The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 15, 2009 VOL. 360 NO. 3

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

Pim A.L. Tonino, M.D., Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Uwe Siebert, M.D., M.P.H., Sc.D., Fumiaki Ikeno, M.D., Marcel van 't Veer, M.Sc., Volker Klauss, M.D., Ph.D., Ganesh Manoharan, M.D., Thomas Engstrøm, M.D., Ph.D., Keith G. Oldroyd, M.D., Peter N. Ver Lee, M.D., Philip A. MacCarthy, M.D., Ph.D., and William F. Fearon, M.D., for the FAME Study Investigators*

ABSTRACT

BACKGROUND

In patients with multivessel coronary artery disease who are undergoing percutaneous coronary intervention (PCI), coronary angiography is the standard method for guiding the placement of the stent. It is unclear whether routine measurement of fractional flow reserve (FFR; the ratio of maximal blood flow in a stenotic artery to normal maximal flow), in addition to angiography, improves outcomes.

METHODS

In 20 medical centers in the United States and Europe, we randomly assigned 1005 patients with multivessel coronary artery disease to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography. Before randomization, lesions requiring PCI were identified on the basis of their angiographic appearance. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was 0.80 or less. The primary end point was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year.

RESULTS

The mean (±SD) number of indicated lesions per patient was 2.7±0.9 in the angiography group and 2.8±1.0 in the FFR group ($P=0.34$). The number of stents used per patient was 2.7±1.2 and 1.9±1.3, respectively ($P<0.001$). The 1-year event rate was 18.3% (91 patients) in the angiography group and 13.2% (67 patients) in the FFR group ($P=0.02$). Seventy-eight percent of the patients in the angiography group were free from angina at 1 year, as compared with 81% of patients in the FFR group ($P=0.20$).

CONCLUSIONS

Routine measurement of FFR in patients with multivessel coronary artery disease who are undergoing PCI with drug-eluting stents significantly reduces the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year. (ClinicalTrials.gov number, NCT00267774.)

From the Catharina Hospital, Eindhoven, the Netherlands (P.A.L.T., N.H.J.P., M.V.); Cardiovascular Center Aalst, Aalst, Belgium (B.D.B.); University of Health Sciences, Medical Informatics, and Technology, Hall in Tirol, Austria, and Massachusetts General Hospital, Harvard Medical School, Boston (U.S.); Stanford University Medical Center and Palo Alto Veterans Affairs Health Care Systems, Stanford, CA (F.I., W.F.F.); Medizinische Poliklinik, Campus-Innenstadt, University Hospital, Munich, Germany (V.K.); the Heart Centre, Royal Victoria Hospital, Belfast, United Kingdom (G.M.); Rigshopitalet, Copenhagen (T.E.); Western Infirmary, Glasgow, United Kingdom (K.G.O.); Northeast Cardiology Associates, Bangor, ME (P.N.V.L.); and King's College Hospital, London (P.A.M.). Address reprint requests to Dr. Pijls at the Department of Cardiology, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands, or at nico.pijls@inter.nl.net.

*The investigators participating in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study are listed in the Appendix.

N Engl J Med 2009;360:213-24.

The presence of myocardial ischemia is an important risk factor for an adverse clinical outcome.[1-3] Revascularization of stenotic coronary lesions that induce ischemia can improve a patient's functional status and outcome.[3-5] For stenotic lesions that do not induce ischemia, however, the benefit of revascularization is less clear, and medical therapy alone is likely to be equally effective.[6,7]

With the introduction of drug-eluting stents, the percentage of patients with multivessel coronary artery disease in whom percutaneous coronary intervention (PCI) is performed has increased.[8,9] Because drug-eluting stents are expensive and are associated with potential late complications, their appropriate use is critical.[10,11] However, in patients with multivessel coronary artery disease, determining which lesions cause ischemia and warrant stenting can be difficult. Noninvasive stress imaging studies are limited in their ability to accurately localize ischemia-producing lesions in these patients.[12] Although coronary angiography often underestimates or overestimates a lesion's functional severity, it is still the standard technique for guiding PCI in patients with multivessel coronary artery disease.[13,14]

Fractional flow reserve (FFR) 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.[15] 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. 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%.[15-17] The information provided by FFR is similar to that obtained with myocardial perfusion studies, but it is more specific and has a better spatial resolution, because every artery or segment is analyzed separately, and masking of one ischemic area by another, more severely ischemic, zone is avoided.[12,18] Deferring PCI in nonischemic stenotic lesions as assessed by FFR is associated with an annual rate of death or myocardial infarction of approximately 1% in patients with single-vessel coronary artery disease, which is lower than the rate after routine stenting.[7] On the other hand, deferring PCI in lesions with an FFR of less than 0.75 to 0.80 may result in worse outcomes than those obtained with revascularization.[19] Retrospective studies suggest that in patients with multivessel coronary artery disease, FFR-guided PCI is associated with a favorable outcome with respect to event-free survival.[20,21]

For patients with multivessel coronary artery disease, identifying an approach to PCI that would result in a more judicious use of stents, while still achieving complete relief of myocardial ischemia, could improve the clinical outcome and decrease health care costs. The objective of this randomized study was to compare treatment based on the measurement of FFR in addition to angiography with the current practice of treatment guided solely by angiography in patients with multivessel coronary artery disease for whom PCI is the appropriate treatment.

