

# Fractional flow reserve to guide percutaneous coronary intervention in multivessel coronary artery disease

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**Fractional Flow Reserve to guide  
Percutaneous Coronary Intervention in  
Multivessel Coronary Artery Disease**

Proefschrift

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Technische Universiteit Eindhoven, op gezag van de  
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commissie aangewezen door het College voor  
Promoties in het openbaar te verdedigen  
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door

Wilhelmus Adrianus Ludovicus Tonino

geboren te Leiden



Dit proefschrift is goedgekeurd door de promotoren:

prof.dr. N.H.J. Pijls  
en  
prof.dr. F. Zijlstra

Copromotor:  
dr. B. De Bruyne

# List of abbreviations

<b>ACE</b>	: angiotensin-converting enzyme
<b>ARB</b>	: angiotensin-receptor blocker
<b>BARI 2D</b>	: Bypass Angioplasty Revascularization Investigation 2 Diabetes (trial)
<b>CABG</b>	: coronary artery bypass surgery
<b>CAD</b>	: coronary artery disease
<b>CCS</b>	: Canadian Cardiovascular Society classification system to assess functional class
<b>CK</b>	: creatine-kinase
<b>CK-MB</b>	: MB fraction of creatine-kinase
<b>COURAGE</b>	: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (trial)
<b>CFR</b>	: coronary flow reserve
<b>DEFER</b>	: Deferral Versus Performance of PCI of Non-Ischemia-Producing Stenoses (trial)
<b>DES</b>	: drug-eluting stent
<b>ECG</b>	: electrocardiogram
<b>EQ-5D</b>	: European Quality of Life-5 Dimensions scale (a questionnaire to assess and follow-up quality-of-life)
<b>FAME</b>	: Fractional Flow Reserve versus Angiography for Multivessel Evaluation (trial)
<b>FAME II</b>	: FFR-Guided PCI plus Optimal Medical Treatment versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease (trial)
<b>FAME III</b>	: Fractional Flow Reserve-Guided Percutaneous Coronary Intervention to Coronary Artery Bypass Graft Surgery in Patients with Multivessel Coronary Disease (trial)
<b>FFR</b>	: fractional flow reserve
<b>GPI</b>	: glycoprotein inhibitor
<b>ICER</b>	: incremental cost-effectiveness ratio
<b>LAD</b>	: left anterior descending coronary artery

<b>LCX</b>	: left circumflex coronary artery
<b>LM</b>	: left main coronary artery
<b>MACCE</b>	: major adverse cardiac and cerebrovascular event
<b>MACE</b>	: major adverse cardiac event
<b>MI</b>	: myocardial infarction
<b>MVD</b>	: multivessel disease
<b>Non-STEMI</b>	: myocardial infarction without ST-elevation
<b>OMT</b>	: optimal medical therapy
<b>Pa</b>	: aortic pressure
<b>PCI</b>	: percutaneous coronary intervention
<b>Pd</b>	: distal pressure
<b>Pv</b>	: venous pressure
<b>QALY</b>	: quality-adjusted life years
<b>QCA</b>	: quantitative coronary analysis
<b>Qnorm</b>	: myocardial blood flow in case of a normal coronary artery
<b>Qsten</b>	: myocardial blood flow in the presence of a stenosis
<b>RCA</b>	: right coronary artery
<b>RR</b>	: relative risk
<b>SD</b>	: standard deviation
<b>STEMI</b>	: ST-elevation myocardial infarction
<b>SYNTAX</b>	: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (trial)
<b>SYNTAX 3VD</b>	: SYNTAX study patient population with three-vessel disease
<b>SYNTAX score</b>	: anatomical assessment of a coronary angiogram, with higher scores indicating more complex coronary artery disease
<b>USD</b>	: United States Dollar
<b>3vd</b>	: three-vessel coronary disease
<b>95%CI</b>	: 95% confidence interval

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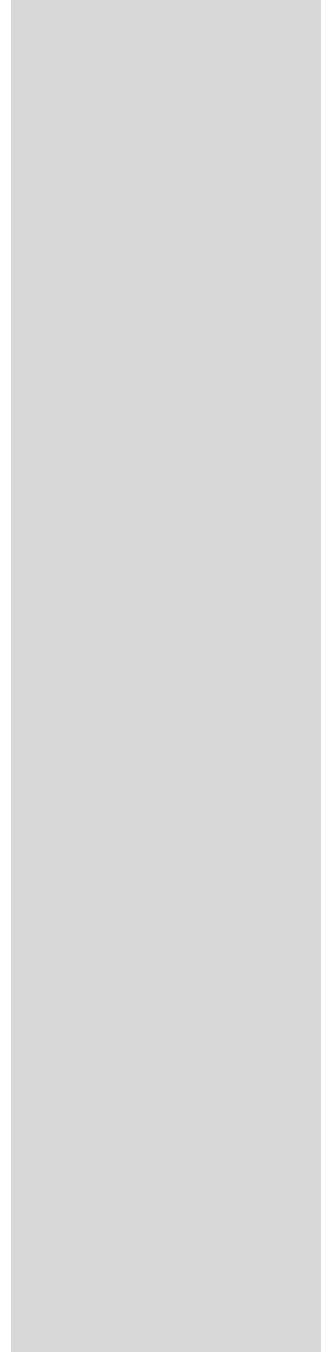
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# 1

## Introduction







## 1.1 Atherosclerosis of the coronary circulation

In Western society, atherosclerosis of the coronary arteries is the most prevalent disease and it is responsible for high numbers of death and non-fatal but disabling myocardial infarction every year. The heart is supplied by blood through the coronary arteries. Blood contains oxygen and nutrients which are essential to contraction of the myocardium. From the aorta, a right and a left coronary artery branch off. The latter usually splits into two major branches, the left anterior descending (LAD) and left circumflex (LCX) artery. Therefore, in clinical practice nomenclature of the coronary arteries is based on the presence of 3 arteries. Significant atherosclerotic disease in only one of these arteries is called single vessel disease and significant disease in 2 or 3 arteries is named multivessel disease. The anatomy and function of the coronary circulation are described in more detail in *chapter 2*.

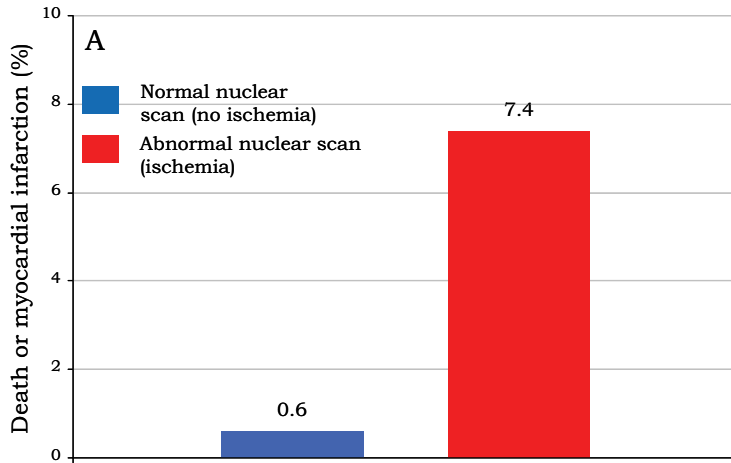
Atherosclerosis leads to diffuse disease and/or local narrowing in these arteries, which in turn impairs blood flow and therefore oxygen supply to the myocardium. Such an imbalance between oxygen supply and oxygen demand induces myocardial ischemia, resulting in chest discomfort known as angina pectoris. The presence of inducible myocardial ischemia not only causes symptoms, but also has significant and unfavorable prognostic implications.<sup>1-4</sup> Treatment options for coronary artery narrowings consist of medical therapy or revascularization by either percutaneous coronary intervention (PCI) or coronary bypass surgery (CABG). As will be explained in the next paragraph, the choice of treatment largely depends on the severity of the patient's complaints and the presence and extent of reversible myocardial ischemia. Non-ischemic (hemodynamically or functionally non-significant) coronary lesions do not cause angina pectoris by definition and are relatively benign

with a chance of causing death or myocardial infarction of less than 1% per year, if treated by appropriate medical therapy. Ischemic (hemodynamically or functionally significant) lesions generally cause chest pain and negatively affect longevity. Therefore, for proper clinical-decision making it is of critical importance to establish whether a coronary artery stenosis is related to myocardial ischemia, or in other words functionally significant. Although in many patients with single vessel disease, non-invasive testing and standard angiography are suitable methods to determine the potentially ischemic nature of a stenosis, in multivessel disease it is often very difficult to judge which out of several lesions are functionally significant and should be revascularized; and vice versa which stenoses could better be left alone and treated medically.

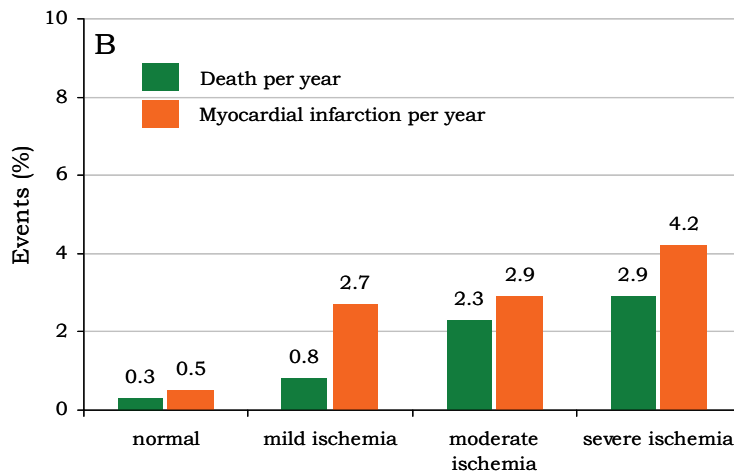
## **1.2 Myocardial ischemia in patients with coronary artery disease**

In patients with coronary artery disease, the presence of inducible myocardial ischemia is an important risk factor for an adverse clinical outcome.<sup>1-4</sup> The extent and severity of myocardial ischemia can be used to risk stratify patients (*figures 1.1A and 1.1B*).<sup>5</sup>

The more inducible myocardial ischemia, the higher the risk of death or myocardial infarction. The medical treatment of patients with coronary artery disease and myocardial ischemia consists of therapy with anti-platelet agents, anti-anginal medications, angiotensin-converting enzyme inhibitors, and statins. Medical treatment can relieve symptoms and improve a patient's prognosis by reducing myocardial ischemia, inhibiting progression of disease (secondary prevention), or avoiding complications of existing plaques. However, in patients with a substantial amount of ischemic myocardium, restoring myocardial blood flow by coronary artery revascularization, results in a greater reduction of myocardial ischemia than medical therapy alone (*see also figure 8.1*).<sup>4</sup> Because it is more effective in reducing myocardial ischemia than medical therapy, coronary artery revascularization results in complete relieve of anginal symptoms in a higher percentage of patients.<sup>6-9</sup>

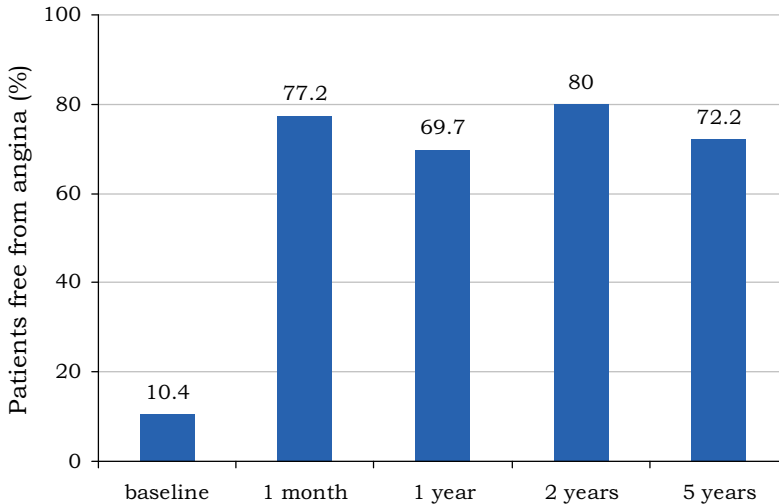


**Figure 1.1A.** Relation between presence of ischemia and outcome according to nuclear perfusion scan results. Panel A shows the annual rate of death or non-fatal myocardial infarction in patients with normal (no ischemia) and abnormal (ischemia) nuclear scan results from 14 published reports comprising more than 12,000 patients. (Adapted from Iskander, Iskandrian. *J Am Coll Cardiol* 1998; 32:57-62; with permission of the ACC)



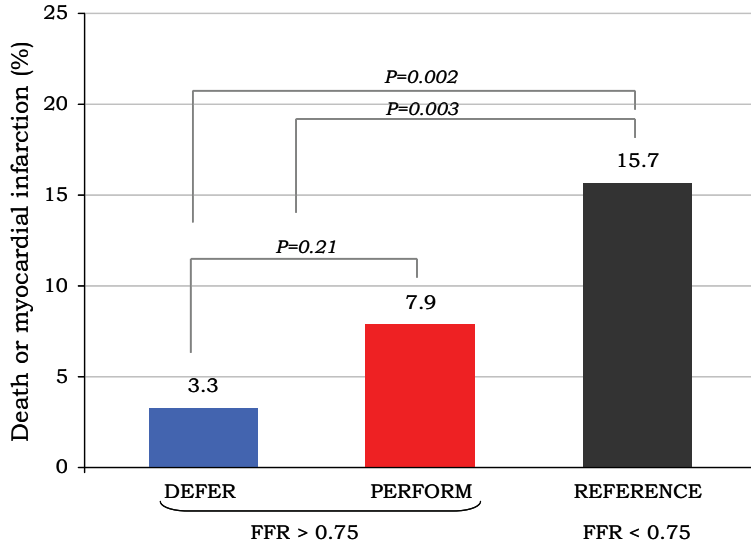
**Figure 1.1B.** Relation between severity of ischemia and outcome according to nuclear perfusion scan results. Panel B shows the rates of cardiac death and myocardial infarction per year as a function of extent of ischemia on a nuclear scan. (Adapted from Hachamovitch et al., *Circulation* 1998; 97: 535-543; with permission of the AHA)

It is shown in *figure 1.2* that this benefit of revascularization on a patient's symptoms is a durable effect. Furthermore, in patients with myocardial ischemia, several studies have shown better clinical outcome results for revascularization when compared to medical therapy alone.<sup>4;10;11</sup>



**Figure 1.2.** Percentage of patients free from angina up to 5 years after percutaneous coronary revascularization (PCI) in patients with single vessel disease and evidence of myocardial ischemia. Almost 80% of the patients became free from anginal symptoms after PCI. This effect is still present after 1, 2, and 5 years. (DEFER study, reference 12; with permission of the ACC)

For patients with stenotic coronary arteries that do not induce myocardial ischemia however, the benefit of revascularization is less clear. After 5 years of follow-up in patients with a single non-ischemic stenosis, there is no advantage of revascularization by PCI over medical therapy (*figure 1.3*).



**Figure 1.3.** Cardiac death and acute myocardial infarction rates after 5 years, for patients with single vessel coronary artery disease. The blue and red column represent patients without inducible myocardial ischemia (as assessed by Fractional Flow Reserve), treated by medical therapy or PCI (stent placement), respectively. The black column represents patients who do have inducible ischemia, treated by PCI and optimal medical therapy. It is striking that such ‘ischemic stenoses’, even if treated by all possible means, have an outcome that is far worse than for non-ischemic stenoses. (DEFER study, reference 12; with permission of the ACC)

One might even suggest a trend towards a higher event rate in such patients revascularized by coronary stenting as compared to patients treated by medical therapy alone.<sup>12</sup> More important, patients with non-ischemic stenoses that are deferred from PCI have an excellent outcome with a very low event rate of less than 1% per year if treated by appropriate medical therapy.

In summary, as underlined in this paragraph and also recommended by current guidelines for the treatment of coronary artery disease, the presence of myocardial ischemia should play a pivotal role in the decision making process about coronary revascularization. Therefore, in patients with coronary artery disease, it is of paramount importance, both with respect to choice of therapy and prognosis, to have adequate information about the extent and localization of myocardial ischemia.

### **1.3 Detection of myocardial ischemia by non-invasive stress studies**

Non-invasive stress tests for the detection of myocardial ischemia play an important role in clinical cardiology. This is reflected by their implementation in guidelines for the diagnosis and treatment of coronary artery disease.<sup>13;14</sup> Although recommended by these guidelines, not all patients undergo non-invasive stress-testing before ending up in the catheterization laboratory for invasive treatment. A retrospective study of a Medicare population showed that less than half of all patients with stable coronary artery disease have documentation of ischemia by non-invasive testing, within 90 days prior to elective percutaneous coronary intervention.<sup>15</sup> Furthermore, the non-invasive detection and documentation of myocardial ischemia in patients with coronary artery disease can be a diagnostic challenge.

Exercise stress-testing with electrocardiography has a limited sensitivity and specificity for the detection of myocardial ischemia and is especially difficult to interpret in patients who cannot exercise maximally or in patients with an abnormal electrocardiogram at rest.<sup>16</sup> Moreover, if such a test is positive for myocardial ischemia, it does not give information about which myocardial territory is, or which territories are, responsible for ischemia. The inability to accurately detect and localize myocardial ischemia is less pronounced in non-invasive stress tests that use imaging modalities. Of these tests, nuclear perfusion imaging is the most widely used. Nuclear imaging, combined with exercise- or pharmacologically-induced stress is more accurate in detecting and localizing myocardial ischemia than exercise testing with electrocardiography.<sup>17</sup> However, several reports have shown that non-invasive tests like nuclear myocardial perfusion imaging can be falsely negative or can underestimate the amount of myocardial ischemia, especially in patients with multivessel disease.<sup>18;19</sup> Such tests are based on the principle of perfusion differences between different myocardial territories and therefore require at least one non-ischemic myocardial territory as a 'normal' reference, in order to be able to detect inducible myocardial ischemia in another territory.<sup>20</sup> The lack of a reference myocardial territory without inducible myocardial ischemia is

most prominent in patients with multivessel disease, thereby limiting diagnostic accuracy of nuclear perfusion tests in this subpopulation significantly. Moreover, in multivessel disease, ischemia in one perfusion territory may be masked by more severe ischemia in another territory (*figure 1.5*). And finally, even if an ischemic territory is correctly identified, ambiguity may remain with respect to the culprit lesion if several stenoses are present in the supplying artery or diffuse disease is present, whether or not superimposed on focal disease. It is likely that non-invasive myocardial nuclear perfusion scintigraphy in multivessel disease provides inadequate information in approximately 50% of the patients.<sup>19;21</sup>

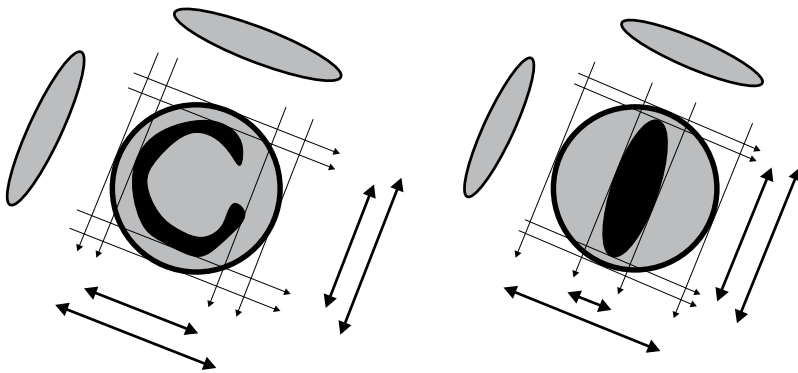
The absence or incompleteness of information about extent and localization of myocardial ischemia in patients with multivessel disease creates difficulties in determining which out of several lesions cause myocardial ischemia and therefore warrant revascularization. Because of this lack or incompleteness of diagnostic information, once a patient with multivessel disease is in the catheterization laboratory for revascularization, the interventional cardiologist will often rely upon the coronary angiogram for decision making about revascularization of coronary artery stenoses, notwithstanding its intrinsic limitations as described in the next paragraph.

#### **1.4 Coronary angiography in guiding percutaneous coronary intervention**

Coronary angiography has played a pivotal role in the diagnosis and treatment of coronary artery disease since the first coronary angiogram was made more than 50 years ago.<sup>22;23</sup> Two decades later, PCI developed rapidly. In 1977 the first balloon coronary angioplasty was performed<sup>24</sup> and nowadays PCI is an indispensable alternative to bypass surgery in many patients even with multivessel coronary artery disease.<sup>24-27</sup> Fueled by improved angioplasty technology and lower restenosis rates with the drug-eluting stents, more and more patients with multivessel disease are treated by PCI worldwide. It is estimated that 4 million PCI's are performed worldwide each year.



For guiding PCI in such patients, i.e. selecting the correct spots where stents have to be placed, coronary angiography is still the standard technique. This implies that in many patients, treatment decisions are largely based on visual angiographic assessment of coronary artery narrowings, together with clinical data. Many clinical trials on revascularization also use coronary angiography as a ‘gold standard’ to define the significance of a coronary artery stenosis. However, coronary angiography has a number of well-recognized limitations.<sup>28-30</sup> Compared to pathological findings at autopsy, a number of studies have reported both significant overestimation of coronary stenosis severity as well as underestimation of coronary artery narrowings. This is explained in part in *figure 1.4*.



**Figure 1.4.** Angiographic projections from different angles can lead to misjudgement of the true anatomic severity of a coronary artery stenosis. The black area within the circle represents the intact lumen of the artery, which is filled by contrast agent during coronary angiography. On the left a schematic example of underestimation by angiography of an anatomically severely narrowed coronary artery. On the right a schematic example of a stenosis that appears severely narrowed in one angiographic projection and normal in another projection. (Adapted from van 't Veer M. Hemodynamic measurements in coronary, valvular, and peripheral vascular disease. PhD thesis, Eindhoven University of Technology, 2008.)

Furthermore, visual estimation of stenosis severity has been proven to be highly variable between different operators and even intra-observer variability is large.<sup>31;32</sup> Above all, visual angiographic stenosis severity assessment poorly predicts the functional significance of a stenosis<sup>32</sup>, whereas the presence of inducible myocardial ischemia related to such a stenosis should be the 'trigger' for revascularization, as discussed in paragraph 1.2. Even a more sophisticated technique like computer automated anatomic estimation of coronary narrowings (QCA) has proven to correlate poorly to physiologic measures of coronary function, especially in the stenosis range between 50-90% diameter stenosis (*see figure 5.1*).<sup>33</sup> This poor concordance between angiography or anatomy on the one hand and function on the other hand, is not only due to the abovementioned shortcomings of coronary angiography.

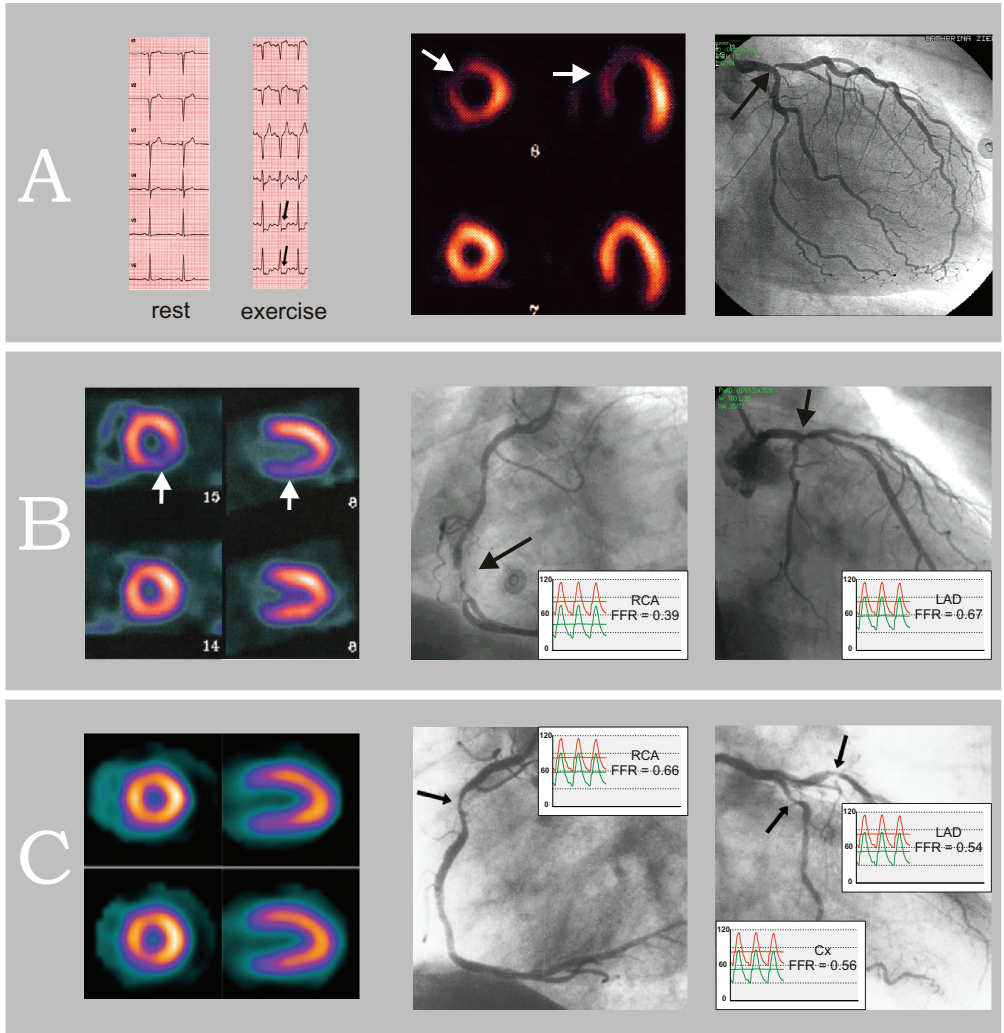
Another explanation why the functional significance of a stenosis often cannot be settled from the coronary angiogram is that differences in morphology of the stenosis or plaque can result in different rheologic and subsequent functional effects, as explained in *figure 1.6*.

Finally, several other, "non-anatomic" factors should be taken into account when determining the physiological severity of a coronary artery stenosis, such as the extent of the myocardial perfusion area that is supplied by that artery and the presence of collateral flow, as will further be explained in *chapter 2*.<sup>34</sup>

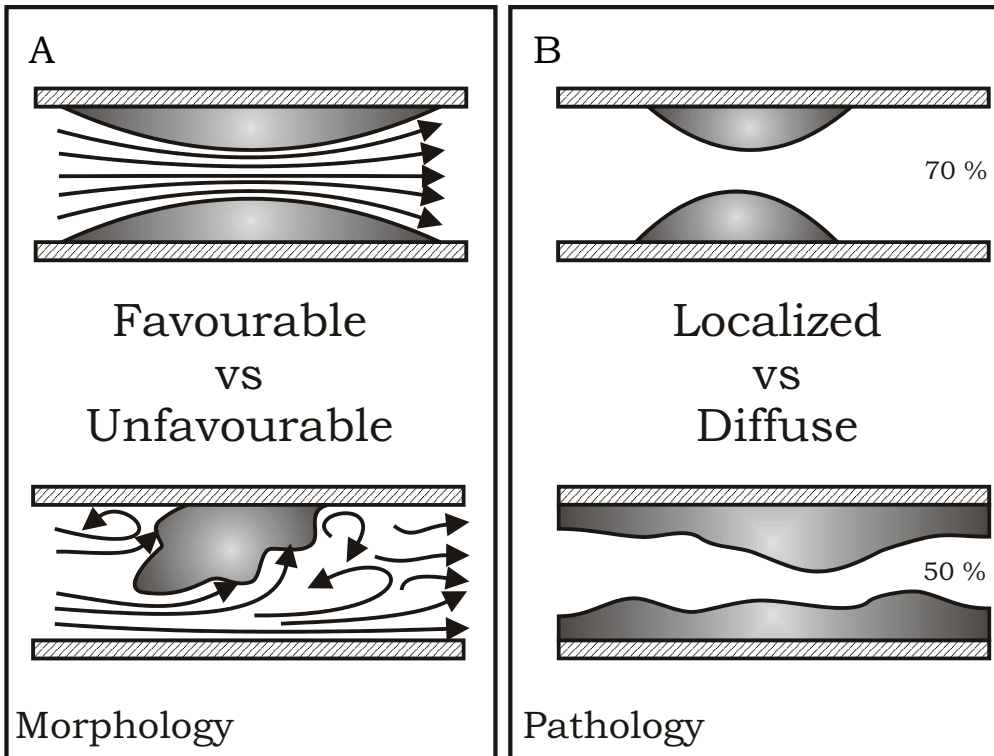
**Figure 1.5.** Three illustrations of patients in whom nuclear stress imaging studies were performed as part of a diagnostic work-up because of chest pain. Patient A (upper row) had typical chest pain during exercise. The left panel of row A shows the exercise ecg of this patient, which is clearly positive for myocardial ischemia (black arrows indicate ST-segment depressions during exercise). In the middle panel, the white arrows indicate reversible myocardial ischemia in the anteroseptal wall on the nuclear scan images. The coronary angiogram of the left coronary artery shows a subtotal stenosis in the proximal left anterior descending artery (LAD; black arrow). So, in patient A, all diagnostic modalities show compatible results. Because all non-invasive tests are correctly positive, it is clear that the proximal LAD stenosis needs to be revascularized.

Patient B (middle row) had typical chest pain, a positive nuclear scan showing reversible ischemia in the inferior wall (white arrows) and the coronary angiogram revealed a subtotal stenosis in the right coronary artery (RCA). Patient B was referred from another hospital for PCI of the RCA. The angiographically mild lesion in the distal left main stem was overlooked by the referring cardiologist, probably also because the nuclear scan did not reveal ischemia in the anterior wall. Functional assessment of both the left main stem and RCA with Fractional Flow Reserve showed not only a functionally significant (ischemic) stenosis in the RCA (FFR 0.39), but also in the left main stem (FFR 0.67). In this case, the nuclear scan result gave incomplete information, because the ischemia in the anterior wall (as detected by FFR) was masked by the more extensive ischemia in the opposing inferior wall. Because of the additional information supplied by the FFR measurements, this patient was referred for bypass surgery (instead of PCI as was originally planned).

Patient C had chest pain with some typical characteristics. The nuclear scan, however, showed no signs of myocardial ischemia. Therefore, initially no therapy was started. Because of ongoing complaints, finally a coronary angiogram was performed, which showed proximal stenoses of moderate angiographic severity in all 3 coronary arteries. FFR was below the ischemic threshold (0.54; 0.56; 0.66, respectively) in all 3 coronary arteries. The nuclear scan in this case showed no myocardial ischemia due to balancing of ischemia. Such a false-negative test results in a potentially dangerous decision in this type of patients.



**Figure 1.5.** See legend on left page.



**Figure 1.6.** Explanations why the morphology of a coronary stenosis plays a role in its functional significance. Panel A shows that a pressure drop due to shear stress and flow separation is much higher if the stenosis is eccentric and of irregular shape, as is often the case. Panel B shows that in the presence of diffuse disease, percentual narrowing will underestimate the significance of a coronary stenosis (Adapted from Pijls N. Maximal myocardial perfusion as a measure of the functional significance of coronary artery disease. PhD thesis, Radboud University of Nijmegen, 1991).

## 1.5 Multivessel disease: selecting the correct lesions for stenting

As outlined in the previous paragraphs, non-invasive stress testing and coronary angiography will not always provide adequate and complete information about the functional importance of coronary artery narrowings. Particularly in patients with multivessel disease, it can therefore be difficult to determine which out of several lesions cause myocardial ischemia and

therefore warrant revascularization. Because of the low restenosis rate, some investigators have proposed stenting of all angiographically significant lesions (i.e. more than 50% diameter stenosis) with drug-eluting stents, irrespective of their physiological significance.<sup>35;36</sup> However, drug-eluting stents are expensive and are associated with potential serious late complications, leading to death or myocardial infarction in at least 2 to 3% per stent per year.<sup>37;38</sup>

Therefore, realizing the relative benign character of non-ischemic stenoses if treated medically (*figure 1.3*), just stenting all visible lesions can increase risk inadvertently and is not an acceptable strategy. More sophisticated ways to detect ischemic stenoses and to stent those lesions selectively, are mandatory. Fractional Flow Reserve (FFR) is an invasive index that can be measured with a coronary pressure wire at the time of angiography and accurately identifies ischemic lesions.<sup>21;39;40</sup> Therefore, in patients with multivessel disease, an easily obtainable physiological index like FFR can be of help in guiding decision making about the choice of those coronary artery stenoses that benefit from stenting.

In patients with single vessel disease and intermediate coronary artery stenoses, a randomized study showed that deferring stenting if the FFR was compatible with absence of ischemia results in excellent 5-year outcome compared to performing stenting.<sup>12</sup> In a retrospective study in patients with multivessel disease who underwent stenting of ischemic lesions according to FFR and deferral of stenting of other lesions because the FFR indicated absence of ischemia, the 3-year event rate related to the deferred lesion was low as well.<sup>41</sup> Both studies indicate that PCI of hemodynamically non-significant stenoses can be safely deferred, even if initially planned on the basis of the angiogram.

Another retrospective analysis of patients with multivessel disease compared a group of patients that underwent PCI based on guidance by angiography to a group of patients that underwent PCI based on guidance by FFR.<sup>42</sup> In the FFR-guided group less vessels were treated and costs were lower. Also the outcome after 30 months was significantly better in the group that underwent PCI based on guidance by FFR.

The main topic of this thesis is a prospective, randomized, multicenter trial to compare a standard, currently used angiography-guided strategy to an FFR-guided strategy in patients with multivessel coronary artery disease undergoing PCI with drug-eluting stents. The theoretical background, clinical validation, and clinical application of FFR are described in detail in *chapter 2* of this thesis.

## 1.6 Outline of this thesis

As outlined in this introduction (*chapter 1*), in patients with coronary artery disease the most important factor, both with respect to functional class (symptoms) and prognosis (outcome), is the presence and extent of inducible myocardial ischemia. However, especially in patients with multivessel disease, coronary angiography and non-invasive stress testing often do not provide sufficient information about presence or localization of inducible myocardial ischemia, and the necessity of a more sophisticated method to guide coronary intervention, is highly needed. In *chapter 2* the concept of FFR and the technique to measure this functional index are reviewed. Also, reference is made to validation studies, confirming the feasibility and reliability of pressure derived FFR to discriminate whether a lesion is capable of inducing myocardial ischemia. FFR is proposed as an innovative technology to guide multivessel PCI and to improve outcome.

The windtunnel for testing the effect of any new treatment on clinical outcome, is a comparison with existing technology in a large, prospective and randomized clinical trial. That is the background for designing and performing the FAME study (Fractional Flow Reserve versus Angiography in Multivessel Evaluation). The rationale and design of this study are presented in *chapter 3* of this thesis. The FAME study was performed in 20 centers in Europe and in the United States of America. The results of this trial, comparing guidance of multivessel PCI by FFR or by standard angiography, are presented in *chapter 4*. The correspondence with respect to the publication of the 1-year results of the FAME study in the New England Journal of Medicine, is presented in

**appendix I.** In **appendix II**, investigators and institutions participating in the FAME Study Group are listed.

In **chapter 5**, an in-depth analysis of the FAME study reports the low accuracy of angiography in predicting a lesion's functional significance as assessed by FFR. This chapter also gives insight into the difference in number of significantly diseased coronary arteries from a functional versus an anatomical point of view.

It is very rare in today's medicine that a novel treatment is not only better but also cost-saving. The FAME study proved to be such a rare exception. A detailed cost-effectiveness analysis and the economic impact of an FFR-guided strategy of drug-eluting stenting in multivessel disease is described in **chapter 6**.

In **chapter 7** the 2-year outcome of the FAME study is described.

Finally, in **chapter 8** a general discussion is presented and future perspectives are overviewed with respect to FFR-guided revascularization, within a wider context of several other landmark studies in this field.



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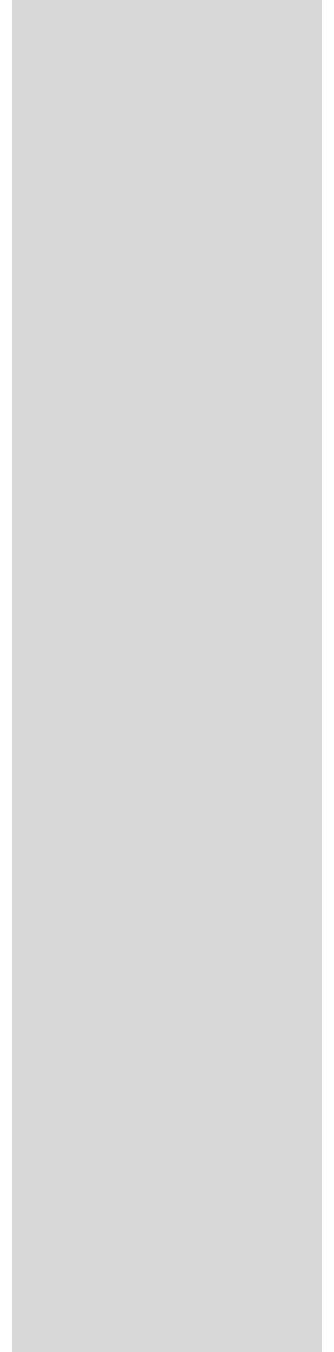
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# 2

## Fractional Flow Reserve





## **2.1 Introduction**

This thesis deals with the routine use of fractional flow reserve (FFR) in guiding percutaneous coronary intervention (PCI) with drug-eluting stents in patients with multivessel coronary artery disease. In the next paragraphs, the anatomy and physiology of the coronary circulation are shortly described and the concept and practical application of FFR is explained.

