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CLINICAL RESEARCH

Fractional Flow Reserve in Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Experience From the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) Study

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Objectives The aim of this study was to study whether there is a difference in benefit of fractional flow reserve (FFR) guidance for percutaneous coronary intervention (PCI) in multivessel coronary disease in patients with unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI), compared with stable angina (SA).

Background The use of FFR to guide PCI has been well established for patients with SA. Its use in patients with UA or NSTEMI has not been investigated prospectively.

Methods In the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study 1,005 patients with multivessel disease amenable to PCI were included and randomized to either angiography-guided PCI of all lesions ≥50% or FFR-guided PCI of lesions with an FFR ≤0.80. Patients admitted for UA or NSTEMI with positive troponin but total creatine kinase <1,000 U/l were eligible for inclusion. We determined 2-year major adverse cardiac event rates of these patients and compared it with stable patients.

Results Of 1,005 patients, 328 had UA or NSTEMI. There was no evidence for heterogeneity among the subgroups for any of the outcome variables (all p values >0.05). Using FFR to guide PCI resulted in similar risk reductions of major adverse cardiac events and its components in patients with UA or NSTEMI, compared with patients with SA (absolute risk reduction of 5.1% vs. 3.7%, respectively, p = 0.92). In patients with UA or NSTEMI, the number of stents was reduced without increase in hospital stay or procedure time and with less contrast use, in similarity to stable patients.

Conclusions The benefit of using FFR to guide PCI in multivessel disease does not differ between patients with UA or NSTEMI, compared with patients with SA. (J Am Coll Cardiol Intv 2011;4: 1183–9) © 2011 by the American College of Cardiology Foundation

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The use of fractional flow reserve (FFR) to select coronary stenoses associated with reversible ischemia and that will benefit most by stenting has been well established in patients undergoing elective percutaneous coronary intervention (PCI) (1–3). Its use in unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) is less well investigated.

Several retrospective and a few small prospective studies have indicated that in such patients FFR can be used in a similar way as in stable angina pectoris (SA), but no large randomized study has been performed so far (4–7). Especially in multivessel disease when several stenoses are present, selection of the culprit lesion in case of UA or NSTEMI might be difficult. Often electrocardiography is helpful and indicates the lesion responsible for the acute ischemia, but sometimes it does not. In addition, even when the culprit lesion is known, doubt might arise about the ischemic potential of other concomitant lesions and the necessity to treat such lesions invasively.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
FFR = fractional flow reserve
MACE = major adverse cardiac event(s)
MI = myocardial infarction
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
SA = stable angina
STEMI = ST-segment elevation myocardial infarction
UA = unstable angina

In the recently published prospective and randomized FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study, FFR-guided PCI in multivessel disease was compared with angiography-guided PCI in 1,005 patients.

The FAME study demonstrated the superiority of FFR-guided PCI over angiography guidance alone in patients with multivessel disease, with a decrease of all types of events by approximately 30% up to 2 years of follow-up without prolongation of the procedure, at lower costs and with less use of contrast agent, a shorter hospital stay, and an at least equal functional class at 1- and 2-year follow-up (3,8,9).

In the FAME study, 328 patients were included who were admitted because of UA or NSTEMI. The outcome of FFR-guided PCI versus angiography-guided PCI in these patients and comparison with the 677 patients with SA is the subject of this study.

Methods

The FAME study design and patient population. The FAME study is a multicenter prospective trial in 1,005 patients with multivessel coronary artery disease undergoing PCI by stenting with drug-eluting stents. Patients were randomly assigned to either angiography-guided PCI or FFR guidance in addition to angiography. The decision and selection of those coronary stenoses that required stenting was based upon visual estimation on the angiogram (angiography-guided group) or upon FFR measurements (FFR-guided group), in addition to clinical data.

Patients assigned to angiography-guided PCI underwent stenting of all stenoses ≥50% by visual estimation of which the operator deemed stenting indicated. In patients assigned to the FFR-guided PCI, FFR was measured first in all such lesions, and stenting was only performed if FFR was ≤0.80.

Exclusion criteria were left main disease, previous CABG, and ST-segment elevation myocardial infarction (STEMI) <5 days before, because the use of FFR is not validated in recent STEMI (10). However, patients admitted for UA (whether or not with transient ST-segment changes) and NSTEMI with positive troponin but total creatine kinase <1,000 U/l could be included.