METHODS

STUDY DESIGN

The design of this study has been described previously (Fig. 1).[22] In eligible patients with multivessel coronary artery disease, the investigator indicated which lesions had stenosis of at least 50% of their diameter and were thought to require PCI on the basis of angiographic appearance and clinical data. Patients were then randomly assigned to either angiography-guided or FFR-guided PCI. Computerized randomization was stratified according to study site and performed in blocks of 25, with the use of sealed envelopes. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions with drug-eluting stents. For patients assigned to FFR-guided PCI, FFR was measured in each diseased coronary artery, and drug-eluting stents (Endeavor [Medtronic], Cypher [Cordis], or Taxus [Boston Scientific], with the choice of stent at the discretion of the surgeon) were placed in indicated lesions only if the FFR was 0.80 or less.

The study protocol was approved by the institutional review board or ethics committee at each participating center; all patients provided written informed consent. An independent clinical events committee whose members were unaware of treatment assignments adjudicated all events. Data management and statistical analysis were performed by an independent data coordinating center (University of Health Sciences, Medical Informatics, and Technology, Hall in Tirol, Austria). The study sponsors (Radi Medical Systems, Stich-

ting Vrienden van het Hart Zuidoost Brabant [Friends of the Heart Foundation], and Medtronic) had no role in the methods, data acquisition, data analysis, reporting, or publication of this study.

STUDY POPULATION

Patients were included in the study if they had multivessel coronary artery disease, which was defined as coronary artery stenoses of at least 50% of the vessel diameter in at least two of the three major epicardial coronary arteries, and if PCI was indicated. Patients who had had a myocardial infarction with ST-segment elevation could be included if the infarction had occurred at least 5 days before PCI. Patients who had had a myocardial infarction without ST-segment elevation could be included earlier than 5 days after the infarction if the peak creatine kinase level was less than 1000 U per liter. Patients who had undergone previous PCI could be included in the study. Patients who had 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, or a contraindication to the placement of drug-eluting stents and patients who were pregnant were excluded.

TREATMENT

PCI was performed with the use of standard techniques. Procedure time was defined as the interval between the introduction of the first guiding catheter and the removal of the last guiding catheter. A record was kept of all materials used, such as guiding catheters, guidewires, balloons, stents, and, if applicable, pressure wires and vials of adenosine. FFR was measured with a coronary pressure guidewire (Radi Medical Systems) at maximal hyperemia induced by intravenous adenosine, which was administered at a rate of 140 μg per kilogram of body weight per minute through a central vein. FFR is calculated as the mean distal coronary pressure (measured with the pressure wire) divided by the mean aortic pressure (measured simultaneously with the guiding catheter) during maximal hyperemia.[23] In the case of diffuse atherosclerosis punctuated by focal areas of more severe stenosis, or in the case of more than one stenosis within the same artery, pressure pullback recordings during hyperemia were performed as described previously.[18,22] Because FFR cannot be measured in a totally occluded artery before an intervention is performed, a default FFR value of 0.50 was recorded in the case of totally occluded arteries in the FFR group. All patients were treated with aspirin and clopidogrel for at least 1 year after PCI. If a patient underwent repeat coronary angiography during follow-up, the initially assigned strategy of angiography guidance or FFR guidance was followed in the case of stent placement.

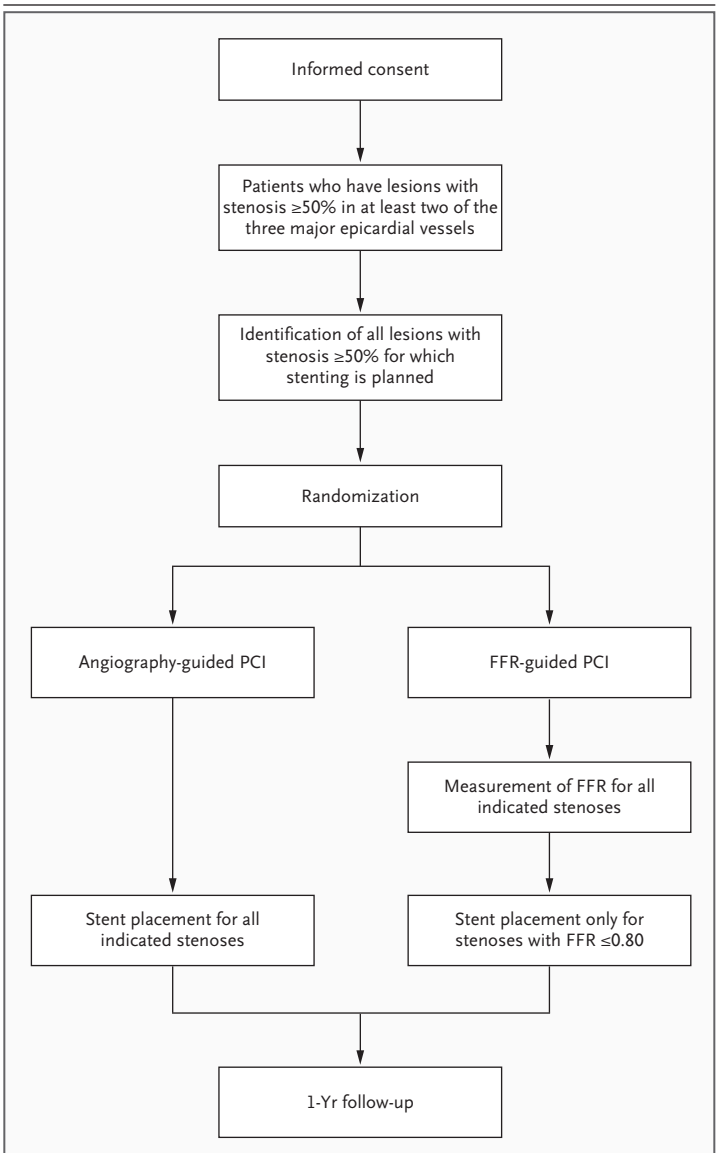

Figure 1. Design of the Study.
FFR denotes fractional flow reserve, and PCI percutaneous coronary intervention.

