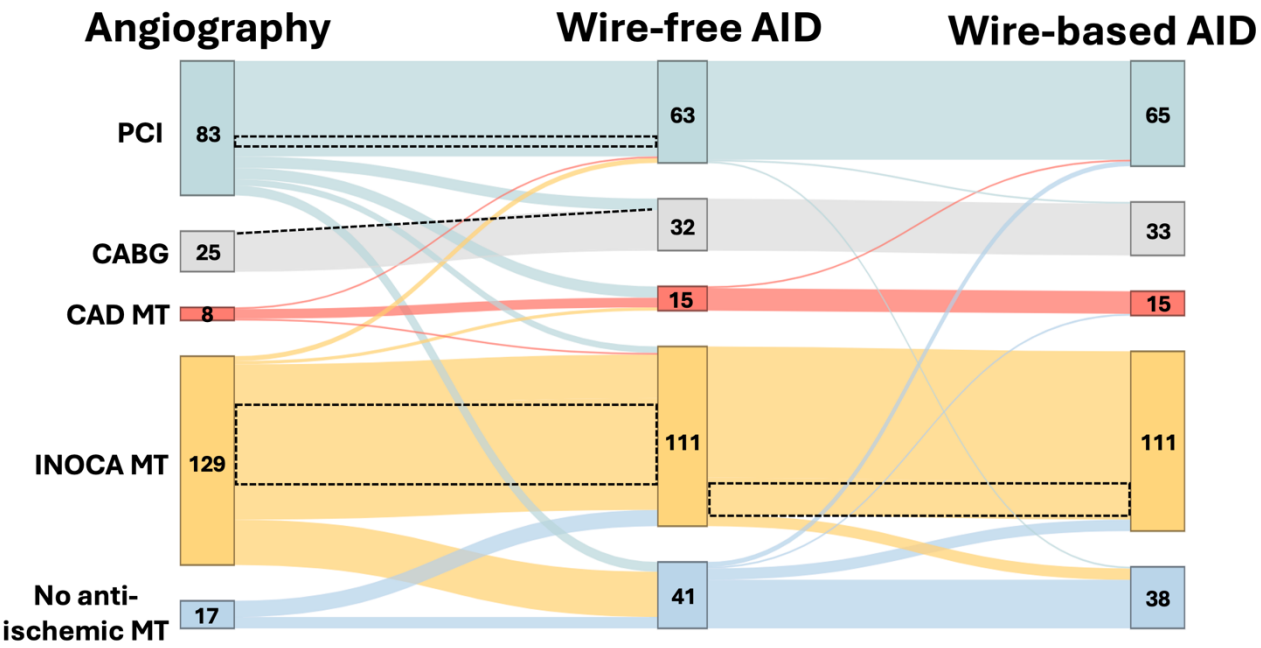
Abbreviations: Angio-IMR: angiography-derived index of coronary microcirculatory resistance; IMR: index of coronary microcirculatory resistance; FFR: fractional flow reserve; QFR: quantitative flow ratio; RFR: resting fullcycle ratio.

Figure 3. Diagnostic yield of coronary angiography alone, wire-free and wire-based AID strategies.



Abbreviations: AID: advanced invasive diagnosis; CMD: coronary microvascular dysfunction.

Figure 4. Impact of the wire-free AID strategy on clinical decision-making compared to wire-based AID strategy and coronary angiography alone.



Dashed lines indicate intragroup changes due to difference in treatment of INOCA endotypes / number of epicardial lesions to treat.

Abbreviations: AID: advanced invasive diagnosis; CABG: coronary artery bypass graft; CAD: coronary artery disease; INOCA: myocardial ischemia with non-obstructive coronary arteries; MT: medical treatment; PCI: percutaneous coronary intervention.

TABLES

Table 1. Baseline characteristics. Data are presented as median (IQR) or n (%).

Characteristics	**N = 262**
Age, years	66 (58-73)
Female sex	113 (43.1)
Hypertension	166 (63.3)
Dyslipidemia	178 (67.9)
Diabetes	80 (30.5)
Insulin dependent	14 (17.5)
Active smoker	45 (17.2)
Former smoker	80 (30.5)
Body mass index, kg/m²	27.7 (25-30)
Family history of CAD	19 (7.2)
Peripheral vascular disease	12 (4.6)
Chronic kidney disease	13 (4.9)
Previous MI	40 (15.3)
Previous PCI	48 (18.3)
Previous ICA	93 (35.5)
Symptoms	**N = 262**
Exertional angina	157 (60)
I	14 (8.9)
II	118 (75.1)
III	25 (15.9)
Episodes of angina at rest	41 (15.6)
Atypical chest pain	46 (17.5)
Dyspnea	43 (16.4)
Symptom assessment	**N = 216**
SAQ - Physical limitation	73.3 (60.0-88.1)
SAQ - Angina stability	50.0 (33.3-66.7)
SAQ - Angina frequency	75.0 (66.7-83.3)
SAQ - Treatment satisfaction	81 (66.7-90.5)
SAQ - Quality of life	53.3 (41.7-66.7)
SAQ - Overall score	71.7 (62-78.8)
Complementary tests	**N = 262**
LVEF on TTE, %	60 (60-60)
Exercise ECG test	102 (38.9)
Positive result	71 (69.6)
Stress echocardiography	42 (16)
Positive result	25 (59.5)
SPECT	30 (11.4)
Positive result	22 (73.3)
CCTA	45 (17.2)

Abbreviations: CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; CCTA: coronary computed tomography angiography; ECG: electrocardiography; ICA: invasive coronary angiography; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MRI: magnetic resonance imaging; PCI: percutaneous coronary intervention; SAQ: Seattle Angina Questionnaire; SPECT: single-photon emission computed tomography; TTE: transthoracic echocardiography

Table 2. Assessment of the cause of myocardial ischemia.

Overall	**N = 262**
Angiographic severe stenoses	**N = 80**
Coronary physiology	**N = 182**
Pd/Pa	0.95 (0.93-0.97)
RFR	0.93 (0.9-0.95)
FFR	0.90 (0.86-0.93)
Patients with ischemic coronary intermediate stenoses	*N = 35*
RFR	0.84 (0.83-0.87)
FFR	0.73 (0.71-0.76)
Patients without coronary stenoses or non-ischemic intermediate stenoses (according to RFR/FFR values)	*N = 147*
RFR	0.93 (0.92-0.95)
FFR	0.91 (0.88-0.93)
CFR	2.8 (2.1-4.3)
IMR	16 (12-25)
Patients with coronary stenoses	*N = 74*
RFR	0.92 (0.87-0.95)
FFR	0.87 (0.81-0.9)
Patients without coronary stenoses	*N = 108*
RFR	0.93 (0.92-0.96)
FFR	0.92 (0.89-0.94)
Acetylcholine test	**N = 144**
Chest pain (similar to patient's previous symptoms)	89 (63.5)
ECG changes	74 (52.8)
Epicardial spasm	45 (32.1)
Functional coronary angiography	**N = 182**
QFR	0.97 (0.89-0.99)
Patients with coronary stenoses	*N = 74*
QFR	0.89 (0.78-0.96)
Patients without coronary stenoses or with non-ischemic stenoses	*N = 147*
Angio-IMR	22 (19-29.75)
3D-QCA	**N = 182**
Vessel length (mm)	57.3 (53.1-66.7)
Reference diameter (mm)	2.6 (2.3-2.9)
%DS	27.8 (19-36.2)
MLD (mm)	1.8 (1.5-2.2)

Abbreviations: %DS: percentage diameter stenosis; Angio-IMR: angiography-derived index of coronary microcirculatory resistance; CFR: coronary flow reserve; IMR: index of coronary microcirculatory resistance; FFR: fractional flow reserve; MLD: minimum lumen diameter; N = number of patiens; Pa: aortic pressure; Pd: distal pressure; RFR: resting full-cycle ratio; QFR: quantitative flow ratio; 3D-QCA: three dimensional quantitative coronary analysis.

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SUPPLEMENTARY MATERIAL

Supplementary Appendix 1. Derivation of contrast Angio-IMR (cAngio-IMR) (1).

$$IMR = (Pd * Tmn)_{hyp}$$

$$cAngio\text{-}IMR = (Pa_{rest} - [0.1 * Pa_{rest}]) * QFR * (L / V)$$

$$Pd_{hyp} = Pa_{hyp} * FFR$$

$$Tmn \approx L / V$$

$$QFR \approx FFR$$

$$Pa_{hyp} \approx Pa_{rest} - (0.1 * Pa_{rest})$$

Abbreviations: Angio-IMR: angiography-derived index of coronary microcirculatory resistance, LAD: left anterior descending artery; LCX: left circumflex artery; QFR: quantitative flow ratio; RCA: right coronary artery.L = vessel length analyzed with QFR; Pa = mean aortic pressure; Pd = mean intracoronary distal pressure; V = flow velocity from frame counting analysis; Tmn = mean transit time.

Supplementary Appendix 2. Recommendations for angiogram acquisition aimed to calculate QFR and Angio-IMR (2).

A. Selecting View Angles Based on Target Coronary Vessel.
Refer to **Supplementary Table 1** for recommended viewing angles.

B. General Guidelines for Optimal Image Quality
- Administer intracoronary nitroglycerin as early as possible.*
- Use a frame rate of at least 15 frames per second.
- Opt for a 5F or 6F catheter.
- Ensure the catheter is filled with contrast before injection.*
- Verify that the catheter is properly engaged to prevent contrast leakage.*
- When manually injecting contrast, apply a steady and continuous injection for three cardiac cycles.*
- Maintain a stable table position during image acquisition (avoid panning).
- Minimize excessive zooming to ensure a broader field of view.

C. Guidelines for 3D Vessel Reconstruction
- Avoid analyzing vessels with ostial lesions that prevent accurate measurement of the proximal reference diameter.
- Select views that minimize overlap and foreshortening.
- If no significant stenosis is present in the left main, position the starting point for vessel segmentation at the proximal LAD or LCX.
- If no distal target stenosis exists, avoid setting the landing zone for QFR segmentation too distally, particularly in the LAD and RCA.

