

# Comparison of Fractional Flow Reserve–Guided PCI and Coronary Bypass Surgery in 3-Vessel Disease

Fearon WF, Zimmerman FM, De Bruyne B, et al. Fractional flow reserve-guided PCI as compared with coronary bypass surgery. *N Engl J Med*. 2022;386(2):128-137. doi:10.1056/NEJMoa2112299

## Study Overview

**Objective:** To determine whether fractional flow reserve (FFR) –guided percutaneous coronary intervention (PCI) is noninferior to coronary-artery bypass grafting (CABG) in patients with 3-vessel coronary artery disease (CAD).

**Design:** Investigator-initiated, multicenter, international, randomized, controlled trial conducted at 48 sites.

**Setting and participants:** A total of 1500 patients with angiographically identified 3-vessel CAD not involving the left main coronary artery were randomly assigned to receive FFR-guided PCI with zotarolimus-eluting stents or CABG in a 1:1 ratio. Randomization was stratified according to trial site and diabetes status.

**Main outcome measures:** The primary endpoint was major adverse cardiac or cerebrovascular event, defined as death from any cause, myocardial infarction (MI), stroke, or repeat revascularization. The secondary endpoint was defined as composite of death, MI, or stroke.

**Results:** At 1 year, the incidence of the composite primary endpoint was 10.6% for patients with FFR-guided PCI, and 6.9% for patients with CABG (hazard ratio [HR], 1.5; 95% CI, 1.1-2.2;  $P = .35$  for noninferiority,) which was not consistent with noninferiority of FFR-guided PCI com-

pared to CABG. The secondary endpoint occurred in 7.3% of patients in the FFR-guided PCI group compared with 5.2% in the CABG group (HR, 1.4; 95% CI, 0.9-2.1). Individual findings for the outcomes comprising the primary endpoint for the FFR-guided PCI group vs the CABG group were as follows: death, 1.6% vs 0.9%; MI, 5.2% vs 3.5%; stroke, 0.9% vs 1.1%; and repeat revascularization, 5.9% vs 3.9%. The CABG group had more extended hospital stays and higher incidences of major bleeding, arrhythmia, acute kidney injury, and rehospitalization within 30 days than the FFR-guided PCI group.

**Conclusion:** FFR-guided PCI was not found to be noninferior to CABG with respect to the incidence of a composite of death, MI, stroke, or repeat revascularization at 1 year.

## Commentary

Revascularization for multivessel coronary artery disease can be performed by CABG or PCI. Previous studies have shown superior outcomes in patients with multivessel CAD who were treated with CABG compared to PCI.<sup>1-3</sup> The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, which compared CABG to PCI in patients with a multivessel disease or unprotected

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left main CAD, stratified the anatomic complexity based on SYNTAX score and found that patients with higher anatomic complexity with a high SYNTAX score derive larger benefit from CABG compared to PCI.<sup>4</sup> Therefore, the current guidelines favor CABG over PCI in patients with severe 3-vessel disease, except for patients with a lower SYNTAX score (<22) without diabetes.<sup>5,6</sup> However, except for a smaller size study,<sup>3</sup> the previous trials that led to this recommendation used mostly first-generation drug-eluting stents and have not evaluated second-generation stents that have lower rates of in-stent restenosis and stent thrombosis. In addition, there have been significant improvements in the PCI techniques since the study period, including the adoption of a radial approach and superior adjunct pharmacologic therapy. Furthermore, previous studies have not systematically investigated the use of PCI guided by FFR, which has been shown to be superior to angiography-guided PCI or medical treatment alone.<sup>7-9</sup>

In this context, Fearon and the investigators of the FAME 3 trial investigated the use of FFR-guided PCI with second-generation zotarolimus drug-eluting stent compared to CABG in patients with 3-vessel CAD. They randomized patients with angiographically identified 3-vessel CAD in a 1:1 ratio to receive FFR-guided PCI or CABG at 48 sites internationally. Patients with left main CAD, recent ST-elevation MI, cardiogenic shock, and left ventricular ejection fraction <30% were excluded. The study results (composite primary endpoint incidence of 10.6% for patients with FFR-guided PCI vs 6.9% in the CABG group (HR, 1.5; 95% CI, 1.1-2.2;  $P=0.35$  for noninferiority) showed that FFR-guided PCI did not meet the noninferiority criterion.