END POINTS AND FOLLOW-UP

The primary end point was the rate of major adverse cardiac events at 1 year. Major adverse cardiac events were defined as a composite of death,

myocardial infarction, and any repeat revascularization. Secondary end points included the procedure time, the amount of contrast agent used, functional class at 1 year as assessed with the use of the Canadian Cardiovascular Society classification system, health-related quality of life (as measured by the score on the European Quality of Life–5 Dimensions [EQ-5D] scale),[24] the number of antianginal medications used, and the individual components of the primary end point at 1 year, as well as the rates of major adverse cardiac events at 30 days and 6 months. Cost-effectiveness was a secondary end point as well. Death was defined as death from all causes. Myocardial infarction was defined as an elevation of the creatine kinase MB fraction by a factor of 3 or more or new Q waves in 2 or more contiguous leads of the electrocardiogram (ECG).[25] Levels of total creatine kinase and the creatine kinase MB fraction were measured in all patients between 12 and 24 hours after PCI. Quantitative coronary angiography was performed offline, and the scoring system used in the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) study (ClinicalTrials.gov number, NCT00114972) was used to assess the extent and severity of coronary artery disease; the SYNTAX score was calculated by the core laboratory.[26,27] After discharge, a follow-up assessment was performed at 1 month, 6 months, and 1 year. Before PCI and at all other time points, the severity of angina, graded according to the Canadian Cardiovascular Society classification system, and the number of antianginal medications prescribed were assessed. An ECG was obtained before PCI, within 24 hours after PCI, and at 1 year after PCI. The quality-of-life questionnaire (EQ-5D) was completed by the patient before PCI, at 1 month, and at 1 year.[24,28]

STATISTICAL ANALYSIS

The primary purpose of the data analysis was to determine whether the 1-year probability of major adverse cardiac events differed significantly between patients who underwent angiography-guided PCI and those who underwent FFR-guided PCI. The estimated minimum sample size of 426 patients in each group was based on a two-sided chi-square test with an alpha level of 0.05 and a statistical power of 0.80, assuming 1-year rates of major adverse cardiac events of 14% in the angiography group and 8% in the FFR group. These rates were based on outcome data in the early studies of drug-eluting stents that were available in 2005 when the present study was designed.[29]

All enrolled patients were included in the analysis of primary and secondary end points according to the intention-to-treat principle. Categorical variables, including the primary end point and its components, are expressed as proportions and were compared with the use of the chi-square test. Continuous variables are expressed as means and standard deviations and were compared with the use of an unpaired t-test or the Mann–Whitney U test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Kaplan–Meier curves are shown for the time-to-event distributions of the primary end point and its individual components. All statistical analyses were performed with the use of SAS software, version 9 (SAS Institute). One interim analysis was performed, immediately after inclusion of the first 50 patients, to monitor safety and to exclude any frank inconsistencies in the study protocol or case-record form.

RESULTS

BASELINE CHARACTERISTICS AND ANGIOGRAPHIC DATA

From January 2006 through September 2007, a total of 1005 patients were enrolled in 20 centers in the United States and Europe (Fig. 2). Of the 1005 patients, 496 were randomly assigned to angiography-guided PCI and 509 to FFR-guided PCI. Baseline characteristics of the two groups were similar, as were the number of indicated lesions, vessel and lesion dimensions as assessed by quantitative coronary angiography, and extent and severity of coronary artery disease as indicated by the SYNTAX score (Table 1). A total of 26.5% of the patients in the angiography group had a left ventricular ejection fraction of 50.0% or less, as compared with 28.6% in the FFR group (P=0.47).

PCI

A total of 2415 stents were placed, of which 2339 (96.9%) were drug-eluting stents. In the case of 76 stenoses, a bare-metal stent had to be placed for technical reasons. Significantly more stents per patient were placed in the angiography group than in the FFR group (2.7±1.2 vs. 1.9±1.3, P<0.001) (Table 2). In the FFR group, FFR was successfully measured in 94.0% of all lesions. In 874 lesions (63.0%), the FFR was 0.80 or less, and stents were

placed in these lesions, per protocol. In 513 lesions (37.0%), the FFR was greater than 0.80, and stents were not placed in these lesions. The procedure time was similar in the two groups (70±44 minutes in the angiography group and 71±43 minutes in the FFR group, P=0.51). Significantly more contrast agent was used in the angiography group than in the FFR group (302±127 ml vs. 272±133 ml, P<0.001).

PRIMARY END POINT

Complete 1-year follow-up data were obtained for 98.1% of the patients (11 were lost to follow-up in the angiography group and 8 were lost to follow-up in the FFR group [P=0.45]). The primary end point (a composite of death, myocardial infarction, and repeat revascularization) occurred in 91 patients (18.3%) in the angiography group and in 67 (13.2%) in the FFR group (P=0.02) (Table 3). Event-free survival is shown by means of a Kaplan–Meier curve (Fig. 3A).

SECONDARY END POINTS

All-cause mortality at 1 year was 3.0% (15 deaths, 10 of which had cardiac causes) in the angiography group and 1.8% (9 deaths, 7 of which had cardiac causes) in the FFR group (P=0.19). Myocardial infarction occurred in 43 patients (8.7%) in the angiography group and in 29 (5.7%) in the FFR group (P=0.07). The numbers of small, periprocedural infarctions (as indicated by a creatine kinase MB fraction that was 3 to 5 times the upper limit of the normal range) were 16 and 12 in the two groups, respectively. A total of 47 patients (9.5%) in the angiography group and 33 (6.5%) in the FFR group required repeat revascularization (P=0.08). The 1-year rate of death or myocardial infarction, which was not a prespecified secondary end point but is an important clinical variable, was 11.1% (55 patients) in the angiography group and 7.3% (37 patients) in the FFR group (P=0.04). At 1 year, 77.9% of the patients in the angiography group were free from angina, as compared with 81.3% in the FFR group (P=0.20). A total of 67.6% of patients in the angiography group and 73.0% in the FFR group did not have an event and were free from angina at 1 year (P=0.07).