Of the 1,005 patients, 328 (32%) had an initial diagnosis of UA or NSTEMI. Strict criteria were used to distinguish between NSTEMI and periprocedural infarction as previously described (11). Further details about the FAME trial have been extensively described elsewhere (11).

FFR. Fractional flow reserve 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. 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 during maximum hyperemia (12). The 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% (13). The information provided by FFR is similar to that obtained with myocardial perfusion studies, but FFR is more specific and has a better spatial resolution, because every artery or segment is analyzed separately and masking of 1 ischemic area by another more-severely ischemic area is avoided (14,15).

Treatment. The interventional treatment of patients in the FAME study has been described previously and was identical for patients with SA and for patients admitted because of UA or NSTEMI (11). Percutaneous coronary intervention was performed with standard techniques and with drug-eluting stents. The FFR was measured with a coronary pressure guidewire (St. Jude Medical Systems, Uppsala, Sweden) at maximum hyperemia induced by intravenous adenosine, administered at a rate of 140 μg/kg/min through a central vein. Pressure pullback recordings were performed in all indicated arteries. All patients were treated with aspirin and clopidogrel for at least 1 year after PCI. Use of periprocedural glycoprotein IIb/IIIa antagonists was at the discretion of the operator.

Endpoints and follow-up. The subject of this study was the occurrence of major adverse cardiac events (MACE) and their individual components at 2 years. Major adverse cardiac events were defined as composite of death from any cause, myocardial

infarction (MI), and any repeat revascularization. Details on these definitions have been described previously (3,11).

Also, functional class at 2 years was assessed.

Statistical analysis. Data management and statistical analysis were performed by an independent data coordinating center (UMIT–University for Health Sciences, Hall in Tirol, Austria).

An independent clinical events committee whose members were unaware of the treatment assignments adjudicated all events. All enrolled patients were included in the analysis of MACE according to the intention-to-treat principle.

To test for heterogeneity for the effect of using FFR in the strata of UA or NSTEMI and SA, Breslow-Day testing was performed—a 2-sided p value <0.05 signifying heterogeneity. For descriptive purposes, we compared the effect of FFR-guided therapy versus angiography-guided therapy within subgroups.

Categorical variables, including the primary endpoint and its individual components, are expressed as proportions and were compared with chi-square test. Continuous variables are expressed as mean ± SD and were compared with an unpaired *t* test or the Mann-Whitney *U* test as appropriate. A 2-sided p value of <0.05 was considered to indicate statistical significance. Kaplan-Meier curves are shown for the time-to-event distributions of MACE in all patients stratified according to diagnosis (UA or NSTEMI or SA) and treatment strategy (angiography- or FFR-guided PCI).

All statistical analyses were performed with SAS software (version 9, SAS Institute, Cary, North Carolina).

Results

Baseline characteristics. Of 1,005 patients enrolled in the FAME study, 328 patients (32%) had UA or NSTEMI, of which 178 were randomized to angiography-guided PCI and 150 were randomized to FFR-guided PCI.

The baseline characteristics of the patients with UA or NSTEMI and patients with SA are mentioned in Table 1. Although most baseline characteristics were equally distributed, patients with UA or NSTEMI in comparison with SA were less likely to be male (69% vs. 77%, $p = 0.01$), more often had previous MI (44% vs. 33%; $p < 0.01$), more often used beta blockade (81% vs. 75%, $p = 0.017$) and clopidogrel (70% vs. 40%, $p < 0.01$), less often used statins (77% vs. 83%, $p = 0.02$), and had a higher Euro-score (2.8 ± 2.2 vs. 3.2 ± 2.3, $p < 0.01$). The angiographic severity of disease (number and severity of lesions and Syntax score) and FFR measurements, however, were not different between patients with UA or NSTEMI and patients with SA.

Next, patients were categorized according to diagnosis (UA or NSTEMI or SA) and treatment strategy (angiography-guided PCI or FFR-guided PCI), thus rendering 4 groups.

Baseline characteristics of these 4 groups are presented in Table 2.

