An Artistic Summary of Hospitalist Year

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Division of Hospital Medicine / Oregon Health & Science University
2018 Annual Scientific Meeting; Oregon Chapter, ACP.
November 10, 2018. Salem, Oregon

Disclosures

• Card-carrying generalist educator (a.k.a.) ABSOLUTELY ZERO
  • Potential funding conflicts
  • Subject-matter specialty expertise (☺) – (beware)
Methods-O-Hunter

• Aim
  • Inpatient (& some outpatient) relevant
  • Potential to change (or NOT) practice
    • RCT’s > Systematic Reviews & Meta’s > obs/retro

• Sources
  • 365 (ish) Days in Review
  • High-impact journals (NEJM, Annals, Archives, JAMA, etc)
    • Major Journals: Bias to higher quality
  • Covet thy neighbor’s selections (Journal Clubs/Talks)
  • EBM syntheses (ACP, Journal Watch)

• NEVER talk about VTE!

(ILIAR)

Today’s Focus: The Arts
Mini Topic Reviews
(45-5)/5 = 8 min per topic

Your Choice
A. Verse
B. Ink
C. Brush
D. Voice
E. Sport
F. Drama
G. Yogi Berra

(Photos – Dug out of family home, not shared here)
Case

A 25-year-old woman with MSSA aortic valve endocarditis has just been admitted to your service. She has issues to address outside of the hospital; is clinically stable, and is felt to be reliable to follow up. She fears needles & does not want a long term catheter and wants an oral regimen

Which statement is best supported by current evidence?
A. There is strong evidence for oral outpatient management of uncomplicated right sided endocarditis, but there is none for left sided endocarditis
B. There is good evidence that left sided endocarditis needs a full intravenous antimicrobial treatment
C. There is evidence that once stabilized with intravenous antibiotics, carefully selected stable patients with left sided endocarditis can be transitioned to oral bioavailable antibiotics to complete their course
D. There is evidence that stable patients with left sided endocarditis can be transitioned from the emergency department to oral bioavailable antibiotics to complete their course

AHA Scientific Statement

Infecive Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications
A Scientific Statement for Healthcare Professionals From the American Heart Association

- Epi
  - Rare (3-7/100K Person/yr) - Not that rare In HOSPITAL
  - S. aureus #1 most common (developed world)
  - Health care contact is #1 risk (valves, card. Devices)
    - ~ 50% nosocomial
    - ~ 50% removable focus
    - Injection drug use...
- Updated Modified Duke’s Criteria
- ~15-45% mortality (most inpt; function of organism)
- Morbid → >1.58 million (disability adjusted) life-yrs lost
- ~ 50% undergo surgery
- Re: antibiotics → per AHA/ACC

Circulation. 2015;132:1435-1486
Antimicrobial Therapy

Therapeutic Principles
The primary goal of antibiotic treatment is to eradicate infection.

• Aim of antibiotics → eradication of infection

• Challenges:
  • high bacterial density in source (~ vegetation)
  • Slow bacterial growth rate within the biofilm
  • Low metabolic activity of microorganism
  • Host immunity
  • Altered pharmacokinetic/dynamic properties of Antibiotics

Therefore, prolonged, parenteral, bactericidal therapy is required for attempted infection cure.

Circulation. 2015;132:1435-1486
Table 10. Therapy for NVE Caused by Staphylococci

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose and Route</th>
<th>Duration, wk</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin-susceptible strains</td>
<td>Nafcillin or oxacillin</td>
<td>12 g/day IV in 4-6 equally divided doses</td>
<td>Class I Level of Evidence C</td>
</tr>
<tr>
<td>For penicillin-allergic (not nephrotoxic type) patients</td>
<td>Gentamicin*</td>
<td>6 g/day IV in 6 equally divided doses</td>
<td>Class I Level of Evidence B</td>
</tr>
<tr>
<td>Oxacillin-resistant strains (uncompromised)</td>
<td>50 mg/kg per 24 h IV in 7 equally divided doses</td>
<td>Class I Level of Evidence C</td>
<td>Adjust vancomycin dose to achieve trough concentration of 15-20 mg/L (see use for vancomycin intolerance).</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>8 mg/kg/day</td>
<td>Class IIb Level of Evidence B</td>
<td>Avoid additional study data to define optimal dosing.</td>
</tr>
</tbody>
</table>

↑ 6wks
Consider 2 wks for uncomplicated R or L I.E.

Therefore, current evidence suggests that either parenteral β-lactam or daptomycin short-course therapy is adequate for the treatment of uncomplicated MSSA RIGHT-sided IE.”

Statement, absent references (P. 1451)

Circulation. 2015;132:1435-1486

There have been numerous observational trials and 3 RTC’s of note evaluating PO abx in endocarditis.

Data is still small but per AHA/ISDA for uncomplicated RIGHT (R? LEFT!??) Staphylococcal endocarditis consider PO antibiotics

Evidence for LEFT is mostly observational (good cure rates) and 3 RCTs (unable to access one; results not available in one) support its use. Quality of trials is limited

RCT

Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci.
POET Trial

ABSTRACT

Background

Patients with infective endocarditis on the left side of the heart are typically treated with intravenous antibiotic agents for 4 to 6 weeks. Although some patients are in stable condition and could be discharged from the hospital early, the morbidity and mortality associated with this condition is high. The main principles for hospital discharge are completion of intravenous antibiotics and prevention of readmission. POET Trial is a randomized, controlled, multicenter, open-label trial that compared PO and IV antibiotics in patients with infective endocarditis on the left side of the heart. The primary outcome was a composite of all-cause mortality, relapse, and stroke within 30 days after discharge. The study was completed in 2017.

Methods

In the POET Trial, patients were randomized to PO or IV antibiotics. The primary outcome was a composite of all-cause mortality, relapse, and stroke within 30 days after discharge. The study was completed in 2017.

Results

The study showed a significant reduction in the primary outcome in the PO group compared to the IV group. The study was completed in 2017.

Conclusions

PO therapy was associated with a significant reduction in the primary outcome compared to IV therapy. The study was completed in 2017.
In clinically stable patients with LEFT sided endocarditis

A shift from intravenously to oral antibiotics

→ Similar efficacy & safety (vs those treated with continued intravenous antibiotics)

Qn/Hypoth: Is switching from IV to oral antibiotics in patients with stable LEFT sided endocarditis efficacious & safe?

Design: Multicentered, randomized, non-inferiority, open label at Danish cardiac centers

Intervention: High bioavail. ABX per ESC guidelines; levels monitored

Patients: Adults, stable, on IV ABX, with Dukes NVE* or PVE*

* NVE = Native valve endocarditis; * PVE = Prosthetic valve endocarditis
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

N = 400, Age > 18; on ≥ 10 d IV antibiotics for stable LEFT sided native- or prosthetic-valve endocarditis*

Published on August 28, 2018, at NEJM.org. DOI: 10.1056/NEJMo1808312

Published online, August 28, 2018, at NEJM.org. DOI: 10.1056/NEJMo1808312
**Antibiotic Options**

**PCN- & MSSA and Coag-Neg Staphylococci**
1. Amoxicillin 1 g x 4 and fusidic acid 0.75 g x 2
2. Amoxicillin 1 g x 4 and rifampin 0.6 g x 2
3. Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2
4. Linezolid 0.6 g x 2 and rifampin 0.6 g x 2

**MSSA and Coag-Neg Staphylococci**
1. Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2. Dicloxacillin 1 g x 4 and rifampin 0.6 g x 2
3. Linezolid 0.6 g x 2 and fusidic acid 0.75g x 2
4. Linezolid 0.6 g x 2 and rifampin 0.6 g x 2

**MRSA**
1. Linezolid 0.6 g x 2 and fusidic acid
2. Linezolid 0.6 g x 2 and rifampin 0.6 g x 2

**Enterococcus faecalis**
1. Amoxicillin 1 g x 4 and rifampin 0.6 g x 2
2. Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
3. Linezolid 0.6 g x 2 and rifampin 0.6 g x 2
4. Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

**Streptococci w/ PCN MIC < 1 mg/L**
1. Amoxicillin 1 g x 4 and rifampin 0.6 g x 2
2. Linezolid 0.6 g x 2 and rifampin 0.6 g x 2
3. Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

**Streptococci w/ PCN MIC ≥ 1 mg/L**
1. Linezolid 0.6 g x 2 and rifampin 0.6 g x 2
2. Moxifloxacin 0.4 g x 1 and rifampin 0.6 g x 2
3. Moxifloxacin 0.4 g x 1 and clindamycin 0.6 g x 3

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**Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis**

Age > 18; on ≥ 10 d IV antibiotics for stable LEFT sided native- or prosthetic-valve endocarditis* with + BCX → streptococcus, *Enterococcus faecalis*, *S. aureus*, or coag neg Staph.

*IF feasible Rx’d as outpatients*

**Oral (N=201)**

**IV (N=199)**

High bioavailability antibiotics per Eur. Soc. Cardiology & AHA

All po abx were assessed for serum levels (last on d5)

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**Qn/Hypoth:** Is switching from IV to oral antibiotics in patients with stable LEFT sided endocarditis efficacious & safe?

**Design:** Multicentered, randomized, non-inferiority, open label at Danish cardiac centers

**Intervention:** High bioavail. ABX per ESC guidelines; abx monitored

**Patients:** Adults, stable, on IV ABX, with Dukes NVE* or PVE*

**Outcomes:**

1. Combined 6 month endpoint
   - All-cause mortality
   - Unplanned cardiac surgery
   - Relapsed infection (same organism)

*NVE = Native valve endocarditis; *PVE = Prosthetic valve endocarditis

Published on August 28, 2018, at NEJM.org. DOI: 10.1056/NEJMoa1808312

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**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment (N=199)</th>
<th>Treatment (N=292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age — y</td>
<td>67.4+12.0</td>
<td>67.8+13.6</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>50 (25.7)</td>
<td>52 (20.4)</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>38.9+0.45</td>
<td>37.7+0.44</td>
</tr>
<tr>
<td>Coexisting condition or risk factor — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>35</td>
<td>35 (15.4)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>35 (15.4)</td>
<td>35 (15.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37 (19)</td>
<td>37 (19)</td>
</tr>
<tr>
<td>COPD</td>
<td>17 (9)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>7 (4)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Cancer</td>
<td>14 (7)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Intraaortic aneurysm</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Pathogen — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pneumonia</td>
<td>104 (52)</td>
<td>64 (28)</td>
</tr>
<tr>
<td>Enterococcus/haemolytic</td>
<td>46 (23)</td>
<td>51 (21.4)</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>40 (20.3)</td>
<td>47 (19.4)</td>
</tr>
<tr>
<td>Coagulase-negative streptococci</td>
<td>38 (19.4)</td>
<td>33 (13.8)</td>
</tr>
<tr>
<td>Laboratory results at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin — g/dL</td>
<td>8.7±1.3</td>
<td>7.2±1.6</td>
</tr>
<tr>
<td>Leukocytes — 3x10⁶/mm³</td>
<td>7.6±3.4</td>
<td>7.2±2.6</td>
</tr>
<tr>
<td>Creatinine — mg/dL</td>
<td>0.9±1.4</td>
<td>1.0±1.7</td>
</tr>
<tr>
<td>Pericardial effusion, pericardial tamponade —  no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>35 (17.6)</td>
<td>34 (15.2)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>31 (31)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Other known valve disease</td>
<td>82 (41.2)</td>
<td>90 (41.5)</td>
</tr>
<tr>
<td>Cardiac involvement at randomization — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve endocarditis</td>
<td>65 (33.7)</td>
<td>71 (30.8)</td>
</tr>
<tr>
<td>Tricuspid valve endocarditis</td>
<td>58 (29.7)</td>
<td>55 (23.2)</td>
</tr>
<tr>
<td>Tricuspid valve endocarditis</td>
<td>65 (33.7)</td>
<td>71 (30.8)</td>
</tr>
<tr>
<td>Tricuspid valve endocarditis in other location</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Aortic valve endocarditis</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Vegetation size &gt; 8 mm</td>
<td>7 (3.5)</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Moderate or severe valve regurgitation</td>
<td>19 (10.5)</td>
<td>19 (7.8)</td>
</tr>
<tr>
<td>Valve surgery during current episode</td>
<td>70 (35.7)</td>
<td>87 (36.4)</td>
</tr>
</tbody>
</table>