The mean cost of materials used in the index procedure was $6,007±2,819 in the angiography group, as compared with $5,332±3,261 in the FFR group (P<0.001). The mean length of stay in the hospital was 3.7±3.5 days in the angiography group, as compared with 3.4±3.3 days in the FFR group (P=0.05).

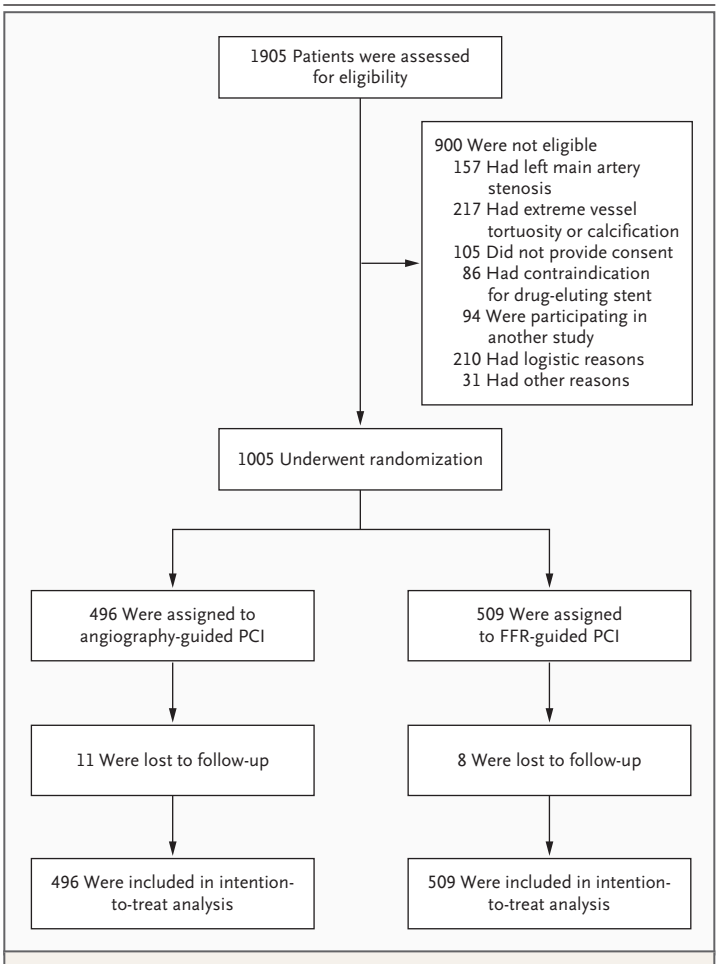

Figure 2. Study Enrollment and Randomization.
FFR denotes fractional flow reserve, and PCI percutaneous coronary intervention.

DISCUSSION

This study showed that in patients with multivessel coronary artery disease, routine measurement of FFR during PCI, as compared with the standard strategy of PCI guided by angiography, significantly reduced the rate of the primary composite end point of death, myocardial infarction, and repeat revascularization at 1 year. The combined rate of death and myocardial infarction was also significantly reduced. Without prolonging the procedure, the FFR-guided strategy reduced the number of stents used, decreased the amount of contrast agent used, and resulted in a similar,

if not improved, functional status with no decrease in health-related quality of life. Furthermore, the procedure-related costs were significantly lower with the FFR-guided strategy. These results were achieved in a patient population with complex disease. The event rate in the angiography group was similar to that in groups in other recent studies evaluating the use of drug-eluting stents for patients with multivessel coronary artery disease.[30-33] Moreover, in 89.6% of the patients assigned to the FFR-guided strategy, at least one stenotic lesion had an FFR of 0.80 or less, indicating ischemia, and stents were placed in these lesions; 63.0% of all lesions that were measured had an FFR of 0.80 or less. These data reflect that in this study, FFR was used in an unselected population, not just in persons with intermediate lesions, of which only approximately 35% have an FFR that indicates ischemia.[7]

In our study, routine measurement of FFR consistently reduced the incidence of all types of adverse events by approximately 30%. The absolute

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Angiography Group (N=496)	FFR Group (N=509)	P Value†
Demographic			
Age — yr	64.2±10.2	64.6±10.3	0.47
Sex — no. (%)			0.30
Male	360 (72.6)	384 (75.4)	
Female	136 (27.4)	125 (24.6)	
Clinical			
Angina classification — no. (%)‡			0.13
I	115 (23.2)	132 (25.9)	
II	165 (33.3)	170 (33.4)	
III	118 (23.8)	132 (25.9)	
IV	98 (19.8)	75 (14.7)	
Previous myocardial infarction — no. (%)	180 (36.3)	187 (36.7)	0.84
Previous PCI — no. (%)	129 (26.0)	146 (28.7)	0.34
Diabetes — no. (%)	125 (25.2)	123 (24.2)	0.65
Hypertension — no. (%)	327 (65.9)	312 (61.3)	0.10
Hypercholesterolemia — no. (%)	362 (73.0)	366 (71.9)	0.62
Family history — no. (%)	190 (38.3)	205 (40.3)	0.49
Current smoker — no. (%)	156 (31.5)	138 (27.1)	0.12
Unstable angina — no. (%)			
With dynamic ECG changes	91 (18.3)	73 (14.3)	0.09
Without dynamic ECG changes	87 (17.5)	77 (15.1)	0.29
Left ventricular ejection fraction — %	57.1±12.0	57.2±11.0	0.92
Medication			
Beta-blocker — no. (%)	377 (76.0)	395 (77.6)	0.55
Calcium antagonist — no. (%)	96 (19.4)	121 (23.8)	0.09
Nitrate — no. (%)	179 (36.1)	167 (32.8)	0.27
ACE inhibitor or ARB — no. (%)	255 (51.4)	267 (52.5)	0.74
Statin — no. (%)	397 (80.0)	417 (81.9)	0.45
Aspirin — no. (%)	454 (91.5)	465 (91.4)	0.92
Clopidogrel — no. (%)	292 (58.9)	310 (60.9)	0.51

Table 1. (Continued.)

