MHIF FEATURED STUDY:
XIENCE 90

DESCRIPTION:
This study evaluates the safety of three months of dual antiplatelet therapy (DAPT) in subjects at a high risk of bleeding (HBR) undergoing PCI with a XIENCE stent. Subjects can be consented to XIENCE 90 up to three days after their PCI procedure (must be prior to discharge).

CRITERIA LIST/ QUALIFICATIONS:

Inclusion
Patients at a high risk of bleeding, defined by one of the following: greater than 75 years of age, clinical indication for at least six months of anticoagulation therapy, history of major bleeding, renal insufficiency (Creatinine > 2.0 mg/dl), anemia with Hgb < 11 g/dl

Exclusion
Patients with implantation of another DES (other than XIENCE) within nine months prior to index procedure
Subjects with known EF <30%.

CONDITION:
Patients at high risk of bleeding who need coronary stents

PI:
Nicholas Burke, MD

RESEARCH CONTACT:
Amy McMeans
Amy.McMeans@allina.com | 612-863-3895

SPONSOR:
Abbott

ACTION: If you have a patient at high risk of bleeding and they are having a coronary angiogram, notify research or the Cath Lab.

• DESCRIPTION:
This study evaluates the safety of three months of dual antiplatelet therapy (DAPT) in subjects at a high risk of bleeding (HBR) undergoing PCI with a XIENCE stent. Subjects can be consented to XIENCE 90 up to three days after their PCI procedure (must be prior to discharge).

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Subjects with known EF <30%.
Daring to be different in STEMI management

*the importance of giving ‘door-to-unload’ a chance*

Allison Hall, MD

December 3, 2018, MHI Grand Rounds

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A Brief History of STEMI
In 1912, James B. Herrick described certain clinical features of sudden coronary obstruction ...

- “My paper on the diagnosis of coronary thrombosis during life rather than only at autopsy, which I presented at the 1912 meeting of the Association of American Physicians, fell like a dud.”

  --James B. Herrick

- In a 2012 review paper, Eugene Braunwald summarized 4 phases in the evolution of STEMI management:

  The treatment of acute myocardial infarction: the Past, the Present, and the Future

  Eugene Braunwald
Phase 1-1912-1961

- Bed rest and ‘expectant’ treatment
  - Bedrest, 6 weeks or so!
  - Emotional rest
  - Morphine
  - Digitalis
  - Caloric and fluid restriction
  - Later, into the 1950s, heparin, coumadin, atropine, paparavine


Phase 1 Outcomes...

- "It was not uncommon for me, when arriving on the medical floor at 6 am to draw blood to be sent for testing, to discover that one of my AMI patients had died quietly during the night."

--Eugene Braunwald
Phase 2 - 1961-1974

- The CCU

- Concept described in 1961
  - (1) segregation of AMI into specialized intensive care units – trained staff, monitors, catheters, pacemakers, drugs and cardiologists at hand
  - (2) continuous rhythm monitoring/arrhythmia alarms
  - (3) training of staff in closed chest resuscitation
  - (4) RN authority to perform resuscitation & defibrillation, in absence of MD

Phase 2 - 1961-1974

- The CCU

- Significantly ↓ deaths from VF, CHB/arrhythmias
  - ↓ early hospital mortality AMI by ½:
    - ~30% in prior decade to ~15%
Phase 3- 1975-present

- **Myocardial Reperfusion**
- 1975 Chazov et al lysed thrombi by infusing streptokinase into blocked coronaries
  - (1) development of more potent tissue plasminogen activators
  - (2) addition of ASA, then more potent antiplatelets to lytic
  - (3) use of percutaneous coronary angioplasty
  - (4) addition of stents – BMS then DES
  - (5) other adjunct tools such as aspiration thrombectomy
  - Door-to-balloon in 90 min

Phase 3- 1975-present

- Each measure improved clinical outcomes
  - AMI in-hospital mortality \( \downarrow \) by 1/2
    - \(-15\% \text{ to } ~7.5\%\)
    - now as low as 3.5\% in clinical trial pts
The Progress...
Where Have we Come From with STEMI Outcomes?

![Mortality Rates Trends](image)

**Figure 1** Early mortality rates in major randomized STEMI trials: 1986–2008.

Van der Werf, European Heart Journal (2014) 35, 2510–2515

Cardiovascular Mortality Rates:

- **↓ 22% in last decade**
  - With DES, 1°PCI, effective OMT (anti-platelets/anti-thrombotics, lipid lowering drugs etc) & preventive care

<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>30–40%</td>
</tr>
<tr>
<td>1975</td>
<td>27%</td>
</tr>
<tr>
<td>1984</td>
<td>19%</td>
</tr>
<tr>
<td>1994</td>
<td>10%</td>
</tr>
<tr>
<td>2009</td>
<td>6%</td>
</tr>
</tbody>
</table>

Table 1: Decreasing mortality of Acute Coronary Syndrome with time.
Well, What’s to Improve Upon?

