Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial

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Summary

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

Methods The FAME study was a multicentre trial done in Belgium, Denmark, Germany, the Netherlands, Sweden, the UK, and the USA. Patients (aged ≥18 years) with multivessel coronary artery disease were randomly assigned to undergo angiography-guided PCI or FFR-guided PCI. Before randomisation, stenoses requiring PCI were identified on the angiogram. Patients allocated to angiography-guided PCI had revascularisation of all identified stenoses. Patients allocated to FFR-guided PCI had FFR measurements of all stenotic arteries and PCI was done only if FFR was 0·80 or less. No one was masked to treatment assignment. The primary endpoint was major adverse cardiac events at 1 year, and the data for the 5-year follow-up are reported here. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00267774.

Findings After 5 years, major adverse cardiac events occurred in 31% of patients (154 of 496) in the angiography-guided group versus 28% (143 of 509 patients) in the FFR-guided group (relative risk 0·91, 95% CI 0·75–1·10; p=0·31). The number of stents placed per patient was significantly higher in the angiography-guided group than in the FFR-guided group (mean 2·7 [SD 1·2] *vs* 1·9 [1·3], p<0·0001).

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

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Introduction

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

Fractional flow reserve (FFR) is defined as the ratio of maximum blood flow in a stenotic coronary artery to maximum blood flow if the same artery were completely normal. An FFR of 0·80 or less, as measured with the use of a coronary pressure wire during invasive coronary angiography, indicates the potential of a specific stenosis to induce myocardial ischaemia with an accuracy of greater than 90%. Therefore, FFR is recommended for the guidance of coronary revascularisation.[7,8]

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

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

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Research in context

Evidence before this study

Fractional flow reserve (FFR) indicates the potential of a specific stenosis to induce myocardial ischaemia with an accuracy of more than 90%. Therefore, FFR is recommended for the guidance of coronary revascularisation, as described by the guidelines of the European Society of Cardiology and American Heart Association–American College of Cardiology. In the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, angiography-guided percutaneous coronary intervention (PCI) was compared with FFR-guided PCI in multivessel disease. At 1 year, the rate of major adverse cardiac events was significantly lower in the FFR-guided group and equally high percentages of patients were free from angina in both groups. At 2 years, an ongoing favourable outcome was noted with significantly lower rates of death and myocardial infarction in the FFR-guided group than in the angiography-guided PCI group. Additionally, FFR-guided PCI was cost-saving.

Added value of this study

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

Implications of all the available evidence

This new evidence of long-term safety of FFR-guided PCI in patients with multivessel disease will further strengthen the evidence of benefit of functional revascularisation over anatomical revascularisation. This is the first study of the long-term results of FFR-guided strategy and the results show that, with optimum medical therapy, revascularisation of only functional significant lesions is safe and will not result in a late catch-up phenomenon because of the progression of atherosclerosis in non-significant lesions.

Methods

Study design and participants

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

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

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

Randomisation and masking

Patients with multivessel coronary artery disease were randomly assigned with a computer-generated allocation sequence to have angiography-guided PCI or FFR-guided PCI. Randomisation was stratified according to the study site and done in blocks of 25, with the use of sealed opaque envelopes. Patients allocated to angiography-guided PCI underwent revascularisation of all angiographic stenoses with drug-eluting stents. Patients allocated to FFR-guided PCI had FFR measurement of all stenotic arteries and PCI was done only if FFR was 0·80 or less. No one was masked to treatment assignment.

Treatment

PCI was done with drug-eluting stents. In the angiography-guided group, all indicated angiographically significant stenoses were stented. In the FFR-guided group, a coronary pressure wire (Radi, St Jude Medical, Uppsala, Sweden) was advanced and equalised with the pressure sensor at the tip of the guiding catheter. Hereafter, the pressure wire was advanced in the coronary artery, sufficiently distal to the lesion under investigation. Maximum coronary hyperaemia was induced with central venous infusion of adenosine (140 µg/kg per min) and FFR was measured. If FFR was less or equal to the ischaemic threshold (ie, 0·80), PCI of the respective stenosis was done. All patients were treated with aspirin and clopidogrel for at least 1 year.

Outcomes

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

Predefined secondary endpoints were major adverse cardiac events at 2 years and 5 years, and the individual components of the major adverse cardiac events at 1 year,

2 years, and 5 years;[12] data for the major adverse cardiac events and the individual components at 5 years are reported here. Although major adverse cardiac events for up to 2 years were adjudicated by a clinical event committee, events thereafter were assessed at the site and verified by source documentation (cardiac enzymes, electrocardiogram [ECG] changes, PCI reports, and cause of death).

