

Considering ISCHEMIA in the Context of FAME and FAME 2: A Call for the Universal Adoption of Invasive Ischemia-Guided Coronary Intervention Approach in Chronic Coronary Syndrome

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Coronary artery disease is the number one cause of death worldwide and the number 2 cause of death in Taiwan. In contrast to the declining death rate of stroke, the death rate of coronary artery disease remains climbing in Taiwan, thus enacting discussions regarding how to curtail this ominous trend. Coronary revascularization by either angioplasty or bypass surgery has been performed in patients with coronary artery disease and being refractory to medical therapy for decades. Despite coronary revascularization in patients with acute coronary syndrome having been shown to reduce morbidity and mortality,¹ the clinical benefits, in terms of myocardial infarction and/or cardiovascular mortality reduction, of coronary revascularization in patients with chronic coronary syndrome (stable ischemic heart disease) remain controversial.² The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed that an initial management strategy of percutaneous coronary intervention (PCI) plus optimal medical therapy, compared with optimal medical therapy alone, in patients with chronic coronary syndrome was not associated with significant difference in all-cause mortality or myocardial infarction during either the initial median 4.6 years or an extended median 7.9 years follow-up.^{3,4} A watchful waiting strategy with continuing optimal medical therapy was thus suggested

for patients with chronic coronary syndrome. However, the high cross-over rate (> 30% shifting to undergoing coronary intervention) in the medical therapy alone group and the use of either bare-metal or first-generation drug-eluting stents in the COURAGE trial raise concerns about its applicability in the modern PCI era.

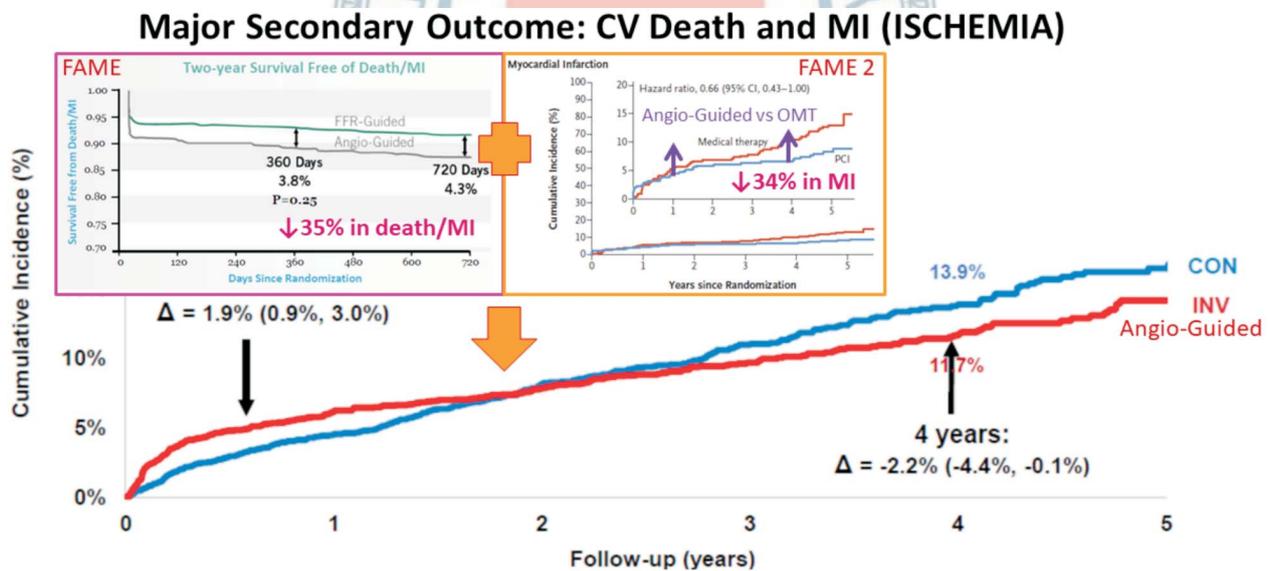
To clarify whether coronary revascularization with the state-of-the-art PCI technology is associated with morbidity and mortality benefits in patients with chronic coronary syndrome and moderate myocardial ischemia ($\geq 10\%$ left ventricular ischemia in nuclear perfusion scan), results of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial had been highly anticipated. The ISCHEMIA trial was presented on November 16, 2019 at the American Heart Association Annual Scientific Session in Philadelphia.⁵ The primary finding of the ISCHEMIA trial was, again, a neutral result: an initial invasive approach with cardiac catheterization and revascularization, compared with optimal medical therapy alone, showed no reduction in major adverse cardiovascular events in patients with moderate-to-severe ischemia on stress testing.⁵ Nevertheless, the ISCHEMIA story is not that simple. The ISCHEMIA trial clearly demonstrated the “double-edged sword” characteristic of PCI: the initial invasive approach improved angina symptoms while also leading to a higher incidence of periprocedural myocardial infarction but a significant 33% reduction of spontaneous myocardial infarction within the median 3.3 years follow-up period, with the curves continuing diverging (Figure 1). The benefit of spontaneous myocardial infarction reduction with an initial PCI approach, compared with optimal medical therapy, in patients with chronic coronary syndrome has also been shown in the Fractional Flow Reserve versus Angiogra-

