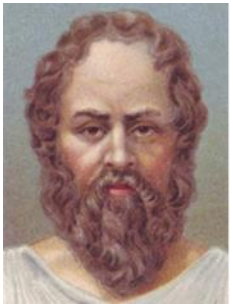
Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock – the DOREMI study

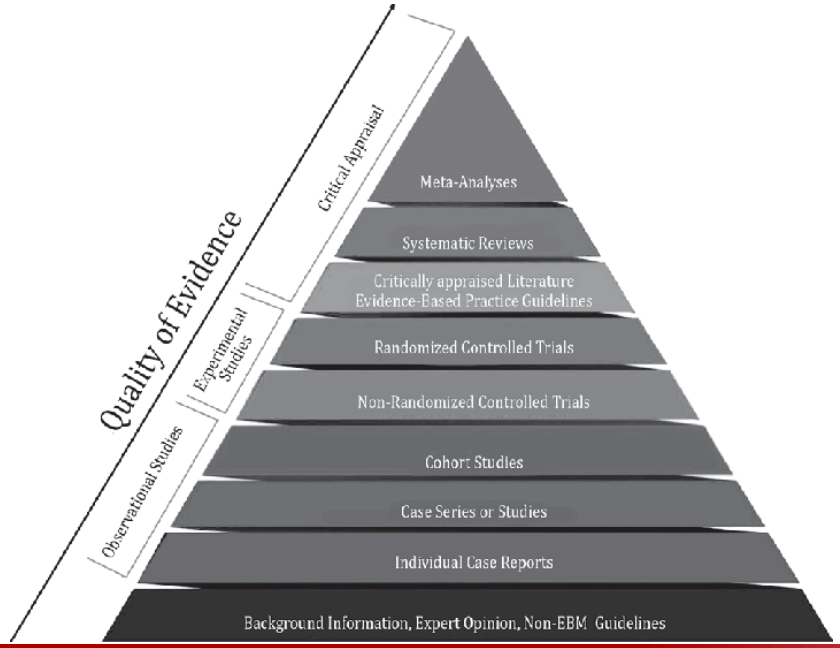
Benjamin Hibbert MD PhD FRCPC
Division of Cardiology, University of Ottawa Heart Institute
Cellular and Molecular Medicine, University of Ottawa
CArdiovascular **P**ercutaneous **I**ntervention **T**ri**AL** Group

Evidence Base and the Knowledge Gap



The only true wisdom is in knowing you known nothing - Socrates

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



Evidence Base and the Knowledge Gap

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**
  - **Funding should be linked to evidence based practices and research resources should be directed at answering fundamental questions**

Cardiogenic Shock

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

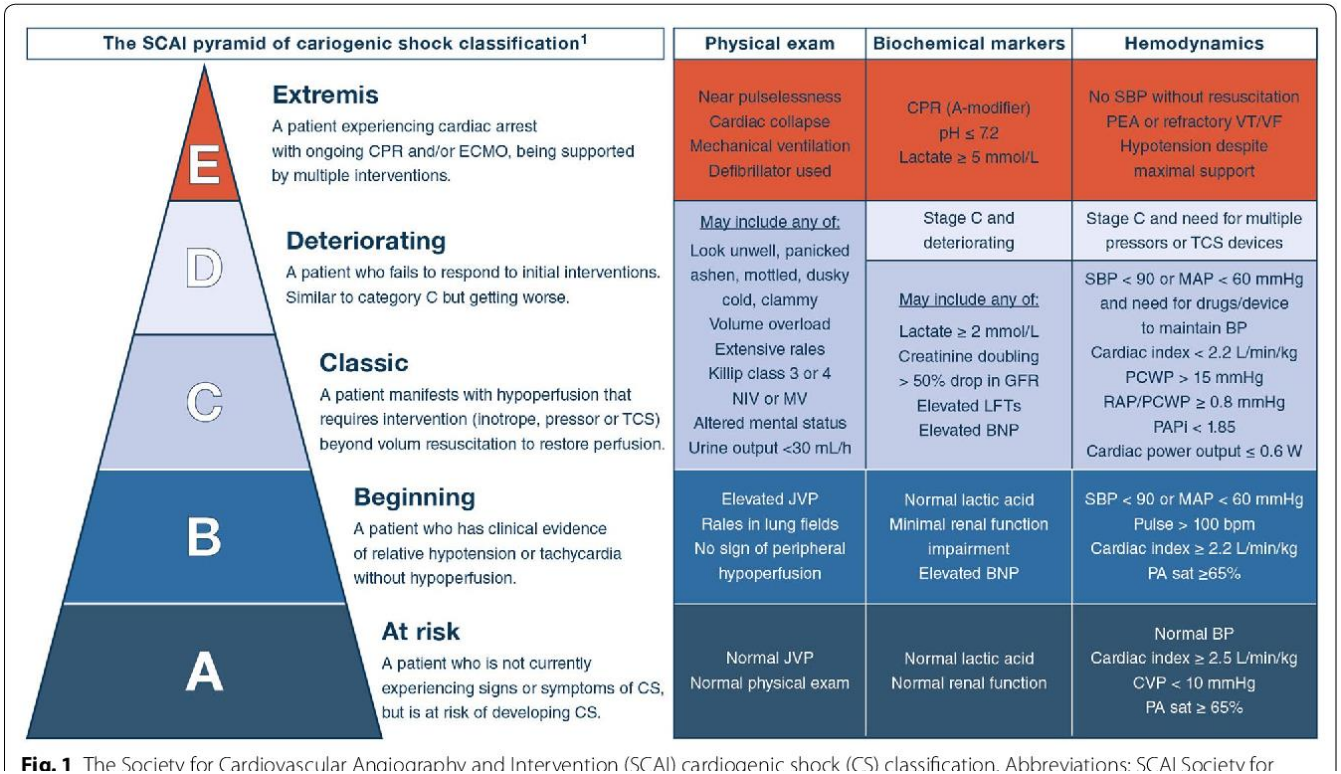
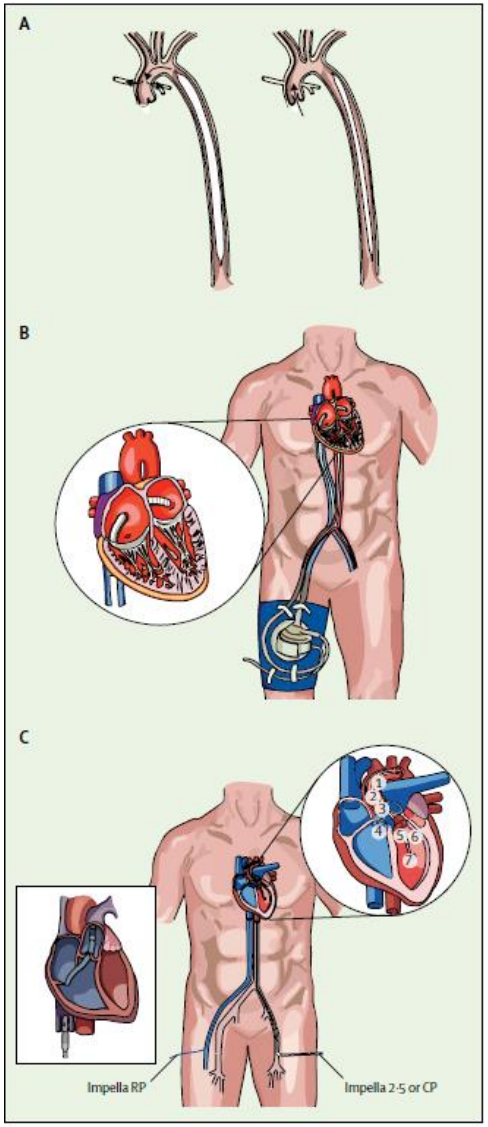


Fig. 1 The Society for Cardiovascular Angiography and Intervention (SCAI) cardiogenic shock (CS) classification. Abbreviations: SCAI Society for