D. Frame Counting for Angio-IMR Analysis
- Assess contrast movement across the vessel in both views, choosing the one where the contrast bolus front is clearly visible.
- Identify the frame where the contrast bolus enters the segment of interest.
- Select the frame where the bolus reaches the end of the segment.
- Repeat the process in the second view and use the one with the higher flow velocity for final analysis.
- Important: Avoid frame counting in views in which dye gets stuck across frames.

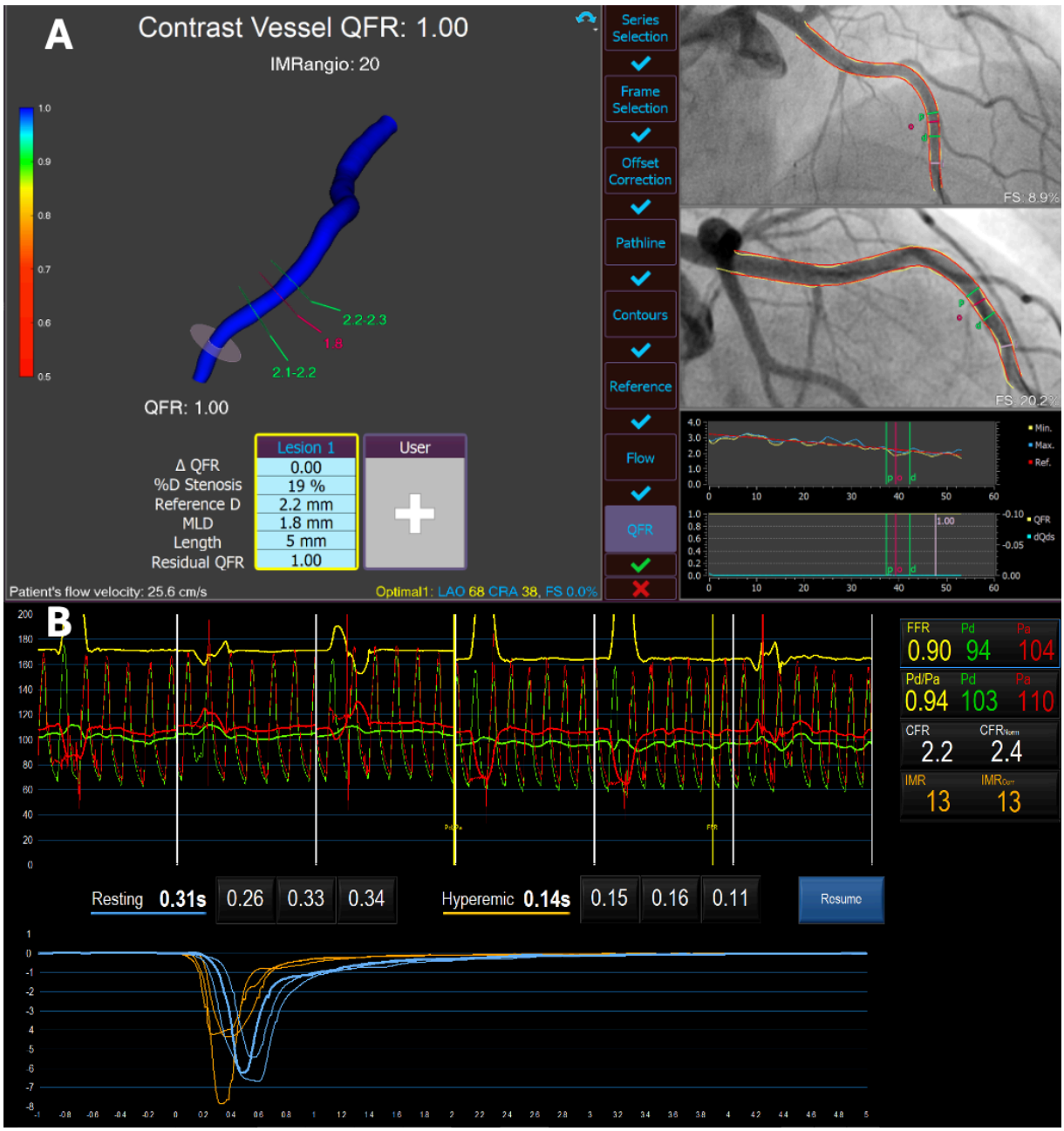
Abbreviations: Angio-IMR: angiography-derived index of coronary microcirculatory resistance, LAD: left anterior descending artery; LCX: left circumflex artery; QFR: quantitative flow ratio; RCA: right coronary artery.

Supplementary Table 1. Recommended angiography views for QFR analysis according to the target vessel (2).

Vessel / Bifurcation	**First view**	**Second view**
LM + LAD/LCX	RAO 20, Caudal 45	AP, caudal 10
LAD/Diag	AP, cranial 45	RAO 35, cranial 20
LCX / OM	LAO 10, caudal 25	RAO 25, Caudal 25
Proximal + mid RCA	LAO 45, Caudal 0	AP, caudal 0
PLA / PDA	LAO 45, Caudal 0	LAO 30, Caudal 30

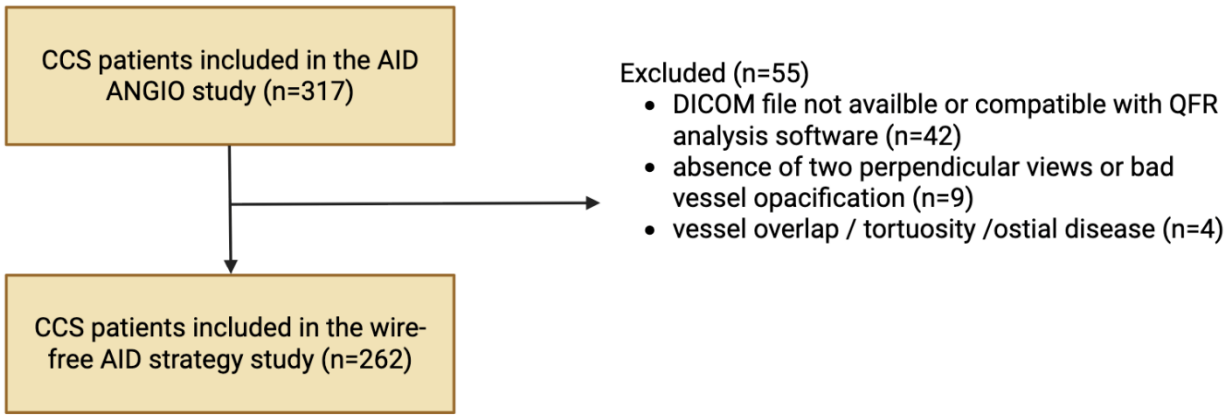
Abbreviations: Diag: diagonal; PDA: posterior descending artery; LAD: left anterior descending artery; LCX: left circumflex artery; OM: obtuse marginal; PLA: posterolateral artery; QFR: quantitative flow ratio; RCA: right coronary artery

Supplementary Figure 1. Example of Angio-IMR analysis (A) compared to the true invasive IMR calculated with bolus thermodilution (B).



Abbreviations: Angio-IMR: angiography-derived index of coronary microcirculatory resistance, CFR: coronary flow reserve; IMR: index of coronary microcirculatory resistance; FFR: fractional flow reserve; QFR: quantitative flow ratio; Pa = mean aortic pressure; Pd = mean intracoronary distal pressure.

Supplementary Figure 2. Causes for patients' exclusion from the wire-free AID strategy study.



Abbreviations: AID: advanced invasive diagnosis; CCS: chronic coronary syndrome; QFR: quantitative flow ratio.

Supplementary Table 2. Enrolment periods at each participating centre.

Centre	**Period**
Hospital Clínico San Carlos	June 2022 – December 2023 (n=131)
Hospital Universitario Severo Ochoa	September 2022 – December 2023 (n=33)
Hospital Universitario Príncipe de Asturias	October 2022 – December 2023 (n=61)
Hospital Universitario de Fuenlabrada	November 2022 – December 2023 (n=37)

Supplementary Table 3. Comparison of baseline characteristics between included and excluded patients. Data are presented as median (IQR) or n (%).

Characteristics	**Included N = 262**	**Excluded N=55**	**P value**
Age, years	66 (58-73)	69 (59.5-75.5)	0.13
Female sex	113 (43.1)	27 (49.1)	0.42
Hypertension	166 (63.3)	31 (56.4)	0.33
Dyslipidemia	178 (67.9)	30 (54.5)	0.06
Diabetes	80 (30.5)	12 (21.8)	0.19
Insulin dependent	14 (17.5)	1 (8.3)	0.68
Active smoker	45 (17.2)	4 (7.3)	0.07
Former smoker	80 (30.5)	23 (41.8)	0.10
Body mass index, kg/m²	27.7 (25-30)	26.9 (24.6-30.7)	0.71
Family history of CAD	19 (7.2)	4 (7.3)	1.00
Peripheral vascular disease	12 (4.6)	3 (5.5)	0.73
Chronic kidney disease	13 (4.9)	5 (9.1)	0.21
Previous MI	40 (15.3)	10 (18.2)	0.59
Previous PCI	48 (18.3)	9 (16.4)	0.73
Previous ICA	93 (35.5)	19 (34.5)	0.89
Symptoms	**N = 262**	**N = 55**	
Exertional angina	157 (60)	28 (51)	0.21
I	14 (8.9)	3 (10.7)	0.72
II	118 (75.1)	24 (85.7)	0.33

III	25 (15.9)	1 (3.5)	0.13
Episodes of angina at rest	41 (15.6)	6 (10.9)	0.37
Atypical chest pain	46 (17.5)	16 (29)	0.05*
Dyspnea	43 (16.4)	14 (25.4)	0.11
Symptom assessment	**N = 216**	**N = 49**	
SAQ - Physical limitation	73.3 (60.0-88.1)	77.8 (56.7-91.1)	0.83
SAQ - Angina stability	50 (33.3-66.7)	50 (33.3-66.7)	0.77
SAQ - Angina frequency	75 (66.7-83.3)	75 (66.7-83.3)	0.37
SAQ - Treatment satisfaction	81 (66.7-90.5)	81 (66.7-90.5)	0.82
SAQ - Quality of life	53.3 (41.7-66.7)	53.3 (40-60)	0.08
SAQ - Overall score	71.7 (62-78.8)	72.1 (58.9-81.5)	0.93
Complementary tests	**N = 262**	**N = 55**	
LVEF on TTE, %	60 (60-60)	60 (55-63.5)	0.27
Exercise ECG test	102 (38.9)	29 (52.7)	0.06
Positive result	71 (69.6)	20 (69)	0.95
Stress echocardiography	42 (16)	13 (23.6)	0.17
Positive result	25 (59.5)	11 (84.6)	0.18
SPECT	30 (11.4)	4 (7.3)	0.47
Positive result	22 (73.3)	3 (75)	1.0
CCTA	45 (17.2)	2 (3.6)	<0.01*

Abbreviations: CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; CCTA: coronary computed tomography angiography; ECG: electrocardiography; ICA: invasive coronary angiography; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MRI: magnetic resonance imaging; PCI: percutaneous coronary intervention; SAQ: Seattle Angina Questionnaire; SPECT: single-photon emission computed tomography; TTE: transthoracic echocardiography
**Statistically significant*

Supplementary Table 4. Characterization with coronary angiography alone of the 262 patients included.

