



## Debate: Revascularization of non-culprit lesions in ACS: physiology, OCT-guided or both? Perspective from physiology

*A debate. Revascularización de lesiones no culpables en SCA. ¿Guiada por fisiología, por OCT o por ambas? Perspectiva desde la fisiología*

Mauro Echavarría-Pinto<sup>a,b,\*</sup>

<sup>a</sup> Servicio de Cardiología, Hospital General ISSSTE Querétaro, Querétaro, Mexico

<sup>b</sup> Facultad de Medicina, Universidad Autónoma de Querétaro, Querétaro, Mexico

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**QUESTION:** What kind of evidence supports the use of the pressure guidewire for the management of nonculprit lesions in patients with multivessel disease? Can you explain to us the controversy surrounding the results of the most recent clinical trials compared to the former ones?

**ANSWER:** I would like to start by contextualizing the change of paradigm we've been experiencing regarding myocardial revascularization. In controlled clinical trials of stable coronary artery disease, compared to optimal medical therapy, unfortunately, myocardial revascularization—the percutaneous one (PCI) in particular—has not been able to reduce clinical events whether angiography-guided (COURAGE and BARI 2D trials) or guided by non-invasive ischemia detection studies (ISCHEMIA trial).<sup>1</sup> It is hard to believe that although there is a significant correlation between the degree of ischemia documented non-invasively and the risk of adverse events, revascularization based on the information that, as interventional cardiologists, we collect from non-invasive studies doesn't lead to better clinical outcomes compared to non-revascularizing the patient leaving him with ischemia and on optimal medical therapy. Here's where the use of the pressure guidewire (PG) during the procedure (and possibly its angiographic alternatives) seems to lead to a different outcome. Currently, 3 randomized clinical trials are being conducted—2 of them in patients with acute coronary syndrome (ACS)—comparing the clinical events associated with PG- and optimal medical therapy-guided myocardial revascularization alone. A recent metaanalysis revealed that, compared to optimal medical therapy, PG-guided myocardial revascularization reduces the risk of cardiac death an infarction significantly at 5 years.<sup>2</sup> We should mention that this is a high-quality metaanalysis that only included randomized clinical trials and «hard» events in its primary outcome. Also, unlike the ISCHEMIA trial that reported more early events associated with revascularization, fewer events were also documented in the PG arm from the beginning of follow-up and, as years went by, this event difference has grown

favorable to revascularization. This and other information suggest that the PG allows us to select more accurately compared to angiography the segments of epicardial arteries where the benefits of PCI exceed risks.<sup>3,4</sup> This evidence has changed the clinical practice guidelines that now recommend the use of the PG for the lack of previous evidence of ischemia and when the use of revascularization is under consideration. However, although this recommendation has been effective for years, the clinical use of PG is still low worldwide.

Recently, some PG studies have shown neutral or negative results: the FUTURE, RIPCORD 2, FAME 3, and the FLOWER-MI.<sup>4</sup> Without smearing the effort made by the investigators, I'll try to share my view on these trials.

The FUTURE trial randomized patients with and without ACS and 2- or 3-vessel disease to routine or PG-guided revascularization.<sup>3,4</sup> The study was interrupted by the safety committee after only 54% of the entire sample was recruited and due to an increased overall mortality rate reported in the PG group. It is always difficult to interpret a study without statistical potential due to the sample size. However, the lack of differences in infarction and cardiac death makes it hard to explain how the PG can increase overall mortality through non-cardiac ways. Also, upon decision by the investigators, over 20% of negative lesions according to the PG were revascularized, which increased the number of procedures performed and stents used in the PG arm. This dropped the rate of revascularization down to 12.6% when, overall, in PG studies where a lower rate of stenting (30%) is often reported.

The RIPCORD-2 included 1100 patients with stable symptoms or ACS without ST-segment elevation randomized to angiography-guided revascularization or systematic use of the PG. The study concluded that the systematic use of the PG did not improve quality of life or reduced costs compared to the angiography-guided PCI.

\* Corresponding author.

E-mail address: [mauroep@hotmail.com](mailto:mauroep@hotmail.com) (M. Echavarría-Pinto).

[@MauroEchavPinto](https://twitter.com/MauroEchavPinto)

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It's surprising to see how the PG was used in this study since, per protocol, PGs were used in all the arteries even in the absence of visible atherosclerosis. In my opinion, this is a complete game changer from the clinical use of PG, prolongs time, and increases risk without a clear justification. We still don't know if this proposal of using PG could be associated with the increased number of events seen at 1 year in the PG arm—close to 9%—which was high compared to many other PG studies. However, statistically, it was similar to the one seen in the angiography-guided PCI group of the same study.

There is nothing controversial about the FAME 3, I think. For years, we've been seeing the same slide in several meetings showing how the PG-related number of events from the FAME trial was similar to the number of events reported in the surgical arm of the SYNTAX trial. That's the origin of the FAME 3 that compared—with a non-inferiority design—PG-guided surgical to percutaneous revascularization for the management of 3-vessel disease. It was a disappointment to see that the PG-guided PCI is not inferior to surgery even accepting a large non-inferiority margin of 45%. Although the use of intracoronary imaging was low in the FAME 3, it's not easy to think of an image-guided PCI study reaching non-inferiority compared to surgery given the results of the recent FLAVOUR trial that assessed PG- vs intracoronary ultrasound-guided PCI. Similar clinical outcomes were seen with both strategies at the expense of a 30% increase in the number of stents from the image group.<sup>5</sup> We hope that, in the future, it'll tell us if the interventional strategy included in the SYNTAX II cohort (combining an optimal selection of patients with PG- and intracoronary imaging-guided PCI including total occlusions) is non-inferior to surgery in a controlled clinical trial.

