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Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis

5-Year Follow-Up of the DEFER Study

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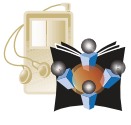
Objectives The purpose of this study was to investigate the appropriateness of stenting a functionally nonsignificant stenosis.

Background Percutaneous coronary intervention (PCI) of an intermediate stenosis without evidence of ischemia is often performed, but its benefit is unproven. Coronary pressure-derived fractional flow reserve (FFR) is an invasive index used to identify a stenosis responsible for reversible ischemia.

Methods In 325 patients scheduled for PCI of an intermediate stenosis, FFR was measured just before the planned intervention. If FFR was ≥0.75, patients were randomly assigned to deferral (Defer group; n = 91) or performance (Perform group; n = 90) of PCI. If FFR was <0.75, PCI was performed as planned (Reference group; n = 144). Clinical follow-up was 5 years.

Results There were no differences in baseline clinical characteristics between the 3 groups. Complete follow-up was obtained in 98% of the patients. Event-free survival was not different between the Defer and Perform groups (80% and 73%, respectively; p = 0.52), but was significantly worse in the Reference group (63%; p = 0.03). The composite rate of cardiac death and acute myocardial infarction in the Defer, Perform, and Reference groups was 3.3%, 7.9%, and 15.7%, respectively (p = 0.21 for Defer vs. Perform group; p = 0.003 for the Reference vs. both other groups). The percentage of patients free from chest pain at follow-up was not different between the Defer and Perform groups.

Conclusions Five-year outcome after deferral of PCI of an intermediate coronary stenosis based on FFR ≥0.75 is excellent. The risk of cardiac death or myocardial infarction related to this stenosis is <1% per year and not decreased by stenting. (J Am Coll Cardiol 2007;49:2105–11) © 2007 by the American College of Cardiology Foundation



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It is generally accepted that revascularization of a coronary stenosis responsible for reversible ischemia is justified as it relieves anginal complaints, and in some situations improves patient outcome (1–6).

In today's interventional practice, however, a stenosis not clearly responsible for symptoms is often stented, even if ischemia cannot be attributed to the lesion and even if it is only of mild or moderate severity (7,8). This applies to either a single intermediate stenosis or to an intermediate stenosis found incidentally in a patient undergoing stenting because of a more severe stenosis elsewhere in the coronary arteries.

Not only is this approach not evidence-based, but it is also unnecessarily expensive and might even be harmful because the risk of periprocedural myocardial infarction or subacute stent thrombosis is not negligible, even when drug-eluting stents are used (9,10). It is unlikely that stenting a hemodynamically nonsignificant stenosis will improve complaints, and there are no data suggesting that it will improve patient prognosis. Defining the hemodynamic significance of a stenosis from the angiogram is difficult (11). In contrast, fractional flow reserve (FFR) is an accurate invasive index to determine in the catheterization laboratory

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Abbreviations and Acronyms

AMI = acute myocardial infarction

FFR = fractional flow reserve

PCI = percutaneous coronary intervention

SPECT = single-photon emission computed tomography

whether an angiographically equivocal stenosis is of functional significance (i.e., responsible for reversible ischemia) (2,12,13). Fractional flow reserve can be simply and rapidly determined just before the planned intervention or during routine diagnostic catheterization. Fractional flow reserve expresses maximum achievable blood flow to the myocardium supplied by a stenotic artery as a fraction of normal maximum flow. Its normal value is 1.0, and a value of 0.75 identifies stenosis associated with inducible ischemia with a high diagnostic accuracy (2,12,13). Although initially applied predominantly in patients with single-vessel disease, FFR has more recently been validated in many other clinical and angiographic conditions such as multivessel disease, previous myocardial infarction, and left main disease (13–19).

Several studies have suggested that FFR-based decision-making about revascularization of an intermediate coronary stenosis results in an excellent short-term outcome (18–20). To date, no long-term outcome data are available.

