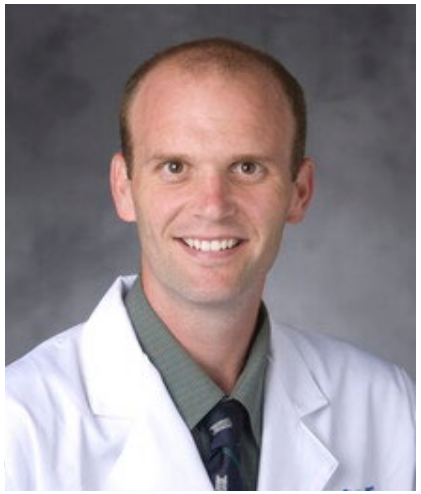
Williams Lecture: The randomized registry trial: A model for cost effective and efficient multi-center trials.

Kevin Hill

Moderators:
Tara Karamlou
Nicolas Madsen



The PC^4/PAC^3 Spring Conference
April 28th-30th

STRESS Trial funded by National Center for Advancing Translational Sciences

CORD-CHD funded by National Heart Lung and Blood Institute

PC^4 PAC^3

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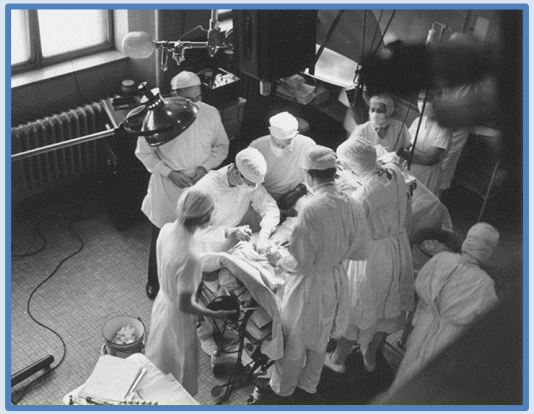
OUR FIELD HAS A LONG HISTORY OF INNOVATION

1936: First ever CHD surgery

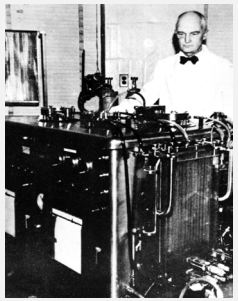
Robert Gross and Lorraine Sweeney

1944: First palliation of complex CHD



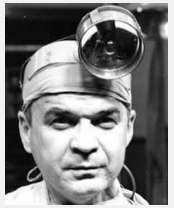
Vivien Thomas, Helen Taussig and Alfred Blalock
1944: Introduced the BTTS to treat "blue babies"

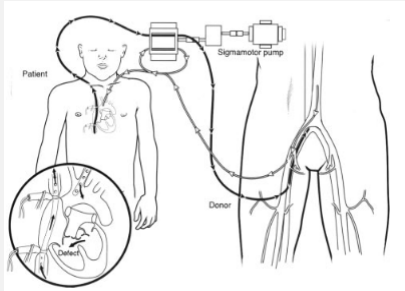
1950's: Origins of CPB

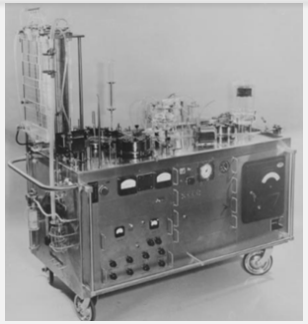


John Gibbon
1953: 1st open heart surgery using bubble oxygenator

C. Welton Lillehei
1955: Human Cross Circulation







John Kirklin
1955: Mechanical CPB

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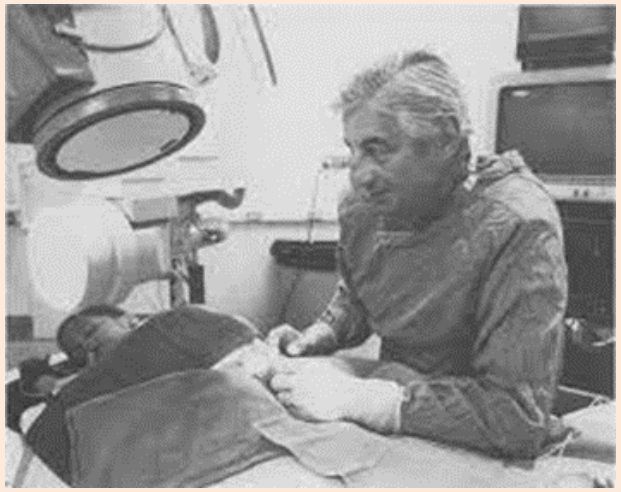
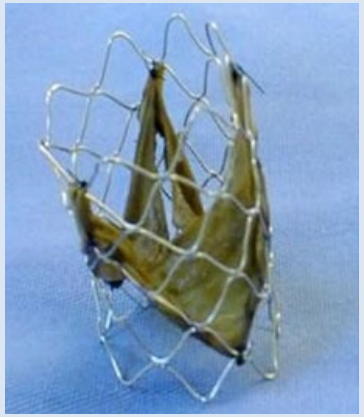
OUR FIELD HAS A LONG HISTORY OF INNOVATION

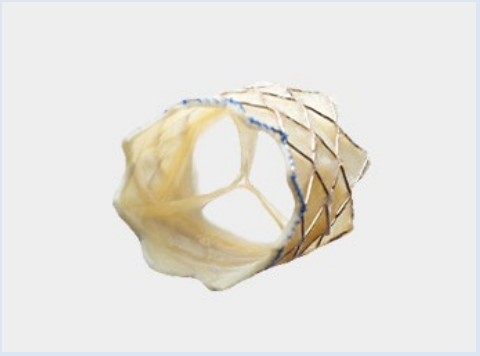
1951: First ever interventional cardiac cath



William Rashkind

2000: First ever trans-catheter valve implantation





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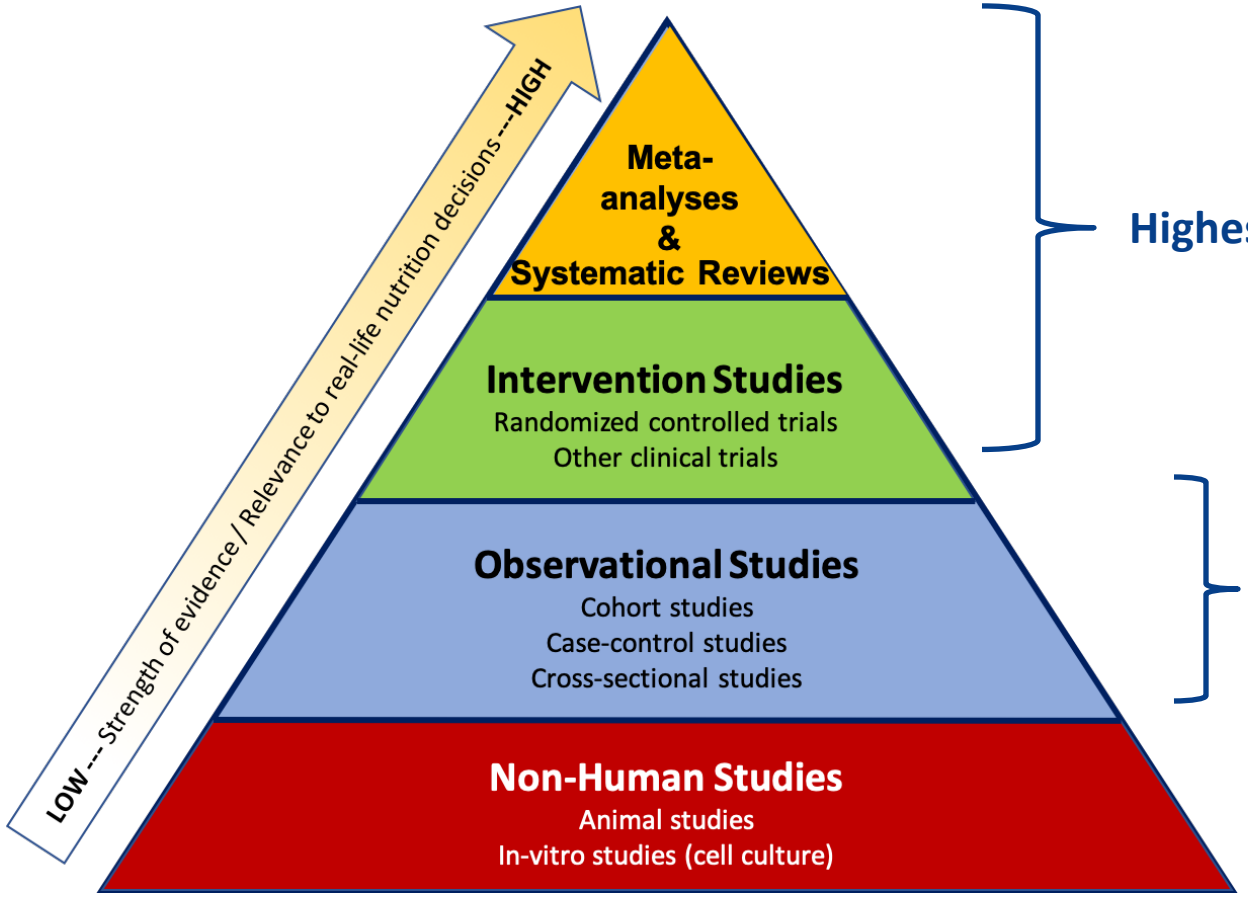
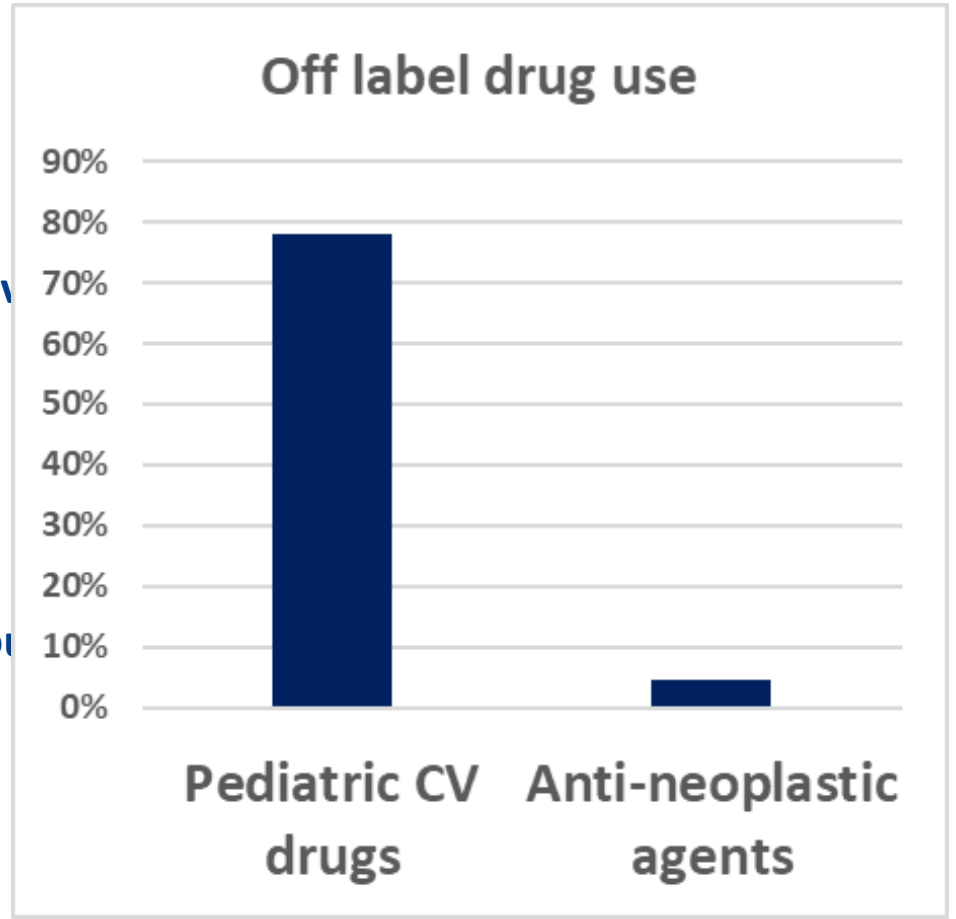
AND YET…