Procedural results. UA OR NSTEMI VERSUS SA. There was no difference between patients with UA or NSTEMI and patients with SA with respect to the number of indicated lesions/patient (2.7 ± 0.9 vs. 2.8 ± 1.0, $p = 0.06$), the percentage of hemodynamically significant lesions within the FFR-guided groups (61.8% vs. 63.5%, $p = 0.54$), or the percentage of successfully treated lesions (97.5% vs. 96.9%, $p = 0.42$).

There was no significant difference in procedure time, contrast use, number or type of stents used, or use of glycoprotein IIb/IIIa inhibitors. Hospital stay was significantly longer for patients with UA or NSTEMI than for patients with SA (4.5 ± 4.5 days vs. 3.1 ± 2.7 days, $p < 0.01$). These data are shown in Table 1.

FFR-GUIDANCE VERSUS ANGIOGRAPHY-GUIDANCE IN UA OR NSTEMI. In the patients with UA or NSTEMI, procedural success, procedure time, and duration of hospital stay were not different between the FFR-guided group and the angiography-guided group, except for contrast use, which was significantly higher in the angiography-guided group (308 ± 134 ml vs. 269 ± 139 ml, $p = 0.01$). In patients with UA or NSTEMI assigned to FFR-guidance group, on average 1 stent less/patient was used than in those assigned to angiography guidance (1.9 ± 1.5 vs. 2.9 ± 1.1, $p < 0.01$), as shown in Table 3.

2-year outcome. BENEFIT OF FFR-GUIDANCE IN UA OR NSTEMI COMPARED WITH SA. We found no evidence for heterogeneity in effect of FFR guidance among the subgroups of UA or NSTEMI and SA.

In the patients with UA or NSTEMI, the absolute reduction of MACE at 2 years by using FFR guidance was 5.1% versus 3.7% in patients with SA. The relative risk reduction of MACE was 19% versus 18%, respectively. The rates of MACE and its individual components, absolute and relative risk reductions by FFR-guidance, and Breslow-Day test for MACE and its components are shown in Table 4.

Kaplan-Meier curves for survival free from MACE for the patients in all groups are presented in Figure 1.

UA OR NSTEMI VERSUS SA. The composite of death, MI, and repeated revascularization at 2 years occurred in 24.1% of all patients with UA or NSTEMI versus 18.2% of patients with SA ($p = 0.03$). There was also a significant difference in occurrence of MI (10.9% vs. 6.5%, $p = 0.02$) and death or MI (13.7% vs. 9.2%, $p = 0.04$). Functional status at 2 years did not differ. These data are shown in Table 1.

Discussion

As previously shown in the FAME study (9), using FFR to guide PCI in multivessel disease resulted in significant reduction of MI and mortality at 2 years. In this subanalysis, we found no evidence for a difference of the effect

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Table 1. Demography, Clinical Characteristics, Procedural Data, Outcome, and Functional Status at 2 Years of Patients With UA or NSTEMI Compared With Patients With SA

