

Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve–Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease

Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation)

BACKGROUND: Previous studies found that percutaneous coronary intervention (PCI) does not improve outcome compared with medical therapy (MT) in patients with stable coronary artery disease, but PCI was guided by angiography alone. FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) compared PCI guided by fractional flow reserve with best MT in patients with stable coronary artery disease to assess clinical outcomes and cost-effectiveness.

METHODS: A total of 888 patients with stable single-vessel or multivessel coronary artery disease with reduced fractional flow reserve were randomly assigned to PCI plus MT (n=447) or MT alone (n=441). Major adverse cardiac events included death, myocardial infarction, and urgent revascularization. Costs were calculated on the basis of resource use and Medicare reimbursement rates. Changes in quality-adjusted life-years were assessed with utilities determined by the European Quality of Life–5 Dimensions health survey at baseline and over follow-up.

RESULTS: Major adverse cardiac events at 3 years were significantly lower in the PCI group compared with the MT group (10.1% versus 22.0%; $P<0.001$), primarily as a result of a lower rate of urgent revascularization (4.3% versus 17.2%; $P<0.001$). Death and myocardial infarction were numerically lower in the PCI group (8.3% versus 10.4%; $P=0.28$). Angina was significantly less severe in the PCI group at all follow-up points to 3 years. Mean initial costs were higher in the PCI group (\$9944 versus \$4440; $P<0.001$) but by 3 years were similar between the 2 groups (\$16792 versus \$16737; $P=0.94$). The incremental cost-effectiveness ratio for PCI compared with MT was \$17300 per quality-adjusted life-year at 2 years and \$1600 per quality-adjusted life-year at 3 years. The above findings were robust in sensitivity analyses.

CONCLUSIONS: PCI of lesions with reduced fractional flow reserve improves long-term outcome and is economically attractive compared with MT alone in patients with stable coronary artery disease.

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Clinical Perspective

What Is New?

- The new findings in this article are that percutaneous coronary intervention in patients with stable coronary disease and abnormal fractional flow reserve results in lower rates of death, myocardial infarction, and urgent revascularization at the 3-year follow-up compared with an initial strategy of best medical therapy.
- Patients who receive percutaneous coronary intervention up-front continue to have significantly improved quality of life at the 3-year follow-up.
- An initial strategy of percutaneous coronary intervention in patients with stable coronary disease and abnormal fractional flow reserve is attractive from an economic standpoint.

What Are the Clinical Implications?

- Percutaneous coronary intervention in patients with stable coronary disease and abnormal fractional flow reserve is advantageous compared with medical therapy alone because it results in improved clinical outcomes and quality of life at no increased cost by the 3-year follow-up.

The optimal treatment strategy for patients with stable angina and coronary artery disease (CAD) remains controversial, especially whether medical therapy (MT) alone or percutaneous coronary intervention (PCI) plus MT is most appropriate. Previous studies such as the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) suggested little difference in clinical outcome and quality of life between these 2 strategies and significantly higher costs with the addition of PCI.^{1,2} These studies were limited, however, by including a significant proportion of patients with CAD causing little or no myocardial ischemia and by the use of older PCI techniques.³

Measuring fractional flow reserve (FFR) with a pressure wire at the time of coronary angiography identifies coronary lesions that are responsible for significant ischemia and identifies patients most likely to benefit from PCI.⁴ The FAME 2 trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) randomized patients with stable angina and at least 1 coronary lesion with an abnormal FFR to either MT alone or PCI with current-generation drug-eluting stents.⁵ The long-term clinical outcomes, effects on quality of life, and cost-effectiveness of these 2 strategies are unknown.

METHODS

Study Design and Oversight

The design of the FAME 2 trial has been reported previously.⁶ Briefly, the FAME 2 trial was a prospective, international,

randomized controlled trial conducted at 28 sites in Europe and North America that enrolled patients with stable angina and angiographically documented CAD (1-, 2-, or 3-vessel disease) suitable for PCI with current-generation drug-eluting stents. Before randomization, FFR was measured across all lesions that appeared to be angiographically significant. Patients who had ≥ 1 stenosis in a major coronary artery with an FFR ≤ 0.80 were randomly assigned to FFR-guided PCI plus the best available MT or to the best available MT alone. Patients with an FFR > 0.80 across all lesions were not randomized, and 50% of these patients were followed up in a registry. The inclusion and exclusion criteria are detailed in the [Appendix in the online-only Data Supplement](#). All patients provided written informed consent, and local Institutional Review boards approved the study protocol.

Treatment

Patients randomly allocated to PCI received a loading dose of clopidogrel (600 mg) and aspirin immediately before the procedure if they were not already taking these medications. All stenoses with an FFR ≤ 0.80 were treated with second-generation drug-eluting stents. All patients who underwent PCI received clopidogrel at a dose of 75 mg daily for at least 12 months, in addition to the best available MT. All patients were given a medication tracking form for recording weekly medication use and doses. Patients who smoked were counseled about smoking cessation. Patients with diabetes mellitus were referred to a diabetes specialist to receive the best available treatment.

Study End Points and Follow-Up

The primary end point was the rate of major adverse cardiac events defined as a composite of death resulting from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization. In this report, we focus on 3-year clinical outcomes, quality of life, and cost-effectiveness. For each outcome event, a detailed narrative was produced. All events were adjudicated by independent clinical events committee members who were unaware of the assigned treatment. Revascularization was considered to be urgent when a patient was admitted to the hospital with persistent or increasing symptoms (with or without changes in the ST segment or T wave or elevated biomarker levels) and the revascularization procedure was performed during the same hospitalization. All urgent revascularizations were adjudicated to determine the type of trigger (myocardial infarction, electrocardiographic evidence of ischemic changes, or clinical features only) and the severity (according to the criteria of the Canadian Cardiovascular Society) of angina that led to the procedure. Follow-up visits were scheduled at 1 and 6 months and at 1, 2, and 3 years.

