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Coronary Physiology in Patients with Stable and Unstable Coronary Artery Disease - Evaluation of Instantaneous Wave-Free Ratio

Berntorp, Karolina

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Coronary Physiology in Patients with Stable and Unstable Coronary Artery Disease

Evaluation of Instantaneous Wave-Free Ratio

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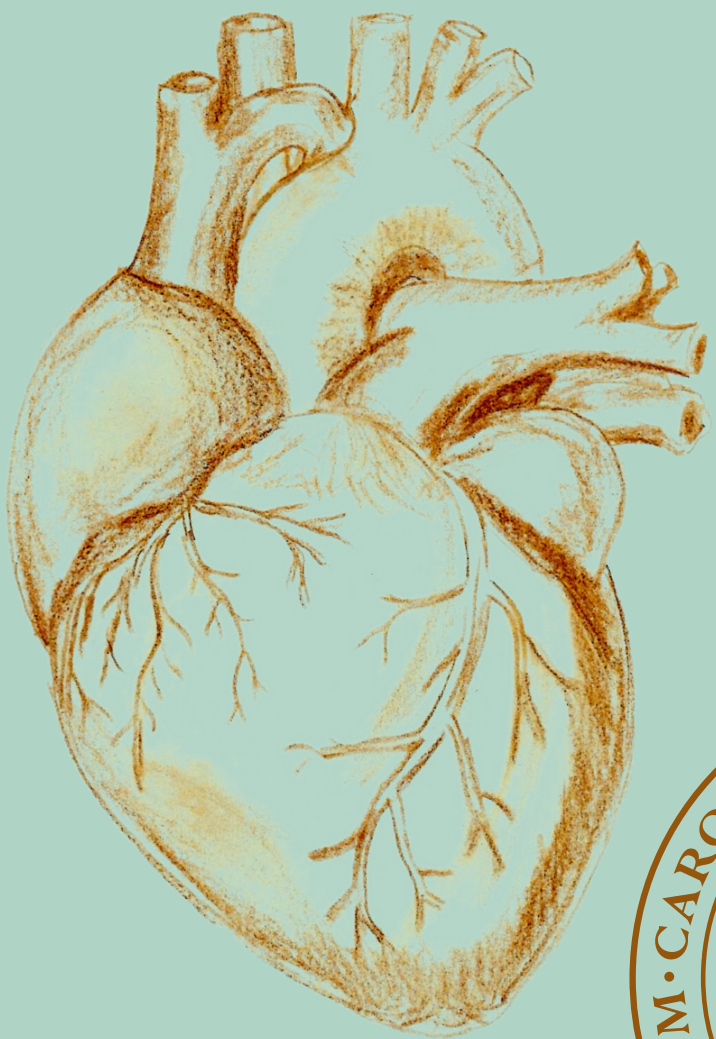

KAROLINA BERNTORP was born in Malmö, Sweden in 1987. She studied medicine at the University of Copenhagen, Denmark, and received her medical degree in 2014. She entered the PhD program at Lund University in 2018, conducting research in interventional cardiology. This doctoral thesis comprises five studies focusing on coronary physiology as represented by the instantaneous wave-free ratio, aiming to expand adoption of coronary physiology assessment in clinical practice. Dr. Berntorp became a specialist in cardiology in 2024 and is currently working as a cardiologist at the Department of Cardiology at Skåne University Hospital in Lund.

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Coronary Physiology in Patients with Stable and Unstable Coronary Artery Disease

Evaluation of Instantaneous Wave-Free Ratio

Karolina Berntorp

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University. To be publicly defended in Segerfalk Hall, BMC, Lund on October 3 at 09.00.

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Title and subtitle: Coronary Physiology in Patients with Stable and Unstable Coronary Artery Disease – Evaluation of Instantaneous Wave-Free Ratio.

Abstract:

Background
Revascularization of a stenosis is warranted when hemodynamically significant. Coronary physiology provides a diagnostic tool for assessment of stenosis severity to aid in the decision to revascularize or defer. The iFR-SWEDEHEART trial demonstrated non-inferiority of the instantaneous wave-free ratio (iFR) compared to fractional flow reserve (FFR) in guiding decision-making in coronary revascularization, with no difference in major adverse cardiac events (MACE) over the course of one year. The goal of the research reported in this thesis was to characterize the efficacy of iFR-guidance of revascularization in patients varying in clinical presentation.

Methods
This thesis comprises five studies. Studies I-III are based on data of the iFR-SWEDEHEART trial, a multicenter randomized clinical trial with 2,037 patients enrolled. Study I was a comparison of costs related to iFR and FFR in the 12 months post-procedure. Study II investigated the five-year rate of prespecified clinical endpoints in the population of the iFR-SWEDEHEART trial. Study III determined rate of MACE in the iFR-SWEDEHEART population with revascularization deferred based on the iFR index compared to FFR, as well as differences in those presenting with stable angina pectoris (SAP) vs. acute coronary syndrome (ACS). Studies IV and V employed data obtained from the nationwide quality registry, SWEDEHEART. Study IV compared MACE rate in patients deferred from revascularization of the left main coronary artery (LMCA) based on intravascular ultrasound (IVUS) to those deferred based on coronary physiology (iFR or FFR). Study V compared deferral rate with iFR to that with FFR in three coronary vessels and determined rate of clinical endpoints of deferred lesions in each vessel over a five-year period.

Results
The iFR-guided revascularization was associated with significant cost savings compared to FFR-guided in the first year following the procedure. Long-term follow-up of the iFR-SWEDEHEART population revealed no difference in clinical endpoints in those undergoing iFR vs. FFR. No difference in MACE rate was observed in the long-term follow-up of the deferred population. The outcomes of the deferred population did not differ with clinical presentation of SAP or ACS. There was no difference in rate of the composite endpoint following deferral of LMCA lesions based on coronary physiology indices vs. IVUS, but higher all-cause death was observed in those deferred with IVUS. The deferral rate was higher when using iFR in all investigated vessels, with preserved clinical outcomes.

Conclusions
Use of iFR to assess severity of coronary stenosis and guide revascularization is comparable to FFR in safety and effectiveness over the long-term and shows financial benefits over FFR. Wider knowledge of its advantages should lead to its broader adoption in clinical practice.

Key words: Coronary physiology, instantaneous wave-free ratio, fractional flow reserve, cost-minimization analysis, acute coronary syndrome, stable angina pectoris, intravascular imaging, left main coronary artery, coronary blood flow, left coronary artery, right coronary artery.

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To my parents, who could climb any mountain

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Paper II Götberg M, **Berntorp K**, Rylance R, Christiansen H E, Yndigegn T, Gudmundsdottir I, Koul S, Sandhall L, Danielewicz M, Jakobsen L, Olsson S-E, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Venetsanos D, James K S, Kåregren A, Carlsson J, Jensen J, Karlsson A-C, Erlinge D, Fröbert O. 5-year outcomes of PCI guided by measurement of instantaneous wave-free ratio versus fractional flow reserve. *Journal of the American College of Cardiology*. 2022 Mar 15;79(10):965-974.

Paper III **Berntorp K**, Rylance R, Yndigegn T, Koul S, Fröbert O, Christiansen H E, Erlinge D, Götberg M. Clinical outcome of revascularization deferral with instantaneous wave-free ratio and fractional flow reserve: A 5-year follow-up substudy from the iFR-SWEDEHEART trial. *Journal of the American Heart Association*. 2023 Feb 7;12(3):e028423.

Paper IV **Berntorp K**, Mohammad MA, Koul S, Yndigegn T, Bergman S, Zwackman S, Linder R, Völz S, Fröbert O, Erlinge D, Götberg M. Deferral of left main coronary artery revascularization via IVUS or coronary physiology – Long-term outcomes from the SWEDEHEART registry. *International Journal of Cardiology*. 2025 Jan 15:419:132726.

Paper V **Berntorp K**, Mohammad MA, Koul S, Yndigegn T, Fröbert O, Myredal A, Persson J, Erlinge D, Götberg M. A vessel-specific analysis of deferred lesions using the instantaneous wave-free ratio and fractional flow reserve. *Journal of the Society for Cardiovascular Angiography & Interventions*. E-publication ahead of print; https://doi.org/10.1016/j.jscai.2025.103823

Abstract

Background: Revascularization of a stenosis is warranted when hemodynamically significant. Coronary physiology provides a diagnostic tool for assessment of stenosis severity to aid in the decision to revascularize or defer. The iFR-SWEDEHEART trial demonstrated non-inferiority of the instantaneous wave-free ratio (iFR) compared to fractional flow reserve (FFR) in guiding decision-making in coronary revascularization, with no difference in major adverse cardiac events (MACE) over the course of one year. The goal of the research reported in this thesis was to characterize the efficacy of iFR-guidance of revascularization in patients varying in clinical presentation.

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Results: The iFR-guided revascularization was associated with significant cost savings compared to FFR-guided in the first year following the procedure. Long-term follow-up of the iFR-SWEDEHEART population revealed no difference in clinical endpoints in those undergoing iFR vs. FFR. No difference in MACE rate was observed in the long-term follow-up of the deferred population. The outcomes of the deferred population did not differ with clinical presentation of SAP or ACS. There was no difference in rate of the composite endpoint following deferral of LMCA lesions based on coronary physiology indices vs. IVUS, but higher all-cause death was observed in those deferred with IVUS. The deferral rate was higher when using iFR in all investigated vessels, with preserved clinical outcomes.

Conclusions: Use of iFR to assess severity of coronary stenosis and guide revascularization is comparable to FFR in safety and effectiveness over the long-term and shows financial benefits over FFR. Wider knowledge of its advantages should lead to its broader adoption in clinical practice.

Overview

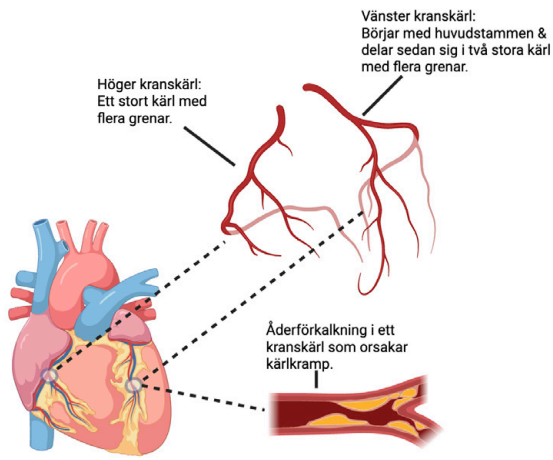
Study	Goals	Data source[a]	Main findings	Conclusions
I	Compare costs incurred with iFR to that of FFR in the 12 months post-procedure.	iFR-SWEDEHEART trial NordDRG Medicare cost data by DRG n = 2,037	Cost saving per patient of $681(95% CI: $641–$723) in a Nordic setting and $1024 (95% CI: $934-$1114) in a USA setting.	iFR-guided revascularization is associated with significantly lower cost compared to FFR-guided revascularization.
II	To quantify predetermined five-year endpoints in the iFR-SWEDEHEART population.	iFR-SWEDEHEART trial n = 2,037	Rate of MACE was 21.5% in the iFR group and 19.9% in the FFR group (HR: 1.09; 95% CI: 0.90–1.33).	At five years post-procedure, an iFR-guided strategy is associated with no difference from FFR in MACE.
III	To quantify predetermined five-year endpoints in the deferred population of the iFR-SWEDEHEART trial.	iFR-SWEDEHEART trial n = 908	Rate of MACE was 18.6% in the iFR group and 16.8% in the FFR group (HR: 1.08; 95% CI: 0.79–1.48). MACE adjusted for clinical presentation did not differ.	After five years, iFR- and FFR-deferred patients show similar outcomes regardless of clinical presentation of ACS or SAP.
IV	Determine long-term clinical outcome in patients with lesions of the LMCA deferred based on IVUS compared to deferral based on coronary physiology (iFR or FFR).	SCAAR 2014–2022 n = 1,552	MACE was 40.2% in the IVUS-deferred group and 35.5% in the coronary physiology group (RR: 1.18; 95% CI: 0.97–1.44) with a higher rate of all-cause death in the IVUS group.	Deferral of revascularization is equally safe whether based on IVUS or coronary physiology. The significantly higher all-cause death seen in the IVUS group should be interpreted with caution.
V	Determine deferral rates and five-year clinical outcomes in lesions deferred based on iFR or FFR, with respect to investigated vessel (RCA, LAD, or LCx).	SCAAR 2014–2022 n = 33,241	Deferral rates with iFR were 18.7% higher in the RCA, 9.5% higher in the LAD, and 5.3% higher in the LCx than with FFR. No significant differences was seen in MACE at five years in deferred lesions in any of the investigated vessels.	iFR is associated with higher deferral rate in the analyzed vessels, especially in the RCA, with preserved clinical outcome.

[a] n represents patients in Studies I-IV and lesions in Study V. ACS=acute coronary syndrome, CI=confidence interval, DRG=Diagnostic Related Group, FFR=fractional flow reserve, HR=hazard ratio, iFR=instantaneous wave-free ratio, IVUS=intravascular ultrasound, LAD=left descending artery, LCx=left circumflex artery, LMCA=left main coronary artery, MACE=major adverse cardiac event, NordDRG=Nordic Diagnosis Related Group, RCA=right coronary artery, RR=risk ratio, SAP=stable angina pectoris, SCAAR=Swedish Coronary Angiography and Angioplasty Registry, USA=United States.

Swedish Summary

Hjärt-kärlsjukdom är den främsta dödsorsaken i Sverige – trots att både insjuknande och dödlighet har minskat markant de senaste decennierna. Bakom utvecklingen ligger årtionden av forskning som lett till bättre förebyggande insatser och mer effektiva behandlingsmetoder.

Kranskärlssjukdom uppstår när de blodkärl som löper på utsidan av hjärtat och in i hjärtmuskeln drabbas av sjukdom. Hjärtat försörjs av tre större kranskärl: ett på höger sida och två på vänster sida. De två vänstra har sitt ursprung i ett gemensamt kärl som kallas huvudstammen. Den vanligaste orsaken till kranskärlssjukdom är åderförkalkning – en process där fett och kalk lagras i kärlväggen och orsakar inflammation. Med tiden kan detta leda till att kärlen blir trängre (förträngningar), vilket försvårar blodflödet. När hjärtmuskeln inte får tillräckligt med syre uppstår kärlkramp. Om åderförkalkningen spricker kan en blodpropp bildas i området. Detta är den vanligaste orsaken till hjärtinfarkt. När blodflödet stoppas helt, eller delvis, når inte syret hjärtmuskeln, vilket leder till skada på hjärtmuskeln.



Vid hjärtinfarkt – och många fall även vid kärlkramp – genomförs en kranskärlsröntgen. Under denna undersökning sprutar man in kontrastvätska i kranskärlen samtidigt som man tar röntgenbilder, vilket gör det möjligt att se eventuella förträngningar. I samband med denna undersökning kan man gå vidare med en så kallad ballongvidgning, eller PCI (perkutan koronar intervention). Då vidgas det trånga utrymmet med en ballong och ett metallnät – ett så kallat stent – placeras i kärlet för att hålla det öppet. Vid hjärtinfarkt är det oftast fråga om ett kärl som är helt eller nästan helt stängt. Då är det oftast tydligt vilket kärl som orsakat symptomen. Vid kärlkramp kan det vara mer svårbedömt. En förträngning

som minskar kärlets diameter med mer än 50% anses i regel vara potentiellt symptomgivande och bör därför övervägas behandling. Att avgöra graden av förträngning enbart med ögonmått kan dock vara en utmaning.

För att bättre kunna bedöma hur en förträngning i ett kranskärl påverkar blodflödet har man utvecklat metoder inom så kallad koronar fysiologi. En av de första och mest etablerade metoderna kallas Fractional flow reserve (FFR). Fractional flow reserve bygger på att man mäter tryckfallet över en förträngning i kärlet. För att göra detta ges ett kärlvidgande läkemedel – adenosin – som får kranskärlen att vidga sig maximalt. Genom att då mäta blodtrycket både före och efter förträngningen kan man räkna ut hur mycket flödet påverkas. Resultatet uttrycks som en fraktion: trycket efter delat med trycket före förträngningen. Till exempel innebär ett FFR-värde på 0,79 att tryckfallet är 21 %, vilket anses kliniskt relevant. Gränsen för när en förträngning bör åtgärdas är satt till 0,80 eller lägre. Detta tröskelvärde är väl underbyggt i forskningen, och FFR har visat sig bidra till bättre behandlingsresultat när det används för att styra beslut om åtgärd. Trots fördelarna används metoden inte i den omfattning man skulle önska. En anledning är att det tar extra tid att genomföra mätningen. Dessutom upplever många patienter tillfälliga, men obehagliga biverkningar av adenosin.

Med tiden har nya metoder tagits fram som kan spara tid och orsakar färre biverkningar, eftersom de inte kräver adenosin. Trots det bygger de på samma princip som FFR – att uppskatta blodflödet genom tryckmätning. Den vanligaste av dessa metoder är Instantaneous wave-Free ratio (iFR), som mäter tryckskillnaden i kärlet under en specifik fas av hjärtcykeln då flödet är mest stabilt.

De båda metoderna, iFR och FFR, jämfördes i en stor nordisk studie iFR-SWEDEHEART studien från 2017, som inkluderade över 2000 patienter. Studien visade att metoderna gav likvärdiga patientresultat efter ett års uppföljning. Dessutom fanns potentiella fördelar med iFR när det gäller både tid och biverkningar för patienten. Man upptäckte också att färre förträngningar behövde åtgärdas hos patienter som undersöktes med iFR. Eftersom iFR då var en relativt ny metod, med mindre omfattande forskning jämfört med FFR, fanns ett behov av ytterligare studier. I min doktorsavhandling har jag därför utvärderat både iFR och FFR i fem olika delstudier.

I **delarbete I** gjorde vi en ekonomisk jämförelse mellan iFR och FFR, baserat på data från iFR-SWEDEHEART studien med ett års uppföljning. Resultatet visade att iFR var mer kostnadseffektivt än FFR, främst tack vare att färre patienter som undersöktes med iFR behövde genomgå revaskularisering. I **delarbete II** följde vi upp patienterna i iFR-SWEDEHEART studien efter fem år och fann inga skillnader i död, ny hjärtinfarkt eller behov av ny kranskärlsåtgärd under uppföljningstiden. Eftersom färre patienter som undersöktes med iFR genomgick åtgärd, var det viktigt att studera hur det gick för dessa patienter. I **delarbete III** undersökte vi därför denna grupp. Efter fem år såg vi ingen skillnad i död, ny hjärtinfarkt eller behov av

nya åtgärder mellan patienter som genomgått iFR utan åtgärd och de som genomgått FFR utan åtgärd. Resultaten var likartade oavsett om patienterna sökt vård för kärlkramp eller hjärtinfarkt.

Tack vare de svenska personnumren är Sverige unikt med sin möjlighet att följa upp patienter över tid på ett effektivt sätt. Vi har nationella kvalitetsregister där patientvården kontinuerligt kan följas upp för att säkerställa hög kvalitet, oavsett var i landet patienten bor. Ett av dessa register är det nationella kvalitetsregistret SWEDEHEART, där bland annat alla patienter som genomgår kranskärlsröntgen i Sverige varje år registreras. Detta ger utmärkta förutsättningar för forskning som syftar till att förbättra vården för patienterna.

Mina två sista delarbeten bygger på data från SWEDEHEART. I **delarbete IV** introducerade vi en ny metod för att värdera förträngningar, så kallat intravaskulärt ultraljud (IVUS). Intravaskulärt ultraljud innebär ultraljud inne i kranskärlet för att bedöma åderförkalkningens uppbyggnad och utbredning. Vi jämförde patienter som avstått åtgärd av en förträngning i huvudstammen baserat på tryckmätningar med iFR eller FFR med IVUS. Studien visade att metoderna övergripande var likvärdiga. Däremot såg vi en högre dödlighet i gruppen som undersöktes med IVUS, vilket sannolikt beror på att dessa patienter var mer sjuka från början. Därför bör resultaten tolkas med försiktighet.

I **delarbete V** undersökte vi om det fanns skillnader i resultat mellan iFR och FFR beroende på om höger eller vänster kranskärl undersöktes. Detta är intressant eftersom blodflödet kan skilja sig mellan höger och vänster kranskärl under hjärtcykeln, vilket potentiellt kan påverka mätningarna och i förlängningen påverka risk för död, ny hjärtinfarkt eller behov av ny åtgärd. Resultaten visade att metoderna gav likvärdiga resultat på lång sikt när man avstod åtgärd oavsett vilket kranskärl som undersöktes. Detta trots att långt färre förträngningar åtgärdades efter undersökning med iFR i alla undersökta kärl.

