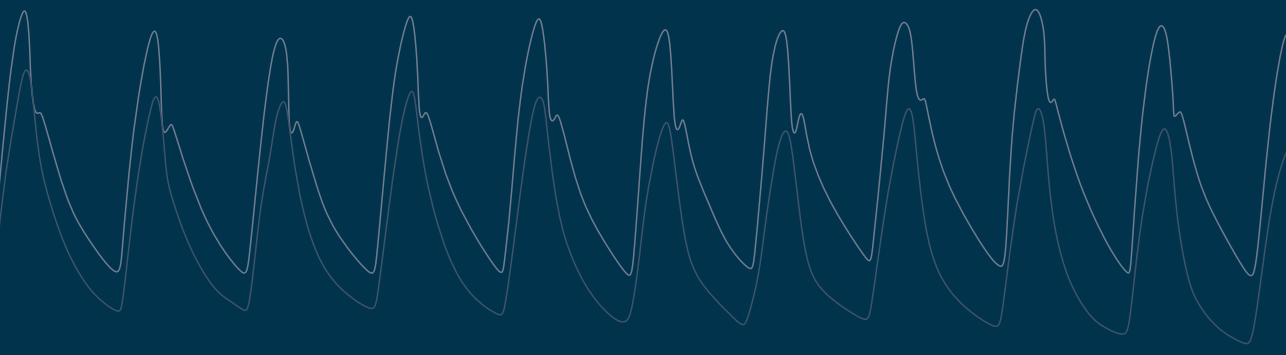
Physiology-guided treatment of complex coronary artery disease

PHYSIOLOGY-GUIDED TREATMENT OF COMPLEX CORONARY ARTERY DISEASE

Frederik M. Zimmermann



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Proefschrift

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voor een commissie aangewezen door het College voor Promoties,
in het openbaar te verdedigen op vrijdag 3 februari 2023 om 13:30 uur

door

Frederik Maria Zimmermann

geboren te Vught

Dit proefschrift is goedgekeurd door de promotoren en de samenstelling van de promotiecommissie is als volgt:

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Voor mijn ouders
Voor Marlies en mijn jongens

Don't bend; don't water it down; don't try to make it logical;
don't edit your own soul according to the fashion.
Rather, follow your most intense obsessions mercilessly.

Franz Kafka

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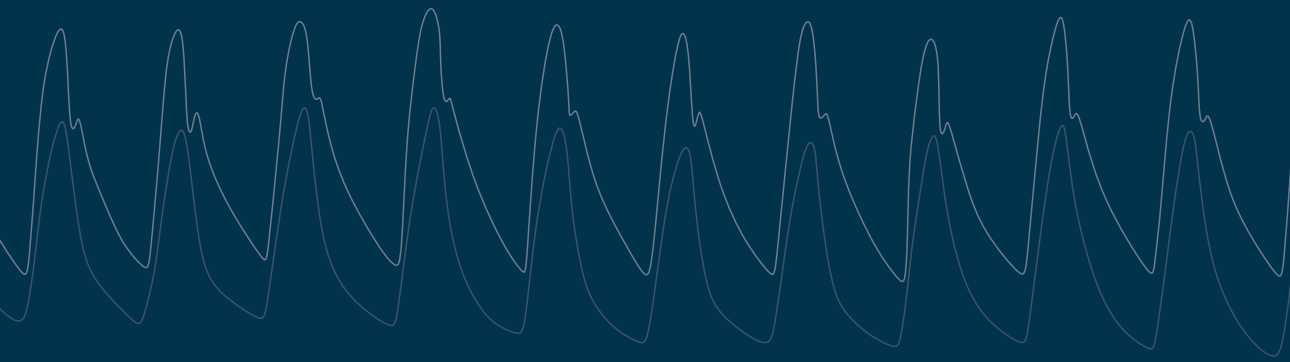

CHAPTER 1

General Introduction and Outline of This Thesis

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Frederik M. Zimmermann, Nico H.J. Pijls, Pim A.L. Tonino. Chapter: Fractional flow reserve. Textbook of Catheter-based Cardiovascular Interventions; Knowledge-based Approach; 2nd edition; Springer Publishers. 2017.

THE CORONARY CIRCULATION

The heart is the engine that powers life. The coronary circulation represents the fuel pipes in this analogy, providing oxygen and other nutrients to keep the heart beating. Under normal physiologic circumstances an equilibrium exists between oxygen demand of the myocardium and oxygen supply provided by the blood flow in the coronary arteries. An ingenious regulatory system in the coronary circulation called autoregulation, maintains this equilibrium. Due to the enormous reserve of the coronary circulation to provide blood to the myocardium, early stages of coronary atherosclerosis and narrowing in the coronary arteries will hardly be noticed. If the coronary arteries become more severely narrowed, complaints will only occur in situations where oxygen demand is increased, such as physical exercise or stress. For these reasons, it is not coronary blood flow at rest that should be studied as a metric for coronary artery disease severity, but rather maximal achievable blood flow.[1,2] The anatomic severity of disease assessed by coronary angiography has only a poor correlation with the degree to which blood flow is decreased. Therefore, it is difficult to assess the physiologic significance of a coronary artery stenosis from the angiogram. As a result, several invasive methods have been developed to quantify the function of the coronary circulation.

Fractional flow reserve (FFR)

The concept of FFR is based on two important principles. First, it is not resting blood flow but maximal achievable blood flow that determines the functional capacity of a patient and is decisive whether myocardium will become ischemic. Second, at maximum vasodilatation (corresponding to maximum hyperemia or maximum exercise), blood flow to the myocardium is proportional to myocardial perfusion pressure. FFR is defined as the ratio of maximal achievable blood flow to a supplied area of myocardium in the presence of a stenosis to normal maximal blood flow to that same area, i.e. maximum blood flow in the hypothetical situation of a normal coronary artery (figure 1).[1]

In a healthy epicardial coronary artery there is only negligible pressure loss along the epicardial vessel, so perfusion pressure equals aortic pressure (Pa) minus coronary sinus (venous) pressure (Pv). A stenosis causes a pressure drop, lowering the distal pressure (Pd), and thus lowering the distal perfusion pressure. Consequently, maximal achievable blood flow beyond the stenosis is impaired.

Therefore the ratio of maximum blood flows (Q) can be calculated via the ratio of the distal perfusion pressure to the normal perfusion pressure, both measured at maximum hyperemia:

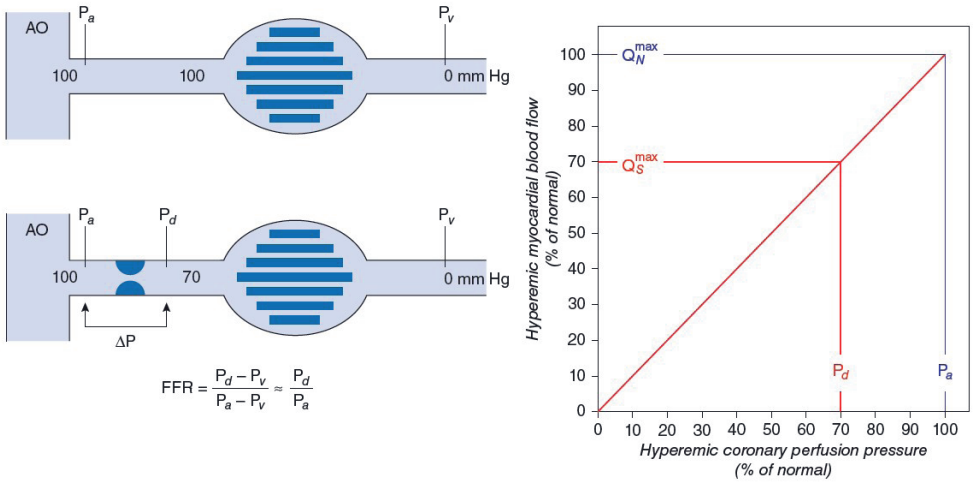

Figure 1. Concept of fractional flow reserve. On the left side, the epicardial coronary vessel and microvascular tree are shown. In the normal coronary artery (upper panel), coronary pressure is equal throughout the epicardial vessel. In case of a coronary stenosis (lower panel) distal coronary pressure decreases. In this example the distal coronary pressure decreases to 70% of its original pressure during maximal hyperemia. Because of the linear relationship between hyperemic perfusion pressure and hyperemic blood flow, the maximal achievable blood flow is also decreased to 70% of its original value. FFR indicates the fraction of normal maximum blood flow that is still achievable in the presence of a stenosis. Reproduced with permission from chapter by Zimmermann et al. Textbook of catheter-based cardiovascular interventions. 2017.

$$FFR = \frac{\text{Qmax stenotic}}{\text{Qmax normal}} = \frac{\text{Pd–Pv}}{\text{Pa- Pv}}$$

Since Pv (venous pressure) is low under normal circumstances, it has a negligible effect on perfusion pressure. The formula can thus be simplified to:

$$FFR = \frac{Pd}{Pa} \quad \text{(at maximum hyperemia)}$$

The most common indication to measure FFR is the precise functional assessment of an intermediate stenosis with uncertain hemodynamic significance. This is a frequently occurring problem, especially since non-invasive tests often produce conflicting results. It has been shown that for angiographically ambiguous stenoses, FFR provides greater accuracy for the determination of inducible ischemia than non-invasive exercise tests and nuclear perfusion imaging.[1,2] In addition, there is a strong and continuous relationship between FFR and subsequent adverse outcomes, with lower FFR values representing more ischemia and worse outcomes.[3] Vice versa, high (i.e. 'negative') FFR is associated

with favorable outcomes. As such, deferring revascularization of coronary lesions on the basis of a negative FFR measurement has proven to be safe up to 5 years of follow-up with an annual risk of cardiac death or myocardial infarction of less than 1%, without added benefit of performing percutaneous coronary intervention (PCI) on these lesions.[4,5] The safety of PCI deferral based on a negative FFR has been demonstrated in randomized controlled trials as well as in large 'real world' cohorts.[6,7] In patients with multivessel disease, selecting lesions that cause ischemia can even be more difficult. For example, exercise testing and nuclear perfusion imaging lack the ability to specifically identify the ischemic territories and responsible stenoses. In addition, nuclear perfusion imaging may appear 'normal' in case of multivessel disease with balanced ischemia. The advantage of FFR-guided PCI for multivessel disease was demonstrated in the landmark FAME trial, showing significantly improved outcomes for FFR-guided PCI versus angiography-guided PCI at a lower cost and equal improvement in symptoms.[5]

Coronary flow reserve (CFR)

The level to which coronary or myocardial blood flow can increase is indicated by coronary flow reserve (CFR). CFR is defined as the ratio between hyperemic and baseline blood flow. CFR is affected by both the epicardial vessel and microcirculation. For that reason, CFR is not able to assess both compartments independently. CFR is a useful parameter to understand the coronary circulation but less suitable in clinical practice. CFR is dependent on several factors, such as blood pressure, heart rate, and age.[8] In addition, CFR depends on resting flow, which can be variable. For example, a patient in the catheterization laboratory may feel anxious which itself influences resting blood flow. Therefore, it can be uncertain if true resting blood flow is present. As a result of these limitations of CFR, its threshold below which coronary ischemia is inducible varies in different studies. This means that the same CFR value of, for example, 2.5 can be normal in one person but severely decreased in another person. Consequently, it is difficult to use CFR for decision making with respect to revascularization. The most commonly used threshold is 2.0. Since CFR is influenced by the epicardial vessel, it is also less reliable to assess the microcirculation.

Index of microcirculatory resistance (IMR)

The index of microcirculatory resistance is an invasive pressure-wire based index to quantify the minimal achievable microcirculatory resistance.[8] IMR is derived from simultaneous coronary pressure and hyperemic temperature measurements. Because the pressure sensor of the pressure-wire also can act as a thermistor, flow can be estimated by using bolus thermodilution to calculate the mean transit time (Tmn) of room temperature saline injected into the coronary artery. Because hyperemic blood flow is inversely proportional to hyperemic mean transit time, IMR can be calculated by:

$$IMR = Pd_{hyperaemia} \times Tmn_{hyperaemia}$$

IMR specifically assesses the microcirculation, in contrast to CFR. In addition, IMR is less influenced by blood pressure, heart rate, and left ventricular contractility. The prognostic value of IMR has been demonstrated in several clinical scenarios, including patients with stable angina and ST-elevation myocardial infarction.[8,9]

Percutaneous coronary intervention versus coronary bypass surgery

For patients with complex coronary artery disease, two types of revascularization are available: percutaneous coronary intervention and coronary bypass surgery (CABG), see figure 2.

The first successful CABG in humans was performed in 1960 by Dr. Robert H. Goetz. Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) by Andreas Grüntzig in 1977 and later the introduction of stents, there has been extensive debate on the optimal indications for both treatments. In patients with a stenosis in one or two coronary arteries, PCI has been shown to be the treatment of choice in the majority of patients. In patients with coronary stenoses in all three coronary arteries – also called 'three-vessel disease'– randomized trials over the course of the past decades have favored CABG instead of PCI. After the introduction of drug-eluting stents, the SYNTAX and FREEDOM trials were conducted, confirming improved outcomes after CABG compared to PCI.[10,11] However, in those studies PCI was guided by the angiogram and first-generation drug-eluting stents were used. As described in this introduction, outcomes after PCI have been improved when guided by FFR. In addition, second-generation DES outperform first-generation DES,

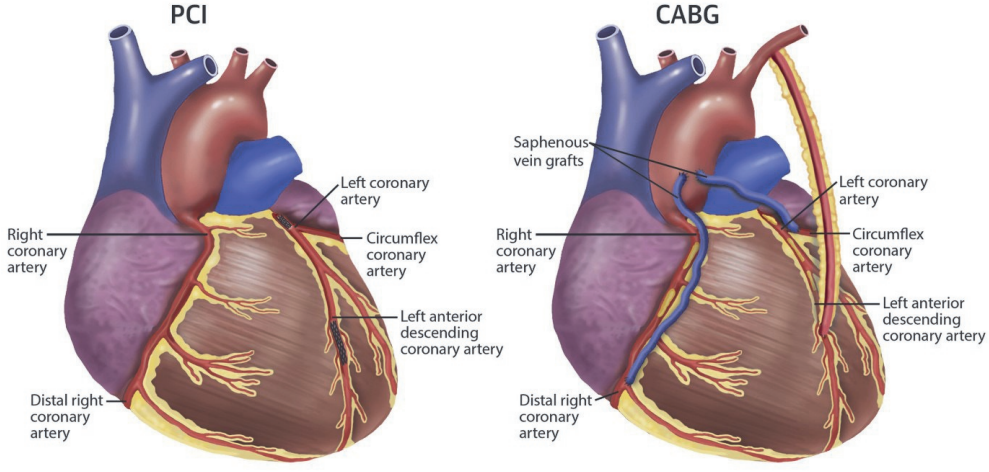

Figure 2. Two main types of revascularization exist to treat coronary disease: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Reproduced with permission from Windecker et al. JACC 2016; 68:1010–1013.

with a lower risk of restenosis, stent thrombosis, and myocardial infarction.[12] Given these improvements in PCI, it may be possible that PCI will result in comparable results to CABG in patients with three-vessel coronary disease. If so, PCI has the advantage over CABG that it is a less invasive treatment. Previous trials have shown that quality of life is superior in the first months after PCI, while CABG outperforms PCI over the long term potentially because of lower subsequent events.[13,14]

Coronary physiology after heart transplantation

Cardiac allograft vasculopathy (CAV), a special form of coronary artery disease in cardiac transplant recipients, is one of the leading causes of death after heart transplantation. According to the International Society for Heart and Lung Transplantation (ISHLT) in 2017, CAV and late graft failure accounted for the majority of mortality at 5-10 years (32.3%), surpassing the contributions of malignancies (24.9%) and infections (10.8%).[15] The pathophysiology of CAV is different from 'classic' coronary artery disease in non-transplant patients, but is not yet completely understood.[16] Historically it has been thought of as a chronic rejection process of the coronary arteries. Indeed, several complex immune processes do play a role in its pathophysiology, such as upregulation of T cells, chemokines, and MHC II molecules. Nevertheless traditional risk factors such as diabetes, tobacco use and dyslipidemia, are also associated with the occurrence and progression of CAV, probably by causing endothelial injury.[16] The diagnosis of CAV is challenging for several reasons. First, patients may not feel angina because of denervation of the heart during transplantation. In addition the angiogram may appear normal as the lumen can be reduced diffusely over its entire length (figure 3). CAV is also known to affect the microvasculature of the heart, which cannot be detected by the angiogram. Given these limitations, there is increased need for methods to better diagnose CAV and predict outcomes. Both intravascular imaging and intracoronary physiology have a potential role in this regard. Intravascular imaging can visualize different layers of the vascular wall. Intimal thickening, most frequently studied with intravascular ultrasound (IVUS), has been associated with poor outcomes.[17] As described in this introduction, intracoronary physiology can assess both the epicardial vessel and microvasculature. Small studies have demonstrated that low FFR (indicating epicardial disease) and high IMR (indicating high microvascular resistance) are associated with death and retransplantation.[18] In addition, single center data have suggested that IMR measured early after heart transplantation may be able to predict acute cellular rejection during follow-up.[19]

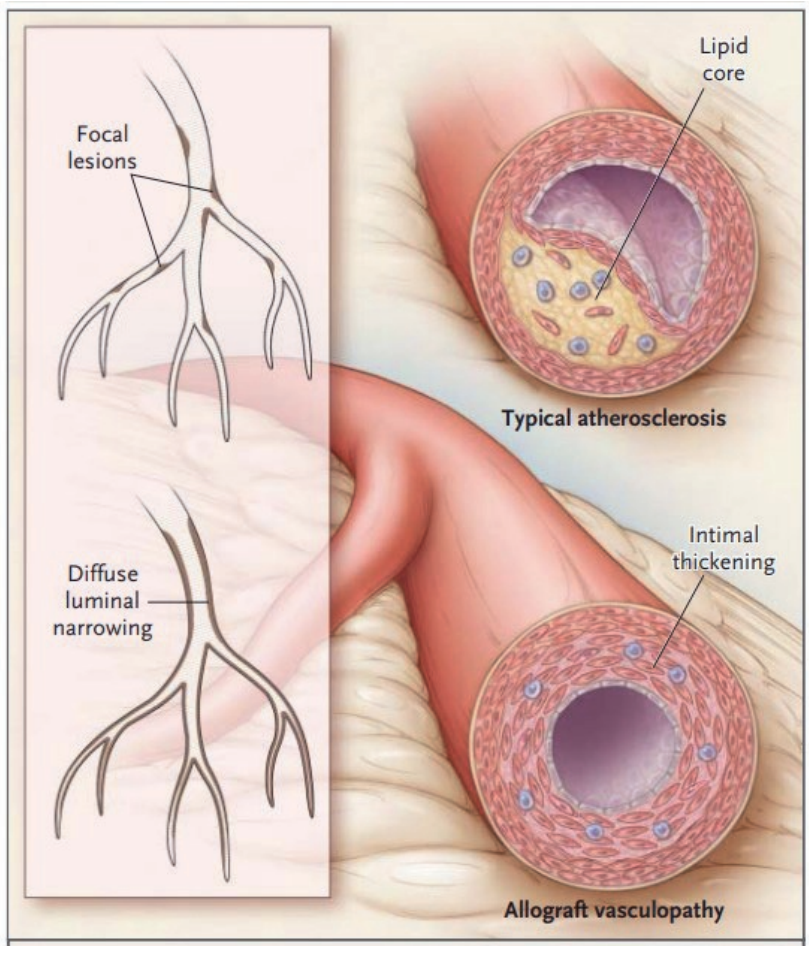

Figure 3. The typical atherosclerotic plaque, with its lipid core, has a focal distribution in major coronary arteries. In allograft vasculopathy, with its characteristic concentric intimal thickening, there is a diffuse distribution throughout the coronary tree. Reproduced with permission from Avery. N Engl J Med 2003; 349:829-830, Copyright Massachusetts Medical Society.

Aims and outline of this thesis

This thesis focuses on the role of intracoronary physiology in the treatment of patients with complex coronary artery disease. The word 'complex' in this setting refers to severe or multivessel coronary artery disease, complex clinical scenarios with conflicting results between diagnostic tests, and complex pathophysiology as observed after heart transplantation.

The first part of this thesis focuses on FFR-guided PCI versus CABG in patients with three-vessel coronary artery disease. Over the past several decades there is ongoing

debate regarding the best treatment of patient with complex coronary disease, usually in favor of CABG.[10,11] However, PCI has improved substantially over these years with the introduction of FFR and second-generation drug-eluting stents.[5,12] In **chapter 2** the rationale and design of the randomized FAME 3 are discussed. The history of CABG versus PCI trials are reviewed and the potential effect of FFR and new stent technology on this debate is described. Following this rationale, **chapter 3** reports the primary 1-year results of the FAME 3 trial in 1500 patients with three-vessel disease comparing FFR-guided PCI with second-generation drug-eluting stents with CABG. Besides clinical outcomes, other health-related metrics such as quality of life and work status may play an important role in clinical decision making. Several measures of quality of life and working status in the FAME 3 trial at 1 year are reported in **chapter 4**.

The second part of this thesis focuses on long term outcomes following FFR-guided decision making. Until recently, little was known about the long-term prognosis of both FFR-negative and FFR-positive lesions. Focusing on FFR-negative lesions, the longest follow-up after deferral of PCI in single vessel disease was 5 years.[4] It may be possible that coronary lesions when treated medically progress later than 5 years and potentially cause adverse events. To study these very long-term effects, the 15-year follow-up of the DEFER trial are reported in **chapter 5** comparing PCI versus medical therapy in FFR-negative lesions. The same uncertainly exists in multivessel disease where other factors besides FFR, such as high plaque burden and disease complexity, may impact long-term prognosis. In **chapter 6**, the 5-year results of the FAME trial are reported comparing FFR-guided PCI versus angiography-guided PCI in patients with multivessel disease.

One of the most debated questions in modern medicine is whether PCI can prevent death or myocardial infarction in stable coronary lesions. Focusing on FFR-positive lesions, randomized trials have found favorable outcomes after FFR-guided PCI versus medical therapy, although none of the trials were powered to assess these 'hard' outcomes.[20-22] For that reason **chapter 7** discusses the results of a patient-level meta-analysis of all randomized trials comparing PCI versus medical therapy in stable coronary lesions. Another method of selecting coronary lesions that may cause a myocardial infarction in the future is intracoronary imaging. It has been suggested that coronary lesions with a negative FFR but 'vulnerable' characteristics on imaging may benefit from PCI by potential 'plaque sealing'.[23] **Chapter 8** discusses the methodological and statistical limitations of such an approach. The final chapter of the second part, **chapter 9**, reviews the best treatment of lesions in the grey zone of FFR.

The third part of this thesis focuses on the prediction of invasive coronary physiology such as FFR and CFR. The adoption of intracoronary physiology may increase if measurement of those well-known physiologic indexes could be simplified. For both indexes induction

of hyperemia is mandatory. **Chapter 10** reports on the use of deep learning, a subfield of artificial intelligence, in order to predict FFR from non-hyperemic pressure curves. An intracoronary bolus of contrast, which also induces some form of hyperemia, may also have a potential role in predicting FFR without the need for a hyperemic drug. Given potential differences in the microvasculature between women and men, **chapter 11** discusses the role of sex differences on the validity of contrast-FFR and other non-hyperemic indexes. It would be also useful if CFR could be predicted from a coronary pressure-only technique. **Chapter 12** describes the rationale and proof-of-concept of such a novel technique called pressure-bounded CFR, while in **chapter 13** pressure-bounded CFR is applied to a large cohort in order to study FFR and CFR discordances.

The fourth part of this thesis focuses on the role of intracoronary physiology in cardiac transplant recipients. Cardiac allograft vasculopathy (CAV) is a major cause of death after heart transplantation.[15,16] Since the coronary angiogram has several limitations to diagnose CAV, intracoronary physiology may play an important role. In **chapter 14** data from a large pooled analysis are reported on the prognostic value of intracoronary physiology. **Chapter 15** investigates whether the index of microcirculatory resistance may predict allograft rejection in a multicenter cohort.

Chapter 16, the final chapter, discusses all research from this thesis and focuses on future directions for ongoing research in the field of coronary physiology and coronary artery disease.

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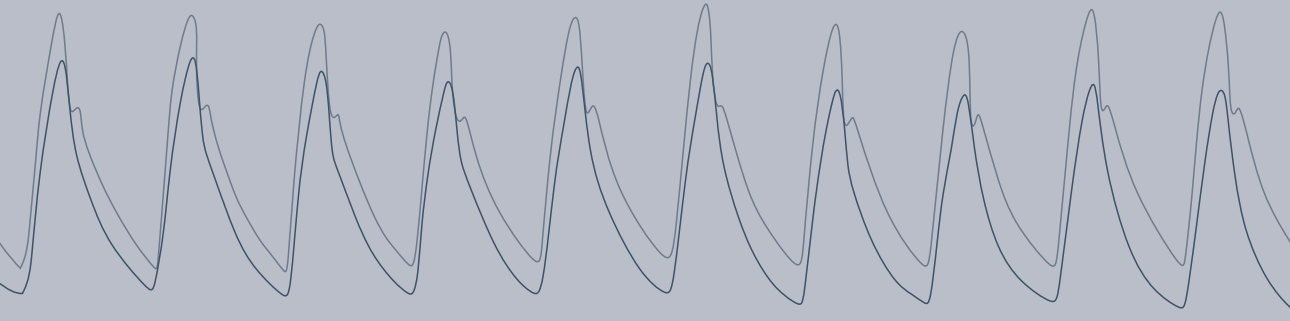
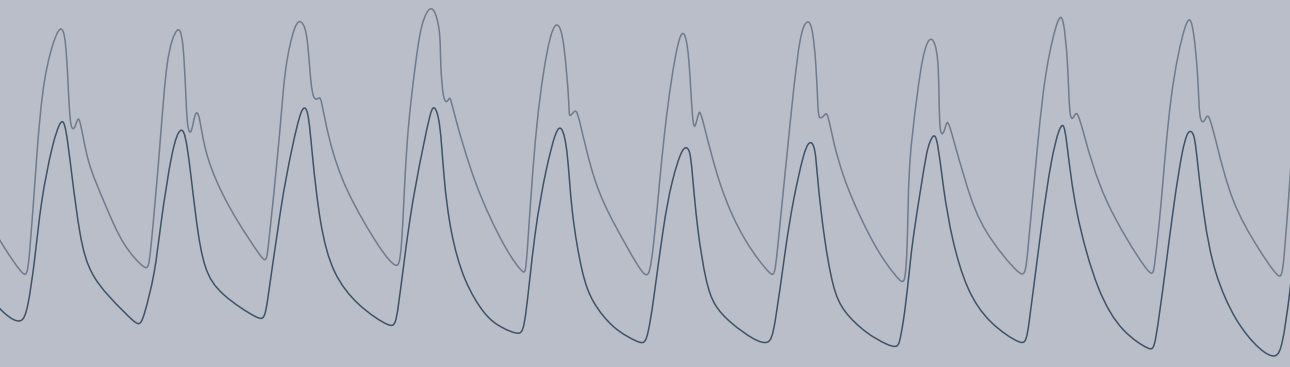
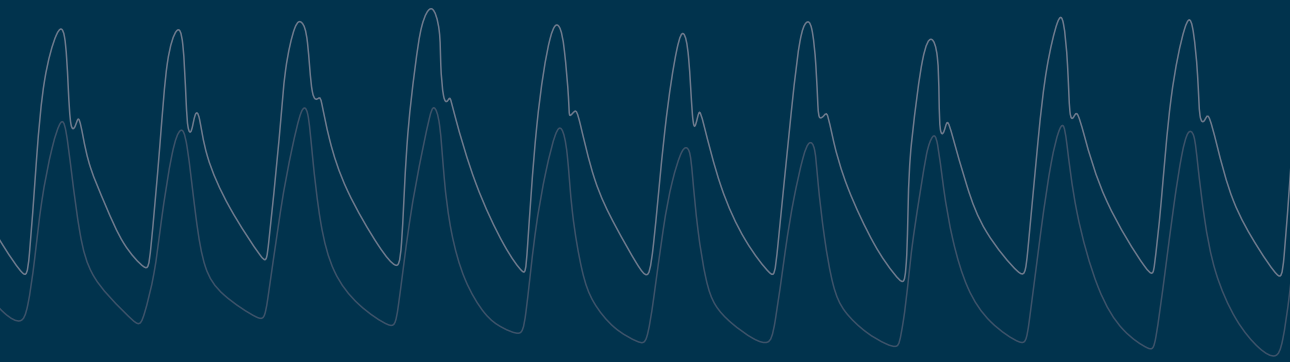


PART I

Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Versus Coronary Bypass Surgery for Three-vessel Disease





CHAPTER 2

Rationale and Design of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 3 Trial

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ABSTRACT

Background

Guidelines recommend coronary artery bypass graft surgery (CABG) over percutaneous coronary intervention (PCI) for the treatment of three-vessel coronary artery disease (3-VD). The inferior results of PCI demonstrated by previous large randomized trials comparing PCI and CABG might be explained by the use of suboptimal stent technology, and by the lack of fractional flow reserve (FFR) guidance of PCI.

Trial design

The objective of this investigator-initiated, multicenter, randomized clinical trial is to investigate whether FFR-guided PCI with new generation stents is non-inferior to CABG in patients with 3-VD, not including the left main coronary artery. Eligible patients must have ⩾50% coronary stenoses in all 3 major epicardial vessels, or major side branches. Patients with a non-dominant right coronary artery may be included only if the left anterior descending artery (LAD) and left circumflex have ⩾50% stenoses. Consecutive patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 fashion to either CABG or FFR-guided PCI. CABG will be performed based on the angiogram as per clinical routine. Patients assigned to FFR guided-PCI will have FFR measured in each diseased vessel and only undergo stenting if the FFR is ⩽0.80. The primary endpoint of the study is a composite of major adverse cardiac and cerebrovascular events, including death, myocardial infarction (MI), repeat coronary revascularization and stroke at 1 year. Key secondary endpoint will be a composite of death, MI and stroke at 3-year follow-up. Other secondary endpoints include the individual adverse events, cost-effectiveness and quality of life at 2-year, 3-year, with up to 5-year follow-up.

Conclusion

The FAME 3 study will compare in a multicenter, randomized fashion FFR-guided PCI with contemporary drug-eluting stents to CABG in patients with three-vessel coronary artery disease.

BACKGROUND

Coronary artery disease (CAD) is the leading cause of death globally.[1] Revascularization of coronary arteries causing ischemia has been shown to improve outcome compared with medical therapy, especially when there is a large ischemic area at risk.[2-4] About 50 years ago, CABG was the first available form of revascularization and several trials showed the superiority of CABG over medical therapy in patients with severe coronary disease.[5,6] Since the introduction of percutaneous coronary intervention (PCI) in 1977 as an alternative to coronary artery bypass surgery (CABG), there has been great debate as to which form of revascularization is the optimal therapy for a patient with three-vessel coronary artery disease (3-VD).[7] In the last decades, outcomes of both CABG and PCI have continuously improved making it challenging to extrapolate older literature to the modern era. Previous studies have shown the superiority of CABG over PCI in patients with 3-VD, and therefore CABG is the recommended therapy in the majority of patients with 3-VD.[8-11] However, the inferior result of PCI in these studies might be improved by the additional use of two technologies that have shown to improve outcome: second generation drug-eluting stents and fractional flow reserve (FFR) guidance of PCI.[2,12-15] Consequently, the purpose of the FAME 3 study is to compare outcome in patients with 3-VD treated by either CABG or by FFR guided multivessel PCI using second generation drug-eluting stents.

METHODS

Study design

The primary objective of the FAME 3 Trial is to demonstrate that FFR-guided PCI is non-inferior to coronary artery bypass graft surgery in patients with three-vessel CAD. FAME 3 is an investigator-initiated, multicenter, multicontinental, prospective, randomized trial including up to 50 sites worldwide, including men and women aged ⩾21 years with 3-VD, defined as ⩾ 50% diameter stenosis by visual estimation in each of the three major epicardial vessels or major side branches, but not involving left main coronary artery. All lesions must be suitable for revascularization by both PCI and CABG as determined by the Heart Team. Patients with a non-dominant right coronary artery may be included only if the left anterior descending artery (LAD) and left circumflex have ⩾50% stenoses. Consecutive patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 fashion to either CABG or FFR-guided PCI with Medtronic Resolute Integrity stents. Randomization will occur via a web-based system stratified by diabetes status and site. Once a patient has been randomized, treatment should occur within 2 weeks, and no longer than 4 weeks. A patient will be considered enrolled, once randomization has occurred. Patients with previous CABG, patients with angiographic evidence of significant left main coronary disease, requirement for other cardiac or non-

cardiac surgical procedures (e.g., valve replacement, carotid revascularization) and known poor left ventricular ejection fraction (i.e. <30%) are excluded. The complete inclusion and exclusion criteria are outlined in Table I.

Every patient will undergo baseline assessment including baseline demographics and clinical characteristics, medications, laboratory studies including complete blood count, basic metabolic panel, lipid panel and glycosylated hemoglobin (HbA1C). All hospitalized patients will have cardiac markers, including troponin checked post-procedure, and if elevated, repeated 4-12 hours later to determine if they are stable or declining, an electrocardiogram and quality of life (EQ-5D) assessment.

CABG will be performed as per routine practice at each participating center. FFR assessment of lesions to help guide bypass is not mandated, but if performed at the time of the diagnostic angiogram, the information can be used by the surgeon. Both off-pump and on-pump surgery are acceptable, as long as the surgeon and the site are experienced in the particular technique. An internal mammary graft to the LAD should be attempted in all cases, if feasible. Complete arterial revascularization is strongly recommended, however, each center should use a conduit strategy with which they are most comfortable. All vessels ≥ 1.5 mm in diameter and with ≥ 50% stenosis should be bypassed, if technically feasible. PCI can be performed via the radial or femoral artery, as per the site's usual routine.

Only those sites with prior experience of measuring FFR will be included in the FAME 3 trial. The FFR tracings from the first 10 patients at every site will be recorded on the QUANTIEN Analyzer and reviewed by the FFR core lab at Stanford immediately after each patient is treated.

Before introducing the wire into the coronary artery, intracoronary nitroglycerin (100-200 micrograms, or its equivalent) will be administered. It is recommended that hyperemia is induced by intravenous adenosine (140 µg/kg/min for at least 2 minutes or until a steady state is obtained) via a large antecubital vein or central venous access. FFR will be measured according to the standard approach as described in the literature and a value ≤0.80 is used to discriminate reversible ischemia, according to the former FAME studies.[16] PCI will be performed solely with the Medtronic Resolute Integrity stent (Medtronic Inc., MN, USA). If the Resolute stent cannot be delivered, an alternative current generation drug-eluting stent can be substituted. Dual antiplatelet therapy is recommended for 12 months post procedure, but should be at least 6 months.

Chronic total occlusion (CTO) should only be revascularized if a patient has persistent symptoms ascribed to the CTO, documented ischemia on non-invasive testing involving the region subtended by the vessel with the CTO, and visible collaterals which fill a vessel

Table 1. Inclusion and exclusion criteria

Inclusion Criteria
1. Age ≥ 21 years with angina and/or evidence of myocardial ischemia
2. Three vessel CAD, defined as ≥ 50% diameter stenosis by visual estimation in each of the three major epicardial vessels or major side branches, but not involving left main coronary artery, and amenable to revascularization by both PCI and CABG as determined by the Heart Team. Patients with a non-dominant right coronary artery may be included if only the left anterior descending artery (LAD) and left circumflex have ≥50% stenosis
3. Willing and able to provide informed, written consent
Exclusion Criteria
1. Requirement for other cardiac or non-cardiac surgical procedure (e.g., valve replacement, carotid revascularization)
2. Cardiogenic shock and/or need for mechanical/pharmacologic hemodynamic support
3. Recent STEMI (<5 days prior to randomization)
4. Ongoing Non STEMI with biomarkers (cardiac troponin) still rising
5. Known left ventricular ejection fraction <30%
6. Life expectancy < 2 years
7. Requiring renal replacement therapy
8. Undergoing evaluation for organ transplantation
9. Participation or planned participation in another clinical trial, except for observational registries
10. Pregnancy
11. Inability to take dual antiplatelet therapy for six months
12. Previous CABG
13. Left main disease requiring revascularization
14. Extremely calcified or tortuous vessels precluding FFR measurement
15. Any target lesion with in-stent drug-eluting stent restenosis

>2.5 mm in diameter. In the case in which the operator decides to revascularize a chronic total occlusion, FFR measurement is not mandatory and a default FFR value of 0.50 can be applied. PCI may be staged if necessary, but this is not encouraged. The plan to stage the PCI of a particular lesion should be declared before instrumenting the lesion. The second portion of the PCI procedure should be performed within four weeks of the first portion.

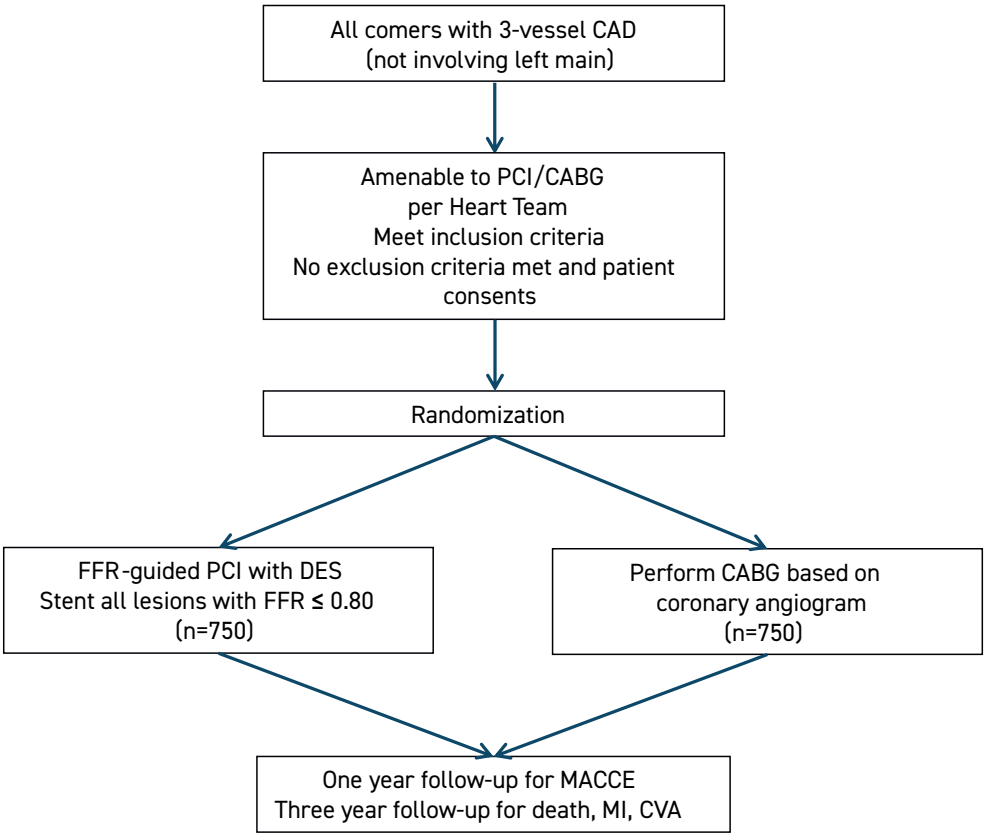
Patients will be seen and evaluated at 1 month (±7 days), and 1 and 3 years (±30 days) after randomization. 5-year follow-up will be performed if funding allows. Phone call follow-up will occur at 6 months, 2 years (and 4 years, if funding allows). During follow-up patients will be assessed for any MACCE, angina severity, and quality of life (EQ-5D). The anginal status of the patient will be assessed according to the Canadian Cardiovascular Society (CCS) Classification at all follow-up contacts. Prior to treatment allocation and at all planned clinical follow-up visits, the patient will be requested to provide information relative to his/her working status or any change therein. Resource utilization data will be collected for each patient at the time of each follow-up contact.
A study flowchart is displayed in figure 1.

Endpoints

The primary end point of the study is the rate of major adverse cardiac events and cerebrovascular events (MACCE) at 1 year. *Major adverse cardiac and cerebrovascular events* are defined as all-cause death, MI, any repeat coronary revascularization, and stroke as adjudicated by the adverse clinical event committee. The key secondary endpoint is the rate of death, MI, and stroke at 3-year follow-up. Other secondary endpoints include the rate of MACCE at 2- and 3-year follow-up, with up to 5-year follow-up, if funding allows. The rate of each individual event, death (cardiac and all-cause), MI, repeat revascularization, stroke, bleeding complications, stent thrombosis, graft occlusion, significant arrhythmia, development of acute renal failure, length of hospital stay, rehospitalisation, number of anti-anginal medications, and functional class at the above time points, will also be evaluated as secondary endpoints. Usefulness of scoring systems for predicting outcomes such as the STS, logistic Euroscore, SYNTAX score, clinical SYNTAX score, ACEF score and Functional SYNTAX score will be evaluated, as well as cost-effectiveness and health-related quality of life index (EQ-5D) at each time point. The complete list of endpoints and pre-specified subgroup analyses is available in the online appendix. Subgroup analysis will include a comparison of the completeness of revascularization, diabetic status and outcomes of patients with and without disease in the proximal LAD. Specific subgroup analysis in the CABG arm will include the comparison of complete vs. incomplete arterial revascularization, on-pump vs. versus off-pump CABG, and outcomes based on left internal mammary artery use alone versus multiple arterial conduits.

Death is defined as all cause death. Cardiac death is defined as any sudden death, death related to acute myocardial infarction, arrhythmia or congestive heart failure, death secondary to a cerebrovascular accident, or death directly related to PCI or CABG, even if the ultimate cause of death is not clearly a cardiac event (e.g., infection). Non-cardiac death is any death not clearly cardiac in etiology.

Figure 1. Study flowchart



Myocardial infarction is defined in two ways, depending on whether or not it is PCI or CABG-related or a spontaneous event, according to the third universal definition of myocardial infarction.[17]

Stroke (cerebrovascular accident, CVA) is diagnosed when the following criteria are met: 1. Rapid onset of a focal/global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphagia/aphasia, hemianopia, amaurosis fugax or other new neurological sign(s)/symptom(s) consistent with stroke 2. Duration of focal/global neurological deficit is ⩾24 hours, or it can be <24 hours if a therapeutic intervention is performed, brain imaging clearly documents a new hemorrhage or infarct, or the neurological deficit results in death. 3. Confirmation of the diagnosis by at least one of the following: a) Neurology or neurosurgical specialist b) Brain imaging (CT, MRI, or cerebral vessel angiography) c) Lumbar puncture diagnostic or intracranial haemorrhage.

Urgent revascularization is defined as an unplanned hospitalization for an acute coronary syndrome with at least one of the following: electrocardiographic changes, biomarker elevation, or new perfusion/wall motion abnormalities to document ischemia and which results in revascularization during the hospitalization. *Repeat revascularization* is defined as any unplanned (elective or urgent) revascularization, whether PCI or CABG. Planned staged PCI procedures do not qualify. *Bleeding* is defined as per the Bleeding Academic Research Consortium (BARC).[18] Other descriptions of bleeding, such as TIMI, will be applied as well. *Stent thrombosis* is defined as per the Academic Research Consortium (ARC). *Graft Occlusion* is defined based on an ARC-like definition.[19] *Significant Arrhythmia* consists of ventricular tachycardia or fibrillation requiring cardioversion, atrial fibrillation lasting > 24 hours, or need for a permanent pacemaker. *Re-hospitalization* is defined as a hospital stay of >36 hours.

Statistics

The objective of this study is to demonstrate non-inferiority of FFR guided PCI to CABG in patients with 3-VD. A hazard ratio of 1.45 or less is assumed not clinically meaningful. More specifically, the null hypothesis is that the hazard of MACCE for PCI patients is greater than that of CABG patients and the alternative hypothesis is that the hazard of MACCE for PCI is not worse (not greater) than that for CABG patients. Let HR_0 be the non-inferiority margin – i.e., the maximum ratio of clinical insignificance. Then the null (H0) and alternative (H1) hypotheses can be expressed as: H_0:HR⩾HR0 vs. H_1:HR<HR0. The primary analysis will be based on the intention-to-treat (ITT) principle.

Kaplan-Meier curves will be used to graphically display differences in MACCE by treatment arm and by diabetes status. In addition, we will use survival analytic techniques such as a log-rank test or, if appropriate, a Cox proportional hazards (PH) model to estimate the difference in hazard of MACCE by treatment arm, stratified by center, and with diabetes status included as a term in the model. The test for non-inferiority of FFR-guided PCI will be one-sided and assessed at the 0.025 level of significance.

We anticipate that within 1 year of follow-up the PCI arm will have a 12% event rate based on the 18% rate in SYNTAX and the decrease in death, MI and revascularization seen with FFR guidance in FAME and with second generation drug-eluting stents. Thus, assuming 12% of subjects in the CABG arm experience MACCE (from the SYNTAX study and FREEDOM trial), given a clinically irrelevant hazard ratio of 1.45, a one-sided 2.5% significance level and 90% power to reject the null hypothesis if it is false, the sample size necessary is 712 patients per group (1424 for the entire study). These calculations are based on assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed death times, and a Wald test statistic. Thus, to account for patients lost to follow-up (we anticipate a <5% loss to follow-up), we will enroll 1500 patients from up to 50 medical centers. In

FAME 1, there was a 2% loss to follow-up at one year and FAME 2 there was <1% loss to follow-up at one year. We do not expect the event rate in the CABG group to be different than in previous studies, however we will have >80% power to reject the null hypothesis if it is false with the current sample size for a wide range of assumptions including event rates in both arms ranging from 10% to 16%.

Organization and ethical concerns

The study protocol will be approved at each participating center by its internal review board. All patients will provide informed written consent before participating. Up to 50 sites will participate. The study is an investigator initiated trial. The Principal Investigators are considered to be the sponsors of this study. Coordinator of the trial is Stanford University. The Principal Investigators will be supported by the clinical research organization, Genae to administer the financial and logistic aspects of the trial. The study is supported by research grants provided by Medtronic Corporation and St. Jude Medical. The Steering Committee (SC) is the main decision making committee of the trial and has final responsibility for the medical and scientific conduct of the trial. The FAME 3 trial is registered at clinicaltrials.gov: NCT02100722.

A minimum of 10% of the CRFs will be randomly selected and monitored to identify inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site. If this is identified, targeted on-site monitoring will be conducted.

The Clinical Events Committee (CEC) is made up of an interventional and non-interventional cardiologist, cardiac surgeon, and a neurologist who are not participants in the trial. The neurologist will review neurologic event adjudication as necessary. The Clinical Events Committee is charged with the development of specific criteria used for the adjudication of clinical events and clinical endpoints in the trial that are based on protocol.

The Clinical Events Committee will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. All members of the Clinical Events Committee will be blinded to the primary results of the trial.

The Data Safety Monitoring Board (DSMB) will be an independent group of physicians including an interventional cardiologist, cardiac surgeon and statistician. The DSMB, in conjunction with the Steering Committee, will develop a charter with specific guidelines regarding monitoring the safety of the subjects enrolled in FAME 3. Based on their clinical judgment, the DSMB can recommend stopping the trial. The final decision regarding stopping enrollment will rest with the Steering Committee.

Enrolment began in August 2014 and is expected to be completed by August 2016. Follow-up for the primary end point will be completed in August 2017, although patients will be followed for a total of 3 years after enrollment, with up to 5-year follow-up, if funding allows.

DISCUSSION

Currently, both United States and European guideline statements recommend CABG for patients with three-vessel disease.[10,11] This recommendation is based primarily on the "Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery" (SYNTAX) study, which randomized 1800 patients with 3-VD or significant left main coronary disease to either PCI or CABG and demonstrated significantly higher rates of the primary endpoint at one year in the PCI arm (17.8 vs. 12.4%, p=0.002).[9] The primary endpoint was defined as a composite of the major adverse cardiovascular and cerebrovascular events (MACCE), death, myocardial infarction (MI), cerebrovascular accident (CVA) and repeat revascularization and the difference was driven primarily by a significant increase in the need for repeat revascularization (13.5 vs. 5.9%, p<0.001), although there was a strong trend towards lower rates of cardiac death (3.7 vs. 2.1%, p=0.05) and MI (4.8 vs. 3.3%, p=0.11) in the CABG arm. These events were counterbalanced to some degree by a significantly lower rate of CVA in the PCI arm (0.6 vs. 2.2%, p=0.003). The five year follow-up in this trial continued to show a significantly higher rate of MACCE in the PCI arm (37.3 vs. 26.9%, p<0.0001), as well as a now significantly higher rate of cardiac death (9.0 vs. 5.3%, p=0.003) and MI (9.7 vs. 3.8%, p=0.0001) in the PCI arm.[20] When comparing the 1095 patients with 3-VD not involving the left main stem, the same differences were noted in MACCE between the two groups at both one and five years (19.2 vs. 11.5%, p<0.001) and (37.5 vs. 24.2%, p<0.0001).

The "Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease" (FREEDOM) trial adds further support to the findings from SYNTAX. This trial randomized 1900 diabetic patients to PCI or CABG and found a significantly higher rate of the primary endpoint (death, MI or CVA) in the PCI arm at 5 year follow-up (26.6 vs. 18.7%, p=0.005). This difference was driven by higher rates of death and MI in the PCI arm with higher rates of CVA in the CABG arm.[8]

Based on these two studies, most patients with 3-VD are now routinely referred for CABG, particularly if they have an intermediate or high SYNTAX score. However, the inferior results of PCI demonstrated by both SYNTAX and FREEDOM might be improved by the use of modern stent technology, and perhaps more importantly, by employing fractional flow reserve (FFR) guidance of PCI.

Patients undergoing PCI in SYNTAX received the paclitaxel-eluting TAXUS stent and patients in the FREEDOM trial received predominantly the sirolimus-eluting Cypher stent and the TAXUS stent. These stents have now been shown to be inferior to second generation drug-eluting stents, which have lower rates of stent thrombosis, target lesion revascularization, and in some cases, death or myocardial infarction.[12-14] Studies directly comparing second generation drug-eluting stents to each other have shown no appreciable difference in these endpoints.[21,22] Thus, one might hypothesize that a comparison of PCI with second generation stent technology to CABG might result in lower rates of death, MI and repeat revascularization compared to that seen with the Taxus stent, and which are more similar to those seen after CABG.

FFR is a coronary pressure wire-based index for assessing the ischemic potential of a coronary stenosis. It is defined as the mean distal coronary pressure divided by the mean proximal coronary pressure during maximal hyperemia. Numerous studies have demonstrated that if the FFR is ≤0.80, then significant ischemia is present related to that particular stenosis and revascularization is warranted. Conversely, if the FFR is >0.80, then the lesion can be safely treated with medication, despite its angiographic appearance, and one can expect an excellent outcome.[2,15,23]

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, randomized 1005 patients with two or three vessel coronary disease and stable symptoms or non ST elevation acute coronary syndromes in whom PCI was indicated to either angiography-guided PCI or to FFR-guided PCI, in which case FFR was measured across every lesion and PCI was performed only if the FFR was ≤ 0.80.[24] The one year primary endpoint of death, MI and repeat revascularization occurred in significantly fewer patients randomized to the FFR-guided strategy (13.2 vs. 18.3%, p=0.02).[24] This reduction is similar in magnitude to the difference between PCI and CABG in the SYNTAX and FREEDOM trials and was driven by numerical reductions in all three components of the primary endpoint: death (1.8 vs. 3.0, p=0.19), MI (5.7 vs. 8.7%, p=0.07) and repeat revascularization (6.5 vs. 9.5, p=0.08). The composite of death and MI was also significantly reduced by FFR-guided PCI (7.3 vs. 11.1, p=0.04). At two year follow-up, there continued to be a significant reduction in death and MI with FFR-guided PCI (8.4 vs. 12.9%, p=0.02) and a trend towards a lower rate of death, MI and repeat revascularization (17.9 vs. 22.4%, p=0.08).[15] The improved outcomes with FFR-guided PCI are likely a result of more judicious PCI whereby only ischemia-producing lesions are revascularized. In this manner, the benefit of PCI can be maximized by relieving ischemia and the risks can be minimized by avoiding unnecessary stenting.

If one compares the results of the FAME study to the results of SYNTAX (excluding the left main subset), the major adverse event rate (excluding stroke) was similar between the angiography-guided arm in FAME and the PCI arm in SYNTAX, reflecting the fact that PCI

in SYNTAX was performed primarily with angiographic guidance alone. On the other hand, the FFR-guided arm in FAME had similar event rates to the CABG arm in SYNTAX. Based on this comparison and the trials showing improved outcomes with second generation drug-eluting stents, one can hypothesize that a comparison between FFR-guided PCI with contemporary stents and CABG in patients with 3-VD would show non-inferiority of PCI to CABG. The purpose of the FAME 3 study is to investigate that hypothesis.

Some clarifying notes should be made with respect to the FAME 3 protocol: In our study PCI vs. CABG is studied for three-vessel disease. However, it should be noted that only those patients are eligible for inclusion in FAME 3 who are candidates for both CABG and PCI from a technical point of view. This might implicate that some patient with extended diffuse and multivessel-disease are not eligible for this study because PCI is not an option at all and vice versa: some patients with a very high surgical risk prohibitive for CABG are not eligible as well. So this study focuses on patients with 3-VD technically suitable for both therapies. The assumption of a drop in event rate in the PCI group has been derived from SYNTAX. One should take in mind that the population of SYNTAX, FAME, and the anticipated population of FAME 3 are not identical. In SYNTAX, many patients had extremely complex disease (highest SYNTAX score tertile) and it is unlikely – following the lessons from SYNTAX – that such patients will be considered by the Heart Team as 'technically suitable for both PCI and CABG' in FAME 3. Nevertheless, we believe that based upon the FAME results, a decrease of event rate by 30% can be anticipated.[15] Furthermore, it should be noted that in the FAME 3 study current generation stents will be used, which might further contribute to the anticipated lower event rate in the PCI group. We have excluded left main disease because in most participating centers, left main disease is still an indication for CABG and not routinely performed.

Summary

The FAME 3 trial is an investigator initiated, multicenter, international, randomized trial including up to 50 sites comparing FFR guided PCI with CABG in three-vessel coronary artery disease (not involving left main). Previous studies comparing CABG and PCI showed superiority of CABG over PCI in three-vessel disease. The hypothesis of this study is that FFR guided PCI with second-generation drug-eluting stents is non-inferior to CABG.

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PROTOCOL UPDATE 2019

Since the initial design of the FAME 3 protocol,[1] the BEST, EXCEL, and NOBLE trials have been published.[2-4] These studies demonstrate a 1 year MACCE rate which is in the 10% or lower range in the CABG arm, compared with the SYNTAX and FREEDOM trials which were in the 12% range.[5,6] In addition, in EXCEL, a clinically acceptable non-inferiority margin for only death, CVA and MI (excluding revascularization) was a hazard ratio in the 1.4 range. Because of the lower event rates after CABG in more recent studies and because we will also be including revascularization as part of MACCE, the FAME 3 Steering Committee feels a hazard ratio of 1.65 is more appropriate for defining a clinically acceptable non-inferiority margin. Based on this change, 1290 total subjects will be necessary to reject the null hypothesis if it is false. To account for subject drop-out and loss of followup and to maximize our statistical power, the original sample size of 1500 subjects will remain unchanged. It is important to note that the decision to change the non-inferiority margin was made by the steering committee without knowledge of the event rates in either of the randomized arms or input from Medtronic or Abbott, which are providing financial support for the study. In addition, we want to emphasize that a claim of non-inferiority can only be made when the upper 95% confidence interval (CI) of the hazard ratio does not exceed the non-inferiority margin. As an example of the difference between the hazard ratio and the upper limit of its 95% CI, in the recent non-randomized SYNTAX II study, contemporary PCI was compared to the equipoise-derived CABG cohort of the SYNTAX I trial.[7] While the rate of major adverse cardiac and cerebrovascular events (MACCE) was numerically lower in the PCI arm, resulting in a hazard ratio of 0.81, the upper limit of the 95% CI was 1.49.

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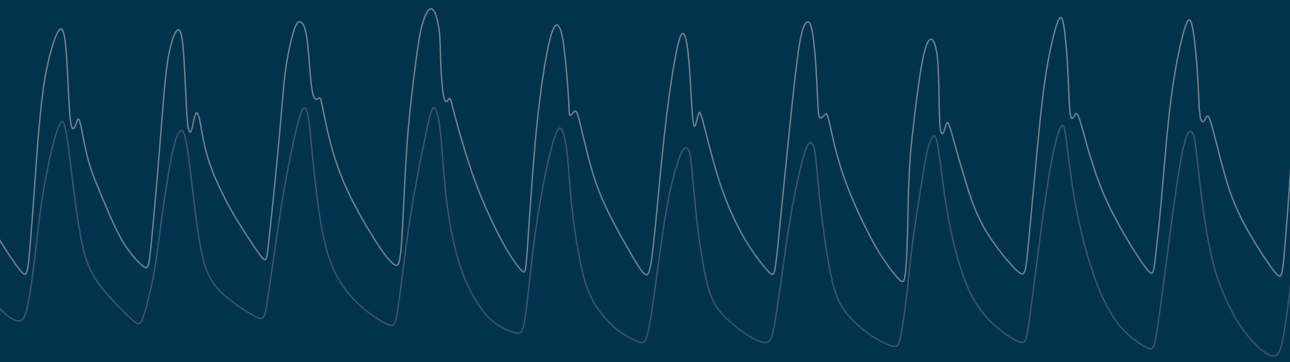

CHAPTER 3

Fractional Flow Reserve-Guided PCI as Compared With Coronary Bypass Surgery

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ABSTRACT

Background

Patients with three-vessel coronary artery disease (3v-CAD) have had better outcomes with coronary artery bypass grafting (CABG) than with percutaneous coronary intervention (PCI), but in these studies PCI was not guided by fractional flow reserve (FFR) measurement.

Methods

In this multicenter, international, noninferiority trial, patients with 3v-CAD were randomly assigned to CABG or FFR-guided PCI using current generation zotarolimus-eluting stents. The primary endpoint was the one-year occurrence of all-cause death, myocardial infarction (MI), stroke or repeat revascularization (MACCE). The noninferiority margin was pre-specified as a hazard ratio (HR) of 1.65.

Results

A total of 1500 patients were randomized at 48 centers. Patients randomized to PCI received mean (standard deviation) 3.7 (±1.9) stents and those randomized to CABG received 3.4 (±1.0) distal anastomoses. The incidence of MACCE at one year was 10.6% in those randomized to FFR-guided PCI and 6.9% in those randomized to CABG (HR 1.5, 95% CI 1.1-2.2), findings that were not consistent with noninferiority of FFR-guided PCI (p=0.35). The incidence of death, MI or stroke was 7.3% vs 5.2%, respectively (HR 1.4, 95% CI 0.9-2.1). As compared with patients randomized to FFR-guided PCI, those randomized to CABG had higher rates of major bleeding, arrhythmia and acute kidney injury.

Conclusion

In patients with 3v-CAD, FFR-guided PCI was not found to be noninferior to CABG with respect to the rate of the composite of death, MI, stroke or repeat revascularization at one year.

INTRODUCTION

In patients with three-vessel coronary artery disease (3v-CAD), large, randomized trials have demonstrated improved outcomes when coronary revascularization is performed with coronary artery bypass grafting (CABG) rather than percutaneous coronary intervention (PCI).[1-3] However, only one of the prior trials used second generation drug-eluting stents (DES) and none routinely measured fractional flow reserve (FFR) to guide PCI. Second generation DES have improved early and late outcomes with lower rates of stent thrombosis, procedural and spontaneous myocardial infarction (MI), restenosis, and death when compared with first-generation DES.[4] FFR is an index measured with a coronary pressure wire which provides more accurate assessment of the hemodynamic significance of a coronary stenosis compared with the angiogram alone. FFR-guided PCI improves short and long-term outcomes compared with angiography-guided PCI and with medical therapy alone.[5-7] We performed the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 trial to compare FFR-guided PCI with current generation DES to CABG with respect to rates of major adverse cardiac and cerebrovascular events (MACCE) in patients with 3v-CAD.

METHODS

Design

Details regarding the design and conduct of the FAME 3 trial have been published previously and are included in the supplement.[8,9] FAME 3 is an investigator-initiated, multicenter, international, randomized, controlled trial performed at 48 sites. The study was supported by research grants to Stanford University from Medtronic, Inc and Abbott Vascular, Inc, which had no role in the study design, conduct or manuscript preparation. Dr. Fearon vouches for the accuracy and completeness of reporting and the fidelity of the report to the study protocol. Patients with angiographic 3v-CAD not involving the left main coronary artery were randomized in a 1:1 fashion to either CABG or FFR-guided PCI. Randomization occurred via a web-based system stratified by diabetes status and site. The major inclusion criterion was the presence of 3v-CAD, defined as ≥ 50% diameter stenosis by visual estimation in each of the three major epicardial vessels or major side branches, but not involving the left main coronary artery, and amenable to revascularization by either PCI or CABG as determined by each site's Heart Team. Major exclusion criteria were recent ST segment elevation myocardial infarction (MI), cardiogenic shock, and left ventricular ejection fraction <30%. The research protocol was approved by relevant institutional review boards or ethics committees, and all participants gave written informed consent.

Study Procedures

CABG was performed using the standard practice at the participating center, with complete arterial revascularization strongly recommended. FFR assessment of lesions to guide bypass surgery was not mandated, but if performed at the time of the diagnostic angiogram, the information could be used by the surgeon. All patients randomized to PCI first underwent FFR assessment with a coronary pressure wire (Abbott Vascular Inc, Santa Clara, CA) and intravenous or intracoronary adenosine. The protocol specified that only stenoses with an FFR≤0.80 were to undergo PCI with durable polymer zotarolimus-eluting stents (Resolute Integrity/Onyx, Medtronic, Minneapolis, MN). Post-PCI FFR measurement was encouraged. Intravascular imaging was performed as deemed necessary by the treating physicians. All patients in both arms were to receive aspirin and high dose statin, as well as guideline-directed medical therapy. Patients undergoing PCI were to receive a second antiplatelet medication for at least 6 months post PCI. Follow-up occurred at hospital discharge, 1, 6 and 12 months.

Endpoints

The primary endpoint of FAME 3 was the occurrence of major adverse cardiac or cerebrovascular events (MACCE) defined as the composite of all-cause death, MI, stroke and repeat revascularization at one year. MI was defined as procedural or spontaneous. In both groups, the biomarker threshold for the definition of procedural MI was any elevation of the cardiac troponin value more than 10 times the 99th percentile of the upper reference limit (URL) in patients with a normal baseline reference level, or an increase of > 20%, if the baseline values were elevated within 72 hours of the procedure. In addition, at least one of the following was required: new pathologic Q waves or new left bundle branch block, angiographic documentation of new graft or major native coronary occlusion, or imaging demonstration of new loss of viable myocardium or new regional wall motion abnormalities. This definition is in line with a Type 5 MI (post-CABG procedural MI) based on the 3rd and 4th Universal Definition of MI. Spontaneous MI was defined as the rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia, development of pathological Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. An independent clinical events committee adjudicated events in a blinded fashion.

