International Journal of Cardiology 291 (2019) 27–28

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

The prognostic importance of silent ischemia

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ARTICLE INFO

Article history:
Received 6 October 2018
Accepted 21 May 2019
Available online 24 May 2019

Invasive testing for ischemia by measuring fractional flow reserve (FFR) has provided support for the importance of ischemia in predicting adverse events. For example, Barbato and colleagues found that in patients treated with medical therapy alone, the lower the FFR value the greater the chance there was for a major adverse cardiac event during follow-up [1]. In a similar cohort of patients, Ciccarelli and colleagues compared outcomes based on an FFR value above or below the ischemic threshold of 0.80 and based on the presence or absence of a lesion with a diameter stenosis above or below 50% [2]. The presence of ischemia was a significant predictor of outcomes, while the anatomy was not. The FAME 2 trial found that FFR-guided PCI improved outcomes compared with medical therapy alone in patients with stable CAD [3]. The five year follow-up of this trial demonstrated lower rates of all MI and of spontaneous MI in those patients who received FFR-guided PCI [4].

The results from FAME 2 favoring PCI occurred despite the fact that approximately 50% of patients in the medical therapy arm crossed over and received PCI. It is possible that these patients who crossed over to PCI were protected from future MI or death. This would suggest that patients with stable CAD and silent ischemia might be at greater risk when treated with medical therapy alone. A substudy from FAME 2 evaluated this possibility by determining outcomes in 98 patients with silent ischemia compared with 789 patients with symptomatic ischemia [5]. The patients with silent ischemia who received medical treatment alone had significantly lower rates of non-urgent revascularization compared with symptomatic patients, which is not surprising. However, the group with silent ischemia had a significantly higher rate of death or MI compared with the symptomatic group when randomized to medical therapy alone. On the other hand, patients with silent ischemia who were randomized to PCI plus medical therapy, had similar and low rates of death and MI when compared with symptomatic patients receiving PCI and medical therapy. From these data, we can conclude that the presence of ischemia portends an adverse outcome, that this is particularly true if the ischemia is silent, and that PCI appears to attenuate this risk.

It is with this backdrop that we read with great interest the study in this issue of the International Journal of Cardiology by Choi and colleagues from Korea [6]. In this single center, observational trial, the investigators identified 1473 patients with myocardial ischemia as determined by noninvasive stress testing and with at least one stenosis ≥50% on invasive coronary angiography. Approximately half of these patients underwent revascularization, primarily with PCI; the other half was managed medically. At a median follow-up of 5 ½ years, the cardiac death rate was significantly lower in the revascularization group as compared with the medical therapy group (25 vs. 34%, $p < 0.001$). Receiving medical treatment alone was an independent predictor of cardiac death. Interestingly, among those patients who did receive revascularization up front for their silent ischemia, in those who had follow-up stress tests, if the ischemia was completely relieved, the cardiac death rate was significantly lower than if there was residual ischemia.

Some things to consider when analyzing this study include the fact that it was an observational study without randomization. Because of this, there were significant differences in the baseline characteristics between the two groups. Even though the authors attempted to account for these differences by various statistical techniques, it is likely that unaccounted variables exist which might have had a significant impact on long-term cardiac death. The medical therapy at baseline was more intense in the patients who underwent revascularization. Unfortunately, we do not have data regarding medical therapy in the two groups at various time points during follow-up. Finally, periprocedural MI was not accounted for in the revascularizton group, meaning the differences in MI rates between the two groups may be exaggerated.

Despite these issues, Choi and colleagues should be congratulated on this important study which adds further support to the concept that myocardial ischemia, even if not responsible for symptoms portends a poor prognosis in patients receiving medical therapy alone and this risk is attenuated by coronary revascularization.

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DOI of original article: https://doi.org/10.1016/j.ijcard.2018.08.006.
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