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**Results**

- 67y/o; ~50% women, ~20% DM, 1% IDU
- ~70% Strep & enterococcus, NO MRSA
- Cardiac involvement
  - 26% Prosthetic valve
  - 41% with predisposing valve pathology
  - ~55% Aortic; ~34% mitral; ~10% both
  - ~5% vegetation > 9 mm
  - ~10% mod-severe regurgitation
- ~40% require valve surgery
Results

1\textsuperscript{st} Outcome

Primary Composite Outcome
Met criteria for non-inferiority
No change in results: Per protocol vs Intention-to-treat

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intravenous Treatment (N=199)</th>
<th>Oral Treatment (N=201)</th>
<th>Difference</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Mortality</td>
<td>24 (12%)</td>
<td>18 (9%)</td>
<td>3% ARR</td>
<td>HR 0.72 (0.37-1.36)</td>
</tr>
<tr>
<td>Unplanned cardiac surgery</td>
<td>6 (3.0)</td>
<td>6 (3.0)</td>
<td>0 (-3.3 to 3.4)</td>
<td>0.99 (0.32 to 3.07)</td>
</tr>
<tr>
<td>Embolic event</td>
<td>3 (1.5)</td>
<td>3 (1.5)</td>
<td>0 (-2.4 to 2.4)</td>
<td>0.97 (0.20 to 4.82)</td>
</tr>
<tr>
<td>Relapse of the positive blood culture\dagger</td>
<td>5 (2.5)</td>
<td>5 (2.5)</td>
<td>0 (-3.1 to 3.1)</td>
<td>0.97 (0.28 to 3.33)</td>
</tr>
</tbody>
</table>

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Components of 1\textsuperscript{st} Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intravenous Treatment (N=199)</th>
<th>Oral Treatment (N=201)</th>
<th>Difference</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Mortality</td>
<td>13 (6.5)</td>
<td>7 (3.5)</td>
<td>3.0 (-1.4 to 7.7)</td>
<td>0.53 (0.21 to 1.32)</td>
</tr>
<tr>
<td>Unplanned cardiac surgery</td>
<td>6 (3.0)</td>
<td>6 (3.0)</td>
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Additional Results:

<table>
<thead>
<tr>
<th>Metric</th>
<th>IV</th>
<th>PO</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to randomization (IV abx!) (avg)</td>
<td>-- 17 days --</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Post randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration-days (avg)</td>
<td>19 days</td>
<td>17 days</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital LOS (Median)</td>
<td>19 days</td>
<td>3 days</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Antibiotic exposure days (Avg)</td>
<td>36 days</td>
<td>36 days</td>
<td>NS</td>
</tr>
</tbody>
</table>

- 80% of PO arm successfully treated as outpatients
- 7 Pts had low antibiotic concentrations (did not impact outcome)

Summary

- In clinically stable LEFT sided endocarditis patients, with ABX-sensitive staphylococcus (no MRSA), streptococcus or enterococcus, who have responded to induction intravenous therapy transitioning to orally bioavailable 2 drug antibiotic was non-inferior to (~) 4 weeks of IV antimicrobial treatment. (Note: 80% of oral patients were treated as outpatients)

Impressive, open-label, RCT, In LEFT sided endocarditis → adds to prior observational & (2) randomized trials (1 good quality RCT)
Comments

- Small (NS) increase in mortality with IV raises qn:
  - Did IV cause harm?
  - Poor randomization? (different populations?)
  - Poor blinding (did sicker pts get into IV arm?)
- Doesn’t guide us with respect to patients with
  - MRSA (or really any resistant organism)
  - IDU (2.5% of population); adherence, access, secure housing, etc
  - cardiac device/pacemaker infections (~3% of population)
  - Unstable, heavy (BMI > 40), or patients with altered GI absorption
  - Poor responders to induction therapy

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Recommendation

- While not standard-of-care, for carefully selected patients (or out of necessity), it is reasonable to transition patients fitting the above characteristics to oral antibiotics, with close follow up, to complete their treatment (AJH: Class IIb; Evidence B)

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Case

• A 45-year-patient with severe sepsis is admitted to the ICU with acute hypoxemic respiratory failure...
• In addition to ALL THOSE THINGS YOU DO (😊)...

What is the best choice for fluid administration?
A. Colloid fluids, as they improve outcomes
B. 0.9% NaCl
C. A balanced crystalloid (e.g. lactated ringers/plasmalyte)
D. Dealer’s choice


2018 Update

Colloids versus crystalloids for fluid resuscitation in critically ill people (Review)

Continued lack of superiority of colloids to crystalloids (Starches & dextrans MAY increase need for dialysis)
F. Fluid Therapy

1. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).

2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).

3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).

5. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).

6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

SPLIT Trial

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

JAMA 2015;314(16):1701-1710
Two 2018 Trials

**Balanced Crystalloids versus Saline in Critically Ill Adults**


**ABSTRACT**

Both balanced crystalloids and saline are used for volume resuscitation in critically ill adults, but it is unclear in which clinical scenarios one is superior to the other.

In a pragmatic, randomized clinical trial involving more than 7600 patients in the ICU, we compared 5% albumin saline to saline or balanced crystalloids (138:2% lactated Ringer’s solution or Plasmalyte 148) in adult patients in the ICU for 5 days in whom need for resuscitation was expected. The primary outcome was death at 14 days after enrollment. Logistic regression analysis was used to compare effects of resuscitation fluid on mortality and other clinical outcomes. Group differences were measured by using random-effects logistic regression with an exchangeable working correlation structure. The trial was stopped early because the primary outcome was not significantly different between groups (9.6% vs 9.2%, 95% CI 0.9% to 14.9%, P = 0.57). Median hospital stay was 9 days in the albumin group and 8.7 days in the balanced crystalloid group (0.5 days, 95% CI 0.0% to 1.0%, P = 0.97). Median time to hospital discharge was 15 days in the albumin group and 14.6 days in the balanced crystalloid group (0.4 days, 95% CI 0.0% to 0.8%, P = 0.24). Median ICU stay was 10 days in the albumin group and 9 days in the balanced crystalloid group (1 day, 95% CI 0.0% to 2.0%, P = 0.11). The incidence of nonrenal-organ complications was 1.9% and 2.0% (P = 0.62). The incidence of nosocomial-pneumonia was 1.9% and 2.3%, respectively (P = 0.40). Adoptions of center-specific clinical practice were similar, and 4% of patients in each group had a duration of stay longer than 28 days (P = 0.11).

**RÉSUMÉ**

Comparaison clinique des fluides cristalloïdes équilibrés et de la saline en milieu critique, particulièrement en chirurgie, est un essai randomisé, double-contre-erreur, en quatre centres, incluant plus de 7 600 patients hospitalisés en réanimation, comparant 5% de solution de sérum albuminé à la sérum de physiologie ou des crystalloïdes équilibrés (138:2% de solutions de Ringer lacté ou de Plasmalyte 148) pour les ressaisissages du volume en milieu critique de 5 jours chez les patients pour lesquels la nécessité de ressaisissages était attendue. L’objectif principal était la mortalité à 14 jours après l’inscription. L’analyse de régression logistique a été utilisée pour comparer les effets des fluides de ressaisissage sur la mortalité et d’autres complications cliniques. Les différences entre les groupes ont été mesurées par l’utilisation de la régression logistique avec un modèle de covariance de type échangeable. L’essai a été arrêté prématurément car les résultats principaux n’étaient pas significativement différents entre les groupes (9,6% vs 9,2%, IC 95% 0,9% à 14,9%, P = 0,57). La durée d’hospitalisation médiane était de 9 jours dans le groupe albumine et de 8,7 jours (0,5 jours, IC 95% 0,0% à 0,8%, P = 0,97). La durée médiane de sortie de l’hôpital était de 15 jours dans le groupe albumine et de 14,6 jours (1 jour, IC 95% 0,0% à 2,0%, P = 0,24). La durée médiane d’hospitalisation en réanimation était de 10 jours dans le groupe albumine et de 9 jours dans le groupe crystalloïdes équilibrés (1 jour, IC 95% 0,0% à 2,0%, P = 0,11). La survenue d’organes non-renal était de 1,9% et 2,0% (P = 0,62), la survenue de pneumonie nosocomiale était respectivement de 1,9% et 2,3% (P = 0,40). Les adoptions de pratique clinique center-spesific étaient similaires, et 4% de patients dans chaque groupe avaient une durée de séjour plus longue que 28 jours (P = 0,11).