Pasquali et al. **Off-Label Use of Cardiovascular Medications in Children Hospitalized With Congenital and Acquired Heart Disease. Circulation: Cardiovascular Quality and Outcomes. 1 (2) 2008**

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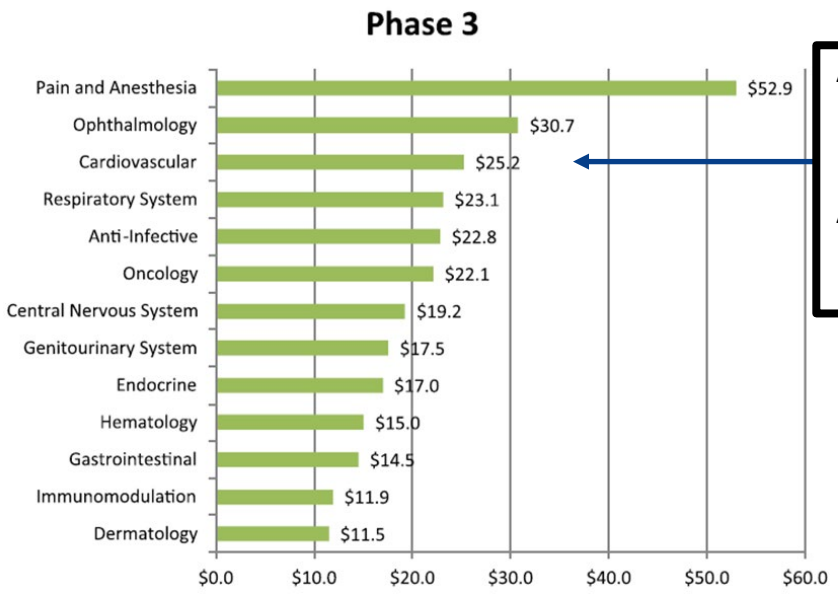
CLINICAL TRIAL BARRIERS

HIGH COST

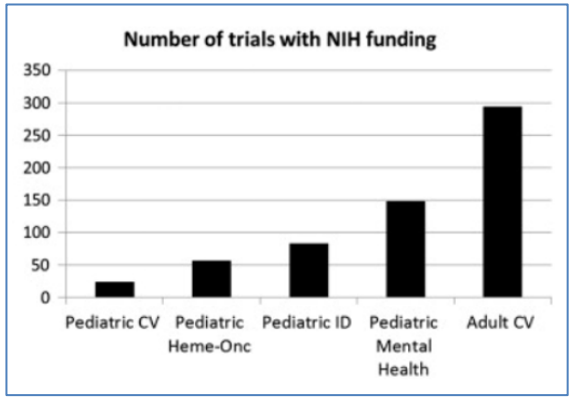


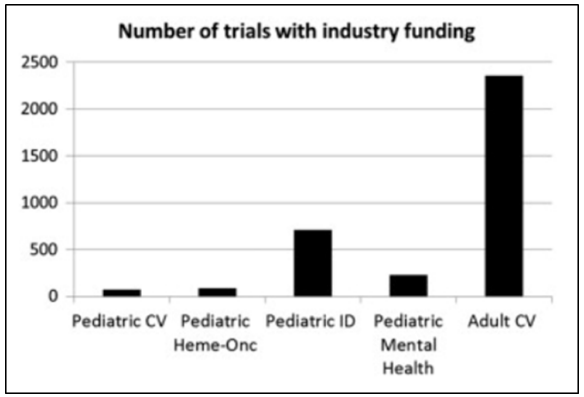
Average cost for a phase III cardiac RCT: $25.2 million.

Average cost per patient enrolled: $13,400

Setkaya et al. **Key cost drivers of pharmaceutical clinical trials in the United States.** Clin Trials. 2016 Apr;13(2):117-26.

LIMITED FUNDING





Hill, KD et al. **Characteristics of pediatric cardiovascular clinical trials registered on ClinicalTrials.gov.** Am Heart J. 2014 Jun;167(6):921-9.e2.

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CLINICAL TRIAL BARRIERS

CHALLENGES CONSENTING AND ENROLLING CHILDREN

Lessons Learned from a Pediatric Clinical Trial: The Pediatric Heart Network Angiotensin Converting Enzyme Inhibition in Mitral Regurgitation Study

Jennifer S. Li, MD MHS[1], Steven D. Colan, MD[2], Lynn A. Sleeper, Sc.D[2], Jane W. Newburger, MD MPH[3], Victoria L. Pemberton, RNC MS[4], Andrew M. Atz, MD[5], Meryl S. Cohen, MD[6], Fraser Golding, MD[7], Gloria L. Klein[2], Ronald V. Lacro, MD[3], Elizabeth Radojewski, RN[7], Marc E. Richmond, MD[8], and L. LuAnn Minich, MD[9] for the Pediatric Heart Network Investigators

Am Heart J. 2011 Feb; 161(2): 233–240.

Target enrollment: 92

10 sites, 18 months, $408,950 → 8 participants

The Study of Antiarrhythmic Medications in Infancy (SAMIS)

A Multicenter, Randomized Controlled Trial Comparing the Efficacy and Safety of Digoxin Versus Propranolol for Prophylaxis of Supraventricular Tachycardia in Infants

Shubhayan Sanatani, MD; James E. Potts, PhD; John H. Reed, MD, MPH; J. Philip Saul, MD; Elizabeth A. Stephenson, MD; Karen A. Gibbs, RN, CCRP; Charles C. Anderson, MD; Andrew S. Mackie, MD; Pamela S. Ro, MD; Svjetlana Tisma-Dupanovic, MD; Ronald J. Kanter, MD; Anjan S. Batra, MD; Anne Fournier, MD; Andrew D. Blaufox, MD; Harinder R. Singh, MBBS, MD, DCH; Bertrand A. Ross, MD; Kenny K. Wong, MD; Yaniv Bar-Cohen, MD; Brian W. McCrindle, MD, MPH; Susan P. Etheridge, MD

Circulation: Arrhythmia and Electrophysiology
Volume 5, Issue 5, October 2012; Pages 984-991
https://doi.org/10.1161/CIRCEP.112.972620

Target enrollment: 220

19 sites, 4 years → 61 participants

Congenital Heart Disease

A Multicenter, Randomized Trial Comparing Heparin/Warfarin and Acetylsalicylic Acid as Primary Thromboprophylaxis for 2 Years After the Fontan Procedure in Children

Paul Monagle, MD, MSc, MBBS,* Andrew Cochrane, MD,* Robin Roberts, MSc,† Cedric Manlhiot, BSc,‡ Robert Weintraub, MBBS,* Barbara Szechtman, BA,† Marina Hughes, DPHIL.,§ Maureen Andrew, MD,‡ Brian W. McCrindle, MD, MPH,‡ for the Fontan Anticoagulation Study Group

JACC Vol. 58, No. 6, 2011
August 2, 2011:645–51

Target enrollment: 224

6 sites, 5 years → 111 participants

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CLINICAL TRIAL BARRIERS

CHALLENGES INTERPRETING RESULTS IN OUR HETEROGENEOUS PATIENT POPULATION

Carvedilol for Children and Adolescents With Heart Failure

A Randomized Controlled Trial

Robert E. Shaddy, MD; Mark M. Boucek, MD; Daphne T. Hsu, MD; et al

Table 2. Primary End Point and Prespecified Subgroup Analyses

	No. (%) of Participants		
	Placebo (n = 54)	Combined Carvedilol (n = 103)	*P* Value
All patients			
Improved	30 (56)	58 (56)	.74
Unchanged	8 (15)	20 (19)	
Worsened	16 (30)	25 (24)	
Dilated cardiomyopathy	(n = 33)	(n = 60)	
Improved	18 (55)	41 (68)	.24
Unchanged	6 (18)	6 (10)	
Worsened	9 (27)	13 (22)	
Congenital heart disease with systemic left ventricle	(n = 6)	(n = 17)	
Improved	2 (33)	8 (47)	.29
Unchanged	1 (17)	6 (35)	
Worsened	3 (50)	3 (18)	
Congenital heart disease without systemic left ventricle	(n = 15)	(n = 26)	
Improved	10 (67)	9 (35)	.14
Unchanged	1 (7)	8 (31)	
Worsened	4 (27)	9 (35)	
Systemic left ventricle[a]	(n = 39)	(n = 77)	
Improved	20 (51)	49 (64)	b
Not improved	19 (49)	28 (36)	
Without systemic left ventricle[c]	(n = 15)	(n = 26)	
Improved	10 (67)	9 (35)	b
Not improved	5 (33)	17 (65)	

Pts with a systemic LV tended to improve, pts with a systemic RV tended to get worse

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SUMMARY

- ❑ High costs
- ❑ Limited funding
- ❑ Difficult to enroll
- ❑ Challenging to interpret

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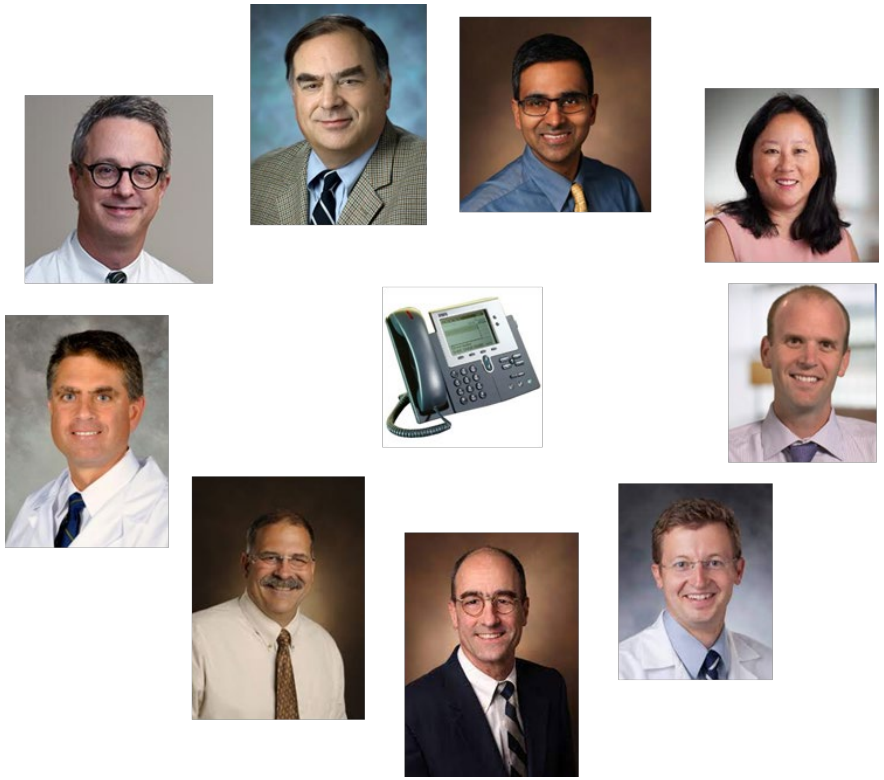
IMPROVING FEASIBILITY OF PEDIATRIC CARDIOLOGY TRIALS

Cheaper, Easier, More efficient, More interpretable



- **Leverage existing resources**
  - Reduce costs, improve efficiency
- **Pragmatic trials**
  - Test hypotheses in real world settings
  - Reduce costs
- **Novel endpoints**
  - Improve study power → smaller "N"

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HISTORY OF CLINICAL RESEARCH IN PEDIATRIC CARDIOLOGY

Data from >96% of children undergoing a cardiac intervention in the U.S. are entered into a CHD registry

Pediatric Cardiac Critical Care Consortium

PAC3 Pediatric Acute Care Cardiology Collaborative

The Society of Thoracic Surgeons Established 1964

UNOS℠

Congenital Cardiac Anesthesia Society CCAS

American College of Cardiology | Quality Improvement for Institutions

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Can we leverage our registry infrastructure to make trials more efficient and cost effective?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2013 VOL. 369 NO. 17

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D., Amra Kåregren, M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertson, M.D., Lennart Sandhall, M.D., Iwar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harnek, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

7259/11709 pts undergoing STEMI in Sweden enrolled

Avg cost per pt enrolled = $50

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

"The randomized registry trial represents a technology that transforms existing standards, procedures, and cost structures."

