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Lessons from the trials

# FAME 2: Reshaping the approach to patients with stable coronary artery disease

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## ABSTRACT

Contrary to its central role in patients with acute coronary syndromes (ACS), percutaneous coronary intervention (PCI) in stable ischemic heart disease (SIHD) remains largely restricted to patients in whom medical treatment fails to control symptoms, or those with a large area of myocardium at risk and/or high risk findings on non-invasive testing.<sup>1,2</sup> These recommendations are based on a number of studies – the largest of which is COURAGE – that failed to show any reduction in mortality or myocardial infarction (MI) with PCI compared to optimal medical therapy (OMT) in this group of patients.<sup>3</sup> A possible limitation in these studies was relying on visual assessment of angiographic stenoses (which is now well-known to be imprecise) to determine lesions responsible for myocardial ischemia. Non-invasive stress testing – including imaging – may also be inaccurate in patients with multivessel coronary artery disease.<sup>4,5</sup> These limitations have inadvertently led to the inclusion of patients with non-ischemic lesions in these studies, which may have diluted any potential benefit with PCI. Given the superiority of fractional flow reserve (FFR) in identifying ischemic lesions compared to angiography, Fractional flow reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) investigators hypothesized that when guided by FFR, PCI plus medical therapy would be superior to medical therapy alone in patients with SIHD.

*Keywords:* FAME 2, fractional flow reserve, stable ischemic heart disease

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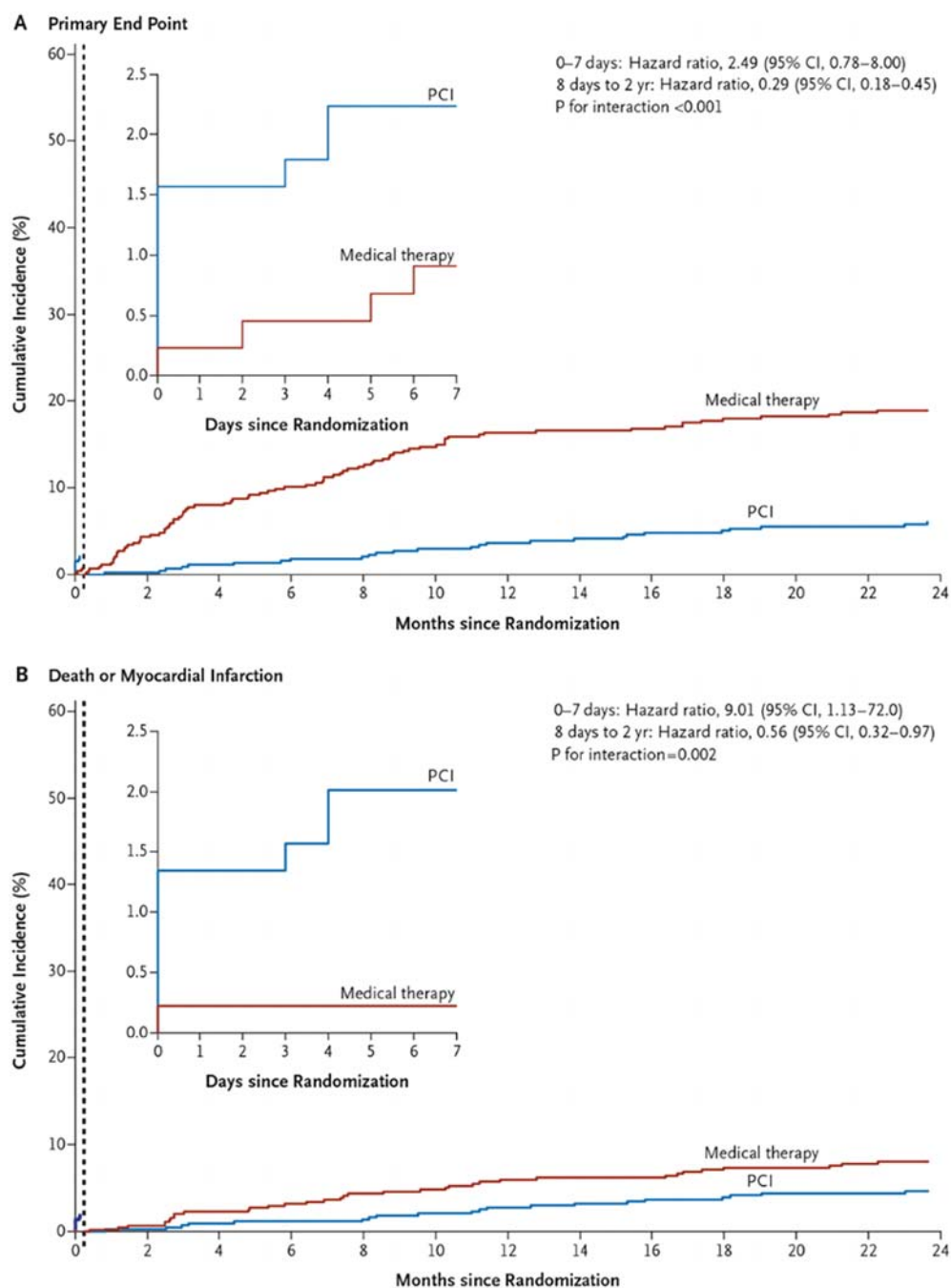
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## STUDY DESIGN