The prospective, randomized DEFER study was undertaken in patients with stable chest pain and a functionally nonsignificant coronary stenosis to investigate if percutaneous coronary intervention (PCI) of such stenosis is justified. The 2-year follow-up in these patients has been published earlier (18). The 5-year follow-up of this study is the subject of the present report.

Methods

Study design and participants. The international multicenter prospective and randomized DEFER study was performed in 12 hospitals in Europe and 2 hospitals in Asia between June 1997 and December 1998.

Patients were eligible if they fulfilled the following inclusion criteria: 1) referral for elective PCI of a single angiographically significant de novo stenosis (more than 50% diameter stenosis by visual assessment) in a native coronary artery with a reference diameter of more than 2.5 mm; and 2) no evidence of reversible ischemia had been documented by noninvasive testing within the last 2 months.

Thus, noninvasive tests were either negative, inconclusive, or simply not performed. Patients with a total occlusion of the target artery, acute Q-wave infarction, or unstable angina documented by transient ST-segment abnormality were excluded. Patients with small-sized target arteries (reference diameter <2.5 mm) were excluded because these patients have less benefit from PCI and their inclusion could bias the outcome in favor of deferral of PCI. There were no further exclusion criteria. The study protocol was approved by the institutional review boards of all the participating centers, and written informed consent was obtained by all patients before entering the study.

Randomization procedure. Figure 1 depicts the flowchart of the study. Immediately after inclusion in the study and before any physiologic measurement was performed, patients were randomized to deferral or performance of PCI. Next, FFR was determined (see the following text). If FFR was <0.75, the randomization was ignored because such FFR reveals clear evidence of ischemia, PCI is of proven benefit, and it was considered unethical not to stent these lesions (3,4,20).

On the contrary, if the FFR was ≥0.75, making it unlikely that the stenosis was responsible for anginal complaints or reversible ischemia, the randomization was executed, resulting in 1 group of patients with an FFR ≥0.75 in whom PCI was deferred and treated medically, and 1 group of patients with an FFR ≥0.75 in whom stenting was performed despite the fact that their stenosis was most likely not of functional significance.

This resulted in 3 groups of patients: 1) patients with an FFR ≥0.75 in whom PCI was deferred (Defer group); 2) patients with an FFR ≥0.75 in whom PCI was performed (Perform group); and 3) patients with an FFR <0.75 in whom PCI was performed anyway as originally planned (Reference group).

The reason behind this randomization scheme was to avoid any selection bias in favor of the Defer group. Firstly, if the FFR would have been determined before the randomization, there would have been a chance that an operator would not include a patient in the study because the FFR measurement did not fit with his visual interpretation or intuition of what would be the best treatment. Secondly,

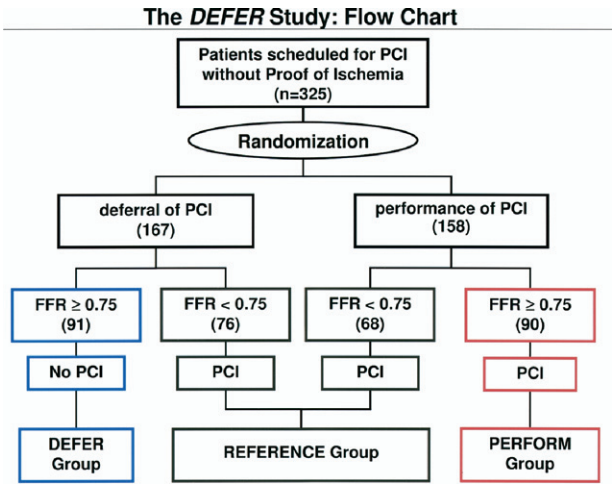

Figure 1 Flowchart of the Study, Randomization, and Definition of the 3 Groups

To avoid bias, randomization was performed before the physiologic measurement (see text). DEFER = deferral of percutaneous coronary intervention; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; PERFORM = performance of percutaneous coronary intervention; REFERENCE = percutaneous coronary intervention anyway because of ischemic fractional flow reserve.

this randomization protocol accounted for possible complications related to the performance of the pressure measurement itself. Thirdly, in this way the unique opportunity was obtained to compare outcome in a group of patients with an ischemic stenosis (Reference group) with a group of patients with a stenosis of similar angiographic severity but not functionally significant (Defer and Perform groups).