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

Statistical analysis

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

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

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

All statistical tests were two-tailed and a p value of less than 0·05 was significant. The acquired data were analysed with IBM SPSS for Windows (version 19.0.0.1). This trial is registered with ClinicalTrials.gov, number NCT00267774.

Role of the funding source

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

Results

1005 patients were included in 20 centres in the USA and Europe between Jan 2, 2006, and Sept 26, 2007 (figure 1). 496 patients were randomly assigned to angiography-guided PCI and 509 patients were assigned to FFR-guided PCI. Baseline characteristics, the number of indicated lesions, and the severity of coronary artery disease were similar between the two groups (appendix). Mean age of the study population was 64 years (SD 10), and about 75% were men (appendix). Most of the patients had more than one risk factor for coronary artery disease (appendix). The incidence of diabetes was not different between the two groups (appendix). 37% of the patients had previous myocardial infarction and 27% had previous PCI (appendix). The severity of coronary artery disease was well balanced between the two groups, with a similar number of lesions per patient and a similar percentage of patients with a proximal LAD stenosis (appendix).

See Online for appendix

The procedure times did not differ between the angiography-guided group and the FFR-guided group (mean 70 min [SD 44] *vs* 71 min [43]; p=0·51). In the FFR-guided group, FFR measurement was done in 1329 (94%) of 1414 indicated lesions. FFR measurement

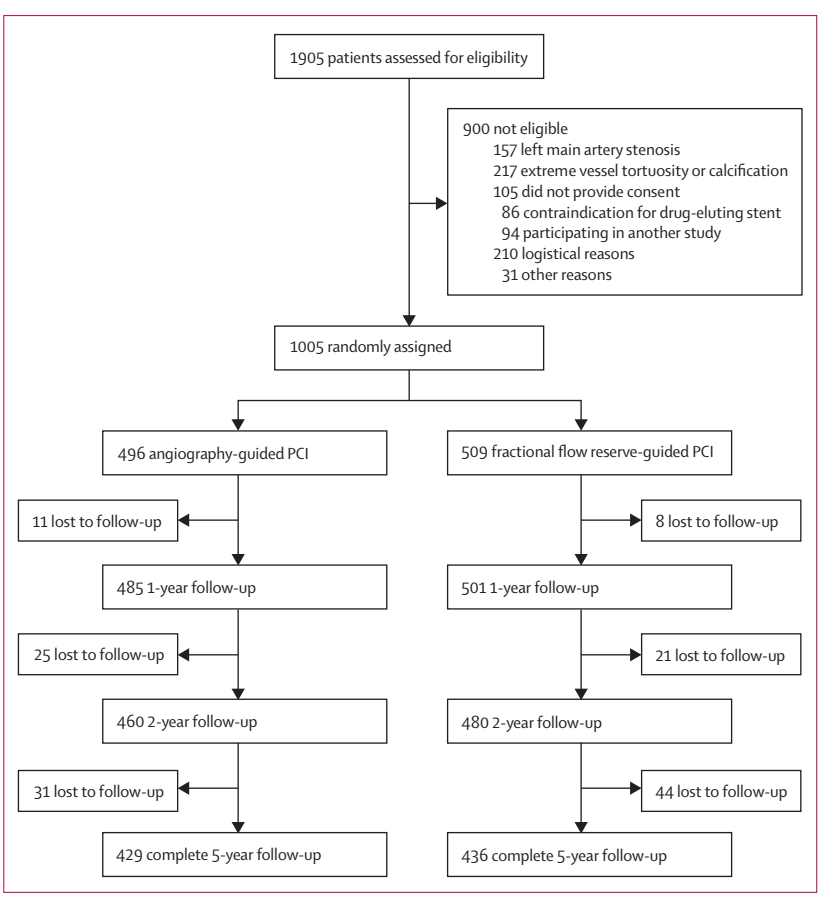

Figure 1: **Trial profile**
PCI=percutaneous coronary intervention.

was not successful in 27 stenoses, and was not done in 58 stenoses with a chronic total occlusion for which a default value of 0·50 was assigned in accordance with the protocol. In 874 (63%) of 1387 stenoses, FFR was 0·80 or less, and these stenoses were treated with PCI as per protocol.