Quality of Life and Resource Use

Healthcare resource use associated with the index hospitalization and with follow-up outpatient visits, diagnostic tests, medications, adverse events, and hospitalizations was recorded prospectively. Use of guiding catheters, coronary guidewires, balloon catheters, and stents; medications; cardiac catheterization laboratory time; and hospital days for each patient

were quantified, and cost weights in US dollars were applied to calculate the cost of the index procedure for each patient. Costs were assigned to postdischarge events on the basis of Medicare's reimbursement rate per diagnosis-related group for hospitalizations and the Medicare fee schedule for outpatient tests and all physician fees. Pharmacy costs for cardiac medications were estimated from internet pharmacy prices. We did not discount costs because of the limited follow-up period. All costs were assessed from the perspective of the US healthcare system and are reported in 2012 US dollars. The cost weights for adverse events and resources are included in [Tables I and II in the online-only Data Supplement](#).

Quality-adjusted life-years (QALYs) were derived from health-related quality of life and survival during the 3-year time horizon of the trial. Quality-of-life indexes (utilities) were evaluated at baseline, 1 month, and 1, 2, and 3 years with the European Quality of Life–5 Dimensions (EQ-5D) instrument with US weights scaled from 0 (death) to 1 (perfect health). Because the protocol did not mandate it, only a minority of patients completed the 3-year EQ-5D. To account for the missing values at the 3-year time point, we used multiple imputation using measured utility values and reported angina, as well as baseline patient characteristics, lesion location, and clinical events. In another analysis, we used a last value carried forward technique to estimate utility at 3 years on the basis of the values at 2 years. The overall QALYs for each patient were estimated as the area under the curve determined by the utility values at baseline, 1 month, and 1, 2, and 3 years. The individual delta QALY was calculated by multiplying years and the change in the health utility from baseline as an increment of utilities gained by the treatment for each patient.

Statistical Analysis

All patients were analyzed according to the group to which they were originally assigned (intention-to-treat analysis). We compared categorical data using the χ^2 test or Fisher exact test and continuous data with *t* tests or the Mann-Whitney *U* test as appropriate. Comparisons between baseline and 1-month and 1-, 2-, or 3-year utilities were made by the paired *t* test, whereas comparisons of differences between groups were made by the 2-sample *t* test. We constructed Kaplan-Meier curves for the primary end point and revascularization and treatment groups. Cox proportional-hazard models were fitted to estimate hazard ratios with 95% confidence intervals for the between-group comparisons, and the log-rank test was used to calculate *P* values. The cost-effectiveness of PCI was expressed as the incremental cost-effectiveness ratio (ICER), defined as the difference in the cumulative costs of PCI and MT divided by the difference in cumulative QALYs of PCI and MT. We computed confidence intervals for differences in costs and QALYs and in the ICER using the bootstrap technique with the percentile method with 10000 replications. Sensitivity analyses were performed for a range of \pm \$400 on the cost of coronary stents, by setting to zero the cost of the coronary pressure wire and adenosine in the initial procedure in the MT group, and by setting to zero the total cost of the initial catheterization procedure in the MT group. Full details of the imputation model are provided in [Methods in the online-only Data Supplement](#). The data, analytical

methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

RESULTS

Patients

Enrollment in the trial was stopped prematurely on the advice of the Data Safety Monitoring Board because a highly significant difference had developed in the primary end point. Among 1220 patients enrolled, 888 patients had at least 1 stenosis with an FFR \leq 0.80 and were randomly assigned to FFR-guided PCI plus MT (447 patients) or to MT alone (441 patients). The 332 patients with an FFR $>$ 0.80 in all stenoses visible on angiography were not randomized to a treatment, and 50% were randomly selected for follow-up in a registry while receiving MT. The numbers of patients with follow-up in the PCI group and the MT group were as follows: 442 (99%) and 434 (98%) at 1 month, 437 (98%) and 429 (97%) at 1 year, 427 (96%) and 424 (96%) at 2 years, and 422 (94%) and 413 (94%) at 3 years, respectively. The numbers of patients with EQ-5D data in the PCI group and the MT group were as follows: 439 (98%) and 432 (98%) at baseline, 422 (94%) and 422 (96%) at 1 month, 406 (91%) and 403 (91%) at 1 year, 378 (85%) and 383 (87%) at 2 years, and 20 (5%) and 19 (4%) at 3 years. The clinical characteristics of the patients at baseline were well balanced between the 2 treatment groups.⁶

Clinical Outcome

After 3 years of follow-up, major adverse cardiac events occurred in 10.1% of the 447 patients (1235 person-years of follow-up) randomized to PCI and in 22.0% of the 441 patients (1090 person-years of follow-up) randomized to MT ($P<0.001$; Figure 1). There was a nonsignificant reduction in death or myocardial infarction in patients randomized to PCI (8.3% versus 10.4%; $P=0.28$), as well as a highly significant difference in the rate of urgent revascularization (4.3% versus 17.2%; $P<0.001$; Table 1). The rates of late revascularization, both urgent and nonurgent, were lower in the PCI group than the MT group, with a widening difference over time ([Figure 1 in the online-only Data Supplement](#)). After 3 years, 195 patients (44.2%) in the MT group had undergone a late PCI, whereas 45 patients (10.3%) in the PCI group had undergone repeat revascularization. The percentage of patients with Canadian Cardiovascular Society class II, III, or IV angina was significantly lower in the PCI group than in the MT group at all time points during 3 years of follow-up (Figure 2). At 3 years, the difference in angina was driven by fewer patients with class II and III angina. Patients assigned to the PCI