Sammanfattningsvis bekräftar mitt doktorandprojekt att iFR och FFR är likvärdiga metoder för att bedöma behovet av åtgärd av en förträngning – både på kort och lång sikt. Vi har inte funnit några säkra skillnader beroende på vilket kranskärl som undersöks. Både iFR och FFR förbättrar patientens långtidsutfall, men iFR har fördelar i form av mindre obehag för patienten, kortare undersökningstid och bättre kostnadseffektivitet.

Abbreviations

ACS	Acute coronary syndrome
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
CFR	Coronary flow reserve
CI	Confidence interval
CV	Cardiovascular
cTn	Cardiac troponin
DRG	Diagnostic related group
ECG	Electrocardiogram
FFR	Fractional flow reserve
HSR	Hyperaemic stenosis resistance
iFR	Instantaneous wave-free ratio
IV	Intravenous
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LCA	Left coronary artery
LCx	Left circumflex artery
LMCA	Left main coronary artery
MACE	Major adverse cardiac event
MI	Myocardial infarction
MLA	Minimum luminal area
NSTEMI	Non-ST-elevation myocardial infarction
NordDRG	Nordic diagnosis related group
OMT	Optimal medical treatment
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty

QFR	Quantitative flow reserve
RCA	Right coronary artery
RCT	Randomized controlled trial
RRCT	Registry-based randomized controlled trial
SAP	Stable angina pectoris
SCAAR	Swedish coronary angiography and angioplasty registry
STEMI	ST-elevation myocardial infarction
SWEDEHEART	Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies
USA	United States of America
USD	US dollar

Introduction

The history of angiography

Coronary angiography had its beginnings in the inspiration and dedication of well-known pioneers in the fields of physics, radiology, and medicine. Over the years, novel techniques were designed and developed, with some abandoned and others modified to provide the next phase of evolution. A crucial step in the progress of invasive cardiology was the discovery of X-rays by Wilhelm Roentgen in 1895. [1] The following year, Francis Williams produced fluoroscopic images of the beating heart, [1] and the first angiograms were produced in animals by Cournand and Richards. [2] The years that followed saw several advances in the development of angiography and contrast agents. In 1919, Carlos Heuser recorded the first angiogram in a living human. [3]

The pioneering work of German surgical resident Werner Forssman in 1929 included the first human cardiac catheterization. [4] He inserted a catheter into his own brachial vein, advancing it to the right atrium, documenting the procedure with roentgenograms. The next step toward modern angiography was visualization of the coronary arteries. Nonselective coronary angiography had been reported over the years, but it was not until 1958 that F. Mason Sones performed the first selective angiography when he inadvertently injected contrast dye into the right coronary artery (RCA). [5] Sones fine-tuned his technique using specially shaped catheters for brachial artery access. The process remained the standard until 1967, when Judkins and Amplatz introduced a more practical and advanced set of catheters to obtain access via the femoral artery. [6] Melvin Judkins visited the University of Lund in 1965/1966 stating, according to his spouse, that 'Sweden was the mecca of radiology, particularly selective angiography'.

Angioplasty became a reality in 1964 when Dotter and Judkins performed the first intentional dilatation of a stenotic popliteal artery. [3, 7] The next crucial turning point in human cardiac angioplasty occurred in 1977, when Andreas Grüntzig opened an occlusion in the left anterior descending artery (LAD) during coronary artery bypass surgery. [8]

Since the advent of coronary balloon angioplasty, the field has evolved through major developments that include, to cite only a few, rotational and laser atherectomy, intravascular lithotripsy, various types of thin-strut stents eluting

antiproliferative drugs, intracoronary imaging, and advanced antithrombotic therapies. Thanks to the pioneers who, over the years, brought ingenuity and resourcefulness to their work, survival rates of myocardial infarction and cardiac disease have increased dramatically. [9]

Coronary artery disease

Coronary artery disease (CAD) can be classified as chronic coronary syndrome (CCS) or acute coronary syndrome (ACS). Chronic coronary syndrome primarily involves mechanisms in the epicardial arteries or in the microvascular system that cause ischemia. [10] Management of CCS includes a general clinical examination, assessment of the likelihood of obstructive atherosclerotic CAD, confirmation of diagnosis through non-invasive or invasive methods, and initiation of appropriate therapy.

Acute coronary syndrome is diagnosed by factors including clinical presentation, electrocardiogram (ECG) findings, and cardiac troponin (cTn) levels. [11] It is further categorized as acute myocardial infarction (MI) or unstable angina. The diagnosis of MI is associated with elevated cTn levels, in contrast to unstable angina, which is characterized by myocardial ischemia at rest or with minimal exertion, without evidence of acute myocardial injury.

Based on ECG findings, myocardial infarction is classified as ST-segment elevation MI (STEMI) or non-ST-segment elevation MI (NSTEMI). According to the Fourth Universal Definition of MI, the condition is further categorized into five types.[12]

Five types of MI according to the Fourth Universal Definition

Type 1: Spontaneous MI precipitated by plaque rupture or erosion, fissuring, or dissection.

Type 2: Ischemic MI related to mismatch of oxygen supply and demand.

Type 3: Sudden cardiac death that is likely due to ischemia, but cardiac markers are not available.

Type 4 a–c: MI related to (a) percutaneous coronary intervention, (b) stent thrombosis, and (c) restenosis.

Type 5: MI associated with cardiac surgery.

Limitations of coronary angiography

Although the accuracy and reproducibility of coronary angiography was being questioned as early as the 1960s, with studies showing intra- and inter-observer discrepancy approaching 50%,[13-15] it is still considered the gold standard in examination of coronary arteries and diagnosing epicardial CAD. The standard cutoff of >50% diameter focal stenosis as threshold for significant cardiac disease is based on animal studies. [16] The angiogram is a lumenogram showing the coronary arteries in a two-dimensional plane, without information of plaque distribution or pathology. It has limited resolution, and factors including vessel tortuosity, overlap of structures, and lumen shape influence interpretation. [17] In particular, the left main coronary artery (LMCA) is a challenge to assess because of its short length and overlap with other structures. Independent of the location of stenosis, dissociation between coronary angiography showing stenosis 40–70% of vessel diameter and clinical manifestations is substantial. [18] Stenoses of 40–90% of vessel diameter are typically defined as intermediate. [19] The limitations of coronary angiography, especially within the range of intermediate stenoses, led to the attempt to develop a physiology-based index to define functional stenosis severity. The goal was to find a technique that would be easy to use, reproducible, and capable of identifying ischemia-producing lesions.

Myocardial ischemia in patients with CAD

The presence of inducible myocardial ischemia is an important risk factor for adverse clinical outcome in patients with CAD. [20-22] The risk of MI and death is correlated to the extent of myocardium exhibiting inducible ischemia. When a substantial proportion of myocardium is involved, medicinal treatment alone does not reduce ischemia to the degree obtained with coronary revascularization. [22, 23] Revascularization relieves angina completely in a greater number of patients than does medication therapy and results in better clinical outcome in many cases. [22, 24] However, whether revascularization is beneficial to patients with a stenotic lesion not associated with inducible myocardial ischemia or in those with inducible ischemia and stable angina pectoris (SAP) remains unknown. [25, 26] Current clinical guidelines recommend that the level of myocardial ischemia be given careful consideration in the decision to perform revascularization. [19]

Non-invasive assessment of myocardial ischemia

Non-invasive assessment of myocardial ischemia is especially critical in patients with stable CAD. Documentation of ischemia is recommended prior to any invasive procedure. Exercise ECG has a low specificity and sensitivity and is therefore not recommended as first line testing for the diagnosis of obstructive CAD. [10] Its interpretation is a challenge when the patient is unable to exercise to a sufficient extent or if the ECG is abnormal at rest. It has no capacity to localize the area of myocardial ischemia.

Coronary computed tomography angiography (CCTA) has a class IA recommendation in clinical guidelines in the initial diagnosis of patients with low to moderate pre-test likelihood of obstructive CAD. [10] It is valuable in ruling out significant CAD with high sensitivity at the cost of low specificity. [27]

In patients with a moderate to high pre-test probability of obstructive CAD, nuclear perfusion imaging has a class IB recommendation in the initial diagnosis. [10] Its accuracy in detecting obstructive CAD is superior to that of exercise ECG. [28] However, in patients with multivessel disease there is a risk of false negative results, and the extent of myocardium at risk can be underestimated. [29] The basic principle of these tests is the level of perfusion differences among myocardial territories. [30] The standard reference is non-ischemic myocardium, which, if not present, limits diagnostic accuracy.

Coronary physiology

As coronary angiography and non-invasive testing often do not provide the desired information regarding the presence and location of myocardial ischemia, assessment of the hemodynamic aspects of CAD through measures of coronary physiology can play a vital role in the management of cardiac disease. Interpretation of coronary physiology indices that have evolved since the late 20th century requires familiarity with the basics of coronary physiology.

Coronary arteries

The coronary arterial system comprises the RCA and the left coronary artery (LCA) that arises in the LMCA and bifurcates into the LAD and the left circumflex artery (LCx). [2] A third branch, the ramus intermedius, is occasionally found arising from the LMCA. The main epicardial arteries divide further into several epicardial branches. The sub-epicardial layer of the myocardium is perfused by multiple branches, while the sub-endocardium is perfused by numerous branches after

penetrating the myocardium; thus, the sub-endocardial system possesses a higher volume of small vessels. [31, 32]

Coronary circulation

Through an intrinsic mechanism known as autoregulation, [33] coronary blood flow can be held constant over a wide range of mean cardiac pressures to ensure a consistent supply of oxygen to the myocardium. Coronary artery resistance changes in response to coronary pressure with subendocardial arteries maximally dilated at a mean pressure of ~40 mmHg. All coronary arteries will show alterations in smooth muscle tone, but the contribution of the epicardial arteries to a drop in resistance is negligible. The microvascular system represents the primary contributor and can expand flow as much as five-fold with vasodilation. [34] An increase in myocardial oxygen demand during exercise increases the autoregulatory plateau via a mechanism referred to as metabolic adaptation (Figure 1). [35]

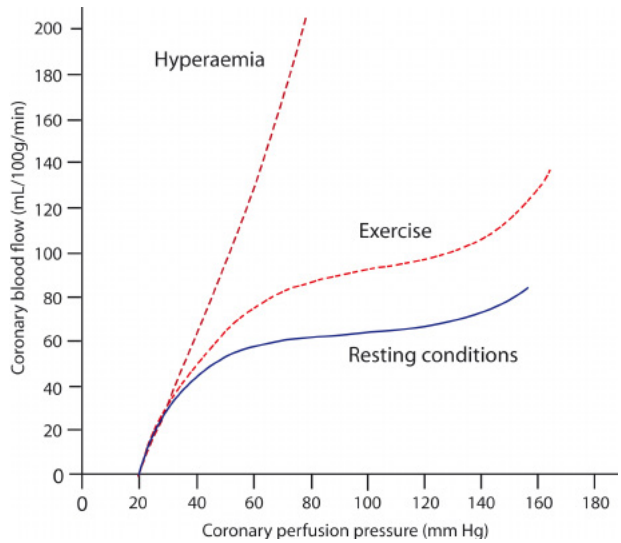


Figure 1. Coronary pressure-flow relationship
Coronary blood flow remains constant within a range of perfusion pressures, a phenomenon known as autoregulation. When myocardial oxygen demand increases, metabolic adaptation increases the autoregulatory plateau. During hyperaemia the relationship becomes linear. Reprinted with permission from Heart 99(22):1699-705(2013).

Ohm's law can be used to describe the relationship among coronary blood flow, pressure drop, and resistance of the coronary vascular bed:

$$Flow = \frac{\Delta \text{Pressure}}{\text{Resistance}} \quad (1)$$

In the absence of coronary artery stenosis, coronary blood flow is determined by the driving pressure and the resistance of the coronary vascular bed. The driving pressure is the aortic pressure minus the backward pressure, approximately the venous pressure. Pressure per se is defined as the driving pressure outward against the vascular wall minus the inward pressure working against expansion.

Pressure reduction and flow in the presence of stenosis

A vessel with no stenosis exhibits laminar flow with pressure moderated by viscous friction. Poiseuille's law calculates the pressure P reduction in a vessel of viscosity μ, specific length L, diameter D, and flow volume Q: [36]

$$\Delta P = \frac{128\mu L}{\pi D^4} Q \quad (2)$$

The equation assumes that, in a vessel of a given diameter and length, resistance is constant along the length of the vessel. Pressure diminishes by the inverse of vessel diameter to the fourth power. Poiseuille's equation is based on three primary assumptions (1) a rigid, straight, uniform tube; (2) steady laminar flow; and (3) consistent viscosity.

Another important equation in blood vessel haemodynamics is the continuity equation, the law of conservation of mass, which states that the volume of blood that enters the vessel per unit time is equal to the volume that leaves, where A is the cross-section area and v is the velocity: [37]

$$Q = A_1 \times v_1 = A_2 \times v_2 = constant \quad (3)$$

Bernoulli's equation describes pressure P relative to flow velocity v and is based on the conservation of energy and momentum. The sum of static pressure, hydrostatic pressure (potential energy), and dynamic pressure (kinetic energy) is held constant [37]

$$P_{tot} = P + \rho g h + 1/2 \rho v^2 = constant \quad (4)$$

where ρ is blood density, g is the gravitational acceleration, and h is a height of a fluid column above a reference level. If the height is constant, the equation can be reduced to [37]

$$P_1 + 1/2\rho v_1^2 = P_2 + 1/2\rho v_2^2 \quad (5)$$

meaning that the velocity of blood entering a vessel section with stenosis will increase proportional to the decrease in cross-section area ($v_2 > v_1$), and pressure will be lost in conversion to kinetic energy ($P_2 < P_1$). Pressure is also reduced because of blood viscosity. Gould et al. used the equations of Poiseuille and Bernoulli to predict decrease in pressure P due to stenosis in a coronary vessel. [16, 38] The formula is

$$\Delta P = AQ + BQ^2 \quad (6)$$

where Q is flow velocity distal to the stenosis, and A describes the pressure reduction from friction along the entrance and throat of the stenosis, which is linearly correlated to flow (Poiseuille's law, Eq. 2). In addition, pressure loss at the entrance of the stenosis is caused by flow contraction with subsequent convective acceleration (Bernoulli's law, Eq. 4 and Eq. 5). This pressure decrease is not recovered distal to the stenosis because of flow separation and formation of eddies and is included as the term B, which increases with the square of the flow velocity (Figure 2).

The primary contributor to pressure drop is cross-section diameter. [39] The resistance is inversely proportional to the vessel diameter to the fourth power. Therefore, resistance increases with degree of stenosis. The loss of pressure due to flow separation becomes increasingly important with stenosis severity. Factors including the length of the lesion and cross-section area distal to it are minor contributors to reduced pressure. Flow velocity parameters such as aortic driving pressure and microvascular resistance can influence the pressure lost across the stenosis.

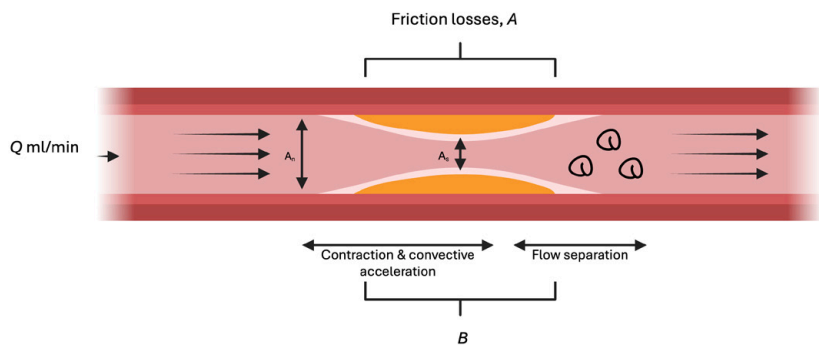


Figure 2. Trans-stenotic pressure gradient
The trans-stenotic pressure gradient is described by the Gould formula: $\Delta P = AQ + BQ^2$. A_n is the area of the normal segment and A_s is the area of the stenosis. Created using BioRender (www.biorender.com).

Wave intensity analysis

Wave intensity analysis originated in the field of gas dynamics and has been used to describe coronary physiology and the contribution to the pattern of flow and pressure of different areas of the coronary arteries. [40] It involves use of a pressure and flow sensor-tipped wire to measure pressure and flow. Wave intensity analysis has contributed to the development of techniques to characterize coronary physiology and assess the significance of a coronary artery stenosis.

With wave intensity analysis, the coronary vessel is viewed in a two-dimensional plane, and the information of pressure and velocity changes are axial. The measured pressure and flow waveforms are decomposed into the summation of wavefronts of different amplitudes. The definition of a wave is a 'disturbance that propagates in space and time'. [41] Wave speed is always greater than blood flow velocity and the intensity is calculated as the sum of wave amplitudes, which may be either positive or negative (Figure 3). The wave can influence blood flow in three ways:

Direction of travel: originating proximally (aortic) as a forward wave or distally (myocardial) as a backward wave.

Effect on pressure: increasing pressure as a compression wave or decreasing pressure as a decompressive wave.

Effect on velocity: acceleration or deceleration.

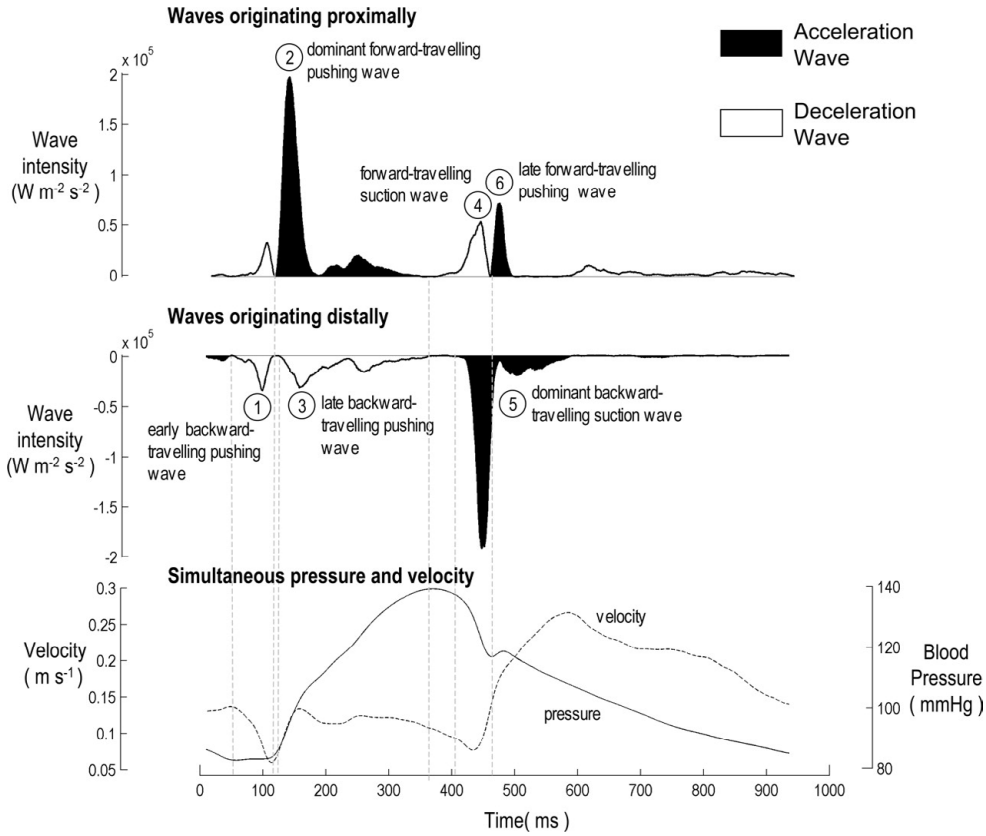


Figure 3. Coronary artery wave intensity profile
Characteristics of waves in the human circumflex artery with left ventricular hyperthrophy. Reprinted with permission from Circulation 113(14):1768-78(2006).

Three types of forward waves originate from the aorta and three originate distally from the intramyocardial blood vessels (Table 1, Figure 3). [42] The most clinically important wave is the backward decompression wave initiated at the end of systole when intramyocardial cells re-expand and generate suction of blood from the aorta into the coronary vessels.