De Chambrun et al. 2020 ICM

Cardiogenic Shock

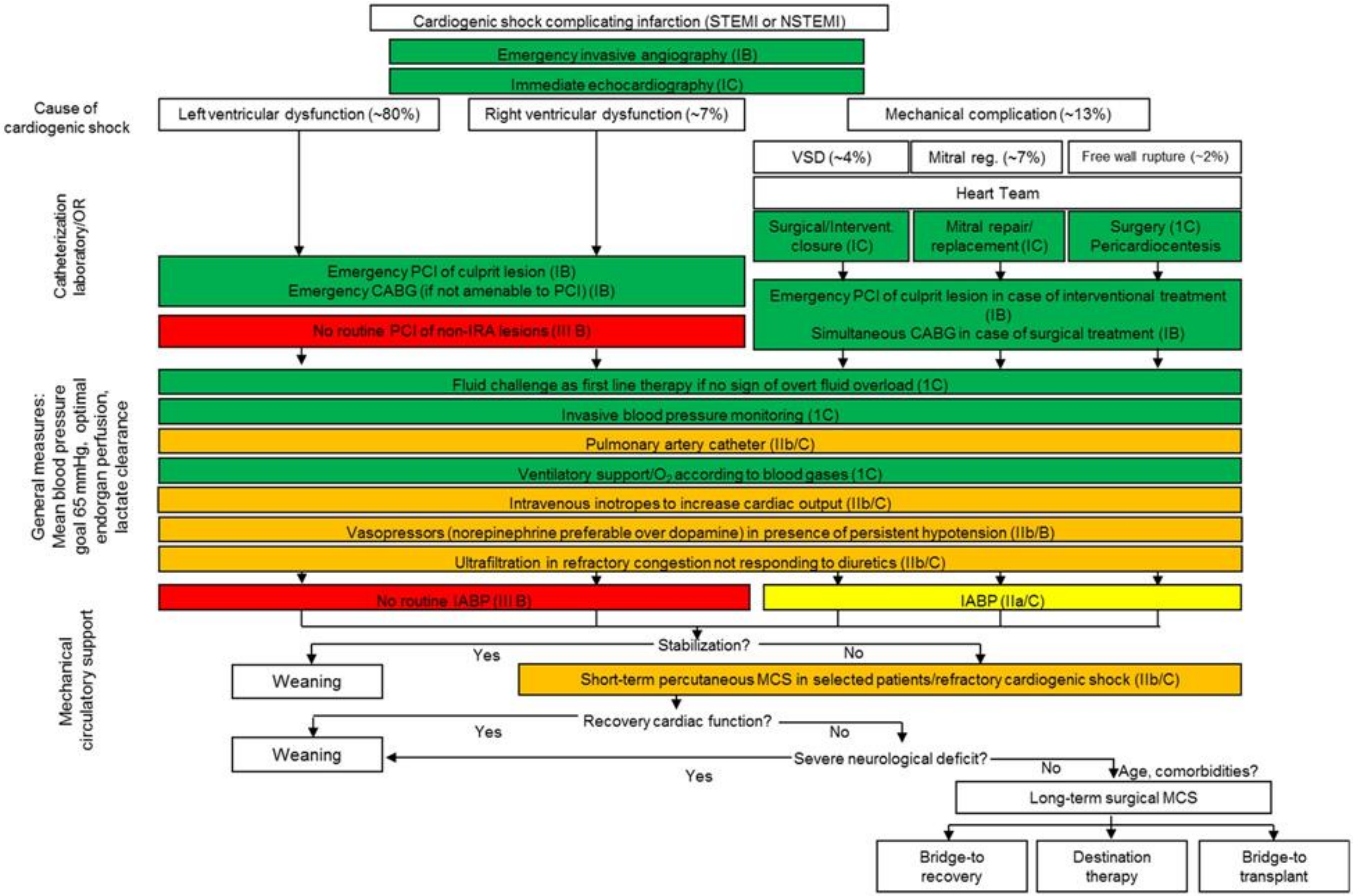
- Prognosis altering therapies are limited
- Revascularization
- Vasopressors
- Inotropes
- NO-Synthase Inhibitors
- MCS
  - IABP
  - Percutaneous VAD
  - ECLS



Combes et al. 2020 Lancet

Cardiogenic Shock

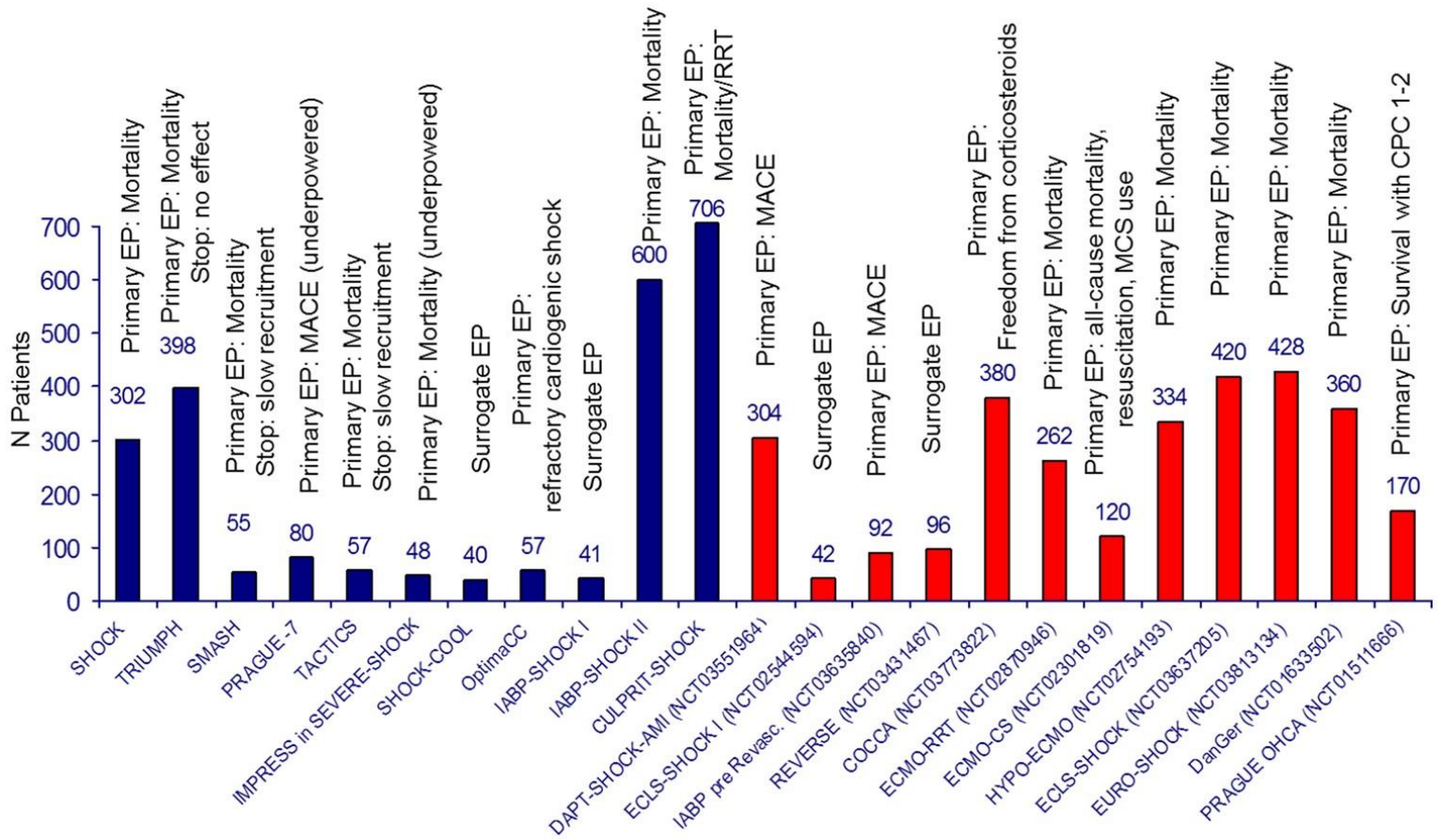
- **Very little data to guide therapy in patients with CS**



Thiele et al. 2020 EHJ

Cardiogenic Shock

- **Very little data to guide therapy in patients with CS**

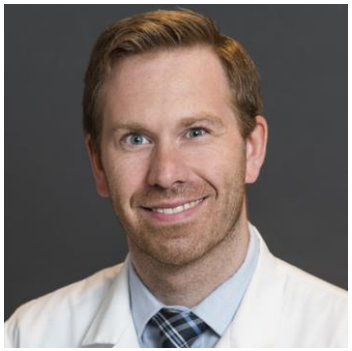


Thiele et al. 2020 EHJ

Cardiogenic Shock

Resident/Fellow led Research

Resident research curriculum

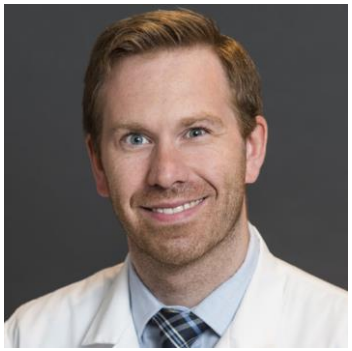


- Formalized competency based curriculum
- Phase 1
  - 1 rotation – all C1s – 4 weeks
  - Didactic lectures in study design, basic statistical analyses, regulatory frame work/training, ethic board processes
- Phase 2
  - Tailored – up to 6 months of electives in research
  - Objective/goal directed rotations – evaluated by research block supervisor
- Phase 3
  - Competency demonstrated through publications, presentations
- Clinician scientist track – CIP – 1 year of training MSc/Phd