Last but not least, the FLOWER MI trial.<sup>6</sup> In my opinion, it is the only one that suggests, in a convincing way, that safety is lower when decisions are based on PGs in patients with ST-segment elevation acute coronary syndrome (STEACS). In the FLOWER MI, a total of 1171 patients with STEACS were randomized to receive angiography- or PG-guided total revascularization after treating the culprit artery. Although the 1-year cumulative rate of the primary event did not change between both arms, a statistically non-significant increase in the risk of infarction (77% in the PG arm) was reported. Also, the estimated cut-off of the effect for the primary endpoint suggests PG-related damage and no benefit. Still, the accuracy of this effect estimate is low and non-significant.

**Q.:** What kind of evidence supports the use of the PG in nonculprit lesions of an ACS? Do you think it's strong enough to recommend it?

**A.:** Currently, 2 large meta-analyses are being conducted including the evidence available on the use of PGs in nonculprit lesions, which is large. The first one conducted by Cerrato et al.<sup>3</sup> of 8579 patients from 5 different cohorts, 6461 of whom had stable symptoms and 2118 ACS.<sup>3</sup> A larger number of events was seen in the group of patients with PG-guided delayed revascularization with ACS compared to the group of patients in stable condition. However, and significantly, patients with ACS treated with PCI had more events compared to patients with ACS and PG-guided delayed treatment. This study suggests that safety of PG-guided delayed PCI depends on the clinical presentation being safer with stable symptoms compared to ACS. Also, that treating nonculprit lesions doesn't reduce the chances of events compared to delaying the procedure unlike what the FLOWER-MI reported. We should mention that this meta-analysis could not distinguish STEACS from other forms of ACS, which is why it should be interpreted in detail.

The second meta-analysis is important because it compares all randomized clinical trials currently available on 3 strategies for

nonculprit lesion revascularization proposed for patients with STEACS: culprit lesion only revascularization, angiography- and PG-guided total revascularization.<sup>4</sup> A total of 8195 patients from 11 randomized clinical trials were included. It was reported that in patients with multivessel disease and STEACS, angiography- or PG-guided total revascularization is associated with a lower rate of adverse events compared to the strategy of revascularizing the culprit lesion only. Also, the PG-guided strategy was associated with a non-significant increased risk of adverse events of 23% (95% confidence interval, 0.78-1.94) compared to the angiography-guided total revascularization strategy. Therefore, in the management of STEACS, angiography-guided total revascularization strategy is far more superior compared to the culprit lesion-only revascularization and similar to PG-guided revascularization. However, the effect estimate of the last comparison is favorable to the total angiography strategy.

**Q.:** Are there any differences based on the type of ACS with or without ST-segment elevation?

**A.:** This is not an easy question to answer because most studies report combined data of ACS without stratifying STEACS and NSTEMI.<sup>2,3,4</sup> What we know so far is that the current evidence that has generated controversy comes specifically from patients with STEACS. This is consistent with the maturity of multiple lines of research that suggest that the nonculprit lesions of patients with STEACS behave more aggressively compared to the same lesions in patients with stable symptoms. We should remember that, overall, PG-related non-significant lesions in stable disease are responsible for 3% to 4% of clinical events per year while contemporary stents are responsible for an annual 6%. Therefore, if treated, we could be inducing damage. However, non-significant lesions according to the PG in patients with STEACS seem to cause more events—with rates close to 8%—like a substudy of the FLOWER-MI suggests.<sup>7</sup> Therefore, any procedure performed here may be associated with more benefits than risks. Therefore, the utility of PG specifically in STEACS seems lower. Finally, we should mention that the results of the COMPLETE and FLOWER MI trials cannot be extrapolated to the STEACS setting. Also, there are many more studies supporting the utility of the PG in this scenario. Therefore, until future studies with robust designs analyze the safety profile of PG to treat NSTEMI, we won't be able to determine whether safety is closer to the one reported in the stable context or discretely lower, as in the case of STEACS.

**Q.:** Are there any differences based on the type of index, whether hyperemic or not?

**A.:** The differences between hyperemic and non-hyperemic indexes does not seem to be very significant from the clinical standpoint. However, when we migrate from clinical trials to physiological indexes (that report, in small series, their findings from combined measurements of pressure and intracoronary flow) it's hard to determine what indexes are better diagnostic tool in the ACS setting since results are controversial. Therefore, there seems to be greater scientific consensus recognizing a transient fatigue of hyperemic response compared to recognizing significant changes to the baseline conditions. This transient fatigue of hyperemic response is characterized by a reduced coronary flow reserve and an increased coronary fractional flow reserve, a situation that could clinically produce more false negatives with hyperemic compared to non-hyperemic indexes.<sup>8</sup> Despite of all this, currently, there are no solid arguments to prefer hyperemic over non-hyperemic indexes.

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## CONFLICTS OF INTEREST

M. Echavarría-Pinto is speaker and proctor for manufacturers of pressure guidewires (BSC, Abbot, and Philips).

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