Table 1. Waves included in the wave intensity analysis

Wave	Origin	Pressure effect	Effect on velocity
Forward compression	Aorta – the contraction of the left ventricle forces blood in an antegrad direction through the coronary arteries.	Increase	Acceleration
Forward decompression	Aorta – at conclusion of systole, suction is created in the aorta at the proximal end of the coronary arteries.	Decrease	Deceleration
Late forward compression	Aorta – closure of the aortic valve.	Increase	Acceleration
Early backward compression	Intramyocardial blood vessels – early systole, isovelumetric contraction causes compression of microcirculation.	Increase	Deceleration
Late backward compression	Intramyocardial blood vessel – early systole causes compression of microcirculation.	Increase	Deceleration
Backward decompression	Intramyocardial blood vessel – conclusion of systole, myocardial cells re-expand.	Decrease	Acceleration

A higher systolic:diastolic wave ratio is seen in the vessels from the RCA to the left ventricle along with low backward decompression in the RCA, reflecting the relaxation force resulting from lower peak cavity pressure in the right ventricle. [41] The flow pattern is also influenced by such factors as the presence of left ventricular hypertrophy and aortic stenosis. [42]

Coronary flow reserve

Calculation of coronary flow reserve (CFR) is a well-established method of assessing coronary physiology to identify coronary blood flow impairment in the investigated territory. [16, 43] It is defined as the ratio of maximal flow during vasodilation to baseline flow under autoregulation conditions (Figure 4). Thus, it describes the extent to which the investigated coronary circulatory area can increase blood flow in response to alterations in oxygen demand. It is the sum of blood flow capacity of epicardial and microcirculatory arteries and will therefore reflect overall impairment.

Coronary flow reserve can be measured to stratify risk through both non-invasive and invasive methods. [44-46] Invasive assessment is conducted via either doppler flow velocity or thermodilution. In a healthy individual, coronary flow should increase more than 4.5-fold when hyperaemia is induced. [47] Association with poor clinical outcomes is seen in individuals without epicardial stenosis and CFR <2.8 as well as in those with epicardial stenosis and CFR <2.0. [45, 48, 49] A dichotomous cutoff value of 2.0 is primarily used in research and clinical practice to define risk of adverse cardiovascular outcome. Several important factors limit CFR use in clinical practice. Measuring CFR is technically challenging and leads to inaccurate results in a considerable number of cases. It represents the level of impaired flow in epicardial arteries as well as in the microvascular system. Its inability to discriminate between the two systems reduces its value in planning treatment strategies. As flow during maximal vasodilatation is affected by changes in pressure, CFR is sensitive to any factor influencing pressure.

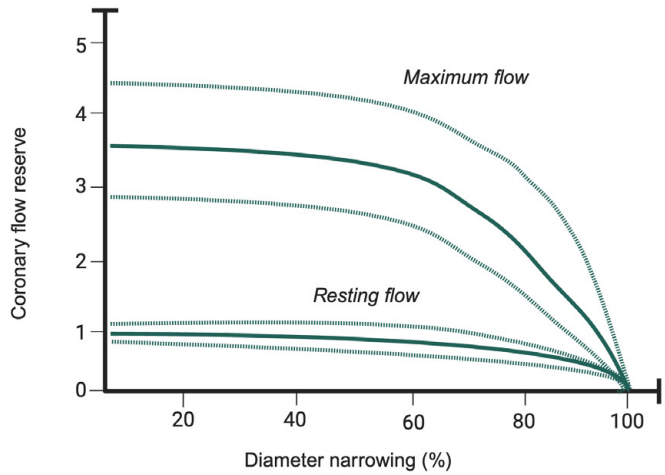


Figure 4. Coronary flow reserve vs. percent diameter stenosis
Autoregulation of flow remains constant as severity of stenosis increases. Under hyperaemia, flow begins to decline at 50% diameter stenosis, while resting flow declines at 80-85% diameter stenosis. Adapted from Am J Cardiol 33(1):87-94(1974) with permission using BioRender (www.biorender.com).

Fractional flow reserve

Definition

Fractional flow reserve (FFR) is based on the principle that during maximal vasodilatation (hyperaemia), the pressure/flow relationship is linear. [33] The measured pressure will therefore correspond to the flow.

> FFR = maximal myocardial blood flow in the presence of stenosis/normal maximal blood flow

This definition can be further described as the ratio of myocardial flow in a stenotic coronary artery Q to normal myocardial flow QN during hyperaemia:

$$FFR = \frac{Q}{QN} \tag{7}$$

As previously mentioned, the relationship of flow Q, pressure P, and resistance R is described by Ohm´s law. The equation can therefore be transformed to

$$FFR = \frac{(P_d - P_v)/R}{(P_a - P_v)/RN} \tag{8}$$

where P_d is the distal pressure and P_a is the proximal pressure. In maximal hyperaemia, the resistance in the coronary artery is negligible and can be omitted from the equation. This also applies to venous pressure P_v in the coronary arteries, thus the equation can be simplified to: [50]

$$FFR = \frac{P_d}{P_a} \tag{9}$$

Simply put, FFR is the ratio of maximal hyperaemic flow in the index myocardial territory to what it would be if the coronary artery was normal. [51, 52] Hence, it represents the extent to which myocardial blood flow is limited by the presence of epicardial stenosis. An FFR of 0.7 means that the maximal myocardial flow is 70% of its normal value (Figure 5). The value of FFR is not influenced by heart rate, blood pressure, or contractility. [51, 53]

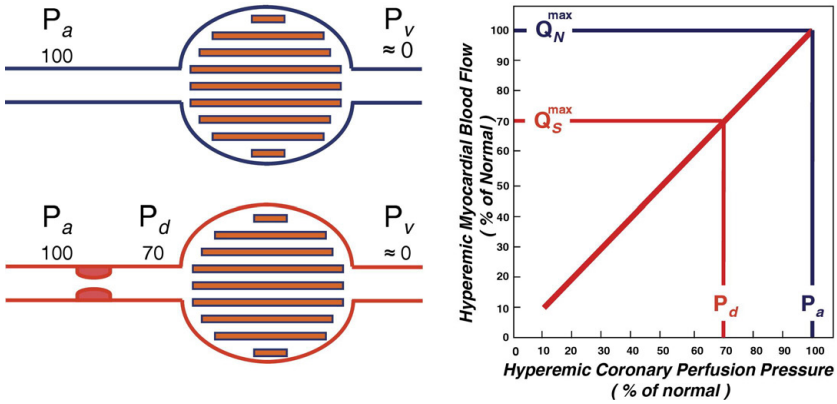


Figure 5. Fractional flow reserve relative to stenosis severity
Upper left: Driving pressure P_a determines normal maximal myocardial blood flow. P_a = aortic pressure. Lower left: Driving pressure decreased by stenosis, in this case to 70 mmHg. P_d = driving pressure downstream of stenosis; P_v = venous pressure. Right: Linear relationship between pressure and flow. Q_N = normal hyperaemic myocardial blood flow; Q_s = stenotic hyperaemic myocardial blood flow. Reprinted with permission from Elsevier J Am Coll Cardiol 59(12):1045-57(2012).

Initially, FFR was termed FFR_{myo}, as it also considers the contribution of collateral flow. When the contribution of collateral flow was excluded in the calculation, FFR was referred to as FFR_{cor}. [51-53] The difference was called fractional collateral flow. FFR_{myo} was considered the most clinically important value, as it incorporates both antegrade and collateral flow. Therefore, FFR_{myo} is currently the definition of FFR.

Adenosine

Administration of adenosine is the standard method of inducing hyperaemia. Adenosine is a nucleoside, naturally synthesized in the heart under conditions of increasing metabolic demand and during ischemia. [47] Adenosine induces angina through stimulation of cardiac-sensitive nerve fibres. Vasodilatation of microcirculation is induced by binding of vessels to A2 receptors in the smooth muscle cells. Adenosine is administered either as an intravenous (IV) infusion or an intracoronary bolus injection. Its half-life is short, and with IV administration, the intended effect is reached within 60–90 seconds and ceases within 60 seconds of ending infusion. The administration often causes chest discomfort, shortness of breath, and facial flushing. [47] It should be avoided in patients with a history of severe chronic obstructive pulmonary disease or asthma because of risk of bronchoconstriction. If this happens, the antidote is theophylline. The most effective administration is via either a peripheral or central vein at 140–170 mg/kg body weight/min. [54, 55]

Intracoronary injection (60–600 mg) reaches peak effect after 10 seconds, and the effect ceases within 20 seconds. [56] It has been demonstrated to be as effective and

safe as IV administration, with lower systemic impact and fewer side-effects. [57, 58] It also allows for repeat measurements to be conducted without delay. [59] However, it is not appropriate for repeat measurements in the same vessel (pullback) and is not to be used in ostial stenoses. [60] The risk of transient atrioventricular block is higher than with IV and needs to be considered, especially at higher doses. [56] There is also greater likelihood of overestimating of the extent of stenosis. [58]

A stable pressure gradient across the stenosis indicates a steady state of hyperaemia. The measured P_d and P_a should become stable, and the patient may experience the mentioned uncomfortable side-effects. It is important to reach hyperaemia, and, if properly conducted, the reliability of obtaining hyperaemia is close to 100%.

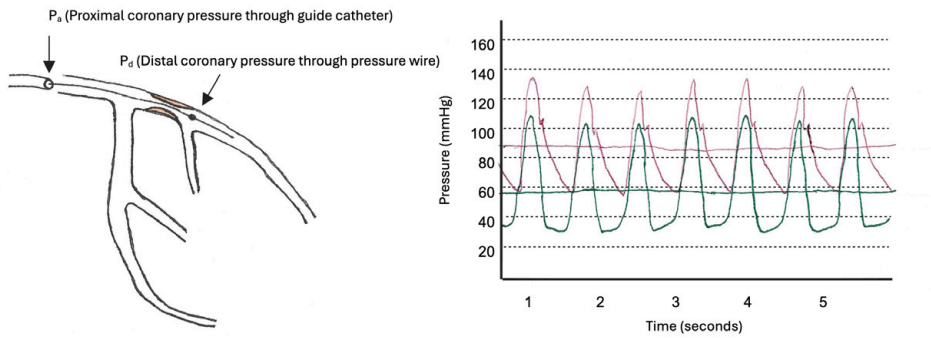


Figure 6. Assessment of a coronary artery stenosis with FFR
Stenosis causing significant ischemia in the LAD. During maximal hyperaemia, myocardial blood flow is proportional to coronary perfusion pressure. With a sensor-tipped guidewire and adequate hyperaemic stimulus, FFR can be calculated as the ratio P_d/P_a as seen in the left panel. The right panel shows pressure tracings as displayed by the sensor-tipped wire with the sensor placed distal to the stenosis (P_d, green) in the LAD and from the tip of the guide catheter (P_a, red). The FFR index value is 0.57, indicating that maximal hyperaemic blood flow to the anterior wall has decreased to 57% of its normal value without stenosis.

Validation of FFR and cutoff values

Studies have compared FFR to non-invasive stress testing including dobutamine stress echocardiogram, exercise stress test, and single-photon emission scintigraphy. [51, 61-63] Patient clinical presentation has ranged from single vessel CAD to multivessel CAD, previous MI, and in-stent restenosis. Cutoff values for recommending revascularization have varied. The value of 0.75 was the first to be adopted in a decision-making trial [64, 65] after being validated in a study including patients with moderate stenosis experiencing chest pain. [63] Participants underwent bicycle exercise testing, myocardial perfusion imaging, and stress echocardiography. All patients with FFR <0.75 demonstrated myocardial ischemia

on at least one of the noninvasive tests. After revascularization, all test results reverted to normal. The accuracy was 93%, specificity 100%, sensitivity 88%, positive predictive value 100%, and negative predictive value 88%.[63]

Later the cutoff value was adjusted to 0.80, [66] increasing the sensitivity at the cost of a greater number of false positive results, and thus lower specificity. However, the interpretation of FFR as a single cutoff value has been questioned. A meta-analysis investigating prognosis after FFR measurement showed that lesions with a lower index value received greater absolute benefit from revascularization. [67]

The FFR grey zone is defined as 0.75–0.85. [68] Outside this range, the likelihood of repeating a single FFR value is >95%. Closer to its cutoff of 0.80, this falls to <80%, indicating that, in the grey zone, a repeat measurement within 10 minutes may result in a different decision with respect to revascularization (Figure 7).

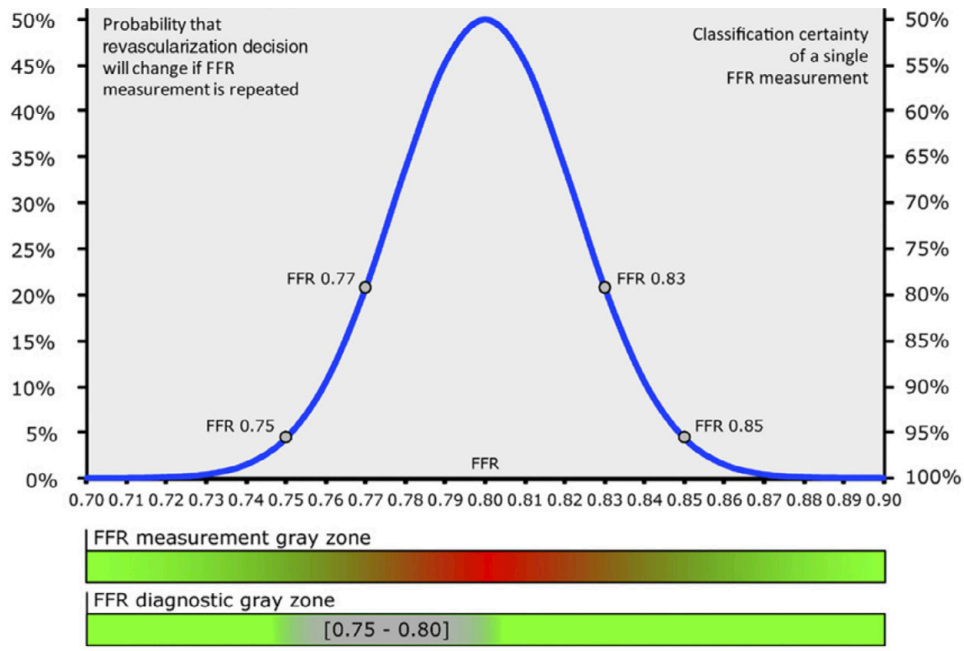


Figure 7. The fractional flow reserve grey zone
The diagnostic grey zone revealed from the DEFER study. The further the FFR value falls from the 0.80 cutoff, the greater the certainty that the recommended treatment strategy will not change with repeat testing. Reprinted with permission from Elsevier JACC CI 6(3):222-5(2012).

Clinical outcome

Fractional flow reserve as a clinical decision-making tool with a single dichotomous cutoff value has been assessed in three pivotal studies.

The Deferral Versus Performance of PTCA (percutaneous transluminal coronary angioplasty) in Patients Without Documented Ischemia (DEFER) study was the first prospective randomized clinal study to evaluate FFR using a cutoff value of >0.75 for revascularization deferral. [64] The study population comprised 325 patients with stable coronary disease and intermediate lesions (>50% stenosis by visual assessment) with no previous documented evidence of ischemia. The patients were randomized to three groups: FFR >0.75 with lesions deferred from PTCA, FFR >0.75 with PTCA, and FFR <0.75 with PTCA. The primary endpoint was the absence of adverse cardiac events during 24 months of follow-up. The conclusion was that patients with FFR >0.75 receive no benefit from PCTA and can be safely deferred. Longer term follow-up of the DEFER study over a span of 15 years revealed similar outcomes. [65, 69]

The next important evaluation of FFR in a clinical setting was the Fractional Flow Reserve versus Angiography for Multi vessel Evaluation (FAME) study. [66] Unlike previous studies, FAME adjusted the cutoff value to ≤0.80 for revascularization. The reasoning was that FFR >0.80 had been shown to rule out ischemia in 90% of cases, [70] and by accepting the upper limit of the grey zone, the ischemic lesions potentially left untreated would decrease. [66] The study population comprised 1005 patients with ≥50% stenosis in two or three epicardial vessels. The patients were randomized to complete revascularization with percutaneous coronary intervention (PCI) based on angiography or on FFR values. The primary outcome was the rate of major adverse cardiac events (MACE) at one year defined as death, nonfatal MI, and repeat revascularization. Revascularization guided by FFR significantly lower MACE at one year compared to angiography alone.

The Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease (FAME) II study assessed whether FFR-guided PCI plus optimal medical therapy (OMT) would be superior to OMT alone. [71] The population consisted of 1220 patients with multivessel disease who were receiving OMT and considered for PCI. If at least one lesion showed FFR ≤0.80, patients were randomized to either PCI in addition to OMT or to OMT alone. Patients with FFR >0.80 in all lesions continued OMT. The primary endpoint was a composite of death, MI, and urgent revascularization. The study was halted prematurely due to a significant reduction in the primary outcome in the PCI group compared to the OMT group driven by significantly fewer urgent revascularizations in the PCI group. This limited the conclusion to decreased rate of urgent revascularization with PCI compared to OMT alone.

Economic impact

Cost-effectiveness is an important factor when introducing a new clinical tool. An FFR evaluation in intermediate coronary lesions without prior functional assessment has been shown to lead to significant cost savings compared to nuclear stress

imaging and stenting of all lesions. [72] The FAME study found significant cost savings with FFR-guided strategy conducted at the index procedure associated with reduced stent costs. [73] During follow-up, the main cost saving was fewer rehospitalizations and reduced incidence of MACE. The analysis of cost-effectiveness in the FAME II trial revealed that PCI in patients with low FFR values was economically superior to OMT alone. [74] In modern medicine it is unusual to introduce new technology that shows a health benefit as well as reducing costs, a factor that is important in a financially challenged health care system.

Primary features of the fractional flow reserve index

- FFR has a normal value of 1.0.
- Cutoff value for revascularization is 0.80 with a grey zone from 0.75-0.80.
- Hemodynamics do not influence the FFR value.
- FFR values include the contribution of collateral blood flow and the mass of the perfusion area.
- Results are highly reproducible.
- FFR-guided strategy for revascularization is financially beneficial.

Instantaneous wave-free ratio

Background

The work of Gould et al. in 1974 showed that, compared to hyperaemic flow, which declines with stenosis >50%, resting coronary flow remains stable until near complete occlusion of the vessel. [16] As previously described, fluctuations in a phasic pattern are present throughout the cardiac cycle. To minimize their effects, FFR is measured during hyperaemia, which shows a linear relationship between pressure and flow when resistance is stable.

Through knowledge of the wave-intensity analysis and measurement of FFR, a wave-free period (WFP) can be identified in diastole. [75] During the WFP, new waves are not generated, and competing waves affecting coronary blood flow are not present. On ECG, the WFP begins 25% into diastole after the dicrotic notch and ceases 5 ms before the end of diastole. This knowledge led to development of a new

diagnostic tool to evaluate hemodynamic significance of a coronary artery stenosis, the instantaneous wave-free ratio (iFR), a non-hyperaemic index.

Features of the WFP

- Flow velocity is 30% greater than whole-cycle resting flow velocity.
- Pressure and flow decline in a linear fashion.
- Microvascular resistance is more stable and lower than in the rest of the cycle.

Definition

The definition of iFR was initially more complex than the definition of FFR. To define iFR, animal studies were replicated in humans. It was demonstrated that the pressure gradient was driven by compensatory vasodilation changes in microvascular resistance associated with coronary autoregulation. [76] Only a gradient detected at rest will have a meaningful physiological impact (Figure 8).

iFR = mean pressure distal to a stenosis during the WFP/mean pressure proximal to a stenosis during the WFP

The iFR can be calculated during the WFP on a beat-by-beat basis compared to FFR that is measured throughout the entire cardiac cycle [37]

$$\text{iFR} = \frac{P_{dWFP}}{P_{aWFP}} \qquad (10)$$

where P_d is the distal pressure and P_a is the proximal pressure.

