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EDITORIAL COMMENT

Cardiogenic Shock a Quarter Century Later

A Dire Outcome Barely Changed*

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Almost a quarter of a century after the SHOCK (Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock) trial showed an absolute 13% reduction from 63.1% to 50.3% in 6-month mortality of patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS)[1] outcomes of these critically ill patients and therapies in CS have changed little.[2,3] Furthermore, by far the majority of studies, randomized controlled trials or observational studies, have focused primarily on CS in the context ST-segment elevation myocardial infarction (STEMI), and even in those that included patients with non-ST-segment elevation myocardial infarction (NSTEMI), little has been written about characteristics and outcomes specific to this latter group of high-risk patients.

In this issue of *JACC: Advances*, Sinha et al[4] provide the most contemporary window into the treatment of patients with CS complicating AMI in the Cardiogenic Shock Working Group (CSWG) registry, a collaboration of 17 community and university hospitals in the United States. The investigators enrolled 1,110 patients between 2016 and 2020, focusing on the interplay between patient characteristics, shock severity, utilization of drugs and mechanical support devices, and patient outcomes.

The authors provide an important contribution with their careful description of the clinical, hemodynamic, and metabolic parameters in STEMI and NSTEMI shock patients. From the report, we find that patients with shock and NSTEMI are older. Those who present after a cardiac arrest have a much worse outcome and require separate analysis in future randomized trials. Importantly, we find that most patients who present with Society for Cardiovascular Angiography and Intervention (SCAI) Stages B and C tend to progress to higher stages over the course of hospitalization, highlighting the need not only for careful vigilance and management but also the need to further improve our initial treatment protocols. Interestingly they have not touched at all on the revascularization practices in these patients, and we can only assume that these were guideline based.

They found the utilization of vasoactive and inotropic drugs, as well as temporary mechanical circulatory support devices, especially in the first 24 hours, to be low with more than one-half of the patients receiving neither treatment modality within this early period. At least in part, this could be due to the relatively high systolic and mean arterial pressure at baseline, suggesting that clinicians may have been responding more to systemic pressures than to pulmonary artery catheter measurements and metabolic parameters of shock severity. Also in part, the evidence to guide the timing and selection of pressor agents, other than a subgroup analysis of randomized trial conducted over a decade ago showing superiority of norepinephrine over dopamine in CS patients, is generally lacking.[5]

High quality evidence guiding the use of temporary mechanical circulatory support is at least as sparse. While the intra-aortic balloon pump (IABP) has been a staple of CS treatment for close to half a century,[6] a

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large randomized controlled trial showed unequivocally that its routine use initiated after percutaneous coronary intervention does not reduce mortality of patients with CS complicating either STEMI or NSTEMI.[7] Yet, in the current study, the CSWG investigators report that the IABP was the most commonly utilized MCS device at all-time points during the hospitalization, a phenomenon even more likely in most other geographies, where newer devices such as the axial flow pump Impella (Abiomed Inc) are simply unaffordable and unavailable as a treatment option.

The authors correctly point out that future trials must be conducted to determine the optimal setting and role of the IABP in the CS spectrum. Some avenues to explore might be in the timing of IABP support. While SHOCK-IABP 2 found no benefit from routine IABP use, the majority of devices were deployed after the PCI procedure, while 10% of patients randomized to control crossed over to IABP support.[7] There is at least a suggestion from a retrospective single-center registry that placement of the IABP within the first hour of onset of shock is associated a 50% lower in-hospital mortality compared to later deployment.[8] The size of the IABP deployed may be important as well. A 50 cc IABP provides significantly greater unloading than a 40 cc device,[9] and in one single-center study its use resulted in very acceptable outcomes in CS patients, when utilized alone, or as a bridge to more advanced therapies.[10]

Of course, as it currently stands, routine use of the IABP in AMI CS patients is actually not recommended in the 2021 European Society of Cardiology guidelines,[11] while a 2021 American Heart Association policy statement goes further to recommend early initiation of advanced mechanical circulatory support.[12] The evidence to support this recommendation remains tenuous. Not only do the few very small randomized trials comparing percutaneous LVADs vs IABP not suggest even the smallest signal of survival benefit,[13] observational U.S. registries actually reveal worse outcomes with use of a percutaneous LVAD compared with the IABP. A propensity-matched analysis of an administrative database from 14 states showed a significantly higher risk of in-hospital mortality with the use of a percutaneous LVAD compared with the IABP (OR: 1.63; 95% CI: 1.32-2.02).[14] In an adjusted multivariable analysis of a very large National Inpatient Sample database of patients with CS secondary to STEMI or NSTEMI between 2005 and 2014, treated with primary PCI in the first 24 hours, the use of a percutaneous LVAD was associated with a doubling of in-hospital mortality risk (OR: 2.21; 95% CI: 2.01-2.54).[15] Of course administrative databases are likely to have unmeasured confounders that may underestimate the risk of a given group, thus adding imprecision to the assessment of the efficacy and safety of any therapy. However, these data do serve to point out the need for carefully designed randomized controlled trials to bring clarity to this important aspect of management of CS patients.

Perhaps the issue is the timing of MCS support. In the majority of patients enrolled in randomized trials, the pLVAD was deployed after the primary PCI procedure. The National Cardiogenic Shock Initiative (NCSI) is a collaboration of 35 U.S. sites that conducted a prospective single-arm study in AMI CS patients utilizing a common algorithm of patient management,[16] including deployment of the Impella CP device (most cases) prior to primary PCI. Inclusion criteria matched those of the SHOCK trial,[1] with the exception that patients already on IABP support were excluded. In-hospital mortality was 28%, considerably lower than observed in previously reported studies in similar shock populations. Furthermore, a recent meta-analysis of 13 observational studies of patients with AMI CS undergoing primary PCI and Impella support suggested an association with lower mortality with pre-PCI deployment of the device.[17] Again, carefully designed and conducted randomized controlled trials are needed to confirm the efficacy of this strategy. The currently enrolling DanGer (Danish-German Cardiogenic Shock) trial, with a planned study size of 360 participants, may well provide the answer.[18]

An intriguing twist to this is the concept of waiting for a period of time after placement of a pMCS device to actually perform the primary PCI. Based on a porcine study in which reperfusion after 30 minutes of unloading with an Impella CP device significantly reduced infarct size by reducing proapoptotic signaling,[19] the STEMI-DTU trial, a randomized controlled trial in patients with an anterior STEMI but no CS is currently in the enrollment phase, with a planned enrollment of 668 patients.[20] If there is a positive outcome for the pre-PCI Impella CP in the DanGer trial and in the STEMI-DTU (Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial

Infarction) trial, STEMI-DTU, this strategy could eventually find its way to application in AMI CS.

Understandably, Sinha et al[4] and the CSWG investigators are vague in their recommendations with respect to these therapies. However, with their careful characterization of STEMI and NSTEMI CS patients, documentation of SCAI stages and progression, as well as drug and device utilization, they add an important chapter to our current knowledge of AMI CS. Their work also suggests that we have a long way to go and much more work to do in order to improve the outcome of these, our most critically ill patients.

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