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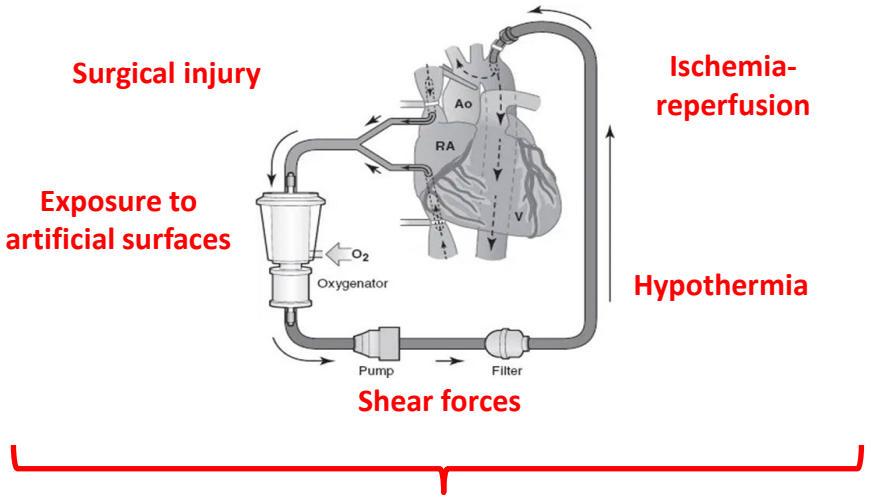
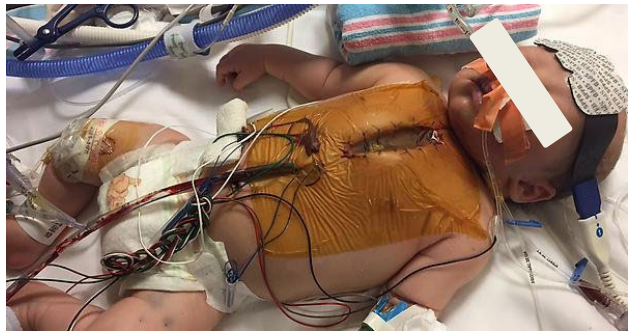
BACKGROUND: PERIOPERATIVE CORTICOSTEROIDS

Used to treat CPB-related systemic inflammatory response





Safety and efficacy not established in children

Registry Data (2011-'16)

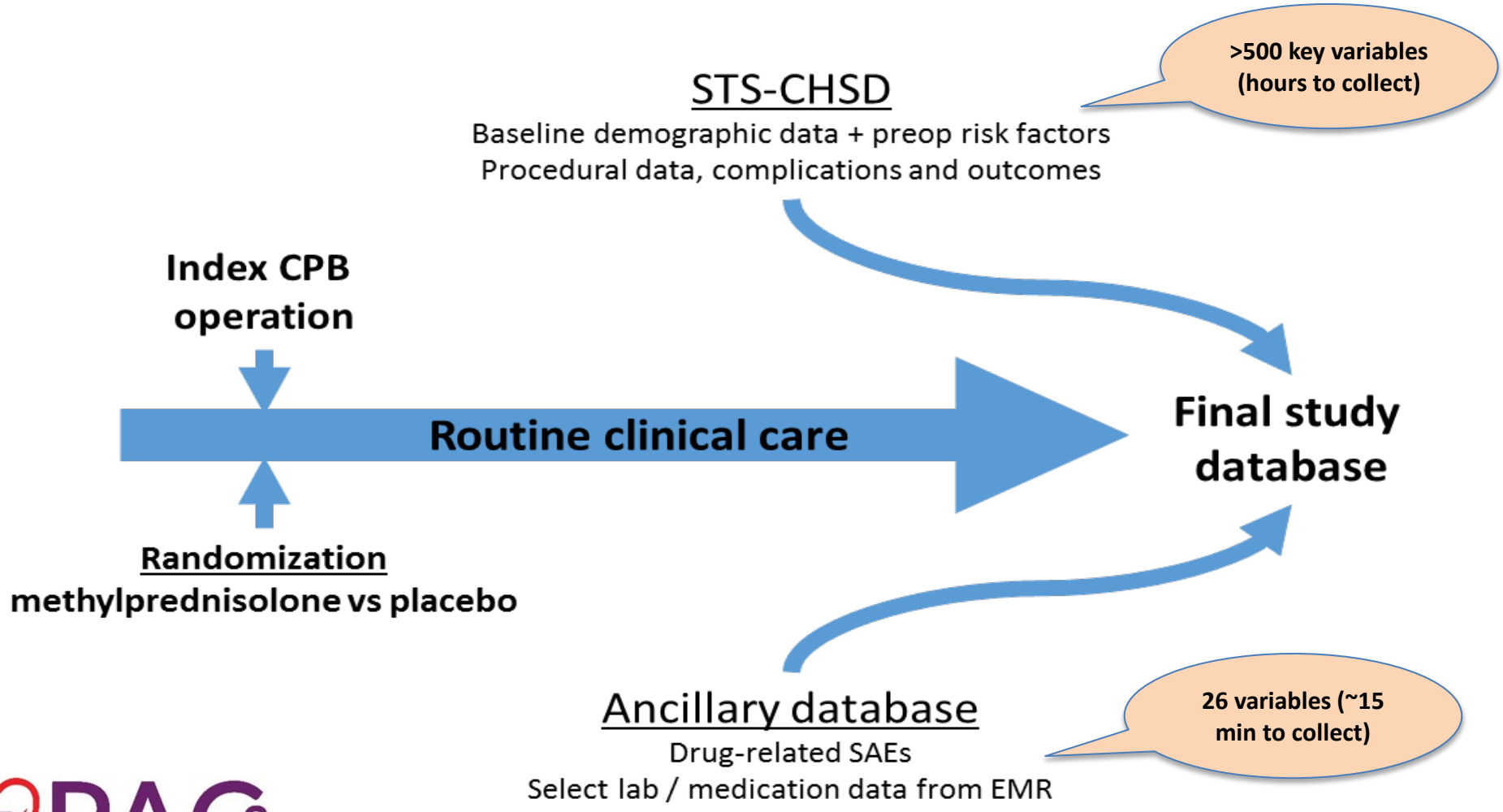
52% of neonatal surgeries used pre/perioperative steroids

- **Adult trials (DECS[1], SIRS[2])**
  - ❑ >12,000 randomized
  - ❑ Meta-analysis[3]:
    - ➢ *No difference in mortality, stroke, renal failure, afib*
    - ➢ *Reduced respiratory failure, infection, LOS*
- **Pediatric trials[4]**
  - ❑ Meta-analysis: 10 RCTs conducted over 4 decades, 768 children enrolled
    - ➢ *Improved fluid balance at 24, 36 hrs*
    - ➢ *No difference in any other endpoints*
    - ➢ *But underpowered*

1. Dieleman et al. JAMA 2012 Nov 7;308(17):1761-7
2. Whitlock et al. Lancet 2015 Sep 26;386(10000):1243-53
3. Dvirnik et al. BRJ Anaesth 2018 Apr;120(4):657-67
4. Bronicki et al. Ann Thorac Surg 2021

TRIAL WITHIN A REGISTRY

Concept: Leverage existing resources to conduct a low cost, pragmatic RCT



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REGISTRY DATA TO EVALUATE NOVEL ENDPOINTS

ELSEVIER

American Heart Journal

Volume 226, August 2020, Pages 188-197

Clinical Investigation

Overcoming underpowering: Trial simulations and a global rank end point to optimize clinical trials in children with heart disease

RANKED ENDPOINTS

Rank	Description
97	Operative mortality
96	Heart transplant (during hospitalization)
95	Renal failure with permanent dialysis
	Neurologic deficit persistent at discharge
	Respiratory failure requiring tracheostomy
94	Post-operative mechanical circulatory support
	Unplanned cardiac reoperation
93	Reoperation for bleeding
	Unplanned delayed sternal closure
	Post-op unplanned interventional catheterization
92	Post-op cardiac arrest
	Multi-system organ failure
	Renal failure with temporary dialysis
	Prolonged ventilator support (> 7 days)
91	Post-operative length of stay > 90 days
1-90	Post-operative length of stay

Advantages

- ❑ Weighting of endpoints consistent with clinical relevance
- ❑ Include more endpoints without diluting out the impact of key endpoints
- ❑ Include binary and continuous outcomes

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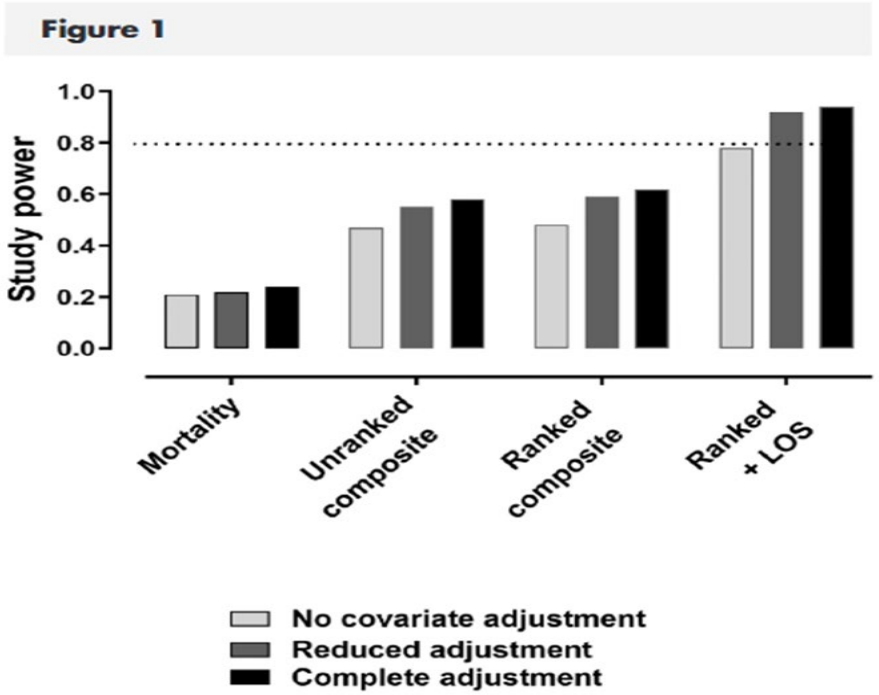
ENDPOINTS