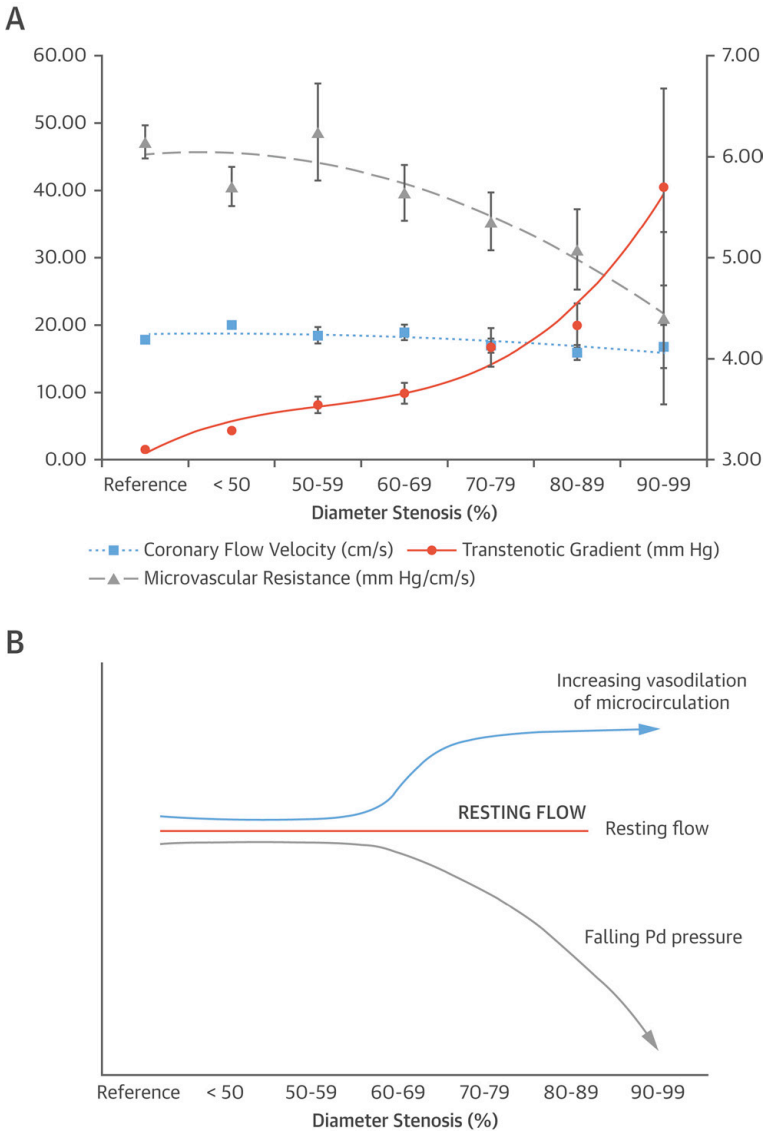


Figure 8. Coronary autoregulation at rest in the presence of stenosis

A) With increasing severity of stenosis, resting coronary flow velocity is maintained at a stable level by reduction in microvascular resistance. B) Resting coronary physiology relative to stenosis severity. The falling distal coronary pressure (P_d) reflects the physiological impact of coronary artery stenosis on the distal coronary bed. Reprinted with permission from Elsevier JACC 70(11):1379–1402(2017), originally adapted from Eur Heart J 2016;37:2069.

Validation of iFR and cutoff values

The aim of validation studies of iFR was to establish an iFR cutoff value with accuracy equivalent to that of FFR in distinguishing hemodynamically important stenoses. The first study to compare iFR with FFR used an iFR cutoff ≤0.83 and an FFR ≤0.80 for revascularization and found close correlation and diagnostic efficiency. [75] A subsequent study using an iFR cutoff value ≤0.80 showed lower diagnostic agreement. [77] The currently used cutoff value of ≤0.89 for revascularization was compared to FFR ≤0.80 in the Adenosine Vasodilator Independent Stenosis Evaluation (ADVISE) II study. [78] The methods provided similar results, and iFR displayed agreement of 82.5% of total stenoses with sensitivity of 73% and specificity of 87.8%. The study also demonstrated that a hybrid approach in which stenoses with iFR index near the cutoff value (0.86–0.93) were further evaluated with FFR resulted in high diagnostic agreement.

The validation of iFR has included studies comparing iFR to other methods, both invasive and non-invasive. In the Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow (CLARIFY) study, iFR was compared to FFR and the hyperaemic stenosis resistance (HSR) index. [79] The latter is a combined pressure and flow index. The study found iFR with and without adenosine to show diagnostic accuracy equivalent to HSR. Administration of adenosine during iFR measurement did not improve diagnostic agreement. A study comparing iFR and FFR to myocardial perfusion scintigraphy combined with HSR to assess level of ischemia showed no difference among indices. [80] When level of ischemia obtained via iFR, FFR, and CFR were compared, iFR showed closer agreement with CFR than with FFR (area under the curve for iFR 0.82 vs. 0.72 for FFR; $p < 0.001$). [81] This agreement was observed over a wide range of index values, but to a greater extent in the 0.60 to 0.90 range of FFR values. The authors suggested that the results provided evidence of iFR suitability as an index to indicate disease severity independent of FFR values.

Clinical outcome

A hybrid approach to evaluating stenoses first with iFR and, for values 0.86–0.93, with supplementary FFR has been proposed, as an unequivocal iFR result is shown to spare 60–70% of patients from adenosine administration. [78, 82] The recommendation was abandoned when two randomized clinical studies confirmed the multiple validation trials showing noninferiority of iFR to FFR.

The Instantaneous Wave-Free Ratio versus Fractional Flow Reserve Guided Intervention (iFR-SWEDEHEART) and the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) trials were conducted to test the hypothesis that iFR-guided revascularization was non-inferior to FFR-guided revascularization. [83, 84] A positive result could lead to wider adoption

of coronary physiology in clinical decision making, as iFR shows potential time and costs benefits and avoiding adenosine administration reduces patient side-effects. The trials included patients with intermediate coronary artery stenoses randomized to undergo either iFR- or FFR-guided revascularization. Indication for the procedure was SAP or ACS with a non-culprit lesion assessed. Cutoff value for revascularization was ≤0.89 for iFR and ≤0.80 for FFR.

The iFR-SWEDEHEART trial was a multicentre, prospective, randomized, controlled, clinical open-label trial that used the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) for enrolment. [84] The primary endpoint was a composite of all-cause death, nonfatal MI, and unplanned revascularization at one year. A total of 2,037 patients were enrolled. The primary endpoint occurred in 68 (6.7%) of 1,012 participants in the iFR group and in 61 (6.1%) of the 1,007 patients in the FFR group (difference in event rates 0.7%; 95% confidence interval (CI): -1.5 – 2.8; p=0.007 for noninferiority; HR: 1.12; 95% CI: 0.79 – 1.58; p=0.53).

The DEFINE-FLAIR trial was a prospective multicentre international double-blinded patient study. [83] The primary endpoint was the rate of MACE at one year. Among 2,492 patients included, the primary endpoint occurred in 78 of 1,148 undergoing iFR (6.8%) and in 83 of 1,182 FFR patients (7.0%) (difference in risk, -0.2%; 95% CI: -2.3 – 1.8; p<0.001 for noninferiority; HR: 0.95; 95% CI: 0.68 – 1.33; p=0.78). Main findings of the trials are presented in Table 2.

Table 2. Findings of the iFR-SWEDEHEART and DEFINE-FLAIR trials assessing iFR vs. FFR

Main findings	iFR-SWEDEHEART	DEFINE-FLAIR
iFR-guided revascularization was non-inferior to FFR-guided revascularization	x	x
Significantly higher proportion of deferred lesions with iFR	x	x
Significantly fewer revascularized patients with iFR		x
Significantly fewer patients with adverse procedure symptoms in the iFR group	x	x
Significantly shorter procedure time with iFR		x

A pooled patient-level analysis was performed on the populations of the DEFINE-FLAIR and iFR-SWEDEHEART studies comprising 4,529 patients with intermediate coronary artery stenoses. As in the earlier studies, iFR-guided revascularization and FFR-guided revascularization demonstrated similar rate of the primary combined endpoint. [85] A significantly greater proportion of patients were deferred from coronary revascularisation with iFR compared to FFR (1,117 (50%) vs. 1,013 (45%) (p<0.01). The one-year MACE rate in the deferred population of the iFR and FFR groups was similar (4.12% vs. 4.05%, respectively; HR:1.13; 95% CI: 0.72 – 1.79; p=0.60).

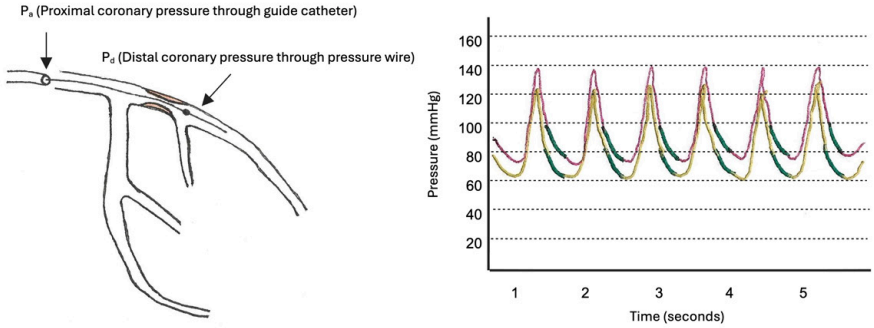


Figure 9. Assessment of coronary artery stenosis with iFR
Stenosis causing significant ischemia in the LAD. Left panel: The LCA with a stenosis in the proximal LAD. With a sensor-tipped guidewire, iFR can be calculated as the ratio P_d/P_a. Right panel: iFR is calculated during the wave-free period of diastole (green). The illustration shows pressure tracings as displayed from the sensor-tipped wire, with the sensor placed distal to the stenosis (P_d, yellow) and from the tip of the guide catheter (P_a, red). The value of iFR is 0.84, indicating that blood flow to the anterior wall has decreased to 84% of its normal value without stenosis.

Primary features of the instantaneous wave-free ratio index

- iFR has a normal value of 1.0.
- Cutoff value for revascularization 0.89.
- Measured in the wave-free period of diastole.
- Hyperaemia not required.
- Non-inferior to FFR with respect to MACE at one year.

Evaluation of left main coronary artery stenoses

The findings related to LMCA lesions should be interpreted with caution, as unprotected lesions left untreated are associated with increased mortality, owing to the extent of myocardial territory at risk. [86, 87] Clinical guidelines recommend revascularization of LMCA with lesions ≥50% of diameter regardless of symptoms. [19] The best approach for revascularization depends on stenosis location, extent, complexity, and patient comorbidities. The visual estimate of intermediate LMCA stenoses with angiography is subject to interobserver variation, emphasising the

importance of methods providing objective detailed information regarding anatomic severity and hemodynamic significance of LMCA lesions. [88]

FFR and iFR in LMCA stenoses

There are technical limitations to the assessment of LMCA disease based on coronary physiology especially related to ostial disease, angulation, and risk of damping the pressure curves. Use of FFR in the presence of distal lesions of the LAD or LCx may produce a high index value, resulting in underestimation of the level of stenosis. [89]

Patients with LMCA lesions have largely been excluded from randomized clinical trials because of high risk of mortality related to untreated LMCA lesions. [87] An observational study has shown poor correlation of visual estimates of angiographic significance with FFR values. [90] The same study demonstrated favourable long-term clinical outcome in patients with LMCA lesions deferred with FFR ≥0.80. Other studies have similarly shown benefits of FFR in guiding revascularization of LMCA lesions. [91, 92] A meta-analysis found an increased rate of revascularizations in FFR-deferred lesions of the LMCA. [93] However, the cutoff value of FFR ≤0.80 was used in only one of the included studies.

Less information is available regarding LMCA revascularization guided by iFR. The iFR and FFR indices have shown agreement in classification of LMCA disease with most discrepancies falling in the grey zone. [94] The safety of deferring LMCA revascularization based on iFR results has been demonstrated in an observational study of 314 patients. [95] Disagreement of iFR and FFR is frequent in LMCA and LAD lesions, [96] and is estimated to occur in approximately 20% of cases in the LMCA. [97] The iFR has been shown to have superior predictive value for adverse cardiovascular events in deferred LMCA stenoses and may be safer than FFR to defer LMCA lesions. [97]

Intravascular ultrasound

Intravascular ultrasound (IVUS) is an invasive method of imaging with the advantage compared to angiogram of providing a tomographic view as well as allowing direct visualisation of the vessel wall. [98] Intravascular ultrasound is conducted by placing a catheter distal to the target area. Grayscale cross-section images are generated during manual or automated pullback, enabling measurement of lumen area and plaque extent and distribution, as well as providing information of plaque composition (Figure 10). Its safety is well documented, with a complication rate of 1–3%. [99, 100]

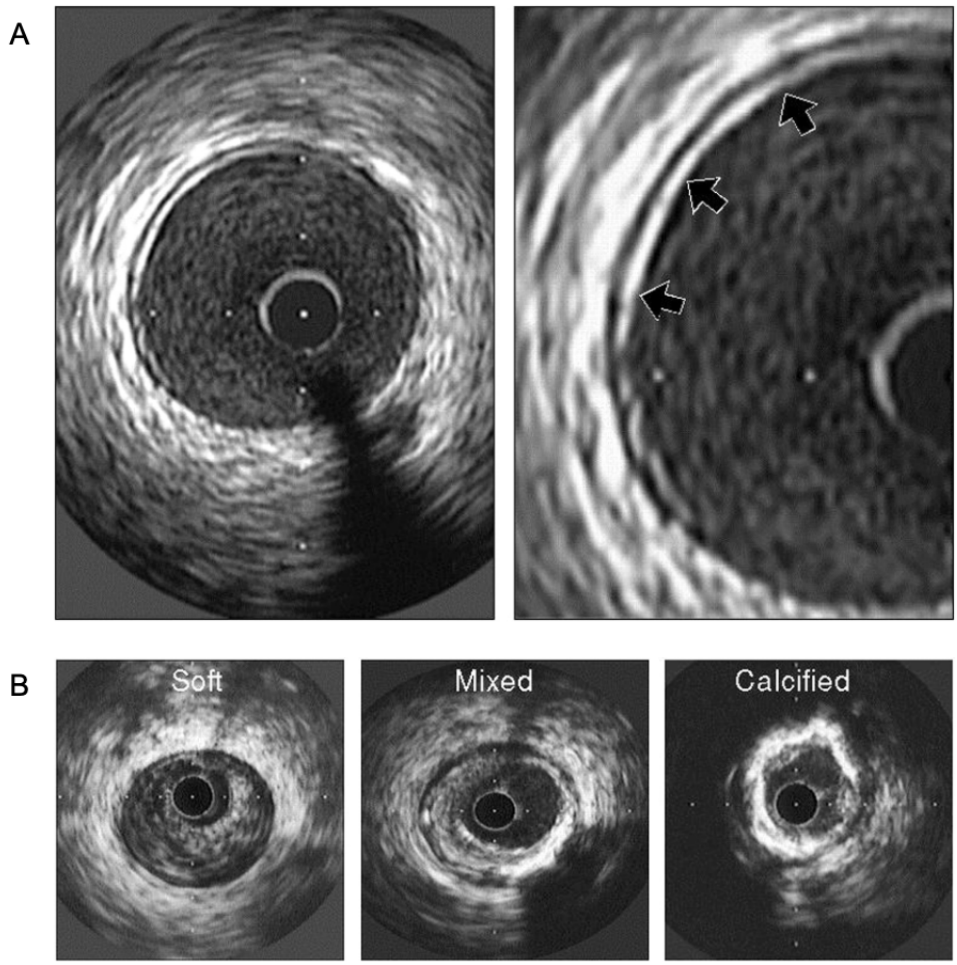


Figure 10. Images of a coronary artery generated by IVUS
A) Normal anatomy. In the right image, arrows show the intimal leading edge. Scale is 1 mm between white dots. B) Atheroma morphology: soft (left), mixed fibrous and calcified (centre), and heavily calcified (right). Reprinted with permission from Circulation 103(4):604-16(2001).

The facility of IVUS to assess plaque extent and involvement of ostial segments of daughter branches improves clinical outcomes when used to guide stent implantation and optimization. [101, 102] Coronary imaging with IVUS currently has a class IIa, level B recommendation in the European Society of Cardiology guidelines for decisions regarding revascularization of unprotected LMCA lesions. [19] As a diagnostic tool to guide revascularization decision-making, IVUS is used to determine the minimum luminal area (MLA). The interpretation of MLA differs among patients, likely because of differences in reference size of the coronary arteries. [103-105] Deferral of an intermediate stenoses of 25–60% on visual estimate

and an MLA ≥6 mm^2 has been found to be safe and associated with favourable outcomes, showing cardiac death-free survival of 97.7% in a Spanish population. [106] A United States (USA) study of the optimal MLA cutoff value for revascularization comparable to FFR <0.75 found MLA ≤5.9 mm^2 to have sensitivity of 93% and specificity of 94%. [103] These cutoff values are currently used in Swedish standard practice.

Vessel-specific coronary blood flow

Blood flow in coronary circulation is predominantly diastolic as a result of compression of the microcirculation by the myocardium in systole and, during diastole, active suction of blood into the coronary arteries due to myocardial relaxation. [42, 107] This flow pattern is present in epicardial arteries and their many branches that penetrate the myocardium. [108-110] The pattern in the LCA is well known, while that of the RCA is less understood. Small-scale studies in animals and humans have produced contradictory findings, demonstrating equal systolic and diastolic flow as well as greater systolic flow. [111, 112] More recently, a human study showed that coronary blood flow is predominantly diastolic in patients with CAD regardless of the investigated vessel. [113]

FFR and iFR in specific vessels

Clinical guidelines recommend assessment of coronary physiology with FFR and iFR to guide revascularization, making no distinction between lesions of the LCA and RCA. [19] Differences in flow pattern could potentially affect the results of the procedures; hence, interpretation could depend on the vessel being assessed. The pressure waveform distal to a stenosis has been demonstrated to differ in the LCA and RCA. [114] The pressure drop with FFR is a predominantly diastolic characteristic in the LCA, while in the RCA the reduction is chiefly due to systolic pressure loss. [114] Whether this phenomenon is present with iFR is not known. Vessel-specific analyses comparing clinical outcome of FFR and iFR are lacking. The DEFINE-FLAIR study showed a significantly lower rate of unplanned revascularizations and numerically fewer MI in the LAD one year after iFR-guided strategy compared with FFR. [115]

Aims

The overall aim of the research reported in this thesis was to compare the efficacy of coronary physiology assessment with iFR to that using FFR in patients with stable and unstable coronary artery disease.

The stated aims of each paper were:

Paper I	To compare the cost associated with iFR-guided revascularization to that with FFR-guided revascularization based on data of the iFR-SWEDEHEART trial.
Paper II	To determine the rate of a prespecified five-year primary composite endpoint of all-cause mortality, myocardial infarction, and unplanned revascularization in patients of the iFR-SWEDEHEART trial.
Paper III	To compare five-year clinical endpoints in patients of the iFR-SWEDEHEART trial deferred from revascularization based on iFR vs. FFR as well as outcomes by clinical presentation.
Paper IV	To compare long-term clinical endpoints in patients with LMCA stenosis deferred from revascularization with IVUS with those deferred by coronary physiology via iFR or FFR in an all-comer real-world population, using the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.
Paper V	(1) To compare deferral rates based on FFR with iFR in the RCA, LAD, and LCx; and (2) to evaluate the long-term clinical outcomes of deferred lesions with FFR vs. iFR in the RCA, LAD, and LCx, respectively, in an all-comer real-world population using the SWEDEHEART registry.

Methods

This section presents an overview of methods used in the studies (Table 3). The details of specific materials and methods used is available in the attached papers.

Table 3. Study methods

Study	Study population[a]	Index	Endpoints	Statistical analysis
I	iFR-SWEDEHEART trial n = 2,037	FFR and iFR	Cost differences per patient in a Nordic setting and a United States setting.	Cost-minimization analysis and senistivity analyses.
II	iFR-SWEDEHEART trial n = 2,037	FFR and iFR	MACE (all-cause death, nonfatal MI, and unplanned revascularization) and outcome of the individual components at five years.	Cox-proportional hazards models and a test for interaction.
III	Deferred patients in the iFR-SWEDEHEART trial n = 908	FFR and iFR	MACE (all-cause death, nonfatal MI, and unplanned revascularization) and outcome of the individual components at five years including CV death and non-CV death. Comparing FFR to iFR and ACS to SAP.	Cox-proportional hazards models and a test for interaction.
IV	SCAAR 2014–2022 n = 1,552	IVUS, FFR and iFR	MACE (all-cause death, MI, and unplanned revascularization) and outcome of the individual components at five years including CV death and non-CV death.	Poisson regression model and a test for interaction.
V	SCAAR 2014–2022 n = 33,241	FFR and iFR	Deferral rates in each vessel. MACE within five years defined as CV death, non-CV death, MI, and unplanned TSR within each vessel and the individual components including TVR.	Cox-proportional hazards models and Poisson regression model.

[a] In Study I–IV, n is number of patients. In Study V, n is number of lesions. ACS=acute coronary syndrome, CV=cardiovascular, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, IVUS=intravascular ultrasound, MACE=major adverse cardiac event, SAP=stable angina pectoris, SCAAR=Swedish Coronary Angiography and Angioplasty Registry, TSR=target segment revascularization, TVR=target vessel revascularization.