## **2.2 Anatomy of the coronary circulation**

The right and the left coronary artery branch off from the proximal part of the aorta, just above the level of the aortic valve. The diameter of these small arteries taper from 3.5 to 1 mm from base to apex and the resistance to blood flow in these epicardial vessels is negligible under normal circumstances. The first part of the left coronary artery is called the left main stem (LM), which after only a short distance divides into two important arteries, the left anterior descending artery (LAD) and left circumflex artery (LCX). In clinical practice therefore, we often speak of three coronary arteries. From these epicardial vessels, perforating arteries branch off and penetrate into the myocardium. These vessels further divide into arterioles with a diameter of 100 to 400  $\mu\text{m}$ . Arterioles are so-called 'resistance vessels', having a muscular sphincter surrounding the vessel that can vary resistance and therefore blood flow, over a wide range. The arterioles further branch into capillaries, which form a dense network for optimal exchange of oxygen and metabolites with the cardiac muscle cells (myocytes). Finally, the capillaries unite into venules, which further unite into veins. The blood in these veins flows into the right atrium via the coronary sinus, and partly via the Thebesian veins.



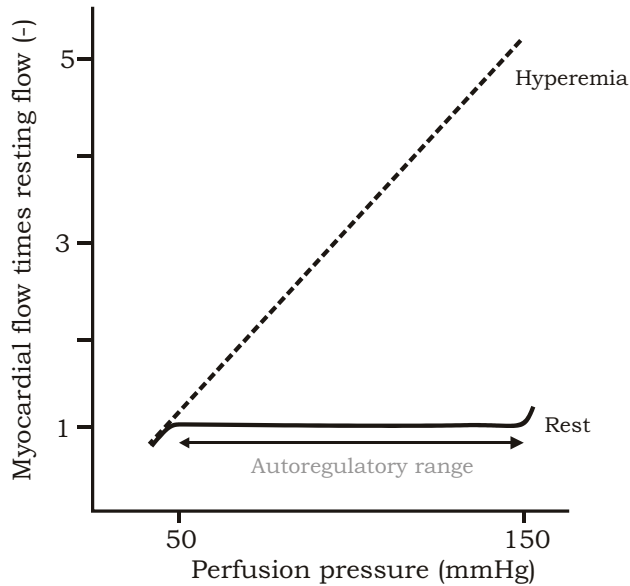
### 2.3 Regulation of coronary blood flow

In a healthy person, cardiac output can be increased from 5 liters per minute at rest to 25 liters per minute at peak exercise in order to sufficiently match the metabolic demands of the body. The coronary blood flow consists of 3-5% of cardiac output and can therefore vary from 200 ml up to 1 liter per minute. In most organs the oxygen saturation of venous blood is approximately 70%. However, the oxygen saturation of blood in the coronary sinus is relatively low, being 30 to 40% at rest. This high oxygen extraction implicates that an increase in oxygen demand by the heart can not be met by a further increase in oxygen extraction and must therefore be accomplished by an increase in coronary blood flow.

The arterioles with their surrounding muscular sphincters have a key function in the regulation of coronary blood flow.<sup>1;2</sup> As noticed, they can vary resistance over a wide range by regulating sphincter tone, mediated by a complex interplay of mechanical and humoral factors. When the oxygen demand of the myocardium increases, vascular resistance decreases by relaxation of the arteriolar sphincters and blood flow will increase. In a similar way this mechanism keeps coronary blood flow constant by increasing or decreasing the resistance, if changes in blood pressure occur. This mechanism is referred to as autoregulation and is illustrated in *figure 2.1*.

Autoregulation can keep resting coronary perfusion constant over a wide range of blood pressure, but in case distal coronary pressure drops below 50 mmHg, which can for instance occur in the presence of a severe epicardial stenosis, even resting flow can become subcritical.<sup>3</sup>

It is clear that under normal physiological circumstances and in the absence of a coronary stenosis, maximum achievable or hyperemic blood flow may exceed by far resting flow, often by a factor 5 or more. The extent to which coronary or myocardial blood flow can increase is termed coronary flow reserve. Coronary flow reserve was introduced as a functional index of the coronary circulation and is defined as the ratio between peak or hyperaemic and basal blood flow.<sup>4;5</sup>



**Figure 2.1.** Coronary autoregulation maintains resting coronary flow constant within a narrow range despite large variations in coronary perfusion pressure. As opposed to the resting situation, at maximum hyperemia, myocardial flow is almost linearly proportional to myocardial perfusion pressure.

Although coronary flow reserve is a beautiful physiologic concept, this index is inadequate for determining hemodynamic or functional severity of a coronary artery stenosis for several reasons. Coronary flow reserve has a large inter-individual variation, is age-dependent and fluctuates with changes in baseline blood flow and blood pressure.<sup>3-7</sup> Because of the absence of a normal value, it is impossible to define a clear threshold value of CFR for the detection of myocardial ischemia related to a coronary stenosis. To overcome these limitations the concept of Fractional Flow Reserve (FFR) was introduced.

## 2.4 Fractional Flow Reserve

FFR is defined as the maximum achievable blood flow to a myocardial territory in the presence of a stenosis as a ratio to the normal maximum achievable blood flow to that same myocardial territory in the hypothetical situation the supplying vessel would be completely normal. In other words, FFR expresses maximal blood flow in the presence of a stenosis as a fraction of normal maximum blood flow. The concept of FFR was developed to investigate the functional significance of a coronary artery stenosis.<sup>4</sup> This index is considered the gold standard for the detection of myocardial ischemia, related to a particular stenosis. Nowadays, FFR is a routinely available diagnostic tool, which is used for clinical decision-making in most catheterization laboratories. And as will be explained, although FFR is a ratio of flows, it can easily be measured by the ratio of distal coronary pressure to aortic pressure at maximum hyperemia.

### 2.4.1 Conceptual background of FFR

The exercise tolerance of patients with stable coronary artery disease is determined by maximum achievable myocardial blood flow. Therefore, from the practical point of view of the patient, maximum achievable myocardial blood flow is the most important parameter to quantify the severity of coronary disease. In the presence of a stenosis, the exercise level at which ischemia occurs is directly related to the maximum coronary blood flow that is still achievable by the stenotic coronary artery. Therefore, not *resting flow* but *maximum achievable blood flow* to the myocardium is the best parameter to determine the functional capacity of the patient. Expressing myocardial blood flow in absolute dimensions (ml/min), however, has considerable disadvantages because this is dependent on the size of the distribution area which is unknown, and will differ between patients, vessels and distribution areas. To overcome this, it is better to express maximum achievable (stenotic) blood flow as a ratio to normal maximum blood flow. Consequently, the ratio between maximum achievable stenotic blood flow and maximum achievable

normal blood flow is called fractional flow reserve of the myocardium ( $FFR_{myo}$ ).<sup>6-8</sup> In general, and also in this thesis,  $FFR_{myo}$  is generally just called FFR.

This index is not dependent on resting flow or changing hemodynamic conditions, has a normal value of 1.0 for every patient and every artery, takes into account the extent of the perfusion area and presence of collaterals, and is therefore not subject to many of the limitations related to the concept of coronary flow reserve. More importantly, for FFR there is a clear threshold value with a narrow gray zone (0.75-0.80), discriminating stenoses which are responsible for inducible myocardial ischemia or not. Therefore, FFR is a very suitable tool for guiding decision making with respect to performing coronary interventions.

#### **2.4.2 Measuring FFR**

Under circumstances generally present in the coronary catheterization laboratory it is difficult to measure flow and flow ratios directly. However, by using a pressure-monitoring guidewire at maximum hyperemia it is possible to calculate this ratio of flows by a ratio of pressures. This can be understood from *figure 2.1* and is further explained in *figure 2.2*. *Figure 2.2A* represents a normal coronary artery and its dependent myocardium. Suppose that this system is studied at maximum vasodilation. In this situation, myocardial resistance is minimal and constant, and maximum myocardial hyperemia is present, as is the case at maximum exercise. At maximum hyperemia, as can be seen in *figure 2.1*, myocardial perfusion pressure and myocardial flow are linearly proportional, and a change in myocardial perfusion pressure results in a proportional change in myocardial flow. In the case of a normal coronary artery (*figure 2.2A*), the epicardial artery does not have any resistance to flow, and the pressure in the distal coronary artery is equal to aortic pressure. In the example, therefore, myocardial perfusion pressure (defined as distal coronary pressure  $P_d$  minus venous pressure  $P_v$ ) equals 100 mm Hg. In case of a stenosis however (*figure 2.2B*), this stenosis creates an additional resistance to blood flow, and distal coronary pressure will be lower than aortic pressure: a pressure gradient exists across the stenosis (in the example  $P_a - P_d = 30$

mmHg) and myocardial perfusion pressure will be diminished (in the example  $P_d - P_v = 70$  mmHg). In the example, therefore (*figure 2.2B*), myocardial perfusion pressure has decreased to 70mm Hg, whereas it should be 100 mmHg in the normal case.

Because during maximum hyperemia, myocardial perfusion pressure is directly proportional to myocardial flow (*figure 2.1*), the ratio of maximum stenotic and normal maximum flow can be expressed as the ratio of distal coronary pressure and aortic pressure at hyperemia and also equals 0.70.

Therefore:

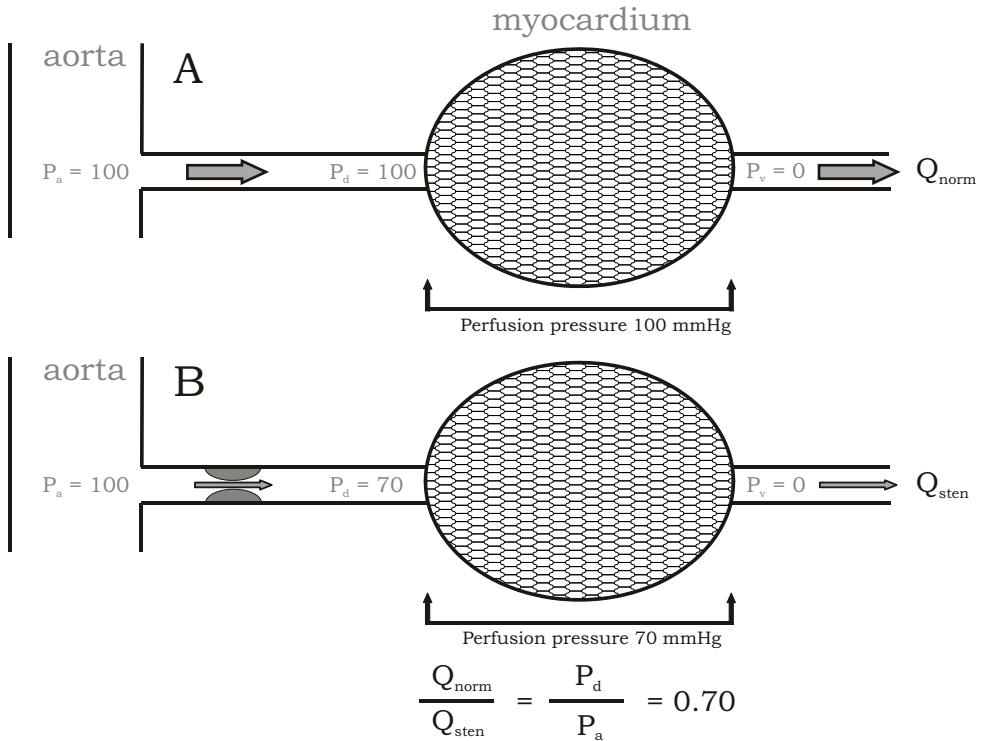
$$FFR_{myo} = \frac{\text{Maximum myocardial blood flow in the presence of a stenosis}}{\text{Normal maximum myocardial blood flow}}$$

Can be expressed as:

$$FFR_{myo} = \frac{(P_d - P_v)}{(P_a - P_v)}$$

Because generally, central venous pressure is much smaller than  $P_d$  and  $P_a$ , and close to zero, the equation can be further simplified to:

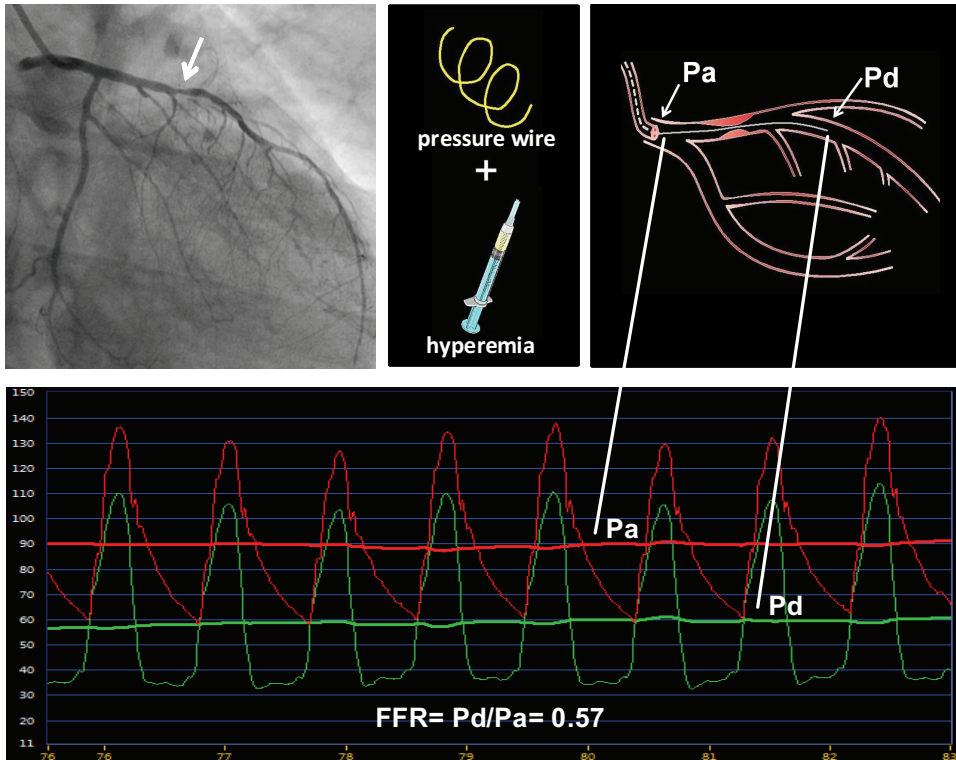
$$FFR_{myo} = \frac{P_d}{P_a}$$



**Figure 2.2A.** Schematic representation of a normal coronary artery and its dependent myocardium, studied at hyperemia. In this normal situation, the (conductive) coronary artery gives no resistance to flow, and thus distal coronary pressure is equal to aortic pressure. Assuming that venous pressure is zero, perfusion pressure across the myocardium is 100 mm Hg.

**Figure 2.2B.** The same coronary artery, now in the presence of a stenosis. In this situation, the stenosis will impede blood flow and thus a pressure gradient across the stenosis will arise ( $\Delta P=30$  mm Hg). Distal coronary pressure is not equal anymore to aortic pressure, but will be lower ( $P_d=70$  mm Hg). Consequently, the perfusion pressure across the myocardium will be lower than in the situation that no stenosis was present (perfusion pressure is now  $100-30=70$  mm Hg). Because during maximum hyperemia, myocardial perfusion pressure and myocardial blood flow are linearly proportional, the ratio of maximum stenotic and normal maximal flow can be expressed as the ratio of distal coronary pressure and aortic pressure at hyperemia:  $FFR=P_d / P_a=70$  mm Hg. Importantly, it is distal coronary pressure at hyperemia which determines myocardial flow, and not the pressure gradient across the stenosis. (Adapted from Aarnoudse W. Invasive assessment of the coronary microcirculation by pressure and temperature measurements, PhD thesis, Eindhoven University of Technology, 2006.)

As  $P_a$  can be measured in a regular way by the coronary or guiding catheter, and  $P_d$  is obtainable simultaneously by crossing the stenosis with a sensor-tipped guidewire, it is clear that  $FFR_{myo}$  can be simply obtained, both during diagnostic and interventional procedures, by measuring the respective pressures at maximum hyperemia (*figure 2.3*). From the equations above it is also obvious that  $FFR_{myo}$  for a normal coronary artery equals 1.0 for every person and for every normal coronary artery.



**Figure 2.3.** With a pressure sensor-tipped guidewire and an adequate hyperemic stimulus, FFR can be calculated as the ratio  $P_d/P_a$ . The lower part of this figure shows pressure tracings as displayed on an analyzer, derived from a sensor-tipped wire, with the sensor placed distal from the stenosis ( $P_d$ , green signal) in the left anterior descending (LAD) artery, and from the tip of a guiding catheter in the ostium of the left main coronary artery ( $P_a$ , red signal). Despite the fact that the narrowing (arrow) does not look very severe on the coronary angiogram, its hemodynamic impact is important as reflected by the low value of FFR.

### **2.4.3 Validation of FFR and cut-off threshold for myocardial ischemia**

FFR has a high accuracy for detecting myocardial ischemia. More specifically,  $FFR < 0.75$  has 100% specificity for indicating inducible ischemia, whereas a  $FFR > 0.80$  has a sensitivity of  $>90\%$  for excluding inducible ischemia. This extremely high accuracy of FFR is unique and FFR is the only index of ischemia which has ever been validated versus a true gold standard in a prospective multi-testing Bayesian approach. These cut-off threshold values have been confirmed in multiple clinical studies in many different populations, comparing FFR measurement to non-invasive tests for inducible myocardial ischemia.<sup>7-12</sup> Identical FFR cut-off threshold values are applicable in a variety of patient populations, including in patients with previous myocardial infarction or diabetes mellitus.<sup>11;13;14</sup>

Several studies have convincingly shown that stenting a coronary stenosis in patients with a fractional flow reserve below 0.75-0.80 improves functional class and prognosis, whereas stenting stenoses above that threshold does not and therefore is not recommended.<sup>8;11;15</sup>

### **2.4.4 Features of FFR**

Besides a very high specificity and sensitivity for the detection of inducible myocardial ischemia related to a coronary artery stenosis, FFR has some additional advantageous and specific features which make it an easy and convenient practical index to be used in the catheterization laboratory. These features are:

- *FFR is independent of heart rate, blood pressure and myocardial contractility*<sup>16</sup>
- *FFR has an unequivocal normal value of 1.0 for every patient, every coronary artery, and every myocardial distribution*
- *FFR takes into account the contribution of collateral blood flow to myocardial perfusion*<sup>17</sup>



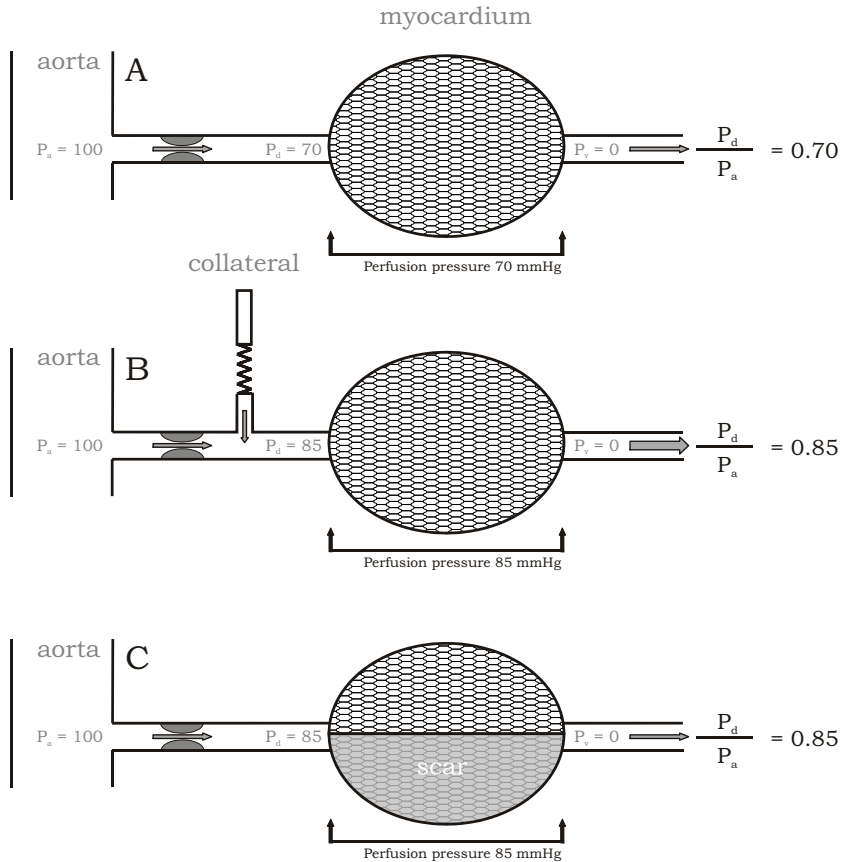
- FFR takes into account the amount of viable myocardial mass <sup>11</sup>
- FFR can be applied in single- and in multivessel disease: there is no need for a normal coronary artery to compare with
- FFR has a higher spatial resolution than any other functional test
- FFR can be easily obtained, both at diagnostic and interventional procedures, by the ratio of the mean hyperaemic distal coronary to aortic pressure <sup>8</sup>
- FFR has a high reproducibility <sup>15</sup>

With respect to the interrogation of patients with multivessel disease by FFR, the fact that there is no need for a normal control artery to compare with is advantageous compared to non-invasive functional tests like nuclear perfusion imaging and other physiologic indices like coronary flow reserve. In addition, as illustrated in *figure 2.4*, FFR takes into account the amount of viable myocardial mass and/or the presence of collateral flow.

Furthermore, FFR has an unsurpassed high spatial resolution. The position of the pressure sensor on the sensor-tipped guidewire can be accurately located by fluoroscopy, and by changing its position along a coronary artery under continuous hyperemia, the pressure changes can be followed real-time. This feature allows an operator to distinguish between diffuse atherosclerosis and focal stenoses, even within a single coronary artery segment. The same feature can also be of help in the assessment of arteries with ostial, serial, or bifurcation stenoses. As outlined in *chapter 1*, other functional tests, in contrast to FFR, only reach an accuracy per patient (exercise stress-testing with ECG) or per coronary artery (nuclear perfusion imaging).

#### **2.4.5 Towards the routine use of FFR in multivessel disease**

Many of the abovementioned specific and advantageous features of FFR are especially applicable to patients with multivessel disease. One might

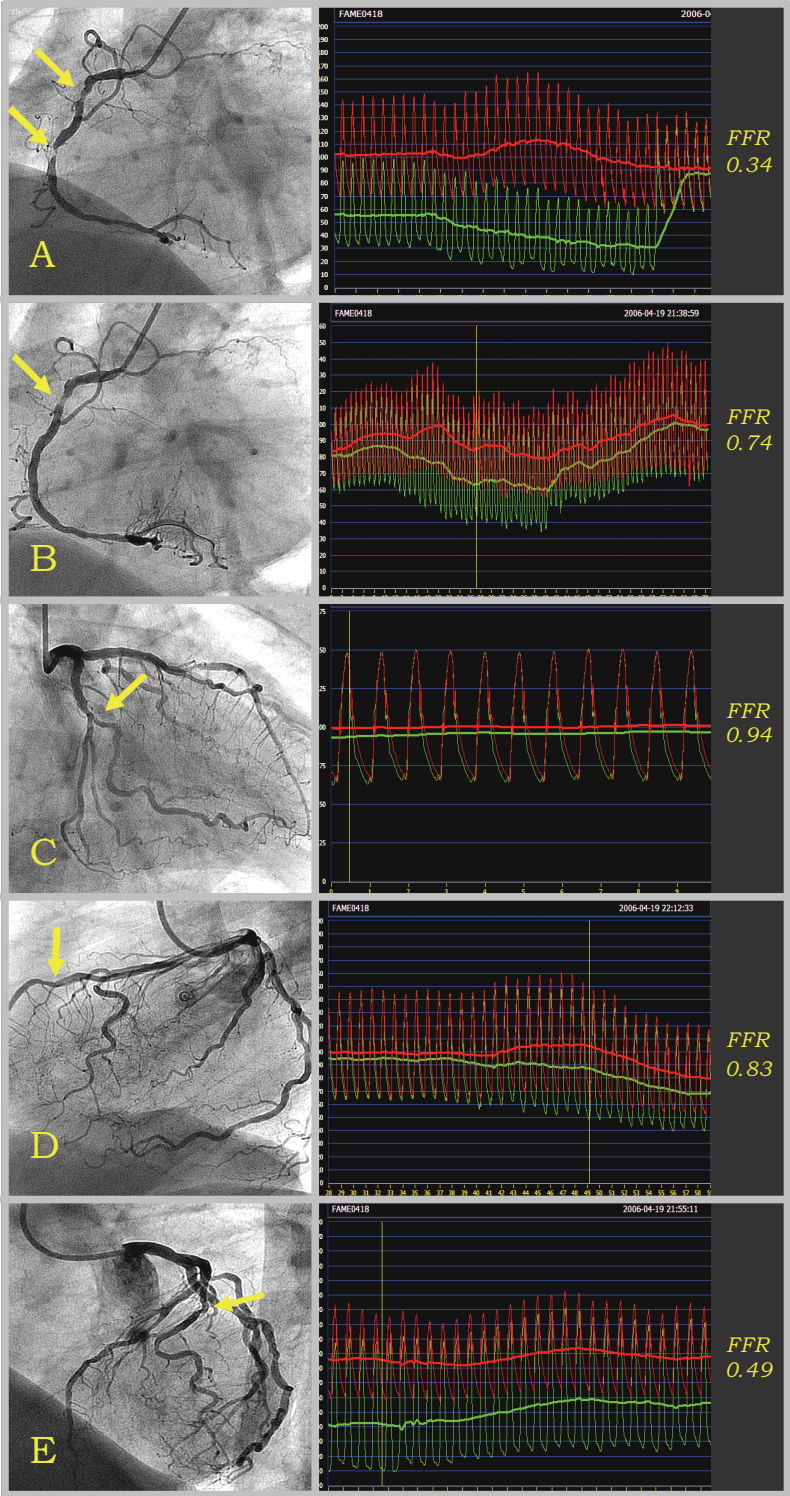


**Figure 2.4.** FFR takes into account the amount of viable myocardial mass and/or collateral flow. In all three examples ( A, B, and C) the same coronary stenosis and the same aortic pressure ( $P_a=100\text{mmHg}$ ) are present under hyperaemic circumstances. However, the physiologic significance of the stenosis is different, due to collaterals or previous infarction. That difference is reflected by a different FFR. In example A there is a normal myocardium, the distal pressure ( $P_d$ ) is 70mmHg and therefore FFR is  $70/100=0.70$ . In example B, a situation with the same stenosis and myocardium as in example A, but now there is collateral flow, resulting in a higher distal pressure ( $P_d$ ) of 85mmHg. FFR in example B is therefore  $85/100=0.85$ . So a higher (no longer significant) FFR in the presence of the same stenosis, due to contribution of collateral flow. In example C, again the same stenosis as in example A, but now the myocardial perfusion area is much smaller as a result of a previous myocardial infarction (scar). The distal pressure ( $P_d$ ) is now higher (85mmHg) because hyperaemic blood flow is decreased due to a smaller myocardial perfusion area to be perfused. FFR is now 0.85 and the stenosis is no longer significant.

hypothesize that the use of FFR in such patients allows more judicious use of stents than with angiography alone, thereby rendering equal relief of ischemia and lower stent- and procedure related complication rates (*figure 2.5*). Retrospective studies have already indicated beneficial effect of the routine use of FFR on outcome and costs in patients with multivessel disease<sup>18;19</sup>. The main subject of this thesis is a randomized comparison between an FFR-guided and an angiography-guided strategy for stenting in patients with multivessel disease and the design of that study will be described in the next chapter.

*(Legend belonging to the figure on the right page)*

**Figure 2.5.** *Example of a FAME study patient (randomization number 418). The FAME study is extensively described in the next chapter. This patient had 5 stenoses that were indicated by the operator as requiring stent placement on the basis of the angiogram and clinical data. Thereafter this patient with multivessel coronary artery disease was randomized to the FFR-guided strategy, which means that only stenoses with  $FFR \leq 0.80$  (below the ischemic threshold) are to be stented. FFR of the 2 tight stenoses in the RCA was 0.34 (Panel A). A stent was placed in the distal stenosis, and FFR after was 0.74 (Panel B). A second stent was placed in the proximal stenosis (FFR after stenting of the RCA was 0.87). FFR of the RCX was 0.94 (Panel C), and this stenosis was therefore not stented. The 50-70% stenosis in the LAD was also not stented because of an FFR above the ischemic threshold of 0.80 (Panel D). The FFR of the 50-70% stenosis in the diagonal branch was 0.49 (Panel E), and a stent was placed with a good angiographic result (FFR after stenting in the diagonal was not recorded). The total procedure time was 46 minutes. Only 3 out of the 5 indicated stenoses needed stent placement after assessment by FFR.*



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# 3

## Rationale and Design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) Study

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*William F. Fearon, M.D.*  
*Pim A.L. Tonino, M.D.*  
*Bernard De Bruyne, M.D.,*  
*Ph.D.*  
*Uwe Siebert, M.D., MSc.,*  
*M.P.H. ScD.*  
*Nico H.J. Pijls, M.D., Ph.D.*  
*for the Fractional Flow*  
*Reserve versus*  
*Angiography for*  
*Multivessel Evaluation*  
*(FAME) Study*  
*Investigators\**

*\*Affiliations of all authors*  
*and all members of the*  
*FAME Study Investigator*  
*Group are listed in*  
*appendix II of this thesis*



## Abstract

**Background** Although its limitations for diagnosing critical coronary artery disease are well-described, coronary angiography remains the predominant method for guiding decisions about stent implantation in patients with multivessel coronary artery disease. However, some have suggested that invasive physiologic guidance may improve decision making.

**Trial Design** The objective of this multicenter, randomized clinical trial is to compare the efficacy of two strategies, one based on angiographic guidance to one based on physiologic guidance with fractional flow reserve (FFR), for deciding which coronary lesions to stent in patients with multivessel coronary disease. Eligible patients must have coronary narrowings  $>50\%$  diameter stenosis in two or more major epicardial vessels, at least two of which the investigator feels require drug-eluting stent placement. Patients with prior coronary bypass surgery or left main disease are excluded. Based on angiographic evaluation, the investigator notes the lesions that require stenting. The patient is then randomly assigned to either angiographic guidance or FFR guidance. Patients assigned to angiographic guidance undergo stenting as planned. Patients assigned to FFR guidance first have FFR measured in each diseased vessel and only undergo stenting if the FFR is  $\leq 0.80$ . The primary endpoint of the study is a composite of major adverse cardiac events, including death, myocardial infarction, and repeat coronary revascularization, at one year. Secondary endpoints will include the individual adverse events, cost-effectiveness, quality of life, and 30 day, 6 month, 2 year and 5 year outcomes.

**Conclusion** The FAME study will examine for the first time in a large, multicenter, randomized fashion the role of measuring FFR in patients undergoing multivessel PCI. (*ClinicalTrials.gov* number, NCT00267774.)

### **3.1 Introduction**

The presence of myocardial ischemia is an important determinant of adverse cardiac outcome.<sup>1</sup> Eliminating myocardial ischemia through coronary revascularization can improve patient outcomes.<sup>2</sup> In patients with multivessel coronary artery disease (CAD), identifying which lesions are responsible for ischemia can be challenging. Noninvasive stress imaging studies are limited in their ability to accurately localize culprit vessels or lesions in patients with multivessel CAD.<sup>3</sup> Coronary angiography remains the standard technique for diagnosing critical coronary disease and for guiding percutaneous coronary intervention (PCI). However, angiography is limited by its two-dimensional nature which can result in both underestimation and overestimation of a coronary stenosis.<sup>4</sup> In addition, angiography documents changes in the coronary lumen, but does not always identify the atherosclerotic burden of a particular vessel, which may impact the ability of the vessel to provide adequate blood flow to the myocardium.<sup>5;6</sup> Finally, angiography provides morphologic information only; in the setting of intermediate coronary stenoses, angiography is unable to accurately predict which lesions will be ischemia-producing.<sup>7</sup>

Fractional flow reserve (FFR) is an invasive index which can be readily measured with a coronary pressure wire at the time of angiography and accurately identifies ischemia-producing coronary lesions.<sup>8</sup> FFR is defined as the mean distal coronary pressure (measured with the pressure wire) divided by the mean proximal coronary or aortic pressure (measured simultaneously with the guiding catheter) during maximal hyperemia.<sup>9</sup> The normal FFR is 0.94-1.0, while an FFR less than 0.75-0.80 correlates with ischemia on noninvasive imaging studies in a variety of patient populations.<sup>10-13</sup>

In a randomized study including patients with single vessel intermediate coronary lesions and chest pain, deferring PCI if the FFR was  $\geq 0.75$  resulted in excellent long-term outcomes compared to performing PCI.<sup>14</sup> In a retrospective review of patients with multivessel CAD who underwent PCI of one lesion and deferral of PCI of another lesion because the FFR was  $\geq 0.75$ , the 3 year event rate related to the deferred lesion was very low.<sup>15</sup> Another retrospective study of patients with multivessel CAD undergoing PCI, compared a group of patients who underwent PCI based on angiographic guidance to another group of patients who underwent PCI based on FFR guidance.<sup>16</sup> The average number of vessels treated with PCI and the cost of the procedure were significantly greater in the angiographic-guided group compared to the FFR-guided cohort. The 30-month event free survival was significantly better in the FFR-guided group.

With the recent introduction of drug-eluting stents (DES) and lower restenosis rates, PCI is being performed more often in patients with multivessel CAD and in patients with increasingly complex CAD.<sup>17</sup> In addition, because of the low restenosis rate, some investigators have proposed stenting all intermediate lesions with DES, irrespective of their physiologic significance.<sup>18</sup> However, DES are expensive and are associated with potential late complications.<sup>19;20</sup> By identifying an approach to PCI in patients with multivessel CAD that would decrease the number of DES deployed, but still result in complete relief of myocardial ischemia, clinical outcomes and health care expenditure could be improved. To date, there has not been a prospective randomized comparison of an FFR-guided strategy to an angiography-guided strategy in patients with multivessel CAD undergoing PCI.

## **3.2 Methods**

### **3.2.1 Study Design**

The objective of the FAME study is to compare the clinical outcomes and cost-effectiveness of an FFR-guided PCI strategy to an angiography-guided one in patients with multivessel CAD. FAME is a multicenter, international,

prospective, randomized trial including men and women aged 18 or older in whom multivessel PCI is planned. Eligible patients must have lesions which are at least 50% narrowed and which the investigator feels require stenting in at least two major epicardial vessels. The vessels must be large enough to accommodate DES.

Patients presenting with ST segment elevation myocardial infarction (MI) are excluded from the study. A patient with a recent ST segment elevation MI who has residual narrowings in two non-culprit epicardial vessels can be enrolled if 5 days have passed since the acute event or sooner if the peak creatinine kinase (CK) was <1000. Patients presenting with non-ST segment elevation MI are included in the study if the peak CK was <1000, otherwise they cannot be enrolled until 5 days have passed from the acute event. These criteria are based on data that show that FFR remains reliable in patients with a previous significant MI as long as sufficient time has elapsed for any myocardial stunning to resolve.<sup>11</sup>

Patients with prior coronary artery bypass surgery or patients with angiographic evidence of significant left main disease are excluded. The complete inclusion and exclusion criteria are outlined in *table 3.1*.

Any patient who is screened, provides consent and meets all inclusion criteria and no exclusion criteria, but is not enrolled (e.g., referred for coronary bypass) will be recorded on an E-CONSORT flowchart.<sup>21</sup> Patients who are enrolled will be prescribed aspirin indefinitely and clopidogrel for at least one year, unless stenting does not occur because the FFR is above 0.80 in both vessels, in which case clopidogrel therapy will be at the discretion of the caring physician.

Once a patient has provided informed, written consent and meets all inclusion and no exclusion criteria and is enrolled in the study, then the investigator must note which lesions will be stented based on visual assessment of the angiogram. The patient is then randomly assigned to one of the two strategies. Computerized randomization will be performed in blocks of 25, using sealed envelopes with assigned strategy mailed to participating centers before enrollment.

**Table 3.1.** In- and exclusion criteria of the FAME study

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**Inclusion Criteria**

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1. 18 years or older
  2. At least two  $\geq 50\%$  diameter stenoses in at least two major epicardial vessels, both of which the investigator feels require stenting
  3. Willing and able to provide informed, written consent
- 

**Exclusion Criteria**

---

1. Left main coronary disease
  2. Previous coronary bypass surgery
  3. Recent ST elevation myocardial infarction (<5 days)
  4. Recent Non ST elevation myocardial infarction (<5 days) if the peak CK is greater than 1000 IU
  5. Cardiogenic shock
  6. Extremely tortuous or calcified coronary vessels
  7. Life expectancy of less than 2 years
  8. Pregnancy
  9. Contraindication for drug-eluting stent placement
- 

If the patient is assigned to the angiography-guided strategy, then the investigator stents the lesions as noted with DES. No other adjunctive technique beyond angiography, such as intravascular ultrasound, can be used to further assess the lesion before stenting.

