

# Fractional flow reserve-guided percutaneous coronary intervention versus medical therapy for stable coronary artery disease: long-term results of the FAME 2 trial

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A list of authors and their affiliations appears at the end of the paper

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In patients with stable coronary artery disease (CAD), the long-term benefits of revascularization over medical therapy remain unclear. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 trial, patients with hemodynamically significant stenoses (fractional flow reserve (FFR)  $\leq 0.80$ ) were randomized to receive FFR-guided percutaneous coronary intervention (PCI) plus medical therapy ( $n = 447$ ) or medical therapy alone ( $n = 441$ ). At 5 years, FFR-guided PCI reduced the risk of the primary composite outcome of time to death, myocardial infarction or urgent revascularization, largely because of fewer urgent revascularizations. We now report the long-term clinical outcomes from this trial. Sixteen hospitals, contributing 748 randomized patients (161 women, 21.5%), participated in the long-term follow-up. The primary composite outcome was analyzed hierarchically using the unstratified win ratio, which addressed differential missingness of data on nonfatal outcomes in deceased patients by prioritizing comparisons on time to death. At a median follow-up of 11.2 years, the primary endpoint occurred in 150 of 447 patients (33.6%) in the PCI group versus 182 of 441 (41.3%) in the medical therapy group. PCI was superior in 29.2% of comparisons, medical therapy in 23.3%, and the two groups were tied in 47.5%, resulting in a win ratio of 1.25 in favor of PCI (95% confidence interval (CI) 1.01–1.56,  $P = 0.043$ ). The corresponding win difference was 5.9% (95% CI 0.2–11.6), and the number needed to treat was 17 (95% CI 9–500). Win ratios were 0.88 for all-cause death (95% CI 0.66–1.17), 1.50 for myocardial infarction (95% CI 0.98–2.31) and 4.57 for urgent revascularization (95% CI 2.53–8.24). During long-term follow-up, FFR-guided PCI in patients with stable CAD and hemodynamically significant stenoses reduced the composite of death, myocardial infarction or urgent revascularization, primarily because of fewer urgent revascularizations. These long-term findings reaffirm the efficacy of FFR-guided PCI over medical therapy in patients with stable CAD. ClinicalTrials.gov registration: [NCT06159231](https://clinicaltrials.gov/ct2/show/NCT06159231).

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality globally, necessitating continuous advancements in diagnostic and therapeutic strategies. Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) has emerged as an essential tool in managing stable CAD. The Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention (FAME) 1 trial showed that FFR-guided PCI significantly reduces the rate of major adverse cardiac events compared to angiography-guided PCI in patients with multivessel disease<sup>1</sup>.

Building on this foundational work, the FAME 2 trial investigated the benefits of FFR-guided PCI compared to medical therapy alone in patients with stable CAD. The main findings showed that FFR-guided PCI significantly reduced the composite endpoint of death, myocardial infarction and urgent revascularization, affirming the clinical value of FFR in guiding revascularization decisions<sup>2,3</sup>. A 5-year follow-up further confirmed that patients randomized to FFR-guided PCI experienced lower rates of the primary composite endpoint compared to those allocated to medical therapy alone, primarily driven by a reduction in urgent revascularization<sup>4</sup>. However, no significant differences were found in the composite of death or myocardial infarction, highlighting the need for continued investigation into the long-term benefits of FFR-guided PCI.

We present an extended clinical follow-up of FAME 2 beyond 10 years to assess whether the benefits observed at 1, 2 and 5 years are sustained over more than a decade, providing insights into the durability of results associated with FFR-guided PCI.

## Results

Between 15 May 2010 and 15 January 2012, 888 patients were enrolled in the randomized trial. Of these, 447 were assigned to PCI plus medical therapy and 441 to medical therapy alone. The baseline characteristics of patients were similar between treatment groups (Table 1). The mean age at randomization was 63.7 years, 694 patients were male (78.2%) and 240 had a diagnosis of diabetes mellitus (27.0%)<sup>2</sup>. Figure 1 presents the flow of patients through the different phases of the trial. Follow-up information beyond 5 years was available for 654 patients (73.6%). Of the remainder, 122 patients withdrew or were lost to follow-up (13.7%), and their censoring was considered potentially informative. An additional 112 patients had survived until their last follow-up (12.6%) but were enrolled at sites that did not participate in the long-term follow-up. Their censoring was considered noninformative, because it was unrelated to patient prognosis. Extended Data Table 1 compares baseline characteristics of patients with follow-up information available beyond 5 years with those without, and Extended Data Table 2 compares baseline characteristics of patients with available long-term follow-up information between PCI and medical therapy groups.

In the 16 sites that participated in the long-term follow-up, median length of follow-up was 11.8 years (interquartile range (IQR), 10.0 to 12.4) in the PCI group and 11.9 years (IQR 10.0 to 12.4) in the medical therapy group. In the 12 sites that did not participate, median length of follow-up was 3.0 years (IQR 2.9 to 5.0) in both the PCI and medical therapy groups. Across all sites, median length of follow-up was 11.2 years (IQR 6.5 to 12.4) in the PCI group and 11.2 years (IQR 7.5 to 12.4) in the medical therapy group.

## Outcomes

Death was documented in 104 (23.3%) of the 447 patients in the PCI group (incidence rate 2.4 per 100 patient-years) and 92 (20.9%) of the 441 patients in the medical therapy group (2.2 per 100 patient-years; Fig. 2 and Table 2). Myocardial infarctions were reported for 47 (10.5%) patients in the PCI group (1.4 per 100 patient-years) and for 64 (14.5%) patients in the medical therapy group (1.9 per 100 patient-years). Urgent revascularizations were found in 45 (10.1%) patients in the PCI group (1.3 per 100 patient-years) and in 111 (25.2%) patients in the medical therapy group (3.8 per 100 patient-years). A primary composite outcome event was observed in 150 (33.6%) patients in the PCI group (4.2

**Table 1 | Demographic and clinical characteristics at baseline**

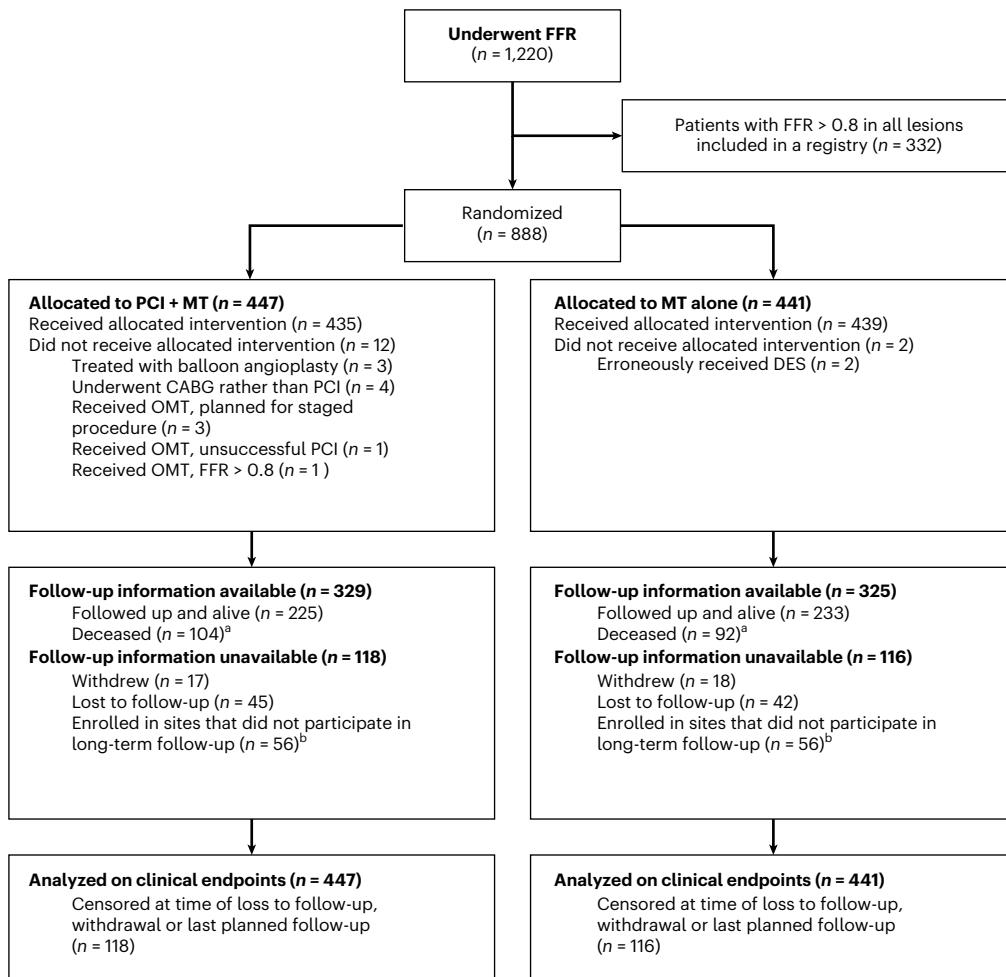
	PCI (n=447)	Medical therapy (n=441)
Age (years)	63.52±9.35	63.86±9.62
Age >60 years	165 (36.9)	162 (36.7)
Male sex	356 (79.6)	338 (76.6)
Body mass index	28.29±4.27	28.44±4.55
Current smoking	89 (19.9)	90 (20.4)
Silent ischemia	73 (16.3)	73 (16.6)
Renal insufficiency	8 (1.8)	12 (2.7)
Diabetes mellitus	123 (27.5)	117 (26.5)
Insulin dependent	39 (8.7)	39 (8.8)
Hypertension	347 (77.6)	343 (77.8)
Peripheral vascular disease	43 (9.6)	47 (10.7)
Family history of CAD	216 (48.4)	207 (46.9)
Hypercholesterolemia	330 (73.8)	348 (78.9)
History of myocardial infarction	164 (36.7)	165 (37.4)
History of stroke or TIA	414 (92.6)	413 (93.7)
History of PCI in target vessel	80 (17.9)	76 (17.2)
Left ventricular ejection fraction ≤50%	83 (18.6)	56 (12.7)
Angina class		
Asymptomatic	53 (11.9)	46 (10.5)
CCS class I	82 (18.3)	98 (22.3)
CCS class II	204 (45.6)	197 (44.8)
CCS class III	80 (17.9)	65 (14.8)
CCS class IV	28 (6.3)	34 (7.7)
Total no. of lesions	890	815
Lesions with stenosis of >50% of diameter	837 (94.0)	764 (93.7)
No. of lesions with >50% of diameter per patient	1.87±1.05	1.73±0.94
Lesions with FFR≤0.80	679 (76.3)	625 (76.7)
No. of lesions with FFR≤0.80 per patient	1.52±0.78	1.42±0.73

Data are presented as means±s.d. or number (%). The body mass index is the weight in kilograms divided by the square of the height in meters. CCS, Canadian Cardiovascular Society; TIA, transient ischemic attack.

per 100 patient-years) and 182 (41.3%) patients in the medical therapy group (5.9 per 100 patient-years).