• Despite achieving goals such as DTB in 90 min & decreased mortality, incidence post-AMI HF remains high
  – At least 1 series in elderly pts w/ AMI, 37% diagnosed w/ new HF during index hospitalization, 71% developed HF by 5 years, 64% within 1st yr

Ezekowitch, JA, JACC Vol 53, Issue 1, 6 Jan 2009, Pages 13-20
MI Size, Myocardial Injury and HF

- Every 5% ↑ MI size, 20% ↑ 1-yr hospitalization for HF & 1-yr mortality

- Some of degree of HF onset is probably population-based:
  - ↑ co-morbidity, complex coronary anatomy
  - Pts ’11-’13 with AMI & cardiogenic shock more likely to have comorbidities i.e. DM, dyslipidemia, prior PCI, ESRD vs. ’05-’06

Kapur et al; LV Unloading with Impella before PCI in STEMI. Circulation 2016
Patel, Manesh, Percutaneous Support Devices For PCI: Having the Science Catch Up with the Technology. Circulation 2018

However, alleged ongoing contributor to MI size/myocardial injury & HF is:

Reperfusion Injury:

- Although it reduces ischemic cell death, reperfusion is double-edged sword:
  - also injures the surviving myocardium
Reperfusion Injury:

- Disordered microvascular fxn & inadequate myocardial tissue perfusion often present despite infarct vessel patency post-revasc
  - Ideally, optimal reperfusion would include intact microvascular flow/restored myocardial perfusion in addition to epicardial patency

Roe et al. JACC Vol. 37, No. 1, 2001 Shifting the Open-Artery Hypothesis Downstream January 2001:9–18

Braunwald’s Phase 4-‘the future’

- “The prevention of lethal reperfusion injury”
- ?regenerative medicine
Estimated that *timely* reperfusion can salvage *50%* of severely ischemic myocardium

**CRISP AMI STUDY**

- **337** pts with acute anterior STEMI w/o cardiogenic shock at 30 sites in 9 countries June ‘09- Feb ’11
  - IABP pre-PCI vs. not

- **Even w/ DTB <90 min ~40%** myocardium both groups infarcted ~4d post-MI
  - unclear how many went on to develop HF

*Kapur, N From Door-to-Balloon to Door-to-Unload Time MARCH/APRIL 2015 CARDIAC INTERVENTIONS TODAY

JAMA, September 28, 2011—Vol 306, No. 12*
Manifestations of Myocardial Ischemia/Reperfusion Injury in Coronary Circulation

- No-reflow & reperfusion injury frequently seen after interventional reperfusion & carry adverse prognosis
  - Vascular Permeability: Edema
  - Vasomotion impairment
  - Microembolization
  - Stasis & intravascular cellular aggregates
  - Capillary Destruction: Hemorrhage

Summary-Microvascular Dysfunction Post-Reperfusion

Figure 1. Pathophysiology of microvascular dysfunction after epicardial perfusion.
Reperfusion Injury

- Complex phenomenon to effectively target therapeutically
  
  – No widely accepted effective Rx for reducing myocardial reperfusion injury in STEMI, though some promising studies/methods

Roe et al. JACC Vol. 37, No. 1, 2001 Shifting the Open-Artery Hypothesis Downstream January 2001:9–18

Ischemic Conditioning

≥1 brief cycle ischemia & reperfusion can protect heart from myocardial reperfusion injury

- Mid 1980s Murry, Jennings & Reimer
  
  – pre-treating dog LCx w/ 4, 5-min cycles occlusion & reflow prior to occlusion for 40 min led to 25% ↓ MI size

- Since replicated in all species tested, including humans

- Extensive investigative efforts, benefit well established pre-clinical models
  
  - Pubmed “ischemic preconditioning” 10,301 results

- Therapeutic potential investigated –last 5-10 yrs : promise, translational challenges

Hauserloy & Yellon, Nature Reviews Cardiology, Online Feb 4, 2016
Reperfusion Injury—it’s real...