If the patient is assigned to the FFR-guided strategy, then FFR is first measured and only if it is  $\leq 0.80$  can the operator stent the lesion. Studies have shown that an FFR  $< 0.75$  is very specific for ischemia, while an FFR  $> 0.80$  essentially rules out significant ischemia. The decision to use a cutpoint of 0.80, instead of the traditional 0.75, is based on the fact that many

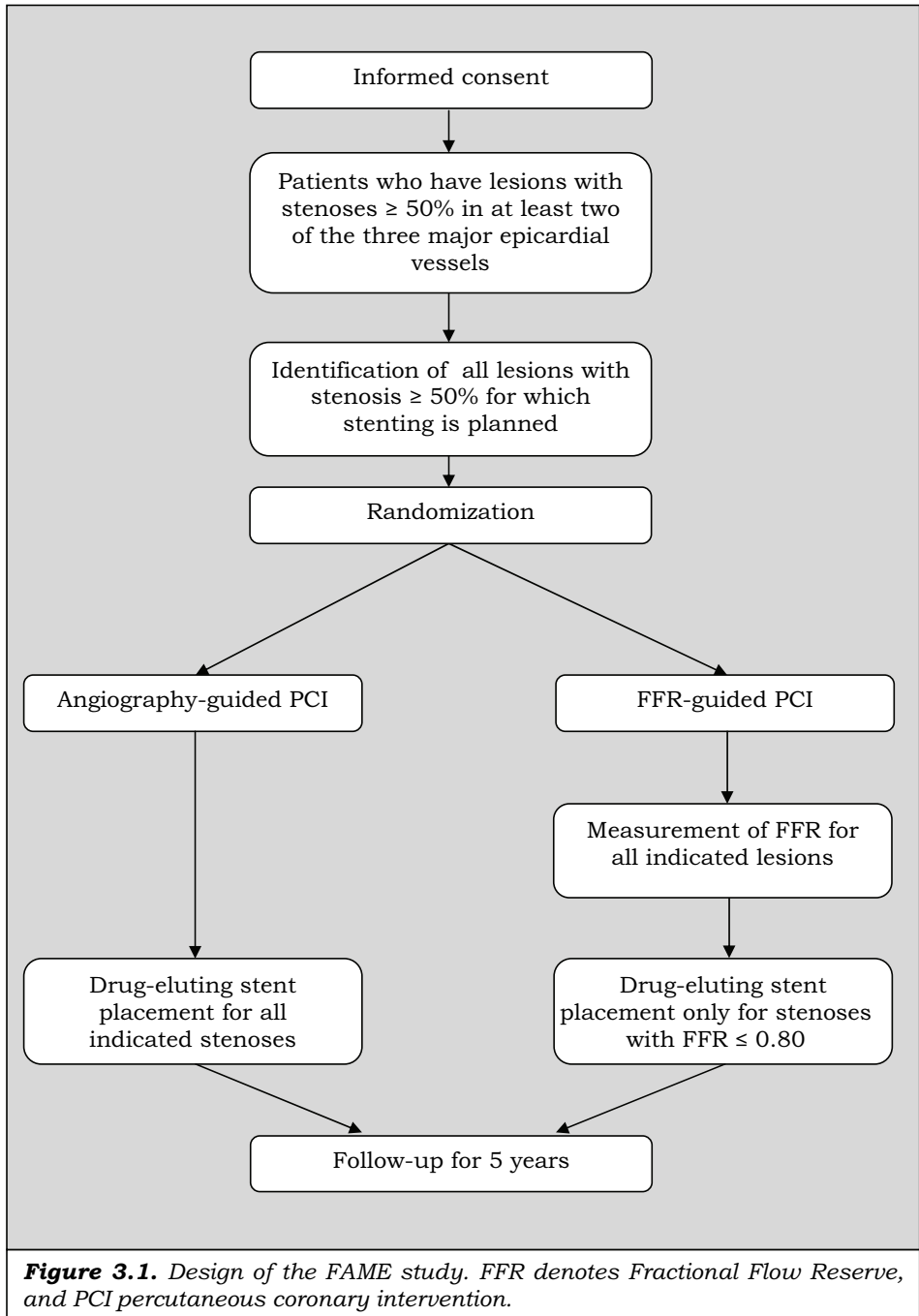
interventional cardiologists elect to perform PCI when the FFR is between 0.75 and 0.80 if the clinical scenario suggests ischemia.<sup>22;23</sup>

FFR is measured with a standard coronary pressure wire (St. Jude/Radi Medical Systems) and after complete hyperemia has been achieved with intravenous adenosine, administered at 140 micrograms/kilogram/minute via a central vein. The investigator can decide not to stent despite an FFR  $\leq 0.80$ , if on slow pullback of the pressure wire the gradient is found to be a result of diffuse CAD and not a focal lesion. In the setting of serial stenoses, stenting is only performed if the FFR beyond all narrowings is  $\leq 0.80$ ; the investigator then stents the narrowing which appears most significant or is responsible for the largest pressure gradient during pullback of the pressure sensor. After stenting the first lesion, FFR is measured again and any residual narrowing causing an FFR  $\leq 0.80$  is stented. Intravenous adenosine is required as opposed to intracoronary adenosine because intravenous adenosine provides prolonged hyperemia which allows adequate time to perform a pullback of the pressure wire and localize pressure gradients. The pressure wire pullback is especially useful in patients with multivessel and diffuse disease.

Patients with a chronically occluded vessel can be included in the study if the investigator feels the vessel warrants PCI and there is another major epicardial vessel which requires PCI. In this case, the patient is not included and randomized until the operator has successfully crossed the chronically occluded vessel. If the patient is then randomized to the FFR strategy, a default FFR value of 0.50 is assigned to the chronically occluded vessel. The rationale for including patients with chronically occluded vessels is to keep the inclusion criteria as broad as possible.

In all FFR-guided patients, the investigator is encouraged to measure a final FFR after completion of PCI. Although the final FFR measurement can be quite useful for assessing the PCI result, it is not mandated in the protocol in an attempt to keep the procedure as simple as possible. If necessary for clinical reasons, the PCI procedure can be staged so that one or more vessels are treated in one setting and the remaining vessels are treated in another setting. If this occurs, follow-up will begin after the first procedure and endpoints such as procedure duration and cost will include both procedures.

Patients will be followed while in hospital for major adverse events. Total CK and CK-MB will be measured in all patients 12-24 hours after PCI is completed. Amount of contrast used and procedure duration will be recorded. A Euroscore and SYNTAX score will be calculated from clinical characteristics and angiographic features, respectively.<sup>24;25</sup> After discharge from the hospital, patients will be followed either by clinic visit or telephone call at 1 month ( $\pm 1$  week), 6 months ( $\pm 1$  month), 12 months ( $\pm 1$  month), 24 months ( $\pm 1$  month) and 60 months ( $\pm 1$  month). An electrocardiogram will be performed in all patients before PCI, within 24 hours after PCI and at 12 months after PCI. Each patient will complete a quality-of-life questionnaire (EQ-5D) before PCI, at 1 month and 12 months after PCI. If a patient requires repeat coronary angiography during follow-up, the strategy to which the patient was originally assigned is followed. In other words, in patients assigned to the FFR-guided strategy, then FFR is measured prior to any repeat PCI; likewise, patients assigned to the angiography-guided strategy undergo repeat PCI based on the angiographic findings alone. By maintaining the treatment strategy during follow-up procedures, patients will not cross over from one strategy to the other, which could hamper the causal interpretation of the results. Follow-up costs will also be prospectively recorded. A study flowchart is displayed in *figure 3.1*.





### 3.2.2 Endpoints

The primary endpoint of the study is the rate of major adverse cardiac events (MACE) at 1 year (*table 3.2*).

**Table 3.2.** Primary and secondary endpoints in the FAME study

<b>Endpoints</b>	
Primary:	The rate of death, myocardial infarction and repeat coronary revascularization (MACE) at 1 year
Secondary:	Cost-effectiveness Health-related quality-of-life index (EQ-5D) MACE at 30 days, 6 months, 2 years and 5 years Individual components of MACE at all timepoints Functional class Number of antianginal medications prescribed Procedure time Contrast usage

MACE is defined as all cause death, MI and any repeat coronary revascularization as adjudicated by the Adverse Clinical Event Committee. Secondary endpoints include the rate of MACE at 1, 6, 24 and 60 months. The rate of each individual event, death (cardiac and all cause), MI, and repeat revascularization at the above time points will also be secondary endpoints. Rehospitalization for chest pain, global cost-effectiveness, number of antianginal medications prescribed, procedure time, contrast usage, functional class, and health-related quality of life at the above time points will be secondary endpoints. Procedural costs will be calculated by determining the number of guiding catheters, guidewires (regular and pressure wire), balloon catheters, DES and adjunctive pharmacology (glycoprotein inhibitor or bivalirudin use). Follow-up resource utilization, such as rehospitalization for

an acute coronary syndrome or repeat PCI will be tracked and assigned a specific cost.

Death will be defined as all cause mortality. Cardiac death will be any death that cannot be attributed to a non-cardiac cause. MI will be defined as greater than 3-fold elevation of CK-MB, with or without chest pain and ECG changes, or as development of new Q-waves in 2 or more contiguous leads on the ECG in the absence of documented abnormal markers of myocardial necrosis. In patients presenting with a non-ST elevation MI and elevated CK-MB before PCI, if the peak CK-MB has not occurred, a periprocedural MI will be defined as recurrent chest pain lasting  $\geq 30$  minutes or new electrocardiographic changes consistent with a second MI and an increase in CK-MB by at least 50% of the pre-procedure CK-MB. If the pre-PCI CK-MB is falling or already normal then a periprocedural MI will be defined as a CK-MB increase  $\geq 3$  times the upper limit of normal and a 50% increase from the pre-PCI CK-MB level.

Repeat revascularization will be defined as any PCI or CABG during the follow-up period. Stent thrombosis will be defined according to the Academic Research Consortium as definite (presence of an acute coronary syndrome and autopsy or angiographic evidence of stent thrombosis), probable (unexplained sudden death  $< 30$  days after PCI or acute myocardial infarction in the target vessel territory without angiographic confirmation) or possible (unexplained death occurring  $> 30$  days after PCI) and early (0-30 days), late (31-360 days) or very late ( $> 360$  days). Procedural time will be defined as the time from first insertion of the guide catheter to removal of the guide catheter. Health-related quality of life index will be determined using the EQ-5D instrument.<sup>26</sup>

### **3.2.3 Statistics**

The objective of this study is to demonstrate the superiority of the FFR-guided strategy over the angiography-guided strategy. To satisfy this objective, the study will test:

Null hypothesis  $H_0$ :  $\pi_1$ (MACE in the FFR-guided strategy group) =  $\pi_2$  (MACE in the angiography-guided strategy group);

Alternative hypothesis HA:  $\pi_1$ (MACE in the FFR-guided strategy group)  $\neq$   $\pi_2$  (MACE in the angiography-guided strategy group).

This hypothesis will be tested using a two-sided Chi<sup>2</sup> test. Using a 0.05 level of significance, a power of 0.80, and 1-year risk of major adverse cardiac events in the FFR-guided strategy of 8%, and 1-year risk of major adverse cardiac events in the angiography-guided group of 14%, at least 852 patients should be enrolled in the trial. These estimates are based on the 5 year results of the Defer Study and on previous studies involving fractional flow reserve in patients with multivessel CAD.<sup>14-16</sup>

If this study fails to show superiority of the FFR-guided strategy, establishing non-inferiority will be of interest. The non-inferiority margin delta for major cardiac events is set at 3%. Non-inferiority will be tested by the confidence interval method. The one-sided confidence interval of the difference of major adverse cardiac event rate in the two compared groups will be calculated. The confidence interval will have a coverage probability of 97.5%. After switching to the non-inferiority analysis, non-inferiority will be shown if the confidence interval does not include the non-inferiority margin delta.<sup>27</sup>

For secondary end-points, angiographic data and laboratory testing comparisons between continuous data will be tested by use of unpaired *t* test or Mann-Whitney U test, as appropriate. Categorical data will be tested by use of Chi<sup>2</sup> test or Fisher's exact test, as appropriate. For endpoints measured at different time points, continuous data will be tested by use of paired *t*-test or Wilcoxon signed rank test, categorical data will be tested by McNemar's test, and repeated measurement analysis will be performed. Costs may be transformed by the log-transformation if necessary. A statistical significance will be determined at the  $P < 0.05$  level; all tests will be two-sided. For all event types, event-free survival curves will be presented using the Kaplan-Meier method.

### **3.2.4 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 prior to participating. Twenty sites are participating. In order to participate, each site

had to demonstrate that they performed 100 FFR measurements during the preceding year. The primary sponsor for the trial is St. Jude/Radi Medical Systems, which will provide the Certus Pressure monitoring guide wires, as well as the costs related to data collection and analysis. Medtronic Inc (Minneapolis, MN) provides limited financial support to some centers by tailoring the prices of the Endeavor stents to the local reimbursement system. It is noteworthy that none of the sponsors will be granted access to the data during any time of the study, nor will their advice be requested before publication of any of the data. Patients will be followed for a total of 5 years after enrollment. The study is being conducted entirely by the principal investigators and participating centers. All data acquisition and analysis will be performed independent of the study sponsor. Events will be adjudicated by an independent adverse clinical event committee. Decisions regarding publication of data will be made independent of the study sponsor.

### **3.3 Summary**

The FAME study is a large, multicenter, international, randomized trial comparing an angiography-guided approach to PCI in patients with multivessel CAD to an FFR-guided approach. The hypothesis is that by measuring FFR to assess the physiologic significance of coronary narrowings, a more informed decision can be made regarding the need for PCI in patients with multivessel CAD. The goal of the study is to determine whether this strategy translates into better clinical outcomes and lower costs.

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# 4

## Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

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*Pim A.L. Tonino, M.D.*  
*Bernard De Bruyne, M.D.,*  
*Ph.D.*  
*Nico H.J. Pijls, M.D., Ph.D.*  
*Uwe Siebert, M.D., MSc.,*  
*M.P.H. ScD.*  
*Fumiaki Ikeno, M.D.*  
*Marcel van 't Veer, MSc.,*  
*Ph.D.*  
*Volker Klauss, M.D., Ph.D.*  
*Ganesh Manoharan, M.D.*  
*Thomas Engström, M.D.,*  
*Ph.D.*  
*Keith G. Oldroyd, M.D.*  
*Peter N. Ver Lee, M.D.*  
*Philip A. MacCarthy, M.D.,*  
*Ph.D.*  
*William F. Fearon, M.D.*  
*for the Fractional Flow*  
*Reserve versus*  
*Angiography for*  
*Multivessel Evaluation*  
*(FAME) Study*  
*Investigators\**

*\*Affiliations of all authors*  
*and all members of the*  
*FAME Study Investigator*  
*Group are listed in*  
*appendix II of this thesis*



## Abstract

**Background** In patients with multivessel coronary artery disease who are undergoing percutaneous coronary intervention (PCI), coronary angiography is the standard method for guiding the placement of the stent. It is unclear whether routine measurement of fractional flow reserve (FFR; the ratio of maximal blood flow in a stenotic artery to normal maximal flow), in addition to angiography, improves outcomes.

**Methods** In 20 medical centers in the United States and Europe, we randomly assigned 1005 patients with multivessel coronary artery disease to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography. Before randomization, lesions requiring PCI were identified on the basis of their angiographic appearance. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was 0.80 or less. The primary endpoint was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year.

**Results** The mean ( $\pm$ SD) number of indicated lesions per patient was  $2.7\pm 0.9$  in the angiography-guided group and  $2.8\pm 1.0$  in the FFR group ( $P=0.34$ ). The number of stents used per patient was  $2.7\pm 1.2$  and  $1.9\pm 1.3$ , respectively ( $P< 0.001$ ). The 1-year event rate was 18.3% (91 patients) in the angiography group and 13.2% (67 patients) in the FFR group ( $P=0.02$ ). Seventy-eight percent of the patients in the angiography group were free from angina at 1 year, as compared with 81% of patients in the FFR group ( $P=0.20$ ).

**Conclusions** Routine measurement of FFR in patients with multivessel coronary artery disease who are undergoing PCI with drug-eluting stents significantly reduces the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year.

## **4.1 Introduction**

The presence of myocardial ischemia is an important risk factor for an adverse clinical outcome.<sup>1-3</sup> Revascularization of stenotic coronary lesions that induce ischemia can improve a patient's functional status and outcome.<sup>3-5</sup> For stenoses that do not induce ischemia, however, benefit of revascularization is less clear and medical therapy alone is likely to be equally effective.<sup>6;7</sup>

With the introduction of drug-eluting stents, the percentage of patients with multivessel coronary artery disease in whom percutaneous coronary intervention (PCI) is performed has increased.<sup>8;9</sup> Because drug-eluting stents are expensive and are associated with potential late complications, their appropriate use is critical.<sup>10;11</sup> However, in patients with multivessel coronary artery disease, identifying which lesions cause ischemia and warrant stenting can be difficult. Noninvasive stress imaging studies are limited in their ability to accurately localize ischemia-producing lesions in these patients.<sup>12</sup> Although coronary angiography often underestimates or overestimates a lesion's functional severity, it is still the standard technique for guiding PCI in patients with multivessel coronary artery disease.<sup>13;14</sup>

Fractional flow reserve (FFR) is an index of the physiological significance of a coronary stenosis and is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow.<sup>15</sup> It can be easily measured during coronary angiography by calculating the ratio of distal coronary pressure measured with a coronary pressure guidewire to aortic pressure measured simultaneously with the guiding catheter. FFR in a normal coronary artery equals 1.0. An FFR value of 0.80 or less identifies ischemia-causing coronary stenoses with an accuracy of more than 90%.<sup>15-17</sup> The information provided by FFR is similar to that provided by myocardial perfusion studies, but it is more

specific and has a better spatial resolution, because every artery or segment is analyzed separately, and masking of one ischemic area by another, more severely ischemic, zone is avoided.<sup>12;18</sup> Deferring PCI in non-ischemic stenotic lesions as assessed by FFR is associated with an annual rate of death or myocardial infarction rate of approximately 1% in patients with single-vessel coronary artery disease, which is lower than the rate after routine stenting.<sup>7</sup> On the other hand, deferring PCI in lesions with an FFR less than 0.75 to 0.80 may result in worse outcomes than those obtained with revascularization.<sup>19</sup> Retrospective studies suggest that in patients with multivessel coronary artery disease, FFR-guided PCI is associated with a favorable outcome with respect to event-free survival.<sup>20;21</sup>

For patients with multivessel coronary artery disease, identifying an approach to PCI that would result in a more judicious use of stents, while still achieving complete relief of myocardial ischemia, could improve the clinical outcome and decrease health care costs. The objective of this randomized study is to compare treatment based on the measurement of FFR in addition to angiography with the current practice of treatment guided solely by angiography in patients with multivessel coronary artery disease for whom PCI is the appropriate treatment.

## **4.2 Methods**

### **4.2.1 Study design**

The design of this study has been described in detail in *figure 3.1*.<sup>22</sup> Shortly, in eligible patients with multivessel coronary artery disease, the investigator indicated which lesions had stenosis of at least 50% of their diameter and were thought to require PCI on the basis of angiographic appearance and clinical data. Patients were then randomly assigned to either angiography-guided or FFR-guided PCI. Computerized randomization was stratified according to study site and performed in blocks of 25, with the use of sealed envelopes. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions with drug-eluting stents. For patients assigned to FFR-

guided PCI, FFR was measured in each diseased coronary artery, and drug-eluting stents (Endeavor [Medtronic], Cypher [Cordis], or Taxus [Boston Scientific], with the choice of stent at the discretion of the surgeon) were placed in indicated lesions only if the FFR was 0.80 or less.

The study protocol was approved by the institutional review board or ethics committee at each participating center; all patients provided written informed consent. An independent clinical events committee whose members were unaware of treatment assignments adjudicated all events. Data management and statistical analysis were performed by an independent data coordinating center (University of Health Sciences, Medical Informatics, and Technology, Hall in Tirol, Austria). The study sponsors (St. Jude/ RADI Medical Systems, Stichting Vrienden van het Hart Zuidoost Brabant [Friends of the Heart Foundation], and Medtronic) had no role in the methods, data acquisition, data analysis, reporting, or publication of this study.

#### **4.2.2 Study population**

Patients were included in the study if they had multivessel coronary artery disease, which was defined as coronary artery stenoses of at least 50% of the vessel diameter in at least two of the three major epicardial coronary arteries, and if PCI was indicated. Patients who had had a myocardial infarction with ST-segment elevation could be included if the infarction had occurred at least 5 days before PCI. Patients who had had a myocardial infarction without ST-segment elevation could be included earlier than 5 days after the infarction if the peak creatine kinase level was less than 1000 U per liter. Patients who had undergone previous PCI could be included in the study. Patients who had 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, or a contraindication to the placement of drug-eluting stents and patients who were pregnant were excluded.

### **4.2.3 Treatment**

PCI was performed with the use of standard techniques. Procedure time was defined as the interval between the introduction of the first guiding catheter and the removal of the last guiding catheter. A record was kept of all materials used, such as guiding catheters, guidewires, balloons, stents, and, if applicable, pressure wires and vials of adenosine. FFR was measured with a coronary pressure guidewire (St. Jude/Radi Medical Systems) at maximal hyperemia induced by intravenous adenosine, which was administered at a rate of 140 µg/kg/min through a central vein. FFR is calculated as the mean distal coronary pressure (measured with the pressure wire) divided by the mean aortic pressure (measured simultaneously with the guiding catheter) during maximal hyperemia.<sup>23</sup> In the case of diffuse atherosclerosis punctuated by focal areas of more severe stenosis, or in the case of more than one stenosis within the same artery, pressure pullback recordings were performed. Because FFR cannot be measured in a totally occluded artery before an intervention is performed, a default FFR value of 0.50 was recorded in the case of totally occluded arteries in the FFR group. All patients were treated with aspirin and clopidogrel for at least 1 year. If a patient underwent repeat coronary angiography during follow-up, the initially assigned strategy of angiography guidance or FFR guidance was followed in the case of stent placement.

### **4.2.4 End points and follow-up**

The primary endpoint was the rate of major adverse cardiac events at 1 year. Major adverse cardiac events was defined as a composite of death, myocardial infarction, and any repeat revascularization. Secondary endpoints included the procedure time, the amount of contrast agent used, functional class at 1 year as assessed with the Canadian Cardiovascular Society classification system, health-related quality of life (as measured by the score on the European Quality of Life-5 Dimensions [EQ5D] scale),<sup>24</sup> the number of antianginal medications used, and the individual components of the primary endpoint at 1 year, as well as the rates of major adverse cardiac events at 30 days and 6 months. Cost-effectiveness was a secondary endpoint as well.

Death was defined as death from all causes. Myocardial infarction was defined as an elevation of the creatine kinase MB fraction by a factor of 3 or more or new Q-waves in 2 or more contiguous leads of the electrocardiogram (ECG).<sup>25</sup> Levels of total creatine kinase and the creatine kinase MB fraction were measured in all patients between 12 and 24 hours after PCI. Quantitative coronary angiography was performed offline, and the scoring system used in the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) study was used to assess the extent and severity of coronary artery disease; the SYNTAX score was calculated by the core laboratory.<sup>26;27</sup> After discharge, follow-up assessment was performed at 1 month, 6 months, and 1 year. Before PCI, and at all other time points, the severity of angina, graded according to the Canadian Cardiovascular Society classification system, and the number of antianginal medications prescribed were assessed. An ECG was obtained before PCI, within 24 hours after PCI, and at 1 year after PCI. A quality-of-life questionnaire (EQ-5D) was completed by the patient before PCI, at 1 month, and at 1 year.<sup>24;28</sup>

#### **4.2.5 Statistical analysis**

The statistical considerations when planning the FAME study have been extensively described in *chapter 3*. Shortly, the primary purpose of the data analysis was to determine whether the 1-year probability of major adverse cardiac events differed significantly between patients who underwent angiography-guided PCI and those who underwent FFR-guided PCI. The estimated minimum sample size of 426 patients in each group was based on a two-sided chi-square test with an alpha level of 0.05 and a statistical power of 0.80, assuming 1-year rates of major adverse cardiac events of 14% in the angiography group and 8% in the FFR group. These rates were based on outcome data in the early studies of drug-eluting stents that were available in 2005 when the present study was designed.<sup>29</sup>

All enrolled patients were included in the analysis of primary and secondary end points according to the intention-to-treat principle. Categorical variables, including the primary endpoint and its components, are expressed as proportions and were compared with the use of the chi-square test.

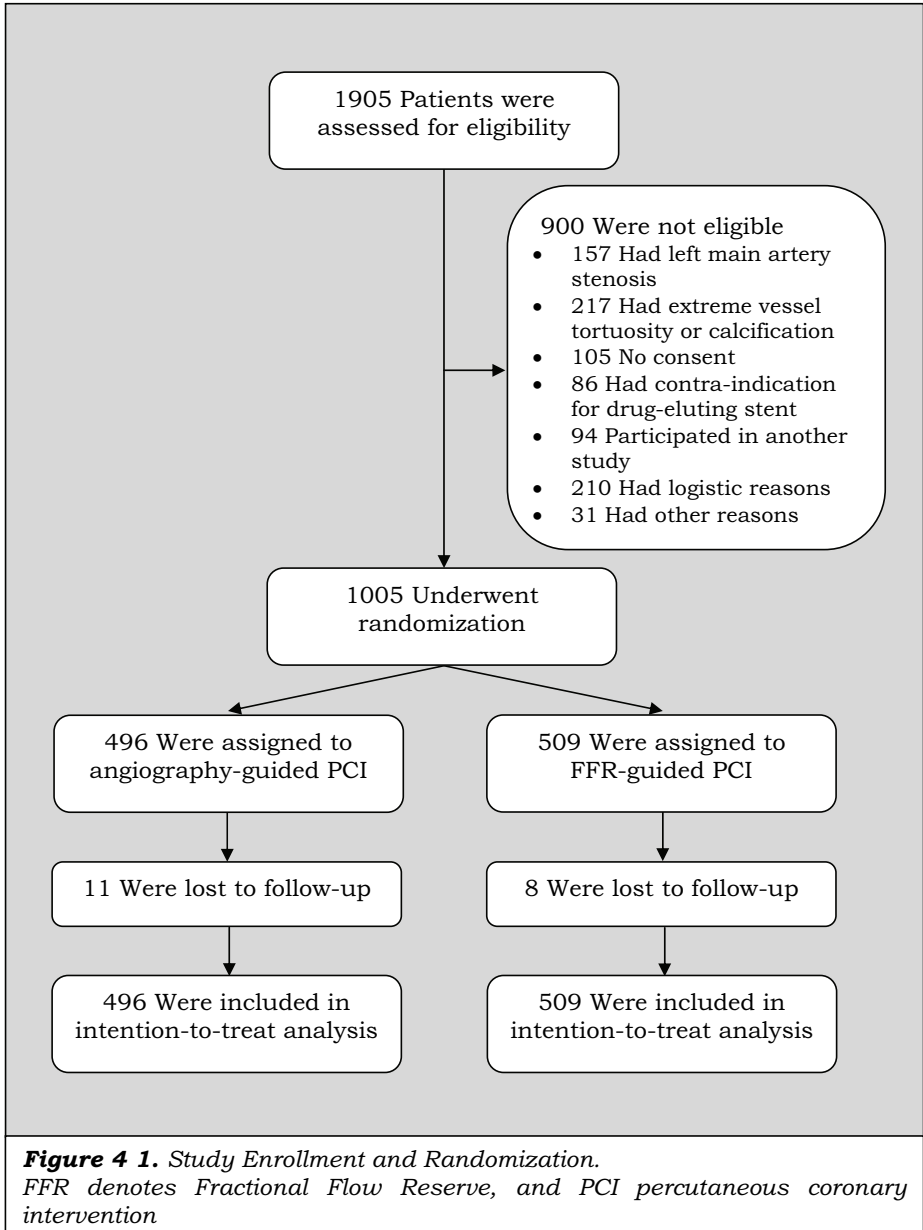
Continuous variables are expressed as means and standard deviations and were compared with the use of an unpaired *t* test or Mann-Whitney U test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Kaplan-Meier curves are shown for the time-to-event distributions for the primary endpoint and its individual components. All statistical analyses were performed with the use of SAS software, version 9 (SAS Institute). One interim analysis was performed, immediately after inclusion of the first 50 patients, to monitor safety and to exclude any frank inconsistencies in the study protocol or case-record form.

## 4.3 Results

### 4.3.1 Baseline characteristics and angiographic data

From January 2006 through September 2007, a total of 1005 patients were enrolled in 20 centers in the United States and Europe (*figure 4.1*). A list of all investigators and institutions participating in the FAME Study group is presented in *appendix II* of this thesis.

Of the 1005 patients, 496 were randomly assigned to angiography-guided PCI and 509 to FFR-guided PCI. Baseline characteristics of the two groups were similar, as were the number of indicated lesions, vessel and lesion dimensions as assessed by quantitative coronary angiography, and extent and severity of coronary artery disease as indicated by the SYNTAX score (*table 4.1*). A total of 26.5% of the patients in the angiography-guided group had a left ventricular ejection fraction of 50% or less, as compared to 28.6% in the FFR-guided group (P=0.47).





**Table 4.1.** Baseline Characteristics of the Patients.\*

<b>Characteristic</b>	<b>Angiography Group N=496</b>	<b>FFR Group N=509</b>	<b>P Value †</b>
<b>Demography</b>			
Age - yr	64.2±10.2	64.6±10.3	0.47
Sex - no. (%)			0.30
Male	360(72.6)	384(75.4)	
Female	136(27.4)	125(24.6)	
<b>Clinical</b>			
Angina (CCS class) - no. (%)			0.13
I	115(23.2)	132(25.9)	
II	165(33.3)	170(33.4)	
III	118(23.8)	132(25.9)	
IV	98(19.8)	75(14.7)	
History - no. (%)			
Previous myocardial infarction	180(36.3)	187(36.7)	0.84
Previous PCI	129(26.0)	146(28.7)	0.34
Diabetes	125(25.2)	123(24.2)	0.65
Hypertension	327(65.9)	312(61.3)	0.10
Current smoker	156(31.5)	138(27.1)	0.12
Hypercholesterolemia	362(73.0)	366(71.9)	0.62
Positive family history	190(38.3)	205(40.3)	0.49
Unstable angina - no. (%)			
with dynamic ECG changes	91(18.3)	73(14.3)	0.09
without dynamic ECG changes	87(17.5)	77(15.1)	0.29
Left ventricular ejection fraction - %	57±12	57±11	0.92
<b>Medication</b>			
Beta-blocker - no. (%)	377(76.0)	395(77.6)	0.55
Calcium-antagonist - no. (%)	96(19.4)	121(23.8)	0.09
Nitrates - no. (%)	179(36.1)	167(32.8)	0.27
ACE-inhibitor/ARB - no. (%)	255(51.4)	267(52.5)	0.74
Statin - no. (%)	397(80.0)	417(81.9)	0.45
Aspirin - no. (%)	454(91.5)	465(91.4)	0.92
Clopidogrel - no. (%)	292(58.9)	310(60.9)	0.51

**Table 4.1.** (continued)

Characteristic	Angiography Group N=496	FFR Group N=509	P Value †
<b>Angiography</b>			
Indicated lesions per patient – no.‡	2.7±0.9	2.8±1.0	0.34
50-70% narrowing – no. (%)	550/1350(40.7)	624/1414(44.1)	
70-90% narrowing – no. (%)	553/1350(41.0)	530/1414(37.5)	
90-99% narrowing – no. (%)	207/1350(15.3)	202/1414(14.3)	
Total occlusion – no. (%)	40/1350(3.0)	58/1414(4.1)	
Patients with total occlusion – no. (%)	37(7.5)	54/1414(10.6)	
<b>Quantitative Coronary Analysis</b>			
Percentage stenosis - %	61.2±16.6	60.4±17.6	0.24
Minimal Luminal Diameter - mm	1.0±0.4	1.0±0.5	0.35
Reference Diameter - mm	2.5±0.6	2.5±0.7	0.81
Lesion Length - mm	12.6±6.9	12.5±6.5	0.42
SYNTAX score §	14.5±8.8	14.5±8.6	0.95
EQ-5D visual analogue scale ¶	64.7±19.2	66.5±18.3	0.24

\* Plus-minus values are means ± SD. CCS denotes Canadian Cardiovascular Society, PCI percutaneous coronary intervention, ECG electrocardiogram, ARB angiotensin-receptor blocker. † All categorical variables were compared by chi-square-test; all continuous variables were compared by Mann-Whitney U test, except age, which was normally distributed and compared by t test. ‡ Before randomization the investigator indicated all lesions to be included in the study and classified them according to severity, by visual estimation, based on the angiogram. § SYNTAX score was performed as described in the methods section of this article. ¶ EQ-5D visual analogue scale is a generic measure of health-related quality of life with a range from 0 to 100; higher scores indicate higher health-related quality of life.

### 4.3.2 PCI

A total of 2415 stents were placed, of which 2339 (96.9%) were drug-eluting stents. In the case of 76 stenoses a bare-metal stent had to be placed for technical reasons. Significantly more stents per patient were placed in the angiography-guided group than in the FFR-guided group (2.7±1.2 vs. 1.9±1.3;  $P<0.001$ ) (table 4.2).

**Table 4.2.** Results of PCI.\*

	<b>Angiography Group N= 496</b>	<b>FFR Group N= 509</b>	<b>P Value †</b>
<b>Procedure time</b> – min.‡	70±44	71±43	0.51
<b>Contrast agent used</b> – ml.	302±127	272±133	<0.001
<b>Drug eluting stents</b>			
Drug eluting stents used per patient– no.	2.7±1.2	1.9±1.3	<0.001
Lesions successfully stented – no. (%) §	1237(92)	819(94)	
Total drug eluting stents used – no.	1359	980	
<b>FFR results</b>			
Lesions successfully measured by FFR – no. (%) ¶	n/a	1329(94)	
FFR (all lesions)	n/a	0.71±0.18	
FFR ≤ 0.80 (ischemic lesions)	n/a	0.60±0.14	
FFR > 0.80 (non-ischemic lesions)	n/a	0.88±0.05	
Lesions with FFR ≤ 0.80 – no. (%)	n/a	874(63%)	
Lesions with FFR > 0.80 – no. (%)	n/a	513(37%)	
<b>Procedural costs</b>			
Materials – USD **	6007±2819	5332±3261	<0.001
Hospital stay at baseline admission - days	3.7±3.5	3.4±3.3	0.05

\* Plus-minus values are means ± SD . PCI denotes percutaneous coronary intervention, FFR fractional flow reserve. † P values were calculated by chi-square test in case of categorical data and Mann-Whitney U test in case of continuous data. ‡ Procedure time was defined as time from introduction of first till removal of last guiding catheter. § Percentage of the lesions indicated at baseline (angiography group), percentage of the lesions with FFR ≤ 0.80 (FFR group). ¶ Percentage of the number of all indicated lesions. Of those 85 lesions without FFR measurement, 58 (4.1%) were the totally occluded arteries to which a default FFR value of 0.50 was assigned , whereas in 27 (1.9%) lesions, FFR could not be measured because of technical reasons. \*\* The materials used during the index procedure (PCI) were recorded and their costs were calculated according to the actual local price and translated into USD.

In the FFR group, FFR was successfully measured in 94.0% of all lesions. In 874 (63.0%), the FFR was 0.80 or less, and stents were placed in these

lesions, per protocol. In 513 lesions (37.0%), FFR was greater than 0.80, and stents were not placed in these lesions. The procedure time was similar in the two groups (70±44 minutes in the angiography group and 71±43 minutes in the FFR group,  $P=0.51$ ). Significantly more contrast agent was used in the angiography group than in the FFR group (302±127 ml vs. 272±133 ml,  $P<0.001$ ).

### **4.3.3 Primary endpoint**

Complete 1-year follow-up were obtained for 98.1% of the patients (11 were lost to follow-up in the angiography group and 8 were lost to follow-up in the FFR group [ $P=0.45$ ]). The primary endpoint (a composite of death, myocardial infarction, and repeat revascularization) occurred in 91 patients (18.3%) in the angiography group and in 67 patients (13.2%) in the FFR group ( $P=0.02$ ) (*table 4.3*). Event-free survival is shown by means of a Kaplan-Meier curve (*figure 4.2A*).

