Patients with coronary stenosis and a fractional flow reserve of ≥ 0.75 measured in daily practice at the VU University Medical Center

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Objectives. The aim of this study was to analyse the rate of major adverse clinical events in patients with coronary artery disease and a fractional flow reserve (FFR) of ≥ 0.75 and deferred for coronary intervention in daily practice.

Methods. From 1 January to 31 December 2006, FFR measurement was initiated in 122 patients (5%) out of 2444 patients referred for coronary angiography. In two patients FFR measurement failed and in one patient the FFR value could no longer be traced in the documents. Thus, 119 patients (84 men, 64 years, range 41-85) were included in the evaluation (145 lesions). Major adverse clinical events (death, myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG)) and the presence of angina were evaluated at follow-up. Furthermore a cost-effectiveness analysis was performed.

Results. In 93 patients (76%) the FFR value was ≥ 0.75 . Seventy of these 93 patients (76%) were treated with medication alone or underwent PCI for a different lesion (medical treatment group). Average duration of follow-up of all 119 patients was 22 months (range 4 days to 30 months). In the medical treatment group seven patients (10%) experienced a major adverse clinical event related to the FFR-evaluated lesion during follow-up. In this study popula-

tion, the use of FFR measurement is cost-reducing provided that at least 65% of the patients in the medical treatment group has had a PCI with stent implantation when the use of FFR measurement is impossible. In this case, the decision to use PCI with stent implantation is purely based on the angiogram.

Conclusions. In patients with a coronary stenosis based on visual assessment and an FFR of ≥ 0.75 deferral of PCI or CABG is safe in daily clinical practice and saves money. (Neth Heart J 2010;18:402-7.)

Keywords: Fractional Flow Reserve; Coronary Artery Disease; Coronary Angioplasty

Defining the haemodynamic significance of a stenosis by visual assessment from the angiogram is difficult. It frequently appears that a stenosis which is not clearly related to symptoms is treated, even if ischaemia can not be attributed to the lesion and even if the stenosis is only of mild or moderate severity.^{1,2} One of the methods to define the pathophysiological significance of an intermediate stenosis (diameter stenosis of 50 to 70%) is the determination of the fractional flow reserve (FFR). The FFR is defined as the ratio of maximal blood flow achievable in a stenotic coronary artery relative to the maximal flow in the same artery if it were normal. Its normal value is 1.0 and a value of < 0.75 identifies lesions which are associated with inducible ischaemia with a high diagnostic accuracy.³ Many studies have demonstrated the safety of deferring revascularisation in patients with moderate coronary stenosis based on FFR results of ≥ 0.75 .⁴⁻⁶

How this concept applies to daily practice is not clear. Therefore, we performed a retrospective analysis of patients with angina pectoris and suspected coronary artery disease who underwent a catheterisation with FFR measurement in the period between 1 January and 31 December 2006. All patients who underwent FFR measurement at our institute were included. The aim of this study

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was to analyse the major adverse clinical event rate in patients with an FFR measurement of ≥ 0.75 and without any further coronary intervention in the FFR-evaluated lesion performed in daily practice in our institution.

In addition a cost-effectiveness analysis was performed with respect to this patient group who would otherwise have had a PCI with stent implantation in the majority of the cases.

Methods

A retrospective observational cohort study was conducted at the VU University Medical Center in Amsterdam. All patients who underwent a coronary angiogram and an FFR measurement between 1 January and 31 December 2006 were evaluated. All patients had a coronary stenosis on the angiogram obtained by visual assessment.

Coronary angiography was performed according to the standard procedure.⁷ In our centre, the severity of each stenosis is classified in the database according to the following criteria based on visual assessment: nonsignificant stenosis (0-50%), moderate stenosis (50-70%), severe stenosis (70-99%) or total occlusion (100%).

After performing coronary angiography, the FFR was measured using a 0.014-inch sensor tipped PCI guidewire. The wire was introduced through a 6- or 7-F guiding catheter, calibrated, advanced into the coronary artery, and positioned distal to the stenosis. Adenosine was administered to induce maximum hyperaemia, either intrave-

nously (140 $\mu\text{g/kg/min}$) or intracoronarily (40 μg in the right or left coronary artery).^{3,8}

The study design is illustrated in figure 1. We divided the patients in two groups. Group 1 consisted of patients with an FFR measurement ≥ 0.75 in a lesion which was indicated as non-significant. Thus, PCI or CABG should be deferred. However, depending on the judgment of the physician and based on complementary clinical data a selected group of patients underwent PCI or CABG. Furthermore, some of the patients with an FFR ≥ 0.75 underwent PCI of a different lesion where no FFR measurement was performed. Group 2 consisted of patients with an FFR of < 0.75 who consequently underwent a PCI with stent implantation or CABG after coronary angiography.