	UA or NSTEMI (n = 328)	SA (n = 677)	p Value
Demography			
Age, yrs	64.8 ± 10.7	64.3 ± 10.0	0.41
Male	226 (69)	518 (77)	0.01*
Clinical characteristics			
History of			
Previous MI	144 (44)	223 (33)	<0.01*
Previous PCI	100 (30)	175 (26)	0.13
Diabetes	71 (22)	177 (26)	0.13
Hypertension	212 (65)	427 (63)	0.68
Current smoker	98 (30)	196 (29)	0.77
Hypercholesterolemia	230 (70)	498 (74)	0.25
Positive family history	142 (43)	253 (37)	0.07
Left ventricular ejection fraction, %	58 ± 11.5	57 ± 11.5	0.16
EuroSCORE	3.2 ± 2.3	2.8 ± 2.2	<0.01*
SYNTAX score	14.7 ± 8.4	14.4 ± 8.9	0.69
Procedural characteristics			
No. of indicated lesions/patient	2.7 ± 0.9	2.8 ± 1.0	0.06
Successfully treated lesions, %	96.9	97.4	0.42
Procedure time, min	70 ± 43	70 ± 44	1.0
Contrast agent used, ml	290 ± 137	286 ± 128	0.60
Drug-eluting stents used/patient, n	2.43 ± 1.38	2.4 ± 1.36	0.71
Hospital stay at baseline admission, days	4.5 ± 4.5	3.1 ± 2.7	<0.01*
GP IIb/IIIa inhibitor	55 (17)	85 (13)	0.08
FFR results			
Lesions successfully measured by FFR	391/420 (93)	938/994 (94)	0.39
FFR (all lesions)			
FFR ≤0.80 (ischemic lesions)	0.60 ± 0.13	0.60 ± 0.14	0.65
FFR >0.80 (nonischemic lesions)	0.87 ± 0.06	0.88 ± 0.05	0.43
Lesions with FFR ≤0.80, %	61.8	63.5	0.54
Endpoints			
Death, MI, CABG, or repeat PCI	79 (24.1)	123 (18.2)	0.03*
Death	12 (3.7)	20 (3.0)	0.44
MI	36 (11)	44 (6.5)	0.02*
Death or MI	45 (13.7)	62 (9.2)	0.04*
CABG or repeat PCI	45 (13.7)	72 (10.6)	0.17
Functional status	n = 282	n = 618	
Functional status at 2 yrs			
Patients without event and free from angina	177 (62.8)	422 (68.3)	0.11
Patients free from angina	209 (74.1)	492 (79.6)	0.07

Values are mean ± SD or n (%). *Significant p value (<0.05).

CABG = coronary artery bypass grafting; FFR = fractional flow reserve; GP = glycoprotein; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SA = stable angina; UA = unstable angina.

of using FFR between patients with UA or NSTEMI and patients with SA. The guidance of PCI by FFR rather than angiography alone was associated with similar relative risk reductions of MACE, death, MI, and death or MI in patients with UA and NSTEMI and patients with SA.

The reduction of events by FFR-guidance in patients with UA or NSTEMI is obtained by using fewer stents, as in patients with SA.

This latter observation can be explained because, also in UA or NSTEMI in patients with multivessel coronary disease, unnecessary stenting of nonischemic lesions increases the chance of stent thrombosis, in-stent restenosis, and periprocedural complications, which—in contrast to ischemic lesions—is not outweighed by the benefit of relieving myocardial ischemia (2). Moreover, if the culprit lesion is not clear from the electrocardiogram, as is some-

Table 2. Baseline Characteristics of Patients Stratified to Diagnosis and Treatment Strategy

	UA or NSTEMI			SA		
	Angiography (n = 178)	FFR (n = 150)	p Value	Angiography (n = 318)	FFR (n = 359)	p Value
Age, yrs	64.2 ± 10.5	65.6 ± 11.0	0.22	64.2 ± 10.0	64.3 ± 10.0	0.95
Male	116 (65)	110 (73)	0.12	244 (77)	274 (76)	0.93
History of						
Previous MI	78 (44)	66 (44)	1.00	102 (32)	121 (34)	0.68
Previous PCI	50 (28)	50 (33)	0.34	79 (25)	96 (27)	0.60
Diabetes	38 (21)	33 (22)	0.89	87 (27)	90 (25)	0.54
Hypertension	122 (69)	90 (60)	0.13	205 (65)	222 (62)	0.52
Current smoker	55 (31)	43 (29)	0.71	101 (32)	95 (26)	0.15
Hypercholesterolemia	129 (72)	101 (67)	0.33	233 (73)	265 (74)	0.93
Positive family history	73 (41)	69 (46)	0.37	117 (37)	136 (39)	0.81
LVEF, %	58.5 ± 12.3	57.3 ± 10.4	0.37	56.4 ± 11.9	57.2 ± 11.3	0.39
EuroSCORE	3.3 ± 2.3	3.8 ± 2.5	0.46	2.6 ± 2.1	2.7 ± 2.1	0.71
SYNTAX score	13.9 ± 7.6	15.6 ± 9.1	0.08	14.8 ± 9.4	14.1 ± 8.4	0.28

Values are mean ± SD or n (%). A p value of <0.05 is considered statistically significant.
EuroSCORE = European Systems for Cardiac Operative Risk Evaluations; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

times the case in UA or NSTEMI, FFR can be helpful to select it. Importantly, at the same time concomitant lesions can be interrogated for being responsible for reversible ischemia, and a better decision can be made as to whether or not to treat those lesions invasively.