Statistical Analysis

The primary analysis was conducted in accordance with the intention-to-treat principle. We initially assumed that 12% of subjects randomized to CABG would experience MACCE at one year and hypothesized that patients randomized to PCI would not have a higher hazard of MACCE than those patients randomized to CABG.[3,10,11] Pre-specifying a noninferiority hazard ratio of 1.45 and a one-sided 2.5% significance level, a sample size of 712 patients per group

(1,424 for the entire study) was required to achieve 90% power to claim noninferiority. To account for patients anticipated to be either lost to follow-up or withdrawn from the study, we enrolled 1,500 patients. During recruitment and without knowledge of event rates, the FAME 3 Trial Steering Committee decided to increase the noninferiority margin to a hazard ratio of 1.65 because it felt it was more appropriate for defining a clinically acceptable non-inferiority margin based on newly published clinical trials comparing CABG with PCI, which reported MACCE rates of 10% or lower in patients randomized to CABG and used noninferiority margins similar to a hazard ratio of 1.65.[9] With this change, a sample size of 645 patients per group (1,290 for the entire study) was required to achieve 90% power to claim noninferiority however, the Steering Committee elected to complete the scheduled enrolment of 1500 subjects.

Differences in MACCE by treatment arm were visualized using cumulative incidence curves and estimated using a Cox proportional hazards model that adjusted for stratification factors (through inclusion of baseline diabetes status as a term in the model and by allowing the baseline hazard for each study center to vary). Each MACCE component was similarly compared between treatment groups, and safety outcomes were compared using the Chi-squared or Fisher's exact test, as appropriate. The proportional hazards assumption was evaluated for the primary analysis using a two-sided score test of the scaled Schoenfeld residuals over time at the 0.05 level. The test for noninferiority was assessed using a Wald test at the 0.025 level of significance. Subgroup analyses were performed under the same Cox proportional hazards framework as the primary analysis and visualized as a forest plot for the following prespecified characteristics: age group (<65 years or older), sex, presence of diabetes , acute coronary syndrome, left ventricular ejection fraction (>50%, versus 50% or lower), previous PCI, and core laboratory-assessed SYNTAX score, an angiography-based scoring system of the complexity of the CAD (<23, 23-32, and >32), with lower score indicating less complexity and predicting a better outcome with PCI.) A post-hoc sensitivity analysis was performed utilizing an alternate accepted definition for procedural MI.[12] Analyses were independently reproduced within the statistical team and conducted using SAS 9.4 (SAS Institute, Cary, North Carolina) and R version 4.0.[13]

RESULTS

Of the 1,500 patients enrolled, 757 were randomized to PCI and 743 were randomized to CABG (Figure S1). The average age of the patients was 65 years, 29% had diabetes, 39% presented with an acute coronary syndrome, and 14% had a previous PCI (Table 1). On average, patients had 4.3 lesions, 22% had a chronically occluded vessel and 67% had at least one bifurcation lesion. The mean SYNTAX score was 26. There was a mean of 4.3 lesions per patient in the PCI group and a mean of 3.7 DES were implanted per patient with

a median stented length of 80 mm. FFR was measured in 82% of lesions. Reasons for not measuring FFR were primarily subtotally or completed occluded vessels.

Table 1. Baseline characteristics

	PCI (n=757)	**CABG** (n=743)
Age – years	65.2±8.6*	65.1±8.3
Male sex – no. (%)	616 (81.4)	619 (83.3)
White/Caucasian – no. (%)	711 (93.9)	686 (92.3)
Body mass index (kg/m^2)†	28.6±4.5	28.7±4.3
Diabetes, no. (%)	214 (28.3)	214 (28.8)
Insulin-dependent	55 (7.3)	61 (8.2)
Non-insulin dependent	159 (21.0)	153 (20.6)
Hypertension – no. (%)	538 (71.2)	556 (75.0)
Dyslipidemia – no. (%)	521 (68.9)	531 (71.7)
Smoking status – no. (%)		
Current tobacco user	145 (19.2)	136 (18.4)
Previous tobacco user	296 (39.2)	296 (39.9)
Family history of CAD – no. (%)	246 (32.5)	213 (28.8)
Previous MI – no. (%)	252 (33.3)	248 (33.5)
Previous PCI – no. (%)	98 (13.0)	104 (14.0)
History of TIA/CVA – no. (%)	49 (6.5)	56 (7.6)
Renal disease (MDRD<60 mL/min/1.73 m2) – no. (%)	37 (4.9)	44 (5.9)
Noninvasive test for ischemia – no. (%)	311 (41.1)	301 (40.6)
Ejection Fraction ≤ 50% – no. (%)	137 (18.2)	130 (17.6)
Hospitalized with NSTE-ACS – no. (%)	300 (39.7)	287 (38.7)

**Plus–minus values are means ±standard deviation (SD).*
†The body-mass index is the weight in kilograms divided by the height in meters squared.
NSTE-ACS denotes non-ST segment elevation acute coronary syndrome, CVA cerebrovascular accident, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

The mean FFR was 0.70, with 24% of lesions intended for treatment having an FFR>0.80. FFR was measured after PCI in 60% of treated lesions, with a mean value of 0.88. Intravascular imaging was utilized in 12% of cases.

Table 2. Angiographic and procedural characteristics

	PCI (n=757)	**CABG** (n=743)
Time to procedure (days) – median (IQR)	4 (1-13)	13 (6-26)
Procedure duration (min) – median (IQR)	87 (67-113)	197 (155-239)
Length of hospital stay (days) – median (IQR)	3 (1-7)	11 (7-16)
Number of lesions – mean	4.3±1.3	4.2±1.2
⩾1 chronic total occlusion – no. (%)	157 (20.8)	171 (23.1)
⩾1 bifurcation lesion – no. (%)	522 (69.1)	491 (66.4)
SYNTAX Score – mean†	26.0±7.1	25.8±7.1
Low (0 to 22) – no. (%)	237 (32.3)	245 (34.5)
Intermediate (23 to 32) – no. (%)	365 (49.7)	343 (48.3)
High (>32) – no. (%)	132 (18.0)	122 (17.2)
PCI‡		
Staged procedure – no. (%)	166 (22.1)	NA
Number of stents – mean	3.7±1.9	NA
Total length of stents placed (mm) – median (IQR)	80 (52-116)	NA
Intravascular imaging used – no. (%)	87 (11.7)	NA
CABG‡		
Multiple arterial grafts – no. (%)	NA	173 (24.5)
Number of distal anastomoses – mean	NA	3.4±1.0
LIMA – no. (%)	NA	684 (97.0)
Off-Pump surgery – no. (%)	NA	168 (24.1)
FFR used prior to CABG – no. (%)	NA	72 (10.0)

**Plus–minus values are means ±SD. IQR denotes interquartile range.*
†The SYNTAX score reflects the angiographic severity of coronary artery disease; higher scores indicate more complex coronary disease. The SYNTAX score was calculated by the core laboratory.
‡Numbers (%) based on the "as treated" population.
CABG denotes coronary artery bypass grafting, FFR fractional flow reserve, LIMA left internal mammary artery, NA not applicable, and PCI percutaneous coronary intervention.

Patients undergoing CABG had 4.2 lesions and received 3.4 distal anastomoses with 97% receiving a left internal mammary artery graft and 25% receiving multiple arterial grafts. FFR was measured before CABG in 10% of patients. Procedural details are listed in Table 2.

Follow-up at one year was achieved in 99.7% of subjects. FFR-guided PCI did not meet the criterion set in this trial for noninferiority (p=0.35). At one year, the incidence of MACCE was 10.6% in patients randomized to FFR-guided PCI vs. 6.9%, in those randomized to CABG (HR 1.5, 95% CI 1.1-2.2, Table 3, figure 1). There was no clear evidence of between groups

differences in the incidence of the individual components of MACCE or the composite of death, MI or stroke (Table 3).

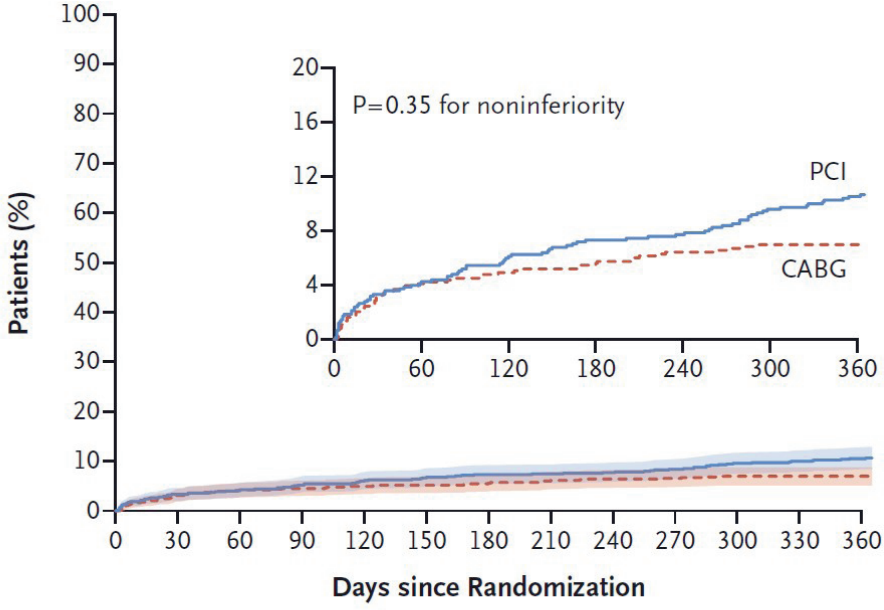
Table 3. One year outcomes

	PCI (n=757)	**CABG** (n=743)	**Hazard Ratio** (95% CI)	***P* value**
Primary Endpoint				
MACCE	80 (10.6)	51 (6.9)	1.5 (1.1, 2.2)	0.35†
Secondary endpoints‡				
Death	12 (1.6)	7 (0.9)	1.7 (0.7, 4.3)	
Cardiac death	6 (0.8)	4 (0.5)		
Myocardial infarction	39 (5.2)	26 (3.5)	1.5 (0.9, 2.5)	
Spontaneous	25 (3.3)	17 (2.3)		
Procedural	13 (1.7)	9 (1.2)		
Stroke	7 (0.9)	8 (1.1)	0.9 (0.3, 2.4)	
Death, myocardial infarction, or stroke	55 (7.3)	39 (5.2)	1.4 (0.9, 2.1)	
Repeat revascularization	45 (5.9)	29 (3.9)	1.5 (0.9, 2.3)	
Percutaneous coronary intervention	39 (5.2)	26 (3.5)		
Coronary bypass surgery	6 (0.8)	3 (0.4)		
Safety endpoints§				
BARC Type 3-5 bleeding	12 (1.6)	28 (3.8)		<0.01
Acute kidney injury	1 (0.1)	7 (0.9)		<0.04
Atrial fibrillation/significant arrhythmia	18 (2.4)	105 (14.1)		<0.001
Definite stent thrombosis	6 (0.8)	NA		
Definite symptomatic graft occlusion	NA	10 (1.3)		
Rehospitalization within 30 days	42 (5.5)	76 (10.2)		<0.001

**Percentages are crude rates based on intention-to-treat analysis.*
†P-value obtained from test of noninferiority for MACCE.
‡95% CIs were not adjusted for multiplicity and should not be interpreted to inform definitive treatment effects.
§P-value from the Chi-squared or Fisher's exact test. Patients lost to follow-up prior to the end of the first year are excluded from comparisons with respect to safety endpoints.
Acute kidney injury was defined as any of the following: Increase in SCr (serum creatinine) by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume 0.5 ml/kg/h for 6 hours.
CABG denotes coronary artery bypass grafting, PCI percutaneous coronary intervention, BARC bleeding academic research consortium

There were no obvious differences between groups in medical therapy at one year, except for a higher rate of dual antiplatelet and nitrate therapy in the patients randomized to PCI. Patients randomized to CABG had longer hospital stays and increased rates of major bleeding, arrhythmia, acute kidney injury and rehospitalization within 30 days (Table 3). Results of prespecified subgroup analyses are shown in Figure 2**.** A post hoc sensitivity analysis evaluating the impact of using a different definition for procedural MI resulted in a 14.7% rate in the patients randomized to CABG and a 10.4% rate in the patients randomized to PCI.[12]

Figure 1. Kaplan–Meier curves for the primary end point.



No. at Risk

PCI	757	728	721	713	707	702	697	696	693	687	678	674	670
CABG	743	709	701	698	695	693	691	686	683	682	679	679	679

Primary end point was the occurrence within 1 year of a major adverse cardiac or cerebrovascular event, defined as death from any cause, myocardial infarction, stroke, or repeat revascularization. The inset shows the same data on an enlarged y axis. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

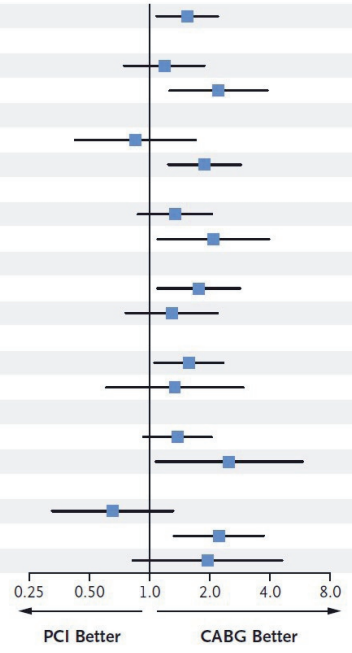
DISCUSSION

The main finding of the FAME 3 trial is that in patients with 3v-CAD at angiography, FFR-guided PCI did not meet the criterion set in this trial for noninferiority. CABG resulted in a lower rate of the composite of death, MI, stroke or repeat revascularization at one year when compared with FFR-guided PCI utilizing current generation zotarolimus-eluting stents. The rates of the composite of death, MI or stroke and the individual components of MACCE were not significantly different between the two groups. Rates of procedural complications such as major bleeding, acute kidney injury, arrhythmia, and rehospitalization within 30 days were higher and hospital length of stay was longer in the patients randomized to CABG.

These findings are consistent with previous studies comparing CABG with PCI, but there are important differences between the current report and earlier trials.[1,3] The current trial involved routine measurement of FFR to guide PCI, with the expectation that FFR

Figure 2. Subgroup analyses of the primary end point.

Subgroup	PCI (total no.)	CABG (total no.)	PCI (1-yr incidence %)	CABG (1-yr incidence %)
All patients	757	743	10.6	6.9
Age				
≥65 yr	434	409	9.4	8.1
<65 yr	323	334	12.1	5.4
Sex				
Female	141	124	11.3	13.7
Male	616	619	10.4	5.5
Diabetes				
No	543	529	9.4	7.0
Yes	214	214	13.6	6.5
NSTE-ACS				
No	456	454	10.1	5.9
Yes	300	287	11.3	8.4
LVEF				
>50%	616	610	10.4	6.6
30–50%	137	130	10.9	8.5
Previous PCI				
No	658	637	9.3	6.8
Yes	98	104	19.4	7.7
SYNTAX score				
0–22	237	245	5.5	8.6
23–32	365	343	13.7	6.1
≥33	132	122	12.1	6.6



The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is an angiography-based score evaluating the severity of coronary artery disease; lower scores indicate less complexity of coronary artery disease and predict a better outcome with PCI (the lowest score is 0, and there is no upper limit). Scores were calculated by the core laboratory. CI denotes confidence interval, LVEF left ventricular ejection fraction, and NSTE-ACS non–ST-segment elevation acute coronary syndrome.

would lead to more judicious stenting by (1) treating only functionally significant lesions, which have been shown to lead to higher rates of adverse events when treated with medications alone, and (2) by avoiding unnecessary stenting of non-flow limiting lesions, which respond as well if not better to medical therapy alone compared with PCI.[5,7] As anticipated, participants in FAME 3, in whom PCI was guided by FFR, received fewer stents (3.7 vs 4.6), compared with the SYNTAX trial, which compared PCI (without FFR guidance) to CABG, while the number of coronary lesions was similar.[1] While these trials are not directly comparable, patients randomized to PCI in FAME 3 also had a lower rate of repeat revascularization (4.9% vs 13.5%) and mortality (1% vs 4%) compared with the SYNTAX trial, despite similar patient characteristics and risk profiles between the trials; plausible explanations include the lower number of stents placed, with reduced risk of stent-related complications like thrombosis or restenosis, improved stent technology, and high rates of adherence to recommended medical therapy. Moreover, the MACCE rate in patients randomized to either FFR- guided PCI (10.6%) or to CABG (6.9%) in FAME 3 was lower compared with the MACCE rate in patients randomized to CABG in the SYNTAX trial (12.4%).[1] Among patients randomized to CABG, the better outcomes in FAME 3 may be due to improvements in operative techniques or more effective medical therapy. For example, the percentage of participants randomized to CABG using statins or beta blockers at 1 year was 94% and 83%, respectively, in FAME 3, versus approximately 70% and 75%, respectively, in the SYNTAX trial.[14]

In FAME 3, FFR was measured in 82% of lesions and FFR was >0.80 in 24% of lesions. These percentages were lower than in a prior trial comparing FFR-guided PCI with angiographically-guided PCI in patients with multivessel CAD (95% and 37%, respectively).[5] The benefit of FFR-guidance is primarily related to avoiding unnecessary stents and their inherent complications. In cases where the FFR measurement and deferral rates are higher, one might anticipate better outcomes with an FFR-guided PCI approach.

FFR was measured prior to CABG in 10% of subjects. Presumably these patients all had functionally significant 3v-CAD. It is likely that a proportion of candidates for the study had FFR measured before randomization and were found to have only one or two vessels with functionally significant disease and therefore were not included in the study, but instead were treated immediately with PCI. This could have skewed the population in this trial towards more severe CAD.

The definition of procedural MI remains controversial. In our primary analysis, we defined periprocedural MI in both the CABG and PCI groups using the 3rd and 4th Universal Definitions for CABG-related MI , which resulted in low rates of procedural MI. A post-hoc sensitivity analysis utilizing a more liberal definition, including a biomarker elevation only criterion, resulted in higher rates of procedural MI, particularly in the patients randomized

to CABG.[12] Because data on symptoms suggestive of ischemia or new ischemic ECG changes after PCI were not routinely recorded, we could not assess the incidence of MI related to PCI based on the 3rd and 4th Universal Definitions for these MIs. If we had been able to calculate the rates of PCI-related MI according to these definitions, which require lower levels of biomarker elevation (troponin elevation more than 5 times the 99th percentile of the upper reference limit) in conjunction with only symptoms of ischemia or ischemic ECG changes, we likely would have seen higher rates of MI in the PCI group.

Other limitations of the present report also warrant consideration. First, the follow-up in this study was only one year; previous studies have shown greater benefit of CABG as compared with PCI during longer term follow-up, particularly with respect to late MI and repeat revascularization. Three and five-year follow-up is ongoing in FAME 3 and will be critical to assessing longer-term effects of these two treatment strategies. Second, the current report does not include information on changes in quality of life and cost-effectiveness; data have been collected to address these outcomes and will be reported subsequently. Third, FFR was not routinely measured in the patients randomized to CABG; however, studies comparing FFR-guided CABG with angiography-guided CABG have not demonstrated the same benefit as seen with FFR-guided PCI.[15,16] Fourth, intravascular imaging was used in only 12% of cases in the patients treated with PCI; prior data support lower rates of repeat revascularization when intravascular imaging is routinely performed, although the revascularization rate at 1 year in a recent study employing intravascular imaging in 84% of PCI cases in a similar population was not lower than in FAME 3 [17,18] Fifth, the completeness of revascularization in both groups has not yet been analyzed and will be the subject of a substudy. Sixth, women and persons of color were underrepresented in the present report. Future studies including a more diverse patient population are necessary before generalizing these findings.

In conclusion, the FAME 3 trial found that in patients with 3v-CAD, FFR-guided PCI was not noninferior to CABG with respect to the composite of death, MI, stroke, or repeat revascularization at one year.

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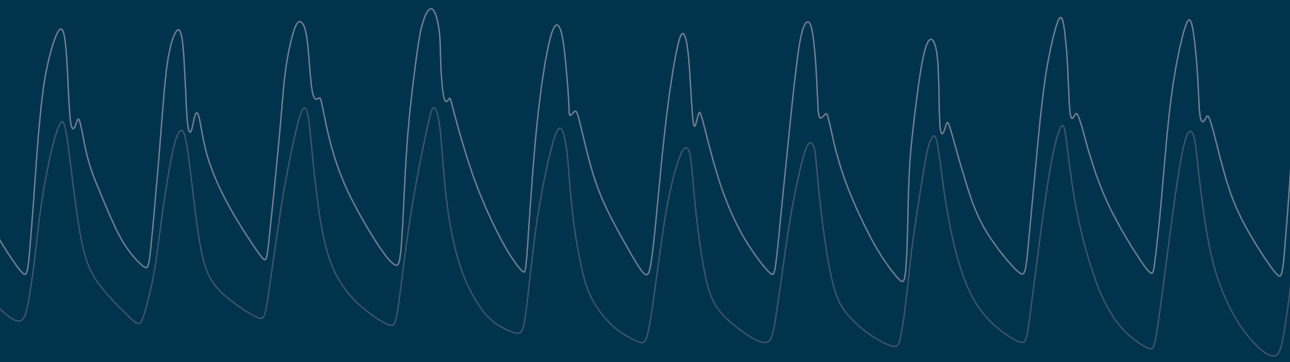

CHAPTER 4

Quality of Life After Fractional Flow Reserve-Guided PCI Compared With Coronary Bypass Surgery

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ABSTRACT

Background

Previous studies have shown quality of life improves after coronary revascularization, more so after coronary artery bypass grafting (CABG) than after percutaneous coronary intervention (PCI). This study aimed to evaluate the impact of fractional flow reserve (FFR) guidance and current generation, zotarolimus drug-eluting stents (DES) on quality of life after PCI compared with CABG.

Methods

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 trial is a multicenter, international trial including 1500 patients with three-vessel coronary artery disease (CAD) who were randomly assigned to either CABG or FFR-guided PCI. Quality of life was measured using the European Quality of Life–5 Dimensions (EQ-5D) questionnaire at baseline, 1 and 12 months. The Canadian Cardiovascular Class (CCS) angina grade and working status were assessed at the same time points and at 6 months. The primary objective was to compare EQ-5D summary index at 12 months. Secondary endpoints included angina grade and work status.

Results

The EQ-5D summary index at 12 months did not differ between the PCI and CABG groups (difference=0.001, 95% confidence interval (CI) -0.016 to 0.017, p=0.946). The trajectory of EQ-5D over the 12 months differed (p<0.001) between PCI and CABG: at 1 month, EQ-5D was 0.063 (95% CI 0.047 to 0.079) higher in the PCI group. A similar trajectory was found for the EQ visual analogue scale. The proportion of patients with CCS 2 or greater angina at 12 months was 6.2% vs 3.1% (OR=2.5, 95% CI 0.96 to 6.8), respectively in the PCI group compared with the CABG group. A greater percentage of younger patients (<65 years-old) were working at 12 months in the PCI group compared with the CABG group (68% vs 57%, OR=3.9, 95% CI 1.7 to 8.8).

Conclusions

In the FAME 3 trial, quality of life after FFR-guided PCI with current generation DES compared with CABG was similar at one year. The rate of significant angina was low in both groups and not significantly different. The trajectory of improvement in quality of life was significantly better after PCI, as was working status in those less than 65 years old.

INTRODUCTION

In patients with three-vessel coronary artery disease (CAD), large, randomized trials have demonstrated that coronary revascularization improves quality of life, with better outcomes (in particular, lower rates of myocardial infarction (MI) and repeat revascularization) after coronary artery bypass grafting (CABG) than after percutaneous coronary intervention (PCI).[1,2] These studies were performed without innovations that significantly improve PCI outcomes, particularly current generation drug-eluting stents (DES) and guidance by fractional flow reserve (FFR).[3-6]

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 trial found that FFR-guided PCI using current generation zotarolimus DES did not meet the criterion set for noninferiority regarding major adverse cardiac and cerebrovascular events (MACCE) at one year compared with CABG. When compared with previous trials the overall event rates were lower after both PCI and CABG, and the difference between the two strategies was smaller.[7] In light of the lower rates of hard events, the impact of these alternative treatments on quality of life, chest pain, and work status becomes more important for clinical decision-making. The goal of this study was to compare the effects of the randomized revascularization strategies on these health-related outcomes.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was approved by each site's institutional review committee and the subjects gave informed consent.

Trial Design

The design and main outcomes of the FAME 3 trial have been reported previously.[7-9] Briefly, both stable patients and those with ongoing unstable angina or non-ST segment elevation MI who had three-vessel CAD not involving the left main coronary artery, amenable to both PCI and CABG, were randomized to either FFR-guided PCI with zotarolimus DES or to CABG and assessed for occurrence of MACCE (a composite outcome consisting of death, MI, stroke and repeat revascularization). Major exclusion criteria were cardiogenic shock, recent ST segment elevation MI (within 5 days), or very low left ventricular ejection fraction (<30%). Patients were followed-up at discharge, one, six and 12 months for clinical events, including rehospitalization, as well as for quality of life, angina, and work status.

Trial Procedures

The European Quality of Life–5 Dimensions (EQ-5D) and its associated visual analogue scale were completed by each subject at baseline, one month and 12 months of follow-up. The EQ-5D summary index was calculated based on responses over five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which was rated on three levels (no problems, some problems, and extreme problems). The responses were translated using U.S. value sets into the EQ-5D summary index, which ranges from -0.1 (worst) to 1 (best).[10] The EQ visual analogue scale was used to record the patient's self-rated health on a scale that ranges from 0 (worst) to 100 (best).

Angina was assessed at baseline, discharge, one, six, and 12 months using the Canadian Cardiovascular Society (CCS) angina classification, ranging from a grade of 0 for asymptomatic patients to a grade of 4 for the most severe, limiting angina. Work status was assessed at baseline, one, six, and 12 months, with patients classified as working (full-time or part-time) or not working (due to retirement, health restriction or other reasons), with a pre-specified subgroup comparison for patients of working age, i.e., <65 years old at baseline.

Endpoints

The primary endpoint for this study was the comparison of the EQ-5D summary index measured at 12-months follow-up between patients randomized to PCI or CABG. Secondary endpoints included the EQ visual analogue scale, presence of clinically significant angina (defined as CCS grade 2 or higher), and employment status (working or not).

Statistical Analysis

The primary analysis was designed to address whether the EQ-5D summary index differed between study arms at 12 months and was conducted in accordance with the intention-to-treat principle. Between-group differences in the primary endpoint over time were visualized using boxplots, and statistical inference was based on a mixed model framework to account for the correlation of repeated observations within individuals. For comparing EQ-5D summary index scores by arm over time, the linear mixed effects regression model included a term for the randomization assignment, post-baseline visit (one or 12 months, modeled categorically), their interaction, as well as baseline diabetes status to account for the randomization stratification. Differences in one-year trajectories between arms were evaluated using a likelihood ratio test of the arm x visit interaction.

The EQ visual analogue scale was analyzed using the mixed effects model specified for the primary analysis. The dichotomized angina grade and work status were analyzed using an analogous generalized linear mixed effects model with a logit link and included

assessments at additional visits (discharge and 6 months for angina grade and 6 months for work status) in characterizing trajectories.

Heterogeneity of the treatment effect at 12 months was tested for key baseline clinical characteristics, based on tests of statistical interaction. Two factors were prespecified to test the hypotheses that quality of life after PCI would be more favorable among (1) patients with less complex coronary disease, as assessed by the angiography-based Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (higher scores indicate greater complexity of coronary artery disease) and (2) patients without an acute coronary syndrome at time of enrollment. Heterogeneity of treatment effect was not expected to be present, but was also tested for, according to additional baseline characteristics: age group (<65 years or ⩾65 years), sex, presence or absence of diabetes, left ventricular ejection fraction (>50% or ⩽50%), and previous PCI.

Sensitivity analyses for the EQ-5D measures were performed with missing data multiply-imputed by chained equations and regression estimates combined using Rubin's rules. The imputation model included baseline factors and nonfatal clinical events, and 20 data sets were imputed for each outcome. Analyses were performed using R software, version 4.0, and multiple imputation was performed using the 'mice' R package.[11,12]

RESULTS

Of the 1,500 patients enrolled, 757 were randomized to PCI and 743 to CABG. The average age was 65 years old, 83% were men, 92% were white, 29% had diabetes and 39% presented with an acute coronary syndrome. Baseline clinical characteristics were well balanced (Table 1). EQ-5D summary index data were available at baseline for 98% of patients randomized to PCI and 97% of patients randomized to CABG, 95% and 90% at 1 month, and 89% and 88% at 12 months. Angina data were available at baseline in 99.6% of patients randomized to PCI and 99.3% of patients randomized to CABG, 96% and 93.3% at one month, and 92.2% and 91.8% at 12 months. Nineteen patients died during the first year of follow-up, 12 in the PCI-assigned group, and seven in the CABG-assigned group. The length of the index hospitalization was significantly longer in patients randomized to CABG (median 11 days vs 3 days, $p < 0.0001$). The percentage of patients with a repeat hospitalization during the first 12 months of follow-up was slightly, but not significantly, higher among patients randomized to CABG than among patients randomized to PCI (21% vs. 18%, $p=0.16$).

Table 1. Baseline characteristics

Characteristic	**PCI** (n=757)	**CABG** (n=743)
Age – years	65.2±8.6	65.1±8.3
Male sex – no. (%)	616 (81%)	619 (83%)
White/Caucasian – no. (%)	711 (94%)	686 (92%)
Body mass index (kg/m^2)	28.6 ±4.5	28.7±4.3
Diabetes – no. (%)	214 (28%)	214 (29%)
Insulin-dependent	55 (7%)	61 (8%)
Non-insulin dependent	159 (21%)	153 (21%)
Hypertension – no. (%)	538 (71%)	556 (75%)
Dyslipidemia – no. (%)	521 (69%)	531 (72%)
Smoking status – no. (%)		
Current tobacco user	145 (19%)	136 (18%)
Previous tobacco user	296 (39%)	296 (40%)
Previous MI – no. (%)	252 (33%)	248 (33%)
Previous PCI – no. (%)	98 (13%)	104 (14%)
Renal disease (MDRD<60 mL/min/1.73 m^2) – no. (%)	37 (5%)	44 (6%)
Ejection Fraction ≤ 50% – no. (%)	137 (18%)	130 (18%)
Hospitalized with NSTE-ACS – no. (%)	300 (40%)	287 (39%)

Quality of life at baseline was impaired in the overall population, with mean scores in all patients of 0.82 for the EQ-5D summary score, and 68 for the visual analogue scale; 71% of patients had CCS class 2 or greater angina and 65% of those <65 years old were working at baseline (Tables 2 and 3).

The primary comparison, the EQ-5D summary index at 12 months, did not differ between the randomized groups: difference = 0.001 (95% confidence interval (CI) -0.016 to 0.017), p=0.946 (Table 2 and Figure 1); both groups improved significantly from their baseline EQ-5D scores (Table S1).

Similarly, the EQ visual analogue scale rating of quality of life did not differ between the randomized groups at 12 months and improved from baseline in both groups (Table 3 and Figure 2). The percentage of patients with CCS Class ≥2 angina was not significantly different at 12 months: 6.2% vs 3.1% (OR=2.5, 95% CI 0.96 to 6.8) respectively for PCI and CABG (Table 3**,** Figure 3, and table S2).

The percentage of patients working full-time or part-time was similar at 12 months in both groups: 35.1% vs. 32.0% (OR=1.2, 95% CI 0.5 to 2.6) respectively for PCI and CABG. In the prespecified subgroup of patients < 65 years of age at baseline, the percentage

Table 2. EQ-5D Summary Index over follow-up

Outcome	PCI	CABG	Difference† (95% CI)	p-value
EQ-5D Summary Index – mean (SD)				<0.001*
Baseline	0.827 (0.157)	0.821 (0.167)	0.007 (-0.009, 0.022)	
1 month	0.891 (0.133)	0.830 (0.147)	0.063 (0.047, 0.079)	
12 months	0.874 (0.152)	0.873 (0.160)	0.001 (-0.016, 0.017)	0.946**

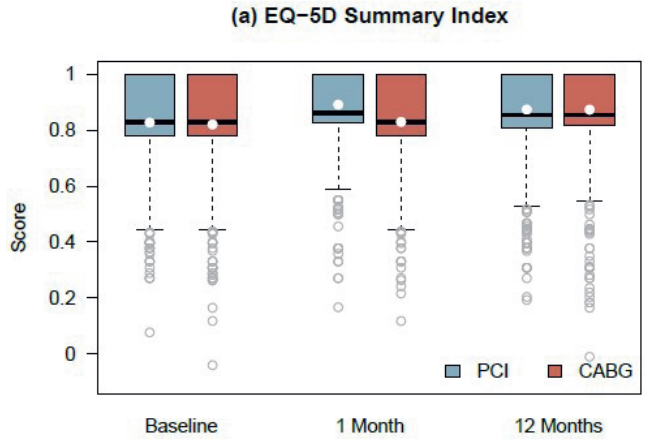
† *Adjusted for baseline diabetes status.*
**p-value for the trajectory of improvement in EQ-5D Summary Index favoring FFR-Guided PCI*
***p-value showing no significant difference in the primary endpoint of EQ-5D summary score at 12 months*
EQ-5D indicates European Quality of Life–5 Dimensions; CCS indicates Canadian Cardiovascular Society

Table 3. Other quality of life outcomes over follow-up

Outcome	PCI	CABG	Difference† (95% CI)
EQ Visual Analog Scale – mean (SD)			
Baseline	68.5 (17.4)	68.0 (17.9)	0.5 (-1.2, 2.2)
1 month	77.0 (14.5)	72.2 (16.2)	5.0 (3.3, 6.7)
12 months	76.3 (15.5)	77.2 (15.7)	-0.8 (-2.5, 1.0)
			Odds Ratio† (95%CI)
CCS Angina › 2 – no. (%)			
Baseline	526 (69.9)	535 (72.3)	0.6 (0.3, 1.1)
1 month	46 (6.3)	17 (2.5)	4.1 (1.5, 11.3)
6 months	38 (5.3)	24 (3.5)	1.3 (0.5, 3.5)
12 months	43 (6.2)	21 (3.1)	2.5 (0.96, 6.8)
Working Full or Part-time – no. (%)			
Baseline	270 (35.8)	249 (33.7)	0.9 (0.4, 1.9)
1 month	234 (32.2)	128 (18.4)	15.5 (6.3, 38.2)
6 months	247 (34.7)	208 (30.6)	1.4 (0.6, 3.2)
12 months	245 (35.1)	217 (32.0)	1.2 (0.5, 2.6)
Working Full or Part-time, Age <65 Years–no. (%)			
Baseline	216 (66.9)	211 (63.6)	1.8 (0.8, 4.0)
1 month	186 (60.2)	104 (33.1)	19.4 (8.5, 44.6)
6 months	203 (67.0)	169 (55.4)	4.2 (1.9, 9.4)
12 months	203 (68.1)	175 (57.4)	3.9 (1.7, 8.8)

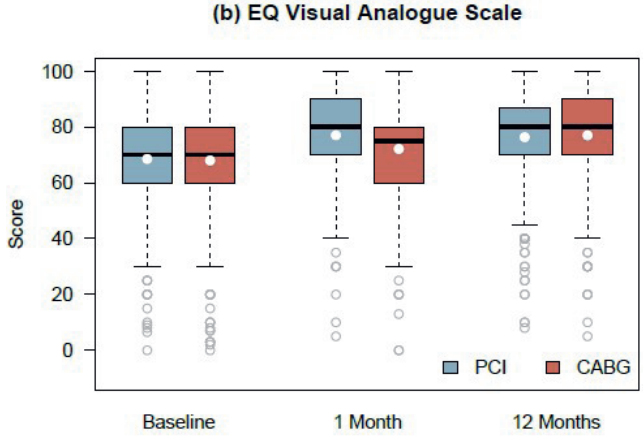
† *Adjusted for baseline diabetes status.*
EQ-5D indicates European Quality of Life–5 Dimensions; CCS indicates Canadian Cardiovascular Society

Figure 1. European Quality of Life–5 Dimensions (EQ-5D) summary index in patients randomized to fractional flow reserve–guided percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) at each time point.



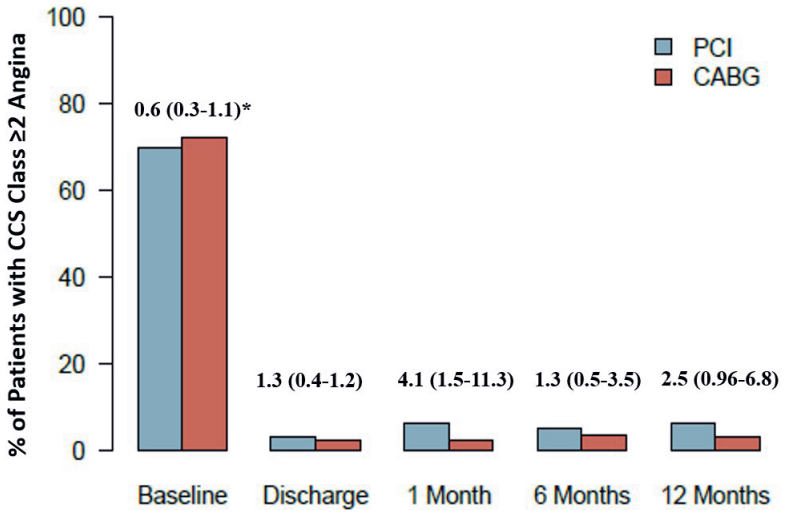
Black line indicates median and white dot indicates mean.

Figure 2. EQ Visual Analogue Scale in patients randomized to fractional flow reserve–guided percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) at each time point.



Black line indicates median and white dot indicates mean.

Figure 3. Angina status in patients randomized to fractional flow reserve–guided percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) at each time point.



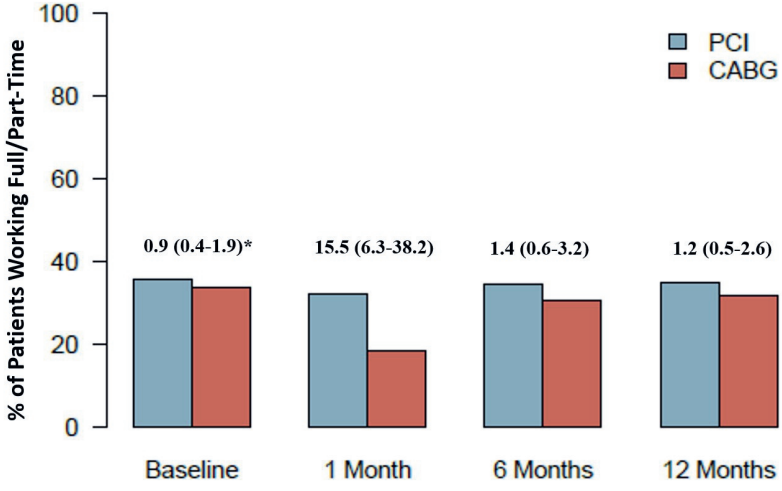
*CCS indicates Canadian Cardiovascular Society; and OR, odds ratio. *OR and 95% CI for comparisons of each time point*

of patients working full-time or part-time at 12 months was significantly higher among patients assigned to PCI: 68.1% vs. 57.4% (OR=3.9, 95% CI 1.7 to 8.8) respectively for PCI and CABG (Table 3 and Figure 4). In the PCI arm, of patients <65 years old who were not working at baseline, 26.0% were working at 12 months compared with 21% of the CABG group. In the PCI arm, of patients <65 years old who were working at baseline, 12% were not working at 12 months compared with 24% of the CABG group.

While 12-month quality of life scores were similar between the two randomized groups, the trajectories of scores over follow-up time differed significantly, with patients assigned to PCI having better quality of life (Tables 2 and 3). The differences in primary outcome (12-month EQ-5D scores) in key clinical subgroups were consistent with the results in the overall population (Figure 5 and Table S3). Results were not materially changed in sensitivity analyses (Table S4).

Figure 4. Working status. A, Percentage of patients randomized to fractional flow reserve–guided percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) working full or part time at each time point. B, Percentage of patients <65 years old randomized to fractional flow reserve–guided PCI compared with CABG working full or part time at each time point.

A



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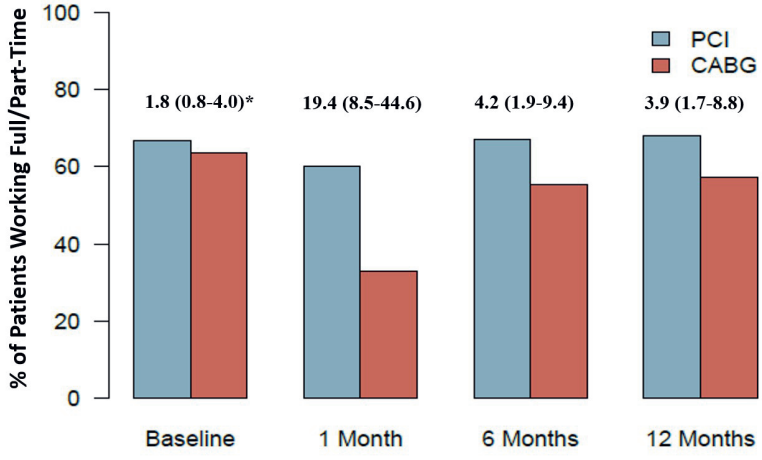
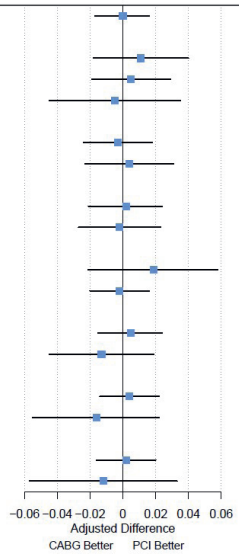


OR indicates odds ratio

Figure 5. Subgroup analyses comparing the European Quality of Life–5 Dimensions Summary Index at 12 months between patients randomized to fractional flow reserve–guided percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG).

Subgroup	PCI Total N	CABG Total N	PCI 1–yr Average	CABG 1–yr Average	Interaction p–value
Overall	757	743	0.874	0.873	
SYNTAX					0.81
0–22	237	245	0.884	0.873	
23–32	365	343	0.874	0.869	
33+	132	122	0.881	0.882	
NSTE–ACS					0.69
No	456	454	0.876	0.878	
Yes	300	287	0.871	0.866	
Age at enrollment					0.85
65+	434	409	0.867	0.864	
<65	323	334	0.883	0.885	
Sex					0.35
Female	141	124	0.818	0.799	
Male	616	619	0.886	0.887	
Diabetes					0.35
No	543	529	0.888	0.883	
Yes	214	214	0.836	0.849	
LVEF					0.35
>50%	616	610	0.876	0.872	
30–50%	137	130	0.865	0.880	
Previous PCI					0.57
No	658	637	0.874	0.871	
Yes	98	104	0.874	0.888	



CABG indicates coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NSTE-ACS, non ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

DISCUSSION

Coronary revascularization reduces angina and, in certain groups of patients, improves survival. CABG and PCI have been compared in many randomized trials, but prior studies have not incorporated the latest developments in PCI, particularly use of FFR guidance. The FAME 3 study was designed to compare CABG and PCI guided by FFR in patients with 3V-CAD, and found that despite these advancements, PCI did not meet the criterion set for noninferiority regarding MACCE at one year when compared with CABG.[7] However, the overall event rates were lower in both groups compared with previous studies and the difference between the two was smaller. This study extends these findings by showing that quality of life, measured by the EQ-5D summary score, did not differ significantly after 12 months between patients randomized to CABG or to FFR-guided PCI. Patients assigned to PCI had faster recoveries, however, with significantly better EQ-5D scores at one month of follow-up. Patients assigned to CABG had later improvement in EQ-5D scores, which did not differ from the scores of PCI-assigned patients at 12 months.

Studies have found that a minimal clinically important difference in the EQ-5D is 0.028.[13] The difference in EQ-5D at one month between PCI and CABG of 0.063 is over twice this minimal clinically important difference. Furthermore, the 0.001 difference in EQ-5D at 12 months is well below this threshold, and the confidence limits exclude a difference as large as 0.028. The longer-term effects of CABG on quality of life may be more important to some patients, and could potentially offset the early decrements due to the inherently more invasive CABG procedure. Given the lower rates of hard outcomes in both groups and the smaller difference between the two groups, the earlier improvements in symptoms and quality of life after FFR-guided PCI may be an important consideration for patients choosing between methods of coronary revascularization.

Other measures in the quality of life battery showed similar patterns over follow-up. The EQ visual analogue scale, a simple yet intuitive measure of quality of life, paralleled the changes in the EQ-5D summary measure over follow-up. Angina was greatly improved in both randomized groups, and the percentage of patients with CCS Class ⩾2 angina at 12 months was similar in the two randomized groups, in contrast to the lower rates of angina after CABG in previous studies.

The effect of coronary revascularization on employment has been small and inconsistent in prior studies, presumably because non-medical factors may be more important than the purely medical outcomes when patients decide whether to continue working. In this study, the percentage of patients of working age (i.e., <65 years old) who were working full or part-time at 12 months was higher among patients assigned to PCI. Consistent with the faster recovery seen in the other quality of life measures, and their shorter initial hospital stays, more patients randomized to PCI had returned to work at one month of follow-up.

In contrast to earlier studies, in which quality of life measures at one year were improved to a greater extent following CABG compared with PCI, we found similar outcomes between the randomized groups at 12 months. Current generation zotarolimus DES, which were used in this study, are associated with lower rates of complications after PCI (e.g., less stent thrombosis and restenosis), which may translate to improved quality of life. Previous studies have shown better quality of life outcomes with FFR-guided PCI compared with either angiography-guided PCI or with medical therapy alone.[14,15] Moreover, there is a strong correlation between the improvement in FFR and improvement in quality of life.[16] We postulate that FFR-guided PCI in this trial allowed more accurate identification of functionally significant coronary disease and more judicious use of stenting, thereby leading to effective relief of myocardial ischemia by optimizing the benefit of PCI and minimizing its inherent risks. FFR guidance, in combination with improved stent technology, resulted in fewer complications and led to greater improvement in quality of life after PCI than seen in previous studies. These results should be interpreted in the light of the patient

population selected for this trial, in which 60% had stable ischemic heart disease and over 80% had an ejection fraction greater than 50% and should not be extrapolated to all patients undergoing coronary revascularization.

A limitation of this study is that the 12-month follow-up is relatively short. The clinical outcomes of CABG compared with PCI may change over longer follow-up periods, including quality of life and angina as well as the "harder outcomes" such as death and MI.[17] Longer follow-up of the FAME 3 study cohort is planned to evaluate these possibilities. The EQ-5D is a general health status measure, which may be less sensitive to changes due to revascularization than disease-specific measures, such as the Seattle Angina Questionnaire, or other general measures, such as the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), or the Patient Health Questionnaire-9. For example, in the SYNTAX trial, the Seattle Angina Questionnaire score was slightly, yet significantly higher at 12 months after CABG compared with PCI, even though the EQ-5D summary quality of life score did not differ between the two groups at 12 months. A disease-specific measure, however, may not capture the full effects of alternative therapies on overall quality of life, especially on more general health outcomes and perceptions. Studies comparing the EQ-5D with these other measures have demonstrated good correlation.[18,19] We used the original EQ-5D-3L questionnaire, which utilizes three possible responses to each question, rather than the more recently developed EQ-5D-5L, which uses five possible responses, and the greater granularity of this newer scale may provide greater power to identify differences between the two treatment strategies. We also did not measure cognitive function during follow-up, an outcome of importance to patients. Prior trials have shown similar long-term cognitive function after PCI and CABG, despite the immediate post-procedure impairments in cognitive function after CABG.

The mean quality of life scores in this study were calculated based only on surviving patients, and would have been slightly lower if we had assigned a score of zero to non-survivors. We would argue that quality of life is a meaningful concept only among living patients, however, so that omitting patients who died is conceptually appropriate. Moreover, the death rate in this study was less than 2% at one year, and did not differ between the randomized groups, so the comparison between randomized groups would not be materially altered. A final limitation is that not all patients completed the quality of life assessments at all time points. However, when these missing values were imputed, the results of the study did not change substantially.

In conclusion, in patients with 3V-CAD, quality of life and angina severity at 12 months are similar after FFR-guided PCI with current generation DES compared with CABG. FFR-guided PCI results in a faster improvement in quality of life than CABG during the first year after revascularization and improved working status at one year.

Funding Sources
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Table S1. Change in EQ-5D Summary Index since baseline, by arm.

Outcome	PCI	CABG	P-value
	Difference† (95% CI)	Difference (95% CI)	
EQ-5D Summary Index			
1 Month vs. Baseline	0.064 (0.052, 0.076)	0.008 (-0.005, 0.021)	<0.001
12 Months vs. Baseline	0.045 (0.033, 0.058)	0.051 (0.039, 0.064)	0.512

† *Adjusted for baseline diabetes status.*

Table S2. CCS Angina Grade for PCI and CABG at baseline and 12 months

	Baseline		12 Months	
CCS Angina Grade	**PCI**	**CABG**	**PCI**	**CABG**
n	753	740	698	682
0 (Asymptomatic)	126 (16.7)	112 (15.1)	542 (77.7)	565 (82.8)
1	101 (13.4)	93 (12.6)	113 (16.2)	96 (14.1)
2	240 (31.9)	249 (33.6)	28 (4.0)	19 (2.8)
3	170 (22.6)	176 (23.8)	13 (1.9)	2 (0.3)
4	116 (15.4)	110 (14.9)	2 (0.3)	0 (0)

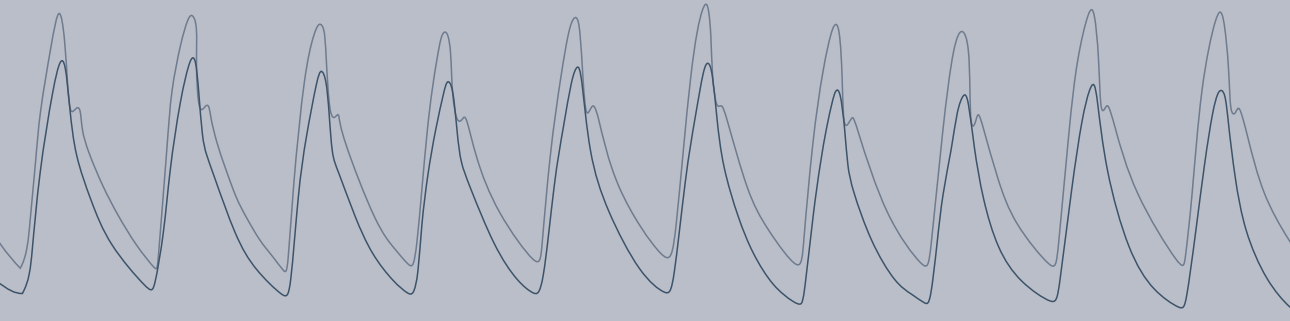
Table S3. EQ-5D Summary Index over follow-up, by baseline ACS status.

Outcome	PCI	CABG	Difference† (95% CI)
EQ-5D Summary Index			
ACS at Baseline – mean (SD)			
Baseline	0.837 (0.168)	0.821 (0.181)	0.016 (-0.011, 0.042)
1 month	0.880 (0.144)	0.816 (0.157)	0.065 (0.038, 0.092)
12 months	0.871 (0.148)	0.866 (0.166)	0.008 (-0.019, 0.036)
No ACS at Baseline – mean (SD)			
Baseline	0.821 (0.149)	0.820 (0.158)	0.001 (-0.019, 0.020)
1 month	0.899 (0.124)	0.838 (0.140)	0.062 (0.042, 0.081)
12 months	0.876 (0.154)	0.878 (0.155)	-0.004 (-0.024, 0.016)

† *Adjusted for baseline diabetes status.*

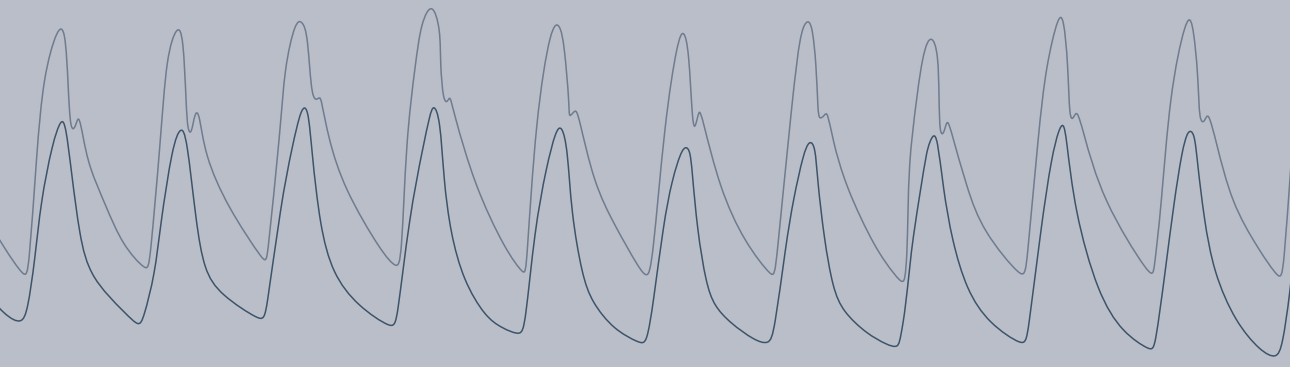
Table S4. Sensitivity analysis of one year outcomes under multiple imputation.

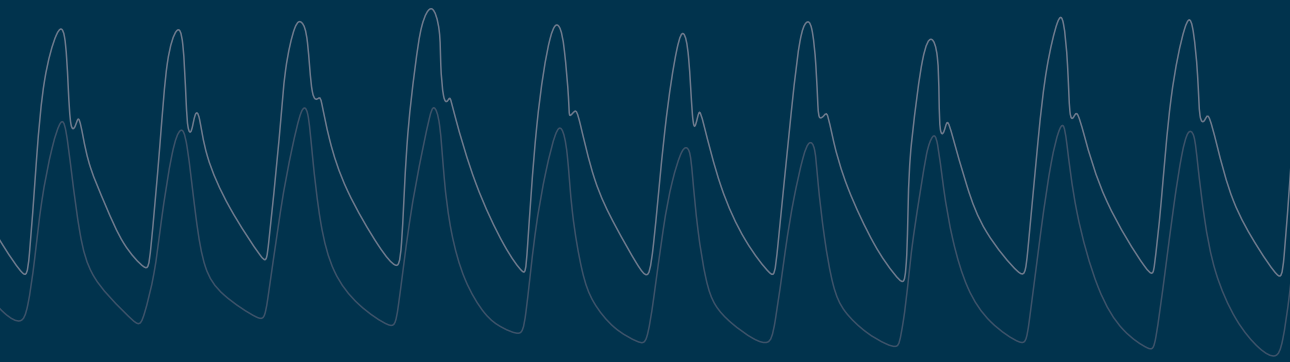
QOL Measure	PCI vs. CABG
EQ-5D Summary Index	Difference (95% CI)
1 Month	0.060 (0.043, 0.077)
12 Months	0.003 (-0.015, 0.021)
EQ Visual Analogue Scale	Difference (95% CI)
1 Month	4.7 (2.9, 6.6)
12 Months	-0.4 (-2.4, 1.6)



PART II

Long-Term Clinical Outcomes Following Fractional Flow Reserve-Guided PCI





CHAPTER 5

Deferral Versus Performance of Percutaneous Coronary Intervention of Functionally Non-Significant Coronary Stenosis. 15-Year Follow-up of the DEFER Trial

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ABSTRACT

Aims

Stenting an angiographically intermediate but functionally non-significant stenosis is controversial. Nevertheless, it has been questioned if deferral of a functionally non-significant lesion on the basis of Fractional Flow Reserve (FFR) measurement, is safe, especially on the long-term. Five-year follow-up of the DEFER trial showed that outcome after deferral of percutaneous coronary intervention (PCI) of an intermediate coronary stenosis based on FFR ⩾0.75 is excellent and was not improved by stenting. The aim of this study was to investigate the validity of this position on the very long term.

Methods and results

In 325 patients scheduled for PCI of an intermediate stenosis, FFR was measured just before the planned intervention. If FFR was ⩾0.75, patients were randomly assigned to deferral (Defer group; n=91) or performance (Perform group; n = 90) of PCI. If FFR was <0.75, PCI was performed as planned (Reference group; n = 144). Clinical follow-up was 15 years. There were no differences in baseline clinical characteristics between the randomized groups. Complete 15-year follow-up was obtained in 92% of patients. After 15 years of follow-up, the rate of death was not different between the 3 groups: 33.0% in the Defer group, 31.1% in the Perform group, and 36.1% in the Reference group (Defer vs. Perform, RR 1.06, 95% CI: 0.69-1.62, p=0.79). The rate of myocardial infarction (MI) was significantly lower in the Defer group (2.2%) compared to the Perform group (10.0%), RR 0.22, 95% CI: 0.05-0.99, p=0.03.

Conclusion

Deferral of PCI of a functionally non-significant stenosis is associated with a favourable very long-term follow-up without signs of late "catch-up" phenomenon.

INTRODUCTION

It has been well documented that decisions with respect to revascularization of coronary stenoses, should take into account not only angiographic criteria but also non-invasive or invasive evidence of reversible myocardial ischemia.[1-7] Stenting an angiographically significant but functionally non-significant stenosis is controversial.[8, 9] Nevertheless, it has been questioned if deferral of revascularization of a functionally non-significant lesion on the basis of fractional flow reserve (FFR) measurement is safe, especially over the long-term. Concerns about future plaque rupture have played a major role in that discussion.[10-13] The DEFER study was the first randomized controlled trial investigating the suitability of FFR to guide coronary interventions.[14] The purpose of the DEFER study was to compare deferral versus performance of percutaneous coronary intervention (PCI) of an anatomic intermediate but functionally non-significant stenosis as indicated by FFR >0.75. The two-year and five-year follow-up showed that, both with respect to outcome and to symptoms, deferral was at least as good as mechanical revascularization of such stenoses. Up to five years, there was no difference with respect to mortality, myocardial infarction or revascularization related to the deferred lesions. No differences were present either with respect to functional class or use of medication.[15] The present report extends that follow-up to fifteen years with respect to the outcome parameters: mortality, myocardial infarction (MI) and revascularization.

METHODS

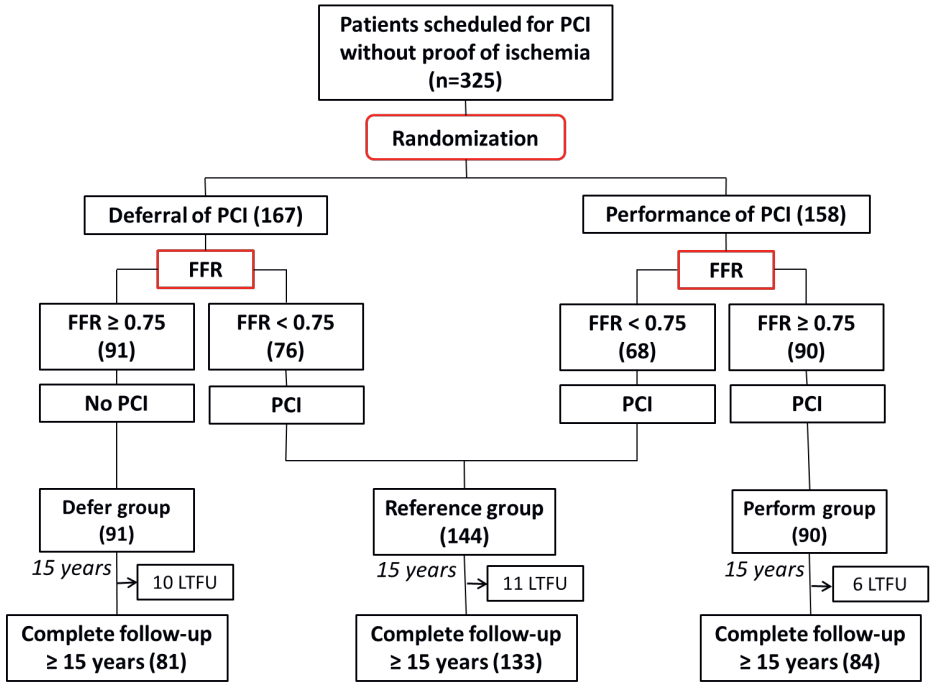
Design and participants

The design and methods of the DEFER study have been described previously and are summarised briefly below.[14] The DEFER study was a multicenter, international, randomized controlled trial performed in 12 European and 2 Asian centers between 1997 and 1998. Patients were enrolled if they met 2 inclusion criteria: 1) referral for elective PCI of a single angiographically significant de novo stenosis (more than 50% diameter reduction by visual assessment) in a native coronary artery with a reference diameter of more than 2.5mm; and 2) no conclusive evidence of reversible ischemia as documented by non-invasive testing within the last 2 months. Main exclusion criteria were total occlusion of the target artery, myocardial infarction or unstable angina. The institutional review boards of all centers approved the study protocol. All patients provided written consent before enrolment.

Randomization

In order to prevent bias, patients were randomized before measuring FFR (Figure 1). After inclusion in the study and before physiological measurement, patients were randomized to deferral or performance of PCI. Thereafter, FFR was measured. If the FFR value was <0.75

Figure 1. Flowchart of the study, randomization, definition of the 3 groups, and 15-year follow-up



indicating reversible ischemia, then randomization was ignored and PCI was performed anyway because it was felt unethical at that time to leave such a stenosis unrevascularized (Reference group). In contrast, if the FFR value was ›0.75, then the stenosis was treated according to the randomization, resulting in one group of patients with FFR›0.75 in whom PCI was performed (Perform group) and a second group of patients with FFR›0.75 in whom PCI was deferred and the further treatment was medically (Defer group). All patients received optimal medical therapy for that era.

Quantitative angiography and fractional flow reserve measurement

Angiograms were performed in at least 2 orthogonal projections after administration intracoronary nitroglycerin. All angiograms were analysed using QCA-CMS system (Medis, Leiden, the Netherlands). FFR was measured with a coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) and adenosine-based hyperemia given intravenously (140 µg per minute per kilogram of body weight) or intracoronary.[16, 17] PCI was performed in the Perform group and in the Reference group according to the interventional standards at the time the study was performed. PCI was performed according to the standards at that time, before the era of drug-eluting stents, by either bare metal stents (BMS) or balloon angioplasty.