This study was performed to evaluate the justification of a conservative approach in patients with an FFR of ≥ 0.75 (medical treatment group) when performed in daily practice. Consequently, patients who underwent PCI or CABG in group I, based on the decision of the cardiologist, were evaluated together with the patients who underwent an intervention based on FFR < 0.75 (intervention group).

The primary clinical endpoints of this evaluation were major clinical events defined as death, myocardial infarction (MI), PCI and coronary artery bypass grafting (CABG). Death was considered cardiac related, unless proved otherwise. MI was defined as a clinical episode of typical chest pain with development of new pathological Q waves on

Figure 1. Flow chart of the study population of patients with angina pectoris and suspected coronary artery disease who underwent a catheterisation with FFR measurement. From the second level of the figure on, all numbers refer to patients, not lesions. FFR=fractional flow reserve, CABG=coronary artery bypass grafting, PCI=percutaneous coronary intervention.

the electrocardiogram or an increase of serum creatinine kinase levels to more than twice the normal value.⁹ The secondary endpoint includes freedom from angina. Angina was defined according to the New York Heart Association classification (NYHA) into class I to IV. All information was obtained by data from our own database, from the municipal personal records database, by phone calls to the patients who were asked questions according to a prespecified protocol and by written correspondence if phone contact failed.

Furthermore a cost-effectiveness analysis was performed. We made the assumption that any uncertainty regarding the use of revascularisation (PCI or CABG), because FFR measurement is not

a possibility, is solved by having the patients undergo PCI with stent implantation. We use an average of 1.2 stents during each PCI. In our institute about 35% of the patients receive a drug-eluting stent (DES).

Statistics

Continuous data are reported as mean (range). Differences between groups were tested by use of the unpaired Student's *t* test. Categorical data are presented as number and percentage. Differences between groups were tested by use of the χ^2 test with continuity correction. Curves for major adverse cardiac events were constructed according to Kaplan and Meier. A *p* value <0.05

Table 1. Baseline clinical and angiographic characteristics of patients with FFR measurement.

		Overall (n=119)	Group I FFR ≥ 0.75 (n=93)	Group II FFR < 0.75 (n=26)	P value
Patients	Age in years (range)	64 (41-85)	64 (41-84)	64 (41-84)	1.000
	Male	84 (71)	65 (70)	19 (73)	0.943
History	Myocardial infarction	37 (31)	26 (28)	11 (42)	0.247
	- Anterior MI	14 (38)	10 (38)	4 (36)	0.761
	- Posterior/ lateral/ inferior MI	23 (62)	16 (62)	7 (64)	0.407
	Previous PCI	65 (55)	51 (55)	14 (54)	1.000
	Previous CABG	7 (6)	3 (3)	4 (15)	0.063
Anginal symptoms	NYHA class I or II	56 (47)	51 (55)	5 (19)	0.003
	NYHA class III or IV	63 (53)	42 (45)	21 (81)	0.003
Indication CAG	Stable angina pectoris	92 (77)	71 (78)	21 (81)	0.833
	Unstable angina pectoris	15 (13)	11 (11)	4 (15)	0.882
	Other indications	12 (10)	11 (11)	1 (4)	0.409
Angiographic characteristics	Minor vessel disease ($<50\%$ stenoses)	29 (24)	29 (31)	0 (0)	0.003
	Single-vessel disease	50 (42)	36 (39)	14 (54)	0.247
	Two-vessel disease	29 (24)	22 (24)	7 (27)	0.933
	Three-vessel disease	11 (10)	6 (6)	5 (19)	0.108
	No. lesions with FFR measurement	145 (100)	119 (100)	26 (100)	
Stenosis severity	0-50%	68 (47)	67 (56)	1 (4)	<0.001
	50-70%	36 (25)	30 (25)	6 (23)	1.000
	70-99%	41 (28)	22 (19)	19 (73)	<0.001
Lesion site	Main stem	6 (4)	4 (3)	2 (7)	0.645
	RCA	24 (17)	21 (18)	3 (12)	0.640
	LAD	80 (55)	63 (53)	17 (65)	0.348
	LCx	33 (23)	30 (25)	3 (12)	0.212
	Vein graft	2 (1)	1 (1)	1 (4)	0.793

Values are presented as number (%) unless otherwise stated. FFR=fractional flow reserve, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, NYHA=New York Heart Association, CAG=coronary angiography, RCA=right coronary artery, LAD=left anterior descending coronary artery, LCx=left circumflex coronary artery.

was considered statistically significant. All tests were two tailed.

Results

Baseline clinical and angiographic characteristics

Table 1 shows baseline, clinical and angiographic data of both groups. Most patients (77%) had stable angina. The majority of patients (45%) were in class III. Of all 145 lesions, 68 (47%) were classified as nonsignificant stenoses (diameter stenosis of 0-50%). Sixty-seven of these 68 lesions (99%) were present in patients with an FFR ≥ 0.75 .