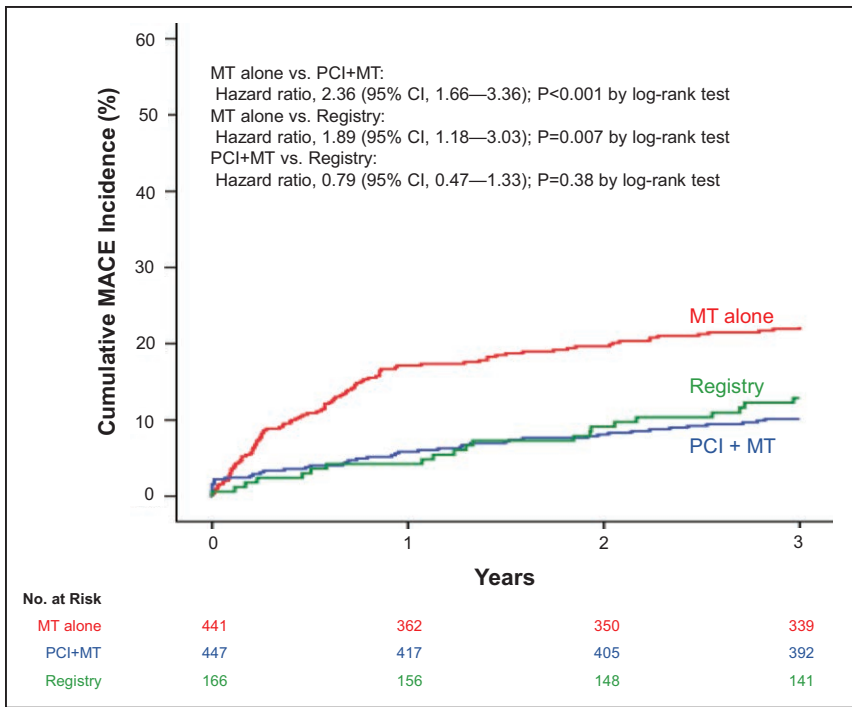


Figure 1. Cumulative incidence of major adverse cardiac events (MACEs).

Kaplan-Meier curves are shown for the cumulative incidence of the MACEs of death, myocardial infarction, or urgent revascularization in the group randomly assigned to percutaneous coronary intervention (PCI) plus medical therapy (MT), the group randomly assigned to the MT alone, and the group who did not undergo randomization and were enrolled in a registry. CI indicates confidence interval.

group received fewer antianginal medications, including calcium channel blockers, β -blockers, and long-acting nitrates, than those assigned to the MT group at all time points (Table III in the online-only Data Supplement).

Costs and Health Outcomes

The initial procedure and hospitalization costs were significantly greater in the PCI group compared with the MT group ($\$9944 \pm 6507$ versus $\$4440 \pm 4462$; $P < 0.001$),

primarily because of the cost of the PCI procedure. Over the subsequent years, follow-up costs were higher in the MT group such that the mean cumulative costs at 3 years were not significantly different between the PCI group and the MT group ($\$16792 \pm 10139$ versus $\$16737 \pm 13108$; $P = 0.94$; Figure 3). The median costs were $\$13248$ (interquartile range, $\$10519$ to $\$19593$) for the PCI group and $\$12132$ (interquartile range, $\$6202$ to $\$22724$) for the MT group. The higher follow-up costs in the MT arm were driven by the higher rate of revascularization and coronary angiography. The higher cost of antiplatelet therapy in the PCI arm was balanced by the higher cost of antianginal agents in the MT arm (Table 2).

Table 1. Clinical Outcomes at the 3-Year Follow-Up

	PCI+MT (n=447), n (%)	MT alone (n=441), n (%)	P Value	Registry (n=166), n (%)
MACEs	45 (10.1)	97 (22.0)	<0.001	21 (12.7)
Death	12 (2.7)	16 (3.6)	0.43	5 (3.0)
MI	28 (6.3)	34 (7.7)	0.41	11 (6.6)
Urgent revascularization	19 (4.3)	76 (17.2)	<0.001	11 (6.6)
Death or MI	37 (8.3)	46 (10.4)	0.28	15 (9.0)
Other end points				
Cardiac death	5 (1.1)	5 (1.1)	0.98	3 (1.8)
Any F/U revascularization	46 (10.3)	195 (44.2)	<0.001	24 (14.5)
Nonurgent	28 (6.3)	133 (30.2)	<0.001	15 (9.0)
Stroke	10 (2.2)	6 (1.4)	0.33	2 (1.2)
Stent thrombosis	7 (1.6)	2 (0.5)	0.10	1 (0.6)

F/U indicates follow-up after the initial procedure; MACE, major adverse cardiac event; MI, myocardial infarction; MT, medical therapy; and PCI, percutaneous coronary intervention.

P values were calculated with the log-rank test for the PCI+MT group compared with the MT group.

In the PCI group, the health utility significantly increased at 1 month and then slightly decreased but remained significantly higher during follow-up compared with baseline. In the MT group, the utility did not significantly improve from baseline at any time point during follow-up (Figure 4). The change in QALYs from baseline to 2 years was significantly greater in the PCI arm compared with the MT arm (0.070 [SE, 0.015] versus 0.006 [SE, 0.015]; $P < 0.002$). QALYs at 3 years were numerically higher in the PCI group compared with the MT group (2.528 [SE, 0.019] versus 2.493 [SE, 0.020]; $P = 0.22$). Because of differences at baseline in QALYs, the individual delta QALYs were significantly greater in the PCI group compared with the MT group at the 3-year follow-up (0.0752 [SE, 0.022] versus -0.0390 [SE, 0.023]; $P < 0.001$).

