# Novel statistical approaches for cardiogenic shock trials: what are the options?

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# "Conventional" RCT Paradigm

- Example: IMPRESS in Severe Shock
- Parallel-group, 2-arm: patients assigned active treatment (pMCS) versus (IABP)
- Power based on guesstimates of benefit (in this case, control mortality < expected)
- Any subgroup analyses must be taken with caution - design does not control type 1 error rate for that multiplicity
- Overall effect on survival at 30 days - HR=0.96; 95%CI 0.42 - 2.18
- Takeaway? - "This probably rules out a huge lifesaving effect of pMCS over IAMP in the CS population; otherwise, not much else without more data"
- None of this meant to pick on IMPRESS investigators; merely illustrates how difficult RCT can be in the CS population

**ABSTRACT**

**BACKGROUND** Despite advances in treatment, mortality in acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) remains high. Short-term mechanical circulatory support devices acutely improve hemodynamic conditions.

**OBJECTIVES** The aim of this study was to determine whether a new percutaneous mechanical circulatory support (pMCS) device (Impella CP, Abiomed, Danvers, Massachusetts) decreases 30-day mortality when compared with an intra-aortic balloon pump (IABP) in patients with severe shock complicating AMI.

**METHODS** In a randomized, prospective, open-label, multicenter trial, 48 patients with severe CS complicating AMI were assigned to pMCS (n = 24) or IABP (n = 24). Severe CS was defined as systolic blood pressure <90 mm Hg or the need for inotropic or vasoactive medication and the requirement for mechanical ventilation. The primary endpoint was 30-day all-cause mortality.

**RESULTS** At 30 days, mortality in patients treated with either IABP or pMCS was similar (50% and 46%, respectively; hazard ratio with pMCS: 0.96; 95% confidence interval: 0.42 to 2.18; p = 0.92). At 6 months, mortality rates for both pMCS and IABP were 50% (hazard ratio: 1.04; 95% confidence interval: 0.47 to 2.32; p = 0.923).

**CONCLUSIONS** In this explorative randomized controlled trial involving mechanically ventilated patients with CS after AMI, routine treatment with pMCS was not associated with reduced 30-day mortality compared with IABP. (IMPRESS in Severe Shock; NTR3450) (J Am Coll Cardiol 2017;69:278-87) © 2017 by the American College of Cardiology Foundation.

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# Issues with "Conventional" RCT in Cardiogenic Shock

- High mortality (>=50%) population

- Increasing reluctance to enroll such high-risk patients in trials where possibility that patients may be assigned to not receive a device (worry about "sentencing patient to death" – even without RCT data proving that pMCS improves survival, must be helpless feeling)

- Therefore, it likely will remain difficult to enroll large numbers in these trials (most prior pMCS trials <50 patients; none showed even a hint of mortality benefit)

- The "Right Patients" Problem: common refrain after negative trials is that the device/drug works, but the trial included too many of the wrong patients or not enough of the right ones to show it

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# Issues with "Conventional" RCT in Cardiogenic Shock

- Therefore, seek design that allows the following:

  - Get a valid answer with as few patients randomized as possible (but also keep recruitment open-ended; minimizes risk of "inconclusive" trials which help nobody)

  - Include design feature that helps with the "right patients" question

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# Adaptive-Enrichment Design with Bayesian Monitoring: What Is It?

- High-profile example is the recent DAWN trial (NEJM 2018)
- Mechanical embolectomy in patients 6-24 hours after stroke
- Trial designed to enroll anywhere from 150 to 500 patients
- First interim at 150 patients (every 50 patients thereafter)
- Population could "enrich" to narrow inclusion criteria based on infarct size (if therapy was having positive effect in smaller infarcts but not large infarcts, design allowed adaptation that would stop enrolling the patients with large infarcts)

**Design Paper -** Jovin TG, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods. *Int J Stroke* 2017; 12(6): 641-652

**Outcomes Paper -** Nogueira RG, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med* 2018; 378(1): 11-21.

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# Adaptive-Enrichment Design with Bayesian Monitoring: What Is It?

- Interim analysis at 150 patients (enrichment/futility stopping only) and every 50 patients thereafter (efficacy, enrichment, or futility)
- Stopping rules for **efficacy**
  - After 200 & 250 patients: stop if BPP of success>95%
  - After 300 & 350 patients: stop if BPP>90%
  - After 400 patients: stop if BPP>85%
  - After 450 patients: stop if BPP>80%
  - If an enrichment rule triggered, trial only stops if at least 100 subjects have been enrolled since last enrichment
  - Final analysis done on the enriched population only
- Stopping rules for **futility**
  - Subgroups are dropped if BPP<40% in that subgroup
  - If early results on first 150 patients were so poor that BPP<40% across the board, all arms would be closed and trial would terminate

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# Adaptive-Enrichment Design with Bayesian Monitoring: Advantages

- <u>Frequent Interim Monitoring</u>: Bayesian statistical approach controls Type I error rate across multiple interim looks better than traditional approach, allowing interim analyses often; by monitoring nearly-continuous we can minimize number of pts randomized to have valid answers

- <u>Adaptive Capability</u>: if trial shows clear evidence of benefit or futility in certain subgroups, trial may discontinue enrollment in the groups where answer is resolved but carry on for the groups not yet definitively answered

# Adaptive-Enrichment Design with Bayesian Monitoring: Application

- Start with broad inclusion criteria, with clinical subgroups specified ahead of time to avoid the "but the right patients" effect

- Schedule frequent interim analyses to allow adaptations to take hold; minimize number of patients randomized once conclusions reached for efficacy and/or futility (overall or within specific subgroups)

- Combination of these 2 points has potential to answer definitively i) does pMCS actually reduce mortality at all in CS patients and ii) if pMCS has benefit in some specific patients but not all, may be able to answer "which patients" get the most (or least) benefit

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# Adaptive-Enrichment Design with Bayesian Monitoring: Scenarios

- Therapy improves survival for everyone
  - Early results will show high BPP of success across the board; trial may terminate quickly if effect so strong that BPP threshold for efficacy is reached early (this happened in DAWN)
- Therapy improves survival for some, not all
  - Early results will show high BPP of success in some groups, which may close once efficacy threshold crossed; trial can still proceed until conclusions reached about likelihood of benefit in some subgroups & futility in others
- Therapy improves survival for nobody
  - Early results will show low BPP of success in all groups, trial will terminate when futility threshold crossed