Endpoints

The primary end point was freedom from major adverse cardiac events (death, MI, and repeat revascularization) after 2 years of follow-up, and 5-year follow-up was a secondary end point. It should be noted that the DEFER study was not powered for a 15-year follow-up and that no a priori hypothesis for such long-term follow-up was defined. The 15-year follow-up was added later due to the importance of understanding long-term clinical outcomes after FFR-guided revascularization. Because non-cardiac mortality will dominate cardiac mortality during such very long-term follow-up, we distinguished among cardiac, unknown, and non-cardiac mortality. Myocardial infarction was defined as a clinical episode of typical chest pain with development of new pathologic Q-waves on the electrocardiogram or an increase of serum creatinine kinase (CK) levels to more than twice the normal value, reflecting the practice pattern during the era of patient recruitment. Repeated angiography was only performed if clinically indicated or in case of an adverse event. While events were adjudicated by a clinical event committee up to 5 years, events thereafter were site determined and verified by source documentation (including related vessel, cardiac enzymes, and cause of death).

National database

In those patients for whom no complete follow-up could be acquired, applicable national databases were queried to obtain the survival status. These data were used only for comparing all-cause mortality.

Statistical analysis

All analyses used an intention-to-treat assignment. Continuous variables are expressed as mean ± 1 SD and were compared using student s t-test. Dichotomous variables are expressed as absolute numbers and percentages (%) and were compared using the chi-square test or Fisher's exact test as appropriate. Myocardial infarction rates were visualized with the use of Kaplan-Meier survival curves, using the log-rank test for the comparison between groups.

A p- value less than 0.05 was considered significant, and applicable tests were always two-sided. All analyses were conducted using SPSS 19.0.0.1 software (IBM corporation, Armonk, NY) or R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics and procedural results.

Out of 325 patients, 167 were randomly assigned to deferral and 158 to performance of PCI (Figure 1). Baseline characteristics of patients in both randomization arms were similar, including angiographic characteristics and FFR (Table 1).

FFR was ⩾0.75 in 181 patients of whom 91 belonged to the group randomized to deferral of PCI (Defer group) and 90 to the group randomized to performance of PCI (Perform group). Fractional flow reserve was <0.75 in 144 patients. In the latter group (Reference group), randomization was ignored and PCI was performed anyway. Mean percent diameter stenosis was more severe in the Reference group (FFR <0.75). However, overlap of data was so large that quantitative coronary angiography was absolutely not useful for predicting the true functional stenosis severity in individual patients. Fractional flow reserve was 0.86 ± 0.06 in the Defer group, 0.87 ± 0.07 in the Perform group, and 0.57 ± 0.16 in the Reference group. In the Performance group 41 patients (46%) were treated by BMS and 85 patients (59%) in the Reference group. Finally, all angiographic parameters after PCI were similar in the Perform and Reference groups, indicating that no difference was present in the quality of stenting between the Perform and Reference group.

15-year follow-up.

Complete follow-up was obtained in 325 patients (100%) after 12 months, in 317 patients (98%) after 24 months, in 313 patients (97%) after 5 years, and in 298 patients (92%) after 15 years. Mean follow-up of patients alive was 16.9 years (interquartile range 16.0-17.5 years). Patients lost to follow-up were similarly distributed among Defer (10 of 91, 11%), Perform (6 of 90, 7%), and Reference (11 of 144, 8%) groups (p=0.62). Follow-up with respect to all-cause mortality after 15 years was obtained in 311 patients (96%) by checking national databases.

Clinical outcome after 15 years

Mortality (Table 2). Mean age of the patients at the start of the study was 61 years. Consequently, after a mean follow-up of 16.9 years, a considerable portion of patients had died from a predominance of non-cardiac causes. There was no difference in all-cause mortality after 15 years among the three groups: 33.0% in the Defer group, 31.1% in the Perform group, and 36.1% in the Reference group (Defer vs. Perform, RR 1.06, 95% CI: 0.69-1.62, p=0.79). Also cardiac death was not different between 5.5% in the Defer group, 4.4% in de Perform group, and 10.4% in the Reference group (Defer vs. Perform p=1.00).

Myocardial infarction. The rate of myocardial infarction was significantly lower in the Defer group (2.2%) compared to the Perform group (10.0%), RR 0.22, 95% CI: 0.05-0.99, p=0.03).

Table 1. Baseline characteristics

	FFR ⩾ 0.75		FFR < 0.75
	Defer group (n=91)	**Perform group (n=90)**	**Reference group (n=144)**
Age (yrs)	61±9	61 ± 11	60 ± 9
Gender (%)			
Male	65	63	80
Female	35	37	20*
Risk factors (%)			
Diabetes	15	9	13
Hypertension	36	34	42
Hyperlipidemia	43	48	49
Current smoker	27	23	29
Familiy history of lkCAD	56	46	45
Ejection fraction (%)	67 ± 9	67 ± 10	68 ± 9
Angiography			
Reference diameter (mm)	3.00 ± 0.64	2.94 ± 0.57	2.97 ± 0.58*
DS (QCA) (%)	48 ± 9	48 ± 10	57 ± 12
MLD (mm)	1.55 ± 0.37	1.50 ± 0.36	1.28 ± 0.39*
Lesion length (mm)	9.8 ± 5.4	10.2 ± 4.3	9.5 ± 3.9*
FFR	0.87 ± 0.07	0.87 ± 0.06	0.56 ± 0.16*

**p < 0.05 for comparison between Defer and Perform groups versus Reference group. CAD–coronary artery disease; DS–diameter stenosis; FFR–fractional flow reserve; MLD - minimum luminal diameter.*

This was almost exclusively due to less target vessel related infarctions (Figure 2). Patients with a baseline FFR⩾0.75 (Defer and Perform group) had a significantly lower rate of MI (6.1%) compared with patients with an FFR<0.75 (Reference group), 12.5%, RR 0.49, 95% CI: 0.24-1.00 p=0.044).

Repeat revascularization. Revascularization occurred in 42.9% of the Defer group, 34.4% in the Perform group and 44.4% of the Reference group, thereby showing a trend towards higher revascularization rate in the Defer group (Defer vs. Perform p=.245). However, when looking at total cumulative events no difference was observed (47 vs. 49 events) regarding PCI, as shown in table 3. In other words, the mean number of percutaneous coronary interventions per patient was not statistically different in both groups.

Table 2. Clinical outcome after 15 years

	Defer group	Perform group	Reference group	*p*-value	
	(n=91)	(n=90)	(n=144)	Defer vs. Perform	Defer and Perform vs. Reference
Mortality					
All-cause	30 (33.0%)	28 (31.1%)	52 (36.1%)	.789	.441
Cardiac	5 (5.5%)	4 (4.4%)	15 (10.4%)	1.000	.062
Unknown	13 (14.3%)	11 (12.2%)	10 (6.9%)	.682	.065
Non-cardiac	12 (13.2%)	13 (14.4%)	27 (18.8%)	.806	.228
Myocardial infarction					
All	2 (2.2%)	9 (10.0%)	18 (12.5%)	**.033**	**.044**
Target vessel$	1 (1.1%)	8 (8.9%)	12 (8.3%)	**.018**	.221
Revascularization					
All	39 (42.9%)	31 (34.4%)	64 (44.4%)	.245	.294
Target vessel	33 (36.3%)	25 (27.8%)	51 (35.4%)	.221	.522

$ Target vessel = target vessel + unknown vessel

Figure 2. Kaplan Meier of myocardial infarction (MI) (panel A) and relation of MI with study vessel territory (Panel B).

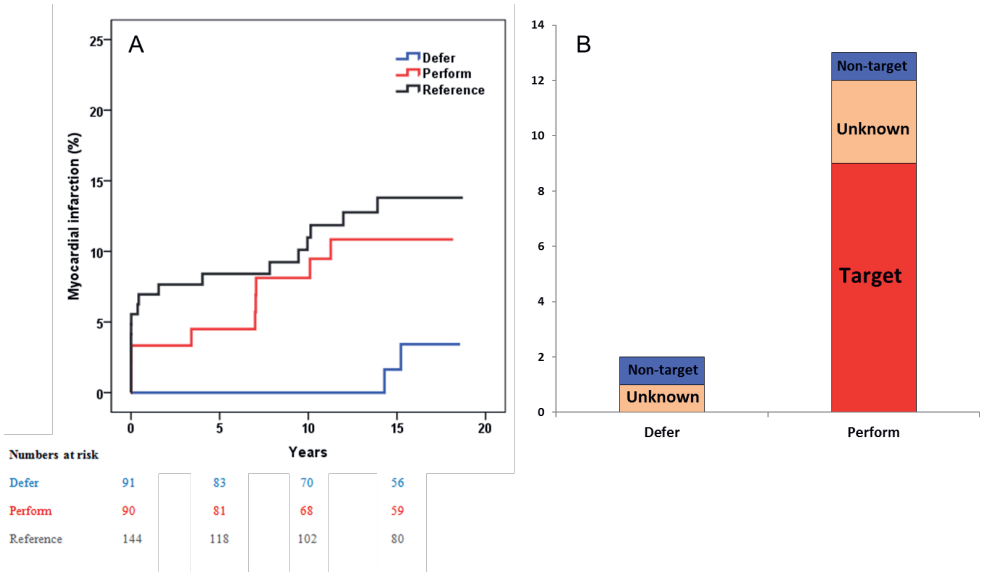


Table 3. Cumulative adverse events after 15 years

	Defer group	Perform group	Reference group
	(n=91)	(n=90)	(n=144)
Myocardial infarction			
All	2	13	19
Target vessel	0	9	13
Unknown vessel	1	3	1
Non-target vessel	1	1	5
PCI			
All	49	47	66
Target vessel	30	28	38
Non-target vessel	19	19	28
CABG			
All	11	7	23
Target vessel	10	7	22
Non-target vessel	1	0	1

DISCUSSION

The DEFER randomized controlled trial investigated the safety of deferring PCI for an angiographically significant but functionally non-significant coronary stenosis as indicated by an FFR ⩾ 0.75. Our results show that even after 15-years of follow-up, the prognosis of functionally non-significant deferred lesions is excellent, that PCI of such stenoses has no advantage and even results in more myocardial infarctions when compared to medical therapy. Our novel results extend earlier findings from the DEFER study at 2- and 5-year follow-up.[14, 15] This is the longest follow-up of a randomized trial using fractional flow reserve for decision making and calls for a number of discussion points.

First, our results show a significant increase in rates of myocardial infarction if a functionally non-significant stenosis is treated by PCI compared to medical therapy alone. These myocardial infarctions not only were peri-procedural but also occurred throughout the complete follow-up, with the majority arising later than 5 years after the index procedure (Figure 2). Interestingly, in the Defer group only one myocardial infarction was possibly related to the study vessel, thereby confirming the excellent natural history of a functionally non-significant stenosis with optimal medical treatment. In contrast, in the Perform group, the majority of myocardial infarctions occurred in the stented artery, suggesting a possible role of neo-atherosclerosis as underlying cause.

Second, despite the increased rate of MI in the Perform group, there was no increased mortality compared to the Defer group. In this respect, it should be noted that after a very long follow-up mortality is more related to advanced age (average age of 78.0 years at mean follow-up) and non-cardiac causes than to cardiac death. Therefore, the potential effects of deferral versus performance of PCI on mortality dilute over time. However, the present data show that concerns about increased mortality after deferral of angiographically significant but functionally non-significant coronary lesions are not justified.[10, 12, 13]

Third, deferring PCI of functionally non-significant stenoses does not result in a significant increase or 'catch-up' of revascularization compared with PCI on the long term. There was a trend towards revascularization occurring in more patients in the Defer group compared with the Perform group, but when looking at total cumulative events no difference was observed (table 3).

Fourth, the current study provides unique insights into the natural course of coronary artery disease over the very-long term when treated medically according to FFR guidance. Several studies have described the follow-up of medically treated coronary stenoses in stable angina, but none of them exceeded 10 years.[18-20] Direct comparison of our results with other studies should be done with caution due to differences in baseline characteristics. Deferral of PCI in angiographically significant but functionally non-significant lesions is safe during the very-long term. The current study presents rates of MI in the Defer group of 2.2% after 15 years, compared with MI rates of 11.2% after 5 years in COURAGE and 4.5% after 7 years in RITA-2, when FFR was not used in comparable patients.[18, 21] In the FAME study, out of 513 deferred lesions based on an FFR > 0.80, only one infarction related to a deferred lesion occurred after 2 years, in line with our extended DEFER results.

Limitations. The present study also has several limitations. First, the study was not designed for a follow-up of 15 years and was therefore not explicitly powered for the reported endpoints.

Second, PCI was performed in an era when drug-eluting stents were not yet available. With contemporary second-generation stents the rate of myocardial infarction might have been lower in the Perform group.[22] Yet, the excellent outcome in the Defer group, with only two myocardial infarctions, is hard to surpass (figure 2).

Third, although treatment was randomized, neither the patients nor the physician was blinded. This might have a created a bias towards more revascularization in the Defer group at follow-up.

Fourth, in contrast to contemporary patients, the majority of patients in the DEFER study had single vessel disease. Extrapolating our long-term data to patients with multivessel disease should be done with caution. Nevertheless, comparable results with respect to deferral of functionally non-significant lesions up to 5 years have been described in patients with multivessel disease in the FAME and FAME 2 studies.[5, 7] Therefore, even in multivessel disease it might be expected that PCI can be safely deferred in functionally non-significant lesions.

Finally, when using FFR to identify ischemic stenoses, a grey zone exists between 0.75 and 0.80. In the DEFER study the lower limit of that grey zone was used, whereas presently the upper limit of the grey zone is used (0.80) to make decisions, thereby increasing sensitivity to almost 100% at the cost of a decreased specificity. We do not believe this choice fundamentally influenced the outcome of the DEFER study because of a continuous relationship between the FFR value and clinical outcomes for both deferral and performance of PCI, as documented recently in a large meta-analysis.[3]

In conclusion, among patients with stable chest pain, coronary stenoses that are not responsible for inducible ischemia as indicated by FFR ⩾ 0.75 have an excellent outcome when treated medically, even after 15 years of follow-up. Performing PCI of such functionally non-significant stenosis has no benefit compared to medical treatment.

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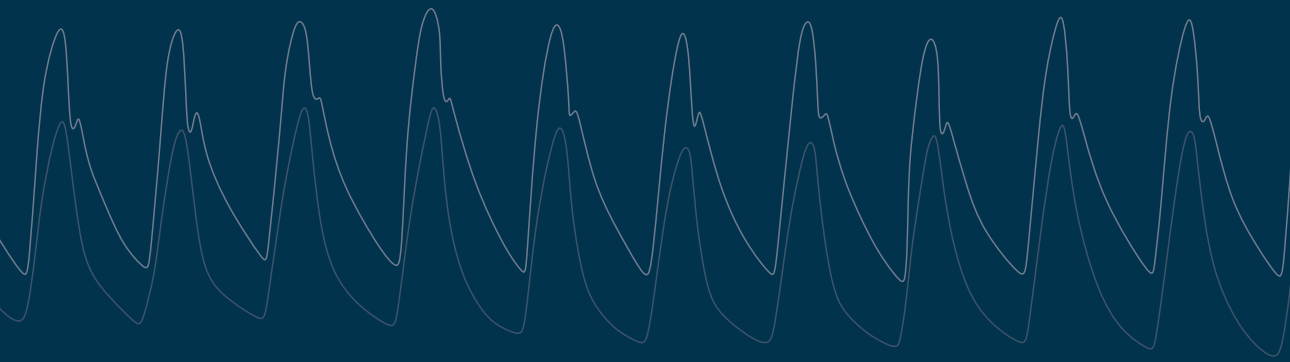

CHAPTER 6

Fractional Flow Reserve Versus Angiography for Guidance of PCI in Patients With Multivessel Coronary Artery Disease (FAME): 5-year Follow-up of a Randomised Controlled Trial

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ABSTRACT

Background

In the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) improved outcome compared with angiography-guided PCI for up to 2 years of follow-up. The aim in this study was to investigate whether the favourable clinical outcome with the FFR-guided PCI in the FAME study persisted over a 5-year follow-up.

Methods

The FAME study was a multicentre trial done in Belgium, Denmark, Germany, the Netherlands, Sweden, the UK, and the USA. Patients (aged ⩾18 years) with multivessel coronary artery disease were randomly assigned to undergo angiography-guided PCI or FFR-guided PCI. Before randomisation, stenoses requiring PCI were identified on the angiogram. Patients allocated to angiography-guided PCI had revascularisation of all identified stenoses. Patients allocated to FFR-guided PCI had FFR measurements of all stenotic arteries and PCI was done only if FFR was 0.80 or less. No one was masked to treatment assignment. The primary endpoint was major adverse cardiac events at 1 year, and the data for the 5-year follow-up are reported here. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00267774.

Findings

After 5 years, major adverse cardiac events occurred in 31% of patients (154 of 496) in the angiography-guided group versus 28% (143 of 509 patients) in the FFR-guided group (relative risk 0.91, 95% CI 0.75-1.10; p=0.31). The number of stents placed per patient was significantly higher in the angiography-guided group than in the FFR-guided group (mean 2.7 [SD 1.2] *vs* 1.9 [1.3], p<0.0001).

Interpretation

The results confirm the long-term safety of FFR-guided PCI in patients with multivessel disease. A strategy of FFR-guided PCI resulted in significant decrease of major adverse cardiac events for up to 2 years after the index procedure. From 2 to 5 years, the risks for both groups developed similarly. This clinical outcome in the FFR-guided group was achieved with a lower number of stented arteries and less resource use. These results indicate that FFR guidance of multivessel PCI should be the standard of care in most patients.

INTRODUCTION

In addition to coronary angiographic abnormalities, the presence and extent of inducible myocardial ischemia is an important prognostic factor in coronary artery disease.[1–3] The absence of inducible myocardial ischemia is associated with excellent outcome during medical treatment.[1,4] Therefore, revascularisation of non-ischemic stenoses is usually not indicated. However, revascularisation of ischemia-inducing stenoses improves symptoms and outcome.[5,6]

Fractional flow reserve (FFR) is defined as the ratio of maximum blood flow in a stenotic coronary artery to maximum blood flow if the same artery were completely normal. An FFR of 0.80 or less, as measured with the use of a coronary pressure wire during invasive coronary angiography, indicates the potential of a specific stenosis to induce myocardial ischemia with an accuracy of greater than 90%. Therefore, FFR is recommended for the guidance of coronary revascularisation.[7,8]

In the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study,[9] we compared angiography-guided percutaneous coronary intervention (PCI) with FFR-guided PCI in multivessel disease. At 1 year, the proportion of major adverse cardiac events was significantly lower and a higher proportion of patients were free from angina in the FFR-guided group than in the angiography-guided PCI group.[9] At 2 years, the rates of death and myocardial infarction were significantly lower in the FFR-guided group.[10] Additionally, use of FFR-guided PCI was cost-saving.[11] The results of the FAME study contributed to a shift from purely anatomical to functional revascularisation strategies. However, the long-term safety of such a strategy has not been studied so far.

The goal in this analysis was to investigate whether the favourable outcome with the FFR-guided PCI in the FAME study persisted over 5 years of follow-up.

METHODS

Study design and participants

The design of the FAME study has been described previously.[12] Briefly, FAME was a multicentre, randomised controlled trial, done in the USA and six European countries (Belgium, Denmark, Germany, the Netherlands, Sweden, and the UK).

The institutional review board of each participating centre provided ethics approval. All patients provided written informed consent.

Patients (aged ⩾18 years) were included in the study if they had coronary artery stenoses of at least 50% of the vessel diameter in at least two major epicardial coronary arteries, and if clinical data and angiographic appearance indicated PCI. Exclusion criteria were angiographically significant left main coronary artery disease, previous coronary artery bypass surgery, cardiogenic shock, extremely tortuous or calcified coronary arteries, a life expectancy of less than 2 years, pregnancy, and contraindication to the placement of a drug-eluting stent. Recent myocardial infarction was not an exclusion criterion if it occurred at least 5 days before PCI. With respect to non-ST-elevation myocardial infarction, patients could be included earlier than 5 days before PCI if the peak creatine kinase concentration was less than 1000 IU.

Randomisation and masking

Patients with multivessel coronary artery disease were randomly assigned with a computer-generated allocation sequence to have angiography-guided PCI or FFR-guided PCI. Randomisation was stratified according to the study site and done in blocks of 25, with the use of sealed opaque envelopes. Patients allocated to angiography-guided PCI underwent revascularisation of all angiographic stenoses with drug-eluting stents. Patients allocated to FFR-guided PCI had FFR measurement of all stenotic arteries and PCI was done only if FFR was 0.80 or less. No one was masked to treatment assignment.

Treatment

PCI was done with drug-eluting stents. In the angiography-guided group, all indicated angiographically significant stenoses were stented. In the FFR-guided group, a coronary pressure wire (Radi, St. Jude Medical, Uppsala, Sweden) was advanced and equalised with the pressure sensor at the tip of the guiding catheter. Hereafter, the pressure wire was advanced in the coronary artery, sufficiently distal to the lesion under investigation. Maximum coronary hyperemia was induced with central venous infusion of adenosine (140 mg/kg per min) and FFR was measured. If FFR was less or equal to the ischemic threshold (ie, 0.80), PCI of the respective stenosis was done. All patients were treated with aspirin and clopidogrel for at least 1 year.

Outcomes

The primary endpoint in the FAME study was the rate of major adverse cardiac events at 1 year; the 5-year follow-up data are reported here. The definition of major adverse cardiac events was a composite of death, myocardial infarction, and any repeat revascularisation. In the FAME study, death was defined as all-cause death.

Predefined secondary endpoints were major adverse cardiac events at 2 years and 5 years, and the individual components of the major adverse cardiac events at 1 year, 2 years, and 5 years;[12] data for the major adverse cardiac events and the individual components at 5

years are reported here. Although major adverse cardiac events for up to 2 years were adjudicated by a clinical event committee, events thereafter were assessed at the site and verified by source documentation (cardiac enzymes, electrocardiogram [ECG] changes, PCI reports, and cause of death).

For the 5-year follow-up, cardiac death was also assessed; this was not a prespecified endpoint. Death from an unknown cause was designated as cardiac death.

Statistical analysis

Primary and secondary endpoints were assessed with the intention-to-treat analysis. For these endpoints, we used the c^2 test to compare the two groups. Endpoints throughout the 5-year follow-up were visualised with the use of Kaplan-Meier curves, using the log-rank test to compare the two groups.

Data were presented as mean (SD). Discrete variables were compared using the chi^2 test or Fisher's exact test as appropriate, whereas continuous variables were compared by use of the Student's *t* test or Mann-Whitney *U* test as appropriate. Patients lost to follow-up were censored at the date of last contact. A sensitivity analysis, assuming all patients lost to follow-up died at the last follow-up, was done to investigate potential effects of under-reporting due to loss to follow-up. To adjust for potential confounders, we did a multivariate logistic regression analysis using the following variables: sex, age, presence of diabetes, unstable angina or non-ST-elevation myocardial infarction, ejection fraction of less than 40%, SYNTAX score,[13] presence of proximal left anterior descending (LAD) involvement, and inclusion site.

Post-hoc subgroup analyses were done, with subgroups defined according to sex, age, presence or absence of diabetes, stable angina versus unstable angina or non-ST-elevation myocardial infarction, ejection fraction of at least 40% or less than 40%, SYNTAX score of 22 or less, 23-32, or 33 or greater, and the presence or absence of proximal LAD involvement. Relative risks (RR) were calculated including 95% CIs and p values for interaction.

All statistical tests were two-tailed and a p value of less than 0.05 was significant. The acquired data were analysed with IBM SPSS for Windows (version 19.0.0.1). This trial is registered with Clinicaltrials.gov, number NCT00267774.

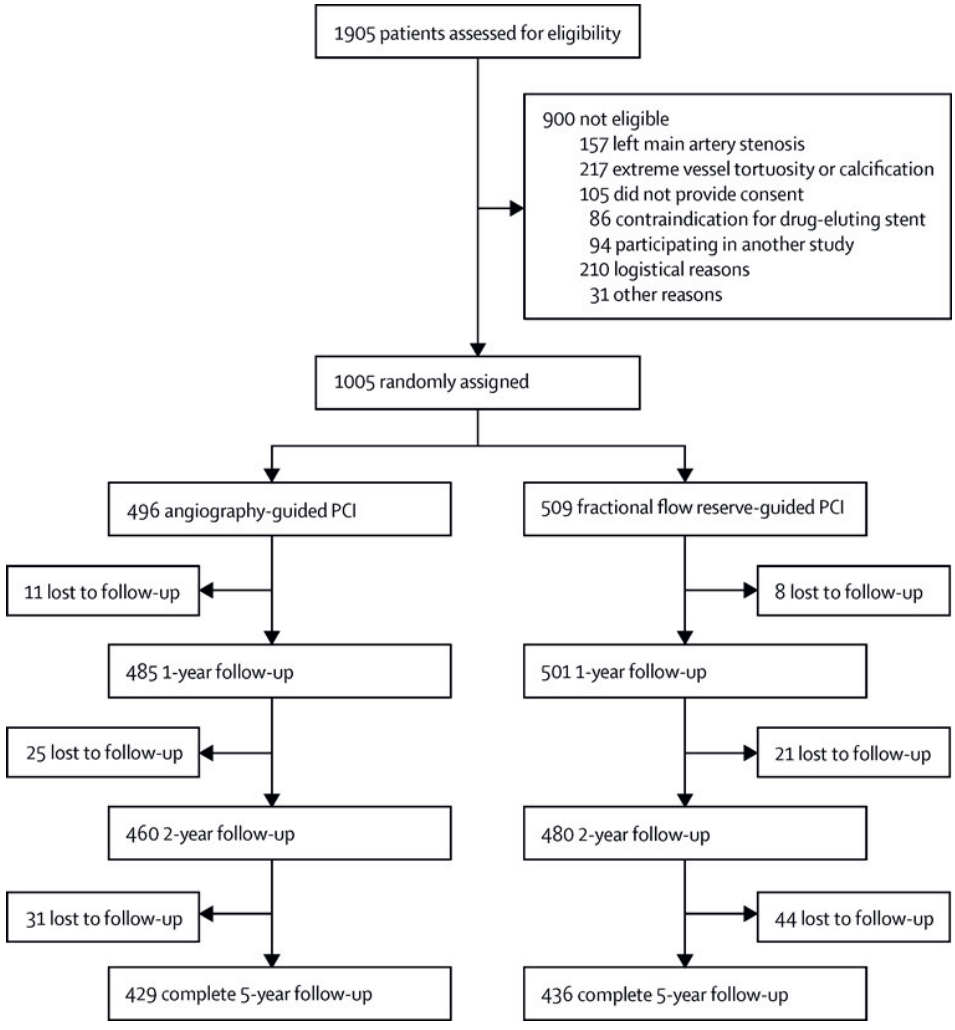
Role of the funding source

The funders of the study had no role in data gathering, analysis, and interpretation, writing of the manuscript, and the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

1005 patients were included in 20 centres in the USA and Europe between Jan 2, 2006 and Sept 26, 2007 (Figure 1). 496 patients were randomly assigned to angiography-guided PCI and 509 patients were assigned to FFR-guided PCI. Baseline characteristics, the number of indicated lesions, and the severity of coronary artery disease were similar between the two groups (Table 1).

Figure 1. Design of the FAME study



Flowchart of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. Patients (n=1005) were randomized to either angiography-guided percutaneous coronary intervention (PCI) (n=496) or fractional flow reserve (FFR)-guided PCI (n=509). DES indicates drug-eluting stent.

Table 1. Patient characteristics at baseline of all patients (left columns) and of patients with complete 5-year follow-up (right columns)

	Baseline		5-year follow-up		*p*-value
	Angiography-guided group (*n*=496)	FFR-guided group (*n*=509)	Angiography-guided group (*n*=429)	FFR-guided group (*n*=436)	
Baseline characteristics					
Age (yrs)	64.2 ± 10.2	64.6 ± 10.3	63.9 ± 10.0	64.5 ± 10.4	
Male / Female	360(73) / 136(27)	384(75) / 125(25)	318(74) / 111(26)	328(75) / 108(25)	0.72
Clinical characteristics					
Angina (CCS class)					0.48
I	115 (23)	132 (26)	97 (23)	111 (25)	
II	165 (33)	170 (33)	142 (33)	143 (33)	
III	118 (24)	132 (26)	105 (24)	115 (26)	
IV	98 (20)	75 (15)	85 (20)	67 (15)	
Diabetes	125 (25)	123 (24)	107 (25)	98 (22)	0.78
Hypertension	327 (66)	312 (61)	277 (65)	259 (59)	0.15
Hypercholesterolemia	362 (74)	366 (72)	316 (74)	307 (70)	0.72
Family history	190 (39)	205 (41)	169 (39)	178 (41)	0.87
Current smoker	156 (32)	138 (27)	130 (30)	111 (25)	0.15
Previous myocardial infarction	180 (36)	187 (37)	155 (36)	154 (35)	0.98
Previous PCI	129 (26)	146 (29)	110 (26)	123 (28)	0.64
Unstable angina					
With ECG changes	91 (18)	73 (14)	81 (19)	61 (14)	0.08
Without ECG changes	87 (18)	77 (15)	74 (17)	67 (15)	0.65
LVEF (%)	57 ± 12	57 ± 11	57 ± 12	57 ± 11	0.99
Medication					
Beta-blocker	377 (76)	395 (78)	321 (75)	334 (77)	0.79
Calcium antagonist	96 (19)	121 (24)	86 (20)	100 (23)	0.26
Nitrates	179 (36)	167 (33)	156 (36)	137 (31)	0.31
ACE inhibitor/ARB	255 (51)	267 (52)	213 (50)	225 (52)	0.86
Statin	397 (80)	417 (82)	341 (79)	358 (82)	0.67
Aspirin	454 (92)	465 (91)	390 (91)	396 (91)	0.98
Clopidogrel	292 (59)	310 (61)	243 (57)	256 (59)	0.63
Angiographic characteristics					
Indicated lesions per patient	2.7 ± 0.9	2.8 ± 1.0	2.7 ± 0.9	2.8 ± 1.0	0.61
Extent of occlusion*					

	Baseline		5-year follow-up		*p*-value
	Angiography-guided group (*n*=496)	FFR-guided group (*n*=509)	Angiography-guided group (*n*=429)	FFR-guided group (*n*=436)	
50%-70% narrowing	550 (41)	624 (44)	508 (43)	549 (45)	
70%-90% narrowing	553 (41)	530 (37)	468 (40)	453 (37)	
90%-99% narrowing	207 (15)	202 (14)	165 (14)	171 (14)	
Total occlusion	40 (3)	58 (4)	30 (3)	48 (4)	
Patients with proximal LAD lesion	186 (38)	210 (41)	160 (37)	178 (41)	0.45
Patients with total occlusion	37 (7.5)	54 (10.6)	28 (6.5)	45 (10.3)	0.07

*Values are mean ± SD or n (%). * The investigator indicated all lesions to be included in the study before randomization and classified them according to severity by visual estimation. ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; FFR, fractional flow reserve; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.*

Mean age of the study population was 64 years (SD 10), and about 75% were men. Most of the patients had more than one risk factor for coronary artery disease. The incidence of diabetes was not different between the two groups. 37% of the patients had previous myocardial infarction and 27% had previous PCI. The severity of coronary artery disease was well balanced between the two groups, with a similar number of lesions per patient and a similar percentage of patients with a proximal LAD stenosis.

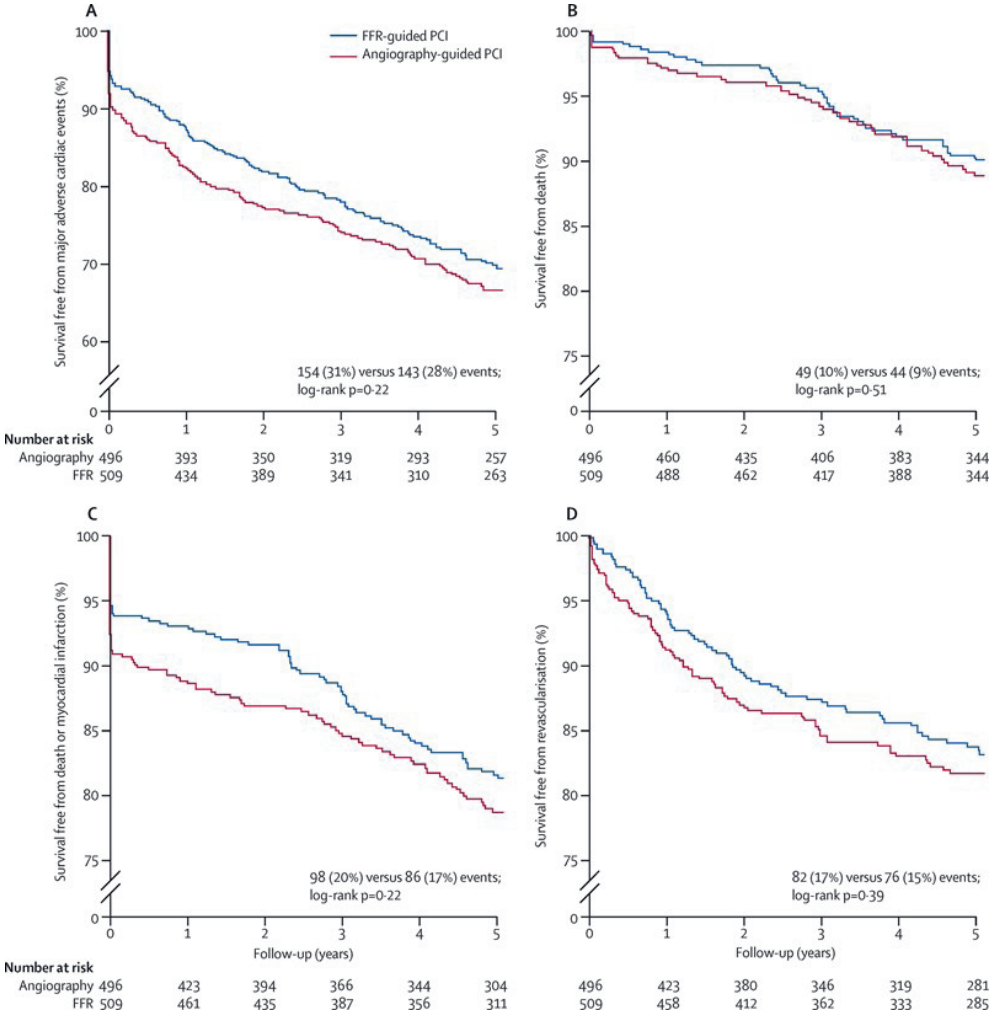
The procedure times did not differ between the angiography-guided group and the FFR-guided group (mean 70 min [SD 44] *vs* 71 min [SD 43]; p=0.51). In the FFR-guided group, FFR measurement was done in 1329 (94%) of 1414 indicated lesions. FFR was not successful in 27 stenoses, and was not done in 58 stenoses with a chronic total occlusion for which a default value of 0.50 was assigned in accordance with the protocol.

In the complete study population, 2415 stents were placed, of which 2339 (97%) were drug-eluting stents. In the angiography-guided group, the number of stents placed per patient was significantly higher than in the FFR-guided group (mean 2.7 [SD 1.2] *vs* 1.9 [1.3], p<0.001).

865 (86%) of 1005 patients had complete 5-year follow-up. 67 patients in the angiography-guided group and 73 patients in the FFR-guided group were lost to follow-up (p=0.70). The characteristics of the patients who completed the 5-year follow-up did not differ from baseline characteristics of the total patient population at the start of the study (Table 1).

After 5 years, the primary end point (major adverse cardiac events) occurred in 31% of patients (154 of 496) in the angiography-guided group versus 28% (143 of 509 patients) in the FFR-guided group (RR 0.91, 95% CI 0.75-1.10, p=0.31). Figure 2 shows event-free survival. Sensitivity analysis showed no difference in major adverse cardiac events if

Figure 2. Kaplan-Meier survival curves



Kaplan-Meier survival curves according to study group (red curve indicates angiography-guided percutaneous coronary intervention (PCI) group, blue curve indicates fractional flow reserve (FFR)-guided PCI group) for survival free from major adverse cardiac events (MACE)(154 versus 143; log-rank p=0·22; panel A), all-cause mortality (49 versus 44; log-rank p=0·51; panel B), all-cause mortality or myocardial infarction (98 versus 86; log-rank p=0·22; panel C), and revascularization (82 versus 76; log-rank p=0·39; panel D).

all patients lost to follow-up had died. Potential confounders did not alter the effect of treatment strategy on event-free survival with multivariate logistic regression.

All-cause mortality at 5 years was 10% (49 of 496 patients) in the angiography-guided group, and 9% (44 of 509 patients) in the FFR-guided group (RR 0.88, 95% CI 0.59-1.29, p=0.50). Myocardial infarction occurred in 12% of patients (n=58) in the angiography-guided group and 9% (n=48) in the FFR-guided group at 5 years (RR 0.81, 95% CI 0.56-1.16, p=0.24).

Three patients (two in the angiography-guided group and one in the FFR-guided group) had a second acute myocardial infarction during follow-up, bringing the total number of myocardial infarctions to 60 versus 49. At 5 years, 20% of patients (n=98) in the angiography-guided group and 17% (n=86) in the FFR-guided group died or had myocardial infarction (RR 0.86, 95% CI 0.66-1.11, p=0.24).

In the angiography-guided group, 17% of patients (n=82) required repeat revascularisation versus 15% (n=76) in the FFR-guided group (RR 0.90, 95% CI 0.68-1.20, p=0.49). 26 patients (12 in the angiography-guided group and 14 in the FFR-guided group) needed two or more revascularisation procedures.

The total number of repeat revascularisations was 101 in the angiography-guided group and 92 in the FFR-guided group. The absolute difference in all-cause mortality between the two groups after 1 year, 2 years, and 5 years remained constant (1.2%, 1.2%, and 1.3%; Table 2). The difference in mortality at 5 years was exclusively due to cardiac mortality,

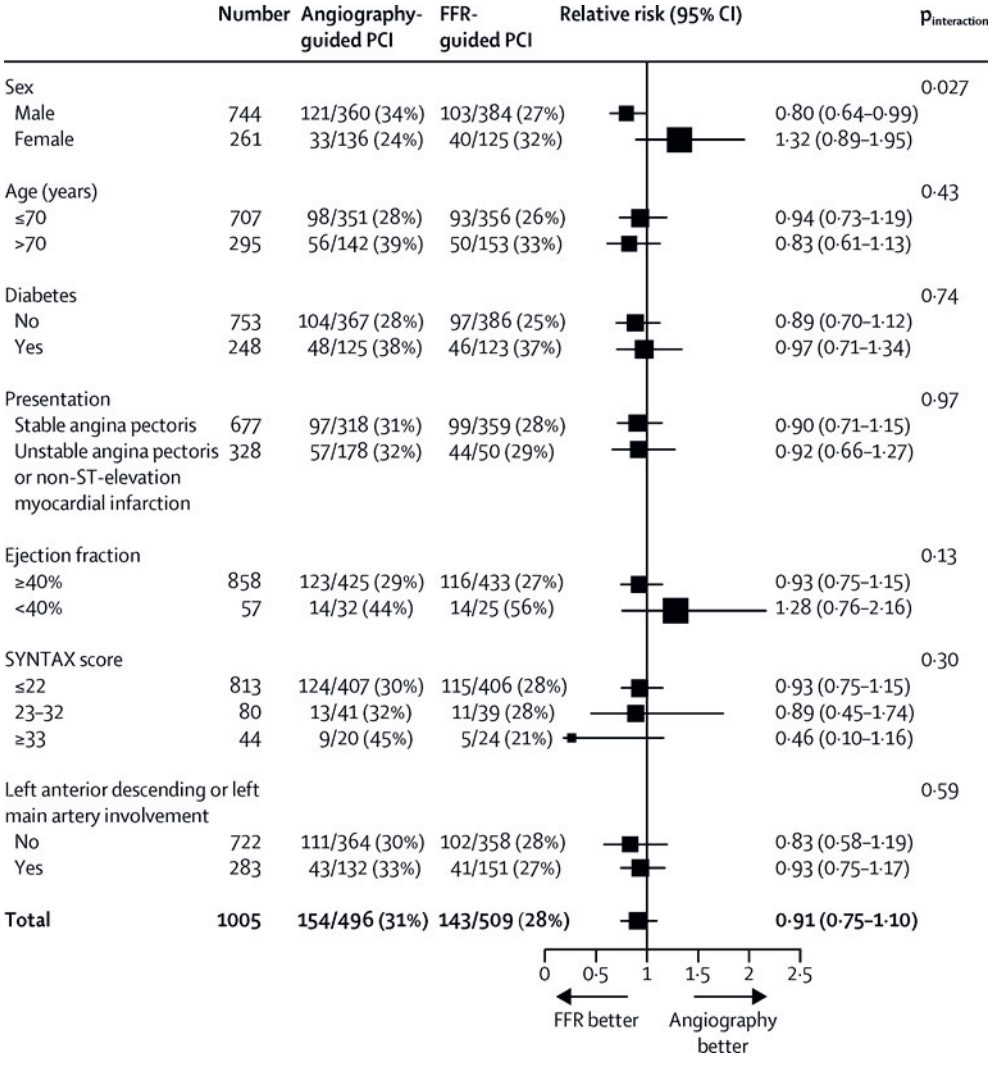
Table 2. Development of reduction of event rates over time (up to 5 years)

	Angio-guided PCI	FFR-guided PCI	Δ
All-cause Mortality (%)			
1-year follow-up	3.0	1.8	1.2
2-year follow-up	3.8	2.6	1.2
5-year follow-up	9.9	8.6	1.3
Cardiac Mortality (%)			
1-year follow-up	2.0	1.4	0.6
2-year follow-up	2.4	1.8	0.6
5-year follow-up	5.6	4.1	1.5
Number of events per patient (n)			
1-year follow-up	0.23±0.53	0.15±0.41	0.08
2-year follow-up	0.29±0.60	0.21±0.48	0.08
5-year follow-up	0.41±0.76	0.35±0.67	0.06

Δ *indicates absolute (percentual) difference.*

which was 6% (28 out of 496 patients) in the angiography-guided group versus 4% (21 of 509 patients) in the FFR-guided group (RR 0.73, 95% CI 0.42-1.27, p=0.26). Also, the differences in mean number of events per patient between angiography-guided and FFR-guided strategies remained constant after 1 year, 2 years, and 5 years (0.08, 0.08, and 0.06; Table 2). In the subgroup analyses, the interaction between sex and treatment strategy was significant, with FFR-guided PCI favouring the male sex ($p_{interaction}$=0.027; Figure 3).

Figure 3. Subgroup analyses of the primary end point



The forest plot shows the relative risk (with 95% confidence intervals) of the primary end point according to subgroups. SA indicates stable angina; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; EF, ejection fraction; LAD, left anterior descending; LM, left main.

With focus solely on the male sex, the primary end point at 5 years occurred in 34% (121 of 360) in the angiography-guided group versus 27% (103 of 384) in the FFR-guided group (RR 0.80, 95% CI 0.64-0.99; p=0·044).

In the angiography-guided group, the mean number of events per patient was 0.42 (SD 0.76) versus 0.36 (0.67) in the FFR-guided group during the 5-year follow-up (p=0.28; Table 3).

The cumulative events per 100 patient-years during follow-up were higher in the angiography-guided group (Figure 4).

Table 3. Total number of events

	Angio-guided PCI	FFR-guided PCI	P-value
Total events (n)	210	185	
Events per patient	0.42 ± 0.76	0.36 ± 0.67	0.28
Total number of events			
All-cause Mortality (n (%))	49 (9.9)	44 (8.6)	0.50
Cardiac Mortality (n (%))	28 (5.6)	21 (4.1)	0.26
Myocardial infarction (n)	60	49	
Revascularization (n)	101	92	
Combined end points			
Primary end point (n (%))	154 (31.0)	143 (28.1)	0.31
All-cause Mortality or MI (n (%))	98 (19.8)	86 (16.9)	0.24
Cardiac Mortality or MI (n (%))	78 (15.7)	66 (12.9)	0.21

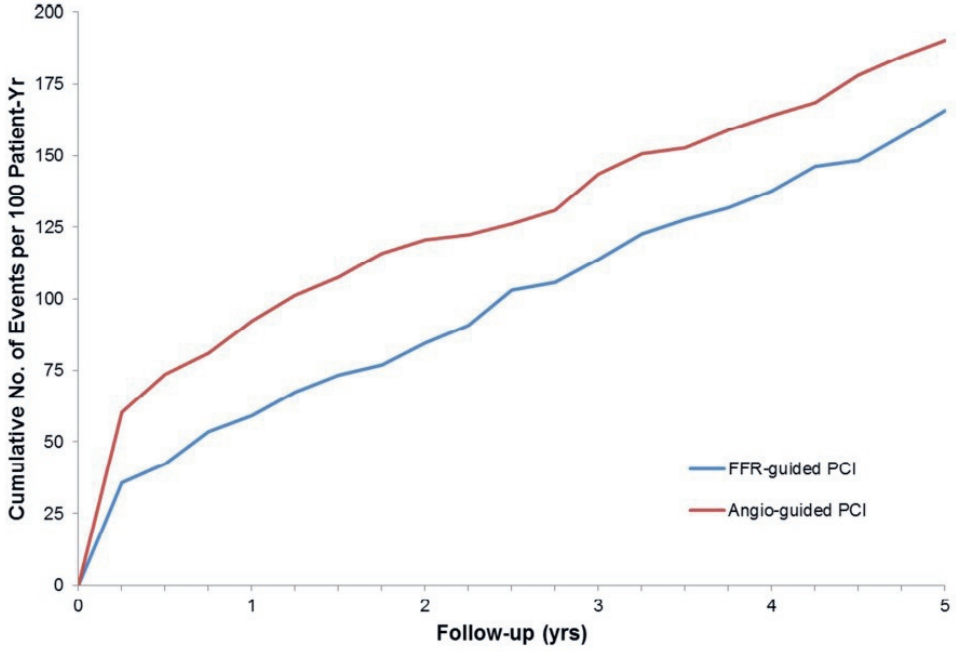
MI indicates myocardial infarction.

DISCUSSION

The current analysis shows that up to 5 years, the absolute difference in cardiac events persists, but is not significant because of the smaller number of patients at risk and the similar incidence of events in both groups beyond 2 years. These results indicate that the benefit of FFR-guided PCI occurs mainly during the first 2 years, thereafter the risks increase similarly in both groups. Moreover, the results confirm the long-term safety of FFR-guided PCI in patients with multivessel disease.[10]

Routine measurement of FFR allows more judicious use of stents than does angiography and equal relief of ischemia. Thus, by systematical measurement of FFR, the benefit of PCI can be maximised by accurate discrimination of the stenoses that benefit most from revascularisation.

Figure 4. Cumulative events per 100 patient-years during 5-year follow-up



Cumulative events of angiography-guided PCI versus FFR-guided PCI during 5-year follow-up are shown in this cumulative event-curve. By not excluding patients after their first events (as in survival curves), but accumulating events per 100 patients-years, a more clear distribution of disease burden is shown.

The potential benefit of revascularisation depends on the extent and degree of myocardial ischemia.[1,14,15] In patients with multivessel disease, non-invasive testing often has too low spatial resolution to identify ischemia associated with individual stenoses.[16] When based solely on anatomical criteria, attempts to achieve complete revascularisation have led to the use of a high number of stents associated with a high rate of major adverse cardiac events.[13] The notion of functional complete revascularisation rather than anatomical complete revascularisation overcomes these limitations by complete relief of ischemia related to the epicardial vessel with better outcome and less resource utilisation.[10,17,18] An FFR-value of 0.80 or less indicates the potential of a particular coronary stenosis to induce myocardial ischemia with an unsurpassed spatial resolution.

With respect to all-cause mortality and cardiac mortality, there were no significant differences between the two groups. There was a reduction in RR of 12% in the FFR-guided group for all-cause mortality, whereas the RR reduction for cardiac mortality was 27%. In a study with such a long follow-up, mortality numbers related to the specific disease studied

are diluted by naturally occurring other causes of death. Therefore, we believe that cardiac mortality in itself is a relevant factor when studying long-term follow-up. Although not significant, the absolute reduction in mortality was constant over time, as was the reduction in mean number of events per patient. As shown in Table 2, the difference in mortality at 5 years is solely due to the difference in cardiac mortality.

The benefit of FFR-guided PCI achieved in the first 2 years remains over the long term and emphasises the safety of such strategy. The present analysis shows that very little catch-up occurs over time in the FFR-guided group. This is in agreement with the results other studies deferring non-significant lesions as indicated by FFR.[18,19]

In the decision-making process with respect to revascularisation in multivessel disease, the SYNTAX score (not yet in existence at the time of writing the FAME protocol), has an important role. Therefore, a subanalysis according to SYNTAX score was done. No significant interaction was noted between the SYNTAX score and the benefit of treatment strategy.

A significant interaction between sex and treatment strategy was noted, favouring the male sex. In the male population, even after 5 years of follow-up, there was still a significant difference favouring FFR-guided therapy. This benefit was not noted in the female population. This sex difference was not present at the 2-year follow-up.[10]

Our 5-year follow-up analysis had limitations. First, this study was designed and powered for 1-year follow-up only. This 5-year follow-up was underpowered. Second, a noteworthy percentage of patients was lost to follow-up. A sensitivity analysis showed that the primary endpoint results were not significantly affected by this loss to follow-up, which was balanced between the two groups. Third, we do not have data for whether events between 2 years and 5 years were related to the index stenoses. Yet, events during the first 2 years in the FFR-guided group were mainly related to stent failure or new stenoses, rather than due to deferred lesions.[10] Fourth, compliance to medical therapy and the presence or absence of anginal symptoms was unknown. Last, the drug-eluting stents used in the FAME study were first generation. These stents have now been shown to be inferior to second-generation drug-eluting stents, which have lower rates of stent thrombosis, target lesion revascularisation, and, in some cases, death and myocardial infarction.[20–22]

Our results confirm the long-term appropriateness and safety of FFR-guided PCI in patients with multivessel disease. Thus, FFR guidance of multivessel PCI should be the standard of care in most patients.

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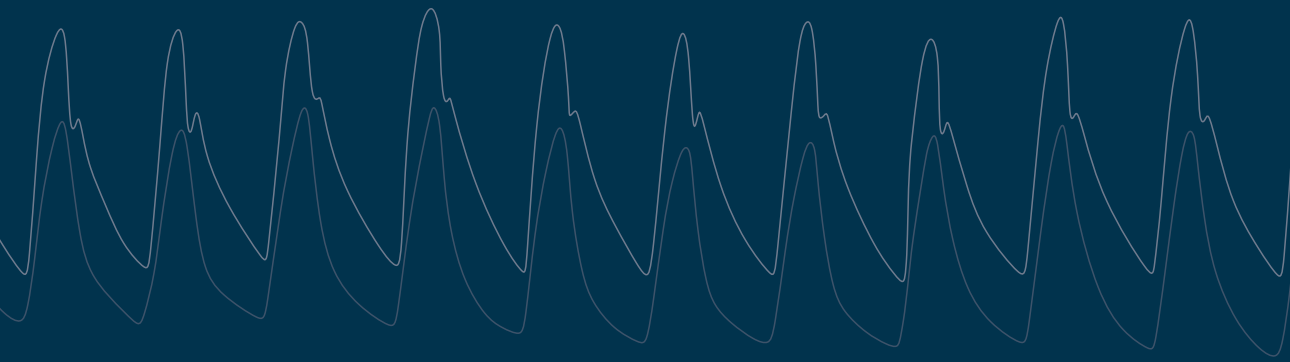

CHAPTER 7

Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Versus Medical Therapy for Patients With Stable Coronary Lesions: Meta-analysis of Individual Patient Data

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ABSTRACT

Aims

To assess the effect of fractional flow reserve (FFR)-guided percutaneous coronary intervention with contemporary drug-eluting stents on the composite of cardiac death or myocardial infarction versus medical therapy in patients with stable coronary lesions.

Methods and results

We performed a systematic review and meta-analysis of individual patient data (IPD) from the 3 available randomized trials of contemporary FFR-guided PCI versus medical therapy for patients with stable coronary lesions: FAME 2 (NCT01132495), DANAMI-3-PRIMULTI (NCT01960933), and Compare-Acute (NCT01399736). FAME 2 enrolled patients with stable coronary artery disease, while the other two focused on non-culprit lesions in stabilized patients after ACS. A total of 2400 subjects were recruited from 54 sites worldwide with 1056 randomly assigned to FFR-guided PCI and 1344 to medical therapy. The pre-specified primary outcome was a composite of cardiac death or myocardial infarction. We included data from extended follow-ups for FAME 2 (up to 5.5 years follow-up) and DANAMI-3-PRIMULTI (up to 4.7 years follow-up). After a median follow-up of 35 months (interquartile range 12 to 60 months), a reduction in the composite of cardiac death or MI was observed with FFR-guided PCI as compared with medical therapy (hazard ratio 0.72, 95% confidence interval 0.54 to 0.96, p=0.02). The difference between groups was driven by myocardial infarction.

Conclusion

In this individual patient data meta-analysis of the 3 available randomized controlled trials to date, FFR-guided PCI resulted in a reduction of the composite of cardiac death or myocardial infarction compared with medical therapy, which was driven by a decreased risk of myocardial infarction.

INTRODUCTION

Controversy exists regarding the role of percutaneous coronary intervention (PCI) of stable epicardial coronary lesions to reduce death and myocardial infarction (MI). While American guidelines state that PCI "has not been demonstrated to improve survival, [...] may increase the short-term risk of MI, [...] [and] does not lower the long-term risk of MI",[1] European guidelines admit that they "suffer from limitations inherent [...] on what is the real benefit from myocardial revascularization".[2] In these discussions, the presence of reversible ischemia plays a pivotal role. As a result of numerous mechanistic studies, randomized clinical trials, and observational series fractional flow reserve (FFR) has emerged as the gold standard to guide revascularization.

At least three randomized trials compared FFR-guided PCI versus medical therapy in hemodynamically stable patients with stable coronary lesions (patients with stable coronary disease or hemodynamically stable patients presenting with ACS with clear non-culprit lesions after successful PCI of their culprit lesion).[3-5] The primary endpoint of such trials is typically a composite of death, MI, or revascularization. Because of the open label design, patients who did not receive PCI might be more likely to seek medical care, and physicians aware of treatment assignment might be more likely to recommend revascularization in patients without previous PCI, thus introducing a risk of bias for the component of revascularization.[6,7] Even though, some trials only included ischemia-driven[4] or urgent revascularizations,[3] the inclusion of revascularization in primary composite endpoints continues to be criticized.[6,8] The ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA; ClinicalTrials.gov number, NCT01471522) therefore specified the composite of cardiovascular death or MI as primary endpoint before initiation of the trial but, in view of limited power to detect a clinically relevant difference, subsequently had to fall back to their original intention[9] and include resuscitated cardiac arrest and hospitalization for unstable angina or heart failure as additional components of the primary endpoint.[10] To resolve a key uncertainty in clinical practice for a frequently performed, invasive and expensive procedure, we did a collaborative individual patient data meta-analysis of trials that compared FFR-guided PCI versus medical therapy in hemodynamically stable patients with stable coronary lesions using cardiac death or MI as pre-specified primary composite endpoint.

METHODS

This individual patient data meta-analysis was performed according to a predefined protocol. We searched MEDLINE, Embase, and the Cochrane Library to identify randomized controlled trials of potential interest without language restriction using the following

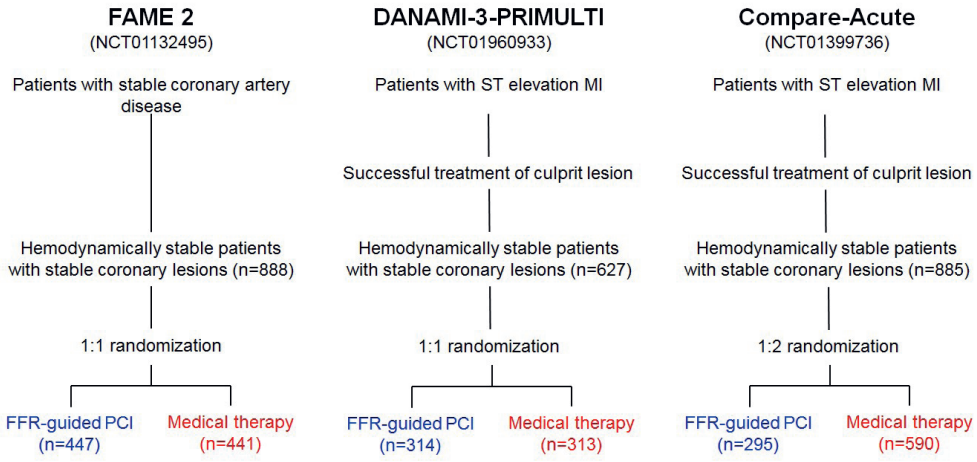
algorithm: ("fractional flow reserve" or FFR) AND ("percutaneous coronary intervention" or "percutaneous coronary interventions" or PCI* or stent*) AND (random* or trial* or control*). The search was started at March 25, 2017 and last updated on April 8, 2018. We included randomized controlled trials comparing PCI guided by fractional flow reserve using second-generation drug-eluting stents versus medical therapy for patients with stable coronary stenoses. Patients with stable coronary stenoses were defined as patients with stable coronary disease or hemodynamically stable patients presenting with ACS with clear non-culprit lesions after successful PCI of their culprit lesion.

FFR-guided PCI was defined as the performance of PCI based on a positive FFR measurement. We excluded trials where PCI was performed without the use of second-generation DES as well as trials on hemodynamically unstable patients. We checked reference lists of relevant studies and contacted experts in the field to identify additional trials. Two independent reviewers (FMZ and NPJ) identified eligible trials and reached consensus in case of discrepancies. After identification of eligible trials, we invited the trials' principal investigators to contribute to the collaborative analysis, reviewed protocols and publications for each trial, and specified the data requirements in agreement with the principal investigators, including most up-to-date follow-up data. Data were checked for missing values and consistency and queries were resolved through consultation with trialists.

Three independent reviewers (FMZ, NPJ, PJ) assessed trials using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials,[11] discrepancies were resolved by consensus. The design of the trials was reported previously.[3-5]

All trials randomized hemodynamically stable patients with stable coronary lesions to FFR-guided PCI or medical therapy (see Figure 1). FAME 2 randomized patients with stable coronary artery disease and at least 1 FFR-positive lesion with an FFR≤0.80 in 1:1 ratio to either FFR-guided PCI or medical therapy; patients in whom all angiographically significant stenoses were FFR negative did not undergo randomization, received medical therapy and were included in a registry. In DANAMI-3-PRIMULTI and Compare-Acute, hemodynamically stabilized subjects initially admitted with an acute STEMI and angiographically significant coronary non-culprit lesions were randomized after successful PCI of the culprit lesion to FFR-guided PCI or medical therapy of non-culprit lesions. Randomization ratios were 1:1 in DANAMI-3-PRIMULTI and 1:2 in Compare-Acute. Ethics committees at each participating institution approved the trial protocols and all subjects signed informed consent before randomization. This report was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[12]

Figure 1. Design of trials included in individual patient data (IPD) meta-analysis.



Outcomes and definitions

The pre-specified primary outcome for this meta-analysis of individual patient data was the composite of cardiac death or MI. Secondary endpoints include the composite of all-cause death or MI and individual components of these composites, myocardial infarction, cardiac death, and all-cause death. Independent clinical events committees adjudicated endpoints in each trial using pre-specified definitions. For the definition of peri-procedural MI, FAME 2 required CK-MB 10-fold above the 99th percentile upper reference limit (URL) or 5-fold above URL with clinical evidence of MI; DANAMI-3-PRIMULTI required troponin 5-fold above URL with clinical evidence of MI; and Compare-Acute required CK-MB 3-fold above URL. For chronic total or subtotal occlusions, a default FFR value of 0.50 was assumed in all trials, consistent with prior studies.[3,13]

Statistical analysis

Baseline categorical variables are reported as counts and percentages and compared using conditional regression analysis stratified by trial. Baseline continuous variables were reported as means and standard deviations and were compared using linear regression stratified by trial. The primary analysis was performed according to the intention-to-treat principle including all randomized patients. Individual patient data were combined in a single data set and analyzed using a mixed-effects Cox regression model with baseline hazards stratified by trial and a random intercept to account for variation between trials in baseline risk, and a random slope to account for variation between trials in treatment effect. Treatment effects are presented as hazard ratios and 95% confidence intervals (CI). Heterogeneity of the treatment effect between trials was quantified using the variance of the random slope[2]. Proportional-hazards assumptions were tested after stratification

by trial using Schoenfeld residuals. We performed sensitivity analyses of the primary outcome using a mixed-effects Poisson regression model with robust sandwich estimators of standard errors,[14] and a mixed-effects flexible parametric model.[15] In addition, we used a competing risk model to simultaneously analyze the two components of the primary outcome, and used a conventional two-stage fixed-effect meta-analysis to combine trial-level hazard ratios. Then, we plotted Kaplan-Meier time-to-first-event curves, superimposing estimates of the cumulative incidence per group predicted from the mixed-effects flexible parametric survival model, and used the cumulative incidences and their 95% CIs at 5 years follow-up, as predicted from the mixed-effects flexible parametric survival model, to derive numbers-needed-to-treat, analogous to calculations done for individual trials.[16] The use of a mixed-effects flexible parametric survival model to predict cumulative incidences and derive numbers-needed-to-treat avoided Simpson's paradox[17] due to the 1:2 randomization in Compare-Acute. All analyses were based on the same data structure, using time-to-first-event analyses throughout.

Pre-specified subgroup analyses of the primary outcome were performed according to clinical presentation (stable CAD versus ACS) and FFR status (patients with at least one stable coronary lesion with a positive FFR of ≤0.80 versus patients with only lesions with a negative FFR of >0.80). In DANAMI-3-PRIMULTI, FFR was only measured in the experimental arm, therefore the trial had to be excluded from the subgroup analysis according to FFR status. Subgroup analyses of the primary endpoint specified post hoc were performed according to age (>60 years or ≤60 years), sex, diabetes status, previous myocardial infarction, and smoking. We separated out within-trial and across-trial interactions and based tests for subgroup-by-treatment interactions on within-trial interactions,[18] except for the subgroup analysis by clinical presentation, which was by design based on an across-trial interaction. Landmark analyses of the primary outcome were performed according to a pre-specified landmark point at 7 days,[3] with hazard ratios calculated separately for events that occurred up to 7 days after randomization and events that occurred between 8 days and the end of follow-up. Landmark analyses were accompanied by a test for interaction between treatment and time (first 7 days vs. subsequent period). The power of our meta-analysis to detect a 30% relative risk reduction in the primary composite outcome was calculated as described by Turner et al.[19] Between-trial heterogeneity was considered to be low if the between-trial variance^2 was 0.04 or less.[20] Analyses were conducted using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata Release 14.2 (Stata Corp, College Station, TX).

