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# Integrating the results of the CULPRIT-SHOCK trial in the 2017 ESC STEMI Guidelines: Viewpoint of the Task Force

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**Spirit of the viewpoint**

The recent 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (STEMI GL).[1] included 159 recommendations based on 477 references. Although the field of acute myocardial infarction is very evidence-based many treatment options have never been tested in prospective randomized clinical trials (RCTs). Under these circumstances the guideline TF is expected to develop clinically useful recommendations using consensus based on available evidence from small trials or observational studies or plain clinical experience (level of evidence (LOE) C). In the recent STEMI guidelines (REF) 49% of the recommendations were labeled as LOE C. Many of these LOE C recommendations were acknowledged as relevant areas for future research in the 2017 STEMI GL document.[1]
Regarding the management of patients with cardiogenic shock complicating STEMI and with severe stenosis apart from the infarct-related artery (IRA), the recent 2017 STEMI GL[1] favoured complete revascularization during the index primary percutaneous coronary intervention (PCI), allocating a class of recommendation IIa with LOE C. After the publication of the STEMI GL,[1] the "Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock" (CULPRIT-SHOCK) trial demonstrated that routine complete revascularization during index PCI procedure in this population is harmful.[2] In light of this outcome, the 2017 STEMI GL task force (TF) considers it important to provide the cardiology community with a viewpoint that can help readers to place these apparent contradictory messages in context and help physicians taking the best therapeutic decision for their patients. A selected group of members of the 2017 STEMI GL TF leading the chapters related to this topic decided to write this document. To get the broadest view of this relevant topic, additional authors were invited to participate in this document, including the principal investigator of CULPRIT-SHOCK (H.T.), the chair of the ESC Committee for Practice Guidelines (CPG) (S.W.), and the chair of the upcoming 2018 ESC Myocardial Revascularization GL (F.-J.N.).

**Complete revascularization in STEMI patients with multi-vessel disease but no cardiogenic shock: evidence leading to the 2017 recommendation**

The recommendation for non-IRA PCI in STEMI was significantly modified from the 2012[3] to the 2017 STEMI GL.[1] In the 2012 GL, it was recommended that primary PCI

should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion (class IIa LOE B).[3] Thus, routine PCI of non-IRA was not recommended. The 2017 document proposed that routine PCI of non-IRA severe stenoses should be considered before hospital discharge (Class IIa, LOE A).[1] Justification for this change was based on the results of four medium-sized randomized controlled trials (RCTs) and several meta-analyses comparing IRA-only PCI vs. complete revascularization in stable STEMI patients[4-7] none of which included patients with cardiogenic shock or resuscitated from cardiac arrest. The primary outcome measure was mainly driven by a reduction in repeat revascularisation rates. While this might be seen as a self-fulfilled prophecy (i.e. revascularisations already done upfront in the active treatment), meta-analyses also revealed ischemic outcomes (death or myocardial infarction) were numerically lower in the non-IRA PCI group in most of the trials.[8] The overall low event rate in conjunction with the relatively small size of all trials precluded the demonstration of a clinical benefit beyond repeat revascularisations. For this reason, the class of recommendation for non-IRA PCI before hospital discharge was set t IIa and not in I.

**Evidence to recommend non-IRA PCI during index procedure in STEMI patients with multivessel disease and cardiogenic shock**

In patients with STEMI and cardiogenic shock, early revascularization of the IRA improves outcomes.[9, 10] Up to 80% of patients with STEMI and shock have multivessel disease, and the mortality in these patients is higher than that of those with single-vessel disease.[11] Prior to the publication of CULPRIT-SHOCK trial, late in 2017,[2] the evidence available on the clinical benefit of complete vs. IRA-only PCI in this population was based on indirect evidence and observational studies. In the SHOCK trial, 40% of patients underwent coronary artery bypass grafting (CABG) likely extending beyond the IRA revascularisation.[12] In the Manitoba Cardiogenic Shock Registry, a retrospective multicentre cohort of patients with cardiogenic shock undergoing coronary angiography, complete revascularization was identified as an independent predictor for hospital survival in the subgroup of STEMI.[13] In the absence of prospective RCTs, these data was considered by the 2012 STEMI GL to recommend non-IRA PCI in STEMI patients with persistent shock after IRA PCI.[3] Similarly, the most recent U.S. appropriate-use criteria defined as appropriate to perform immediate PCI of a non-IRA if cardiogenic shock

persisted after IRA PCI.[14] Owing to the mentioned benefits of non-IRA PCI in STEMI patients without cardiogenic shock of and the absence of evidence of harm, the 2017 STEMI GL document maintained the 2012 recommendation for non-IRA in STEMI patients with multi-vessel disease in cardiogenic shock although the wording was less stringent by eliminating the consideration that this should be done in patients with persistent shock after IRA PCI.