In total,  $447 \times 441 = 197,127$  comparisons of patient pairs were performed. In the win ratio analysis of the hierarchical primary composite of time to all-cause death, myocardial infarction or urgent revascularization, there were 57,533 wins (29.2%) and 45,882 losses (23.3%) for PCI, while 93,712 comparisons (47.5%) were tied, resulting in a win ratio of 1.25 in favor of PCI (95% confidence interval (CI) 1.01–1.56,  $P = 0.043$ ) (Fig. 3). The win difference was 5.9% (95% CI 0.2–11.6) and the number needed to treat (NNT) was 17, suggesting that 17 patients (95% CI 19–500) would need to be treated with PCI plus medical therapy, rather than medical therapy alone, to achieve one additional patient with a better outcome.

In the analysis of individual components of the primary outcome, there were 28,694 wins (14.6%) for PCI, 32,692 losses (16.6%) and 135,741 ties (68.9%) on time to all-cause death, resulting in a win ratio of 0.88 (95% CI 0.66–1.17,  $P = 0.38$ ). Among the 135,741 patient pairs with ties on time to all-cause death, there were 15,404 wins (7.8%) for PCI, 10,250 losses (5.2%) and 110,087 ties (55.8%) on time to myocardial infarction,

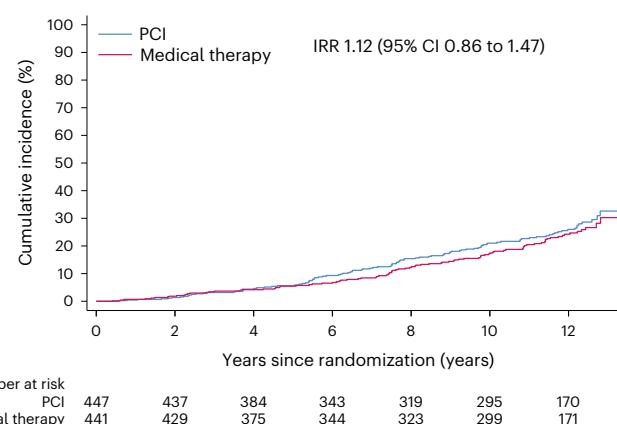


**Fig. 1 | Study flowchart.** <sup>a</sup>Among deceased patients, 72 had incomplete data on myocardial infarction and/or urgent revascularization in the PCI group, and 59 had incomplete data in the medical therapy group; this was considered to have minimal impact on the win ratio for the hierarchical primary composite outcome (Extended Data Table 5). <sup>b</sup>Seventy patients in each of the PCI and medical therapy groups were enrolled at sites that did not participate in the long-term follow-up study;

of these patients, 2 in the PCI group and 1 in the medical therapy group withdrew their consent, 9 in the PCI group and 11 in the medical therapy group were lost to follow-up, and 3 in the PCI group and 2 in the medical therapy group died, leaving 56 patients in each group as listed in the flowchart. Censoring of these 56 patients in each group was considered to be noninformative. CABG, coronary artery bypass grafting; DES, drug-eluting stents; MT, medical therapy; OMT, optimal medical therapy.

resulting in a conditional win ratio of 1.50 (95% CI 0.98–2.31,  $P = 0.063$ ). Further analysis of the remaining 110,087 patient pairs with ties on time to myocardial infarction found 13,435 wins (6.8%) for PCI, 2,940 losses (1.5%) and 93,712 ties (47.5%) on time to urgent revascularization, resulting in a conditional win ratio of 4.57 (95% CI 2.53–8.24,  $P < 0.001$ ) (Fig. 3).

Prespecified subgroup analyses are shown in Fig. 4. There were significant treatment-by-subgroup interactions between treatment and the presence or absence of severe lesions defined either functionally or angiographically. In patients with an FFR < 0.65, the win ratio for PCI was 1.58 (95% CI 1.15–2.16), favoring PCI, whereas in patients with an FFR ≥ 0.65, the win ratio was 1.00 (95% CI 0.74–1.37;  $P$  for interaction = 0.044). Similarly, in patients with a diameter stenosis ≥ 70%, the win ratio for PCI was 1.46 (95% CI 1.13–1.89), favoring PCI, whereas in those with less-severe stenosis (<70%), the win ratio was 0.77 (95% CI 0.50–1.19;  $P$  for interaction = 0.013). Extended Data Table 3 presents exploratory post hoc calculations of the win ratio at each level of the hierarchical primary outcome for subgroups defined by FFR. In patients with FFR < 0.65, there was a significant benefit for myocardial infarction (conditional win ratio 1.90, 95% CI 1.01–3.56), with an even more pronounced benefit for urgent revascularization (conditional win ratio 7.07, 95% CI 3.16–15.8). By contrast, patients with FFR ≥ 0.65 showed no significant benefit for myocardial infarction (conditional win ratio 1.23, 95% CI 0.68–2.21) and a smaller benefit for urgent revascularization (conditional win ratio 2.85,



**Fig. 2 | Cumulative incidence of death from any cause.** Cumulative incidence curves for death from any cause. IRR, incidence rate ratio.

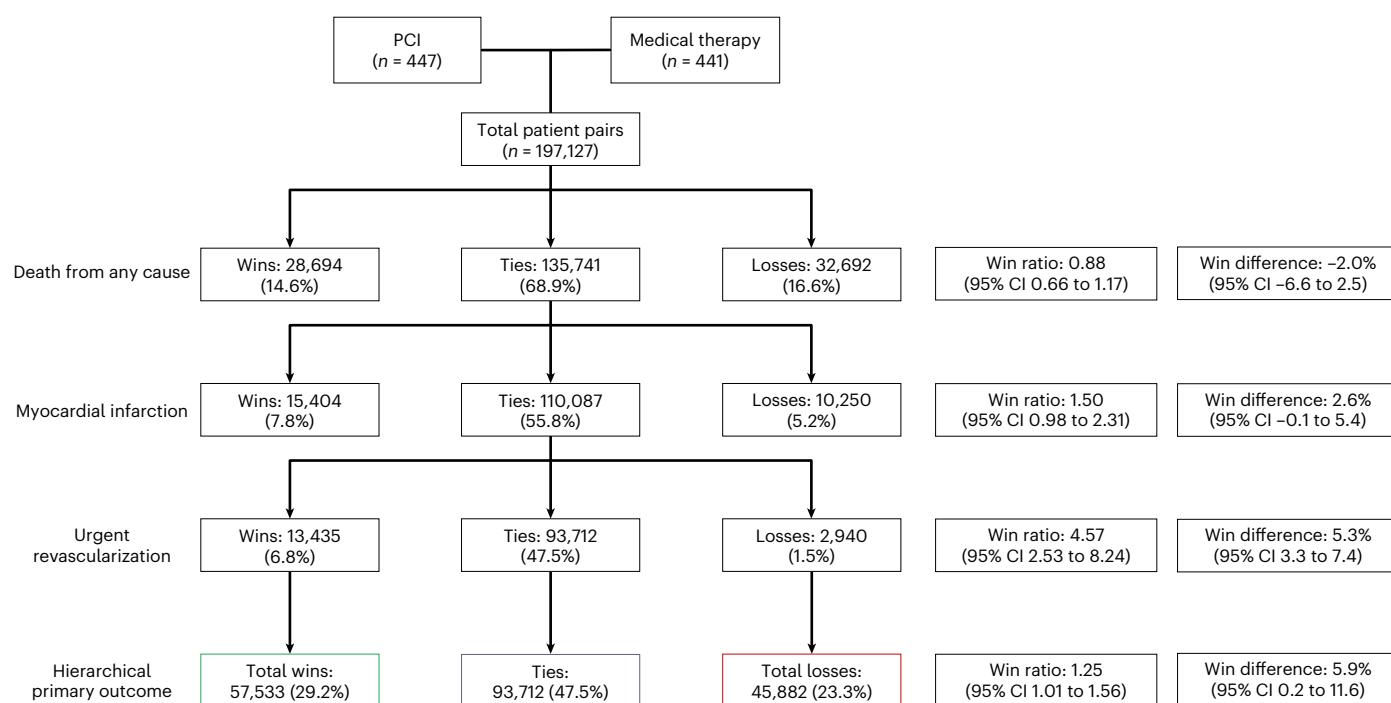
95% CI 1.17–6.91). No clear differences in win ratios for all-cause death were observed between subgroups defined by FFR.