FAME 2 trial randomized patients with SIHD and one or more stenoses with  $\text{FFR} \leq 0.80$  to PCI plus OMT or to OMT alone. Patients were enrolled in the registry if they did not have FFR values less than 0.80 in any of the stenoses seen on their angiograms. The primary endpoint was the composite of death,



**Figure 1. Kaplan–Meier curves for the landmark analyses.** Shown are the cumulative incidences of the primary end point (a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization) (Panel A) and of death or myocardial infarction (Panel B) in the two study groups, stratified on the basis of a landmark point at 7 days after randomization (vertical dashed line). Hazard ratios for PCI versus medical therapy were calculated separately for events that occurred within 7 days and those that occurred between 8 days and the end of follow-up at 2 years. Data for the first 7 days are not included in the period after 7 days. The insets show the data for days 0 to 7 on an expanded y axis. P values for interaction were calculated from tests of heterogeneity between time periods. Hazard ratios below 1.00 denote a lower incidence of the primary end point in the PCI group than in the medical-therapy group. Reproduced from De Bruyne et al. [8].

non-fatal MI and urgent revascularization. Patient recruitment was stopped prematurely after randomizing 888 patients (originally targeting 1623) at the request of an independent data and safety monitoring board as a result of a highly significant difference in the incidence rates of the composite primary end-point between both groups.<sup>6</sup> The study's design in detail, as well as early results, have previously been discussed in the Journal.<sup>7</sup> The investigators published 2-year follow-up results late last year in the *New England Journal of Medicine* (Figure 1).<sup>8</sup>

## RESULTS AND DISCUSSION

At two years, the rate of the primary end point was significantly lower in the PCI group compared to the OMT group (8.1% vs. 19.5%, hazard ratio with PCI = 0.39; 95% CI = 0.26 – 0.57;  $p < 0.001$ ). This reduction was primarily driven by a lower rate of urgent revascularization in the PCI group, with approximately one half of those triggered by myocardial infarction or ischemic electrocardiographic changes (Table 1). Restricting analysis to the latter subgroup also revealed a lower rate of urgent revascularization with PCI compared to OMT (3.4% vs. 7.0%,  $p = 0.01$ ). To exclude periprocedural MI, a landmark analysis showed lower rates of death or MI between 8 days and two years in the PCI group (4.6% vs. 8%,  $p = 0.04$ ). The composite primary end point occurred in 9% in patients enrolled in the registry.

**Table 1. Clinical end points and triggers of urgent revascularization.**

End point	PCI (n = 447)	Medical therapy (n = 441)	Hazard ratio	P value
Primary composite of death, MI, or urgent revascularization	8.1%	19.5%	0.39 (0.26–0.57)	<0.001
Death from any cause	1.3%	1.8%	0.74 (0.26–2.14)	0.58
MI	5.8%	6.8%	0.85 (0.50–1.45)	0.56
Urgent revascularization	4.0%	16.3%	0.23 (0.14–0.38)	<0.001
Triggered by clinical features only	0.7%	9.8%	0.07 (0.02–0.21)	<0.001
Triggered by MI or ECG changes	3.4%	7.0%	0.47 (0.25–0.86)	0.01
Death or MI	6.5%	8.2%	0.79 (0.49–1.29)	0.35

Two-year results from FAME 2 confirm the earlier message from the same study: when second-generation drug eluting stents are used and PCI is restricted to functionally significant lesions, the need for urgent revascularization is significantly reduced compared to medical therapy alone. It is also plausible that this strategy reduces other hard clinical end points (i.e. death or MI). The latter possibility is supported by the landmark analysis that excluded periprocedural MI, which is known to carry a better prognosis compared to spontaneous MI.<sup>9,10</sup> Limitations of FAME 2 including its premature termination and non-blinded design (which may have influenced the decision to perform PCI to a known functionally significant stenosis during follow-up) have previously been addressed. However, the lack of blinding is unlikely to affect the overall conclusion in light of the results of the landmark analysis where only deaths or myocardial infarctions were analyzed. In addition, the higher rate of events observed in the OMT group compared to patients enrolled in the registry cannot be explained by the lack of blinding. These results emphasize the importance of accurate identification of the functional significance of coronary stenoses in patients with SIHD.

## WHAT HAVE WE LEARNED?

FFR-guided PCI in patients with SIHD using second-generation drug-eluting stents reduces the need for urgent revascularization, and possibly death and MI. On the other hand, patients with hemodynamically non-significant stenosis (defined as FFR >0.80) have excellent prognosis with medical treatment alone, regardless of the angiographic appearance of their coronary lesions.

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