Completing the job: The advantage of complete revascularization in ST-elevation myocardial infarction over culprit-only revascularization strategies

Almost half of patients acutely presenting with ST-elevation myocardial infarction (STEMI) have multivessel coronary artery disease (CAD) [1]. In this setting, multivessel disease is associated with less ST-segment resolution after primary percutaneous coronary intervention (PCI) and higher 1-year mortality, with a direct proportionality with CAD extent in non-culprit vessels [2].

Multiple mechanisms have been advocated to explain why a more widespread atherosclerotic involvement of the coronary arteries reduces survival in STEMI patients. First, subjects with multivessel disease tend to have a higher burden of comorbidities. Second, the extent of epicardial CAD might be a marker of microvascular disease which may directly impact on reperfusion (and prognosis) following STEMI. Third, obstructive stenoses in non-culprit vessels directly cause myocardial ischemia [2]. Fourth, atherosclerotic non-culprit plaques may harbor features of vulnerability which associate with recurrent atherothrombosis [3].

All this considered, whether treatment of non-culprit lesions might result in better outcomes in STEMI setting has been a matter of heated debate and research over the last decade.

Initial conflicting results, primarily derived from observational cohorts or underpowered randomized controlled trials (RCTs), led to a IIb recommendation for the treatment of non-culprit lesions in both European and American guidelines [1,4]. More recently, some well-conducted RCTs and the large Complete Revascularization with Multivessel PCI for Myocardial Infarction (COMPLETE) trial have shown significant reductions in major adverse cardiovascular events (MACE) providing robust evidence in support of a complete revascularization strategy [5].

The study by Gupta and colleagues published in the present issue of International Journal of Cardiology, Heart and Vasculature [6] reports a systematic review and metanalysis of RCTs comparing complete versus culprit-only revascularization strategies in patients presenting with STEMI and multivessel disease.

The Authors report a significant reduction in MACE, consisting in the composite of all-cause mortality, ischemia-driven revascularization and recurrent myocardial infarction (12.6% vs. 23.0%, risk-ratio [RR] 0.51, 95% CI 0.42, 0.61, p < 0.001) with the complete revascularization strategy [6]. The reduction in MACE was primarily driven by a reduction in repeated revascularization and recurrent myocardial infarction, consistently with the COMPLETE trial.

However, thanks to the higher statistical power by pooling all available published evidence on the topic, this meta-analysis also shows a significant 29% reduction in cardiovascular mortality, which was inapparent by COMPLETE trial results alone (RR 0.93, 95% CI 0.65–1.32).

In this perspective, several considerations arise. First, optimal timing of revascularization completion between index PCI, staged PCI before hospital discharge (early) and staged PCI after discharge (delayed) remains unclear. Second, the question whether a physiology- versus angiography-guided non-culprit lesion revascularization is superior to the other is unknown.

1. Timing of revascularization completion

Gupta and colleagues present a subgroup analysis of early vs delayed complete revascularization showing similar MACE rates for either strategy (11.3% vs. 14.3%, RR 0.82, 95% CI 0.66, 1.01, p = 0.067) [6].

A recent meta-analysis concluded that the benefit on mortality and myocardial infarction observed with complete revascularization was driven by immediate-revascularization (i.e. during primary PCI) only, as opposed to the staged (<30 days) approach, but the strategies were not directly compared [7]. In this study immediate revascularization subgroup included trials with >50% cases of complete revascularization during index PCI [7]. Other Authors found a ~50% MACE reduction with a strategy of early (<72 h from index PCI) vs culprit-only/staged complete revascularization, without differences between immediate vs non-immediate early revascularization [8]. Direct comparison between early vs delayed strategies from a network meta-analysis did not measure any differences between the two approaches, while reinforced the superiority of an early vs culprit-only approach [9]. In this study early subgroup included both immediate and before-discharge procedures [9]. While hinting at a superiority of an early revascularization completion, different and inconsistent definitions of non-culprit lesions PCI timing used in the three publications make it difficult to reconcile their findings and do not allow to draw definitive conclusions [10]; moreover, these studies were published before the results of the COMPLETE trial were available.

In the COMLPETE trial no interaction between timing of revascularization (left at physicians' discretion) and study outcomes was found [5,11]. The majority (68%) of patients randomized to

the complete revascularization arm received a non-culprit lesion staged PCI at a median of one day after primary PCI (vs 23 days in the delayed group). It is possible that, secured that revascularization is completed within a reasonable time-span from index STEMI, rates of MACE are sufficiently low to be either clinically or statistically not significant. Indeed, a focused landmark analysis of the COMPLETE trial shows that benefit of complete revascularization begin to emerge only after 45 days from randomization [11].

2. Optimal guidance for revascularization completion

Beyond optimal timing, the best strategy to guide revascularization of non-culprit lesions following STEMI remains unsettled. In their meta-analysis, the authors report a similar reduction in MACE occurrence with a physiology (fractional flow reserve [FFR]-guided) as compared to an angiography-guided strategy. Unfortunately, since data regarding individual outcomes are not provided, a differential effect of a physiology- versus angiography-guided strategy on myocardial infarction, repeat revascularization and cardiovascular death endpoints cannot be excluded.

This is of importance, as the prognostic implications of preventing a repeat revascularization or a spontaneous atherothrombotic event are radically different. Moreover, the recent optical coherence tomography (OCT) substudy of the COMPLETE trial, showed that nearly half of patients among those assessed by OCT had obstructive non-culprit lesions with vulnerable plaque features, suggesting the benefit of intervening in obstructive non-culprit lesions after primary PCI might be related to the effect of stenting vulnerable plaques [12]. It remains however unclear which - between the degree of angiographic obstruction and hemodynamical significance of a stenosis - is a better marker to predict the evolution of a plaque towards atherothrombotic events.

Some Authors postulated that a normal FFR, regardless of angiographic severity, may rule-out plaque characteristics heralding atherothrombosis, possibly representing a safe gatekeeper to defer revascularization [13]. While these concepts may apply to the stable CAD setting they may not be generalizable to non-culprit lesions in STEMI. Following an atherothrombotic event plaque characteristics are intensely dynamic and non-culprit vessels hemodynamic is altered, entailing falsely normal FFR values [14].

Conversely, in STEMI setting, an angiography-guided approach might lower the threshold to undertake PCI potentially translating into stenting (and thus "silencing") of a higher number of vulnerable plaques. While these concepts remain speculative, meta-analysis of relevant trials seems to point in this direction, by showing that angiography-guided complete revascularization reduces myocardial infarction, myocardial infarction/cardiovascular mortality, and repeat revascularization, while physiology-guided approach is associated exclusively with a reduced need for repeat revascularization [15].

Waiting for prospective evidence comparing these two approaches, it seems prudent not to transfer evidence deriving from stable CAD trials to this acute, inherently different setting.

In conclusion, the study by Gupta and colleagues provides an interesting, systematic and quantitative synthesis of currently available data, hinting at a fundamental role for complete revascularization in the quest for long-awaited strategies to improve outcomes in STEMI.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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