Top Cardio Trials of 2019

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Hello!

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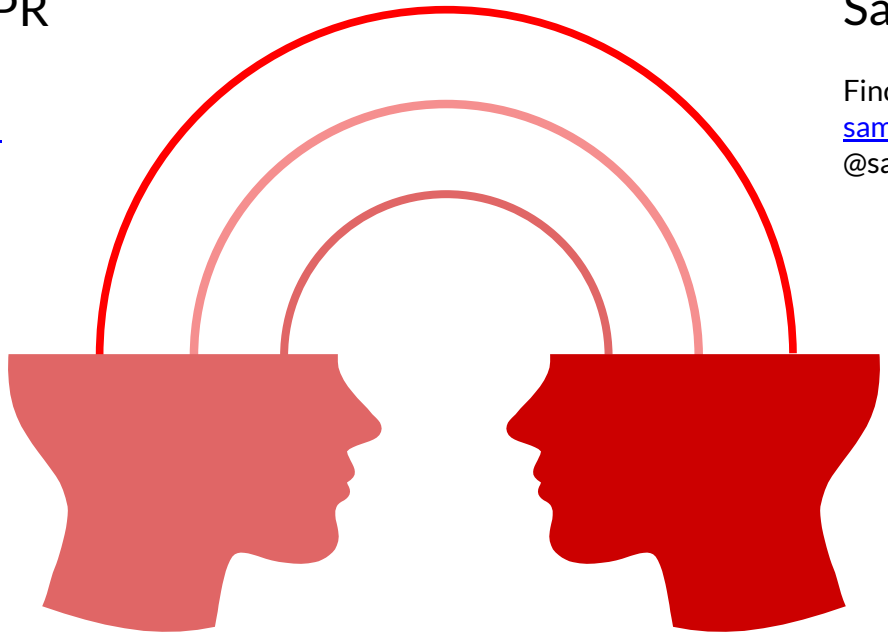

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Presenter Disclosures

- Presenter Name: Aleina Haines, BSP ACPR
  - I have no conflicts of interest to declare
  - I have no current or past relationships with commercial entities
  - I have received an honoraria for this presentation from CCPN

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ex·pert

/ˈekˌspərt/

noun

a person who has a comprehensive and authoritative knowledge of or skill in a particular area.
"a financial expert"
synonyms: specialist, authority, pundit, oracle, resource person; More

We are not critical appraisal experts but we like to practice evidence-based medicine

Learning Objectives

By the end of this presentation, attendees will be able to...

1. Summarize the main results, strengths, and limitations of new cardiology trials presented
2. Determine the applicability of these trials to inpatient and community populations
3. Describe how their practice may change based on the evidence presented

The Trials

- **Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation**
  - Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. New England Journal of Medicine. 2019 Apr 18;380(16):1509-24.
- **Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant**
  - Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. *JAMA Intern Med*. Published online August 05, 2019. doi:10.1001/jamainternmed.2019.2431
- **Comparative Effectiveness of β-Blocker Use Beyond 3 Years After Myocardial Infarction and Long-Term Outcomes Among Elderly Patients**
  - Shavadia JS, Holmes DN, Thomas L, Peterson ED, Granger CB, Roe MT, Wang TY. Comparative Effectiveness of β-Blocker Use Beyond 3 Years After Myocardial Infarction and Long-Term Outcomes Among Elderly Patients. Circ Cardiovasc Qual Outcomes. 2019 Jul;12(7):e005103.

Critical Appraisal of Clinical Trials

- Does the study address a clinical question I care about?
- Are the results of this study valid?
- What were the results?
- Can I apply these results to my patients?

AUGUSTUS:

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

March 2019; NEJM

AUGUSTUS - Trial Background

In AFib patients with ACS or undergone PCI, how does an antithrombotic regimen with apixaban + P2Y12 Inhibitor +/- ASA compare to a VKA + P2Y12 Inhibitor +/- ASA?