Characteristic	Angiography Group (N=496)	FFR Group (N=509)	P Value†
Angiographic Findings			
Indicated lesions per patient — no.§	2.7±0.9	2.8±1.0	0.34
Extent of occlusion — no. of lesions/total no. (%)			
50–70% narrowing	550/1350 (40.7)	624/1414 (44.1)	
71–90% narrowing	553/1350 (41.0)	530/1414 (37.5)	
91–99% narrowing	207/1350 (15.3)	202/1414 (14.3)	
Total occlusion	40/1350 (3.0)	58/1414 (4.1)	
Patients with total occlusion — no. (%)	37 (7.5)	54 (10.6)	
Quantitative coronary analysis			
Extent of stenosis — %	61.2±16.6	60.4±17.6	0.24
Minimal luminal diameter — mm	1.0±0.4	1.0±0.5	0.35
Reference diameter — mm	2.5±0.6	2.5±0.7	0.81
Lesion length — mm	12.6±6.9	12.5±6.5	0.42
SYNTAX score¶	14.5±8.8	14.5±8.6	0.95
EQ-5D score‖	64.7±19.2	66.5±18.3	0.24

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin II–receptor blocker, ECG electrocardiogram, FFR fractional flow reserve, and PCI percutaneous coronary intervention.
† All categorical variables were compared with the use of the chi-square test; all continuous variables were compared with the use of the Mann–Whitney U test.
‡ Angina was assessed according to the Canadian Cardiovascular Society Functional Classification of Angina Pectoris.
§ Before randomization, the physician who performed the procedure indicated all lesions to be included in the study and classified them according to severity by visual estimation, on the basis of the angiogram.
¶ The SYNTAX score is the scoring system used in the SYNTAX study to assess the extent and severity of coronary artery disease. A score of 0 indicates no angiographically significant coronary disease. There is no designated highest score. A score of 14.5 indicates rather extensive disease.
‖ The European Quality of Life–5 Dimensions (EQ-5D) scale is a visual-analogue scale that measures health-related quality of life. Scores range from 0 to 100, with higher scores indicating higher health-related quality of life.

risk of major adverse cardiac events was reduced by 5 percentage points, which means that measuring FFR in 20 patients can prevent one adverse event. Routine measurement of FFR probably improved the outcomes by allowing more judicious use of stents and equal relief of ischemia. It has been known for decades that the most important prognostic factor among patients with coronary artery disease is the presence and extent of inducible ischemia.[1] It might be speculated that PCI of a stenotic lesion that is inducing ischemia (indicated by an FFR ≤0.80) is beneficial overall because the risk of stent thrombosis or restenosis is outweighed by the significant reduction in the risk of ischemic events with stent placement. On the other hand, PCI of a stenotic lesion that is not inducing ischemia (FFR >0.80) increases the chance of an adverse event because the risk of thrombosis and restenosis associated with the placement of the stent, with the attendant risk of subsequent death, myocardial infarction, or repeat revascularization, exceeds by far the low risk associated with a hemodynamically nonsignificant stenosis in which a stent has not been placed.[7] Thus, performing PCI on all stenoses that have been identified by angiography, regardless of their potential to induce ischemia, diminishes the benefit of relieving ischemia by exposing the patient to an increased stent-related risk, whereas systematically measuring FFR can maximize the benefit of PCI by accurately discriminating the lesions for which revascularization will provide the most benefit from those for which PCI may only increase the risk.

Our results also suggest that the outcomes with PCI as compared with those achieved with medical treatment, such as in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggres-

Table 2. Results of PCI.*

Variable	Angiography Group (N=496)	FFR Group (N=509)	P Value†
Procedure time — min‡	70±44	71±43	0.51
Volume of contrast agent used — ml	302±127	272±133	<0.001
Drug-eluting stents			
No. of stents per patient			
Mean	2.7±1.2	1.9±1.3	<0.001
Median (interquartile range)	3 (2–3)	2 (1–3)	
Total length per patient — mm	51.9±24.6	37.9±27.8	<0.001
Average diameter per patient — mm	2.96±0.33	2.92±0.36	0.13
Total no. of stents	1359	980	
Zotarolimus-eluting — no. (%)	603 (44.4)	403 (41.1)	
Sirolimus-eluting — no. (%)	273 (20.1)	202 (20.6)	
Paclitaxel-eluting — no. (%)	414 (30.5)	316 (32.2)	
Other — no. (%)	69 (5.1)	59 (6.0)	
Lesions in which stents successfully placed — no./total no. (%)§	1237/1350 (91.6)	819/874 (93.7)	
FFR-guided strategy			
Lesions successfully measured for FFR — no./total no. (%)¶	NA	1329/1414 (94.0)	
FFR	NA	0.71±0.18	
Ischemic lesions	NA	0.60±0.14	
Nonischemic lesions	NA	0.88±0.05	
Lesions with FFR ≤0.80 — no./total no. (%)	NA	874/1387 (63.0)	
Lesions with FFR >0.80 — no./total no. (%)	NA	513/1387 (37.0)	
Cost of materials — $‖	6,007±2,819	5,332±3,261	<0.001
Hospital stay at baseline admission — days	3.7±3.5	3.4±3.3	0.05