The analysis of the hierarchical composite of time to all-cause death or myocardial infarction showed 44,098 wins for PCI (22.4%),

**Table 2 | Outcomes**

Outcome	PCI (n=447)			Medical therapy (n=441)		
	No.	%	Events per 100 PY	No.	%	Events per 100 PY
All-cause death	104	23.3	2.4	92	20.9	2.2
MI	47	10.5	1.4	64	14.5	1.9
Stroke	20	4.5	0.6	19	4.3	0.5
Urgent revascularization	45	10.1	1.3	111	25.2	3.8
Death, MI or urgent revascularization	150	33.6	4.2	182	41.3	5.9
Death or MI	137	30.6	3.5	141	32.0	3.7
Nonurgent revascularization	51	11.4	1.5	170	38.5	5.8
Any revascularization	91	20.4	2.9	246	55.8	12.7

Event rates for nonfatal events are underestimated because of a high proportion of missing data on nonfatal events in patients who died in the interval between 5 years and long-term follow-up. Events per 100 PY, number of first events per 100 patient-years; MI, myocardial infarction; No., number of patients who experienced at least one event; PY, patient-years accumulated until censoring due to the first event or last follow-up, whichever occurred first; %, percentage of patients with at least one event.



**Fig. 3 | Win ratio analysis.** In a comparison of the PCI group with the medical therapy group on time to all-cause death, time to myocardial infarction and time to urgent revascularization, the number and percentage of wins, ties and losses at each level of the hierarchical primary outcome are shown, along with the corresponding win ratios and win differences. There were a total of  $447 \times 441 = 197,127$  pairs of participants. The win ratio and win difference for time

to myocardial infarction are conditional, calculated in the 135,741 patient pairs with a tie on time to all-cause death. The win ratio and win difference for time to urgent revascularization are also conditional, calculated in the 110,087 patient pairs with ties on both time to all-cause death and myocardial infarction. All percentages were calculated using the denominator of 197,127 total patient pairs.

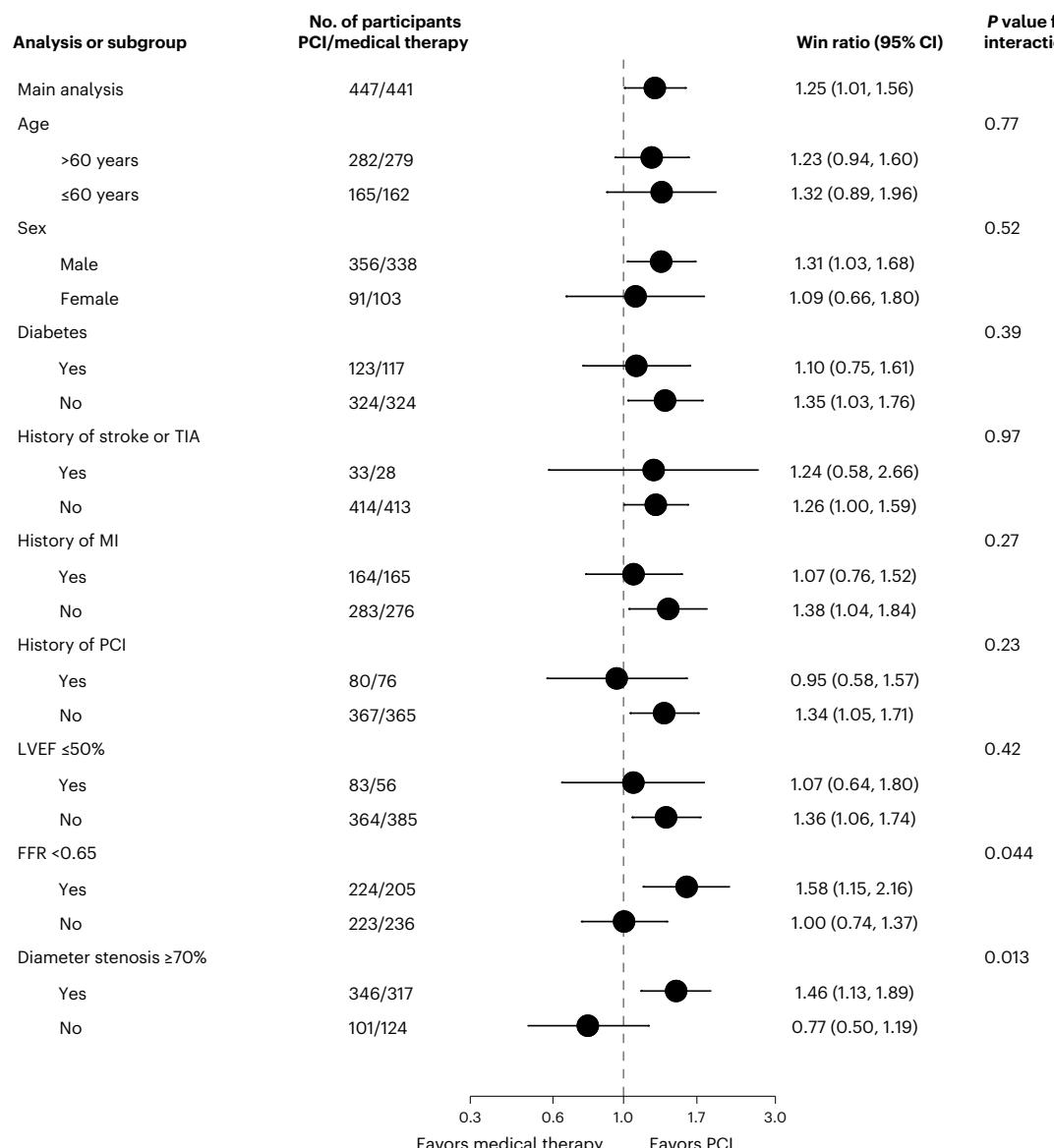
42,942 losses for PCI (21.8%) and 110,087 ties (55.8%), resulting in a win ratio of 1.03 (95% CI 0.81–1.31). Win ratios for remaining outcomes are presented in Extended Data Table 4. Incidence rate ratios for the primary composite outcome and its individual components, with analyses conducted by either censoring patients or applying multiple imputation, are shown in Extended Data Fig. 1. Corresponding sensitivity analyses using hazard ratios (HR) are presented in Extended Data Fig. 2. Extended Data Fig. 3 displays time-to-event curves for the composite outcome and its components following multiple imputation.

## Discussion

The long-term follow-up of the FAME 2 trial reaffirms the efficacy of FFR-guided PCI compared to medical therapy in patients with stable

CAD. Based on 29.2% wins in the PCI group, 23.3% wins in the medical therapy group and 47.5% ties at a median follow-up of 11.2 years, the win ratio for the hierarchical composite of time to death, myocardial infarction or urgent revascularization was 1.25, indicating that patients assigned to PCI were 25% more likely to win than those assigned to medical therapy alone. The corresponding win difference was 5.9%, and the NNT was 17, meaning that 17 patients would need to be treated with PCI plus medical therapy, rather than medical therapy alone, to achieve one additional patient with a better outcome. A summary of the main study findings is provided in Extended Data Fig. 4.

The benefit of PCI was primarily driven by a reduction in urgent revascularizations, with no difference observed in the hierarchical composite of time to death or myocardial infarction. Based on 6.8% wins in



**Fig. 4 | Subgroup analyses for the primary composite endpoint for the two randomized groups.** Subgroup analyses for the hierarchical primary outcome of death, myocardial infarction or urgent revascularization. Presented are numbers of patients in the two randomized groups for each subgroup, win ratios with corresponding 95% CI and P values for interaction between treatment and

subgroup. Two-sided P values for interaction are from z-tests. A win ratio >1 indicates a benefit with PCI compared to medical therapy alone. The 95% CI and P values for interaction were not adjusted for multiple testing. LVEF, left ventricular ejection fraction.

the PCI group, 1.5% wins in the medical therapy group and 47.5% ties, the conditional win ratio for time to urgent revascularization was 4.57, indicating that, among patient pairs with ties on time to death and time to myocardial infarction, those assigned to PCI were approximately 4.6 times more likely to win than those assigned to medical therapy alone. This benefit of PCI in reducing urgent revascularizations aligns with earlier findings from short-term and 5-year follow-ups<sup>2–4</sup>. As in the 5-year follow-up<sup>4</sup>, there was also a statistical trend toward fewer myocardial infarctions in the PCI group compared to medical therapy. Based on 7.8% wins in the PCI group, 5.2% wins in the medical therapy group and 55.8% ties, the conditional win ratio for time to myocardial infarction was 1.5, indicating that among patient pairs with ties on time to death, those assigned to PCI were 50% more likely to win than those assigned to medical therapy alone, although this difference did not reach statistical significance ( $P = 0.063$ ). By contrast, there was no evident trend for all-cause mortality. Based on 14.6% wins in the PCI group, 16.6% wins in the medical therapy group and 68.9% ties, the

win ratio for time to all-cause death was 0.88, indicating that patients assigned to PCI were 12% less likely to win on time to death than those assigned to medical therapy. However, the 95% CI was wide, and this difference did not reach statistical significance ( $P = 0.38$ ), suggesting little evidence for a difference between PCI and medical therapy.

Our results should be interpreted in the context of the placebo-controlled Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA)<sup>5</sup> and ORBITA-2 trials<sup>6</sup>, as well as the randomized International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)<sup>7</sup>. In ORBITA, which studied patients with stable angina and single-vessel coronary disease on multiple antianginal medications, PCI did not significantly improve exercise capacity compared to placebo<sup>5</sup> but improved stress echocardiography scores and increased the percentage of patients who were angina-free (odds ratio 2.47; 95% CI 1.30–4.72)<sup>8</sup>. ORBITA-2, which excluded background antianginal medications, demonstrated significant improvements in

angina symptom scores, daily angina episodes and exercise capacity with PCI compared to placebo<sup>6</sup>. In ISCHEMIA, an early invasive strategy halved the risk of hospitalization for unstable angina (HR 0.50, 95% CI 0.27–0.91) and reduced nonprocedural myocardial infarctions (HR 0.67, 95% CI 0.53–0.83), although there was no significant difference in myocardial infarctions overall (HR 0.91, 95% CI 0.76–1.10) or all-cause mortality (HR 1.05, 95% CI 0.83–1.32)<sup>7,9</sup>. Taken together, the findings from these three<sup>5–7</sup> and our own trial provide robust evidence that early PCI can improve subjective outcomes and reduce nonfatal adverse events, such as hospitalization for unstable angina and non-procedural myocardial infarctions. However, both ISCHEMIA and our trial indicate that an invasive treatment strategy is unlikely to offer a survival benefit compared to an initially conservative strategy with medical therapy alone.