The SWEDEHEART registry

The Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry is a national quality registry created in 2009 by merging four existing quality registries (Figure 11): [116] The Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA) became a national quality registry in 1995, collecting data of patients hospitalized with MI. The SCAAR, established in 1998, collects procedural data pertaining to all patients undergoing coronary angiography and coronary interventions in Sweden. Approximately 40,000 patients each year are registered in SCAAR for each procedure, recording up to 150 variables including baseline characteristics, angiographic findings, type of stenosis, type of stent, antithrombotic treatment, and details of complications. The National Registry of Secondary Prevention (SEPHIA) registers, and follows up for 12 months, all patients with a diagnosis of MI under age 80 with the aim of improving secondary prevention. The Swedish Cardiac Surgery Registry holds data of all patients with thoracic heart surgery performed in the thoracic surgery centres in Sweden since 1992. The SWEDEHEART registry currently includes percutaneous valve interventions in SWENTRY, patients with heart failure in SwedeHF, and includes a cardiogenetic registry. Hospitals recording data in SWEDEHEART in Sweden include those treating patients with ACS as well as all intervention centres.

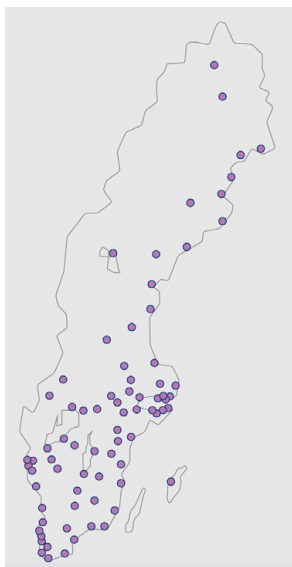


Figure 11. Locations of hospitals participating in SWEDEHEART
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The primary purpose of the SWEDEHEART registry is to monitor and improve acute and chronic coronary artery disease care in Sweden. The long-term goal is to decrease mortality and morbidity and to improve cost-effectiveness. The registry allows for medical research with an unselected patient population, nationwide coverage, and high rate of participation. The personal identification number issued to all residents of Sweden makes it possible to cross-reference information with other national registries. The SWEDEHEART data is merged with the National Cause of Death Register and the National Patient Registry, recording cause of death and diagnosis at hospital discharge, respectively, as well as with the National Registry of Drug prescriptions containing information regarding prescribed drugs.

The iFR-SWEDEHEART trial

Study design

The Instantaneous Wave-Free Ratio versus Fractional Flow Reserve guided intervention (iFR-SWEDEHEART) trial was a multicentre, prospective, randomized, controlled, clinical open-label trial in patients with SAP or ACS undergoing coronary angiography. [84] The objective was to investigate the hypothesis that iFR-guided revascularization was non-inferior to FFR-guided revascularization.

The study was conducted in Sweden, Denmark, and Iceland in accordance with the declaration of Helsinki and approved by the ethical review boards in each country. Thirteen hospitals in Sweden participated as well as one hospital in Denmark and one in Iceland.

Patients were randomized 1:1 to either iFR- or FFR-guided revascularization. The SCAAR was used for inclusion, randomization, and obtaining baseline and procedural data.

Cutoff for revascularization was ≤0.89 for iFR and ≤0.80 for FFR. Hyperaemia when FFR was conducted was induced with adenosine according to standard clinical practice. Revascularization was performed according to standard clinical practice. The type of P_2Y_{12} inhibitor was left to the discretion of the attending physician. A flowchart showing study design is presented in Figure 12.

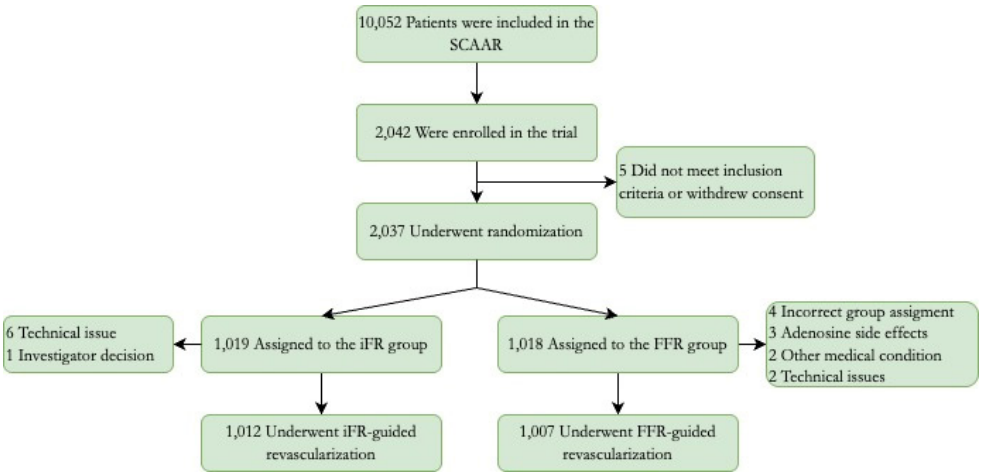

Figure 12. Flowchart showing study design of the iFR-SWEDEHEART trial
FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, SCAAR= the Swedish Coronary Angiography and Angioplasty Registry.

Study population

Patients scheduled for angiography who exhibited SAP, unstable angina pectoris, or NSTEMI were eligible for inclusion. Any lesion could be accessed in patients with SAP and only non-culprit lesions in patients with unstable angina and NSTEMI. Stenosis of 40–80% on visual estimation was required as indication for physiology-guided revascularization. All included patients provided written informed consent. Exclusion criteria were inability to give informed consent, age below 18 years, previous participation in the study, life expectancy less than one-year, hemodynamic instability, intolerance to adenosine, previous coronary artery bypass grafting (CABG) with patent grafts to the investigated vessel, expected inability to cross the lesion with a pressure wire, and difficulty in identifying culprit lesion.

Endpoints

The primary endpoint was a composite of all-cause death, nonfatal MI, and unplanned revascularization at one year. The key secondary endpoints were the individual components of the composite endpoint and chest discomfort during the procedure. Information of all-cause death was obtained from national population registries, while data of nonfatal MI and unplanned revascularization was obtained from the SWEDEHEART registry in Sweden, the Danish National Patient Registry and the Western Denmark Heart Registry in Denmark, and, in Iceland, through clinical follow-up conducted by a research nurse.

Results

A total of 2,037 patients were enrolled from May 2014 through October 2015. The primary endpoint occurred in 68 of 1,012 (6.7%) patients in the iFR group and in 61 of 1,007 (6.1%) patients in the FFR group (95% CI, -1.5 – 2.8; p=0.007 for noninferiority) (Figure 13). The upper limit of the difference in event rates fell within the prespecified noninferiority margin of 3.2 percentage points. The unadjusted HR was 1.12 (95% CI, 0.79 – 1.58; p=0.53). There was no significant difference in rate of occurrence of the individual components of the composite endpoint. In the iFR group, 29.1% of lesions were deemed hemodynamically important, compared to 36.8% in the FFR group (p<0.001). In the iFR group, numerically fewer stents per patient were placed (1.58 ± 1.08 vs. 1.73 ± 1.19, p=0.05) and numerically fewer revascularizations with PCI were performed (443 vs. 456, p=0.50). Numerically fewer CABGs were conducted in the iFR group than in the FFR group (93 vs. 113, p=0.13). A significantly greater proportion of patients in the FFR group reported chest discomfort during the procedure (68.3% with FFR vs. 3.0% with iFR, p<0.001).

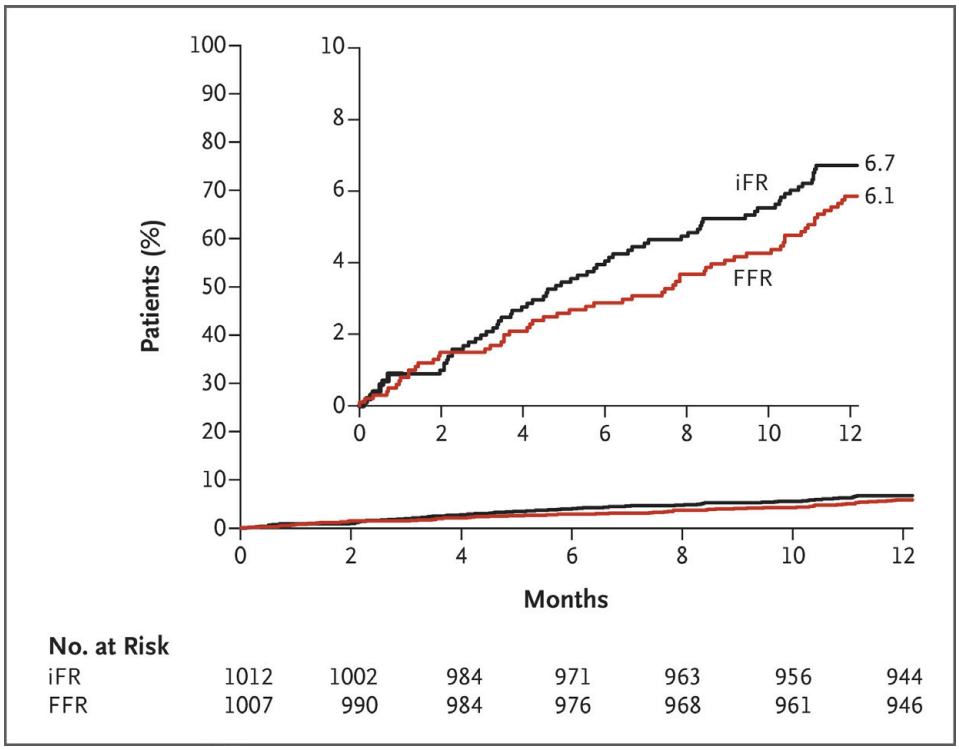

Figure 13. Kaplan-Meier curves depicting rate of the primary endpoint of the iFR-SWEDEHEART trial

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Study population and study design

Paper I

The study population comprised all patients included in the final analysis of the iFR-SWEDEHEART trial.

We designed a decision-tree model for a hypothetical cohort of 1000 patients to compare health-care costs with respect to iFR and FFR during the 12 months post-procedure (Figure 14). The model is initiated with a decision to use either iFR or FFR to assess coronary physiology as basis for deferring or conducting revascularization. Each technique carried a possible choice of PCI, CABG, or medicinal treatment. Patients undergoing each treatment had the potential for fatal MI, nonfatal MI, or unplanned revascularization. The model was applied to both a Nordic and a USA setting.

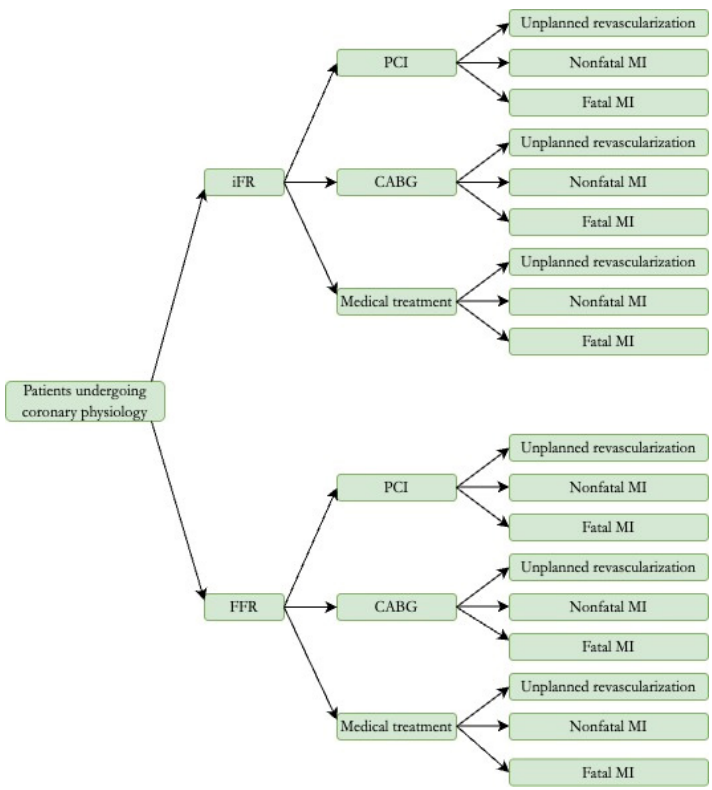

Figure 14. Decision-tree model to compare cost of iFR vs. FFR over the course of one year post-procedure

CABG=coronary artery bypass grafting, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, MI=myocardial infarction, PCI=percutaneous coronary intervention.

Paper II

The cohort of Paper II comprised all patients included in the final analysis of the iFR-SWEDEHEART trial. The patients were followed for five years with no patients lost to follow-up. The study population and design has previously been described in the summary of the iFR-SWEDEHEART trial.

Paper III

This sub-study of the iFR-SWEDEHEART trial compared outcomes over the course of five years in patients deferred from revascularization based on iFR with those based on FFR. Patients were categorized according to indication for the procedure (SAP or ACS) (Figure 15). Lesions were considered of nonhemodynamic relevance and safe for deferral with iFR >0.89 or FFR >0.80.

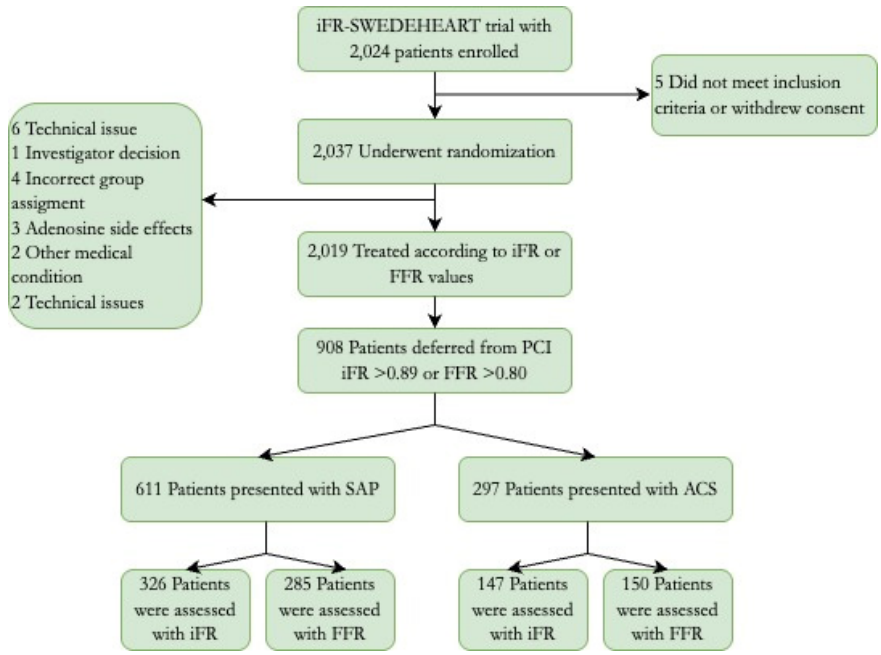

Figure 15. Design of Paper III comparing five-year endpoints in patients deferred from revascularization based on iFR or on FFR

ACS=acute coronary syndrome, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, PCI=percutaneous coronary intervention, SAP=stable angina pectoris.

Paper IV

Individuals with data recorded in SCAAR from January 1, 2014 through February 16, 2022 in whom revascularization of the LMCA was guided by IVUS, iFR, or FFR were included. Patients were excluded from the analysis if ad hoc PCI was performed in LMCA, LAD, or LCx; elective revascularization or valve surgery was planned; MLA <6 mm2; iFR ≤0.89; FFR ≤0.80; or if previously included in the study. Study design is shown in Figure 16.

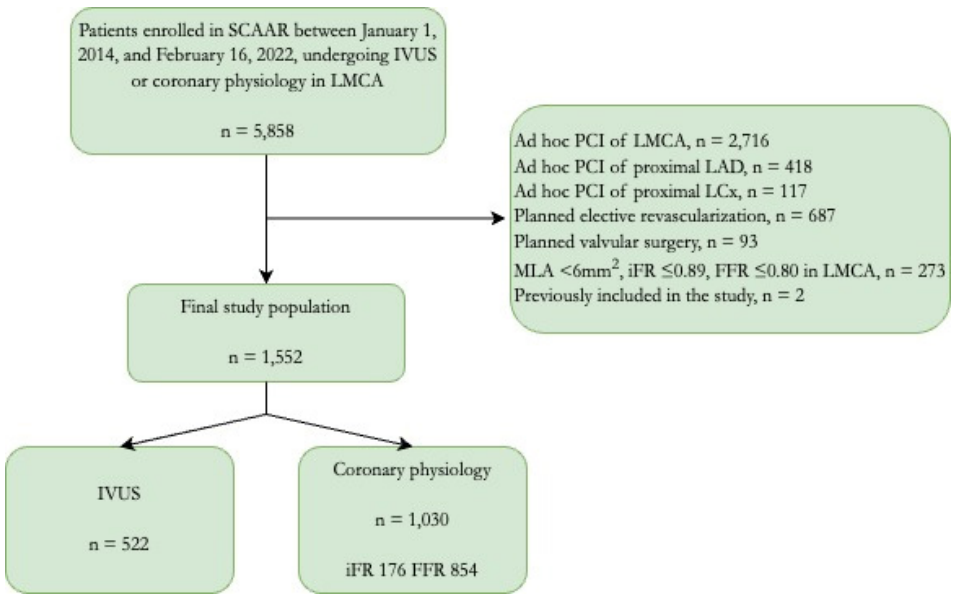

Figure 16. Design of Paper IV comparing deferral of revascularization of the LMCA guided by IVUS or iFR/FFR

FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, IVUS=intravascular ultrasound, LAD=left anterior descending artery, LCx=left circumflex artery, LMCA=left main coronary artery, MLA=minimum luminal area, SCAAR= Swedish Coronary Angiography and Angioplasty Registry.

Paper V

The analysis included data of all lesions assessed with iFR or FFR reported in SCAAR from January 1, 2014 through February 16, 2022. Lesions of the intermediate coronary artery and LMCA were excluded. Exclusion criteria also included instances of both FFR and iFR having been conducted in the target vessel, more than one lesion assessed in a single vessel, and previous CABG. Study design is shown in Figure 17.

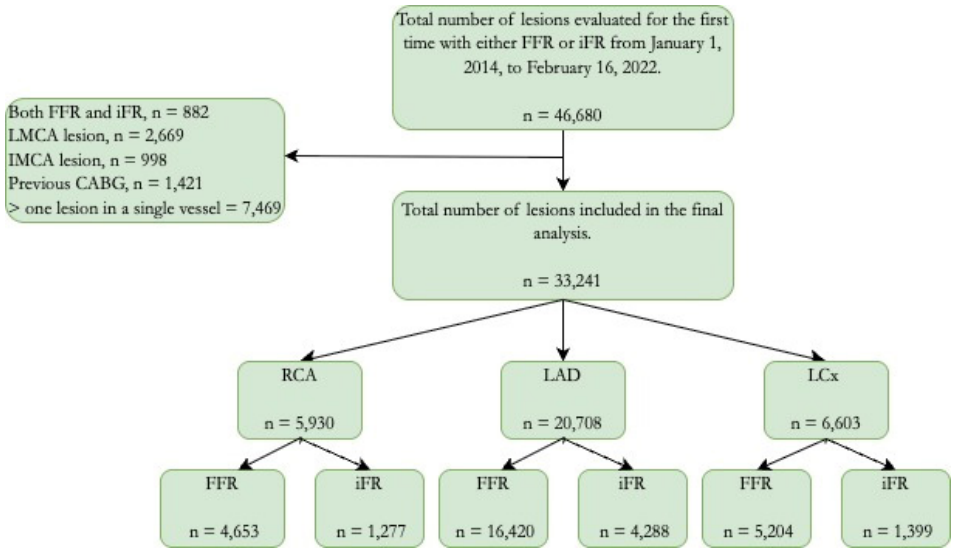

Figure 17. Design of Paper V comparing deferral rates and clinical outcome with FFR vs. IFR in a vessel-specific analysis

CABG=coronary artery bypass grafting, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, IMCA=intermediate coronary artery, LAD=left anterior descending artery, LCx=left circumflex artery, LMCA=left main coronary artery, RCA=right coronary artery.

Study endpoints

Paper I

The outcome of the decision-analytic model was an estimate of the cost associated with iFR and FFR in a Nordic and in a USA setting. Nordic Diagnosis Related Group (NordDRG) codes for uncomplicated conditions were used to estimate patient-specific costs during hospital stay. The Medicare cost data by Diagnostic Related Group (DRG) codes were used for the USA setting. The cost of adenosine administration and cost per stent placed were based on the average cost among centres participating in the trial. The cost per stent placed is included in the NordDRG. The cost in the Nordic setting was presented in US dollars (USD) with an exchange rate of 0.12 SEK to USD as per December 16, 2020.

Paper II

The primary endpoint of the study was the composite of MACE at five years, defined as all-cause death, non-fatal MI, and unplanned revascularization. The

secondary endpoints were the individual components of MACE, including cardiovascular (CV) death and non-CV death.