### **4.3.4 Secondary endpoints**

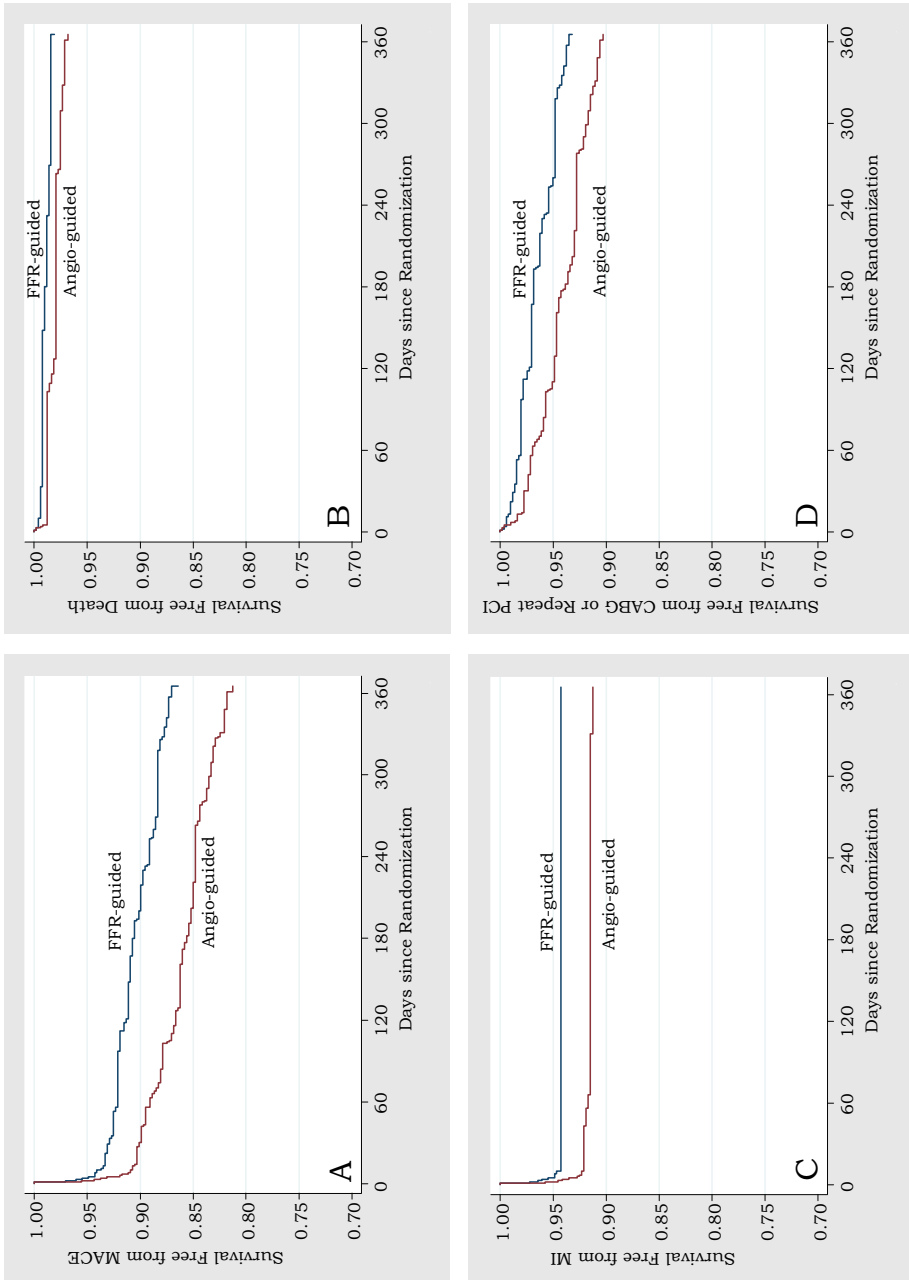
All-cause mortality at 1 year was 3.0% (15 deaths, 10 of which had cardiac causes) in the angiography group and 1.8% (9 deaths, 7 of which had cardiac causes) in the FFR group ( $P=0.19$ ). Myocardial infarction occurred in 43 patients (8.7%) in the angiography group and in 29 (5.7%) in the FFR group ( $P=0.07$ ). The numbers of small, periprocedural infarctions (as indicated by a creatine kinase MB fraction that was 3 to 5 times the upper limit of the normal range) were 16 and 12 in the two groups, respectively. A total of 47 patients (9.5%) in the angiography group and 33 (6.5%) in the FFR group required repeat revascularization ( $P=0.08$ ). The 1-year rate of death or myocardial infarction, which was not a prespecified secondary endpoint, but is an important clinical variable, was 11.1% (55 patients) in the angiography group and 7.3% (37 patients) in the FFR group ( $P=0.04$ ). At 1 year 77.9% of the patients in the angiography group were free from angina, as compared to 81.3% in the FFR group ( $P=0.20$ ). A total of 67.6% of patients in the angiography group and 73.0% in the FFR group did not have an event and were free from angina at 1 year ( $P=0.07$ ). The mean costs of materials used in

the index procedure was \$6007±2819 in the angiography group, as compared with \$5332±3261 in the FFR group (P<0.001). The mean length of stay in the hospital was 3.7±3.5 days in the angiography group, as compared with 3.4±3.3 days in the FFR group (P=0.05).

**Table 4.3.** Primary and Secondary End Points at 1 Year.\*

	<b>Angiography Group N= 496</b>	<b>FFR Group N= 509</b>	<b>P value †</b>	<b>RR with FFR guidance (95%CI)</b>
<b>Events at 1 year – no. (%)</b>				
Death, myocardial infarction, CABG, repeat PCI ‡	91(18.3)	67(13.2)	0.02	0.72 (0.54-0.96)
Death	15(3.0)	9(1.8)	0.19	0.58 (0.26-1.32)
Myocardial infarction	43(8.7)	29(5.7)	0.07	0.66 (0.42-1.04)
Death or myocardial infarction	55(11.1)	37(7.3)	0.04	0.68 (0.45-1.05)
CABG or repeat PCI	47(9.5)	33(6.5)	0.08	0.66 (0.44-0.98)
Total no. of events	113	76		
Average no. of events per pat.	0.23±0.53	0.15±0.41	0.02	
<b>Functional status at 1 year</b>				
Patients without event and free from angina §	326(68)	360(73)	0.07	
Patients free from angina – no. (%) ¶	374(78)	399(81)	0.20	
Number of anti-anginal medications – no **	1.23±0.74	1.20±0.76	0.48	
EQ-5D visual analogue scale §§	73.7±16.0	74.5±15.7	0.65	

\* Plus-minus values are means ± SD. RR denotes relative risk, 95%CI 95% confidence interval, CABG coronary artery bypass grafting, PCI percutaneous coronary intervention, pat. patient. † All categorical variables were compared by chi-square test; all continuous variables were compared by Mann-Whitney U test.. ‡ This is the primary endpoint of the study. § 30 patients with missing information on angina status were excluded from the analysis. ¶ 34 patients with missing information on angina status were excluded from the analysis. \*\* Anti-anginal medications included beta-blockers, calcium antagonists, nitrates. §§ EQ-5D visual analogue scale is a generic measure of health-related quality of life with a range from 0 to 100; higher scores indicate higher health-related quality of life.



**Figure 4.2.** Kaplan-Meier Survival Curves According to Study Group. FFR denotes fractional flow reserve, CABG coronary artery bypass surgery, MACE major adverse cardiac events, MI myocardial infarction, and PCI percutaneous coronary intervention.

## 4.4 Discussion

This study showed that in patients with multivessel coronary artery disease, routine measurement of FFR during PCI, as compared with the standard strategy of PCI guided by angiography, significantly reduced the rate of the primary composite end point of death, myocardial infarction, and repeat revascularization at 1 year. The combined rate of death and myocardial infarction was also significantly reduced. Without prolonging the procedure, the FFR-guided strategy reduced the number of stents used, decreased the amount of contrast agent used, and resulted in a similar, if not improved, functional status with no decrease in health-related quality of life. Furthermore, the procedure-related costs were significantly lower with the FFR-guided strategy. These results were achieved in a patient population with complex disease. The event rate in the angiography group was similar to that in groups in other recent studies evaluating the use of drug-eluting stents for patients with multivessel coronary artery disease.<sup>30-33</sup> Moreover, in 89.6% of the patients assigned to the FFR-guided strategy, at least one stenotic lesion had an FFR of 0.80 or less, indicating ischemia, and stents were placed in these lesions; 63% of all lesions that were measured had an FFR of 0.80 or less. These data reflect that in this study, FFR was used in an unselected population, not just in persons with intermediate lesions, of which only approximately 35% have an FFR that indicates ischemia.<sup>7</sup>

In our study, routine measurement of FFR consistently reduced the incidence of all types of adverse events by approximately 30%. The absolute risk of major adverse cardiac events was reduced by 5 percentage points, which means that measuring FFR in 20 patients can prevent one adverse event. Routine measurement of FFR probably improved outcomes by allowing more judicious use of stents and equal relief of ischemia. It has been known for decades that the most important prognostic factor among patients with coronary artery disease is the presence and extent of inducible ischemia. It might be speculated that PCI of a stenotic lesion that is inducing ischemia (indicated by an FFR less than or equal to 0.80) is beneficial overall because the risk of stent thrombosis or restenosis is outweighed by the significant

reduction in the risk of ischemic events with stent placement. On the other hand, PCI of a stenotic lesion that is not inducing ischemia (indicated by an FFR greater than 0.80) increases the chance of an adverse event because the risk of thrombosis and restenosis associated with the placement of the stent, with the attendant risk of subsequent death, myocardial infarction, or repeat revascularization, exceeds by far the low risk associated with a hemodynamically nonsignificant stenosis in which a stent has not been placed. Thus, performing PCI on all stenoses that have been identified by angiography, regardless of their potential to induce ischemia, diminishes the benefit of relieving ischemia by exposing the patient to an increased stent-related risk, whereas systematically measuring FFR can maximize the benefit of PCI by accurately discriminating the lesions for which revascularization will provide the most benefit from those for which PCI may only increase the risk. Our results also suggest that the outcomes with PCI as compared with medical treatment, such as in the COURAGE trial<sup>6</sup>, or with coronary-artery bypass grafting, such as in the SYNTAX trial<sup>34</sup>, might be improved if the PCI is performed with FFR guidance and might ensure functionally complete revascularization with more appropriate use of stents. A comparison of the FAME study with other recent landmark studies in the field of multivessel disease treatment is described in more detail in *chapter 8* and in *appendix II*. A substudy of the COURAGE trial<sup>3</sup>, which showed that patients with the greatest relief of ischemia had the lowest rates of death or myocardial infarction, further supports the concept that PCI should be guided by physiological considerations and not solely by anatomical ones. Earlier studies have suggested that incomplete revascularization results in an outcome that is not optimal.<sup>35;36</sup> However, in those studies the decision not to perform PCI for a particular lesion was made on the basis of an angiographical or anatomical assessment. The FFR-guided strategy in this study resulted in functionally complete revascularization but with fewer stents placed. In this study we tried to reflect routine practice with respect to multivessel PCI. Therefore, patients with angiographically significant left main coronary artery disease were excluded, as were patients presenting with a recent myocardial infarction with ST-segment elevation, since multivessel PCI is



generally deferred in such patients. Patients in the latter group could be included 5 days or later after the acute event, if at least two angiographically significant lesions were present. Patients who had undergone previous PCI were included in the present study, which is often not the case in randomized trials of coronary revascularization.<sup>6;34;37</sup>

Other potential limitations of this study include the use of an FFR cutoff value of 0.80 as reflecting inducible ischemia. In previous studies, in a variety of clinical and angiographic conditions, FFR cutoff values between 0.75 and 0.80 have been used.<sup>15-18</sup> We decided to take the upper limit of that small transition zone in order to limit the number of ischemic lesions left untreated. Finally, the current data are restricted to a 1-year follow-up. Theoretically, lesions in the FFR group in which stents were not placed could progress and lead to events beyond 1 year. However, from previous studies it is known that lesions with an FFR greater than 0.80, if optimally treated with medications, have an excellent prognosis, with an event rate of approximately 1% per year up to 5 years after measurement.<sup>7</sup> We intend to collect follow-up data up for a total period of 5 years for the present study.

In *conclusion*, in patients with multivessel coronary artery disease undergoing PCI with drug-eluting stents, routine measurement of FFR in addition to angiographic guidance, as compared with PCI guided by angiography alone, results in a significant reduction of major adverse events at 1 year, a finding that supports the evolving strategy of revascularization of ischemic lesions and medical treatment of nonischemic lesions.

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# 5

## Angiographic versus Functional Severity of Coronary Artery Stenoses in the FAME Study

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*Pim A.L. Tonino, M.D.  
William F. Fearon, M.D.  
Bernard De Bruyne, M.D.,  
Ph.D.  
Keith G. Oldroyd, M.D.  
Massoud A. Leesar, M.D.  
Peter N. Ver Lee, M.D.  
Philip A. MacCarthy, M.D.,  
Ph.D.  
Marcel van 't Veer, MSc.,  
Ph.D.  
Nico H.J.Pijls, M.D., Ph.D.*

*\*Affiliations of all authors  
and all members of the  
FAME Study Investigator  
Group are listed in  
appendix II of this thesis*

## Abstract

**Background** It can be difficult to determine on the coronary angiogram which lesions cause ischemia. Revascularization of coronary stenoses that induce ischemia improves a patient's functional status and outcome. For stenoses that do not induce ischemia, however, the benefit of revascularization is less clear.

**Methods** In the FAME study, routine measurement of Fractional Flow Reserve (FFR) was compared to angiography for guiding PCI in patients with multivessel coronary artery disease. The use of FFR in addition to angiography significantly reduced the rate of all major adverse cardiac events at 1 year by 30-35%. Out of the 1414 lesions (509 patients) in the FFR-guided arm of the FAME study, 1329 were successfully assessed by FFR, and included in this analysis.

**Results** Before FFR measurement, all these lesions were categorized into 50-70% (47% of all lesions), 71-90% (39% of all lesions), and 91-99% (15% of all lesions) diameter stenosis by visual assessment. In the category 50-70% stenosis, 35% was functionally significant (FFR  $\leq$ 0.80) and 65% was not (FFR  $>$ 0.80). In the category 71-90% stenosis, 80% was functionally significant and 20% was not. In the category of subtotal stenoses, 96% was functionally significant and 4% was not. Of all 509 patients with angiographically defined multivessel disease, only 235 (46%) had functional multivessel disease ( $\geq$ 2 coronary arteries with FFR  $\leq$ 0.80).

**Conclusions** Angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared to FFR, not only in the 50-70% range, but also in the 70-90% angiographic severity category. Therefore, revascularization in the setting of multivessel disease should be routinely guided by FFR.

## 5.1 Introduction

The presence of inducible ischemia related to a coronary artery stenosis is an important factor in decision making, whether to revascularize such a stenosis. Reducing myocardial ischemia by revascularization improves a patient's functional status and outcome, whereas revascularization of non-ischemic lesions is controversial.<sup>1-4</sup> The recently published results of the FAME study support the evolving strategy of revascularization of ischemic lesions and medical treatment of non-schemic ones.<sup>5</sup>

In patients with multivessel coronary artery disease (CAD) it is often difficult to determine which lesions are responsible for reversible ischemia. Non-invasive stress tests are often not able to accurately detect and localize ischemia.<sup>6</sup> Therefore, the coronary angiogram is the standard for decision making about revascularization in such patients. In randomized trials evaluating coronary revascularization, as well as in daily practice in most catheterization laboratories, lesions with a diameter stenosis of  $\geq 50\%$  on the angiogram are generally considered for revascularization.<sup>7-9</sup> Coronary angiography, however, may result in both under- and overestimation of a lesion's severity and is often inaccurate in predicting which lesions cause ischemia.<sup>10;11</sup>

Fractional Flow Reserve (FFR) is an accurate and selective index of the physiological significance of a coronary stenosis that can be easily measured during coronary angiography. An FFR value of 0.80 or less identifies ischemia-causing coronary stenoses with an accuracy of more than 90%.<sup>12;13</sup> In the randomized FAME (Fractional Flow Reserve versus Angiography in Multivessel Evaluation) study, FFR-guided percutaneous coronary intervention (PCI) with drug-eluting stents was compared to angiography-guided PCI in patients with multivessel CAD.<sup>5</sup> The 1-year results of this study, as described in *chapter 4*,



showed that FFR-guidance of PCI significantly decreased the combined endpoint of death, myocardial infarction and repeat revascularization. In this current analysis, we analyze the relation between angiographic stenosis severity and functional stenosis severity as measured by FFR. We also analyze classification of the number of functionally significant diseased coronary arteries (coronary arteries with  $\text{FFR} \leq 0.80$ ) in all patients with angiographic 2- and 3-vessel disease in the FFR-guided arm of the FAME study.

## 5.2 Methods

### 5.2.1 Study population

In this sub-analysis of the FAME study, the relationship between angiography and FFR in all patients in the FFR-guided arm ( $n=509$ ) is analyzed. The FAME study protocol is described in detail in *chapter 3*.<sup>14</sup> In brief, 1005 patients with multivessel disease were randomly assigned to angiography-guided PCI ( $n=496$ ) or FFR-guided PCI ( $n=509$ ). Before randomization the operator indicated all lesions with a diameter stenosis percentage of  $\geq 50\%$  requiring stenting. In case of angiography-guided PCI all indicated lesions were stented. In case of FFR-guided PCI, patients had first FFR measured in each diseased coronary artery and only underwent stenting if the FFR was  $\leq 0.80$ . The FAME study had liberal inclusion criteria to reflect daily practice of PCI in patients with multivessel CAD. More than 50% of all screened patients actually participated in the study and the inclusion rate per participating center was 40 patients per year, which is high compared to other studies in this field. Exclusion criteria for the FAME study were angiographically significant left main coronary artery disease, previous coronary artery bypass surgery, cardiogenic shock or extremely tortuous or calcified coronary arteries. The FAME study protocol was approved for all participating centers by their respective internal review board or ethics committee.

### **5.2.2 Definitions of angiographic multivessel disease and functional multivessel disease**

Angiographic multivessel CAD was defined as stenoses  $\geq 50\%$  in at least 2 of the 3 major epicardial coronary arteries (angiographic 2- or 3-vessel disease), which the operator deemed required stenting. Prior to randomization, the operator categorized the lesions according to visual angiographic stenosis severity, into 50-70%, 71-90% and 91-100% diameter stenosis. In those randomized to FFR guidance, if the FFR of a particular stenosis,  $>50\%$  by angiography, was  $>0.80$ , this stenosis was considered as *functionally non-significant* and no stent was placed. The *angiographic significant* disease in the respective artery was classified as *functionally not significant*. The definition of “functional” 0-, 1-, 2-, or 3-vessel disease was made on the basis of the number of main arteries with  $\text{FFR} \leq 0.80$ . So a patient with “angiographic 3-vessel disease” could be classified as “functional 0-, 1-, 2-, or 3-vessel disease”, after FFR measurements.

### **5.2.3 Fractional Flow Reserve measurements**

FFR is defined as the ratio between distal coronary pressure and aortic pressure, both measured simultaneously at maximal hyperemia. Distal coronary pressure was measured with a coronary pressure guidewire (Certus Pressure Wire, St. Jude Medical, St. Paul, Minnesota, USA). Maximal hyperemia was induced by intravenous adenosine, administered at 140 micrograms/kilogram/minute via a central vein. Hyperemic pullback recordings were performed in all diseased arteries to discriminate focal from diffuse disease.

### **5.2.4 Clinical events**

Major adverse cardiac events were defined as a composite of death, myocardial infarction, and any repeat revascularization. Death was defined as all-cause mortality. Myocardial infarction was defined as  $\geq 3$ -fold elevation of CK-MB level or new Q-waves in  $\geq 2$  contiguous leads of the electrocardiogram (ECG). Total CK and CK-MB levels were measured in all patients 12 to 24 hours after PCI. After discharge, follow-up was performed at 1 month, 6 months and 1

year. An ECG was performed before PCI, within 24 hours after PCI, and at 1 year.

### **5.2.5 Statistical analysis**

Categorical variables are expressed as proportions. Continuous variables are expressed as means and standard deviations. Angiographic lesion severity per category and the respective FFR value of each specific lesion were plotted in a Box-and-Whisker plot, to show the degree of dispersion and skewness in the data, and to identify potential outliers. The Box-and-Whisker plot was created with GraphPad Prism 2.01 software. Kaplan-Meier curves (1 minus survival free from MACE) are presented to describe the time-to-event distributions for MACE in the respective subcategories of table 5.3. The Kaplan-Meier curves were performed with SPSS software, version 17.0.

## **5.3 Results**

### **5.3.1 Angiographic versus functional stenosis severity**

In the FFR-guided arm of the FAME study, 509 patients with angiographic multivessel CAD were included. Their baseline characteristics are listed in *table 5.1*.

In these 509 patients, 1414 lesions were indicated before randomization ( $2.8 \pm 1.0$  lesions per patient). FFR was measured successfully in 1329 (94%) of the 1414 lesions. Of the 85 lesions across which FFR was not measured, in 58 it was because they were chronically occluded and in 27 it was due to technical reasons. These lesions were not included in this analysis.

**Table 5.1.** Baseline Characteristics.\*

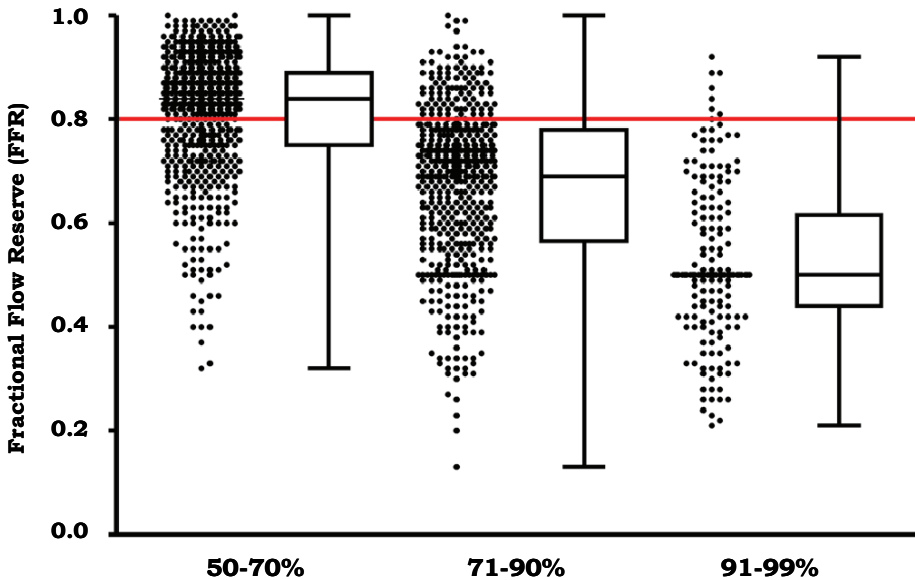
<b>Characteristic</b>	<b>FFR Group N=509</b>
<b>Demography</b>	
Age - yr	64.6±10.3
Male sex – no. (%)	384(75)
<b>Clinical</b>	
History – no. (%)	
Previous myocardial infarction	187(37)
Previous PCI	146(29)
Diabetes	123(24)
Unstable angina – no. (%)	147(29)
Left ventricular ejection fraction - %	57±11
<b>Angiography</b>	
Indicated lesions per patient – no.†	2.8±1.0
Total indicated lesions – no.	1414
Lesions measured by FFR – no.‡	1329
Chronic total occlusions – no.§	58

\* Plus-minus values are means ± SD. PCI denotes percutaneous coronary intervention, FFR Fractional Flow Reserve. † Before randomization the investigator indicated all lesions to be included in the study and classified them according to severity, by visual estimation, based on the angiogram. ‡ All lesions successfully measured by FFR, thus excluding all chronic total occlusions (n=58) and all lesions not assessed by FFR due to technical reasons (n=27). § Chronic total occlusions were assigned a default FFR value of 0.50 in the FAME study.

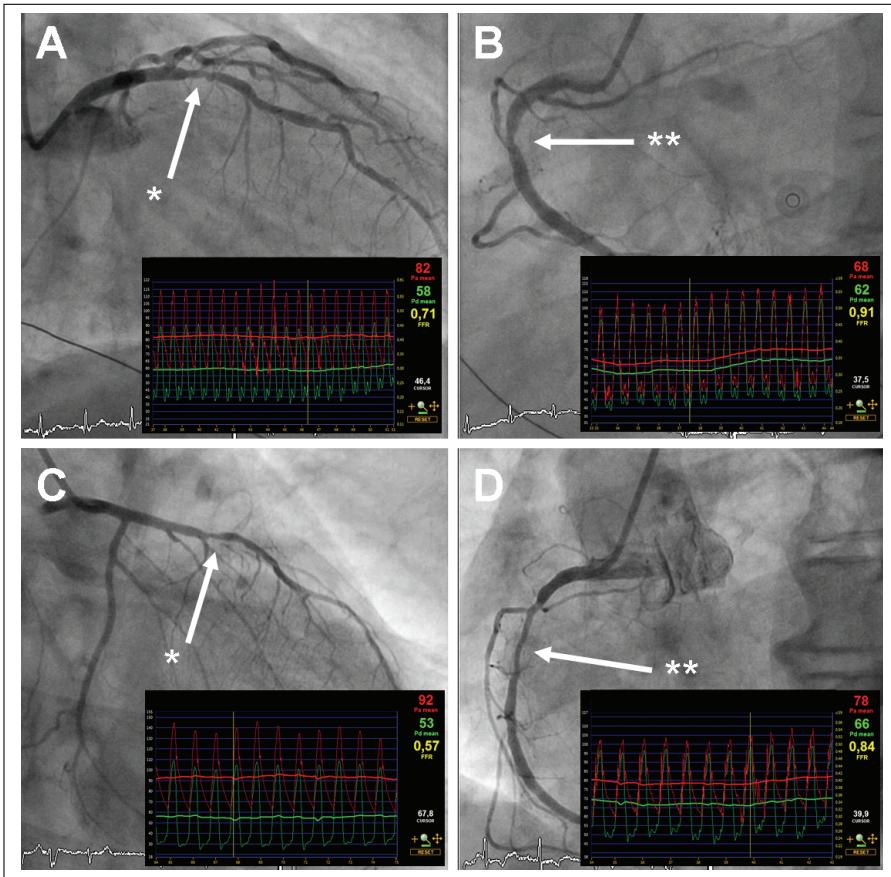
Of all 1329 analyzed lesions, 620 (47%) were categorized in the 50-70% category, 513 (39%) in the 71-90% category, and 196 (15%) in the 91-99% category (table 5. 2, figure 5.1).

Of all 1329 lesions, 816 (61%) were below the ischemic threshold (FFR  $\leq 0.80$ ). Of the stenoses 50-70% by visual estimation, in 402 (65%) FFR was  $>0.80$  and in 218 (35%) FFR was  $\leq 0.80$ . Of the stenoses in the 71-90% category, in 104 (20%) FFR was  $>0.80$  and in 409 (80%) FFR was  $\leq 0.80$ . In the 91-99% category, 7 (4%) stenoses had a FFR  $>0.80$  and 189 (96%) had a FFR  $\leq 0.80$ .

In figure 5.2 examples of discrepancy between angiographic and functional stenosis severity are shown.



**Figure 5.1.** Angiographic severity versus functional severity of coronary artery stenoses. Box-and-Whisker plot showing the FFR values of the lesions in the categories of 50-70%, 71-90%, and 91-99% diameter stenosis, as visually estimated on the basis of the angiogram.



**Figure 5.2.** Two patients with two equally severe stenoses by angiography, but completely different functional importance as assessed by FFR. Panels A and B show a stenosis in the left anterior descending (LAD) artery (panel A, arrow with asterisk) and a stenosis in the right coronary artery (RCA) (panel B, arrow with double asterisk) of a patient in the FAME study. Both lesions were categorized as 50-70% stenosis severity by the operator by eyeballing. After randomization to the FFR-guided arm of the FAME study, FFR was measured in both arteries. FFR was below the ischemic threshold of 0.80 in the LAD (0.71; functionally significant). Subsequently the LAD was stented according to FAME study protocol. FFR of the RCA was 0.91, indicating a functionally non-significant stenosis, and was therefore not stented. Panels C and D show another patient in the FAME study in which the operator categorized both lesions as 70-90%. The LAD stenosis (panel C, arrow with asterisk) was functionally significant (FFR 0.57) and treated by stent placement. FFR of the RCA stenosis (0.84) (panel D, arrow with double asterisk) was above the ischemic threshold of 0.80 and consequently this stenosis was not stented.

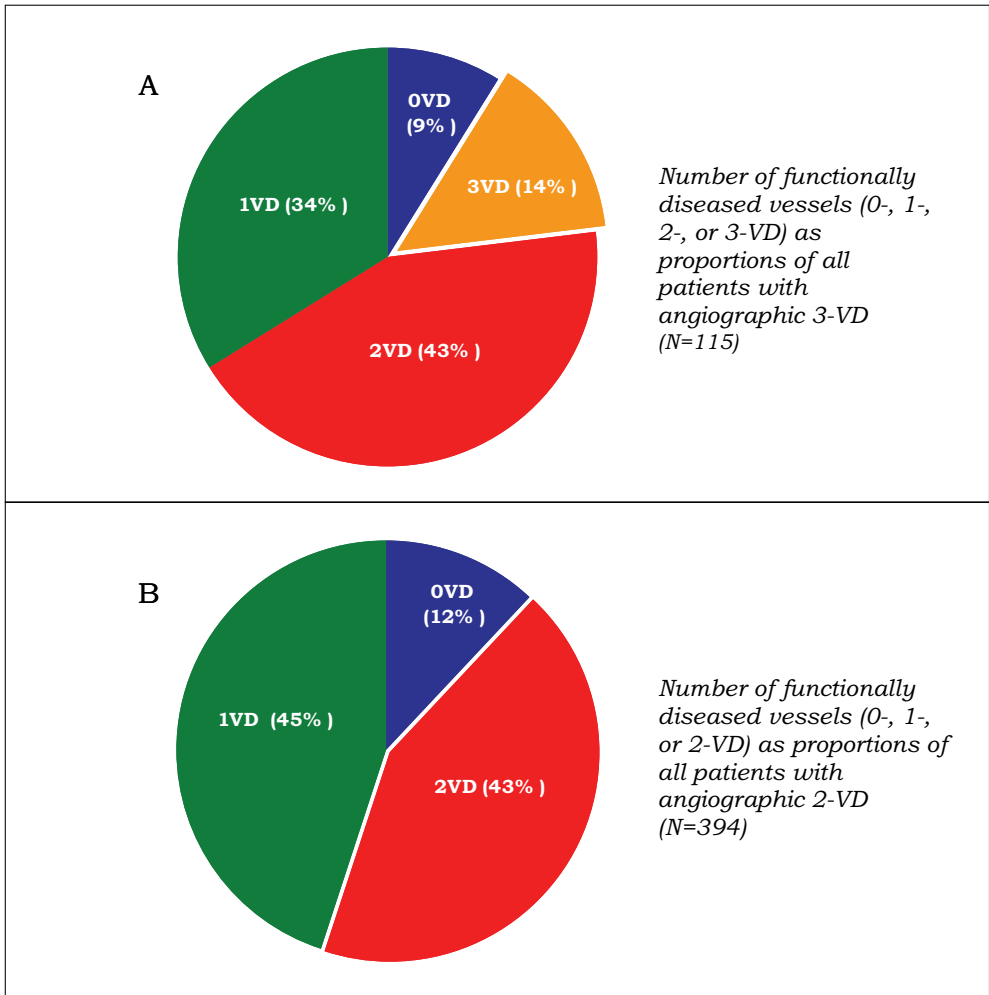
**Table 5.2.** Lesion characteristics per category of angiographic stenosis severity.\*

	Percentage stenosis by angiography†		
	50-70% N=620 (47%)	71-90% N=513 (39%)	91-99% N=196 (15%)
<b>FFR</b>			
FFR > 0.80 – no. (%)	402(65)	104(20)	7(4)
FFR ≤ 0.80 – no. (%)	218(35)	409(80)	189(96)
Mean FFR all lesions	0.81±0.12	0.67±0.15	0.52±0.15
Mean FFR > 0.80	0.89±0.05	0.87±0.05	0.87±0.04
Mean FFR ≤ 0.80	0.68±0.10	0.62±0.13	0.51±0.13

\* Plus-minus values are means ± SD. FFR denotes Fractional Flow Reserve. † Before randomization the investigator indicated all lesions to be included in the study and classified them according to severity, by visual estimation, based on the angiogram. Only lesions successfully measured by FFR were included in this analysis.

### 5.3.2 Number of significantly diseased coronary arteries from the angiographic and functional point of view

Of the 509 patients in the FFR-guided arm, 115 (23%) had angiographic 3-vessel disease, and 394 (77%) had angiographic 2-vessel disease (*figure 5.3*). Of all 115 patients with angiographic 3-vessel disease, 16 (14%) had functional 3-vessel disease, 49 (43%) had functional 2-vessel disease, 39 (34%) had functional single-vessel disease, and 11 (9%) had no functional disease at all. Of all 394 patients with angiographic 2-vessel disease, 170 (43%) had functional 2-vessel disease, 176 (45%) had functional single-vessel disease, and 48 (12%) had no functional disease at all.



**Figure 5.3.** Proportions of functionally diseased coronary arteries in patients with angiographic 3- or 2-vessel disease. All 509 patients had 3- or 2-vessel disease (corresponding respectively to panel A and panel B) by the angiographic coronary artery disease definition (the number of major epicardial coronary arteries with at least one stenosis of  $\geq 50\%$ ; minimum is two and maximum is three). In all these patients FFR was measured in all angiographically diseased coronary arteries. The respective numbers of diseased coronary arteries by the definition of functional coronary artery disease (the number of major epicardial coronary arteries with at least one stenosis with an FFR  $\leq 0.80$ ; minimum is zero and maximum is three) are displayed in the respective segments.

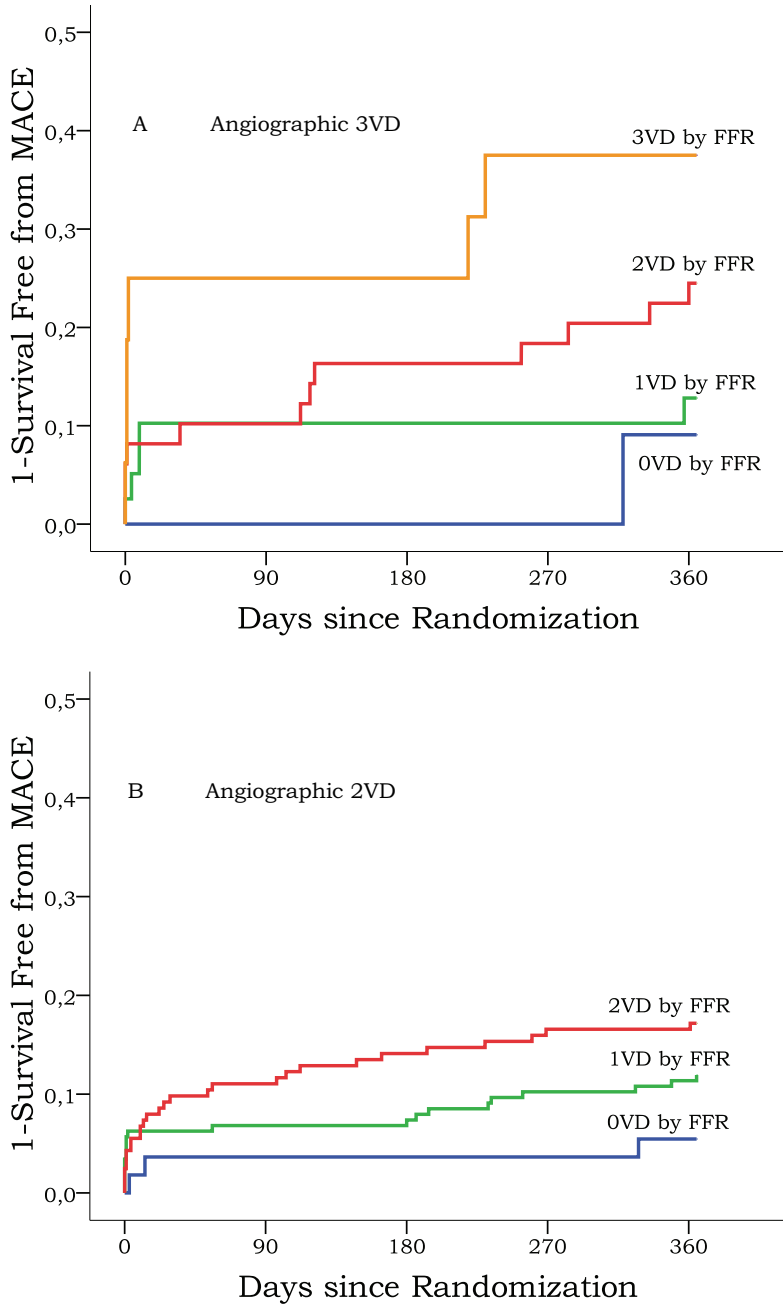


Because stent placement in these patients was based upon FFR measurements, only 60% of all stenoses received a stent, corresponding with an average of  $1.9 \pm 1.3$  stents per patient. The 1-year MACE rate after PCI in the group of patients with angiographic 3-vessel disease was 18.3%, versus 11.7% in the angiographic 2-vessel group (*table 5.3*). Within the angiographic 3-vessel group the rate of MACE after PCI was lowest in the subcategory of patients with no functionally diseased coronary arteries (9.1%) and increased to 10.3% for functional single-vessel disease, 20.4% for functional 2-vessel disease and 37.5% for functional 3-vessel disease. Within the angiographic 2-vessel group a similar increment in MACE rate occurred from 6.3% (no functional disease) to 11.4% (single-vessel functional disease) and 13.5% (two-vessel functional disease). One minus survival free from MACE is shown for all these functional subcategories by Kaplan-Meier curves (*figure 5.4*).