**DISCUSSION**

Comparative clinical trials of balanced crystalloids and saline are common, particularly in critically ill patients cared for in a specific center (507).
Two 2018 Trials

15,904 ADULT PATIENTS

ICU ADMISSION

WARD ADMISSION

Balanced Crystalloids versus Saline in Critically Ill Adults
SMART TRIAL

SMART-MED (N=5383)
SMART-SURG (SICU)

Balanced Crystalloids versus Saline in Noncritically Ill Adults
SALT-ED TRIAL

Only parsing SMART Trial (will share SALT-ED results)

Balanced Crystalloids versus Saline in Critically Ill Adults

<table>
<thead>
<tr>
<th>Question</th>
<th>Impact of isotonic crystalloids on outcomes in ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothesis</td>
<td>Balanced crystalloid $\rightarrow$ persistent AKI, Mort, RRT</td>
</tr>
<tr>
<td>Methods</td>
<td>Pragmatic, cluster RCT (Multiple cross over), 5 US ICU's (Single Center - Vanderbilt)</td>
</tr>
</tbody>
</table>

## Balanced Crystalloids versus Saline in Critically Ill Adults

**Plan: “60-unit-months” (12 mos in 5 ICU’s)**

- 5 Vanderbilt ICU’s
- 15,802 adult critically (ICU) patients
- Randomly assigned NaCl or Buffered Crystalloid (per MD)
  - LR or Plasma-Lyte A
  - Alternate q mos (odd/even)

### ICU Assignments

<table>
<thead>
<tr>
<th>Month</th>
<th>MICU</th>
<th>TICU</th>
<th>SICU</th>
<th>NICU</th>
<th>CVICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAN</td>
<td>NaCl</td>
<td>LR/PL</td>
<td>NaCl</td>
<td>LR/PL</td>
<td>NaCl</td>
</tr>
<tr>
<td>FEB</td>
<td>LR/PL</td>
<td>NaCl</td>
<td>LR/PL</td>
<td>NaCl</td>
<td>LR/PL</td>
</tr>
<tr>
<td>MAR</td>
<td>NaCl</td>
<td>LR/PL</td>
<td>NaCl</td>
<td>LR/PL</td>
<td>NaCl</td>
</tr>
<tr>
<td>MAR</td>
<td>LR/PL</td>
<td>NaCl</td>
<td>LR/PL</td>
<td>NaCl</td>
<td>LR/PL</td>
</tr>
</tbody>
</table>

Common Crystalloid Components

<table>
<thead>
<tr>
<th>Component</th>
<th>0.9% NaCl</th>
<th>Lactated Ringers</th>
<th>Plasma-lyte 148</th>
<th>You &amp; Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na]</td>
<td>154</td>
<td>130</td>
<td>140 ✓</td>
<td>140</td>
</tr>
<tr>
<td>[Cl]</td>
<td>154</td>
<td>109</td>
<td>98 ✓</td>
<td>100</td>
</tr>
<tr>
<td>[K]</td>
<td>4 ✓</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>[Ca]</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>[Mg]</td>
<td></td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>[Lactate]</td>
<td>28</td>
<td>24</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>[Acetate]</td>
<td></td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Gluconate]</td>
<td></td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>5.5</td>
<td>6.5</td>
<td>5.5</td>
<td>7.4</td>
</tr>
<tr>
<td>mOSM/L</td>
<td>308</td>
<td>273</td>
<td>294 ✓</td>
<td>285-95</td>
</tr>
</tbody>
</table>

Balanced Crystalloids versus Saline in Critically Ill Adults

Patients | 15,802 adult critically (ICU) patients
Intervent’n | NaCl vs buffered crystalloid (LR or plasma-Lyte A)
Outcomes | 1°: Major Adverse Kidney Event @ 30d (MAKE30) (composite outcome)

In-Hospital Mortality
Death prior to hospital discharge

New Receipt of RRT
Receipt of any modality of RRT prior to hospital discharge in a patient not known to have received RRT prior to ICU admission.

Persistent Renal Dysfunction
Final plasma creatinine value before hospital discharge ≥ 200% of the baseline creatinine value in a patient not known to have received RRT prior to ICU admission.

Patient Characteristics

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Balanced Crystalloids (N=7942)</th>
<th>Saline (N=7940)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - yr</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Intermittent range</td>
<td>66-49</td>
<td>66-49</td>
</tr>
<tr>
<td>Males - no. (%)</td>
<td>4540 (57.2)</td>
<td>4557 (58.0)</td>
</tr>
<tr>
<td>White race - no. (%)</td>
<td>6384 (80.4)</td>
<td>6322 (80.4)</td>
</tr>
<tr>
<td>Weight - kg</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Intermittent range</td>
<td>65-96</td>
<td>63-95</td>
</tr>
<tr>
<td>Chronic kidney disease of stage 3 or higher</td>
<td>1388 (17.3)</td>
<td>1360 (17.3)</td>
</tr>
<tr>
<td>Previous receipt of renal replacement therapy - no. (%)</td>
<td>384 (4.8)</td>
<td>402 (5.1)</td>
</tr>
<tr>
<td>Source of admission to ICU - no. (%)</td>
<td>3875 (50.4)</td>
<td>3907 (50.0)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>1732 (21.0)</td>
<td>1649 (21.0)</td>
</tr>
<tr>
<td>Operating room</td>
<td>1038 (13.1)</td>
<td>1018 (13.0)</td>
</tr>
<tr>
<td>Hospital ward</td>
<td>738 (9.3)</td>
<td>780 (9.9)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>364 (4.6)</td>
<td>339 (4.4)</td>
</tr>
<tr>
<td>Another ICU within hospital</td>
<td>46 (0.6)</td>
<td>57 (0.7)</td>
</tr>
<tr>
<td>Diagnosis of ICU admission - no. (%)</td>
<td>1187 (14.7)</td>
<td>1169 (14.9)</td>
</tr>
<tr>
<td>Sepsis or septic shock</td>
<td>1187 (14.7)</td>
<td>1169 (14.9)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>698 (8.8)</td>
<td>645 (8.3)</td>
</tr>
<tr>
<td>Mechanical ventilation - no. (%)</td>
<td>2722 (34.3)</td>
<td>2733 (34.7)</td>
</tr>
<tr>
<td>Hypoglycemia - no. (%)</td>
<td>3050 (40.4)</td>
<td>3058 (40.4)</td>
</tr>
<tr>
<td>Mean predicted risk of in-hospital death — % (95% CI)</td>
<td>9.4 (5.0-9.9)</td>
<td>9.1 (5.0-10.9)</td>
</tr>
<tr>
<td>Solute reabsorption level - mg/dL</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Intermittent range</td>
<td>0.74-1.10</td>
<td>0.74-1.10</td>
</tr>
<tr>
<td>Acute kidney injury of stage 3 or higher - no. (%)</td>
<td>687 (8.6)</td>
<td>645 (8.2)</td>
</tr>
</tbody>
</table>

**Source**
- 50% from ED
- ~22% post op (OR)
- 10% from ward

**Admission Diagnosis**
- (Incomplete)
- 15% sepsis/septic shock
- ~23% population noted
- Not in supplemental mat’l

**Predicted mortality 9.5%**
- APACHE ~ 9-11
- OHSU APACHE ~ 20 (estimate)

---

Balanced Crystalloids versus Saline in Critically Ill Adults

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Buffered</th>
<th>0.9% NaCl</th>
<th>ARR (NNT)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAKE30</td>
<td>14.3%</td>
<td>15.4%</td>
<td>1.1 (91)</td>
<td>0.04</td>
</tr>
<tr>
<td>• In-Hosp. &lt; 30-d death</td>
<td>10.3%</td>
<td>11.1%</td>
<td>0.8 (125)</td>
<td>0.06</td>
</tr>
<tr>
<td>• New Renal Replac. Therapy (~ dialysis)</td>
<td>2.5%</td>
<td>2.9%</td>
<td>0.4 (250)</td>
<td>0.08</td>
</tr>
<tr>
<td>• Persistent Renal dysfn (&gt;200% adm)</td>
<td>6.4%</td>
<td>6.6%</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

MAKE30 = Major Adverse Kidney Event @ 30 days
Balanced Crystalloids versus Saline in Critically Ill Adults

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Buffered</th>
<th>0.9% NaCl</th>
<th>ARR (NNT)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PRE – ICU discharge</td>
<td>6.6%</td>
<td>7.3%</td>
<td>0.7% (143)</td>
<td>0.08</td>
</tr>
<tr>
<td>• Pre 60 days</td>
<td>11.7%</td>
<td>12.4%</td>
<td>0.7 (143)</td>
<td>0.13</td>
</tr>
<tr>
<td>• Renal Replacement free days (???)</td>
<td>28</td>
<td>28</td>
<td>OR 1.11 (?)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

From Supplemental Appendix (post-hoc manipulation)

• 30 day mortality-Sepsis 25.2% 29.4% 4.2% (24) 0.02


Fig S3, Supplemental Appendix, N Engl J Med (March) 2018;378:829-39
Balanced Crystalloids versus Saline in Critically Ill Adults

**Electrolytes**

**Chloride**
- Balanced crystalloid: ~ 1.2 mmol/L
- Saline: ~ 1 mmol/L
- P < 0.001

**Bicarbonate**
- Balanced crystalloid: ~ 1 mmol/L
- Saline: ~ 1 mmol/L
- P < 0.001

**Sodium**
- Balanced crystalloid: P < 0.001

*N Engl J Med (March) 2018;378:829-39*

**Balanced Crystalloids versus Saline in Critically Ill Adults**

**Chloride**
- Median
- P value for interaction < 0.001
- Highest [Cl⁻] (mmol/L)

**Sodium**
- Balanced crystalloid: P < 0.001

*Total isotonic crystalloid through day 30 (mL)*
Table S9. MAKE-30 (Multivariate Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Group (Balanced crystalloids : Saline)</td>
<td>0.90</td>
<td>0.82 – 0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.02</td>
<td>1.01 – 1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (Male : Female)</td>
<td>1.06</td>
<td>0.96 – 1.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Race (Non-White : White)</td>
<td>1.16</td>
<td>1.03 – 1.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Source of Admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department (referent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating Room</td>
<td>0.25</td>
<td>0.21 – 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inter-Hospital Transfer</td>
<td>1.44</td>
<td>1.25 – 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital ward (Intra-Hosp. X-fer)</td>
<td>2.01</td>
<td>1.74 – 2.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>0.79</td>
<td>0.62 – 1.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Mechanical Ventilation (Yes : No)</td>
<td>2.41</td>
<td>2.17 – 2.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor Receipt (Yes : No)</td>
<td>2.45</td>
<td>2.18 – 2.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis or Septic Shock (Yes : No)</td>
<td>2.50</td>
<td>2.22 – 2.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traumatic Brain Injury (Yes : No)</td>
<td>2.66</td>
<td>2.11 – 3.35</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table S8, Supplemental Appendix, N Engl J Med (March) 2018;378:829-39

Balanced Crystalloids versus Saline in Critically Ill Adults

- Authors → **struck gold**
  - While only 1.1% reduction in $1^0$ (composite) outcome
    - Improved electrolytes, HCO3
  - If apply to > 5 million ICU admission’s per year (NNT 91)
    - Could save ~55,000 from the composite endpoint

- Editorial → caution
  - Single center, pragmatic design (all comers) surrogate outcomes
  - Variable acuity @ different sites (site may have influenced)
  - The composite outcome is not patient centered
  - Doubling of creatinine? (Yes mortality & RRT)

How calculate maintenance fluids?

A. Adult → 125 ml/h (~ 3L per day)

B. 4-3-2-1 x 20-30-90-232 = \[ \lim_{h \to 0} \frac{f(t+h)-f(t)}{h} \]

(What I preach) – JUST LIKE Peds

25-35 cc/kg/24 hrs (use 30)

~ 1-1.3 cc/kg/hr

x

70 kg = 70-90 cc/hr

1.7 – 2.5L / day

Balanced Crystalloids versus Saline in Critically Ill Adults

<table>
<thead>
<tr>
<th></th>
<th>Balanced</th>
<th>NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TOTAL fluid volume (ICU → Disch)</td>
<td>1000 ml (0-3120)</td>
<td>1020 ml (0-3500)</td>
</tr>
<tr>
<td>Median TOTAL fluids PRE-Randomization (e.g. in ED or OR)</td>
<td>0 ml (13 ± 136)</td>
<td>0 mL (13 ± 115)</td>
</tr>
<tr>
<td>Median TOTAL supplemental fluids (e.g. meds, blood, etc)</td>
<td>100 ml (0-446)</td>
<td>100 ml (0-400)</td>
</tr>
<tr>
<td>Median TOTAL NG supplemental fluids</td>
<td>Not Rec</td>
<td>Not Rec</td>
</tr>
<tr>
<td>Median TOTAL fluids (NG not recorded)</td>
<td>1100 ml (0-3700)</td>
<td>1120 ml (0-4015)</td>
</tr>
<tr>
<td>Median LOS</td>
<td>4.9 days (2.6-8.7 d)</td>
<td>4.9 days (2.6-8.7 d)</td>
</tr>
<tr>
<td>Avg fluid volume /day</td>
<td>224 ml (0 – 755)</td>
<td>229 mL (0 – 819)</td>
</tr>
</tbody>
</table>

Data from Table S9, Supplemental Appendix; N Engl J Med (March) 2018;378:829-39
Balanced Crystalloids versus Saline in Critically Ill Adults

- I have no idea what to make the total (low) volume of crystalloid delivered

- Probably a function of the pragmatic design (all ICU admissions) → thus many didn't require much at all.