- An example

Day 0, initial ECG
Reperfusion Injury - Pt Initial Cath Images

Patient Cath Post-Stenting: *attention to MBG*
Day 3, 72 hrs post-revasc/ ‘open artery’

Better Defining Reperfusion

Roe et al. JACC Vol. 37, No. 1, 2001 Shifting the Open-Artery Hypothesis Downstream January 2001:9–18
Door-to-Unload (DTU): The Concept

• Excessive myocardial oxygen demand relative to supply is fundamental mechanism of MI
  
  — *LV mechanical unloading could minimize* $O_2$ demand, reducing infarct size & preventing subsequent HF

Door-to-Unload (DTU): The Concept

• Similar to CV Surgical approach to STEMI + shock:
  
  — 1st initiate cardiopulmonary bypass to unload RV & LV
  
  — time to harvest grafts while culprit artery remains occluded
  
  — then, ultimately reperfusion
Door-to-Unload (DTU): The Concept

- By contrast, in PCI world, current climate is for ASAP rapid coronary reperfusion
- So, typically insufficient time for cardioprotective therapy targeted at reperfusion injury

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Door-to-Unload (DTU)

- Pre-clinically:
  - In canine, sheep & pig models, as recently as 2018, mechanical unloading of LV during ischemic period prior to revasc shown to reduce infarct size & subsequent HF
  - Also activates cardio-protective signaling program
    - (decreased degradation SDF-1α)

Kapur et al; LV Unloading with Impella before PCI in STEMI, Circulation 2018
Applying DTU in Humans-What is Impella CP?

- Percutaneous mechanical circulatory support (MCS) device
- Part of Impella family of devices from ABIOMED, series of microaxial pumps
  - Impella 2.5®, Impella 5.0®, Impella LD® & Impella CP®
    - Various levels of support provided
  - There is also an RV support version, the Impella RP®

What is the Impella CP?

*Impella® Ventricular Support Systems for Use During Cardiogenic Shock and High-Risk PCI-ABIOMED product*
How is an Impella CP Inserted?

- Percutaneous femoral arterial insertion
  - most common
- Femoral cutdown, axillary insertion, sidearm grafting insertion also possible; Impella LD can be inserted directly into ascending Ao
Physiologic Effects of Impella

- 1) unloads LV, reducing LVEDP & LV wall tension, decreasing LV work & myocardial oxygen demand

International Journal of Cardiology 201 (2015) 684-691
Physiologic Effects of Impella

• 2) Increased mean arterial pressure, diastolic pressure, CO + cardiac power output
  – improved systemic perfusion + increased coronary flow
  – improved coronary perfusion through combined increased Ao pressure + LV unloading + decreased wall tension

• 3) Decreased pulmonary capillary pressure + secondary reduction in RV afterload
Fig. 3. Pressure-volume loop: Normal conditions (brown), Acute Heart Failure without hemodynamic support (blue), with Impella CP support (green) and with ECMO support (red). The loop area is an estimate of the mechanical work performed by the ventricle. Note the area reduction (work reduction) by the Impella device and the characteristic oblique vertical lines in the latter, indicating continuous emptying of the ventricle even in the “isovolumic” phases.


Why is Impella & its study in DTU or even at all, often met with harsh criticism?
Because overall, *Randomized* Impella (& IABP)-based studies have turned up empty-handed for altering hard outcomes:

Prior studies in AMI w/o shock + IABP unloading generally negative for MACE/re-occlusion

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**Table: Randomized Trials with Percutaneous Support Devices**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Description</th>
<th>Comparison</th>
<th>Sample Size</th>
<th>AMI</th>
<th>Shock</th>
<th>Trial Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohman et. al. (1994) (8)</td>
<td>Primary PTCA in AMI</td>
<td>IABP + PTCA vs. PTCA</td>
<td>96 / 86</td>
<td>Yes</td>
<td>No</td>
<td>Less re-occlusion and MACE with IABP</td>
</tr>
<tr>
<td>PAMI II (1997) (9)</td>
<td>Primary PTCA in AMI</td>
<td>IABP + PTCA vs. PTCA</td>
<td>211 / 226</td>
<td>Yes</td>
<td>No</td>
<td>No change in re-occlusion or MACE w/IABP</td>
</tr>
<tr>
<td>van’t Hof et. al (1999) (10)</td>
<td>Primary or rescue PCI in AMI</td>
<td>IABP + PCI vs. PCI</td>
<td>118 / 120</td>
<td>Yes</td>
<td>No</td>
<td>No change in re-occlusion or MACE w/IABP</td>
</tr>
<tr>
<td>CRISP AMI (2011) (11)</td>
<td>Primary PCI in Anterior AMI</td>
<td>IABP + PCI vs. PCI</td>
<td>161 / 176</td>
<td>Yes</td>
<td>No</td>
<td>No change in infarct size</td>
</tr>
<tr>
<td>Kapur et. al. (2018) (4)</td>
<td>Primary PCI in Anterior AMI</td>
<td>Impella CP = immediate PCI vs. Impella CP + delayed PCI</td>
<td>25 / 25</td>
<td>Yes</td>
<td>No</td>
<td>Similar Infarct size, similar MACE</td>
</tr>
</tbody>
</table>