Diagnostic group	**Characterization**	**N= 262**
Ischemic	Severe stenoses	80
	Severe + intermediate stenoses	18
Non-ischemic	Intermediate stenoses	56
	No stenoses	108

Supplementary Table 5. Characterization of significant coronary lesions in patients with obstructive CAD according to the wire-free AID strategy.

Significant coronary lesions	N=110
LM alone	2 (1.8%)
1-vessel disease*	52 (47.3%)
2-vessel disease*	24 (21.8%)
3-vessel disease*	14 (12.7%)
LM + 1-vessel disease	6 (5.4%)
LM + 2-vessel disease	7 (6.4%)
LM + 3-vessel disease	5 (4.5%)

**Except for LM*

Abbreviations: AID: advanced invasive diagnosis; CAD: coronary artery disease; LM: left main

Supplementary Table 6. Further details about discordance between the wire-free and wire-based AID strategies for the primary endpoint (diagnostic yield of wire-free strategy).

Cause of discordance	Total discordant cases (N=41)
CFR<2.0	16
Normal IMR / High Angio-IMR	21
Low RFR or FFR / Normal QFR	4

Abbreviations: Angio-IMR: angiography-derived index of coronary microcirculatory resistance; CFR: coronary flow reserve; IMR: index of coronary microcirculatory resistance; FFR: fractional flow reserve; N = number of patiens; RFR: resting full-cycle ratio; QFR: quantitative flow ratio.

Supplementary Table 7. Further details on the changes performed in the therapeutic plan according to the information obtained with the wire-free AID strategy (right) compared to coronary angiography alone (left).

Angiography alone	Wire-free AID	
From	**To**	**N=145**
PCI	No anti-ischemic treatment	6
PCI	PCI*	6
PCI	CABG	7
PCI	Medical treatment for obstructive CAD	7
PCI	Medical treatment for INOCA Vasomotor disorder CMD Mixed	4 1 2 1
CABG	CABG*	1
Medical treatment for obstructive CAD	Medical treatment for INOCA Vasomotor disorder	1 1

Medical treatment for obstructive CAD	PCI	1
Medical treatment for INOCA Vasomotor disorder CMD Mixed	No anti-ischemic treatment	28 10 13 5
Medical treatment for INOCA CMD	PCI	3 3
Medical treatment for INOCA Vasomotor disorder CMD	Medical treatment for obstructive CAD	2 1 1
Medical treatment for INOCA Vasomotor disorder CMD Mixed	Medical treatment for INOCA CMD Mixed Vasomotor disorder Mixed Vasomotor disorder CMD	69 8 5 20 19 12 5
No anti-ischemic treatment	Medical treatment for INOCA Vasomotor disorder CMD Mixed	10 5 3 2

**Change in the number of lesions to treat.*

Abbreviations: AID: advanced invasive diagnosis; CABG: coronary artery bypass graft; CAD: coronary artery disease; CMD: coronary microvascular dysfunction; INOCA: myocardial ischemia with non-obstructive coronary arteries; PCI: percutaneous coronary intervention.

Supplementary Table 8. Further details on the changes performed in the therapeutic plan according to the information obtained with the wire-free compared to wire-based AID strategies.

Wire-free AID	**Wire-based AID**	
From	**To**	**N=44**
PCI	No anti-ischemic treatment	1
PCI	CABG*	1
Medical treatment for obstructive CAD	PCI	1
Medical treatment for INOCA CMD	No anti-ischemic treatment	7 7

Medical treatment for INOCA Vasomotor disorder Mixed	Medical treatment for INOCA Mixed Vasomotor disorder	23 9 14
No anti-ischemic treatment	PCI	3
No anti-ischemic treatment	Medical treatment for obstructive CAD	1
No anti-ischemic treatment	Medical treatment for INOCA CMD	7 7

**Change in the number of lesions to treat.*

Abbreviations: AID: advanced invasive diagnosis; CABG: coronary artery bypass graft; CAD: coronary artery disease; CMD: coronary microvascular dysfunction; INOCA: myocardial ischemia with non-obstructive coronary arteries; PCI: percutaneous coronary intervention.

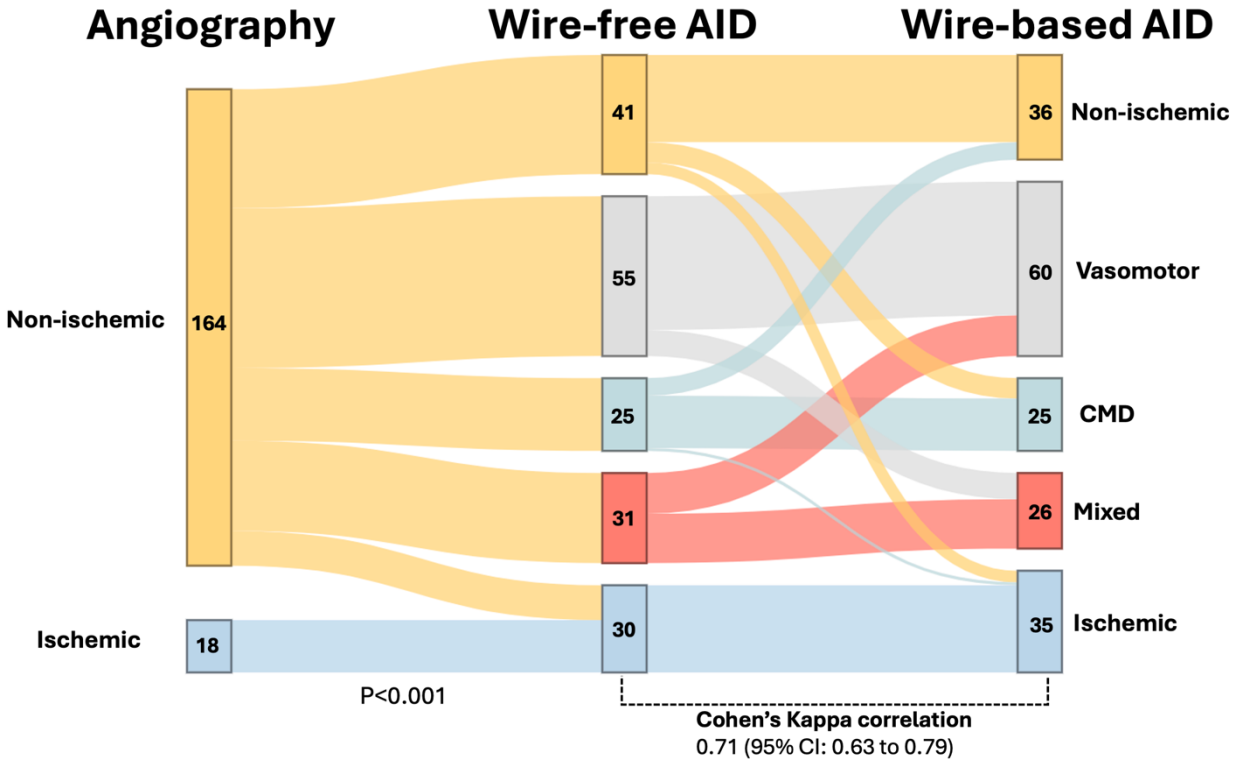
Supplementary Table 9. Cases where the change in therapeutic plan between wire-free AID strategy and angiography was due to a misclassification of the wire-free strategy, as compared to the standard of reference (wire-based AID).