Paper III

The primary endpoint was MACE at five years in patients deferred based on iFR or FFR, defined as all-cause death, non-fatal MI, and unplanned revascularization. The secondary endpoints were the individual components of MACE, as well as CV death and non-CV death. The endpoints were adjusted for indication for procedure, SAP or ACS.

Paper IV

The primary endpoint was MACE following deferral with IVUS compared to that with coronary physiology (iFR or FFR) in the LMCA within five years, defined as a composite of all-cause death, MI, and unplanned revascularization with PCI or CABG. The secondary endpoints were the individual components of MACE, including CV death and non-CV death. All outcomes were calculated for iFR and FFR separately.

Paper V

Deferral rates for FFR and iFR were calculated separately for the RCA, LAD, and LCx. The primary endpoint was MACE in deferred lesions within five years calculated for each of the target coronary arteries relative to index used. The definition of MACE was the composite of CV death, non-CV death, MI, and unplanned target segment revascularization. The secondary endpoints included the individual components of MACE and unplanned revascularization in each vessel.

Statistical analysis

Paper I

The primary outcome of the decision-analytic model was to estimate the costs associated with each strategy in a Nordic setting and in a USA setting. Since iFR has been shown non-inferior to FFR, a cost-minimization analysis was conducted using the decision-analytic model. One-way deterministic sensitivity analysis was conducted to assess the impact of each separate cost. A probabilistic sensitivity analysis of the statistical uncertainty of parameters was conducted using a Monte

Carlo simulation. The parameters included probability and costs for 1000 bootstrap replicates. The probabilities were modelled with beta distribution chosen according to the number of patients observed in each pathway in the iFR-SWEDEHEART trial.

Papers II-V

Categorical data were expressed as counts and percentages and compared with a chi-square test or Fisher exact test. Continuous variables were expressed as median and interquartile range, tested with the Mann-Whitney U test, or expressed as mean ± standard deviation, tested with a two-tailed Student´s t-test. Kaplan-Meier survival curves were used for visual comparison of two groups. The primary and secondary endpoints were analysed using Cox proportional hazards models, presented with 95% CI. The validity was tested with the proportional hazards assumption. If the proportional hazards assumption was not met, a Poisson regression model was applied to calculate the risk ratio and 95% CI. Unadjusted analyses were conducted, along with those adjusted for prespecified confounders. Subgroup analyses were conducted and tests for interaction were performed. A two-sided p-value <0.05 was considered to indicate statistical significance.

Statistical analysis in Paper I was conducted with Microsoft Excel (Microsoft, Redmond, WA, US); Paper II using SAS; Papers III and IV, STATA v.17 (StataCorp); and, in Paper V, using STATA v.18 (StataCorp).

Ethics

The iFR-SWEDEHEART trial was conducted in accordance with the declaration of Helsinki. The trial was approved by the ethical review boards of Sweden, Denmark, and Iceland. The ethics approval included obtaining data for prespecified secondary outcomes conducted in papers I–III. The trial was registered under www.clinicaltrials.gov:NCT02166736. Monitors had regular contact with the participating centres during the study period to ensure conduction in compliance with the study protocol and regulatory requirements. All patients provided written informed consent.

The SWEDEHEART registry is a national quality registry, and accessing its data does not require written informed consent. Patients are informed of their participation with the option to opt out of the registry. As previously described, the SWEDEHEART data is merged with the National Cause of Death Register, the National Patient Registry, and with the National Registry of Drug prescriptions to obtain information regarding prescribed drugs. When merged, patient identity is removed from the database. Approval was obtained from the Swedish Ethical

Review Authority to use the merged dataset in scientific research. Further approval was needed from the SWEDEHEART steering committee to initiate a study.

Results

Paper I

Paper I: Instantaneous wave-free ratio compared with fractional flow reserve in PCI: A cost-minimization analysis

Aim: To compare the cost associated with iFR-guided revascularization to that with FFR-guided revascularization based on data of the iFR-SWEDEHEART trial.

Main findings

Patient baseline characteristics are presented in Table 4. The parameters for the probabilities used in the decision-tree model, together with data used for estimation of the cost in the Nordic and USA setting are presented in Table 5. The probability of PCI with iFR was 44% compared to 45% in the FFR group. The probabilities for CABG with iFR and FFR were 9% vs. 11%, respectively.

The cost-minimization analysis demonstrated a cost saving per patient of $681 (95% CI $641 – $723) with iFR in the Nordic setting and $1024 ($934 – $1114) in the USA setting. The results were not sensitive to major differences in cost input. The most sensitive cost inputs are illustrated in Figure 18.

Table 4. Patient baseline characteristics

	iFR Group (n = 1,019)	FFR Group (n = 1,018)
Age, yr	67.6 ± 9.6	67.4 ± 9.2
Male	756 (74.2)	766 (75.2)
BMI, kg/m^2	27.6 ± 4.3	27.6 ± 4.3
Indication for angiography		
Stable angina	632 (62.0)	632 (62.1)
Unstable angina	211 (20.7)	208 (20.4)
NSTEMI	176 (17.3)	178 (17.5)
CCS angina class[a]		
I	153/632 (24.2)	121/632 (19.1)
II	355/632 (56.2)	343/632 (54.3)
III	49/632 (7.8)	74/632 (11.7)
IV	0/632 (0.0)	3/632 (0.5)
Missing data	75/632 (11.9)	91/632 (14.4)
Diabetes mellitus	232 (22.8)	213 (20.9)
Hypertension	730 (71.6)	710 (69.7)
Hyperlipidemia	733 (71.9)	704 (69.2)
Smoking status		
Never smoked	351 (34.4)	368 (36.1)
Former smoker	501 (49.2)	467 (45.9)
Current smoker	159 (15.6)	167 (16.3)
Missing data	8 (0.8)	16 (1.6)
Previous MI	337 (33.1)	335 (32.9)
Previous PCI	429 (42.1)	425 (41.7)
Previous CABG	49 (4.8)	43 (4.2)
Angiographic findings		
Nonsignificant coronary artery disease	203 (20.0)	198 (19.4)
One-vessel disease	452 (44.3)	453 (44.5)
Two-vessel disease	256 (25.1)	267 (26.2)
Three-vessel disease	108 (10.6)	101 (9.9)

Values are mean ± SD, n (%), or n/N (%). [a] Values are n/N with stable angina (%). BMI=body mass index, CABG=coronary artery bypass grafting, CCS=Canadian Cardiovascular Society, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, MI=myocardial infarction, NSTEMI=non-ST-segment elevation myocardial infarction, PCI=percutaneous coronary intervention.

Table 5. Parameters assessed in a cost-minimization analysis

Parameters	Proportion of patients	
iFR		
IV adenosine	0% (0/1012)	
PCI	44% (443/1012)	
CABG	9% (93/1012)	
Unplanned revascularization	5% (47/1012)	
Stents placed per patient Mean (SD)	1.58 (±1.08)	
Nonfatal MI	2% (22/1012)	
Fatal MI	0.2% (2/2012)	
FFR		
IV adenosine	100% (1007/1007)	
PCI	45% (459/1007)	
CABG	11% (113/1007)	
Unplanned revascularization	5% (46/1007)	
Stents placed per patient Mean (SD)	1.73 (±1.19)	
Nonfatal MI	2% (17/1007)	
Fatal MI	0.2% (2/1007)	
Costs in Nordic setting (SEK)		**Range[a]**
IV adenosine	400	110–980
PCI	63,131	50,505–75,757
CABG	224,113	179,290–268,936
Unplanned revascularization	56,370	45,096–67,644
Nonfatal MI	33,250	26,600–39,900
Fatal MI	22,411	17,929–26,893
Costs in USA setting (USD)		**Range[a]**
IV adenosine	61	50–73
PCI	18,137	14,510–21,764
CABG	34,221	27,377–41,065
Unplanned revascularization	18,137	14,510–21,764
Nonfatal MI	9,323	7,458–11,188
Fatal MI	10,288	8,230–12,346

[a] range is ± 20%, CABG=coronary artery bypass grafting, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, IV=intravenous, MI=myocardial infarction, PCI=percutaneous coronary intervention, SD=standard deviation, USA=United States of America, USD=US dollar.

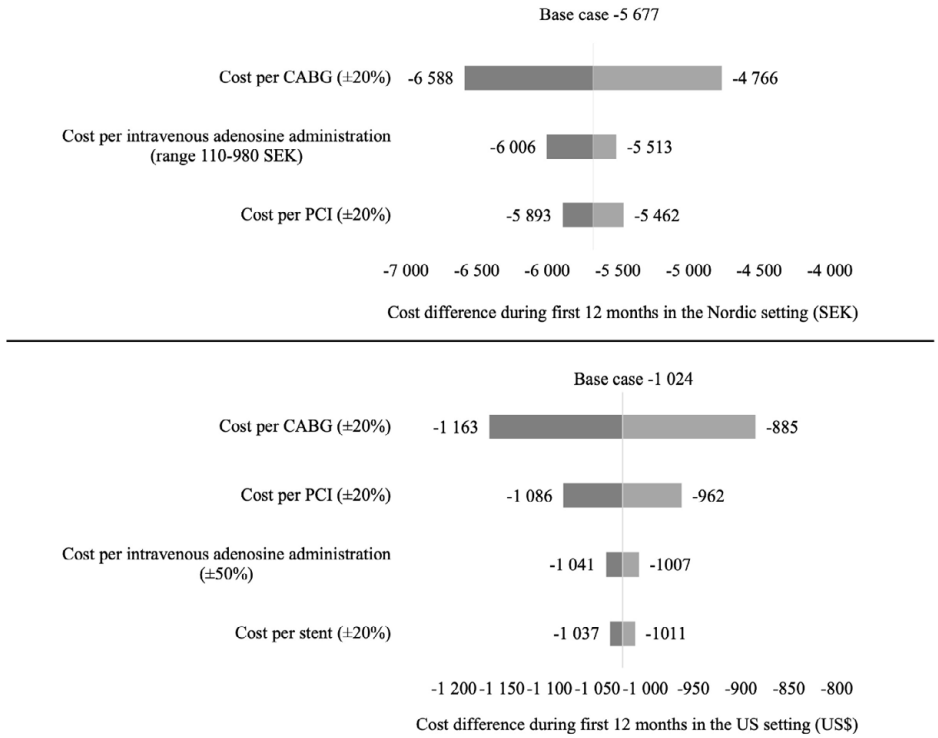

Figure 18. Cost inputs relative to the output with iFR and FFR
Tornado diagrams of the one-way sensitivity analyses illustrating the most sensitive cost inputs relative to the output differences with instantaneous wave-free ratio and fractional flow reserve. Upper panel represents the Nordic setting; lower panel represents the USA setting. Centre line provides results from the base-case models. CABG=coronary artery bypass grafting, PCI=percutaneous coronary intervention, US=United States of America.

Paper II

Paper II: 5-year outcomes of PCI guided by measurement of instantaneous wave-free ratio versus fractional flow reserve

Aim: To determine the rate of a prespecified five-year primary composite endpoint of all-cause mortality, myocardial infarction, and unplanned revascularization in patients of the iFR-SWEDEHEART trial.

Study population and baseline characteristics

Baseline characteristics of the iFR and FFR groups were well balanced (Table 4). [84] Mean age was 68 years, and 75% of participants were male. The indication for the procedure was SAP in 62%, 22% had diabetes mellitus, 33% had previous MI, 42% previous PCI, and 44% had one vessel disease. Procedures are presented in Table 6.

Table 6. Details of procedures used in patients undergoing iFR and FFR

	iFR Group (n = 1,012)	FFR Group (n = 1,007)	*P* value
Radial-artery approach	841 (83.1)	811 (80.5)	0.13
Contrast used per patient, mL	110 (80–155)	115 (80–160)	
Procedure time, min	50.8 (13.8–87.8)	53.1 (18.1–88.1)	0.09
IV adenosine administered		695 (69.0)	
Lesions evaluated	1,568	1,436	
Lesions evaluated per patient	1.55 ± 0.86	1.43 ± 0.70	0.002
Hemodynamically impotant lesions[a]	457 (29.1)	528 (36.8)	<0.001
Mean number of functionally significant lesions per patient	0.45 ± 0.71	0.52 ± 0.68	0.05
iFR	0.91 ± 0.10		
iFR in hemodynamically important lesions	0.80 ± 0.13		
FFR		0.82 ± 0.10	
FFR in hemodynamically important lesions		0.72 ± 0.08	
Total n of stents placed	698	787	
Stents placed per patients undergoing PCI	1.58 ± 1.08	1.73 ± 1.19	0.05
Stent length per patient, mm	34.2 ± 21.9	36.8 ± 24.5	0.10
Stent diameter, mm	2.97 ± 0.47	3.01 ± 0.49	0.27
Drug-eluting stents placed	696 (99.7)	770 (97.8)	0.50
PCI as primary revascularization procedure	443 (43.8)	456 (45.3)	0.50
CABG as primary revascularization procedure	93 (9.2)	113 (11.2)	0.13
Revascularization performed	536 (53.0)	569 (56.5)	0.11

Values are n (%), median (IQR), n, or mean ± SD, unless otherwise indicated. [a] Values are n (% of total lesions evaluated). CABG=coronary artery bypass grafting, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, IV=intravenous, PCI=percutaneous coronary intervention.

Main findings

No patient was lost to follow-up. The primary outcome of MACE occurred in 21.5% of patients in the iFR group and 19.9% of the patients in the FFR group (HR 1.09; 95% CI: 0.90 – 1.33). Kaplan-Meier curves of the primary endpoint are presented in Figure 19.

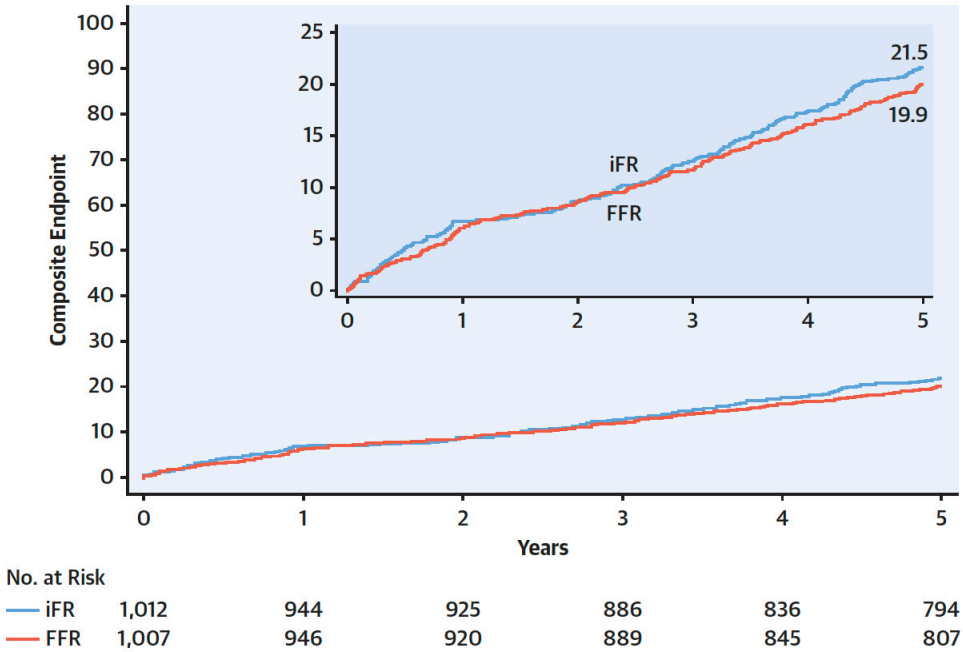

Figure 19. Kaplan-Meier curves illustrating rate of MACE within five years

Kaplan-Meier curves illustrating the primary endpoint of MACE defined as all-cause mortality, nonfatal myocardial infarction, or unplanned revascularization within five years. y-axis represents percent of total patients. FFR=fractional flow reserve, iFR=instantaneous wave-free ratio.

The secondary endpoints of individual components of MACE, including CV and non-CV death, did not differ significantly between groups (Table 7), although the rate of non-CV death was borderline higher in the iFR group. When a test for interaction was conducted in predefined subgroups for MACE no significant difference in treatment effect was observed.

Table 7. Endpoints at five years in patients undergoing iFR vs. FFR

	iFR (n = 1,012)	FFR (n = 1,007)	HR	95% CI
Composite endpoint	218 (21.5)	200 (19.9)	1.09	0.90–1.33
All-cause mortality	95 (9.4)	79 (7.9)	1.20	0.89–1.62
Nonfatal myocardial infarction	58 (5.7)	58 (5.8)	1.00	0.70–1.44
Unplanned revascularization	117 (11.6)	114 (11.3)	1.02	0.79–1.32
Cardiovascular death	28 (2.8)	33 (3.3)	0.85	0.51–1.40
Noncardiovascular death	67 (6.6)	46 (4.6)	1.46	1.00–2.12

Values are n (%). CI=confidence interval, FFR=fractional flow reserve, HR=hazard ratio, iFR=instantaneous wave-free ratio.

Paper III

Paper III: Clinical outcome of revascularization deferral with instantaneous wave-free ratio and fractional flow reserve: A 5-year follow-up substudy from the iFR-SWEDEHEART trial

Aim: To compare five-year clinical endpoints in patients of the iFR-SWEDEHEART trial deferred from revascularization based on iFR vs. FFR as well as outcomes by clinical presentation.

Study population and baseline characteristics

The number of patients included in the analysis was 908, with 473 (52%) deferred with iFR and 435 (48%) deferred with FFR. The number of patients presenting with SAP was 611 and, with ACS, 297. Patient baseline characteristics were similar, with the exception of a significant difference in Canadian Cardiovascular Society grade of angina between iFR and FFR ($p<0.05$) and a difference in smoking status ($p<0.05$).

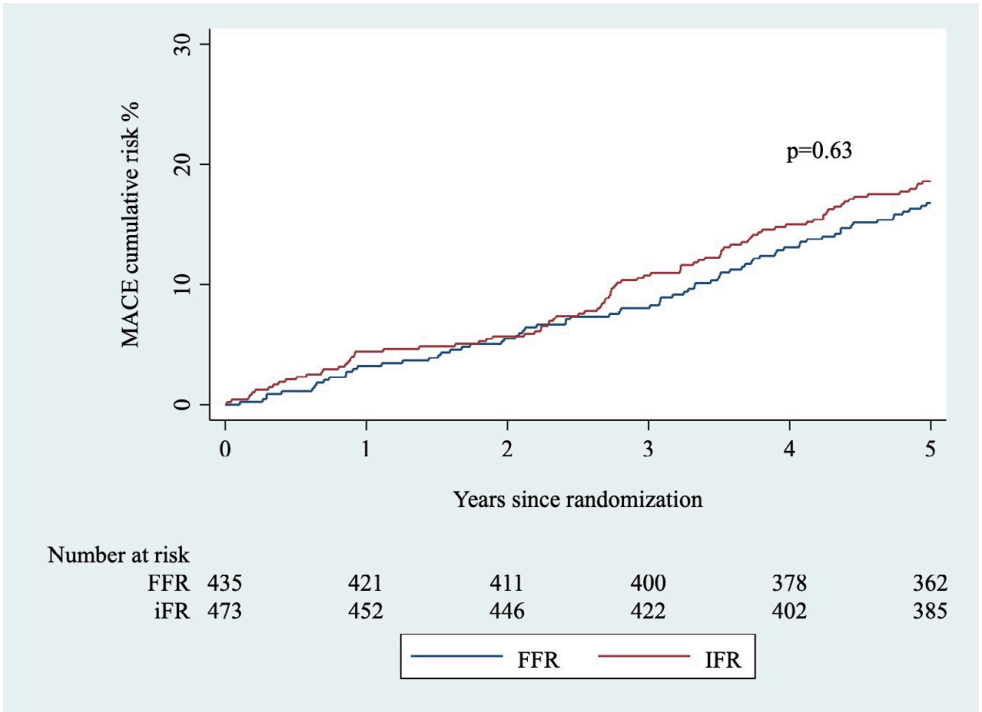

Figure 20. Kaplan-Meier survival curve illustrating the cumulative risk of MACE in patients with lesions deferred based on iFR and FFR

Cumulative risk of a MACE over the course of five years, iFR vs. FFR. FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, MACE=major adverse cardiac event.

Main findings

The primary endpoint of MACE did not differ significantly between patients deferred with iFR and those deferred based on FFR over five years (iFR 18.6% vs. FFR 16.8%; adjusted HR 1.08; 95% CI: 0.79 – 1.48) (Figure 20). No significant difference was seen in the individual components of MACE, including CV and non-CV death. When adjusting results according to indication for the procedure (SAP or ACS), no significant difference was seen in MACE (SAP 16.7% vs. ACS 19.9%, adjusted HR 0.85; 95% CI: 0.61 – 1.19), and no significant difference was seen in the individual components of MACE (Table 8). Deferral with iFR or FFR did not influence results when a test for interaction was conducted.