In the complete study population, 2415 stents were placed, of which 2339 (97%) were drug-eluting stents. In the angiography-guided group, the number of stents placed per patient was significantly higher than in the FFR-guided group (mean 2·7 [SD 1·2] *vs* 1·9 [1·3], p<0·0001).

865 (86%) of 1005 patients had complete 5-year follow-up. 67 patients in the angiography-guided group and 73 in the FFR-guided group were lost to follow-up (p=0·70). The characteristics of the patients who completed the 5-year follow-up are shown in table 1, and did not differ from baseline characteristics of the total patient population at the start of the study (appendix).

After 5 years, the primary endpoint (major adverse cardiac events) occurred in 31% of patients (154 of 496) in the angiography-guided group versus 28% (143 of 509 patients) in the FFR-guided group (RR 0·91, 95% CI 0·75–1·10; p=0·31). Sensitivity analysis showed no difference in major adverse cardiac events if all patients lost to follow-up had died (appendix). Figure 2 shows event-free survival. Potential confounders did not alter the effect of treatment strategy on event-free survival with multivariate logistic regression (data not shown).

All-cause mortality at 5 years was 10% (49 of 496 patients) in the angiography-guided group, and 9% (44 of 509 patients) in the FFR-guided group (RR 0·88, 95% CI 0·59–1·29; p=0·50). Myocardial infarction occurred in 12% of patients (n=58) in the angiography-guided group and 9% (n=48) in the FFR-guided group at 5 years (RR 0·81, 95% CI 0·56–1·16; p=0·24). Three patients (two in the angiography-guided group and one in the FFR-guided group) had a second acute myocardial infarction during follow-up, bringing the total number of myocardial infarctions to 60 versus 49. At 5 years, 20% of patients (n=98) in the angiography-guided group and 17% (n=86) in the FFR-guided group died or had myocardial infarction (RR 0·86, 95% CI 0·66–1·11; p=0·24). In the angiography-guided group, 17% of patients (n=82) required repeat revascularisation versus 15% (n=76) in the FFR-guided group (RR 0·90, 95% CI 0·68–1·20; p=0·49). 26 patients (12 in the angiography-guided group and 14 in the FFR-guided group) needed two or more revascularisation procedures. The total number of repeat revascularisations was 101 in the angiography-guided group and 92 in the FFR-guided group.

The absolute difference in all-cause mortality between the two groups after 1 year, 2 years, and 5 years remained constant (1·2%, 1·2%, and 1·3%; table 2). The difference in mortality at 5 years was exclusively due to cardiac mortality, which was 6% (28 of 496 patients) in the angiography-guided group versus 4% (21 of 509 patients) in the FFR-guided group (RR 0·73, 95% CI 0·42–1·27; p=0·26). Also, the differences in mean number of events per patient between angiography-guided and FFR-guided strategies remained constant after 1 year, 2 years, and 5 years (0·08, 0·08, and 0·06; table 2).

In the subgroup analyses, the interaction between sex and treatment strategy was significant, with FFR-

	Angiography-guided PCI (n=429)	Fractional flow reserve-guided PCI (n=436)	p value
Baseline characteristics			
Age (years)	63·9 (10·0)	64·5 (10·4)	0·41
Men/women	318 (74%)/111 (26%)	328 (75%)/108 (25%)	0·71
Clinical characteristics			
Angina (Canadian Cardiovascular Society class)			0·32
I	97 (23%)	111 (25%)	
II	142 (33%)	143 (33%)	
III	105 (24%)	115 (26%)	
IV	85 (20%)	67 (15%)	
Diabetes	107 (25%)	98 (22%)	0·36
Hypertension	277 (65%)	259 (59%)	0·09
Hypercholesterolaemia	316 (74%)	307 (70%)	0·26
Family history of ischaemic heart disease	169 (39%)	178 (41%)	0·69
Current smoker	130 (30%)	111 (25%)	0·11
Previous myocardial infarction	155 (36%)	154 (35%)	0·86
Previous PCI	110 (26%)	123 (28%)	0·39
Unstable angina			
With ECG changes	81 (19%)	61 (14%)	0·05
Without ECG changes	74 (17%)	67 (15%)	0·44
Left ventricular ejection fraction	57% (12)	57% (11)	0·75
Medication			
β blocker	321 (75%)	334 (77%)	0·54
Calcium antagonist	86 (20%)	100 (23%)	0·30
Nitrates	156 (36%)	137 (31%)	0·13
Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker	213 (50%)	225 (52%)	0·57
Statin	341 (79%)	358 (82%)	0·33
Aspirin	390 (91%)	396 (91%)	0·97
Clopidogrel	243 (57%)	256 (59%)	0·54
Angiographic characteristics			
Indicated lesions per patient	2·7 (0·9)	2·8 (1·0)	0·37
Extent of occlusion*	1171	1221	
50–70% narrowing	508 (43%)	549 (45%)	
70–90% narrowing	468 (40%)	453 (37%)	
90–99% narrowing	165 (14%)	171 (14%)	
Total occlusion	30 (3%)	48 (4%)	
Patients with proximal left anterior descending artery lesion	160 (37%)	178 (41%)	0·29
Patients with total occlusion	28 (7%)	45 (10%)	0·05

