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The Benefit of Ischemia-Based Revascularization for Stable Ischemic Heart Disease: The Impact of FAME 2

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In the past decade, remarkable advances have been made in the treatment of coronary artery disease. The approval of the first drug-eluting stent (DES) in 2002 ushered in an era where millions of patients became better candidates for minimally invasive percutaneous coronary intervention (PCI), which could be performed with low rates of subsequent revascularization procedures. Through this advance, in conjunction with other iterative improvements in PCI-related technologies [such as further refinements in device design, modifications of access techniques, and PCI pharmacology, and the more defined use of adjunctive ischemic testing such as fractional flow reserve (FFR)], PCI has become safer than ever, with some of the lowest rates of adverse events that have ever been observed following an invasive cardiac procedure.

However, in part due to concerns about the rising costs of healthcare, there has been a recent move to scrutinize the overall utility of PCI, particularly for the treatment of stable ischemic heart disease (SIHD). Since the publication of the COURAGE trial, in 2007, PCI has since been repeatedly—and in our opinion, often unfairly—stereotypically portrayed as a procedure that is overused, with benefits that are limited to a modest and transient relief of symptoms. Indeed, the finding of no significant difference in death or myocardial infarction (MI) with PCI over optimal medical therapy in the COURAGE population has oft been used by detractors of PCI as superficial evidence that PCI has marginal overall benefit compared to medical therapy. One recent editorial stated that PCI "performed in patients with stable disease is probably widely used as an expensive placebo for pain control."[1] In addition to a potential cost harm of PCI, others have linked

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the performance of PCI to other patient-related deleterious effects, stating that upfront PCI for SIHD has "no known benefit [and] definite harms."[2]

These provocative editorial comments disregard a large body of research showing that even for patients without severe proximal disease, PCI has been shown to be a highly effective therapy for reducing the frequency and severity of anginal symptoms [3]. Independent of effects on death or MI, the demonstrable effectiveness of PCI in improving quality of life is clearly meaningful for our patients and is an important and relevant stand-alone clinical outcome. Detractors of PCI are also quick to point out that while PCI performed for patients with acute coronary syndromes (ACS) has been demonstrated to reduce the occurrence of death and MI, there are at present limited prospective randomized data showing that PCI can provide prognostic benefits for patients with SIHD. However, the absence of adequately powered prospective randomized data does not necessarily equal absence of effect.

In fact, there are several sources of data supporting the prognostic benefits of revascularization in SIHD, in particular, revascularization of vessels that have been shown to subtend ischemic myocardium. In observational data from the Cedars Sinai nuclear database, patients with moderate-to-severe ischemia who underwent subsequent revascularization had lower rates of cardiac death within 2 years compared to those who did not undergo revascularization [4]. Corroborative prospective findings using the same imaging protocols were observed in the nuclear substudy of the COURAGE trial, a trial that included lower-risk patients (only 1/3 of patients with moderate-to-severe ischemia) and notably included a randomized study design. In this analysis, patients treated with PCI had a greater reduction in ischemia compared to optimal medical therapy (which in fact did not reduce ischemia at all), and reductions in ischemia were associated with lower rates of death or MI over the follow-up period [5]. That these findings were observed among patients in COURAGE is notable, particularly given both the strict inclusion/exclusion criteria (10% of screened patients were enrolled) and the high rate of crossover from medical therapy to PCI within the trial.

There have been two additional recent randomized trials assessing the prognostic role of PCI-based revascularization for patients with SIHD. A modest-sized 384 patient trial that received very little attention in the post-COURAGE era was the JSAP trial, a randomized multicenter study conducted in Japan, enrolling low-risk patients with single and double-vessel disease with lesions that were eligible for PCI [6]. Patients were randomized to PCI plus medical therapy versus medical therapy alone, and while the overall rates of death or MI were similar with both treatments, the rate of subsequent ACS over the 3.3-year follow-up period was lower with the PCI-based strategy (11.7 vs. 5.0%, $P = 0.012$). Although these effects were modest, JSAP did nonetheless demonstrate that even among a low-risk population of patients with SIHD, a higher rate of subsequent ACS events was observed among patients for whom PCI was deferred. These findings are remarkably similar to the results of the FAME 2 trial [7].