*Patel, Manesh, Percutaneous Support Devices For PCI: Having the Science Catch Up with the Technology. Circulation 2018*
Prior studies in AMI w/shock- no differences in 30 d mortality, some hemodynamic improvements; however lots of individual operator/centre/database experience with Impella in shock; remains one of the ‘formal indications’ for its use

### MI with Shock

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Description</th>
<th>Comparison</th>
<th>Sample Size</th>
<th>AMI</th>
<th>Shock</th>
<th>Trial Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiele et al (2005) (15)</td>
<td>AMI and Shock</td>
<td>TandemHeart™ vs IABP</td>
<td>21 / 20</td>
<td>Yes</td>
<td>Yes</td>
<td>Improved cardiac power, more bleeding, similar 30-day mortality</td>
</tr>
<tr>
<td>Burkoff et al. (2006) (16)</td>
<td>Cardiogenic Shock – Not all AMI</td>
<td>TandemHeart™ vs IABP</td>
<td>19 / 14</td>
<td>Some</td>
<td>Yes</td>
<td>Improved cardiac hemodynamics, similar 30-day mortality</td>
</tr>
<tr>
<td>ISAR-SHOCK (2008) (17)</td>
<td>AMI and Shock</td>
<td>Impella 2.5 vs IABP</td>
<td>13 / 13</td>
<td>Yes</td>
<td>Yes</td>
<td>Improved Cardiac index</td>
</tr>
<tr>
<td>IMPRESS in severe shock (2017) (18)</td>
<td>AMI and Shock, 100% with mechanical ventilation, 100% with catecholamines at baseline</td>
<td>Impella CP vs IABP</td>
<td>24 / 24</td>
<td>Yes</td>
<td>Yes</td>
<td>30-day mortality – no difference</td>
</tr>
<tr>
<td>IABP-SHOCK II (2012) (19)</td>
<td>Primary PCI with Shock</td>
<td>IABP + PCI vs PCI</td>
<td>300 / 298</td>
<td>Yes</td>
<td>Yes</td>
<td>30-day mortality – no difference</td>
</tr>
</tbody>
</table>

Prior studies in high risk PCI-again no clear data for benefit, however individual operator/centre/database experience with Impella in this setting continues to build & remains one of the ‘formal indications’ for its use

### High Risk PCI

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Description</th>
<th>Comparison</th>
<th>Sample Size</th>
<th>AMI</th>
<th>Shock</th>
<th>Trial Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vijayalakshmi et al. (2007) (12)</td>
<td>High-risk PCI (hypotension, tachycardia, no-flow, ST segment elevation, pulmonary edema)</td>
<td>IABP + PCI vs PCI</td>
<td>17 / 16</td>
<td>No</td>
<td>No</td>
<td>No change coronary flow – TIMI grade</td>
</tr>
<tr>
<td>BCIS-1 (2010) (13)</td>
<td>High-risk PCI (LVEF ≤30%, unprotected LM, TV supply &gt;40% of myocardium)</td>
<td>IABP+PCI vs PCI</td>
<td>150 / 150</td>
<td>No</td>
<td>No</td>
<td>No Change in MACE 30 days,</td>
</tr>
<tr>
<td>PROTECT II (2012) (14)</td>
<td>High-risk PCI (fast patent vessel PCI with LVEF ≤35%, Unprotected LM, 3VD with LVEF ≤30%)</td>
<td>Impella 2.5 vs IABP + PCI</td>
<td>225 / 222</td>
<td>No</td>
<td>No</td>
<td>No Difference MACE at 30 days – trend for Impella at 90 days (stopped for futility)</td>
</tr>
</tbody>
</table>
Why do some people still really believe in Impella-based therapies?

- Registry/Retrospective data
- Positive local experiences

Recent Impella enthusiasm in CS

Physician-led National Cardiogenic Shock Initiative (NCSI)
- Best practices: Impella before PCI, reducing inotropes, use hemodynamic monitoring
- At TCT, Dr. O’Neill (Henry Ford, Detroit) also presented initial data from 104 pts with NCSI protocol
  - 77% survival to discharge with 99% native heart recovery
More Impella enthusiasm-AMI, LM & CS

- Meraj et al published multi-center retrospective (cVAD registry) study looking at insertion of Impella 2.5 prior to PCI on ULMCA vs. pts supported post-PCI & found significantly better survival to discharge (55.0% vs 18.8%, P = 0.041)

Impella enthusiasm-AMI & CS

- 154 pts in 38 US sites w/AMI & CS; Impella insertion pre-PCI vs. after
- ‘Pre’ pts significantly better survival to discharge vs. ‘post’ pts
  - (65.1% vs.40.7%, P = 0.003).  