Quantitative angiography. After administration of 200 μg of intracoronary nitroglycerine, angiography was performed in at least 2 orthogonal projections both before the procedure and after PCI was performed. All angiograms were analyzed by using the QCA-CMS system (Medis, Leiden, the Netherlands). Using the guiding catheter as a scaling device, reference diameter, minimal lumen diameter, and percent diameter stenosis were calculated as the mean of the values obtained from the 2 projections (21).

Coronary pressure measurement and calculation of FFR. After eligibility was established and immediately after coronary angiography, patients were randomized as described whereafter coronary pressure was measured using a 0.014-inch sensor-tipped PCI guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden). The wire was introduced through a 6- or 7-F guiding catheter, calibrated, advanced into the coronary artery, and positioned distal to the stenosis as previously described (12,13). Adenosine was administered to induce maximum hyperemia, either intravenously (140 μg/kg/min) or intracoronary (15 μg in the right or 20 μg in the left coronary artery) (12,22).

Fractional flow reserve was calculated as the ratio of mean hyperemic distal coronary pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter. The measurement was performed twice, and FFR was taken as the average of both measurements.

Next, PCI was performed in the patients in the Perform and Reference groups, according to local routine of the participating centers. The study was performed in 1997 and 1998, and, therefore, as a matter of fact, only bare-metal stents were used. Coronary pressure measurement after stenting was not allowed, and evaluation of the result of stenting was performed according to the regular routine in the participating centers.

End points and follow-up. Clinical follow-up was performed at hospital discharge and after 1, 3, 6, 12, 24, and 60 months.

The primary end point (outcome) was freedom from adverse cardiac events after 2 years of follow-up. The 5-year follow-up was a secondary end point but is the primary focus of this paper. Adverse cardiac events were defined as all-cause mortality, myocardial infarction, coronary artery bypass grafting, and coronary angioplasty. Cardiac mortality was defined as any death not clearly attributable to a noncardiac cause. An independent end points committee reviewed all events, and analysis was based on the committee's adjucation.

Myocardial infarction was defined as a clinical episode of typical chest pain with development of new pathologic Q waves on the electrocardiogram or an increase of serum kreatinine kinase levels to more than twice the normal value (23,24).

The other secondary end points (quality of life) included freedom from angina (Canadian Cardiovascular Society class I) at 1, 3, 6, 12, 24, and 60 months of follow-up and the usage of antianginal drugs.

Repeated angiography was only performed if clinically indicated or in case of an adverse event. Decision on further treatment and medications during follow-up were entirely left to the discretion of the referring cardiologist.

Statistical analysis. All comparisons were made on an intention-to-treat basis. Continuous variables are described as mean value ± 1 SD, whereas dichotomous variables are described as numbers and percentages. Differences in baseline characteristics between patients in the different groups were analyzed by unpaired Student *t* tests (continuous data) or chi-square tests (dichotomous data).

Patient's survival curves for absence of adverse cardiac events were constructed accorded to the method of Kaplan and Meier and compared by the log-rank test. A p value of <0.05 was considered significant; all tests were 2-tailed.

Results

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

Fractional flow reserve was ≥0.75 in 181 patients of whom 91 belonged to the group randomized to deferral of

Table 1 Baseline Characteristics of the Patients in the 3 Groups

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

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

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PCI (Defer group) and 90 to the group randomized to performance of PCI (Perform group). Fractional flow reserve was <0.75 in 144 patients. In the latter group (Reference group), randomization was ignored and PCI performed anyway. The angiographic stenosis severity in these 3 groups is presented in Figure 2.

Average percent diameter stenosis was more severe in the Reference group (FFR <0.75). However, overlap of data was so large that quantitative coronary angiography was absolutely not useful for predicting the true stenosis severity in individual patients.