FAME 2 was a randomized trial initially designed to enroll a total of 1,632 patients with ischemia-producing stenoses (as defined by FFR 0.80), with randomization to either PCI or medical therapy. The primary hypothesis of the trial was that, compared to medical therapy alone, PCI of an FFR-positive lesion would reduce the incidence of death, MI, or unplanned hospitalization leading to an urgent revascularization procedure. The trial was stopped early after randomization of 888 patients, due to a "highly significant difference in the incidence rates of the primary endpoint between the PCI and medical therapy groups" (favoring PCI). In other words, the independent data safety and monitoring board determined it to be unsafe and/or unethical to continue randomizing patients in the trial given the observed benefit of PCI in patients with FFR-positive lesions. The specific finding that led to the early cessation of FAME 2 related to the marked reduction of unplanned hospitalizations leading to urgent revascularization observed among patients randomized to PCI. This endpoint occurred in seven patients in the PCI arm compared with 49 patients in the medical therapy arm at a median follow-up of 7 months, a highly significant difference in an important patient-oriented outcome (hazard ratio of 0.13, 95% confidence interval 0.06–0.30, $P < 0.001$).

Although longer-term data are at present incomplete, by examining the cumulative incidence curves shown in Figure 1 of the published manuscript, the absolute difference in event rates at 1 year was even more pronounced (~15%) for both the primary study endpoint as well as for the specific component of unplanned hospitalization leading to urgent revascularization. If this effect size is maintained with longer follow-up, this would equate to one resultant unplanned hospitalization leading to urgent revascularization for approximately every seven patients treated with medical therapy that could have been entirely prevented with upfront PCI at the time of the initial diagnostic procedure. Unfortunately, because FAME 2 was terminated early, it is difficult to assess whether upfront PCI of FFR-positive lesions could lead to other benefits such as prevention of MI events or deaths. The ongoing NIH-funded ISCHEMIA trial specifically testing this hypothesis will provide further clarity when its results are eventually available (~2018–2019).

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What is clear from FAME 2, however, is that in addition to the observed benefits of PCI in reducing unplanned hospitalizations, there was no harm observed with a strategy of upfront PCI compared to medical therapy, a finding that is often underemphasized but mirrored in the COURAGE trial. Moreover, in FAME 2, patients treated with PCI were treated less frequently with antianginal medications; despite this reduction in antianginal medications, PCI-treated patients had significantly less angina compared to patients randomized to medical therapy. The improvement in symptom status afforded by PCI, in addition to the reduction in unplanned hospitalizations leading to subsequent revascularization, further supports the quality of life benefits of PCI for ischemia-producing stenoses over medical therapy alone.

Notwithstanding the early cessation of the trial, the findings from FAME 2 represent a further critical piece of evidence in favor of the ischemia hypothesis in SIHD; namely, that the safe and effective revascularization of ischemia-producing lesions can lead to improved patient outcomes and quality of life metrics above and beyond symptom relief. It is now 5 years since the initial publication of COURAGE, and the practice of PCI has changed dramatically since that time. As interventionalists in an increasingly cost-conscious time, we are continually charged with demonstrating improvements in patient outcomes. It is our belief that FAME 2 offers the best data currently available to guide the treatment of patients with SIHD and ischemia-producing stenoses. The study reflects the most cutting-edge use of evidence-based ischemic testing (including FFR) and in-lab treatment options (97% DES use, the vast majority with second-generation stents), and examined their combined ability to improve patient outcomes over medical therapy alone. The FAME 2 trial demonstrates that PCI of appropriately selected patients and lesions can indeed safely provide that benefit within a very short timeframe (1 year). The reduction in unplanned admissions in this "all comers" trial is yet another reason to consider PCI plus medical therapy as an initial strategy in these economically challenging times. We thus eagerly await the ascertainment of longer-term follow-up to determine the ongoing and enduring results of this important trial.

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