Addition of Impella to VA-ECMO (ECPELLA) associated with improved survival, improved weaning, less inotropes, no complication differences
- Mortality
  - 30 d. 5.7% vs. 7.8%, HR 0.40 [0.19–0.84], p = 0.016
  - 1-yr: 6.9% vs 8.7% HR 0.39 [0.19–0.81], p = 0.011
- Limited by selection bias, small sample size, confounding, expertise

The European Impella Experience
- From 2014, group of European MDs looking at collective experiences w/ Impella, to establish best clinical practices
- Over 8 yrs > 8000 pts supported outside USA & as of publication, >800 US hospitals had supported > 20,000 pts
Hot off the Press in DTU

Unloading the Left Ventricle Before Reperfusion in Patients with Anterior ST-Segment Elevation Myocardial Infarction:
A Pilot Study Using the Impella CP®

Running Title: Kapur et al.; LV Unloading with Impella before PCI in STEMI

Navin K. Kapur et al.

DTU Pilot Study-Objective

- Multi-center (14 US), prospective, randomized exploratory safety & feasibility trial

- Pts received acute mechanical unloading with Impella CP, then randomized to either:
  - LV unloading followed by immediate reperfusion (U-IR)
  - LV unloading with 30- min delay to reperfusion (U-DR)
Included:

- 21-80 yrs
- Presenting 1-6 hrs from CP onset
- STE $\geq 2$ mm in $\geq 2$ contiguous anterior leads or
  $\geq 4$ mm total STD sum in anterior leads

Excluded:

- Prior MI or CABG
- OOH cardiac arrest requiring CPR
- Cardiogenic shock
- Inability to undergo Impella CP insertion
- Fibrinolysis within 72 hrs
- Contraindications to CMR
Primary Safety Outcome

- Composite MACCE including CV mortality, reinfarction, stroke, or major vascular events at 30 d

Additional Safety Parameters

- All-cause mortality
- Hemolysis
- Acute renal dysfunction
- Hospitalization for HF
- Ventricular arrhythmias
- LV thrombus
- Bleeding
- Minor vascular events
Primary Efficacy Endpoint:

- Infarct size as percent of total LV mass at 30 days using CMR

Secondary Efficacy Endpoints:

- Infarct size by CMR at 3-5 d & 30 d

Exploratory Endpoints:

- Infarct size normalized to area at risk at 3-5 d
- Qualifying 12-lead ECGs evaluated to quantify STE Sum (ΣSTE), marker of area at risk in STEMI
50 patients presenting with Acute Anterior Myocardial Infarction were enrolled and randomized (1:1)

Impella CP implanted and support initiated

Assignment to U-DR (n=25)
30min of LV unloading with Impella CP
Diagnostic angiogram
Percutaneous Coronary Intervention

Assignment to UHR (n=25)
Diagnostic angiogram
Percutaneous Coronary Intervention

Impella CP explanted after 3-4 hours of support (n=50)

9 patients did not undergo CMR at 3-5 days:
- 2 expired
- 2 due to claustrophobia
- 1 had acute (on chronic) kidney injury
- 2 due to body habitus
- 1 had a metallic IUD
- 1 was outside the test window

Infarct size assessed by CMR at 3-5 days post-PCI (n=41)

10 patients did not undergo CMR at 30 days:
- 2 expired
- 2 due to claustrophobia
- 1 had chronic kidney disease
- 2 due to size
- 1 had a metallic IUD
- 1 was outside the test window
- 1 moved to a different state

Infarct size assessed by CMR (n=40*)
MACCE rate at 30 days (n=50)
Results

- Impella CP successfully implanted in all 50 pts
  - mean power (P-level) 7.6±1.0
  - mean device flow 2.8±0.4 L/min
    - felt to represent successful unloading of LV
### Results - Timing Elements