Angiography	**Wire-free AID**	**Wire-based AID**	**N=11**
PCI	No anti-ischemic treatment	PCI	2
PCI	Medical treatment for obstructive CAD*	PCI	1
Medical treatment for INOCA Vasomotor disorder Mixed	Medical treatment for INOCA Mixed Vasomotor disorder	Medical treatment for INOCA Vasomotor disorder Mixed	5 2 3
Medical treatment for INOCA	No anti-ischemic treatment	Medical treatment for INOCA	3

**due to negative QFR*

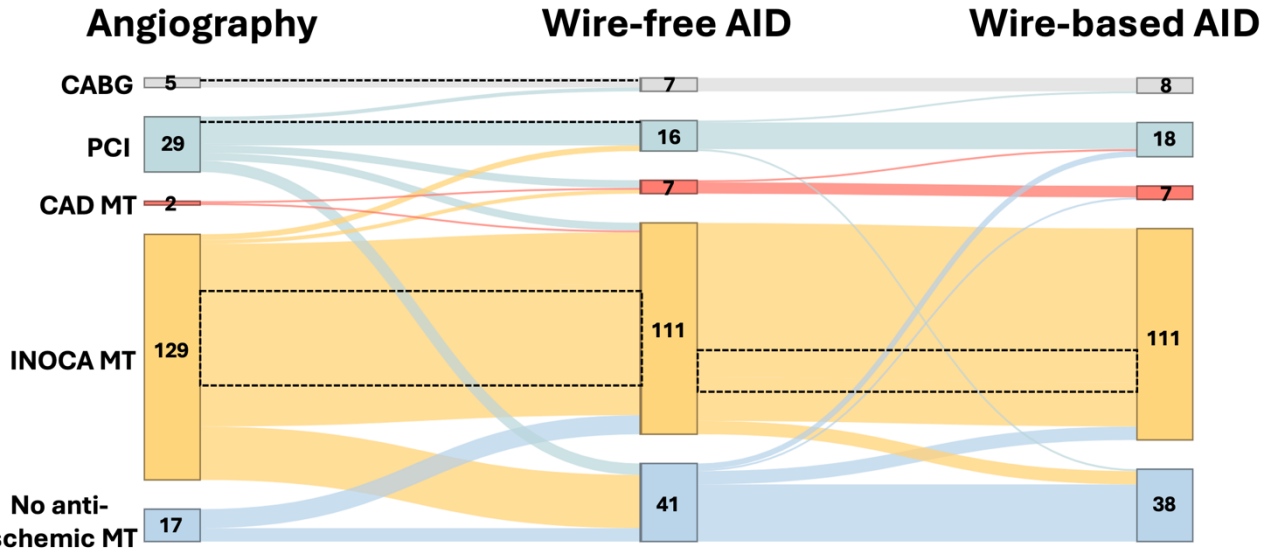
Abbreviations: AID: advanced invasive diagnosis; CAD: coronary artery disease; INOCA: myocardial ischemia with non-obstructive coronary arteries; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio.

Supplementary Figure 3. Diagnostic yield of coronary angiography alone, wire-free and wire-based AID strategies, after excluding patients with angiographic stenosis ≥90%.



Abbreviations: AID: advanced invasive diagnosis; CMD: coronary microvascular dysfunction.

Supplementary Figure 4. Impact of the wire-free AID strategy on clinical decision-making compared to wire-based AID strategy and coronary angiography alone, after excluding patients with angiographic stenosis ≥90%.



Dashed lines indicate intragroup changes due to difference in treatment of INOCA endotypes / number of epicardial lesions to treat.

Abbreviations: AID: advanced invasive diagnosis; CABG: coronary artery bypass graft; CAD: coronary artery disease; INOCA: myocardial ischemia with non-obstructive coronary arteries; MT: medical treatment; PCI: percutaneous coronary intervention

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Chapter 4.

Predictors of side branch compromise during stepwise provisional stenting: the OCT-Bifurcation score

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) using a stepwise provisional approach is the default strategy for the treatment of most coronary bifurcation lesions. However, side branch (SB) compromise after main vessel (MV) stenting remains unpredictable based on angiography alone. This study aimed to identify optical coherence tomography (OCT)-based predictors of SB compromise and to develop a predictive OCT-Bifurcation score.

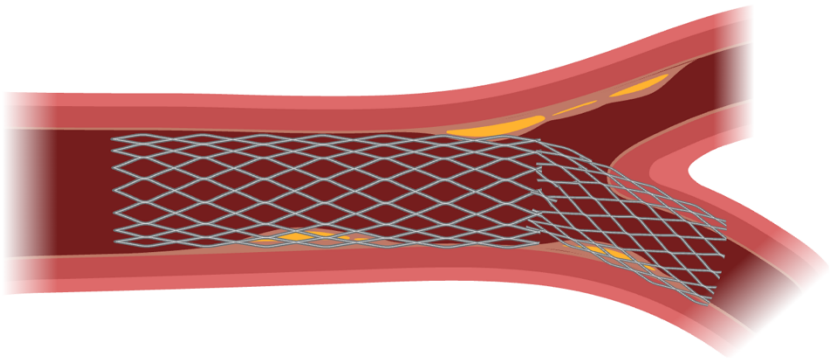
Methods: The OCT-Bifurcation score was developed in a derivation cohort of 105 coronary bifurcation lesions and validated in an external cohort of 101 lesions. SB compromise was defined as angiographic SB ostial diameter stenosis ≥90% after MV stenting.

Results: In the derivation cohort, multivariate analysis (adjusted for SB stenosis >50%, SB pre-dilation, and stent-to-artery ratio) identified three independent predictors: 1) calcified plaque at the SB side (odds ratio [OR] 3.9 per segment; 95% confidence interval [CI], 1.8–8.4; p=0.001); 2) carina length ≥1 mm (OR 4.5; 95% CI, 1.3–15.7; p=0.016); and 3) SB orifice length <1.7 mm (OR 6.1; 95% CI, 1.7–22.2; p=0.006). A score from 0 to 4 was assigned based on these parameters. A score ≥2 predicted SB compromise with 83% sensitivity and 83% specificity (AUC 0.852; 95% CI, 0.773–0.931). These findings were confirmed in the validation cohort (AUC 0.878).

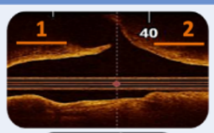
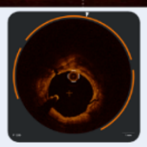
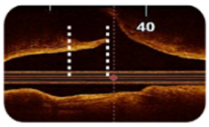
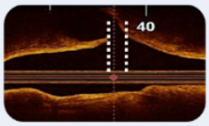
Conclusions: In patients undergoing provisional stenting, a pre-PCI OCT score was able to identify SB compromise after MV stenting. Coronary bifurcation lesions with calcified plaque at the SB side, carina length≥1 mm, and SB orifice length<1.7 mm may be at risk of SB compromise.

GRAPHIC ABSTRACT

Prediction of SB compromise during provisional stenting



OCT-Bifurcation score

OCT features	Example	Cut-off	Score
Calcification at the SB side		1 segment	+1
		2 segments	+2
Carina length		≥ 1 mm	+1
SB orifice length		< 1.7 mm	+1
		Total OCT-Bifurcation score	0 – 4

INTRODUCTION

Coronary bifurcation lesions account for approximately 15-20% of all percutaneous coronary interventions (PCI) and are considered a hallmark of procedural complexity (1). The stepwise provisional stenting approach is the default strategy for the treatment of most coronary bifurcation lesions, as it simplifies the procedural PCI pathway while providing optimal procedural and long-term outcomes (2–5). However, side branch (SB) compromise can occur after main vessel (MV) stenting (6), and identifying which coronary bifurcation lesions are at risk for SB compromise is sometimes unpredictable - particularly when relying solely on angiographic findings.

Recent international guidelines emphasize the importance of intracoronary imaging use in complex scenarios, including bifurcation lesions, recommending its use for PCI-guidance with a class IA recommendation (7,8). Optical coherence tomography (OCT) is an intracoronary imaging modality that, with its high axial resolution (<20 micron), provides detailed insights for procedural planning (9). OCT enables a detailed evaluation of vessel morphology and sizing, allowing accurate stent deployment and post-PCI optimization, making it particularly valuable in the context of bifurcation PCI (10,11).

The aim of the present study was to determine the predictors of SB compromise after MV provisional bifurcation stenting using OCT imaging, and to develop an OCT-based bifurcation scoring system to predict SB compromise.

METHODS

This was a retrospective, observational study aimed to develop and validate an OCT score to predict SB compromise after stepwise provisional stenting in coronary bifurcation lesions. This study consisted of two independent cohorts: the derivation cohort (cohort A) was used to develop the OCT-Bifurcation score, and the validation cohort (cohort B) was used to externally validate the predictability of this OCT-Bifurcation score on SB compromise (**Figure 1**).

We included all consecutive patients who underwent intracoronary imaging with OCT before PCI of an atherosclerotic lesion involving a bifurcation site at IRCCS Ospedale Policlinico San Martino, Genova, Italy from January 2021 to September 2024 (derivation cohort - cohort A) and at Hospital Clinico San Carlos, Madrid, Spain from March 2019 to October 2024 (validation cohort - cohort B). The study was conducted according to the Declaration of Helsinki.

The main inclusion criteria were: 1) presence of a bifurcation lesion (within 5 mm of the bifurcation site) treated with PCI using drug-eluting stent (DES) via a stepwise provisional approach; 2) pre-PCI OCT assessment of the MV of analyzable quality; 3) availability of at least two angiographic projections (>30° apart) at baseline and after stenting (before any optimization technique such as kissing balloon inflation) to enable quantitative coronary angiography (QCA) analysis of SB stenosis; 4) SB diameter greater than 2.00 mm; 5) in cases where the MV lesion involved multiple bifurcations, more than one bifurcation was analyzed only if the distance between them was >15 mm, otherwise the bifurcation involving the greater SB diameter was selected. Patients with in-stent restenosis, previous coronary artery bypass grafting of the target lesion, chronic total occlusion, or those who underwent elective SB stenting prior MV stenting (e.g. during double kissing (DK)-crush technique) were excluded.

Coronary angiography acquisition and analysis

Angiograms were obtained at baseline before stent deployment and were analyzed using a computer-based system dedicated (CAAS 8.5.1 Pie Medical, Imaging BV, Maastricht, The Netherlands) by two independent investigators who were blinded to clinical and OCT information, a consensus reading was achieved with a third senior investigator.

Quantitative angiographic measurements of the 4 segments of the bifurcation lesion were obtained: the proximal MV segment, the distal MV segment, the SB segment, and the bifurcation core segment. The bifurcation angle (the angle between the distal MV and the SB) from the analysis system was also obtained.

SB compromise was defined as an angiographic diameter stenosis ≥90% at the SB ostium immediately after MV stent deployment or post-dilation. In cases where significant SB stenosis was present before PCI, pre-dilation was performed. If pre-dilation was successful (i.e., resulted in no residual significant stenosis), SB compromise was defined as the reappearance of significant (≥90%) stenosis at the SB ostium following MV stent implantation.