- True benefit of the balanced/buffered crystalloid will likely be seen with larger volume resuscitations (a la the supplemental, post hoc analysis data)

PLEASE


SALT-ED

- Ditto (Same group/Similar methods)
- Pragmatic, Single Ctr, multiple crossover - 16 month trial
- Saline vs balanced crystalloid in the Emergency Dept only (not after)
- 13,347 Patients from ED to floor (Alt ED fluids q mos)
- 1^0 Outcome: Hospital free days @ d28

Results:

- 70% admitted to medicine
- ~1000 ml in ED in both groups (med)
- 1^0: No difference
- 2^0: 1.1% ARR MAKE-30 with buffered
  - Primarily a fn of “final creat >200% adm”
Balanced Crystalloids versus Saline in Critically Ill Adults

- I am not sure what to make of the 3rd low resuscitative volume study of saline vs crystalloids, in only (relatively) low mortality patients.

- Not convinced that choice of maintenance fluid matters

- PROBABLY → with sicker patients (more fluids) it will

- So – sure use a buffered crystalloid, but don’t be flustered if during the next medication shortage you need to use 0.9 NaCl instead of a buffered crystalloid


Case

- A 45-year-patient with severe sepsis is admitted to the ICU with acute hypoxemic respiratory failure...

- In addition to ALL THOSE THINGS YOU DO (😊)...

What is the best choice for fluid administration?

A. Colloid fluids, as they improve outcomes
B. 0.9% NaCl
C. A balanced crystalloid (e.g. lactated ringers/ plasmalyte)
D. Dealer’s choice
Case

• A 65-year-old African American man with hypertension & diabetes presents with Left sided weakness & slurred speech, lasting < 90 minutes (now resolved)

• TO
  A) The ED 8 hours after onset of the episode (neg CT)
  B) YOUR clinic 2-3 weeks later

• He is assessed as NIHSS = 2 & ABCD2 that his ‘high risk’

• What are your options?
  A. Thrombolysis (Scenario A: No; Too long; too mild)
  B. Anticoagulate?
  C. Antiplatelet therapy?
  D. More Antiplatelet therapy?
  E. EVEN MORE antiplatelet therapy?

Mild Strokes or High Risk TIA’s

• What are recurrent rates for high risk TIA’s?

• How are we doing with (mgt?) secondary prevention?
ABCD & ABCD2 Scores to Predict Recurrent CVA’s

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Future Stroke Risk Following TIA</th>
<th>2-day</th>
<th>7-day</th>
<th>30-day</th>
<th>90-day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ABCD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk (≤ 3)</td>
<td></td>
<td>1.2%</td>
<td>0.5-9%</td>
<td>0.5-4%</td>
<td>0.3-2%</td>
</tr>
<tr>
<td>High risk (≥ 4)</td>
<td></td>
<td><strong>4.9-7.9%</strong></td>
<td><strong>4.2-15.9%</strong></td>
<td><strong>6.9-17.6%</strong></td>
<td><strong>11.3-18.9%</strong></td>
</tr>
<tr>
<td><strong>ABCD2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk (≤ 3)</td>
<td></td>
<td>0.5-2%</td>
<td>1.2-5%</td>
<td>1.2-5%</td>
<td>5.3-6%</td>
</tr>
<tr>
<td>High risk (≥ 4)</td>
<td></td>
<td><strong>4.2-8.9%</strong></td>
<td><strong>5.9-14.7%</strong></td>
<td><strong>9.6-26.9%</strong></td>
<td></td>
</tr>
</tbody>
</table>


Summary of **30-day** Findings of ASA (160-300 mg) vs no ASA in Pts w Acute TIA /Ischem. CVA (*& Anticoag)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N (studies)</th>
<th>Evid Grade</th>
<th>ASA</th>
<th>No ASA</th>
<th>ARR</th>
<th>NNT</th>
<th>Anticoag*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Mortality</td>
<td>41,291 (4)</td>
<td>High</td>
<td>11.1%</td>
<td>12.0%</td>
<td>0.9</td>
<td>111</td>
<td>13%</td>
</tr>
<tr>
<td>Good Functional Outcome (Rankin Score ≤ 1)</td>
<td>41,291 (4)</td>
<td>High</td>
<td>35.7%</td>
<td>35%</td>
<td>0.7%</td>
<td>143</td>
<td>34.3%</td>
</tr>
<tr>
<td>Non-fatal major hemorrhage; Bleeding req. transfusion</td>
<td>40,850 (4)</td>
<td>High</td>
<td>1%</td>
<td>0.6%</td>
<td><strong>(0.4%)</strong></td>
<td>(250)</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

*B* Between trial, not within trial comparison; N ~ 12,000 (4/5 Studies)

Scenario’s are Different

Scenario A

→ Non-thrombolytic management* of acute mild stroke (NIHSS < 3) or high risk TIA (ABCD ≥ 4)

* Or is this EARLY secondary prevention

Scenario B

→ Secondary prophylaxis of subacute/chronic mild stroke (NIHSS < 3) or high risk TIA (ABCD ≥ 4)

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

Scenario A

→ Non-thrombolytic management* of acute mild stroke (NIHSS < 3) or high risk TIA (ABCD ≥ 4)

<table>
<thead>
<tr>
<th>Recommendation (new)</th>
<th>Strength of Rec</th>
<th>Level of Evid</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin &amp; clopid) begun within 24 hours can be beneficial for early 2nd stroke prevention for up to 90 days from symptom onset</td>
<td>IIa (Moderate)</td>
<td>B-R Mod-qual evid from ≥1 RCT Meta-anal of mod-qual RCT’s</td>
</tr>
</tbody>
</table>

The CHANCE trial (presented here 2013) was a large well done Chinese trial comparing 21 days DAPT, then clopidogrel vs ASA.
The CHANCE trial (presented here 2013) was a large well done Chinese trial comparing 21 days DAPT, then clopidogrel vs ASA (started within 24 hours)

~5100 Chinese patients with acute minor CVA (72%) or high risk TIA who were essentially ASA non-responders (90% on ASA prior)

**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASA (N=2586)</th>
<th>Clopid + ASA (N=2584)</th>
<th>ARR</th>
<th>NNT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome Stroke</td>
<td>11.7%</td>
<td>8.2%</td>
<td>3.5%</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, MI</td>
<td>11.9%</td>
<td>8.4%</td>
<td>3.5%</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular Death</td>
<td>11.4%</td>
<td>7.9%</td>
<td>3.5%</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isch. Stroke</td>
<td>11.7%</td>
<td>8.2%</td>
<td>3.5%</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Summary/take home → Qns remain, applicability?

**Recommendation** → Reasonable in right population

(At that time) Two trials ongoing: POINT & TARDIS

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

(S. Claiborne Johnston, M.D., Ph.D., J. Donald Easton, M.D., Mary Farrant, M.B.A., William Barsan, M.D., Robin A. Conwit, M.D., Jordan J. Elm, Ph.D., Anthony S. Kim, M.D., Anne S. Lindblad, Ph.D., and Yuko Y. Palesch, Ph.D., for the Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators) POINT Trial - 2018


POINT Trial

(Platelet-Oriented Inhibition in New TIA & minor stroke)

• Randomized, double-blinded, placebo cont. (2010-17)
• No. America (83% US), Europe, Australia & New Zealand
• Adults; mild stroke (NIHSS ≤ 3) or high risk TIA (ABCD ≥ 4)
• If could be randomized < 12 h

**Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA**  
**POINT Trial**

4881 patients; > 18, minor stroke (NIHSS ≤ 3) or high risk TIA (ABCD ≥ 4)

- Clopidogrel 600 mg load, then 75 mg daily + Aspirin (50-325 mg)
- Aspirin 162 mg x 5d, then 81 mg daily + Placebo

1\(^{st}\) Outcome: Composite
1. Ischemic stroke
2. Myocardial infarction
3. Death from ischemic vascular disease

• Trial stopped early (Major bleeding) (Aug 2017)
  • DID NOT meet desired 5840 patients
  • 98% followed 7 days
  • 93.4% followed (or died) by 90 days
  • ~ 29% med discontinuation rate (both arms)
• 45% Women; 75% white; 3.3% Asian; 58% on ASA prior presenting
• ~57% Strokes (NIHSS avg 2)
• ~43% high risk TIA (ABCD avg 5)


### Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA  POINT Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopid Aspirin (N=2432)</th>
<th>ASA (N=2449)</th>
<th>ARR (NNT)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isch. Stroke, MI, ischemic vasc. death</td>
<td>5.0%</td>
<td>6.5%</td>
<td>1.5% (67)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>4.6%</td>
<td>6.3%</td>
<td>1.7% (59)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Primary Safety Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>0.9%</td>
<td>0.4%</td>
<td>0.5% (200)</td>
<td>0.02</td>
</tr>
<tr>
<td>Minor hemorrhage</td>
<td><strong>40 (1.6%)</strong></td>
<td>13 (0.5%)</td>
<td>1.1% (91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA  
**POINT Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopid Aspirin (N=2432)</th>
<th>ASA (N=2449)</th>
<th>ARR (NNT)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isch. Stroke, MI, ischemic vasc. death</td>
<td>5.0%</td>
<td>6.5%</td>
<td>1.5% (67)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Primary Outcome &amp; Major Hemorrhage</strong></td>
<td>5.9%</td>
<td>6.9%</td>
<td>1.0% (100)</td>
<td>?</td>
</tr>
<tr>
<td><strong>Primary Outcome &amp; Major Hemorrhage &amp; Minor hemorrhage</strong></td>
<td>7.5%</td>
<td>7.4%</td>
<td>-0.1%</td>
<td>?</td>
</tr>
</tbody>
</table>


### Summary,

- In adult patients with minor stroke (NIHSS avg 2) or high risk TIA (ABCD avg 5) NOT candidates for thrombolysis or anticoagulation, clopidogrel + ASA resulted in improved ischemic stroke, MI or vasc. Death…but more hemorrhage than ASA alone

- Providers & patients must weigh relative concerns/desires re: the bleeding / stroke prevention trade off.

Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial

Open label, (blinded endpoint) RCT of 3096 adults w/an acute ischemic stroke or TIA (< 48hr)

TAPT*
ASA 75 mg
Clopidogrel 75 mg
Dipyridamole 200 mg bid

Guideline Directed

Clopidogrel 75 mg
Dipyridamole 200 mg bid

Aspirin 75 mg
Dipyridamole 200 mg bid

90-Day
Aspirin
Clopidogrel
Dipyridamole

Even More antiplatelet exposure

1st (combined) Outcome: 90-day incidence & severity of stroke

Results: No Change in Primary; but 2x the bleeding

Lancet 2018; 391: 850–59
Putting the 3 trials together

<table>
<thead>
<tr>
<th>CHANCE (2013)</th>
<th>CEER</th>
<th>ARR</th>
<th>Mi Bld</th>
<th>ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Hours</td>
<td>Clopidogrel</td>
<td>8.2%</td>
<td>3.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>ASA</td>
<td>11.7%</td>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pβ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TARDIS (2018)</th>
<th>CEER</th>
<th>ARR</th>
<th>Mi Bld</th>
<th>ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 Hours</td>
<td>Clopidogrel</td>
<td>6.0%</td>
<td>1.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>7.0%</td>
<td></td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>Dipyridamole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>POINT (2018)</th>
<th>CEER</th>
<th>ARR</th>
<th>Mi Bld</th>
<th>ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Hours</td>
<td>Clopidogrel</td>
<td>5.0%</td>
<td>1.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>6.5%</td>
<td></td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>Pβ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scenario A: Acute antiplatelet mgt
What to do?

- New 2018 AHA/ASA Guidelines note IIa (reasonable) to treat minor stroke of high risk TIA with 21 days of DAPT (then switch to clopidogrel – presuming) – Based on 2013 CHANCE trial in China

- New trials are mixed
  - POINT suggests anti-ischemic benefit is real, but at a risk of bleeding (Used DAPT x 90 days)
  - TARDIS really says... **NO** to TAPT (for now)

- It is reasonable after a shared decision-making conversation with our patients, to treat acute mild strokes and high risk TIA’s with DAPT, but *(per CHANCE)*

- limit DAPT to 21 days recognizing;
  - we are not guided by US trial data or
  - whether dropping clopidogrel is equal to or better than dropping ASA after 21 days
Scenario’s are Different

Scenario A

→ Non-thrombolytic management* of acute mild stroke (NIHSS < 3) or high risk TIA (ABCD ≥ 4)

* Or is this EARLY secondary prevention

(±)

Scenario B

→ Secondary prophylaxis of subacute/chronic mild stroke (NIHSS < 3) or high risk TIA (ABCD ≥ 4)

Summary of Findings: Clopidogrel vs ASA in Patients with Hx of non-embolic ischemic CVA or TIA

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ASA (n=1058)</th>
<th>Clopidogrel (n=1058)</th>
<th>ASA ARR NNT</th>
<th>Clopidogrel ARR NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All case mortality</td>
<td>3.1%</td>
<td>2.9%</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Non-fatal recurrent ischemic stroke</td>
<td>0.6%</td>
<td>0.6%</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.6%</td>
<td>0.6%</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Non-fatal major intracranial hemorrhage</td>
<td>0.6%</td>
<td>0.6%</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

Adapted from Table 17, Lansberg MG, et al. Chest 2012;141(2):Suppl:S311-S320

Secondary Prevention of TIA/Stroke

• In the web version
• summary of all the secondary prevention therapy for TIA/Stroke

Your REFERENCE ONLY
New Approach: Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Asx To Prevent Embolism in ESUS NAVIGATE-ESUS Trial

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

• “ESUS” (proposed new term in prior studies)
  • Cryptogenic strokes not assoc. w/ prox. arterial stenosis or recognized cardioembolic source (e.g. A Fib, LV thrombus, valve, etc) & not ‘lacunar’
  • ~ 20% of ischemic CVA’s (Rec rate ~
  • Of note: Atrial Fib may occur in up to 40% of ESUS*

• With success of anticoagulants (vs antiplatelet) for embolic strokes (e.g. A fib), why not anticoag?

• International, randomized, phase 3 trial at 459 centers in 31 countries (Pharma intertwined; but described)

• Adults, > 49 y/o (if 50-50 required 1 risk factor), with ischemic stroke (7 d to 6 mos prior)

  N Engl J Med (May) 2018;378:2191-201
**Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source**

New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Aspirin To Prevent Embolism in ESUS

**NAVIGATE-ESUS Trial**

~ 7000 patients

- Rivaroxaban 15 mg + Placebo
- Aspirin 100 mg + Placebo

1, 6, & 13 mos clinic

Outcomes (Time-to-Event: 2 yr duration)

1ª: 1str recurrent stroke or systemic embolism
2ª: Numerous
1ª Safety: Major bleeding

Telemetry x ≥ 20 h to evaluate for A. Fib

N Engl J Med (May) 2018;378:2191-201

---

**YOU CAN’T READ THIS**

Post Stroke Atrial Fibrillation Detection Rates (previous trials)

- Range: 0-30% atrial fibrillation rate
- Clearly different populations
- ESUS – Probably ~ 9.2% *
- Variable monitoring techniques
  - Holter, Implantable loop recorder, ICD, Mobile Cardiac outpatient tele, flash monitor
- Hours: 24 – 25,920 (14 mos)
- 20-24 reasonable, but likely missing some atrial fib

Hariri E. et al. BioMed Research International 2016; Article ID 5704963, 10 pages
http://dx.doi.org/10.1155/2016/5704963
### Characteristics

- **Patients**
  - Age 67
  - 38% Women
  - 72% white

- **Where**
  - ~60% Europe
  - 13% US; 19% Asia

- Median NIHSS = 1 minor stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban Group (N = 3609)</th>
<th>Aspirin Group (N = 3604)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age—yr</td>
<td>66.5±8.8</td>
<td>66.6±8.8</td>
</tr>
<tr>
<td>Male—no. (%)</td>
<td>2212 (61)</td>
<td>2200 (61)</td>
</tr>
<tr>
<td>Race—no. (%)</td>
<td>White only: 2912 (80)</td>
<td>2804 (78)</td>
</tr>
<tr>
<td>Black only: 11 (3)</td>
<td>69 (2)</td>
<td></td>
</tr>
<tr>
<td>Other: 130 (4)</td>
<td>241 (7)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.1±4.9</td>
<td>27.3±5.1</td>
</tr>
<tr>
<td>Blood pressure—mm Hg</td>
<td>135.1±17.0</td>
<td>134.4±18.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.0±10.8</td>
<td>78.4±10.8</td>
</tr>
<tr>
<td>Statin use after randomization—no. (%)</td>
<td>2035 (71)</td>
<td>1988 (72)</td>
</tr>
<tr>
<td>Hypertension—no. (%)</td>
<td>2182 (77)</td>
<td>2390 (76)</td>
</tr>
<tr>
<td>Diabetes mellitus—no. (%)</td>
<td>189 (5)</td>
<td>917 (25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NIH Stroke Scale Score</th>
<th>Stroke Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stroke symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to severe stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe stroke</td>
</tr>
</tbody>
</table>


### Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

#### Table 2. Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (N = 3609)</th>
<th>Aspirin (N = 3604)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1° Outcomes:</td>
<td></td>
<td>5.1% Riv vs 4.8% Asa</td>
<td>HR 1.07 (.87-1.33)</td>
</tr>
<tr>
<td>2° Outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1° Safety Outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Bleeding:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8% Riv vs 0.7% Asa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 2.72 (1.68-4.39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening Bld:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More w/Rivarox</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 2.34 (0.28-4.29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

In older patients with cryptic embolic strokes (ESUS), (7 days → 6 mos old), there was no benefit of rivaroxaban vs aspirin, but with double the bleeding risk.

Scenario’s are Different

**Scenario A** (early mgt of mild CVA/high risk TIA)

It is *reasonable* after a shared decision-making conversation with our patients, to treat acute mild strokes and high risk TIA’s with DAPT, but I’d limit DAPT to 21 days (as per CHANCE).

**Scenario B** (2° & delayed mgt of ESUS strokes)

No current role for anticoagulation for sub-acute secondary management of mild sub-acute ESUS / strokes.
Case

- 52-year-old woman, with ‘COPD’ and ongoing smoking, presents with 5 days of cough, dyspnea, increased sputum production and chills
- Exam is notable for ill appearance, low grade fever, and diffuse course crackles & wheezes

What is the role of procalcitonin in guiding decision to treat her with antibiotics?

A. No role, nada, nyet, nein, etc..
B. Should routinely be obtained to guide diagnosis of pneumonia
C. Procalcitonin-guided decision-making reduces antibiotic exposure in a variety of infections (vs non-infectious syndromes)
D. Hm... wasn’t there a new study....
Commentary

Up to 72% of ambulatory ARI patients receive antibiotics (1); the clinical challenge is that viral and bacterial ARI symptoms overlap, and there is no accurate culture-based gold standard to differentiate these diagnoses. PCT-guided antibiotic prescribing offers 1 approach to improve antibiotic stewardship.

The updated meta-analysis by Schuetz and colleagues shows that, in various clinical settings, PCT-guided antibiotic therapy reduces mortality compared with usual care, but positive effects on treatment failures, as seen in the 2012 meta-analysis (2), were no longer statistically significant. The mechanism by which PCT guidance reduces mortality without reducing treatment failures, which would seem to be the root cause of preventable ARI-related deaths, is a mystery. However, a rational take-home message is that antibiotics can be avoided, or the duration of therapy reduced, without increasing mortality in a broad range of ARI patients with non-elevated PCT levels.

PCT-guided antibiotic prescribing for ARI offers a personalized approach to patients more likely to have an acute or acutely resolved bacterial infection. The PCT threshold above which antibiotics are indicated can be adjusted for lower- and higher-risk settings (3). However, implementation barriers abound, including clinician acceptance and access to PCT. More RCTs are underway because some investigators want confirmation of the safety and acceptability of PCT guidance within their healthcare systems (4). Real-world application of PCT-guided ARI management could devolve into a slippery slope of indiscriminate testing for every sore throat or runny nose, which could paradoxically increase antibiotic prescribing (5).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection


Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

- 14 US Hospitals with high adherence to quality measures for pneumonia management
- Provided guidance for PNA mgt & PCT application
- Patients in whom providers unclear if required antibiotics for LRTI (aka pneumonia)


Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

Patients in whom providers unclear if required antibiotics for LRTI (aka pneumonia)

Procalcitonin Group

Usual Care Group

- Serum procalcitonin
- Real time to MD’s
- Serial-if hospitalized

<table>
<thead>
<tr>
<th>PCT Value</th>
<th>Antibiotic Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1 μg/L</td>
<td>Strongly discourage</td>
</tr>
<tr>
<td>0.1-0.25 μg/L</td>
<td>Discourage</td>
</tr>
<tr>
<td>0.25 – 0.5 μg/L</td>
<td>Recommend</td>
</tr>
<tr>
<td>&gt; 0.5 μg/L</td>
<td>Strongly recommend</td>
</tr>
</tbody>
</table>

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

Patients in whom providers unclear if required antibiotics for LRTI (aka pneumonia)

Procalcitonin Group
• Real-time & serial PCT
• Antibiotic use guideline

Usual Care Group
• Pre-enrollment PCT Drawn (result not shared)
• No contact from study coordinators & treating MD’s

Outcome:
• Total antibiotic exposure (30 days of enroll)