Cost-Effectiveness Analysis

At the 2-year follow-up, QALYs were numerically higher in the PCI group than in the MT group (1.716

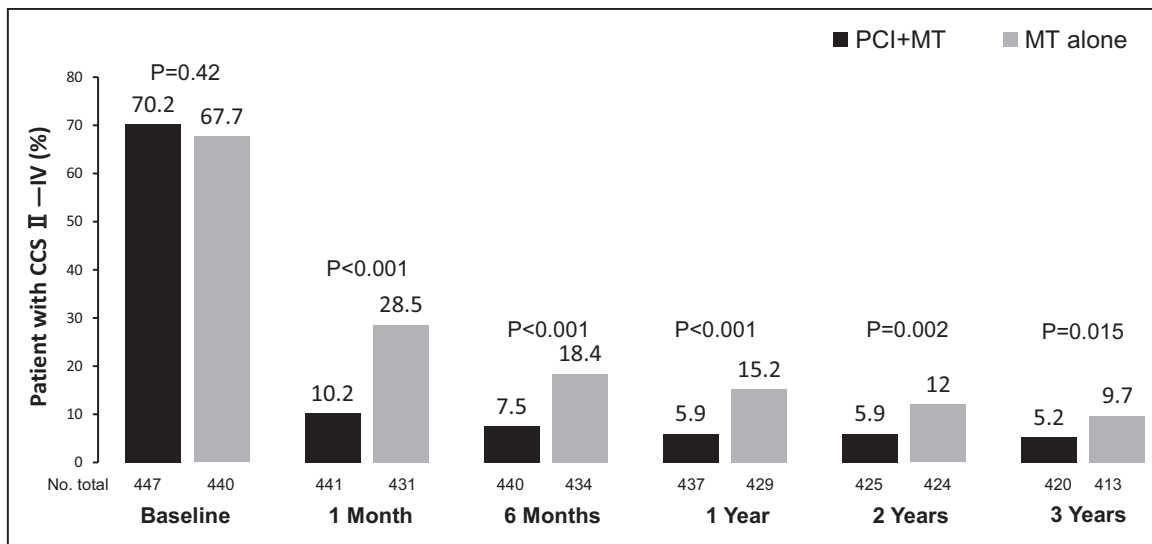


Figure 2. Differences in angina.

Presented are numbers of patients with Canadian Cardiovascular Society (CCS) class II to IV angina in the randomized trial at different time points. MT indicates medical therapy; and PCI, percutaneous coronary intervention.

[SE, 0.015] versus 1.691 [SE, 0.015]; $P=0.23$), and the mean cumulative costs in patients with 2-year QALY data were numerically higher in the PCI group than in the MT group (\$14 853±8741 versus \$14 421±11 561, respectively; $P=0.56$), resulting in an ICER for PCI at 2 years of \$17 300/QALY. At the 3-year follow-up, the ICER for PCI compared with MT was \$1600/QALY and was below a willingness-to-pay threshold of \$50 000/QALY in 85% of the 10 000

bootstrap replications (Figures II and III in the online-only Data Supplement).

The ICER for PCI changed numerically in several sensitivity analyses but remained less than \$50 000/QALY. When we assumed that the cost of a drug-eluting stent was \$400 higher than our base case estimate of \$1656 per stent, the ICER increased to \$21 100/QALY, whereas if we assumed that the stent cost was \$400 lower than the base case, the overall cost was lower in the

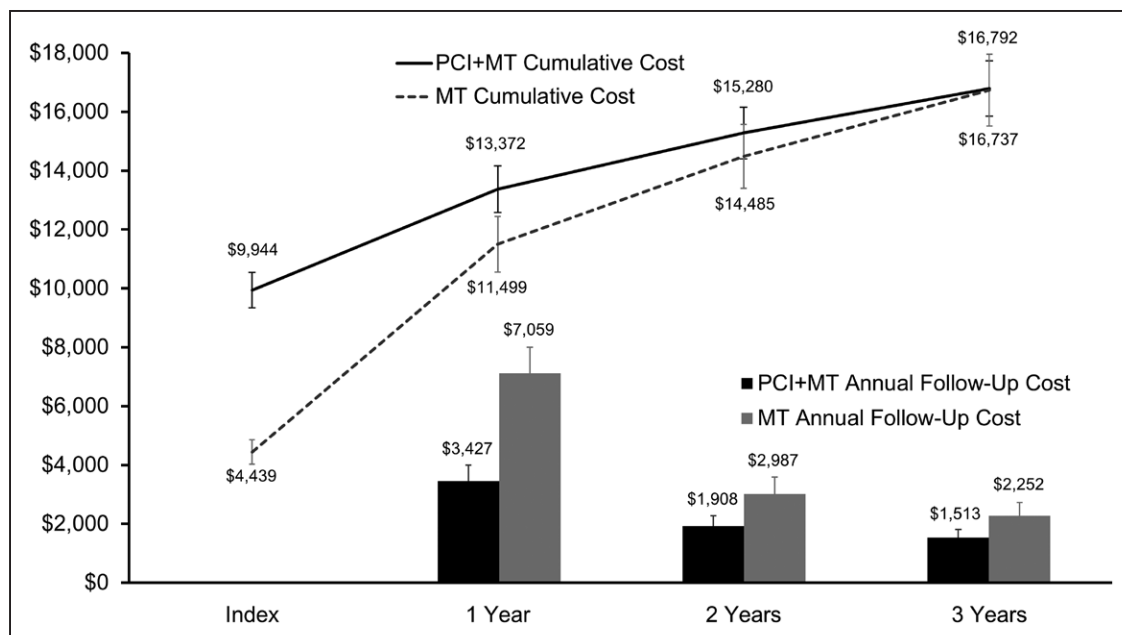


Figure 3. Differences in costs.

Mean cumulative medical costs (lines) at index hospitalization and at 1, 2, and 3 years and mean annual follow-up costs (bars) for the percutaneous coronary intervention (PCI) plus medical therapy (MT) and MT alone groups after hospital discharge up to 1 year, between 1 and 2 years, and between 2 and 3 years. Error bars and values in parentheses indicate 95% confidence intervals.