<table>
<thead>
<tr>
<th></th>
<th>U-DR</th>
<th>U-IR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Door to Balloon</strong></td>
<td>n=24*</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>DTB, mean (±SD), minutes</td>
<td>96.7 (25.1)</td>
<td>72.6 (24.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>DTB, median (IQR), minutes</td>
<td>98.0 (76.0–112.5)</td>
<td>68.9 (55.0–87.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Door to Unload</strong></td>
<td>n=25</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Door to Unload, mean (±SD), minutes</td>
<td>64.0 (25.5)</td>
<td>62.1 (24.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>Door to Unload, median (IQR), minutes</td>
<td>63.0 (43.0–83.5)</td>
<td>56.0 (42.0–79.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom to Unload</strong></td>
<td>n=25</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Symptom to Unload, mean (±SD), minutes</td>
<td>176.2 (73.4)</td>
<td>200.2 (151.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Symptom to Unload, median (IQR), minutes</td>
<td>125.0 (119.0–190.0)</td>
<td>149.0 (124.0–225.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Procedural Start to Impella Insertion</strong></td>
<td>n=25</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Procedure Start to Impella Insertion, mean (±SD), minutes</td>
<td>15.1 (7.9)</td>
<td>15.8 (9.0)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Insertion Time, mean (±SD), minutes</strong></td>
<td>n=24*</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Insertion Time, mean (±SD), minutes</td>
<td>15.0 (8.0–20.0)</td>
<td>15.0 (12.0–20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Unload to Coronary Balloon</strong></td>
<td>n=24*</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Unload to Coronary Balloon, mean (±SD), minutes</td>
<td>34.1 (2.6)</td>
<td>10.5 (6.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Unload to Balloon, median (IQR), minutes</strong></td>
<td>n=25</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Unload to Balloon, median (IQR), minutes</td>
<td>34.0 (32.0–35.3)</td>
<td>10.0 (5.0–12.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of Support</strong></td>
<td>n=75</td>
<td>n=75</td>
<td></td>
</tr>
<tr>
<td>Duration of Support, mean (±SD), hours</td>
<td>8.2 (7.9)</td>
<td>5.2 (3.9)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Duration of Support, median (IQR), hours</strong></td>
<td>n=25</td>
<td>n=25</td>
<td></td>
</tr>
<tr>
<td>Duration of Support, median (IQR), hours</td>
<td>3.9 (3.1–11.9)</td>
<td>4.2 (3.4–14.9)</td>
<td></td>
</tr>
</tbody>
</table>

*One patient in the U-DR arm did not have a PCI U-DR, delayed reperfusion after 30 minutes of LV unloading by the Impella CP. U-IR, immediate reperfusion after placement of the Impella CP, DTB, door-to-balloon; IQR, interquartile range; SD, standard deviation; CP, cardiac power; LV, left ventricle; PCI, percutaneous coronary intervention.

### Supplemental Table 3. Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>U-DR</th>
<th>U-IR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct-related artery, n (%)</td>
<td>n=25</td>
<td>n=25</td>
<td>0.99</td>
</tr>
<tr>
<td>Left main</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>24 (96.0)</td>
<td>25 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Right coronary</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>No infarct-related artery identified</td>
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<td>0 (0.0)</td>
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<tr>
<td>Infarct-related artery stenosis location, n (%)</td>
<td>n=25</td>
<td>n=25</td>
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<tr>
<td>Proximal</td>
<td>16 (66.7)</td>
<td>16 (64.0)</td>
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</tr>
<tr>
<td>Mid</td>
<td>5 (20.8)</td>
<td>8 (32.0)</td>
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</tr>
<tr>
<td>Ostial</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Ostial</td>
<td>3 (12.5)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (4.2)</td>
<td>0 (0.0)</td>
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<tr>
<td>Infarct-related artery TIMI flow</td>
<td>n=25</td>
<td>n=25</td>
<td>0.33</td>
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<tr>
<td>Postintervention grade, n (%)</td>
<td>9 (36.0)</td>
<td>13 (52.0)</td>
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</tr>
<tr>
<td>0</td>
<td>1 (4.0)</td>
<td>3 (12.0)</td>
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<tr>
<td>1</td>
<td>5 (20.0)</td>
<td>2 (8.0)</td>
<td></td>
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<tr>
<td>2</td>
<td>10 (40.0)</td>
<td>7 (28.0)</td>
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</tr>
<tr>
<td>P value</td>
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<td>n=25</td>
<td>0.99</td>
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<td>0</td>
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<tr>
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<tr>
<td>2</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25 (100.0)</td>
<td>24 (96.0)</td>
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<tr>
<td>Interventions on non-infarct-related arteries, n (%)</td>
<td>n=25</td>
<td>n=25</td>
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<td>Left main</td>
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<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>1 (4.3)</td>
<td>3 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>1 (4.3)</td>
<td>2 (8.0)</td>
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<tr>
<td>Diagonal</td>
<td>2 (8.0)</td>
<td>2 (8.0)</td>
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<tr>
<td>RCA</td>
<td>2 (8.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Other</td>
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<tr>
<td>Type of Stent, n (%)</td>
<td>n=25</td>
<td>n=25</td>
<td></td>
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<tr>
<td>Drug eluting</td>
<td>24 (100.0)</td>
<td>25 (100.0)</td>
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<tr>
<td>Bare metal, No</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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Results - Procedural Characteristics