* Plus–minus values are means ±SD. FFR denotes fractional flow reserve, and PCI percutaneous coronary intervention.
† All categorical variables were compared with the use of the chi-square test; all continuous variables and the number of drug-eluting stents per patient were compared with the use of the Mann–Whitney U test.
‡ Procedure time was defined as the time from the introduction of the first guiding catheter until the removal of the last guiding catheter.
§ For the angiography group, the data shown are the number and percentage of lesions indicated at baseline; for the FFR group, the data are the number and percentage of lesions with an FFR of 0.80 or less.
¶ The data shown are the number and percentage of all indicated lesions. A total of 85 lesions were not measured for FFR: 58 (4.1%) that were in totally occluded arteries, for which a default FFR value of 0.50 was assigned, and 27 (1.9%) that could not be measured for FFR because of technical reasons.
‖ The materials used during PCI (e.g., guiding catheters, guidewires, balloons, stents, and, if applicable, pressure wires and vials of adenosine) were recorded, and their costs were calculated according to the actual local price and translated into U.S. dollars.

sive Drug Evaluation) trial (NCT00007657),[6] or with coronary-artery bypass grafting, such as in the SYNTAX trial,[34] might be improved if the PCI is performed with FFR guidance and might ensure functionally complete revascularization with more appropriate use of stents. A substudy of the COURAGE trial,[3] which showed that patients with the greatest relief of ischemia had the lowest rates of death or myocardial infarction, further supports the concept that PCI should be guided by physiological considerations and not solely by anatomical ones.

Earlier studies have suggested that incomplete revascularization results in an outcome that is not optimal.[35,36] However, in those studies the decision not to perform PCI for a particular lesion was

Table 3. Primary and Secondary End Points at 1 Year.*

End Point	Angiography Group (N=496)	FFR Group (N=509)	P Value†	Relative Risk with FFR Guidance (95%CI)
Events at 1 year				
Composite of death, myocardial infarction, and repeat vascularization — no. (%)‡	91 (18.3)	67 (13.2)	0.02	0.72 (0.54–0.96)
Death — no. (%)	15 (3.0)	9 (1.8)	0.19	0.58 (0.26–1.32)
Myocardial infarction — no. (%)	43 (8.7)	29 (5.7)	0.07	0.66 (0.42–1.04)
Repeat vascularization — no. (%)	47 (9.5)	33 (6.5)	0.08	0.68 (0.45–1.05)
Death or myocardial infarction — no. (%)	55 (11.1)	37 (7.3)	0.04	0.66 (0.44–0.98)
Total events — no.	113	76		
Events per patient — no.	0.23±0.53	0.15±0.41	0.02	
Functional status at 1 year				
Patients without event and free from angina — no./total no. (%)	326/482 (67.6)	360/493 (73.0)	0.07	
Patients free from angina — no./total no. (%)	374/480 (77.9)	399/491 (81.3)	0.20	
Antianginal medications — no.§	1.23±0.74	1.20±0.76	0.48	
Score on EQ-5D visual-analogue scale¶	73.7±16.0	74.5±15.7	0.65	

* Plus–minus values are means ±SD. FFR denotes fractional flow reserve.
† All categorical variables were compared with the use of the chi-square test; all continuous variables and the number of events per patient were compared with the use of the Mann–Whitney U test.
‡ This was the primary end point of the study.
§ Antianginal medications included beta-blockers, calcium antagonists, and nitrates.
¶ The European Quality of Life–5 Dimensions (EQ-5D) scale is a visual-analogue scale that measures health-related quality of life. Scores range from 0 to 100, with higher scores indicating higher health-related quality of life.

made on the basis of an angiographic or anatomical assessment. The FFR-guided strategy in this study resulted in functionally complete revascularization but with fewer stents placed.

In this study we tried to reflect routine practice with respect to multivessel PCI. Therefore, patients with angiographically significant left main coronary artery disease were excluded, as were patients presenting with a recent myocardial infarction with ST-segment elevation, since multivessel PCI is generally deferred in such patients. Patients in the latter group could be included 5 days or later after the acute event, if at least two angiographically significant lesions were present. Patients who had undergone previous PCI were included in the present study, which is often not the case in randomized trials of coronary revascularization.[6,34,37]

Other potential limitations of this study include the use of an FFR cutoff value of 0.80 as reflecting inducible ischemia. In previous studies, in a variety of clinical and angiographic conditions, FFR cutoff values between 0.75 and 0.80 have been used.[15-18] We decided to take the upper limit of that small transition zone in order to limit the number of ischemic lesions left untreated. Finally, the current data are restricted to a 1-year follow-up period. Theoretically, lesions in the FFR group in which stents were not placed could progress and lead to events after 1 year. However, from previous studies it is known that persons who have lesions with an FFR of more than 0.80, if optimally treated with medication, have an excellent prognosis, with an event rate of approximately 1% per year up to 5 years after measurement.[7] We intend to collect follow-up data for a total period of 5 years for the present study.

In conclusion, in patients with multivessel coronary artery disease undergoing PCI with drug-eluting stents, routine measurement of FFR in addition to angiographic guidance, as compared with PCI guided by angiography alone, results in a significant reduction in major adverse events at 1 year, a finding that supports the evolving strategy of revascularization of ischemic lesions and medical treatment of nonischemic lesions.