Table 2. Costs During Index Admission and 3-Year Follow-Up

	PCI+MT (n=447)	MT Alone (n=441)	P Value
Initial costs per patient, \$			
Procedure (including staged procedure) and hospital stay cost	9836±5758	4383±4326	<0.001
Other costs	108±1318	57±611	0.46
Total costs	9944±6507	4440±4462	<0.001
Follow-up costs per patient, \$			
Revascularization	1967±5227	7178±9877	<0.001
Coronary angiography	534±1235	1024±1781	<0.001
Noninvasive diagnostic tests	269±371	276±440	0.82
Outpatient visits	357±361	361±534	0.91
Adverse events (other than revascularization)	1449±3905	1159±2807	0.21
Medication	2272±653	2300±638	0.43
Antiplatelet medication	332±265	265±275	<0.001
Antianginal medication*	510±336	600±357	<0.001
3-y total costs per patient, \$	16792±10139	16737±13108	0.94

MT indicates medical therapy; and PCI, percutaneous coronary intervention.
*The antianginal medications include calcium channel blocker, β-blockers, and long-acting nitrates.

PCI group by \$590 (\$16 142 versus \$16 732), and PCI became the dominant strategy. When we set the cost of the pressure wire and adenosine to zero in the MT

arm, the ICER became \$22 400/QALY. When we set the entire cost of the index catheterization procedure and FFR measurement in the MT arm to \$0, the ICER became \$46 200/QALY.

To explore the validity of imputing 3-year utility values to calculate ICERs, we evaluated the correlation between change in angina classification from 1 to 2 years and change in EQ-5D from 1 to 2 years. In the 86 patients who had an improvement in angina class, the EQ-5D improved (0.032±0.17, mean±SD); in the 529 patients with no change in angina class, the EQ-5D changed very little (−0.005±0.15); and in the 112 patients who had a decline in angina class, the EQ-5D decreased (−0.020±0.17; *P*<0.001 for trend). From these findings, because the relative reduction in the percentage of patients with class II to IV angina in the PCI arm compared with the MT alone arm was similar at 3 years (for which we have complete data) compared with the relative reduction at 2 years, we would expect the utility values at 3 years to be similar to the values at 2 years.

When QALYs were quantified with a last value carried forward technique for the utilities rather than multiple imputation, the QALYs at 3 years were numerically higher in the PCI group compared with the MT group (2.552 [SE, 0.024] versus 2.519 [SE, 0.024]; *P*=0.34). The mean cumulative costs of the corresponding population were numerically lower in the PCI group (\$16 376±9466 versus \$16 664±12 995; *P*=0.73), and hence, FFR-guided PCI was the dominant strategy.

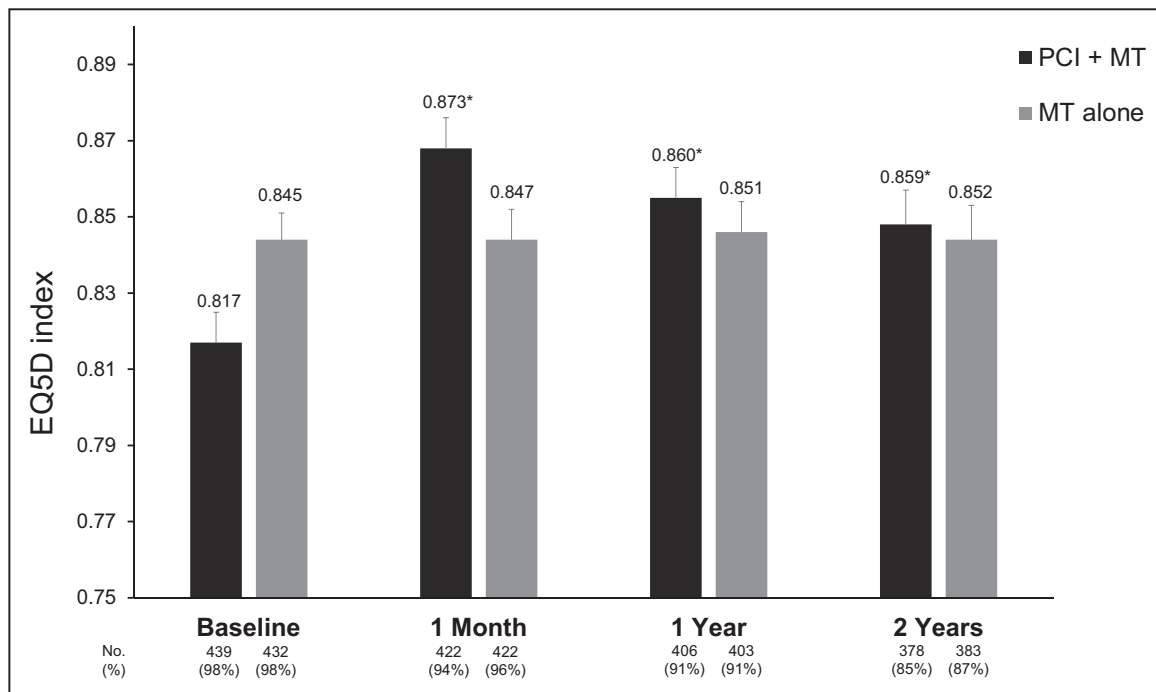


Figure 4. Changes in European Quality of Life–5 Dimensions (EQ-5D).

Values are means calculated from multiple imputation data. Error bars represent SEM. Between-group difference was significant at baseline and at 1 month. MT indicates medical therapy; and PCI, percutaneous coronary intervention. **P*<0.05 vs baseline.