Resident research curriculum

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 70, NO. 21, 2017

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jacc.2017.10.032

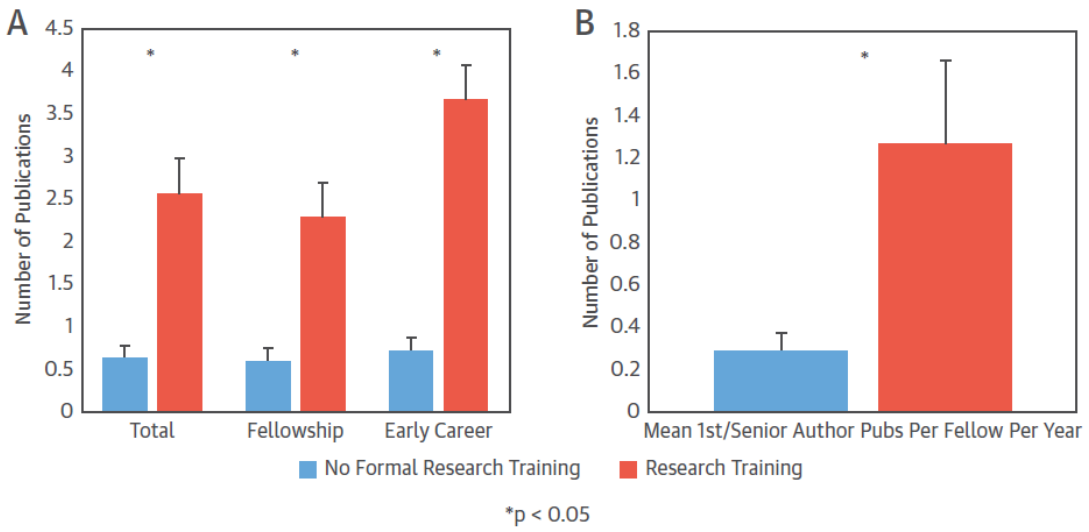


FELLOWS-IN-TRAINING & EARLY CAREER PAGE

Effect of a Formalized Research Curriculum on Fellows-in-Training and Early Career Research Productivity

Jeffrey A. Marbach, MBBS, MSc,[a] Robert Moreland, MD,[b] Trevor Simard, MD[a,c]

FIGURE 1 Research Productivity of Fellows Who Received and Did Not Receive Research Training



Resident initiated/led trials

- RAPID GENE/STEMI – Dr Jason Roberts – Lancet
- CAPITAL OPTI-CROSS – Dr Ali Pourdjabbar – Thr & Hemostasis
- CAPITAL CHILL – Dr Ronnen Maze – ACC/under review
- CAPITAL iRADIAL – Dr Pietro Di Santo – CMAJ
- CAPITAL iRADIAL2 – Dr Simon Parlow – recruiting
- CAPITAL RAPTOR – Dr Pietro Di Santo – 1800 patient RCT – recruiting
- CAPITAL Do-Re-MI trial – Dr Rebecca Mathew - NEJM

CAPITAL Do-Re-Mi

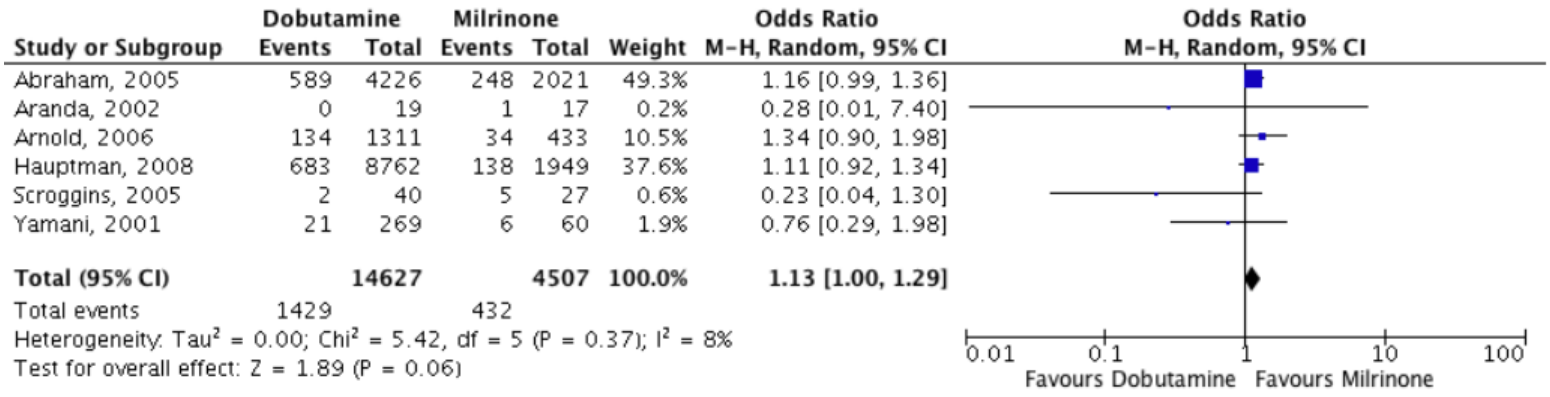
- **Milrinone versus Dobutamine in the Treatment of Cardiogenic Shock**

- ***Mathew, R., Di Santo, P., Jung, R., Marbach, J., Hutson, J., Simard, T., Ramirez, F.D., Harnett, D.T., Merdad, A., Almufleh, A., Weng, W., Abdel-Razek, O., Fernando, S.,*** Kyeremanteg, K., Bernick, J., Wells, G.A., Chan, V., Froeschl, M., Labinaz, M., Le May, M., ***Russo, J.,*** Hibbert, B.

Background

- 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

FIGURE 2A.

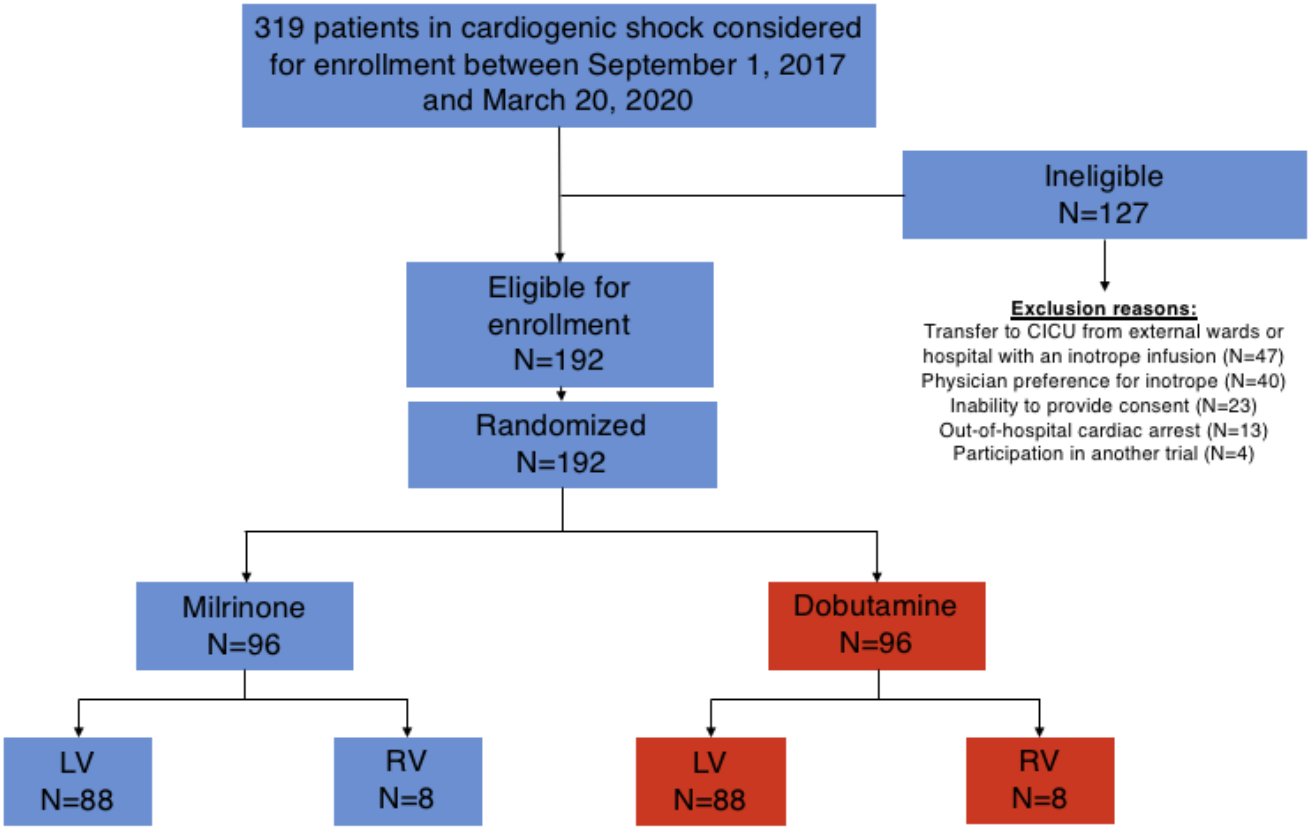


Forest plot of in-hospital mortality with dobutamine versus milrinone inotrope therapy.

