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Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis

5-Year Follow-Up of the DEFER Study

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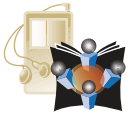
Objectives The purpose of this study was to investigate the appropriateness of stenting a functionally nonsignificant stenosis.

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,

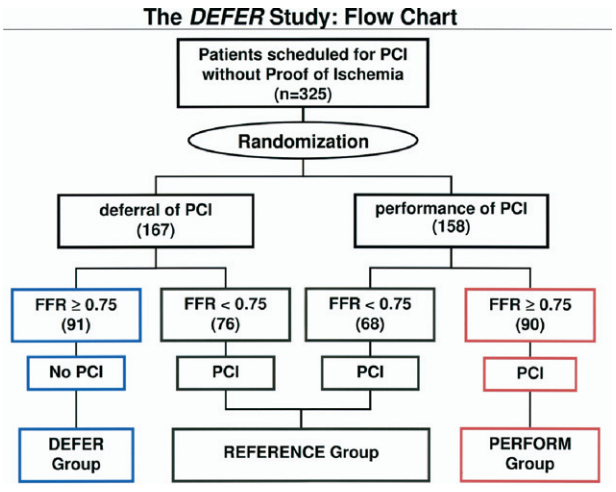

Figure 1 Flowchart of the Study, Randomization, and Definition of the 3 Groups

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.