DISCUSSION

The main finding of this study is that compared with best MT alone, performing PCI in patients with stable CAD and at least 1 coronary lesion with an abnormal FFR leads to improved clinical outcome, less angina, and improved quality of life at a similar cost over 3 years of follow-up. With better clinical outcomes at a similar cost, PCI of coronary lesions with reduced FFR is an economically attractive strategy.

We previously reported that the FFR-guided PCI strategy in the FAME 2 trial was cost-effective compared with MT alone.⁷ However, the previous analysis was limited by only 7 months of follow-up and extrapolation of the 1-month quality-of-life assessment. In this study, we have quality-of-life data out to 2 years in the majority of patients and cost and angina data at 3 years. By 3 years of follow-up, there was no difference in cost between the 2 groups, and significantly fewer patients in the PCI arm had class II to IV angina. The persistent difference in angina may be the result of low referral for PCI to control angina in the MT arm, which may result in additional PCIs in this group during longer-term follow-up.

The cost-effectiveness of FFR-guided PCI was quite favorable in this study and remained under the benchmark value of \$50 000/QALY in several alternative formulations and in several sensitivity analyses. Collection of the EQ-5D data used to estimate utility was not mandatory at the 3-year follow-up point, and these data were collected in relatively few patients. The 2-year ICER was \$17 300/QALY, and we estimate it to be more favorable at 3 years because of a smaller cost difference. The point estimates of the ICER varied because of the relatively small cost differences, but all were economically favorable. The cost-effectiveness of FFR-guided PCI remained favorable even when we set the cost of FFR and the cost of invasive angiography to zero in the MT group. These sensitivity analyses do not, however, assess the cost-effectiveness of PCI compared with a noninvasive diagnostic approach, because all patients in FAME 2 required an invasive evaluation with these procedures to identify the subset with myocardial ischemia suitable for PCI.

The measurement of FFR in this study may explain why our results differ from those of previous trials comparing PCI with MT in patients with stable CAD. Because of the inclusion of only patients with at least 1 narrowing in a major epicardial coronary vessel with an abnormal FFR, the FAME 2 trial population was restricted to patients with well-documented myocardial ischemia. A previous study from this same cohort has shown a direct correlation between the FFR value and major adverse cardiac event rates, including a strong trend toward higher rates of death or myocardial infarction in patients with lower FFR values who received

MT.⁸ Other studies have shown that the benefit of revascularization compared with MT is larger the lower the FFR or the greater the degree of myocardial ischemia.^{9,10} Moreover, in patients who have no coronary lesions with an abnormal FFR, MT is just as effective, if not more effective, at preventing major adverse cardiac events compared with PCI.¹¹ One quarter of the patients considered for PCI in this study were not randomized because none of their angiographically apparent stenoses had an abnormal FFR. Patients who did not have significant ischemia and were unlikely to benefit from PCI were almost certainly included in previous trials, diluting any potential benefit of PCI while driving up costs.

Limitations of this study include that enrollment in the trial was stopped early at the advice of the Data Safety Monitoring Board, which could have exaggerated differences between the 2 strategies.¹² Both the patients and the treating physicians were not blinded to the FFR results, and it is possible that the awareness of an abnormal FFR value may have influenced the decision to perform late coronary revascularization. Another limitation was the lack of any significant difference between death and myocardial infarction between the 2 treatment strategies; the study was not powered to detect a difference in death or myocardial infarction. A fourth limitation is that the EQ-5D scores were obtained in only a minority of patients at the 3-year follow-up, requiring the use of imputation to assess cost-effectiveness at 3 years.

CONCLUSIONS

The 3-year results of the FAME 2 trial show that PCI improves outcomes and is economically attractive compared with MT alone in patients with stable CAD.

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FOOTNOTES

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SUPPLEMENTAL MATERIAL.

Supplementary Methods

A. Patients inclusion and exclusion criteria

Eligible subjects include patients with stable clinical condition and one-, two- or three vessel disease at coronary angiography and amenable for PCI. Inclusion is based on the combination of the clinical data, the non-invasive testing, when available, and the angiographic data.

Inclusion criteria:

1. Stable angina pectoris (Canadian Cardiovascular Society Class [CCS] 1, 2, 3); or angina pectoris CCS class 4 subsequently stabilized medically (minimum 7 days); or atypical or no chest pain but documented ischemia on noninvasive testing
2. At least one stenosis of at least 50% diameter reduction in at least one major native epicardial coronary artery with a diameter of at least 2.5 mm and supplying viable myocardium
3. Eligible for PCI
4. Signed written informed consent obtained

Note: a) Patients with restenosis in native coronary arteries can be included

b) Patients with previous stents and restenosis may be included.

c) Total occlusion can be included if this vessel supplies viable myocardium, and if recanalization is deemed likely and useful by the operator and if it is not the only lesion with a significant FFR. In total chronic occlusions it is not mandated to measure FFR. The FFR value will be set at an arbitrary value of 0.5.

d) Patients who sustained a STEMI or a NSTEMI more than one week ago can be included in the trial (see exclusion criteria)

Exclusion Criteria

1. Patients in whom the preferred treatment is CABG
2. Patients with left main coronary artery disease requiring revascularization
3. Patients with a recent (less than 1 week) STEMI or Non-STEMI
4. Prior CABG
5. Contra-indication to dual antiplatelet therapy
6. LVEF < 30%
7. Severe LV hypertrophy (defined as a septal wall thickness at echocardiography of more than 13 mm)
8. Planned need for concomitant valvular or aortic surgery
9. Extremely tortuous or calcified coronary arteries precluding FFR measurements
10. A life expectancy of less than 2 years
11. Age under 21
12. Pregnancy or intention to become pregnant during the course of the trial
13. Refusal or inability to sign an informed consent. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the trial or mental retardation or language barrier such that the patient is unable to give informed consent
14. Potential for non-compliance towards the requirements in the trial protocol (especially the medical treatment) or follow-up visits