---

MHIF CV Grand Rounds – Dec. 3, 2018
### Results - Infarct Size by CMR, 30d

<table>
<thead>
<tr>
<th>30 Days</th>
<th>U-DR</th>
<th>U-IR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct Size, Number assessed, n (%)</td>
<td>21 (84.0)</td>
<td>19 (76.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), %</td>
<td>13.1 (11.3)</td>
<td>15.3 (11.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>10.4 (5.0-26.1)</td>
<td>13.0 (3.8-22.9)</td>
<td></td>
</tr>
<tr>
<td>LVEF, Number assessed, n (%)</td>
<td>21 (84.0)</td>
<td>19 (76.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), %</td>
<td>49.2 (12.9)</td>
<td>48.5 (13.4)</td>
<td>0.87</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>47.4 (39.4-61.0)</td>
<td>47.2 (35.9-59.9)</td>
<td></td>
</tr>
<tr>
<td>LVESV, Number assessed, n (%)</td>
<td>20 (80.0)</td>
<td>19 (76.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), ml</td>
<td>76.0 (43.9)</td>
<td>78.3 (34.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>median (IQR), ml</td>
<td>69.0 (38.7-106.0)</td>
<td>65.5 (50.2-106.0)</td>
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</tr>
<tr>
<td>LVEDV, Number assessed, n (%)</td>
<td>20 (80.0)</td>
<td>19 (76.0)</td>
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</tr>
<tr>
<td>mean (±SD), ml</td>
<td>140.9 (50.8)</td>
<td>147.9 (37.1)</td>
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</tr>
<tr>
<td>median (IQR), ml</td>
<td>147.8 (97.8-171.6)</td>
<td>149.6 (119.2-171.0)</td>
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### Results - Infarct Size by CMR, 3-5d

<table>
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<tr>
<th>3 to 5 Days</th>
<th>U-DR*</th>
<th>U-IR</th>
<th>P value</th>
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<tbody>
<tr>
<td>Infarct Size, Number assessed, n (%)</td>
<td>20 (80.0)</td>
<td>20 (80.0)</td>
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<tr>
<td>mean (±SD), %</td>
<td>16.7 (13.3)</td>
<td>19.1 (14.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>15.2 (6.7-23.9)</td>
<td>15.3 (7.4-30.5)</td>
<td></td>
</tr>
<tr>
<td>Infarct/AAR, Number assessed, n (%)</td>
<td>20 (80.0)</td>
<td>20 (80.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), %</td>
<td>44.2 (18.9)</td>
<td>51.6 (23.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>47.3 (38.8-59.5)</td>
<td>57.1 (38.4-71.8)</td>
<td></td>
</tr>
<tr>
<td>MVO, Number assessed, n (%)</td>
<td>20 (80.0)</td>
<td>20 (80.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), %</td>
<td>1.3 (2.7)</td>
<td>2.7 (4.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>0.0 (0.0-1.7)</td>
<td>0.7 (0.0-3.0)</td>
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</tr>
<tr>
<td>Salvage Index, Number assessed, n (%)</td>
<td>20 (80.0)</td>
<td>20 (80.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), %</td>
<td>55.8 (18.9)</td>
<td>48.4 (23.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>52.7 (41.3-71.0)</td>
<td>43.0 (38.2-59.8)</td>
<td></td>
</tr>
<tr>
<td>LVEF, Number assessed, n (%)</td>
<td>21 (84.0)</td>
<td>20 (80.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), %</td>
<td>44.7 (9.2)</td>
<td>46.2 (14.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>median (IQR), %</td>
<td>45.0 (37.9-52.2)</td>
<td>47.3 (32.6-54.9)</td>
<td></td>
</tr>
<tr>
<td>LVESV, n (%)</td>
<td>20 (80.0)</td>
<td>20 (80.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), ml</td>
<td>82.7 (39.4)</td>
<td>78.3 (30.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>median (IQR), ml</td>
<td>79.6 (60.6-93.8)</td>
<td>80.8 (57.8-102.9)</td>
<td></td>
</tr>
<tr>
<td>LVEDV, n (%)</td>
<td>20 (80.0)</td>
<td>20 (80.0)</td>
<td></td>
</tr>
<tr>
<td>mean (±SD), ml</td>
<td>145.1 (47.8)</td>
<td>143.1 (32.5)</td>
<td>0.88</td>
</tr>
<tr>
<td>median (IQR), ml</td>
<td>143.9 (118.0-167.4)</td>
<td>143.6 (123.7-167.4)</td>
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</table>
Results-MACCE

Table 4. MACCE at 30 Days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>U-DR n=25</th>
<th>95% CI</th>
<th>U-IR n=25</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE, n (%)</td>
<td>3 (12%)</td>
<td>[2.55%, 31.22%]</td>
<td>2 (8%)</td>
<td>[0.98%, 26.03%]</td>
<td>0.99</td>
</tr>
<tr>
<td>CV Mortality, n (%)</td>
<td>1 (4%)</td>
<td>[0.10%, 20.35%]</td>
<td>1 (4%)</td>
<td>[0.10%, 20.35%]</td>
<td>0.99</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>0 (0%)</td>
<td>[0.00%, 13.72%]</td>
<td>0 (0%)</td>
<td>[0.00%, 13.72%]</td>
<td>-</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>0 (0%)</td>
<td>[0.00%, 13.72%]</td>
<td>1 (4%)</td>
<td>[0.10%, 20.35%]</td>
<td>0.99</td>
</tr>
<tr>
<td>Major Vascular Events, n (%)</td>
<td>2 (8%)</td>
<td>[0.98%, 26.03%]</td>
<td>0 (0%)</td>
<td>[0.00%, 13.72%]</td>
<td>0.49</td>
</tr>
</tbody>
</table>