OCT imaging acquisition and analysis

OCT was performed using frequency-domain OCT (ILUMIEN™ C7-XR™, OPTIS™ or OPTIS NEXT™), and Dragonfly™ Duo, OPTIS or OPSTAR catheter (Abbott Vascular, Santa Clara, CA, USA). Pre-stent OCT was performed before intervention and stent size selection was based on OCT measurements made in the segment distal to the bifurcation; however, if the OCT catheter did not cross the lesion, OCT was performed immediately after dilation using a small balloon.

OCT image analysis was performed offline using a proprietary software (LightLab Imaging) by two independent expert investigators who were blinded to clinical data; in case of discordance, a consensus reading was achieved with a third senior investigator. All OCT analyses were performed in accordance with the joint consensus on the use of OCT in coronary bifurcation lesions endorsed by the European and Japanese bifurcation clubs (1).

OCT analysis was performed to assess: 1) plaque morphology (fibrous, lipid-rich, thin-cap fibroatheroma [TCFA], calcified, thrombus); 2) plaque distribution across the bifurcation (5 segments: proximal MV, SB side; proximal MV, opposite to SB; bifurcation site; distal MV, SB side [flow divider]; distal MV, opposite to SB); 3) carina length (in mm); 4) bifurcation angle (in degrees, °); 5) minimum lumen area (in mm^2); 6) SB ostium diameter (in mm); 7) SB orifice length (i.e., distance in mm between proximal branching point and carina tip).

Details on OCT image acquisition and analysis are reported in the **Figure 1**.

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages, and were compared using the $\chi 2$ or Fisher's exact test. After assessing data distribution by the Kolmogorov-Smirnov test, continuous variables were expressed as mean±standard deviation or median (interquartile range), and compared using the independent samples Student's t test or Mann–Whitney U test. Logistic regression analysis was used to define the predictors of SB compromise. All the variables exhibiting a $p<0.1$ at univariate analysis were entered in a backward, stepwise multivariate model (criterion for retention: $p<0.1$) in order to determine the independent predictors. The model was adjusted for potential cofounders. Receiver operating characteristics (ROC) with area under the curve (AUC) were used to test predictive value of risk score model, which was externally validated. All tests were two-sided. A $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (v.21.0, Inc, Chicago, IL).

RESULTS

Study participants

A flowchart of the patient entry into the study is shown in **Figure 2**, reasons and numbers for exclusion are provided in **Supplementary Table 1**.

In the derivation cohort (cohort A), 105 coronary bifurcation lesions were included from 81 consecutive patients (chronic coronary syndrome [CCS], n=43; acute coronary syndrome [ACS], n=38). The validation cohort (cohort B) included 101 bifurcation lesions from 93 consecutive patients (CCS, n=43; ACS, n=50).

Baseline characteristics of both cohorts are reported in **Table 1**.

Angiographic and procedural characteristics

Left anterior descending (LAD) artery-diagonal branch bifurcation was involved in 58% of cases, and left main stem bifurcation in 27% of cases. A Medina 1.1.1 lesion was present in 47 cases (44.8%), and SB pre-dilation was performed in 26 cases (25%). SB compromise after MV stenting was observed in 42 cases (40%) (**Table 2**).

OCT analysis

SB compromise was significantly associated with plaque distribution in specific regions of the MV. Plaques on the SB side of the proximal MV were more frequent in the SB compromise group (85.7% vs. 23.8%, $p < 0.001$), as well as plaques at the distal MV flow divider (61.9% vs. 27.0%, $p < 0.001$).

Geometric differences were also observed: the SB compromise group had a shorter SB orifice length (1.4 mm vs. 2.0 mm, $p < 0.001$), smaller SB ostium diameter (1.8 mm vs. 2.1 mm, $p < 0.001$), and longer carina length (0.9 mm vs. 0.7 mm, $p = 0.027$) (**Table 3**).

Additionally, increased SB compromise was progressively observed with the number of segments involved (from 0 to 2) in patients presenting with lipid-rich plaque, TCFA and calcification (**Supplementary Figure 1**).

Score development

In univariate analysis, each additional SB-side segment involved was associated with higher odds of SB compromise for calcification (OR 3.9; 95% CI, 2.2–7.0; p < 0.001), fibrous plaque (OR 2.9; 95% CI, 1.6–5.1; p < 0.001), and lipid-rich plaque (OR 1.7; 95% CI, 1.0–2.8; p = 0.047) (**Table 4**). Anatomic features associated with SB compromise included carina length ≥ 1 mm (OR 3.5; 95% CI, 1.5–8.3; p = 0.004), SB orifice length < 1.7 mm (OR 5.6; 95% CI, 2.4–13.0; p < 0.001), and SB ostium diameter < 1.9 mm (OR 4.1; 95% CI, 1.8–9.3; p = 0.001) (**Table 4**).

Multivariate logistic regression analysis, adjusted for SB angiographic stenosis >50%, SB pre-dilation, and stent-to-artery ratio, identified three independent predictors of SB compromise: the presence of calcified plaque at the SB side (OR 3.9 per involved segment; 95% CI, 1.8–8.4, p=0.001), carina length ≥ 1 mm (OR 4.5, 95% CI, 1.3–15.7, p=0.016), and SB orifice length < 1.7 mm (OR 6.1, 95% CI, 1.7–22.2, p=0.006) (**Table 5**). Based on these predictors, an OCT-Bifurcation Score (range 0–4) was developed: 1 point for each SB-side segment containing calcified plaque (from 0 [no segment] to 2 [both segments]); 1 point for carina length ≥ 1 mm; and 1 point for SB orifice length < 1.7 mm (**Figure 3**). **Figure 3, Panel A** shows SB compromise prevalence according to increasing OCT-Bifurcation score. An OCT-Bifurcation score ≥ 2 predicted SB compromise with a sensitivity of 83% and a specificity of 83% (AUC, 0.852; 95% CI, 0.773-0.931; p<0.001) (**Figure 3, Panel B**).

Validation of the OCT-Bifurcation score

In the validation cohort, LAD-diagonal branch bifurcation was involved in 73% of cases, and left main stem bifurcation in 18% of cases. A Medina 1.1.1 lesion was present in 27 cases (26.7%), and SB pre-dilation was performed in 8 cases (7.9%). SB compromise after MV stenting was observed in 41 cases (41%). **Figure 4, Panel A** shows SB compromise prevalence according to increasing OCT-Bifurcation score pointing, showing similar results to the cohort A. An OCT-Bifurcation score ≥ 2 predicted SB compromise with a sensitivity of 85% and a specificity of 82% (AUC, 0.878; 95% CI, 0.806-0.950; p<0.001) (**Figure 4, Panel B**).

DISCUSSION

In the present study, we developed and validated an OCT-derived scoring system—termed the OCT-Bifurcation score—designed to predict SB compromise following MV stenting in coronary bifurcation lesions treated with a stepwise provisional approach. Our findings demonstrate that specific pre-PCI morphological features visualized by OCT of the MV—namely the presence of calcified plaque at the SB side, carina length ≥ 1 mm, and SB orifice length < 1.7 mm—were independently associated with a higher risk of SB compromise after MV stenting. The OCT-Bifurcation score, derived from these parameters, achieved a good sensitivity and specificity for identifying patients at risk of SB compromise. Notably, these findings were confirmed in an independent validation cohort, highlighting the reproducibility and robustness of the OCT-Bifurcation score.

SB compromise is a common and often unpredictable event during provisional stenting and has been associated with worse clinical outcomes, including increased rates of cardiac death and myocardial infarction (6). Angiography, although widely used, is limited by its two-dimensional projection, subjectivity, and inability to characterize plaque distribution or vessel geometry accurately (12,13). In contrast, OCT provides high-resolution cross-sectional imaging that enables a more detailed understanding of bifurcation anatomy (1). While prior studies have identified factors such as carina shift and plaque burden at the SB ostium as contributors to SB occlusion (14–16), few have integrated these features into a structured, imaging-based scoring tool. Angiographic models, such as the RESOLVE score (17), have attempted to quantify SB occlusion risk using QCA-derived metrics. However, QCA lacks the spatial resolution necessary to assess key structural features like plaque morphology or carina configuration—parameters that have emerged as central predictors in our OCT-based model. As intracoronary imaging gains traction, especially in complex cases as recommended by current guidelines (7,8), an OCT-based approach to bifurcation risk assessment may provide a

more direct and mechanistically grounded assessment of SB compromise risk, further emphasizing the need for personalized medicine based on the optimized use of available tools.

Previous intracoronary imaging studies have explored either bifurcation geometry or plaque morphology as predictors of SB compromise following MV stenting. Some models focused solely on geometric parameters derived from 3D-OCT reconstructions—often complex and not routinely accessible in daily practice (18). Others examined qualitative plaque features without integrating anatomical geometry (19,20). In contrast, the OCT-Bifurcation score combines both geometric and morphologic parameters, all of which can be readily assessed using standard OCT consoles without the need for external software or 3D reconstruction and can be assessed through a single OCT pullback in the MV. This represents a significant advantage in routine practice, where contrast volume, procedural time, and guide-catheter stability often limit OCT imaging of the SB (21).

Importantly, the presence of calcification at the side-branch side has emerged as a strong predictor of SB compromise, with an OR 3.9 per involved segment. This OCT parameter was therefore incorporated into the OCT-Bifurcation score, assigning one point for the presence of calcifications at the SB side, at the level of the MV or of the flow divider. While prior studies have not investigated the impact of bifurcation calcifications in a comprehensive manner (20), our findings highlight its relevance during provisional stepwise stenting. The mechanistic rationale is supported by simulation data showing that the presence of calcified plaques are associated with greater SB lumen compromise by inducing an elliptic lumen cross-section and reducing the lumen area (22).

Alongside calcifications, the two geometric parameters—carina length and SB orifice length—reflect distinct yet complementary mechanisms of SB compromise. A long carina length (≥ 1 mm) represents a protruding anatomical structure between the MV and SB lumens, which, when displaced during MV stent expansion, shifts toward the SB ostium and narrows its lumen—a process known as carina shift (14,23). Unlike plaque shift, which involves atheromatous material protruding into the SB ostium, carina shift is a dynamic geometric alteration driven by stent expansion and vessel

remodeling, causing the flow divider (carina) to move toward the SB (22), resulting in luminal narrowing, particularly when the carina is elongated or with a spiky morphology (15). Conversely, a short SB orifice length (<1.7 mm) identifies bifurcations with a narrow side-branch entry that lacks the geometric compliance needed to accommodate plaque redistribution or carina displacement (1). This configuration is more prone to collapse under mechanical stress during MV stenting (24).