15. Participation or planned participation in another cardiovascular clinical trial before two year follow-up is completed

B. Statistical Methods

Multiple imputation was used to replace any missing values of EQ-5D index data. Data were imputed and analyzed using the SPSS multiple imputations procedure (version 24, IBM Corp., Armonk, New York). The automatic method scans the data and uses the monotone method if the data show a monotone pattern of missing values; otherwise, fully conditional specification which is an iterative Markov chain Monte Carlo (MCMC) method. Twenty imputed datasets were generated. The imputation model included: EQ-5D index at each time point (baseline, 1 month, 1, 2, and 3 years); treatment group (the PCI+MT group and the MT group); adverse events (death, cardiac death, stent thrombosis, urgent and nonurgent revascularization, bleeding, myocardial infarction, and stroke); days to the adverse events; enrolled site; baseline characteristics (gender, height, body weight, smoking, medical history of renal failure, dialysis, diabetes mellitus, diabetes mellitus treatment (diet, insulin, or oral med], stroke, TIA, peripheral artery disease, and CAD; and ejection fraction); lesion location; Canadian Cardiovascular Society scale at each time point (baseline, 1 and 6 months, and 1, 2, and 3 years).

Supplementary Tables

Supplementary Table 1. Cost Weights for Adverse Events (US\$)

	Index admission	post-discharge
Bleed	650	5765
Stroke	1250	5012
Myocardial Infarction (MI)	900	4424
Death	200	500
Urgent revascularization		11166
Nonurgent revascularization		11166
Coronary artery bypass graft	1400	27207
Coronary angiography	200	1594
Pacemaker	20000	11464
Embolism	200	3742
Pericardial Effusion	200	1000
Peripheral vascular disease	650	3742
Heart failure	500	3804
Chest pain	200	3060
Atrial fibrillation	200	4592
Fatal MI (additional over death)	2800	9139

The cost for revascularization during the index hospitalization was calculated in the same way with the index procedure.

Supplementary Table 2. Cost Weights for Resources

Resource	Cost-weight (US\$)
Index procedure	
Guide catheter	52
Guidewire	51
Pressure Wire	650
Balloon catheter	166
Drug-eluting stent	1656
Bare-metal stent	809
Adenosine vial	150
Adenosine ampule/syringe	30
Glycoprotein IIb/IIIa inhibitor	500
Bivalirudin vial	50
Hospital day	2000
Professional fee	796
Procedure duration, min	17
Medication (per day)	
Aspirin	0.05
Statin	0.82
Angiotensin-converting enzyme inhibitor	0.55
Angiotensin II receptor blocker	0.74
Beta Blocker	0.27
Calcium channel blocker	0.64
Nitrates	0.3
Clopidogrel	0.55
Other antiplatelet therapy	1.75
Follow-up	
Outpatient Visit	90
Echocardiography	197
Coronary Angiography	1594
Exercise stress test	105
Nuclear Scan	637
Cardiac magnetic resonance imaging	653

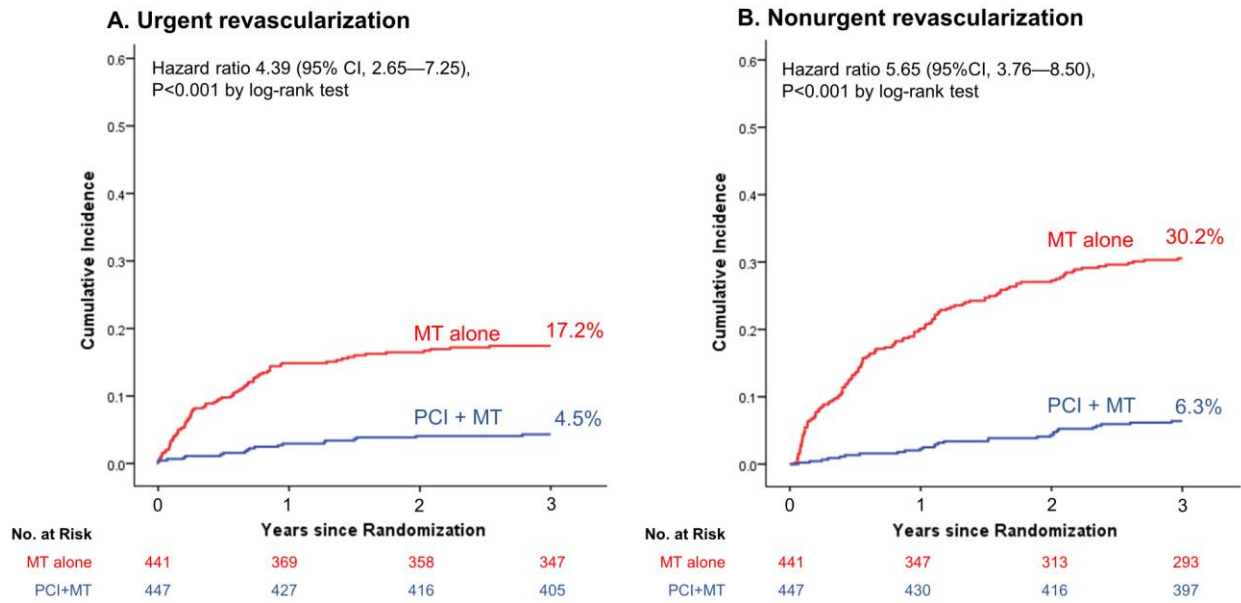
Supplementary Table 3. Number of Antianginal Medications