**Table 5.3** . One year event rates per subcategory of functional disease.\*

	MACE(%)		MACE(%)
<b>Angiographic 3VD (n=115)†</b>	18.3	<b>Angiographic 2VD (n=394)†</b>	11.7
0vd by FFR (n=11)‡	9.1	0vd by FFR (n=55)‡	6.3
1vd by FFR (n=39)‡	10.3	1vd by FFR (n=176)‡	11.4
2vd by FFR (n=49)‡	20.4	2vd by FFR (n=163)‡	13.5
3vd by FFR (n=16)‡	37.5		

\* MACE denotes Major Adverse Cardiac Events, vd vessel disease, and FFR Fractional Flow Reserve. † Number of significantly diseased coronary arteries (at least 1 stenosis  $\geq 50\%$ ) based on the angiogram. ‡ Number of significantly diseased coronary arteries ( $FFR \leq 0.80$ ) based on FFR.



**Figure 5.4.** One minus Survival free from MACE Kaplan-Meier curves per number of functionally diseased coronary arteries. Angiographic 3-vessel disease (panel A) and angiographic 2-vessel disease (panel B) and their different subcategories of numbers of functionally diseased coronary arteries.

## 5.4 Discussion

The most important finding in this study is that of all stenoses with an angiographic severity of 50-70%, two-thirds are functionally non-significant and one-third is functionally significant. This means that if the decision for revascularization is merely based upon angiographic stenosis severity, a strategy to stent such lesions routinely, based upon the angiogram, results in probably unnecessary stenting in two-thirds of such lesions leading to unnecessary adverse events, whereas a strategy of routinely deferring such lesions leaves one-third of ischemic stenoses untreated and negatively affects functional class and outcome. Even in more severe stenoses between 71 and 90% angiographic stenosis severity, 20% of all lesions are not functionally significant and also in these cases, stent placement might be inadvertent. Therefore, in patients with multivessel CAD, whether or not taking into account clinical data one cannot rely on the angiogram to identify ischemia-producing lesions when assessing stenoses between 50 and 90%. In this setting, routine stenting without FFR guidance is justified only for truly subtotal lesions (diameter stenosis >90%), because in a coronary artery supplying a non-infarcted area, almost all of these lesions are functionally significant.

Another important finding of this study is that outcome of FFR-guided PCI in patients with angiographic multivessel disease is not only influenced by the number of angiographically diseased coronary arteries, but even more by the number of functionally diseased coronary arteries. Assessing the number of functionally significant diseased coronary arteries in patients with angiographic 2-, or 3-vessel disease often leads to a reduction in the 'number of diseased coronary arteries', thereby challenging the commonly used definition of multivessel disease, based on the coronary angiogram. Angiographic 3-vessel disease, for example, was surprisingly often reduced to 2- or even single vessel disease after assessment by FFR, thereby creating a potentially less complex revascularization procedure and a potential shift from CABG to PCI. The smaller the number of functionally diseased coronary arteries, the lower the 1-year MACE rate after FFR-guided PCI. Since the

number of functionally diseased coronary arteries reflects the amount of myocardium that is jeopardized by ischemia, these findings fully comply with those of numerous previous studies, which showed that the extent of myocardial ischemia is the most important prognostic factor in patients with coronary artery disease.<sup>3;15-17</sup>

Myocardial ischemia causes symptoms and affects outcome.<sup>1-4</sup> Therefore the decision about revascularization of a coronary artery stenosis should be guided by the presence of myocardial ischemia. Non-invasive stress testing is performed in less than half of the patients undergoing elective PCI<sup>18</sup>, and if performed, especially in the setting of multivessel CAD, it is often inaccurate in selecting which out of several lesions are responsible for reversible myocardial ischemia.<sup>6</sup> As a consequence, selection of stenoses to be stented is mostly just guided by the standard coronary angiogram. Additional functional information by FFR, can however be obtained online, is more specific and has a better spatial resolution.<sup>13;19-21</sup> From this and other studies it is obvious that angiographic stenosis severity corresponds poorly with the presence of myocardial ischemia and is inferior to FFR measurements.<sup>22-24</sup> This is also the most probable explanation for the favorable results of the FAME study, that showed a consistent decrease of 30 to 35% for all types of events in the FFR-guided group at 1 year after PCI with drug-eluting stents in multivessel disease patients, with at least equal, if not better functional class.

It should be realized that in all previous randomized studies that compared the different treatment modalities of CAD, i.e. optimal medical therapy alone (OMT), OMT with PCI, or OMT with coronary artery bypass surgery (CABG), the selection of lesions to be treated by PCI with stenting was based upon angiographic assessment alone – in the best case combined with clinical data – without certainty that only those lesions responsible for inducible ischemia were stented. In the recently published SYNTAX study PCI with drug-eluting stents was inferior to coronary artery bypass surgery (CABG) in patients with angiographic 3-vessel disease.<sup>25</sup> In that study the decision about revascularization of a stenosis was based on clinical data and the coronary angiogram alone. In both arms of the SYNTAX study the treatment goal was complete revascularization from an angiographic point of view. In contrast, in

the FFR-guided arm of the FAME study, the goal was complete functional revascularization and according to the results of the FAME study, such a strategy was superior to the strategy of complete anatomical revascularization. Although indirect comparison between studies should be made with caution, one might speculate that if the PCI arms in the SYNTAX trial, COURAGE trial, and BARI 2D trial had been FFR-guided, it would have improved the outcome of PCI compared to the other treatment modalities. Further randomized studies are mandatory to prove this hypothesis.

In addition to improving prognosis a critically important goal of revascularization is improvement of angina. Although fewer stents were used, FFR-guided PCI in the FAME study resulted in freedom from angina after 1 year in 81% of the patients, which is high compared to other studies with comparable patients treated by angiographically guided stenting or medical therapy alone.<sup>7;25</sup> This means that selective stenting based on FFR is very effective in eliminating angina (*figure 7.2*).

#### **5.4.1 Limitations**

The selection of lesions in the FAME study was based upon the operator's visual interpretation of the angiogram, together with clinical data. It is well known that there is a high interobserver variability in assessing anatomical coronary stenosis severity, but we do not believe that this induced bias in the class of lesions in this study, because FFR was measured after the lesions had been classified. This reflects daily practice in the catheterization laboratory. Moreover, the operator knew there was a 50% chance that the patient would be randomized to angiographic guidance alone and that stenting of all identified lesions would be required by the protocol. Thus the operator was forced to only identify those lesions which he or she truly deemed worthy of PCI, based on the angiogram and clinical data.

### **5.4.2 Conclusions**

In patients with multivessel disease, coronary angiography is an inappropriate tool to assess the functional severity of a coronary artery stenosis as measured by FFR, not only in the 50-70% stenosis range, but also in the 71-90% stenosis range. Therefore, FFR in addition to standard angiography should be used for the decision making whether or not to stent such lesions in almost all patients with multivessel coronary artery disease. Finally, in many patients angiographic 3-vessel disease can be converted to functional 2-vessel disease with potential implications for choice of appropriate treatment (medical therapy, PCI, or CABG).

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# 6

## Economic Evaluation of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients with Multivessel Disease

*Under review*

*William F. Fearon, M.D.*

*Bernhard Bornschein,  
M.D., M.P.H.*

*Pim A.L. Tonino, M.D.*

*Raffaella M. Gothe*

*Bernard De Bruyne, M.D.,  
Ph.D.*

*Nico H.J.Pijls, M.D., Ph.D.*

*Uwe Siebert, M.D., MSc.,  
M.P.H. ScD.*

*\*Affiliations of all authors  
and all members of the  
FAME Study Investigator  
Group are listed in  
appendix II of this thesis*

## Abstract

**Background** The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) Study demonstrated significantly improved health outcomes at 1 year in patients randomized to multivessel percutaneous coronary intervention (PCI) guided by FFR compared to PCI guided by angiography alone. The economic impact of routine measurement of FFR in this setting is not known.

**Methods and Results** 1005 patients were randomly assigned to FFR-guided PCI or angiography-guided PCI and followed for 1 year. A prospective cost utility analysis comparing costs vs. quality-adjusted life years (QALY) was performed with a time horizon of 1 year. QALYs were calculated using utilities determined by the EQ-5D with US weights. Direct medical costs included those of the index procedure and hospitalization, as well as those for major adverse cardiac events (MACE) during follow-up. Confidence intervals for both QALYs and costs were estimated by the bootstrap percentile method.

MACE at 1 year occurred in 13.2% of those in the FFR-guided arm and 18.3% of those in the angiography-guided arm ( $p=0.02$ ). QALYs were significantly greater in the FFR-guided arm (0.86 vs 0.83,  $p=0.03$ ). Mean overall costs at 1 year were significantly less in the FFR-guided arm (\$16,524 vs. \$19,351,  $p<0.001$ ). Bootstrap simulation indicated that the FFR-guided strategy was cost-saving in 99.96%, and cost-effective in all 10,000 samples. Sensitivity analyses demonstrated robust results.

**Conclusion** Economic evaluation of the FAME study reveals that FFR-guided PCI in patients with multivessel coronary disease is one of those rare situations in medicine in which a new technology not only improves outcomes, but also saves resources.

## 6.1 Introduction

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study was a large, multicenter, international, randomized, clinical trial comparing outcomes in patients with multivessel coronary artery disease undergoing percutaneous coronary intervention (PCI) with either angiographic guidance alone or with the addition of fractional flow reserve (FFR) guidance. The primary outcome of the trial was a significant decrease at one year in the composite endpoint of death, myocardial infarction or the need for repeat revascularization in the group receiving FFR guidance (13.2% vs. 18.3%,  $p=0.02$ ). The economic ramifications of the additional costs incurred by the routine measurement of FFR in this scenario are unknown. The goal of this prospective economic evaluation is to determine the cost effectiveness of the FFR-guided strategy in the US health care context.

## 6.2 Methods

### 6.2.1 Study design

The design of the FAME trial has been previously reported and is described extensively in *chapter 3* of this thesis.<sup>1,2</sup> In brief, the study included patients undergoing PCI for multivessel coronary artery disease, defined as two or three major epicardial arteries, each with a 50% or greater stenosis warranting PCI. Patients with angiographically significant left main coronary artery disease, prior coronary artery bypass grafting, extremely tortuous or calcified vessels, or within 5 days of an ST segment elevation myocardial infarction were excluded. After a baseline coronary angiogram was performed, the

investigator indicated which lesions should be stented based on the angiographic appearance and clinical information available. Patients were then randomized to either angiographic guidance, in which case the investigator performed PCI of the indicated lesions, or to FFR guidance, in which case FFR was first measured in each diseased vessel with a coronary pressure wire and intravenous adenosine. If the FFR was  $\leq 0.80$ , then PCI of the respective stenosis was performed, otherwise PCI was deferred. Patients received drug-eluting stents and clopidogrel during the first year. Major adverse cardiac events (MACE), defined as all cause death, myocardial infarction, or need for repeat coronary revascularization were assessed at one year, as previously described.<sup>1</sup>

### **6.2.2 Framework of the economic evaluation**

In the present study, an economic evaluation along the FAME trial in the context of the US health care system was performed. The incremental cost-effectiveness ratio (ICER), that is, the net incremental cost of the FFR-guided and angiography-guided strategies divided by the net incremental health outcomes of each strategy was calculated.<sup>3</sup> The time horizon was one year (i.e., the duration of follow-up in the primary clinical study) and analyses were performed from a societal perspective using direct costs. Given the short time horizon, no discounting was performed. The primary analysis was a cost-utility analysis (i.e., cost vs. quality-adjusted life years [QALYs]), with a secondary analysis of cost-effectiveness (cost vs. MACE).

### **6.2.3 Costs**

Costs for each strategy included the initial procedural costs and costs during the 1 year follow-up. The costs of the index procedures were calculated from the actual resource consumption, by determining the amount of guiding catheters, regular wires, pressure wires, balloon dilatation catheters, stents, antiplatelet therapy, adenosine, contrast media, and hospital days utilized for each patient's index procedure. These were multiplied by the cost of each resource in US dollars. Based on a recent publication, the cost of a hospital day was estimated at \$2,400.<sup>4</sup> The costs of the other resources were obtained

from a US participating site. Personnel and laboratory time costs were not included as they were exactly similar between the two strategies.<sup>2</sup> Costs of repeat PCI, CABG, and MI were based on recent literature.<sup>4;5</sup> Indirect costs due to productivity losses were assumed to be captured by the denominator of the ICER (i.e., QALY), and therefore, not included in the numerator of the ICER.<sup>6</sup> All costs were converted to 2008 US dollars using the consumer price index ([www.bls.gov](http://www.bls.gov)).

#### **6.2.4 Health outcomes**

QALYs were derived from health-related quality of life and survival during the 1-year time horizon of the trial. Quality-of-life indices (utilities) were evaluated at baseline, after one month and after 1 year using the EQ-5D with US weights.<sup>7;8</sup> EQ-5D is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The overall QALY was estimated as the area under the curve determined by these three values. Data for quality of life were missing for 9.7% of patients at baseline, for 15.4% at 1 months' follow-up examination and for 17.5% at 1 year. We imputed missing values at baseline by replacement with the overall mean at baseline. For missing values during later follow-up periods (i.e., 1 month, 1 year) and for patients lost to follow-up (n=19), we used the last available values (last value carried forward, LVCF, if necessary at all).<sup>9</sup> Observation time was used exactly from randomization to a maximum of 365 days, unless death occurred before then.

#### **6.2.5 Statistical analysis**

Categorical data are reported as frequencies, and continuous data as mean +/- standard deviation. Categorical data were compared using the Chi<sup>2</sup> test. Given non-normal distributions, continuous data (including costs and QALYs) were compared using the Mann-Whitney U test. Ninety-five percent confidence intervals are reported where appropriate. Confidence intervals for both differences in QALYs and costs were estimated by the bootstrap method using the percentile-method and 10,000 replications. The bootstrap method creates

artificial datasets by resampling from all available datasets.<sup>10</sup> A two-sided p-value of less than 0.05 was considered to indicate statistical significance. Sensitivity analyses were performed for a range of  $\pm 20\%$  on all prices and for  $\pm 10\%$  on utilities. We performed additional sensitivity analyses for missing values and patients lost-to follow-up, applying a complete-case analysis. All analyses were performed with the use of SAS software, version 9.1 (SAS Institute).

### 6.3 Results

The baseline characteristics of the patients enrolled in the FAME trial are displayed in *table 6.1*.

**Table 6.1.** Baseline Characteristics

	<b>Angiography Group N= 496</b>	<b>FFR Group N= 509</b>
Age (years)	64.2±10.2	64.6±10.3
Male (%)	72.6	75.4
Diabetes (%)	25.2	24.2
Hypertension (%)	65.9	61.3
Dyslipidemia (%)	73.0	71.9
Tobacco use (%)	31.5	27.1
Previous MI (%)	36.3	36.7
Previous PCI (%)	26.0	28.7
Unstable angina (%)		
With dynamic ECG changes	18.3	14.3
Without dynamic ECG changes	17.5	15.1
Ejection fraction (%)	57±12	57±11
Indicated lesions - no.	2.7±0.9	2.8±1.0
Mean utility ate baseline (EQ5D)	0.793	0.820

*Values are means  $\pm$  SD, unless otherwise specified.  $P > 0.05$  for all comparisons.*

At one year, the rate of MACE was 13.2% in the FFR-guided arm and 18.3% in the angiography-guided arm ( $p=0.02$ ). The rate of death or myocardial infarction was 7.3% in the FFR-guided arm versus 11.1% in the angiography-guided arm ( $p=0.04$ ). There was a similar improvement in freedom from angina (81 vs. 78%, respectively,  $p=0.20$ ). Mean utilities for patients in the angiography-guided group were 0.793 at baseline, 0.881 after one month and 0.882 after 1 year. The respective values for the FFR-guided group were 0.820, 0.898 and 0.898, respectively ( $p>0.05$  between study groups at any follow-up time). In both groups, mean utilities increased from baseline to 1 month, ( $p<0.0001$ ), and remained stable until end of follow-up.

Mean QALYs at 1 year were significantly higher in the FFR-guided arm compared to the angiography-guided arm (0.86 vs. 0.83,  $p=0.03$ ). Overall QALYs ranged from zero to one in both groups. The mean index procedural costs were significantly lower in the FFR-guided arm ( $\$14,068 \pm 9,048$  vs.  $\$15,527 \pm 8,770$ ,  $p<0.0001$ ).

Resources utilized at the index procedure for each arm and their costs are listed in *table 6.2*. Overall costs at one year ranged from \$3,045 to \$84,240 in the FFR-guided strategy and from \$4,445 to \$130,219 in the angiography-guided strategy. At one year, the mean overall costs were significantly lower in the FFR-guided arm ( $\$16,524$  vs.  $\$19,351$ ,  $p<0.0001$ ).

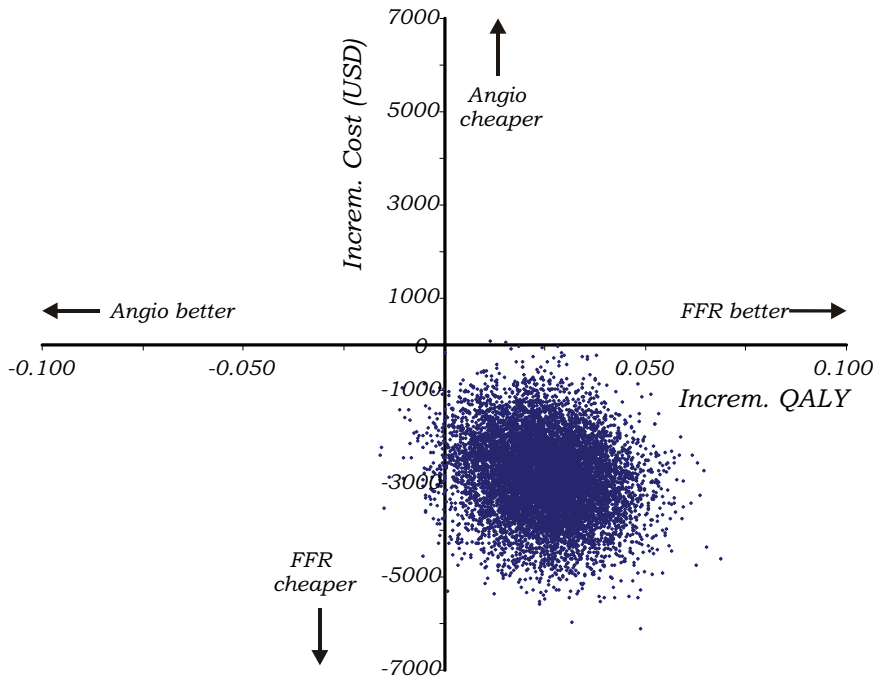


**Table 6.2.** Resources Utilized and Costs

<b>Resource</b> (Cost)	<b>Angio-guided</b>		<b>FFR-guided</b>	
	No. of resource units	Mean cost/pat. (\$)	No. of resource units	Mean cost/pat. (\$)
Guide Catheter (\$35)	2.2 (2.1-2.3)	77	2.0 (1.9-2.1)	71
Guidewire (\$85)	2.2 (2.1-2.3)	184	1.2 (1.1-1.3)	95
Pressure Wire (\$650)	0	---	1.3 (1.2-1.3)	818
Balloon Catheter (\$150)	2.1 (1.9-2.2)	302	1.7 (1.5-1.9)	245
Contrast Agent (\$0.5/ml)	302 (291-314)	150	272 (261-284)	135
DES (\$2,100)	2.7 (2.6-2.9)	5,755	1.9 (1.8-2.0)	4,042
Bare-Metal Stent (\$1,000)	0.1 (0.06-0.14)	101	0.06 (0.03-0.09)	59
Adenosine (\$150/vial)	0	---	1.5 (1.4-1.6)	222
GPI (\$500/vial)	0.4 (0.3-0.5)	157	0.3 (0.26-0.40)	137
Hospital Day (\$2,400/day)	3.7 (3.4-4.0)	8,805	3.5 (3.2-3.7)	8,239
Repeat PCI (\$15,634)	0.08 (0.06-0.12)	1,325	0.06 (0.04-0.09)	982
CABG (\$31,320)	0.03 (0.01-0.04)	823	0.01 (0-0.02)	371
MI (\$19,369)	0.09 (0.06-0.11)	1,683	0.06 (0.04-0.08)	1,104
<b>Total 1 Year Costs:</b>		<b>\$19,351</b>		<b>\$16,524</b>

Values are mean number of resource units (95% CI) or mean cost per patient. GPI indicates glycoprotein inhibitor, DES, drug-eluting stent; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; MI, myocardial infarction.

The angiography-guided strategy is therefore strongly dominated, as it is more expensive, but clinically less effective with respect to QALYs gained or MACE rates. The bootstrap simulation demonstrates that the FFR-guided strategy is cost-saving in 99.96% and cost-effective (at a threshold of \$50,000 per QALY gained) in all 10,000 bootstrap samples (*figure 6.1*). Absolute and incremental QALYs and costs are presented in *table 6.3*.



**Figure 6.1.** Bootstrap simulation of incremental costs and effects. Numbers on axes represent differences between FFR-guided and Angio-guided strategies. Positive incremental QALYs indicate higher effectiveness for FFR-guided treatment. Negative incremental costs indicate lower costs for FFR-guided treatment, when compared to Angio-guided strategy. Data are from 10,000 bootstrap replications. The data show that FFR is cost-saving in 99.96% and cost-effective in 100% of all bootstrap samples.

All sensitivity analyses showed robust results. Reducing the utilities calculated from the EQ-5D by 10% resulted in 0.74 QALY on average for the angiography-guided group and 0.77 for the FFR-group. Increasing the utilities by 10% resulted in 0.86 and 0.89 QALYs, respectively. In both cases the difference between the groups remained statistically significant ( $p=0.02$ ). Sensitivity analyses varying resource prices by  $\pm 20\%$  led to cost differences between the study groups between \$2,485 and \$3,169 (basecase: \$2,827),

always favoring the FFR-guided strategy. The cost components with the largest impact on overall cost were the price of DES (increasing the difference of overall costs between strategies by \$342 if costs were increased by 20%), the price of the pressure wire (reducing the difference by \$164), the cost of a myocardial infarction (increasing by \$115) and for a hospital day (increasing by \$112).

**Table 6.3.** Overall Health Outcomes and Costs

<b>Outcome</b>	<b>Angio-guided</b>	<b>FFR-guided</b>	<b>Difference (95% CI)</b>
MACE (%)	18.3	13.2	5.1 (0.6-9.7)
MI or death (%)	11.1	7.3	3.8 (0.3-7.4)
QALY	0.83	0.86	0.03 (0.004-0.05)
Overall costs (US\$)	19,351	16,524	-2,827 (-4,542 to -1,201)

*Values are means with 95%-confidence intervals. MACE indicates major adverse cardiac events; MI, myocardial infarction; QALY, quality adjusted life years.*

## 6.4 Discussion

The principle finding of this study is that performing PCI guided by FFR in patients with multivessel coronary artery disease saves health care resources and improves health outcomes at 1 year compared to a traditional standard strategy of angiographic guidance. The cost savings occurs both at the index procedure, primarily due to a decrease in drug-eluting stent use, which more than offsets the increased cost of the pressure wire and adenosine, and it occurs during follow-up as a result of a decrease in rehospitalization and fewer MACE. The improvement in QALY occurs by 1 month after the index procedure and persists at 1 year. These results appear to be robust, as the bootstrap simulation demonstrated that an FFR-guided strategy was

dominant (cost-saving, i.e., costs less and provides better health outcomes) in 99.96% of the samples. In addition, sensitivity analyses varying costs and utilities did not change these results.

The presumed explanation for these results has already been explained in extension in the preceding chapters of this thesis and lies in the fact that the coronary angiogram, although our reference standard for diagnosing coronary artery disease, is a poor predictor of ischemia-producing lesions. For example, in the FAME trial, 65% of lesions with 50-70% diameter stenosis were not responsible for an abnormal FFR ( $\leq 0.80$ ), and 20% of lesions with a 71-90% diameter stenosis were not responsible for an abnormal FFR (*chapter 5*). Yet, the angiographic appearance of lesions causing ischemia is identical to lesions not responsible for ischemia, particularly when in the moderate range of stenosis.<sup>11</sup> Prior studies have demonstrated the importance of identifying ischemia and the improved outcomes which occur with the relief of ischemia.<sup>12</sup> Likewise, the lack of benefit of PCI on non-ischemia producing lesions also has been clearly documented.<sup>13</sup>

In the current study, the angiography-guided arm likely received a number of stents for lesions not responsible for ischemia. This increased the costs without improving the health outcome. In fact, the additional stents may have resulted in harm, that is, more MACE due to both procedural complications and late complications, such as restenosis, as will be further discussed in *chapter 8*. Conversely, it is possible that relief of ischemia was not complete in some patients in the angiography-guided arm because mild ischemia-producing lesions were not recognized, translating into a higher adverse event rate and loss of quality of life. In contrast, in the FFR-guided arm, presumably only those lesions responsible for ischemia, and hence at higher likelihood for causing adverse events were treated with PCI. This approach resulted in fewer stents being placed and hence lower costs, despite the cost of the pressure wire and adenosine, and better outcomes because the benefit of the stents was maximized and the risk minimized.

It is unusual in modern medicine to find a new technology or treatment strategy which not only improves the intended health benefit, reduces risk and unintended effects, but also saves costs. A strategy of providing free

medications to patients after myocardial infarction to improve compliance may be cost-saving.<sup>14</sup> Radiofrequency ablation for Wolff-Parkinson-White Syndrome, statins after myocardial infarction and ace inhibitors in congestive heart failure are other examples.<sup>15</sup> A unique finding from the current analysis is the fact that not only was an FFR-guided strategy to PCI in multivessel coronary artery disease cost-saving, but it achieved these results within just one year, a remarkably short period of time.

The cost-effectiveness of FFR has been previously evaluated in other settings. Using a decision-tree model, measuring FFR in patients with single vessel intermediate lesions and no prior noninvasive stress test was found to be cost effective compared to deferring the decision to perform PCI in order to obtain a nuclear perfusion study and compared to a routine strategy of performing PCI on all intermediate lesions.<sup>16</sup> Similar results have been reported by a recent European health technology assessment report.<sup>17</sup> A small, single center randomized study compared an FFR-guided strategy to a nuclear perfusion imaging strategy in patients presenting with non ST elevation acute coronary syndromes with single vessel intermediate disease and found equivalent outcomes and lower costs with the FFR-guided strategy.<sup>18</sup> In a nonrandomized, single center study of 137 patients with multivessel coronary artery disease, costs were lower and outcomes better in the 57 patients who had FFR-guided PCI compared to the 80 patients with angiography-guided PCI.<sup>19</sup> Based on its large size, multicenter nature and randomized, prospective design, the current study further strengthens the evidence supporting the economic advantage to measuring FFR to guide PCI routinely.

As potential limitations, it should be said that the analysis in this chapter is limited by its relatively short time horizon; the durability of these findings will need to be confirmed after longer follow-up. However, given that the difference in expenditure is limited to the index procedure and most benefits would be expected during the first year, a short time horizon may be sufficient.<sup>20</sup> With respect to our assessment of quality of life, there were missing values and relatively large time intervals, however, sensitivity analyses suggested consistent results over a wide range of potential quality of life parameters and for different imputation methods for missing values. We did not explicitly

account for indirect costs, such as loss of productivity, or for nonmedical costs; but this most likely does not limit this analysis at all, because such indirect costs probably bias the results in favor of the angiography-guided arm given that there was a higher event rate in this group, which would have increased indirect costs. Finally, these results apply to the US healthcare system and cannot be directly generalized to other healthcare systems, although based on the significant differences between the two strategies, it is unlikely that the direction of the overall results will be very different.

In conclusion, FFR-guided PCI with DES in patients with multivessel coronary artery disease compared to standard angiographic guidance improves outcomes and saves costs at 1 year and hence is a dominant strategy in this setting. Therefore, FFR is one of those rare situations in medicine in which a new technology not only improves outcomes, but also saves resources.

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# 7

## Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention in Patients with Multivessel Coronary Artery Disease: 2-Year Follow-Up of The FAME Study

*Under review*

*Nico H.J. Pijls, M.D., Ph.D.*

*William F. Fearon, M.D.*

*Pim A.L. Tonino, M.D.*

*Uwe Siebert, M.D., MSc.,  
M.P.H. ScD.*

*Fumiaki Ikeno, M.D.*

*Bernhard Borschein,  
M.D., M.P.H.*

*Marcel van 't Veer, MSc.,  
Ph.D.*

*Volker Klauss, M.D., Ph.D.*

*Ganesh Manoharan, M.D.*

*Thomas Engström, M.D.,  
Ph.D.*

*Keith G. Oldroyd, M.D.*

*Peter N. Ver Lee, M.D.*

*Philip A. MacCarthy, M.D.,  
Ph.D.*

*Bernard De Bruyne, M.D.,  
Ph.D.*

*for the Fractional Flow  
Reserve versus  
Angiography for  
Multivessel Evaluation  
(FAME) Study  
Investigators\**

*\*Affiliations of all authors  
and all members of the  
FAME Study Investigator  
Group are listed in  
appendix II of this thesis*

## Abstract

**Background** In patients with multivessel coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) coronary angiography is the standard method for guiding stent placement. The FAME study showed that routine measurement of fractional flow reserve (FFR) in addition to angiography improves outcomes of PCI at 1 year. It is unknown if these favorable results are maintained at 2 years of follow-up.

**Methods** At 20 U.S. and European medical centers, 1005 patients with multivessel CAD were randomized to PCI with drug-eluting stents (DES) guided by angiography alone or guided by FFR measurements. Prior to randomization, lesions requiring PCI were identified based on their angiographic appearance. Patients randomized to angiography-guided PCI underwent stenting of all indicated lesions, while those randomized to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was  $\leq 0.80$ . Follow-up was 2 years.

**Results** The number of indicated lesions was  $2.7 \pm 0.9$  in the angiography-guided group and  $2.8 \pm 1.0$  in the FFR-guided group ( $P=0.34$ ). The number of stents used was  $2.7 \pm 1.2$  and  $1.9 \pm 1.3$  respectively ( $P < 0.001$ ). The 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group ( $P=0.02$ ). Rates of PCI or coronary artery bypass surgery were 12.7% and 10.6%, respectively ( $P=0.30$ ). The combined rates of death, non-fatal myocardial infarction and revascularization were 22.4% and 17.9%, respectively ( $p=0.08$ ). In the angiography-guided group, 76% of all patients were free from angina, as compared to 80% in the FFR-guided group ( $P=0.14$ ). In lesions deferred on the basis of  $FFR > 0.80$ , rate of myocardial infarction was 0.2 % and revascularization rate was 3.2 % after 2 years.

**Conclusions** Routine measurement of FFR in patients with multivessel CAD undergoing PCI with DES, significantly reduces mortality and myocardial infarction at 2 years when compared to standard angiography-guided PCI and is associated with excellent functional outcome.

## **7.1 Introduction**

With the introduction of drug-eluting stents (DES), the percentage of patients with multivessel coronary artery disease (CAD) in whom percutaneous coronary intervention (PCI) is performed, has increased.<sup>1</sup> Because drug-eluting stents are expensive and are associated with potential late complications, their appropriate use is critical.<sup>2</sup> However, in patients with multivessel CAD, identifying which lesions cause ischemia and warrant stenting can be difficult. Although coronary angiography often underestimates or overestimates a lesion's functional severity, it is still the standard technique for guiding PCI in patients with multivessel coronary artery disease.<sup>3</sup>

Fractional flow reserve (FFR) is an index of the physiologic significance of a coronary stenosis and is defined as maximal blood flow in a stenotic artery as a ratio to normal maximal flow.<sup>4</sup> It can be easily measured during coronary angiography by the ratio of distal coronary pressure measured with a coronary pressure guidewire to aortic pressure measured simultaneously with the guiding catheter. An FFR value of 0.80 discriminates coronary stenoses responsible for ischemia with an accuracy of more than 90%.<sup>4-7</sup> Retrospective studies suggest that in patients with multivessel CAD, FFR-guided PCI is associated with a favorable outcome with respect to event-free survival.<sup>8;9</sup>

For patients with multivessel coronary artery disease, identifying an approach to PCI that would result in a more judicious use of stents, while still achieving complete relief of myocardial ischemia, could improve clinical outcome and decrease health care costs. The objective of the FAME study was to compare treatment based on measurement of FFR in addition to angiography to the current practice of treatment solely guided by angiography in patients with multivessel CAD amenable for PCI. The FAME study showed that after a follow-up of one year, the rate of major adverse cardiac events was

reduced significantly by 5.1% whereas similar high percentages of patients were free from angina.<sup>10</sup> The purpose of this paper is to investigate if the favorable outcome of FFR-guided PCI in the FAME study, is maintained at 2 years.

## **7.2 Methods**

### **7.2.1 Study design**

The design of this study has been described previously (*chapter 3 of this thesis*).<sup>11</sup> Shortly, in eligible patients with multivessel CAD the investigator indicated which lesions had stenosis of at least 50% and were thought to require PCI on the basis of angiographic appearance and clinical data. Patients were then randomly assigned to either angiography-guided or FFR-guided PCI. Patients assigned to angiographic guidance underwent stenting of all indicated lesions with drug-eluting stents. In patients assigned to FFR guidance, first FFR was measured in each diseased coronary artery and drug-eluting stents were placed in indicated lesions only if the FFR was 0.80 or less. The study protocol was approved by the internal review board of each participating center. An independent clinical event committee blinded to treatment assignment adjudicated all events. Data management and statistical analysis were performed by an independent data coordinating center. The study sponsors had no role in the methods, data acquisition, data analysis, reporting, or publication of this study.

### **7.2.2 Study population**

Patients were included in the study if they had multivessel coronary artery disease, defined as coronary artery stenoses  $\geq 50\%$  diameter stenosis in at least 2 of the 3 major epicardial coronary arteries, which were felt to require PCI. Patients with ST-segment elevation myocardial infarction could be included if the infarction had occurred at least 5 days before PCI. Enrolment and PCI in patients with non-ST-segment elevation myocardial infarction could occur earlier than 5 days if the peak creatinine kinase was  $<1000$  IU.

Patients who had undergone previous PCI could be included in the study. Patients with 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, or a contra-indication to DES placement were excluded.

### **7.2.3 Treatment**

PCI was performed using standard techniques. FFR was measured with a coronary pressure guidewire (Radi/St Jude Medical, Uppsala, Sweden) at maximal hyperemia induced by intravenous adenosine, administered at 140 µg/kg/min through a central vein. Hyperemic pressure pull back recordings were performed as described previously.<sup>7,11</sup> All included patients were treated with aspirin and clopidogrel for at least 1 year. If a patient underwent repeat coronary angiography during follow-up, decision making with respect to repeat revascularization was based on the initially assigned strategy of angiography guidance or FFR guidance.

### **7.2.4 Endpoints and 2-year follow-up**

MACE was defined as a composite of death, myocardial infarction or any repeat revascularization. The primary endpoint was the rate of major adverse cardiac events (MACE) by 1 year. Secondary endpoints included death and myocardial infarction rates and MACE and its individual components at 2 years, procedure time, amount of contrast agent used, functional class at 1 and 2 years, and number of anti-anginal medications. Cost-effectiveness was a secondary endpoint as well. Death was defined as all-cause mortality. Myocardial infarction was defined as  $\geq 3$ -fold elevation of CK-MB level or new Q-waves in  $\geq 2$  contiguous leads of the electrocardiogram (ECG).<sup>12</sup> Total CK and CK-MB levels were measured in all patients between 12 and 24 hours after PCI. After discharge, follow-up was performed at 1 month, 6 months, 1 year, and 2 years.

### **7.2.5 Statistical analysis**

The power analysis for this study was extensively described in *chapter 4*. All enrolled patients were included in the analysis of primary and secondary endpoints according to the intention-to-treat principle. Categorical variables including the primary endpoint and its components are described as proportions and were compared by chi-square test. Continuous variables are described as mean and standard deviation and were compared by unpaired *t* test or Mann-Whitney U test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Kaplan-Meier curves are presented to describe the time-to-event distributions for the different endpoints. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA) and STATA, version 11 SE (StataCorp, College Station, TX, USA).

## **7.3 Results**

### **7.3.1 Baseline characteristics and angiographic data**

Between January 2006 and September 2007, a total of 1005 patients were included in 20 centers in the U.S. and Europe. Of these, 496 were randomized to angiography-guided PCI and 509 to FFR-guided PCI. Baseline demographic and clinical characteristics of the two groups were similar (*table 4.1*). Also the number of indicated lesions, and angiographic extent and severity of coronary artery disease were similar (*table 7.1*).

**Table 7.1.** Baseline Angiographic Characteristics.\*

<b>Angiographic Characteristic</b>	<b>Angiography Group N=496</b>	<b>FFR Group N=509</b>	<b>P Value †</b>
<b>Angiography</b>			
Indicated lesions per patient – no.‡	2.7±0.9	2.8±1.0	0.34
50-70% narrowing – no. (%)	550(41)	624(44)	
70-90% narrowing – no. (%)	553(41)	530(37)	
90-99% narrowing – no. (%)	207(15)	202(14)	
Total occlusion – no. (%)	40(3)	58(4)	
Lesions in segment 1,2,3,6,7,11 -- no. (%)	960(71)	1032(73)	0.27
Patients with proximal LAD lesion– no. (%)	186(38)	210(41)	0.22
Patients with total occlusion – no. (%)	37(7.5)	54(10.6)	0.08

\* Plus-minus values are means ± SD. LAD denotes left anterior descending artery. † All categorical variables were compared by chi-square-test; all continuous variables were compared by Mann-Whitney U test. ‡ Before randomization the investigator indicated all lesions to be included in the study and classified them according to severity, by visual estimation, based on the angiogram.