Methodology

- Randomized clinical trial, with blinding of both physicians and patients
- Hypothesis was that Milrinone would reduce the composite outcome compared to Dobutamine
- Drug titration by clinical evaluation using a standardized scale
- 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*

Patient recruitment



Baseline Characteristics

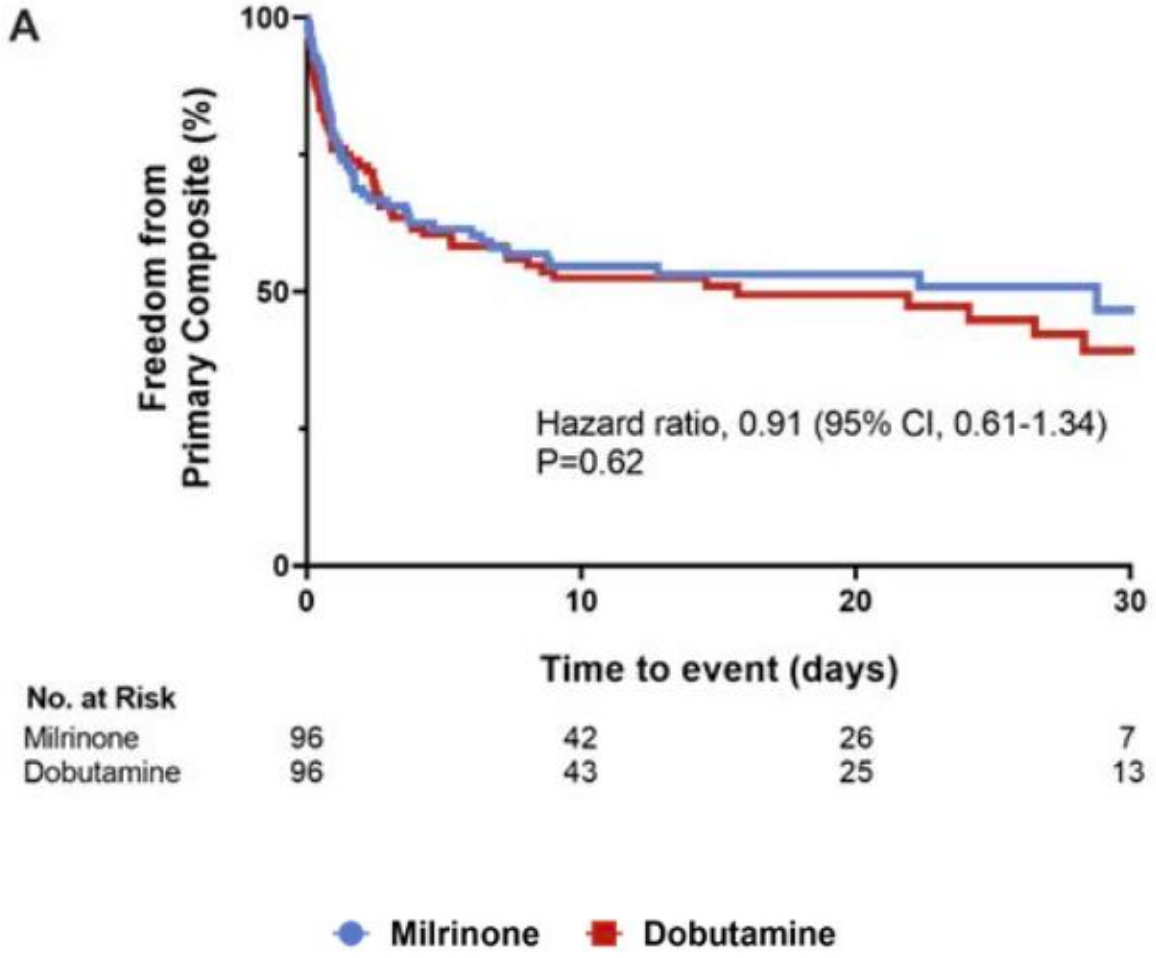
Table 1. Baseline Characteristics of the Participants.*

Characteristic	Milrinone (N=96)	Dobutamine (N=96)
Age — yr	68.9±13.8	72.0±11.3
Female sex — no. (%)	36 (38)	34 (35)
Median body-mass index (IQR)†	26.4 (23.7–31.0)	26.0 (22.5–30.5)
Race — no. (%)‡		
White	86 (90)	79 (82)
Non-White	10 (10)	17 (18)
Left ventricular function		
Median left ventricular ejection fraction (IQR) — %	25 (20–40)	25 (20–40)
Cause of ventricular dysfunction — no. (%)		
Ischemic	66 (69)	62 (65)
Nonischemic	30 (31)	33 (34)
Coexisting conditions — no. (%)		
Previous myocardial infarction	39 (41)	29 (30)
Previous percutaneous coronary intervention	30 (31)	19 (20)
Previous coronary-artery bypass grafting	20 (21)	19 (20)
Previous stroke or transient ischemic attack	13 (14)	15 (16)
Atrial fibrillation	49 (51)	46 (48)
Chronic kidney disease§	38 (40)	40 (42)
Chronic liver disease	6 (6)	7 (7)
Chronic obstructive pulmonary disease	11 (11)	14 (15)
SCAI cardiogenic shock class — no. (%)¶		
A	0	0
B	6 (6)	5 (5)
C	77 (80)	78 (81)
D	10 (10)	12 (12)
E	3 (3)	1 (1)
Time from admission to the cardiac ICU to randomization — hr	23.4±92.6	17.9±50.6

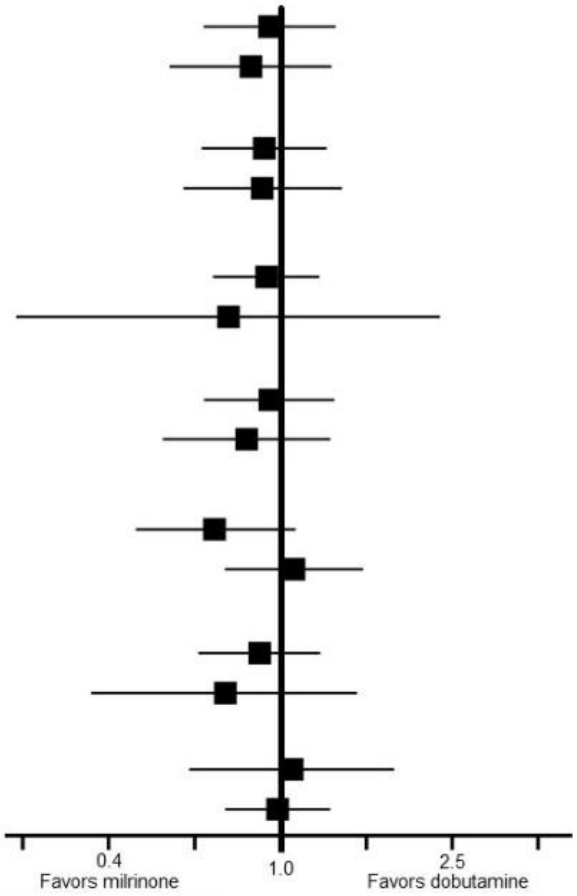
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ICU denotes intensive care unit, and IQR interquartile range.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the participants.
§ Chronic kidney disease was defined as an estimated glomerular filtration of less than 60 ml per minute per 1.73 m^2 of body-surface area, in accordance with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.
¶ Society for Cardiovascular Angiography and Interventions (SCAI) class A indicates a risk of the development of cardiogenic shock in the absence of signs or symptoms; class B, compensated shock with relative hypotension; class C, hypoperfusion that requires an initial set of interventions to restore perfusion; class D, deteriorating shock after interventions have failed to stabilize the patient's condition; and class E, cardiovascular collapse with ongoing cardiopulmonary resuscitation.