RESULTS

We identified 1286 reports, of which 345 were duplicates and removed. After reviewing the remaining 941 unique reports, we found 16 potentially eligible randomized controlled trials, of these five trials were excluded as a wrong comparator was used,[13,21-24] seven trials were excluded as PCI was not based on a positive FFR measurement,[24-30] and one trial because PCI did not include the use of second-generation DES.[32] Three trials met our inclusion criteria: the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial (NCT01132495),[3] the Third DANish Study of Optimal Acute Treatment of Patients With STEMI: PRImary PCI in MULTIvessel Disease (DANAMI-3-PRIMULTI, NCT01960933),[4] and the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD (Compare-Acute) trial (NCT01399736)[5]. The principal investigators of all three eligible trials agreed to provide individual patient data.

All 3 trials had adequate generation of allocation sequences and concealment of allocation using central randomization in two[3,4] and sealed opaque sequentially number envelopes in one trial.[5] All trials used independent, blinded event adjudication and analyzed all randomized patients in the groups they were originally allocated to according to the intention-to-treat principle. By design, blinding of patients and care provider was not possible in any of the trials. As this is unlikely to result in relevant bias for the types of outcomes analyzed,[33] all trials were classified as having low risk of bias.

2400 subjects from 54 sites were included in Europe, North America, and Asia, of whom 1056 were randomly assigned to FFR-guided PCI and 1344 to medical therapy. Baseline characteristics are summarized in Table S1.

Patients in the two groups were well balanced with regard to most of the baseline demographic, medical history, and discharge medication. Over three quarters of patients were male in both groups. Approximately 19% of patients had diabetes, and about 19% a history of myocardial infarction. Due to the 1:2 randomization in Compare-Acute, the crude percentages of patients with stable CAD were 42% versus 33%; after stratification by trial, the difference between groups was 0.0% (95% CI -0.7 to 0.7%, p=1.00). As expected, more subjects were discharged on dual antiplatelet therapy in the FFR-guided PCI arm than the medical therapy arm (99% versus 82%, p<0.001). The percentage of randomized patients with FFR-negative lesions only was 0% in FAME-2 and 49% in Compare-Acute. In DANAMI-3-PRIMULTI, FFR was only measured in the experimental arm, and 31% of randomized patients in this arm had FFR-negative lesions only.

Primary and secondary endpoints

Table 1 presents the cumulative incidence estimates at 5 years of follow-up and hazard ratios of primary and secondary endpoints.

Table 1. Clinical events: primary and secondary endpoints.

	Estimated cumulative incidence at 5 years		Hazard ratio	P-
	FFR-guided PCI	Medical therapy	(95% CI)	value
Cardiac death or MI*	10.7% (8.4 to 13.6%)	16.4% (13.3 to 20.1%)	0.72 (0.54 to 0.96)	0.02
Death or MI	13.9% (11.2 to 17.2%)	19.4% (16.0 to 23.4%)	0.76 (0.59 to 0.99)	0.04
MI	8.5% (6.5 to 11.1%)	13.4% (10.7 to 16.8%)	0.70 (0.51 to 0.97)	0.03
Cardiac death	3.2% (2.1 to 5.1%)	3.0% (1.9 to 4.8%)	1.04 (0.58 to 1.78)	0.89
All-cause mortality	7.0% (5.2 to 9.6%)	6.5% (4.7 to 8.9%)	1.03 (0.69 to 1.54)	0.89

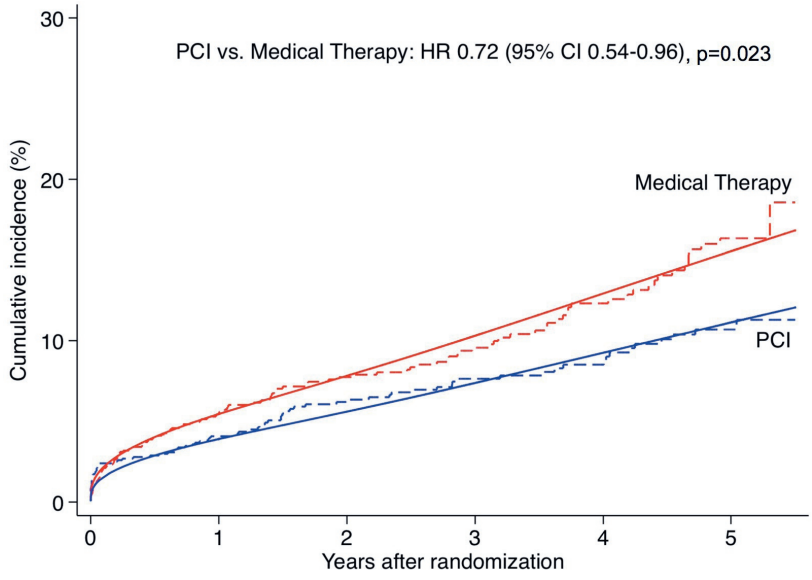
**Pre-specified primary outcome. Abbreviations: CI – confidence interval, FFR–fractional flow reserve, MI–myocardial infarction, PCI –percutaneous coronary intervention. FFR-guided PCI (N=1056) Medical therapy (N=1344)*

Figure 1 shows the crude and fitted cumulative incidence curves for the primary composite endpoint of cardiac death or MI. After a median follow-up of 35 months (interquartile range 12 to 60 months), a 28% relative reduction was observed with FFR-guided PCI as compared with medical therapy (hazard ratio 0.72, 95% CI 0.54 to 0.96, p=0.02). The estimated cumulative incidence at 5 years was 10.7% (95% CI 8.4 to 13.6%) for FFR-guided PCI group and 16.4% (95% CI 13.3 to 20.1%) for medical therapy, which resulted in an estimated number-needed-to-treat to prevent 1 event up to 5 years of 18 (95% CI 10 to 72).

The between-group difference in the primary composite endpoint was driven by a between-group difference in myocardial infarction (HR 0.71, 95% CI 0.51 to 0.97, p=0.03), with an estimated number-needed-to-treat to prevent 1 event up to 5 years of 20 (95% CI 11 to 87). Conversely, there was little evidence for a difference between groups in cardiac or all-cause deaths. For the secondary composite endpoint of all-cause death or myocardial infarction, there was 23% relative reduction with FFR-guided PCI (HR 0.77, 95% CI 0.59 to 0.99, p=0.04).

Figure 3 presents subgroup analyses of the primary endpoint. We found little evidence for hazard ratios differing across type of initial presentation (p for interaction=0.78), but a statistical trend towards an interaction between treatment and FFR (p for interaction=0.065), with a particularly pronounced benefit of FFR-guided PCI in patients who had at least one lesion with an FFR of 0.80 or less (HR 0.62, 95% CI 0.43 to 0.89, p=0.01).

Figure 2. Cumulative incidence curves of primary composite outcome of cardiac death or myocardial infarction.

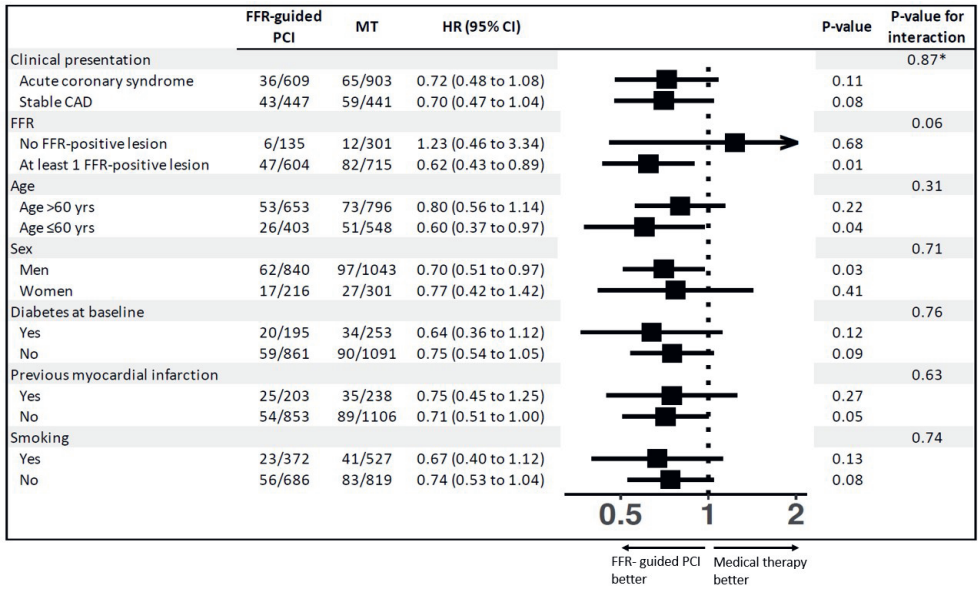


The cumulative incidence of the primary endpoint of cardiac death or myocardial infarction was significantly reduced in subjects randomized to FFR-guided PCI instead of medical therapy. Dashed lines are crude time-to-event curves, solid lines are fitted cumulative incidence curves as predicted from a mixed effects flexible parametric model. Only the fitted curves should be used for inferences about the treatment effect.

Figure 4 present landmark analyses. For the primary composite endpoint of cardiac death or MI we found a strongly positive interaction between treatment and time (p for interaction=0.0029), with a non-significant risk increase with FFR-guided PCI up to 7 days (HR 1.94, 95% CI 0.85 to 4.42, p=0.12), but a statistically significant risk reduction with FFR-guided PCI 8 days or more after randomization (HR 0.62, 95% CI 0.46 to 0.85, p=0.003). The interaction was entirely driven by myocardial infarction (p for interaction 0.0015), with a statistical trend towards an increase in events in the FFR-guided PCI arm up to 7 days (HR 2.51 95% CI 0.96 to 6.57, p=0.06), but a statistically significant reduction of events 8 days or more after randomization with FFR-guided PCI (HR 0.59, 95% CI 0.42 to 0.83, p=0.003). There was no evidence for an interaction between treatment and time for cardiac death (p for interaction=0.83).

Results of sensitivity analyses were much the same as those of primary analyses, as were results of competing risk model and two-stage meta-analysis. Tests of proportional hazards assumption were negative for the primary composite outcome (p=0.15) and all secondary outcomes (p⩾0.09). Heterogeneity in treatment effects between trials was low for all

Figure 3. Subgroup analyses of primary composite endpoint of cardiac death or myocardial infarction



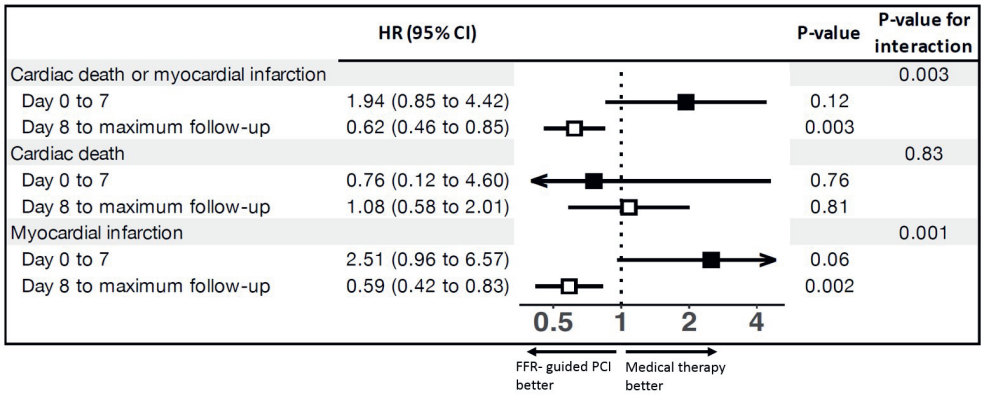
*Pre-specified subgroup analyses of the primary outcome are shown according to clinical presentation (stable CAD versus ACS) and FFR status (patients with at least one stable coronary lesion with a positive FFR of ≤0.80 versus patients with only lesions with a negative FFR of >0.80). Post-hoc subgroup analyses of the primary endpoint specified are shown according to age (>60 years or ≤60 years), sex, diabetes status, previous myocardial infarction, and smoking. Abbreviations: CAD–coronary artery disease. FFR–fractional flow reserve, HR–hazard ratio, MT–medical therapy, PCI–percutaneous coronary intervention. P-values are for within-trial interaction unless indicated otherwise. * p-value is for across-trial interaction.*

outcomes (τ^2<0.001). The power of the meta-analysis to detect a 30% relative reduction was 68%. We identified no issues regarding the integrity of the individual patient data.

DISCUSSION

Our individual patient data meta-analysis of 3 randomized trials showed a statistically significant reduction in the pre-specified composite endpoint of cardiac death or myocardial infarction favoring FFR-guided PCI over medical therapy. FFR-guided PCI also reduced the composite of all-cause death or MI. Differences were driven by a reduction in myocardial infarction, with little evidence for a reduction in cardiac or all-cause death. The relative risk reduction of PCI of about 28% corresponds to an estimated 5.7% absolute risk reduction at 5 years and a number-needed-to-treat of 18, which is clinically relevant and in keeping with many other standard treatments.

Figure 4. Landmark analyses of primary composite endpoint and its components



The hazard ratios of the primary composite outcome of cardiac death or myocardial infarction and of components of the primary composite outcome shown according to the time from randomization (7 days or less versus 8 days or more). The solid boxes represent hazard ratios for 7 days or less after randomization, the open boxes represent hazard ratios for 8 days or more from randomization. Arrows indicate that the ends of the confidence interval are either less than 0.4 or more than 5. Abbreviations: FFR–fractional flow reserve, HR–hazard ratio, PCI–percutaneous coronary intervention

Two factors are likely to explain negative results for outcomes seen in individual trials. First, each trial by itself was underpowered for a composite of cardiac death or MI. Because all of these trials were powered for a primary composite endpoint that included various definitions of revascularization as one of its components, it cannot be expected that a statistically significant reduction in cardiac death or MI would be found in any single trial. Each component trial in our analysis had recruited less than 1000 patients and ascertained its primary endpoint between 1 and 2 years of follow-up, and none of the trials had more than 25% power to detect, for example, a 30% relative risk reduction in the composite of cardiac death or MI. Our analysis included 2400 patients at a median of almost 3 years of follow-up, accordingly, its power to detect a 30% relative risk reduction[20] is above 65%. While this is still below the optimum of 80 to 90%, it is considerably above the average observed in meta-analyses of cardiovascular trials.[20] Second, prior randomized trials, such as COURAGE,[27] used PCI with bare-metal or early generation drug-eluting stents guided by angiography, which was found inferior to modern PCI with modern generation drug-eluting stents[34] and FFR-guidance.[14]

This meta-analysis included stable lesions from subjects presenting with both stable coronary disease and stabilized acute STEMI. While the clinical presentation differs, both physiologic and statistical arguments plus recent guideline recommendations justify combining these studies. First, in contrast to culprit lesions,[35] FFR-values in non-culprit vessels usually do not change much between assessments made during the acute phase

of a STEMI and assessments weeks or months later during the stable phase of coronary disease.[36-39] Therefore, the vast majority of lesions which were classified as FFR-positive during the acute phase will also be classified as FFR-positive during the subsequent stable phase of coronary disease. Second, STEMI patients were only included in the trials after successful opening of the culprit vessel, when they were hemodynamically stable. Third, the heterogeneity in treatment effects between trials was low and there was no evidence for an interaction between clinical presentation and treatment effect, with near identical relative reductions of the primary endpoint of 30% observed in patients with stable CAD and 28% in patients who initially presented with stabilized ACS. Finally, the recent European guidelines on myocardial revascularization[40] state that "after PCI of the culprit lesion in [an acute coronary syndrome], the choice of further revascularization modality should follow the criteria applied to patients with [stable coronary artery disease]."

Lesion selection is critically important when assessing the benefit of FFR-guided PCI over medical therapy. If patients who only have FFR-negative lesions are randomized and included in the analysis – as in DANAMI-3-PRIMULTI[4] and Compare-Acute[5] based on angiographic inclusion criteria – then a substantial proportion of patients receives the same, typically conservative treatment regardless of randomization and the effect of FFR-guided PCI will be diluted in an intention-to-treat analysis. In our meta-analysis, an estimated 26% of randomized patients had only FFR-negative lesions. Nevertheless, a statistically significant 28% reduction in the composite of cardiac death or MI was found. In a subgroup analysis by FFR, a more pronounced, 38% reduction was indeed found in patients with at least one FFR-positive lesion. While we acknowledge that the test for interaction between FFR status and treatment effect showed only a statistical trend (p=0.06) and DANAMI-3-PRIMULTI could not be included in this analysis as FFR status was unknown for the control group of this trial,[4] we consider it likely that the 38% relative reduction of the primary endpoint in the FFR positive subgroup of patients is a true reflection of the benefit of modern FFR-guided PCI in patients with hemodynamically significant stable coronary lesions. Of note, the recent ORBITA trial comparing PCI with a sham intervention included 29% of patients with FFR negative lesions only.[26] In contrast to the trials included in our analysis, these patients typically received PCI if they were allocated to the experimental arm, even though PCI unlikely to improve symptoms or prognosis in patients without hemodynamically significant lesions.[7,14,28]

Several ongoing trials have the potential to corroborate or refute our findings. In the ISCHEMIA trial, an invasive strategy will be compared with initial medical therapy in patients with stable CAD and moderate ischemia (NCT01471522), using a primary composite endpoint of cardiovascular death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure. ISCHEMIA recently completed recruitment of almost 5200 subjects. Despite its complex design, it may be possible to isolate a subset of patients with

FFR-positive lesions randomized to revascularization or medical therapy. In the FULL REVASC trial, FFR-guided PCI will be compared with initial medical therapy of non-culprit lesions in STEMI patients (NCT02862119). The trial will randomize about 4000 patients with a primary composite endpoint of all-cause mortality or MI. Notably, it will include both patients with FFR-positive and FFR-negative lesions, which will dilute the benefit of the experimental strategy as seen in Compare-Acute and DANAMI-PRIMULTI.[4,5]

This analysis should be interpreted in view of several limitations. First, patients and their physicians were not blinded to the allocated strategy. In addition, there was variation between trials in the disclosure of FFR values to patients and physicians. However, knowledge of the allocated strategy and of FFR values is unlikely to bias estimates of our primary composite outcome of cardiac death or myocardial infarction in favour of the experimental strategy.[12] If anything, knowledge of the treatment strategy and FFR values might have rendered patients in control groups more likely to cross over to an invasive strategy. Therefore, an intention- to-treat analysis is likely to underestimate the potential benefit of FFR-guided PCI as compared with medical therapy with regard to our primary outcome of cardiac death or myocardial infarction.[7] The higher use of dual antiplatelet therapy in the FFR-guided PCI group could provide an alternative or complementary explanation for the observed benefit instead of FFR-guided PCI itself, especially since many subsequent events occur in non-target vessels.[39] Nevertheless the curves continue to diverge beyond 1 year follow-up, where the majority of patients in both groups is assumed to receive single antiplatelet therapy.

Although FFR provides a lesion- or vessel-specific diagnostic tool, subsequent clinical events were not adjudicated with this level of specificity. Non-target vessel events (for example, a subsequent MI in a vessel not interrogated with FFR) have little or no mechanistic link to FFR in the target vessel. The distinction between cardiac and non-cardiac death can be complex and subjective. However, all trials had a blind, independent adjudication of events, including death and MI. Finally, we did not distinguish between peri-procedural and spontaneous MI. In addition, information on infarction size or presence of Q waves was not obtained. However, our landmark analysis confirmed an early increase in MI with early FFR-guided PCI within 7 days, followed by a pronounced benefit, with a 41% relative reduction of MI beyond 7 days (p=0.003), as also seen in FAME 2 alone.[3]

Conclusion

In this individual patient data meta-analysis of the 3 available randomized controlled trials to date, FFR-guided PCI resulted in a reduction of the composite of cardiac death or myocardial infarction compared with medical therapy, which was driven by a decreased risk of myocardial infarction.

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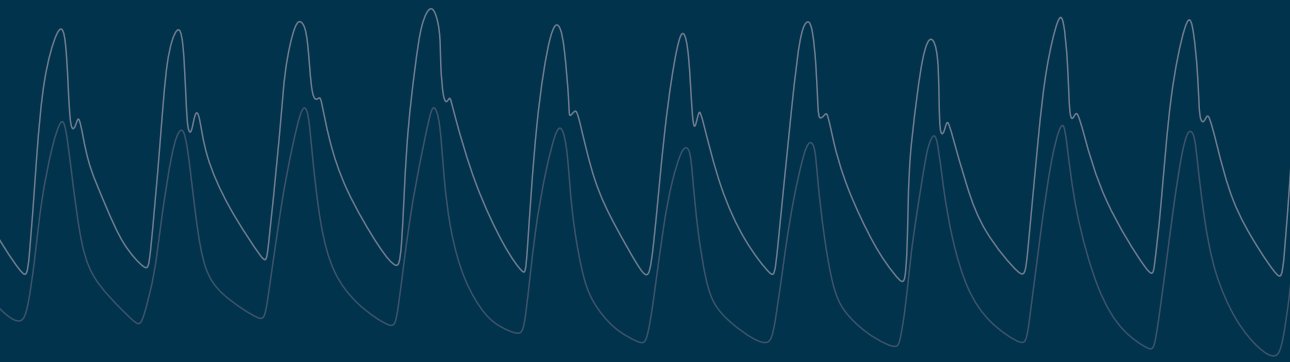
Table S1. Baseline characteristics of patients

	FFR-guided PCI	Medical therapy	p value
Patient characteristics			
Number of subjects	1056	1344	
Age (years)	63.1±10.2	62.7±10.5	0.78
Male sex	840 (79.5%)	1043 (77.6%)	0.25
BMI (kg/m^2)	27.7±4.3	27.7±4.4	0.71
Medical history			
Family history of CAD	465 (44.4%)	577 (43.2%)	0.87
Current smoking	370 (35.1%)	525 (39.1%)	0.34
Hypertension	613 (58.0%)	770 (57.3%)	0.32
Hypercholesterolemia	533 (50.6%)	642 (47.8%)	0.28
Any diabetes	195 (18.5%)	253 (18.8%)	0.45
Diabetes requiring insulin	56 (5.3%)	76 (5.7%)	0.48
Peripheral artery disease	69 (6.8%)	79 (6.1%)	0.95
History of stroke or TIA	62 (6.0%)	68 (5.2%)	0.09
Previous MI	203 (19.2%)	238 (17.7%)	0.42
Previous PCI	118 (11.2%)	140 (10.4%)	>0.99
Clinical presentation			
Stable coronary disease	447 (42.3%)	441 (32.8%)	>0.99
Angiographic findings			
*Number of diseased vessels per patient**			0.83
1-vessel	340 (32.2%)	354 (26.3%)	
2-vessel	518 (49.1%)	705 (52.5%)	
3-vessel	198 (18.8%)	285 (21.2%)	
Number of angiographically significant lesions per patient#	1.8±1.0	1.8±0.9	0.15

*Plus–minus values are means ± standard deviation. Abbreviations: BMI–body mass index, FFR–fractional flow reserve, MI–myocardial infarction, PCI–percutaneous coronary intervention, STEMI–ST-segment elevation myocardial infarction, TIA–transient ischemic attack. P-values are for differences between groups after stratification by trial. *Estimated using multilevel Poisson regression. # not including culprit lesion in case of STEMI*



CHAPTER 8

Stenting "Vulnerable" but FFR Negative Lesions: Potential Statistical Limitations of Ongoing and Future Trials

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INTRODUCTION

For some patients, acute myocardial infarction (MI) or sudden cardiac death represent the first manifestations of atherosclerotic coronary artery disease. Each year in the United States, approximately 600000 patients experience an initial acute MI and another 350000 suffer an out-of-hospital cardiac arrest.[1] While risk factor modification and medical therapy remain the foundation for reducing the incidence of this serious and common problem, it is natural to wonder if percutaneous coronary intervention (PCI) could play a role. This notion has received names in the literature like "plaque sealing", "prophylactic PCI", or "preventive PCI".

Intravascular ultrasound (IVUS), optical coherence tomography (OCT), near infrared spectroscopy (NIRS), and computed tomographic angiography (CTA) have identified "vulnerable" features of coronary plaques that associate with higher subsequent event rates. Can imaging provide sufficient risk stratification to warrant PCI of a stable plaque in the absence of refractory symptoms? This question has moved beyond the abstract by several ongoing randomized trials whose results are expected soon.

While characterizing high risk plaque by CT or intracoronary imaging may evolve to a future solution, for current technology and published data, a hypothetical statistical analysis provides a sobering, possibly realistic limitation for planning future interventional studies. In this paper we critically examine the hypothesis of plaque sealing not only to predict the results of upcoming studies but also to understand what type of tool and trial would be necessary to obtain a positive result. We examine it separately from the related but distinct hypothesis regarding imaging-guided customization of medical treatment, like statin or PCSK9 therapy.

Small gradient, low events

Because lesions with a positive fractional flow reserve (FFR) are indicated for revascularization in the guidelines due to a broad evidence base[2], the critical issue for the plaque sealing hypothesis regards lesions with negative FFR. In addition, all ongoing randomized controlled trials (RCTs) on plaque sealing are focusing on lesions with negative FFR. These lesions do well with medical therapy alone, as seen in many studies. In the FAME study, only 1 acute MI from 513 deferred lesions with negative FFR occurred during 2 years of follow-up,[3] approximately 0.1%/year. After 15 years of follow-up in the DEFER trial, only 2 acute MI occurred from 91 deferred lesions with FFR⩾0.75,[4] a rate of 0.15%/year. Vessel-related cardiovascular death or MI in the FAME 2 study showed 14 events from approximately 514 lesions over 2 years when FFR⩾0.78 (top 2 quartiles) for a composite rate of 1.4%/year.[5] For combined target and non-target events – not adjudicated separately – a Korean registry of 6468 lesions deferred after FFR assessment (including some lesions

with low FFR) recorded 26 cardiac or MI events during a median follow-up of almost 2 years for an incidence of 0.21%/year.[6] Taking vulnerable and non-vulnerable lesions together, the event rate for medical treatment with FFR>0.80 varies among these studies, but at worst reaches 1% per year for death or MI related specifically to the interrogated lesion or vessel.

Stenting as an iatrogenic disease

If PCI had no acute risk or long-term complications, then it could be applied almost universally depending on financial circumstances. However, despite enormous improvements in device design, implantation technique, and pharmacologic therapy, PCI carries both immediate and delayed consequences. For stable lesions whose causal symptoms or natural history reach sufficiently adverse levels, the substitution of "stent disease" for "atherosclerotic disease" brings a net clinical advantage. Since medical treatment of a lesion with high FFR has a target vessel event rate of death or MI of approximately 1%/year, we must compare this rate against the rate after modern PCI.

Two randomized trials examining latest-generation drug-eluting stent platforms implanted in 2015 and 2016 – thus representing contemporary PCI under carefully controlled circumstances – found similar event rates during the subsequent year.[7,8] Target vessel MI occurred in 2.9% of subjects, with peri-procedural MI accounting for 1.7% of this total that remains a source of controversy regarding its prognostic implications.[9] Furthermore, clinically driven target lesion revascularization – implying device failure sufficient to cause new symptoms – occurred in 2.2%. Finally, 0.6% of subjects suffered cardiac death potentially attributable to the stent.

Whether complication rates would be lower for FFR negative lesions with vulnerable imaging features remains a hypothesis unsupported by pilot data.[10] Additionally, so-called bioresorbable vascular scaffolds (BVS) had been touted as uniquely suited to preventative PCI for a variety of reasons.[11] However, emerging data regarding inferior clinical outcomes prompted commercial withdrawal of the first-generation version of this device.[12]

Imaging markers of risk

It is clear that prophylactic PCI could at best be applied selectively since the composite group of FFR negative lesions has a death or MI rate of approximately 1%/year or less but modern stents have a rate of 2-3.5%/year (depending on the inclusion of peri-procedural MI) plus 2% repeat PCI for clinically-driven, device-related symptoms. Currently several imaging tools have been studied to identify higher risk plaques.

IVUS provided one of the most impressive natural history studies of non-culprit lesions studied at the time of an acute coronary syndrome, mostly acute MI.[10] Over the subsequent 3 years, only 6 of 697 subjects experienced a spontaneous MI (with no death or cardiac

arrest) due to a non-culprit lesion, or 0.3%/year. While certain imaging parameters stratified a composite of events that mainly included revascularization and rehospitalization with hazard ratios ranging from 5 to 18, lesion-related death or acute MI remained exceedingly rare.

NIRS investigated the natural history study of stabilized subjects undergoing invasive angiography and IVUS assessment.[13] After 2 years, only 10 non-fatal MI occurred among 1271 subjects and were attributed to an imaged, non-culprit plaque, or 0.4%/year. Intriguingly, 7 of these 10 events arose from segments with a maximum 4mm lipid core burden index ($maxLCBI_{4mm}$) below the 400 threshold suggested as high risk, indicating that an outcomes trial applying this criterion would not have treated the majority of future culprits. While $maxLCBI_{4mm}$>400 at a plaque level increased the risk of composite events that also included revascularization, rehospitalization, angina, and angiographic progression, lesion-related death or acute MI remained exceedingly rare.

OCT studied the natural history study of patients undergoing clinical angiography for a variety of indications.[14] During the next 1 year, cardiac death and target-vessel MI occurred in 3.7% of subjects. However, in the 3.6% of subjects with 4 simultaneous vulnerable features (thin fibrous cap, minimum lumen area <3.5mm2, wide lipid arc, and presence of macrophages), 18.9% experienced this outcome. These event rates far exceed those of FFR negative lesions or natural history studies using IVUS or NIRS, potentially suggesting that this particular cohort included some vessels that would have been FFR positive if measured.

CTA with added computational fluid dynamic simulation used a case-control design to study culprit lesions preceding an acute coronary syndrome, mostly acute MI.[16] Well over half of culprit lesions had a low simulated FFR value with a mean FFR_{CT} of 0.72±0.17 and largely focal lesions with an average ΔFFR_{CT} of 0.17 over 19mm of vessel. Conversely, non-culprit lesions in the same subjects had a significantly higher FFR_{CT} of 0.79±0.14 and less focal gradient with an average ΔFFR_{CT} of 0.06 over 16mm of vessel. While these results undergo replication (clinicaltrials.gov NCT03591328), it is important to note that only 3% of culprit lesions had no features of vulnerability, either hemodynamic (like low vessel FFR_{CT} or high lesion ΔFFR_{CT}) or anatomic (like low density plaque or positive remodeling). Over half of all lesions with both types of vulnerability became culprit lesions, and almost 70% of all culprit lesions possessed both types of vulnerable features. These CTA results again emphasize that high FFR lesions infrequently lead to death or spontaneous MI.

Ongoing randomized trials

To the best of our knowledge and as summarized in the Table, 3 ongoing randomized controlled trials are testing the concept of plaque sealing in FFR negative lesions. Each

started out using BVS, but completed enrollment before BVS withdrawal from the market, switched to a standard metallic drug-eluting stent midway through enrollment, or stopped the treatment arm and continued as a non-randomized observational cohort. Based on the preceding review of the literature, two points bear keeping in mind. First, plaque sealing can only change vessel-level events, not death or MI due to other vessels or non-coronary mechanisms. Tracking all events dilutes any potential benefit by including off-target and thus non-modifiable outcomes.

Second, all of the trials include target-vessel revascularization in their composite endpoint. Because most subjects are asymptomatic, and even symptoms in the setting of a negative FFR do not improve with PCI, revascularization represents an inappropriate endpoint. After all, if a patient develops medically refractory or unstable angina, then urgent PCI can be performed without loss of life or myocardial tissue.

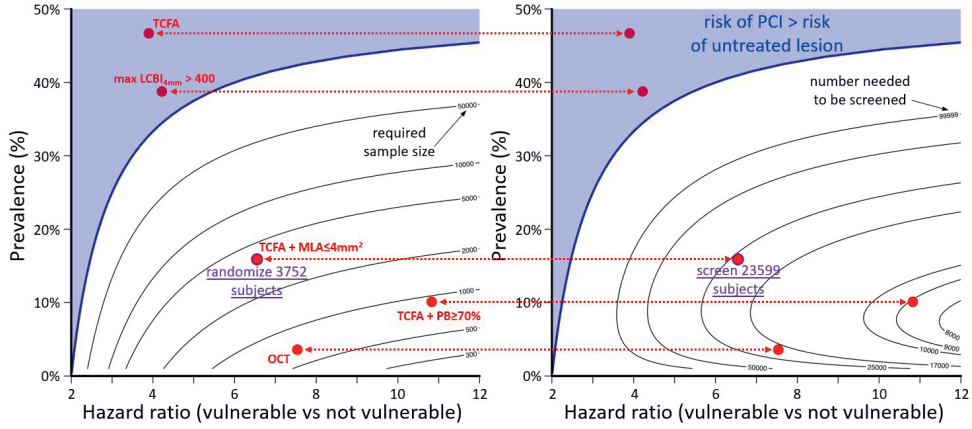
Can we ever expect a positive randomized trial?

Given very low event rates in unselected lesions with negative FFR, imaging enrichment remains necessary to gain advantage over post-PCI outcomes. However, a higher background event rate via enrichment comes at a cost of screening failures that make it more difficult to enroll the required sample size. Based on the prior summary of the literature, assume an average background event rate for cardiac death and MI of 1%/year. How much enrichment is necessary for PCI to offer an advantage, assuming a very conservative 2%/year risk of stent-related death or MI?[7,8]

The Figure shows a contour plot for enrolled and screened sample sizes given arbitrary combinations of the enrichment magnitude (expressed as the hazard ratio between vulnerable and non-vulnerable plaque risk) and its prevalence among subjects with negative FFR. It is important to realize that such hazard ratio only indicates the *relative* risk of patients with vulnerable features versus the minimal risk of patients without these features. Therefore, this relative risk only translates in small *absolute* increased rate, as the event rate of FFR-negative lesions in total will still remain about 1%/year.

Reported combinations in the literature using IVUS,[10] OCT,[14] and NIRS[13] are shown, with the caveats that these hazard ratios include a much larger number of clinical events besides cardiac death and MI, often 10:1 or greater, and did not explicitly ensure that FFR was negative. Note that hazard ratio and prevalence show an inverse relationship (higher risk occurs in a smaller subgroup of the entire population). Currently available technologies still require screening approximately 9000 patients invasively even under the most optimistic scenario.

Figure. Randomized trial to validate or refute plaque sealing hypothesis.



Assume a 1%/year rate of cardiac death or acute myocardial infarction from a plaque with negative fractional flow reserve, and a 2%/year risk of the same endpoints from percutaneous coronary intervention (PCI). Imaging can enhance the risk by identifying vulnerable features like thin-cap fibroatheroma (TCFA), small minimum lumen area (MLA), high plaque burden (PB), high lipid content (maximum 4mm lipid core burden index, LCBI), or a composite of 4 findings by optical coherence tomography (OCT). Vulnerable features increase the hazard ratio (population with vulnerable features versus population without vulnerable features), but exist only in a subset. These panels quantify the required sample size – and upstream screening – necessary for a randomized controlled trial. Hazard ratios and prevalence (of vulnerable features within a population) were taken from large natural history studies.[10,13,14]

For example, the combination of thin-cap fibroatheroma plus small lumen area (4mm^2 or less) by IVUS increased the hazard ratio to 6.55 but occurred in only 16% of lesions.[10] Because this criterion is similar to the largest ongoing trial, let us use it to illustrate the impact on trial design. For the 16% of lesions meeting “vulnerable” criteria, the event rate rises to 1%/(0.16+0.84/6.55)=3.47% for medical therapy versus 2% after PCI. The sample size for a two-sided t-test with typical a=0.05 and 1-b=0.80 demands 3752 subjects. Furthermore, a total of 23599 patients would need to be screened to enroll this “vulnerable” 16% population. These estimates are actually conservative given that some patients will not provide informed consent and others will drop out because of clinical and angiographical exclusion criteria. Accounting for adverse events related to invasive imaging, reaching 1.6% dissections or perforations producing 0.4% MI in one study using IVUS[10] and 0.4% events in another study using NIRS[13] implies over 3-fold more adverse events during enrichment (0.4% of 23599 equals 94 events) than saved with prophylactic PCI (3.47% versus 2% in the 3752 randomized subjects equals 28 net saves).

Table. Ongoing randomized trials of prophylactic PCI for vulnerable but FFR negative lesions.

	PREVENT	**PROSPECT ABSORB**	**PECTUS**
Registration(s)	NCT02316886	NCT02171065	NL4177 NCT03857971
Sample size	1600	300	500
Clinical scenario	All comers	After acute MI	After acute MI
Imaging tool(s)			
IVUS	X	X	
OCT	X		X
NIRS	X		
Stent type(s)	BVS and EES	BVS	BVS
Clinical endpoints			
Cardiac death	X	X	X
Target vessel MI	X	X	X
TVR	X	X	X
Non-cardiac death	X		X
Off-target MI	X		X
Non-TVR	X		X
Follow-up	2 years	2 years	1 year
Estimated completion	2022	2019	2022
Comments	Switched to EES in 2017 because of concerns with BVS.	Completed enrollment. Data safety monitoring board has not raised any concerns related to BVS.	Stopped treatment arm in 2018 related to concerns with BVS and continued as non-randomized observational cohort.

Abbreviations: BVS = bioresorbable vascular scaffold; EES = everolimus-eluting stent; IVUS = intravascular ultrasound; MI = myocardial infarction; NIRS = near infra-red spectroscopy; OCT = optical coherence tomography; TVR = target vessel revascularization.

Atherosclerosis is bad. More is worse.

In conclusion, preventive PCI of a "vulnerable" plaque with negative FFR depends on such a small effect that sample sizes to validate or refute its benefit become prohibitive. The small risk from invasive imaging quickly outsizes any potential downstream benefits when applied to suitably sized populations. Therefore, ongoing randomized trials are underpowered even if pooled. Potentially non-invasive imaging could identify an asymptomatic population with elevated risk despite negative FFR but without the risk from vessel instrumentation. However, existing data suggests that the more fruitful target from non-invasive imaging is an asymptomatic subject with adverse stress hemodynamics plus vulnerable plaque features.[16]

Seen another way, FFR provides a quick, quantitative, straightforward, and reproducible “imaging” metric of plaque vulnerability and burden without the need for or expense of additional catheter devices. While plaque features associate with higher global risk, likely through increased total plaque burden, they cannot be modified via local plaque sealing, only systemic medical therapy. Therefore, the data implies that IVUS, OCT, and NIRS cannot meaningfully guide prophylactic PCI when faced with a negative FFR

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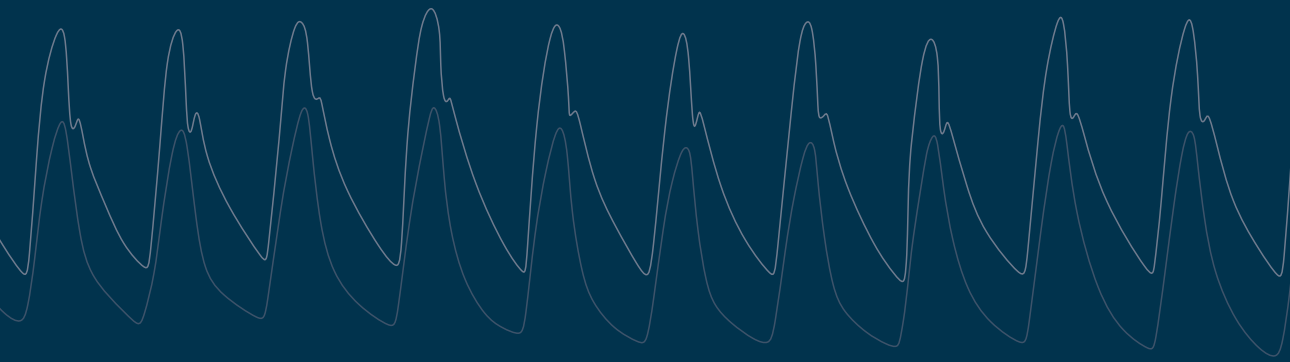


CHAPTER 9

Yellow Traffic Lights and Grey Zone Fractional Flow Reserve Values: Stop or go?

Nils P. Johnson, Frederik M. Zimmermann

European Heart Journal 2018 May 7;39(18):1620-1622.

SLAVE TO THE TRAFFIC LIGHT

Traffic lights represent a type of decision common to many aspects of medicine: do (green), don't (red), or maybe (yellow). While traffic lights remain a powerful guideline for driving safely, we have on rare occasion stopped at a green light (when a child ran into the intersection) or ran a red light (when racing to the hospital for an emergency at 2 o'clock in the morning). And how do we react to a yellow light? While perhaps befuddling to novice drivers (the formal rule demands that we stop unless unable to 'stop safely'), with experience we all reach a common, practical answer: it depends. Wet roads, late for work, fast speed, or vehicle on your tail? Go! Lazy weekend, unfamiliar city, slow speed, or police car nearby? Stop!

Fittingly, cardiology guidelines[1] have now taken to coding their recommendations using a traffic light colour scheme: class I (recommended, green), class III (not recommended, red), and class II (with divisions IIa = should consider, yellow; and IIb = may consider, orange). Much of clinical medicine focuses on a narrow application of the guidelines in class I and class III scenarios, while—perhaps befuddling to trainees—with experience we all reach a pragmatic answer for class II options: patient preference (coupled with education and informed consent) and clinical judgement.

With this analogy in mind, we turn to the article by Kang et al.[2] Their manuscript addresses the so-called 'grey zone' of fractional flow reserve (FFR), denoting values between 0.75–0.80. While the initial DEFER trial[3] used an FFR < 0.75 threshold for revascularization based on a unique multitest validation before and after revascularization,[4] the subsequent FAME family of studies,[5–7] and other trials[8] moved to an FFR ⩽0.80 threshold in a desire to avoid undertreatment. Because FFR = 0.75–0.80 values occur in approximately 15% of lesions (about one in seven patients),[9] their optimal treatment deserves further examination.

IRIS-FFR registry

Using a large, prospective Korean registry, the authors analysed a total of 1334 de novo coronary lesions in the grey zone from 1334 patients, representing the largest such cohort to date.[2] About half of the lesions underwent revascularization in non-randomized fashion based on unspecified and unknowable clinical factors. The revascularized patients had more frequent multivessel disease and acute coronary syndrome presentations, as well as angiographically more severe and complex lesions. During a median follow-up of 2.9 years, no statistically significant difference in outcomes [composite of all-cause mortality, target vessel myocardial infarction, and target vessel revascularization (TVR)] existed between the deferred and revascularized lesions. However, a significant increase in myocardial infarction occurred in the revascularized group, mainly due to an increase in periprocedural infarction. These results persisted even after adjustment for several potential confounders.

The authors deserve compliments for a rigorous analysis. Particular strengths include its prospective design, large size, event adjudication by an independent committee, adjustment for potential confounders, and vessel-level outcomes. The unanswerable question remains why some lesions were revascularized and why some were deferred despite similar FFR values. Unfortunately, the authors did not report baseline symptoms, an important contributor to decision making. How abnormal were upstream stress tests? Were lesions in the revascularized group more focal and therefore more suitable for percutaneous coronary intervention (PCI)? Finally, the remarkably low rate of spontaneous myocardial infarction in the IRIS-FFR registry (<1% during 3 years of follow-up) implies some combination of a very low-risk population, excellent medical therapy, and/or insufficient ascertainment of events.

Synthesis of existing literature

In addition to the new results from Korea,[2] several non-randomized, observational studies have examined revascularization vs. deferral for grey zone FFR lesions in cohorts varying from 97 to 453 patients.[10–14] While we urge caution when combining observational data using a 'back-of-the-envelope' meta-analysis, what can we learn from a synthesis of the literature?

First, death and myocardial infarction remain uncommon in the FFR grey zone. Among the 2357 patients from all publications, less than 100 hard events were observed during an average 2.5 years of follow-up (4.4% or 50 of 1129 treated conservatively, and 3.3% or 41 of 1228 treated with revascularization).[2,10–14] A random effects meta-analysis suggests that the difference does not reach significance (risk ratio 1.86, 95% confidence interval 0.92–3.75, P=0.08). When accounting for the length of follow-up, these numbers imply an approximate 1.5% per year rate of death or myocardial infarction. Only two of the six studies found significant differences in hard endpoints but were mutually inconsistent: one study in favour[2] and one study against10 conservative treatment. The other cohorts did not observe a significant difference, probably due to lack of power in small populations.[11–14]

Second, subsequent TVR takes place in a small minority of stenoses with FFR values in the grey zone. Although numerically greater in conservatively treated lesions (8.0% or 90 of 1129 treated conservatively, and 5.9% or 72 of 1228 treated with revascularization), a random effects meta-analysis did not reach statistical significance (risk ratio 1.55, 95% confidence interval 0.91–2.65, P=0.11). Scaling for the average 2.5 years of follow-up implies an approximate 2–3% per year rate of TVR. It is important to realize that most studies discount initial revascularizations in the PCI group. Indeed, TVR would be much higher in the PCI arm if those procedures were counted. TVR for grey zone FFR lesions will always be lower with a strategy of initial medical therapy because 100% of the revascularization group receives an immediate TVR. As a counterargument, initial revascularization may

prevent the need for a second procedure and its accompanying burden, highlighting the importance of patient preference, especially in the presence of limiting symptoms.

Similarly, composite major adverse cardiac events, although somewhat heterogeneously defined among the studies, reached every possible conclusion: neutral in the two largest series,[2,10] favouring revascularization,[11–13] and favouring conservative treatment.[14]

Stop or go?

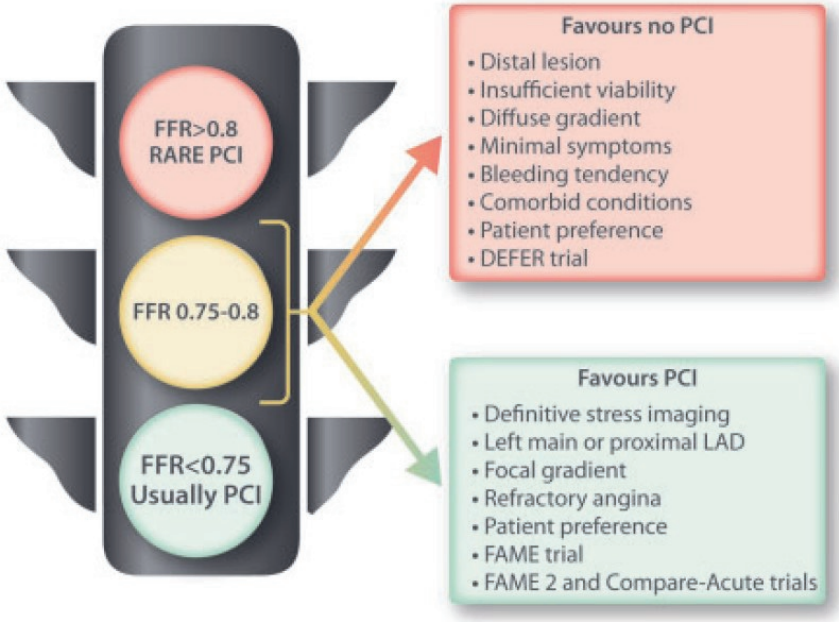
Take home figure summarizes the clinical factors and randomized literature organized using the traffic light analogy for grey zone FFR. Several aspects warrant specific comment. First, we know already from the FFR risk continuum[9] that lesions with a value 0.75–0.80 have a worse natural history than those >0.80. Therefore, the relevant clinical question must focus on medical therapy vs. revascularization for lesions within the 0.75–0.80 range, not how these grey zone stenoses fare in relation to different stenoses with higher or lower FFR values.

Second, all published studies employed observational designs,[2,10–14] whereby treatment was determined by the physician, thereby creating the serious potential for allocation bias. The awaited GzFFR results (clinicaltrials.govNCT02425969) will be the first to randomize lesions within the specific FFR range 0.75–0.82, with its 108-subject sample size powered for angina status as the primary outcome.

Third, the existing observational literature—with its important caveat regarding potential bias—does not indicate a consistent adverse signal for hard endpoints of death or myocardial infarction. Given the low lesion-related event rates in the FFR grey zone coupled with its 15% prevalence,[9] an enormous (and perhaps prohibitive) number of subjects would need to be screened for a properly powered randomized controlled trial. Fourth, because even best-generation drug-eluting stents still carry a 1-year risk of target lesion death or myocardial infarction around 4–8% and clinically driven repeat revascularization of 2%,[15] the natural history of a grey zone FFR lesion would need to be sufficiently greater to offer a reasonable trade-off.

In conclusion, when approaching a grey zone FFR value—or yellow traffic light—we should not always stop or always go. Rather, we must incorporate patient preference and our clinical judgement to make the decision. Although it may not always seem like it, we thankfully have more time in the catheterization laboratory to weigh the options than when hurtling towards an intersection!

Take home figure



Traffic light analogy for fractional flow reserve (FFR). When confronted with an FFR value above 0.80 (red traffic light), the usual response should be to avoid revascularization (stop!). Conversely, a lesion whose FFR value falls below 0.75 (green traffic light) should most often be revascularized (go!). In between falls the FFR 'grey zone'—much like a yellow traffic light—where patient preference and clinical judgement decide.

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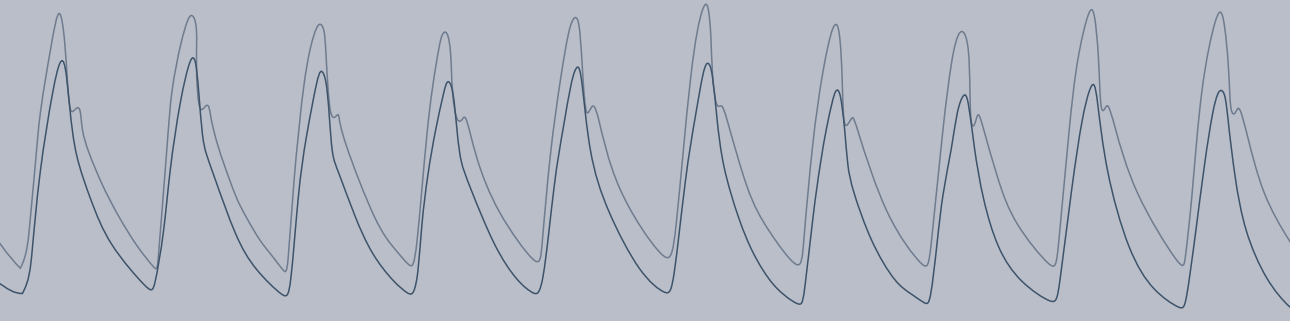
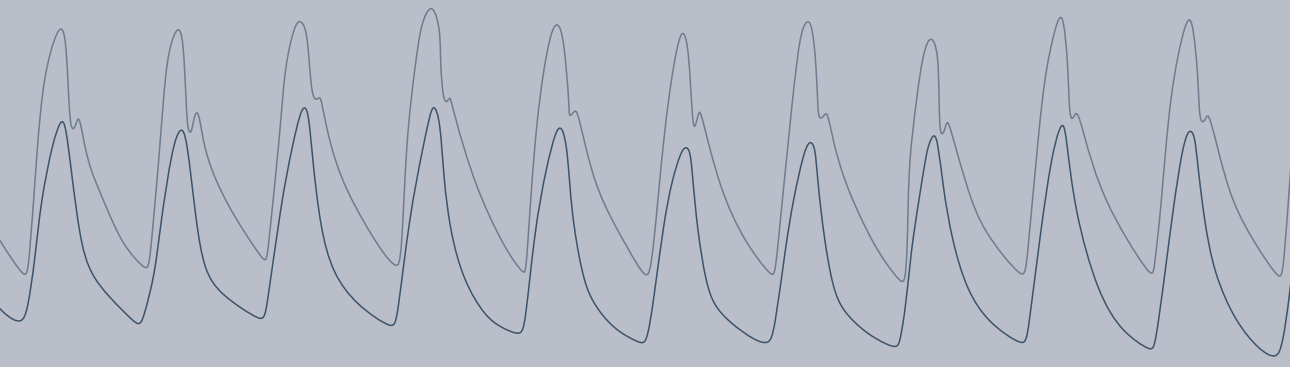
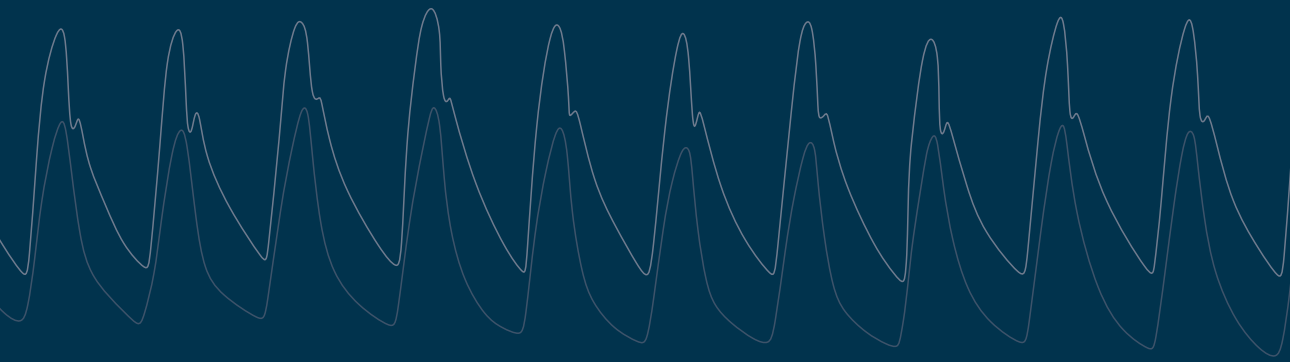


PART III

Prediction of Invasive Coronary Physiology





CHAPTER 10

Deep Learning for Prediction of Fractional Flow Reserve From Resting Coronary Pressure Curves (ARTIST Study)

Frederik M. Zimmermann, Thomas P. Mast, Nils P. Johnson, Ivo Everts, Barry Hennigan, Colin Berry, Daniel T. Johnson, Bernard De Bruyne, William F. Fearon, Keith G. Oldroyd, Nico H.J. Pijls, Pim A.L. Tonino, Marcel van 't Veer

EuroIntervention. 2021 May 17;17(1):51-58.

ABSTRACT

Aims

It would be ideal for a non-hyperemic index to predict fractional flow reserve (FFR) more accurately, given FFR's extensive validation in a multitude of clinical settings. The aim of this study was to derive a novel non-hyperemic algorithm based on deep learning and to validate it in an internal validation cohort against FFR.

Methods and Results

The ARTIST study is a post hoc analysis of 3 previously published studies. In a derivation cohort (random 80% sample of the total cohort) a deep neural network was trained (deep learning) with paired examples of resting coronary pressure curves and their FFR values. The resulting algorithm was validated against unseen resting pressure curves from a random 20% sample of the total cohort. The primary endpoint was diagnostic accuracy of the deep learning-derived algorithms against binary FFR≤0.8. To reduce the variance in the precision, we used a 5-fold cross-validation procedure. A total of 1666 patients with 1718 coronary lesions and 2928 coronary pressure tracings were included. Diagnostic accuracy of our convolutional neural network (CNN) and recurrent neural networks (RNN) against binary FFR≤0.80 were 79.6±1.9%, and 77.6±2.3%, respectively. There was no statistically significant difference between the accuracy of our neural networks to predict binary FFR and the most accurate non-hyperemic pressure ratio (NHPR).

Conclusions

Compared to standard derivation of resting pressure ratios, we did not find a significant improvement in FFR prediction when resting data is analysed using artificial intelligence approaches. Our findings strongly suggest that a larger class of hidden information within resting pressure traces is not the main cause for the known disagreement between resting indices and FFR. Therefore, if clinicians want to use FFR for clinical decision making, hyperaemia induction should remain the standard practice.

INTRODUCTION

Fractional flow reserve (FFR) has become the invasive reference standard for assessing the physiological significance of a coronary stenosis based on randomized clinical outcome trials and mechanistic studies.[1-4] Guidance of percutaneous coronary intervention (PCI) by FFR has been shown to be superior to angiography-guided PCI and medical therapy for improving both symptoms and prognosis and is recommended by current guidelines.[1-6]

In order to measure FFR, adenosine (or another vasodilator drug) is required to induce hyperemia, which adds some cost and might cause transient, short-lasting symptoms.[1] Therefore, several non-hyperemic indexes have been proposed that do not require adenosine but are derived from non-hyperemic (resting) coronary pressure curves.[7-10]

Such a resting index usually assesses the pressure ratio during a specific period within the cardiac cycle or focuses on qualitative parameters. Unfortunately, the accuracy of existing non-hyperemic indexes to predict FFR≤0.80 has consistently been shown to be approximately 80%.[7-10]

A possible explanation for this suboptimal predictive value of resting indexes is that the information needed to predict FFR from resting curves exists in a more complex and subtle manner beyond simplistic pressure ratios or known qualitative features. In addition, traditional waveform analysis might have limits to discover complex information contained within the pressure curves. Yet, it would be ideal for a non-hyperemic index to predict FFR more accurately, given its extensive validation in a multitude of clinical settings.

Deep learning, a subfield of artificial intelligence, can model extremely complicated relationships between inputs and outputs, and has shown potential to improve health care in several areas.[11-12] A deep learning algorithm, a so-called deep neural network, can train itself when provided with a sufficient number of correct examples of input and output. Therefore, we hypothesised that a deep neural network could be trained to predict FFR after receiving many examples of resting pressure curves and their corresponding FFR values.

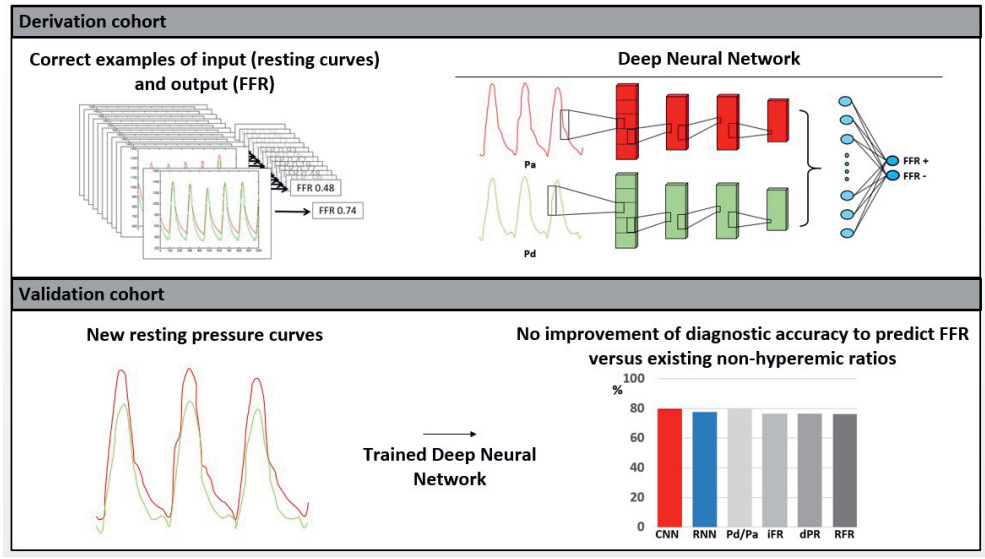
The aim of this study was to derive a novel non-hyperemic algorithm based on deep learning and to validate it in an internal validation cohort against FFR.

METHODS

Study population

The ARTIST study (ARTificial Intelligence to identify functionally SignificanT coronary stenoses) is a post hoc analysis of 3 previously published studies: CONTRAST (clinicaltrials.gov NCT02184117), VERIFY (clinicaltrials.gov NCT01559493), and VERIFY 2 (clinicaltrials.gov NCT02377310). All studies included in this analysis were approved by the institutional review boards of the individual sites. Detailed descriptions and primary results of these studies have been published previously.[13-15] In short, all three studies recorded raw tracings of simultaneous aortic (Pa) and distal coronary pressure (Pd) during both resting (non-hyperemic) conditions and maximal hyperemia induced by either intravenous or intracoronary adenosine.

Visual summary



Abbreviations: CNN–convolutional neural network; dPR–Diastolic pressure ratio; FFR–fractional flow reserve; iFR–instantaneous wave free ratio; Pa – aortic pressure; Pd – distal coronary pressure; Pd/Pa – ratio of distal coronary pressure to aortic pressure

Fractional flow reserve (FFR)

In order to uniformly assess FFR among trials, all hyperemic pressure curves were anonymized and independently analyzed for calculation of smart minimum FFR (smFFR) using an automated algorithm[16] at the Weatherhead PET Imaging Center in Houston, Texas. Calculation of smFFR occurred without knowledge of matching non-hyperemic data.

Non-hyperemic pressure ratios (NHPR)

The following definitions were used to calculate various non-hyperemic pressure ratios; dPR: average Pd/Pa from dicrotic notch to 5ms before end of diastole resting; Pd/Pa: average Pd/Pa over the entire heart cycle; instantaneous wave-free ratio (iFR): average Pd/Pa from 25% into diastole until 5 ms before end of diastole; RFR; value at which the filtered ratio of Pd and Pa is lowest during the entire cardiac cycle. According to the literature, a binary cut-off of ≤0.92, was used for resting Pd/Pa and ≤0.89 for other NHPR.[8]

Derivation cohort

The visual summary provides an overview of the study design. In a derivation cohort (random 80% sample of the total cohort) a deep neural network was trained (deep learning) with paired examples of resting coronary pressure curves and their FFR values. To reduce the variance in the precision, we used a 5-fold cross-validation procedure.

Artificial Neural Network

A one-dimensional convolutional neural network (CNN) was used to classify resting pressure recordings into FFR positive (FFR≤0.80) or FFR negative (FFR>0.80) binary categories, and to predict FFR as a continuous outcome. A CNN can automatically learn and identify features that are present among the resting coronary pressure curves.[11,12] The architecture of the CNN consisted of five layers (figure 1, panel A) to provide feature extraction on different levels. Several variations of this CNN architecture were tested (Table 1). A detailed description of neural architectures are provided in the supplements.

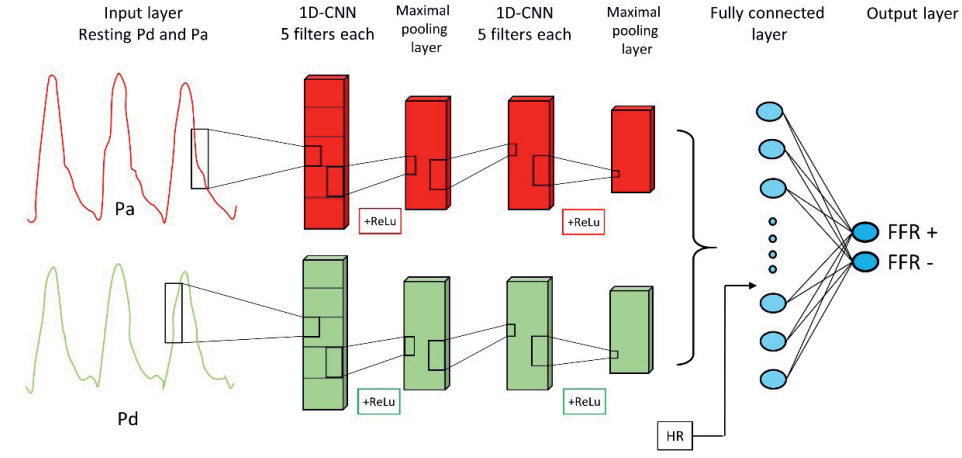
In addition to a CNN, we tested a different deep learning architecture: a recurrent neural network (RNN), see figure 1, panel B. A recurrent neural network is especially designed to incorporate temporal-dependency among features by adding information of a previous interval to the next interval.[17] This contrasts with a CNN, which is insensitive to the temporal location of the feature within the pressure curve itself. Two different RNN variations were used mutually exclusive: long short term memory cells (LSTM) and gated recurrent units (GRU).