In prespecified subgroup analyses, we found significant interactions between treatment and lesion severity, defined either functionally or angiographically. In patients with an FFR < 0.65, a win ratio of 1.58 indicated that PCI patients were 58% more likely to win than those assigned to medical therapy, while no difference was observed for patients with FFR ≥ 0.65 (*P* for interaction = 0.044). This interaction with FFR was consistently seen over time, with varying levels of significance: significant at 1 year (*P* = 0.010)<sup>2</sup>, a statistical trend at 2 years (*P* = 0.07)<sup>3</sup> and not significant at 5 years (*P* = 0.15)<sup>4</sup>. The consistency of these findings over time suggests that an FFR < 0.65 may be a reliable predictor of benefit from PCI. Conversely, the interaction with angiographic severity was not evident in previous analyses<sup>2–4</sup> and may be a chance finding. Previous studies, including ref. 10, have shown an association between continuous FFR values and subsequent clinical outcomes, with the risk of clinical events increasing as FFR decreases. Our own exploratory post hoc analysis suggests that patients with FFR < 0.65 derived significant benefit from PCI in reducing myocardial infarction and urgent revascularization. This effect was considerably less pronounced in patients with FFR ≥ 0.65. Our exploratory findings, along with those in ref. 10, further support the notion that revascularization offers greater benefits in patients with low FFR values at baseline (<0.65). In addition, advancements in invasive coronary physiology, such as the quantification of the pullback curve, are being explored to improve the identification of patients with hemodynamically significant lesions (FFR < 0.80) who are likely to benefit most from revascularization<sup>11,12</sup>.

The long-term follow-up of the FAME 2 trial has several limitations. Of 888 patients, 131 had incomplete data on myocardial infarction and urgent revascularization because they had died in the interval between 5 years and long-term follow-up, before the long-term follow-up was initiated. Traditional time-to-first event analyses, used in earlier FAME 2 reports<sup>2–4</sup>, would be impacted by this pattern of missing data. We therefore performed a hierarchical analysis using an unstratified win ratio that prioritized time to death over nonfatal events. Despite 14.8% of patients with this type of incomplete data, its impact on the analysis was minimal: only 2.3% of the pairwise comparisons used to calculate the win ratio were affected. An additional 122 patients (13.7%) withdrew or were lost to follow-up, leading to potentially informative censoring at their last follow-up and affecting 15.9% of the pairwise comparisons required to calculate the win ratio. Given the median follow-up period of 11.2 years, this attrition rate is relatively low. A further 112 patients (12.6%) were prematurely censored because of their enrollment at sites that did not participate in the long-term follow-up. Their censoring was evenly distributed across treatment groups and is likely noninformative, because the sites' decisions not to participate were unrelated to patient prognosis.

Beyond 5 years, the classification of myocardial infarction subtype (spontaneous versus periprocedural) and its temporal association with revascularization procedures could no longer be reliably determined. Given that periprocedural myocardial infarctions represented only a minority of all events over 5 years, this limitation is unlikely

to materially affect the interpretation of the long-term treatment effect. In addition, patients, physicians and nurses were aware of the assigned treatment group. Although the urgent revascularization endpoint was defined using objective criteria, knowledge of a functionally significant stenosis or confidence in the efficacy of PCI may have influenced clinical decisions during follow-up. Revascularization procedures in the PCI group may therefore have been less likely to be pursued or described in a way that led the adjudication committee to classify them as urgent, regardless of the actual clinical course. Finally, we did not capture patient-reported outcomes, which could have provided insights into the long-term benefits of PCI for symptom management, and the evolving nature of medical therapy and PCI technology over the past decade may limit the applicability of our findings to contemporary practice.

In conclusion, long-term follow-up of the FAME 2 trial over a median of 11.2 years shows that FFR-guided PCI in patients with stable CAD reduced the composite of death, myocardial infarction and urgent revascularization, primarily because of fewer urgent revascularizations.

## Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-025-04132-5>.

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**Carlos Collet**<sup>1,27</sup>, **Thabo Mahendiran**  <sup>1,2,27</sup>, **William F. Fearon**<sup>3</sup>, **Takuya Mizukami**<sup>1,4</sup>, **Daniel Munhoz**<sup>1</sup>, **Nico H. J. Pijls**<sup>5</sup>, **Pim A. L. Tonino**<sup>5,6</sup>, **Emanuele Barbato**<sup>7</sup>, **Zsolt Piroth**  <sup>8</sup>, **Miodrag Sreckovic**<sup>9</sup>, **Holger Thiele**  <sup>10</sup>, **Mohamed El Farissi**<sup>5</sup>, **Nils Witt**<sup>11</sup>, **Gilles Rioufol**<sup>12</sup>, **Petr Kala**<sup>13</sup>, **Thomas Engström**<sup>14</sup>, **Kreton Mavromatis**<sup>15</sup>, **Ole Fröbert**<sup>16,17,18,19</sup>, **Peter Verlee**<sup>20</sup>, **Stefan Brunner**<sup>21</sup>, **Martin Mates**<sup>22</sup>, **Nikola Jagic**<sup>23</sup>, **Gianluca Campo**<sup>24</sup>, **Sofie Pardaens**<sup>1</sup>, **Kazumasa Ikeda**  <sup>1,25</sup>, **Tiago Veiga Pereira**<sup>26</sup>, **Bruno R. da Costa**  <sup>26</sup>, **Stephane Fournier**<sup>2</sup>, **Bernard De Bruyne**  <sup>1,2,28</sup>  & **Peter Jüni**  <sup>1,26,28</sup> 

<sup>1</sup>Cardiovascular Center Aalst, AZORG, Aalst, Belgium. <sup>2</sup>Department of Cardiology, Lausanne University Hospital, Lausanne, Switzerland. <sup>3</sup>Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine and VA Palo Alto Health Care System, Palo Alto, CA, USA. <sup>4</sup>Division of Clinical Pharmacology, Department of Pharmacology, Showa University, Tokyo, Japan. <sup>5</sup>Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands. <sup>6</sup>Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands. <sup>7</sup>Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy. <sup>8</sup>Gottsegen National Cardiovascular Center, Budapest, Hungary. <sup>9</sup>Department of Internal Medicine, University of Kragujevac, Kragujevac, Serbia. <sup>10</sup>Heart Center Leipzig at University of Leipzig, Leipzig, Germany. <sup>11</sup>Department of Clinical Science and Education, Unit of Cardiology, Karolinska Institute, Södersjukhuset, Stockholm, Sweden. <sup>12</sup>Hospices Civils de Lyon and Claude Bernard University, Lyon, France. <sup>13</sup>Medical Faculty of Masaryk University and University Hospital Brno, Brno, Czech Republic. <sup>14</sup>Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. <sup>15</sup>Atlanta VA Medical Center, Emory University, Atlanta, GA, USA. <sup>16</sup>Department of Cardiology, Örebro University Hospital, Örebro, Sweden. <sup>17</sup>Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. <sup>18</sup>Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark. <sup>19</sup>Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark. <sup>20</sup>Northeast Cardiology Associates, Bangor, ME, USA. <sup>21</sup>Department of Medicine I, University Hospital Munich, Ludwig Maximilian University of Munich (LMU), Munich, Germany. <sup>22</sup>Na Homolce Hospital, Prague, Czech Republic. <sup>23</sup>Clinical Hospital Center Zemun, Beograd, Serbia. <sup>24</sup>Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy. <sup>25</sup>Department of Cardiology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan. <sup>26</sup>Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK. <sup>27</sup>These authors contributed equally: Carlos Collet, Thabo Mahendiran. <sup>28</sup>These authors jointly supervised this work: Bernard De Bruyne, Peter Jüni.  e-mail: [bernard.de.bruyne@azorg.be](mailto:bernard.de.bruyne@azorg.be); [peter.juni@ndph.ox.ac.uk](mailto:peter.juni@ndph.ox.ac.uk)

## Methods

### Study design and oversight

The FAME 2 trial was a randomized, parallel, multicenter two-arm trial with blind adjudication of clinical outcomes, comparing FFR-guided PCI plus medical therapy with medical therapy alone in patients with stable CAD<sup>2</sup>. Conducted at 28 sites across Europe and North America (Supplementary Table 1), the trial was prematurely stopped after the randomization of 888 patients, of an originally planned 1,632, following a recommendation from the Data and Safety Monitoring Board because of a highly significant difference in the primary endpoint favoring the PCI group<sup>2</sup>.

Patients provided informed consent for both the initial trial and the long-term follow-up, which received renewed approval from the institutional review board at each participating site. The long-term follow-up was funded by Abbott Vascular. The funder was not involved in data collection, trial design or conduct, subsequent data collection, writing and review of the manuscript, or the decision to submit it for publication. The first two authors and the last two authors had full access to all the data in the trial and vouch for the accuracy and completeness of the data and analyses and the fidelity of the trial to the protocol. The long-term follow-up was registered at ClinicalTrials.gov, number [NCT06159231](#). The study protocol and the statistical analysis plan are provided in Supplementary Information.

### Participants, randomization and treatment

Eligible participants included those with stable angina or documented silent ischemia, with at least one stenosis with a 50% diameter reduction in a large epicardial artery suitable for PCI. Detailed inclusion criteria were: stable angina pectoris (CCS class 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; 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; coronary stenoses amenable to PCI. Patients in the following specific situations could be included if they met the inclusion criteria: patients with previous stents and restenosis; chronic total occlusions if the supplied myocardium was deemed viable, recanalization was deemed likely and useful, and if the chronic total occlusion was not the only lesion with a significant FFR; patients who sustained a ST-segment elevation myocardial infarction (STEMI) or a non-STEMI more than one week before randomization. Exclusion criteria were patients in whom the preferred treatment was coronary artery bypass grafting; left main CAD requiring revascularization; STEMI or non-STEMI within the past week; prior coronary artery bypass grafting; contraindication to dual antiplatelet therapy; left ventricular ejection fraction <30%; severe left ventricular hypertrophy (defined as a septal wall thickness at echocardiography of >13 mm); planned need for concomitant valvular or aortic surgery; extremely tortuous or calcified coronary arteries precluding FFR measurements; life expectancy of less than 2 years; age under 21 years; pregnancy or intention to become pregnant during the trial; refusal or inability to provide informed consent; existence of a mental condition (psychiatric or organ cerebral disease) that rendered the subject unable to understand the nature, scope and possible consequences of the trial, preventing the patient from providing informed consent; potential for noncompliance toward the requirements in the trial protocol (especially the medical treatment) or follow-up visits; and participation or planned participation in another cardiovascular clinical trial before the 2-year follow-up was completed.