Safety outcome: Numerous outcomes assessing risk of holding antibiotics

### Patients

- ~ Age 50; 57% women
- 36% black
- 33% COPD/~40% asthma
- ~10% on home oxygen
- ~ 33% chills / ~ 55% sputum
- WBC median 8.8/mm³
- PCT levels (μg/L)
  - < 0.1  73%p  (82% UC)
  - 0.1-0.25 20%p   (9% UC)
  - 0.25-0.5 ~3%
  - >0.5 ~5%
- ~25% CAP/other (need abx)

### Table 1: Baseline Characteristics of No Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Procalcitonin (ns-only)</th>
<th>Usual Care (ns-only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — y</td>
<td>52 (43-64)</td>
<td>54 (43-67)</td>
</tr>
<tr>
<td>Sex — m/f</td>
<td>50% (26/28)</td>
<td>47% (26/28)</td>
</tr>
<tr>
<td>Race or ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White — %</td>
<td>42% (23/55)</td>
<td>45% (25/55)</td>
</tr>
<tr>
<td>Black — %</td>
<td>35% (20/58)</td>
<td>37% (20/58)</td>
</tr>
<tr>
<td>Hispanic — %</td>
<td>20% (10/51)</td>
<td>22% (12/51)</td>
</tr>
<tr>
<td>PCT levels (μg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>73%p (82% UC)</td>
<td></td>
</tr>
<tr>
<td>0.1-0.25</td>
<td>20%p (9% UC)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.25</td>
<td>3% (1/32)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>5% (1/21)</td>
<td></td>
</tr>
<tr>
<td>WBC median</td>
<td>8.8 (7.3-10.3)</td>
<td>8.8 (7.3-10.3)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>60% (40/67)</td>
<td>62% (40/67)</td>
</tr>
<tr>
<td>Monocyte</td>
<td>14% (10/67)</td>
<td>14% (10/67)</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>14% (9/67)</td>
<td>12% (9/67)</td>
</tr>
<tr>
<td>Basophil</td>
<td>1% (1/67)</td>
<td>1% (1/67)</td>
</tr>
</tbody>
</table>

### ProACT Trial

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

**Assimilation**

- I was a convert for PCT for respiratory infections
- Deliberately picked hospital with “high adherence to quality measures” – may have diluted the effect
  - Likely aware of PCT in control arm
  - Likely aware of stewardship
- ED adherence to PCT guideline only 73%
- (thus almost more of an effectiveness trial)
- Does highlight the better the ‘system’ – LIKELY will see more of a benefit

ProACT Trial

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

Recommendation (I really struggled with this)

• Don’t give up!
• Prior data in respiratory infections is good
• Analogous to PE Decision Rules? (Gestalt vs Rules)
  • For a system I think it makes sense, as it normalizes those with less experience

Case

• You are caring for a 58-year-old man with Class IV, Stage C, acute on chronic systolic heart failure.
• As you near discharge you recall receiving some enthusiastic recommendations to assure maximum diuresis by checking pre-discharge NT-proBNP

• What is true about a pre-discharge BNP value?
  A. Discharge BNP does not correlate with outcomes
  B. If the pre-discharge BNP has not reduced from admission, treatment should be intensified prior to discharge
  C. Patients with higher pre-discharge BNP have worse long term outcomes
  D. Patients do better if BNP is not checked prior to discharge
Acute Decompensated Heart Failure Morbidity

Observational data
- 50% readmitted within 6 mos.
- ↑ discharge JVP assoc w/20% 1-yr mortality
- Discharge change & absolute NT-proBNP predicts adverse events

Circulation. 2017;136:e137–e161

“insufficient data to inform specific guideline recommendations related to serial NT-proBNP or BNP levels for the purpose of reducing hospitalization, or death” - AHA
Consecutive patients hospitalized for ADHF

Screened (N=311)

NT-proBNP Guided
N = 137 (3 lost to f/u)

Control
N = 133 (6 lost to f/u)

Randomized (N=280)

NT-proBNP ≥ 3000 ng/L

NT-proBNP < 3000 ng/L

NT-proBNP ≥ 3000 ng/L

NT-proBNP < 3000 ng/L

Screening failure n = 31

Therapy optimization diuretics, BB, ACEI, ARBs, MRA

Clinical follow-up

6 Month outcomes BNP guided vs control mgt of ADHM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-DC NT-pro BNP ≥3000</th>
<th>Pre-DC NT-pro BNP &lt; 3000</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mos CV Death or Rehosp</td>
<td>Control 47% Guided 44%</td>
<td>Control 33% Guided 42% P=0.232 (NS)</td>
</tr>
</tbody>
</table>

Low BNP (Control)

Everyone else

• Low BNP (Intervention)
• Made them WORSE
• High BNP (Control)
• High BNP (Intervention)

Survival (probability)

Study day 180
N-terminal pro-B-type natriuretic peptide-guided therapy in patients hospitalized for acute heart failure
Valentina Carbellia, Carlo Lombardiia, Valentina Lazzarinia, Ivan Bonadiea, Anna I. Castrini, Elio Gorgaa, Arthur M. Richardb and Marco Metraa

- 2016, 1st RCT addressing if NT-proBNP guided therapy in 271 consecutive patients hospitalized for “ADHF”
- IF pre DC NT-proBNP > 3000 ng/L* → intensify diuresis (*point of randomization)
  - Control group MD’s didn’t know NT-ProBNP
- 1st Outcome: 6 mos CV death or CV rehospitalization

- Results: Using a PRE-DC Pro-NTBNP value of > 3000 to guide up-escalation of diuresis
  - Did not change in primary outcome
  - Did result in more diuretics (intervention arm 😊)
  - Pts with LOW BNP (blinded MD’s) has best outcomes


Original research article

NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)-Guided Therapy in Acute Decompensated Heart Failure
PRIMA II Randomized Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?)

Susan Steiner, MD
Khabar Salahi, MD
Anna M. Messina, MD, PhD
Aikatino L. Bala, MD
Pietro van Phl, MD
R. A. Michael Kuntz, MD
Jado Pedro Remia, MD
Irene Mazipes, MD
Anna M. Schneider-Soika, MD, PhD
Jan T. Kripk, MD, PhD
Antonio Bytof, MD, PhD
Joe G. Tjipura, MD, PhD
Vigila K. Kuri, MD, PhD
Wouter E. Kwik, MD, PhD

Circulation (April) 2018;137:1671–1683

What about % change?
**Question:**
Whether a NT-proBNP-guided therapy targeting a 30% ↓ would improve outcomes

**Design:**
investigator-initiated, prospective, multicenter, international, randomized controlled, prospective

**Intervention:**
Aim to reduce NT-proBNP by 30% (DC vs admission)

**Patients:**
405 pts w/ stabilized ADHF (NT-proBNP / 3000 ng/L)

**Outcomes:**
6 month composite endpoint
1. All cause mortality
2. Re-admissions
3. Out of hospital days-alive (6 mos)

*Circulation (April) 2018;137:1671–1683*
405 patients w/ ADHF (NT-proBNP > 1700 ng/L) who had achieved clinical stability* (Ready for discharge)

NT-proBNP Guided  |  NT-proBNP Drawn  |  Control

> 30% ↓  |  < 30% ↓  |
Plan DC & FU  |  Follow the Guide

Serial BNP Suggest Δ's for:
- ACE
- BB
- Aldo blockade
Cardiac resync tx
Diuretics (MD discret.)

Circulation. 2018;137:1671–1683


c| NT-proBNP Guided | Conventional (Non-Guided) | P |
---|---|---|---|
Achieved 30% ↓ by randomization | 64% | 63% | 0.75 |
Remaining 36% (achieved by DC) | **52%** | 14% | < 0.001 |
Overall (% ≥ 30% by DC) | **80%** | 64% | < 0.001 |

- 3 day longer LOS if needed ‘intensification’
- Same DC med packages (guided vs conventional)
  - prescription rates and dosages of ACE inhibitors or ARBs, β-blockers, MRAs, and diuretics.
### Results

<table>
<thead>
<tr>
<th>NT-proBNP Guided</th>
<th>Conventional (Non-Guided)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved 30%↓ by randomization</td>
<td>64%</td>
<td>63%</td>
</tr>
<tr>
<td>Remaining 36% (achieved by DC)</td>
<td>52%</td>
<td>14%</td>
</tr>
<tr>
<td>Overall (% ≥ 30% by DC)</td>
<td>80%</td>
<td>64%</td>
</tr>
</tbody>
</table>

**NT-proBNP-guided therapy vs conventional therapy in stabilized patients admitted for acute decompensated heart failure (HF)†**

**Outcomes**
- Composite of readmission for HF or all-cause mortality: 36% (NT-proBNP) vs 36% (Conventional)
- Readmission for HF: 24% (NT-proBNP) vs 26% (Conventional)
- All-cause mortality: 19% (NT-proBNP) vs 17% (Conventional)

**Results (6 Months)**

- Hazard ratio for NT-proBNP-guided therapy: 0.36 (99% CI 0.72-1.37)
- P = 0.33

**% CHF Readmit/Death (6-mos)**

- Conventional = 36%
- NT-proBNP = 36%

---

**All-cause mortality / HF readmissions**

- Hazard ratios and P-values for interaction are provided for various factors:
  - Age: < 75 yrs vs ≥ 75 yrs
  - Gender: female vs male
  - Prior HF: acute vs chronic
  - CAD
  - LVEF: < 60% vs ≥ 60%
  - NT-proBNP: < 500 pg/mL vs ≥ 500 pg/mL

- NT-proBNP Guided vs Conventional Guided
Post-Hoc Analysis

<table>
<thead>
<tr>
<th>≤30% ↓ (Unsuccessfully Guided)</th>
<th>&gt;30% ↓ (Successfully Guided)</th>
<th>Non-guided</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Mos mortality or re-admit</td>
<td>59%</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

Circulation (April) 2018;137:1671–1683

• No apparent benefit in targeting NT-proBNP of “3000” or a “30% reduction’ in pre-discharge BNP for pts hospitalized w/ ADHF

• Are we hurting patients?
  • Over diuresing ? →
  • Is poor response a marker for sicker patients?

NT-proBNP (N-Terminal pro-B-Type Natriuretic Peptide)-Guided Therapy in Acute Decompensated Heart Failure
PRIMA II Randomized Controlled Trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?)

Circulation (April) 2018;137:1671–1683
Future: New Targets?
• 1500 ng/dL
• 50% decline in NT-proBNP (admit to DC?)
• (but remember the non-guided group had the BEST 6 month outcomes)

Take Home:
• Diurese until clinically stable
• No role for routinely employing NT-proBNP targets in routine management of patients hospitalized with acute decompensated heart failure

Case
• You are caring for a 58-year-old man with Class IV, Stage C, acute on chronic systolic heart failure.
• As you near discharge you recall receiving some enthusiastic recommendations to assure maximum diuresis by checking pre-discharge NT-proBNP

• What is true about a pre-discharge BNP value?
  A. Discharge BNP does not correlate with outcomes
  B. If the pre-discharge BNP has not reduced from admission, treatment should be intensified prior to discharge
  C. Patients with higher pre-discharge BNP have worse long term outcomes
  D. Patients do better if BNP is not checked prior to discharge
Case

Full Length Article

Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis

Ang Li¹, David A. Garcia¹, Gary H. Lyman², Marc Carrier²

¹Division of Hematology, University of Washington School of Medicine, Seattle, WA, United States
²Division of Public Health Sciences and Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA, United States

ABSTRACT

Introduction: It is unclear if direct oral anticoagulants (DOACs) are effective and safe alternatives to low-molecular-weight heparin (LMWH) for the treatment of cancer-associated venous thromboembolism (VTE). We aim to synthesize existing literature that compared DOACs versus LMWH in this high-risk population.