All deep learning models were implemented using scikit-learn in Python™.

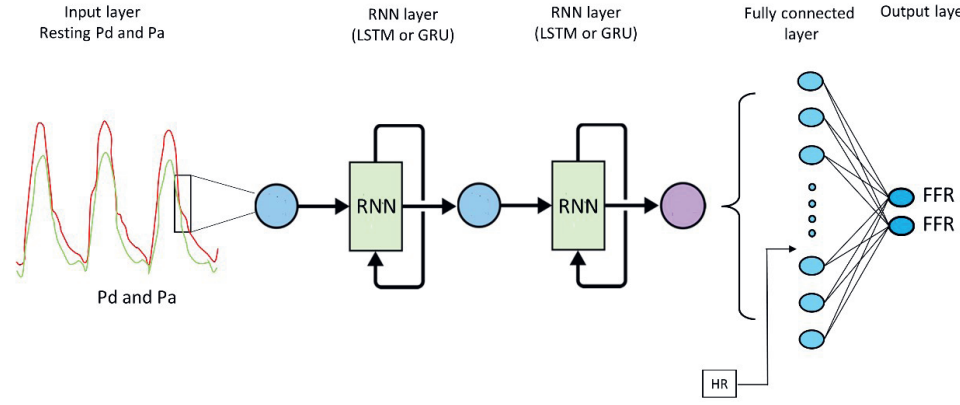
Validation cohort

After a neural network was trained, its resulting algorithm was validated against unseen resting pressure curves from a random 20% sample of the total cohort. The primary endpoint of the validation cohort was diagnostic accuracy of the deep learning-derived algorithms against binary FFR≤0.8. In addition, sensitivity, specificity, positive predictive value, and negative predictive value were calculated, with FFR≤0.80 as reference standard. The diagnostic performance were presented as mean and standard deviation of the 5-fold cross-validation procedure.

Figure 1. Detailed architecture of deep neural networks (1A: CNN, 1B: RNN)



A



B

Abbreviations: CNN – convolutional neural network; FFR – fractional flow reserve; GRU–gated recurrent unit; HR – heart rate; LSMT–long short-term memory; Pa – aortic pressure; Pd – distal coronary pressure; ReLU–rectified linear unit; RNN – recurrent neural network

The diagnostic performance of several non-hyperemic pressure ratios were also calculated and compared using a McNemar test. A mean and 95% confidence interval for the diagnostic performance was calculated for the non-hyperemic pressure ratios based on these data. Prediction of FFR as continuous variable was analyzed using the area under the receiver-operating characteristic (ROC) curve (compared using the DeLong method). Applicable tests were 2 tailed, and $p < 0.05$ was considered statistically significant. Analysis was conducted using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

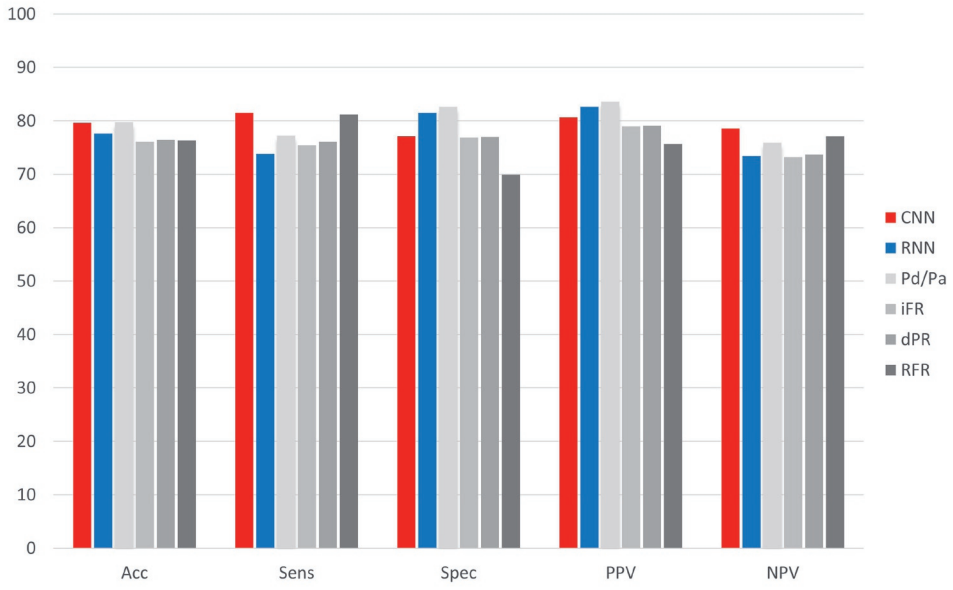
RESULTS

A total of 1666 patients with 1718 coronary lesions and 2928 coronary pressure tracings were included. Approximately 71% of patients were male, and the majority of patients had one or more classical risk factors for coronary artery disease. Baseline characteristics and angiographic data in the individual trials have been reported previously.[13-15] Median resting Pd/Pa was 0.92 (interquartile range [IQR] 0.88 – 0.96), median iFR was 0.89 (interquartile range [IQR] 0.83 – 0.94,) and median FFR was 0.80 (interquartile range [IQR] 0.72 – 0.86). Out of 1718 coronary lesions, 923 (54%) had FFR≤0.80.

Endpoints

Figure 2 shows the diagnostic performance of our deep neural architectures compared to FFR. Diagnostic accuracy (acc), sensitivity (sens), specificity (spec), positive predictive value (PPV), and negative predictive value (NPV) of our convolutional neural network (CNN) against binary FFR≤0.80 using 5-fold cross-validation was 79.6±1.9%, 81.5±3.2%, and 77,1±6.4%, 80.6±3.6%, 78,5±2.4%, respectively. Acc, sens, spec, PPV, and NPV for our

Figure 2. Diagnostic performance of our deep learning-based algorithms and other NHPRs, against binary FFR ≤0.80.*



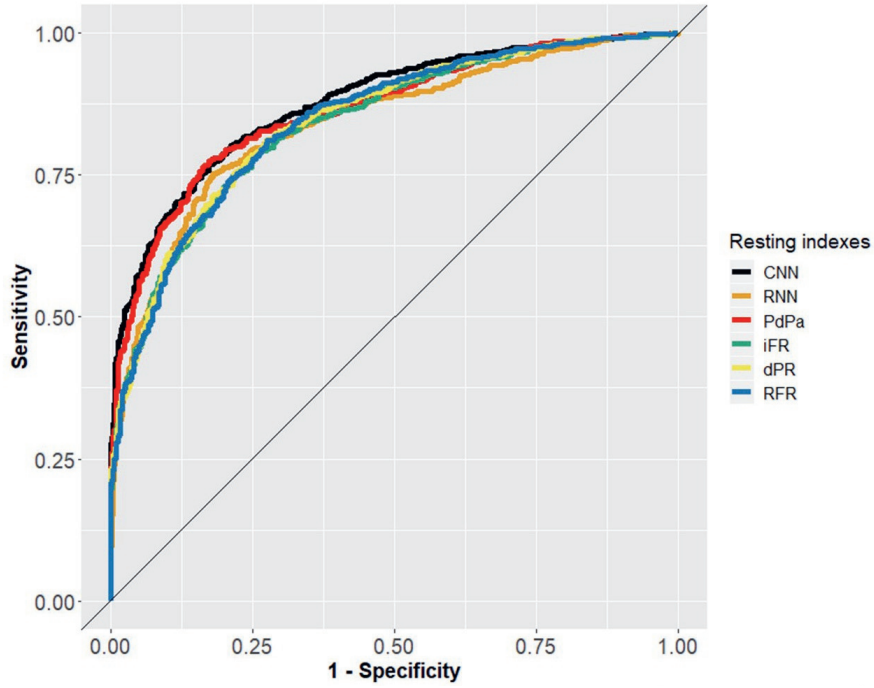
**diagnostic accuracy of both neural networks not statistically different against most accurate NHPR. Abbreviations: Acc – accuracy; CNN–convolutional neural network; dPR–Diastolic pressure ratio; FFR–fractional flow reserve; iFR–instantaneous wave free ratio; Pd/Pa – ratio of distal coronary pressure to aortic pressure; NPV – negative predictive value; PPV–positive predictive value, RFR–relative flow reserve; RNN–recurrent neural network; Sens – sensitivity; Spec – specificity;*

recurrent neural network (RNN) against FFR using 5-fold cross-validation were 77.6±2.3%, 73.8±6.1%, and 81.5%±6.4%, 82.6±3.5%, 73.4±3.8%, respectively.

The diagnostic accuracy of NHPR were 79.7% for Pd/Pa, 76.1% for iFR, 76.4% for dPR, and 76.3% for RFR. There was no statistically significant difference between the diagnostic accuracy of both neural networks and the NHPR with the highest accuracy (Pd/Pa), p>0.40 for both comparisons. Optimal cut-off values for existing NHPR to predict binary FFR≤0.80 in our large cohort were near-identical to published cut-off values.

As detailed in Figure 3, the area under the ROC curve of our CNN and RNN were 0.88 and 0.84, respectively. Compared to other NHPR the AUC of the CNN was larger compared to 0.86 for Pd/Pa, 0.84 for iFR, 0.85 for dPR, and 0.85 for RFR (DeLong p<0.01 vs. other NHPR), although neither analysis was pre-specified or adjusted for multiple comparisons.

Figure 3. Receiver-operating characteristic curve (ROC) of several indexes to predict binary FFR ≤0.80



Abbreviations: AUC–Area under the receiver-operating characteristic curve; CI – Confidence Interval; CNN – convolutional neural network; dPR–Diastolic pressure ratio; iFR–instantaneous wave free ratio; FFR–fractional flow reserve; Pd/Pa–resting distal coronary pressure to aortic pressure ratio; RFR–relative flow reserve; RNN – recurrent neural network

Sensitivity analyses using 16 variations in CNN and RNN architectures did not result in an increase in the diagnostic performance against binary FFR≤0.80 (table 1). In addition, a pressure-recording-level analysis (multiple pressure recordings per lesions allowed) or patient-level analysis (randomly selecting 1 coronary lesion per patient in case of multiple lesions per patient; ~4% of patients) instead of a lesion-level analysis did not alter the diagnostic performance.

DISCUSSION

The ARTIST study is the first to assess deep learning for the prediction of fractional flow reserve (FFR) from resting coronary pressure curves. We found that deep learning-based algorithms did not clinically relevant improve the diagnostic accuracy of predicting FFR compared to other non-hyperemic indexes. Our findings eliminate a larger class of possible hidden information than has been examined before. Therefore, inducing maximal hyperemia remains a prerequisite for accurate FFR assessment.

The need for FFR (prediction) in the era of non-hyperemic pressure ratios (NHPR)
Recently, two large randomized clinical trials have demonstrated that iFR-guided PCI (one of several NHPR) is non-inferior to FFR-guided PCI in a low-risk population at maximal two-year follow-up, when including ~80% of concordant FFR/iFR cases.[9,18,19] Although NHPRs are a welcome addition to the interventional armamentarium to assess coronary physiology in such low-risk populations, it is still desirable to measure FFR itself (or predict it accurately) for several reasons.

First, only FFR has been tested against a true gold standard of myocardial ischemia.[1] Second, FFR is the only index that has been proven superior to both medical therapy and angio-guided PCI in randomized clinical trials with follow-up extending to 15 years.[2-4]

Third, FFR has been clinically validated in many subgroups, including non-culprit lesions of acute coronary syndromes, left main disease, pre-coronary bypass surgery, and bifurcations lesions.[2-4,20-22] Finally, the clinical benefit and safety of FFR-guided PCI has been tested not only in randomized trials, but also in large real-world observational studies.[23-24] For example, in the randomized DEFINE-FLAIR study on iFR, only about half of PCIs were guided by physiology, related to the protocol-based requirement to confine physiology assessment to lesions with 40-70% diameter stenosis.[9] How NHPRs perform in a real world setting, including frequently occurring 70-90% lesions, remains an important yet unanswered clinical question.

Table 1. Diagnostic performance of 16 deep learning-based architectures against binary FFR ≤0.80.

	Neural network	Hidden conv. layers	Hidden RNN layers	Filter size	ReLU	GRU or LSTM	HR	Acc*	Sens*	Spec*	PPV*	NPV*
1	CNN	1	N/A	60	No	N/A	No	0.79 ±0.03	0.75 ±0.08	0.83 ±0.06	0.83 ±0.05	0.75 ±0.07
2	CNN	1	N/A	60	No	N/A	Yes	0.79 ±0.02	0.80 ±0.03	0.78 ±0.07	0.80 ±0.05	0.77 ±0.03
3	CNN	1	N/A	60	Yes	N/A	No	0.76 ±0.02	0.75 ±0.06	0.78 ±0.04	0.79 ±0.03	0.73 ±0.03
4	CNN	1	N/A	60	Yes	N/A	Yes	0.75 ±0.05	0.75 ±0.06	0.75 ±0.09	0.78 ±0.08	0.73 ±0.03
5	CNN	2	N/A	30	No	N/A	No	0.79 ±0.02	0.80 ±0.04	0.78 ±0.07	0.81 ±0.05	0.77 ±0.04
6	CNN	2	N/A	30	No	N/A	Yes	0.80 ±0.02	0.82 ±0.03	0.77 ±0.06	0.81 ±0.04	0.79 ±0.02
7	CNN	2	N/A	30	Yes	N/A	No	0.71 ±0.09	0.65 ±0.18	0.78 ±0.11	0.76 ±0.12	0.67 ±0.07
8	CNN	2	N/A	30	Yes	N/A	Yes	0.71 ±0.09	0.74 ±0.08	0.66 ±0.12	0.72 ±0.12	0.69 ±0.07
9	RNN	N/A	1	N/A	N/A	GRU	No	0.78 ±0.02	0.74 ±0.06	0.81 ±0.06	0.83 ±0.04	0.73 ±0.04
10	RNN	N/A	1	N/A	N/A	GRU	Yes	0.74 ±0.04	0.70 ±0.09	0.79 ±0.04	0.79 ±0.04	0.70 ±0.07
11	RNN	N/A	1	N/A	N/A	LSTM	No	0.77 ±0.02	0.74 ±0.05	0.80 ±0.06	0.81 ±0.03	0.73 ±0.03
12	RNN	N/A	1	N/A	N/A	LSTM	Yes	0.74 ±0.04	0.71 ±0.10	0.79 ±0.06	0.79 ±0.05	0.71 ±0.08
13	RNN	N/A	2	N/A	N/A	GRU	No	0.75 ±0.03	0.75 ±0.06	0.76 ±0.07	0.82 ±0.10	0.73 ±0.04
14	RNN	N/A	2	N/A	N/A	GRU	Yes	0.77 ±0.01	0.81 ±0.02	0.72 ±0.02	0.77 ±0.02	0.77 ±0.02
15	RNN	N/A	2	N/A	N/A	LSTM	No	0.76 ±0.03	0.76 ±0.06	0.75 ±0.06	0.78 ±0.05	0.74 ±0.05
16	RNN	N/A	2	N/A	N/A	LSTM	Yes	0.77 ±0.01	0.81 ±0.02	0.73 ±0.01	0.77 ±0.02	0.77 ±0.03

**Using 5-fold cross-validation. Abbreviations: ±–standard deviation; Acc – accuracy; CNN – convolutional neural network; conv – convolutional; GRU–gated recurrent unit; LSMT–long short-term memory; HR – heart rate; N/A – not applicable; NPV – negative predictive value; PPV – positive predictive value; RNN – recurrent neural network; ReLU–rectified linear unit; Sens – sensitivity; Spec – specificity*

The quest for hidden information in resting coronary pressure curves

Over the past decade, there has been increasing interest in predicting FFR from resting coronary pressure curves, aiming at simplifying the procedure and preventing the need for adenosine.[7-9] Since this time, the results of multiple studies in this field can be summarized by two simple conclusions. First, all proposed NHPRs are numerically equivalent. Second, the diagnostic accuracy of NHPRs to predict binary FFR ≤0.80 is around 80% regardless of the timing within the cardiac cycle.[7-9]

In order to create a non-hyperemic index that is able to predict FFR more accurately, the ARTIST study was designed to overcome limitations of previous studies. Table 2 summarizes the potential advantages of our design compared to pivotal studies in this field.

First, ARTIST was structured to create a new index with the highest possible agreement with FFR, in contrast to several previous studies that only validated an existing index.

Second, almost all previous studies focused only on the ratio of distal to aortic pressure during a specific period of the cardiac cycle and neglected *qualitative* information. For example, it is known that the distal coronary pressure curve changes, not only numerically, but also in morphology with increasing stenosis severity.[10] Only two previous studies incorporated pre-specified qualitative features, such as the presence of the dicrotic notch and diastolic dipping[10] or wave-intensity analysis,[25] without significant success. Although some of these qualitative features were chosen on a physiological basis, such assumptions neglect the existence of possible additional information outside of the underlying theory.

Third, to our best knowledge this study was the first to use deep learning to predict FFR from resting pressure curves. Over the past years, deep neural networks have shown impressive results in several areas of medicine.[11,12] A deep neural network uses multiple layers to abstract features on different levels of the data.[12] As such, even non-prespecified features have the potential to be identified. Therefore, we hypothesized that deep learning would be capable of identifying complex interactions among features contained in the resting pressure curve that might be pivotal to more accurately predict FFR.

Finally, ARTIST was among the largest cohorts to date studying the prediction of FFR from resting coronary pressure curves.

Despite these numerous advantages in study design, including the use of deep-learning, the current study reached an accuracy to predict FFR of approximately 80%, in accordance with previously reported NHPRs.

Table 2. Comparison of the potential advantages in design of the ARTIST study with pivotal studies on the prediction of FFR from resting coronary pressure curves

Study	Nr of patients	Nr of lesions	Deep Learning	Designed to create new index	Focus beyond distal to aortic pressure during a specific period of the cardiac cycle	Potential to identify non-prespecified qualitative features	Resting index	Accuracy against binary FFR ≤0.80 (%)
ARTIST	1666	1718	+	+	+	+	Deep-learning derived algorithm	80%
ADVISE	131	157	-	+	-	-	iFR	88%
Johnson et al. JACC 2013	1129	1129	-	-	-	-	Pd/Pa iFR	NA
VERIFY[14]	706	706	-	-	-	-	iFR	60%
VERIFY 2[15]	197	257	-	-	-	-	Pd/Pa iFR	80% 79%
CONTRAST[13]	763	763	-	-	-	-	Pd/Pa iFR	79% 80%
RESOLVE	1768	1593	-	-	-	-	Pd/Pa iFR	82% 80%
Van 't Veer et al.[7]	197	197	-	+	-	-	Several NHPR	76-77%
Matsumura et al.[10]	592	592	-	+	+	-	Qualitative parameters in addition to Pd/Pa and iFR	NA
Svanerud et al. Eurointervention 2018	1137	1305	-	+	-	-	RFR	81%
Johnson et al. EHJ 2019	833	893	-	+	-	-	dPR	NA

Abbreviations: iFR–instantaneous wave free ratio; dPR–Diastolic pressure ratio FFR–fractional flow reserve; NHPR–non-hyperaemic pressure ratio; Pd/Pa–resting distal coronary pressure to aortic pressure ratio; RFR–relative flow reserve

Given the small changes in AUC among NHPR largely considered to be clinically equivalent (largest delta 0.02, with baseline Pd/Pa actually having the largest AUC) and lack of prespecification between CNN and RNN architectures (delta 0.04 between the two methods), we feel that the statistically larger AUC for CNN versus other NHPR (deltas 0.02 to 0.04) should not be overinterpreted as providing a meaningful clinical advantage.

Why is it not possible to accurately predict FFR from resting pressure curves?

Several factors might explain why FFR cannot accurately be predicted from resting coronary pressure curves. The hyperemic trans-stenotic pressure gradient is dependent on several unpredictable factors, including hyperemic coronary flow and a complex stenosis-specific pressure-flow relationships.[26-27] Beyond epicardial disease, hyperemic coronary flow is mostly dependent on the amount of myocardial mass and microvascular function, which appear to be unpredictable from resting coronary pressure curves. The pressure-flow relationship between the trans-stenotic pressure gradient (ΔP) and average whole-cycle flow is a curvilinear function: $\Delta P = f \cdot Q + s \cdot Q^2$.[26,27] This relationship is dependent on both friction (f) and separation (s) pressure loss. Both coefficients depend on vessel size, stenosis geometry, and blood rheology, [26,27] which apparently do not affect resting coronary pressure morphology in a way that can be picked up by a neural network. Future studies might increase the diagnostic accuracy of deep-learning based algorithms when incorporating additional information like stenosis geometry or myocardial mass. In addition, if one could measure the pressure gradient at different flow rates, then one could assess the corresponding pressure-flow relationship. Since the resting pressure gradient is obtained only at single flow rate, predictions about hyperemic conditions cannot be made with acceptable precision. Finally, it would be of interest for future deep-learning models to incorporate clinical outcome. These models might be able to find hidden information in (non-)hyperemic curves useful to predict future events or symptoms.

We observed a lower accuracy in CNNs including a rectified linear unit (ReLU). One of the potential advantages of using a ReLU is that it decreases overfitting in complex datasets, although some information is lost in the process. It might be possible that useful information to predict FFR was lost due to the ReLU, although this might also be related to a play of chance.

Limitations

This study has several limitations. First, this was a post-hoc analysis. Second, although our cohort is the largest reported to predict FFR from resting coronary pressure curves, deep learning usually requires huge amounts of data to function optimally. Nevertheless, given the fact that our results do not provide a hint for a possible improvement in accuracy, we believe that a much bigger cohort would not change the conclusion of this paper relevantly.

Third, although we already tested multiple deep neural architectures, it cannot be excluded that other architectures would yield a different result. Yet, given the near-identical accuracy between the architectures used in our study, we do not expect that a different architecture would increase the predictable value in a clinically meaningful manner.

Conclusions

Compared to standard derivation of resting pressure ratios, we did not find a significant improvement in FFR prediction when resting data is analysed using artificial intelligence approaches. Our findings strongly suggest that a larger class of hidden information within resting pressure traces is not the main cause for the known disagreement between resting indices and FFR. Therefore, if clinicians want to use FFR for clinical decision making, hyperaemia induction should remain the standard practice.

Funding

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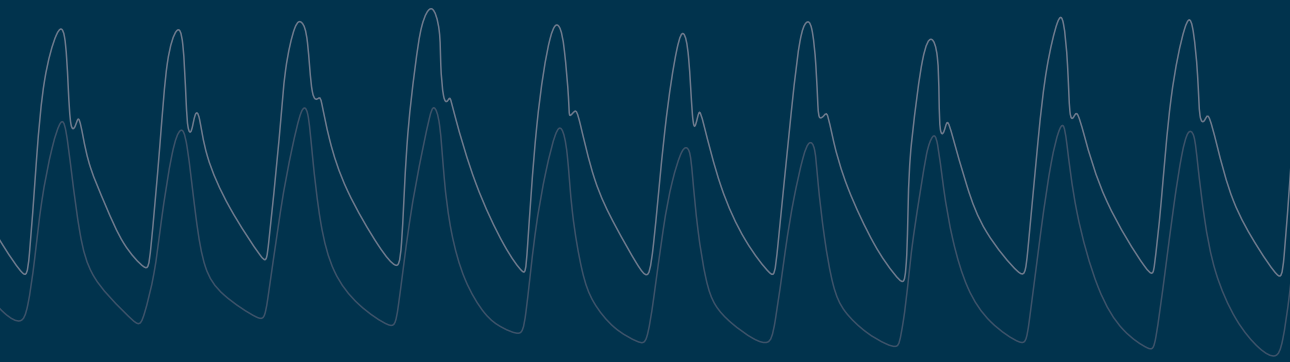

CHAPTER 11

Sex Differences in Adenosine-Free Coronary Pressure Indexes. A CONTRAST Substudy

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ABSTRACT

Objectives

The goal of this study was to investigate sex differences in adenosine-free coronary pressure indexes.

Background

Several adenosine-free coronary pressure wire indexes have been proposed to assess the functional significance of coronary artery lesions; however, there is a theoretical concern that sex differences may affect diagnostic performance because of differences in resting flow and distal myocardial mass.

Methods

In this CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) substudy, contrast fractional flow reserve (cFFR), obtained during contrast-induced submaximal hyperemia, the instantaneous wave-free ratio (iFR), and distal/proximal coronary pressure ratio (Pd/Pa) were compared with fractional flow reserve (FFR) in 547 men and 216 women. Using FFR ≤0.8 as a reference, the diagnostic performance of each index was compared.

Results

Men and women had similar diameter stenosis (p = 0.78), but women were less likely to have FFR ≤0.80 than men (42.5% vs. 51.5%, p = 0.04). Sensitivity was similar among cFFR, iFR, and Pd/Pa when comparing women and men, respectively (cFFR, 77.5% vs. 75.3%; p = 0.69; iFR, 84.9% vs. 79.4%; p = 0.30; Pd/Pa, 78.8% vs. 77.3%; p = 0.78). cFFR was more specific than iFR or Pd/Pa regardless of sex (cFFR, 94.3% vs. 95.8%; p = 0.56; iFR, 75.6% vs. 80.1%; p = 0.38; Pd/Pa, 80.6% vs. 78.7%; p = 0.69). By receiver-operating characteristic curve analysis, cFFR provided better diagnostic accuracy than resting indexes irrespective of sex (p ≤ 0.0001).

Conclusions

Despite the theoretical concern, the diagnostic sensitivity and specificity of cFFR, iFR, and Pd/Pa did not differ between the sexes. Irrespective of sex, cFFR provides the best diagnostic performance.

INTRODUCTION

Physiological assessment of coronary stenosis by fractional flow reserve (FFR) has emerged as the gold standard to facilitate decisions regarding coronary revascularization (1–4). Studies of sex differences in FFR measurements have shown that in comparison with men, angiographic lesions of similar visual severity are less likely to be ischemia producing in women (5–7). In light of multiple prior studies that have found women undergoing percutaneous coronary intervention to have worse short- and long-term outcomes compared with men (8–10), an FFR-guided approach is particularly appealing in women to guide appropriate revascularization. FFR measurement requires the induction of maximal hyperemia, which adds a small amount of time and cost to the procedure (11–13). Use of resting pressure indexes, which avoid the need for hyperemia, has been proposed, but studies have found these indexes to be less accurate compared with FFR (9,12,14–18). Recently, the CONTRAST (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) study investigated whether contrast medium (contrast FFR [cFFR]), which is ubiquitous in the catheterization laboratory and creates partial hyperemia, could provide an easy alternative and inexpensive tool for assessing FFR. The study found that cFFR was diagnostically superior to resting measurements, specifically resting distal pressure/aortic pressure (Pd/Pa) and the instantaneous wave-free ratio (iFR), in predicting FFR (19).

The reason for higher FFR values observed in women at maximum hyperemia is not entirely clear, but studies speculate this difference may be due to the smaller myocardial mass, vessel size, and territory associated with women (5,20). Other studies have cited microvascular dysfunction and impaired coronary autoregulation in women as a possible explanation for the greater anatomic-functional mismatch (5,21–26). There is a theoretical concern that microvascular dysfunction and differences in coronary physiology between men and women may also affect the diagnostic accuracy of adenosine-free indexes. Given this uncertainty, the primary goal of this study was to determine: 1) if the accuracy of adenosine-free indexes (cFFR, Pd/Pa, and iFR) varies by sex; and 2) if cFFR is diagnostically superior to resting pressure indexes regardless of sex.

METHODS

We explored the impact of sex in a post hoc analysis of the CONTRAST study (NCT02184117). The detailed study protocol and primary results have been published previously (19). In brief, the CONTRAST study is a multicenter, prospective, investigator-initiated observational study evaluating the diagnostic performance of cFFR, Pd/Pa, and iFR to predict FFR.

Study population

Subjects were recruited from 12 centers between June 2014 and April 2015. This study was approved by an institutional review committee from each participating site, and informed consent was obtained from all participants. Subjects underwent invasive physiological assessment of coronary artery lesions for standard clinical indications with comprehensive coronary physiological assessment, including both adenosine free indexes and FFR. Subjects were excluded if they had previous coronary artery bypass surgery, an extremely tortuous or calcified coronary artery, known severe left ventricular hypertrophy, left ventricular ejection fraction of <30%, inability to receive adenosine, renal insufficiency such that additional contrast would pose unwarranted risk, or recent ST-segment elevation myocardial infarction. Culprit lesions for either ST-segment elevation myocardial infarction or non–ST-segment elevation myocardial infarction were excluded. Standard demographic, clinical, and catheterization parameters were collected for each subject.

Study design

The physiology protocol and core laboratory analysis used for the study have been previously described (19). Briefly, an initial period of at least 1 min provided a stable assessment of resting physiology without further contrast injection. This formed the basis of resting Pd/Pa and iFR determinations. Next, a manual or injector-based intracoronary (IC) bolus of contrast medium was given as per local practice for diagnostic angiography.

After pressure recovery, this was repeated. Following the return of baseline conditions, 100 to 200 mg of IC adenosine was administered as per local practice and repeated after pressure recovery. Next, intravenous adenosine was administered at a standard rate of 140 mg/kg/min for at least 2 min after pressure recovery through a central or antecubital vein. After stopping the intravenous infusion and waiting for the return of baseline conditions, another intravenous adenosine infusion at the same rate was performed.

Both IC and intravenous adenosine were allowed for the calculation of FFR in order to allow sites to choose their preferred technique. Sites were encouraged to use both methods and to repeat each, meaning that a total of 4 possible FFR values could be obtained. The recorded FFR value was computed by the following hierarchy: the mean of the 2 intravenous adenosine values, a single intravenous value, the mean of 2 IC values, or a single IC value.

All pressure tracings were sent to the Cardiovascular Research Foundation physiology core laboratory for standardized and centralized review. The core laboratory carried out its post hoc analysis without knowledge of the locally determined Pd/Pa value, IC substance (contrast medium or adenosine), enrolling site, or subject and lesion characteristics.

FFR was measured as the mean distal coronary pressure divided by aortic pressure during maximal hyperemia. cFFR was measured during submaximal hyperemia with IC injection of contrast, and Pd/Pa was measured at rest. iFR was defined as the ratio of distal coronary pressure to aortic pressure during the wave-free period (approximately 75% of late diastole) at rest.

Statistical analysis

The primary endpoints were sensitivity and specificity using FFR ≤0.80 as the gold standard and compared using a McNemar test between metrics. Secondary endpoints included accuracy and the area under the receiver-operating characteristic (ROC) curve (compared using the DeLong method). All analyses were performed in men and women. On the basis of previous evidence (27), the binary thresholds were as follows: FFR ≤0.80, cFFR ≤0.83, Pd/Pa <0.92, and iFR <0.90. Continuous variables are presented as mean ±SD and were compared using independent-samples Student's t-tests. Categorical variables are expressed as counts and percentages and were compared using chi-square or Fisher exact tests as appropriate. Correlations between FFR and other adenosine-free indexes were tested using the Pearson correlation coefficient. ROC curve analysis was performed to examine diagnostic performance of adenosine-free indexes using FFR ≤0.80 as a reference standard; the DeLong method was used to compare curves (28). A p value of <0.05 was considered significant. All analyses were performed using SPSS version 21 (SPSS, Chicago, Illinois), except for ROC curve analysis and the DeLong method, which were performed using MedCalc software version 12.7.2 (MedCalc, Ostend, Belgium).

RESULTS

Baseline characteristics

Of 763 subjects, 216 (28.3%) were female. Compared with men, women were older (67.9 ± 9.1 years vs. 64.9 ± 9.8 years; p < 0.0001), had a higher body mass index (27.9 ± 5.7 kg/m2 vs. 27.1 ± 4.2 kg/m2; p = 0.028), and more frequently had diabetes (39.2% vs. 19.7%; p < 0.0001), hypertension (76.9% vs. 69.3%; p < 0.0001), and renal dysfunction (17.6% vs. 6.6%; p < 0.0001) (Table 1). Men were more likely to use tobacco (38.8% vs. 23.6%; p < 0.0001). The 2 groups were well balanced for clinical presentation (stable or unstable), coronary vessel studied, and volume of IC adenosine. However, type of contrast medium varied by sex, with a smaller volume of IC contrast used in women (7.4 ± 1.5 ml vs. 8.0 ± 1.8 ml; p < 0.0001).

Table 1. Baseline characteristics

	Male (n=547) (71.7%)	Female (n=216) (28.3%)	P value
Age (yrs)	64.9 ± 9.8	67.9 ± 9.1	<0.0001
Diabetes	19.7 (108)	32.9% (71)	<0.0001
BMI (kg/m2)	27.1 ± 4.2	27.9 ± 5.7	0.03
Smoking	38.3 (212)	23.6 (51)	<0.0001
Hypertension	69.3 (379)	76.9 (166)	0.04
Dyslipidemia	66.0 (361)	68.1 (147)	0.59
Family history of CAD	23.9 (131)	27.8 (60)	0.27
Renal dysfunction (eGFR <60ml/min)	6.6 (36)	17.6 (38)	<0.0001
Prior MI	27.6 (151)	21.8 (47)	0.10
Prior PCI	16.3 (89)	11.6 (25)	0.10
Peripheral vascular disease	4.8 (26)	3.7 (8)	0.53
Clinical presentation			0.78
Stable	79.2 (426)	79.6 (172)	
ACS	20.8 (121)	20.4 (44)	
Unstable angina	10.8 (59)	11.6 (25)	
NSTEMI	10.2 (56)	7.9 (17)	
STEMI	1.1 (6)	0.9 (2)	
Coronary vessel			0.22
LM	2.6 (14)	5.2 (11)	
LAD	59.6 (326)	62.0 (134)	
LCx	18.5 (101)	17.1 (37)	
RCA	19.4 (106)	15.7 (34)	
Contrast medium			<0.0001
Iobitridol	5.9 (32)	3.7 (8)	
Iodixanol	20.8 (114)	34.7 (75)	
Iohexol	13.5 (74)	14.8 (32)	
Iomeprol	30.9 (169)	26.9 (58)	
Iopamidol	0.9 (5)	1.4 (3)	
Iopromide	11.2 (61)	3.7 (8)	
Ioversol	8.4 (46)	10.2 (22)	
Ioxaglate	8.4 (46)	4.6 (10)	
Volume of IC contrast (ml)	8.0±1.8	7.4±1.5	<0.0001
5	2.6 (14)	1.4(3)	
6-7	38.2 (209)	53.3 (115)	
8-9	27.8 (152)	26.9 (58)	

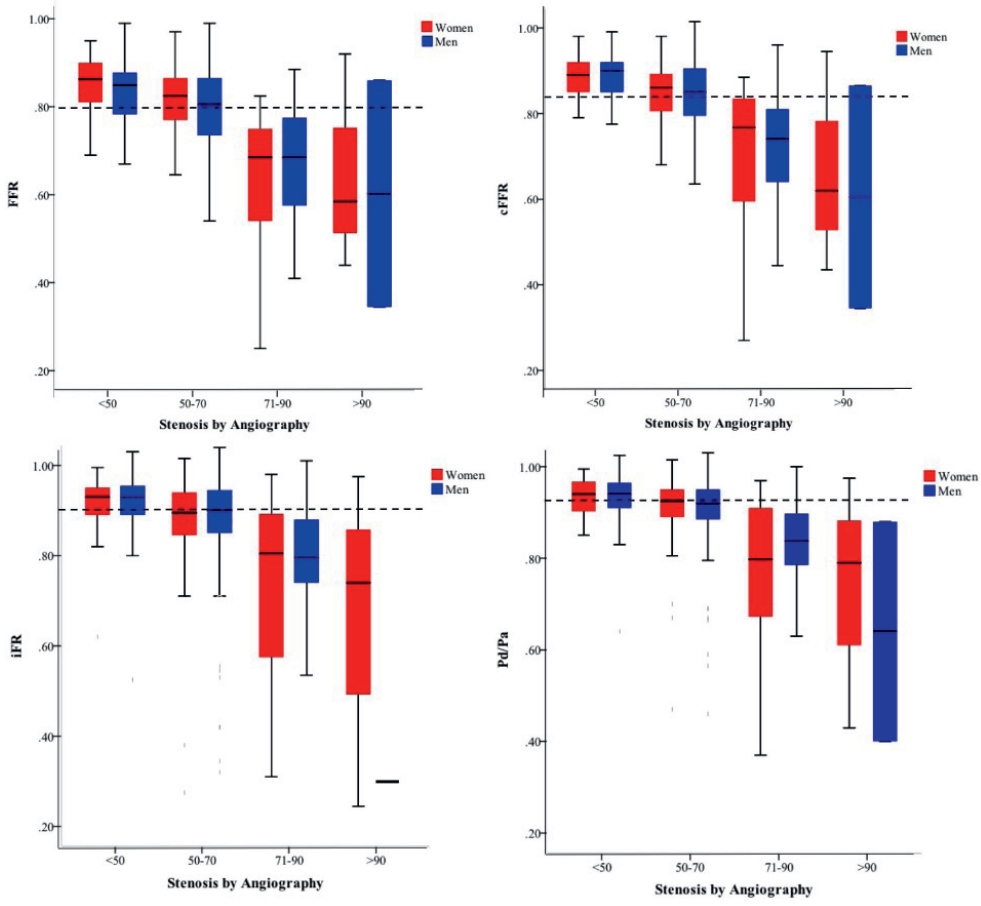
	Male (n=547) (71.7%)	Female (n=216) (28.3%)	P value
10	31.3 (171)	18.5 (40)	
12	0.2 (1)	0 (0)	
Dose of IC adenosine* (mg)	167.8 ±46.5	167.5 ± 46.3	0.95
<80	1.3 (7)	1.0 (2)	
80-90	5.9 (32)	3.3 (7)	
100-150	14.8 (81)	13.9 (30)	
160-200	20.5 (112)	32.9 (71)	
>200	10.8 (59)	10.2 (22)	
Visual stenosis			0.12
<50%	14.2 (77)	17.7 (38)	
51%-70%	74.3 (404)	73.5 (158)	
71%-90%	11.2 (61)	7.4 (16)	
>90%	0.4 (2)	1.4 (3)	

*Values are mean ± SD or % (n). *Only 549 of 763 patients received IC adenosine, while all other rows are based on 763 total.*
ACS = acute coronary syndrome(s); BMI = body mass index; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; IC = intracoronary; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

Visual diameter stenosis

Mean angiographic diameter stenosis (DS) by visual estimation was similar between women and men (57.0 ± 13.2% vs. 57.8 ±12.9%; p = 0.78). Lesions were further categorized into <50%, 51% to 70%, 71% to 90%, and >90% DS by visual estimation. The proportion of women and men presenting in each category was similar (p =0.12), with the largest proportion of both sexes with DS between 51% and 70%. Additionally, the proportion of functionally significant lesions using previously described binary thresholds (FFR ⩽0.80, cFFR ⩽0.83, iFR <0.90, and Pd/Pa <0.92) was similar in women and men for all lesions with 51% to 70% stenosis, 71% to 90% stenosis, and >90% stenosis (Figure 1) for each index. Using the rough criterion of DS >50%, rates of mismatch (DS >50% and FFR >0.80, cFFR >0.83, iFR ⩾0.90, or Pd/Pa ⩾0.92) were high regardless of sex, and mismatch was more frequent, though not statistically significant, in female patients for FFR (50.5% vs. 48.2%; p = 0.09), cFFR (44.0% vs. 39.3%; p =0.23), iFR (41.0% vs. 39.2%; p = 0.71), and Pd/Pa (44.4% vs. 39.8%; p = 0.10) (Figure 2).

Figure 1. Fractional flow reserve, contrast fractional flow reserve, instantaneous wave-free ratio, and resting distal pressure/aortic pressure values according to angiographic stenosis severity

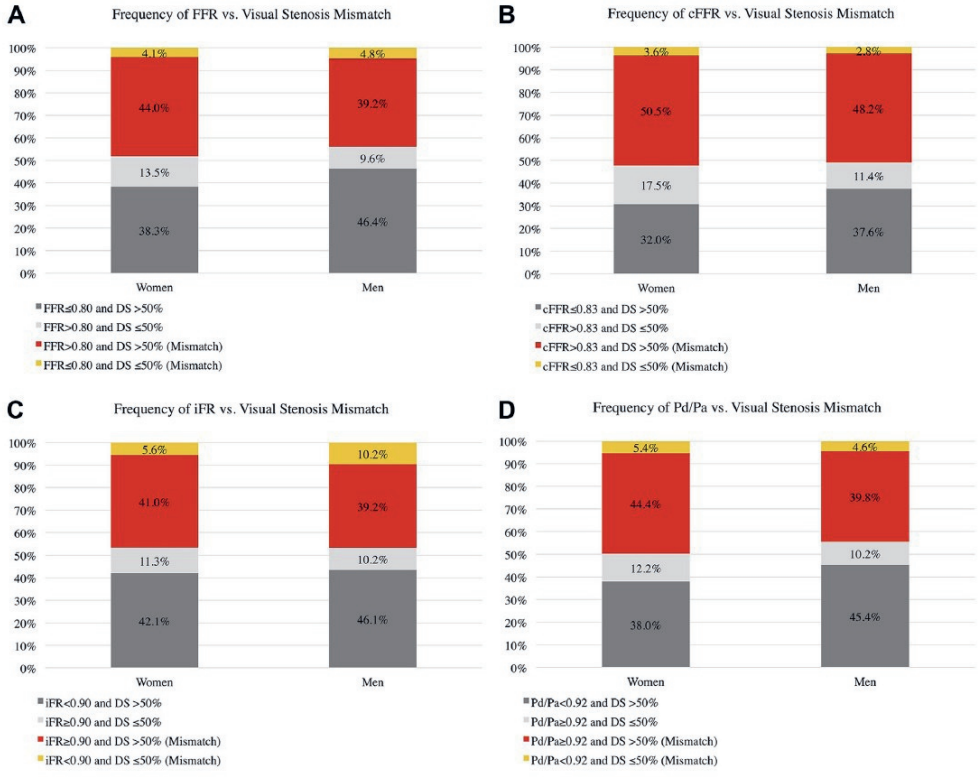


Boxplot of fractional flow reserve (FFR), contrast fractional flow reserve (cFFR), instantaneous wave-free ratio (iFR), and resting distal pressure/aortic pressure (Pd/Pa) values according to angiographic stenosis severity for women (red bars) and men (blue bars) displaying median values (solid line), upper and lower quartiles (box), and maximum and minimum values excluding outliers (whiskers). Dotted lines indicate the binary threshold for each index.

Comparison of diagnostic performance

FFR values were similar in women and men (0.80 ± 0.11 vs. 0.78 ± 0.12; p = 0.12), but women were less likely to have FFR ≤0.8 than men (42.5% vs. 51.5%; p = 0.04). There was no sex difference in the rate of binary threshold achieved by cFFR (≤0.83; 35.6% vs. 40.4%; p = 0.25), iFR (<0.90; 49.7% vs. 50.4%; p = 0.87), or Pd/Pa (<0.92; 43.3% vs. 49.8%; p = 0.12) (Table 2). Comparisons of diagnostic sensitivity, specificity, and accuracy between men and women using FFR as the gold standard are shown in Figure 3. Overall, sensitivity

Figure 2. Frequencies of mismatch in fractional flow reserve, contrast fractional flow reserve, instantaneous wave-free ratio, and resting distal pressure/aortic pressure versus visual stenosis



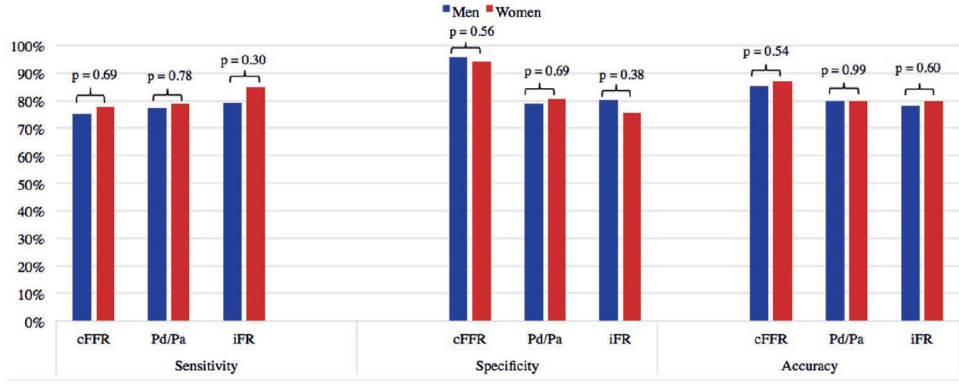
Frequency of discordance between angiographic diameter stenosis (DS) and (A) fractional flow reserve (FFR), (B) contrast fractional flow reserve (cFFR), (C) instantaneous wave-free ratio (iFR), and (D) resting distal pressure/aortic pressure (Pd/Pa) for women and men.

Table 2. Measures of adenosine-free coronary perfusion indexes in men and women

Mean FFR	0.78 ± 0.12	0.80 ± 0.11	0.12
Mean cFFR	0.83 ± 0.11	0.84 ± 0.11	0.14
Mean iFR	0.88 ± 0.11	0.87 ± 0.12	0.54
Mean Pd/Pa	0.90 ± 0.08	0.90 ± 0.10	0.44
FFR <0.80	51.5 (256)	42.5 (82)	0.04
cFFR ⩽0.83	40.4 (203)	35.6 (69)	0.25
iFR <0.90	50.4 (227)	49.7 (88)	0.87
Pd/Pa <0.92	49.8 (263)	43.4 (89)	0.12

Values are mean ± SD or % (n).
cFFR = contrast fractional flow reserve; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; Pd/Pa = resting distal pressure/aortic pressure.

Figure 3 Diagnostic performance for adenosine-free coronary pressure indexes



Diagnostic performance of contrast fractional flow reserve (cFFR), instantaneous wave-free ratio (iFR), and resting distal pressure/aortic pressure (Pd/Pa). Accuracy, specificity, and sensitivity of each metric are reported for women (red bars) and men (blue bars), demonstrating absence of heterogeneity in these subgroups.

was similar among the 3 metrics when comparing women and men, respectively (cFFR, 77.5% vs. 75.3%; p = 0.69; iFR, 84.9% vs. 79.4%; p = 0.30; Pd/Pa, 78.8% vs. 77.3%; p = 0.78), but cFFR had greater specificity compared with iFR or Pd/Pa and there was no significant interaction with sex (cFFR, 94.3% vs. 95.8%; p = 0.56; iFR, 75.6% vs. 80.1%; p = 0.38; Pd/Pa, 80.6% vs. 78.7%; p = 0.69). As previously reported, a binary threshold of cFFR ≤0.83 produced accuracy of 85.8%, superior to both Pd/Pa (78.5%) and iFR (79.3%) (McNemar p < 0.001 vs. both resting metrics) when compared with FFR ≤0.8. In this substudy, there was no significant interaction between sex and accuracy. Accuracy in subgroups of women and men was similar for cFFR (87.1% vs. 85.2%, respectively; p = 0.76), iFR (79.8% vs. 78.0%, respectively; p = 0.60), and Pd/Pa (79.8% vs. 79.7%, respectively; p = 0.992).

A small but nonsignificant improvement in accuracy was seen after adjusting for diabetes, with higher accuracy in both men and women with diabetes compared with subjects without diabetes (Table 3).

There was no significant difference in rates of mismatch between men and women. The false positive rate (FFR negative [>0.80], adenosine-free index positive) was lower for cFFR compared with Pd/Pa and iFR regardless of sex but numerically higher in women compared with men (cFFR, 5.7% vs. 4.2%; iFR, 24.4% vs. 19.9%; Pd/Pa, 21.3% vs. 19.4%). The false negative rate (FFR positive [≤0.80], adenosine-free index negative) for all 3 metrics was numerically lower in women than men (cFFR, 22.5% vs. 24.7%; iFR, 15.1% vs. 20.6%; Pd/Pa, 21.3% vs. 22.7%). The area under the ROC curve was largest for cFFR

Table 3. Accuracy of adenosine-free indices after adjustment for diabetes

Index	Women	Men	P value
iFR	78.6	77.7	0.85
Pd/Pa	79.2	77.1	0.66
cFFR	86.3	85.1	0.71
DM			
iFR	85.2	81.8	0.49
Pd/Pa	81.2	80.6	0.93
cFFR	88.7	86.0	0.64

Diagnostic accuracy of adenosine-free indices compared to FFR in men and women after adjustment for diabetes. DM = diabetes mellitus; other abbreviations as in Table 2.

compared with Pd/Pa and iFR, which were equivalent in both women (0.966 for cFFR, 0.890 for Pd/Pa, and 0.872 for iFR; DeLong $p < 0.001$ for cFFR vs. iFR, $p < 0.0001$ for cFFR vs. Pd/Pa) (Figure 2) and men (0.931 for cFFR, 0.882 for Pd/Pa, and 0.882 for iFR; DeLong $p < 0.0001$ for cFFR vs. iFR, $p < 0.0001$ for cFFR vs. Pd/Pa) (Figure 4).

Correlation between FFR and adenosine-free indexes

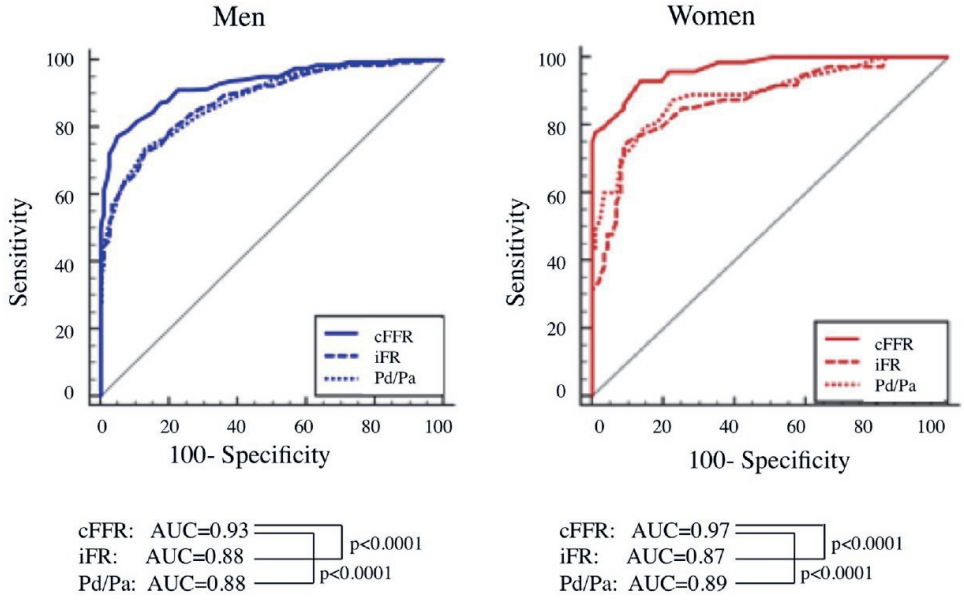
Compared with Pd/Pa and iFR, the correlation of cFFR with FFR was superior in both women ($r = 0.94$ and intraclass correlation coefficient [ICC] = 0.94 for cFFR, $r = 0.80$ and ICC = 0.79 for iFR, and $r = 0.87$ and ICC = 0.86 for Pd/Pa) and men ($r = 0.92$ and ICC = 0.92 for cFFR, $r = 0.82$ and ICC = 0.82 for iFR, and $r = 0.85$ and ICC = 0.80 for Pd/Pa) (Figure 5).

DISCUSSION

The main finding of this study is that adenosine-free pressure wire–derived indexes of stenosis severity are similarly sensitive and specific in men and women when using FFR as the gold standard. In addition, cFFR provides superior diagnostic performance compared with resting metrics (iFR and Pd/Pa) irrespective of sex. Our study is consistent with prior studies, which found that women are less likely to have functionally significant stenosis with FFR ≤0.80 than men (5–7). In addition, rates of mismatch between visual versus functional stenosis were higher, though not significantly so, in women than men. Kang et al. (5) similarly found that both angiographic and intravascular ultrasound criteria were more likely to overestimate the true functional significance of stenosis in female patients.

Prior studies have speculated that the higher FFR values at maximum hyperemia in women may be due to the smaller myocardial mass, vessel size, and territory associated with women (5,20). Other studies have cited microvascular dysfunction and impaired coronary

Figure 4. Comparison of receiver-operating characteristic curves among contrast fractional flow reserve, instantaneous wave-free ratio, and resting distal pressure/aortic pressure

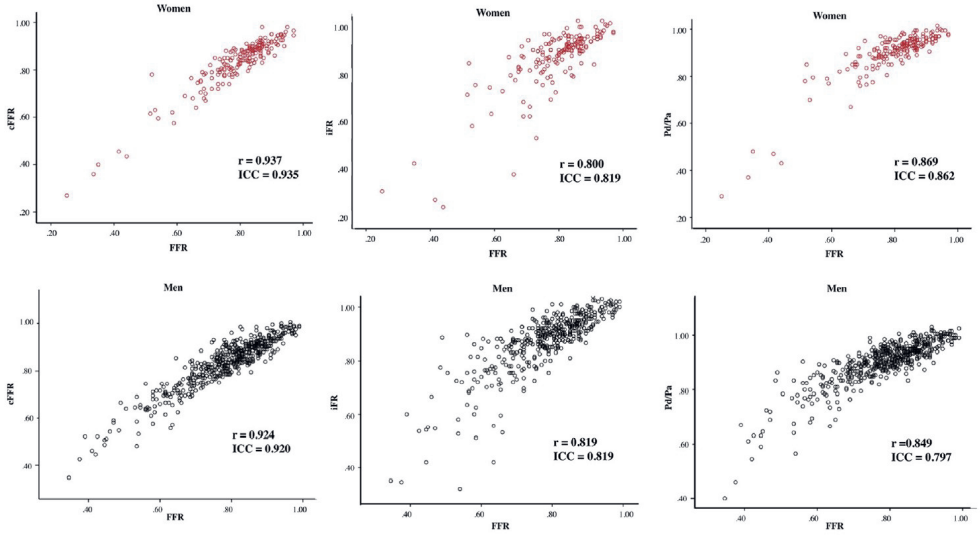


Diagnostic performance expressed by the area under the receiver-operating characteristic curve for each metric in men (blue) and women (red). AUC = area under the curve; cFFR = contrast fractional flow reserve; iFR = instantaneous wave-free ratio; Pd/Pa = resting distal pressure/aortic pressure.

autoregulation in women as a possible explanation for the greater anatomic-functional mismatch (5,21–25). Indeed, multiple studies have found that women with suspected coronary artery disease have lower coronary flow reserve, a frequently used marker for microvascular dysfunction, than men (22,24,29). More recently, a study by Taqueti et al. (30) found that impaired coronary flow reserve is strongly associated with excess cardiovascular risk in women.

However, studies have found that the lower CFR observed in women is likely a result of higher resting coronary flow rather than impaired augmentation of hyperemic flow (26). The increased resting flow in women also raises the possibility that iFR and resting Pd/Pa might correlate more closely with FFR in women compared with men. However, in our study, although the accuracy was numerically higher in women than men for iFR, this was not statistically significant. Furthermore, after adjusting for diabetes, a known risk factor for coronary microvascular dysfunction that has been associated with increased resting flow (31,32), accuracy of adenosine-free coronary indexes not surprisingly improved slightly for both men and women. In our study, iFR, Pd/Pa, and cFFR best correlated with

Figure 5 Scatterplots of each metric with fractional flow reserve



Scatterplots of each metric with fractional flow reserve (FFR) in men (black) and women (red). Resting physiology (resting distal pressure/aortic pressure [Pd/Pa] and instantaneous wave-free ratio [iFR]) displays a more scattered relationship with FFR than does modest hyperemia (contrast fractional flow reserve [cFFR]) in both men and women, as shown visually by the raw data and quantified by correlation coefficients. ICC = intraclass correlation coefficient; r = Pearson correlation coefficient.

FFR in women with diabetes and were least correlated in men without diabetes. These findings further support the theory that higher resting flow affects adenosine-free coronary perfusion indexes.

Still, further study is needed to better understand sex differences in resting and hyperemic coronary flow and the diagnostic accuracy of FFR in women. Although multiple studies have examined the utility of resting indexes to guide coronary revascularization, data on sex differences in resting coronary pressure indexes are limited. One study by Fineschi et al. (33) on 317 patients with intermediate coronary stenosis found no difference in resting Pd/Pa measurements for men and women but found that women had a significantly smaller Pd/Pa. A post hoc analysis from the 3V FFR-FRIENDS study showed women were more likely to present with high FFR but low iFR than men (34). Our study found no sex difference in resting Pd/Pa, iFR, or cFFR measurements. Furthermore, diagnostic accuracy using FFR as the gold standard was similar in men and women, although the accuracy of cFFR was superior to Pd/Pa and iFR irrespective of sex. The sensitivity of all adenosine-free indexes was low regardless of sex, suggesting that a negative value from an adenosine-free index does not necessarily rule out a significant coronary artery stenosis.

The specificity of cFFR was high in women and men, while the specificity of iFR and Pd/Pa was low for both sexes. Thus, positive cFFR strongly indicates a significant stenosis, but positive iFR or Pd/Pa may not.

When a dichotomous cutoff was applied, all adenosine-free indexes showed a slightly higher incidence of false negative values in men, which is consistent with prior studies (35). This could be explained by the higher likelihood of FFR's being significant in men compared with women because of a greater hyperemic response in the setting of healthy microcirculation in men.

The false positive rate was lower using cFFR compared with Pd/Pa and iFR in both women and men, likely because of the moderate vasodilatation induced by contrast medium. In concordance with the 3V FFR-FRIENDS substudy previously described (34), we found higher false positive rates in women than men across all indexes. Finally, among the adenosine-free indexes tested in this study, cFFR provides the best diagnostic performance by ROC curve analysis. iFR and Pd/Pa provide similar results regardless of sex. It is important to remember that given the wealth of outcomes data and randomized clinical trial data validating FFR in a vast array of clinical settings, it remains the gold standard for invasively identifying functionally significant epicardial coronary disease. Any small prolongation of procedural time, transient side effects, and increase in cost from adenosine are outweighed by the improved accuracy of FFR compared with adenosine-free indexes, particularly when compared with the expense and risk of placing a coronary pressure wire in a vessel. However, some operators prefer to avoid using adenosine. To that end, this study provides important data regarding the effect of sex on the accuracy of various adenosine free indexes.

Study limitations

First, this post hoc analysis of the CONTRAST study was not designed or powered to investigate the subgroup of women specifically, and our analysis should be considered hypothesis generating. Furthermore, long-term data are needed to determine outcomes in patients who undergo a cFFR-guided revascularization strategy. Second, data from quantitative coronary angiography, which has the benefit of objectivity and reproducibility, were not available for most lesions, and thus visual stenosis measures were based on subjective assessment by the operator. Additionally, the small difference in the amount of contrast used to obtain cFFR between the 2 lesion subsets may theoretically have affected the results, although a substudy from CONTRAST looking at this question found no practical effect (36).

Conclusions

Adenosine-free pressure wire–derived indexes of stenosis severity are similarly sensitive and specific in men and women. However, cFFR provides the best diagnostic performance among the adenosine-free indexes, regardless of sex. Thus, if an adenosine-free approach to assess the functional significance of a coronary stenosis is desired, use of cFFR should be considered.

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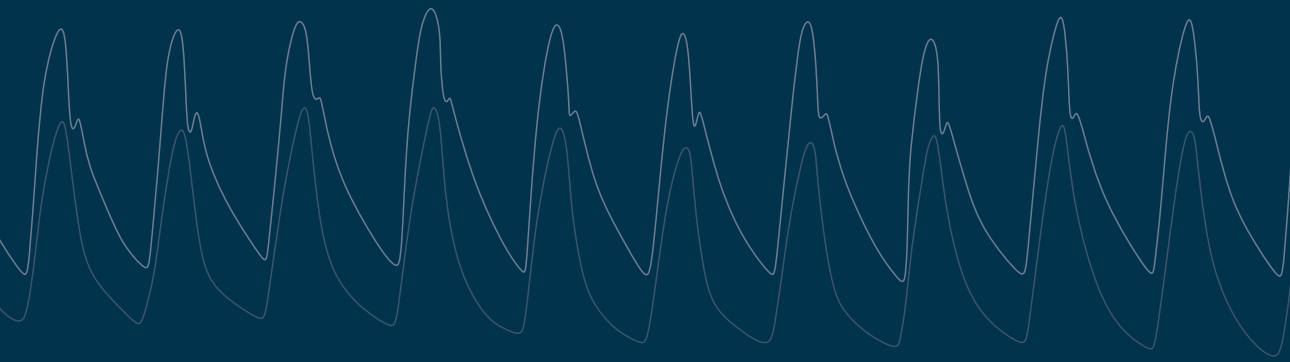

CHAPTER 12

What can Intracoronary Pressure Measurements Tell us About Flow Reserve? Pressure-Bounded Coronary Flow Reserve (CFR) and Example Application to the Randomized DEFER Trial

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ABSTRACT

Objective

We propose a novel technique called pressure-bounded coronary flow reserve (pb-CFR) and demonstrate its application to the randomized DEFER trial.

Background

Intracoronary flow reserve assessment remains underutilized relative to pressure measurements partly due to less robust tools.

Methods

While rest and hyperemic intracoronary pressure measurements cannot quantify CFR exactly, they do provide upper and lower bounds. We validated pb-CFR invasively against traditional CFR, then applied it to high fractional flow reserve (FFR≥0.75) lesions in DEFER randomized to revascularization or medical therapy.

Results

pb-CFR showed an 84.4% accuracy to predict invasive CFR<2 or CFR≥2 in 107 lesions. In its proof of concept application to DEFER lesions with FFR≥0.75, the 28 with pb-CFR<2 compared to 16 with pb-CFR≥2 had a non-significant trend towards less freedom from angina (61% versus 71% at 5 years, p=0.57) and a higher rate of major adverse cardiac events (MACE, 25% versus 15%, p=0.34). Lesions with FFR≥0.75 but pb-CFR<2 showed no difference in freedom from angina (61% versus 50%, p=0.54) or MACE (25% versus 38%, p=0.27) between the 28 randomized to medical therapy and the 16 randomized to revascularization.

Conclusions

pb-CFR offers a new method for studying FFR/CFR discordances using regular pressure wire measurement. As an example application, DEFER suggested that low pb-CFR with high FFR may be a risk marker for more angina and worse outcomes, but that this risk cannot be modified by revascularization.

INTRODUCTION

Both randomized [1-3] and observational [4] evidence has documented that coronary lesions with high fractional flow reserve (FFR) do well without intervention. For that reason, guidelines in the United States give a class III (harm, or "should not be performed") recommendation for revascularization of an epicardial stenosis with FFR>0.8 [5]. Similarly, European guidelines for stable patients also rate as class III ("is not recommended") revascularization of an intermediate lesion without low FFR [6].

