Inotropes and Cardiogenic Shock
DoReMi Trial

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Evidence Base and the Knowledge Gap

• Cardiology and critical care as fields produce large amounts of low-quality evidence
• Both specialties utilize poorly-justified beliefs to guide therapy of patients in absence of robust data

A thing is not necessarily true because a man dies for it – Oscar Wilde

• NICE sugar – intensive glucose control in ICU – NNH 33 for death
• CAST I trial – suppression of PVCs post MI – NNH of 21 for death
• CAST II trial – suppression of PVCs post MI – NNH of 50 for death
• TTM2 – therapeutic hypothermia post ROSC – NNH 14 for unstable arrhythmia
• PARAMEDIC2 – epinephrine in OHCA – NNH 166 for survival with severe neurological impairment
Evidence Base and the Knowledge Gap

Success is most often achieved by those who don’t know that failure is inevitable – Coco Chanel

- We need guidelines to better reflect uncertainty of recommendations
  - Road map of future research
  - Help clinicians understand the limitations of current data

- We need randomized clinical trials that address fundamental beliefs of cardiac/critical care
  - The most complex analysis of the largest dataset cannot overcome the power of randomization

- We need iterative processes that evaluates evidence and data in context of advancing technology and care

Cardiogenic Shock

- Primary cardiac dysfunction leading to critical organ hypoperfusion
- Common presentation for both ischemic and non-ischemic HD
- High mortality and morbidity
Cardiogenic Shock

- Prognosis altering therapies are limited
- Revascularization
- Vasopressors
- Inotropes
- NO-Synthase Inhibitors
- MCS
  - IABP
  - Percutaneous VAD
  - ECLS

Combes et al. 2020 Lancet

148 studies over 25 years
2.3M patients
In-hospital/30d mortality 36%

Jung & Hibbert 2024 under review
Cardiogenic Shock

- Very little data to guide therapy in patients with CS

- DoReMi – 196 patients
- ECLS shock – 420 patients
- ECMO CS trial – 122 patients
- DANGER shock – 360 patients
- RECOVER IV – 560 patients
- DoReMi 2 – 346 patients
Cardiogenic Shock

• The Storm on the Sea of Galilee
  • Rembrandt's only sea scape
  • Stolen 1990 in Boston – remains missing
  • Estimated worth 500M

Objectives

• Understand the evidence gaps in CS management
• Understand the evidence supporting the use of inotropes in CS
• Review outcomes of DoReMi trial
• Review integration of resident training into running a clinical trial
• Future directions
Milrinone & advanced heart failure

- **PROMISE trial**
  - 1088 patients with NYHA III/IV heart failure ambulatory
  - Randomized to milrinone vs. placebo
  - Increase in mortality by 28% - worse in most symptomatic
  - Increase hospitalization, adverse events

- **OPTIME CHF**
  - 951 patients with acute exacerbation of chronic heart failure
  - 48 hour infusion of milrinone or placebo
  - No difference in death or median number of days in hospital
  - Increased hypotension and new atrial arrhythmias

Guidelines in Cardiogenic Shock

- **ESC**
  - IIb – C – continues inotropes may be considered in patients with low output and hypoperfusion as a bridge to MCS or transplant

- **ACC/AHA HF**
  - IIa – B – Patients with advanced HF who are eligible for and awaiting MCS/transplant – inotrope therapy as bridge is reasonable
  - IIb – B – In select patients who are ineligible for MCS/transplant – as a palliative therapy
  - III – B – In patients with HF – long-term use of either continuous or intermittent for reasons other than above is potentially harmful
Background in CS

- Medical management relies on vasopressors/inotropes but prospective, randomized data is lacking
- Milrinone and dobutamine are among the two most widely used agents, but clinical equipoise remains