Fractional flow reserve was 0.86 ± 0.06 in the Defer group, 0.87 ± 0.07 in the Perform group, and 0.57 ± 0.16 in the Reference group. The absolute difference between the first and second FFR measurement was 0.03 ± 0.02.

Finally, all angiographic parameters after PCI were similar in the Perform and Reference groups, indicating that no difference was present in the quality of stenting.

In-hospital adverse events. Table 2 shows the in-hospital adverse events. None of the patients in the Defer group had an in-hospital event. In the Perform group, 5 patients (5.5%) had an in-hospital event (p = 0.03 for comparison with the Defer group). In the Reference group, 12 patients (8.3%) experienced an in-hospital event (no difference with the Perform group, p = 0.61; p = 0.004 for comparison with the Defer group).

Long-term follow-up. Complete follow-up was obtained in 325 patients (100%) after 12 months, in 317 patients (98%) after 24 months, and in 313 patients (97%) after 5 years.

In Figure 3, the Kaplan-Meier curves of the 3 groups are presented. At first, it can be noted that despite PCI, event-free survival in patients with a functionally significant stenosis (Reference group, FFR <0.75) was significantly lower than in patients with a functionally nonsignificant stenosis (61% vs. 76%; p = 0.03). Secondly, in the patients with a functionally nonsignificant stenosis (FFR ≥0.75), event-free survival was significantly higher irrespective of whether the stenosis was stented or not. Event-free survival of 5 years in the Defer group was 79% and in the Perform group 73% (p = 0.52).

Of all cardiac events, 67%, 70%, and 72%, respectively, could be attributed to the index stenosis in the Defer, Perform, and Reference groups. The different events are specified in Table 2.

The proportion of patients experiencing cardiac death or acute myocardial infarction (AMI) after 5 years is presented in Figure 3, middle panel. For patients with a functionally significant stenosis that was treated by PCI, the rate of cardiac death or AMI was more than 5 times higher than in patients with a similar angiographic but functionally nonsignificant stenosis that was treated medically (p = 0.002).

However, the prognosis of a functionally nonsignificant stenosis was excellent anyway, and, if treated medically, the rate of death or AMI related to that stenosis was <1% per year and not decreased by PCI (Table 2, Fig. 3).

Functional class and use of medication. Figure 3, bottom panel, shows the percentage of patients free from angina at follow-up. This percentage increased significantly in all groups after the index procedure, and this increase persisted throughout the study.

Table 2 In-Hospital Events and Cumulative Events After 5 Years

	FFR ≥0.75		FFR <0.75
	Defer Group (n = 91)	Perform Group (n = 90)	Reference Group (n = 144)
In-hospital events, n (%)	0	5 (5.5)	12 (8.3)
Death	0	0	0
Q-wave MI	0	1 (1.1)	3 (2.1)
Non–Q-wave MI	0	2 (2.2)	6 (4.2)
CABG	0	0	3 (2.1)
(Re)-PCI	0	1 (1.1)	1 (0.7)
Other serious events	0	1 (1.1)	2 (1.4)
Events after 5 yrs, n (%)			
Lost to follow-up	1 (1.1)	2 (2.2)	10 (6.9)
Cardiac death	3 (3.3)	2 (2.3)	8 (6.0)
Noncardiac death	3 (3.3)	3 (3.4)	4 (3.0)
Q-wave MI	0	4 (4.5)	6 (4.5)
Non–Q-wave MI	0	2 (1.1)	7 (5.2)
CABG	1 (1.1)	4 (4.5)	14 (10.4)
TVR	8 (8.9)	8 (9.1)	18 (13.4)
Non-TVR	6 (6.7)	6 (6.8)	11 (8.2)
Other	0	1 (1.1)	2 (1.5)
Total events after 5 yrs, n (%)	21	30	70
Patients with ≥1 event	19 (21)	24 (27)	52 (39)*
Patients free of chest pain	61 (67)	51 (57)	104 (72)†

*p = 0.03 as compared to both other groups; †p = 0.028 as compared to both other groups; p = 0.015 compared to the Perform group.