FFR measurements were taken for all angiographically significant lesions. Patients with at least one hemodynamically significant stenosis ( $\text{FFR} \leq 0.80$ ) were randomly assigned in a 1:1 ratio to either FFR-guided PCI plus medical therapy (PCI group) or medical therapy alone (medical therapy group)<sup>2</sup>. The randomized allocation sequence was computer-generated, stratified according to site, blocked with

randomly varied block sizes and concealed using central randomization. Patients with only hemodynamically nonsignificant stenoses ( $\text{FFR} > 0.80$ ) did not undergo randomization but received medical therapy and were included in a registry<sup>2</sup>.

All patients were prescribed aspirin, metoprolol or another beta-1-selective blocker (alone or combined with a calcium-channel blocker or long-acting nitrate), lisinopril or an alternative angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker, and atorvastatin or a comparable statin (with or without ezetimibe) to reduce low-density lipoprotein levels below 1.8 mmol l<sup>-1</sup>. Smoking cessation counseling was provided to smokers, and patients with diabetes were referred to specialists for optimal management. Patients in the PCI group received a loading dose of clopidogrel and aspirin before PCI if not already on these medications. Stenoses with an FFR of 0.80 or less were treated with second- or third-generation drug-eluting stents. After PCI, clopidogrel 75 mg per day was continued for at least 12 months. In the medical therapy group, clopidogrel use was left to the clinician's discretion<sup>2</sup>.

### Outcomes and follow-up

The primary outcome of FAME 2 was a composite of all-cause death, myocardial infarction or urgent revascularization<sup>2</sup>. Secondary outcomes included the individual components of the primary outcome, nonurgent revascularization, as well as cardiac death and stroke<sup>2</sup>. However, cardiac death could not be ascertained reliably during long-term follow-up because of insufficient information in the majority of deceased patients.

Myocardial infarction was diagnosed using different criteria depending on whether it occurred within 24 h of randomization or PCI, or later during follow-up. Within 24 h after randomization or any PCI, a myocardial infarction was diagnosed if creatine kinase-MB exceeded ten times the 99th percentile upper reference limit (URL), or exceeded five times the URL together with at least one of the following: new pathological Q waves in two or more contiguous leads or new persistent nonrate-related left bundle branch block; angiographically documented native coronary artery occlusion; or imaging evidence of new loss of viable myocardium. Beyond 24 h, myocardial infarction was defined by a rise and/or fall in creatine kinase-MB or troponin with at least one value above the 99th percentile URL, along with evidence of myocardial ischemia as indicated by ischemic symptoms, new ST-T changes or left bundle branch block on electrocardiogram, development of pathological Q waves, or imaging evidence of new regional wall motion abnormality. All myocardial infarctions were further classified as ST elevation or non-ST elevation myocardial infarction, and as Q wave or non-Q wave myocardial infarction when electrocardiogram data permitted. Urgent revascularization was defined as any unplanned hospital admission because of symptoms (persisting or increasing chest pain with or without ST-T changes or elevated biomarkers) that led to revascularization during the same hospitalization. This was distinguished from elective crossover revascularization, which was performed on a nonurgent basis. A detailed clinical narrative was reviewed for each case to determine whether the criteria for urgent revascularization were met.

The objective of the long-term follow-up, conducted 10 years or more after randomization, was to assess the long-term efficacy and safety of FFR-guided PCI compared to medical therapy alone. All 28 sites were invited to participate. Sixteen sites, contributing 748 randomized patients (84.2%), participated in the long-term follow-up (Supplementary Table 2), while 12 sites, contributing 140 randomized patients, did not. Data on all-cause death, myocardial infarction and urgent revascularization were collected through clinic visits or telephone follow-up. Vital status was additionally ascertained using national death registers, ensuring complete data on all-cause death in patients from participating sites. All events were adjudicated by two cardiologists who were not involved in the trial and were unaware of assigned treatments.

## Statistical analysis

**Win ratio analyses.** A total of 131 patients (14.8%) had incomplete data on myocardial infarction and urgent revascularization because they had died in the interval between 5 years and long-term follow-up: 72 of 104 deceased patients (69.2%) in the PCI group and 59 of 92 deceased patients (64.1%) in the medical therapy group. Traditional time-to-first event analyses would be impacted by this pattern of missing data<sup>13</sup>. Therefore, we performed a hierarchical analysis using the unstratified, unmatched win ratio<sup>14</sup>, which prioritizes time to all-cause death over time to myocardial infarction, and time to myocardial infarction over time to urgent revascularization, thereby minimizing the impact of this type of missing data. The analysis first compared all patients randomized to FFR-guided PCI plus medical therapy with all patients randomized to medical therapy alone based on time to all-cause death, for which complete information was available across all participating sites. In each possible patient pair, the comparison determined whether FFR-guided PCI or medical therapy was superior, based on which patient died first. Only for patient pairs in which neither patient died during their shared follow-up period did the analysis proceed to compare patients on time to myocardial infarction and, if necessary, time to urgent revascularization to resolve a tie. Thus, the impact of incomplete data for nonfatal events in deceased patients on the overall win ratio was minimal.

For the primary outcome and its components, we also calculated the win difference, defined as the absolute difference between the proportion of patient pairs won by the FFR-guided PCI group and the proportion won by the medical therapy group<sup>15</sup>. We then derived an estimate of the NNT for the primary outcome as the reciprocal of the win difference<sup>16</sup>. The NNT represents the number of participants who need to be treated with FFR-guided PCI rather than medical therapy to achieve one additional patient with a better outcome, taking into account the frequency, hierarchy and timing of events.

Extended Data Table 5 shows that of a total of 197,127 patient pairs analyzed to calculate the win ratio, 61,386 pairs (31.1%) had definitive outcomes on time to death. Of these, 32,931 pairs (16.7%) would have been affected by incomplete data on myocardial infarction and urgent revascularization in deceased patients, but because the analysis was hierarchical, the missing data did not affect these pairs. The remaining 135,741 pairs (68.9%) involved comparisons of nonfatal events. While 30,915 pairs (15.7%) were affected by missing data from living patients, only 4,572 pairs (2.3%) were impacted by incomplete data from deceased patients. Thus, the actual impact of incomplete data from deceased patients on the overall win ratio was minimal.

To identify which component of the primary composite endpoint drove the overall win ratio, we first calculated the win ratio for time to all-cause death. Next, we determined the conditional win ratio for time to myocardial infarction in patient pairs with a tie on time to all-cause death. Finally, we calculated the conditional win ratio for time to urgent revascularization in remaining pairs with a tie on time to myocardial infarction. To ensure consistency with previous analyses<sup>2–4</sup>, we also calculated the win ratio for the hierarchical composite of time to all-cause death or myocardial infarction. All analyses adhered to the intention-to-treat principle, including all randomized patients in their originally assigned groups. Patients from the 12 nonparticipating sites and patients who withdrew or were lost to follow-up were censored at the time when the last follow-up information was available.

**Subgroup analyses.** Subgroup analyses of the primary composite endpoint were conducted using the win ratio and accompanied by z-tests for interaction between treatment and subgroups. The following baseline characteristics were used for subgroup analysis as originally specified<sup>2</sup>: age (>60 versus ≤60), sex, diabetes, history of stroke or TIA, history of myocardial infarction, history of PCI, left ventricular ejection fraction (<50% versus >50%), FFR (<0.65 versus ≥0.65), diameter stenosis (≥70% versus <70%). Given the previously observed interaction

between treatment and FFR<sup>2–4</sup>, we also conducted exploratory post hoc calculations of the win ratio for subgroups defined by FFR at each level of the hierarchical primary outcome.

**Sensitivity analyses.** Sensitivity analyses were conducted to evaluate the robustness of the primary findings under different analytic assumptions. First, we calculated unconditional win ratios on time to nonfatal events (myocardial infarction and urgent revascularization) to assess treatment effects in all 197,127 patient pairs, without restricting comparisons to those tied on outcomes higher in the hierarchy. In these analyses, patients who died were censored at the time of death, rather than counted as having had an event, ensuring that death did not result in a loss for either treatment group.

Second, we calculated incidence rate ratios for the primary composite outcome and its components using a Poisson model with robust standard errors. This prespecified analysis was performed both using complete-case data, with censoring at the earliest of event occurrence or last known follow-up, and using multiple imputation to address missing outcome data. The Poisson model was selected for its ability to accommodate varying follow-up times and for its relative robustness when using multiple imputation in the presence of missing data. Corresponding time-to-event curves were plotted as the cumulative incidence of events over time derived from the Kaplan–Meier estimate of the survival function. For all-cause death, we present time-to-event curves both using complete-case data (Fig. 2), with censoring at the earliest of event occurrence or last known follow-up, because vital status was near completely ascertained, and using multiple imputation (Extended Data Fig. 3). For the nonfatal outcomes of myocardial infarction and urgent revascularization and the primary composite outcome, we present time-to-event curves solely following multiple imputation (Extended Data Fig. 3). Complete-case analyses would result in an underestimation of the cumulative incidence of nonfatal events due to incomplete data on these events for patients who died between their previous follow-up and the current long-term follow-up.

Third, we estimated HRs for the primary composite outcome and its components using Cox proportional hazards models, with and without multiple imputation for missing data. These post hoc analyses were conducted in response to peer reviewer requests to enable direct comparison with earlier FAME 2 publications<sup>2–4</sup>.