Because the number of patients with non-significant stenoses was rather high, we took a random sample of seven patients with a total of 13 nonsignificant stenoses and reviewed the coronary angiogram to explore the indication for FFR measurement. Based on the results of this sample we can assume that FFR measurement in patients with one or more nonsignificant stenoses was performed in patients with stenosis severity of just about 50%.

Procedural outcome and choice of treatment

From 1 January to 31 December 2006, FFR measurement was initiated in 122 patients (5%) out of 2444 patients referred for coronary angiography. In two patients, no FFR measurements were performed due to technical reasons (failure to cross the lesion). In one patient the FFR value could no longer be traced in the documents. Thus, 119 patients were included in this evaluation (145 lesions).

The results of the FFR measurements are demonstrated in table 2. The average FFR value

in 119 lesions in group I was 0.89. In 17 lesions (14%) FFR was between 0.75 and 0.80.

The choice of treatment after FFR measurement is demonstrated in figure 1. In group I the cardiologist decided to perform a PCI in the FFR-evaluated lesion in 19 patients (20%) and to perform CABG in four patients (4%) despite an FFR value of ≥ 0.75 . The average FFR value in the 23 lesions in this group (23 patients) was 0.81 and in 15 of these 23 lesions (65%) the FFR value was between 0.75 and 0.80.

In group II, PCI was performed in 23 out of 26 patients (88%). In the remaining three patients CABG (12%) was performed within a few weeks after the CAG.

Clinical follow-up

In 107 patients (90%) follow-up was obtained by data from our own database and by phone calls. In the remaining 12 patients (10%) follow-up was not completed for several reasons: in all these patients phone contact failed (two patients had emigrated and were lost to follow-up, three patients refused to cooperate, in seven patients contact failed). With information from our own database and the municipal personal records database, we know that ten of these 12 patients are alive and did not undergo any cardiac interventions in the VU University Medical Center.

Of all patients (n=119) who underwent a successful FFR measurement, 31 (26%) experienced a major adverse clinical event during follow-up (table 3). A total of nine patients (8%) died during follow-up. In three patients (3%) the cause of death was cardiac, one patient (1%) in group I and

Table 2. FFR measurements results.

		Group I FFR ≥ 0.75		Group II FFR < 0.75	
		Mean FFR (range)	No segments	Mean FFR (range)	No segments
Stenosis severity by visual assessment	Total	0.89 (0.75-1.0)	119 (100)	0.68 (0.60-0.74)	26 (100)
	0-50%	0.91 (0.78-1.0)	67 (56)	0.71 (0.71)	1 (4)
	50-70%	0.89 (0.77-0.99)	30 (25)	0.70 (0.66-0.73)	6 (23)
	70-99%	0.82 (0.75-0.98)	22 (19)	0.68 (0.60-0.74)	19 (73)
Lesion site	Total	0.89 (0.75-1.0)	119 (100)	0.68 (0.60-0.74)	26 (100)
	Left main stem	0.87 (0.77-0.95)	4 (3)	0.67 (0.66-0.68)	2 (7)
	RCA	0.91 (0.76-1.0)	21 (18)	0.73 (0.72-0.74)	3 (12)
	LAD	0.86 (0.75-1.0)	63 (53)	0.68 (0.60-0.74)	17 (65)
	LCx	0.94 (0.82-1.0)	30 (25)	0.67 (0.60-0.74)	3 (12)
	Vein graft	0.94 (0.94)	1 (1)	0.71 (0.71)	1 (4)

Values are presented as number (percentage) or number (range). FFR=fractional flow reserve, RCA=right coronary artery, LAD=left anterior descending coronary artery, LCx=left circumflex coronary artery.

Table 3. Patients with major adverse clinical events after an average follow-up of 22 months (range 4 days to 30 months).

	Overall (n=119)	Medical treatment group (n=70)	Intervention group (n=49)	P value
No. of patients with an event	31 (26)	16 (23)	15 (31)	0.461
No. of patients with >1 event	11 (10)	6 (9)	5 (10)	1.000
No. of patients with 1 or more events related to TV	15 (13)	7 (10)	8 (16)	0.458
No. of patients free from angina	78 (66)	48 (68)	30 (62)	0.526
Total number of events	43	22	21	0.279
Cardiac death	3 (3)	1 (1)	2 (4)	0.753
Non-cardiac death	6 (5)	3 (4)	3 (6)	0.980
Myocardial infarction related to target vessel	6 (5)	4 (6)	2 (4)	1.000
CABG, including target vessel	3 (3)	0 (0)	3 (6)	0.133
TVR	15 (13)	7 (10)	8 (16)	0.458
Non-TVR	10 (8)	7 (10)	3 (6)	0.712

Values are presented as number (percentage). MI=myocardial infarction, TV=target vessel, CABG=coronary artery bypass graft, TVR=target vessel revascularization, non-TVR=revascularisation of a vessel where no FFR measurement was performed.

two patients (4%) in group II. In the remaining six patients (5%) the cause of death was noncardiac.