### 7.3.2 Procedural results

A total of 2415 stents were placed, of which 2339 (96.9%) were drug-eluting stents. Significantly more stents per patient were placed in the angiography-guided group compared to the FFR-guided group (2.7±1.2 versus 1.9±1.3;  $P<0.001$ ; table 7.2).

In the FFR-guided group, FFR was successfully measured in 94% of all lesions. In 874 (63%) lesions FFR was 0.80 or less and these lesions were stented as per protocol. In 513 (37%) lesions FFR was greater than 0.80 and these lesions were not stented. The procedure time was similar in the two groups (70±44 minutes in the angiography-guided group and 71±43 minutes in the FFR-guided group;  $P=0.51$ ). Significantly more contrast agent was used in the angiography-guided group than in the FFR-guided group (302±127 ml versus 272±133 ml;  $P<0.001$ ).

Length of hospital stay was 3.7±3.5 days in the angiography-guided group versus 3.4±3.3 days in the FFR-guided group ( $P=0.05$ )



**Table 7.2.** Procedural results.\*

	<b>Angiography Group N= 496</b>	<b>FFR Group N= 509</b>	<b>P Value †</b>
<b>Procedure time</b> – min.‡	70±44	71±43	0.51
<b>Contrast agent used</b> – ml.	302±127	272±133	<0.001
<b>Drug eluting stents</b>			
Drug eluting stents used per patient – no.	2.7±1.2	1.9±1.3	<0.001
Total stent length – mm.	51.9±24.6	37.9±27.8	<0.001
Lesions successfully stented – no. (%) §	1237(92)	819(94)	0.07
Total drug eluting stents used – no.	1359	980	<0.001
<b>FFR results</b> – no. (%)			
Lesions successfully measured by FFR¶	n/a	1329(94)	
Lesions with FFR ≤ 0.80	n/a	874(63%)	
Lesions with FFR > 0.80	n/a	513(37%)	

\* Plus-minus values are means ± SD . PCI denotes percutaneous coronary intervention, FFR fractional flow reserve. † All categorical variables were compared by chi-square test; all continuous variables and the variable ‘drug eluting stents used per patient’ were compared by Mann-Whitney U test. ‡ Procedure time was defined as time from introduction of first till removal of last guiding catheter. § Percentage of the lesions indicated at baseline (angiography group), percentage of the lesions with FFR ≤ 0.80 (FFR group). ¶ Percentage of the number of all indicated lesions. Of those 85 lesions without FFR measurement, 58 (4.1%) were the totally occluded arteries to which a default FFR value of 0.50 was assigned , whereas in 27 (1.9%) lesions, FFR could not be measured because of technical reasons.

### 7.3.3 Adverse events and freedom from angina at 2 years

Complete 2-year follow-up was obtained in 93.6% of patients (36 were lost to follow-up in the angiography-guided group and 29 were lost to follow-up in the FFR-guided group (P=0.31). All-cause mortality at 2 years was 3.8% (19 patients) in the angiography-guided group and 2.6% (13 patients) in the FFR-guided group (P=0.25; table 7.3).

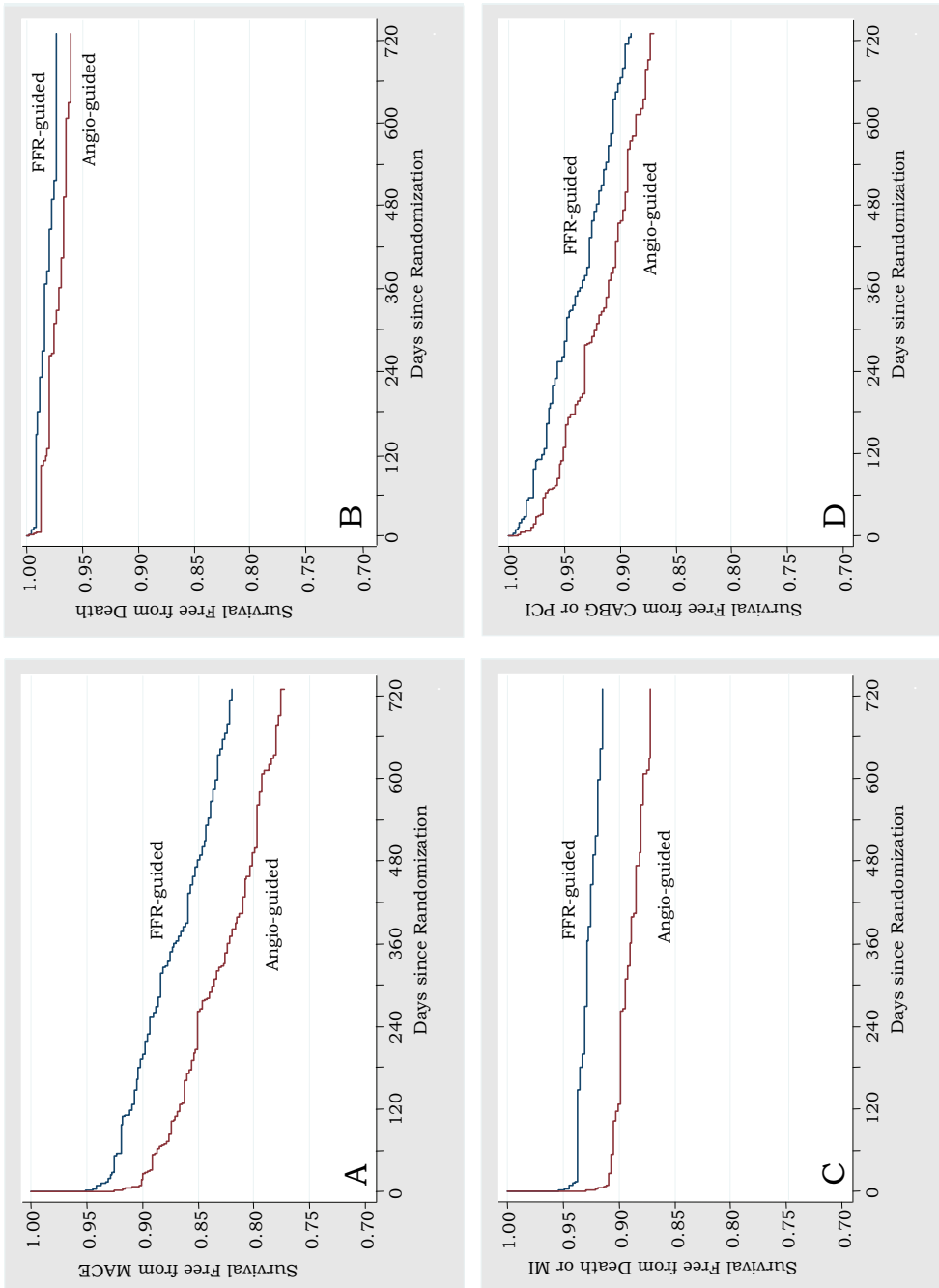
**Table 7.3.** Endpoints at 2 years.\*

	<b>Angiography Group N= 496</b>	<b>FFR Group N= 509</b>	<b>P Value †</b>	<b>RR with FFR guidance (95%CI)</b>
<b>Events at 2 years – no. (%)</b>				
Total no. of events	142	106		
No. of events per patient	0.29±0.60	0.21±0.48	0.17	
Death	19(3.8)	13(2.6)	0.25	0.67 (0.33-1.34)
Myocardial infarction	49(9.9)	31(6.1)	0.03	0.62 (0.40-0.95)
CABG or repeat PCI	63(12.7)	54(10.6)	0.30	0.84 (0.59-1.18)
Death or MI	64(12.9)	43(8.4)	0.02	0.65 (0.45-0.94)
Death, MI, CABG or repeat PCI	111(22.4)	91(17.9)	0.08	0.80 (0.62-1.02)
<b>Functional status at 2 years - no. (%)</b>				
Pts. without event and free from angina ‡	284(64.8)	315(68.2)	0.29	
Pts. free from angina ‡	332(75.8)	369(79.9)	0.14	
N° of anti-anginal medications §	1.2±0.8	1.2±0.7	0.68	

\* Plus-minus values are means ± SD. RRR denotes relative risk reduction, 95%CI 95% confidence interval, MI myocardial infarction, CABG coronary artery bypass grafting, PCI percutaneous coronary intervention, Pts. patients. † All categorical variables were compared by chi-square test; all continuous variables and the variable ‘number of events per patient’ were compared by Mann-Whitney U test.

‡ patients with missing information on angina status were excluded from the analysis.

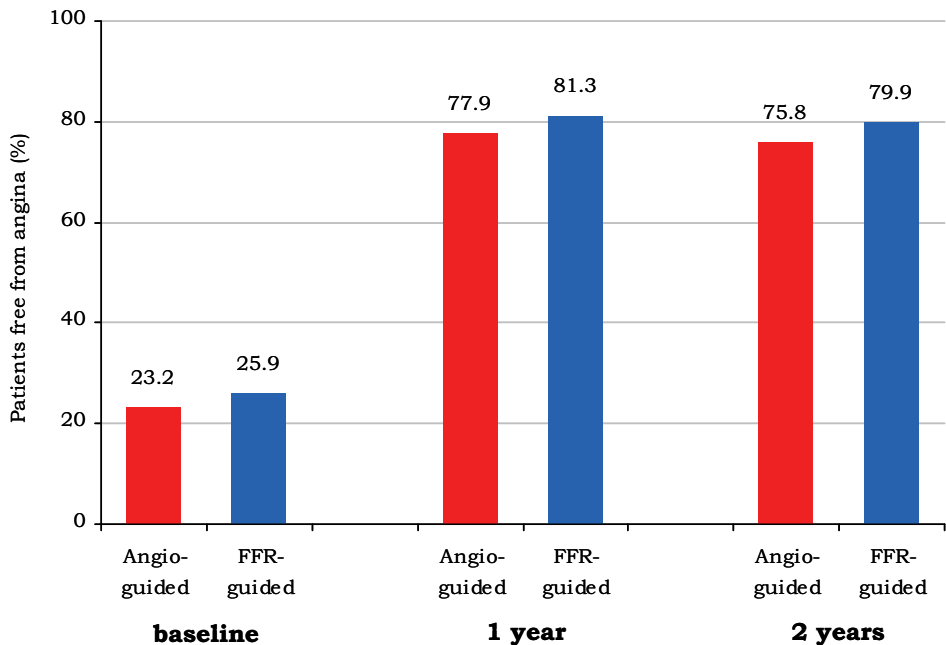
§ Anti-anginal medications included beta-blockers, calcium antagonists, nitrates.



**Figure 7.1.** Kaplan-Meier Survival Curves According to Study Group. FFR denotes fractional flow reserve, CABG coronary artery bypass surgery, MACE major adverse cardiac events, MI myocardial infarction, and PCI percutaneous coronary intervention.

Myocardial infarction occurred in 9.9% (49 patients) in the angiography-guided group and 6.1% (31 patients) in the FFR-guided group ( $P=0.03$ ). The 2-year rate of death or myocardial infarction, which was not a prespecified secondary endpoint, but is an important clinical variable, was 12.9% (64 patients) in the angiography guided group and 8.4% (43 patients) in the FFR guided group ( $P=0.02$ ). Revascularization rate was 12.7% (63 patients) in the angiography-guided group and 10.6% (54 patients) in the FFR-guided group ( $P=0.30$ ). After 2 years, MACE had occurred in 111 patients (22.4%) in the angiography-guided group and in 91 patients (17.9%) in the FFR group ( $P=0.08$ ). Event-free survival is shown by Kaplan-Meier curves (*figure 7.1*).

At 2 years the percentage of patients free from angina 76% of the patients in the angiography-guided group compared to 80% in the FFR-guided group ( $P=0.14$ ; *figure 7.2*).

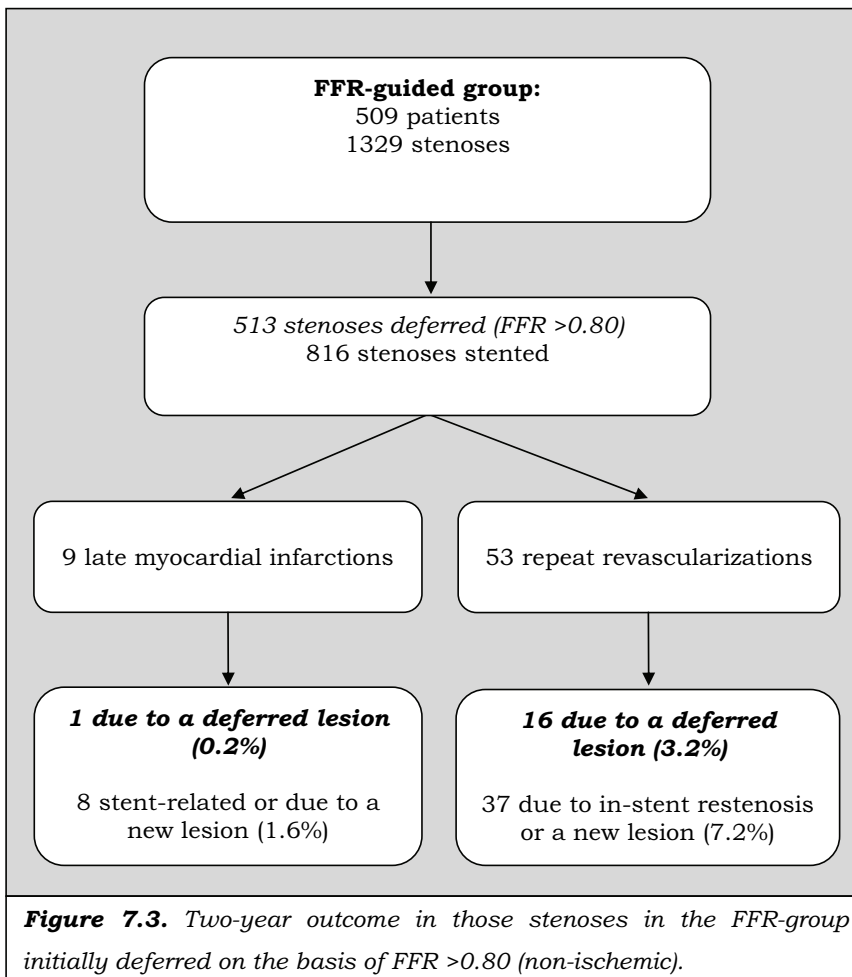


**Figure 7.2.** Percentage of patients completely free from angina at baseline, 1 year, and 2 years follow-up.

Material costs at the index procedure were 6007±2819 USD in the angiography-guided group versus 5332±3261 USD in the FFR-guided group (P<0.001).

### 7.3.4 Outcome of the deferred lesions in the FFR-guided group

In the 509 patients in the FFR-guided group, 1329 stenoses were successfully measured by FFR of which 816 were stented (FFR≤0.80) and 513 were deferred (FFR>0.80). During the follow-up of two years, in these 509 patients 9 myocardial infarctions (1.8%) occurred after the index hospitalization of which 8 (1.6%) were related to a new lesion or were stent-related, whereas only 1 myocardial infarction (0.2%) occurred in an originally deferred lesion (figure 7.3).



In 53 patients (10.4%) in the FFR-guided group one or more repeat revascularizations were performed of which 37 (7.2%) were related to a new or restenotic lesion and only 16 (3.2%) in an originally deferred lesion. The data in figure 7.3 underline the safety of an FFR-guided approach in stenting multivessel CAD.

## 7.4 Discussion

The FAME study showed that in patients with multivessel coronary artery disease, routine measurement of FFR during PCI as compared with the standard strategy of PCI guided by angiography alone, significantly reduces the rate of the composite endpoint of death, myocardial infarction or repeat revascularization at 1 year and the present paper shows that these favorable results are maintained at 2-year follow-up. Although the composite endpoint of death, myocardial infarction, or the need for revascularization was no longer significantly lower in the FFR-guided group ( $p=0.08$ ), the absolute difference in event rates was similar to what was demonstrated at one year. Perhaps more important, the combined rate of death and myocardial infarction ( $p=0.02$ ) as well as rate of myocardial infarction alone ( $p=0.03$ ) were significantly lower in patients in the FFR-guided group. The high percentage of patients free from angina was maintained at 2 years and the FFR-guided strategy resulted in a similar, if not improved, functional status. Moreover, the outcome in initially deferred lesions on the basis of  $FFR > 0.80$ , was excellent underscoring the safety of the FFR-guided approach. These results were achieved in a complex patient population with a similar event rate in the angiography-guided arm compared to other recent studies evaluating the use of drug-eluting stents in patients with multivessel coronary artery disease.<sup>13;14</sup> Moreover, in 90% of the patients assigned to the FFR-guided strategy, at least one stenosis had an  $FFR \leq 0.80$  and was stented, while more than 60% of all lesions interrogated had an ischemic  $FFR (\leq 0.80)$ . These data demonstrate that FFR was routinely used in an unselected population, and not just in

vessels with intermediate lesions where generally only 35% will have ischemic FFRs.<sup>15</sup>

In our study, the incidence of all types of adverse events was consistently reduced by roughly 30%. The absolute risk for MACE was reduced by 4.5%, which means that using FFR in 22 patients can prevent one adverse event. Routine measurement of FFR probably improved outcomes by allowing more judicious use of stents and equal relief of ischemia. It has been well known for decades that the most important prognostic factor in patients with CAD is the presence and extent of inducible ischemia.<sup>16</sup> It might be speculated that PCI of an ischemic stenosis ( $FFR \leq 0.80$ ) is beneficial overall because the risk of stent thrombosis or restenosis is outweighed by the significant reduction in the risk of ischemic events without stent placement. On the other hand, PCI of a non-ischemia-producing stenosis ( $FFR > 0.80$ ) increases the chance for an adverse event because the stent-associated risk of thrombosis and restenosis with subsequent death, myocardial infarction or repeat revascularization exceeds by far the low risk of an unstented hemodynamically non-significant stenosis.<sup>15</sup> Thus, performing PCI on all angiographic stenoses, regardless of their ischemic potential, diminishes the benefit of relieving ischemia by exposing the patient to additional stent-related risk. Whereas by systematically measuring FFR, the benefit of PCI can be maximized by accurately discriminating the lesions for which revascularization will provide the most benefit from those for which PCI may only increase risk.

#### **7.4.1 Strengths and limitations of the FAME study**

The FAME study has several specific strengths which should be mentioned. In the first place, due to the liberal inclusion and few exclusion criteria, the study truly reflects everyday practice in performing PCI in multivessel disease. This position is further corroborated by the fact that 53% percent of all screened patients were actually included in the study<sup>10</sup> and that 43 patients were included per center per year, both numbers exceptionally high for this kind of studies.<sup>14;17</sup>

Secondly, the majority of the stenoses was located in the proximal or mid-segments of the 3 major coronary arteries and in almost 40% of the patients, a

proximal LAD artery stenosis was one of the target lesions. Furthermore, patients who had undergone PCI in the past were not excluded, as is mostly the case in other studies comparing outcome after different treatment modalities in multivessel coronary artery disease.<sup>13;14;17;18</sup> Thirdly, all types of events were reduced by FFR guidance very consistently by approximately 30%. Fourth, the high percentage of patients free from angina after 2 years underlines that PCI – especially when applied appropriately – is a very effective way to eliminate ischemia and improve quality of life. Lastly, the very low late infarction and late revascularization rate of initially deferred lesions underscores the safety of an FFR-guided approach to PCI in multivessel disease.

Our results also suggest that outcomes with PCI as compared with those achieved with medical treatment, such as in the COURAGE trial <sup>17</sup>, or with coronary-artery bypass grafting, such as in the SYNTAX trial <sup>14</sup>, might be improved if the PCI is performed with FFR guidance, ensuring a functionally complete revascularization with more appropriate use of stents. A substudy of the COURAGE trial <sup>19</sup>, which demonstrated lower rates of death or myocardial infarction in those patients with the greatest relief of ischemia, further supports the concept that PCI should be guided by physiologic considerations and not solely by anatomic ones.

In this study we tried to reflect routine daily practice in multivessel PCI. Therefore, patients with left main disease were excluded, as were patients presenting with recent ST-elevation myocardial infarction in whom multivessel PCI is generally deferred. Patients in the latter group could be included from 5 days after the acute event, if at least 2 angiographically significant lesions were present.

It has been suggested that including stenoses of 50-70% in the FAME study, might have biased the outcome because many interventionalists would not stent such lesions. However, just in these lesions (1174 out of a total of 2764 stenoses) the correlation between anatomic and physiologic severity was worst. Not stenting such stenoses on the basis of the angiogram, would have left untreated a hemodynamically significant stenosis in 35% of all lesions (*see chapter 5 of this thesis*).



Finally, the current data are restricted to a 2-year follow-up. Theoretically, unstented lesions in the FFR-guided group could progress and lead to future events beyond this time horizon. However, from former studies it is known that lesions with an FFR > 0.80 - if optimally treated by medication – have an excellent prognosis with an event rate of approximately 1% per year up to 5 years after measurement.<sup>15</sup> We intend to collect data up to a follow-up of 5 years for the present study.

In *conclusion*, in patients with multivessel coronary artery disease undergoing PCI with drug-eluting stents, routine measurement of FFR as compared with PCI guided by angiography alone, results in a significant reduction of the rate of mortality and myocardial infarction at 2 years and supports the evolving paradigm of revascularization of ischemic lesions and medical treatment of non-ischemic ones.

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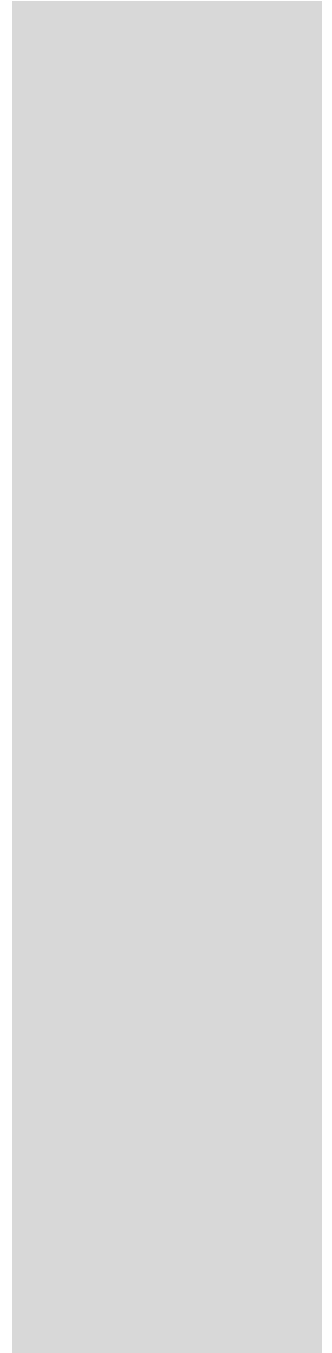
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# 8

## General Discussion

Treatment of multivessel  
coronary artery disease:  
current and future  
perspectives





## **8.1 Introduction**

Atherosclerotic narrowing of the coronary arteries, causing impairment of blood flow to the myocardium, constitutes the most common cause of death and morbidity in the United States and Europe.<sup>1,2</sup> Treatment of coronary artery disease is targeted at relieving or preventing myocardial ischemia by restoring blood flow to the myocardium, thereby improving prognosis and symptoms. Because invasive therapeutic modalities like percutaneous coronary intervention (PCI) are highly effective in relieving myocardial ischemia and the technique of PCI was significantly improved in the last two decades, its use has increased almost exponentially. Nowadays, PCI is even performed in multivessel disease, which is found in more than 50% of all patients presenting with coronary artery disease. It should be realized that information in such patients from non-invasive tests is frequently insufficient or lacking, and that – although it might be clear that stenting is indicated – it is often completely unclear which out of several stenoses are responsible for the angina, ischemia, and decreased prognosis in these patients. Practically this means that coronary angiography is still the most important tool to decide which lesions warrant revascularization in patients with multivessel disease. However, coronary angiography poorly predicts the presence of myocardial ischemia related to a particular stenosis. It is of paramount importance to understand that stenting of functionally (or hemodynamically) significant stenoses is beneficial, but placing a drug-eluting stent in stenoses that do not induce myocardial ischemia is not only ineffective, but also potentially harmful for a patient. Fortunately, selective stenting of only ischemia-producing stenoses in patients with multivessel disease is possible with the help of fractional flow reserve (FFR) measurements.

Whether a strategy of FFR-guided drug-eluting stent placement in patients with multivessel disease is superior to the common angiography-guided approach, was the central hypothesis in this thesis. To test this hypothesis the international, prospective, randomized, multicenter FAME study was designed in order to be able to randomly compare these two treatment strategies. The FAME trial showed convincingly that the routine use of FFR-guided stent placement in patients with multivessel disease reduces the rates of death, myocardial infarction, and repeat revascularization after 1 year by roughly 30% as compared to angiography-guided PCI. Also after 2 years, the reduction in events was maintained, and the FFR-guided strategy showed a significant reduction in hard clinical endpoints, as demonstrated by significant reductions in the combination of death and myocardial infarction, as well as in myocardial infarction alone. In addition, the high percentage of patients free from angina, being approximately 80% at 1 year, was maintained after 2 years of follow-up for both treatment strategies. Therefore, it can be concluded that FFR-guided stent placement in patients with multivessel disease improves prognosis significantly and is highly effective in eradicating symptoms of angina. Probably, routine measurement of FFR improved outcomes by allowing more judicious use of stents, while achieving equal relief of ischemia. Moreover, the outcome in initially deferred lesions on the basis of FFR was excellent, underscoring the safety of the FFR-guided approach.

The FAME study not only demonstrated improvements in clinical outcome and symptoms. Performing FFR-guided PCI in patients with multivessel disease also reduced the amount of contrast agent used and did not prolong procedure time. Moreover, FFR-guided PCI saves health care resources and improves health outcomes at 1 year compared to angiography-guided PCI. The cost savings occurs both at the index procedure due to a decrease in drug-eluting stent use, and it occurs during follow-up as a result of decreased repeat hospitalization and fewer major adverse cardiac events. It is unusual in modern medicine to find a new technology or treatment strategy which not only improves health, and reduces risk, but also saves costs.

Some specifically strong characteristics of the FAME study should be addressed. At first, the patient population in the FAME study was unselected

and certainly not overrepresented by only mild or moderate lesions, as reflected by the findings that the majority of patients (90%) had at least one ischemic stenosis and two-thirds of all stenoses were related to ischemia by FFR. Second, because of the limited number of in-and exclusion criteria and the fact that more than 50% of all screened patients were truly included, the FAME study truly represents the population with multivessel disease as encountered in daily practice in the cath lab. Finally, it should be highlighted that randomization was only performed after the operator had decided which stenoses were at least 50% and required stenting based on his or her clinical judgement. In this manner only those lesions were indicated for stenting which would have been stented anyway when using standard angiography alone and any bias in favour of FFR was avoided.

The shortcomings of coronary angiography, and more specifically its poor performance in detecting myocardial ischemia related to coronary stenoses, are reinforced by the findings in *chapter 5* of this thesis. In patients with multivessel CAD, whether or not taking into account clinical data, one can simply not rely on the angiogram to identify ischemia-producing lesions when assessing stenoses between 50 and 90%. Only for stenoses more than 90%, routine stenting without FFR guidance is justified because almost all of these lesions are functionally significant. It has been suggested that including stenoses of 50-70% in the FAME study, might have biased the outcome because a number of interventionalists would not stent such lesions. However, just in these lesions (1174 out of a total of 2764 stenoses) the correlation between anatomic and physiologic severity was worst. Not stenting such stenoses on the basis of the angiogram, would have left untreated a hemodynamically significant stenosis in 35% of all lesions.

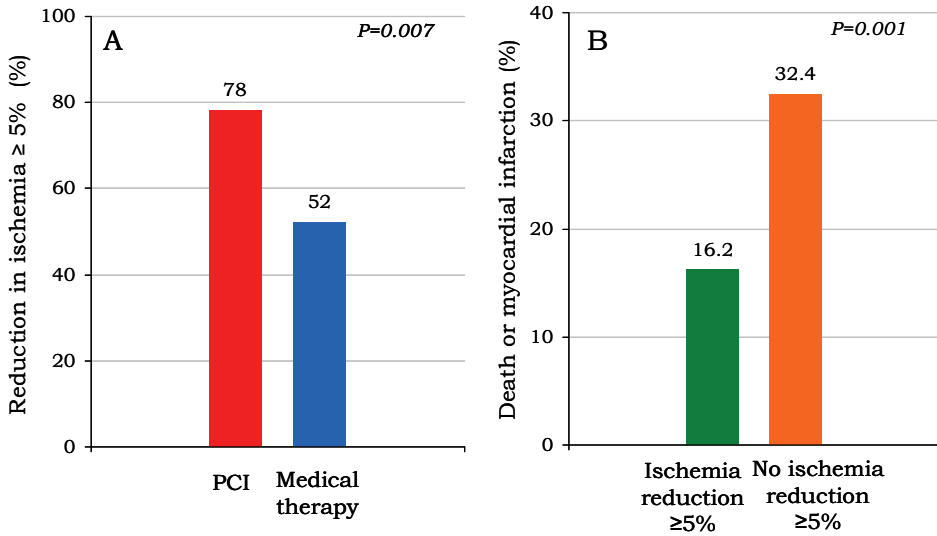


## **8.2 Treatment of multivessel disease: current and future perspectives**

Because of the high incidence, high prevalence and large impact on clinical outcome of multivessel coronary artery disease, effective treatment is mandatory. However, which patients, under which circumstances, benefit most from coronary bypass surgery (CABG), percutaneous coronary intervention (PCI), or medical therapy alone, is still subject to discussion. Many trials comparing these three treatment modalities have been conducted before the introduction of important innovations in treatment and techniques, like the optimal medical therapy as we apply in current practice, the drug-eluting stent, improvements in the technique of bypass surgery, and last but not least, the introduction of coronary pressure measurements and the concept of FFR. Recently, several large trials have been conducted, comparing the currently available treatment modalities for multivessel disease.<sup>3-5</sup> In this chapter the results of the FAME study and its implications for the treatment of multivessel disease are viewed within a wide scope, provided by other recent landmark studies in this field.

### **8.2.1 FAME: functionally complete revascularization**

PCI is increasingly being used in patients with various manifestations of coronary artery disease, and clearly improves survival and reduces recurrence of myocardial infarction in patients with acute coronary syndromes.<sup>6;7</sup> In patients with stable coronary artery disease, PCI is more effective in relieving anginal symptoms than medical therapy alone. Moreover, compared to medical therapy alone, restoring myocardial blood flow by revascularization is more effective in reducing the extent of myocardial ischemia and can even further reduce the risk of death or myocardial infarction (*figure 8.1*).<sup>8-10</sup>



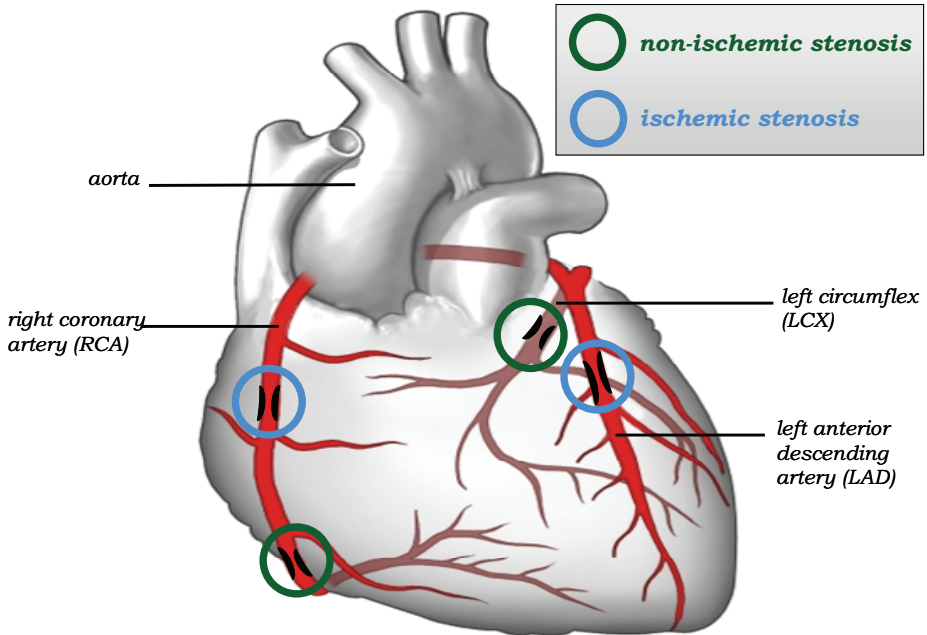
**Figure 8.1.** In the COURAGE nuclear substudy, the reduction in ischemic myocardium by medical therapy alone or PCI in addition to medical therapy was quantified by nuclear imaging tests, before and after treatment. In case moderate to severe myocardial ischemia was present before treatment, significant reduction of the amount of ischemic myocardium was achieved in 78% of patients treated with PCI and in 52% of patients treated with medical therapy alone (**panel A**). This study also showed that patients with a significant reduction ( $\geq 5\%$ ) in the amount of ischemic myocardium, had higher event-free survival rates than patients without such a significant reduction (**panel B**). (Data from Shaw et al. COURAGE trial nuclear substudy. *Circulation* 2008; 117: 1283-91; with permission of the AHA)

Although a recent meta-analysis, comprising 17 randomized trials, demonstrated improved long-term survival for PCI over medical treatment in patients with stable coronary artery disease, not all randomized trials on this subject confirm these findings.<sup>11-13</sup> However, in all these trials, PCI was guided by angiography, targeting at complete revascularization from an anatomical point of view. Such a strategy implies that not only ischemia-producing lesions, but also angiographically important, but hemodynamically non-

significant lesions are treated by stent placement. It is important to realize that stents, more specifically drug-eluting stents, and the procedure of placing a stent are not without risk for a patient.<sup>14;15</sup> It might be speculated that PCI of a stenotic lesion that is inducing ischemia is beneficial overall because the risk of stent thrombosis or restenosis is outweighed by the significantly higher risk of ischemic events without stent placement. On the other hand, PCI of a stenotic lesion that is not inducing ischemia increases the chance of an adverse event because the risk of thrombosis and restenosis associated with the placement of the stent, with the attendant risk of subsequent death, myocardial infarction, or repeat revascularization, exceeds by far the low intrinsic risk associated with a hemodynamically nonsignificant stenosis, appropriately treated by medical treatment alone.<sup>16</sup>

The FAME study hypothesized, as schematically explained in *figure 8.2*, that a selective PCI strategy of stent placement in ischemic lesions only, without the potential ‘collateral damage’ (in war terms) associated with the placement of stents in non-ischemic lesions, will improve outcome. Such a selective strategy is based upon the principle of what we propose to call functionally complete revascularization.

The FAME study included 1005 patients with multivessel coronary artery disease, comparing angiography-guided stenting with Fractional Flow Reserve (FFR)-guided stenting.<sup>5</sup> The results of this study are described in *chapters 4 and 7*. All patients were treated with optimal medical therapy in addition to stenting. In this study, FFR-guided selection of lesions for drug-eluting stent placement reduced the rates of death and myocardial infarction significantly at 1 year. This reduction in hard clinical endpoints even became more pronounced after 2 years of follow-up, whereas a mild catch-up in repeat revascularization occurred in the FFR-guided group. In the FFR-guided group, only lesions with an FFR of less than or equal to 0.80, indicating ischemia, were stented. While using less stents per patient, this FFR-guided approach resulted in similar relief of myocardial ischemia and subsequent anginal symptoms, as with the common angiography-guided approach.



**Figure 8.2.** Schematic explanation of the hypothesis of the FAME study. In this example of a patient with multivessel coronary artery disease there are 4 coronary artery stenoses present with similar angiographic severity (encircled). In this example, two of these 4 stenoses are supposed to be ischemic (blue circles) and 2 are non-ischemic (green circles). If the risk of death or myocardial infarction per year is 5% for an ischemic stenosis and 1% for a non-ischemic stenosis, this patient's risk is  $5\%+5\%+1\%+1\%=12\%$ . The 'intrinsic' risk of death or myocardial infarction for a stent (due to stent thrombosis or restenosis) is about 3% per year. If all 4 lesions in this patient would be stented, angina pectoris is effectively eliminated, but the risk for the patient to die or experience myocardial infarction in the next year would still be 12% ( $3\%+3\%+3\%+3\%=12\%$ ). If, by measuring FFR, one can specifically detect which stenoses are ischemic and which are not, and subsequently only stent the ischemic stenoses, the risk of death or myocardial infarction for this hypothetical patient would be  $1\%+1\%+3\%+3\%=8\%$ , and be reduced by 33% (from 12% to 8%), while angina pectoris is still effectively eliminated.

Therefore, the FAME study results support the strategy of functionally compete revascularization, consisting of revascularization of ischemic lesions and medical treatment of non-ischemic lesions.