Primary composite outcome

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

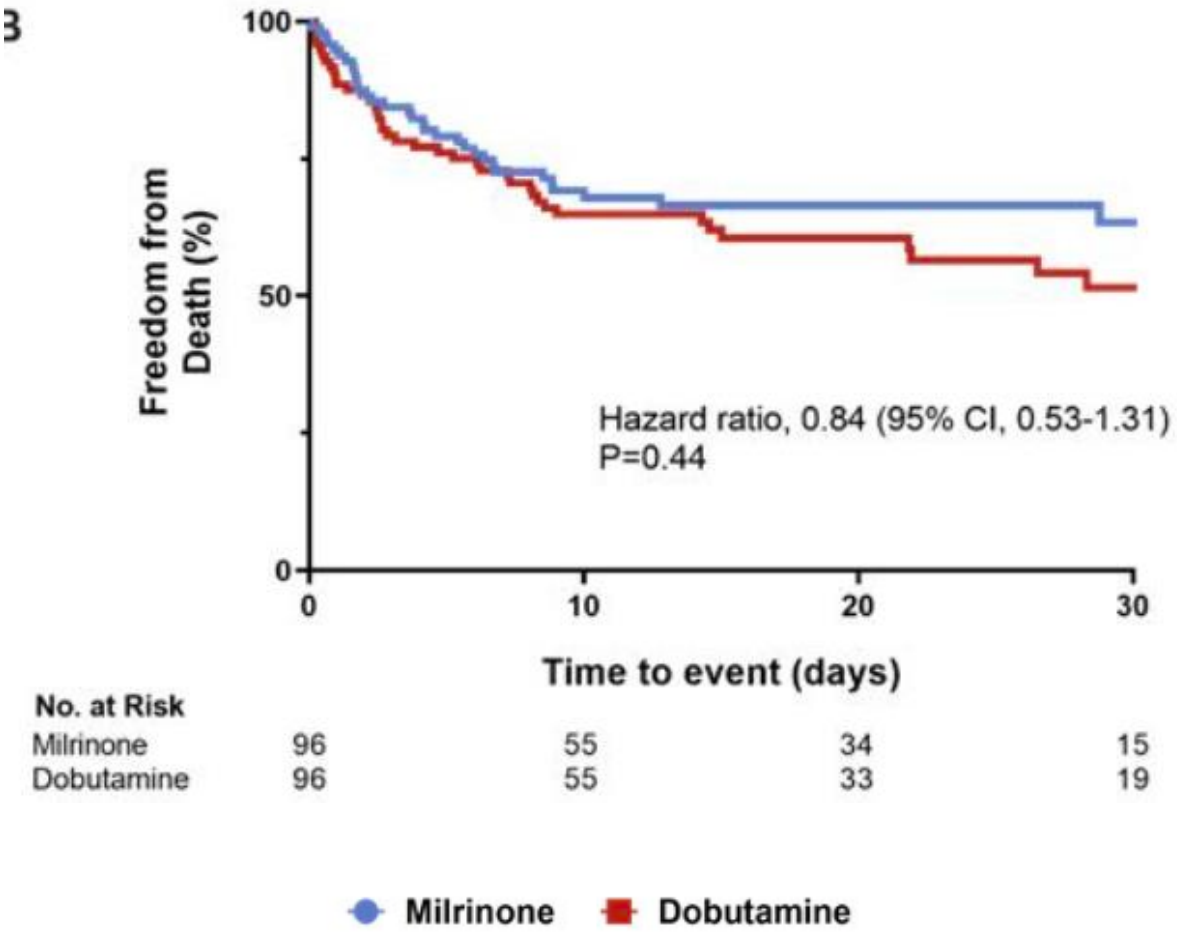


	Milrinone	Dobutamine	Relative Risk (95% CI)	p-value	Interaction p-value
Sex					
Males	29/60 (48.3%)	32/62 (51.6%)	0.94 (0.66-1.34)	0.71	0.73
Females	18/36 (50.0%)	20/34 (58.8%)	0.85 (0.55-1.31)	0.46	
Age					
≥75	24/40 (60.0%)	27/41 (65.9%)	0.91 (0.65-1.27)	0.59	0.98
<75	23/56 (41.1%)	25/55 (45.5%)	0.90 (0.59-1.38)	0.64	
Ventricular subgroup					
Left/biventricular	44/88 (50.0%)	48/88 (54.5%)	0.92 (0.69-1.22)	0.55	0.73
Right ventricular	3/8 (37.5%)	4/8 (50.0%)	0.75 (0.24-2.33)	1.00*	
Etiology of left ventricular dysfunction					
Ischemic	32/66 (48.5%)	32/62 (51.6%)	0.94 (0.66-1.33)	0.72	0.65
Non-ischemic	15/30 (50.0%)	20/33 (60.6%)	0.83 (0.53-1.30)	0.40	
Severity of left ventricular dysfunction					
Mild/moderate	17/38 (44.7%)	23/36 (63.9%)	0.70 (0.46-1.08)	0.10	0.14
Severe	29/57 (50.9%)	28/59 (47.5%)	1.07 (0.74-1.55)	0.71	
Baseline renal dysfunction					
Mild/moderate	35/78 (44.9%)	39/77 (50.6%)	0.89 (0.64-1.23)	0.47	0.65
Severe	5/9 (55.6%)	6/8 (75%)	0.74 (0.36-1.50)	0.62*	
Concomitant vasopressor use at inotrope initiation					
No	21/58 (36.2%)	14/41 (34.1%)	1.06 (0.61-1.83)	0.83	0.80
Yes	25/37 (67.6%)	38/55 (69.1%)	0.98 (0.74-1.30)	0.88	