MACCE, major adverse cardiac and cerebrovascular events; U-DR, delayed reperfusion after 30 minutes of LV unloading by the Impella CP; U-IR, immediate reperfusion after placement of the Impella CP; CV, cardiovascular; TIA, transient ischemic attack; CI, confidence interval; LV, left ventricle; CP, cardiac power.

Results-Safety Parameters at 30d

Supplemental Table 5. Additional Safety Parameters at 30 days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>U-DR n=25</th>
<th>U-IR n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Renal Dysfunction, n (%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Cardiogenic Shock, n (%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hemolysis, n (%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Re-hospitalization for heart failure, n (%)</td>
<td>3^1 (12)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>LV Thrombus, n (%)</td>
<td>3 (12)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Seen only with CMR and not on d/c Echo, n (%)</td>
<td>2 (8)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>VT/VF events requiring defibrillation, n (%)</td>
<td>5 (20)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Minor vascular events, n (%)</td>
<td>5 (20)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Closure device related, n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
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<tr>
<td>Impella access related, n (%)</td>
<td>3^0 (12)</td>
<td>2^0 (8)</td>
</tr>
<tr>
<td>PCI access (radial artery), n (%)</td>
<td>1^0 (4)</td>
<td>0 (0)</td>
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</tbody>
</table>

^1: n = 24; ^0: n = 25
### Results - Bleeding Events

**Supplemental Table 6. Bleeding Events**

<table>
<thead>
<tr>
<th></th>
<th>U-DR n=25</th>
<th>U-IR n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>3a</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>3b</td>
<td>3 (12%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>3c</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients receiving transfusions, n (%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

### Results - CMR Results by STE

**Supplemental Figure 1. Cardiac Magnetic Resonance Studies by ST Segment Elevation**

- **A**: Infarct Size (as % of LV Mass)
  - Total: p = 0.33, n = 48
  - STE+4: p = 0.33, n = 48
  - STE=0: p = 0.33, n = 48
  - STE-4: p = 0.33, n = 48

- **B**: Infarct Size Area as % of RLS
  - Total: p = 0.03, n = 48
  - STE+4: p = 0.03, n = 48
  - STE=0: p = 0.03, n = 48
  - STE-4: p = 0.03, n = 48

- **C**: Accumulation (Displacement, % LV)
  - Total: p = 0.33, n = 48
  - STE+4: p = 0.33, n = 48
  - STE=0: p = 0.33, n = 48
  - STE-4: p = 0.33, n = 48
Limitations/Discussion

- **Study lacks standard of care control group (1° PCI w/o LV unloading in anterior MI)**
  - Limits ability to understand safety of approach/have confidence in no penalty of waiting
    - BARC 2 or more bleeding
    - Vascular events
    - Need to compare such things to standard of care
  - Of note, by randomized chance, ischemic time from symptom onset to unloading 24 min longer in U-IR i.e. total ischemic time in 2 arms, even after protocol, similar

- **Challenges in translation of animal studies to human side-heterogeneity of human subjects**

- **Infarct size not clinical outcome**
  - interest in endpoints like death/HF as changes
  - ? more readily motivate pursuing such therapy
Limitations/Discussion

- Criticisms exist of undertaking such studies i.e. delayed revasc & of further studying Impella, yet not wrong to consider new ways to improve STEMI outcomes
  - Too early to write off DTU concept; await impending larger trial with proper control

- Can debate where to invest effort-MCS, upstream 1° prevention, care access, enforcing OMT, pt education, risk factor management, cardiac rehab...

Practicality of Approach & ‘Buy-in’

- Expense
- Time consumption/cath lab throughput
- Vascular access challenges/complications
- Subacute device complications
- Lack of strong support from previous RCT with Impella in other contexts
  - would need compelling clinical outcome impact in larger, properly controlled trial to motivate any broad uptake of this practice
Concluding Thoughts-

*It is Important to:*

- be proud of how far we have come in STEMI care
- not waste time chasing the wrong things
  - right to critically appraise approaches/technologies being studied
- keep an open mind so that care innovation can continue to evolve and not stagnate

So-Have we Hit a Wall in STEMI Outcomes?

Time will tell...
Thank You!

• allisonhall7@gmail.com
• @A_B_Hall