Multiple imputation of time-to-event data was done for patients who withdrew or were lost to follow-up, patients who had died since the previous follow-up with incomplete information on myocardial infarction and/or urgent revascularization after the previous follow-up, and patients from nonparticipating hospitals, using chained equations to create 50 imputed datasets. The following variables were used as covariates in the imputation model: randomized treatment, age, sex, geographic region, smoking status, diabetes, number of lesions, time since randomization, FFR < 0.65, history of stroke or TIA, history of myocardial infarction, ejection fraction (<50% versus >50%) and history of PCI. Time to event (in days) was imputed using a nearest neighbor algorithm<sup>17</sup>, matching on prognostic scores derived from a Cox proportional hazards model based on the same covariates. Statistical analyses were performed using Stata 18 (StataCorp).

## Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

## Data availability

The data underlying this study consist of clinical information from human participants. Participants provided informed consent for use of their data in this specific study but not for unrestricted public sharing. As such, open access to the dataset would compromise participant confidentiality and breach ethical and legal obligations under applicable data protection regulations. To balance participant

privacy with scientific transparency, anonymized derived data will be made available upon reasonable request to qualified researchers with a methodologically sound proposal, subject to approval by the sponsoring institutions and, if required, relevant ethics committees. Requests for data should be sent to the corresponding authors, with a response expected within 4 weeks.

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## Author contributions

The study was conceptualized by B.D.B., N.H.J.P., W.F.F., C.C. and P.J. All authors were involved in data curation. Study methodology was developed by C.C., B.D.B. and P.J. Data analysis was performed by T.V.P., B.R.d.C., T. Mizukami and T. Mahendirian, under the supervision of B.D.B. and P.J. The original draft was written by C.C., T. Mahendirian, B.D.B. and P.J. All authors contributed to the review, editing and approval of the final version of the manuscript.

## Competing interests

C.C. reports receiving research grants from Biosensor, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, CathWorks,

Boston Scientific, Siemens, HeartFlow Inc. and Abbott Vascular and consultancy fees from HeartFlow Inc., OpSens, Abbott Vascular and Philips Volcano. T. Mahendirian is supported by a grant from the Swiss National Science Foundation (SNSF). W.F.F. has received institutional research support from Abbott Vascular, Boston Scientific and Medtronic; has a consulting relationship with CathWorks and Siemens; and has stock options with HeartFlow. N.H.J.P. has received institutional research grants from Abbott; has consulting relationships with and receives fees from Abbott and Coroventis; has equity in ASML Holding N.V., General Electric, HeartFlow and Philips; is a member of the Scientific Advisory Board of HeartFlow; and has patents pending in the field of the coronary microcirculation and aortic valve stenosis. B.D.B. has a consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens and Coroventis Research; receives research grants from Abbott Vascular, Coroventis Research, CathWorks and Boston Scientific; and holds minor equities in Philips Volcano, Siemens, GE Healthcare, Edwards Lifesciences, HeartFlow, Sanofi and Celyad. The other authors declare no competing interests.

## Additional information

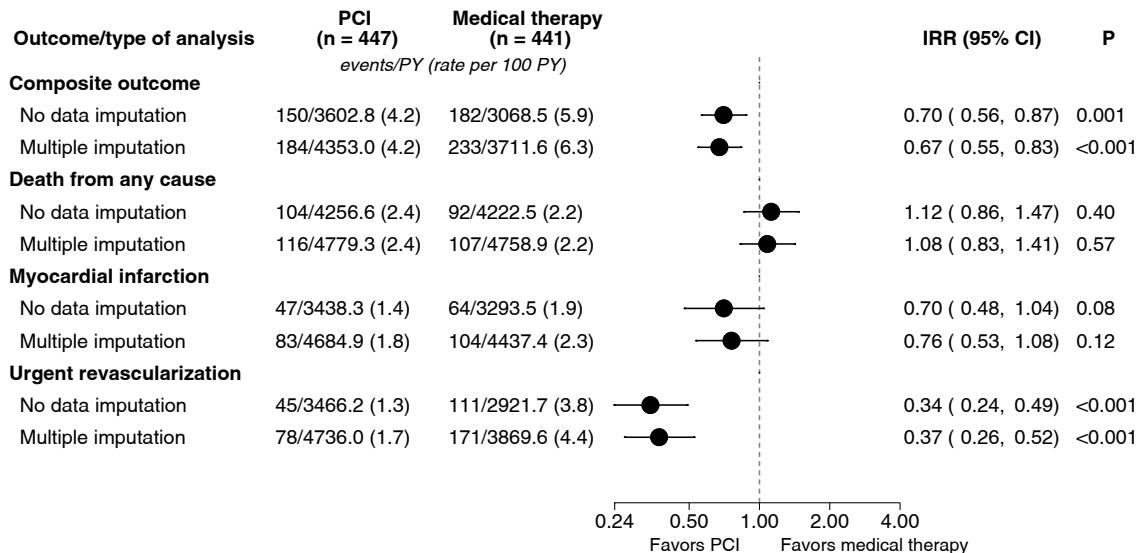
**Extended data** is available for this paper at  
<https://doi.org/10.1038/s41591-025-04132-5>.

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**Correspondence and requests for materials** should be addressed to Bernard De Bruyne or Peter Jüni.

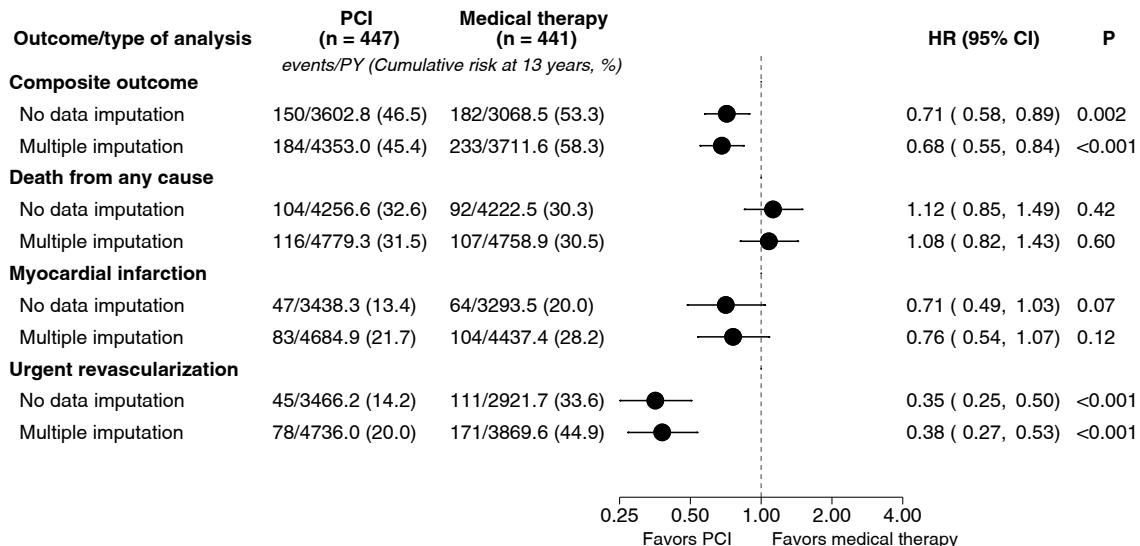
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**Extended Data Fig. 1 | Sensitivity analyses based on the incidence rate ratio.**

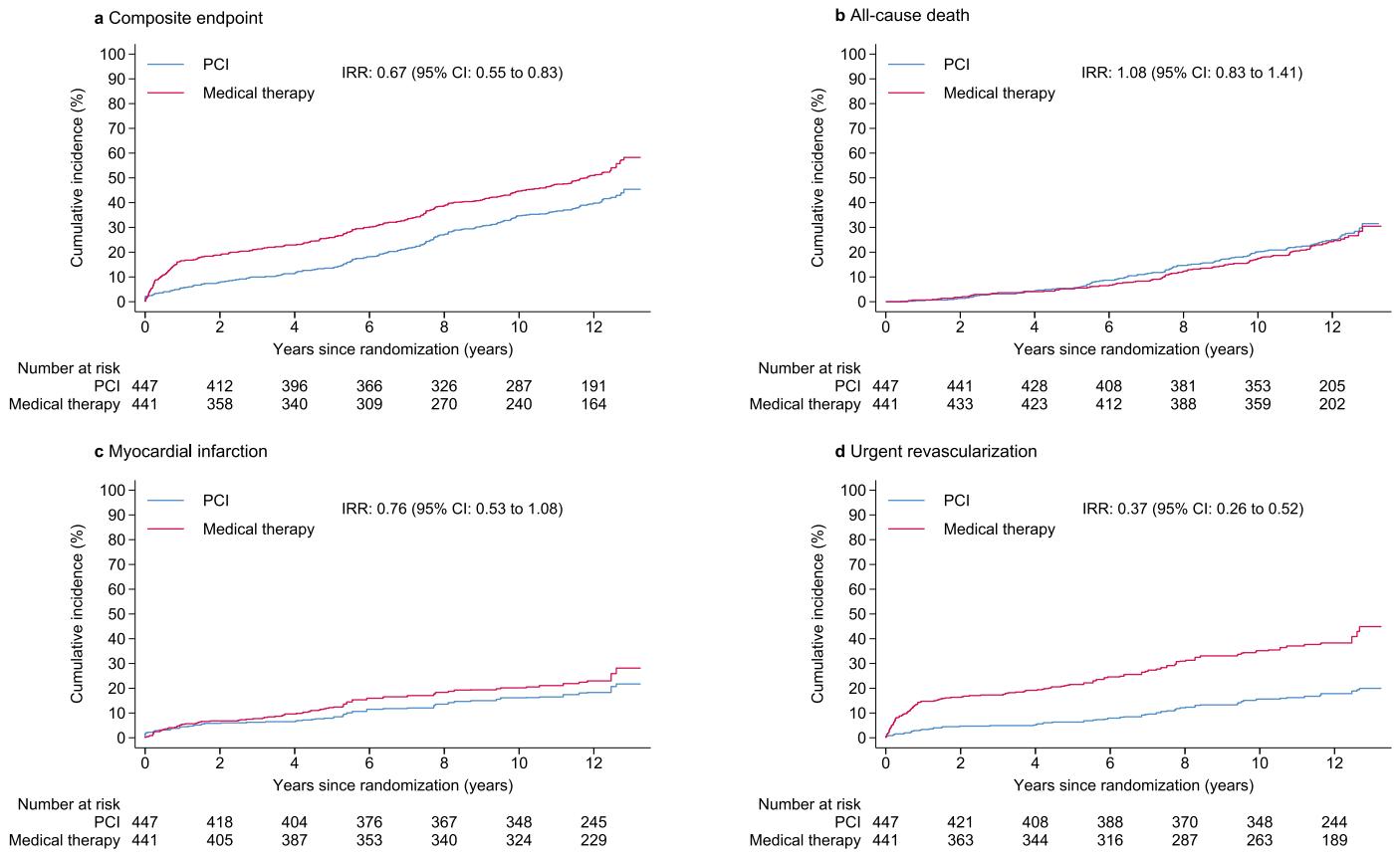
Prespecified sensitivity analyses using Poisson regression with robust standard errors to estimate incidence rate ratios with 95% confidence intervals. In the model without data imputation, participants who dropped out or were lost to