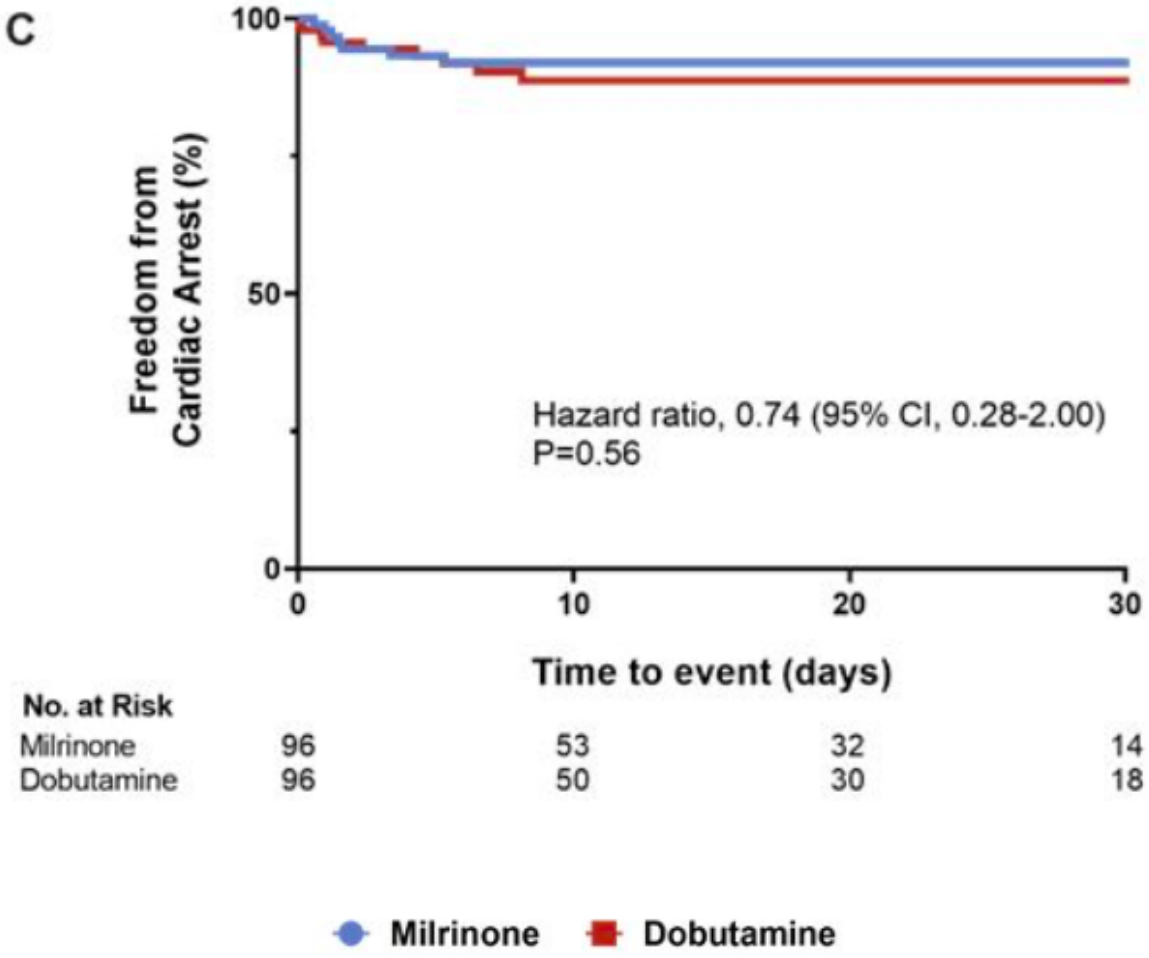
All-cause in-hospital mortality

35 (37%) in milrinone versus 41 (43%) in dobutamine



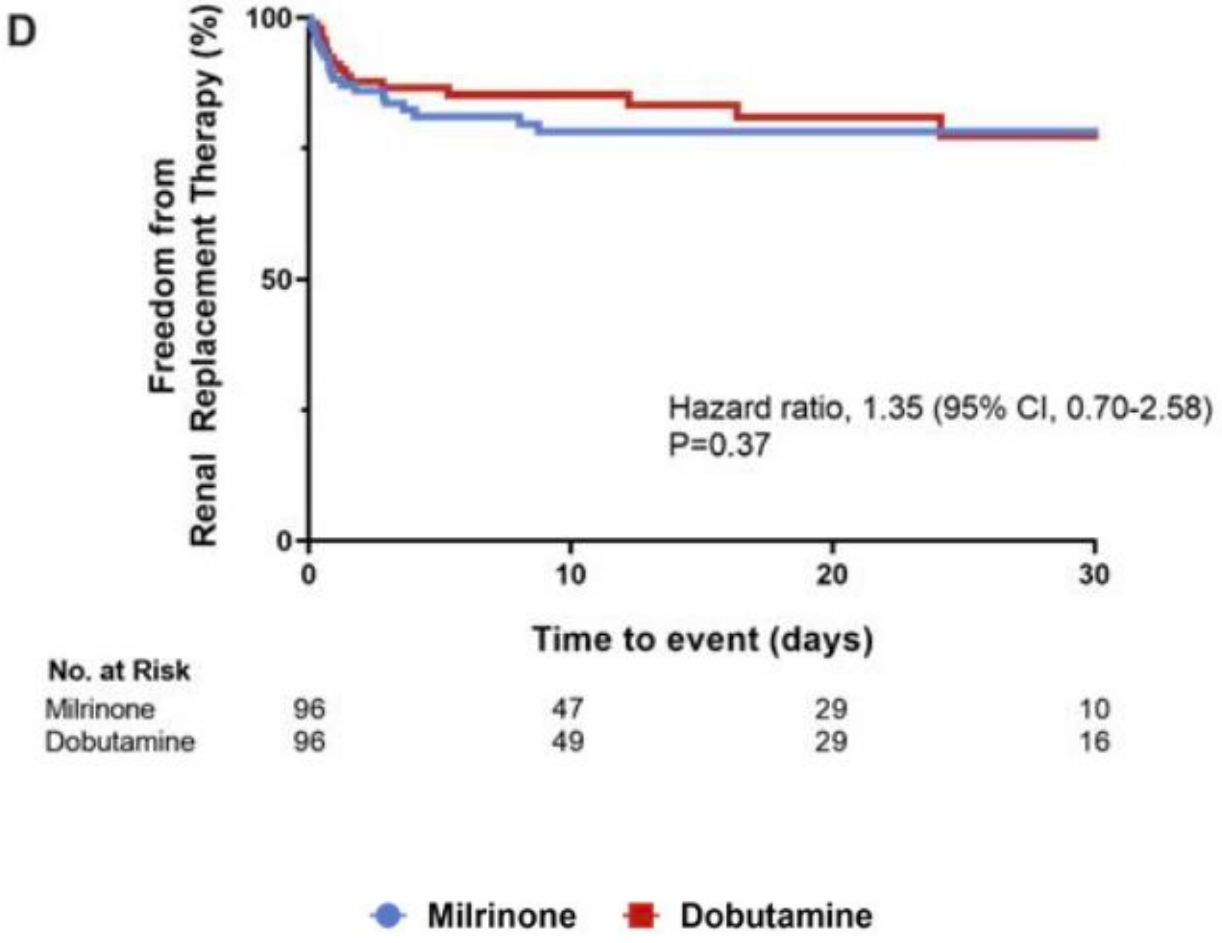
Resuscitated cardiac arrest

7 (7%) in milrinone versus 9 (9%) in dobutamine

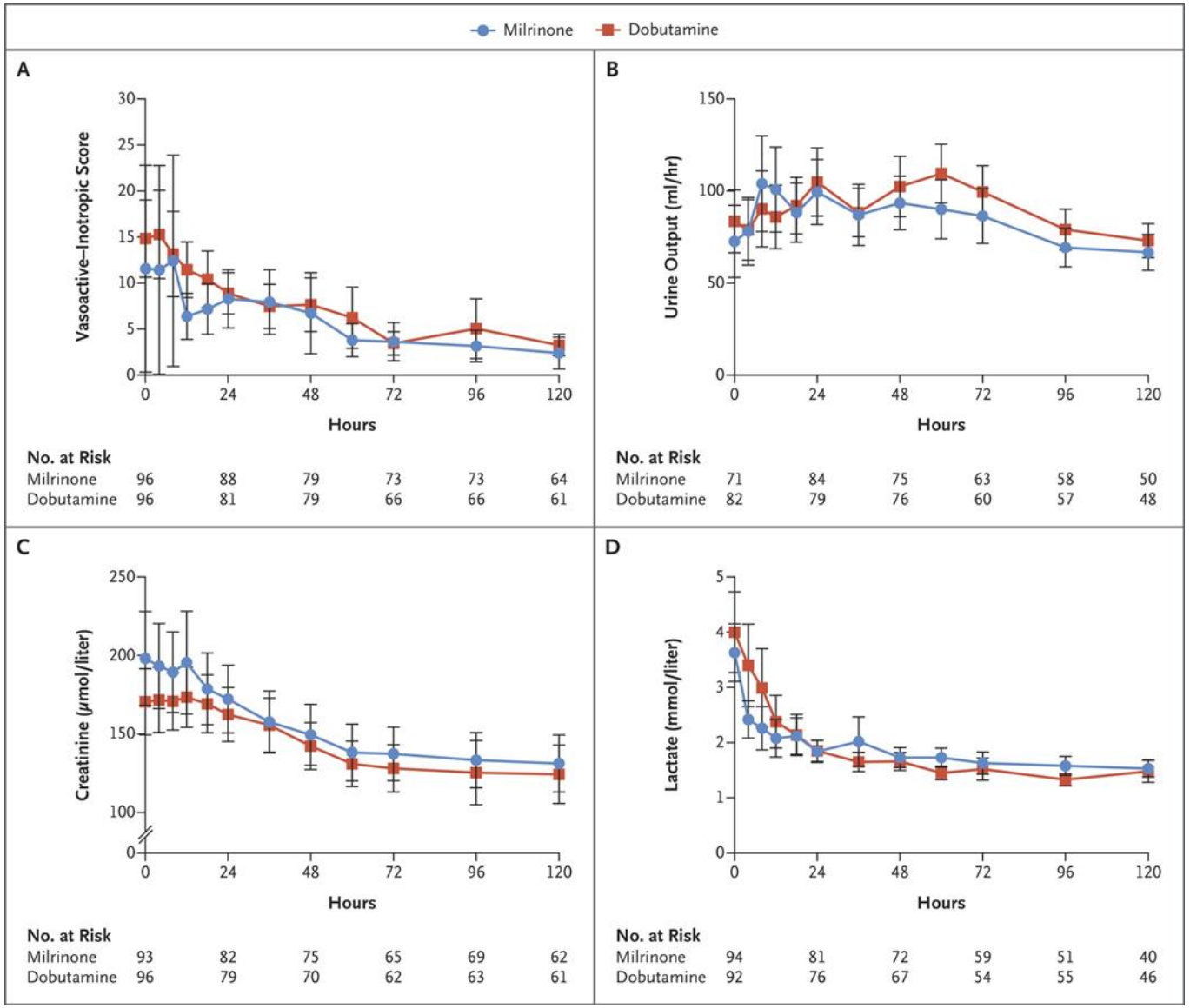


Initiation of renal replacement therapy

21 (22%) in milrinone versus 16 (17%) in dobutamine



Key Clinical and Biochemical Measures



Conclusions

- In contrast to the hypothesis we did not identify a significant advantage of Milrinone over Dobutamine in the composite primary outcome or important secondary outcomes

- There were no differences in important surrogate markers of resuscitation including lactate clearance, HR, BP or vasoactive support

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

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

- Power calculation was based on a large treatment effect for a combined outcome. Thus, we are underpowered to detect smaller differences as reflected in the wide CI

CAPITAL Do-Re-Mi

American Heart Association.
Resuscitation Science

The NEW ENGLAND JOURNAL of MEDICINE

- **Milrinone versus Dobutamine in the Treatment of Cardiogenic Shock**

- ***Mathew, R., Di Santo, P., Jung, R., Marbach, J., Hutson, J., Simard, T., Ramirez, F.D., Harnett, D.T., Merdad, A., Almufleh, A., Weng, W., Abdel-Razek, O., Fernando, S.,*** Kyeremanteg, K., Bernick, J., Wells, G.A., Chan, V., Froeschl, M., Labinaz, M., Le May, M., ***Russo, J.,*** Hibbert, B.