Power gains



- **Primary endpoint: Ranked composite**
  - ❑ Covariate adjusted primary analysis
    - ➢ 1200 participants: > 90% power
- **Secondary endpoints**
  - ❑ Unadjusted analysis and “Win Ratio”
  - ❑ Composite mortality/major morbidity (>91)
  - ❑ Safety Endpoints
    - *Composite infection, Hyperglycemia, Insulin administration*

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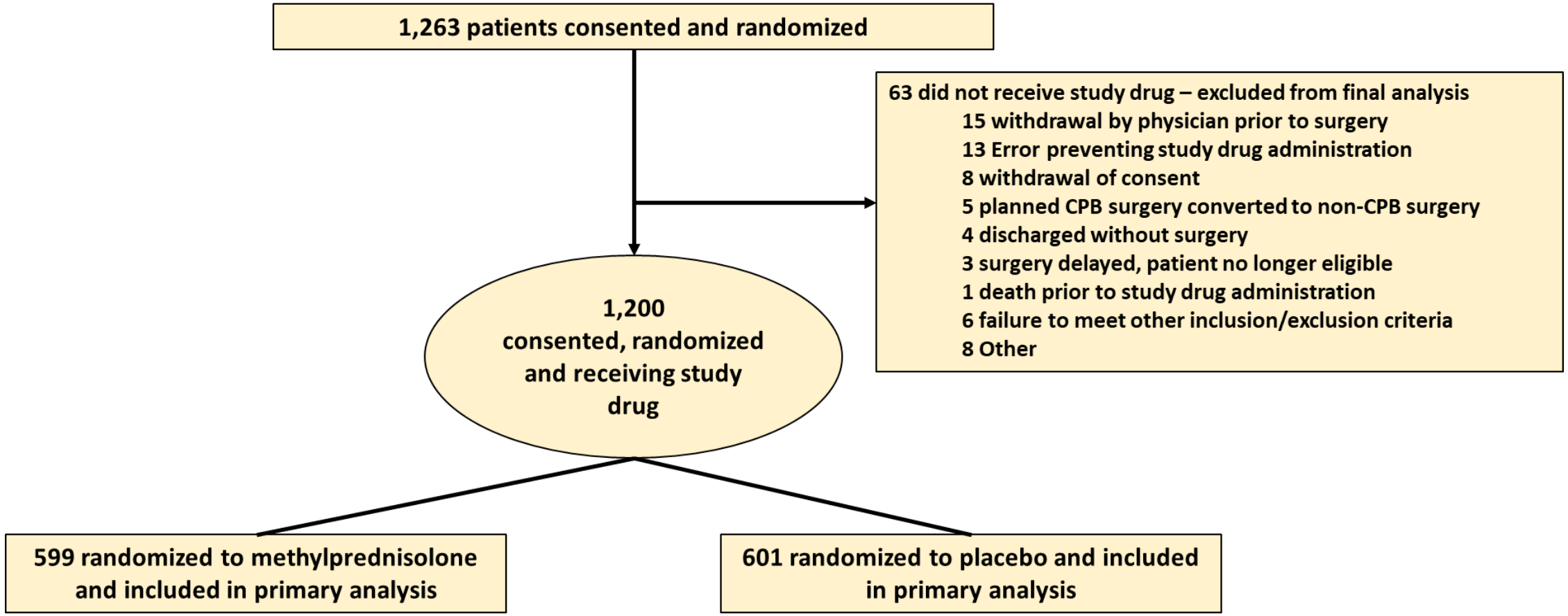
STRESS TRIAL NETWORK

RESULTS: TRIAL COHORT



RESULTS: BASELINE CHARACTERISTICS

Similar distribution of baseline characteristics

Characteristic	Steroids N=599	Placebo N=601
Median age at surgery, days (Q1, Q3)	126 (14, 191)	124 (14, 182)
Age Category		
≤30 days	177/599 (29.5%)	187/601 (31.1%)
Median wt at surgery, kg (Q1, Q3)	5.2 (3.7, 6.4)	5.0 (3.6, 6.3)
Male sex	320/599 (53.4%)	334/600 (55.7%)
Premature	100/598 (16.7%)	93/599 (15.5%)
Non-cardiac congenital anatomic abn.	26/599 (4.3%)	15/600 (2.5%)
Chromosomal abnormality or syndrome	200/599 (33.4%)	183/600 (30.5%)
Prior cardiothoracic operation	81/599 (13.5%)	110/600 (18.3%)
Any preoperative risk factor	223/594 (37.5%)	212/594 (35.7%)
Median CPB time, min (Q1, Q3)	122.0 (88, 161)	121.0 (90, 160)

Diverse participant cohort

Characteristics	Steroids N=599	Placebo N=601
Ethnicity[2]		
Hispanic or Latino	80/580 (13.8%)	63/584 (10.8%)
Not Hispanic or Latino	500/580 (86.2%)	521/584 (89.2%)
Race[3]		
Caucasian	428/585 (73.2%)	425/583 (72.9%)
Black/African American	90/585 (15.4%)	102/583 (17.5%)
Asian	15/585 (2.6%)	12/583 (2.1%)
American Indian/Alaska Native	5/585 (0.9%)	4/583 (0.7%)
Native Hawaiian/Pacific Islander	4/585 (0.7%)	0
Multiracial	13/585 (2.2%)	15/583 (2.6%)
Other	30/585 (5.1%)	25/583 (4.3%)

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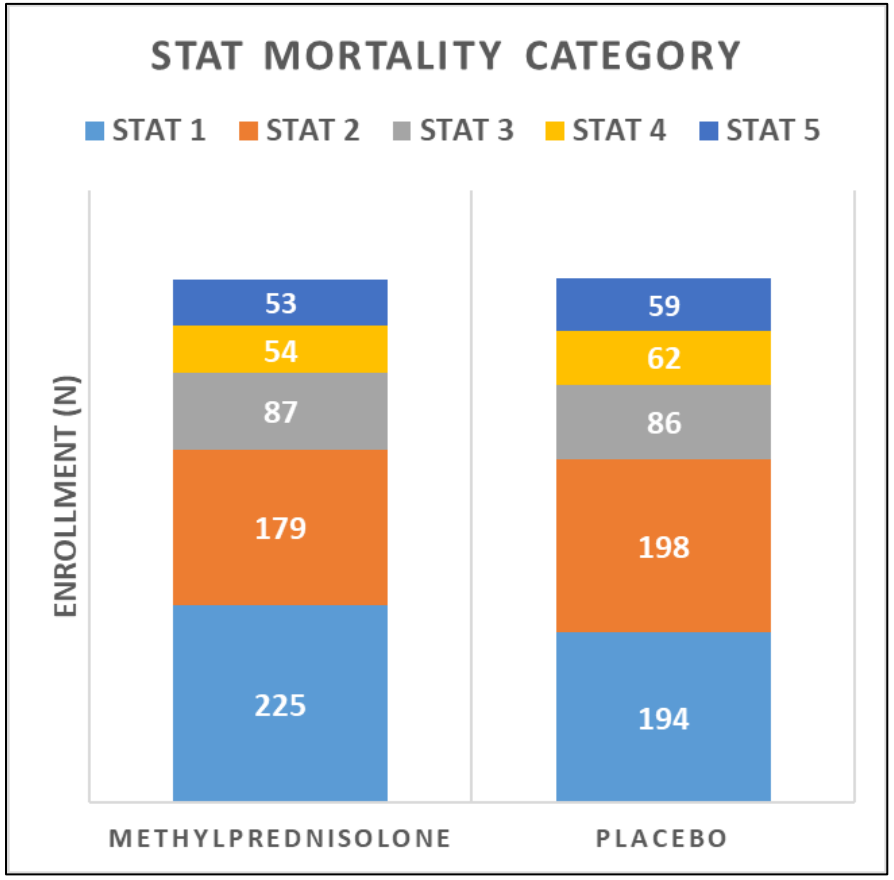
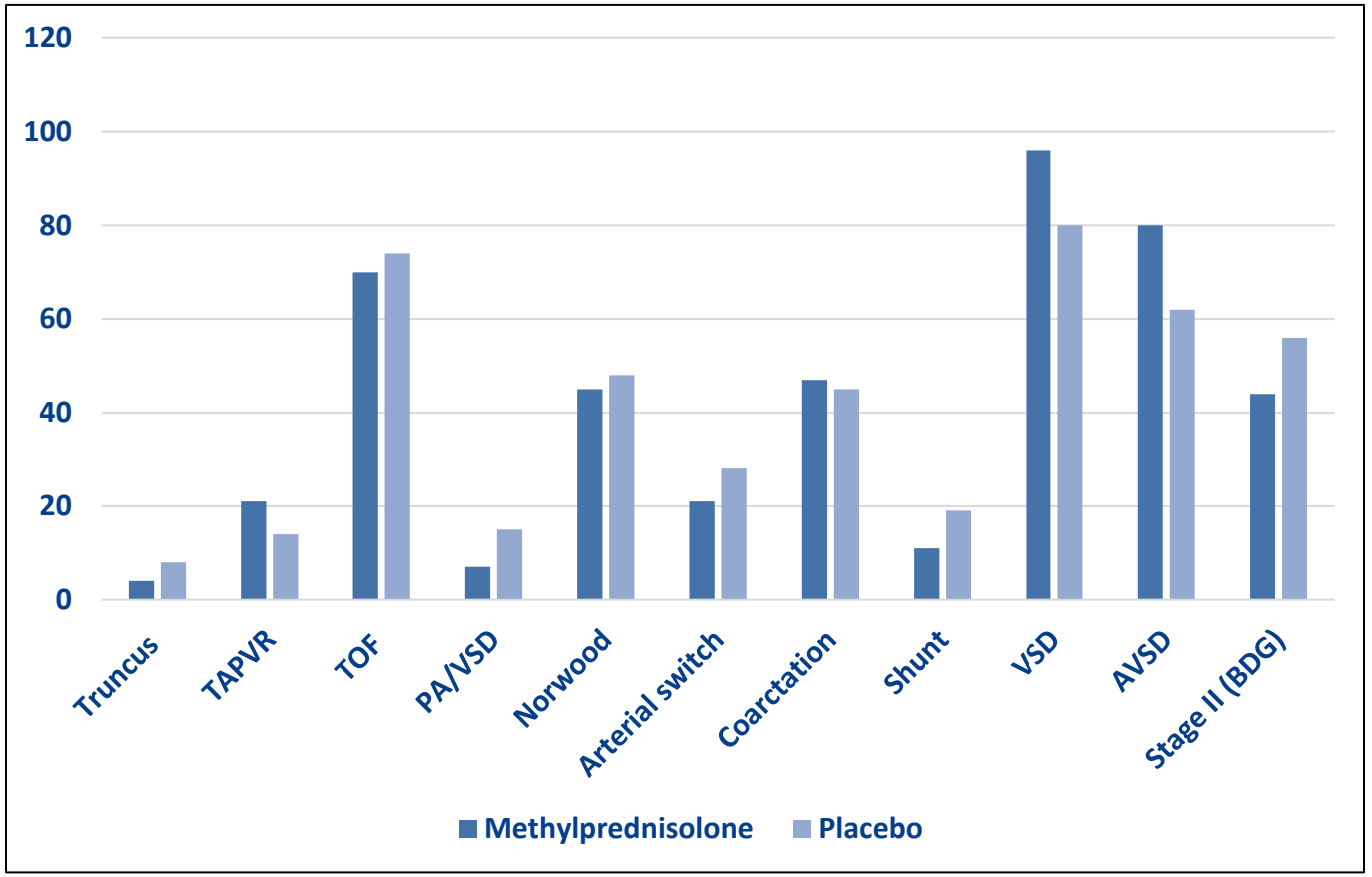
STRESS TRIAL NETWORK