However, some investigators have suggested that a high-risk subset exists within the larger, benign group of FFR negative stenoses. Specifically, lesions with a high FFR but a low coronary flow reserve (CFR) might have worse outcomes and more angina and could potentially benefit from percutaneous coronary intervention (PCI) [7,8]. Possible mechanisms include repressurization-induced changes in myocardial resistance after revascularization, thereby reversing microvascular dysfunction.

It would be ideal to test these hypotheses in a randomized trial. However, the invasive assessment of CFR has remained challenging for both Doppler and thermodilution techniques [9]. As a result, multicenter studies linking simultaneous FFR and CFR to outcomes remain limited compared to the much broader FFR literature. Given the ease and widespread availability of intracoronary pressure wires, it would be useful if we could leverage pressure measurements to study flow reserve.

Here we propose a novel yet physiologically grounded technique to bound CFR using only pressure measurements at baseline and hyperemia. As a proof of concept, we apply the technique to the randomized DEFER trial to study the influence of CFR and treatment on high FFR lesions.

MATERIALS AND METHODS

Pressure-bounded CFR (pb-CFR)

Fluid mechanics theory coupled with empiric animal and human measurements over the past 40 years support a relationship between the pressure loss over a vascular stenosis (ΔP) and the average whole-cycle flow (Q) [10-14]:

$$\Delta P = f \cdot Q + s \cdot Q^2$$

The coefficients f (representing friction or viscous pressure loss) and s (representing separation or expansion pressure loss) depend on vessel size, stenosis geometry, and blood rheology. After intracoronary nitrate administration, generally f and s do not depend on Q, although a small and typically neglected component of s depends on the shape of

the flow waveform [14] and stenosis interactions in branching systems can produce more complex relationships [15].

Prior work to predict CFR from pressure measurements assumed f=0 and assigned all pressure loss to separation forces [16]. However, empiric data showed that this assumption performed poorly in humans, implying that friction or viscous loss contributes significantly and unpredictably [17]. While deriving CFR exactly thus remains impossible when measuring pressure only, we can however place lower and upper bounds on its value. Figure 1 provides a visual explanation of the following derivation.

At one extreme, the pressure loss across a stenosis arises solely due to friction or viscous effects. In this extreme case,

$$\Delta P = f \cdot Q,$$

and the highest boundary for CFR equals

$$\text{upper CFR bound} = (\text{hyperemic } Q) / (\text{baseline } Q) = (\text{hyperemic } \Delta P) / (\text{baseline } \Delta P).$$

At the other extreme, the pressure loss across a stenosis arises solely due to separation or expansion effects. In this other extreme case,

$$\Delta P = s \cdot Q^2,$$

and, by analogy to the above equation, the lowest boundary for CFR equals

$$\text{lower CFR bound} = \sqrt{[(\text{hyperemic } \Delta P) / (\text{baseline } \Delta P)]}.$$

Therefore we propose "pressure-bounded" CFR (pb-CFR) using these natural limits:

$$\sqrt{[(\text{hyperemic } \Delta P) / (\text{baseline } \Delta P)]} \leq \text{CFR} \leq (\text{hyperemic } \Delta P) / (\text{baseline } \Delta P).$$

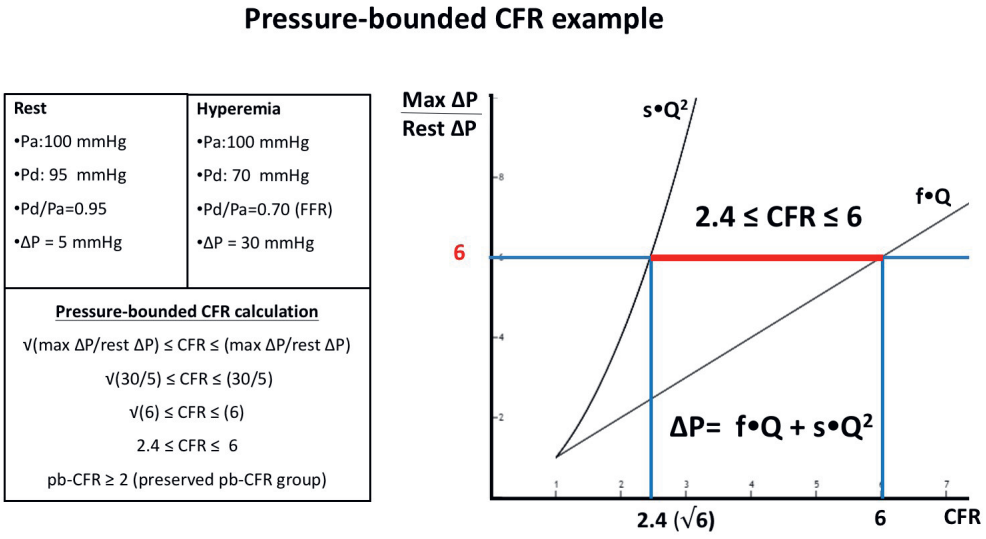
By assuming that the mean aortic pressure (Pa) remains constant during baseline and maximal hyperemia, the ratio of hyperemic and baseline pressure can be used even if the absolute gradient is unknown. Because ΔP = (Pa-Pd), where Pd represents the distal coronary pressure, ΔP/Pa = 1-Pd/Pa. Hence CFR will be bounded by

$$\sqrt{[(1 - \text{FFR}) / (1 - \text{baseline Pd/Pa})]} \leq \text{CFR} \leq (1 - \text{FFR}) / (1 - \text{baseline Pd/Pa}).$$

Overview of the DEFER trial

The design, methods, and primary endpoints of the DEFER trial have been previously described and the following summary follows existing publications closely [1-3]. DEFER was a multicenter, international, randomized controlled trial that enrolled from 12 European and 2 Asian hospitals between 1997 and 1998. Eligible subjects met 2 inclusion criteria: 1) referral for elective PCI of a single, angiographically significant, de novo stenosis of more than 50% diameter reduction (by visual assessment) in a native coronary artery with a reference diameter of more than 2.5mm; and 2) no conclusive evidence of reversible ischemia as documented by non-invasive testing within the last 2 months. Exclusion criteria

Figure 1. Visual explanation of pressure-bounded CFR (pb-CFR).



As detailed in the text, the relative increase in the pressure gradient between baseline and hyperemia provides lower and upper bounds on CFR. At the upper extreme, flow and pressure loss have a linear relationship. At the lower extreme, flow increases as the square root of pressure loss. In some cases (like the example here), pb-CFR can be definitively classified as preserved (pb-CFR›2).

were a total occlusion of the target artery, acute Q-wave infarction, or unstable angina documented by transient ST-segment abnormality. The study protocol was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all subjects before entering the study.

In order to prevent bias, subjects were randomized immediately after enrollment but before FFR measurement. If FFR was ›0.75, indicating a hemodynamically non-significant stenosis [18], treatment proceeded according to randomization between medical therapy and PCI. If FFR was <0.75, randomization was ignored and PCI was performed as planned because it was felt unethical at that time to defer PCI (the FAME 2 trial would not start for over 10 more years [19]). This resulted in 3 non-overlapping groups of subjects: 1) FFR›0.75 in whom PCI was deferred (defer group); 2) FFR›0.75 in whom PCI was performed (perform group); and 3) FFR<0.75 in whom PCI was performed (reference group).

Invasive angiography took place using at least two orthogonal projections after the intracoronary administration of 200 µg of nitroglycerin. All angiograms were analyzed using QCA-CMS (Medis, Leiden, the Netherlands). After angiography, FFR was measured using an intracoronary pressure wire (manufactured at the time by Radi Medical Systems, Uppsala, Sweden) during hyperemia produced via intravenous or intracoronary adenosine.

Since patients were enrolled before the era of drug-eluting stents, PCI was performed according to the standards at that time (bare-metal stents or balloon angioplasty).

Application of pb-CFR to DEFER

Case report forms in the DEFER study asked operators to record Pa and Pd at baseline and hyperemia. From this data we computed the trans-stenosis pressure gradient (ΔP) and bounded CFR using pb-CFR as above. In an exploratory analysis, we also bounded CFR using the Pd/Pa-based relationship and examined classification agreement.

In some DEFER subjects both pb-CFR limits were above or below 2.0 completely, allowing definitive binary categorization into pb-CFR<2 (low pb-CFR group) and pb-CFR≥2 (preserved pb-CFR group). In other cases, the pb-CFR limits overlapped 2.0 and pressure measurements alone could not categorize the flow reserve definitively (uncertain pb-CFR group). We selected a threshold of CFR=2 since generally a CFR<2 indicates a significant reduction, while a CFR≥2 has been associated with a reasonable prognosis [20].

Because pb-CFR requires a non-zero baseline ΔP, we assigned an arbitrary value of 1mmHg to those cases were baseline Pa equaled Pd. We excluded subjects with missing values for Pa and/or Pd. Mid pb-CFR was calculated as the average of the upper and lower pb-CFR limits.

Endpoints

The primary endpoint of the DEFER study was freedom from major adverse cardiac events (MACE) after 2 years of follow-up. MACE was defined as the composite of death, myocardial infarction, and revascularization. Secondary endpoints included the rate of MACE after 5 years, and freedom from angina at 1 month, 1 year, 2 years, and 5 years. Long-term outcomes after approximately 15 years have also been published for DEFER although it was not a pre-specified substudy and did not include symptoms [3].

An independent end points committee reviewed all events within 5 years of follow-up, and analysis was based on the committee's adjudication. Myocardial infarction was defined as a clinical episode of typical chest pain with development of new pathologic Q-waves on the electrocardiogram or an increase of serum creatinine kinase (CK) levels to more than twice the normal value, reflecting the practice pattern during the era of subject recruitment. Importantly, angiography was only repeated if clinically indicated or in case of an adverse event, and was not part of the study protocol.

For our current post-hoc substudy we used MACE and angina follow-up out to 5 years in order to focus on both prognosis and symptoms. To study the association of a low CFR with adverse outcomes and angina, we compared subjects with an FFR≥0.75 in the defer group

between pb-CFR<2 and pb-CFR⩾2. To assess the ability of revascularization to improve outcomes or angina, we compared subjects with an FFR⩾0.75 but pb-CFR<2 between the defer and perform PCI groups.

Statistical analysis

Analyses were performed in R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). We employed standard statistical techniques. Applicable tests were two-tailed, and p<0.05 was considered statistically significant as per historical, arbitrary convention.

RESULTS

Invasive validation of pb-CFR

We pooled 107 lesions from 3 prior publications [12, 16-17] that contained invasive CFR as well as sufficient data to compute pb-CFR. The pb-CFR range was clearly low (<2) or intact (⩾2) in 64 of the 107 (59.8%) cases. Overall pb-CFR demonstrated a pooled accuracy of 84.4% (agreement in 54 of 64). Sensitivity was 42/44 = 95.5% (both CFR and pb-CFR<2) with a specificity of 12/20 = 60.0% (both CFR and pb-CFR⩾2).

pb-CFR in DEFER

Prior publications have already detailed the general results from the DEFER trial [1-3]. Figure 2 provides a visual overview of subgroups in our substudy after randomization, measurement of FFR, and calculation of pb-CFR. In 47 subjects the baseline trans-lesion gradient ΔP was 0mmHg and thus changed to 1mmHg. A total of 44 subjects were excluded for missing or incomplete DP.

In a narrow majority of subjects (186 of 325, or 57%), pb-CFR was available and could be definitively categorized as <2 or ⩾2; in 95 cases the pb-CFR interval overlapped 2. Using Pd/Pa instead of DP produced very similar categorical agreement among low, uncertain, and preserved assignments. Complete agreement occurred in 254 of 281 cases (90.4%) and only 1 case (0.4%) changed from preserved to low or vice versa, with a k=0.855 and a Spearman r=0.921.

Does low CFR associate with worse outcomes and symptoms?

Table 1 compares baseline characteristics between low versus preserved pb-CFR groups with FFR³0.75 that were treated medically. Notably a low pb-CFR associated with diabetes (29% versus 11%, p=0.18), albeit not significantly. Subjects with low pb-CFR trended towards less freedom from angina at baseline (7% versus 18%, p=0.42) despite a higher number of anti-anginal medications (2.0 versus 1.3, p=0.004). FFR did not differ significantly between groups (0.88 versus 0.86, p=0.59).

Table 1. Baseline characteristics of subjects with FFR›0.75 treated medically.

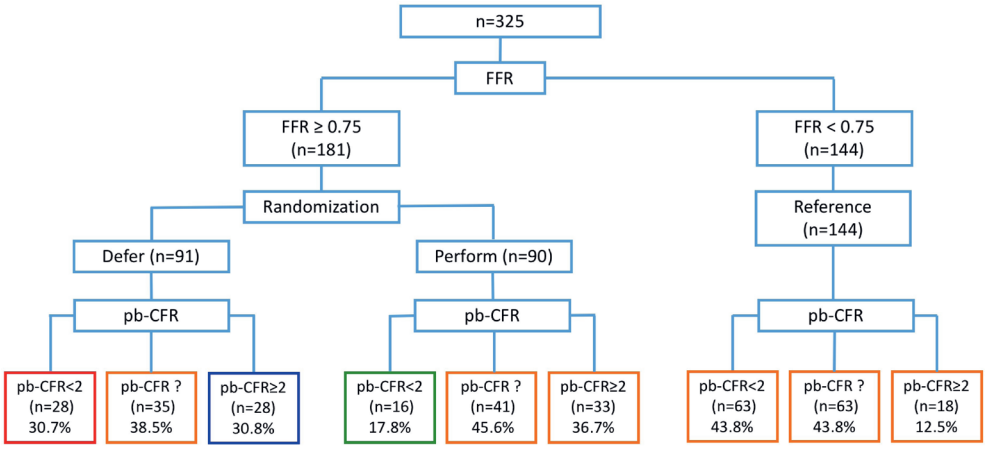
	pb-CFR<2	pb-CFR›2	p value
n	28	28	NA
Age (years)	79 ± 12	76 ± 9	0.23
Male	64%	71%	0.78
Tobacco	18%	46%	0.044
Family history	61%	61%	1.00
Diabetes	29%	11%	0.18
Hypertension	29%	43%	0.40
Dyslipidemia	36%	48%	0.56
Prior MI	22%	32%	0.72
Prior PCI	20%	33%	0.46
Prior CABG	0%	0%	1.00
Antianginals (#)	2.0 ± 0.8	1.3 ± 1.0	0.004
Beta blockers	75%	68%	0.77
Calcium blockers	64%	29%	0.015
Nitrates	64%	36%	0.06
LVEF (%)	67 ± 8	65 ± 9	0.50
RVD by QCA (mm)	2.97 ± 0.74	2.97 ± 0.49	0.98
MLD by QCA (mm)	1.59 ± 0.37	1.48 ± 0.29	0.23
%DS by QCA (%)	46 ± 7	50 ± 9	0.07
Baseline Pd/Pa	0.91 (0.89-0.94)	1.00 (0.98-1.00)	<0.001
FFR	0.88 (0.82-0.91)	0.86 (0.81-0.90)	0.59
pb-CFR (mid)	1.3 (1.2-1.4)	5.6 (3.7-9.9)	<0.001

As shown in Figure 3, low pb-CFR subjects with a high FFR had a non-significant but persistent trend over 5 years towards more angina compared to those with a high pb-CFR. A non-significant trend also existed towards more MACE (p=0.34) in the low pb-CFR group over the follow-up period.

Can PCI improve outcomes or angina for a low CFR?

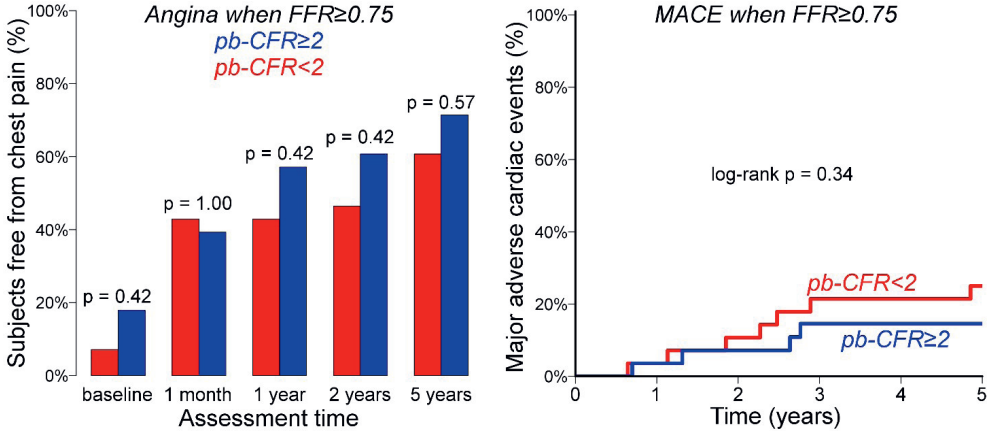
Table 2 compares baseline characteristics between medical treatment versus PCI for subjects with an FFR›0.75 but low pb-CFR. As expected due to randomization of treatment assignment, these characteristics were similar for both groups. Over 5 years of follow-up, PCI did not improve freedom from angina when pb-CFR was low but FFR›0.75. Indeed, initial PCI produced a non-significant trend towards higher MACE rates (p=0.27), as detailed in Figure 4.

Figure 2. Flowchart of DEFER randomized trial and this pb-CFR substudy.



For subjects with an FFR<0.75, PCI was always performed. For subjects with an FFR≥0.75, treatment was randomized between medical therapy (defer) and PCI (perform). For each group, the number of subjects and their pb-CFR classification is provided. Notably, a majority of lesions could be definitively classified as pb-CFR<2 or pb-CFR›2. The text "pb-CFR ?" implies that the pb-CFR range overlapped the 2.0 threshold or that pb-CFR could not be calculated due to missing data. Colors in the bottom row match Figure 3 (compares red and blue) and Figure 4 (compares red and green) with orange denoting unused subsets.

Figure 3. Natural history of medically treated lesions with FFR≥0.75.



Using pb-CFR, the group of subjects with a high FFR randomized to medical treatment was compared between preserved (›2) or low (<2) pb-CFR. Generally pb-CFR<2 showed a non-significant trend towards more angina (left panel) and worse outcomes (right panel).

Table 2. Baseline characteristics of subjects with FFR›0.75 and a low pb-CFR<2.

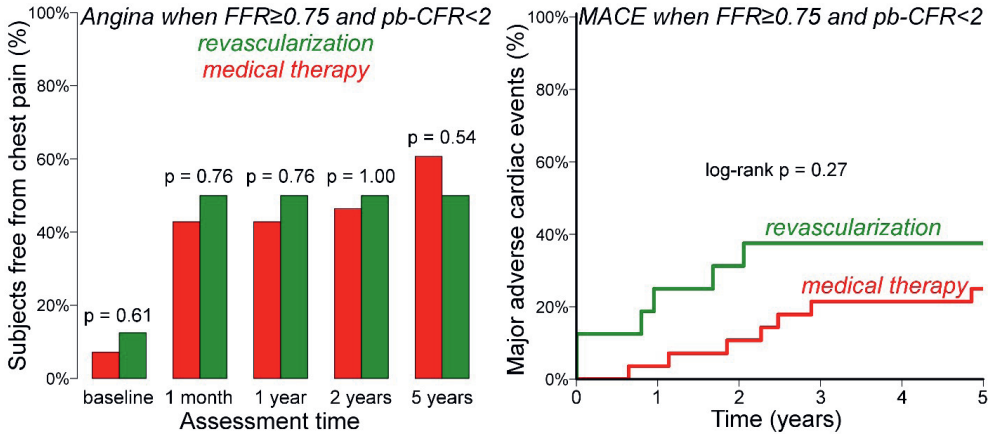
	Defer	Perform	p value
n	28	16	NA
Age (years)	79 ± 12	81 ± 8	0.63
Male	64%	62%	1.00
Tobacco	18%	19%	1.00
Family history	61%	50%	0.54
Diabetes	29%	12%	0.28
Hypertension	29%	38%	0.74
Dyslipidemia	36%	33%	1.00
Prior MI	22%	18%	1.00
Prior PCI	20%	64%	0.043
Prior CABG	0%	0%	1.00
Antianginals (#)	2.0 ± 0.8	1.9 ± 1.0	0.57
Beta blockers	75%	69%	0.73
Calcium blockers	64%	69%	1.00
Nitrates	64%	50%	0.53
LVEF (%)	67 ± 8	74 ± 10	0.05
RVD by QCA (mm)	2.97 ± 0.74	2.87 ± 0.47	0.61
MLD by QCA (mm)	1.59 ± 0.37	1.52 ± 0.37	0.55
%DS by QCA (%)	46 ± 7	47 ± 8	0.55
Baseline Pd/Pa	0.91 (0.89-0.94)	0.92 (0.89-0.94)	0.66
FFR	0.88 (0.82-0.91)	0.86 (0.85-0.93)	0.63
pb-CFR (mid)	1.3 (1.2-1.4)	1.2 (1.0-1.3)	0.12

DISCUSSION

Since its introduction in 1974, CFR and the associated notion of relative CFR have influenced the development of FFR as well as myocardial perfusion imaging [20]. However, its routine, invasive assessment has suffered from technical limitations especially compared to the ease and reliability of making intracoronary pressure measurements. As a result, the link among invasive CFR, clinical outcomes, and revascularization has a weaker evidence base than FFR.

Pressure-bounded CFR (pb-CFR) provides an easy technique for gaining information about CFR when measuring intracoronary pressure, but without having to perform additional measurements or purchase special equipment. Potentially existing outcomes databases

Figure 4. Impact of revascularization in lesions with FFR≥0.75 but pb-CFR<2.



Using pb-CFR to identify subjects with low flow reserve, angina (left panel) and outcomes (right panel) could be compared between medical therapy and revascularization. Generally PCI did not improve symptoms and led to a non-significant trend towards worse outcomes.

with baseline and hyperemic intracoronary pressure gradients could apply pb-CFR retrospectively, as we have done here. Future studies could easily incorporate pb-CFR when making FFR measurements.

As a proof of concept, we applied pb-CFR to the randomized DEFER trial to study CFR/FFR discordance. While the small sample size of high FFR but classifiable pb-CFR in our substudy prevents definitive conclusions, our results suggest that low pb-CFR associates with more angina and MACE compared with preserved pb-CFR, but that PCI cannot modify this risk compared to medical therapy. This analysis supports, but does not prove, the hypothesis that low CFR may be an unmodifiable risk factor by PCI in the absence of a large epicardial pressure gradient during hyperemia.

The associations between a low CFR and more frequent diabetes and worse angina have been long known in the literature and we found similar results with pb-CFR. Assuming the causal mechanism is a variable combination of diffuse epicardial disease plus microvascular dysfunction, it would be plausible that focal PCI of the epicardial artery would not improve the situation. However, our findings do not exclude other potential therapies that might benefit this pathophysiologic milieu.

Comparison with existing literature

Prior work suggested using the difference between rest Pd/Pa and FFR as a marker of lesion severity and predictor of future events [21]. However, fundamental coronary hemodynamics implies that the same delta value carries different bounds for CFR depending on the exact gradients. For example, both Δ = Pd/Pa–FFR of 0.2 = 0.79-0.59 and 0.2 = 0.95-0.75 have the same delta, yet the first case has a pb-CFR<2.0 while the second scenario has a pb-CFR>2.2.

A limited amount of outcomes data exists after simultaneous, invasive measurement of FFR and CFR [7,22]. As such, our pb-CFR substudy of DEFER provides a relevant addition to the literature despite its modest size. Table 3 summarizes key features of published results. Uniquely, DEFER randomized treatment assignment for high FFR lesions. Additionally, pb-CFR was unknown to the DEFER investigators and subjects, thereby providing natural "blinding".

In contrast to prior results [7], we and others [22] could not replicate the very high MACE rate seen in medically treated lesions with intact FFR≥0.75 but a low CFR<2. After 5 years cumulative MACE reached 50% in a previously published cohort, although largely driven by revascularization [7]. A cohort from Korea using observed just 15% [22]. The analogous physiologic cohort in DEFER but using pb-CFR had 5-year event rate of only 25% when treated medically. Notably neither of these other studies had an active treatment arm, unlike Perform in the DEFER study. Additionally, non-target vessel revascularization

Table 3. Comparison with existing literature on outcomes in high FFR/low CFR lesions.

Reference	*DEFER substudy*	*AMC*[7]	*Korea*[22]
Country	*International*	*Netherlands*	*Korea*
Multicenter	Yes	No	Yes
CFR technique	pb-CFR	Doppler	thermodilution
Lesions with FFR and conclusive CFR measurement	186	148	663 lesions 313 patients
Lesions with FFR≥0.75 and CFR<2	44	22	47** (used FFR>0.80)
5-year MACE for FFR≥0.75 and CFR<2, initially treated medically	25%	50%	15%***
5-year MACE for FFR≥0.75 and CFR<2, initially treated by PCI	38%*	N/A	N/A

** = not significantly different than initial medical treatment*
*** = used FFR>0.80 threshold instead of FFR≥0.75*
**** = median follow-up was 1.8 years, but estimate taken from 5-year mark in Kaplan-Meier presented in their Figure 2B [22]*
N/A = not available

accounted for a majority of events in the Korean study, vessels with a potentially different and unmeasured physiologic profile [22].

Limitations

Two sources of limitations should be distinguished in our study, as some arose from the technique of pb-CFR and others from the DEFER protocol. In a large minority (43%) of subjects in DEFER, pb-CFR produced an interval that overlapped with the CFR=2 threshold, thereby reducing further the already modest number of high FFR lesions. In its invasive validation, pb-CFR similarly showed an overlapped range with CFR=2 in 40.2% of lesions. Future studies using pb-CFR should anticipate about a 40-50% loss of sample size due to this inherent limitation of establishing flow reserve bounds instead of assessing CFR exactly.

We validated pb-CFR against existing publications that measured CFR directly, showing a reasonable, but not perfect, classification agreement. As such, pb-CFR should be considered an approximate tool rather than a definitive assessment. Like many approximations, pb-CFR offers tradeoffs – in this case, imperfect classification versus improved ease of use and accessibility. Notably, invasive Doppler and thermodilution CFR measurement have themselves been shown to have an accuracy of only about 85% versus an external flow probe in an animal model [9]. Therefore, the 84.4% accuracy of pb-CFR seems reasonable for clinical application.

Finally, because pb-CFR relies on a ratio of pressure gradients, a small baseline DP can preclude reliable assessment. Generally pressure wires have an approximate ±2mmHg precision, so gradients under 5mmHg have a large relative error.

DEFER enrolled a stable, single-vessel disease population, necessarily employed treatment methods from over 15 years ago, and was designed and powered to address a different question than the current, post-hoc substudy. More importantly, DEFER mandated PCI for all lesions with FFR<0.75, thereby precluding the possibility of studying the natural history of FFR/CFR discordance and impact of PCI for low FFR stenoses. This lesion subset is being addressed in the ongoing DEFINE-FLOW study (clinicaltrials.gov NCT02328820).

Conclusion

Pressure-bounded CFR (pb-CFR) offers a new method for studying FFR/CFR discordance using regular pressure wire measurements. After validating pb-CFR against invasive CFR, we applied it to the randomized DEFER trial as a proof of concept. While limited by sample size, our analysis suggests that low pb-CFR may be a risk marker for more angina and worse outcomes in patients with stable chest pain and a single coronary stenosis with an FFR⩾0.75, but that this risk cannot be modified by PCI.

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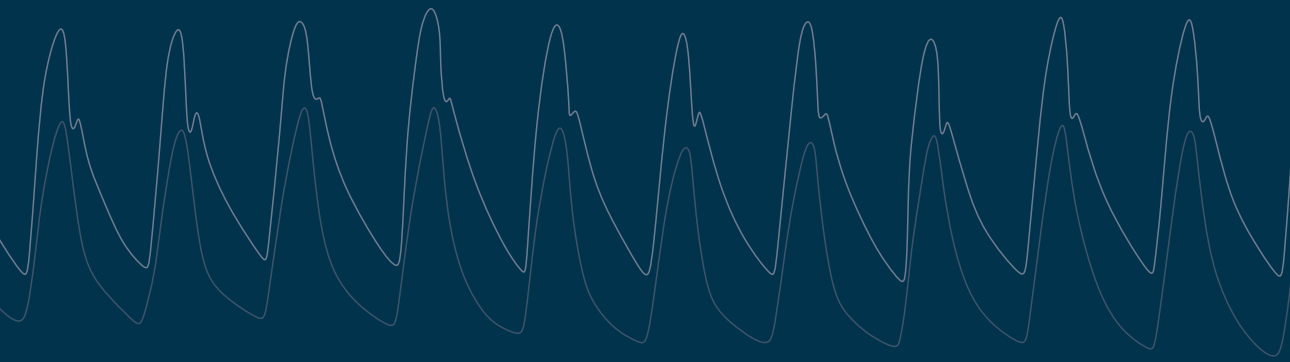

CHAPTER 13

Fractional Flow Reserve and Pressure-Bounded Coronary Flow Reserve to Predict Outcomes in Coronary Artery Disease

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ABSTRACT

Aim

Fractional flow reserve (FFR) has proven to its prognostic and therapeutic value. However, the additive prognostic value of coronary flow reserve (CFR) remains unclear. This study sought to investigate the clinical utility of combined FFR and CFR measurements to predict outcomes.

Methods and Results

Using the prospective, multicenter IRIS-FFR (Interventional Cardiology Research Incooperation Society-Fractional Flow Reserve) registry, a total of 2088 lesions from 1837 patients were included in this substudy. Based on baseline and hyperemic pressure gradients, we computed physiologic limits of CFR (so called pressure-bounded CFR) and classified lesions as low (<2) or high (⩾2). The primary endpoint was major adverse cardiac events (MACE, a composite of cardiac death, myocardial infarction, and revascularization) analyzed on a per-patient basis. During a median follow-up of 1.9 years (interquartile range: 1.0 to 3.0 years), MACE occurred in 5.7% of patients with FFR ⩽0.80 vs. 2.8% of patients with FFR >0.80 (adjusted hazard ratio [aHR]: 2.15, 95% confidence interval [CI]: 1.19 to 3.89; P=0.011. In contrast, the incidence of MACE did not differ between patients with pb-CFR<2 vs. pb-CFR⩾2 (4.2% vs. 4.2%; aHR: 0.98, CI: 0.60 to 1.58; P=0.92). Incorporation of FFR significantly improved model prediction of MACE (global c^2 38.8 to 48.1, P=0.002). However, pb-CFR demonstrated no incremental utility to classify outcomes (global c^2 48.1 to 48.2, P>0.99).

Conclusions

In this large, prospective registry of over 2000 coronary lesions, FFR was strongly associated with clinical outcomes. In contrast, a significant association between pb-CFR and clinical events could not be determined and adding knowledge of pb-CFR did not improve prognostication over FFR alone.

INTRODUCTION

During the last two decades, fractional flow reserve (FFR) has established itself as the invasive standard for identifying flow-limiting coronary artery disease. Several prospective randomized trials and observational studies have shown that FFR-guided percutaneous coronary intervention (PCI) outperforms angiography-guided PCI. Therefore, FFR receives strong recommendations in current clinical guidelines.[1] FFR is characterized by a simple, practical, pressure-derived index specifically assessing the influence of epicardial coronary disease on myocardial perfusion, independent of microvascular (dys)function.[1-8]

In contrast, coronary flow reserve (CFR) provides combined physiologic information on epicardial stenosis plus microvascular function, although a single distal measurement cannot discriminate their relative contributions.[9-11] Considering the frequent, multi-level involvement of coronary artery disease, CFR could remain advantageous and additive to FFR.[12-14] However, measurement of invasive CFR with present techniques remains technically more challenging and less reproducible than FFR.[15] Due to the distinct physiologic nature of CFR and FFR, their integrated assessment might be helpful to more accurately identify risk and guide treatment.

Therefore, we used the large prospective IRIS-FFR (Interventional cardiology Research Incooperation Society-Fractional Flow Reserve) registry to compare the incremental usefulness of CFR and FFR for predicting clinical outcomes. To overcome the technical limitations of current invasive CFR techniques, we applied the novel concept of pressure bounded CFR (pb-CFR), which enables robust classification of "low" and "high" CFR using only routine pressure measurements.[16]

METHODS

Study Design

The IRIS FFR registry (clinicaltrials.gov NCT01366404) is a prospective multicenter study designed to investigate the natural history of coronary stenosis assessed by FFR. A total of 30 heart centers in South Korea participated. The registry consecutively enrolled all patients who underwent FFR measurement of at least one coronary lesion between August 2009 and August 2015. Exclusion criteria were minimal: Thrombolysis In Myocardial Infarction (TIMI) flow <3, bypass graft lesion, severe heart failure, and technical unsuitability for FFR evaluation. The study protocol was approved by the institutional review board or ethical committee at each participating center, and all patients provided written informed consent.

Fractional Flow Measurement and Revascularization

FFR was measured with a commercially available coronary pressure wire during coronary angiography in standard fashion.[3] After administration of intracoronary nitrates (100 to 200mg), the pressure wire was positioned distal to the target lesion. Intravenous adenosine infusion (140µg/kg/min) via a central line or large antecubital vein induced coronary hyperemia. FFR was calculated from the proximal aortic pressure (Pa) and distal coronary pressure (Pd) during hyperemia, as mean Pd/Pa. Revascularization was generally performed in coronary lesions with FFR ≤ 0.75, and deferred in those with FFR > 0.80. For FFR values between 0.75 and 0.80, the decision regarding revascularization was left to the operator's discretion.

Pressure Bounded Coronary Flow Reserve

A well-established fluid dynamics equation quantifies the pressure gradient induced by an epicardial coronary artery stenosis[11]:

$$\Delta P = f \cdot Q + s \cdot Q^2$$

(where f: friction or viscous coefficient, s: separation or expansion coefficient, ΔP: pressure gradient, Q: coronary blood flow)

If all the pressure gradient was caused by frictional loss, then $\Delta P = f \cdot Q$; conversely, if all pressure gradient was caused by separation loss, then $\Delta P = s \cdot Q^2$. Therefore, for any given combination of resting and hyperemic pressure gradients, CFR (the ratio of hyperemic flow to resting flow) is bounded as follows (Figure 1):[16]

$$\sqrt{\frac{hyperemic\ \Delta P}{Resting\ \Delta P}} \leq CFR \leq \frac{hyperemic\ \Delta P}{Resting\ \Delta P} \quad \text{(Equation 1)}$$

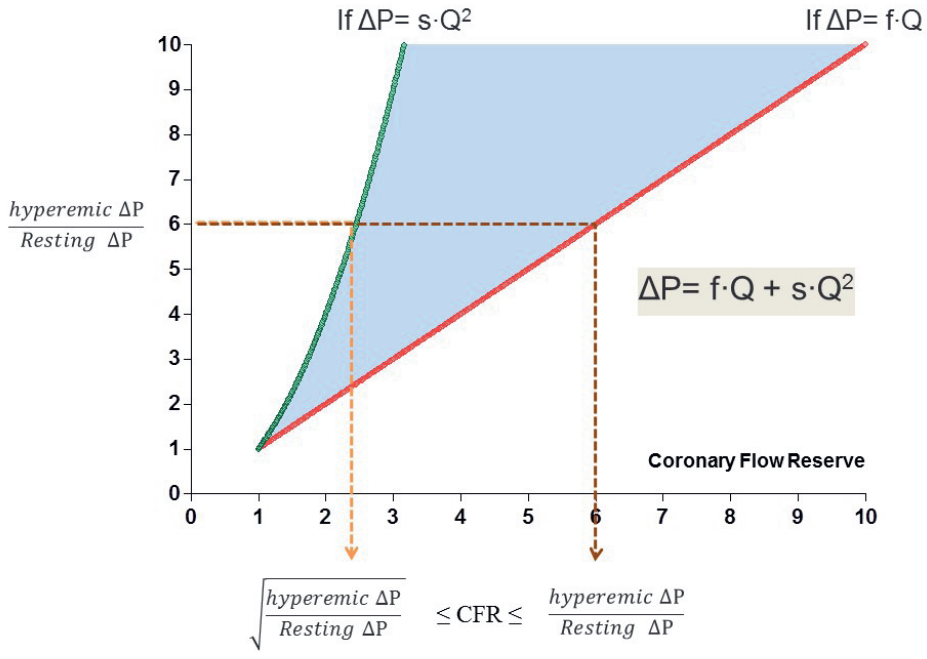
We classified lesions into three distinct pb-CFR groups based on equation 1: low when the upper boundary of CFR (i.e., $\frac{hyperemic\ \Delta P}{Resting\ \Delta P}$) was <2; high when lower boundary of CFR (i.e., $\sqrt{\frac{hyperemic\ \Delta P}{Resting\ \Delta P}}$) was ≥2; and indeterminate when the boundary crossed the value of 2.

To make the calculation more straightforward since only Pd/Pa was available, equation 1 can also be rewritten as:

$$\sqrt{\frac{1-hyperemic\ Pd/Pa}{1-Resting\ Pd/Pa}} \leq CFR \leq \frac{1-hyperemic\ Pd/Pa}{1-Resting\ Pd/Pa} \quad \text{(Equation 2)}$$

under the assumption that aortic pressure does not change, we excluded lesions with missing resting Pd/Pa and lesions with resting Pd/Pa of 0.99 or 1 because the intrinsic error of a pressure measurement is 2%.[17, 18] For the latter group, we performed a sensitivity

Figure 1. Theory of pressure-bounded coronary flow reserve.



Fundamental fluid dynamics demonstrate that the pressure gradient (ΔP) induced by an epicardial coronary stenosis can be described as $\Delta P = f \cdot Q + s \cdot Q^2$. If all of the pressure gradient is caused by frictional loss, then $\Delta P = f \cdot Q$ (red line); conversely, if all of the pressure gradient is caused by separation loss, then $\Delta P = s \cdot Q^2$ (green line). Therefore, for any resting and hyperemic pressure gradient, coronary flow reserve (CFR) is bounded between $\sqrt{\frac{hyperemic\ \Delta P}{Resting\ \Delta P}}$ *and* $\frac{hyperemic\ \Delta P}{Resting\ \Delta P}$ *(blue area). Accordingly, if the upper bound of CFR estimated from resting and hyperemic pressure gradient is <2, then CFR is definitely <2 (low CFR group); and if the lower bound of CFR estimated from resting and hyperemic pressure gradient is ›2, then CFR is definitely ›2 (high CFR group). In the remaining patients, CFR cannot be classified with certainty in this way, and is called indeterminate. CFR denotes coronary flow reserve; f, friction coefficient; s, separation coefficient; ΔP, pressure gradient; Q, coronary blood flow.*

analysis to evaluate the impact of this exclusion criterion on overall findings, hypothesizing that for FFR › 0.99, CFR will frequently be > 2.

End Points and Definitions

The primary endpoint was a major adverse cardiac event (MACE) consisting of composite cardiac death, myocardial infarction, and subsequent revascularization. MACE was analyzed on a per-lesion and per-patient basis. For per-patients analysis, the lowest value of FFR

and its pb-CFR was selected as the representative value of patient. Cardiac death was defined as any death due to cardiac causes including cardiac arrest, myocardial infarction, low-output failure, or fatal arrhythmia. Myocardial infarction was defined as follows: 1) within the first 48 hours after revascularization, ischemic symptoms with an elevation of creatinine kinase-MB (CK-MB) fraction concentration > 5 times normal; or 2) 48 or more hours after revascularization, any CK-MB or troponin increase above the upper range plus ischemic signs or symptoms. Subsequent revascularization was defined as any PCI or coronary artery bypass surgery of an index lesion. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee.

Data and Follow-Up

Baseline characteristics and outcome data were collected using a dedicated, electronic case report form by specialized personnel at each center. Monitoring and verification of registry data were periodically performed in participating hospitals by members of the academic coordinating center (Clinical Research Center, Asan Medical Center, Seoul, Korea). Clinical follow-up was conducted during the index hospitalization and at 30 days, 6 months, and 12 months, then every 6 months thereafter. At these visits, data pertaining to the patient's clinical status, all interventions, and adverse events were recorded.

Statistical Analysis

Continuous variables were expressed as means ± one standard deviation; categorical variables were shown as counts and percentages. Continuous variables were compared using unpaired t-tests, non-parametric Mann-Whitney tests, or one-way analysis of variance; categorical variables were compared using $\chi 2$ statistics or Fisher's exact test, as appropriate. Time-to-event data were presented as Kaplan–Meier estimates and compared using the log-rank test. Baseline variables that were considered clinically relevant or that showed significant univariate relationships with MACE were entered into multivariable Cox proportional-hazards regression models.[19] Variables for inclusion were carefully chosen, given the number of events, to ensure parsimony of the final models. A marginal Cox model was used to account for patients with multiple lesions.[20] A nested Cox proportional hazard regression analysis was used to investigate the incremental prognostic value of the predictors. Statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute). Applicable P values were two-sided, and $P<0.05$ was considered statistically significant.

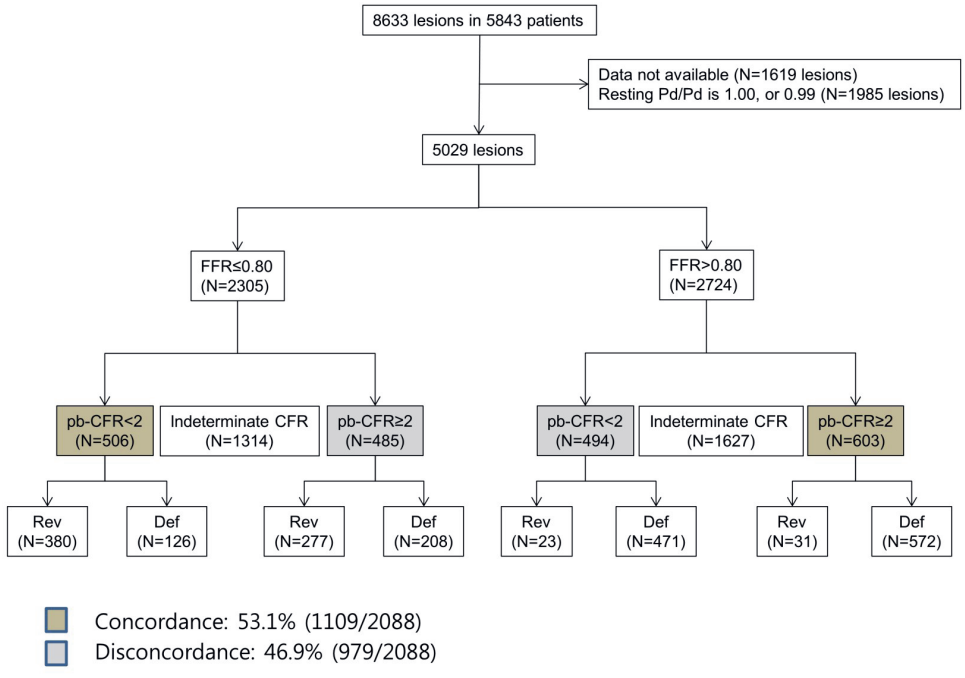
RESULTS

Patient characteristics

Between August 2009 and August 2015, 8633 lesions from 5843 patients were prospectively enrolled, of which pressure bounded CFR could be calculated in 5029 lesions. Excluding 2941 lesions with indeterminate CFR, 1000 lesions were classified as low pb-CFR <2 and 1088 as high pb-CFR ⩾2 within 1837 patients (Figure 2). The concordance and discordance rates between FFR and pb-CFR were 53.1% and 46.9%, respectively, using traditional thresholds of FFR=0.80 and pb-CFR=2. Figure 3 depicts the distribution of pb-CFR, resting Pd/Pa, and hyperemic Pd/Pa.

Significant associations with low pb-CFR included older age, female sex, acute coronary syndrome, hypertension, diabetes, and chronic renal failure. In contrast, low FFR was significantly associated with older age, male sex, and hyperlipidemia. Table 1 describes the patient and lesion characteristics of the 4 groups of binary FFR and pb-CFR. In general, the group with low pb-CFR and low FFR had the most cardiac risk factors.

Figure 2. Flow chart



Pb-CFR denotes pressure-bounded coronary flow reserve; Def, deferral of revascularization; FFR, fractional flow reserve; REV, revascularization

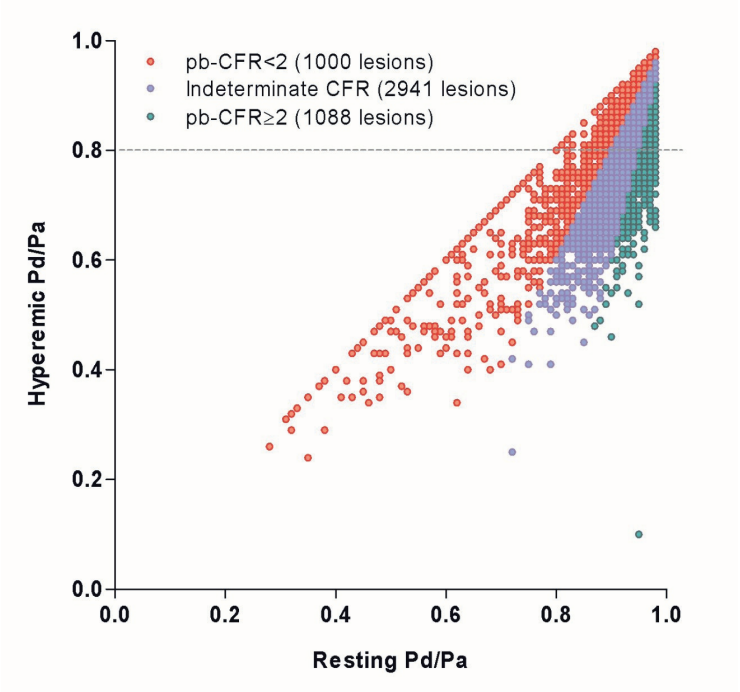
Table 1. Patient and lesion characteristics among combinations of fractional flow reserve and pressure bounded coronary flow reserve

	FFR>0.80 pb-CFR›2	FFR>0.80 pb-CFR<2	FFR‹0.80 pb-CFR›2	FFR‹0.80 pb-CFR<2	P value
Patient Characteristics	**N=513**	**N=425**	**N=434**	**N=465**	
Age	63.0±9.5	65.5±10.0	60.7±9.5	64.4±10.3	<0.001
Gender	380 (74.1)	240 (56.5)	373 (85.9)	330 (71.0)	<0.001
Clinical presentation					<0.001
Stable angina	418 (81.5)	347 (81.6)	359 (82.7)	334 (71.8)	
Unstable angina	74 (14.4)	61 (14.4)	69 (15.9)	85 (18.3)	
NSTEMI	15 (2.9)	14 (3.3)	5 (1.2)	34 (7.3)	
STEMI	6 (1.2)	3 (0.7)	1 (0.2)	12 (2.6)	
Hypertension	319 (62.2)	299 (70.4)	278 (64.1)	313 (67.3)	0.047
Diabetes	136 (26.5)	150 (35.3)	99 (22.8)	196 (42.2)	<0.001
Current smoking	138 (26.9)	79 (18.6)	122 (28.1)	102 (21.9)	0.003
Hyperlipidemia	338 (65.9)	218 (51.3)	279 (64.3)	305 (65.6)	<0.001
Previous MI	24 (4.7)	26 (6.1)	23 (5.3)	24 (5.2)	0.81
Previous PCI	98 (19.1)	83 (19.5)	79 (18.2)	89 (19.1)	0.97
Family history	72 (14.0)	37 (8.7)	43 (9.9)	58 (12.5)	0.045
Previous congestive heart failure	9 (1.8)	5 (1.2)	5 (1.2)	6 (1.3)	0.84
Previous stroke	32 (6.2)	24 (5.6)	29 (6.7)	39 (8.4)	0.39
Peripheral vascular disease	13 (2.5)	7 (1.6)	12 (2.8)	17 (3.7)	0.32
Chronic renal failure	11 (2.1)	13 (3.1)	3 (0.7)	29 (6.2)	<0.001
Chronic obstructive lung disease	13 (2.5)	14 (3.3)	11 (2.5)	6 (1.3)	0.26
Lesion Characteristics	**N=603**	**N=494**	**N=485**	**N=506**	
Resting Pd/Pa	0.97±0.01	0.93±0.03	0.95±0.02	0.74±0.13	<0.001
Hyperemic Pd/Pa (FFR)	0.86±0.03	0.89±0.04	0.73±0.07	0.65±0.12	<0.001
Lower Limit of pb-CFR	2.42±0.29	1.23±0.12	2.41±0.46	1.20±0.14	<0.001
Higher Limit of pb-CFR	5.47±1.44	1.54±0.28	6.04±2.55	1.45±0.33	<0.001
Revascularization	31 (5.1)	23 (4.7)	277 (57.1)	380 (75.1)	<0.001
Lesion territory					<0.001
Left main	14 (2.3)	17 (3.4)	39 (8.0)	58 (11.5)	
Left anterior descending artery	255 (42.3)	352 (71.3)	233 (48.0)	310 (61.3)	
Right coronary artery	206 (34.2)	58 (11.7)	117 (24.1)	59 (11.7)	
Left circumflex artery	91 (15.1)	46 (9.3)	70 (14.4)	53 (10.5)	
Others	37 (6.1)	21 (4.3)	26 (5.4)	26 (5.1)	

	FFR>0.80 pb-CFR≥2	FFR>0.80 pb-CFR<2	FFR≤0.80 pb-CFR≥2	FFR≤0.80 pb-CFR<2	P value
Lesion location					<0.001
Proximal	298 (49.4)	188 (38.1)	279 (57.5)	306 (60.5)	
Mid	175 (29.0)	222 (44.9)	112 (23.1)	129 (25.5)	
Distal	130 (21.6)	84 (17.0)	94 (19.4)	71 (14.0)	
Diameter stenosis					<0.001
≥70%	63 (10.4)	45 (9.1)	217 (44.7)	302 (59.7)	
50-69%	347 (57.5)	243 (49.2)	228 (47.0)	185 (36.6)	
30-49%	193 (32.0)	206 (41.7)	40 (8.2)	19 (3.8)	
AHA/ACC lesion B2C lesion	327 (54.2)	227 (46.0)	346 (71.3)	403 (79.6)	<0.001
Long lesion (>20mm)	247 (41.0)	185 (37.4)	268 (55.3)	333 (65.8)	<0.001
Moderate to severely calcified lesion	13 (2.2)	20 (4.0)	15 (3.1)	21 (4.2)	0.21
Thrombus containing lesion	5 (0.8)	2 (0.4)	4 (0.8)	7 (1.4)	0.42
Angiographic ulcerated lesion	7 (1.2)	1 (0.2)	2 (0.4)	3 (0.6)	0.21

Mean±SD and Number (%)
FFR denotes fractional flow reserve; NSTEMI, non ST segment elevated myocardial infarction; pb-CFR, pressure bounded coronary flow reserve; STEMI, ST segment elevated myocardial infarction

Figure 3. Distribution of pressure-bounded coronary flow Reserve



Overall Clinical Outcomes

During a median follow-up of 1.9 years (interquartile range: 1.0 to 3.0 years), MACE occurred in 84 lesions in 77 patients (cardiac death or myocardial infarction in 18 lesions in 15 patients, repeat revascularization in 71 lesions in 65 patients).

Association of FFR with Clinical Outcomes

A significantly higher incidence of MACE occurred in lesions with low FFR (≤0.80) than those with high FFR (>0.80) (Figure 4A). In addition, the risk of MACE in lesions with low FFR remained significantly higher even after adjustment for other significant covariates or multiple potential confounders (Table 2). The risk of revascularization also remained significantly higher in lesions with FFR≤0.80.

Table 2. Clinical outcomes according to fractional flow reserve

	Total No. of Events (%)		P value	aHR†	95% CI	P value
	Low FFR (≤0.80)	High FFR (>0.80)				
Per Patient Analysis	**N=899**	**N=938**				
Primary Endpoint (MACE): the composite of cardiac death, myocardial infarction, or subsequent revascularization						
All lesion	51 (5.7)	26 (2.8)	0.002	2.15	1.19-3.89	0.011
Deferred lesion	20 (6.9)	25 (2.8)	0.002	2.14	1.15-3.99	0.017
Revascularized lesion	31 (5.1)	1 (2.3)	0.72	1.37	0.18-10.2	0.76
Secondary Endpoint:						
Cardiac death or myocardial infarction	11 (1.2)	4 (0.4)	0.06	1.89	0.38-9.38	0.44
Repeat revascularization	43 (4.8)	22 (2.3)	0.005	2.29	1.22-4.28	0.01
Per Lesion Analysis‡	**N=991**	**N=1097**				
Primary Endpoint						
All lesion	57 (5.8)	27 (2.5)	NA	2.46	1.40-4.31	0.002
Deferred lesion	23 (6.9)	26 (2.5)	NA	2.38	1.32-4.30	0.004
Revascularized lesion	34 (5.2)	1 (1.9)	NA	1.88	0.25-14.0	0.54
Secondary Endpoint:						
Cardiac death or myocardial infarction	14 (1.4)	4 (0.4)	NA	3.61	0.90-14.5	0.07
Repeat revascularization	48 (4.8)	23 (2.1)	NA	2.62	1.44-4.75	0.002

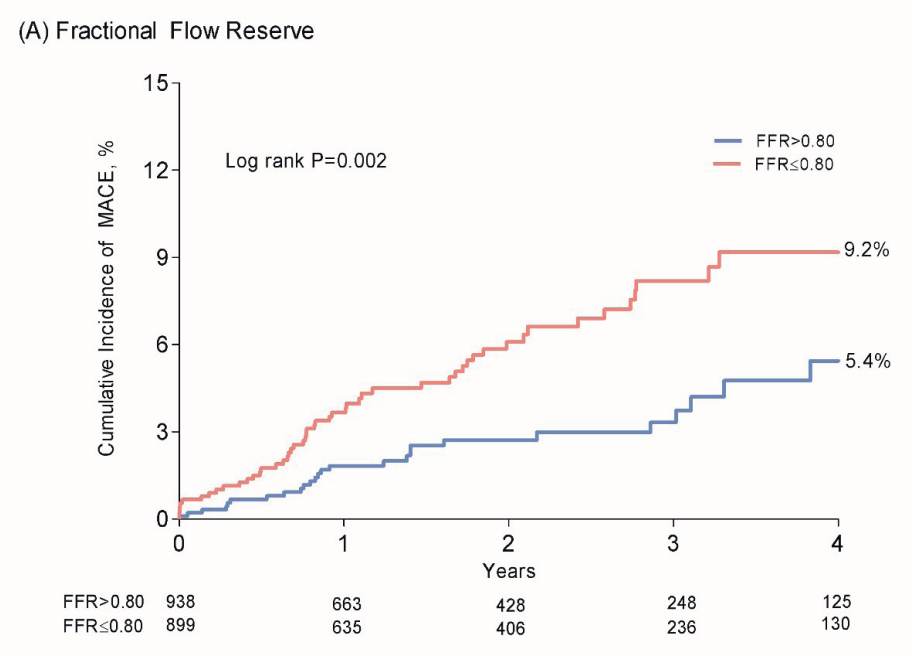
aHR denotes adjusted hazard ratio; CFR, coronary flow reserve; CI, confidence interval; MACE, major adverse cardiac event; NA, not available

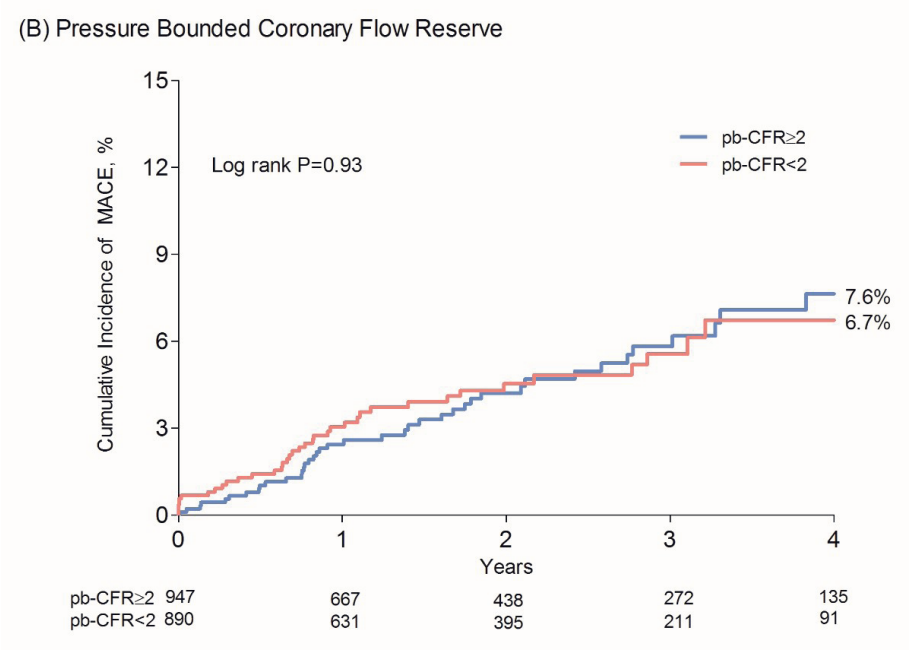
**Log-rank P value*

†Adjusted for age, male sex, clinical presentation, hypertension, diabetes, current smoking, hyperlipidemia, revascularization, lesion territory, lesion location, and diameter stenosis

‡ The models accounted for the clustering of lesions in patients

Figure 4. Kaplan-Meier curves for MACE when using fractional flow reserve and coronary flow reserve in all patients independent of chosen treatment





Association of pb-CFR with Clinical Outcomes

The risk of MACE was similar between patients with low (<2) and high (⩾2) pb-CFR (Table 3). The Kaplan-Meier curves are presented in Figure 4B.

Incremental Value of Coronary Physiology for Predicting MACE

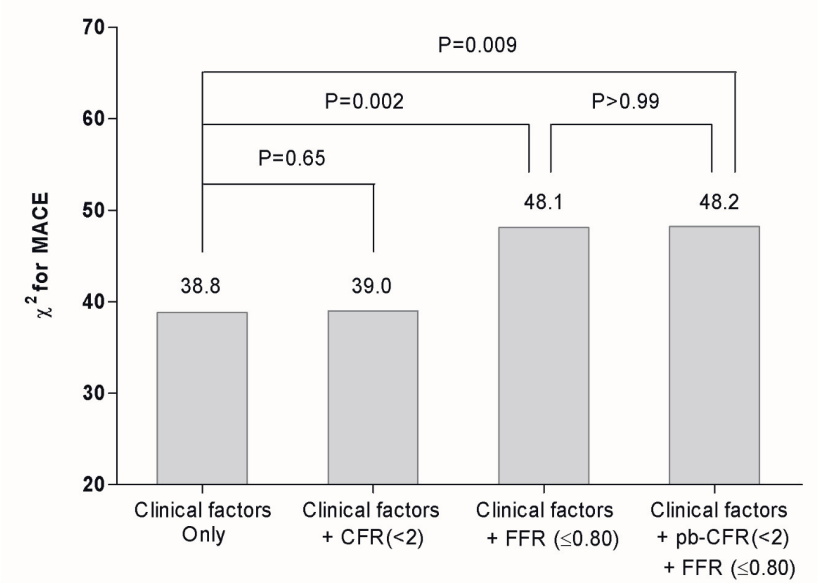
Figure 5 visually summarizes the improvement in predicting MACE by adding FFR or pb-CFR to a model including conventional clinical and lesion factors. When FFR was incorporated into the model, the global $\chi 2$ increased significantly. However, the addition of pb-CFR did not significantly improve the global $\chi 2$ for predicting MACE. Figure 6 shows Kaplan-Meier curves of cumulative events by groupings of physiologic (FFR and pb-CFR subsets) and treatment status (medical or revascularization). For deferred lesions, there was a continuous separation of the events curves according to low versus high pb-CFR in lesions with low FFR; however, in lesions with high FFR, the overall event rate for low and high pb-CFR was low and not different (P=0.05 for interaction). In contrast, for all

Table 3. Clinical outcomes according to pressure bounded coronary flow reserve

	Total No. of Events (%)		P value	aHR	95% CI	P value
	Low pb-CFR (<2)	High pb-CFR (⩾2)				
Per Patient Analysis	**N=890**	**N=947**				
Primary Endpoint (MACE): the composite of cardiac death, myocardial infarction, or subsequent revascularization						
All lesion	37 (4.2)	40 (4.2)	0.93	0.98	0.60-1.58	0.92
Deferred lesion	18 (3.5)	27 (4.1)	0.85	0.84	0.46-1.55	0.57
Revascularized lesion	19 (5.1)	13 (4.6)	0.88	1.32	0.64-2.72	0.45
Secondary Endpoint:						
Cardiac death or myocardial infarction	12 (1.3)	3 (0.3)	0.012	2.60	0.69-9.85	0.16
Repeat revascularization	27 (3.0)	38 (4.0)	0.33	0.85	0.50-1.45	0.55
Per Lesion Analysis‡	**N=1000**	**N=1088**				
Primary Endpoint						
All lesion	40 (4.0)	44 (4.0)	NA	0.93	0.59-1.48	0.76
Deferred lesion	20 (3.4)	29 (3.7)	NA	0.84	0.46-1.55	0.57
Revascularized lesion	20 (5.0)	15 (4.9)	NA	1.32	0.64-2.72	0.45
Secondary Endpoint:						
Cardiac death or myocardial infarction	15 (1.5)	3 (0.3)	NA	3.77	1.04-13.7	0.044
Repeat revascularization	29 (2.9)	42 (3.9)	NA	0.79	0.47-1.32	0.37

aHR denotes adjusted hazard ratio; pb-CFR, pressure bounded coronary flow reserve; CI, confidence interval; MACE, major adverse cardiac event; NA, not available

Figure 5. Incremental utility to predict MACE by adding coronary flow reserve and fractional flow reserve to traditional risk factors



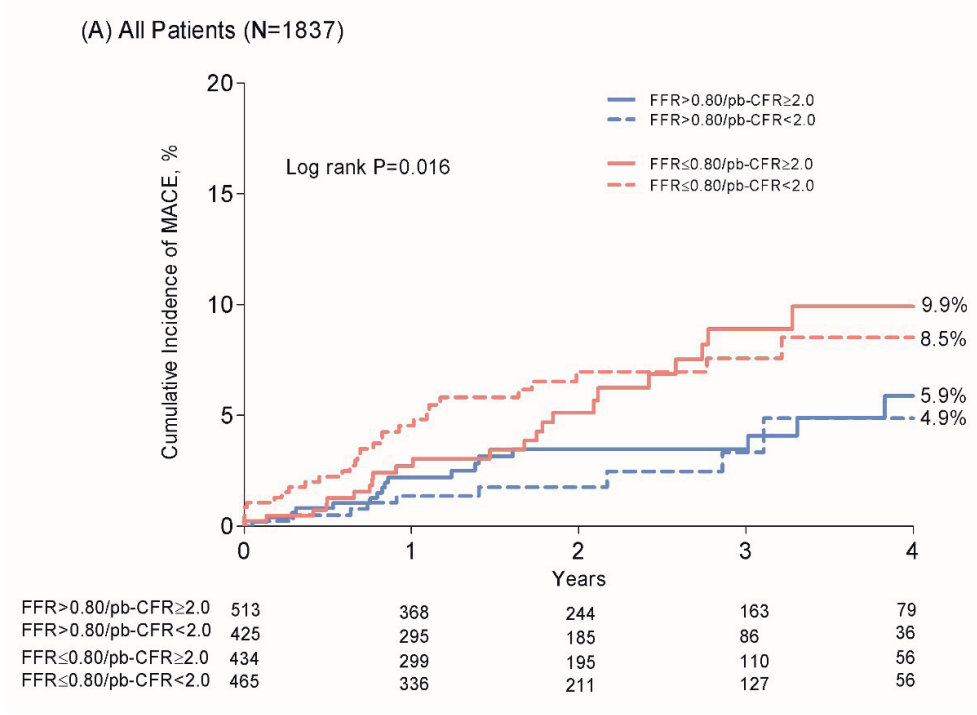
Included clinical factors for model construction were clinical presentation, smoking, hyperlipidemia, previous PCI, peripheral vascular disease, chronic renal failure, chronic obstructive lung disease, revascularization, lesion location, percent diameter stenosis, AHA/ACC lesion B2C lesion, and moderate to severe lesion calcification. MACE denotes major adverse cardiac events as a composite of cardiac death, myocardial infarction, and subsequent revascularization.