Do-Re-MI subpapers

- Biomarker identification and validation
- Impact of BB at baseline (Crit Care)
- Impact of achieved MAP on outcomes (EHJ ACC)
- Impact of inotropes on clinical and hemodynamic outcomes in renal patients
- Impact of baseline arrhythmia on outcomes and management of patients with CS
- Impact of valvular disease on outcomes of CS: insights from the DOREMI trial
- Impact of ACS on outcomes in the DOREMI trial
- Lactate clearance as a prognostic marker in cardiogenic shock

CS – current evidence

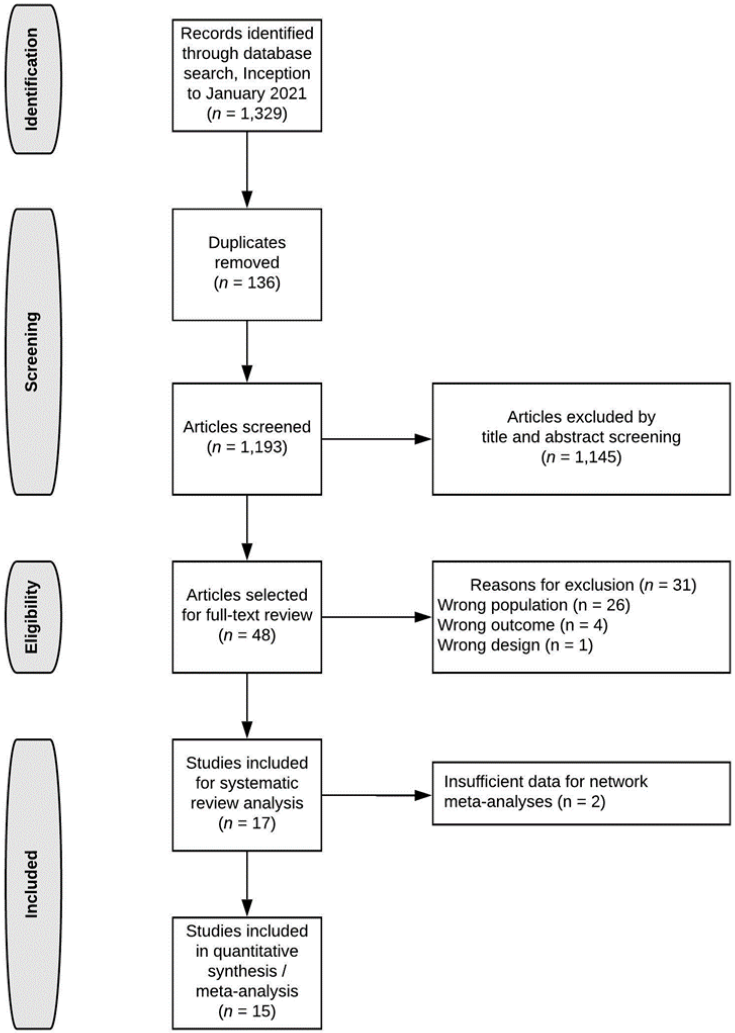
- **Inotropes, Vasopressors and Mechanical Circulatory Support for the Treatment of Cardiogenic Shock – A network meta-analysis**

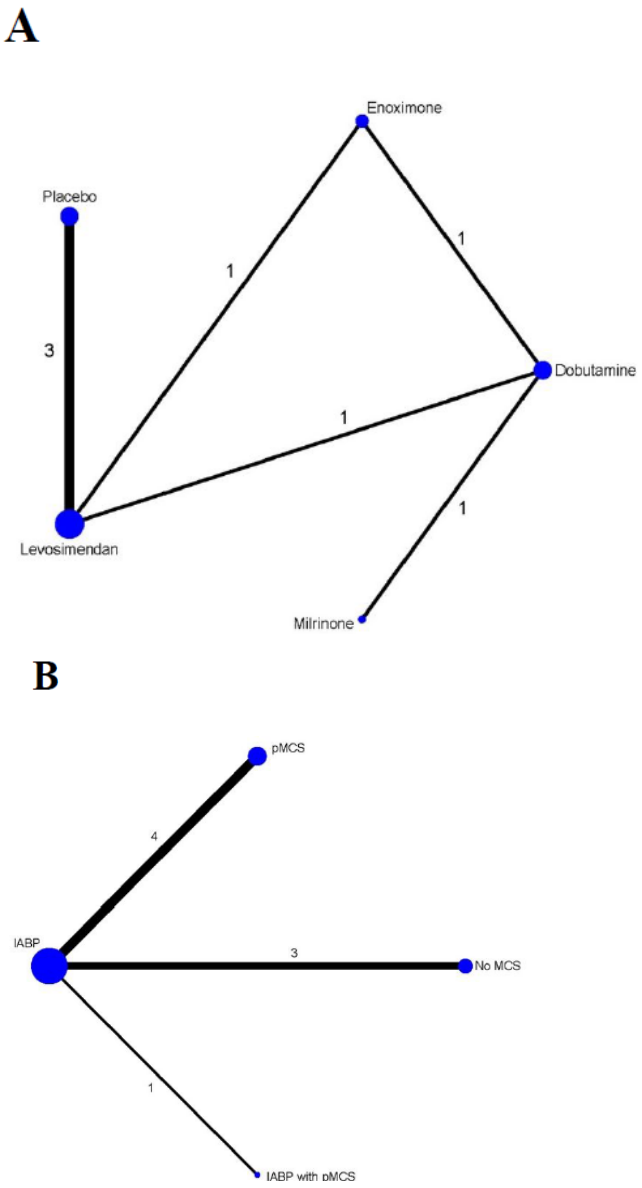
- ***Fernando, S., Mathew, R.,*** Sadeghirad, B., Brodie, D., Belley-Cote, E., Thiele, H., van Diepen, S., Fan, E., ***Di Santo, P., Simard, T., Russo, J.J.,*** Tran, A., Levy, B., Combes, A., Hibbert, B.*, Rochwerg, B* (co-senior)

Background

- A robust evidence base of randomized trials and their impact on clinical outcomes in CS is lacking
- Therapies are largely restricted to vasopressors, inotropes, MCS +/- revascularization
- There remains no definitive therapies that improve prognosis in CS

Results


Identification
Screening
Eligibility
Included
Records identified through database search, Inception to January 2021 (n = 1,329)
Duplicates removed (n = 136)
Articles screened (n = 1,193)
Articles excluded by title and abstract screening (n = 1,145)
Articles selected for full-text review (n = 48)
Reasons for exclusion (n = 31)
Wrong population (n = 26)
Wrong outcome (n = 4)
Wrong design (n = 1)
Studies included for systematic review analysis (n = 17)
Insufficient data for network meta-analyses (n = 2)
Studies included in quantitative synthesis / meta-analysis (n = 15)


A
Enoximone
Placebo
Dobutamine
Levosimendan
Milrinone
1
1
3
1
1
B
pMCS
IABP
No MCS
IABP with pMCS
4
3
1