Mathew et al. 2019 CIM

CAPITAL Do-Re-Mi

- Milrinone versus Dobutamine in the Treatment of Cardiogenic Shock

Methodology

- Randomized clinical trial, with blinding of both physicians and patients
- Stratified by LV/BiV versus RV dysfunction
- Drug titration by clinical evaluation

Composite primary end point of:
- All cause in-hospital mortality
- Resuscitated CA
- Need for transplant or MCS
- Non-fatal MI
- TIA or stroke
- New initiation of RRT

Secondary Outcomes

**Efficacy**
- Individual components of primary outcome
- Total time on inotropes
- Need for, and total days on, NIV and/or IMV
- Incidence of AKI
- Normalization of lactate
- Arrhythmia requiring medical team intervention

**Safety**
- Arrhythmia requiring medical intervention
- Need for, or an increase, in oral or IV anti-arrhythmic therapy
- Ventricular arrhythmias
- Need for, or an increase, in vasopressor therapy
Results

- Patients reflected population
- Average age 70
- Predominantly white, male
- LVEF 25%
- 92% SCAI C,D shock
Primary composite outcome

47 (49%) in milrinone versus 52 (54%) in dobutamine (RR 0.90; CI 0.69-1.19; P=0.47)

All-cause in-hospital mortality

35 (37%) in milrinone versus 41 (43%) in dobutamine (RR 0.85; CI 0.60-1.21; P=0.38)
Secondary outcomes

- No difference in any outcome measured

Results

- No identified subgroup with divergent results
Hemodynamic outcomes and biomarkers

Limitations

- Only in-hospital outcomes were evaluated and differences in outcomes may exist beyond the index hospitalization, as seen in the SHOCK trial

- Our study was designed to be pragmatic, and replicate clinical practice, in which shock is most often defined clinically, rather than hemodynamically

- Our study found a mortality rate of 40%, which is similar to trials that used hemodynamic parameters for enrollment
Conclusions

• We were unable to demonstrate a difference between Milrinone and Dobutamine in the primary composite outcome or in important secondary outcomes

• Selection of inotropes could reasonably be based on physician comfort, cost and response to therapy

CAPITAL Do-Re-Mi

• Milrinone versus Dobutamine in the Treatment of Cardiogenic Shock

BB use and inotrope selection

- Impact of baseline beta-blocker use on inotrope response and clinical outcomes in cardiogenic shock: a subgroup analysis of the DOREMI trial


Background

- Classic teaching and some observational data suggests Milrinone may be preferred in patients on BB
- ESC guidelines recommend against Dobutamine if BBs have been used
Clinical outcomes

Primary composite outcome, mortality and cardiac arrest

Conclusions

• BB therapy in the preceding 24hrs to developing CS was **protective** from cardiac arrest and death in the early resuscitation period

• BB therapy was not predictive of response to inotrope therapy either in hemodynamic or clinical parameters

• Modulating arrhythmic risk in CS may offer mechanisms to reduce adverse outcomes in CS patients
Biomarkers and outcomes

- Lactate Clearance as a surrogate for mortality in CS: Insights from the DOREMI trial


Background

- Risk stratification with selection of high-risk biomarkers for CS patients can be used clinically for therapy augmentation and in research as validated surrogates

- Lactate clearance has been suggested as a potential therapeutic target for CS management, but validation studies are few

- Unclear if inotrope selection preferentially impacts LC in populations of CS
Results

- 75% of patients had a baseline lactate available before initiation of therapy

- Clinical characteristics differed between survivors and non survivors
  - Higher MAPs
  - Age
  - Less mechanical ventilation
  - Vasoactive agents use was lower amongst survivors but when adjusted for where no longer predictive

Results

- MV model strongest predictor of mortality at all time points out to 24 hours – lactate clearance
Conclusions

• LC is a strong independent predictor of survival at all time points from 8-36 hours.

• Complete lactate normalization by 8 hours increases chance of survival 4-fold.