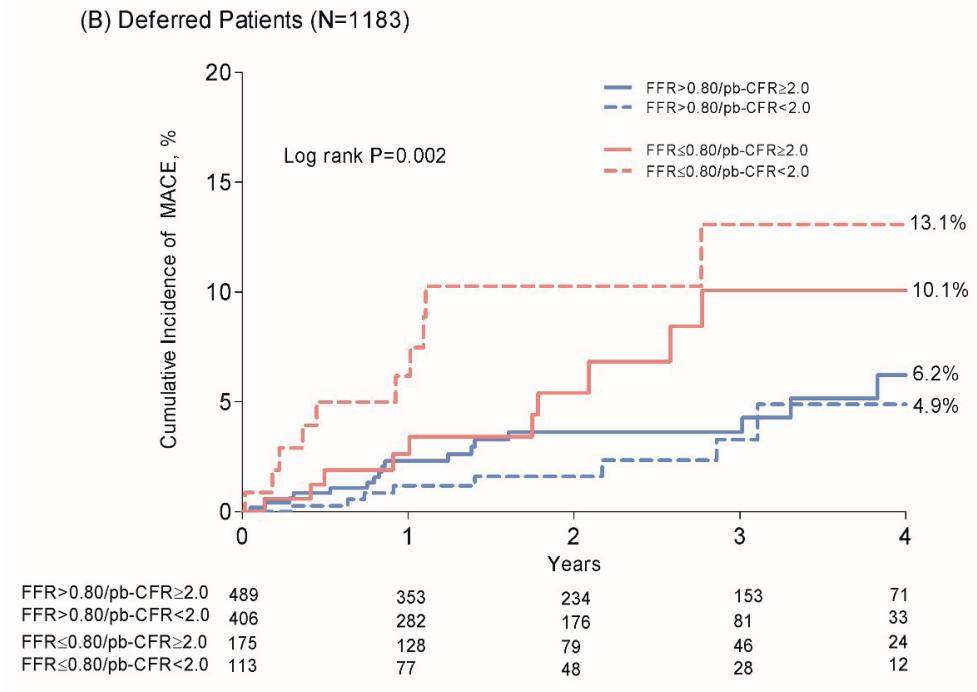
lesions and for revascularized lesions, pb-CFR did not separate event rates between high and low FFR.

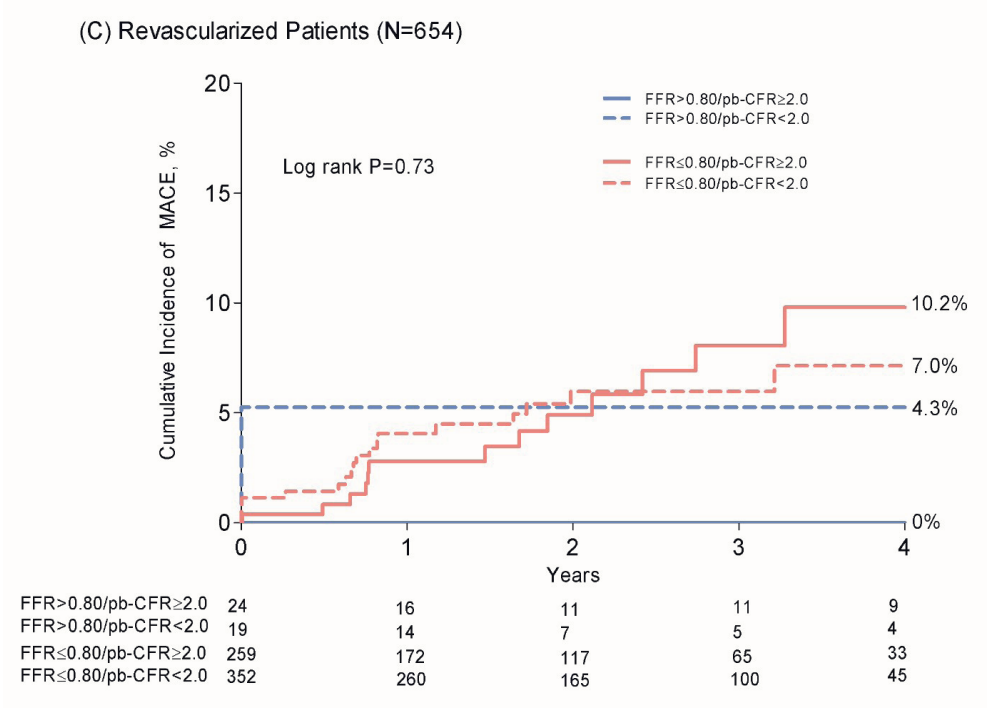
Sensitive Analysis

We performed a sensitivity analysis by including lesions with resting Pd/Pa ratio of 1.0 and 0.99 in the high pb-CFR group. These lesions were excluded from the original analysis, because pb-CFR is theoretically limited in cases with no or mild resting pressure gradients. We hypothesized that for lesions with FFR ⩾0.99, CFR will frequently be > 2. This sensitivity analysis increased the number of lesions from 2088 to 4073 (from 1837 to 3032 patient) adding about 2000 functionally completely normal arteries to the analysis. By doing so, the event rates for patients with the “normal” CFR group decreased from 7.6% to 5.5% and was slightly lower now than the event rate in lesions with pb-CFR<2 . However, even with this sensitivity analysis, pb-CFR showed no incremental value to predict MACE in the multiple risk factor model.

Figure 6. Kaplan-Meier curves for MACE by FFR>0.80/≤0.80 and pb-CFR≥2/<2 for all patients, deferred patients, and revascularized patients







DISCUSSION

This large, prospective registry confirmed that FFR is significantly associated with MACE (composite of cardiac death, myocardial infarction, and revascularization). In contrast, pb-CFR failed to predict adverse cardiac events. Additionally, regardless of pb-CFR, for lesions with FFR>0.80, clinical outcomes were excellent and performance of PCI did not improve them. Incorporation of FFR into a model with clinical factors improved prediction of MACE. However, pb-CFR demonstrated no incremental utility. Therefore, despite the value of pb-CFR to understand coronary physiology, FFR remains the more useful index for prognosis and revascularization decisions.

To overcome the well-recognized technical challenges of invasive CFR measurement,[9] there have been several attempts to derive CFR from coronary pressure.[17, 18, 21] By refining such a concept, we estimated the upper and lower boundaries of CFR from resting and hyperemic trans-lesional coronary pressure gradients based on fundamental fluid dynamics[11] and discriminated groups as low (<2) and high (⩾2) CFR.[16] A unique strength of this study arises from our post-hoc analysis of pb-CFR that was blinded from operators and patients, implying that it did not affect clinical decision making and, thereby reduced bias.

Previous studies into prognostic value of invasively measured CFR have been comparatively small and had conflicting results.[10, 12] In one recent retrospective study, low CFR and high FFR showed worse outcomes than high CFR with low FFR, suggesting that CFR might be more important than FFR in predicting clinical events.[12] However, that conclusion was based on a small number of patients and events, essentially driven completely by subsequent revascularization within 1 year after the unblinded index measurement.

In the present study, pb-CFR did not demonstrate independent prognostic value with respective to clinical outcome. In addition, a post-hoc sensitivity analysis assigning lesions and patients with no or mild pressure gradients to the high pb-CFR group showed consistent findings and did not change the results. Furthermore, pb-CFR did not provide incremental value for predicting MACE in addition to FFR. By contrast, and in agreement with previous findings,[7, 22] FFR itself was strongly associated with MACE. Therefore, our study favors FFR measurement for guiding clinical decision making and predicting outcomes in daily practice.

Despite the lack of independent prognostic value for pb-CFR in this study, combined pb-CFR and FFR assessment provided several important insights. First, we found that the event rate of lesions with FFR >0.80 was very low regardless of pb-CFR, suggesting that the presence of microvascular disease, although it may cause angina, plays a limited role regarding hard outcomes in the presence of a patent epicardial coronary artery. Second, lesions with a low pb-CFR in addition to a low FFR showed the highest clinical risk and benefited the most from revascularization. The event rate for revascularized lesions was lower in that subgroup than was the case for deferred lesions in that group. The ongoing DEFINE-FLOW (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect–Combined Pressure and Doppler FLOW Velocity Measurements, clinicaltrials.gov NCT02328820) study will provide more detailed information about the prognostic value of the different combinations of FFR and CFR, not only as binary indices but also as continuous variables.

This study also confirms epidemiologic links between low CFR and traditional risk factors. Low pb-CFR were associated with old age, female sex, hypertension, diabetes, previous MI, and chronic renal failure. As those risk factors also associate with microvascular disease, our findings favor pb-CFR as an index of flow decrease in the complete coronary circulation rather than the epicardial coronary artery. In addition, such clustering would explain the observed worse outcomes for low CFR.[12, 23]

This study has several limitations. First, there are the inherent limitations of any observational study. Second, in cases with a small pressure gradient at rest or hyperemia, the estimation of pb-CFR might become inaccurate. Therefore, such lesions were excluded

from the primary analysis. Nevertheless, when we included lesions with resting Pd/Pa of 1.0 and 0.99 (worst case scenario), the sensitivity analysis showed that the overall results were not greatly changed. Third, because of low event rates, our study was underpowered to assess the impact of FFR and pb-CFR regarding hard endpoints of cardiac death or myocardial infarction, separately. Finally, slightly more than half of lesions were not included in the analysis due to being assigned to the indeterminate pb-CFR group due to the intrinsic limitation of using pb-CFR instead of measuring CFR directly.

In conclusion, this large, prospective, multicenter registry showed that FFR was strongly associated with long-term outcomes, whereas CFR failed to independently predict the risk of cardiac events. As such, our results confirmed the primacy of FFR for risk stratification and clinical decision making in patients with coronary artery disease. Nevertheless, the technique of pressure-bounded CFR appears useful to study the clinical impact of FFR/CFR discordances.

Acknowledgments
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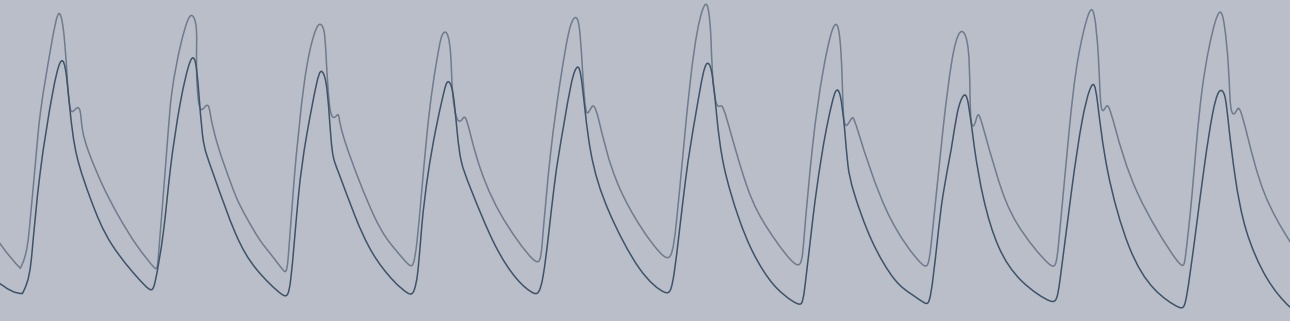
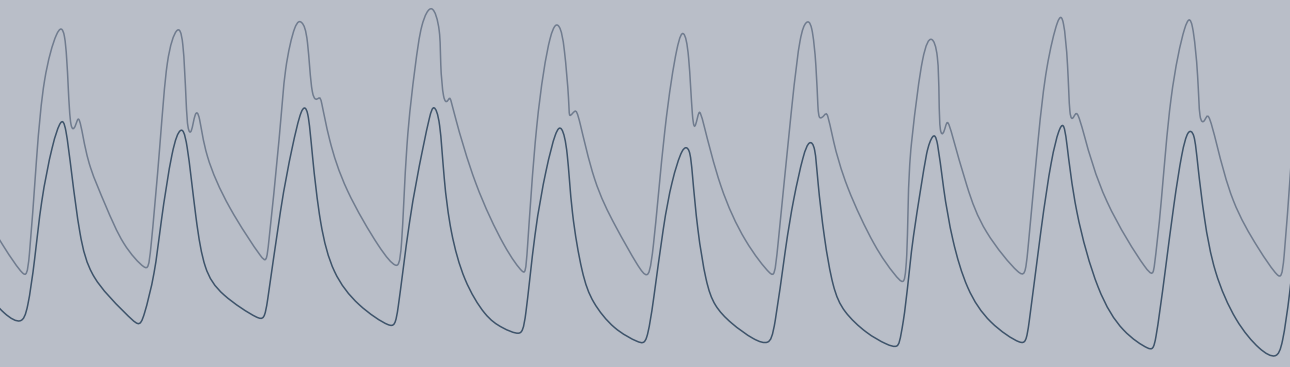
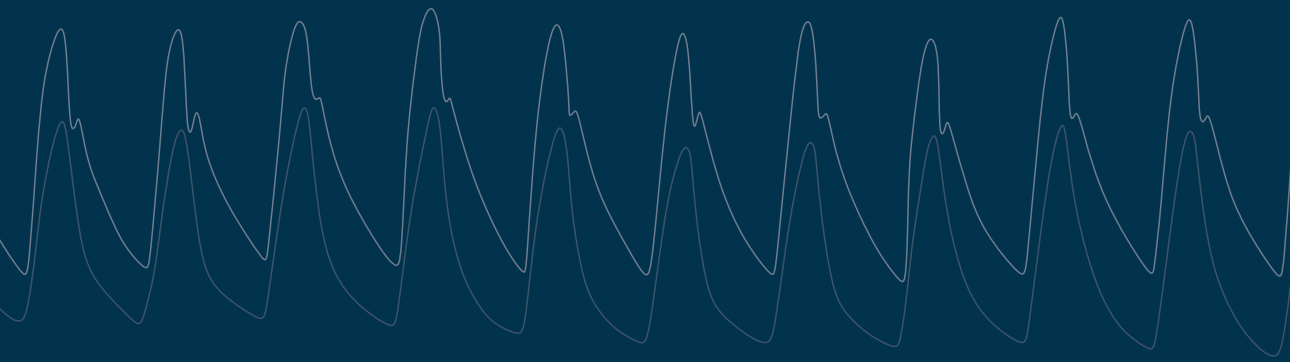


PART IV

Coronary Physiology in Cardiac Transplant Recipients





CHAPTER 14

Prognostic Value of Comprehensive Intracoronary Physiology Assessment Early After Heart Transplantation

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ABSTRACT

Aims

We evaluated the long-term prognostic value of invasively assessing coronary physiology after cardiac transplantation in a large multicenter registry.

Methods and Results

Comprehensive intracoronary physiology assessment measuring fractional flow reserve (FFR), the index of microcirculatory resistance (IMR), and coronary flow reserve (CFR) was performed in 254 patients at baseline (a median of 7.2 weeks) and in 240 patients at 1 year after transplantation (199 patients had both baseline and 1-year measurement). Patients were classified into those with normal physiology, reduced FFR (FFR≤0.80), and microvascular dysfunction (either IMR≥25 or CFR≤2.0 with FFR>0.80). The primary outcome was the composite of death or re-transplantation at 10 years. At baseline, 5.5% had reduced FFR; 36.6% had microvascular dysfunction. Baseline reduced FFR (adjusted hazard ratio [HR], 2.33; 95% confidence interval [CI], 0.88-6.15; P=0.088) and microvascular dysfunction (aHR, 0.88; 95% CI, 0.44-1.79; P=0.73) were not predictors of death and re-transplantation at 10 years. At 1 year, 5.0% had reduced FFR; 23.8% had microvascular dysfunction. One-year reduced FFR (aHR, 2.98; 95% CI, 1.13-7.87; P=0.028) and microvascular dysfunction (aHR, 2.33; 95% CI, 1.19-4.59; P=0.015) were associated with significantly increased risk of death and re-transplantation at 10 years. Invasive measures of coronary physiology improved the prognostic performance of clinical variables (χ^2 improvement: 7.41, P=0.006). However, intravascular ultrasound-derived changes in maximal intimal thickness was not predictive of outcomes.

Conclusion

Abnormal coronary physiology 1 year after cardiac transplantation was common and was a significant predictor of death or re-transplantation at 10 years.

INTRODUCTION

Cardiac allograft vasculopathy (CAV) is the leading cause of late morbidity and mortality (› 1 year) after cardiac transplantation.[1] CAV is a panarterial disease with a progressive and diffuse process involving both the epicardial coronary artery and the microcirculation. Approximately, 10% of patients have angiographic coronary artery disease at 1 year, 50% at 5 years, 80% at 15 years, with long-term mortality increasing with angiographic severity.[2] CAV can also manifest as a microvasculopathy, which occurs more frequently than epicardial coronary artery stenosis at 1 year after transplantation and is associated with a higher risk of cardiac events, independent of epicardial coronary artery stenosis.[3]

Clinical guidelines recommend annual or biannual coronary angiography to assess the development of CAV.[4] Intravascular ultrasound (IVUS) is often used to more accurately detect progression of CAV that is not readily apparent with coronary angiography.[5] However, anatomical evaluation is limited to assessing to the physiological consequences of epicardial coronary artery disease and is not able to assess microvascular dysfunction. In addition, the presence of epicardial CAV does not necessarily indicate that microvascular dysfunction is present and vice versa.[6, 7]

Assessing coronary physiology using a pressure-temperature sensor-tipped guidewire has been well validated in non-transplant patients.[8] The comprehensive physiologic assessment of the epicardial coronary artery and microcirculation has helped to characterize the physiologic phenotype of patients and to better predict their prognosis.[9, 10] Similarly, in transplant patients, fractional flow reserve (FFR) correlates with plaque volume assessed by IVUS, and the index of microcirculatory resistance (IMR) measured after transplantation has been shown to predict the development of CAV, poor graft function, and long-term mortality in single-center studies.[11, 12] The prognostic value of invasively assessing coronary physiology early after heart transplantation has not been adequately validated in a large multicenter study.

This international multicenter registry enrolled cardiac transplant recipients who underwent a comprehensive intracoronary physiology assessment at baseline and 1 year after transplantation. We then characterized the coronary physiologic abnormality into abnormal epicardial coronary physiology and/or microvascular dysfunction and evaluated their long-term prognostic value.

METHODS

Study Population

Patients were pooled from five prospective cohorts (three prospective randomized trials and two prospective observational studies conducted in four countries [USA, Norway, Sweden, and Korea]).[13-17] The study design, detailed entry criteria of each study, and the key features are summarized in Supplementary Table 1. For this analysis, only patients evaluated by comprehensive coronary physiologic assessment including FFR, IMR, and coronary flow reserve (CFR) at baseline and/or at 1 year after transplantation were included.

Immunosuppressive Therapy and Surveillance Endomyocardial Biopsy

All patients received standard immunosuppressive therapy according to the clinical protocol of each participating center.[13-15, 18-20] Briefly, patients received induction therapy with anti-thymocyte globulin, daclizumab, or dasiliximab. Maintenance immunosuppression was based on calcineurin inhibitors (cyclosporin or tacrolimus), antimetabolites (azathioprine or mycophenolate mofetil), and prednisone, which was tapered during the first year at some

Table 1. Baseline characteristics

	Physiologic Dysfunction at 1 Year			P value
	Normal Physiology (N=171)	Microvascular Dysfunction (N=57)	Reduced FFR (N=12)	
Recipient profile				
Age, year	50.3±12.0	50.2±14.7	50.2±13.0	>0.99
Male	119 (69.6%)	44 (77.2%)	11 (91.7%)	0.17
Race-White	148 (86.5%)	50 (87.7%)	9 (75.0%)	0.50
Hypertension	43 (25.1%)	14 (24.6%)	2 (16.7%)	0.81
Diabetes	23 (13.5%)	6 (10.5%)	3 (25.0%)	0.41
Smoking	53 (31.0%)	20 (35.1%)	4 (33.3%)	0.85
CMV IgG positive	114 (66.7%)	40 (70.2%)	11 (91.7%)	0.19
Etiology				
Ischemic cardiomyopathy	93 (54.4%)	27 (47.4%)	5 (41.7%)	0.50
Dilated cardiomyopathy	42 (24.6%)	19 (33.3%)	4 (33.3%)	0.38
Donor profile				
Age	36.1±13.7	38.6±14.3	37.6±12.9	0.48
Male	118 (69.0%)	43 (75.4%)	9 (75.0%)	0.62
CMV IgG positive	115 (67.3%)	37 (64.9%)	9 (75.0%)	0.79
Cold ischemic time, minute	200.5±66.0	208.0±66.0	225.4±57.2	0.38

	Physiologic Dysfunction at 1 Year			P value
	Normal Physiology (N=171)	Microvascular Dysfunction (N=57)	Reduced FFR (N=12)	
Sex mismatch	55 (32.2%)	13 (22.8%)	2 (16.7%)	0.25
ABO mismatch	3 (1.8%)	2 (3.5%)	0	0.63
Ejection fraction at baseline	58.9±7.76	59.4±6.4	59.2±10.5	0.92
Medication at baseline				
Statins	159 (93.0%)	55 (96.5%)	12 (100%)	0.42
Induction therapy	169 (98.8%)	54 (94.7%)	12 (100%)	0.15
Maintenance therapy				
Tacrolimus	56 (32.7%)	11 (19.3%)	3 (25.0%)	0.15
Cyclosporine	114 (66.7%)	46 (80.7%)	10 (83.3%)	0.081
Mycophenolate	155 (90.6%)	53 (93.0%)	11 (91.7%)	0.86
mTOR inhibitor	52 (30.4%)	21 (36.8%)	3 (25.0%)	0.58
ISHLT CAV classification at 1 year				0.40
CAV 0 (Nonsignificant)	150 (87.7%)	45 (78.9%)	10 (83.3%)	
CAV 1 (Mild)	18 (10.5%)	9 (15.8%)	2 (16.7%)	
CAV 2 (Moderate)	3 (1.8%)	3 (5.3%)	0	
CAV 3 (Severe)	0	0	0	
Physiologic measurement at 1 year				
FFR	0.90±0.05	0.92±0.05	0.77±0.03	<0.001
IMR	13.9±4.7	28.3±20.2	15.8±9.6	<0.001
CFR	4.7±2.4	2.2±1.0	3.1±1.3	<0.001
Cardiac events within 1 year				
Overall	47 (27.5%)	15 (26.3%)	3 (25.0%)	0.97
Acute cellular rejection (≥Grade 2)	35 (20.5%)	14 (24.6%)	3 (25.0%)	0.78
Myocardial infarction	0	0	0	
Coronary revascularization	1 (0.6%)	0	0	0.82
Stroke	4 (2.3%)	0	0	0.44
Graft dysfunction (ejection fraction≤45%)	1 (0.6%)	0	0	0.82
Readmission due to cardiac causes	13 (7.6%)	3 (5.3%)	1 (8.3%)	0.83

CAV indicates cardiac allograft vasculopathy; CFR, coronary flow reserve; CMV, cytomegalovirus; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; ISHLT, international society of heart lung transplantation; mTOR, mammalian target of rapamycin.

centers. Calcineurin inhibitors were partially or completely replaced with mammalian target of rapamycin inhibitors (everolimus or sirolimus) in selected patients according to the clinical status or protocol. Therapeutic levels of immunosuppressive agents and associated side effects were carefully monitored and titrated accordingly. Concomitant medications including statins and, in some cases, aspirin were initiated as soon as the patient was able to comply with oral intake. As part of standard clinical care, patients were monitored for the occurrence of acute cellular rejection by endomyocardial biopsies performed at the standard interval according to the clinical protocol of each participating center and at the time of any suspected episode of rejection. Specimens were graded with respect to rejection by each center's pathologist according to the criteria of the International Society for Heart and Lung Transplantation (ISHLT) 2004 version.[21]

Intracoronary Physiologic Assessment

At baseline and at 1 year after successful heart transplantation, intracoronary physiologic assessment was performed in conjunction with a coronary angiogram and intravascular imaging.[22] After performance of coronary angiography, FFR, IMR, and CFR were measured in the usual fashion with a pressure-temperature sensor-tipped guidewire (Abbott Vascular) placed in the distal two thirds of the left anterior descending artery.[12, 18] FFR was defined as the mean distal coronary pressure divided by the mean aortic pressure at maximal hyperemia. IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of hyperemic mean transit time.[23] CFR was calculated as resting mean transit time divided by hyperemic mean transit time. Resting and hyperemic mean transit time were measured using standard thermodilution techniques.[24] Maximal hyperemia was induced with intravenous adenosine at 140 μg/kg/min through a central vein or large antecubital vein.

Definition of Physiologic Abnormality

According to intracoronary physiology assessment, the study population was classified into 3 categories: normal coronary physiology, reduced FFR, and microvascular dysfunction. Patients with reduced FFR were defined as those having an FFR ⩽ 0.80 regardless of IMR and CFR values.[25] Microvascular dysfunction was defined according to standardized COVADIS (Coronary Vasomotion Disorders International Study Group) diagnostic criteria: IMR ⩾25 or CFR⩽2.0 in the absence of significant epicardial disease (FFR>0.80).[26] In addition, sustained abnormal physiology was defined when coronary physiology was abnormal at baseline and at 1 year, and newly developed abnormal physiology was defined when coronary physiology was normal at baseline and abnormal at 1 year.

Coronary Angiography and Intravascular Ultrasound Assessment

The angiographic severity of CAV after transplantation was evaluated by ISHLT classification based on 1-year coronary angiography.[5] ISHLT-CAV_0 indicates no detectable angiographic

lesion; ISHLT-CAV_1 (mild) indicates angiographic left main <50%, or primary vessel with a maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction; ISHLT-CAV_2 (moderate) indicates angiographic left main <50%, a single primary vessel ⩾ 70%, or isolated branch stenosis ⩾ 70% in branches of 2 systems, without allograft dysfunction; and ISHLT-CAV_3 (severe) indicates angiographic left main ⩾ 50%, or two or more primary vessels with ⩾ 70% stenosis, or isolated branch stenosis ⩾ 70% in all 3 systems, or ISHLT-CAV_1 or ISHLT-CAV_2 with allograft dysfunction.

Intravascular ultrasound (IVUS) was performed in the left anterior descending artery with a 20-MHz (Volcano Corporation Inc, CA, USA) or 40-MHz IVUS catheter (Boston scientific, Natick, Massachusetts, USA) and an automatic pullback at 0.5 mm/s. Offline IVUS analyses (EchoPlaque, Indec Systems, Santa Clara, CA) were performed in the IVUS core laboratory of individual participating centers according to the American College of Cardiology clinical expert consensus document.[27] Maximal intimal thickness (MIT) at baseline and at 1 year and the change in MIT was measured. An increase of ⩾ 0.5mm in MIT within 1 year after transplantation was considered as the rapid progression group.[28, 29]

Outcomes

The primary outcome of this study was the composite of death from any cause or re-heart transplantation. A major secondary outcome was the rate of major adverse cardiac events (MACE), the composite of death from any cause, re-heart transplantation, myocardial infarction defined by ischemic symptom and sign with cardiac enzyme elevation more than the upper reference limit, coronary revascularization including percutaneous coronary intervention or coronary bypass surgery, stroke, graft dysfunction defined by newly developed left ventricular dysfunction (ejection fraction of ⩽ 45%), or readmission due to a cardiac cause. Patients were censored at 10 years or when an event occurred.

Data Collection and Follow-up

Individual patient data from each study was sent to the study coordinating committee at Stanford University and merged for analysis. The pooled database was checked for completeness and consistency. Patients were followed until May of 2020. The independent ethics committee for each center/country approved each study protocol.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR); categorical variables are shown as counts and percentages. Continuous variables were compared using one-way analysis of variance (ANOVA); categorical variables were compared using χ^2 statistics or Fisher's exact test. Paired samples were compared using Wilcoxon test or McNemar test. Time-to-event data are presented as Kaplan–Meier estimates. The multivariable Cox regression model was used

to identify statistically significant predictors and potential confounders for the primary outcome. In addition, the treatment effect was estimated separately for each study, and the estimates were combined to provide an overall estimate of the treatment effect using a stratified Cox regression analysis. Variables listed in Table 1 were selected by the backward elimination methods and those with a significant association with death from cardiac causes and MACE were entered into the final model. To evaluate the prognostic value of physiology study at 1 year, patients who experienced clinical events before the physiology study at 1 year were censored in the multivariable model. Additionally, a time-varying cox proportional model using the physiology study at 1 year as time-varying covariate was performed. The proportional hazards assumption was tested using Schoenfeld residuals. A nested Cox proportional hazard regression analysis was used to investigate the incremental prognostic value of physiology abnormality. The cut-off value of coronary physiology indices was additionally assessed by time-dependent receiver operator characteristic curve analyses. Statistical analyses were performed using the SPSS version 21.0 software (IBM, Chicago, Illinois, USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). All applicable P-values were two-sided, and a value of $P < 0.05$ was considered statistically significant.

RESULTS

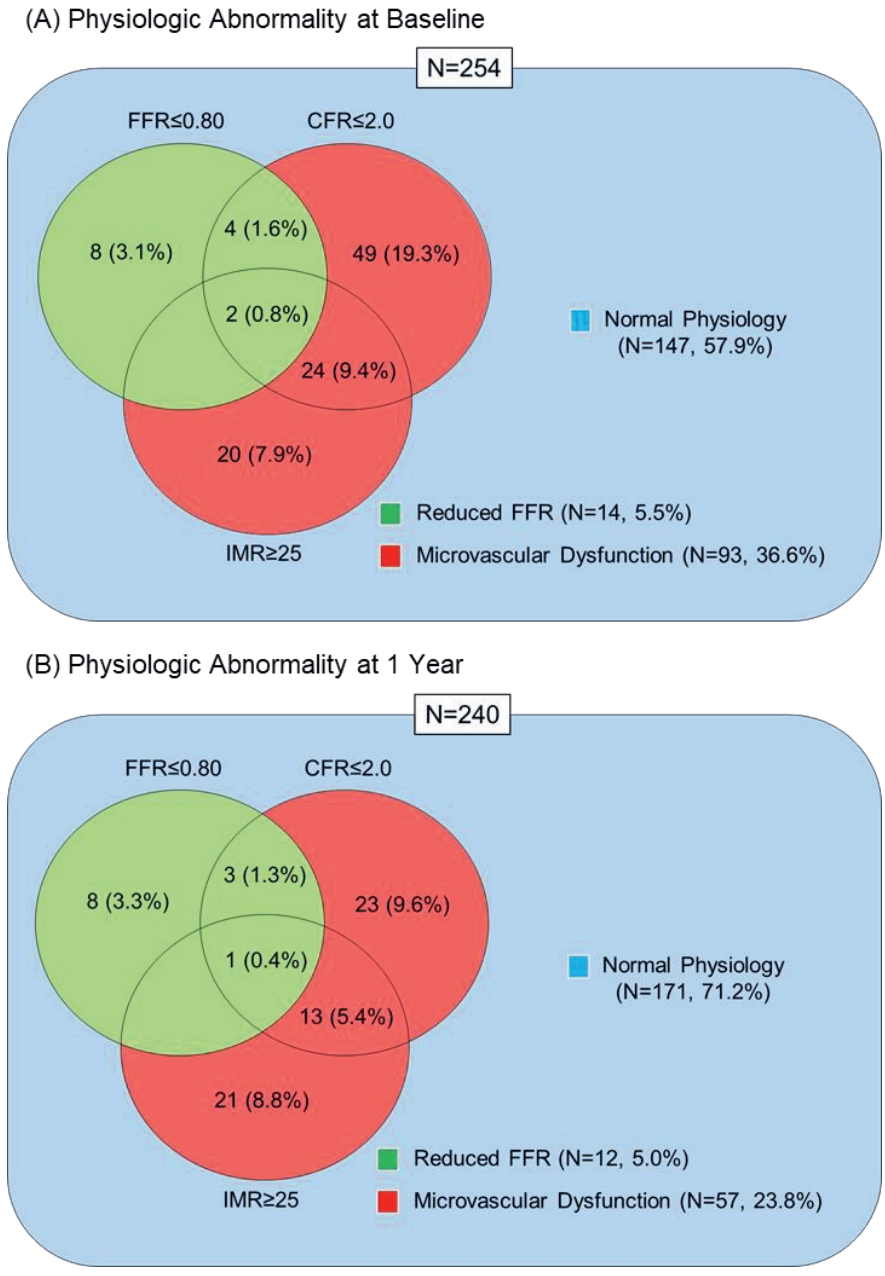
Baseline Characteristics

Comprehensive intracoronary physiologic evaluation for epicardial coronary artery and coronary microcirculation using FFR, IMR, and CFR were performed in 254 patients at baseline (7.2 weeks [Q1 to Q3, 4.1-10.3] after transplantation) and in 240 patients at 1 year (1.0 year [Q1 to Q3, 0.99-1.01]). Of those, 199 patients had both baseline and 1-year measurement (Figure 1). Overall, the recipient mean age was 50.3±12.7 years with 72.5% male sex. The donor mean age was 36.8±13.8 years with 70.8% male sex. Most patients were Caucasian (86.3%), with 3.3% Asian and 6.3% Black. Sex, blood type, and cytomegalovirus IgG mismatch occurred in 29.2%, 2.1%, and 20.8%, respectively. All patients received standard induction and maintenance immunosuppressive therapy. Patient characteristics are summarized in Table 1.

Changes in Coronary Physiology

FFR value did not change significantly (0.92 [Q1 to Q3, 0.88-0.94] at baseline to 0.91 [Q1 to Q3, 0.86-0.95] at 1 year, P=0.45). However, IMR decreased significantly from a median of 16.0 (Q1 to Q3, 11.3-22.8) to a median of 13.7 (Q1 to Q3, 10.2-19.6) (P=0.001) and CFR increased significantly from a median of 3.1 (Q1 to Q3, 2.0-4.1) to a median of 3.7 (Q1 to Q3, 2.5-5.2) (P<0.001).

Figure 1. Distribution of coronary physiologic abnormality at baseline and 1 year



Regarding the physiology phenotype, 5.5% of patients had reduced FFR and 36.6% of patients had microvascular dysfunction at baseline; 5.0% of patients had reduced FFR and 23.8% of patients had microvascular dysfunction at 1 year (Figure 1). The incidence of patients with reduced FFR was not significantly changed (P=0.79) from baseline to 1 year after transplantation while the incidence of those with microvascular dysfunction was significantly decreased (P=0.002) (Figure 1). Smoking status and donor age were statistically significantly associated with microvascular dysfunction.

Clinical Outcomes and Coronary Physiology

At 10 years, the primary outcome of the composite of death from any cause or re-transplantation occurred in 44 patients (40 death from any cause, and 4 re-transplantation). In addition, coronary revascularization occurred in 8 patients, stroke in 6 patients, graft dysfunction in 25 patients and re-admission in 54 patients among the cohort with physiology evaluation at 1 year.

At baseline physiologic assessment, reduced FFR was not associated with a higher risk of death or re-transplantation (adjusted hazard ratio [aHR], 2.33; 95% confidence interval, 0.88-6.15; P=0.088) and MACE (aHR, 1.69; 95% CI, 0.77-3.71; P=0.19) at 10 years. In addition, microvascular dysfunction at baseline was not associated with the higher risk of death or re-transplantation (aHR, 0.88; 95% CI, 0.44-1.79; P=0.73) and MACE (aHR, 0.88; 95% CI, 0.54-1.41; P=0.58) at 10 years (Table 2, Figure 2).

At 1 year assessment, reduced FFR was significantly associated with an increased risk of death or re-transplantation (aHR, 2.98; 95% CI, 1.13-7.87; P=0.028) but was not associated with the risk of MACE (aHR, 1.90; 95% CI, 0.68-5.34; P=0.22). Microvascular dysfunction was significantly associated with both the risk of death or re-transplantation (aHR, 2.33; 95% CI, 1.19-4.59; P=0.015) and the risk of MACE (aHR, 2.52; 95% CI, 1.45-4.35; <0.001) (Table 2 and Figure 2). Additional analysis using time varying Cox proportional model using physiology study at 1 year as time-varying covariate showed consistent results.

Sustained abnormal epicardial coronary physiology (reduced FFR) between baseline and 1 year (aHR, 11.4; 95% CI, 1.68-77.4; P=0.013), and newly developed microvascular dysfunction after baseline assessment (aHR, 7.12; 95% CI, 2.53-20.0; P<0.001) (Table 2 and Figure 3) contributed significantly to the prognostic value of the coronary physiologic assessment. Adding comprehensive invasive measures of coronary physiology into model including only clinical variables improved the prognostic performance to predict the death and re-transplantation and MACE at 10 years (Table 3). FFR ≤ 0.80 was not associated with long-term clinical outcomes after adjustments.

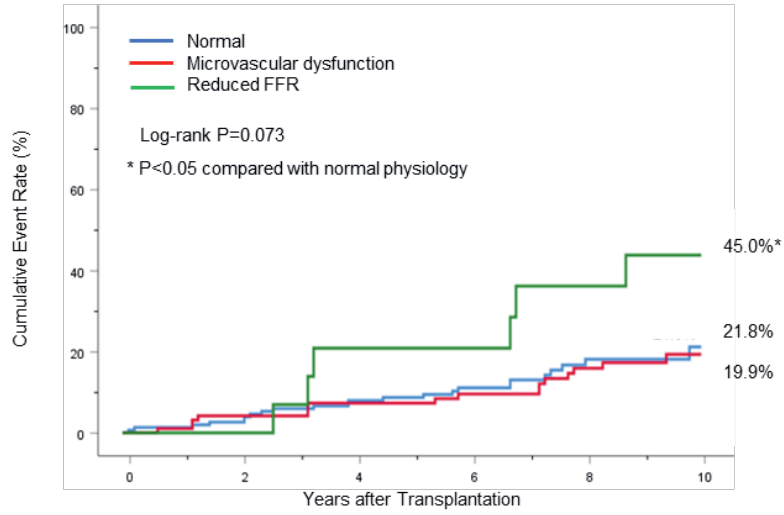
Table 2. Physiologic abnormality at baseline and 1 year and long-term outcome of death and re-transplantation at 10 years

	Event Rate* at 10 years No. (%)	Unadjusted Hazard Ratio (95% Confidence Interval)	P-Value	Adjusted Hazard Ratio† (95% Confidence Interval)	P-Value
At Baseline (N=254)					
Reduced FFR (N=14)	6 (45.0)	2.27 (0.89-5.77)	0.086	2.33 (0.88-6.15)	0.088
Microvascular dysfunction (N=93)	16 (19.9)	0.78 (0.40-1.50)	0.45	0.88 (0.44-1.79)	0.73
Normal coronary physiology (N=147)	23 (21.8)	1 (reference)		1 (reference)	
At 1 Year (N=240)					
Reduced FFR (N=12)	6 (55.6)	2.55 (1.00-6.47)	0.050	2.98 (1.13-7.87)	0.028
Microvascular dysfunction (N=57)	17 (33.1)	2.28 (1.18-4.42)	0.015	2.33 (1.19-4.59)	0.015
Normal coronary physiology (N=171)	21 (17.6)	1 (reference)		1 (reference)	
Changes between baseline and 1 year (N=199)					
Reduced FFR (at baseline – at 1-year)					
Abnormal – Abnormal physiology (N=2)	2 (100)	14.9 (2.96-75.1)	0.001	11.4 (1.68-77.4)	0.013
Normal – Abnormal physiology (N=6)	2 (40.0)	1.33 (0.31-5.75)	0.70	1.85 (0.39-8.82)	0.44
Abnormal – Normal physiology (N=8)	2 (27.1)	1.80 (0.41-7.88)	0.44	1.29 (0.26-6.61)	0.76
Normal – Normal physiology (N=183)	25 (19.5)	1 (reference)		1 (reference)	
Microvascular dysfunction (at baseline – at 1-year)					
Abnormal – Abnormal physiology (N=22)	2 (9.8)	0.36 (0.05-2.83)	0.33	0.38 (0.05-3.14)	0.37
Normal – Abnormal physiology (N=21)	8 (46.1)	7.04 (2.63-18.8)	<0.001	7.12 (2.53-20.0)	<0.001
Abnormal – Normal physiology (N=47)	10 (25.4)	1.21 (0.51-2.91)	0.66	1.47 (0.56-3.87)	0.44
Normal – Normal physiology (N=109)	11 (17.6)	1 (reference)		1 (reference)	

**Event rates were derived from Kaplan-Meier estimates.*
†Adjusted by recipient age, recipient race-white, etiology – ischemic cardiomyopathy, etiology – dilated cardiomyopathy, donor sex, induction therapy, maintenance therapy – mycophenolate

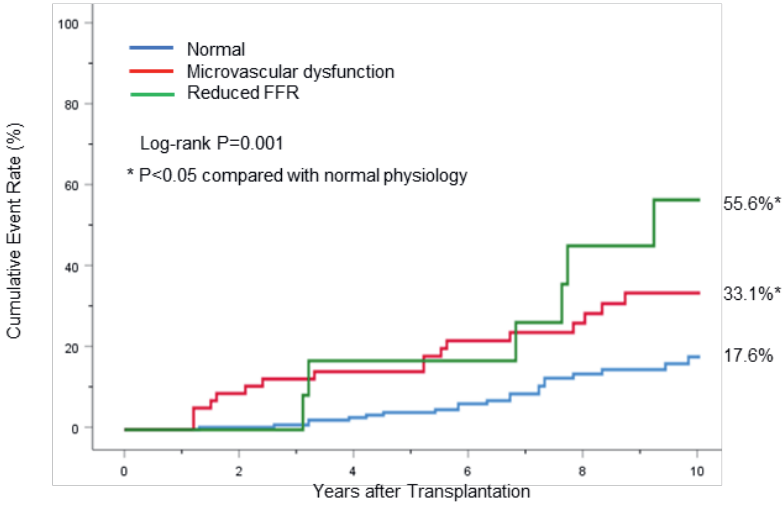
Figure 2. Physiologic abnormality at baseline and 1 year and the risk of death and re-transplantation at 10 years

(A) Physiologic Abnormality at Baseline



Reduced FFR	14	14	11	10	8	3
Microvascular dysfunction	93	89	85	78	64	24
Normal physiology	147	143	130	101	57	17

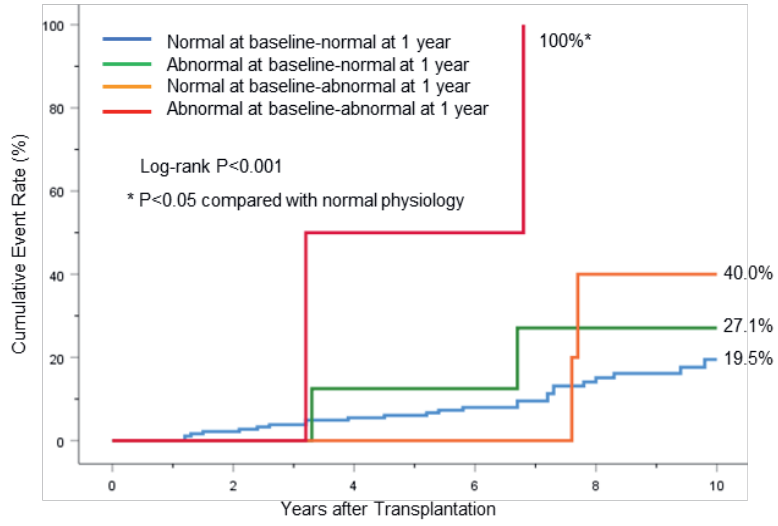
(B) Physiologic Abnormality at 1 Year



Reduced FFR	12	12	10	10	6	3
Microvascular dysfunction	57	52	48	39	32	15
Normal Physiology	171	170	161	128	83	44

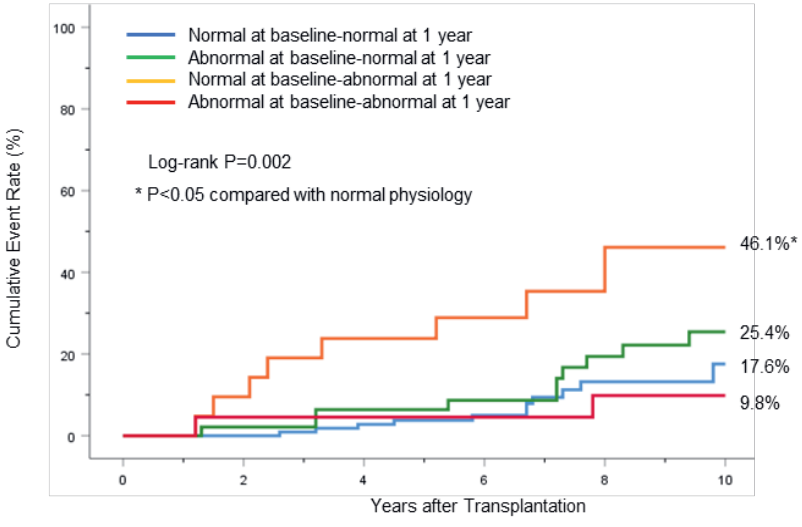
Figure 3. Changes in physiologic abnormality between baseline and 1 year and the risk of death and re-transplantation at 10 years

(A) Reduced FFR



Abnormal Abnormal	2	1	1	1	0	0
Normal Abnormal	6	6	6	6	5	1
Abnormal Norrmal	8	8	7	6	5	2
Normal Normal	183	179	167	135	85	35

(B) Microvascular Dysfunction



Abnormal Abnormal	22	21	21	19	17	7
Normal Abnormal	21	19	15	11	6	1
Abnormal Norrmal	47	46	43	40	30	16
Normal Normal	109	109	102	78	40	14

Table 3. Significant predictors of death and re-transplantation at 10 years

	Hazard Ratio	95% CI	P value	Chi-square improvement	P value
Model 1 – Baseline characteristics*					
Recipient age	0.98	0.95-1.00	0.037		
Etiology – ischemic cardiomyopathy	2.43	1.02-5.79	0.044		
Induction therapy	0.27	0.08-0.85	0.026		
Model 2 – Baseline characteristics + physiology abnormality at baseline				1.01	0.32
Abnormal epicardial physiology at baseline	2.33	0.88-6.15	0.088		
Microvascular dysfunction at baseline	0.88	0.43-1.79	0.73		
Model 3 – Baseline characteristics + physiology abnormality at 1 year				7.41	0.006
Recipient race-white	0.50	0.22-1.12	0.092		
Etiology – ischemic cardiomyopathy	2.53	0.94-6.84	0.067		
Abnormal epicardial physiology at 1year	2.98	1.18-4.59	0.015		
Microvascular dysfunction at 1year	2.33	1.18-4.59	0.028		
Model 4 – Baseline characteristics + changes in physiology between baseline and 1 year				14.0	<0.001
Recipient race-white	0.38	0.13-1.08	0.068		
Newly developed abnormal epicardial physiology	2.17	0.45-10.4	0.33		
Newly developed microvascular dysfunction	7.28	2.76-19.2	<0.001		

**Final model included recipient age, recipient race-white, etiology – ischemic cardiomyopathy, etiology – dilated cardiomyopathy, donor sex, induction therapy, maintenance therapy – mycophenolate*

Prognostic Value of Coronary Angiography and Intravascular Ultrasound Parameter

In our cohort (N=240) who underwent coronary physiology measurement at 1-year, angiographically detected ISHLT-CAV occurred in 35 patients (14.6%): 29 (12.1%) had ISHLT-CAV$_1$, and 6 (2.5%) had ISHLT-CAV$_2$, while most patients (N=203, 84.6%) had no angiographic evidence of CAV and no patients had ISHLT-CAV$_3$. The presence of any ISHLT-CAV (≥ ISHLT-CAV$_1$) was significantly associated with a higher risk of the composite of death or re-transplantation (aHR, 4.34; 95% CI, 1.29-14.6; P=0.018) and MACE (aHR, 4.34; 95% CI, 1.29-14.6; P=0.018) at 10 years. Nevertheless, the presence of microvascular dysfunction 1 year was significantly associated with the composite of death or re-transplantation (aHR, 2.16; 95% CI, 1.09-4.30; P=0.028) and MACE (aHR, 2.10; 95% CI, 1.12-3.34; P=0.008) even

after adjusting for angiographic severity of CAV. In addition, adding coronary physiology assessment improved the prognostic performance of a model including clinical variables plus angiographic severity of CAV.

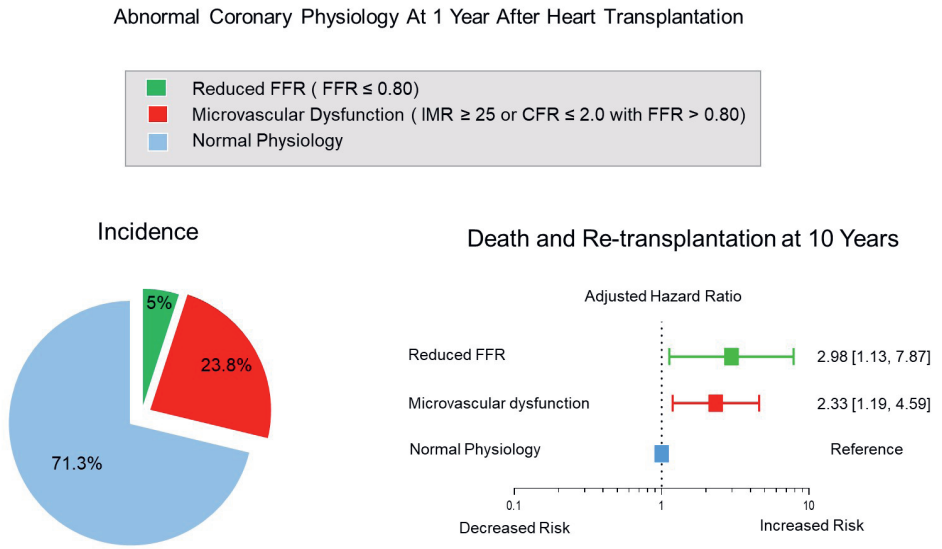
In our cohort, 206 patients underwent serial IVUS analysis at baseline and at 1 year. An increase of ≥ 0.5mm in MIT from baseline to 1 year after transplantation was observed in 10 (4.9%) patients and was not associated with long-term risk of death and re-transplantation (HR, 1.09; 95% CI, 0.26-4.55; P=0.91). The prognostic significance of reduced FFR (HR, 2.53; 95% CI, 1.24-5.18; P=0.011) and microvascular dysfunction (HR, 4.43; 95% CI, 1.52-13.0; P=0.007) was maintained even after putting an increase of ≥ 0.5mm in MIT into multivariable model.

DISCUSSION

This is the largest cohort to date studying the prognostic value of intracoronary physiology assessment in cardiac transplant recipients. The primary finding of this international multicenter registry is that either abnormal epicardial coronary physiology or microvascular dysfunction is common, occurring in 42.1% at baseline and 28.8% at 1 year after cardiac transplantation and both abnormal epicardial coronary physiology and microvascular dysfunction at 1 year were statistically significant predictors of the composite of death or re-transplantation at 10-year follow-up. This study suggests that for the management of the cardiac transplant recipient, a comprehensive intracoronary physiology assessment has an important clinical role in characterizing the patient's physiologic phenotype and predicting long-term outcomes and thus, should be considered as a routine monitoring strategy for CAV. Key questions which remain are how a clinician should respond to these abnormal phenotypes and whether adjunctive therapy will prevent future adverse events.

This study confirms a previous pathologic study on the prognostic value of microvascular dysfunction using comprehensive physiologic assessment based in a larger multicenter population [3, 10]. Microvascular dysfunction occurred more frequently than abnormal epicardial coronary physiology and had contrasting temporal trends in its incidence and prognostic value. Early after transplantation, 39.2% of patients had microvascular dysfunction, which decreased significantly by 1 year to 29.2% of patients. The prognostic value of microvascular dysfunction at baseline was not significant while microvascular dysfunction at 1 year was strongly associated with 10-year risk of death or re-transplantation; this was mostly a result of newly developed microvascular dysfunction. These findings suggest different underlying mechanisms of microvascular dysfunction according to the post-transplantation period.

Graphical abstract



Early after transplantation, microvascular dysfunction is likely to be associated with post-operative changes, reperfusion injury or an early immunologic or inflammatory reaction which are presumed to be temporary and reversible, and, thus, unlikely to mediate long-term outcomes. Microvascular dysfunction at 1 year is likely due to structural changes or overt functional deterioration.[3, 18] The incidence of pathologic microvasculopathy significantly increased during the 1-year post-transplantation period [3] and microvascular dysfunction at 1 year has been shown to be associated with impaired ventricular function, a decrease in cardiac index and stroke volume index and more hemodynamically compromising rejection [18]. Therefore, microvascular dysfunction at 1 year could be considered as a clinically relevant surrogate marker for long-term survival after heart transplantation and a potential therapeutic target for medical management, although this needs to be validated in further studies.[14, 30]

Currently, there is no standard criteria for detecting microvascular dysfunction after cardiac transplantation although CFR and IMR measured with a coronary wire in the catheterization laboratory are the best studied. In this study, we defined microvascular dysfunction in this study as either IMR ⩾ 25 or CFR ⩽ 2.0 in the absence of significant epicardial coronary stenosis (FFR > 0.80) according to COVADIS diagnostic criteria.[26] CFR is a dynamic test to evaluate the coronary vasodilatory capacity, defined as hyperemic coronary blood flow divided by resting flow, and represents the ability of the microcirculation to appropriately

increase myocardial blood flow. It is important to recognize that CFR interrogates the entire coronary circulation, both the epicardial vessel and the microvasculature, so an abnormal value can be indicative of abnormal physiology in either location. Additionally, an abnormal CFR may occur due to increased resting flow, with a normal hyperemic flow. This has been suggested as a specific endotype of microvascular dysfunction, which cannot be detected by measuring IMR alone. IMR measures the minimum achievable coronary microvascular resistance during hyperemia. Because it is measured during hyperemia, it is less dependent on hemodynamic changes and more reproducible than CFR,[31] which incorporates resting flow into its equation. Previous studies showed that both IMR[11, 12] and CFR[32, 33] were associated with the progression of CAV and decreased long-term survival after transplantation, although there were conflicting results.[34, 35] In this study, CFR ≤ 2.0 was associated with a higher risk of death and re-transplantation at 10 years and IMR ≥ 25 at baseline and year 1 were both associated with a higher risk of MACE at 10 years.

Abnormal epicardial coronary physiology assessed by FFR ≤0.80 was associated with 10-year mortality or re-transplantation in this study. However, an increase of ≥ 0.5mm in MIT based on serial IVUS was not. This could be explained by the low incidence of rapid progression of MIT: 4.9% in our study compared with 29.1% in previous studies,[28, 29] probably due to more extensive use of statin therapy and advances in immunosuppressive therapy. In addition, the diffuse nature of CAV can lead to a significant decline in myocardial perfusion pressure without a remarkable increase in MIT in a single plane measurement.[36] Finally, negative vascular remodeling, without intimal thickening can lead to a decrease in FFR.[37] Physicians should be aware that microvascular dysfunction after transplantation can attenuate hyperemia resulting in higher FFR values. Nevertheless, FFR continues to provide information about the impact of an epicardial stenosis on the percentage of maximum achievable myocardial flow. In addition, a previous study and this one found that microvascular dysfunction improved during the first year after transplantation, and worsened again thereafter.[36] In addition, simultaneous evaluation with microvascular function using IMR and CFR helps to interpret FFR more appropriately in cardiac transplant recipients.

There is some controversy about the prognostic significance of donor transmitted atherosclerosis. A previous study suggested that donor lesions do not accelerate plaque progression early after transplantation.[38] However, volumetric IVUS analysis demonstrated a significant association between donor transmitted atherosclerosis and worsening of CAV.[39, 40] Similarly, this study shows the prognostic value of donor transmitted atherosclerosis based on functional significance for predicting the risk of death or re-transplantation at 10 years, particularly when it sustained during the first year after transplantation.

This study has several limitations. First, this is a post hoc analysis of prospectively collected data. Second, given the wide confidence intervals for the estimate of effect, the findings do not allow for a conclusive interpretation, although this is the largest study to evaluate the prognostic value of coronary physiology measurements in heart transplant recipients. Third, coronary physiology and IVUS evaluations were performed only in the left anterior descending artery from a selected population. Fourth, the lack of a uniform immunosuppressive regimen partially due to long enrollment period could have affected the results. Fifth, endothelial dependent epicardial and microvascular dysfunction was not evaluated and may also be an important physiologic predictor of outcomes.[11] Sixth, because of the invasive study protocol performing intracoronary physiology assessment both at baseline and at 1 year, unstable patients were not included. Seventh, we had few patients with very low FFR compared with some earlier studies. It may be that more recent improvements in medical management after heart transplantation have led to less CAV and higher FFR values. Finally, this study included 3 randomized clinical trials. Study randomization may have affected our results.

In conclusion, coronary physiologic abnormalities at 1 year after cardiac transplantation are common and are statistically significant predictors of death and re-transplantation at 10 years. Therefore, invasively assessing coronary physiology may help identify cardiac transplant recipients at high-risk for future adverse events who may benefit from close follow-up and individualized medical therapy. However, it should be taken into consideration that the diagnostic criteria for physiology abnormalities used in this study were derived from patients with non-transplant heart disease, and further study to determine the optimal cut-off values of each physiology index in the heart transplantation population will be necessary.

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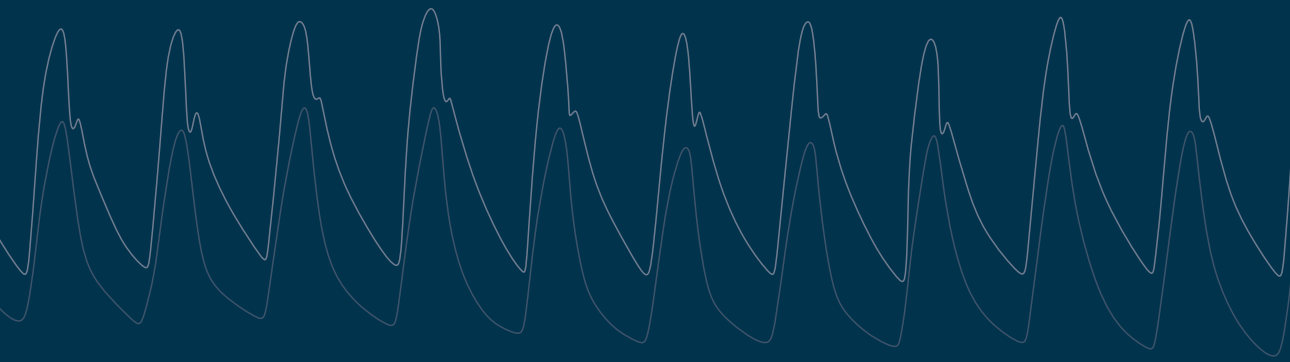
Supplementary Table 1. Key features of each study

	CMV Study	ACEi Study	SCHEDULE	HITTS	IRIS FFR
Enrolling period	2002-2005	2009-2014	2009-2011	2012-2016	2010-2012
Patient Number	69	50	70	66	40
Location	USA	USA	Norway/Sweden	Norway/Sweden	Korea
Study	Prospective Registry	Prospective Randomized	Prospective Randomized	Prospective Randomized	Prospective Registry
Intervention	CMV specific T cell immunity	Ramipril	Everolimus	High-intensity interval training	NA
Immunosuppressive therapy					
Induction therapy	Daclizumab	ATG/daclizumab	ATG	ATG/Basiliximab	ATG/Basiliximab
Maintenance therapy	Cyclosporine MMF Corticosteroid	Cyclosporin/ Tacrolimus MMF Corticosteroid	Cyclosporine/ Everolimus MMF Corticosteroid	Calcineurin inhibitors Everolimus MMF Corticosteroid	Cyclosporin/Tacrolimus MMF Sirolimus/Everolimus Corticosteroid
Findings	Early post-transplantation CMV specific CD4 T-cell responses was associated with lower allograft rejection and coronary allograft vasculopathy	Ramipril improved microvascular function, the number and function of circulating endothelial progenitor cells, and lowered blood pressure	Everolimus with early withdrawal of cyclosporin improved renal function and attenuated the development of coronary allograft vasculopathy	High-intensity interval training resulted in a greater change in exercise capacity	NA



CHAPTER 15

Index of Microcirculatory Resistance to Predict Acute Allograft Rejection and Cardiac Events After Heart Transplantation

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ABSTRACT

Background

Single center data suggest that the index of microcirculatory resistance (IMR) measured early after heart transplantation predicts subsequent acute rejection.

Objectives

To validate whether IMR measured early after transplantation can predict subsequent acute rejection and long-term outcome in a large multicenter cohort.

Methods

From 5 international cohorts, 237 patients who underwent IMR measurement early after transplantation were enrolled. The primary outcome was acute allograft rejection (AAR) within 1 year after transplantation. A key secondary outcome was major adverse cardiac events (MACE, the composite of death, re-transplantation, myocardial infarction, stroke, graft dysfunction, and readmission) at 10 years.

Results

IMR was measured at a median of 7 weeks (interquartile range: 3-10 weeks) post-transplantation. At 1 year, the incidence of AAR was 14.4%. IMR was associated proportionally with the risk of AAR (per increase of 1-unit IMR; adjusted hazard ratio [aHR], 1.04; 95% confidence interval [CI], 1.02-1.06; P=0.001). The incidence of AAR in patients with IMR ≥ 18 was 23.8%, while the incidence of AAR in those with IMR < 18 was 6.3% (aHR, 3.93; 95% CI, 1.77-8.73; P=0.001). At 10 years, MACE occurred in 86 (36.3%) patients. IMR was significantly associated with the risk of MACE (per increase of 1-unit IMR; aHR, 1.02; 95% CI, 1.01-1.04; P=0.005).