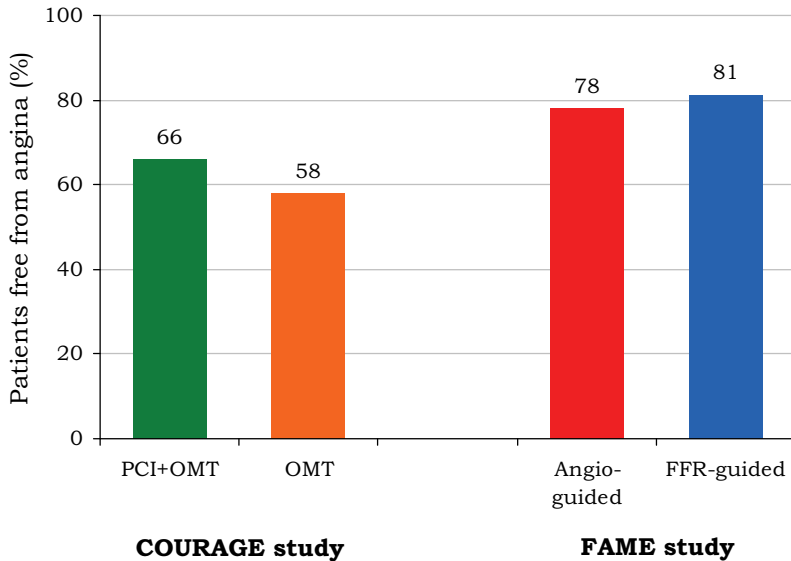
In most previous studies in this field, and particularly in the COURAGE study and the SYNTAX study, PCI was performed by angiography-guidance and compared to optimal medical treatment or CABG, respectively.<sup>3;4</sup> Hypothetically, if PCI would have been performed by FFR-guidance in both studies this might have changed the results and even conclusions of these studies significantly.

### **8.2.2 Medical therapy alone versus revascularization by PCI: COURAGE and FAME**

The COURAGE trial compared current optimal medical therapy only with PCI in addition to medical treatment. Of the 2287 patients with stable coronary artery disease in this trial, 69% had multivessel disease.<sup>19</sup> The population in this study had significantly less severe coronary artery disease as compared to the FAME study. After a median follow-up of 4.6 years, no differences were found in the primary, combined endpoint of death and non-fatal myocardial infarction between the two treatment strategies. These results suggest that an initial approach with medical therapy, also in patients with multivessel disease, is a considerable option. However, there are several issues that need to be addressed in this context.

First of all, only less than 10% of all screened patients were eventually randomized into the study. Therefore, it can be questioned if the COURAGE trial was really representative for the average patient with multivessel disease. Patients with more complex coronary artery disease or extensive myocardial ischemia could be excluded from the study 'at the discretion of the operator, creating a selection-bias in favour of medical therapy. Furthermore, the success rate of PCI in COURAGE was only 89%. This is a low percentage when compared to the high PCI success rates in the FAME study (93%) and SYNTAX study, which were accomplished in patient populations with more complex coronary artery disease.<sup>4;5</sup> Finally, even though almost 33% of all patients in the medical treatment arm of the COURAGE study were eventually treated by

PCI, the percentage of patients free from angina, both with medical therapy alone and PCI in addition to medical therapy, was much lower than in the FAME study (figure 8.3).



**Figure 8.3.** Percentage of freedom from angina, 1 year after randomization. In the FAME study 78% of the patients treated with angiography-guided PCI (red bar) were free from angina. Of the patients treated with FFR-guided PCI (blue bar), 81% were free from angina. In the COURAGE study, of the patients treated with PCI in addition to optimal medical therapy (OMT), 66% were free from angina. In the group of patients treated with OMT alone, the rate of freedom from angina was 58%. (Data from the FAME study (this thesis), and from the COURAGE study (reference 3)).

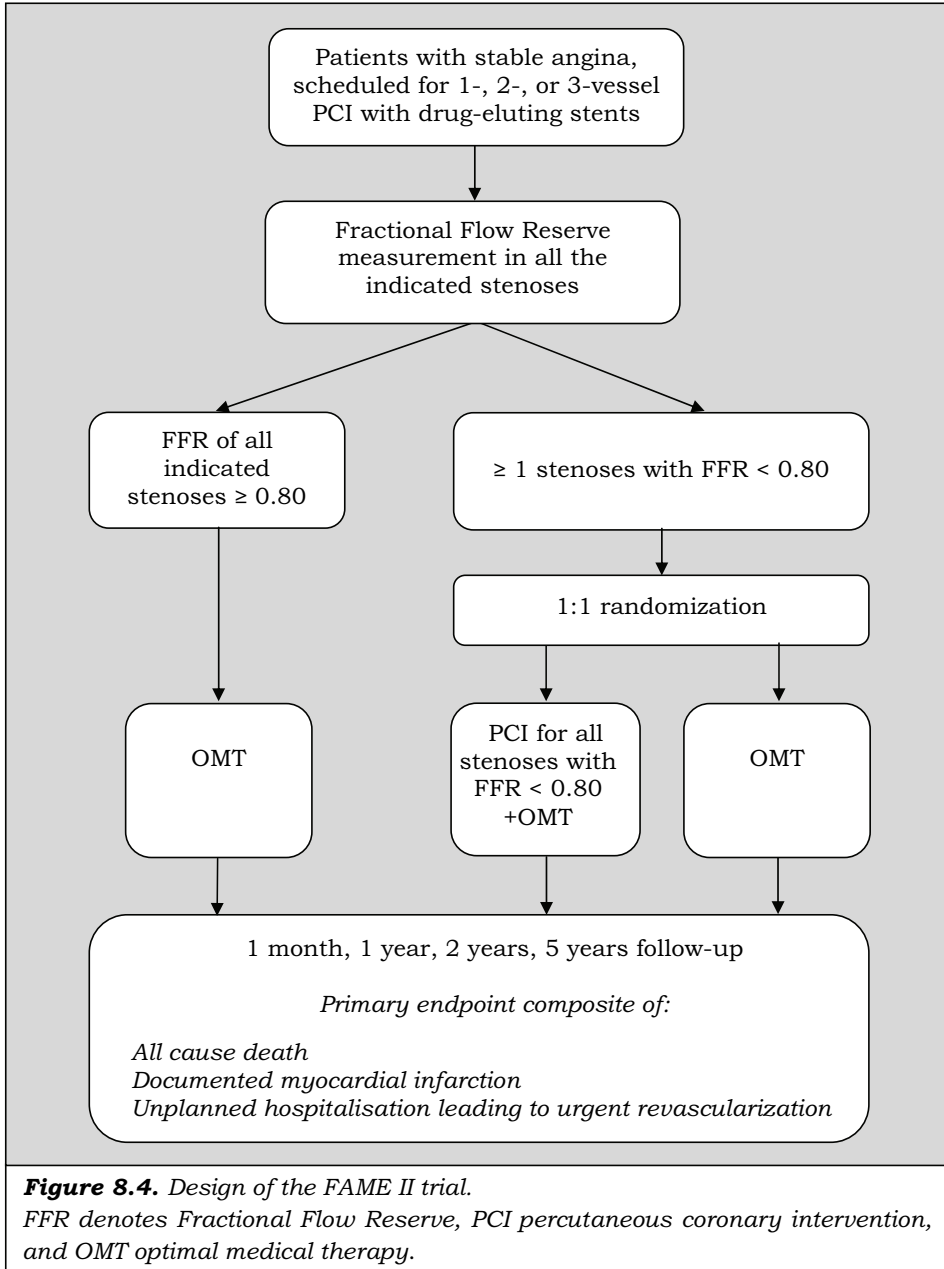
This latter criticism, together with the relatively low PCI success rate, and much less representative population in COURAGE, enforces the assumption that PCI in this study was performed in a less optimal way than in other studies on coronary revascularization. More importantly, in the COURAGE trial PCI was performed angiography-guided, whereas the FAME study showed that outcomes with PCI can be improved by 30% at least by using an FFR-guided approach instead. To hypothesize what would have happened with the results of the COURAGE study, if PCI was performed like in the FFR-guided

arm of the FAME study, is interesting, but speculative. Probably, FFR-guided revascularization would have lowered the rates of death and myocardial infarction in the PCI arm of the COURAGE study, but to what extent this change in outcome would have influenced the conclusions of this trial remains to be proven. At this moment, a couple of studies are under way, comparing optimal medical treatment with PCI with drug-eluting stents on top of medical treatment. One of these studies is the FAME II trial.

This international, multicenter study will test the hypothesis that FFR-guided PCI plus optimal medical treatment (OMT) is superior to OMT alone, in patients with stable coronary artery disease, not only with respect to functional class and total MACE rate, but also in terms of survival. The primary endpoint of the FAME II trial will be a combination of all cause death, myocardial infarction, and unplanned hospitalization leading to urgent revascularization at 1 year. Important secondary endpoints will be all individual components alone and combinations of the individual components of MACE, cost-effectiveness, the rate of non-urgent revascularization, and functional status. We intend to follow-up the patients in the trial for 5 years. The flow-chart of the FAME II trial is displayed in *figure 8.4*. The FAME II trial is expected to start inclusion in the second quarter of 2010 and will answer the question definitely, whether functionally complete revascularization by PCI is better than medical therapy alone, and whether PCI prolongs life.

### **8.2.3 Revascularization with CABG or PCI: SYNTAX and FAME**

When Andreas Gruentzig introduced PCI as an alternative treatment for coronary artery disease, it was initially applied in very selective patients with single-vessel disease. Over the years, with improving skills and techniques, and with the introduction of drug-eluting stents, the domain of PCI expanded largely to patients with more and more complex coronary artery disease.<sup>20;21</sup> Nowadays, for many interventional cardiologists, even 3-vessel disease and left main coronary disease are considered for stenting. Currently, CABG and PCI are both safe and established modalities of revascularization in patients with multivessel disease.



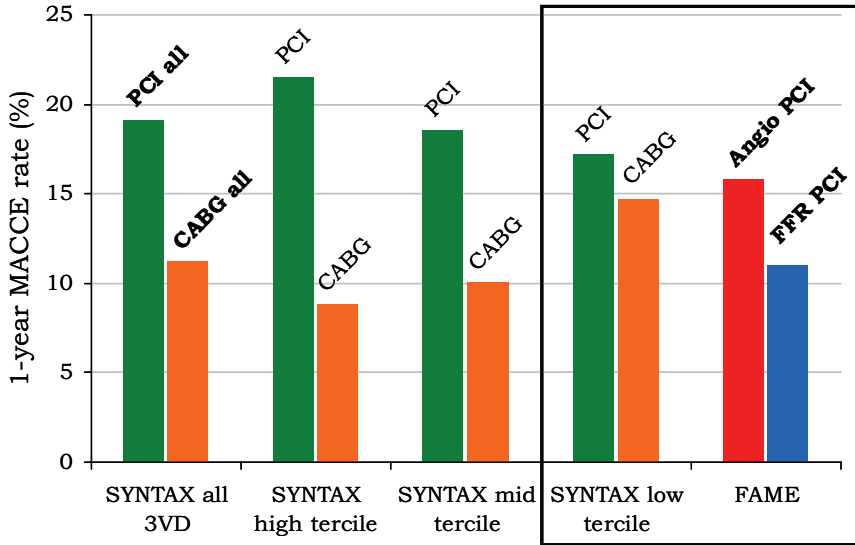
However, CABG is still regarded by many cardiologists as the preferred treatment, especially in patients with 3-vessel disease. Several large trials, comparing CABG and PCI in patients with multivessel disease have been



conducted.<sup>22-24</sup> Despite differences in their study design and differences in the included patient populations, these trials consistently showed similar survival rates for CABG and PCI, but higher rates of repeat revascularization for PCI. However, PCI was performed with bare-metal stents in many of these trials, whereas drug-eluting stents have shown to significantly reduce the rate of restenosis and subsequent necessity for repeat revascularization. Until recently, only small, or non-randomized studies compared PCI with drug-eluting stents to CABG. This was changed by the landmark SYNTAX trial. In the SYNTAX study, 1800 patients with 3-vessel coronary artery disease or left main disease were randomized to PCI with drug-eluting stents or CABG.<sup>4</sup> The primary endpoint in this study was a combination of death, myocardial infarction, stroke, and repeat revascularization. A pre-specified criterion for non-inferiority of PCI was not met. To include the SYNTAX results in the discussion about optimizing treatment of multivessel disease, we should focus on the outcome of the SYNTAX 3-vessel disease patients (N=1095).<sup>25</sup> It is of paramount importance to state that PCI in the SYNTAX study was a strategy of angiography-guided PCI. It is also important to state that, because the non-inferiority criterion for the primary endpoint was not met, comparisons of subgroups in that study are hypothesis generating only. Of the 1095 patients with 3-vessel disease in SYNTAX, 546 were treated by PCI and 549 by CABG. At 1 year, the abovementioned, combined endpoint occurred in 19.1% and 11.2%, respectively. This difference in outcome was predominantly driven by repeat revascularization, which was performed in 14.7% of the patients in the PCI-arm and in 5.4% of the patients in the CABG-arm. In other words, in patients with 3-vessel coronary artery disease, performing PCI with drug-eluting stents has CABG-like results with respect to death and myocardial infarction, but a toll of higher rates of repeat revascularization has to be paid.

The patients in SYNTAX had complex multivessel coronary artery disease as reflected by a high average SYNTAX score. The group of 3-vessel disease patients can be divided into three subgroups of SYNTAX score terciles (*figure 8.5*). The tercile with the lowest SYNTAX score, ranging from zero to 22, shows 1-year outcome results that are similar for PCI and CABG. In the groups of

patients with intermediate and high SYNTAX scores, compatible with more complex coronary artery disease, CABG results in significantly lower rates of the combined endpoint as compared to PCI. The average SYNTAX score in the FAME study is comparable to the average score in the lower tercile of 3-vessel disease patients in SYNTAX.



**Figure 8.5.** Rates of a combination of death, myocardial infarction, stroke, and repeat revascularization (MACCE) are displayed for the SYNTAX 3-vessel disease patients (green column=PCI, orange column=CABG). The 6 columns in the middle of this figure represent the patient cohorts with the highest tercile, mid tercile, and lowest tercile of SYNTAX score in the SYNTAX 3-vessel disease population, treated by either PCI (green) or CABG (orange). The FAME study angiography group results (red column) and FFR group results (blue column) were adapted according to the definitions of MACCE as used in the SYNTAX study, for comparison. Based on their average SYNTAX scores, the FAME population can best be compared to the SYNTAX 3-vessel low tercile group (black frame work). PCI denotes percutaneous coronary intervention and CABG coronary bypass surgery. The SYNTAX score is the scoring system used in the SYNTAX study to assess the extent and severity of coronary artery disease. A score of 0 indicates no angiographically significant coronary disease. There is no designated highest score (Data from the FAME study (this thesis), and from the SYNTAX study, presented by Mohr F. TCT congress, Washington, 2008.)

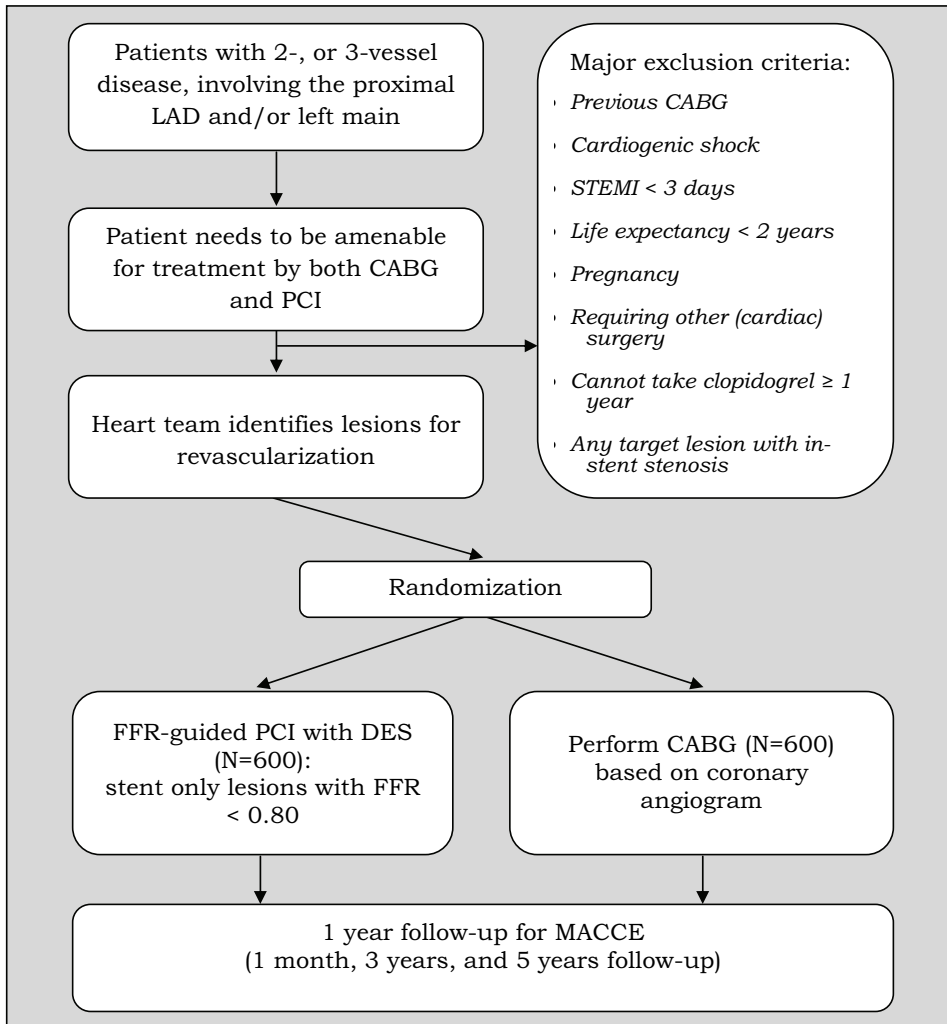
However, the FAME population had more complex patient characteristics, because also patients with previous PCI were included and a high percentage of the patients had proximal LAD disease. A speculative comparison between the 1-year outcome of the lower SYNTAX score tercile group in the SYNTAX study and the outcome of both treatment arms in FAME is displayed in figure 8.5.

As illustrated by this figure, outcome of standard angiography-guided PCI in the lower SYNTAX score tercile cohort is equal to the standard angiography-guided arm in FAME (which is very reinforcing: 'same patients, same treatment, same outcome'), whereas FFR-guided PCI improves outcome compared to both. In addition, FFR-guided PCI shows similar results with respect to outcome as for the whole group of 3-vessel disease patients in SYNTAX, treated by CABG. From this comparison, the hypothesis might be generated that in patients with multivessel coronary artery disease, FFR-guided PCI with drug-eluting stents yields an outcome truly as good as CABG in all regards. Such hypothesis is expected to be tested in the FAME III trial in the near future, of which the flow chart is presented in *figure 8.6*.

### **8.3 Synopsis and future perspectives**

COURAGE, SYNTAX and FAME have expanded the knowledge, skills, and techniques of treatment of multivessel coronary artery disease tremendously. Important factors, like the presence and extent of inducible myocardial ischemia, the severity and complexity of coronary artery disease, patient preference, and more, need to be weighed, before making a decision about which treatment modality is the best option for a specific patient. Although there will never be one simple, general, optimal treatment modality for all patients with multivessel coronary artery disease, and decision making will always need to be based upon an individual patient, the results of the FAME study implicate that outcome after PCI in patients with multivessel disease can significantly be improved with the routine use of FFR. By comparing the

results of FFR-guided PCI in FAME with the results of medical treatment and CABG from other recent important landmark trials, new research questions are generated.



**Figure 8.6.** Design of the FAME III trial.

LAD denotes left anterior descending artery, STEMI st-elevation myocardial infarction, FFR Fractional Flow Reserve, PCI percutaneous coronary intervention, CABG coronary bypass surgery, MACCE major adverse cardiac and cerebrovascular events.

The FAME II and FAME III studies have been designed to answer these questions. They will further expand our knowledge on how to optimize the treatment of patients with multivessel disease. For the time being, we believe that the FAME study has been a major contribution in this field and we would like to summarize the conclusions of this study as follows.

## 8.4 Conclusions

The main findings from this thesis can be summarized as follows:

1. In patients with multivessel coronary artery disease undergoing PCI with drug-eluting stents, routine measurement of FFR in addition to angiographic guidance, as compared with PCI guided by angiography alone, results in a significant reduction of all major adverse events at 1 year by 30-35%.
2. This is achieved without prolonging the procedure time and with less contrast agent.
3. Performing PCI guided by FFR in patients with multivessel coronary artery disease also saves health care resources compared to a traditional strategy of angiographic guidance. Thus, PCI guided by FFR in patients with multivessel disease is one of those rare situations in medicine in which a new technology not only improves outcomes, but also saves resources.
4. This advantage of an FFR-guided strategy is maintained at 2 years. Although there is a mild catch up for repeat revascularization, the difference between both strategies in the combined rate of death and myocardial infarction, and also in the rate of myocardial infarction alone, further strengthens the findings favouring the FFR-guided strategy.

5. In patients with multivessel coronary artery disease one cannot rely on the angiogram to identify ischemia-producing lesions when assessing stenoses between 50 and 90%.
  
6. Thus, the findings in this thesis support the evolving paradigm of 'functionally complete revascularization'; stenting of ischemic lesions and medical treatment of non-ischemic lesions.

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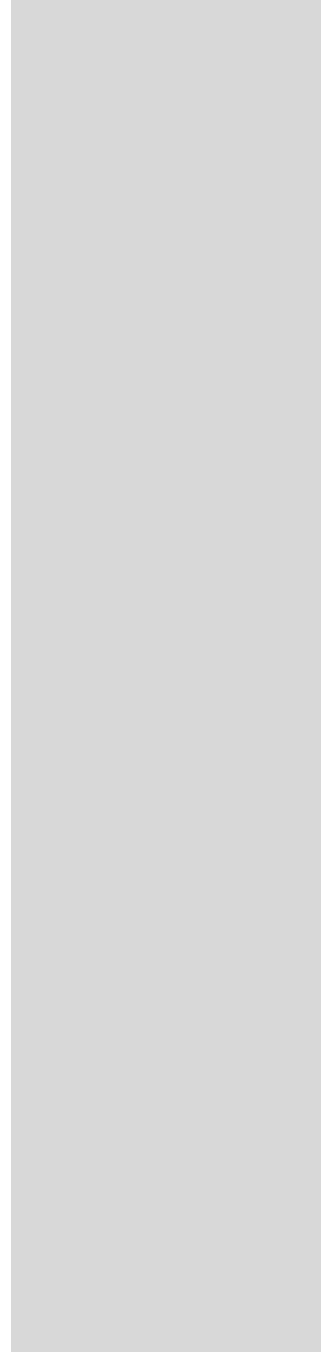
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# 9

## Summary





Coronary heart disease is a leading cause of death, morbidity, and substantial economic costs in the United States and Europe. The pathological process responsible for coronary heart disease is atherosclerosis. It can cause diffuse disease or local narrowings in the coronary arteries, which impair blood flow and therefore oxygen supply to the myocardium. In case oxygen demand by the heart exceeds oxygen supply through the narrowed coronary arteries, for instance during exercise, myocardial ischemia is induced, resulting in chest discomfort known as angina pectoris. In patients with coronary artery disease, the presence of inducible myocardial ischemia not only causes symptoms, but it also has significant prognostic implications i.e. increased chance for myocardial infarction or sudden death. Restoring blood flow and thereby oxygen supply to the myocardium relieves myocardial ischemia, improves symptoms, and reduces the risk of death and myocardial infarction. Revascularization by percutaneous coronary intervention (PCI) with stent placement or by coronary bypass surgery, should therefore be targeted at relieving myocardial ischemia. In **chapter 1**, the introduction of this thesis, it is explained that non-invasive stress testing and coronary angiography will not always provide adequate or complete information about the functional importance of coronary artery narrowings. Particularly in patients with multivessel disease, it can be difficult to determine which out of several lesions cause myocardial ischemia and therefore warrant revascularization. Because of the low restenosis rate, some investigators have proposed stenting of all intermediate lesions with drug-eluting stents, irrespective of their physiological significance. However, drug-eluting stents are expensive and are associated with potential late serious complications, occurring in 2 to 3% of stents per year. Therefore, a more judicious use of coronary stents is paramount.

The index Fractional Flow Reserve (FFR) is considered as the gold standard for the detection of myocardial ischemia, related to a particular stenosis. The concept and practical application of this diagnostic tool in the catheterization laboratory are described in **chapter 2**. By using FFR in patients with multivessel disease, the interventional cardiologist is able to accurately distinguish between coronary stenoses that induce myocardial ischemia and stenoses that do not induce myocardial ischemia. Consequently, it is possible to treat selectively the functionally significant stenoses (those responsible for reversible ischemia, also called ‘ischemic stenoses’) by stent placement and leave the non-ischemic stenoses for medical treatment in such patients. This led to the hypothesis that, compared to commonly practiced angiography-guided stenting, a strategy of FFR-guided stenting would decrease the number of stents and stent-related complications, but still result in complete relief of myocardial ischemia, thereby improving clinical outcome and decreasing health care expenditure. The ‘windtunnel’ for testing a novel strategy or treatment is a randomized trial, in which the new treatment can be tested against the treatment that is commonly used in daily practice. That was the rationale to perform the Fractional Flow Reserve versus Angiography in Multivessel Evaluation (FAME) study. **Chapter 3** describes the design of the FAME study. This international, multicenter study compares angiography-guided PCI with FFR-guided PCI in patients with multivessel coronary disease. In both treatment arms the coronary intervention is performed with drug-eluting stents. In little more than a year, 1005 patients were randomized in 20 centers in Europe and in the USA. Only a limited number of in- and exclusion criteria were applied and an exceptionally high percentage of 53% of all screened patients entered into the study. Among others, these two factors paved the way for an unselected patient population with complex multivessel coronary artery disease, truly reflecting daily practice as much as possible. The results of the FAME study after 1 year of follow-up are discussed in **chapter 4**, and showed a significant reduction in the primary, combined endpoint of death, myocardial infarction, and repeat revascularization for the FFR-guided strategy. In fact not only the primary endpoint, but also the rates of all its individual components were decreased consistently by roughly 30%

with this strategy. Moreover, while using less stents per patient, the FFR-guided approach results in a similar relief of myocardial ischemia and subsequent anginal symptoms as with the common angiography-guided approach. It is important to stress that the use of FFR in these patients did not prolong procedure time and even reduced the amount of contrast agent used.

In **chapter 5**, an in-depth analysis of the patients in the FFR-guided treatment arm of the FAME study confirms the poor performance of coronary angiography in predicting the presence of inducible myocardial ischemia, related to a coronary stenosis. Generally, coronary narrowings with a stenosis percentage of 50% or more of the vessel diameter on the angiogram are defined as clinically significant and are therefore revascularized. However, this analysis shows that of all coronary stenoses with an angiographic severity of 50-70%, two-thirds are functionally non-significant and only one-third is functionally significant. Even in more severe stenoses between 71 and 90% angiographic stenosis severity, 20% of such lesions are not functionally significant. Therefore, in patients with multivessel CAD, one cannot rely on the angiogram to identify ischemia-producing lesions when assessing stenoses between 50 and 90%. In fact, this is probably one of the key explanations for the superior clinical outcome of FFR-guided stenting in the FAME study; by selectively stenting ischemic stenoses, 'collateral damage' from unnecessary stenting of non-ischemic coronary stenoses is prevented, with similar relief of myocardial ischemia as with angiography-guided stenting.

Coronary heart disease not only affects clinical outcome, but it also consumes large parts of health care budgets. An extensive economic evaluation of the FAME study is described in **chapter 6**. This evaluation shows that a FFR-guided strategy also saves health care resources and improves health outcomes at 1 year. The cost savings occur at the index procedure due to a decrease in drug-eluting stent use, and during follow-up as a result of a decrease in events and re-hospitalization. Combining the economic and clinical outcome of the FAME study reveals that FFR-guided placement of drug-eluting stents in patients with multivessel coronary disease is one of

those rare situations in which a new technology not only improves outcomes, but also saves resources.

After 2 years of follow-up in the FAME study, the favorable results of an FFR-guided strategy were maintained, as discussed in **chapter 7**. The combination of death and myocardial infarction, but also the rate of myocardial infarction alone, both very important endpoints from a clinical and patient's perspective, were significantly reduced at 2 years when compared to the common angiography-guided approach. The high percentage of patients free from anginal symptoms was maintained after 2 years for both treatment strategies. This chapter also describes the outcome of the 513 stenoses in the FFR-guided treatment arm, that were deferred from stenting, because they were functionally non-significant at the index procedure. After 2 years, only 0.2% of the deferred stenoses led to a myocardial infarction and only 3.2% of these stenoses needed revascularization because of progression of atherosclerosis. These findings confirm the excellent long-term safety of deferral of non-ischemic stenoses from stenting. The 2-year results of the FAME study show durability of the improved outcomes noted at 1 year. Thereby they continue to support the evolving paradigm of functionally complete revascularization, or in other words revascularization of ischemic stenoses and medical treatment of non-ischemic stenoses. It is intended to collect data up to a follow-up of 5 years for the FAME study

In **chapter 8**, the findings in this thesis are presented in a general discussion and the following conclusions are drawn:

1. In patients with multivessel coronary artery disease undergoing PCI with drug-eluting stents, routine measurement of FFR in addition to angiographic guidance, as compared with PCI guided by angiography alone, results in a significant reduction of all major adverse events at 1 year by 30-35%.

2. This is achieved without prolonging the procedure time and with less contrast agent.
3. Performing PCI guided by FFR in patients with multivessel coronary artery disease also saves health care resources and improves health outcomes at 1 year compared to a traditional strategy of angiographic guidance. Thus, PCI guided by FFR in patients with multivessel disease is one of those rare situations in medicine in which a new technology not only improves outcomes, but also saves resources.
4. This advantage of an FFR-guided strategy is maintained at 2 years. Although there is a mild catch up for repeat revascularization, the difference between both strategies in the combined rate of death and myocardial infarction, and also in the rate of myocardial infarction alone, further increases in favour of the FFR-guided strategy.
5. In patients with multivessel coronary artery disease one cannot rely on the angiogram to identify ischemia-producing lesions when assessing stenoses between 50 and 90%.
6. The findings in this thesis support the evolving paradigm of 'functionally complete revascularization', i.e. stenting of ischemic lesions and medical treatment of non-ischemic lesions.

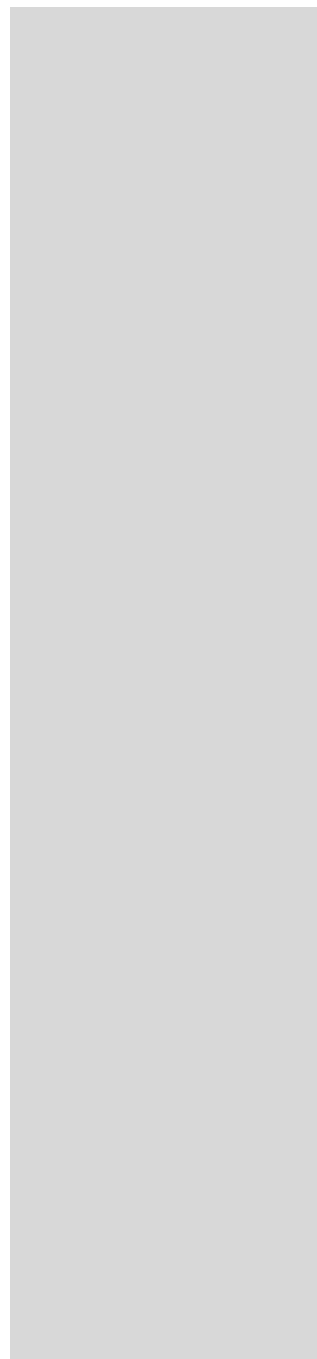
Finally, the FAME study and its implications for the treatment of multivessel coronary disease are discussed within a wide scope in **chapter 8** and **appendix I**, and reflected to other recent landmark studies in the field of treatment of patients with multivessel coronary artery disease: the COURAGE and the SYNTAX trial. These recent, large trials compared PCI with medical therapy and coronary bypass surgery, respectively. In the COURAGE trial PCI did not show better results than medical therapy, and in the SYNTAX trial PCI



was inferior to coronary bypass surgery. However, PCI in those trials was performed with the standard angiography-guided strategy and not with an FFR-guided strategy. Although great caution should be taken when comparing different studies, due to the many similarities in patient populations and characteristics, it might be speculated that the results and even conclusions of these studies might have significantly changed in favour of PCI if performed with the guidance of FFR, like in the FAME study (**figure 8.5**). To prove this standpoint definitely, this theme has resulted in starting two new prospective, large, multicenter trials to show the superiority of FFR-guided PCI over medical treatment (FAME II study) and equality to coronary bypass surgery in patients with multivessel coronary disease (FAME III study). With the unequalled support of the excellent group of investigators and institutions who performed the FAME study, an extensive but exciting future task is waiting for us. In **appendix II** of this thesis, all authors and members of the FAME Study Group, and their affiliations are listed.

# 10

Samenvatting





Hart- en vaatziekten en met name vernauwingen in de kransslagaders van het hart, zijn een belangrijke oorzaak van sterfte en morbiditeit en leiden tot substantiële economische lasten in de westerse wereld. Het pathologische proces dat verantwoordelijk is voor het ontstaan van kransslagadervernauwingen wordt atherosclerose genoemd. Atherosclerose leidt tot diffuse of lokale vernauwing in de kransslagaders, waardoor de bloedstroom en diens gevolgde zuurstoftoevoer naar de hartspier (het myocard) afneemt. Dit wordt met name manifest tijdens inspanning of in andere situaties waarin de zuurstofbehoefte van het myocard toeneemt en er dus een verstoring plaats vindt in de balans tussen zuurstofvraag en -aanbod van het myocard. Indien, tijdens inspanning, de zuurstofvraag van het hart het door de vernauwde kransslagaders aangevoerde zuurstofaanbod overstijgt, ontstaat zuurstofgebrek van het hart (myocardischemie), hetgeen resulteert in pijn op de borst (angina pectoris). Induceerbare myocardischemie bij patiënten met kransslagadervernauwingen leidt niet alleen tot klachten, maar verhoogt ook de kans op het krijgen van een myocardinfarct of voortijdig overlijden. Omgekeerd leidt het herstellen van de bloedstroom en zuurstoftoevoer door de kransslagaders tot het opheffen van myocardischemie, waardoor klachten van pijn op de borst verminderen en de kans op overlijden of myocardinfarct afneemt. Revascularisatie door middel van een percutane coronaire interventie (PCI) met stentplaatsing of door middel van bypass chirurgie is derhalve gericht op het opheffen van myocardischemie.

In **hoofdstuk 1**, de inleiding van dit proefschrift, wordt uitgelegd dat reguliere non-invasieve onderzoeksmethoden naar myocardischemie (zoals coronairangiografie) niet altijd adequate of complete informatie geven over de functionele betekenis van kransslagadervernauwingen. Met name bij patiënten met vernauwingen in meerdere kransslagaders (meervatslijden) kan het

moeilijk zijn om te bepalen welke vernauwingen verantwoordelijk zijn voor myocardischemie en dus in aanmerking komen voor revascularisatie. Omwille van de lage kans op in-stent restenose van een moderne drug-eluting stent, hebben sommige onderzoekers voorgesteld om alle angiografische vernauwingen van meer dan 50%, ongeacht de functionele ernst, te behandelen met zo'n stent. Drug-eluting stents zijn echter duur en veroorzaken potentiële, ernstige complicaties die optreden in minimaal 2 tot 3% van de stents per jaar. Een meer afgewogen gebruik van stents is derhalve van groot belang.

De index fractionele flow reserve (FFR) wordt hedentendage gezien als de 'gouden standaard' voor het vaststellen van myocardischemie ten gevolge van een vernauwing in de kransslagaders. Het concept en de praktische toepasbaarheid van deze diagnostische methode in de catheterisatiekamer wordt besproken in **hoofdstuk 2** van dit proefschrift.

Het gebruik van FFR in patiënten met meervatslijden stelt de interventiecardioloog in staat om op een betrouwbare wijze onderscheid te maken tussen vernauwingen die zuurstofgebrek van het hart kunnen veroorzaken en vernauwingen die dat niet doen. Met die door FFR verkregen informatie is het in dergelijke patiënten vervolgens mogelijk om, op selectieve wijze, de functioneel of hemodynamisch belangrijke vernauwingen (die verantwoordelijk zijn voor zuurstofgebreken, ook wel ischemische vernauwingen worden genoemd) te behandelen door het plaatsen van een stent, terwijl de niet-ischemische vernauwingen behandeld kunnen worden met uitsluitend medicijnen. Dit heeft geleid tot de hypothese dat een op FFR gebaseerde strategie van stentplaatsing, vergeleken met de gangbare op angiografie gebaseerde strategie, tot betere uitkomsten van PCI zou leiden in patiënten met meervatslijden. Een op FFR gebaseerde strategie zou resulteren in complete opheffing van myocardischemie, maar met plaatsing van minder stents en daardoor minder stent-gerelateerde complicaties. Dit zou dan lijden tot een verbetering van de klinische uitkomst en ook een afname van de kosten in de gezondheidszorg.

