

# Revascularization and optimal medical therapy: shattering new evidence

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Hot Topics

In 2007, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial found that percutaneous coronary intervention (PCI) on top of optimal medical therapy (OMT) versus OMT alone, did not reduce the risk of death, myocardial infarction (MI), or other major cardiovascular events of patients with coronary artery disease (CAD) [1].

In 2009, the FAME study showed that the routine measurement of fractional flow reserve (FFR) in patients with multivessel CAD undergoing PCI with drug-eluting stents significantly reduced mortality and MI when compared with standard angiography-guided PCI [2].

The FAME-2 study published in 2012 somehow attempted to test the findings of the COURAGE and FAME studies together, and investigated the efficacy of FFR-guided PCI versus OMT in stable CAD [3]. There was a highly significant difference in the incidence rate of the primary endpoint (a composite of death from any cause, nonfatal MI, or unplanned hospitalization leading to urgent revascularization during the first 2 years) between treatment arms, which was driven by a lower incidence of urgent revascularization in the PCI group. The study was terminated prematurely and the authors concluded that an FFR-guided PCI strategy significantly improved clinical outcomes.

In that study the overall number of events was small (only 56 patients required urgent revascularization) and the definition of the need for urgent revascularization was primarily clinical in the vast majority of patients. However, a careful analysis of the data allows for completely different and seemingly contradictory conclusions.

First of all, stenting was once again shown not to save lives or prevent heart attacks, whereas the OMT strategy was confirmed to be quite effective, with more than 80% of patients presenting symptom free and only 19.2% with a Canadian Cardiovascular Society angina scale of II–IV. Bearing in mind the limitations when comparing data from different studies, the FAME-2 trial also showed that the recurrence rate of angina in patients treated with medical therapy has decreased from 42% at 1 year in the COURAGE trial to 19.2% at 6 months in the FAME-2 trial. Conversely, despite coronary revascularization, 10% of the treatment group was still symptomatic at 6 months. Of note, patients in the registry cohort, who by definition had an FFR of more than 0.80 in all vessels, had comparable angina symptoms to those in the two study groups.

What is more, the PCI group had a 104% chance of undergoing revascularization, whereas only 12.7% of patients required a similar intervention in the medically managed group. In other

words, a patient with stable angina treated with medical therapy is much less likely to require coronary intervention even when presenting with significant CAD and low FFR.

Importantly, following invasive assessment with FFR, 11 patients with significant obstructions need to be treated in order to prevent one urgent revascularization (number needed to treat = 10.53). In this way, one would unnecessarily and prematurely expose 10 patients to revascularization-related complications (ie, stent thrombosis, restenosis, etc.), an aspect that could not be assessed in the present work because of the short follow-up. Keeping in mind that coronary revascularization would not change patient outcomes in terms of death and MI, would it not be more prudent and cost-effective to manage patients with OMT until and if “urgent revascularization” is needed?

Indeed, the FAME trial documented a lower mortality rate in patients undergoing evaluation with FFR; however, also because of a short follow-up, a similar result could not be documented in the FAME-2 study. Nonetheless, the main difference between the two trials is that FFR led to fewer PCI procedures in the earlier study [2].

However, there is some disturbing new evidence with regards to OMT as well! In clinical practice OMT is represented by an association of angiotensin-converting enzyme inhibitors, aspirin,  $\beta$ -blockers and lipid-lowering therapy (statins). The efficacy of angiotensin-converting enzyme inhibitors [4], aspirin [5] and statins [6] for the primary or secondary prevention of cardiovascular events has been confirmed in recently published studies; however, the rationale for using  $\beta$ -blockers for primary and secondary prevention has been extrapolated from the benefit obtained with these agents in patients post MI, with no data directly testing the effect of  $\beta$ -blockers in the primary and secondary prevention of cardiovascular disease.

A recently published observational, propensity score matching study compared outcomes with and without  $\beta$ -blocker therapy in about half of more than 44 000 participants in the REACH registry who had previous MI, CAD without MI, or CAD risk factors

only. In both cohorts with CAD, the risk of cardiovascular death, MI, or stroke did not differ significantly between  $\beta$ -blocker recipients and non-recipients, whereas in the risk factor-only group, the risk was significantly higher (by 18%) in  $\beta$ -blocker recipients than in non-recipients. Only in patients with recent MI (1 year), were  $\beta$ -blockers associated with a significant reduction in the risk of major coronary events, including hospitalization for an atherothrombotic event or revascularization (odds ratio 0.77; 95% CI 0.64–0.92) [7].

### Conclusions

In conclusion, how should this new evidence affect the treatment of patients with established, or risk factors for, ischemic heart disease?

Although the results of these studies unsettle some of our common beliefs and leave many open questions, what we learn is that, in stable angina, revascularization might be confidently reserved only for those patients with refractory angina after intense medical management, bearing in mind that omitting  $\beta$ -blockers might not affect the outcome in terms of cardiovascular events. •

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