**CULPRIT-SHOCK trial**

The CULPRIT-SHOCK trial is the largest RCT in cardiogenic shock complicating myocardial infarction (62% STEMI) to date comparing IRA-only PCI with immediate PCI of all severe lesions.[2] The CULPRIT-SHOCK trial addressed a contemporary, very high-risk patient population. Roughly half of enrolled patients had been resuscitated prior to randomization, and almost one third received some form of hemodynamic support. The primary endpoint (composite of death or severe renal failure leading to renal-replacement therapy at one month) was higher in the immediate multivessel PCI than in the IRA-only PCI group (55.4% vs. 45.9%; P=0.01).[2] The results were mainly driven by an absolute 8.2% difference in 30-day all-cause mortality (51.5% vs. 43.3%, P=0.03). Results were consistent across pre-specified subgroups including all age groups, sex, presence/absence of diabetes, presence/absence of hypertension, STEMI or non-STEMI, anterior/non-anterior STEMI, previous/no previous infarction2/3-vessel disease, or presence/absence of chronic total occlusion (CTO). In the multivessel PCI group, complete revascularization was achieved in 81.0% of the patients. Staged revascularization was performed in 17.7% of the patients in the IRA -only PCI group, and the cross-over rate was limited (12.5% in the IRA -only PCI group and 9.4% in the multivessel PCI group). The consistent risk estimates for the primary end point in the intention-to-treat, per-protocol, and as-treated analyses support the robustness of the findings.

It is well known that presence of a CTO is frequent in cardiogenic shock and associated with high mortality.[15] At least one CTO was present in 22.4% in the IRA-only PCI arm and in 24.0% in the immediate multivessel PCI arm. In CULPRIT-SHOCK, immediate CTO recanalization was attempted in roughly 50% of patients in the immediate

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multivessel PCI group and was successful in approximately one third of attempts. The results for the primary study endpoint were consistent for CTO presence or absence. The mechanisms leading to the higher 30-day mortality in the immediate multivessel PCI group in CULPRIT-SHOCK might be related to the significantly higher amount of contrast medium given (250 cc versus 190 cc; p<0.001) with subsequent impairment of renal function. There was a lower estimated glomerular filtration rate in the immediate multivessel PCI group at days 3 and 4, although differences in the incidence of severe renal failure leading to renal replacement therapy failed to reach conventional levels of statistical significance (11.6% versus 16.4%; p=0.07). The higher dose of contrast medium in the immediate multivessel PCI group may also have led to acute left ventricular volume overload with a negative effect on myocardial function and recovery. In addition, the prolonged duration of the multivessel PCI procedure may be hazardous at a time when the patient is hemodynamically compromised. Additional myocardial damage may also have been induced by PCI in non-IRA stable lesions.

Interestingly, the 30-day mortality rate in the IRA-only PCI group was nearly identical with that of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial performed 2 decades ago.[9, 12] This similar mortality rate may be partly explained by the higher risk profile in the CULPRIT-SHOCK trial because patients with single vessel coronary artery disease were excluded.

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**Position of the TF after publication of Culprit Shock**

Based on the new robust evidence from the adequately powered CULPRIT-SHOCK trial, it is now the opinion of the 2017 STEMI TF that in patients with cardiogenic shock complicating STEMI, primary PCI should be restricted to the IRA. Immediate multivessel PCI may be justified in the rare cases where the IRA is difficult to identify or incorrectly defined initially or when multiple culprit lesions are identified. Selected cases in which there is a flow-limiting non-IRA very severe stenosis irrigating a large myocardial area may also justify immediate non-IRA PCI. Staged non-IRA PCI might be an option, carefully balancing the benefits and risks of a new procedure with additional contrast loading and risk of complications. The new edition of the ESC/EACTS guidelines on myocardial revascularization will be released this year, incorporating the results of all published data so far. In the meantime, decision making in STEMI patients with

cardiogenic shock and multi-vessel disease should be based on available data from CULPRIT SHOCK trial taking into consideration the individual patient using medical judgement based on the available evidence.

**How to deal with evidence arising soon after guidelines release**

The results of the CULPRIT-SHOCK trial were presented on October 30th 2017 approximately two months after the release of the new 2017 ESC STEMI GL. The 2018 ESC/EACTS Guidelines on Myocardial Revascularization will be the next upcoming guideline document to address CULPRIT-SHOCK. Given the potential difference in survival related to changes in management based on CULPRIT-SHOCK, the ESC took advantage of this communication to increase awareness regarding this important outcome.

The inclusion of upcoming evidence is a general conundrum of guidelines. As illustrated by our current example, some of the guideline recommendations may become outdated shortly after their publication. Currently, the life cycle of the ESC guidelines documents is roughly 4-5 years for major topics to allow for the extensive and careful review process that ensures credibility of the recommendations. It is not feasible or desirable to update for any new evidence that appears during the life cycle of a guideline with the same diligence for any given guideline document. However, there is a plethora of ESC guideline topics with overlap between different documents as exemplified by the publication of ESC guidelines on the topics of myocardial revascularization, STEMI, NSTE-ACS and stable coronary artery disease that allow to update within various documents as deemed necessary.

**Conclusion**

Evidence regarding the best approach for cardiogenic shock complicating STEMI and multivessel disease is constantly being generated, and several metaanalyses from non-RCT are being published with mix, even contradictory results to each other.[16-18] We have learnt that data from non-randomized, retrospective and observational studies is potentially affected by important bias and might not represent a real effect. Data from RCT represent the best evidence to guide therapies. The CULPRIT-SHOCK trial is the

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only RCT performed addressing this issue, and demonstrated that routine multivessel PCI during the index procedure in STEMI patients and cardiogenic shock is not safe.

**Summary Key Points**

In patients with cardiogenic shock complicating STEMI and NSTEMI:

Primary PCI should routinely be restricted to the IRA

Immediate multivessel PCI may be justified if the IRA is difficult to identify or incorrectly defined initially or when multiple culprit lesions are identified.

Immediate multivessel PCI may be justified in selected cases in which there is a flow-limiting non-IRA very severe stenosis irrigating a large myocardial area.

Staged non-IRA PCI might be an option, carefully balancing the benefits and risks.

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