CABG = coronary artery bypass surgery; FFR = fractional flow reserve; MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target vessel revascularization.

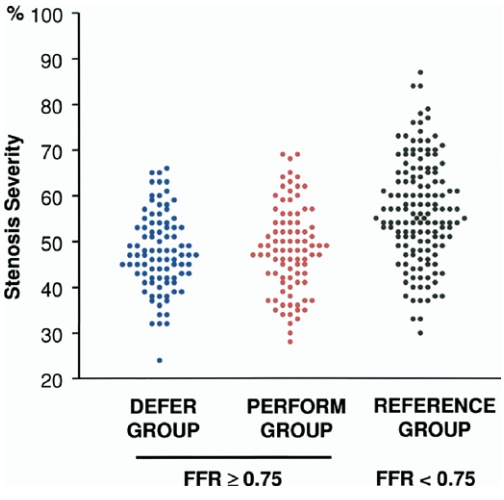

Figure 2 Stenosis Severity at Baseline Assessed by Quantitative Coronary Angiography in the 3 Groups

Abbreviations as in Figure 1.

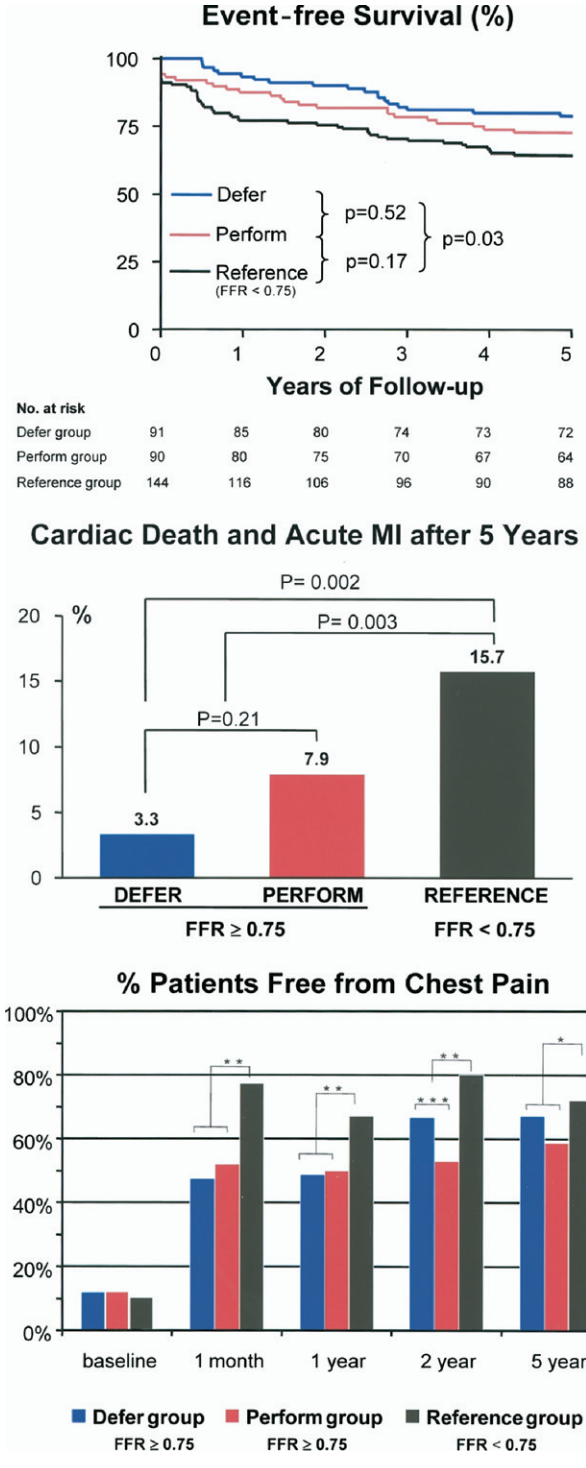

Figure 3 Survival and Adverse Events

(Top) Kaplan-Meier survival curves for freedom from adverse cardiac events during 5 years follow-up for the 3 groups. **(Middle)** Cardiac death and acute myocardial infarction rate in the 3 groups after a follow-up of 5 years. **(Bottom)** Percentage of patients free from chest pain in the 3 groups at baseline and during follow-up. *p = 0.028; **p = <0.001; ***p = 0.021. MI = myocardial infarction; other abbreviations as in Figure 1.