Results

- No placebo controlled trials of vasopressors

Comparison	Direct	*GRADE*	Indirect	*GRADE*	Network	*GRADE*
	OR (95% CI)		**OR (95% CI)**		OR (95% CI)	
Levosimendan vs Placebo[A-B]	0.53 (0.33,0.87)	HIGH	No indirect estimate		0.53 (0.33, 0.87)	HIGH
Enoximone vs Dobutamine[A-B]	1.00 (0.05,18.92)	VERY LOW[1,3]	3.05 (0.62,15.08)		2.36 (0.58,9.63)	VERY LOW[1,2]
Levosimendan vs Dobutamine[A-B]	0.83 (0.44,1.59)	MODERATE[3]	0.27 (0.01,7.29)		0.80 (0.42, 1.50)	LOW[2]
Milrinone vs Dobutamine[C]	0.77 (0.43,1.37)	MODERATE[3]	No indirect estimate		0.77 (0.43, 1.37)	LOW[2,3]
Levosimendan vs Enoximone[C]	0.27 (0.06,1.18)	LOW[1,3]	0.83 (0.04,16.85)		0.34 (0.09,1.26)	LOW[1,3]
Dobutamine vs Placebo	No direct estimate		0.67 (0.30, 1.49)	MODERATE	0.67 (0.30, 1.49)	LOW[2]
Enoximone vs Placebo	No direct estimate		1.58 (0.39,6.45)	LOW	1.58 (0.39,6.45)	VERY LOW[1,2]
Milrinone vs Placebo	No direct estimate		0.52 (0.19,1.39)	MODERATE	0.52 (0.19,1.39)	LOW[2]
Milrinone vs Enoximone	No direct estimate		0.33 (0.07, 1.49)	VERY LOW	0.33 (0.07, 1.49)	VERY LOW[1,2]

Results

- No benefit of MCS on mortality

Comparison	Direct	*GRADE*	Indirect	GRADE	Network	GRADE
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
IABP vs No MCS	0.94 (0.69,1.28)	LOW[1,2]	No Indirect estimate		0.94 (0.69, 1.28)	LOW[1,2]
IABP vs pMCS	0.98 (0.51,1.88)	LOW[1,2]	No Indirect estimate		0.98 (0.51, 1.88)	LOW[1,2]
IABP + pMCS vs IABP	5.91 (0.23,151.15)	VERY LOW[1,3]	No indirect estimate		5.91 (0.23,151.15)	VERY LOW[1,3]
pMCS vs No MCS	No Direct estimate		0.96 (0.47, 1.98)	LOW	0.96 (0.47, 1.98)	LOW[1,2]
IABP + pMCS vs pMCS	No Direct estimate		5.78 (0.21, 157.66)	VERY LOW	5.78 (0.21, 157.66)	VERY LOW[1,3]
IABP + pMCS vs no MCS	No Direct estimate		5.56 (0.21, 144.20)	VERY LOW	5.56 (0.21, 144.20)	VERY LOW[1,3]

- Significant increased risk of bleeding

Comparison	Direct	GRADE	Indirect	GRADE	Network	GRADE
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
IABP vs No MCS	1.00 (0.69,1.45)	LOW[1,2]	No Indirect estimate		1.00 (0.69,1.45)	LOW[1,2]
IABP vs pMCS	0.20 (0.06,0.69)	LOW[1,3]	No Indirect estimate		0.20 (0.06,0.69)	LOW[1,3]
IABP + pMCS vs IABP	28.50 (1.12,723.38)	VERY LOW[1,4]	No indirect estimate		28.50 (1.12,723.38)	VERY LOW[1,4]
pMCS vs No MCS	No Direct estimate		4.91 (1.38, 17.44)	LOW	4.91 (1.38, 17.44)	LOW[1,3]
IABP + pMCS vs pMCS	No Direct estimate		5.81 (0.18, 184.98)	VERY LOW	5.81 (0.18, 184.98)	VERY LOW[1,4]
IABP + pMCS vs no MCS	No Direct estimate		28.49 (1.09, 744.72)	VERY LOW	28.49 (1.09, 744.72)	VERY LOW[1,4]

Conclusions

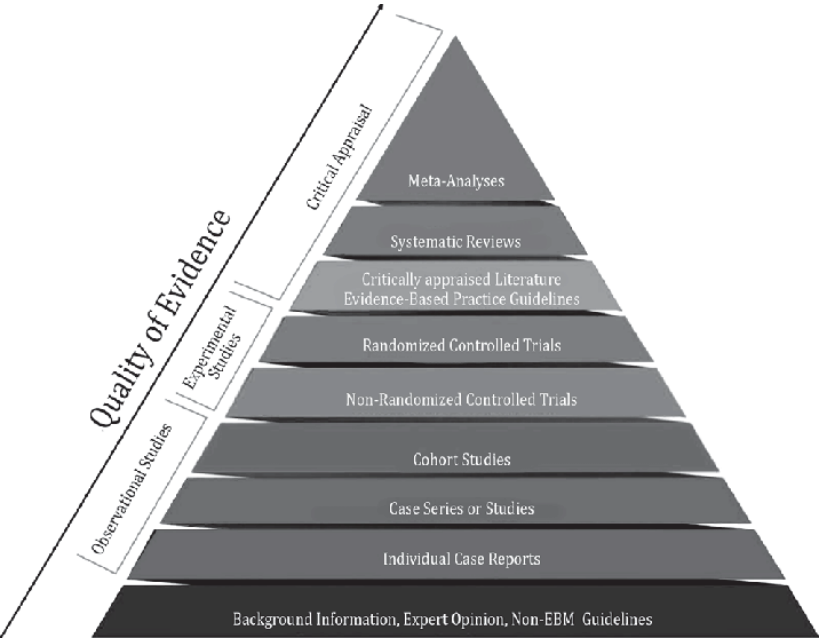
- Levosimendan may reduce mortality compared to placebo among patients with low severity cardiogenic shock
- Dobutamine and Milrinone do not have proven benefit relative to each other or to placebo
- MCS likely increases bleeding and does not appear to impact mortality

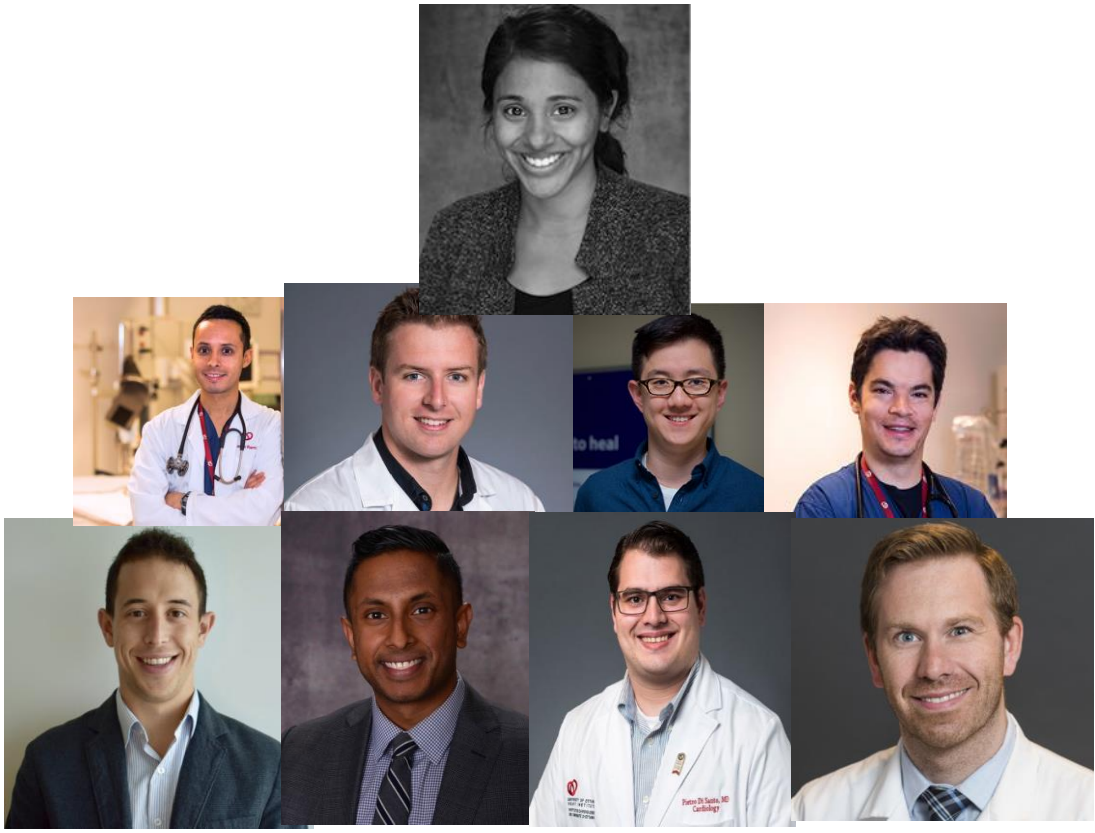
Future Directions

- CAPITAL 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

- CAPITAL MINOS
  - Multicenter international trial of mitraclip for stage C/D shock in patients with >/= 3+ MR

Questions?





Benjamin Hibbert MD PhD FRCPC

Division of Cardiology, University of Ottawa Heart Institute
CArdiovascular **P**ercutaneous **I**ntervention **T**ri**AL** Group