Although the FAME-3 study is an important study, there are a few points to consider. First, the 24% of the lesions had a FFR measured at >0.80. The benefit of FFR-guided PCI lies in the number of lesions that are safely deferred compared to angiography-guided PCI. The small number of deferred lesions could have limited the benefit of FFR guidance compared with angiography. Second, this study did not include all comers who had angiographic 3-vessel disease. Patients who had FFR assessment of moderate lesions at the time of diagnostic angiogram and were found to have FFR >0.80 or were

deemed single- or 2-vessel disease were likely treated with PCI. Therefore, as the authors point out, the patients included in this study may have been skewed to a higher-risk population compared to previous studies.

Third, the study may not reflect contemporary interventional practice, as the use of intravascular ultrasound was very low (12%). Intravascular ultrasound-guided PCI has been associated with increased luminal gain and improved outcomes compared to angiography-guided PCI.<sup>10</sup> Although 20% of the patients in each arm were found to have chronic total occlusions, the completeness of revascularization has not yet been reported. It is possible that the PCI arm had fewer complete revascularizations, which has been shown in previous observational studies to be associated with worse clinical outcomes.<sup>11,12</sup>

Although the current guidelines favor CABG over PCI in patients with multivessel disease, this recommendation is stratified by anatomic complexity.<sup>6</sup> In fact, in the European guidelines, CABG and PCI are both class I recommendation for the treatment of 3-vessel disease with low SYNTAX score in patients without diabetes.<sup>5</sup> Although the FAME-3 study failed to show noninferiority in the overall population, when stratified by the SYNTAX score, the major adverse cardiac event rate for the PCI group was numerically lower than that of the CABG group. The results from the FAME-3 study are overall in line with the previous studies and the current guidelines. Future studies are necessary to assess the outcomes of multivessel PCI compared to CABG using the most contemporary interventional practice and achieving complete revascularization in the PCI arm.

### Applications for Clinical Practice

In patients with 3-vessel disease, FFR-guided PCI was not found to be noninferior to CABG; this finding is consistent with previous studies.

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*Disclosures: None.*

*doi:10.12788/jcom.0082*

### References

1. Farkouh ME, Domanski M, Sleeper LA, et al; FREEDOM Trial Investigators. Strategies for multivessel revascularization in

- patients with diabetes. *N Engl J Med.* 2012;367(25):2375-2384. doi:10.1056/NEJMoa1211585.
2. Serruys PW, Morice MC, Kappetein AP, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360(10):961-972. doi: 10.1056/NEJMoa0804626
  3. Park SJ, Ahn JM, Kim YH, et al; BEST Trial Investigators. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med.* 2015;372(13):1204-1212. doi:10.1056/NEJMoa1415447
  4. Stone GW, Kappetein AP, Sabik JF, et al; EXCEL Trial Investigators. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med.* 2019; 381(19):1820-1830. doi:10.1056/NEJMoa1909406
  5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019;40(2):87-165. doi:10.1093/eurheartj/ehy394
  6. Writing Committee Members, Lawton JS, Tamis-Holland JE, Bangalore S, et al et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79(2):e21-e129. doi:10.1016/j.jacc.2021.09.006
  7. Tonino PAL, De Bruyne B, Pijls NHJ, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360(3):213-224. doi:10.1056/NEJMoa0807611
  8. De Bruyne B, Fearon WF, Pijls NHJ, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371(13):1208-1217. doi:10.1056/NEJMoa1408758
  9. Xaplanteris P, Fournier S, Pijls NHJ, et al; FAME 2 Investigators. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med.* 2018;379(3):250-259. doi:10.1056/NEJMoa1803538
  10. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: The ULTIMATE trial. *J Am Coll Cardiol.* 2018;72:3126-3137. doi:10.1016/j.jacc.2018.09.013
  11. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol.* 2013;62:1421-1431. doi:10.1016/j.jacc.2013.05.033
  12. Farooq V, Serruys PW, Garcia-Garcia HM et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol.* 2013;61:282-294. doi: 10.1016/j.jacc.2012.10.017