It has been widely advocated that acute coronary syndromes primarily occur in nonsignificant lesions, and sometimes so-called plaque sealing of all lesions in UA or NSTEMI is advocated on the basis of morphological characteristics of plaque vulnerability (16–19). However, we found no evidence that guiding treatment by FFR and thus only treating ischemia-causing lesions would be less beneficial in UA or NSTEMI than in SA. An important observation in this respect is that in the patients with UA or NSTEMI none of the MIs at follow-up in the FFR-guided group occurred on previously deferred lesions, underlining the safety of deferring nonsignificant lesions even in unstable coronary disease (9).

The present data also indicate that the 2-year event rate is higher for patients who present with UA or NSTEMI than for patients with SA (24.1% vs. 18.2%), stressing the negative impact of unstable coronary disease on prognosis and at the same time showing that these patients in the FAME population are in fact at increased risk of MACE, compared with stable patients. This is reflected in similar relative risk reduction but larger absolute risk reduction by using FFR in these patients.

Study limitations. First of all, the FAME study was powered to show a difference in outcome at 1 year between angiography-guided and FFR-guided PCI with an alpha level of 0.05 and a statistical power of 0.80, assuming event rates at 1 year in the complete study population of 14% in the angiography-guided group and 8% in the FFR-guided group. This means that, for analysis of smaller subgroups, this study in fact is not powered to show superiority of 1 treatment modality above the other. Moreover, the study

Table 3. Angiographic and Procedural Data of Patients Stratified According to Diagnosis and Treatment Strategy

	UA or NSTEMI			SA		
	Angiography (n = 178)	FFR (n = 150)	p Value	Angiography (n = 318)	FFR (n = 359)	p Value
No. of indicated lesions/patient	2.6 ± 0.8	2.7 ± 1.0	0.61	2.8 ± 0.9	2.8 ± 1.0	0.54
Procedural success rate	97	98.4	0.32	96.4	97.6	0.23
Drug-eluting stents used/patient	2.9 ± 1.1	1.9 ± 1.5	<0.01*	2.8 ± 1.2	2.0 ± 1.4	<0.01*
Procedure time, min†	71 ± 48	69 ± 35	0.72	69 ± 41	71 ± 46	0.54
Contrast agent used, ml	308 ± 134	269 ± 139	0.01*	299 ± 124	273 ± 130	0.08
GP IIb/IIIa inhibitor	31 (17)	24 (16)	0.77	45 (15)	40 (11)	0.24
Hospital stay at baseline admission, days	4.6 ± 4.2	4.5 ± 4.7	0.76	3.2 ± 2.9	3.0 ± 2.5	0.42

Values are mean ± SD, %, or n (%). *Significant p value (<0.05). †Plus-minus values are means ± SD.
Abbreviations as in Table 1.

Table 4. Outcome and Functional Status at 2 Years of Patients Stratified to Diagnosis and Treatment Strategy

	UA or NSTEMI				SA				
	Angiography	FFR	ARR (%)*	RRR (%)	Angiography	FFR	ARR (%)*	RRR (%)	Breslow-Day p Value†
Events at 2 yrs	n = 178	n = 150			n = 318	n = 359			
MACE (death, MI, CABG, or repeat PCI)	47 (26.4)	32 (21.3)	5.1	19	64 (20.1)	59 (16.4)	3.7	18	0.922
Death	8 (4.5)	4 (2.7)	1.8	40	11 (3.5)	9 (2.5)	1.0	29	0.786
MI	24 (13.5)	12 (8.0)	5.5	41	25 (7.9)	19 (5.3)	2.6	33	0.742
Death or MI	30 (16.9)	15 (10.0)	6.9	41	34 (10.7)	28 (7.8)	2.9	27	0.556
CABG or repeat PCI	25 (14.0)	20 (13.3)	0.7	5	38 (11.9)	34 (9.5)	2.4	20	0.624
All events	57 (32)	36 (24)	8.0	25	74 (23.3)	62 (17.3)	6.0	26	0.933
Functional status at 2 yrs	n = 147	n = 135	p value		n = 291	n = 327	p value		
Patients without event and free from angina	95 (64.6)	82 (60.7)	0.54		189 (64.9)	233 (71.3)	0.10		
Patients free from angina	110 (74.8)	99 (73.3)	0.78		222 (76.3)	270 (82.6)	0.06		