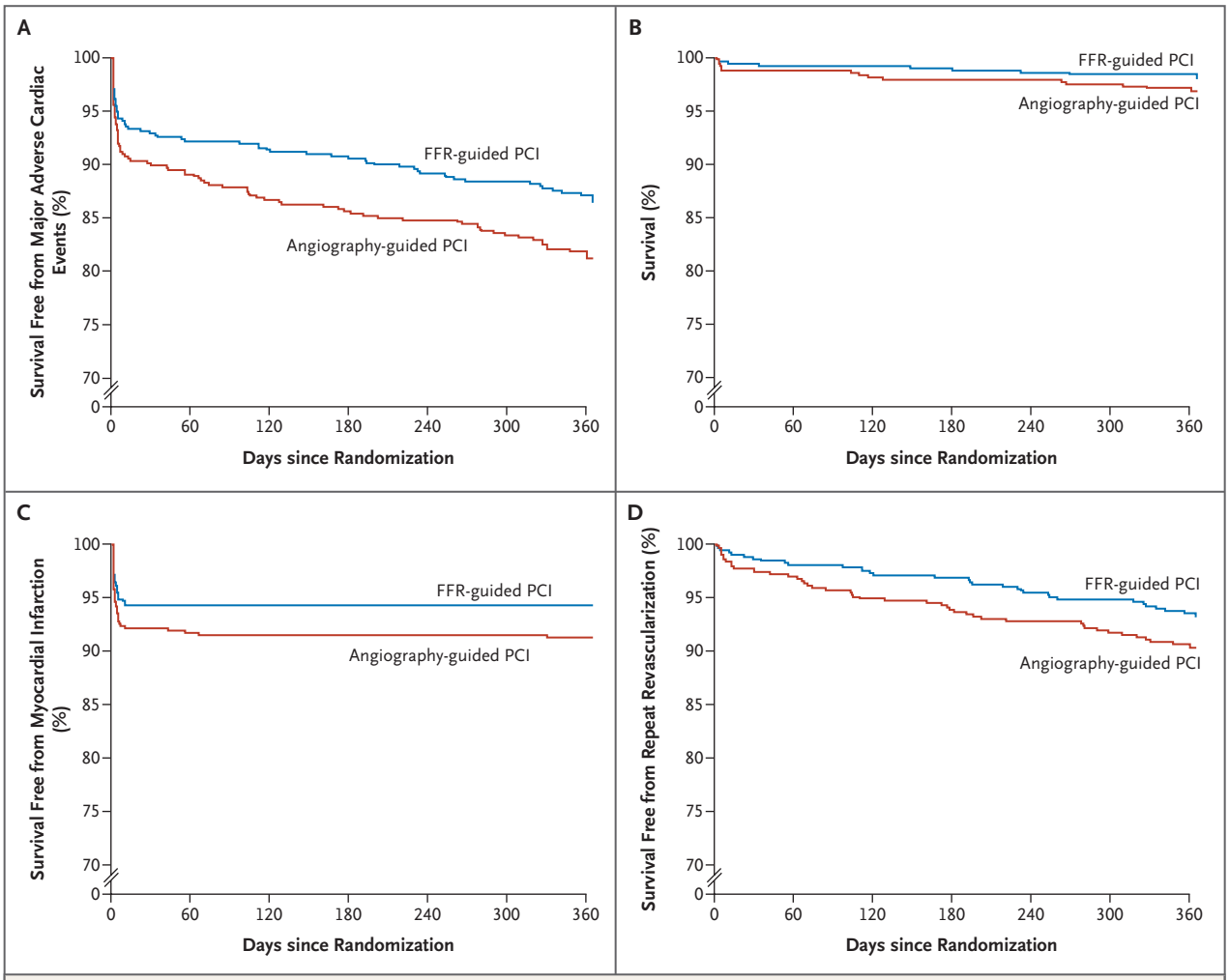

Figure 3. Kaplan–Meier Survival Curves According to Study Group.
FFR denotes fractional flow reserve, and PCI percutaneous coronary intervention.

Supported by unrestricted research grants from Radi Medical Systems and Stichting Vrienden van het Hart Zuidoost Brabant. Medtronic provided limited financial support to some centers by tailoring the price of the Endeavor stents to the local reimbursement system.

Dr. Pijls reports receiving an institutional research grant for the Catharina Hospital Eindhoven from Radi Medical Systems; Dr. Engstrøm, lecture fees from Nycomed Denmark; Dr. Oldroyd, consulting fees from Radi Medical Systems, Boston Scientific, and Cordis and lecture fees and grant support from Boston Scientific; Dr. Ver Lee, lecture fees from Radi Medical Systems; and Dr. Fearon, consulting fees from Abbott Vascular. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The members of the FAME study group are as follows: **Steering Committee —** N. Pijls (principal investigator), W. Fearon (principal investigator), B. De Bruyne, P. Tonino; **Writing Committee —** N. Pijls, W. Fearon, B. De Bruyne, U. Siebert, P. Tonino; **Clinical Events Committee —** E. Eeckhout, M. El Gamal, E. Barbato, M. Kern; J. Hodgson; **Data Analysis Committee —** U. Siebert, R. Gothe, B. Bornschein; **Study investigators: United States —** *Stanford University Medical Center and Palo Alto Veterans Affairs Health Care Systems, Stanford, CA:* W. Fearon, F. Ikeno, T. Brinton, D. Lee, S. Williams, A. Yeung; *Northeast Cardiology Associates, Bangor, ME:* P. Ver Lee, A. Wiseman, G. Crespo, R. Fincke, P. Vom Eigen; *Saint Louis University, St. Louis:* M. Lim, R. Longnecker; *University of Louisville, Louisville, KY,* M. Leesar, V. Yalamanchili, S. Ikram; *University of Virginia Health System, Charlottesville:* M. Ragosta, L. Gimple, L. Lipson; *Medical University of South Carolina, Charleston:* E. Powers. **United Kingdom —** *Western Infirmary, Glasgow:* K. Oldroyd, M. Lindsay, S. Robb, S. Watkins; *Heart Centre, Royal Victoria Hospital, Belfast:* G. Manoharan, P. Tierney; *King's College Hospital, London:* P. MacCarthy, A. Shah, M. Thomas, J. Hill; *Bristol Royal In-*