This study has important clinical implications, potentially enhancing procedural planning and risk stratification in bifurcation PCI. Identifying high-risk anatomical configurations prior to stent deployment could allow interventional cardiologists to anticipate complications and adapt the procedural strategy accordingly, such as by opting for more aggressive plaque preparation, further SB protection strategies (e.g., jailed balloon or microcatheter techniques), or an upfront two-stent technique (25).

Limitations

Nonetheless, some limitations should be acknowledged. First, this was a retrospective study, and prospective validation in larger, multicenter populations will be necessary to confirm these findings and assess the OCT score's impact on clinical decision-making and outcomes. Second, the assessment of SB compromise was based on angiographic criteria rather than functional measurements such as fractional flow reserve, which may better reflect the physiological relevance of SB involvement (27). Lastly, the long-term clinical impact of using the OCT-Bifurcation score in guiding PCI strategy remains to be established.

Future directions

Future directions should include prospective, randomized studies to evaluate whether use of the OCT-Bifurcation score can guide real-time decision-making and improve clinical outcomes. Importantly, advances in imaging software and artificial intelligence (AI) are rapidly expanding the feasibility of automated analysis in the catheterization laboratory. For example, the Ultreon™ 2.0

software (Abbott Vascular), currently available in commercial OCT platforms, already incorporates AI-driven algorithms capable of automatically detecting and quantifying key features such as calcifications, lumen contours and stent-related metrics. This functionality not only enhances efficiency and standardization of image interpretation but also might allow the real-time and automated computation of risk scores. Given that all three components of the OCT-Bifurcation score—calcification at the SB side, carina length, and SB orifice length—are directly measurable from OCT pullbacks and two of them (e.g., calcification and lumen morphology) are already automatically detected by the Ultreon™ 2.0 software, further developments could enable full automation of this risk score. Such integration would facilitate broader adoption regardless of operator experience or case volume (21).

CONCLUSIONS

In patients undergoing PCI of coronary bifurcation lesions using stepwise provisional approach, pre-PCI OCT imaging of the MV was able to identify independent morphological predictors of SB compromise after MV stenting. A newly developed OCT-Bifurcation scoring system (based on the presence of calcified plaque at the SB side, carina length ≥ 1 mm, and SB orifice length < 1.7 mm) was able to predict SB compromise with good sensitivity and specificity.

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TABLES

Table 1. Baseline characteristics in both derivation and validation cohorts.

	Derivation cohort (n=81)	**Validation cohort (n=93)**
Male sex	69 (85.2%)	66 (71.0%)
Age, years	69 (62 – 78)	69 (59 – 78)
Cardiovascular risk factors		
Hypertension	58 (71.6%)	68 (73.1%)
Dyslipidemia	49 (60.5%)	59 (63.4%)
Diabetes	23 (28.4%)	27 (29.0%)
Current smoking	23 (21.9%)	24 (25.8%)
Clinical presentation		
Chronic coronary syndrome	39 (48.1%)	43 (46.2%)
Acute coronary syndrome	42 (51.9%)	50 (53.8%)
Prior MI	19 (23.5%)	15 (16.1%)
Prior PCI	23 (28.4%)	41 (44.1%)
Prior CABG	3 (3.7%)	0 (0.0%)
LVEF, %	55 (45 – 55)	60 (50 – 60)
eGFR, ml/min/1.73 m^2	75 (55 – 91)	81 (70 – 88)

Abbreviations: CABG, coronary artery by-pass graft; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention

Table 2. Angiographic analysis.

	Overall (n=105)	No SB compromise (n=63)	SB compromise (n=42)	P value
Target bifurcation				0.863
Left main stem	28 (26.7%)	22 (34.9%)	6 (14.3%)	
LAD-diagonal	61 (58.0%)	33 (52.4%)	28 (66.7%)	
LCx-OM	13 (12.4%)	6 (9.5%)	7 (16.7%)	
RCA-PDA-PLA	3 (2.9%)	2 (3.2%)	1 (2.4%)	
True bifurcation	55 (52.4%)	24 (38.1%)	31 (73.8%)	<0.001
Medina 1.1.1	47 (44.8%)	19 (30.2%)	28 (66.7%)	<0.001
Bifurcation angle, °	65.8 ± 26.6	70.6 ± 27.1	58.7 ± 24.3	0.023
Main vessel measures				
Proximal reference diameter, mm	3.5 ± 0.7	3.6 ± 0.7	3.4 ± 0.6	0.113
Distal reference diameter, mm	2.8 ± 0.5	2.8 ± 0.5	2.8 ± 0.5	0.842
Diameter stenosis, %	78.5 ± 13.8	78.2 ± 13.4	79.0 ± 14.4	0.809
Main vessel stent				
Diameter, mm	3.3 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	0.411
Length, mm	32.2 ± 8.9	32.8 ± 9.2	31.2 ± 8.5	0.356
Stent inflation pressure (atm)	12.2 ± 1.6	12.0 ± 1.0	12.4 ± 2.2	0.280
Stent-to-artery ratio	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.1	0.789
Side branch diameter stenosis, %	43.7 ± 28.6	32.9 ± 25.4	60.1 ± 25.4	<0.001
SB pre-dilation	26 (24.8%)	16 (25.4%)	10 (23.8%)	0.854

Abbreviations: LAD, left anterior descending; LCx, left cirumflex; RCA, right coronary artery; PDA, posterior descending artery; PLA, postero-lateral artery; SB, side branch

Table 3. OCT analysis.

	Overall (n=105)	No SB compromise (n=63)	SB compromise (n=42)	P value
Plaque distribution				
Proximal MV, SB side	51 (48.6%)	15 (23.8%)	36 (85.7%)	<0.001
Proximal MV, opposite to SB	67 (63.8%)	44 (69.8%)	23 (54.8%)	0.148
Bifurcation site	88 (83.8%)	50 (79.4%)	38 (90.5%)	0.178
Distal MV, Flow divider	43 (41.0%)	17 (27.0%)	26 (61.9%)	<0.001
Distal MV, opposite to SB	76 (72.4%)	49 (77.8%)	27 (64.3%)	0.181
Plaque type				
Lipid-rich plaque	53 (50.5%)	34 (54.0%)	19 (45.2%)	0.381
TCFA	15 (14.3%)	6 (9.5%)	9 (21.4%)	0.088
Calcifications	78 (74.3%)	46 (73.0%)	32 (76.2%)	0.715
Thrombus	16 (15.2%)	11 (17.5%)	5 (11.9%)	0.438
Bifurcation measures				
Carina length, mm	0.8 (0.4 – 1.2)	0.7 (0.4 – 0.9)	0.9 (0.6 – 1.3)	0.027
SB orifice length, mm	1.8 (1.3 – 2.4)	2.0 (1.5 – 2.6)	1.4 (1.0 – 2.0)	<0.001
SB ostium diameter, mm	2.0 (1.6 – 2.6)	2.1 (1.8 – 2.7)	1.8 (1.1 – 2.2)	<0.001
MLA, mm^2	2.7 (2.0 – 3.8)	2.9 (2.1 – 4.0)	2.5 (1.8 – 3.6)	0.133
Bifurcation angle, °	60 (50 – 70)	60 (50 – 70)	60 (44 – 70)	0.328

Abbreviations: MLA, minimum lumen area; MV, main vessel; SB, side branch; TCFA, thin-cap fibroatheroma

Table 4. Univariate logistic regression analysis.

	Odds ratio	95% CI	P value
Fibrous plaque (*per* each segment at SB side)	2.9	1.6 – 5.1	< 0.001
Lipid-rich plaque (*per* each segment at SB side)	1.7	1.0 – 2.8	0.047
TCFA (*per* each segment at SB side)	2.0	0.9 – 4.4	0.064
Calcification (*per* each segment at SB side)	3.9	2.2 – 7.0	< 0.001
Thrombus	0.6	0.2 – 2.0	0.440
Carina length ≥ 1 mm	3.5	1.5 – 8.3	0.004
SB orifice length < 1.7 mm	5.6	2.4 – 13.0	< 0.001
SB ostium diameter < 1.9 mm	4.1	1.8 – 9.3	0.001
MLA < 2.0 mm^2	2.1	0.9 – 5.1	0.090
Bifurcation angle < 70°	1.3	0.6 – 3.0	0.510

Abbreviations: CI, confidence interval; MLA, minimum lumen area; SB, side branch; TCFA, thin-cap fibroatheroma