Values are n (%) or %. Absolute (ARR) and relative risk reductions (RRR) by using FFR for both patients with UA or NSTEMI and patients with SA are shown. Interaction between UA or NSTEMI and SA and treatment for the different outcomes are also shown. A p value <0.05 is considered statistically significant. *Differences in endpoints between treatment strata within diagnosis subgroups are all statistically nonsignificant. †Breslow-Day indicates Breslow-Day test for heterogeneity of odds ratio of FFR-guided PCI versus the odds ratio of angiography-guided PCI within each diagnosis subgroup.
MACE = major adverse cardiac events; other abbreviations as in Table 1.

was not powered to detect differences in subgroups, and therefore, the statistically nonsignificant heterogeneity test must be interpreted as absence of evidence for different effects but is not a proof for the equality of effects across subgroups. If, in studies like this, statistical significance is present in 1 of the complementary subgroups (UA or NSTEMI and SA), it either indicates absence of an effect in the other subgroup or overpowering of the study. Therefore, testing for (or showing evidence against) heterogeneity is the correct purpose of an analysis like this. Nevertheless, it is desirable to confirm these findings of the utility of FFR in patients with UA or NSTEMI in a separate prospective study.

Second, the use of FFR in acute coronary syndromes can be limited by microvascular obstruction, which is often present with extensive MI, although this is still debated (20–24). However, in UA or NSTEMI with creatine kinase <1,000 U/l as defined in the FAME study, obviously the degree of microvascular obstruction—if present—was so limited or rapidly transient that the usefulness of FFR for selection of lesions to be treated was not affected.

This is different from extensive STEMI, excluded in the FAME study, where microvascular obstruction in the infarcted area can be extensive and stunning can last for several days. In such situations, FFR should not be used

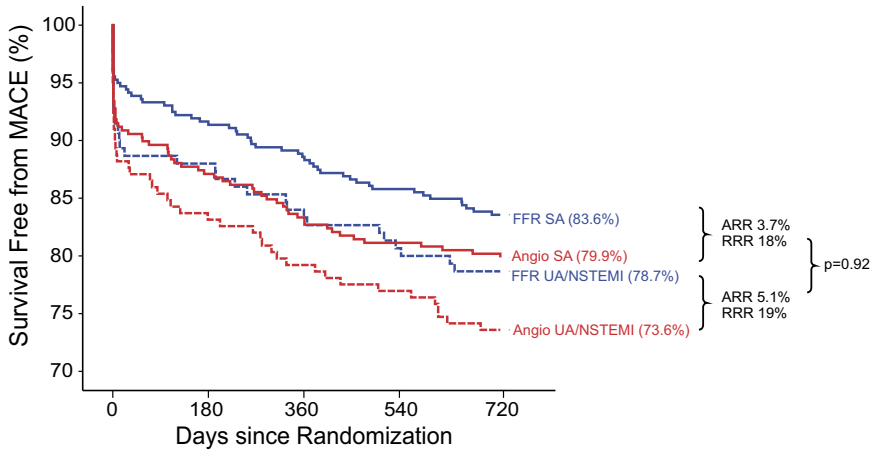

Figure 1. Kaplan-Meier Curves for Survival Free From MACE at 2 Years Stratified to Diagnosis and Treatment Strategy

Kaplan-Meier curves for the percentage survival free from major adverse cardiac events (MACE) at 2 years in the 4 different groups. Also indicated are absolute risk reduction (AAR) and relative risk reduction (RRR) of MACE by fractional flow reserve (FFR)-guided percutaneous coronary intervention in patients with unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI) and patients with stable angina (SA).

until transient microvascular obstruction has resolved and demarcation between vital and necrotic tissue has occurred. Previous studies have indicated that, after STEMI, FFR should not be used to make decisions within the first 5 days after the acute event, which was an exclusion criterion in the FAME study (10).

Conclusions

In patients with UA or NSTEMI in the FAME study, there is no heterogeneity in benefit of FFR guidance of PCI, compared with patients with SA.

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