RESULTS

CASE COMPLEXITY AND PROCEDURAL DISTRIBUTION

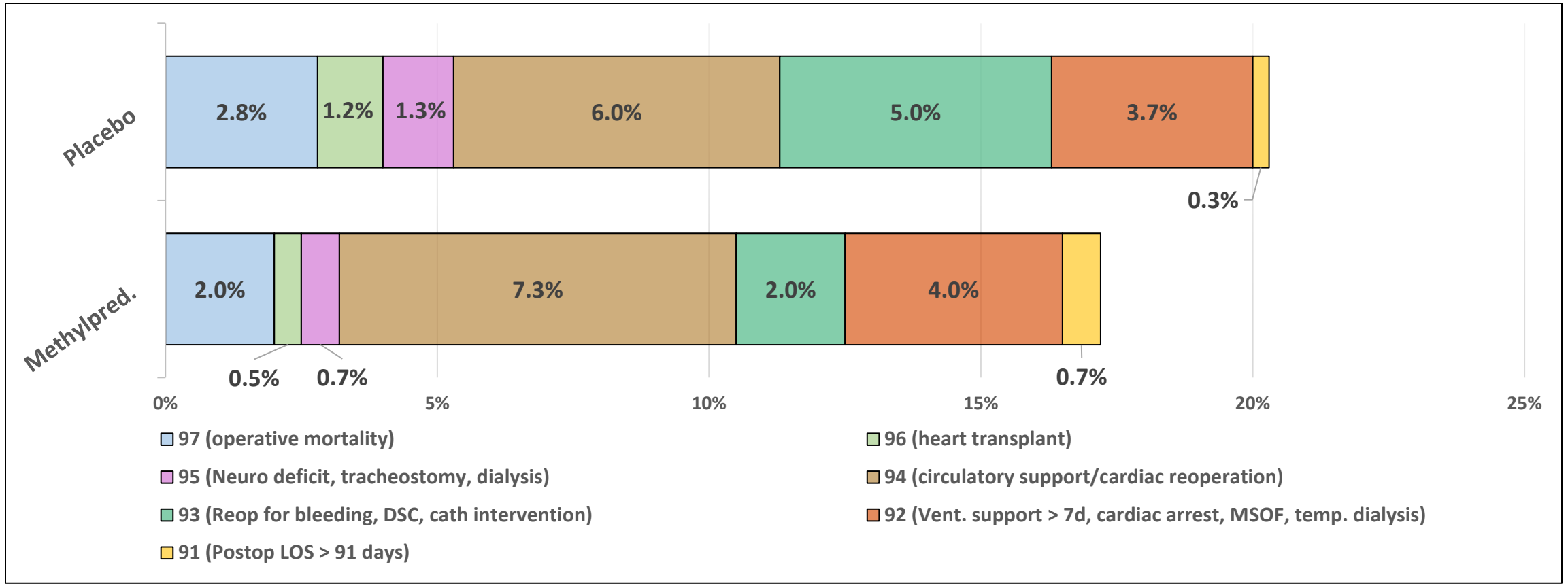




STRESS TRIAL NETWORK

RESULTS: PRIMARY OUTCOME

Adjusted OR = 0.86, 95% CI 0.71 to 1.05; p=0.14



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STRESS TRIAL NETWORK

RESULTS: SECONDARY OUTCOMES

Component	Steroids N=599	Placebo N=601	OR	95% CI	P-value
Unadjusted analysis of primary outcome	**NA**	**NA**	**0.82**	**0.67, 1.00**	**0.047**
Win ratio analysis of primary outcome	**NA**	**NA**	**1.15**	**1.00, 1.32**	**0.046**
Operative mortality	2.0%	2.8%	0.74	0.34, 1.57	0.428
Composite morbidity/mortality (Rank > 91)	17.2%	20.3%	0.83	0.61, 1.13	0.228
Prolonged (> 7 days) post-operative mechanical ventilation	6.8%	8.5%	0.79	0.50, 1.25	0.309
Post-op low cardiac output syndrome	5.2%	6.2%	0.91	0.52, 1.57	0.723
Post-operative infectious complication	5.2%	4.0%	1.39	0.80, 2.42	0.242
Bleeding requiring reoperation	**1.2%**	**3.5%**	**0.34**	**0.14, 0.81**	**0.016**
Post-operative hospital LOS, median (IQR)	10 (6, 20)	11 (6, 23)	1.11	0.99, 1.25	0.066

Favor MP

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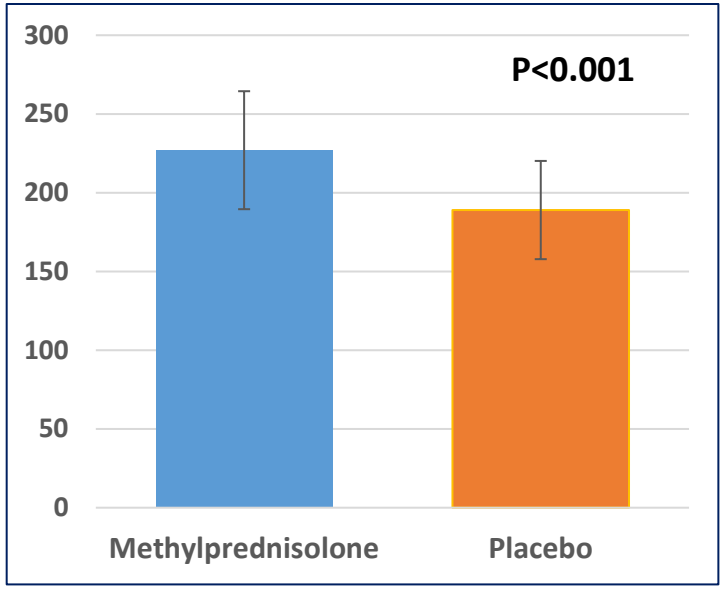
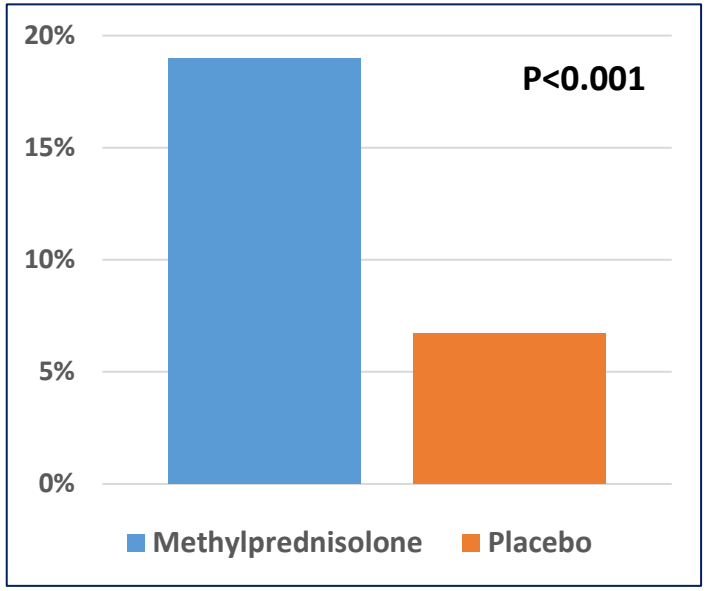
STRESS TRIAL NETWORK

RESULTS: SAFETY AND OTHER OUTCOMES

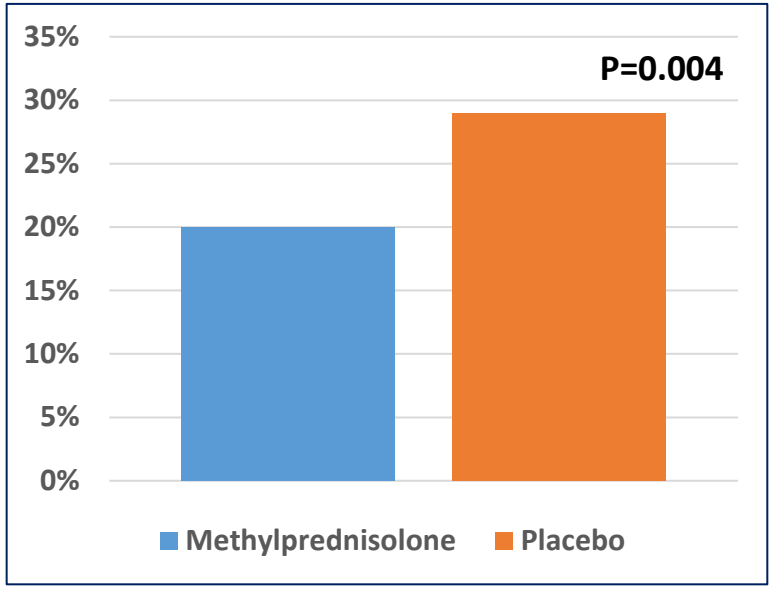
Methylprednisolone with higher post-operative blood glucose