Table 8. Major adverse cardiac events and its individual components at five years in patients presenting with SAP and ACS

			SAP vs ACS		
	SAP (n = 611)	**ACS (n = 297)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	***P* value**
MACE	102 (16.7)	59 (19.9)	0.82 (0.60–1.13)	0.85 (0.61–1.19)	0.35
All-cause death	41 (6.7)	24 (8.1)	0.82 (0.49–1.36)	0.86 (0.51–1.44)	0.57
Cardiovascular death	10 (1.6)	8 (2.7)	0.60 (0.24–1.52)	0.60 (0.23–1.57)	0.30
Noncardiovascular death	31 (5.1)	16 (5.4)	0.93 (0.51–1.70)	0.97 (0.52–1.80)	0.92
Nonfatal MI	32 (5.2)	17 (5.7)	0.91 (0.51–1.65)	0.96 (0.53–1.74)	0.89
Unplanned revascularizaation	57 (9.3)	29 (9.8)	0.95 (0.61–1.49)	0.96 (0.60–1.52)	0.85

Values are n (%) unless indicted otherwise. ACS=acute coronary syndrome, CI=confidence interval, HR=hazard ratio, MACE=major adverse cardiac event, MI=myocardial infarction, SAP=stable angina pectoris.

Paper IV

Paper IV: Deferral of left main coronary artery revascularization via IVUS or coronary physiology – Long-term outcomes from the SWEDEHEART registry

Aim: To compare long-term clinical endpoints in patients with LMCA stenosis deferred from revascularization with IVUS with those deferred by coronary physiology via iFR or FFR in an all-comer real-world population, using the SWEDEHEART registry.

Baseline population characteristics

The number of patients included in the final study population was 1,552, with 522 (33.6%) deferred based on IVUS and 1,030 (66.4%) deferred based on coronary physiology [iFR 176 (11.3%) and FFR 854 (55.0%)]. Mean age in both groups was 71 years with 74.5% male. The groups differed in the profile of comorbidities with a significantly greater proportion of patients with diabetes mellitus (p=0.03), hypertension (p=0.001), and previous MI (p=0.04) in the coronary physiology group and a significantly higher rate of renal failure (p=0.03) in the IVUS group. The indication for the procedure differed significantly between groups with a greater

proportion of patients in the coronary physiology group presenting with CCS and a greater proportion presenting with ACS in the IVUS group.

The two groups were similar with respect to the number of vessels showing significant disease and the anatomic distribution of significant disease in middle and distal segments of the vessel. The median iFR index was 0.96 (0.94−0.98) and, for FFR, the median value was 0.89 (0.85−0.93). The median value of MLA in the IVUS group was 8.5 mm^2 (7.5−11.0).

Table 9. Rate of MACE and its components in patients deferred from revascularization based on IVUS compared to coronary physiology

Endpoint	IVUS	Coronary physiology	Unadjusted RR (95%CI)	Adjusted[a] RR (95%CI)
MACE	163 (40.2)	306 (35.5)	1.08 (0.90–1.31) p=0.41	1.18 (0.97–1.44) p=0.09
Myocardial infarction	51 (12.4)	96 (11.3)	1.05 (0.75–1.47) p=0.79	1.12 (0.79–1.59) p=0.53
Unplanned revascularization	61 (12.9)	159 (17.4)	0.76 (0.56–1.02) p=0.07	0.87 (0.64–1.18) p=0.37
All-cause death	80 (22.4)	126 (16.4)	1.30 (0.82–2.08) p=0.27	1.38 (1.03–1.83) p=0.03
Cardiovascular death	38 (10.7)	49 (6.4)	1.69 (1.12–2.55) p=0.01	1.90 (1.23–2.92) p=0.004
Non-cardiovascular death	42 (13.1)	77 (10.7)	1.10 (0.76–1.60) p=0.61	1.08 (0.73–1.59) p=0.71
Endpoint	**IVUS**	**iFR**	**Unadjusted RR (95%CI)**	**Adjusted[a] RR (95%CI)**
MACE	163 (40.2)	42 (31.3)	1.35 (0.96–1.89) p=0.08	1.34 (0.95–1.90) p=0.10
Myocardial infarction	51 (12.4)	16 (11.5)	1.04 (0.73–1.48) p=0.81	1.14 (0.79–1.64) p=0.47
Unplanned revascularization	61 (12.9)	17 (10.8)	1.21 (0.71–2.07) p=0.49	1.15 (0.66–2.00) p=0.62
All-cause death	80 (22.4)	22 (17.6)	1.21 (0.78–1.86) p=0.40	1.34 (0.82–2.19) p=0.24
Cardiovascular death	38 (10.7)	9 (6.9)	1.57 (0.77–3.23) p=0.22	1.55 (0.73–3.32) p=0.26
Non-cardiovascular death	42 (13.1)	13 (11.5)	1.12 (0.60–2.07) p=0.73	1.15 (0.61–2.20) p=0.66
Endpoint	**IVUS**	**FFR**	**Unadjusted RR (95%CI)**	**Adjusted[a] RR (95%CI)**
MACE	163 (40.2)	264 (36.5)	1.04 (0.86–1.26) p=0.68	1.15 (0.94–1.41) p=0.17
Myocardial infarction	51 (12.4)	51 (12.4)	1.07 (0.61–1.88) p=0.80	0.99 (0.55–1.79) p=0.98

Unplanned revascularization	61 (12.9)	142 (18.7)	0.70 (0.52–0.95) p=0.02	0.82 (0.60–1.13) p=0.23
All-cause death	80 (22.4)	104 (16.2)	1.38 (1.00–1.78) p=0.05	1.38 (1.02–1.86) p=0.04
Cardiovascular death	38 (10.7)	40 (6.2)	1.71 (1.11–2.65) p=0.01	2.01 (1.27–3.17) p=0.003
Non-cardiovascular death	42 (13.1)	64 (10.6)	1.10 (0.75–1.62) p=0.63	1.05 (0.70–1.57) p=0.83

Values are n (%) unless indicated otherwise. [a] Adjusted for age, sex, year of inclusion, smoking status, diabetes mellitus, hypertension, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke, chronic heart failure, peripheral artery disease, chronic obstructive pulmonary disease, renal failure, cancer, indication for the procedure and diseased vessels. CI=confidence interval, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, MACE=major adverse cardiac event, RR=risk ratio.

Main findings

No patient was lost to follow-up during a median of 2.7 years. The primary outcome of MACE did not differ between groups (IVUS, 40.2% vs. coronary physiology 35.5%; adjusted HR 1.18; 95% CI: 0.97 – 1.44) (Table 9; Figure 21). The rate of MACE did not differ when comparing IVUS to either iFR or to FFR. There was a significant difference in all-cause death, driven by a significantly greater proportion of CV deaths in the IVUS group compared to those in the coronary physiology group, as well as when comparing IVUS to FFR alone.

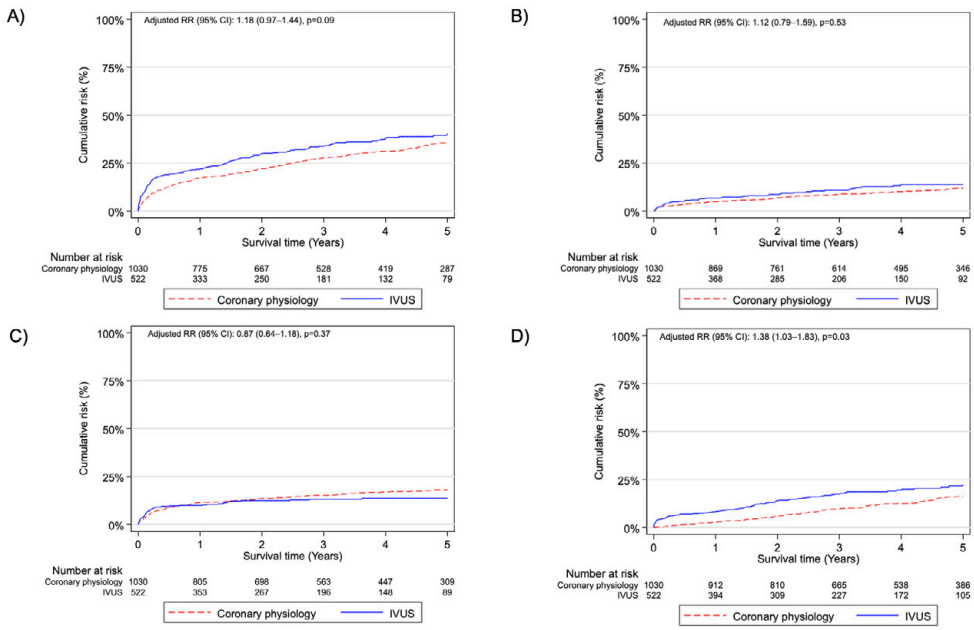

Figure 21. Five year rate of MACE and individual components in patients with revascularization deferred based on IVUS compared to coronary physiology

Cumulative risk visualized in Kaplan-Meier curves over five years for the IVUS and coronary physiology groups. A) MACE, B) myocardial infarction, C) unplanned revascularization, D) all-cause death. CI=confidence interval, FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, IVUS=intravascular ultrasound, RR=risk ratio.

Paper V

Paper V: A vessel-specific analysis of deferred lesions using the instantaneous wave-free ratio and fractional flow reserve

Aim: (1) To compare deferral rates based on FFR with iFR in the RCA, LAD, and LCx; and (2) to evaluate the long-term clinical outcomes of deferred lesions with FFR vs. iFR in the RCA, LAD, and LCx, respectively, in an all-comer real-world population using the SWEDEHEART registry.

Study population and lesion characteristics

A total of 33,241 lesions were included in the analysis. Lesion distribution is presented in Table 10.

Table 10. Location of investigated lesions and physiology index obtained in each vessel

	RCA		LAD		LCx	
Number of lesions (%)	**5,930 (17.8)**		**20,708 (62.3)**		**6,603 (19.9)**	
	FFR	iFR	FFR	iFR	FFR	iFR
Proportion of lesions/index	78.5%	21.5%	79.3%	20.7%	78.8%	21.2%

FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, LAD=left anterior descending artery, LCx=left circumflex artery, RCA=right coronary artery.

The median patient age in the physiology index groups was 69 years with 67–77% male. In the RCA, the iFR group contained a significantly greater proportion of females ($p<0.001$) and patients with previous stroke ($p=0.01$). In the LAD, the iFR group had a significantly higher proportion of females ($p<0.001$), previous stroke ($p=0.02$), and chronic obstructive pulmonary disease ($p=0.01$).

Main findings

The median follow-up time was 3.4 years. The deferral rates in the RCA were 69.8% with FFR vs. 82.6% with iFR ($p<0.001$); 59.8% vs. 65.5%, respectively, in the LAD ($p<0.001$); and 70.1% vs. 73.8%, respectively, in the LCx ($p=0.007$). The deferral rate with iFR was 10.6% greater ($p<0.001$) in all surveyed arteries, 18.7% higher in the RCA, 9.5% higher in the LAD, and 5.3% higher in the LCx (Figure 22).

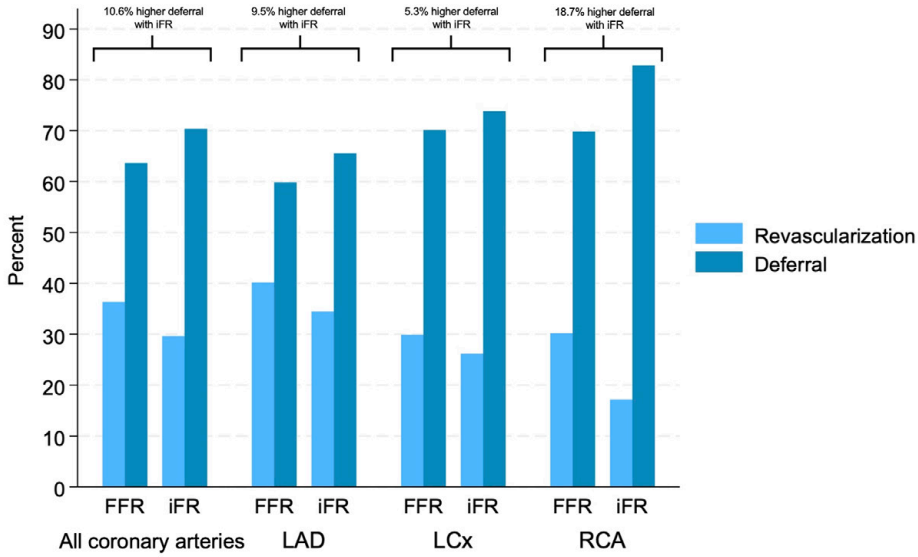

Figure 22. Revascularization/deferral rates based on FFR and iFR relative to affected artery
Revascularization and deferral rates across all analysed coronary arteries. The difference (%) in deferral rate with iFR from that with FFR is shown. FFR=fractional flow reserve, iFR=instantaneous wave-free ratio, LAD=left anterior descending artery, LCx=left circumflex artery, RCA=right coronary artery.

No significant differences were found in MACE rates at five years in lesions with revascularization deferred based on FFR vs. iFR in any investigated vessel: RCA (adjusted HR: 1.14; 95% CI: 0.96 – 1.36; p=0.13), LAD (adjusted RR: 0.93; 95% CI: 0.84 – 1.04; p=0.19), and LCx (adjusted RR: 0.96; 95% CI: 0.81 – 1.13; p=0.60). There were no significant differences in rate of secondary endpoints in the RCA, LAD, or LCx.

Discussion

Despite awareness of the advantages of basing decisions of revascularization on coronary physiology, especially the hyperaemic FFR index, its adoption rate in clinical practice has been low worldwide. [51, 63-66, 69, 84] Possible reasons are the time and costs involved, patient discomfort associated with adenosine administration, contraindications, and lack of monetary reimbursement. [117] The introduction of iFR as a non-hyperaemic index may encourage broader use of coronary physiology in clinical practice. [75] The DEFINE-FLAIR and iFR-SWEDEHEART randomized clinical trials demonstrated noninferiority of iFR compared to FFR with respect to clinical outcomes after one year follow-up. [83, 84] Information obtained from the iFR-SWEDEHEART trial formed the foundation of the investigations reported in this PhD thesis. The present research addresses important aspects of the assessment of CAD using coronary physiology and contributes information applicable to iFR assessment in clinical practice in patients varying in demographics and disease presentation.

Economic aspects of coronary physiology assessment

Cost of iFR compared to FFR

The demonstration of noninferiority of iFR to FFR in guiding coronary revascularization led to its class IA recommendation in clinical guidelines applied to intermediate coronary artery stenoses. [19] The two methods being found equally safe favours the method showing advantages, one of which is the financial aspects in an economically challenged health care system. Before the introduction of iFR, FFR was considered to be cost-effective. [19, 72-74] **Paper I** reported that an iFR-guided revascularization strategy provided significant cost savings over an FFR-guided strategy, with comparable clinical outcome. [118] The savings were driven by eliminating administration of adenosine as well as a higher rate of deferral leading to reduced revascularization with PCI or CABG at the index procedure. The DEFINE-FLAIR trial conducted in Europe, Asia, North America, and Africa demonstrated an average one-year reduction in cost of 896.00 USD. [119] Our findings corresponded with these results, and, taken together, indicate that costs savings with iFR can be expected in most of the world.

Adenosine and procedure time

Ensuring a period of maximum hyperaemia is critical when conducting FFR, as less than maximum will lead to overestimation of the FFR value, thus underestimating stenosis severity. [52, 63, 70, 120] The cost and availability of adenosine varies with time and place, and the volume needed can depend on patient response and method of administration. Eliminating adenosine administration was an important and predictable factor in cost reduction. It is, however, a relatively small fraction of the overall cost and not the largest contributor to savings. An iFR strategy also limits patient discomfort and adverse side-effects [121] that potentially increase costs in the longer term. While it was not a part of our analysis, practitioner time is always a major financial consideration. The DEFINE-FLAIR trial demonstrated significantly shorter procedure time when iFR was used to guide revascularization. [83]

Revascularization and deferral

In the iFR-SWEDEHEART trial, a significantly greater proportion of lesions were considered hemodynamically important with FFR (36.8%) compared to iFR (29.1%), $p<0.001$. [84] However, revascularizations with PCI and CABG were only numerically higher with FFR, and number of stents placed per patient was higher with borderline significance. These differences were the primary source of the lower cost of iFR-guided revascularization. The more frequent deferral of coronary artery stenosis treatment was also the primary reason behind the significantly lower cost with iFR in the DEFINE-FLAIR trial. [119] Safe deferral with iFR was confirmed when merging the datasets of the two studies, which included 4,486 patients in whom 50% of the iFR group was deferred vs. 45% in the FFR group ($p<0.01$) with comparable clinical outcome. [85] This demonstrates that patients can be safely deferred, reducing costs without impacting clinical outcome.

Implementing findings in clinical practice

The main contribution of these results is the potential to influence adoption of basing CAD treatment on coronary physiology indices in clinical practice, possibly having important implications for patient outcomes. The benefits of choosing an iFR-guided strategy include reducing patient discomfort, a more effective cath-lab workflow, financial benefits and potentially fewer adverse side-effects related to adenosine and unnecessary revascularization.

Long-term clinical outcomes with iFR

Outcome of iFR

The approval of iFR use in clinical practice was based on validation trials comparing iFR to other assessments of myocardial ischemia. [75, 79-81, 122] Uncertainty with respect to clinical outcome was addressed in the DEFINE-FLAIR and iFR-SWEDEHEART trials, which confirmed the noninferiority of iFR to FFR. [83, 84] Although data of long-term benefits in guiding PCI were available for FFR, the mentioned trials contributed only one-year outcome data of iFR. [65, 69, 123, 124] Our five-year results presented in **Study II** contributed the first long-term randomized clinical outcome data of iFR. [125] With no patient lost to follow-up, the event rates were similar for iFR and FFR in MACE and its individual components of all-cause death, nonfatal MI, and unplanned revascularization. Five-year outcome data of the DEFINE-FLAIR trial are currently available and show similar outcomes regarding MACE in iFR- and FFR-guided revascularization. [126]

Higher rate of all-cause death

The long-term outcome data obtained in the mentioned randomized trials raised concerns with respect to iFR. The DEFINE-FLAIR trial MACE rate echoed the results of the iFR-SWEDEHEART trial, finding no difference at five years. However, its observed rate of all-cause death was significantly higher with iFR (9.0%) than with FFR (6.2%) ($p<0.01$), driven by higher CV death with iFR. No difference was seen in rate of MI or unplanned revascularization. DEFINE-FLAIR found no difference in MACE rates, including all-cause death, in patients in whom treatment had been deferred based on iFR and FFR. In patients who underwent revascularization, the incidence of MACE was significantly higher with iFR (24.6% vs. 19.2%, $p=0.01$), including all-cause death (11.0% vs. 5.7%, $p=0.001$), and CV death (5.9% vs. 3.0%, $p=0.01$). The difference was striking and not seen in earlier studies. These results are important, as MACE following deferral could be seen as an indicator that the coronary physiology index was inadequate, while MACE following revascularization is more likely related to the revascularization procedure itself. The long-term follow-up of the iFR-SWEDEHEART trial found no significant differences in all-cause death, although there was a borderline higher non-CV death rate in the iFR group ($p=0.05$), along with higher event rates of cancer, septicaemia, and kidney failure. Two external study-level analyses of pooled data from the DEFINE-FLAIR and iFR-SWEDEHEART trial five-year results have been conducted. One study revealed a greater rate of all-cause death at five years in the iFR group, driven by higher incidence of death for which cause was unavailable without difference in CV death, nonfatal MI, or unplanned revascularization. [127] The

second analysis used the same dataset to create a reconstruction of time-to-event data from Kaplan-Meier curves and risk tables, revealing higher risk of MACE with iFR-guided revascularization driven by a higher risk of all-cause mortality. [128] However, these studies should be interpreted with caution, as they are study-level analyses with no access to patient-specific data regarding outcomes or potentially contributing factors. More recent trials have not confirmed the increased rate of mortality with iFR found in the DEFINE-FLAIR trial and the pooled analyses. A recently published report using SWEDEHEART registry data of 24,623 patients undergoing coronary revascularization based on either FFR or iFR revealed no difference in MACE or all-cause mortality between the two indices. [129] This large body of real-world data reflects coronary physiology index use in clinical practice and supplements existing knowledge of its procedures and interpretation.