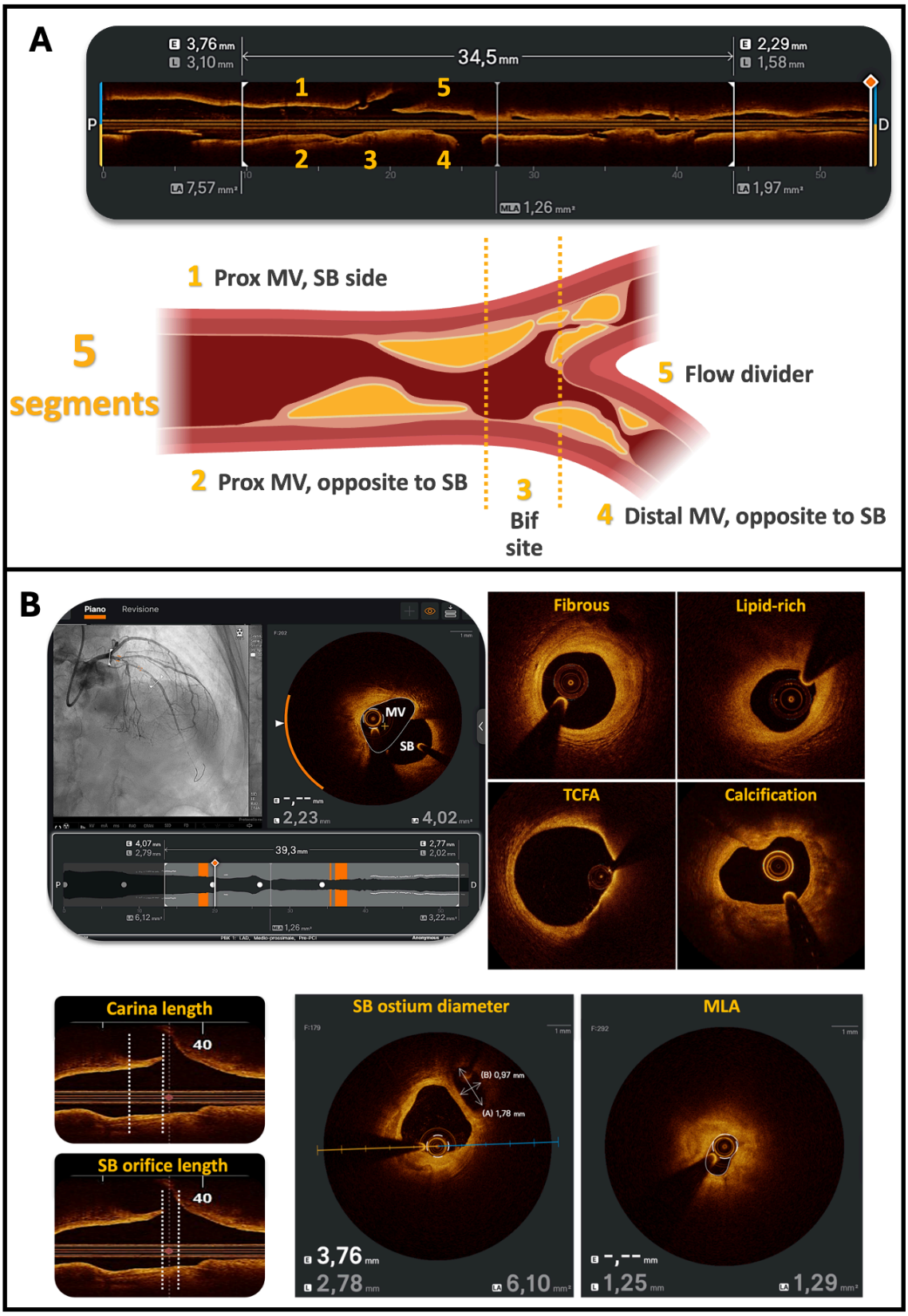
Table 5. Multivariate regression logistic analysis adjusted for angiographic baseline SB stenosis >50%, SB pre-dilation, stent-to-artery ratio.

	Odds ratio	95% CI	P value
Calcification (*per* each segment at SB side)	3.9	1.8–8.4	0.001
Carina length ≥ 1 mm	4.5	1.3–15.7	0.016
SB orifice length < 1.7 mm	6.1	1.7–22.2	0.006
Angiographic SB stenosis pre >50%	5.1	1.5–17.9	0.010
SB pre-dilation	0.1	0.0-0.8	0.034
Maximum stent-to-artery ratio	0.3	0.0-31.4	0.606
Lipid rich plaque	1.1	0.5-2.4	0.847
Fibrous plaque	1.5	0.6-3.6	0.368
SB ostium diameter < 1.9 mm	2.4	0.6-9.1	0.197

Abbreviations: CI, confidence interval; SB, side branch

FIGURES

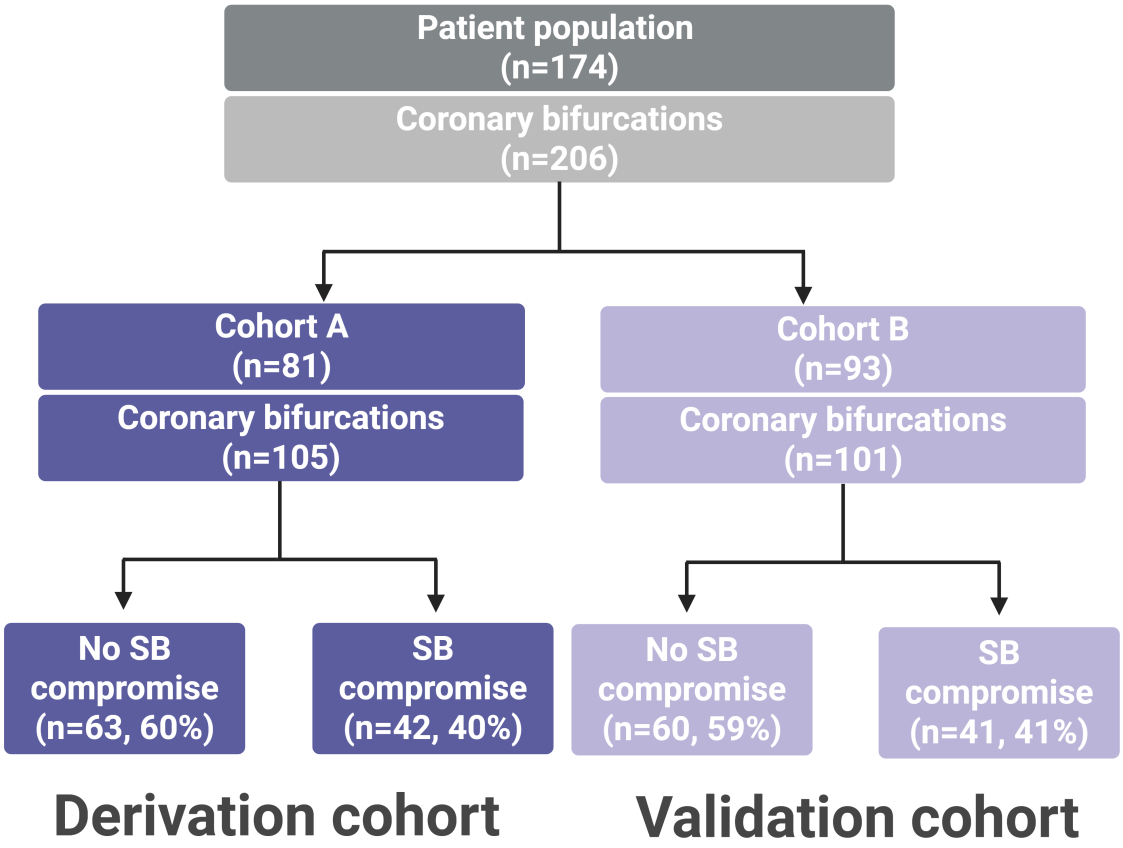
Figure 1. Optical coherence tomography (OCT) imaging analysis.



In the panel A, optical coherence tomography (OCT) analysis of coronary bifurcation anatomy was performed by optimizing the longitudinal reconstruction to clearly visualize both the carina and the side branch (SB) ostium, while selecting the frame showing the narrowest carina angle. The main vessel (MV) was analyzed at five specific segments: 1) Proximal MV, on the same side as the SB; 2) Proximal MV, opposite to the SB; 3) The bifurcation site (between the proximal branching point and the tip of the carina); 4) Distal MV, opposite to the SB; 5) Distal MV at the flow divider (facing the SB).

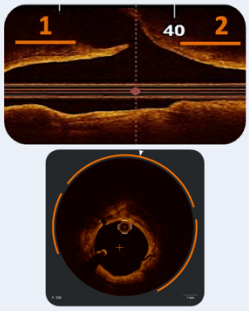
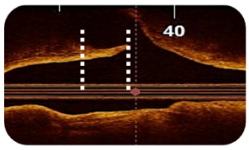
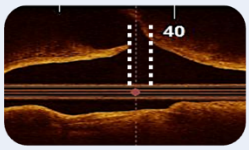
In the panel B, plaque distribution was assessed qualitatively at each of these segments and was characterized in cross-sectional images as: a) Lipid-rich plaque: diffusely bordered signal-poor region with an overlying signal-rich band; b) Thin-cap fibroatheroma (TCFA): lipid-rich plaque with a fibrous cap thickness <65 μm; c) Calcifications: signal-poor regions with sharply delineated borders; d) Thrombus: as an irregular mass protruding into the lumen. Bifurcation geometry was assessed as follows: a) Carina length (mm): measured in the longitudinal view as the distance between the proximal branching point and the tip of the carina; b) SB orifice length (mm): distance from the proximal branching point to the distal end of the SB ostium (in the same plane as carina length); c) SB ostium diameter (mm): measured in the cross-sectional view at the level of the carina; d) Minimum lumen area (MLA, mm^2): smallest luminal cross-sectional area identified within the MV in the bifurcation segment; e) Bifurcation angle (°): angle formed between the distal MV and the SB, measured using the longitudinal reconstruction.

Figure 2. Study flowchart.