Methylprednisolone more likely to receive post-op insulin



Methylprednisolone less likely to receive post-op hydrocortisone



No differences in rates of any other complications

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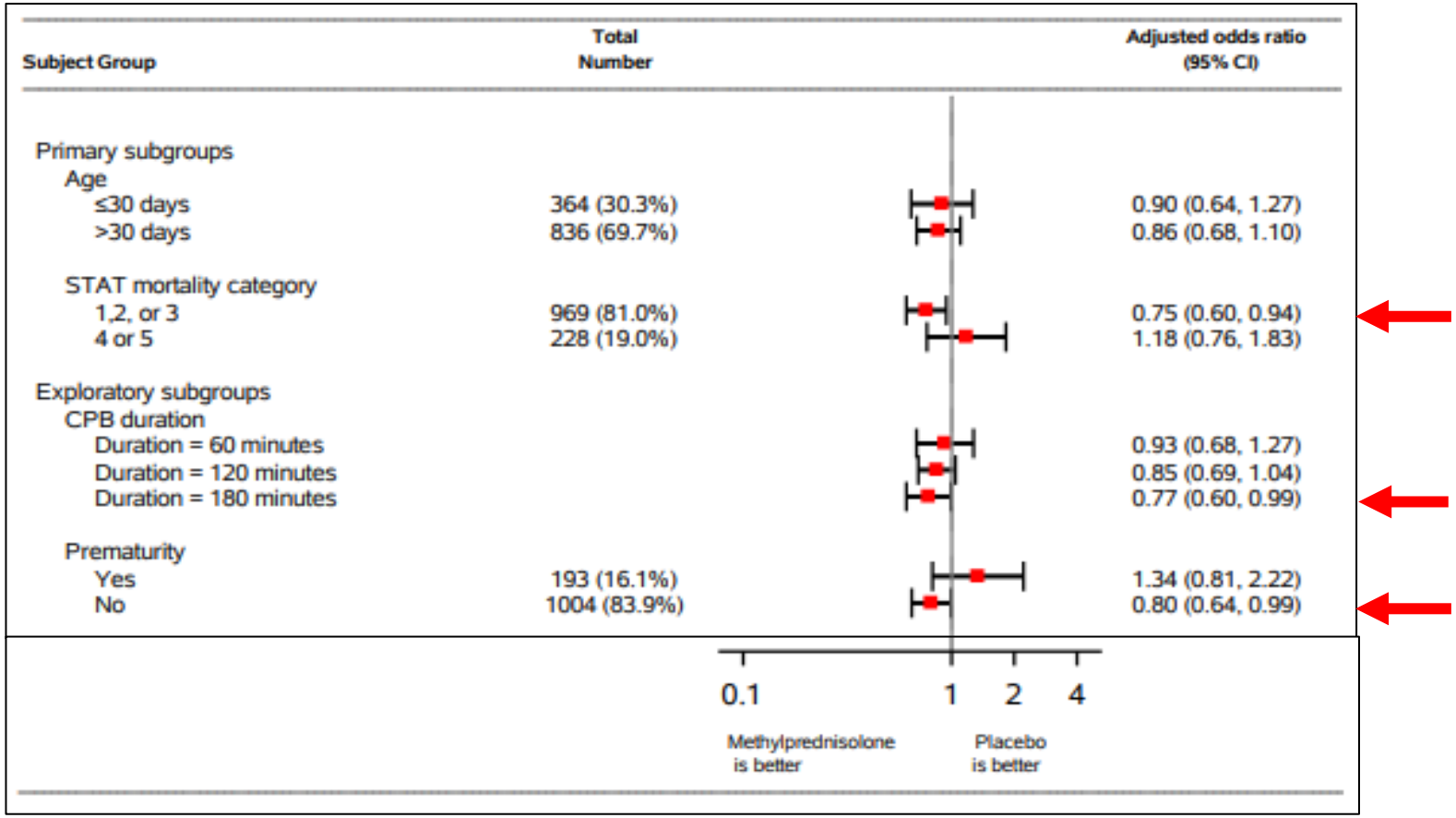
STRESS TRIAL NETWORK

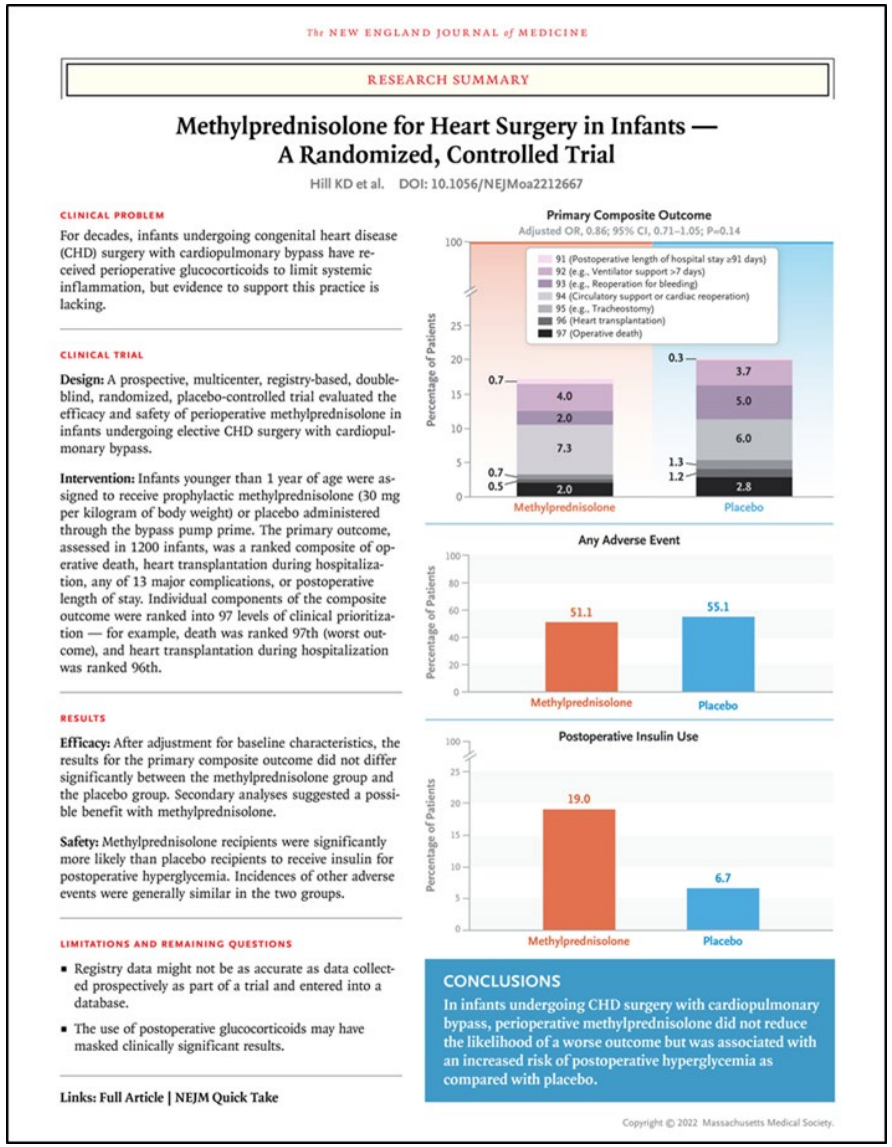
RESULTS: SUBGROUP ANALYSES

Potential benefit in STAT 1,2,3 cases, longer bypass duration and non-premature infants



STRESS CONCLUSIONS

- MP did not decrease the likelihood of the risk adjusted composite primary endpoint but did reduce the likelihood of the primary endpoint when analyzed without risk adjustment and increased the “Win Ratio”
- MP increased the likelihood of hyperglycemia
- Participants receiving MP were less likely to receive post-op hydrocortisone
- In subgroup analysis, there was benefit for:
  - Lower complexity operations (STAT 1,2,3)
  - Infants with longer CPB times
  - Non-premature infants



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RESEARCH SUMMARY

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

Hill KD et al. DOI: 10.1056/NEJMoa2212667

CLINICAL PROBLEM

For decades, infants undergoing congenital heart disease (CHD) surgery with cardiopulmonary bypass have received perioperative glucocorticoids to limit systemic inflammation, but evidence to support this practice is lacking.

CLINICAL TRIAL

Design: A prospective, multicenter, registry-based, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of perioperative methylprednisolone in infants undergoing elective CHD surgery with cardiopulmonary bypass.

Intervention: Infants younger than 1 year of age were assigned to receive prophylactic methylprednisolone (30 mg per kilogram of body weight) or placebo administered through the bypass pump prime. The primary outcome, assessed in 1200 infants, was a ranked composite of operative death, heart transplantation during hospitalization, any of 13 major complications, or postoperative length of stay. Individual components of the composite outcome were ranked into 97 levels of clinical prioritization — for example, death was ranked 97th (worst outcome), and heart transplantation during hospitalization was ranked 96th.

RESULTS

Efficacy: After adjustment for baseline characteristics, the results for the primary composite outcome did not differ significantly between the methylprednisolone group and the placebo group. Secondary analyses suggested a possible benefit with methylprednisolone.

Safety: Methylprednisolone recipients were significantly more likely than placebo recipients to receive insulin for postoperative hyperglycemia. Incidences of other adverse events were generally similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Registry data might not be as accurate as data collected prospectively as part of a trial and entered into a database.
- The use of postoperative glucocorticoids may have masked clinically significant results.

Links: Full Article | NEJM Quick Take

Primary Composite Outcome

Adjusted OR, 0.86; 95% CI, 0.71–1.05; P=0.14

91 (Postoperative length of hospital stay ≥91 days)
92 (e.g., Ventilator support >7 days)
93 (e.g., Reoperation for bleeding)
94 (Circulatory support or cardiac reoperation)
95 (e.g., Tracheostomy)
96 (Heart transplantation)
97 (Operative death)

Percentage of Patients

0.7, 4.0, 2.0, 7.3, 0.7, 0.5, 2.0 — Methylprednisolone

0.3, 3.7, 5.0, 6.0, 1.3, 1.2, 2.8 — Placebo

Any Adverse Event

Percentage of Patients

51.1 — Methylprednisolone

55.1 — Placebo

Postoperative Insulin Use

Percentage of Patients

19.0 — Methylprednisolone

6.7 — Placebo

CONCLUSIONS

In infants undergoing CHD surgery with cardiopulmonary bypass, perioperative methylprednisolone did not reduce the likelihood of a worse outcome but was associated with an increased risk of postoperative hyperglycemia as compared with placebo.

WAS STRESS A SUCCESS?

Successfully enrolled CHD patients in a surgical RCT at 24 centers

Trial	Publication date (Journal)	# enrolled	Centers	Country	Comparison
NITRIC	2022 (JAMA)	1371	6	Aus/NZ	iNO in CPB circuit vs Usual Care
STRESS	2022 (NEJM)	1200	24	US	Methylprednisolone vs Placebo
SPECS	2012 (NEJM)	980	2	US	Tight glycemic control vs UC
SVR	2009 (NEJM)	549	15	US	Sano vs MBTT shunt
DECISION	2020 (JAMA)	394	4	Russia	Dexamethasone vs Placebo
TRICC	2010 (Circ)	198	5	US	T3 vs Placebo
Graham et al.	2019 (Circ)	176	2	US	Methylprednisolone vs Placebo
Boston Circ. Arrest	1993 (NEJM)	171	1	US	Circ Arrest vs. Low Flow Bypass

WAS STRESS A SUCCESS?

Inclusive investigator initiated trial (no network support)

24 centers, 8 with > 50 subjects enrolled

WAS STRESS A SUCCESS?

Pragmatic, cost effective design

Line item	STRESS	PRAGMATIC	TRADITIONAL
STS (Data Access etc)	$158,531	$0	$0
Site payments ($7,500 start up, $1,000 per patient)	$1,430,006	$2,104,706	$5,928,232
Leadership (faculty, DSMB, steering com, project management)	$530,819	$533,342	$942,986
Site management and monitoring	$426,905	$670,119	$1,024,864
Data management and stats	$400,961	$523,293	$1,343,372
Total budget	**$3,268,504**	**$4,164,862**	**$10,140,263**
Cost per patient enrolled	**$2,724**	**$3,470**	**$8,450**

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WAS STRESS A SUCCESS?