One might question whether decision-making based on coronary physiology should be considered a factor in the endpoint of all-cause death. Nonfatal MI and unplanned revascularization are the most likely endpoints to be directly affected by a miscalculation in coronary physiology assessment. In the FAME II trial, a greater rate of unplanned revascularization after three years was revealed in patients deferred from revascularization with FFR <0.80 compared to patients revascularized with FFR <0.80. [130]

In the light of subsequent research, alternative causes as well as the possibility of study methodological differences should be considered when interpreting the higher rate of all-cause mortality and CV death observed with iFR in the DEFINE-FLAIR trial. The authors of the study mention lack of information regarding cause of death in 50% of the cases and differences with the iFR-SWEDEHEART trial in event reporting, as well as the COVID-19 pandemic impact on the multinational DEFINE-FLAIR study compared with European Nordic countries in the iFR-SWEDEHEART trial. [131] The trial was not powered for the detection of all-cause mortality as an individual endpoint, which should also be considered when interpreting the results.

Deferral with respect to coronary physiology index

The lower number of hemodynamically important lesions identified in the iFR-SWEDEHEART trial with iFR compared to FFR, and thus higher proportion of deferral, points to the importance of evaluating outcome in the deferred population. [84] Deferral of revascularization based on the FFR index was confirmed to be safe up to 15 years when using the cutoff >0.75 in the DEFER trial. [64, 65, 69] However, the standard cutoff value has since changed, and drug eluting stents and medical treatment have evolved. The procedures of the FAME study were more in line with current FFR and revascularization practises and confirmed the safety of deferral with FFR in the short and long term. [66, 123] An analysis of outcomes in patients deferred from revascularization was made in a pooled population of the DEFINE-

FLAIR and iFR-SWEDEHEART trials. [85] In total, 2,130 patients were deferred (45% based on FFR vs. 50% based on iFR, p<0.01). The rate of MACE was approximately 4.0% in both groups after one year with no significant difference between indices in the individual MACE components. Thus, deferral with iFR and FFR were found equally safe. The reported event rates were approximately half those reported for deferral with FFR in older studies, reflecting the evolution of interventional cardiology and medical therapy. [64] A registry study from SWEDEHEART including 11,324 patients deferred based on either iFR or FFR showed no significant difference in clinical outcomes over a median follow-up time of two years. [132] In **Study III**, we compared five-year clinical endpoints in patients deferred from revascularization based on iFR or FFR using data of the iFR-SWEDEHEART trial. [133] Our study confirmed the favourable outcome in the DEFINE-FLAIR and iFR-SWEDEHEART pooled population after one year with respect to MACE and its individual components. The event rate in the FFR-deferred group (16.8%) was lower than that reported in the DEFER trial (21%) but not as low as might be expected relative to one-year outcomes of the trials (4.0% in the DEFINE-FLAIR and iFR-SWEDEHEART pooled analysis vs. 8.0% in DEFER). Our study population was older at inclusion than that of DEFER and included a greater proportion of patients with ACS as indication for evaluation, potentially explaining the higher MACE rate observed than may have been expected.

Deferral relative to indication for procedure

Concern has been raised regarding use of FFR in myocardial regions of recent infarction because of abnormal microvascular function in the infarcted area. [134, 135] Decrease in the total mass of viable myocardium in the area affected by stenosis may lead to overestimating the FFR value. [136] Two large randomized clinical trials focusing on patients presenting with STEMI revealed that FFR-guided revascularization of non-culprit lesions prior to discharge after PCI of culprit lesions was associated with higher rate of MACE-free survival than seen in those with PCI of culprit lesion only. [137, 138] A limitation of these studies is that they included only patients with ACS and did not compare results to those with SAP. Fractional flow reserve values determined in non-culprit lesions at the time of MI did not show change at 35 ± 4 days, confirming the reliability of FFR results obtained at the time of MI. [139]

Data of non-culprit lesion assessment with iFR, like that of FFR, are limited. The negative predictive value of iFR has been shown to be high (89%) in the presence of acute STEMI and in the evaluation of non-culprit lesions. [140] In the pooled analysis of the DEFINE-FLAIR and iFR-SWEDEHEART trials, the MACE rate in patients deferred from revascularization was higher in those who presented with ACS than in those with SAP. [85] The rate was proportionally higher in patients presenting with ACS than with SAP when deferred with FFR (6.42% vs. 3.42%)

compared to iFR (5.41% vs. 3.84%), with a non-significant test for interaction (p=0.46). These results are consistent with other studies showing higher rate of MACE in patients with deferred lesions presenting with ACS than SAP when evaluated with FFR. [141-143] In **Study III**, our five-year follow-up of deferred patients revealed no significant difference in outcomes when classified by clinical presentation of ACS or SAP or with respect to index used. [133] Our results add valuable information to that of previous studies of deferral based on iFR and FFR relative to clinical presentation and should be interpreted in light of other studies.

Left main coronary artery lesions

Significant LMCA disease is associated with poor prognosis and high mortality. [86, 87, 144] The LMCA is the most challenging segment to assess with angiography and is vulnerable to interobserver variation. [88, 145] While revascularization of a vessel with significant stenosis is crucial, revascularization of non-significant stenosis with CABG using the left internal mammary carries high risk of atresia. [146] In European clinical guidelines, coronary physiology as represented by FFR and iFR indices has a class IA recommendation to guide revascularization of intermediate stenoses in patients with CCS, while IVUS has a class IIa, level B recommendation in assessing the severity of unprotected LMCA lesions. [19]

Coronary physiology indices and left main coronary artery lesions

Patients with LMCA stenoses have largely been excluded from randomized controlled trials (RCT) because of risks involved in deferring treatment of significant lesions. Observational studies support the use of FFR to guide revascularization in patients with LMCA lesions, [93] however, a large meta-analysis found a greater rate of later revascularizations in the deferred group. [93] Only one included study used the current cutoff value, deferring patients with FFR ≥0.80 and conducting CABG in those with FFR <0.80, with similar five-year clinical outcome in the groups. [90]

Studies of assessment of LMCA lesions with iFR are limited. The largest observational study (n=314) to date revealed no difference in survival of patients with iFR-deferred vs. revascularized lesions after four years. [95] A comparison of FFR and iFR indices in the LMCA have shown overall agreement of 80%. [147] Thus, FFR and iFR are reported as safe for guidance in the LMCA in most studies, but those available are observational and should be interpreted with caution. European guidelines provide no specific recommendations regarding choice of coronary physiology index, as there is currently no indication of a need for individualising

procedures. An RCT focusing on intervention in LMCA lesions and coronary physiology indices would be of value.

Concern is raised regarding the evaluation of LMCA lesions in the presence of distal stenosis, often in the LAD and/or LCx. These stenoses can affect the obtained results depending on which vessel is interrogated. [148] The presence of downstream serial stenoses when conducting FFR tends to lead to underestimating the severity of LMCA lesions if stenosis is present distal to the sensor tip. [149] A pull-back technique may overcome this, but, when investigating the LMCA, the possibility of distal stenosis should always be considered. A proximal stenosis influences results more than does one in a distal side branch. [150] This is not considered to be a major factor with iFR, as the microcirculation keeps coronary flow constant and stable regardless of stenosis severity, and pressure changes across serial stenoses are more predictable. [135] Warisawa et al. revealed that hyperaemic pull-back quantification of lesion-specific ischemia differed from non-hyperaemic results in 20% of cases, posing a diagnostic challenge with assessment of serial coronary artery lesions, especially under hyperaemic conditions. [151] Agreement of FFR and iFR appears to be higher in the LCx than in the LAD. [147] This problematic situation with downstream lesions and interpretation of FFR and iFR values was the rationale for excluding patients with significant LAD or LCx disease from **Study IV**. [152] Given that this was a registry study, information regarding the specific vessel interrogated was not available, making it necessary to exclude the possibility of interrogation of a vessel with distal lesions.

IVUS in left main coronary artery lesions

Intravascular ultrasound shows an advantage over coronary physiology techniques in its facility to directly reveal level of stenosis and plaque morphology, thus aiding in planning of revascularization and stent placement. On the other hand, IVUS does not indicate the hemodynamic importance of a stenosis. The decision of whether an LMCA lesion would benefit from revascularization is based on the MLA. A cutoff value of ≥ 6 mm^2 for deferral has high sensitivity and specificity compared to the FFR cutoff of ≥ 0.75 and has been shown to be safe. [103, 106] An IVUS of ≤ 6 mm^2 has also been shown to correlate to iFR ≤ 0.89. [153] However, the cutoff value should always be interpreted in relation to individual patient characteristics, as the recommended values may differ among populations. [103-105]

Coronary physiology and IVUS

An optimal procedure for assessment of LMCA lesions has not been recommended, and, in clinical practice, coronary physiology and IVUS are often used as primary, sometimes complementary, methods. Patients undergoing IVUS or FFR have shown similar rates of adverse events in a mid-term follow-up. [154] The use of IVUS with

MLA ≥6 mm^2 for deferral in cases of conflicting iFR and FFR results appears to be safe. [147] In **Paper IV** we report deferral of LMCA lesions with IVUS compared to that based on coronary physiology indices. [152] The rationale for this was evaluating the methods in a real-world setting in which FFR and iFR are considered equally safe and act as a homogenic group to compare to IVUS as standard procedure to assess LMCA lesions. As RCTs seldom include patients with LMCA lesions, further studies are needed to confirm results. The adverse event rates observed in our study were higher than reported in previous studies, with 40.2% rate of MACE in the IVUS group and 35.5% in the coronary physiology group over a median follow-up of 2.7 years. In previously mentioned studies, [90, 95, 106] the MACE rate in patients with iFR-deferred lesions was 9.2% at 30 months, five-year event-free survival in the FFR-deferred group was 74.2%, and, in those with lesions deferred based on IVUS, 87.3%. after two years. A recently published study of IVUS used when iFR and FFR showed conflicting results reported a cardiac event rate of 8.3% in the iFR and IVUS-deferred group after 20 months. [147] Multiple factors could explain differences in results of these studies from those of our work, including the nature of real-world data in which unknown confounders, as well as a higher rate of comorbidities in an unselected population, may influence results. Other factors may be differences in study design, length of follow-up, and our endpoint of unplanned revascularization not being restricted to target lesions.

Our study revealed a greater rate of all-cause death and CV mortality in the IVUS group, probably due to a higher proportion of patients presenting with STEMI and renal failure – factors strongly correlated with adverse outcome early in follow-up. Selection bias is a possibility in observational data. The interventionist is also more likely to choose IVUS for a patient exhibiting frailty, when the LMCA is not well visualized on angiography, or when IVUS is felt more likely to accurately guide PCI. As previously mentioned, MI and unplanned revascularization are the target endpoints liable to be impacted if IVUS fails to correctly characterize LMCA lesions. They were not proportionally greater in our study, and the higher rates of all-cause death should therefore be interpreted with caution.

Vessel-specific coronary flow and clinical outcome

Flow patterns in the RCA and LCA

The flow pattern in the coronary arteries differs from that in systemic circulation in that compression of the microcirculation in systole, along with decompression in diastole, results in active suction into the coronary vessels during diastole. [42, 107, 155] Haemodynamic patterns have been suggested to differ in the RCA and the LCAs, [108, 156-158] with the RCA exhibiting a predominance of systolic flow. [156, 157] A recent

study based on a large cohort of clinically representative CAD patients revealed diastolic flow predominance in all vessels, although its magnitude was lower in the RCA than in the LCAs. [113] More pronounced systolic flow was rare and observed at similar levels in the three vessels. The prevalence of diastolic flow was observed in dominant, non-dominant, and co-dominant RCAs and not affected by stenosis severity. According to the conclusions of that study, clinical interpretation of coronary physiology index values should not differ among the RCA and LCAs. This is in accordance with European clinical guidelines, which do not discriminate among vessels. [19] In **Study V** we aimed to determine whether potential differences in coronary vessel blood flow affect clinical outcome in patients with lesions deferred with FFR vs. iFR. We did not observe vessel-specific differences in the primary endpoint of MACE or its individual components in the large real-world patient population included in the analysis. Any difference in blood flow patterns of coronary vessels would hypothetically have affected index values and thus clinical outcome. This did not occur and suggests that FFR and iFR can be used in all three coronary vessels without vessel-specific interpretation or cutoff values.

Deferral rates with respect to physiology index and investigated vessel

A higher deferral rate with iFR compared to FFR has not been shown to affect clinical outcomes. [83, 84] **Study V** confirmed higher deferral rate with iFR in all investigated vessels with no difference in clinical outcome. The considerable difference in deferral rate is worth noting and likely reflects iFR use in clinical practice. It is simpler to conduct than the other techniques, consequently lowering the threshold for evaluating a lesion, leading to more lesions examined per patient. [84] These are often low-grade lesions, resulting in a higher proportion deferred.

In **Study V**, deferral rates were found higher in the RCA and LCx compared to the LAD, irrespective of technique used. In addition to factors such as hydrostatic differences in the LAD and the potential for lower FFR values in the LAD due to the greater myocardial mass supplied by the vessel, our study design could have influenced results. [159, 160] In clinical practice, the decision to perform or defer revascularization is at the discretion of the attending operator, who may be more likely to revascularize a stenosis in the LAD than in the RCA or LCx, especially when the FFR or iFR values are of borderline significance. In an RCT, the impact of clinical context is minimized, while, in an observational study like **Study V**, it can influence interpretation and bias results. This is both a limitation and a strength, as it reflects actual practice and is applicable in a wider range of conditions than is a randomized trial.

The higher deferral rate with the iFR index observed in **Study V** was particularly pronounced in the RCA. This could reflect the difference in flow pattern, which influences the calculation of iFR to a greater extent than it does FFR as iFR is assessed during diastole, while FFR is measured throughout the entire cardiac cycle.

The relatively lower magnitude of diastolic blood flow observed in the RCA may result in a higher obtained iFR value. [113] Despite the potential flow pattern discrepancies, target endpoints in our study did not differ relative to index used in any investigated vessel, as would likely have been the case if the flow pattern was of clinical importance.

Study limitations and considerations

Registry-based studies and randomized controlled trials

Randomized control trials are considered the gold standard for medical research. Randomization minimizes influence of extraneous confounding factors on outcome, thus giving the best evidence of impact of a treatment or exposure. [161] Despite their advantages, RCT results can be of limited value in cases of highly selected patient populations following narrow study protocols that limit external validity. Their association with high costs and frequent failure in meeting recruitment goals is a limitation. [162] The iFR-SWEDEHEART trial was a subtype of RCT, the registry-based randomized controlled trial (RRCT), an option with the potential to incorporate large samples that derive information from real-world clinical practice. The potential for lengthy follow-up with minimal loss of patient data makes RRCTs time- and cost-effective. [162]

This thesis integrates the findings of five investigations. **Studies I–III** relied on robust data with the strength of an RRCT, while **Studies IV and V** were observational and carried limitations accompanying that type of study as outlined below. **Studies IV–V** were registry-based and benefitted from the strengths of a large sample population reflecting real-world conditions with no patient lost to follow-up. Registry based studies have lower strength of evidence than RRCTs but can provide externally valid data with long-term follow-up at low cost. [163]

Limitations of the studies

In **Study I**, cost-effectiveness was not a prespecified endpoint, and patient/procedure-specific financial information was lacking. Therefore, average costs of procedures were used to calculate differences. This could have affected the validity of the results.

Study II was an analysis of prespecified five-year endpoints of an RCT, with the strengths of an RRCT. Although no patient was lost to follow-up, when tracking MI based on hospital cardiology unit discharge diagnosis, there is a possibility of missing an MI treated conservatively outside a cardiology unit.

Study III was a sub-study of the iFR-SWEDEHEART trial and considered a post hoc observational study, which carries a risk of residual confounders. The iFR-SWEDEHEART trial was not powered for this specific subgroup analysis, implying a risk of type II errors when comparing outcomes relative to index used as well as relative to clinical presentation. Another limitation was that, as MACE was not analysed at the vessel/segment level, it was not possible to differentiate a target vessel outcome from that involving a nontarget vessel.

Study IV was a registry-based observational study, and residual confounders cannot be ruled out. As mentioned, tracking MI based on hospital admission can lead to events being missed. The SWEDEHEART registry allows for recording approximately 150 variables. It is not always possible, when time is limited, to record all potentially useful data, and missing values for some variables may preclude their inclusion in the analyses.

Study V was a registry-based observational study and, like **Study IV**, carried limitations related to residual confounders and tracking of MI diagnosis. The decision to defer or to revascularize was made during the intervention at the discretion of the operating physician and was not always based on a discrete cutoff value. This needs to be considered when interpreting the results, as it may influence deferral rates.

The study was designed to compare endpoints in patients with lesions deferred based on FFR vs. iFR in the RCA, LAD, and the LCx. Including patients with both FFR and iFR measurements in a given vessel would be of interest, but was not within the scope of the study.

Conclusions

The cumulative findings of these works provide evidence of iFR association with favourable long-term clinical outcome and significant cost savings and support its use to guide coronary revascularization decision-making in patients varying in clinical presentation. The results will contribute to broader adoption of assessment of coronary physiology in clinical practice.

Study-specific conclusions:

Paper I — An iFR-guided revascularization strategy is associated with significant cost-savings compared to an FFR-guided strategy in the 12 months post-procedure. In addition to fewer patient side-effects, an iFR strategy is financially beneficial from a health care perspective.

Paper II — Major adverse cardiac event rates following iFR-guided and FFR-guided revascularization strategies do not differ in the five years post-procedure. Safety of the iFR-guided strategy is confirmed for the long-term.

Paper III — Based on the population of the iFR-SWEDEHEART trial, rate of prespecified clinical endpoints in patients deferred from revascularization based on iFR compared to FFR does not differ after five years. There is no difference in outcomes of ACS and SAP. This suggests that patients can safely be deferred with iFR or FFR regardless of clinical presentation of ACS or SAP.

Paper IV — Deferral of LMCA lesions with IVUS and deferral based on coronary physiology (FFR or iFR) show no difference in patient rate of MACE as composite endpoint up to five years post-procedure. All-cause death and CV death are significantly lower when the revascularization decision is made based on coronary physiology than when based on IVUS. This difference should be interpreted with caution, as the patient population undergoing IVUS may have more severe disease and comorbidities. The results indicate that some LMCA lesions can be safely deferred based on IVUS or physiological index.

Paper V — The proportion of deferral in the RCA, LAD, and LCx is higher with iFR with no associated increased risk of MACE. The difference is particularly pronounced in the RCA. It is not necessary to establish vessel-specific coronary physiology index cutoff values.

Future perspectives

The key to success of coronary physiology assessment will be the development of an optimal non-invasive method. Although results of the five studies presented here demonstrate that basing treatment decisions on coronary physiology is associated with favourable patient outcome, barriers to its broad adoption in clinical practice exist. These include operator confidence in the ability to accurately estimate severity of ischemia from the angiogram, longer procedure time, the risks involved in placing multiple wires into the coronary artery, side-effects of adenosine, and cost of a single-use pressure wire. [117, 164] The future will bring further development of assessment techniques that overcome these barriers while preserving outcome.

Quantitative flow ratio (QFR), an alternative to wire-based methods, shows potential. [165] It is an angiography-based computational method of estimating FFR that has demonstrated feasibility as well as diagnostic accuracy when results are compared with FFR. [166-168] Its clinical value was first tested in the Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis (FAVOR) III China trial. Results showed clinical outcome of QFR-guided PCI superior to angiography-guided PCI. [169] Therefore, QFR has reached class IB recommendation in clinical guidelines. [10] Recently, the randomized FAVOR III Europe trial comparing outcomes following QFR-guided revascularization compared to FFR-guided revascularization failed to show noninferiority of QFR to FFR, indicating that QFR-guidance needs further development. [170] The QFR strategy led to a greater proportion of lesions being revascularized, which could question its potential cost-effectiveness. The use of QFR to guide revascularization shows possibilities in a population with intermediate stenosis, however FFR seems to be the preferred method when available.

The prediction of FFR values has become possible through CCTA. The FFR_{CT} uses computational fluid dynamics to generate an image of the coronary tree. The technique estimates the physiological impact of a stenosis at maximum hyperaemia with the same threshold as conventional FFR but without the use of adenosine. Studies have shown accuracy of FFR_{CT} superior to conventional CCTA, with high positive and negative predictive values. [171, 172] Its lower rate of false positive findings than with CCTA reduces the number of angiographies required. [173] Although this method is promising, its use in Sweden has not expanded, as interpretation of images is not available here, and general data protection regulations and costs associated with international transfer of images have stalled implementation.

Other angiography-derived FFR methods are under development with promising results and possibilities for clinical practice. Non-invasive methods based on iFR are not currently available but may be in the near future. The ability to use characteristics of coronary physiology to evaluate stenoses non-invasively will dramatically improve disease assessment and treatment decision-making for patients with CAD and intermediate-level stenosis.

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