De windtunnel voor het testen van een nieuwe strategie of behandeling is een gerandomiseerde studie, waarin de nieuwe behandeling afgezet kan worden

tegen de tot dan toe in de dagelijkse praktijk gebruikelijke manier van behandelen. Dit was dan ook de reden om de 'Fractional Flow Reserve versus Angiography in Multivessel Evaluation' (FAME) studie te verrichten. In **hoofdstuk 3** wordt het ontwerp van de FAME studie beschreven. Deze internationale, multicenter studie vergelijkt angiografie-geleide stentplaatsing met FFR-geleide stentplaatsing in patiënten met meervatslijden. In beide behandelgroepen van deze studie werd de coronaire interventie uitgevoerd met drug-eluting stents. In 20 centra in europa en de verenigde staten werden 1005 patiënten gerandomiseerd in een periode van iets meer dan een jaar. Voor deze studie golden eenvoudige in- en exclusiecriteria, waardoor een bijzonder hoog percentage van 53% van alle gescreende patiënten kon worden gerandomiseerd voor deelname in de studie. Daardoor bevat de FAME studie een voor de dagelijkse praktijk zo representatief mogelijke patiëntenpopulatie met meervatscoronairlijden en zijn de resultaten breed toepasbaar. De resultaten van de FAME studie na 1 jaar follow-up worden beschreven in **hoofdstuk 4** en tonen een significante afname van het gecombineerde primaire eindpunt van dood, myocardinfarct en (hernieuwde) revascularisatie in de groep die op geleide van FFR werd behandeld. Ook was er met de FFR-geleide strategie sprake van een consistente afname van alle individuele componenten van het primaire eindpunt met ongeveer 30%. En hoewel er met de FFR-geleide strategie minder stents per patiënt worden geplaatst, is er blijkbaar sprake van een afname van myocardischemie en klachten die tenminste vergelijkbaar is met de gangbare angiografie-geleide strategie. Van belang is daarbij dat het gebruik van FFR in patiënten met meervatslijden niet leidde tot een toename in de tijdsduur van de procedure en dat de hoeveelheid benodigd contrastmiddel zelfs werd verlaagd. Ook de lengte van de ziekenhuisopname was korter dan bij de traditionele manier van behandelen. In **hoofdstuk 5** wordt een analyse beschreven over de waarde van de klassieke coronairangiografie om te kunnen voorspellen of een vernauwing gepaard gaat met induceerbaar zuurstofgebrek. Het blijkt dat het angiogram daartoe een slecht middel is. Dit heeft belangrijke klinische consequenties. Het is gebruikelijk dat kransslagadervernauwingen met een vernauwing van meer dan 50% ten opzichte van de referentiediameter van het bloedvat worden

gedefinieerd als klinisch significant en derhalve worden gestent. De analyse in hoofdstuk 5 toont echter dat van alle vernauwingen met een stenosepercentage tussen de 50 en 70%, tweederde functioneel niet significant is en slechts een derde wel functioneel significant is. Zelfs in de categorie van angiografisch ernstigere vernauwingen, tussen de 71 en 90%, is 20% functioneel niet significant. Als het gaat om vernauwingen tussen de 50 en 90% kunnen we dus niet vertrouwen op het coronairangiogram om ischemische vernauwingen te onderscheiden. Dit is waarschijnlijk ook een van de belangrijkste verklaringen voor de superieure klinische uitkomst van FFR-geleide revascularisatie; door uitsluitend ischemische vernauwingen selectief te stenten wordt iatrogene schade ten gevolge van het onnodig stenten van niet-ischemische vernauwingen voorkomen, terwijl er een vergelijkbare afname van myocardischemie wordt bereikt met tenminste evenveel verbetering van de functionele klasse van de patiënt.

Kransslagadervernauwingen hebben niet alleen een effect op prognose, maar zijn ook verantwoordelijk voor een aanzienlijk deel van het gezondheidszorgbudget. Een uitgebreide economische analyse op basis van de 1-jaars resultaten van de FAME studie wordt beschreven in **hoofdstuk 6**. De resultaten van deze analyse tonen dat een FFR-geleide PCI-strategie leidt tot een aanzienlijke besparing van kosten. Deze kostenbesparing bestaat uit twee componenten. Allereerst is er bij de index-procedure sprake van een daling in de kosten tengevolge van het gebruik van minder stents. Ten tweede is er gedurende de follow-up ook een kostenbesparing ten gevolge van minder myocardinfarcten en revascularisaties en daaraan gerelateerde heropnamen in het ziekenhuis. Plaatsing van drug-eluting stents in patiënten met meervatslijden op geleide van FFR is blijkbaar een van de zeldzame nieuwe behandelmethodes in de moderne geneeskunde die niet alleen beter, maar ook nog eens goedkoper zijn.

In **hoofdstuk 7** worden de 2-jaars resultaten van de FAME-studie beschreven. De gunstige resultaten van op FFR meting gebaseerde behandeling blijven ook na 2 jaar bestaan. De combinatie van dood en myocardinfarct, maar ook myocardinfarct alleen, kwamen significant minder vaak voor in vergelijking met de op angiografie gebaseerde behandeling. Het zeer hoge percentage

patiënten zonder symptomen van angina pectoris na 1 jaar bleef in beide behandelarmen gehandhaafd na 2 jaar. Dit hoofdstuk beschrijft ook de uitkomst van de 513 vernauwingen in de FFR-geleide arm die niet gestent werden tijdens de index-procedure, omdat ze niet functioneel significant waren. Na 2 jaar veroorzaakte slechts 0.2% van deze vernauwingen een myocardinfarct en was in slechts 3.2% van deze vernauwingen alsnog stentplaatsing nodig omwille van progressie van atherosclerose. Deze bevindingen ondersteunen de grote veiligheid op lange termijn van het niet stenten van niet-ischemische vernauwingen en het behandelen van dergelijke vernauwingen met (preventieve) medicamenten als aspirine en statines. De 2-jaars resultaten van de FAME studie ondersteunen het paradigma van functioneel complete revascularisatie, of met andere woorden, revascularisatie van ischemische vernauwingen en medicamenteuze therapie van niet-ischemische vernauwingen. Het is de bedoeling om gegevens van de patiënten in de FAME studie te blijven verzamelen tot een termijn van 5 jaar na inclusie. Tot slot worden in **hoofdstuk 8** en in **appendix I** de implicaties van de resultaten van de FAME studie voor de behandeling van patiënten met meervatslijden besproken in het licht van andere recente studies op dit gebied: de COURAGE studie en de SYNTAX studie. Deze recente grote studies vergeleken stenten met medicamenteuze therapie en met bypass chirurgie. In de COURAGE studie leidde PCI niet tot betere resultaten dan medicamenteuze therapie en in de SYNTAX studie bleek PCI inferieur aan bypass chirurgie. PCI werd in deze studies echter op basis van het traditioneel angiogram uitgevoerd en niet op geleide van FFR. Men dient voorzichtig te zijn als het gaat om het vergelijken van de resultaten van verschillende studies. Echter, omwille van de vele overeenkomsten in de patiëntenpopulaties en overige karakteristieken, kan men speculeren dat de resultaten en mogelijk zelfs conclusies van deze studies significant anders hadden kunnen zijn ten gunste van PCI, als deze, zoals in de FAME studie, op geleide van FFR was uitgevoerd (figuur 8.4). Om deze hypothese definitief te bewijzen, heeft dit proefschrift geresulteerd in de opzet van twee nieuwe, prospectieve, gandomiseerde, multicenter studies om, in patiënten met meervatslijden, de superioriteit aan te tonen van FFR-geleide PCI ten opzichte van respectievelijk medicamenteuze therapie enerzijds



(FAME II studie), en de gelijkwaardigheid van FFR-geleide PCI ten opzichte van bypass chirurgie anderzijds (FAME III studie). Met de ongeëvenaarde steun van de uitmuntende groep van onderzoekers en instituten die de FAME studie hebben uitgevoerd, ligt dus een mooie nieuwe uitdaging voor ons. **Appendix II** van dit proefschrift bevat tot slot een lijst van alle centra en onderzoekers van de 'FAME Study Group'.

De volgende conclusies kunnen op basis van de studies in dit proefschrift worden getrokken:

1. Het routinematig meten van FFR in patiënten met meervatscoronairlijden, behandeld met drug-eluting stents leidt, in vergelijking met angiografie-geleide PCI, tot een significante afname na 1 jaar van alle belangrijke klinische eindpunten met 30-35%. Dit geldt voor sterfte, de kans op een hartinfarct en de kans op (hernieuwde) revascularisatie.
2. Deze resultaten worden bereikt met minder contrastmiddel en zonder een toename van de tijdsduur die nodig is voor het verrichten van de procedure.
3. Het verrichten van PCI in patiënten met meervatscoronairlijden op basis van FFR metingen resulteert ook tot een besparing in de kosten van de behandeling (zowel tijdens de initiële behandeling als in het jaar daarna).
4. Het voordeel van de op FFR gebaseerde strategie is ook na 2 jaar nog aanwezig. Hoewel er een lichte afname is in het verschil in (hernieuwde) revascularisatie, is het verschil in optreden van de combinatie van dood en myocardinfarct en ook van myocardinfarct alleen, verder toegenomen in het voordeel van de FFR-geleide strategie.

5. Om ischemische vernauwingen in patiënten met meervatscoronairlijden te herkennen, kan men in het geval van vernauwingen met een ernst tussen de 50 en 90%, niet vertrouwen op het angiogram.
  
6. De bevindingen in dit proefschrift ondersteunen het paradigma van 'functioneel complete revascularisatie' d.w.z. het stenten van ischemische vernauwingen en medicamenteuze behandeling van niet-ischemische vernauwingen.



# Appendix I

## Correspondence: Fractional Flow Reserve for Guiding PCI

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*Somjot S. Brar, M.D.*  
*William A. Gray, M.D.*

*Columbia University*  
*Medical Center*  
*New York, NY, USA*

*Nagapradeep Nagajothi,*  
*M.D.*  
*Rohit Arora, M.D.*  
*Sandeep Khosla, M.D.*

*Rosalind Franklin*  
*University of Medicine and*  
*Science*  
*North Chicago, IL, USA*

*Scot Garg, M.B., Ch.B.†*  
*Tessa Rademaker, M.Sc.#*  
*Patrick Serruys, M.D.,*  
*Ph.D.†*

*†Erasmus Medical Center,*  
*Rotterdam*

*#Cardialysis, Rotterdam,*  
*The Netherlands*

*Nico H.J. Pijls, M.D.,*  
*Ph.D.\**  
*Pim A.L. Tonino, M.D.\**  
*William F. Fearon, M.D.\**

*\*Affiliations of all authors and all*  
*members of the FAME Study*  
*Investigator Group are listed in*  
*appendix II of this thesis*



**Correspondence:**

*To the Editor:* Tonino et al.<sup>1</sup> report on the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study (ClinicalTrials.gov number, NCT00267774), which compared an angiography-only strategy with routine measurement of fractional flow reserve (FFR) in addition to angiography in patients with multivessel disease who were undergoing percutaneous coronary intervention (PCI). The authors report a lower 1-year rate of adverse events with angiography guided by FFR measurement. Although their findings provide an encouraging perspective on the relative safety of selective stenting with the use of FFR measurement, some aspects of the trial design may have led to a bias in favor of the FFR group. Forty-one percent of the lesions in the angiography group and 44% of those in the FFR group were of intermediate severity, as defined by 50 to 70% occlusion on visual estimation. On the basis of quantitative coronary analysis, the mean extent of stenosis was 61% or less (intermediate severity). If the FFR evaluation was negative in a sizable proportion of lesions of intermediate severity, the protocol-mandated stenting of these stenoses in the angiography group probably accounted for the higher use of stents and increased costs and therefore the differences in clinical outcomes, primarily driven by early, periprocedural infarctions. Thus, the results of this trial may not have elucidated the role of FFR measurement in multivessel disease but instead may have reaffirmed that mandated stenting of stenoses of intermediate severity is neither cost-effective nor associated with improved outcomes.

*Somjot S. Brar, M.D.*

*William A. Gray, M.D.*

*To the Editor:* In the FAME study, 40.7% of lesions in the angiography group and 44.1% in the FFR group had stenosis of 50 to 70%. Moreover, more than 55% of patients had class I or II angina. In this study, noninvasive evidence of inducible ischemia was not a prerequisite for coronary angiography.<sup>2</sup> In the absence of demonstrable ischemia or a large area of at-risk myocardium, PCI is not recommended for these lesions.<sup>3-5</sup> It is likely that most of the 513 lesions in the FFR group that did not warrant PCI (37.0%) were from the 44.1% of lesions with stenosis of 50 to 70% (624 lesions). Routine use of PCI for these lesions in the angiography group could have contributed to the worse outcomes in that group. A larger study specifically evaluating the FFR strategy in lesions of more than 70% stenosis or at least an analysis of this subgroup in the FAME study is needed before one concludes that routine use of FFR measurement in all lesions is beneficial. The angiographic details of the lesions in the FFR group that did not warrant PCI would also be useful information.

*Nagapradeep Nagajothi, M.D.*

*Rohit Arora, M.D.*

*Sandeep Khosla, M.D.*

*To the Editor:* Tonino et al. show the importance of FFR in patients with multivessel coronary disease, continuing the long-standing debate regarding the question of whether all coronary-artery lesions require immediate angioplasty. Previously, we were encouraged by the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study (NCT00007657), which showed that it is safe to defer coronary angioplasty until symptoms cannot be controlled with optimal medical therapy.<sup>6</sup>

Although the current study adds compelling arguments to the ongoing discussion, we are surprised by the absence of any reference to the patient outcomes in the Arterial Revascularization Therapies Study Part II (ARTS II)

(NCT00235170).<sup>7</sup> Table 1 shows that a population with a similar, if not higher, risk was enrolled in ARTS II, as compared with the population in the FAME study; however, the rates of death, repeat revascularization, and myocardial infarction were all higher in the FAME angiography group than in ARTS II (3.0% vs. 1.0%, 9.5% vs. 8.5%, and 8.7% vs. 3.3%, respectively).

**Table 1.** Patient and Procedural Characteristics in the ARTS II and FAME Studies.\*

	ARTS II N= 607	FAME	
		Angio-guided PCI N= 496	FFR-guided PCI N= 509
Mean age – yr.	63	64.2	64.6
Male sex (%)	77	72.6	75.4
Previous myocardial infarction (%)	34	36.3	36.7
Diabetes mellitus (%)	26	25.2	24.2
Unstable angina (%)	36	35.8	29.4
Mean ejection fraction (%)	60	57.1	57.2
Mean Syntax score <sup>†</sup>	20.7	14.5	14.5
Mean no. of lesions/pt.	3.7	2.7	2.8
Mean no. of stents/pt.	3.7	2.7	1.9
Mean total length of stents/pt. (mm)	72.5	51.9	37.9
Mean procedural duration (min)	85	70	71
Mean hospital stay (days)	3.4	3.7	3.4

\*ARTS II denotes Arterial Revascularization Therapies Study Part II, FAME Fractional Flow Reserve versus Angiography for Multivessel Evaluation, FFR fractional flow reserve, and SYNTAX Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. <sup>†</sup> Higher SYNTAX scores indicate a greater extent and severity of coronary disease; there is no designated highest score.

This group of patients receiving the standard intervention in the FAME study may just have been unfortunate; however, the authors' conclusions might



have been significantly different had the outcomes in this group been similar to these published results.

*Scot Garg, M.B., Ch.B.*

*Tessa Rademaker, M.Sc.*

*Patrick Serruys, M.D., Ph.D.*

*The authors reply:* In response to the comments by Brar and Gray and by Nagajothi et al.: we do not believe that inclusion of lesions involving stenosis of 50 to 70% created a bias in favor of the FFR group. The FAME protocol directed the investigator to stent a lesion if it involved stenosis of at least 50% and if the investigator thought that stenting was warranted on the basis of the available clinical data, including the results of noninvasive testing, if performed. The protocol did not mandate treatment of all stenoses of 50% or more. Lesions to be stented had to be indicated before randomization, in order to avoid any possible bias. Currently, some interventionalists do not stent stenoses of 50 to 70% routinely, but many others do. The FAME study showed that without measuring FFR, the first group of operators neglects to revascularize 40% of ischemia-producing lesions in patients with multivessel coronary disease, and the second group unnecessarily stents 60% of such lesions. The FAME study provides strong evidence that coronary angiography and clinical data alone are not sufficient for decision making about appropriate revascularization in patients with multivessel disease.

The difference in clinical outcome between the FAME study groups was not driven by small periprocedural infarctions (creatinine kinase MB fraction, 3 to 5 times the normal value). The rates of periprocedural infarction were 3.2% and 2.4% in the angiography and FFR groups, respectively, and did not significantly affect the statistical difference in outcome between the two groups.

**Table 2.** Patient characteristics and outcome in SYNTAX and FAME.\*

	SYNTAX 3-VESSEL DISEASE		FAME	
	Angio-guided PCI N= 546	CABG N= 549	Angio-guided PCI N= 496	FFR-guided PCI N= 509
Age – yr.	65.1	64.5	64.2	64.6
Previous MI (%)	34.2	39.1	36.3	36.7
Previous PCI (%)	0	0	26.0	28.7
Diabetes (%)	unknown	unknown	25.2	24.2
Unstable angina (%)	27.8	27.3	35.8	29.4
Euroscore	3.7	3.7	3.7	3.8
Syntax score			14.5	14.5
Lower tercile	17.3	17.3		
Middle tercile	27.4	27.5		
Higher tercile	39.8	41.0		
MACCE *				
All patients (%)	19.1	11.2	15.8	11.0
MACCE per SYNTAX score				
Lower tercile (%)	17.2	14.7		
Middle tercile (%)	18.6	10.1		
Higher tercile (%)	21.5	8.8		
Death and MI (%) *	7.9	6.4	7.9	5.1
Hospital stay - days	3.5	9.3	3.7	3.4

\* To make event rates comparable, the definitions of major adverse cardiac and cerebrovascular events are similar to those used in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial. Higher SYNTAX scores indicate a greater extent and severity of coronary disease, with a score of 14.5 indicating rather extensive disease; there is no designated highest score. CABG denotes coronary-artery bypass grafting, EuroSCORE European System for Cardiac Operative Risk Evaluation, FAME Fractional Flow Reserve versus Angiography for Multivessel Evaluation, MI myocardial infarction, and PCI percutaneous coronary intervention.

In response to the question posed by Garg et al.: we believe that it makes little sense to compare the randomized FAME study with the ARTS II registry, which excluded vessels smaller than 2.5 mm and patients with previous PCI.<sup>7</sup> It seems more appropriate to compare FAME with the only other large, randomized, controlled trial of drug-eluting stents for the treatment of multivessel disease — that is, the recently published Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) study.<sup>8</sup> In the SYNTAX study, PCI was guided by angiography alone. Not surprisingly, the clinical outcome was similar to that in the angiography group in the FAME study. In contrast, the clinical outcome in the FFR group in the FAME study was similar to that in the group of patients in SYNTAX who underwent coronary-artery bypass grafting (*table 2*).

*Nico H.J. Pijls, M.D., Ph.D.*

*Pim A.L. Tonino, M.D.*

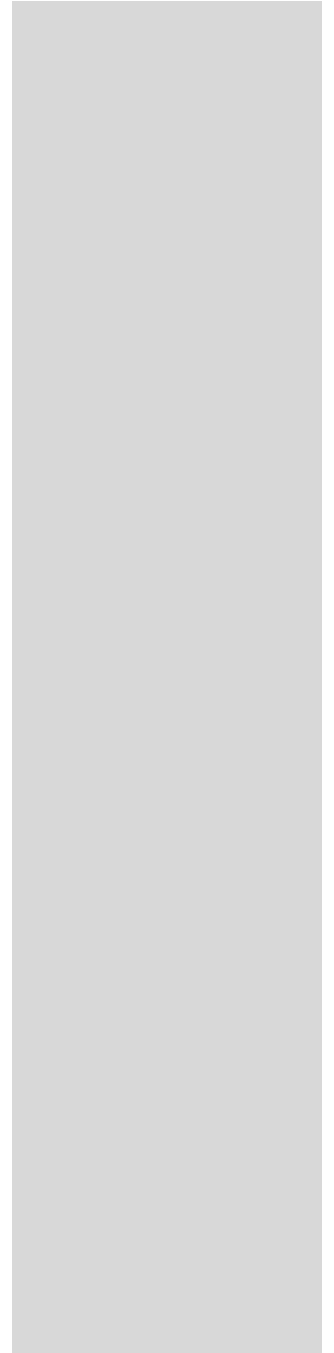
*William F. Fearon, M.D.*

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# **Appendix II**

List of FAME study sites





## List of FAME study sites and investigator's affiliations

### United States of America

*Stanford University Medical Center, Palo Alto VA Health Care Systems,  
Stanford, CA*

W. Fearon, F. Ikeno, T. Brinton, D. Lee, S. Williams, A. Yeung

*Northeast Cardiology Associates, Bangor, Maine*

P. Ver Lee, A. Wiseman, G. Crespo, R. Fincke, P. Vom Eigen

*Saint Louis University, St. Louis, MO*

M. Lim, R. Longnecker

*University of Louisville, Louisville, KY*

M. Leesar (currently University of Cincinnati), V. Yalamanchili, S. Ikram

*University of Virginia Health System, Charlottesville, VA*

M. Ragosta, L. Gimple, L. Lipson

*Medical university of South Carolina, Charleston, SC*

E. Powers

*Massachusetts General Hospital, Harvard Medical School, Boston, MA*

U. Siebert

## **United Kingdom**

*Golden Jubilee National Hospital, Glasgow, Scotland*

K. Oldroyd, M. Lindsay, S. Robb, S. Watkins

*The Heart Centre, Royal Victoria Hospital, Belfast, Northern Ireland*

G. Manoharan, P. Tierney

*King's College Hospital, London, England*

P. MacCarthy, A. Shah, M. Thomas, J. Hill

*Bristol Royal Infirmary, Bristol, England*

A. Baumbach, P. Wilde, A. Nightingale, A. Skyme-Jones, E. Barnes

## **Sweden**

*Södersjukhuset, Stockholm*

I. Herzfeld, M. Törnerud, P. Alström, N. Witt

*Helsingborgs Lasarett, Helsingborg*

F. Schersten

## **Netherlands**

*Catharina Hospital, Eindhoven*

J. Bonnier, C. Botman, B. Brueren, J. van Dantzig, J. Koolen, H. Michels, C.

Peels, N. Pijls, P. Tonino, M. van 't Veer

## **Germany**

*Medizinische Poliklinik, Campus-Innenstadt, University Hospital, Munich*

V. Klauss, J. Rieber, T. Schiele, M. Leibig, Y. Sohn, J. Söllner



*University Hospital Bergmannsheil, Bochum*

W. Bojara, M. Lindstaedt, A. Yazar

*Klinikum Bogenhausen, Munich*

G. Riess

*Klinikum Darmstadt, Darmstadt*

G. Werner

## **Denmark**

*Rigshospitalet, Copenhagen*

T. Engstrøm, H. Kelbaek, E. Jørgensen, S. Helqvist, K. Saunamäki, P.

Clemmensen, J. Kastrup

*Aalborg Sygehus Syd, Aalborg*

K. Rasmussen, O. Frobert (currently Örebro University Hospital, Sweden)

## **Belgium**

*Cardiovascular Center Aalst, Aalst*

B. De Bruyne, N. Melikian, J. Bartunek, E. Wyffels, G. Heyndrickx, W. Wijns,

M. Vanderheyden, H. Batjoens

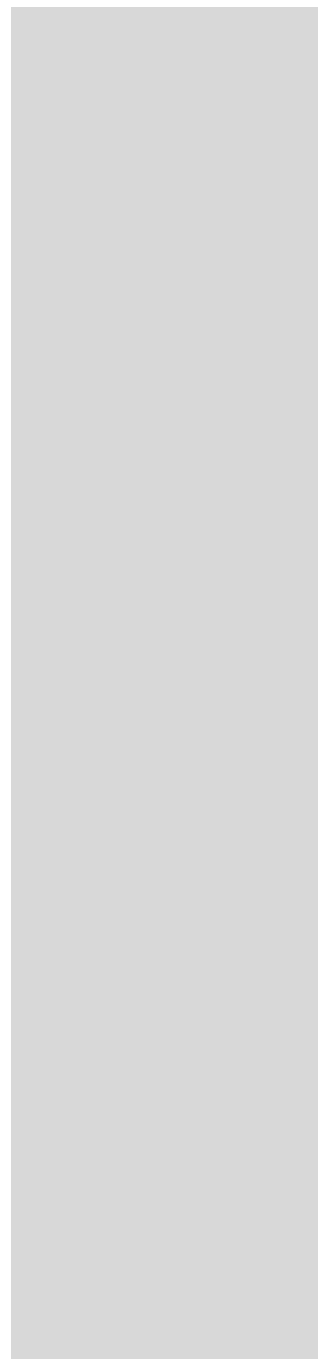
## **Austria**

*University of Health Sciences, Medical Informatics and Technology, Hall i.T.*

U. Siebert, B. Bornschein, R. Gothe.

*List of FAME study sites*

# Nawoord





## Nawoord

Het fundament van dit proefschrift, de FAME studie, betreft een internationaal wetenschappelijk project waar een grote groep mensen aan heeft meegewerkt. Deze studie is verricht met een, binnen de wereld van grote, gerandomiseerde trials, relatief klein budget en de succesvolle uitvoering hiervan is dan ook in bijzonder grote mate te danken aan de tomeloze en gepassioneerde inzet van deze mensen. Met alle radertjes aanwezig en op de goede plek was het aanbrenge van wat olie en licht aanzwengelen al genoeg om de 'FAME-machine' in volle vaart te brengen. Een werkelijk unieke, gezamenlijke prestatie. Ik ben iedereen die heeft bijgedragen aan de FAME studie en dit proefschrift dan ook veel dank verschuldigd.

In het bijzonder professor dr. N.H.J. Pijls, mijn eerste promotor. Beste Nico, ik zal je altijd dankbaar blijven voor de kans die je me hebt gegeven door me eind 2005 voor dit promotieonderzoek te vragen. Je bent een optimale mentor voor me geweest in de wetenschap, het cath lab en de wereld van presentaties en congressen. Het feit dat je me veel vrijheid gaf en op de juiste momenten de touwtjes wat strakker in handen nam, heeft geresulteerd in een voor mij uiterst plezierige en productieve promotietijd. Ik hoop dat dit proefschrift en de FAME studie slechts het begin zijn van een nog lange en constructieve samenwerking. Bedankt voor je vertrouwen!

Dr. B. De Bruyne, mijn co-promotor. Beste Bernard, ik heb je de afgelopen jaren leren kennen als een bevlogen en intelligente cardioloog en wetenschapper. Tijdens de bijeenkomsten in Eindhoven om het CRF van de FAME studie te ontwerpen, internationale congressen en de schrijfsessies voor het artikel in 'de New England', heb ik erg veel van je geleerd. Het frietje in het frietkot bij het Catharina Ziekenhuis, tussen de New England schrijfsessies door, was toch wel een speciaal moment. Ik kijk uit naar de start van FAME II.

Dr. W.F. Fearon, dear Bill, despite the 6,587 miles as the crow flies between Stanford and Eindhoven, you made our cooperation with respect to acquiring and merging the US and European data work great. Thanks! Your well thought-out reasoning and scientific writing were inspiring to me. A highlight for me was your brilliant presentation of the 2 year results of FAME at TCT 2009.

Ik wil Professor dr. F. Zijlstra, mijn tweede promotor en ook de overige leden van de beoordelingscommissie, prof. dr. D.J.G.M. Duncker, prof. ir. F.N. van de Vosse en prof. dr. E. Korsten bedanken voor het zitting nemen in de promotiecommissie. Ik ben de Technische Universiteit Eindhoven en de faculteit Biomedische Technologie erkentelijk voor de samenwerking en de mogelijkheid tot promotie.

Dr. Ir. M. van 't Veer. Beste Marcel, 'chief', wat ben jij onmisbaar geweest. Al die keren dat ik je kamer ben binnengestormd om simpelweg een verhaal kwijt te kunnen, om gedachten te wisselen over wetenschap en statistiek, om je hulp te vragen bij berekeningen en lay-out. Bijna niet te tellen. Daar weegt het schilderen van je bijkeuken niet tegen op. Hoogtepunten waren toch wel jouw promotie en de 'continue infusie van whiskey' op het Loch Lomond landgoed in Schotland. Bedankt voor al je hulp.

A special thanks to Huub Oomes, Eva Tegner and Mona Tiren. Huub, thank you for introducing me to a lot of FAME study investigators, accompanying me on my first trips to the participating centers, and for the relaxed time in Terschelling. Eva, thanks for your kindness and all the trips to hospitals and congresses you arranged for me. Mona, you have a gift in making people feel at ease and respected, thanks for all the work you have done behind the scenes. Bert Mols, Johan Svanerudh, and all other co-workers of formerly RADI, now St. Jude, thank you for your help in this project.

Marjolijn Pijls. Beste Marjolijn, ik vond het erg gezellig als je weer eens FAME gegevens kwam invoeren. Succes met je verdere carrière.

Uwe Siebert, Bernhard Bornschein and Raffaella Göthe, thank you for your great help with the statistical analysis of the FAME study, the beating of deadlines, and the hospitality during our visit to Hall in Tirol.

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All investigators and research nurses of the centers that participated in FAME did a tremendous job including patients and provided us with high quality data. Thanks, and I'm looking forward to working with you in future research projects.

Dr. J.M. van Dantzig, beste Jan-Melle, als opleider weet jij assistenten als geen ander scherp te houden, bedankt voor al je opleidingsmomenten in de afgelopen jaren.

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Alle verpleegkundigen van het cathlab: Marie-José Aben, Berry van Gelder, Eduard van Hagen, Henk Kusters, Arjen Bazelmans, Ruud Boogers, Peter Bastings, Boudewijn Steerneman, Alex Laurensen, Kees de Bruijn, Jan Flerackers, Lex Lakerveld, Claudia Zimmerman, Hanneke van der Heijden Roy Nathoe, Gert Hendrix, Hans Römers, Bonnie Ter Burg, Hans Schroemges, Rudy Bressers, Peter Julien, Ingrid Giepmans, Marjo Buskes, Anja van den Berg en Amber Verbeek, bedankt voor alles wat ik van jullie heb mogen en nog hoop te leren op het gebied van dotteren en pacemakers. Jullie bereidwilligheid en inzet, bijvoorbeeld bij de soms tot middernacht durende stamcelprocedures, is werkelijk uniek in zijn soort. Ik wil Boudewijn, Henk, Arjen, Peter en Eduard speciaal bedanken voor hun analyses van de films van de FAME studie patiënten.

Nicole Bartels, Petry Aangenendt, Herman Massar, Ellen Reuver en Lisette Aarts, bedankt voor alle uitdraaien van wachtlijsten en de flexibiliteit en vindingrijkheid wanneer het programma weer eens aangepast moest worden in verband met een studie patiënt.

Alle huidige collega-assistenten en diegenen die dat ooit waren, bedankt voor een prettige werksfeer en veel collegialiteit. Buiten het Cathrien waren de benevelde weekendjes Ardennen en de (après)-ski trip van afgelopen januari mooie hoogtepuntjes. Sam en Frans, bedankt voor de gezellige zondagen met 'top'hockey. Jan-Willem, 'Circulating Sels', strijdmakker, bedankt voor het gezellige samenwonen in ons kamertje bij het secretariaat, je ongekende humor en het elkaar scherp houden op gebied van cardiologie, wetenschap en andere zaken.

Antoinette Spierings en Ingrid Aarts, bedankt voor jullie hulp en secretariële ondersteuning. Het secretariaat van de poli: Anne Hol, Monique van de Broek en Melanie Yspelder, bedankt dat jullie mij al die tijd in het kamertje van 'Annie' hebben geduld. Harold Helmes, beste Harold, bedankt voor de gezelligheid tijdens onze stamceltripjes naar Gent. Margriet, Anneke en alle 'dames van de poli', bedankt voor het maken van ecg's en afspraken voor vele FAME patiënten. Jan Kalter en Guy van Dael, bedankt voor alle hulp bij technische en audiovisuele zaken.

De verpleging van 7 west en Harry Jansen, bedankt voor jullie zorg voor de FAME studiepatiënten.

Mijn vader, lieve pa, ik vond het geweldig toen je, vanuit het publiek, een scherpe vraag aan me stelde tijdens een van mijn presentaties. Je hebt altijd uitgebreide interesse en trots getoond met betrekking tot mijn promotieonderzoek. Dat jij mijn paranimf wilt zijn is een grote eer voor mij.

Frans, paranimf en goede vriend, we hebben wel vaker samen in rokkostuum gestaan.

Mijn moeder, lieve ma, je weet dat ik je geweldig vind. Bedankt voor je onvoorwaardelijke steun en liefde.

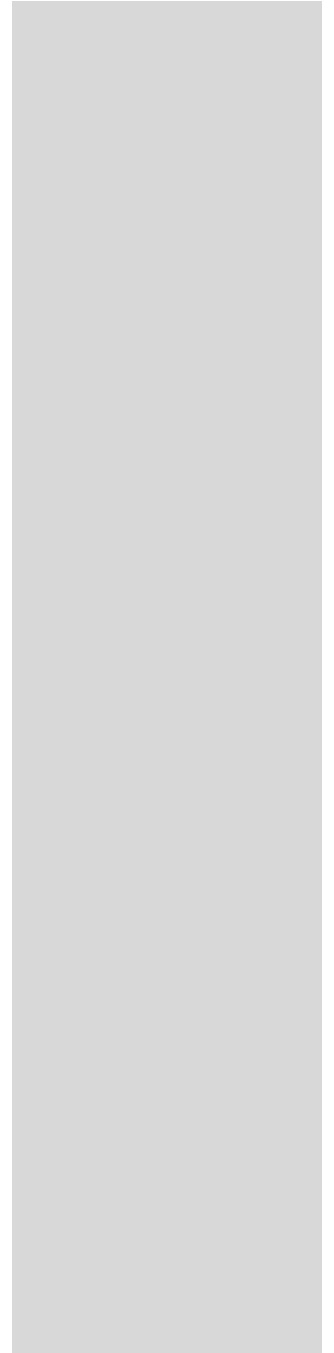
Mijn schoonouders, Jan en Diny, bedankt voor jullie steun, gezelligheid en het 'babysitten'.

Lieve Sandra, zonder jou was me dit simpelweg niet gelukt. Je bent al die tijd pal achter me blijven staan en je hebt jezelf vaak weggecijferd voor mij, het onderzoek en de kindjes. Het is altijd weer een feestje om thuis te komen bij jou, Justus en Sofie. Ik hou ontzettend veel van jullie.



# **Curriculum Vitae**

## **List of papers**





## **Curriculum vitae**

The author of this thesis was born on December 20<sup>th</sup> , 1974, in Leiden, the Netherlands. After primary school, he attended secondary school at the Philips van Horne Scholengemeenschap in Weert. He entered medical school in 1993, at Erasmus University in Rotterdam. Before obtaining his Master's degree on March 26<sup>th</sup> , 1998, he participated in research at the department of Experimental Cardiology of the Erasmus University, under supervision of Prof. Dr. P. D. Verdouw and Prof. Dr. D.J.G.M. Duncker. On July 14<sup>th</sup> , 2000 he obtained his medical degree. That same year he started working as a resident in cardiology in the Reinier de Graaf Hospital in Delft. In 2001 he started working as a resident in cardiology in the Catharina Hospital Eindhoven, where he started his training in cardiology in 2001, under supervision of Dr. J.J. Koolen, Dr. J.M. van Dantzig, and Prof. Dr. N.H.J. Pijls. From 2006, his training in cardiology was combined with this thesis. He expects to be registered as a cardiologist on October 1<sup>st</sup>, 2010.

## List of papers

Fractional Flow Reserve and Myocardial Perfusion Imaging in Patients With Angiographic Multivessel Coronary Artery Disease

***J Am Coll Cardiol Intv* 2010;3 307-314**

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention.

***N Eng J Med.* 2009; 360: 213-24**

Biomechanical properties of abdominal aortic aneurysms assessed by simultaneously measured pressure and volume changes in humans.

***J Vasc Surg* 2008 Dec;48(6):1401-7**

Direct volumetric blood flow measurement in coronary arteries by thermodilution.

***J Am Coll Cardiol.* 2007 Dec 11;50(24):2294-304**

Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study.

***Am Heart J.* 2007 Oct;154(4):632-6**

The twiddler syndrome.

***N Eng J Med.* 2006 Mar 2;354(9):956**

Accelerated idioventricular rhythm: a sign of reperfusion.

***Neth Heart J 2005;13(12):464***

The effect of ITF-1697 on reperfusion in patients undergoing primary angioplasty. Safety and efficacy of a novel tetrapeptide, ITF-1697.

***Eur Heart J. 2004 Mar;25(5):392-400***

Nitric oxide contributes to the regulation of vasomotor tone but does not Modulate O<sub>2</sub> consumption in exercising swine.

***Cardiovasc Res. 2000 Sep;47(4):738-48***

Angiographic versus Functional Severity of Coronary Artery Stenoses in the FAME Study.

***Accepted for publication in JACC***

Economic Evaluation of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients with Multivessel Disease.

***Under review Circulation***

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention in Patients with Multivessel Coronary Artery Disease: 2-Year Follow-Up of The FAME Study.

***Under review JACC***