follow-up were censored at the time of the event or at the time of last available follow-up. IRR, incidence rate ratio. 95% CI, 95% confidence interval. PCI, percutaneous coronary intervention. PY, person-years. Two-sided P-values are from Wald tests of the regression coefficients in the Poisson regression models.

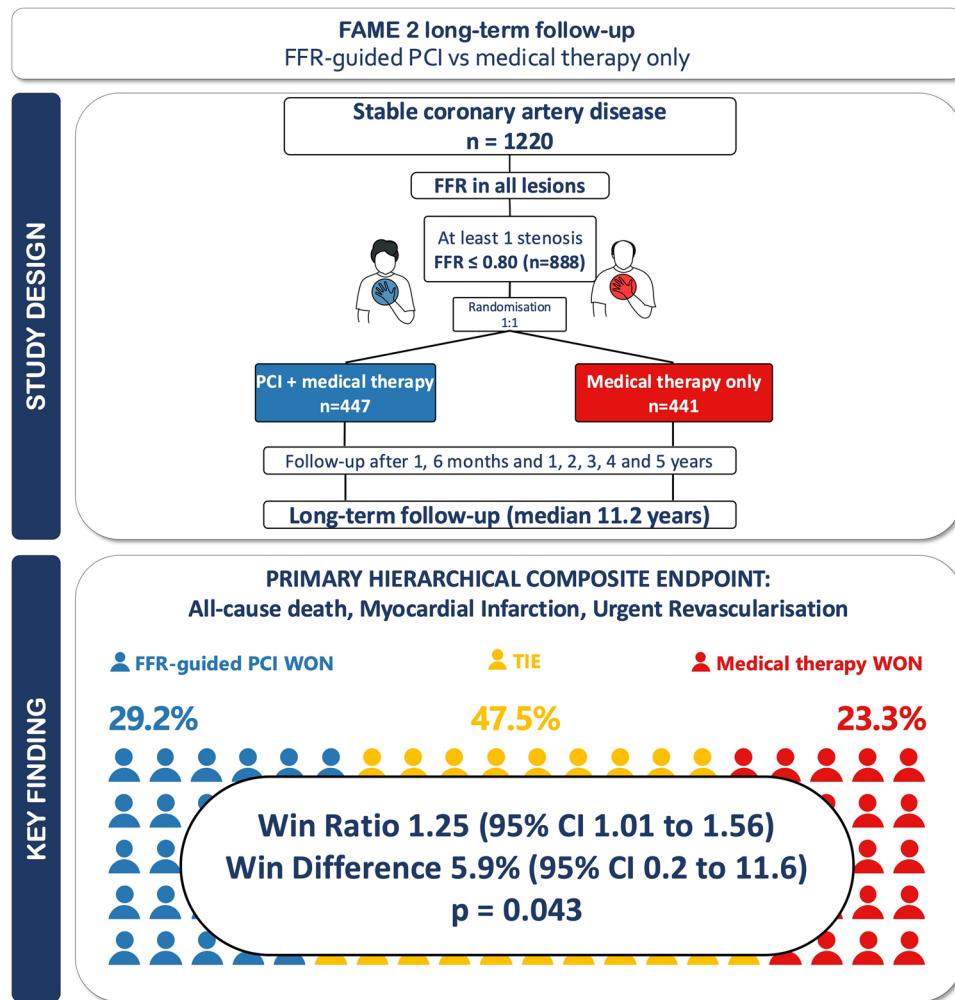
**Extended Data Fig. 2 | Post hoc sensitivity analyses based on the hazard ratio.**

**Post hoc sensitivity analyses** using Cox proportional hazards models to estimate hazard ratios with 95% confidence intervals. In the model without data imputation, participants who dropped out or were lost to follow-up were

censored at the time of the event or at the time of last available follow-up. HR, hazard ratio. 95% CI, 95% confidence interval. PCI, percutaneous coronary intervention. PY, person-years. Two-sided P-values are from Wald tests of the regression coefficients in the Cox proportional hazards models.



**Extended Data Fig. 3 | Time-to-event curves after multiple imputation.** Cumulative incidence curves for primary composite outcome (a) and its components (b) all-cause death, (c) myocardial infarction, and (d) urgent revascularization, after multiple imputation. IRR, incidence rate ratio. 95% CI, 95% confidence interval. PCI, percutaneous coronary intervention.



**Extended Data Fig. 4 | Summary of the main study findings.** The two-sided P-value for the win ratio was calculated using a Z test based on the Finkelstein and Schoenfeld method.

**Extended Data Table 1 | Comparison of baseline clinical characteristics between participants with available long-term follow-up and those without**

	Long-term follow-up available (N=654)	Long-term follow-up unavailable Lost to follow-up/withdrew (N = 122)	Enrolled in non-participating sites (N = 112)*
Age – yr	64.3 ± 9.5	63.1 ± 8.8	61.0 ± 9.7
Age >60 yr – no. (%)	424 (64.8)	81 (66.4)	56 (50.0)
Male sex – no. (%)	523 (80.0)	87 (71.3)	84 (75.0)
Body-mass index	28.1 ± 4.3	28.6 ± 4.8	29.5 ± 4.6
Current smoking – no. (%)	124 (19.0)	29 (23.8)	26 (23.2)
Silent ischemia – no. (%)	100 (15.3)	34 (27.9)	12 (10.7)
Renal insufficiency – no. (%)	15 (2.3)	3 (2.5)	2 (1.8)
Diabetes mellitus – no. (%)	180 (27.5)	40 (32.8)	20 (17.9)
Insulin-dependent – no. (%)	58 (8.9)	14 (11.5)	6 (5.4)
Hypertension – no. (%)	513 (78.4)	96 (78.7)	81 (72.3)
Peripheral vascular disease – no. (%)	70 (10.7)	15 (12.3)	5 (4.5)
Family history of coronary artery disease – no. (%)	297 (45.5)	61 (50.0)	65 (58.0)
Hypercholesterolemia – no. (%)	498 (76.1)	80 (65.6)	100 (89.3)
History of myocardial infarction – no. (%)	251 (38.4)	39 (32.0)	39 (34.8)
History of stroke/ TIA – no. (%)	49 (7.5)	6 (4.9)	6 (5.4)
History of PCI in target vessel – no. (%)	119 (18.2)	23 (18.9)	14 (12.5)
Left ventricular ejection fraction ≤50% – no. (%)	107 (16.4)	19 (15.6)	13 (11.6)
Angina class			
Asymptomatic – no. (%)	70 (10.7)	20 (16.4)	9 (8.1)
CCS class I – no. (%)	128 (19.6)	18 (14.8)	34 (30.6)
CCS class II – no. (%)	292 (44.6)	58 (47.5)	51 (45.9)
CCS class III – no. (%)	110 (16.8)	21 (17.2)	14 (12.6)
CCS class IV – no. (%)	54 (8.3)	5 (4.1)	3 (2.7)

Presented are means±SD or numbers (percentages). \*Of the 140 patients enrolled at non-participating sites, 5 died during the 5-year follow-up and had complete follow-up data recorded for the long-term follow-up and 23 were lost to follow-up or withdrew consent before the 5-year follow-up, which leaves 112 patients in this group.

**Extended Data Table 2 | Comparison of baseline clinical characteristics between participants randomized to PCI or medical therapy with available long-term follow-up**

	PCI (N=329)	Medical therapy (N=325)
Age – yr	64.2 ± 9.2	64.3 ± 9.8
Age >60 yr – no. (%)	216 (65.7)	208 (64.0)
Male sex – no. (%)	271 (82.4)	252 (77.5)
Body-mass index	28.0 ± 4.1	28.3 ± 4.5
Current smoking – no. (%)	60 (18.2)	64 (19.7)
Silent ischemia – no. (%)	54 (16.4)	46 (14.2)
Renal insufficiency – no. (%)	8 (2.4)	7 (2.2)
Diabetes mellitus – no. (%)	96 (29.2)	84 (25.8)
Insulin-dependent – no. (%)	32 (9.7)	26 (8.0)
Hypertension – no. (%)	256 (77.8)	257 (79.1)
Peripheral vascular disease – no. (%)	35 (10.6)	35 (10.8)
Family history of coronary artery disease – no. (%)	151 (46.0)	146 (44.9)
Hypercholesterolemia – no. (%)	244 (74.2)	254 (78.2)
History of myocardial infarction – no. (%)	133 (40.4)	118 (36.3)
History of stroke/ TIA – no. (%)	25 (7.6)	24 (7.4)
History of PCI in target vessel – no. (%)	68 (20.7)	51 (15.7)
Left ventricular ejection fraction ≤50% – no. (%)	67 (20.4)	40 (12.3)
Angina class		
Asymptomatic – no. (%)	40 (12.2)	30 (9.2)
CCS class I – no. (%)	63 (19.1)	65 (20.0)
CCS class II – no. (%)	137 (41.6)	155 (47.7)
CCS class III – no. (%)	63 (19.1)	47 (14.5)
CCS class IV – no. (%)	26 (7.9)	28 (8.6)

Presented are means±SD or numbers (percentages).