	PCI+MT	MT alone	P value
Baseline	1.33 ± 0.76 1 [1, 2]	1.35 ± 0.76 1 [1, 2]	0.63 0.70
1 month	1.36 ± 0.71 1 [1, 2]	1.79 ± 0.74 2 [1, 2]	<0.001 <0.001
6 month	1.32 ± 0.74 1 [1, 2]	1.68 ± 0.79 2 [1, 2]	<0.001 <0.001
1 Year	1.35 ± 0.78 1 [0, 1]	1.62 ± 0.79 2 [1, 2]	<0.001 <0.001
2 Years	1.36 ± 0.80 1 [1, 2]	1.53 ± 0.82 1 [1, 2]	0.003 0.007
3 Years	1.29 ± 0.78 1 [1, 2]	1.52 ± 0.81 1 [1, 2]	<0.001 <0.001

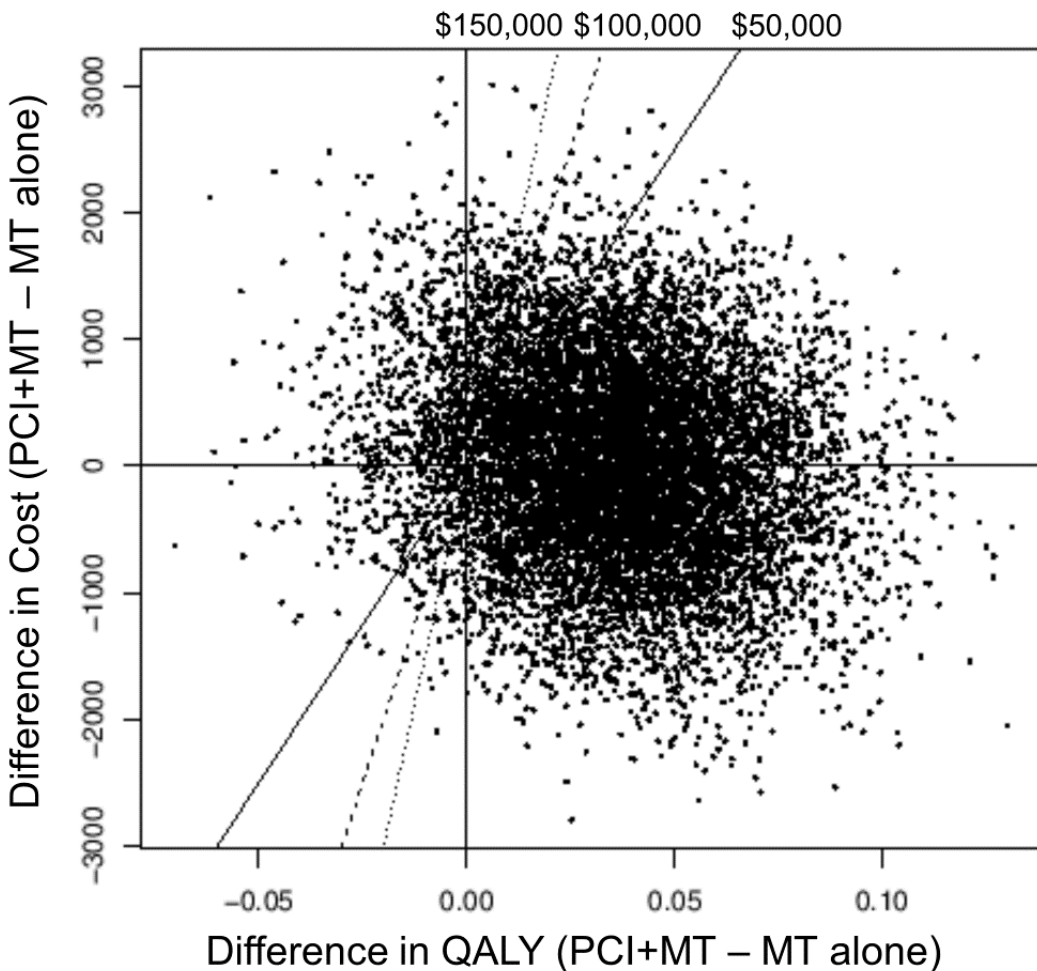
MT denotes medical therapy and PCI percutaneous coronary intervention. The antianginal medications include calcium channel blockers, beta-blockers, and long-acting nitrates. Values are mean ± standard deviation and median [interquartile range] and corresponding P values by t-test and non-parametric test.

Supplementary Figures

Supplementary Figure 1. Cumulative Incidence of the urgent and nonurgent revascularization. Kaplan–Meier curves are shown for the cumulative incidence of the urgent revascularization (A) and the nonurgent revascularization (B) in the percutaneous coronary intervention plus medical therapy (PCI+MT) and the medical therapy alone (MT alone) group.



Supplementary Figure 2. Bootstrap Simulation. Replications of the incremental cost-effectiveness of the strategy of percutaneous coronary intervention (PCI) plus medical therapy (MT) compared with medical therapy alone. Each of the 10,000 points represents the results of 1 bootstrap replication. The difference in cumulative costs is displayed in the vertical axis, and the difference in quality-adjusted life-years (QALYs) is displayed on the horizontal axis. The average QALY value for each case from 20 imputed datasets were used. Willingness-to-pay thresholds of \$50,000 per QALY added (solid line), \$100,000 per QALY added (dashed line), and \$150,000 per QALY added (dotted line) are indicated in the plane.



Supplementary Figure 3. Cost-effectiveness Acceptability Curve. The incremental cost-effectiveness of the fractional flow reserve–guided strategy compared with best medical therapy, based on 10,000 bootstrap replications. The cumulative percentage of replications (vertical axis) below various willingness-to-pay thresholds (horizontal axis) in dollars per quality-adjusted life-year (QALY) is shown. The points on the curve indicate the cumulative proportion of replications below thresholds of \$0/QALY (47%), \$25,000/QALY (77%), \$50,000/QALY (85%), \$75,000/QALY (87%), \$100,000/QALY (88.1%), \$125,000/QALY (88.8%), and \$150,000/QALY (89.2%).