Design: multicenter RCT, **2x2 factorial**, open-label trial (apixaban vs VKA arm), 6 months follow-up

- N = 4614
  - Apixaban (n = 2306) vs. VKA (n=2308); Aspirin (n=2307) vs placebo (n=2307)

Population:

- **Inclusion:** 18 years of age, AFib, planned long-term use of OAC, recent ACS or PCI (within 14 days)
- **Exclusion**: OAC for other indication, SCr > 221 umol/L or CrCl < 30 mL/min, history of ICH, recent or planned CABG, coagulopathy or ongoing bleeding, and/or contraindication to any study drug

Outcomes:

1) Major Bleeding or clinically relevant non-major bleeding
2) Composite death or hospitalization; Composite death or ischemic events

AUGUSTUS - Trial Background

Baseline Characteristics:

- Age (median) = 70.7 years; Male = 71% ; White = 91.8 %
- CHA_2DS_2-VASc score = 3.9 +/- 1.6; HASBLED = 2.9 +/- 0.6
- P2Y12 Inhibitor:
  - Clopidogrel = 92.6% ; Ticagrelor = 6.2% ; Prasugrel = 1.1%
- Event:
  - ACS + PCI = 37.3%
  - ACS + Medical Mgmt = 23.9%
  - Elective PCI = 38.8%
- Days to randomization (mean +/- SD) = 6.6 +/- 4.2
- Apixaban 2.5mg BID = 10%
- Median time in therapeutic INR range = 59%
  - Above range = 3%; Below range = 23%

AUGUSTUS – Trial Results

Outcome	Apixaban vs. VKA	Hazard Ratio (95% CI)
Major or clinically relevant non-major bleeding	10.5% vs 14.7%	0.69 (0.58 - 0.81) p<0.001 NNT = 24
Death or Hospitalization	23.5% vs 27.4%	0.83 (0.74 - 0.93) p 0.002 NNT = 26
Death or Ischemic Event	6.7% vs 7.1%	0.93 (0.75 - 1.16)
	ASA vs Placebo	
Major or clinically relevant non-major bleeding	16.1 % vs 9.0%	1.89 (1.59 -2.24) p<0.001 NNH = 14
Death or Hospitalization	26.2% vs 24.7%	1.08 (0.96 - 1.21)
Death or Ischemic Event	6.5% vs 7.3%	0.89 (0.71 - 1.11)

AUGUSTUS - Strengths and Limitations

Strengths

- 2x2 factorial design
- Same dosing as stroke prophylaxis

Limitations

- Open-label trial
- Time in therapeutic INR range = 59%
- 92.6% of patients received clopidogrel
- Study not powered to detect difference in incidence of ischemic events

AUGUSTUS - Conclusions

- Apixaban decreases risk of bleeding event compared to VKA
- Also decreases risk of death and hospitalization
    - Primarily driven by hospitalization
- Use of ASA in “triple therapy” increases risk of bleeding compared to use of placebo
- There is a trend toward increased incidence of ischemic event without ASA
    - Potentially beneficial to keep high risk patients on ASA + apixaban + P2Y12 Inhibitor for a period of time

PAUSE:

Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant

August 2019; JAMA Internal Medicine - Online

PAUSE - Trial Background

In patients with AFib who use a direct oral anticoagulant (DOAC) and request elective surgery or procedure, what is the effect of standardized intervention on rates of bleeding?

Design:

- Prospective cohort; N = 3007 - Apixaban (41.8%), dabigatran (22.2%), rivaroxaban (36%)

Population:

- **Inclusion:** 18 years of age, AFib, planned long-term us of DOAC, scheduled for an elective surgery or procedure; adherence to DOAC therapy interruption protocol
- **Exclusion**: CrCl < 25 ml/min (Apixaban) or CrCl < 30 ml/min (Rivaroxaban, Dabigatran), cognitive impairment or psychiatric illness, did not consent to participate, previous study participation, or more than 1 procedure planned within 30 days

Outcomes:

1) Major Bleeding or arterial thromboembolism (ischemic stroke, systemic embolism, TIA)
2) Clinically relevant non-major bleeding, minor bleeding, death, myocardial infarction, deep vein thrombosis, pulmonary embolism, and catheter-associated venous or arterial thrombosis, undetectable or minimal residual anticoagulant level (<50 ng/mL) at the time of the procedure

PAUSE - Trial Background

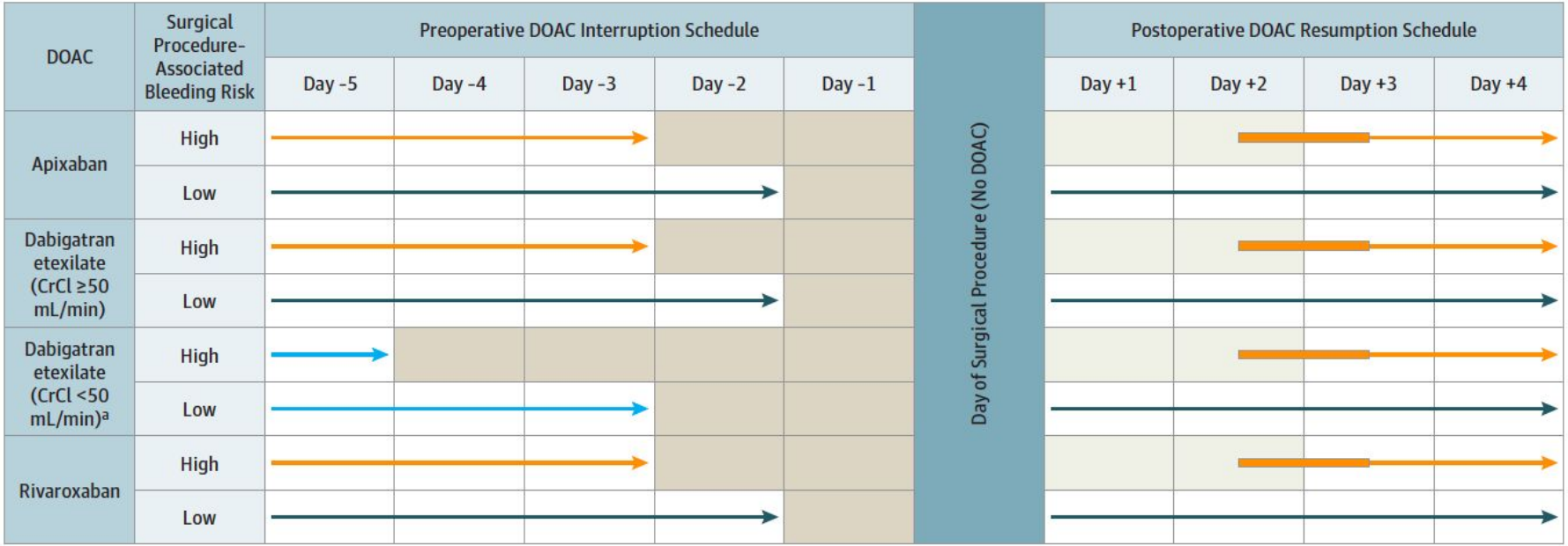
Baseline Characteristics:

- Age: 72.5 [SD 9.39] years; 66.1% men; approx. 95% white ethnicity

	Apixaban (n=1257)	Dabigatran (n=668)	Rivaroxaban (n=1082)
CHADS2 (mean +/- SD)	2.1 (+/- 1.3)	2.2 (+/- 1.3)	2.0 (+/- 1.3)
CrCl, mL/min (mean)	77.9	85.9	82.2
Lower-dose regimen	20%	37.1%	16.7%
High Bleeding Risk Procedure	32.3%	34.1%	34.5%
Low Bleeding Risk Procedure	67.7%	65.9%	65.5%