Data are mean (SD) or number (%). PCI=percutaneous coronary intervention. ECG=electrocardiogram. *The investigator indicated all lesions to be included in the study before randomisation and classified them according to severity by visual estimation.

Table 1: **Baseline and angiographic characteristics of patients with complete 5-year follow-up**

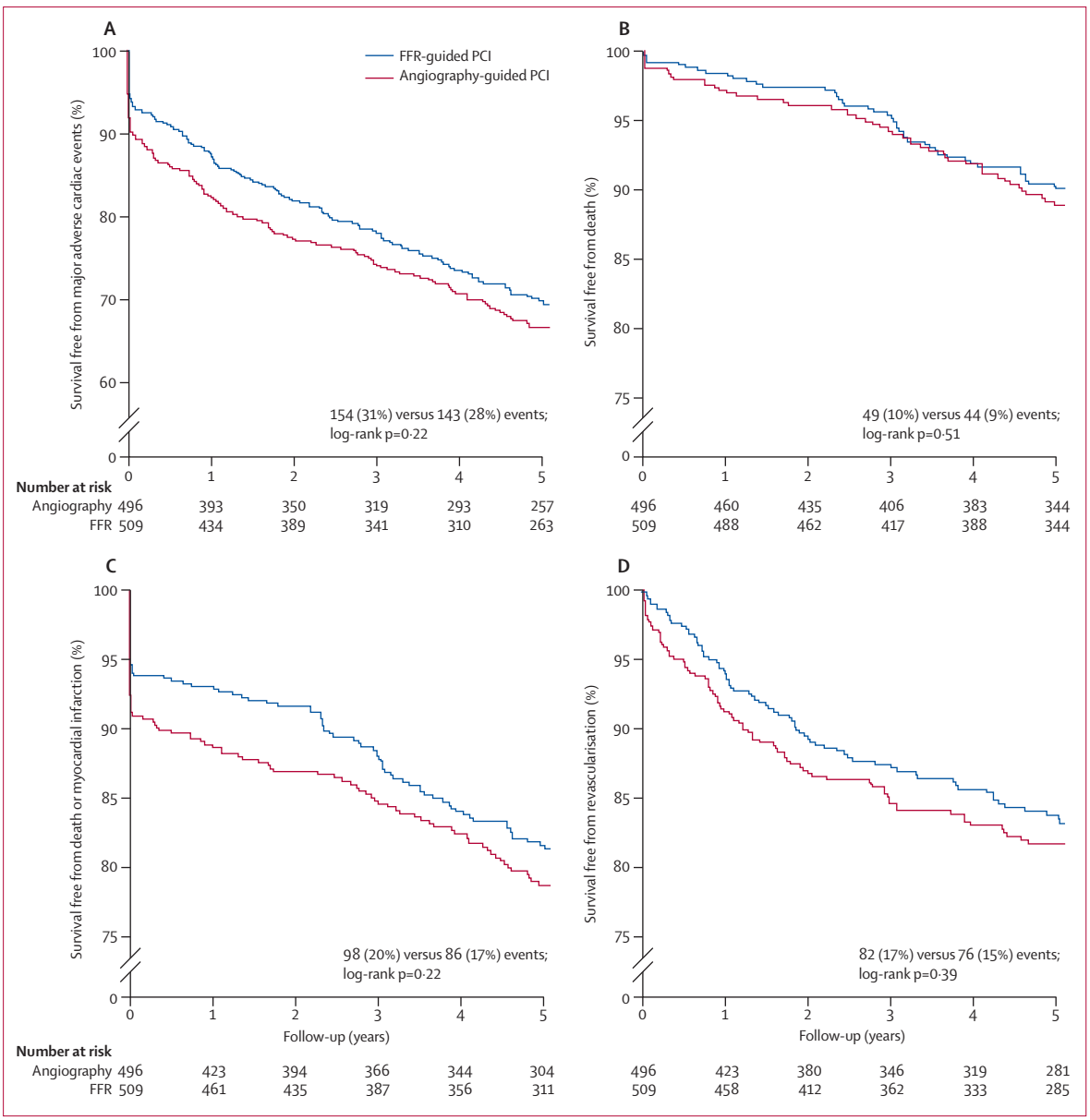

Figure 2: **Kaplan-Meier curves for survival free from major adverse cardiac events (A), all-cause mortality (B), all-cause mortality or myocardial infarction (C), and revascularisation (D)**
FFR=fractional flow reserve. PCI=percutaneous coronary intervention.

guided PCI favouring the male sex ($p_{interaction}$=0·027; figure 3).

With focus solely on the male sex, the primary endpoint at 5 years occurred in 34% of patients (121 of 360) in the angiography-guided group versus 27% (103 of 384) in the FFR-guided group (RR 0·80, 95% CI 0·64–0·99; p=0·044).

In the angiography-guided group, the mean number of events per patient was 0·42 (SD 0·76) versus 0·36 (0·67) in the FFR-guided group during the 5-year follow-up (p=0·28; table 3). The cumulative events per 100 patient-years during follow-up were higher in the angiography-guided group (appendix).

Discussion

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

