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Management of Stable Coronary Artery Disease: From COURAGE, FAME II, to ISCHEMIA

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Coronary Artery Disease (CAD) is the leading cause of death worldwide. Medical therapy including medication and lifestyle modification should always be used to treat CAD. Percutaneous Coronary Intervention (PCI), in addition to medical therapy, has been shown to decrease morality and Myocardial Infarction (MI) in patients presenting with acute coronary syndromes [1]. However, it is unknown if PCI is superior to medical therapy alone as the initial treatment strategy for patients with stable CAD [2].

Many studies have failed to show benefit of PCI in reducing hard cardiac events including death and MI in stable CAD [3]. Among those is the widely publicized COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial [4]. This trial included 2287 patients who had objective evidence of myocardial ischemia and significant CAD defined as stenosis of at least 70% in at least one proximal epicardial coronary artery. Published in 2007, this landmark trial demonstrated that as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death or MI when added to optimal medical therapy. COURAGE trial demonstrated that the risk of complications in chronic stable angina is not negligible but relatively low. It confirmed that optimal medical therapy is as effective as PCI in treatment of stable CAD in the era of bare metal stenting.

Since its publication, COURAGE trial has elicited continued debate and challenge in the cardiology community. First, the intensity of optimal medical therapy implemented in COURAGE trial is difficult to reproduce in real world practice. Recent registry data with more than 460,000 patients suggested that among patients with stable CAD undergoing PCI, less than half were receiving optimal medical therapy before PCI and approximately two-thirds were receiving optimal medical therapy at discharge following PCI, with relatively little change in these practice patterns after publication of the COURAGE trial [5]. This questioned whether the benefit of optimal medical therapy observed in COURAGE trial could be realized in routine clinical practice. Second, one third of the patients initially assigned to the optimal medical therapy group crossed over to receive PCI. Therefore the real benefit of PCI may be diluted by intention to treat analysis. Finally, the patients enrolled in COURAGE trial were of relatively low risk with low incidence of hard cardiac events during follow up. Nearly 80% had minimal or mild angina (Canadian Cardiovascular Society class II or less) with mild to moderate ischemia on stress test.

Ever since the COURAGE trial demonstrated that patients with stable CAD do not benefit from PCI, the interventional cardiology community has been exploring more precise ways to identify which patients will benefit most from PCI. PCI outcomes have improved in the years since COURAGE, with second generation drug eluting stents now the standard of care and dramatic increases in the use of FFR (Fractional Flow Reserve) and intravascular ultrasound. Evidence continues to accumulate that using the physiology or the functional evaluation of a lesion is better than relying on angiography alone as was practiced in COURAGE trial [6].

The recently published FAME II (Fractional Flow Reserve-Guided PCI vs. Medical Therapy in Stable Coronary Disease) attempted to further address this question [7]. FAME II trial enrolled 1220 stable patients with coronary disease and took a completely different approach by performing FFR to determine significant flow-limiting lesions, defined as an FFR <0.80. Patients with at least one such lesion (n=888) were randomized to either PCI or optimal medical therapy. Patients with no flow-limiting lesions shown by FFR were put into a registry and treated with medical therapy (n=332). FAME II trial showed that patients receiving PCI with proven ischemia by FFR had 66% fewer primary endpoint events including death, MI and urgent revascularization compared with patients treated with medical therapy alone (4.3% vs 12.7%, $P<0.001$). The difference in the primary endpoint was driven entirely by the lower rate of urgent revascularization in the PCI group (0.7%) compared to medical therapy group (9.5%). There was no significant difference in mortality or MI between patients with PCI plus medical therapy and patients with medical therapy alone. The registry arm showed that patients with a negative FFR suggesting absence of ischemia did very well treated with just medical therapy with a primary endpoint event rate of 3.0%. It is important to note that FAME II trial was terminated early because it was determined unethical to continue enrolling patients in the medical therapy only arm due to the increased risk of unplanned revascularization. The FAME II study is important in that it shows angiography alone, as was practiced in COURAGE, may not be sufficient in identifying patients at risk of complications. When deciding between medical therapy and PCI the presence of ischemia as measured by FFR makes a difference. The FAME II investigators advocated that FFR should become the standard of care for treating most patients with stable CAD.

How do we put COURAGE and FAME II into perspective? First of all, both trials consistently showed that PCI did not prevent death or MI although it improved angina and quality of life in stable CAD. Second, FAME II took us one step further by showing that FFR can accurately identify a subset of patients who do not need PCI, i.e. those with FFR>0.8. Third, the FAME II trial did provide new evidence that FFR and second-generation drug eluding stents can improve secondary cardiac outcomes by reducing the need for unplanned revascularization. However, the degree of benefit and the significance of this finding are controversial since PCI did not reduce hard cardiac events. As we

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strive to improve outcomes and control costs at the same time, the cost-effectiveness of routine FFR in stable CAD is debatable. It should be noted that more than 50% of urgent revascularization in FAME II was performed in patients with unstable angina diagnosed purely on clinical grounds. This may lead to selection bias in determining which patient should undergo PCI in such a nonblinded trial. In addition, it is not clear whether urgent revascularization was performed on significant stenosis based on previous FFR or as a result of progression of disease that was initially considered noncritical. As the investigator acknowledged, the medical therapy implemented in FAME II was not as intense as in COURAGE. Suboptimal medical therapy could destabilize previously non-significant stenosis requiring urgent PCI. Finally, the short follow up period and the early termination of the study raised more questions than the answers it provided. It is not possible to derive information on prognostically important long-term clinical outcomes.

Thus there are still clinically relevant questions unanswered by COURAGE and FAME II. First, in both trials the patients were randomized after coronary angiogram. However, if as COURAGE advocated that stable angina patient can be managed initially with optimal medical therapy, is there a need for routine coronary angiogram? Certainly left main disease needing immediate revascularization has to be evaluated. However with the advent of advanced imaging modality such as cardiac computed tomography (CT) angiography that could be addressed non-invasively. Second, lessons from COURAGE and FAME II tell us that stable CAD in general is at low risk for future hard events including death and MI and therefore it is difficult for PCI to further reduce the risk. Observational data and the COURAGE nuclear substudy suggested that subset of stable CAD with moderate to severe ischemia on stress test portend a higher risk [8,9]. It is hypothesized that patients with the most severe ischemia might benefit from early revascularization strategy. FFR and stress test may complement each other in terms of further risk stratification and decision making. It is tempting to postulate that patients with severe ischemia on stress test and an FFR ≤0.8 would most likely to benefit from PCI compared with medical therapy.

With improvement in both medical therapy and PCI technique, there is a clear need for a new trial for stable CAD patients uniformly at higher risk. The ongoing ISCHEMIA (The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial is a randomized controlled trial that will study 8,000 patients with stable CAD and moderate to severe ischemia on stress test [10]. Patients will undergo a coronary CT angiography to exclude left main disease and to confirm the presence of obstructive coronary disease. Patients will then be randomized to invasive angiography and revascularization plus optimal medical therapy or optimal medical therapy alone. We anticipate ISCHEMIA trial to fill the gap in our understanding of the optimal initial management strategy for stable coronary disease.

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