Editorial

The CULPRIT SHOCK trial: a favourable verdict for the only-culprit percutaneous coronary intervention strategy

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Falsifiability is the heart of science, and I could add, falsifiability affects also the science of the heart. In August 2017 the back then new released guidelines of the European Society of Cardiology for management of ST elevated myocardial infarction (STEMI) included as a recommendation class IIa (level C) the percutaneous coronary intervention (PCI) of non-infarct related artery during the index procedure in patients with STEMI, multivessel disease (MVD) presenting with cardiogenic shock (CS) (1). Just few weeks later, this statement was seriously challenged by the CULPRIT-SHOCK trial (2), and one year later, the new European guidelines for myocardial revascularization downgraded the aforementioned recommendation to class III (3).

This was the second instance in which Thiele *et al*. knocked down a seemingly established therapeutic strategy, the first had to do with the intra-aortic balloon pump in the context of STEMI with CS (4). Definitely, both turned out to be landmark and game-changers trials.

The prevalence of MVD in patients with STEMI is roughly 50% and such condition worsens significantly the patient´s outcomes, doubling mortality rates at short and long term (5). This fact provided a strong rationale for the design and execution of many trials. These, albeit not large separately, pointed out in the same direction, supporting the beneficial effect of multivessel-PCI on prognosis. This strategy leads to a reduction in overall cardiac adverse events, mostly driven by reductions in revascularization; it is associated to a significant reduction of the composite of death and myocardial infarction but it shows no significant effect on mortality (6). Benefits from multivessel PCI seem to be extended to the very elderly population when performed in staged fashion (7).

However, there is lack of evidence on the optimal timing for such approach, since no properly sized trials have compared head to head the different possible alternatives, index complete *vs*. staged, or staged during index admission *vs*. staged afterwards. It is remarkable that patients with CS were systematically excluded for enrollment in these trials.

CS is reported in 5–10% of patients with STEMI, increasing dramatically the short-term fatality (8,9). In the elderly population the risk of CS in STEMI results higher, along with the prevalence of MVD, and the associated mortality is overwhelmingly high (10).

Initial observations focused on the impact of revascularization in patients with STEMI and CS were just coming from the SHOCK trial in which revascularization either with PCI or CABG was related with a lower death rate (8,11). The time delay between first medical contact and primary PCI was a significant predictor of an adverse outcome (12). On these grounds, the European 2017 guidelines for STEMI endorsed the multivessel PCI approach in patients suffering CS with a class IIa (but level evidence C) (1).

More recently, two meta-analysis of observational registries in patients with STEMI and MVD complicated by CS found a short term, but not long term, benefit for culprit only PCI (13,14) A more recent meta-analysis of observational studies suggested immediate multi-vessel PCI being harmful, with higher short-term mortality (9).

At this point is when the results of the landmark CULPRIT-SHOCK trial were presented, as primary analysis at 30 days and as secondary analysis at 1 year (2,15).

In this trial 706 patients (out of 1,075 screened) with STEMI who had MVD (defined by >70% stenosis in at least two vessels ≥2 mm in diameter) and CS were randomly assigned to either PCI of the culprit lesion only, with the option of staged revascularisation of non-culprit lesions, or immediate multivessel PCI.

At 30 days follow up, 158 out of 344 patients (45.9%) in the culprit lesion-only PCI group and 189 out of 341 (55.4%) in the multivessel PCI group met the primary endpoint, a composite of death or renal replacement therapy (RR 0.83, 95% CI: 0.71–0.96; P=0.01). The reduced primary endpoint was mostly driven by a lower mortality (RR 0.84, 95% CI: 0.72–0.98; P=0.03) and to a lesser extent by a lower need of renal replacement therapy (RR 0.71, 95% CI: 0.49–1.03; P=0.07). Secondary outcomes such as the time to haemodynamic stabilisation, the need of adrenergic therapy and its duration, the levels of myocardial enzymes, as well as the bleeding and stroke rates did not differ significantly (2,15).

Secondary analysis at 1 year follow up showed no significant differences for any of the endpoints (15). The culprit-lesion only PCI group had significantly higher staged or urgent repeat revascularisation and rehospitalization for congestive heart failure.

Needless to say, this is a truly landmark trial, totally pertinent, well designed and thoroughly conducted.

Nonetheless, the following concerns could be raised. First, the exploratory condition for the analysis at 1 year, since the trial was only powered for the 30-day analysis of the primary end point. Second, the open label nature of the study introduces the bias in the ascertainment of outcomes (e.g., patients known to be randomised to culprit lesion-only PCI may be more likely to undergo urgent revascularisation). Third, there was a certain (43 patients) cross over from culprit-lesion only PCI to multi-vessel PCI due to the haemodynamic condition, identification of new lesions after initial PCI or other clinical reasons, potentially leading to bias towards the inclusión or more complex and co-morbid patients in the multi-vessel PCI group. Fourth, in 24% of patients of the multi-vessel PCI arm revascularisation of a chronic total occlusion was attempted according to protocol, showing an 81% success rate, though under the advised limit for contrast volume set at 300 mL. The mandated revascularisation of these lesions may have contributed to the worse outcomes observed in the multi-vessel PCI group. In fact, in the EXPLORE trial, revascularization of non-culprit CTO lesions in patients with STEMI failed to improve left ventricular function and was related with a trend to a higher mortality at 4 months (2.7% *vs.* 0%, P=0.056) (16). Finally, because in half of patients' resuscitation was required prior to PCI, it would have been interesting to have neurological status as a more patient-centered outcome.

Noteworthy, mechanical circulatory support was used in only 28% of the patients and intra-aortic balloon pump was used in 27% in the multivessel PCI group. It remains a matter of debate whether a higher use of mechanical circulatory support [extracorporeal membrane oxygenation (ECMO), Impella and others] could improve outcomes in this complex scenario, enhancing safety for multivessel revascularization procedures.

As mentioned at the beginning of this editorial comment, the CULPRIT SHOCK trial induced a radical change in guidelines, downgrading non-infarct related artery PCI to class III. Yet, this is not a dogma, but a general recommendation. Multivessel PCI during index procedure could be contemplated in specific situations such as the presence of critical flow-limiting lesions in large vessels or in case of difficult identification of the culprit lesion. Likewise, a staged complete revascularization could be attempted in carefully selected cases.

As a more general lesson to derive from this story, recommendations in guidelines based on a C level of evidence should be taken cautiously, until clear evidences are generated.

In this case, the verdict was favourable to the only-culprit lesion PCI, but I bet someone, somewhere, is working on the appeal.

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Footnote

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