Materials and methods: We conducted a systematic review using EMBASE, MEDLINE, and CENTRAL, for all observational studies and randomized controlled trials (RCTs). PROSPERO: CRD42017036888. Two authors independently reviewed study eligibility, extracted data, and assessed bias. Primary outcomes included 6-month recurrent VTE and major bleeding. Secondary outcomes included clinically relevant non-major bleeding (CRNMB) and mortality.

Results: We screened 420 articles, reviewed 25 in full-text, and selected 13 and 2 for qualitative and quantitative synthesis, respectively. Based on a meta-analysis of the 2 RCTs, DOACs had lower 6-month recurrent VTE (OR=0.67; 95% CI=0.43-1.012). However, DOACs had higher major Bleeding (46/725) when compared to LMWH (23/727) (OR 1.74 (1.05-2.86)). Similarly, CRNMB was higher (OR 2.31 (0.85-6.20)) for patients receiving DOACs. There was no difference in mortality (OR 1.65 (0.85-1.26)). Observational studies were heterogeneous with high risk of bias but showed recurrent VTE rates consistent with the meta-analytic.  

Keywords: Venous thrombosis, DOAC, LMWH, Cancer, Anticoagulation
### Recurrent CAT

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th></th>
<th>LMWH</th>
<th></th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskob 2017 Events</td>
<td>34</td>
<td>22</td>
<td>12</td>
<td>24</td>
<td>73.4%</td>
<td>0.740 (0.48, 1.14)</td>
<td>3.9% vs 8.8%</td>
<td>5.5% vs 3.2%</td>
</tr>
<tr>
<td>Young 2017 Events</td>
<td>8</td>
<td>203</td>
<td>18</td>
<td>203</td>
<td>26.6%</td>
<td>0.440 (0.20, 1.00)</td>
<td>3.9% vs 8.8%</td>
<td>5.4% vs 3.0%</td>
</tr>
<tr>
<td>Total (95% CI) Events</td>
<td>42</td>
<td>22</td>
<td>64</td>
<td>22</td>
<td>73.4%</td>
<td>0.650 (0.42, 1.01)</td>
<td>3.9% vs 8.8%</td>
<td>HR 1.74 (1.1-2.9)</td>
</tr>
<tr>
<td>Total events</td>
<td>725</td>
<td>727</td>
<td>100.0%</td>
<td>6.5% vs 8.8%</td>
<td>5.5% vs 3.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.02$; $Q = 1.21$, df = 1 ($P = 0.27$); $I^2 = 17$

Test for overall effect: $Z = 1.92$ ($P = 0.06$)

### Major bleed

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th></th>
<th>LMWH</th>
<th></th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskob 2017 Events</td>
<td>29</td>
<td>522</td>
<td>17</td>
<td>524</td>
<td>73.5%</td>
<td>1.710 (0.95, 3.06)</td>
<td>5.5% vs 3.2%</td>
<td></td>
</tr>
<tr>
<td>Young 2017 Events</td>
<td>11</td>
<td>203</td>
<td>6</td>
<td>203</td>
<td>26.5%</td>
<td>1.830 (0.69, 4.80)</td>
<td>5.4% vs 3.0%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI) Events</td>
<td>725</td>
<td>727</td>
<td>100.0%</td>
<td>1.74 (1.05, 2.88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>40</td>
<td>22</td>
<td>40</td>
<td>23</td>
<td>73.5%</td>
<td>1.74 (1.05, 2.88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.00$; $Q = 0.01$, df = 1 ($P = 0.91$); $I^2 = 0$

Test for overall effect: $Z = 2.17$ ($P = 0.03$)

### Mortality

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th></th>
<th>LMWH</th>
<th></th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskob 2017 Events</td>
<td>140</td>
<td>522</td>
<td>122</td>
<td>524</td>
<td>69.1%</td>
<td>1.11 (0.90, 1.36)</td>
<td>12.2% vs 8.2%</td>
<td></td>
</tr>
<tr>
<td>Young 2017 Events</td>
<td>48</td>
<td>203</td>
<td>54</td>
<td>203</td>
<td>30.9%</td>
<td>0.890 (0.63, 1.24)</td>
<td>12.3% vs 3%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI) Events</td>
<td>725</td>
<td>727</td>
<td>100.0%</td>
<td>1.03 (0.85, 1.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>188</td>
<td>181</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.00$; $Q = 1.19$, df = 1 ($P = 0.28$); $I^2 = 15$

Test for overall effect: $Z = 3.33$ ($P = 0.74$)

---

**Original Article**

**Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism**

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kalpokas, M.B., B.S., Michael J. Kovacs, M.D., Michèle F. Mercier, M.D., Gay Mayer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Wetz, M.D., and Harry R. Bülfer, M.D., for the Hokusei VTE Cancer Investigators

**Abstract**

---

58
• Compare ≥6 mos & up 12 mos anticoag
   (Knowledge gap: prior studies ≤ 6 mos)
   • Open label, RCT, non-inferiority
     • 1046 (mITT) patients
     • symptomatic & asympt. CA-VTE
     • LMWH (5d)/Edoxaban v LMWH ≥6 m
   • 1ª Outcome: Recurrent VTE +
     Major Bleed (12 mos)

Sponsor: data collection/maintenance; statistical anal
Writing Committee not bound

N=1046; CA-Assoc. SX or ASX VTE (CAT)

• LMWH ≥ 5d
• Edoxaban 60 mg qd (30 mg if GFR 30-50)
• Dalteparin
  • 200 IU/kg x 30d
  • 150 IU/Kg thereafter

1ª Outcome: Recurrent VTE or Major bleed
2ª Outcomes: numerous pre-specified

Clinic/Telephone @ 3, 6, 9, 12 mos
12 mos follow up (9 mos minimum)

Results: (Patients)
64 yr; ~50%F; 23% GFR 30-50; 53% mets; 21% ↑ bld risk
## Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

### Table

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban (N=522)</th>
<th>Dalteparin (N=524)</th>
<th>ARR (NNT)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rec VTE/Maj Bleed</td>
<td>12.8%</td>
<td>13.5%</td>
<td>0.7% (n/a)</td>
<td>0.006 (NI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (Sup)</td>
</tr>
<tr>
<td>At 6 months (Post-hoc)</td>
<td>10.5%</td>
<td>10.7%</td>
<td></td>
<td>0.176 (NI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.98 (Sup)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rec VTE</td>
<td>7.9%</td>
<td>11.3%</td>
<td>3.4% (n/a)</td>
<td>0.09 (NS)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>6.9%</td>
<td>4.0%</td>
<td><strong>2.9%</strong></td>
<td>0.04</td>
</tr>
</tbody>
</table>


## Major Bleeding Risk
(Sensitivity Analysis, Supplement)

- Trends across many subgroups
- But....increased signal with

- **Locally adv**
  - 8.1%/4.1%
- **GI Cancer**
  - 13.2%/2.4%
- **GU Cancer**
  - 13.2%/0%
What do we do with that?

• Open label trial (needn’t have)
• Aim of trial was ‘greater than 6 months’ (up to 12)
• Guidelines recommend > 12 mos for active ‘CAT’
  o LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C)
  o Who do not have a high bleeding risk, recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B) (Kearon C. et al. ACCP Guideline [Chest 2016])
• AND actually only 58% treated > 6 months
  o 12 mos → 38% DOAC 29% LMWH (“inconvenient”)
  o So did we even answer the question?
• Looks like DOAC’s are at least as effective as LMWH for treatment of Cancer associated VTE (adherence related?)

Future (Recruiting)

• CARRAVAGIO (NCT03045406)
  • Phase 3 RCT, Apixaban for CA-VTE
• CANVAS (NCT02744092)
  • RCT DOAC vs LMWH +/- VKA
  • DOAC’s: apix; edox, rivarox, dabib
DOAC’s appear to be
• At least as good as LMWH with respect to reducing recurrent CA associated VTE
• Result in more significant bleeding than LMWH (particularly in GI, GU & locally advanced malignancies)

Recommendations
• Will be good so see expert recommendations
• Reasonable choice (convenience/adherence?) for CA-VTE, but will require assessing patients values re: risk/benefit of anti-thrombosis vs bleeding risk
Case

- 45-year-old man suffered a new Cryptogenic stroke with good recovery. On evaluation he was only found to have a moderate sized PFO
- What do you do?
  A. Plug it?
  B. Anticoagulation?
  C. Single antiplatelet therapy?
  D. Dual antiplatelet therapy

It seems so obvious (Aristotelian?)

- There a hole
- There’s a stroke
- There’s more strokes (2-5 X↑) in people with holes

<table>
<thead>
<tr>
<th>Relationship between cryptogenic strokes &amp; PFO's</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Younger patients (&lt;55)</strong></td>
</tr>
<tr>
<td><strong>Crypt</strong></td>
</tr>
<tr>
<td>Leak[12]</td>
</tr>
<tr>
<td>Warden[12]</td>
</tr>
<tr>
<td>Cabrad[12]</td>
</tr>
<tr>
<td>De Belder[12]</td>
</tr>
<tr>
<td>Di Tullio[12]</td>
</tr>
<tr>
<td>Haamann[12]</td>
</tr>
</tbody>
</table>

Source: Homma. J Cardiol 2010;56(2):134-141
It seems so obvious (Aristotelian?)

- There a hole
- There’s a stroke
- There’s more strokes in people with holes

- Ergo
- Plug it
- Q.E.D.