Routine measurement of FFR allows more judicious use of stents than does angiography and equal relief of

	Angiography-guided PCI (n=496)	Fractional flow reserve-guided PCI (n=509)	Absolute difference*
All-cause mortality			
1-year follow-up	3·0%	1·8%	1·2%
2-year follow-up	3·8%	2·6%	1·2%
5-year follow-up	9·9%	8·6%	1·3%
Cardiac mortality			
1-year follow-up	2·0%	1·4%	0·6%
2-year follow-up	2·4%	1·8%	0·6%
5-year follow-up	5·6%	4·1%	1·5%
Number of events per patient			
1-year follow-up	0·23 (0·53)	0·15 (0·41)	0·08
2-year follow-up	0·29 (0·60)	0·21 (0·48)	0·08
5-year follow-up	0·41 (0·76)	0·35 (0·67)	0·06

Data are number (%) or mean (SD). PCI=percutaneous coronary intervention.
*None of the differences were significant.

Table 2: **Event rates during follow-up**

	Angiography-guided PCI (n=496)	Fractional flow reserve-guided PCI (n=509)	p value
Total events	210	185	
Events per patient	0·42 (0·76)	0·36 (0·67)	0·28
Endpoints			
All-cause mortality	49 (10%)	44 (9%)	0·50
Cardiac mortality	28 (6%)	21 (4%)	0·26
Myocardial infarction	60	49	
Revascularisation	101	92	
Combined endpoints			
Major adverse cardiac events (primary endpoint)	154 (31%)	143 (28%)	0·31
All-cause mortality or myocardial infarction	98 (20%)	86 (17%)	0·24
Cardiac mortality or myocardial infarction	78 (16%)	66 (13%)	0·21

Data are number, mean (SD), or number (%). PCI=percutaneous coronary intervention.