In the medically treated group (70 patients) 16 patients (23%) experienced a major adverse clinical event during follow-up. In seven (10%) patients the event was related to the FFR-evaluated lesion. In the intervention group (49 patients), 15 patients (31%) experienced a major adverse clinical event during follow-up. In eight patients (16%) the event was related to the FFR-evaluated lesion. After an average of 22 months of follow-up 48 patients (68%) of the medical treatment group were free from angina compared with 30 patients (62%) of the intervention group ($p=0.526$).

Kaplan-Meier estimate of the time to cardiac event related to the FFR-evaluated lesion is presented in figure 2. At 29 months the estimated event-free survival (related to the FFR evaluated lesion) was 90% in the medical group and 84% in the intervention group.

Cost-effectiveness analysis

In this study population PCI was deferred in 70 patients (59%) based on the results of FFR measurement. If all these patients underwent a PCI with stent implantation (65% bare metal stents (45.5 patients) and 35% DES (24.5 patients)) purely based on visual assessment of the stenosis, €47,439 would be saved. However, it is likely that some of these patients would not have received PCI based on the angiogram and/or other clinical parameters. If more than 65% (45 of 70) of the medically treated patients in this study population had received PCI with stent implantation (without availability of FFR measurement) costs would be lower by using FFR measurement.

Discussion

In this unselected cohort of 122 patients undergoing FFR measurement, the overall incidence of cardiac events related to the FFR-evaluated lesion was 13% unrelated to any following intervention. There was no significant difference between the medically treated group and the intervention group (10 and 16% respectively, ($p=0.458$)). The incidence in the medically treated group is comparable with the reported incidence of cardiac events of 5 to 10% during a two-year follow-up in larger studies.¹⁰⁻¹²

Although the patients in the medical group were at less risk, the cardiac event rate was 10% after an average follow-up of 22 months, which is

Figure 2. Kaplan-Meier estimates of the time to cardiac events related to the target vessel during an average follow-up of 22 months (range 4 days to 30 months) for the medical treatment group and the intervention group.

still several times higher than in an aged-matched population without any heart disease.¹³ Therefore, it is obvious that the presence of a functionally nonsignificant stenosis reflects some increased risk. However, the issue addressed here is whether the risk can be reduced by invasive treatment including stenting.

In daily practice, there can be several reasons to perform a PCI despite an FFR ≥ 0.75 . First, there is a so-called 'grey zone' in which FFR is ≥ 0.75 and < 0.80 . FFR values in the 'grey zone' can indicate inducible ischaemia according to recent studies.^{11,14,15} In our group 17 patients (14%) had a lesion with an FFR value between 0.75 and 0.80. Fifteen of these 17 lesions (88%) were revascularised. Second, it must be stated that not all interventional cardiologists are 'believers' of the measurements and some still rely on their experience, the patients' symptoms and visual assessment of the angiogram in patients with typical chest pain. Third, in several cases other methods (positive exercise test or myoview) which demonstrated ischaemia were used to justify the PCI despite an FFR of ≥ 0.75 .

In this study population the FFR-guided PCI strategy is cost saving if more than 45 of the 70 medically treated patients (65%) receive PCI purely based on the angiogram without knowledge of the FFR measurement. However, we have made a lot of assumptions in this study. First, we assumed an average use of 1.2 stents during each PCI. This is probably an underestimation as we know from other reports that the average stent use is nearly 1.5 per patient. Second, in our institute about 35% of the patients receive a DES. In other institutes significantly more patients receive DES (sometimes nearly 90% of the patients). If costs of PCI increase, more money will be saved by FFR measurement. Consequently, cost savings using FFR are underestimated in this evaluation.

Limitations

There are several limitations to this study. First, this study was non-randomised. Second, the process of initial visual assessment was subjective and based on experience, but still more accurately reflects what happens in the real world. Third, in 12 patients (10%) follow-up was not completed for several reasons. It was unknown whether or not these 12 patients experienced an event (except cardiac and noncardiac death) which was not treated in the VU University Medical Center. Finally, the cardiac risk profile of all patients was partially unknown.

Conclusion

In patients with a coronary stenosis based on visual assessment, and an FFR ≥ 0.75 deferral is safe in daily practice and saves money. Furthermore, this analysis demonstrates that, although it is a non-randomised retrospective trial, the results are comparable with recent clinical randomised data. ■

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