• Lactate normalization/clearance may be used as a surrogate end-point in exploratory studies for early CS therapies.
Valvular HD in CS

- Significant valvular dysfunction and outcomes in cardiogenic shock: a substudy of the DOREMI trial

- Parlow, S., Weng, W., Di Santo, P., Jung, R., Simard, T., Goh, CY, Chan, V., Labinaz, M., Froeschl, M., Mathew, R., Hibbert, B.

Valvular HD and CS

- Concomitant valvular lesions in patients with CS is common
  - 40% of patients in CS had one significant valvular lesion
  - 5% significant AS, 21% significant MR, 17% significant TR
Conclusions

• Valvular HD is common in unrestricted populations of CS

• Presence of significant AS or significant MR is associated with a 2-fold and 60% increased risk of mortality

• Valve disease is a potential novel therapeutic target in CS

Lessons learned from DoReMi

• Pragmatic trials in “difficult” populations can be run in a low cost/high yield fashion

• Fundamental questions in critical care cardiology should be addressed despite prior beliefs

• Integrating residents in trial development and execution is a high yield endeavor
MR as a therapeutic target in CS

Results

- Age 70 years
- 87% SCAI C-E
- Predominantly male
- Individual patient data on 141
Results

• In hospital mortality of 15.6%, 90 day mortality 29.5%

- MR reduction strongly associated with improved outcomes
- Differences may exist between patients in whom MR reduction can be achieved and in those in whom it cannot
- Efficacy was excellent (device success 87% - 2+ or less) and no adverse procedural events noted
Mitral regurgitation as a therapeutic target

- **TEER**
  - TVT registry tracks cases in USA
  - Reports baseline characteristics
  - Reports procedural outcomes

**Transcatheter Edge-to-Edge Mitral Valve Repair in Patients With Severe Mitral Regurgitation and Cardiogenic Shock**

Simard et al. JACC 2022

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MR and TEER – TVT analysis

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Simard et al. JACC 2022
MR and TEER – TVT analysis

• TEER in CS
  • In-hospital mortality of 9.1% vs. 16.4% in case of device failure
  • By 1 year 20% absolute reduction in mortality with procedural success

Conclusions

• Mitraclip therapy in selected patients is safe with no major procedural complications and has similar efficacy to other treated populations

• Observed mortality is significantly lower than expected and successful MR reduction is strongly associated with improved outcome

• A better procedural outcome is predictive of better clinical outcome

• A randomized clinical trial is needed to confirm these findings

Simard et al. JACC 2022
Future Directions

- DOREMI – 2
  - Multicenter trial of inotrope vs. placebo in the early resuscitation of stage C/D cardiogenic shock
  - Establish safety/necessity of inotropes in CS

- MINOS
  - Multicenter trial of mitraclip for stage C/D shock in patients with \( \geq 3+ \) MR

DoReMi -2

- DOREMI – 2 (n = 346)
  - Inotrope (mil or dob) vs. placebo in initial resuscitation – 12 hours
  - Inclusion criteria
    - SCAI C/D shock and over 18 years of age
  - Exclusion criteria
    - OHCA
    - On inotrope in preceding 24 hours
    - Severe obstructive valve lesion/dynamic outflow obstruction

- Primary Outcome
  - All cause mortality in hospital or sustained hypotension, lactate >3.5 at 6 hours, need for MCS, arrhythmia leading to emergent CV or cardiac arrest
MINOS trial

- **MINOS (n=144)**
  - Mitraclip vs. standard of care in patients with SCAI C/D shock and 3+ or greater MR
- **Inclusion criteria**
  - SCAI C/D shock
  - Or unable to wean inotrope/ventilator support
- **Exclusion criteria**
  - Revascularization in preceding 48 hours
  - Degenerative MR and surgical candidate
  - Prior intervention on mitral valve/IE or left sided mass/thrombus
- **Primary Outcome**
  - In hospital all cause mortality, transplant, implantation of durable LVAD or discharge on palliative inotropes

Questions?

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