Table 3: **Outcomes at 5-year follow-up**

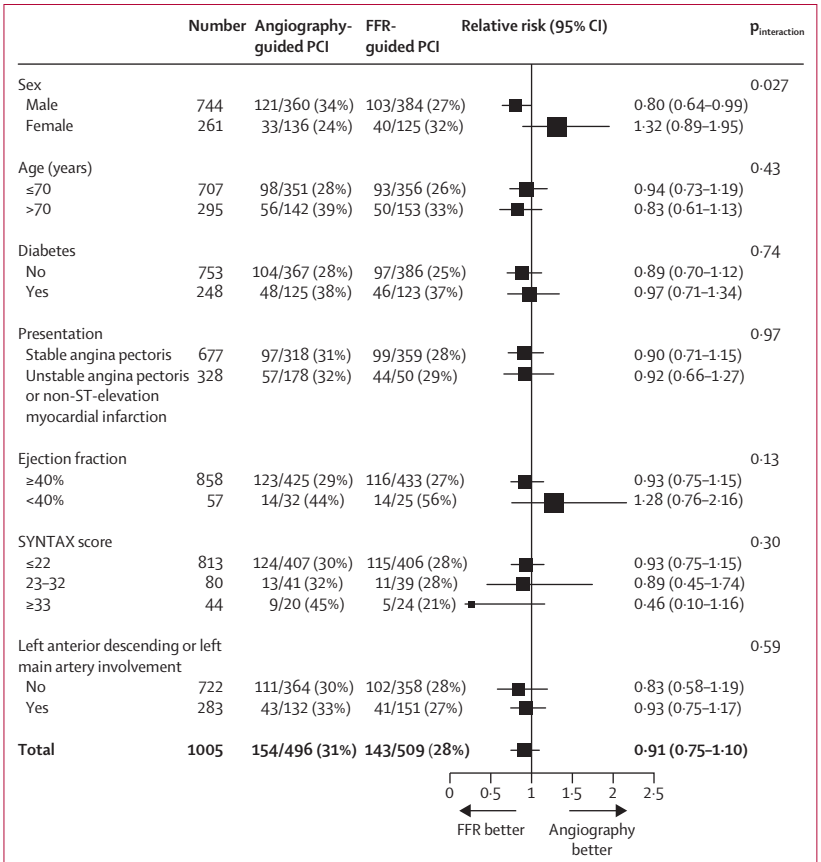

Figure 3: **Subgroup analyses of the primary endpoint major cardiac adverse events at 5 years**
Data are n/N (%), unless otherwise indicated. Relative risks (with 95% CI) of the primary endpoint are shown by subgroup. FFR=fractional flow reserve. PCI=percutaneous coronary intervention.

ischaemia. Thus, by systematic measurement of FFR, the benefit of PCI can be maximised by accurate discrimination of the stenoses that benefit most from revascularisation.

The potential benefit of revascularisation depends on the extent and degree of myocardial ischaemia.[1,14,15] In patients with multivessel disease, non-invasive testing often has too low spatial resolution to identify ischaemia associated with individual stenoses.[16] When based solely on anatomical criteria, attempts to achieve complete revascularisation have led to the use of a high number of stents associated with a high rate of major adverse cardiac events.[13] The notion of functional complete revascularisation rather than anatomical complete revascularisation overcomes these limitations by complete relief of ischaemia related to the epicardial vessel with better outcome and less resource use.[10,17,18] An FFR value of 0·80 or less indicates the potential of a particular coronary stenosis to induce myocardial ischaemia with an unsurpassed spatial resolution.

With respect to all-cause mortality and cardiac mortality, there were no significant differences between the two groups. There was reduction in the RR of 12% in the FFR-guided group for all-cause mortality, whereas the RR reduction for cardiac mortality was 27%. In a study with such a long follow-up, mortality numbers related to the specific disease studied are diluted by naturally occurring other causes of death. Therefore, we believe that cardiac mortality in itself is a relevant factor when studying long-term follow-up. Although not significant, the absolute reduction in mortality was constant over time, as was the reduction in mean number of events per patient. As shown in table 2, the difference in mortality at 5 years is solely due to the difference in cardiac mortality.

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

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

A significant interaction between sex and treatment strategy was noted, favouring the male sex. In the male population, even after 5 years of follow-up, there was still a significant difference favouring FFR-guided therapy. This benefit was not noted in the female population. This sex difference was not present at the 2-year follow-up.[19]

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

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

Contributors

LXvN, FMZ, PALT, EB, WFF, BDB, and NHJP analysed the data and wrote the report. AB, TE, VK, PAM, GM, KGO, PNVL, and MvV were involved in data acquisition and contributed to writing of the manuscript.

Declaration of interests

PALT reports grants from St Jude Medical. EB reports grants from St Jude Medical to the Cardiovascular Research Center Aalst. AB reports personal fees from St Jude Medical, outside the submitted work. GM received consultant fees from St Jude Medical, Medtronic, and Boston Scientific outside the submitted work. KGO reports that his institution receives grant support and consulting fees on his behalf from St Jude Medical. MvV reports consultancy for St Jude Medical. WFF reports grants from St Jude Medical, and grants and personal fees from Medtronic. BDB reports grants from St Jude Medical, Medtronic, and Abbott, institutional fees from St Jude Medical, Boston Scientific, and Opsens, and is a stockholder in Omega Pharma, Siemens, Edwards, General Electric, Sanofi, HeartFlow, and Bayer. NHJP reports that his institution receives research grants from St Jude Medical, he is consultant for St Jude Medical, Boston Scientific, and Opsens Medical, and he holds equity interest in Philips, General Electric, and HeartFlow. The other authors declare no competing interests.

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