**Extended Data Table 3 | Exploratory post-hoc calculations of the win ratio at each level of the hierarchical primary outcome for subgroups defined by FFR**

Subgroup/Outcome	Analyzed pairs	Wins		Ties		Losses		Win ratio (95% CI)
		No	%	No	%	No	%	
<b>FFR&lt;0.65</b>								
All-cause death	45,920	7211	15.7	31615	68.8	7094	15.4	1.02 (0.67, 1.55)
Myocardial infarction*	31,615	3736	11.8	25909	82	1970	6.2	1.90 (1.01, 3.56)
Urgent revascularization**	25,909	4327	16.7	20970	80.9	612	2.4	7.07 (3.16, 15.8)
Hierarchical primary outcome	45,920	15274	33.3	20970	45.7	9676	21.1	1.58 (1.15, 2.16)
<b>FFR≥0.65</b>								
All-cause death	52,628	7120	13.5	36143	68.7	9365	17.8	0.76 (0.51, 1.14)
Myocardial infarction*	36,143	3937	10.9	28994	80.2	3212	8.9	1.23 (0.68, 2.21)
Urgent revascularization**	28,994	2424	8.4	25719	88.7	851	2.9	2.85 (1.17, 6.91)
Hierarchical primary outcome	52,628	13481	25.6	25719	48.9	13428	25.5	1.00 (0.74, 1.37)

For FFR<0.65, there were 224 participants in the PCI group and 205 in the medical therapy group, resulting in a total of 45,920 pairs (224×205). For FFR≥0.65, there were 223 in the PCI group and 236 in the medical therapy group, resulting in a total of 52,628 pairs (223×236). Win ratios are unconditional unless otherwise specified. \*Conditional win ratio for time to myocardial infarction calculated in patient pairs with ties on time to death. \*\*Conditional win ratio for time to revascularization calculated in patient pairs with ties on both time to death and time to myocardial infarction. 95% CI, 95% confidence interval. FFR, fractional flow reserve.

## Extended Data Table 4 | Win ratios for all outcomes

Subgroup/Outcome	Analyzed pairs	Wins		Ties		Losses		Win ratio (95% CI)
		No	%	No	%	No	%	
All-cause death	197127	28694	14.6	135741	68.9	32692	16.6	0.88 (0.66, 1.17)
Myocardial infarction	197127	23052	11.7	157581	79.9	16494	8.4	1.40 (0.95, 2.06)
Conditional*	135741	15404	11.3	110087	81.1	10250	7.6	1.50 (0.98, 2.31)
Stroke	197127	5321	2.7	185323	94.0	6483	3.3	0.82 (0.42, 1.60)
Conditional*	135741	4327	3.2	127309	93.8	4105	3.0	1.05 (0.52, 2.13)
Urgent revascularization	197127	42354	21.5	141615	71.8	13158	6.7	3.22 (2.26, 4.59)
Conditional**	110087	13435	12.2	93712	85.1	2940	2.7	4.57 (2.53, 8.24)
Death or myocardial infarction	197127	44098	22.4	110087	55.8	42942	21.8	1.03 (0.81, 1.31)
Non-urgent revascularization	197127	61289	31.1	125341	63.6	10497	5.3	5.84 (4.20, 8.13)
Conditional**	110087	13152	11.9	87786	79.7	9149	8.3	1.44 (0.77, 2.68)
Any revascularization	197127	95926	48.7	81021	41.1	20180	10.2	4.75 (3.70, 6.11)
Conditional**	110087	13151	11.9	85168	77.4	11768	10.7	1.12 (0.60, 2.09)

Win ratios are unconditional unless otherwise specified. \* Conditional win ratio for time to myocardial infarction calculated in patient pairs with ties on time to death. \*\* Conditional win ratio for time to revascularization calculated in patient pairs with ties on both time to death and time to myocardial infarction.

**Extended Data Table 5 | Summary of pairwise comparisons in the win ratio analysis for the primary outcome**

Pairwise comparisons*	No. (%)
Analyzed pairs	197,127 (100.0%)
Pairs with wins or losses on time to death	61,386 (31.1%)
Incomplete data in deceased patient, not affecting comparison	32,931 (16.7%)
Incomplete data in living patient, not affecting comparison	2,291 (1.2%)
Not affected by incomplete data	26,164 (13.3%)
Pairs with ties on time to death	13,5741 (68.9%)
Affected by incomplete data in deceased patient	4,553 (2.3%)
Affected by incomplete data in living patient	30,915 (15.7%)
Not affected by incomplete data	100,273 (50.9%)

\* There was a total of  $447 \times 441 = 197,127$  pairs of participants.

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### Reporting on sex and gender

No sex or gender-specific analysis were performed except for a subgroup analysis for the primary endpoint which compared outcomes for the different sexes and found no difference (Figure 3). 694 patients were male (78.2%).

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No specific reporting on race, ethnicity, or other socially relevant groupings.

### Population characteristics

This has been detailed in the methods and results. Briefly, Eligible participants included those with stable angina or documented silent ischemia, with at least one stenosis with a 50% diameter reduction in a large epicardial artery suitable for PCI. FFR measurements were taken for all angiographically significant lesions. The baseline characteristics of patients were similar between treatment groups (Table 1). The mean age at randomisation was 63.7 years, 694 patients were male (78.2%), and 240 had a diagnosis of diabetes mellitus (27.0%).

### Recruitment

The FAME 2 trial was a randomised, parallel, multicentre two-arm trial with blind adjudication of clinical outcomes, comparing FFR-guided PCI plus medical therapy with medical therapy alone in patients with stable coronary artery disease. Conducted at 28 sites across Europe and North America. The steering committee members designed the initial trial protocol and long-term follow-up. Patients were reconsented for the long-term follow-up, and the trial received new approval from the institutional review board at each participating site.

### Ethics oversight

Each study center's ethical committee provided approval, as per original study protocol available here: <https://www.nejm.org/doi/full/10.1056/NEJMoa1205361#APPNEJMoa1205361PRO>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

### Sample size

The original trial sample size calculation was performed as follows: We project a rate of the primary end-point of 18% in the optimal medical treatment arm and of 12.6% in the PCI + OMT group (relative risk reduction of 30% and absolute risk reduction of 5.4%) at a median follow-up duration of 36 months, assuming a duration of patient recruitment of 24 months, and a minimum follow-up duration of 24 months. A sample size of approximately 1600 patients randomized 1:1 will have a power larger than 84% to detect a relative risk reduction of 30% at a two-sided alpha of 0.05. Considering a 2% rate of loss during the follow-up, a total of 1632 patients will have to be recruited and randomized.

However, the trial was prematurely stopped after the randomisation of 888 patients, out of an originally planned 1632, following a recommendation from the Data and Safety Monitoring Board (DSMB) due to a highly significant difference in the primary endpoint favouring the PCI group

The objective of the long-term follow-up, conducted 10 years or more after randomisation, was to assess the long-term efficacy and safety of FFR-guided PCI compared to medical therapy alone. All 28 sites were invited to participate. Sixteen sites, contributing 748 randomised patients (84.2%), participated in the long-term follow-up (Supplementary Table S1), while 12 sites, contributing 140 randomised patients, did not.

### Data exclusions

No data exclusions to report

### Replication

No replication of the data was performed due to the nature of the study design: randomized controlled trial.

### Randomization

Patients with at least one hemodynamically significant stenosis ( $\text{FFR} \leq 0.80$ ) were randomly assigned in a 1:1 ratio to either FFR-guided PCI plus medical therapy (PCI group), or medical therapy alone (medical therapy group).<sup>2</sup> The randomised allocation sequence was computer-generated, stratified according to site, blocked with randomly varied block sizes, and concealed using central randomisation. Patients with only hemodynamically non-significant stenoses ( $\text{FFR} > 0.80$ ) did not undergo randomisation but received medical therapy and were included in a registry.

### Blinding

This was a multicentre, open-label, randomised trial with blind adjudication of clinical outcomes.

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Clinical trial registration [ClinicalTrials.gov](#), number NCT06159231

Study protocol The full study protocol and statistical analysis plan are available in the Supplementary Information

Data collection The original trial: between May 15, 2010, and January 15, 2012, a total of 1220 patients were enrolled. All 28 sites were invited to participate in the long-term follow-up. Sixteen sites, contributing 748 randomised patients (84.2%), participated in the long-term follow-up (Supplementary Table S2), while 12 sites, contributing 140 randomised patients, did not.

Outcomes The primary outcome of FAME 2 was a composite of all-cause death, myocardial infarction, or urgent revascularization.<sup>2</sup> Urgent revascularization was defined as any unplanned hospital admission due to symptoms that led to revascularization during the same hospitalization. Secondary outcomes included the individual components of the primary outcome, non-urgent revascularization, as well as cardiac death and stroke (Supplementary Appendix).<sup>2</sup> However, cardiac death could not be ascertained reliably during long-term follow-up due to insufficient information in the majority of deceased patients.  
The objective of the long-term follow-up, conducted 10 years or more after randomisation, was to assess the long-term efficacy and safety of FFR-guided PCI compared to medical therapy alone. All 28 sites were invited to participate. Sixteen sites, contributing 748 randomised patients (84.2%), participated in the long-term follow-up (Supplementary Table S1), while 12 sites, contributing 140 randomised patients, did not. Data on all-cause death, myocardial infarction, and urgent revascularization were collected through clinic visit or telephone follow-up. Vital status was additionally ascertained using national death registers, ensuring complete data on all-cause death in patients from participating sites. All events were adjudicated by two cardiologists who were not involved in the trial and were unaware of assigned treatments.

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