The improvement in anginal status was most pronounced in the Reference group (i.e., the patients with a stenosis able to induce myocardial ischemia) thereby confirming the functional benefit of performing PCI in these patients ($p < 0.001$ at 1 month, 1 year, and 2 years, and $p = 0.028$ at 5 years).

In the patients with a functionally nonsignificant stenosis, there was also significant benefit in terms of anginal class, irrespective of whether the stenosis was stented or not. At 2 years, there was even a significant benefit in favor of the Defer group ($p = 0.021$).

Use of antianginal medication and lipid-lowering drugs was similar in all 3 groups, both at baseline, during, and at the end of the study (Table 3). Aspirin was used by the vast majority of patients during the study (Table 3). Clopidogrel was not a standard drug when the study started and not used at that time, but was started during the course of the study by a number of patients undergoing re-PCI (i.e., after an end point had been reached).

Discussion

From the present study, 2 important conclusions can be drawn. First, PCI of a functionally nonsignificant stenosis (i.e., not responsible for reversible ischemia), as indicated by an FFR ≥0.75, is not of benefit for the patient, neither from a prognostic nor from a symptomatic point of view. Therefore, PCI of such stenosis should be discouraged.

Secondly, the lesions at greatest risk of causing cardiac death or AMI are those that are functionally significant as identified by an FFR <0.75. Even when treated by PCI, the chance of dying or experiencing an AMI related to such a stenosis in the next 5 years is 5 times higher than for a stenosis of similar angiographic severity but not associated with reversible ischemia and treated medically.

In fact, these observations are in line with earlier noninvasive studies by MIBI single-photon emission computed

Table 3 Use of Antianginal and Lipid-Lowering Medication

	FFR ≥0.75		FFR <0.75
	Defer Group	Perform Group	Reference Group
Use at baseline (%)	n = 91	n = 90	n = 144
Beta-blockers	71	62	61
Calcium-channel blockers	43	47	44
Nitrates	56	53	58
Use of any antianginal drug	87	83	88
Statins	37	37	35
Aspirin	92	92	95
Use at 5 yrs (%)	n = 84	n = 83	n = 122
Beta-blockers	55	53	56
Calcium-channel blockers	38	38	37
Nitrates	41	39	32
Use of any antianginal drug	63	64	65
Statins	73	73	72
Aspirin	77	86	89

FFR = fractional flow reserve.

tomography (SPECT) in large numbers of patients indicating that the most important prognostic factor in patients with coronary artery disease is the presence and extent of inducible ischemia (25–29).

The incidence of angiographically visible coronary artery disease increases with age and is at least 40% in a 60-year old population (30). Therefore, when angiography is performed without previous evidence of ischemia, it is not obvious that any abnormality seen at subsequent angiography is responsible for reversible ischemia. This issue is even more relevant today, with an increasing number of patients with multivessel disease, where often 1 or more equivocal, concomitant lesion is seen on the angiogram in addition to 1 or more severe stenoses for which PCI is not disputed (13,14,17,19).

Some previous studies suggested that acute ischemic events not infrequently occur at the site of previously insignificant or mild stenosis (31,32). This has been extended into the general belief that a mild stenosis could have a worse prognosis and that use of PCI in such a lesion might be beneficial (8). However, the present study shows that PCI of such lesions without functional significance does not improve outcome or anginal status and does not reduce the use of antianginal medication. In contrast, our study indicates that significantly greater risk is associated with stenoses responsible for inducible ischemia.