firmary, Bristol: A. Baumbach, P. Wilde, A. Nightingale, A. Skyme-Jones, E. Barnes; **Sweden —** *Södersjukhuset, Stockholm:* I. Herzfeld, M. Törnerud, P. Alström, N. Witt; *Helsinborgs Lasarett, Helsingborg:* F. Schersten; **the Netherlands —** *Catharina Hospital, Eindhoven:* J. Bonnier, C. Botman, B. Brueren, J. van Dantzig, J. Koolen, H. Michels, C. Peels, N. Pijls, P. Tonino; **Germany —** *Medizinische Poliklinik, Campus-Innenstadt, University Hospital, Munich:* V. Klauss, J. Rieber, T. Schiele, M. Leibig, Y. Sohn, J. Söllner; *University Hospital Bergmannsheil, Bochum:* W. Bojara, M. Lindstaedt, A. Yazar; *Klinikum Bogenhausen, Munich:* G. Riess; *Klinikum Darmstadt, Darmstadt:* G. Werner; **Denmark —** *Rigshospitalet, Copenhagen:* T. Engstrøm, H. Kelbaek, E. Jørgensen, S. Helqvist, K. Saunamäki, P. Clemmensen, J. Kastrup; *Aalborg Sygehus Syd, Aalborg:* K. Rasmussen, O. Frobert; **Belgium —** *Cardiovascular Center Aalst, Aalst:* B. De Bruyne, N. Melikian, J. Bartunek, E. Wyffels, G. Heyndrickx, W. Wijns, M. Vanderheyden, H. Batjoens.

REFERENCES

1. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000;101:1465-78.
2. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171-85.
3. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283-91.
4. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037-43.
5. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. JAMA 2007; 297:1985-91.
6. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-16.
7. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007; 49:2105-11.
8. Moses JW, Stone GW, Nikolsky E, et al. Drug-eluting stents in the treatment of intermediate lesions: pooled analysis from four randomized trials. J Am Coll Cardiol 2006;47:2164-71.
9. Ong AT, van Domburg RT, Aoki J, Sonnenschein K, Lemos PA, Serruys PW. Sirolimus-eluting stents remain superior to bare-metal stents at two years: medium-term results from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2006;47:1356-60.
10. Kaiser C, Brunner-La Rocca HP, Buser PT, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitäts Trial (BASKET). Lancet 2005;366:921-9. [Erratum, Lancet 2005;366: 2086.]
11. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006;48: 2584-91.
12. Lima RS, Watson DD, Goode AR, et al. Incremental value of combined perfusion and function over perfusion alone by gated SPECT myocardial perfusion imaging for detection of severe three-vessel coronary artery disease. J Am Coll Cardiol 2003;42:64-70.
13. Fischer JJ, Samady H, McPherson JA, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. Am J Cardiol 2002;90:210-5.
14. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995;92:2333-42.
15. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334: 1703-8.
16. De Bruyne B, Pijls NH, Bartunek J, et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation 2001;104:157-62.
17. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995;92:3183-93.
18. Pijls NH. Optimum guidance of complex PCI by coronary pressure measurement. Heart 2004;90:1085-93.
19. Legalery P, Schiele F, Seronde MF, et al. One-year outcome of patients submitted to routine fractional flow reserve assessment to determine the need for angioplasty. Eur Heart J 2005;26:2623-9.
20. Berger A, Botman KJ, MacCarthy PA, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. J Am Coll Cardiol 2005;46:438-42.
21. Wongpraparut N, Yalamanchili V, Pasnoori V, et al. Thirty-month outcome after fractional flow reserve-guided versus conventional multivessel percutaneous coronary intervention. Am J Cardiol 2005;96: 877-84.
22. Fearon WF, Tonino PA, De Bruyne B, Siebert U, Pijls NH. Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study. Am Heart J 2007;154:632-6. [Erratum, Am Heart J 2007;154:1243.]
23. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993;87:1354-67.
24. The EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990; 16:199-208.
25. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.
26. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1: 219-27.
27. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the SYNTAX score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072-81.
28. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
29. Kastrati A, Dibra A, Eberle S, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. JAMA 2005;294:819-25.
30. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331-41.
31. Stankovic G, Cosgrave J, Chieffo A, et al. Impact of sirolimus-eluting and paclitaxel-eluting stents on outcome in patients with diabetes mellitus and stenting in more than one coronary artery. Am J Cardiol 2006;98:362-6.

32. Tanimoto S, Daemen J, Tsuchida K, et al. Two-year clinical outcome after coronary stenting of small vessels using 2.25-mm sirolimus- and paclitaxel-eluting stents: insight into the RESEARCH and T-SEARCH registries. Catheter Cardiovasc Interv 2007; 69:94-103.
33. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001-9.
34. Ong AT, Serruys PW, Mohr FW, et al. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. Am Heart J 2006;151: 1194-204.
35. Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. Circulation 2006;113:2406-12.
36. Teirstein PS. The dueling hazards of incomplete revascularization and incomplete data. Circulation 2006;113:2380-2.
37. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001; 344:1117-24.