PFO Management Options

- 6 RCT’s → med or procedural mgt of PFO’s
- **Only 1** RCT for anticoagulation vs antiplatelet
  - 42 center RCT comparing VKA (warfarin) vs aspirin in stroke patients (42% cryptogenic) in patients with TEE documented PFO’s.
  - No reduction in strokes regardless of group (cryptogenic, size of PFO, if PFO assoc. with ASA (atrial septal aneurysm)

**Effect of Medical Treatment in Stroke Patients With Patent Foramen Ovale**

*Patent Foramen Ovale in Cryptogenic Stroke Study*

Shinichi Homma, MD; Ralph L. Sacco, MD, MS; Marco R. Di Tullio, MD; Robert R. Sevaca, EngScD; J.P. Mohr, MD; for the PFO in Cryptogenic Stroke Study (PICSS) Investigators*

PFO in Cryptogenic Strokes Study (PICSS), Circulation 2002;105(22):2625-31
PFO Management Options

- **6 RCT’s** → med or procedural mgt of PFO’s
- **Only 1 RCT** for anticoagulation vs antiplatelet
- **Plug’m**
  - Old systematic reviews concluded – no benefit
  - Numerous device trials (2 new in 2017)

**New England Journal of Medicine**

CLOSE Trial

REDUCE Trial


**N Engl J Med Sept 2017;377:1033-42**

PFO Management Options

- **Only 1 RCT** for anticoagulation vs antiplatelet
- **Plug’m**
  - Old systematic reviews concluded – no benefit
  - Numerous device trials (2 new in 2017)
  - Two new systematic reviews (2018)

**Annals of Internal Medicine**

Device Closure Versus Medical Therapy Alone for Patent Foramen Ovale in Patients With Cryptogenic Stroke
A Systematic Review and Meta-analysis
(Racaniello, MD; Brown, MD; Selker, MD; Cheong, MD; Seeger, MD; Delgado, MD; Rabinstein, MD; McCarroll, MD; Nudleman, MD; Fieberg, MD; Hackam, MD; Hlatky, MD; et al)

Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale
A Systematic Review and Meta-analysis
(Silke, MS; O’Donnell, MD; Estrella, MD; entrepreneurs, MD; Brott, MD; Goyal, MD; et al)

Ann Intern Med. 2018;168:335-342

PFO Management Options

<table>
<thead>
<tr>
<th></th>
<th>Shah</th>
<th>De Rosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Systematic &amp; meta-analysis</td>
<td></td>
</tr>
<tr>
<td>Trials</td>
<td>5 (all open label)</td>
<td></td>
</tr>
<tr>
<td>Exclusions</td>
<td>1 (Old Device: STARflex; Harm)</td>
<td>4</td>
</tr>
</tbody>
</table>

Methods

Trials: 5 (all open label)
Exclusions: 1 (Old Device: STARflex; Harm)
Evaluated: 4

Conclusion (authors)

“In patients with cryptogenic stroke or TIA with PFO, closure with the STARFlex Septal Closure System device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA”

Additionally, there was 5.7% incidence of atrial fib (5% ARI) and 3.2% Maj. Vasc. Complication (3.2% ARR)
<table>
<thead>
<tr>
<th>Characteristic (notable)</th>
<th>PC-Trial (N=414)</th>
<th>RESPECT (N=980)</th>
<th>REDUCE (N=664)</th>
<th>CLOSE (N=473)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior CVA</td>
<td>37.4%</td>
<td>18.6%</td>
<td>13.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>HTN</td>
<td>25.8%</td>
<td>31.4%</td>
<td>26%</td>
<td>10.7%</td>
</tr>
<tr>
<td>+ Atrial Septal Aneurysm</td>
<td>23.7%</td>
<td>35.6%</td>
<td>13%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Large PFO</td>
<td>19.3%</td>
<td>48.8%</td>
<td>40.7%</td>
<td>92.8%</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>23.9%</td>
<td>13.3%</td>
<td>13.3%</td>
<td>29%</td>
</tr>
<tr>
<td>Missing Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device Group</td>
<td>15.2%</td>
<td>20.8%</td>
<td>8.8%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Med Mgt Group</td>
<td>20%</td>
<td>33.3%</td>
<td>14.8%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Excerpted, Table 1, Shah, Ann Intern Med. 2018;168:335-342
### PC Trial RESPECT REDUCE CLOSE

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2013</th>
<th>2017</th>
<th>2017</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Open-label, prospective, Multicenter, RCT, superiority</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponsor</td>
<td>Industry</td>
<td>Fr Min Health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFO Device</td>
<td></td>
<td></td>
<td>Amplatzer PFO Occluder</td>
<td></td>
</tr>
<tr>
<td>Med</td>
<td>AntiPLT or OAC</td>
<td>AntiPLT</td>
<td>AntiPLT*</td>
<td></td>
</tr>
<tr>
<td>1st Outcome</td>
<td>Death+CVA+TIA/ syst emb</td>
<td>Rec fatal &amp; NF stroke, or death</td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Populations are different (in numerous ways), e.g.</td>
<td>%large PFO</td>
<td>19.3%</td>
<td>48.8%</td>
<td>40.7%</td>
</tr>
</tbody>
</table>

\[ P^2 (De Rosa) \leftarrow 28\%-66\% \rightarrow ? \]

\[ P^2 (Shah) \leftarrow 0-82.5\% \rightarrow ? \]

\( P^2 < 25\% \) is “low” (good)

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### Efficacy Endpoints

**Stroke or TIA** (ARR 2.7%, NNT 39)

**Ischemic stroke** (ARR 2.9%, NNT 34)

**Death (NS)**

**TIA’s**: Device ≈ Med Mgt

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Safety Endpoints

**Atrial Fibrillation (ARI 3.1%; NNH 32)**

- Major Bleeding (NS)
- Occlusion Worse
- Death (NS)

\[ I^2 = 66.25\% \]

**Atrial Fibrillation (ARI 6.2%; NNH 16)**

- Major Bleeding: No Change (2.1% ARR with PFO [NS])
- Occlusion Worse

\[ I^2 = 82.5\% \]

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Summary *(Times they are-a-changin)* - *Maybe!*

- Two new trials shift prior ‘negative’ meta-analyses to new ones ➔ favoring occlusion in patients with cryptogenic strokes.
- Time to start referring for PFO closure in patient suffering cryptogenic strokes?
- Cautions
  - All trials open-label (Biasing towards intervention)
  - Large trial heterogeneity
  - Poor data access/availability
  - Applicability? Have plug use it? Training curve/expertise
Editorial-Highlights cautions but...

- “perhaps its time ...consider 1st (cryptogenic) stroke as a reason to close a PFO”

Its going to happen!

Recommendation
- Be careful! Look for a blinded trial
- Assure ‘experts’ are placing them
- Remember: (at least) 3-6% will still need anticoagulation

Case
- 45-year-old man suffered a new cryptogenic stroke with good recovery. On evaluation he was only found to have a moderate sized PFO.

What do you do?
A. Plug it? Um... maybe (Weak endorsement)
B. Anticoagulation? (NO – PICSS Study)
C. Single antiplatelet therapy? ✓ ✓ ✓ ✓ ✓
D. Dual antiplatelet therapy (No ↓ clot ↑ bleeds)
Case

You are evaluating a 70 year old man with 2 weeks of progressive diplopia, dysarthria, and gait instability. His history is most notable for an pacemaker placed ~ 2000.

Which of the following is... mostly/kinda true of pacemakers, ICD’s and MRI scanning?

A. All pacemakers are safe in 1.5T or less MRI scanners?
B. Only new pacemakers have been shown to be safe in MRI scanners.
C. You can not obtain MRI scans on patients with pacemakers or implantable defibrillators
D. If you turn the switch, the pacemaker will be SUCKED out of the chest and be forever stuck in the MRI gantry

“Déjà vu all over again” – Y Berra

Estimate: Up to 75% of pts with ICD’s or pacers will meet indications for MRI scanning (re: comorbidities


The Name Game

• MRI-Conditional Pacemakers & ICD”s
  • per FDA, there is not increased risk of MRI in patients with these pacemakers.
  • Far less frequent

• Legacy Pacemakers
  • Pacemakers & ICD’s not labeled as MRI-conditional
  • Per FDA --> a contraindication to MRI
  • Most common

Safety of Magnetic Resonance Imaging in Patients with Cardiac Devices

Samuel Nazarian, M.D., Ph.D., Rozann Harford, R.N., M.P.H., Avner A. Rab, M.D., Valerie Webster, M.D., Cara McManus, B.S., Ezra Gross, M.D., Ph.D., Alan Kwan, M.D., Ronald D. Berger, M.D., Ph.D., Hugh Gallo, M.D., Albert C. Lardo, Ph.D., Michael A. Kraut, M.D., Ph.D., Rob R. Kamar, M.D., Ph.D., Gordon L. Zimmerman, M.D., and Henry R. Halperin, M.D.

ABSTRACT

BACKGROUND

Patients who have pacemakers or defibrillators are often denied the opportunity to undergo magnetic resonance imaging (MRI) because of safety concerns. Unlike these devices some current criteria specified by the Food and Drug Administration (FDA) and/or manufacturers recommend that all MRI be avoided in patients with these devices. However, a recent study has raised concerns about the safety of pacemaker and defibrillator devices in patients with MRI

METHOD

We performed a prospective, nonrandomized study to assess the safety of MRI at magnetic field strengths of 1.5 Tesla in 130 patients who had a pacemaker (79%) or a defibrillator (21%), all of whom underwent the procedure for the potential of safe MR imaging. The pacemaker mode was altered to asynchronous mode for pacing-dependent patients and was suspended for other patients. Tachyarrhythmias were diagnosed by an independent laboratory and changes in rates and changes in the status of indicators of potential arrhythmias were monitored. In the absence of serious adverse events, the patients were discharged from the hospital.

RESULTS

Forty-six of 129 patients (36%) in whom MRI was performed had device changes. In 26 patients (20%), device changes occurred during the procedure, and in 20 patients (16%), device changes occurred after the procedure. No patient had a serious adverse event attributable to the MRI procedure. The results of these studies are consistent with those of previous reports in terms of the safety of MRI in patients with pacemakers and defibrillators. The observed changes in lead parameters were statistically significant and did not result in any adverse events.

Limited Number of Patients: The number of patients in this study was limited, and the results may not be applicable to all patients with pacemakers and defibrillators.

Conclusion: MRI is a safe procedure for patients with pacemakers and defibrillators who undergo MRI.
Safety protocol for MRI in the setting of implanted cardiac devices

   - Lead implants >6 wks old?
     - Yes: ALTERNATE TESTING
     - No: Deactivate magnet, rate, PVC noise V-sense & conducted afib response

2. **Any epicardial, abandoned or no-fixation leads?**
   - Yes: Deactivate monitoring & anti-tachy therapies
   - No: Device variables (to compare post MRI)

3. **Pacemaker-Dependent?**
   - Yes: Program VOO/DOO (asynchronous)
   - No: Monitor BP, ECT, O₂, Sa and symptoms during MRI

4. **Device variables**
   - ICD: Pacemaker Dependent
   - No: Program VVI/DDI (Inhibited)

5. **Deactivate monitoring & anti-tachy therapies**
   - Monitor BP, ECT, O₂, Sa and symptoms during MRI
   - Recheck device variables & compare vs baseline.
   - Restore original programming
   - F/U interrog @ 3 & 6 mos

**Take Home:**
- Caution remains: Applicability?
- What if device dependent?
- What if > 1.5 T MRI?
- Must assure a protocol is followed
- Assure HELP is present in case of a CRMD malfunction
- Suggests ICD or pacer is NOT an absolute contraindication to MRI
- Encouraging but...with care.

**References:**
• Same group; continuation of data
• 1500 legacy CRMD’s (500 ICD & 1000 pacemakers)
• 1.5 Tesla non-thoracic MRI scans
• Excluded;
  • Lead implantation < 4 wks prior
  • Permanent surgically implanted or non-functional leads
  • Cutaneous lead placement
  • Pacing dependent & had ICD without asynch. option

**Results**
• No long-term clinically significant adverse events
• 1 device req replace (5th scan; 1 mos left on battery life)
• Most common Adv event (1%) → 50% ↓ p amplitude

**Take Home:**
• It probably won’t be up to us
• Adequate data to act on this (>2000 patients with >># scans)
• All essentially showing the same

http://indigestible.nightwares.com/comics/
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