Conclusion

IMR measured early after heart transplantation is associated with subsequent AAR at 1 year and clinical events at 10 years. Early IMR measurement after transplantation identifies patients at higher risk and may guide personalized post-transplantation management.

INTRODUCTION

Acute allograft rejection has been a major barrier to favorable long-term outcomes after heart transplantation. While the rates of acute rejection continue to decline with the advance of effective immunosuppression, the risk of rejection remains significant particularly within the first year after transplantation (1). Moreover, patients with rejection within 1 year have a higher risk of late cardiac allograft vasculopathy, graft loss and mortality (2). Endomyocardial biopsy has been a routine method of surveillance for rejection in asymptomatic patients, but the pathologic diagnosis of acute rejection is made only after myocyte damage (3,4). Therefore, earlier prediction of subsequent acute allograft rejection could allow for preemptive modification in immunosuppression and surveillance which might improve outcomes.

The index of microcirculatory resistance (IMR) is an invasive physiologic index which measures minimal coronary microvascular resistance and is predictive of cardiac events in various clinical settings associated with microvascular dysfunction (5). In heart transplant recipients, IMR at 1-year post-transplantation is predictive of development of cardiac allograft vasculopathy, poor graft function, and late death or re-transplantation (6,7). In addition, a small, single center study suggested that IMR early after transplantation is associated with subsequent acute allograft rejection during the first 1 year (8). The aim of this large international, multicenter registry is to validate whether IMR measured early after transplantation predicts subsequent acute allograft rejection and long-term cardiac events.

METHODS

Study Population

Patients were pooled from five prospective cohorts (three prospective randomized trials and two prospective observational studies conducted in four countries [USA, Norway, Sweden, and Korea]) (9-13). For this analysis, only patients evaluated by physiologic assessment including IMR early after transplantation were included and patients with acute cellular rejection of ≥ grade 2R or antibody-mediated rejection of ≥ pAMR2 before intracoronary physiologic assessment were excluded.

Immunosuppressive Therapy and Surveillance Endomyocardial Biopsy

All patients received standard immunosuppressive therapy according to the clinical protocol of each participating center (7,9-11,14). Briefly, patients received induction therapy with anti-thymocyte globulin, daclizumab, or basiliximab. Maintenance immunosuppression was based on calcineurin inhibitors (cyclosporin or tacrolimus), antimetabolites (azathioprine

or mycophenolate mofetil) as well as prednisone, which at some centers were tapered during the first year. Calcineurin inhibitors were partially or completely replaced with mammalian target of rapamycin inhibitors (everolimus or sirolimus) in selected patients according to the clinical status or protocol. Therapeutic levels of immunosuppressive agents and associated side effects were carefully monitored and titrated accordingly. Concomitant medication, including statins and in some centers aspirin, were initiated as soon as the patient was able to tolerate oral intake. As part of standard clinical care, patients were monitored for the occurrence of acute rejection by endomyocardial biopsies performed at a standard interval according to the clinical protocol of each participating center and at the time of any suspected episode of rejection. Specimens were graded by each center's pathologist according to the criteria of the International Society for Heart and Lung Transplantation (ISHLT) 2004 version for acute cellular rejection (4) and the criteria of ISHLT 2013 version for antibody-mediated rejection (15) blinded to the IMR result.

Intracoronary Physiology Assessment

Early after successful heart transplantation, intracoronary physiologic assessment was performed in conjunction with a coronary angiogram (16). After performance of coronary angiography, IMR and coronary flow reserve (CFR) as well as fractional flow reserve (FFR) were measured in the usual fashion with a pressure-temperature sensor-tipped guidewire (Abbott Vascular) placed in the distal two thirds of the left anterior descending artery (6,7). IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of hyperemic mean transit time (17). Maximal hyperemia was induced with intravenous adenosine at 140 μg/kg/min through a central vein or large antecubital vein. Patients were grouped according to an IMR of 18, which was found to be the best cut-off value to predict acute allograft rejection. CFR was calculated as resting mean transit time divided by hyperemic mean transit time. Resting and hyperemic mean transit times were measured using a standard thermodilution techniques (18). FFR was defined as the mean distal coronary pressure divided by the mean aortic pressure at maximal hyperemia.

Outcomes

The primary outcome was acute allograft rejection including acute cellular rejection of ≥ grade 2R and/or antibody-mediated rejection of ≥ pAMR2 within 1 year after heart transplantation (4,15). A key secondary outcome was the rate of major adverse cardiac events (MACE) at 10 years, defined as the composite of death from any cause, re- transplantation, myocardial infarction (defined by ischemic symptoms and signs with cardiac enzyme elevation more than the upper reference limit), coronary revascularization including percutaneous coronary intervention and coronary bypass surgery, stroke, graft dysfunction (defined by newly developed left ventricular dysfunction with ejection fraction of ≤ 45%), or readmission due to a cardiac cause. Patients were censored at 10 years or when events occurred.

Data Collection and Follow-up

The principal investigators in each study collected data according to a protocol with pre-specified outcomes and a common set of baseline variables. Individual patient data from each study were sent to the study coordinating committee at Stanford University and merged for analysis. The pooled database was checked for completeness and consistency by all participating centers. Patients were followed until May 31th 2020. The independent ethics committee for each center/country approved the original study protocols.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation; categorical variables are shown as counts and percentages. Continuous variables were compared using unpaired t-tests or non-parametric Mann-Whitney tests; categorical variables were compared using $\chi 2$ statistics or Fisher's exact test. The best cutoff value to predict acute allograft rejection within 1 year and MACE at 10 years were calculated by using areas under the receiver-operating characteristic (ROC) curve analysis with Youden index. The 95% confidence interval (CI) for cut-off points were obtained through bootstrapping with percentile method (1000 replicates). Time-to-event data are presented as Kaplan–Meier estimates. The multivariable Cox regression model was used to identify independent predictors and potential confounders for the primary outcome and the key secondary outcome. The proportional hazards assumption was tested using Schoenfeld residuals test and log-log plot; no relevant violations of the assumption were found. Variables listed in Table 1 were selected by the backward elimination methods and those with a significant association with the outcome were entered into the final model. Final model included variables including recipient race-white, male donor, maintenance therapy at baseline – tacrolimus for acute allograft rejection at 1 year and recipient race-white, etiology-ischemic cardiomyopathy, induction therapy, maintenance therapy at baseline – mycophenolate for MACE at 10 years. As a secondary analysis, mixed effects Cox model was used to account for center effect (19). Also, stratified Cox proportional hazards models were used to determine whether the merged data would influence the primary outcome and a likelihood-ratio test was performed to assess the homogeneity of data. Prognostic performance of IMR was assessed using Harrell's C-index. Statistical analyses were performed using the SPSS version 21.0 software (IBM, Chicago, Illinois, USA) and R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All applicable P-values were two-sided, and a value of $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 254 patients had invasive coronary physiology evaluation at a median of 7 weeks (interquartile range [IQR], 3 weeks to 10 weeks) after heart transplantation. Seventeen patients who had acute cellular rejection grade 2 or 3 before IMR measurement were excluded leaving 237 patients in the final analysis. Patient characteristics are summarized in Table 1. Overall, the recipient mean age was 50.0±12.8 years with 73% male sex. The donor mean age was 34.7±13.2 years with 69% male sex. All patients received standard induction and maintenance immunosuppressive therapy. The median IMR was 16.3 (IQR, 11.7 to 22.9).

Acute Allograft Rejection and IMR

Follow-up of vital status and the occurrence of acute allograft rejection was complete in all patients at 1 year after heart transplantation: 33 (14.0%) patients had acute cellular rejection ≥ grade 2R, 1 (0.4%) patient had antibody-mediated rejection of ≥ pAMR2, and 3 (1.3%) patients died during the first year, but after baseline IMR evaluation. No patient underwent re-heart transplantation during the first year. All acute allograft rejection events resolved with intensification of immunosuppressive therapy, as confirmed by follow-up endomyocardial biopsy.

IMR measured early after transplantation was independently associated with the risk of acute allograft rejection within 1 year (per increase of 1-unit IMR; adjusted hazard ratio [aHR], 1.04; 95% CI, 1.01-1.06; P=0.003). Based on ROC curve analysis, the best cut-off value to predict acute allograft rejection was an IMR ≥ 18 (95% CI, 16-36).

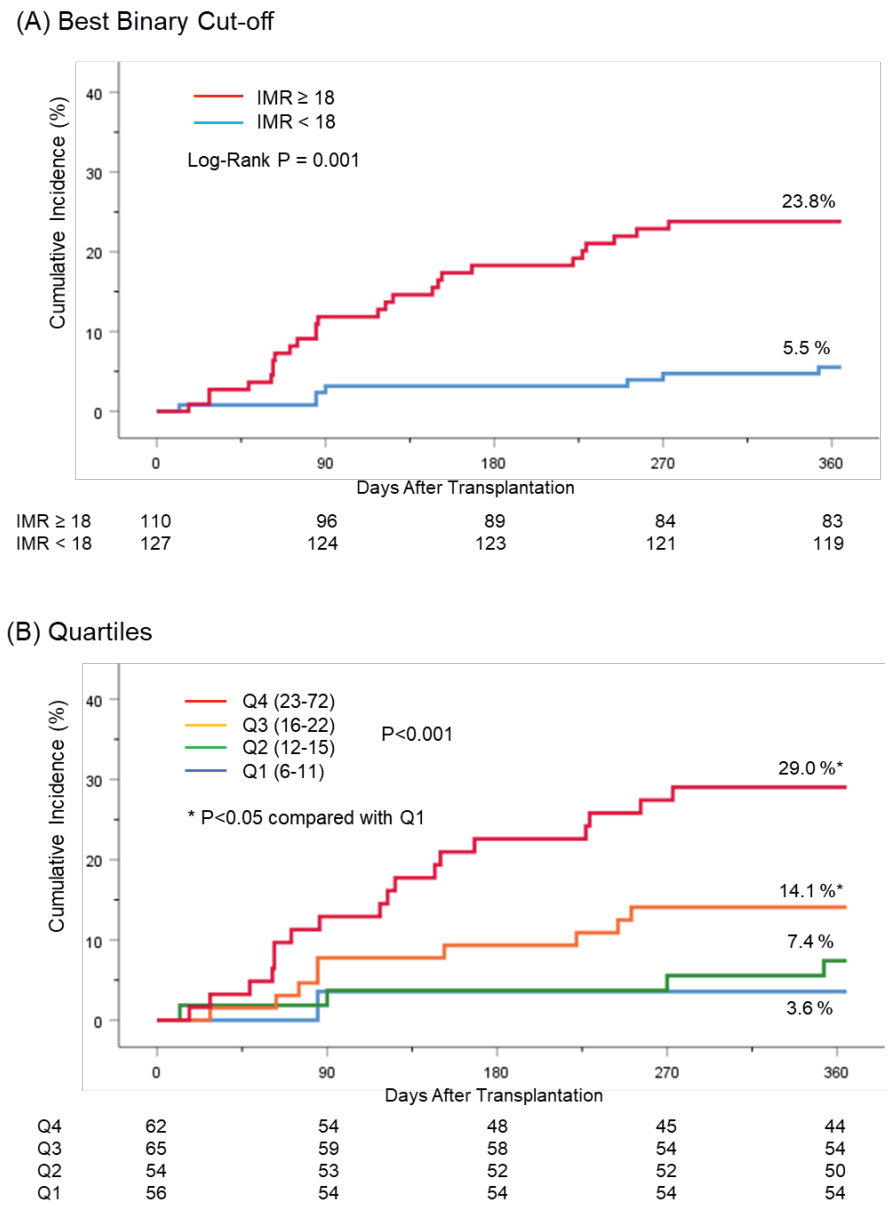
The incidence of acute allograft rejection in patients with IMR ≥ 18 was 23.8%, while the incidence of acute cellular rejection in those with IMR < 18 was 6.3% (P<0.001) indicating a negative predictive value of 93.7% (Figure 1A). Even after adjustment, IMR ≥ 18 was significantly associated with the risk of acute allograft rejection (aHR, 3.93; 95% CI, 1.77-8.73; P=0.001). In addition, the 1-year incidence of acute allograft rejection increased in proportion to quartiles of IMR (Table 2 and Figure 1B). As the immunosuppressive regimen was not uniform according to the study site (Supplementary Table 1), we performed the subgroup analysis according to the immunosuppressive agents. The predictive value of IMR on acute allograft rejection at 1 year was consistent across different immunosuppressive agents. Stratified Cox proportional hazards models also showed similar findings for the primary and key secondary outcomes. A likelihood-ratio test demonstrated the assumption of homogeneity was not violated (P=0.84 for the primary outcome).

Table 1. Baseline characteristics

	All patients (N=237)	The index of microcirculatory resistance		
		IMR ⩾ 18.0 (N=110)	IMR < 18.0 (N=127)	P value
Recipient profile				
Age, year	50.4±12.6	51.0±11.6	49.9±13.5	0.53
Male	173 (73.0%)	80 (72.7%)	93 (73.2%)	0.93
Diabetes	31 (13.1%)	12 (10.9%)	19 (15.0%)	0.36
Hypertension	59 (24.9%)	30 (27.3%)	29 (22.8%)	0.43
CMV IgG positive	158 (66.7%)	74 (67.3%)	84 (66.1%)	0.85
Ischemic cardiomyopathy	61 (25.7%)	30 (27.3%)	31 (24.4%)	0.62
Race				0.60
White	171 (72.2%)	77 (70.0%)	94 (74.0%)	
Asian	47 (19.8%)	23 (20.9%)	24 (18.9%)	
Black	11 (4.6%)	5 (4.5%)	6 (4.7%)	
Hispanic	5 (2.1%)	4 (3.6%)	1 (0.8%)	
Donor profile				
Age, year	35.3±13.5	36.2±13.3	34.5±13.7	0.35
Male	167 (70.5%)	83 (75.5%)	84 (66.1%)	0.12
CMV IgG positive	160 (67.5%)	74 (67.3%)	86 (67.7%)	0.94
Cold ischemic time, minute	191.9±68.3	202.0±61.4	186.6±72.8	0.084
Ejection fraction after transplantation	59.7±7.3	59.7±8.0	59.7±6.7	0.98
ABO mismatch	4 (1.7%)	1 (0.9%)	3 (2.4%)	0.39
Sex mismatch	66 (27.8%)	25 (22.7%)	41 (32.3%)	0.10
Coronary physiology indexes				
Fractional flow reserve	0.91±0.06	0.91±0.05	0.90±0.07	0.023
Coronary flow reserve	3.2±1.8	2.5±1.1	3.8±2.1	<0.001
IMR	18.8±10.5	26.8±10.3	11.9±3.0	<0.001
Medication at baseline				
Statins	221 (93.2%)	101 (91.8%)	120 (94.5%)	0.41
Induction therapy	234 (98.7%)	109 (99.1%)	125 (98.4%)	0.65
Maintenance at baseline				
Tacrolimus	95 (39.7%)	39 (35.5%)	55 (43.3%)	0.22
Cyclosporine	142 (59.9%)	70 (63.6%)	72 (56.7%)	0.28
Mycophenolate	221 (93.2%)	100 (90.9%)	121 (95.3%)	0.18
mTOR inhibitor	65 (27.4%)	26 (23.6%)	39 (30.7%)	0.22

CMV, cytomegalovirus; IMR, index of microcirculatory resistance; mTOR, mammalian target of rapamycin

Figure 1. The Incidence of acute allograft rejection at 1 year



Kaplan-Meier curve shows a higher rate of acute allograft rejection at 1 year in patients with the index of microcirculatory resistance (IMR) of › 18 at baseline (A). In addition, the 1-year incidence of acute allograft rejection increases in proportion to quartiles of IMR (B).

Table 2. Predictive value of IMR for acute allograft rejection at 1 year post transplantation

	Even Rate (%)*	Unadjusted HR	P value	Adjusted HR†	P value
Continuous variable					
IMR as increase of 1-unit	NA	1.05 (1.03-1.07)	<0.001	1.04 (1.02-1.06)	<0.001
Binary variable‡					
IMR ⩾ 18 (N=110)	26 (23.8%)	4.14 (1.88-9.16)	<0.001	3.93 (1.77-8.73)	0.001
IMR < 18 (N=127)	8 (6.3%)	1.0 (reference)		1.0 (reference)	
Categorical variable according to quartiles			0.003		0.001
Q4 (IMR 23-72, N=62)	18 (29.0%)	6.22 (1.83-21.1)	0.003	5.21 (1.53-17.8)	0.008
Q3 (IMR 16-22, N=65)	9 (14.1%)	2.75 (0.75-10.2)	0.13	1.88 (0.50-7.07)	0.35
Q2 (IMR 12-15, N=54)	4 (7.4%)	1.44 (0.32-6.44)	0.63	0.96 (0.21-4.38)	0.96
Q1 (IMR 6-11, N=56)	3 (5.4%)	1.0 (reference)		1.0 (reference)	

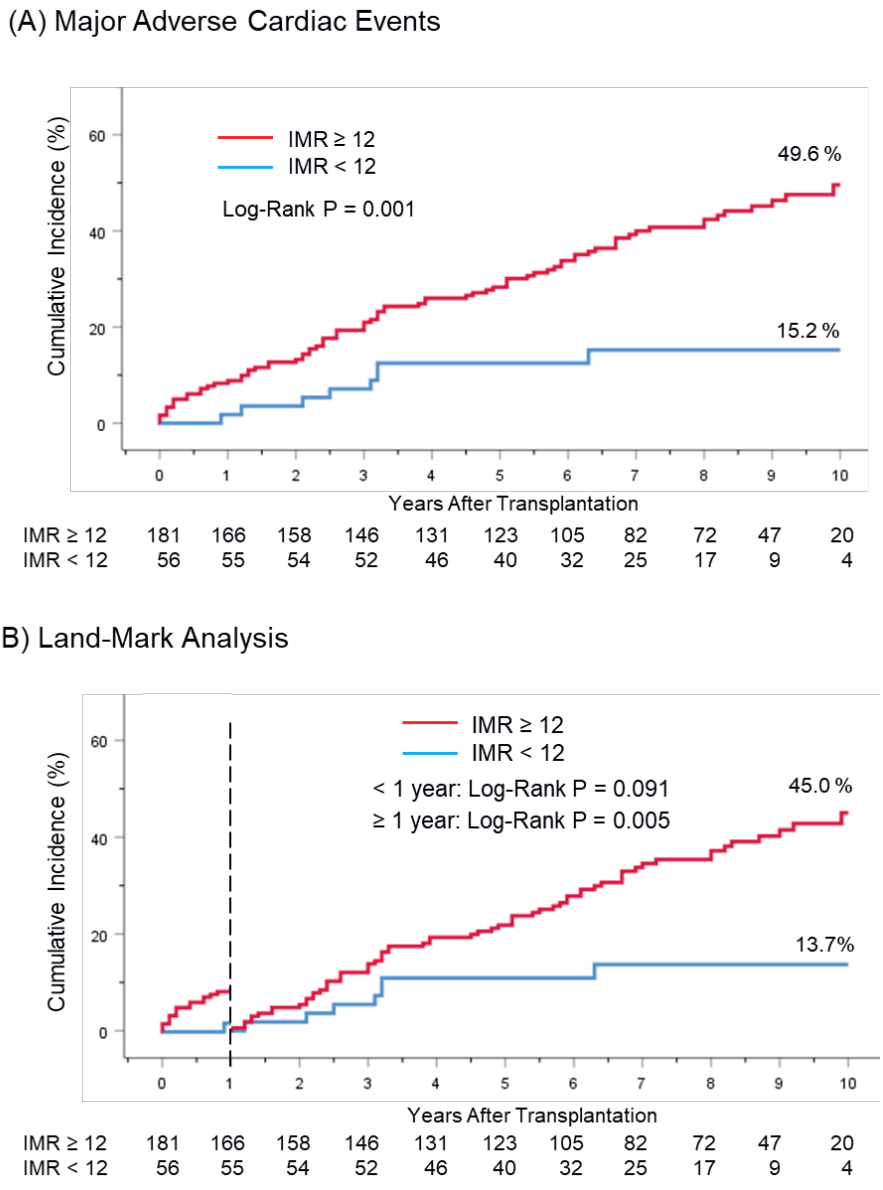
**Derived from Kaplan-Meier estimate*
†Adjusted by recipient race-white, male donor, maintenance therapy at baseline – tacrolimus.‡Cut-off value was derived from receiver operating characteristic curve analysis.
HR, hazard ratio; IMR, index of microcirculatory resistance; NA, not accessible

A multivariable Cox model showed that IMR was an independent predictor for acute allograft rejection at 1 year while CFR was not an independent predictor for acute allograft rejection at 1 year (Table 3), although a lower CFR was associated with the risk of acute allograft rejection at 1 year.

Long-Term Clinical Outcomes

At 10 years after transplantation, 88 MACEs occurred. IMR at baseline was significantly associated with the risk of MACE at 10 years (per increase of 1-unit IMR; aHR, 1.02; 95% CI, 1.01-1.04; P=0.005). ROC curve analysis showed the best cut-off value to predict MACE at 10 years was IMR ⩾ 12 (95% CI, 11-23). IMR ⩾ 12 was significantly associated with the risk of MACE (aHR, 2.60; 95% CI, 1.24-5.42; P=0.011) (Figure 2A), which was mostly driven by higher risk of admission due to cardiac causes (Table 4). Land-mark analysis showed that the event rate continued to diverge after 1 year after transplantation (Figure 2B). Multivariable Cox model showed that IMR was an independent predictor for MACE at 10 years while CRF was not associated with MACE at 10 years. IMR was serially measured in 172 patients at 1 year and IMR ⩾ 21 (95% CI, 11-22) at 1 year was also significantly associated with the risk of MACE at 10 years (aHR, 2.17; 95% CI, 1.21-3.88; P=0.009).

Figure 2. The Incidence of major adverse cardiac events at 10 years



Kaplan-Meier curve shows a higher rate of major adverse cardiac events at 10 years in patients with the index of microcirculatory resistance of › 12 at baseline (A). Landmark analysis shows that the event rate continues to diverge after 1 year after heart transplantation (B).

Table 3. Independent predictors for acute allograft rejection at 1 year

	Hazard Ratio	95% CI	P value	C-index	P Value*
Model 1 – Baseline characteristics*				0.66	
Recipient race-white	0.34	0.16-0.73	0.006		
Maintenance therapy – Tacrolimus	0.23	0.09-0.57	0.002		
Model 2 – Baseline characteristics + Coronary physiology at baseline				0.76	0.014
Recipient race-white	0.39	0.18-0.83	0.015		
Maintenance therapy – Tacrolimus	0.29	0.12-0.72	0.008		
CFR ⩽ 3.8	2.55	0.63-12.3	0.18		
IMR ⩾ 18	3.68	1.39-7.23	0.006		

** P value for C-index improvement † Included variables were selected by a backward stepwise multivariate Cox regression model from variables listed in Table 1. Final model included recipient race-white, male donor, maintenance therapy at baseline – tacrolimus.*

Prognostic performance of IMR

Adding IMR on top of clinical variables improved prediction of acute allograft rejection at 1 year (C-index improvement: 0.10, P=0.014) and MACE at 10 years (C-index improvement: 0.04, P=0.038) (Table 3).

DISCUSSION

This large international multicenter study demonstrates that IMR measured early after heart transplantation is highly predictive of subsequent acute allograft rejection during the first year after transplantation and long-term cardiac events at 10 years. In addition, IMR is a stronger predictor of acute allograft rejection and long-term cardiac events than clinical variables alone.

IMR is a measure of minimal coronary microvascular resistance, defined as distal coronary pressure divided by flow during maximal hyperemia (17). Compared with CFR (a traditional index of microvascular function), IMR interrogates the microcirculation specifically, is less effected by epicardial coronary artery disease, more reproducible and affected less by changes in hemodynamics (20).

A number of risk factors for acute rejection have been suggested such as age, gender, race, circulating anti-HLA antibodies, induction therapy, HLA mismatch, and genetic polymorphisms (21-23). In this study, we demonstrated the value of IMR to predict acute allograft rejection at a single time point, a median of 7 weeks after heart transplantation. Even after adjusting for clinical risk factors, a high IMR (⩾18) showed 3.52-fold higher risk

Table 4. Predictive value of IMR for major adverse cardiac events at 1 year and 10 years post transplantation

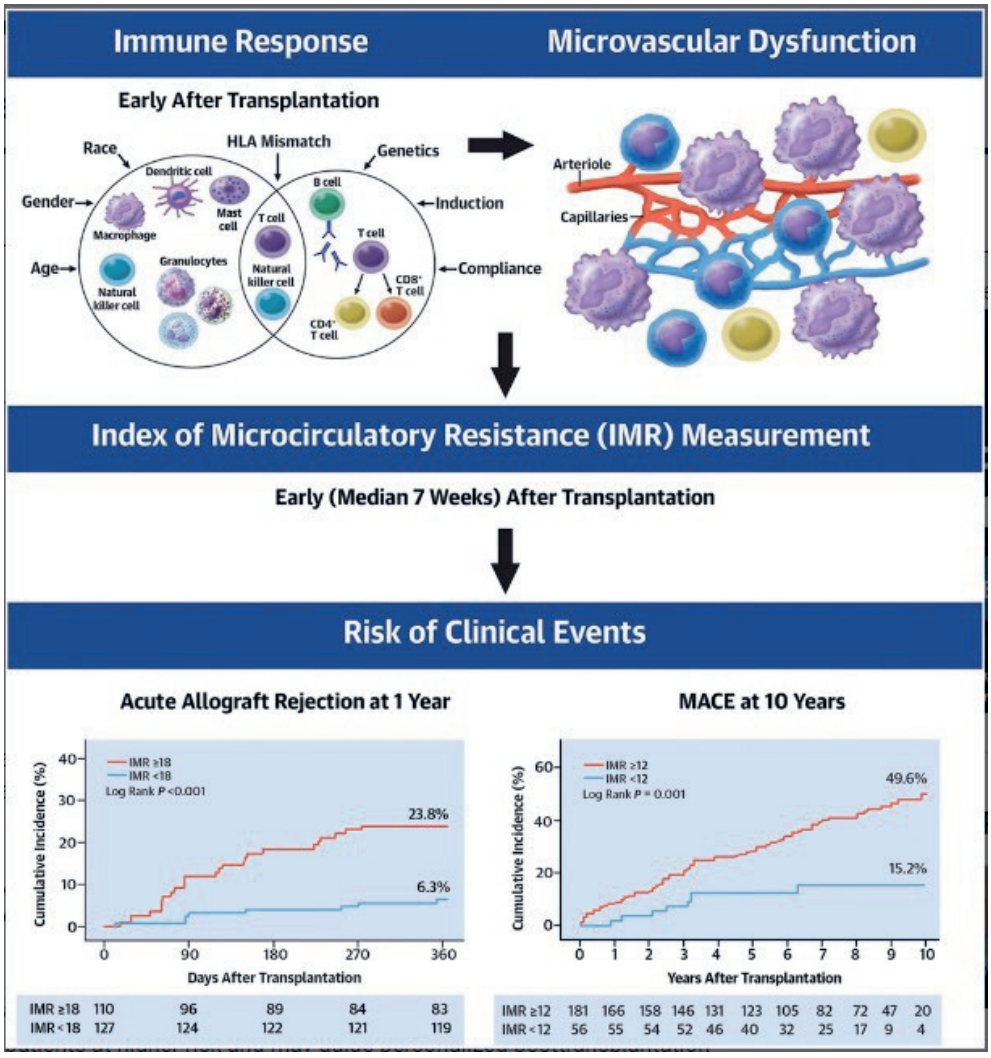
	IMR ⩾ 12 (N=181)	IMR < 12* (N=56)	Unadjusted HR	P value	Adjusted HR‡	P value
	Number (%)†					
Major adverse cardiac events at 1 year	15 (8.3%)	1 (1.8%)	4.85 (0.64-36.7)	0.13	3.84 (0.50-29.8)	0.20
Death or re-transplantation	3 (1.7%)	0				
Myocardial infarction	1 (0.6%)	0				
Stroke	2 (1.1%)	1 (1.8%)				
Repeat revascularization	0	0				
Graft dysfunction (ejection fraction⩽45%)	1 (0.6%)	0				
Admission due to cardiac cause	12 (6.7%)	0				
Major adverse cardiac events at 10 years	78 (49.6%)	8 (15.2%)	3.12 (1.51-6.47)	0.002	2.60 (1.24-5.42)	0.011
Death or re-transplantation	39 (26.5%)	4 (7.1%)				
Myocardial infarction	1 (0.6%)	0				
Stroke	4 (3.2%)	1 (1.8%)				
Repeat revascularization	9 (6.3%)	0				
Graft dysfunction (ejection fraction⩽45%)	29 (19.7%)	1 (2.0%)				
Admission due to cardiac cause	43 (29.8%)	4 (8.4%)				

** Cut-off value was derived from receiver operating characteristic curve analysis.*
†Derived from Kaplan-Meier estimate
‡Adjusted by recipient race-white, etiology-ischemic cardiomyopathy, induction therapy, maintenance therapy at baseline – mycophenolate.
HR, hazard ratio; IMR, index of microcirculatory resistance; NA, not accessible

of acute allograft rejection compared with a low IMR (<18). The optimal cut-off value in our cohort is close to the optimal value (IMR⩾16) defined in a previous single center study (8). More importantly, IMR showed a very high negative predictive value for acute allograft rejection. In addition, using a lower cut-off value resulted in an even higher negative predictive value as IMR and the incidence of subsequent acute allograft rejection were proportional; the incidence of acute allograft rejection was only 5.4% in patients with the lowest quartile of IMR (6-11).

The underlying mechanism for the association between IMR and subsequent acute allograft rejection may be that microvascular dysfunction early after transplantation develops due to an immune response before the adverse effects of the immune response actually manifest as acute rejection (24) (Central Illustration). IMR may be a physiologic surrogate of the immune response in a transplanted heart, with a high IMR implying a heightened immune

Central Illustration: The index of microcirculatory resistance and acute allograft rejection



The index of microcirculatory resistance (IMR) measured early after heart transplantation predicts subsequent acute allograft rejection and long-term clinical outcome. The underlying mechanism for the association between IMR and subsequent acute allograft rejection may be that microvascular dysfunction early after transplantation develops due to an immune response before the adverse effects of the immune response actually manifest as acute rejection.

response between donor heart and recipient immune system. A low IMR may indicate that the donor heart has achieved a state of immune quiescence and the risk of future acute rejection is low. The clinical implications of these findings are that IMR may allow a personalized medical approach. For patients with low IMR, immunosuppressive therapy could potentially be reduced to limit side effects and/or endomyocardial biopsy could be performed less frequently to limit patient discomfort and complications (25). For patients with high IMR, therapy intensity and surveillance may be increased to avoid or minimize the effect of rejection (2).

Another major finding is the association of IMR early after transplantation and the risk of MACE at 10 years, which was mostly driven by higher risk of readmission due to cardiac causes. A previous study showed that the presence of rejection during the first year is the dominant risk factor for recurrent rejection after 1 year (26). Although acute rejection within 1 year could be pathologically reversible after intensive immunosuppressive therapy, the functional and structural sequelae may persist or worsen. Several studies have demonstrated that an episode of acute rejection during the first 1 year is associated with cardiac allograft vasculopathy, graft dysfunction, and late mortality (2,27,28), which was supported by further divergence of the MACE curves after 1 year in this study. In addition, an increased IMR has been associated with the subsequent progression of cardiac allograft vasculopathy (29).

The limitations of this study include that this is a post hoc analysis of prospectively collected data. Second, intracoronary physiology was performed only in the left anterior descending artery from a somewhat select population. Third, although the overall rate of rejection was relatively low, this incidence is in line with that observed in the ISHLT thoracic organ transplant registry, enrolled between 2010-2016 (N=36,883) (1). Nevertheless, the low number of events limits the ability to further control for possible confounding. Fourth, we could not evaluate the incidence of subclinical cardiac allograft vasculopathy at 10 years due to the lack of routine coronary angiographic follow-up after 1 year post transplantation. The higher rate of coronary revascularization at 10 years indirectly suggested the relationship between IMR and cardiac allograft vasculopathy at long-term. Fifth, the lack of a uniform immunosuppressive regimen could be a limitation. Nevertheless, we performed statistical adjustment for different immunosuppressive agents and the effect of study site. The predictive value of IMR on acute allograft rejection at 1 year was consistent across different immunosuppressive regimes and different sites. Sixth, because of the invasive study protocol performing intracoronary physiology assessment, unstable patients probably did not undergo such physiological assessment resulting in potential selection bias. Seventh, the lack of a central core lab could be a limitation because there is significant inter-observer variability between pathologists in the interpreting biopsy samples. Finally, it should be taken into account that the diagnosis of antibody-mediated rejection remains

technically more challenging and a consensus on the definition has recently evolved (15). Special staining for AMR was not routinely performed in our participating centers in the absence of clinical symptoms or signs. Therefore, subclinical antibody-mediated rejection may be underdiagnosed in this cohort.

In conclusion, IMR measured early after heart transplantation predicts the incidence of subsequent acute allograft rejection and long-term clinical outcome. These data suggest that acute allograft rejection induces microvascular dysfunction prior to histological changes of the myocardium. Therefore, early IMR measurement after transplantation identifies patients at higher risk and may guide personalized post-transplantation management. Futures studies will not only need to validate our findings but also to focus on whether IMR measurement allows a more personalized post-transplantation management strategy.

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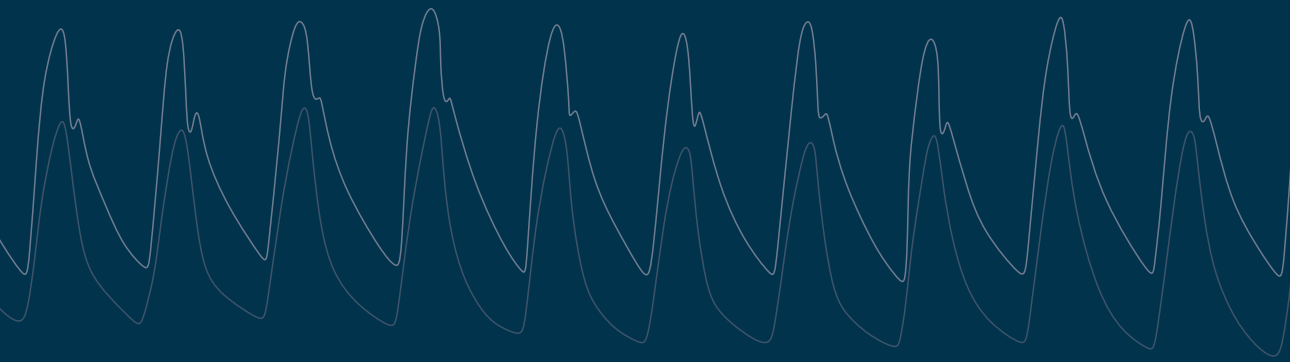
Supplementary Table 1. Immunosuppressive regimen according to the study site

	Stanford	Oslo	Sahlgrenska	Seoul	P value
Induction therapy	96.6%	100%	100%	100%	0.16
Maintenance therapy					
Calcineurin inhibitor					
Cyclosporin	46.6%	84.5%	100%	17.5%	<0.001
Tacrolimus	52.3%	15.5%	0	82.5%	<0.001
mTOR inhibitor	15.9%	43.3%	50.0%	7.5%	<0.001
Mycophenolate	86.4%	100%	100%	90%	0.002



CHAPTER 16

General Discussion and Future Perspectives

More than 2000 years ago, Aristotle spoke the famous words: "The more you know, the more you know you don't know." This timeless phrase is highly relevant in the current era of coronary artery disease. Clinicians possess an almost unlimited variety of diagnostic tools. Highly advanced non-invasive methods such as CT, CMR, and PET are able to assess the coronary tree and myocardium both in structure and function. Intracoronary imaging such as IVUS and OCT with a spatial resolution down to 10 microns can identify the smallest changes in anatomy and composition of the coronary wall. Intracoronary physiology, including fractional flow reserve (FFR), can accurately identify changes in flow among the different compartments of the coronary tree and their associated ischemic potential. Although these diagnostic methods have tremendously pushed the field forward, concordant findings between tests seems to be the exception rather than the rule. The increased knowledge creates complex clinical scenarios in daily practice. For example, what to do with a severe stenosis on the angiogram but preserved coronary blood flow? How to treat stenoses with preserved flow but 'vulnerable characteristics' on intracoronary imaging? In addition, the rising average age of patients and improved treatment options increase complexity of coronary artery disease in the catheterization laboratory, such that three-vessel disease, chronic occlusions, and coronary disease after heart transplantation have become routine nowadays. Non-invasive methods have well-known limitations in these scenarios, such as balanced ischemia accounting for false-negative SPECT or severe calcification obscuring interpretation of CTA. Intracoronary physiology may play a key role in these complex scenarios. For that reason, the main goal of this thesis is to assess what role intracoronary physiology can play in guiding the treatment of complex coronary artery disease.

Fractional flow reserve-guided percutaneous coronary intervention versus coronary bypass surgery

Over the past decades numerous randomized trials have compared PCI with CABG in the setting of multivessel disease. Despite the development of first-generation drug-eluting stents, studies such as SYNTAX and FREEDOM still demonstrated superior outcomes for CABG over PCI in patients with multivessel disease.[1,2] Nevertheless, first-generation stents were associated with higher risk of stent thrombosis. Second-generation drug-eluting stents were developed to overcome these limitations and have demonstrated a lower risk of stent thrombosis and myocardial infarction.[3] In addition, all prior trials comparing CABG and PCI used the angiogram to guide PCI. As comprehensibly discussed in this thesis, FFR-guided PCI has demonstrated superior outcomes versus angiography-guided PCI.[4-7] For these reasons, the randomized FAME 3 trial compared FFR-guided PCI using second generation drug-eluting stents versus CABG in patients with three-vessel disease. As presented in this thesis, FAME 3 showed that after 1 year FFR-guided PCI was not found to be non-inferior to CABG. Importantly, we found that event rates were considerably lower compared with previous trials and the differences between PCI and CABG narrowed. The

main driver away from non-inferiority was repeat revascularization. The main lesson of FAME 3 is that while both PCI and CABG have greatly improved over the last decade, CABG remains the preferred treatment in many patients with three-vessel disease, in particular those with a high (functional) SYNTAX score.[8] As presented in this thesis, quality of life improved faster after PCI – as expected given the technical aspects of the procedures – but converging to no difference after 1 year. Based on the small differences in events between both treatments, shared decision making becomes increasingly important. A potential limitation of the FAME 3 trial is the relatively low use of intravascular imaging in the PCI arm. Although the outcomes of the PCI group potentially could have been improved using intravascular imaging, it is interesting to note that in FAME 3 outcomes were similar between patients who had intravascular imaging guidance and those who did not.[9] In addition, the rate of repeat-revascularization was comparable to that of the single-arm SYNTAX II study that routinely incorporated intracoronary imaging.[10] In FAME 3, the third universal definition of myocardial infarction was used to define both spontaneous and periprocedural infarction. However, ongoing debate continues regarding the optimal definition of periprocedual myocardial infarction. If another common definition had been used in FAME 3 – the SCAI definition[11] – then no difference between PCI and CABG would have been observed. In the opinion of the author of this thesis, completing the FAME 3 trial by itself was already a major achievement. With increasing regulation and its dynamic landscape, enrollment of patients into clinical trials becomes increasingly challenging. In addition, as CABG and PCI have such a differential impact on quality of life over the short term, patients are reluctant to participate in such studies. As a result, another large study comparing CABG and PCI – the Hybrid Trial (Hybrid Coronary Revascularization Trial; NCT03089398) – was prematurely discontinued due to slow enrolment.

Long-term outcomes after FFR-guided decision making

Until the publications from this thesis were available, uncertainty existed about the long-term safety of deferring lesions based on a negative FFR. Critics were afraid that untreated plaques, despite being not flow-limiting, could still progress or become unstable and cause an acute coronary syndrome. This concern was referred to as a potential 'late catch-up phenomenon'. Long-term data from the randomized DEFER and FAME trials reported in this thesis showed that outcomes remained excellent (even after 15 years of follow-up) and that concerns of late catch-up were unjustified. The findings of these randomized trials have also been confirmed in sizable 'real world' cohorts.[7,12] For example, in the large IRIS registry including 5846 patients, the rate of cardiac death or myocardial infarction was lower than 1% at 3-year follow-up.[7] One may ask why an FFR-negative lesions has such a good prognosis? A combination of potential mechanisms can play a role: low mechanical forces on the plaque itself, an association with low plaque burden, and lack of ischemia.[13] With the increased use of non-hyperemic pressure ratios (NHPR) an important question raises whether the good prognosis after deferral of PCI based on NHPR also holds over

the long term. Long-term outcomes of the DEFINE-FLAIR trial, among others, are eagerly awaited. In addition, it would be of great interest to know the safety of deferral of PCI based on NHPR in a 'real world' setting.

Since the introduction of PCI, ongoing debate asked whether PCI could improve so-called 'hard' outcomes in stable coronary lesions. The results of a large, patient-level meta-analysis in patients with an FFR-positive lesion are reported in this thesis showing – for the first time – that FFR-guided PCI reduces myocardial infarction versus medical therapy. The results of the ISCHEMIA trial are actually rather similar when studied carefully.[14] Most importantly, both studies showed a significant decrease of ~30% in spontaneous myocardial infarction in favor of PCI over medical therapy. A limitation of several PCI versus OMT trials, including ISCHEMIA, is their mixing of both FFR-positive and FFR-negative lesions with patient-level, not vessel-level, outcomes. Such mixing affects both types of trials: angio-guided PCI as well as FFR-guided PCI. We know that performing PCI on FFR-negative lesions does not improve outcomes. In addition, some trials focusing on FFR-guided PCI such as DANAMI-PRIMULTI and COMPARE-ACUTE included patients without a single FFR-positive lesion.[15,16] Consequently, both strategies (FFR-guided PCI and medical therapy) result in the same treatment of the target lesion: medical therapy. Any potential benefit of PCI is diluted by such trial designs.

Prediction of invasive coronary physiology

With the broad evidence base that FFR-guided PCI improves symptoms and outcomes, the question remains why physiology is not used in most patients in the catheterization laboratory around the world. If these invasive indexes could be predicted more easily, yet reliably, it could potentially improve the adoption of physiology. Several methods have been applied to predict FFR from non-hyperemic pressure curves, mostly focusing on a specific period within the cardiac cycle or qualitative parameters.[17] With the use of artificial intelligence, we prove in this thesis that no additional 'hidden' information exists in baseline pressure curves to predict FFR in a meaningful manner. The studies presented in this thesis on pressure-bounded CFR introduce a pressure-wire only method to estimate CFR. Pressure-bounded CFR showed a reasonable accuracy of 84% to predict CFR. While this method is not perfect, it provides an pressure-wire only alternative to gain insights into CFR. Given that invasive Doppler and thermodilution CFR measurements have been shown to have an accuracy of only about 85% versus an external flow probe in experimental studies, the pressure-wire only predictions should not be discounted.[18] Other methods have been developed as well during the past years to assess the coronary microcirculation. Using continuous thermodilution, absolute flow and resistance can be measured.[19] In addition, the methods of continuous thermodilution allow for the calculation of the microvascular resistance reserve (MRR), a specific, quantitative, and operator-independent metric to quantify coronary microvascular dysfunction.[20]

Intracoronary physiology in cardiac transplant recipients

Cardiac allograft vasculopathy (CAV) is a major cause of death after heart transplantation.[21] The diagnosis of CAV is challenging given the diffuse nature of the disease.[22] In addition, patients may not feel angina because of the denervated heart after transplantation. As CAV results in diffuse luminal narrowing, the angiogram may appear generally normal. Since FFR is affected by diffuse luminal narrowing, it is a more sensitive tool to detect CAV than the angiogram. In addition, it is known that CAV may also affect the microvasculature, which cannot be detected by the angiogram or intravascular imaging. The findings from the largest international collaboration on intracoronary physiology after heart transplantation were reported in this thesis and confirmed the prognostic value of the index of microvascular resistance (IMR) and FFR. In the opinion of the author of this thesis, current guidelines should incorporate coronary physiology into the diagnosis and risk stratification of CAV. In addition we found from the same collaboration that IMR measured early after transplantation was highly predictive of subsequent rejection. At the time of our publication, an independent Korean cohort showed similar results.[23] It is truly fascinating to the author of this thesis that IMR can pick up the earliest signs of rejection, while the biopsy at that moment appears normal. It would be of interest to study whether microvascular dysfunction could be detected in early stages of rejection after transplantation of other organs. The potential clinical implications of these findings are discussed in the Future perspectives.

Future perspectives

In this thesis several hypotheses are postulated that need to be tested in the future. As the physicist Richard Feynman stated: "It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong."

In the following years, the long-term outcomes of the FAME 3 trial will be reported. The key secondary endpoints are the composite of death, myocardial infarction, or stroke at 3- and 5-year follow-up. If it turns out that CABG and PCI do not differ on these 'hard endpoints' over the long-term, then it may have major clinical implications. In such a future, the major tradeoff for a patient for both methods of revascularization are superior quality of life during the first months after PCI versus an decreased risk of repeat revascularization after CABG. Shared decision making will be of increasing importance in this situation. Ten year outcomes of the BEST trial (NCT00997828), comparing CABG versus PCI with second generation drug-eluting stents (without FFR guidance), will also be of importance in this discussion, and are expected in late 2022.

An important part of the assessment of coronary physiology in the future will be angiography-based (pressure-wire free) and non-invasive methods, such as FFR-CT. An open question is how these pressure-wire free methods will perform in a real world

setting. As well known, angiographic image quality and adequate angulation are of critical importance. In this regard, one of the great strengths of FFR has always been its high operator independence and reproducibility. Another pitfall of too many non-inferiority trials against FFR-guided PCI is whether new methods still outperform angiography-guided PCI. For example, it has been demonstrated that FFR-guided PCI is superior to angiography-guided PCI. Next, iFR-guided PCI was claimed to be non-inferior versus FFR-guided PCI in a low-risk population, but only when including a majority of concordant lesions.[24] If future studies show that a pressure-wire free method achieves non-inferiority against iFR-guided PCI, then it would still be unclear whether this new method continues to outperform angiography-guided PCI.

Will there ever be a randomized trial showing that PCI reduces myocardial infarction in FFR-negative lesions but with vulnerable characteristics on intravascular imaging? Work in this thesis demonstrates that this situation is very unlikely to occur, but it will be put to the test in the near future. The largest ongoing trial testing the plaque sealing hypothesis is the PREVENT trial (NCT02316886). PREVENT will randomize 1600 patients with a negative FFR but vulnerable characteristics on intravascular imaging to either PCI or optimal medical therapy. The primary endpoint will be target-vessel failure after 2 years.

Since the prognostic value of coronary physiology early after transplantation is now confirmed, the next important steps will be to improve patient outcomes based on these measurements. Future studies need to address whether intensified treatment may lower the risk of allograft vasculopathy for patients with abnormal coronary physiology. In addition, FFR and IMR can be used as surrogate endpoints for future trials. For example, an ongoing trial (NCT03537742) is randomizing 120 patients early after heart transplantation to a PCSK-9 inhibitor or placebo on top of statin therapy. Important endpoints include the effects on coronary physiology, including FFR and IMR. Given the highly predictive value of IMR on allograft rejection, future studies need to address whether IMR can be used to guide treatment. One possible design for a study includes measurement of IMR early after transplantation and, in case of an abnormal IMR, randomizing patients to either standard of care or an intensified immunosuppressant regime. Another interesting strategy in this regard is to study whether patients with a low IMR after transplantation could have less frequent biopsies during the first year, thereby potentially improving quality of life and decreasing procedure-related complications.

Finally, further and extensive studies will be performed – and are already ongoing–to establish the role of absolute microvascular resistance and MRR in better understanding and truly quantifying the microcirculation.

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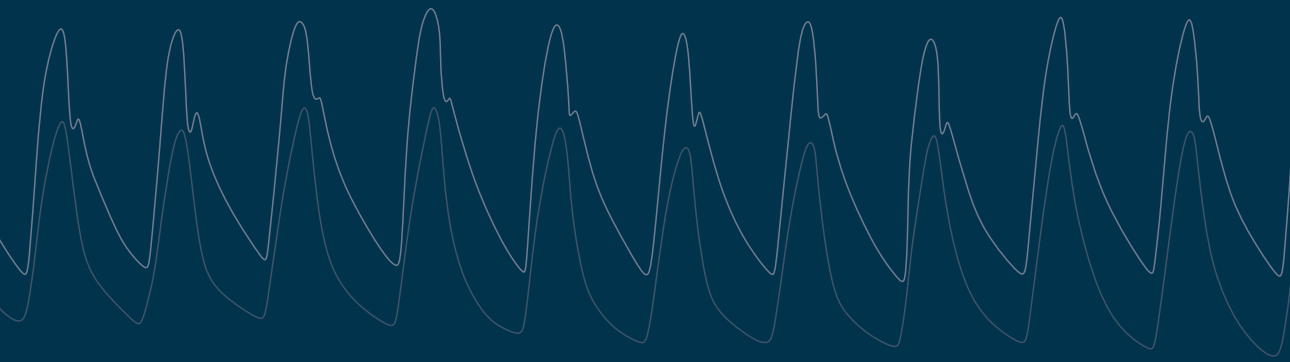

APPENDIX

Summary

Samenvatting

Curriculum Vitae

Dankwoord

List of Publications

Summary

The main focus of this thesis is to use coronary physiology to improve symptoms and outcomes of patients with complex coronary artery disease. In clinical practice complex scenarios often emerge. The word 'complex' in this context refers not only to severe coronary artery disease, but also to advanced clinical scenarios or pathophysiology, such as after heart transplantation.

Chapter 1 is a general introduction into the concepts of coronary physiology, fractional flow reserve (FFR), and coronary revascularization.

The first part of this thesis focuses on FFR-guided percutaneous coronary intervention (PCI) versus coronary bypass surgery (CABG) in patients with three-vessel disease. In **chapter 2** the historical perspective of the CABG versus PCI debate is discussed. In addition, the potential effect of FFR-guidance and current-generation stents on this debate are outlined. The design of the randomized FAME 3 is reported comparing FFR-guided PCI with current-generation drug-eluting stents with coronary bypass surgery in 1500 patients with multivessel disease. The primary results of the FAME 3 trial are reported in **chapter 3**, showing that FFR-guided PCI did not meet the criteria set for non-inferiority versus CABG after 1 year follow-up with respect to the composite primary endpoint of death, myocardial infarction, stroke, or repeat revascularization. Nonetheless, the event rates after both PCI and CABG were much lower compared to previous trials in similar patients and the differences between CABG and PCI narrowed. In light of those smaller differences in event rates, with no significant differences in 'hard endpoints', other health related outcomes become even more important for clinical decision making. Therefore, in **chapter 4**, the quality of life analyses of the FAME 3 trial are discussed, showing that quality of life improves faster after FFR-guided PCI compared with CABG, but converges between treatment arms after 1 year.

The second part of this thesis focuses on long-term outcomes after FFR-guided PCI. Up until the studies presented in this thesis, little was known about the long-term safety of deferring revascularization based on a negative FFR. Critics warned for a potential 'late catch-up phenomenon', whereby lesions not treated with PCI may cause events in the future. For that reason the 15 year follow-up of the DEFER trial was conducted and reported in **chapter 5**, randomizing patients with single-vessel disease and an intermediate coronary stenosis but a negative FFR to either PCI or medical therapy. After 15 years of follow-up, deferral of PCI resulted in an excellent prognosis and even significantly decreased the risk of myocardial infarction compared to patients undergoing PCI despite negative FFR.

The same uncertainty regarding long-term outcomes existed for patients with multivessel disease. In **chapter 6,** the 5-year results of the FAME trial are reported, comparing FFR-guided PCI with angiography-guided PCI in patients with multivessel disease. The main findings were that the absolute benefit of FFR-guided PCI over angiography guided PCI during the first 2 year persisted up until 5 years follow-up. The long-term follow-up analyses of both landmark trials confirmed that FFR-guidance during PCI should be the standard of care for most patients.

Since the introduction of PCI, there has been extensive debate as to whether PCI can reduce myocardial infarction in stable coronary lesions. In **chapter 7**, the results of a patient-level meta-analysis of randomized clinical trials are reported showing that FFR-guided PCI indeed reduces myocardial infarction versus medical therapy in patents with a positive FFR. **Chapter 8** is a viewpoint addressing why, from a statistical standpoint, it will be very unlikely that there will ever be an RCT showing that PCI prevents myocardial infarction in patients with a negative FFR but 'vulnerable' characteristics on intravascular imaging. The best treatment of lesions with FFR in the grey zone, are discussed in an editorial in **chapter 9**, highlighting the importance of clinical judgement in this subset.

The third part of this thesis focuses on the prediction of FFR and coronary flow reserve (CFR). The adoption of invasive coronary physiology may be improved when these measurements are simplified. In **chapter 10**, the results of a deep learning analysis to predict FFR from non-hyperemic pressure curves are presented. The results show that deep learning did not improve the predictive value compared with existing non-hyperemic indexes. This finding suggests that no significant 'hidden information' is present in baseline pressure curves and that a hyperemic drug is still required to reliably obtain FFR. Compared to non-hyperemic indexes, the diagnostic performance can be improved by giving a bolus of intracoronary contrast, which induces some form of hyperemia. In this regard, we show in **chapter 11** that the diagnostic performance of adenosine-free indexes is independent of gender, despite theoretical concerns. In **chapter 12** we introduce a new concept called 'pressure-bounded CFR' in order to estimate CFR using only coronary pressure measurements and without the need for a thermodilution or Doppler wire. This novel method is subsequently applied to a large Korean database (IRIS-FFR registry) in **chapter 13**, demonstrating that FFR was independently associated with clinical outcomes, while CFR was not.

The fourth part of this thesis focuses on the role of intracoronary physiology in cardiac transplant recipients. The coronary angiogram has several limitations to diagnose cardiac allograft vasculopathy. Data from a large international collaboration are reported in **chapter 14**, showing that abnormal coronary physiology was associated with adverse outcomes after heart transplantation. In **chapter 15**, results from the same international collaboration

found that IMR early after transplantation was highly predictive of subsequent acute allograft rejection. These results suggest that coronary physiology may play an important role in clinical decision making after heart transplantation.

The final chapter of this thesis, **chapter 16** presents a general discussion and provides future directions.

Samenvatting

De focus van dit proefschrift is het onderzoeken van de rol van coronaire fysiologie in de behandeling van complex coronairlijden. Het woord 'complex' in deze setting heeft een brede betekenis. Complex coronairlijden kan duiden op ernstig coronairlijden zoals dat bijvoorbeeld gezien wordt bij drievats-coronairlijden, maar ook op complexe klinische scenario's met tegenstijdige diagnostische testen. Tot slot duidt complex coronairlijden in dit proefschrift ook op complexe pathofysiologie, zoals aanwezig kan zijn na harttransplantatie.

Hoofdstuk 1 is een algemene inleiding in de coronaire fysiologie, fractionele flow reserve (FFR) en coronaire revascularisatie.

Het eerste deel van dit proefschrift gaat over de beste wijze van revascularisatie bij patiënten met drievats-coronairlijden: percutane coronaire interventie (PCI) op geleide van FFR versus coronaire bypass chirurgie (CABG). In **hoofdstuk 2** wordt de achtergrond en opzet van de gerandomiseerde FAME 3 studie uiteengezet. Het hoofdstuk begint met een historisch perspectief omtrent de PCI versus CABG discussie bij patiënten met 3-vatslijden. Vervolgens wordt beschreven wat het mogelijke effect op deze discussie is van de ontwikkeling van nieuwe generatie stents in combinatie met het gebruik van FFR-geleide PCI. Tegen deze achtergrond wordt de opzet van de FAME 3 studie besproken, waarbij 1500 patiënten met drievats-coronairlijden worden gerandomiseerd naar CABG versus FFR-geleide PCI met tweede-generatie drug-eluting stents. In **hoofdstuk 3** worden de primaire uitkomsten van de FAME 3 studie beschreven, waarbij CABG bij patiënten met uitgebreid drievats-coronairlijden tot betere uitkomsten leidde dan FFR-geleide PCI. In patiënten met minder uitgebreid drievats-coronairlijden was FFR-geleide PCI even goed of beter. Een belangrijke conclusie van dit onderzoek is dat de uitkomsten na zowel PCI als CABG sterk verbeterd waren ten opzichte van eerdere vergelijkbare cohorten van patiënten en dat de verschillen tussen CABG en PCI steeds kleiner worden. Mede gezien dat er geen verschil was in 'harde eindpunten', spelen andere aspecten zoals kwaliteit van leven een steeds grotere rol. De resultaten met betrekking tot kwaliteit van leven in de FAME 3 studie worden beschreven in **hoofdstuk 4**. De studie laat zien dat patiënten na PCI sneller herstellen dan na een CABG, met vergelijkbare kwaliteit van leven een jaar na de behandeling.

Het tweede deel van dit proefschrift gaat over de lange-termijn uitkomsten na FFR-geleide PCI. Of het afzien van dotteren van een stenose met een negatieve FFR veilig is op de lange termijn was tot aan de studies die in dit proefschrift verschenen zijn onduidelijk. Critici waarschuwden dat deze vernauwingen op termijn mogelijk toch een myocardinfarct

kunnen veroorzaken en daardoor beter preventief konden worden gedotterd. Die zorg blijkt ongegrond te zijn, in **hoofdstuk 5** worden de 15-jaars resultaten van de gerandomiseerde DEFER studie besproken. In deze studie werden patiënten met éénvats-coronairlijden en een intermediaire stenose met negatieve FFR gerandomiseerd naar PCI of alleen medicatie. Zelfs gedurende deze zeer lange follow-up blijken FFR-negatieve vernauwingen die enkel medicamenteus behandeld werden een uitstekende prognose te hebben. De studie laat zelfs zien dat een significant hoger percentage van myocard infarcten werd gezien in patiënten die een PCI hadden ondergaan. In patiënten met meervatslijden werden deze lange-termijn uitkomsten onderzocht in de FAME studie. De 5-jaars resultaten van de FAME studie worden besproken in **hoofdstuk 6,** waar patiënten met meervatslijden werden gerandomiseerd naar FFR-geleide PCI versus angio-geleide PCI. De conclusie van deze studie is dat de voordelen die gepaard gaan met FFR-geleide PCI gedurende de eerste 2 jaar ten opzichte van angio-geleide PCI, behouden blijven gedurende 5 jaar follow-up.

Een belangrijke vraag in de cardiologie is of PCI een hartinfarct kan voorkomen bij stabiele vernauwingen in de kransslagaders. De resultaten van een meta-analyse op basis van individuele-patiëntengegevens van gerandomiseerde studies die FFR-geleide PCI vergeleken met alleen medicamenteuze therapie bij vernauwingen met een positieve FFR worden besproken in **hoofdstuk 7**. Deze studie laat zien dat het preventief uitvoeren van FFR-geleide PCI het risico op een hartinfarct vermindert. In **hoofdstuk 8** wordt uiteengezet waarom het methodologisch waarschijnlijk onhaalbaar is om een studie te ontwerpen die aantoont dat vernauwingen met een negatieve FFR maar met 'vulnerabele kernmerken' bij intracoronaire beeldvorming, preventief een PCI moeten ondergaan om een hartinfarct te voorkomen. **Hoofdstuk 9** is een editorial over de beste behandeling van vernauwingen in het grijze gebied van FFR (FFR waarde tussen 0.75 en 0.80).

In het derde deel van dit proefschrift worden verschillende potentiële technieken onderzocht om verschillende indices van coronaire fysiologie, zoals FFR en coronaire flow reserve (CFR) op een vereenvoudigde manier te voorspellen. Voor dit doel wordt in **hoofdstuk 10** geconcludeerd dat, ondanks het gebruik van deep learning, het niet mogelijk is om uit non-hyperemische drukcurves, FFR betrouwbaar te voorspellen. In **hoofdstuk 11** wordt een studie gepresenteerd die laat zien dat de diagnostisch waarde van non-hyperemische indices om FFR te voorspellen onafhankelijk is van geslacht. Voor het invasief meten van CFR is Doppler of thermodilutie nodig. Wij introduceren een nieuwe techniek in **hoofdstuk 12** om CFR te voorspellen met enkel het gebruik van een intracoronaire drukmeting: pressure-bounded CFR. Een voordeel van deze methode is dat deze retrospectief toegepast kan worden op bestaande databases. In **hoofdstuk 13** wordt pressure-bounded CFR toegepast op een grote Koreaanse database. De conclusie van de studie is dat FFR een grote prognostische betekenis heeft, terwijl CFR geen onafhankelijk prognostische waarde laat zien.

In het vierde en laatste deel van dit proefschrift wordt de klinische betekenis van coronaire fysiologie onderzocht in patiënten die een harttransplantatie hebben ondergaan. In eerdere kleine studies is gesuggereerd dat een verhoogde microvasculaire weerstand na een harttransplantatie, gemeten met behulp van de index of microcirculatory resistance (IMR) van prognostische betekenis is. In **hoofdstuk 14** worden de resultaten gepresenteerd van een grote internationale registratiestudie. Uit invasieve metingen blijkt inderdaad dat epicardiaal- en microvasculairlijden na een harttransplantatie sterk geassocieerd is met een slechte uitkomst. Het meten van IMR kort na een harttransplantatie blijkt zelfs een sterke voorspeller te zijn van rejectie in het eerste jaar, in **hoofdstuk 15**. Dit resultaat is met name interessant omdat een biopt ten tijde van de IMR meting nog geen rejectie laat zien.

Hoofdstuk 16 is een algemene discussie en blikt vooruit op de implicaties van dit proefschrift voor de toekomst.

Curriculum Vitae

Frederik Zimmermann was born on March 16th 1987 in Vught, The Netherlands. He attended secondary school at Gymnasium Beekvliet in Sint-Michielsgestel. In 2005 he entered medical school at Maastricht University. Before obtaining his Master's degree in 2011, he participated in research at the department of Cardiology of Maastricht University on the role of monocytes in acute myocardial infarction, under supervision of Prof. J. Waltenberger. In 2012 he started his training in cardiology, under supervision of Dr. J.M. van Dantzig, Prof. N.H.J. Pijls, and Dr. P. Houthuizen at the Catharina Hospital Eindhoven. In 2014 he interrupted his clinical fellowship to perform 4 years of clinical research that formed the basis of this thesis under supervision of Prof. N.H.J. Pijls, Prof. W.F. Fearon, and Dr. P.A.L. Tonino. During that period, he was a visiting research fellow at the department of cardiovascular medicine at Stanford University, under supervision of Prof. W.F. Fearon. After registering as a cardiologist in 2021, he started his fellowship in interventional cardiology, under supervision of Dr. I.F. Wijnbergen and Dr. B.R.G. Brueren. Since 2020 he is an associate editor of EuroIntervention, responsible for coronary physiology. From 2022-2024, he is a committee member of the European Association of Percutaneous Cardiovascular Interventions (EAPCI).

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