In this context, it should be emphasized that in our study the total event rate in the patients of the Defer group was 21% after 5 years, which is still several times higher than in an age-matched population without any heart disease (32). 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 stenting. In these patients, modifying risk factors and adequate medical treatment are probably of greater prognostic value than a mechanical coronary intervention (33–36). The fact that acute coronary syndromes do not infrequently occur at the site of a nonsignificant stenosis merely reflects the ubiquity of such plaques, not its individual property for rupture.

According to the current guidelines, PCI should be performed after having documented inducible ischemia (1,2). Nevertheless, prior noninvasive evidence of ischemia is present in a minority of patients undergoing PCI (7). Fractional flow reserve, calculated from coronary pressure measurement, is a reliable, invasive index to indicate if a stenosis is ischemia-related and can be determined in the catheterization laboratory in a simple and rapid way (12,18–20). In patients with multivessel disease, in whom MIBI SPECT is often less reliable for indicating the functional significance of individual stenoses (37), FFR reliably interrogates any individual stenosis and, therefore, can be used for immediate decision-making in the catheterization laboratory whether to stent or not (14,17–19).

Our study has several limitations. In the first place, it was performed in an era when drug-eluting stents were not yet available. However, although drug-eluting stents do reduce target vessel revascularization, they do not decrease mortality or the risk of AMI after PCI, which is still 3% to 5% in the first year (7,9,10,38–40). Therefore, if drug-eluting stents would have been available at the time of the study, target vessel revascularization could have been lower in the Perform group, but the mortality and AMI rate as presented in Figure 3, would most likely not have been affected, and the conclusions of the study would have remained unchanged in this respect.

Secondly, the majority of the patients in the DEFER study had a single stenosis of uncertain functional severity in 1 single coronary artery. Today, patients in the catheterization laboratory more often have multivessel disease, often with 1 or more angiographically severe stenoses and concomitant intermediate stenoses (13,14,17,19,20). Although some caution is warranted in extrapolating our study results to the population of today, our study suggests that stenting these coincidental intermediate stenoses without measuring FFR to demonstrate their physiologic significance does not improve outcome and is questionable.

In the third place, our study does not provide data regarding what the adverse cardiac event rate would have been in the Reference group—patients with FFR <0.75—if stenting had not occurred. As explained in the introduction and confirmed in this study, however, stenting ischemia-producing lesions improves symptoms. Therefore, not performing PCI in these patients was not allowed for ethical reasons (1–6). In addition, recent data indicate that not performing revascularization in patients with a hemodynamically significant stenosis with FFR <0.75 is detrimental (20).

Finally, it should be emphasized that the DEFER study was performed in patients with stable chest pain, and no conclusions can be drawn for unstable coronary syndromes with transient electrocardiogram changes or elevated enzymes.

In conclusion, our study indicates that in patients with stable chest pain, the most important prognostic factor of a given coronary artery stenosis with respect to cardiac death or AMI is its ability to produce myocardial ischemia as reflected by an FFR <0.75. In those patients, even when treated by PCI, clinical outcome is significantly worse than in patients with a functionally nonsignificant stenosis (FFR ≥ 0.75).

The risk that a hemodynamically nonsignificant stenosis will cause death or AMI is $<1\%$ per year and is not decreased by stenting.

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APPENDIX

The following centers participated in the study: Academic Hospital Maastricht, Maastricht, the Netherlands; Hospital De Weezenlanden, Zwolle, the Netherlands; University Hospital San Carlos, Madrid, Spain; University Medical Center, Utrecht, the Netherlands; Samsung Medical Center, Seoul, South Korea; Centre Hospitalier Unversitaire Sart-Tilman, Liège, Belgium; Center for Cardiologie, Hamburg, Germany; Sahlgrenska Hospital Göteborg, Göteborg, Sweden; Universitätsklinikum Essen, Essen, Germany; Academisch Medisch Centrum, Amsterdam, the Netherlands; University Hospital Rotterdam Dijkzigt, Rotterdam, the Netherlands; Osaka Police Hospital, Osaka, Japan; Catharina Hospital Eindhoven, Eindhoven, the Netherlands; Cardiovascular Center Aalst, Aalst, Belgium.