Novel endpoint: The Global Rank

Component	Steroids N=599	Placebo N=601
Operative Mortality	12/599 (2.0%)	17/601 (2.8%)
Heart Transplant	4/599 (0.7%)	7/601 (1.2%)
Neurologic deficit persistent at discharge	1/599 (0.2%)	2/601 (0.3%)
Respiratory failure requiring tracheostomy	5/599 (0.8%)	9/601 (1.5%)
Post-operative mechanical circulatory support	31/599 (5.2%)	25/601 (4.2%)
Unplanned cardiac reoperation (exclusive of reop for bleeding)	30/599 (5.0%)	35/601 (5.8%)
Reoperation for bleeding	7/599 (1.2%)	21/601 (3.5%)
Unplanned delayed sternal closure	9/599 (1.5%)	7/601 (1.2%)
Post-op unplanned interventional cardiac catheterization	22/599 (3.7%)	33/601 (5.5%)
Post-op cardiac arrest	14/599 (2.3%)	21/601 (3.5%)
Multi-system organ failure	39/599 (6.5%)	35/601 (5.8%)
Renal failure with temporary dialysis	4/599 (0.7%)	4/601 (0.7%)
Prolonged ventilator support (> 7 days)	41/599 (6.8%)	51/601 (8.5%)
Length of stay > 90	18/599 (3.0%)	29/601 (4.8%)
Mean (SD) LOS (days)	20 ± 34.5	22.5 ± 35.2

Trends reassuring

- *11/15 favor MP*
- *3/15 favor placebo*

All other endpoints vastly underpowered

- *Mortality*
- *Composite M/M*
- *Prolonged Ventilation*
- *Post-op LCOS*

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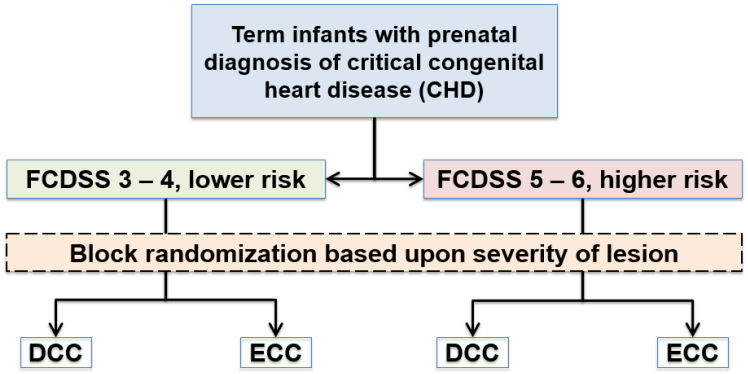
WAS STRESS A SUCCESS?

Springboard for future trials!

CORD-CHD
Clamp OR Delay among neonates with Congenital Heart Disease

500 neonates randomized to early versus delayed cord clamping (19 sites)



FCDSS: Fetal Cardiac Disease Severity Score

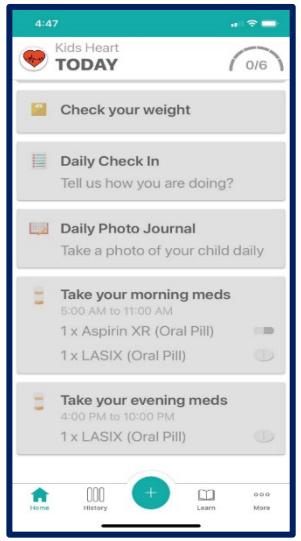
NIH National Heart, Lung, and Blood Institute

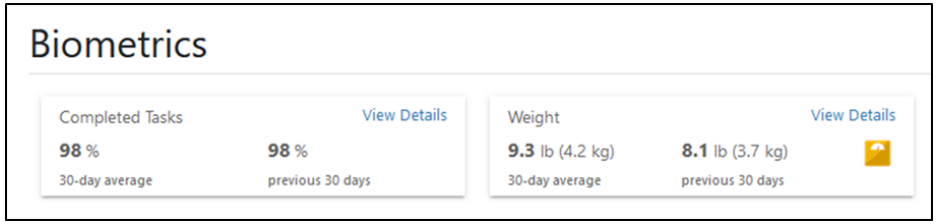
Endpoint	Rank
Death	97
Heart transplant	96
Postnatal complication preventing cardiac intervention Neurological deficit persistent at discharge Tracheostomy Permanent renal failure requiring dialysis	95
Unplanned surgery/cath after initial cardiac intervention Cardiac arrest Pre-intervention mechanical circulatory support Post-intervention multi-system organ failure	94
Pre-surgery/cath polycythemia preventing or delaying intervention Pre-intervention mechanical ventilation Pre-intervention shock	93
Post-intervention RF Post-intervention prolonged mechanical ventilatory support (>7 d)	92
Total hospital LOS >90 d	91
Total hospital LOS ≤90 d	1-90

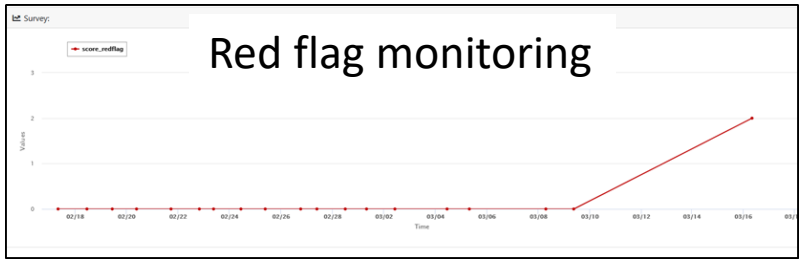
STRESS LIMITATIONS (FUTURE DIRECTIONS)

Longitudinal Follow-up

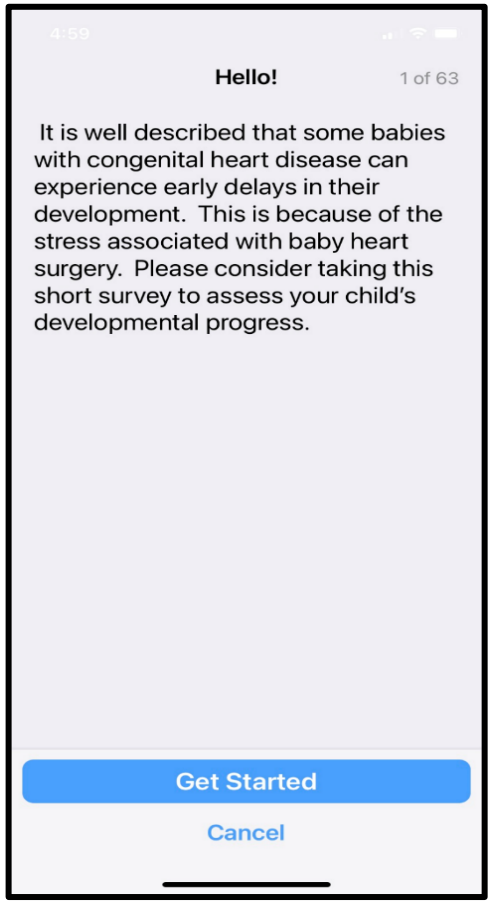
Track daily progress



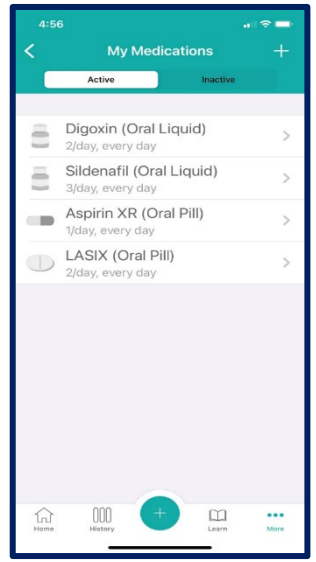


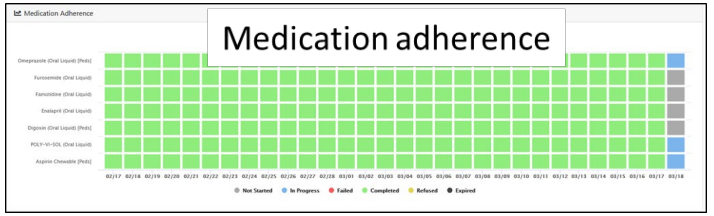


Neurodevelopment surveys



Track meds and compliance





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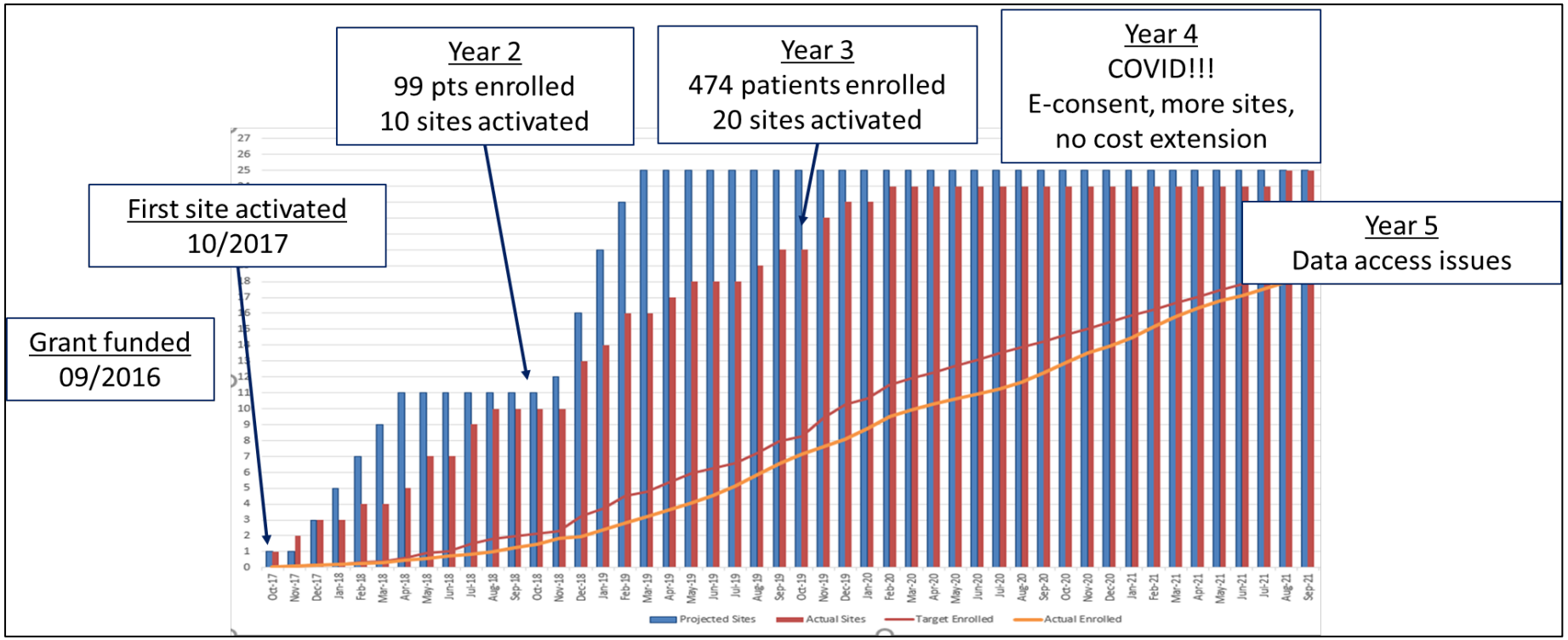
STRESS LIMITATIONS

- **The challenges of consenting and enrollment**
  - *Delays at every step!!!*
    - ➢ *6 years to finish*
    - ➢ *Twice as many sites as originally anticipated*