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phy for Multivessel Evaluation (FAME) 2 trial.⁶ In the FAME 2 trial, the rate of the primary endpoint (death, myocardial infarction, and urgent revascularization) was significantly lower in the fractional flow reserve (FFR)-guided (FFR ≤ 0.80) PCI group than in the medical-therapy group at 5 years (Figure 1). The FFR-guided PCI was associated with a similar 34% reduction in myocardial infarction, whilst a numerically increased number of peri-procedural myocardial infarction within the first 7 days after PCI.⁶ The two major differences between FAME 2 and ISCHEMIA with regard to myocardial infarction are: first, the absolute increase in peri-procedural myocardial infarction with the initial invasive approach (~2%) was too high in ISCHEMIA which offset the later-on benefit of PCI on spontaneous myocardial infarction; and second, in ISCHEMIA, the invasive PCI procedure was guided by angiography, whereas FFR-guided PCI was universally adopted in FAME 2. The advantages of FFR-guided PCI versus angiography-guided PCI with regard to myocardial infarction and death in patients with chronic coronary syndrome has been clearly demonstrated in the FAME trial.⁷ In the FAME trial, FFR-guided PCI consis-

tently reduced myocardial infarction and mortality since the peri-procedural period till 2 years (35% reduction), when compared with angiography-guided PCI, in patients with multivessel chronic coronary syndrome (Figure 1). If we consider FAME, FAME 2, and ISCHEMIA together, we can draw the following conclusions: in patients with chronic coronary syndrome, angiography-guided PCI plus optimal medical therapy and optimal medical therapy alone achieve similar rates of myocardial infarction and mortality, whereas FFR-guided PCI plus optimal medical therapy can provide the best cardiovascular outcome and should be generally recommended in patients with chronic coronary syndrome (Figure 1). This hypothesis-generating observation should be validated in the post-hoc analysis of the ISCHEMIA trial in patients assigned the initial invasive approach and undergoing FFR-guided PCI.

In this issue of the *Journal*, we published two articles regarding cardiac catheterization and revascularization in patients with chronic coronary syndrome. In the first article, Tsai ML et al. demonstrated that patients treated with second-generation durable polymer



FFR-Guided PCI > Anglo-Guided PCI (FAME)
 FFR-Guided PCI > OMT (FAME-2)
 Anglo-Guided PCI = OMT (ISCHEMIA)

Modified from Hochman JS, et al. AHA 2019.



Figure 1. Kaplan-Meier curves for the major secondary outcome (non-fatal myocardial infarction and cardiovascular death) in ISCHEMIA (lower panel), myocardial infarction in FAME 2 (upper right panel), and all-cause death and non-fatal myocardial infarction in FAME (upper left panel). OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

drug-eluting stents, compared with those treated with biodegradable polymer drug-eluting stents, showed similar late loss (0.38 mm vs. 0.26 mm, $p = 0.147$) and binary restenosis (5.4% vs. 8.7%, $p = 0.276$) at 9-month angiographic follow-up and no significant differences in major adverse cardiac events (15.0% vs. 11.6%, $p = 0.577$) at 5 years in 436 Taiwanese patients with single coronary lesion.⁸ In the second article, Hong CS et al. showed that, for patients who underwent one- or two-vessel angioplasty, the average fluoroscopy time in patients managed with biplane imaging was significantly longer than that with monoplane imaging.⁹ Whereas for patients who underwent diagnostic angiography alone or three-vessel angioplasty, there were no significant differences in the fluoroscopy time. These observations are of clinical significance in determining the optimal choice of stents and reducing the radiation dosages during PCI.

In the recent 2 years, our *Journal* published guidelines, interventional studies, and outcome correlation studies with regard to acute and chronic coronary syndrome. We summarized the articles as cited herein for the readers' interest.¹⁰⁻³⁷ We hope you enjoy the *Acta Cardiologica Sinica*, and wish our articles can really help you not only in your clinical practice, but also in your research career.

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