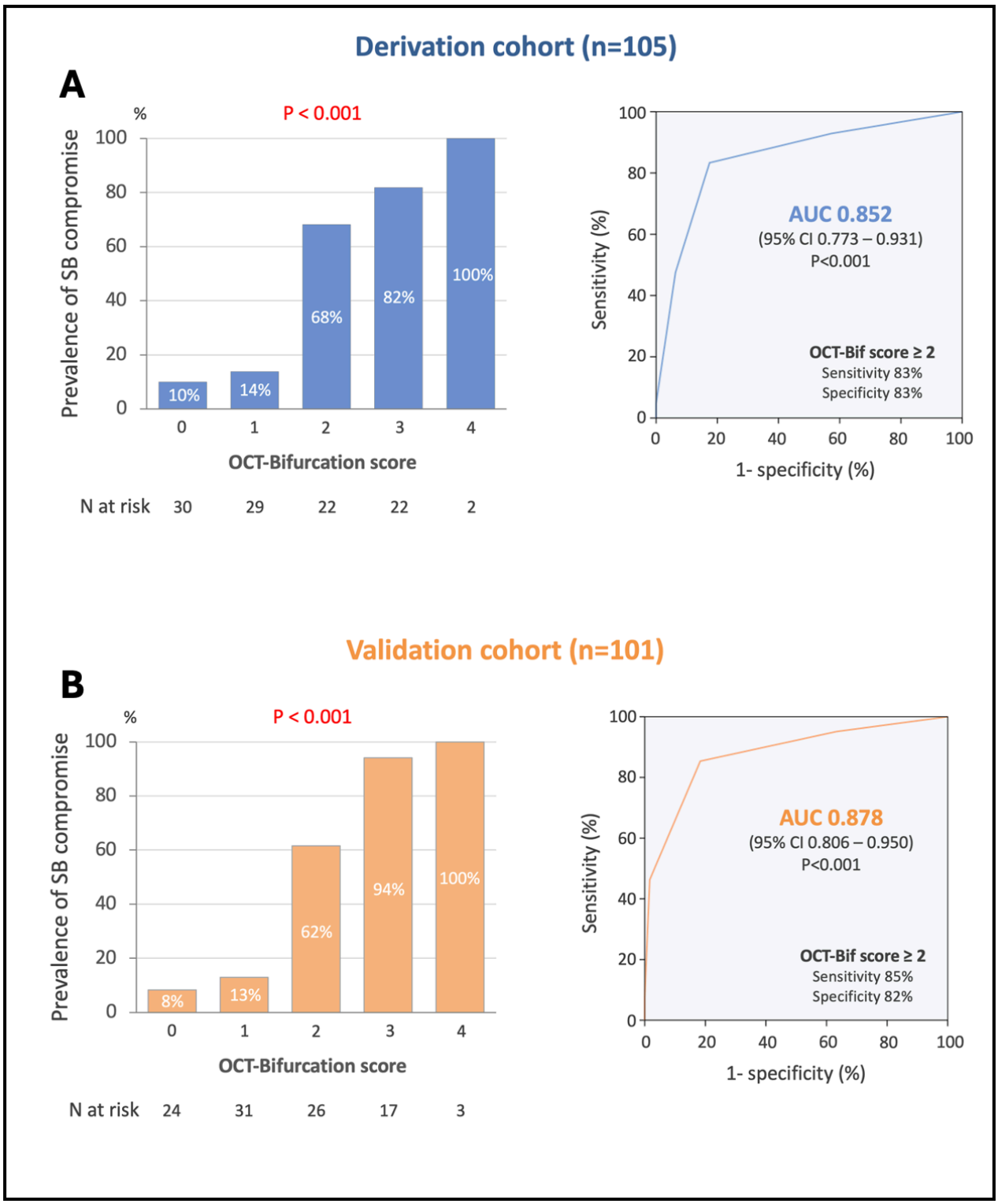
Abbreviation: SB, side branch

Figure 3. OCT-Bifurcation score.

OCT features	Example	Cut-off	Score
Calcification at the SB side		1 segment	+1
		2 segments	+2
Carina length		≥ 1 mm	+1
SB orifice length		< 1.7 mm	+1
		Total OCT-Bifurcation score	**0 – 4**

Abbreviations: OCT, optical coherence tomography; SB, side branch

Figure 4. Prevalence of SB compromise among the different point of the OCT-Bifurcation score and receiver operating curve (ROC) in the derivation cohort (Panel A) and validation cohort (Panel B).



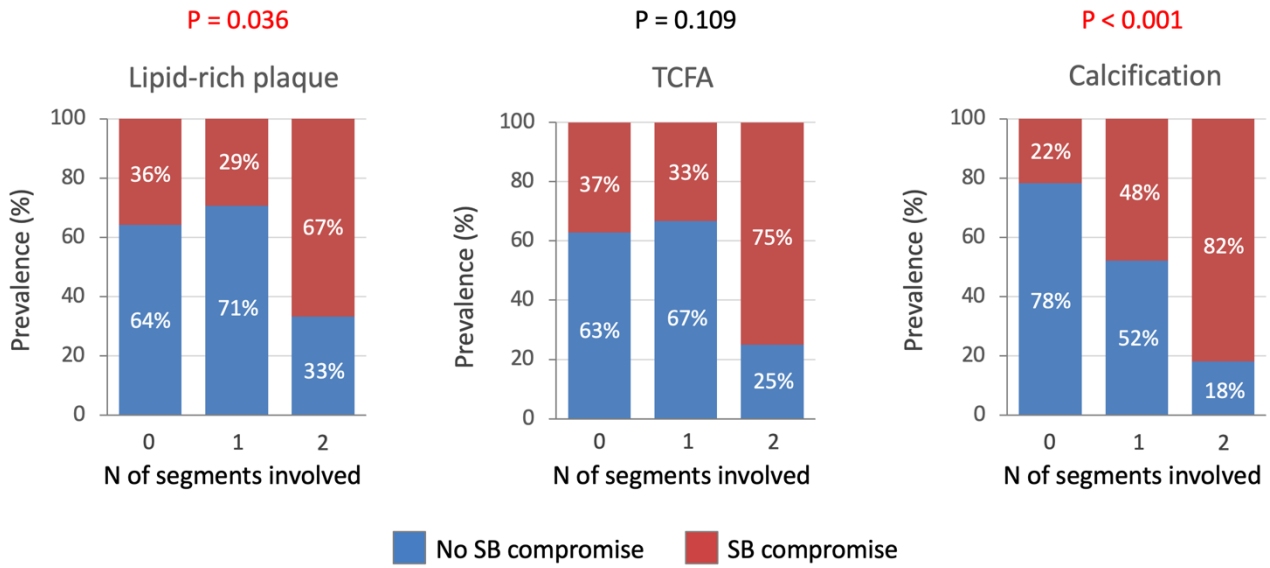
Abbreviations: AUC, area under the curve; CI, confidence interval; OCT, optical coherence tomography; SB, side branch

SUPPLEMENTARY MATERIAL.

Supplementary Table 1. Reason for exclusion from the study.

Reason for exclusion	Cohort A (N= 25)	Cohort B (N=55)
In stent restenosis	19	25
SB<2.00 mm	1	1
Abscence of OCT imaging pre-	4	21
Absence of angiographic evaluation pre- or post-stenting	1	8

Supplementary Figure 1. Involvement of SB side and risk of SB compromise.



Abbreviations: SB, side branch; TCFA, thin-cap fibroatheroma

Part C.

Conclusions

This thesis investigated contemporary applications of coronary physiology and intracoronary imaging across a range of clinically relevant scenarios, with the overarching aim of improving diagnostic precision, procedural planning, and long-term patient management in CAD.

First, the prognostic implications of physiology-guided decision-making were examined. The systematic review and meta-analysis demonstrated that deferral of revascularization based on intracoronary physiological assessment is associated with a lower incidence of adverse cardiovascular events compared with revascularization, suggesting that pressure wire assessment has prognostic implications besides the indication for revascularization.

Second, the long-term comparative performance of iFR and FFR was evaluated using pooled data from the DEFINE-FLAIR and iFR-SWEDEHEART trials. At five years of follow-up, iFR-guided revascularisation was associated with a higher incidence of major adverse cardiovascular events and all-cause mortality compared with FFR-guided revascularization, while rates of non-cardiovascular death, non-fatal myocardial infarction, and unplanned revascularization were similar between the two strategies. Importantly, these differences were predominantly driven by patients undergoing revascularization, whereas outcomes among patients in whom revascularization was deferred were comparable between iFR- and FFR-guided strategies.

Third, recognizing persistent barriers to the adoption of invasive coronary physiology, this thesis assessed the clinical utility of a comprehensive wire-free invasive diagnostic strategy. The wire-free strategy substantially increased the identification of both obstructive and non-obstructive causes of myocardial ischemia compared with angiography alone, demonstrated good agreement with wire-based assessment, and frequently altered therapeutic decision-making. These results support the feasibility of a pragmatic diagnostic pathway capable of broadening access to comprehensive ischemia assessment in routine clinical practice.

Finally, the role of intracoronary imaging as a predictive and decision-support tool was explored through the development and validation of an OCT-based bifurcation score. This score reliably identified lesions at risk of side branch compromise during provisional stenting, providing a practical imaging-guided method to anticipate procedural complexity and tailor interventional strategy in coronary bifurcation PCI.

In summary, this thesis demonstrates that coronary physiology and imaging have broad clinical applications, providing prognostic information, enhancing diagnostic yield, and supporting personalized procedural planning in the clinical decision-making of patients with CAD.

Part D.

List of scientific publications and book chapters published during the PhD

1. Boivin-Proulx LA, Haddad K, **Lombardi M**, Chong AY, Escaned J, Mukherjee S, Forcillo J, Potter BJ, Coutinho T, Pacheco C. Pathophysiology of Myocardial Infarction With Nonobstructive Coronary Artery Disease: A Contemporary Systematic Review. **CJC Open.** 2023 Nov 18;6(2Part B):380-390.
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9. Gonzalo N, **Lombardi M**. Intermediate coronary stenosis evaluation in patients with or without diabetes: are FFR and IVUS equally “sweet”? **EuroIntervention**. 2025;21:e147-e148.
10. **Lombardi M**, Chavez-Solsol J, Salinas P, Cerrato E, Vergallo R, Porto I, Varbella F, Gonzalo N, Escaned J, Macaya-Ten F. The role of percutaneous coronary intervention in spontaneous coronary artery dissection: between Scylla and Charybdis. **Minerva Cardiol Angiol** 2025;73:000–000.
11. **Lombardi M**, Paolucci L, Fernández Ortiz A, Núñez-Gil IJ. Right Coronary Artery Calcified Nodule Pre-TAVI Treatment Facilitated by ELCA Atherectomy. **JACC: Case Reports** 2025;30(5):103029.
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21. **Lombardi M**, Travieso A, Cerrato E, Mohammad MA, Götberg M, Davies J, Escaned J. Cardiovascular Outcomes in Patients with Deferred and Performed Coronary Revascularization Based on Intracoronary Physiology: A Systematic Review and Meta-Analysis. **J Am Heart Assoc**. 2026 Apr 22:e042044. doi: 10.1161/JAHA.125.042044. Epub ahead of print. PMID: 42017344