-



FUTURE DIRECTIONS

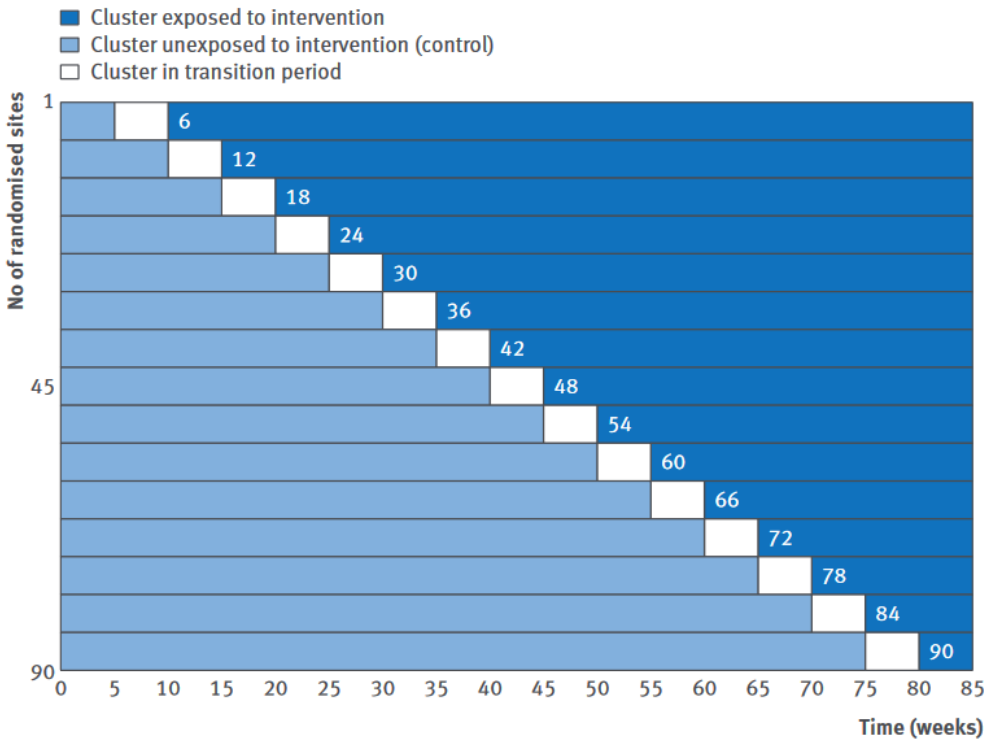
Are their more efficient trial designs?

Cluster Randomization

- Eliminates burden of consent
- Works for center-level interventions
  - *Infection control*
  - *Modified ultrafiltration*

Stepped wedge cluster RCT

Centers sequentially eliminate or alternatively implement the practice change



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FUTURE DIRECTIONS

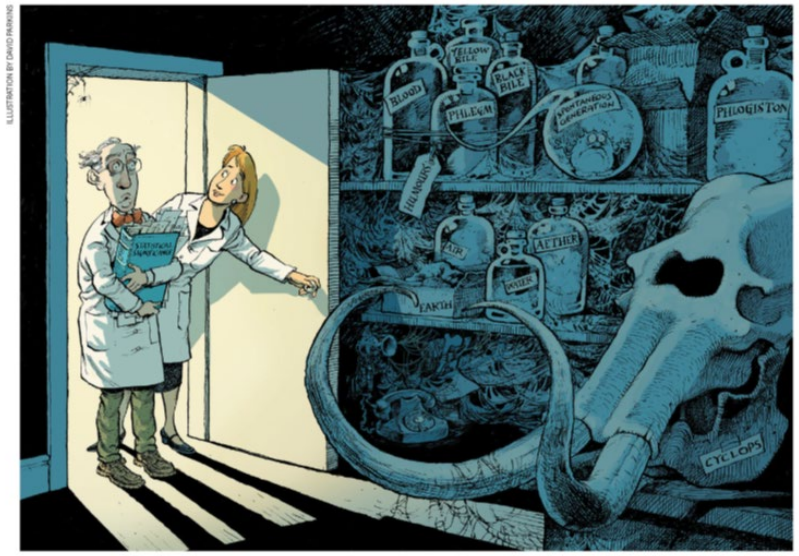
Probability instead of p values

COMMENT | 20 March 2019

nature

Scientists rise up against statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.



Retire statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

"How do statistics so often lead scientists to deny differences that those not educated in statistics can plainly see? For several generations, researchers have been warned that a statistically non-significant result does not 'prove' the null hypothesis (the hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome)"

ORIGINAL ARTICLE

Methylprednisolone for Heart Surgery in Infants — A Randomized, Controlled Trial

Kevin D. Hill, M.D., M.S.C.I., Prince J. Kannankeril, M.D., M.S.C.I., Jeffrey P. Jacobs, M.D., H. Scott Baldwin, M.D., Marshall L. Jacobs, M.D., Sean M. O'Brien, Ph.D., David P. Bichel, M.D., Eric M. Graham, M.D., Brian Blasiole, M.D., Ph.D., Ashraf Resheidat, M.D., Adil S. Husain, M.D., S. Ram Kumar, M.D., Ph.D., et al., for the STRESS Network Investigators*

RESULTS

A total of 1263 infants underwent randomization, of whom 1200 received either methylprednisolone (599 infants) or placebo (601 infants). The likelihood of a worse outcome did not differ significantly between the methylprednisolone group and the placebo group (adjusted odds ratio, 0.86; 95% confidence interval [CI], 0.71 to 1.05; P=0.14). Secondary analyses (unadjusted for risk factors) showed an odds ratio for a worse outcome of 0.82 (95% CI, 0.67 to 1.00) and a win ratio of 1.15 (95% CI, 1.00 to 1.32) in the methylprednisolone group as compared with the placebo group, findings suggestive of a benefit with methylprednisolone; however, patients in the methylprednisolone group were more likely than those in the placebo group to receive postoperative insulin for hyperglycemia (19.0% vs. 6.7%, P<0.001).

CONCLUSIONS

Among infants undergoing surgery with cardiopulmonary bypass, prophylactic use of methylprednisolone did not significantly reduce the likelihood of a worse outcome in an adjusted analysis and was associated with postoperative development of hyperglycemia warranting insulin in a higher percentage of infants than placebo. (Funded by the National Center for Advancing Translational Sciences and others; STRESS ClinicalTrials.gov number, NCT03229538.)

FUTURE DIRECTIONS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

RESULTS

A total of 295 patients underwent randomization. Among the 260 patients with data that could be evaluated and who had a VABS-II score of at least 70 before cardiac arrest, there was no significant difference in the primary outcome between the hypothermia group and the normothermia group (20% vs. 12%; relative likelihood, 1.54; 95% confidence interval [CI], 0.86 to 2.76; P=0.14). Among all the patients with data that

CONCLUSIONS

In comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a good functional outcome at 1 year. (Funded by the Na-

Moler et al. NEJM. 2015;372:1898-1908. DOI: 10.1056/NEJMoa1411480.

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FUTURE DIRECTIONS

NEJM Evidence

Published December 14, 2022
NEJM Evid 2022; 2 (1)
DOI: 10.1056/EVIDoa2200196

ORIGINAL ARTICLE

A Bayesian Interpretation of a Pediatric Cardiac Arrest Trial (THAPCA-OH)

METHODS We performed a Bayesian analysis, interpreting the trial in probabilistic terms (i.e., the probability that therapeutic hypothermia had any benefit, and overall absolute improvements greater than 2%, 5%, and 10% for 1-year neurobehavioral outcome and

RESULTS In the primary analyses, the probability of any benefit from hypothermia was 94% for both the neurobehavioral outcome and survival at 1 year. For both outcomes, the

CONCLUSIONS There is a high probability that hypothermia provides a modest benefit in neurobehavioral outcome and survival at 1 year. (ClinicalTrials.gov number, NCT00878644.)

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SUMMARY

- ***We need more clinical trials!!!***
  - ***Cannot rely solely on networks***
  - ***The pragmatic, randomized registry trial leverages our strengths (registry infrastructure and a collaborative community) and improves trial feasibility***
    - *Doable with existing funding mechanisms and infrastructure*
    - *We need good questions*
    - *Innovation to address our persisting challenges?*
      - *Longitudinal follow up*
      - *Challenges consenting/enrolling children*
      - *Challenges interpreting results*

PC4 PAC3

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THANK YOU TO OUR STRESS NETWORK

Duke University Pediatric and Congenital Heart Center, Vanderbilt University Medical Center, University of Florida Congenital Heart Center, Johns Hopkins University School of Medicine, Medical University of South Carolina, UPMC Children's Hospital of Pittsburgh, Texas Children's Hospital, Baylor College of Medicine, University of Utah/Primary Children's Hospital, University of Southern California; Heart Institute, Children's Hospital of Los Angeles, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Cleveland Clinic Children's, Advocate Children's Hospital, Children's Minnesota, Washington University School of Medicine, University of Texas Southwestern, Children's Hospital Colorado, University of Colorado School of Medicine, Children's Wisconsin, Medical College of Wisconsin, NewYork-Presbyterian/Columbia University Irving Medical Center, University of Rochester Medical Center, Nationwide Children's Hospital; The Ohio State University, Children's Mercy Kansas City, University of California San Francisco Benioff Children's Hospital.

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NCATS Program Officer: Soju Chang MD MPH

Steering committee: Eric M. Graham MD, Jane Newburger MD, James Tweddel MD, Lori Smoot (Parent)

Site PIs/Co-Is: Brian Blasiole MD PhD, Ashraf Resheidat MD, Adil S. Husain MD, S. Ram Kumar MD PhD, Joseph W. Turek, MD PhD, Mark Bleiweis MD, Bret Mettler MD, Alexis Benscoter MD, Eric Wald MD, Tara Karamlou MD MSc, Andrew H Van Bergen MD, David Overman MD, Pirooz Eghtesady MD, Ryan Butts MD, John S. Kim MD, John P. Scott MD, Brett R. Anderson MD MBA MS, Michael F. Swartz PhD, Patrick I. McConnell MD, David F. Vener MD, Venugopal Amula, MD, Nick Andersen, MD, Jean Ballweg, MD, Scott M. Bradley, MD, Jason R. Buckley, MD, Reid C. Chamberlain, MD, Karla G. Christian, MD, John D. Cleveland, MD, Nhue Do, MD, Will Gibson, MD, Christoph P. Hornik, MD MS PhD, James Jaggers, MD, Minoo N. Kavarana, MD, William Ravekes, M.D., Jennifer Schuette, MD, MS, Sarah Tabutt, MD PhD, Richard V. Williams, MD, Sinai C. Zyblewski, MD

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STRESS Trial Coordinating Center (DCRI): Sergei Avdiushko, Susan Bartone, Gail Beaulieu, Darwin Chavez, Stephanie Decker, Deborah Drosdick, Laura Edwards, Carrie Elliott, Alicia Ellis, Claire Evans, Julie Fly, Dianne Gallup, Cindy Green, Jesse Hickerson, Valerie Jackson, Theresa Jasion, David Jensen, Jerry Kirchner, Cheryl Mayton, Annette McDaniel, Rania Metry, Carol Pereira, Thomas Phillips, Gudaye Tasissa, Tinisha Turner, Kadie Wells, Vanderbilt University Darlene Fountain, Central IRB coordination

STRESS TRIAL NETWORK

CHECKLIST: DESIGNING A TRIAL WITH A REGISTRY

Question	Registry	Trial infrastructure	Regulatory support	Trial network	Funding
☐ Simple is better	☐ The right data	☐ DCC	☐ Central IRB	☐ More sites = better	☐ Pay sites well
☐ Interesting	☐ Quality assurance	☐ Steering committee			
☐ With equipoise	☐ Data accessible	☐ DSMB			
☐ Measurable outcome					

Capitated pay structure encourages enrollment

DCC responsibilities

- ***Write protocol***
- ***Day to day oversight (Project lead)***
- ***Site monitoring***
- ***Safety surveillance***
- ***Stats support***
- ***Blinded → develop SAP, final analysis***
- ***Unblinded → prep data for DSMB, safety reports***

PC4 PAC3

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