- 2624 (87.3%) were adherent to protocol

PAUSE - Trial Design



PAUSE - Trial Results

Outcome at 30 days No. (%)	**Apixaban** (n=1257)	**Dabigatran** (n=668)	**Rivaroxaban** (n=1082)
Major Bleeding	17 (1.35%)	6 (0.90%)	20 (1.85%)
Arterial Thromboembolism	2 (0.16%)	4 (0.60%)	4 (0.37%)
Procedure-Associated Bleeding Rate at 30 days %, (95% CI)			
High Bleeding Risk	2.96% (0 - 4.68)	0.88% (0.2.63)	2.95% (0-4.76)
Low Bleeding Risk	0.59% (0 - 1.20)	0.91% (0 - 2.01)	1.27% (0 - 2.17)

- More than 90% of patients had a minimal or no residual anticoagulant level at the time of procedure

PAUSE - Strengths and Limitations

Strengths

- Definition of thromboembolic and bleed risk
- Follow-up period (30 days)
- Prospective design to identify event rate
- Blinding of assessors

Limitations

- Cohort design - selection bias
- Applicability for higher-risk procedures
- Feasibility of measuring DOAC levels in clinical practice

PAUSE - Conclusions

- A standardized, simple approach to perioperative management of DOACs
    - Eliminates variability in practice
- Low rates of major bleeding and thromboembolism
- No need for bridging with heparin products
- No need for coagulation function testing

Comparative Effectiveness of B-Blocker Use Beyond 3-Years After Myocardial Infarction and Long-Term Outcomes Among Elderly Patients

July 2019; Circulation: Cardiovascular Quality and Outcomes

β-Blockers - Trial Background

In elderly patients (≥ 65 years), discharged on a β-blocker and alive at 3 years post-infarction without recurrent MI, what is the impact of β-blocker therapy?

Design: Observational - retrospective analysis of registry data

- Determined B-blocker use at 3 years and dose compared to target (none, <50%, and >/=50%)
- Followed clinical outcomes over the subsequent 5 years

Population:

- **Inclusion:** 65 years of age or older, post-MI without recurrent MI in 3 year follow-up, on β-blocker at discharge, eligible for Medicare
- **Exclusion**: did not survive first 3 years, hospitalization for recurrent MI, discontinued Medicare coverage within first 3 years of indexed MI

Outcomes:

1) Composite death or hospitalization for MI, ischemic stroke, heart failure
2) Subgroup analysis of primary composite and HF, female sex, MI type, DM, ACEI/ARB use, and age < vs. ≥75y

β-Blockers - Trial Background

Baseline Characteristics:

- N = 6893 patients (28 562 eligible, 24% inclusion)
- Age (median) = 75 years; Female = 53.7% ; White = 86.2%
- Charlson comorbidity index > 3 = 30.9%
- Index MI characteristics:
  - STEMI - 8.3%
  - PCI - 57.3%; CABG - 14.4%
- HFrEF (less than 40%) = 21.8%
- Concurrent medications at discharge:
  - Clopidogrel - 74.9%; ACEi/ARB - 71.7%; Statin - 83.6%
- β-blocker use: 43% using ≥ 50% of the recommended target beta-blocker dose
- Follow-up = mean 8 years (5.2 - 9.2 y)

Trial Results - β-Blocker Use

- 4980 (72.2%) were on a β-blocker at 3 years
- More likely to be female, have diabetes, prior CABG, discharged on other evidence based therapies, to have been seen by a cardiologist in the previous 12 months
- Incidence of Primary Composite Outcome (On vs Not On β-blocker)
  - 52.4% vs. 55.4% (HR, 0.95; 95% CI 0.88-1.03; p = 0.23)
  - There was no statistically significant difference in individual components of the primary composite outcome
    - Not modified by any of the evaluated patient subgroups, including patients with heart failure or systolic dysfunction

Trial Results - β-blocker Dose

- Incidence of primary composite outcome
  - No B-blocker - 55.4%
  - <50% of target dose - 50.8%
  - ≥50%of target dose - 54.2%
- Dosing comparisons:
  - No beta blocker vs. <50% target dose
    - (HR, 0.93; 95% CI 0.85-1.02; p = 0.1)
  - No beta blocker vs. ≥50% target dose
    - (HR, 0.98; 95% CI 0.89-1.07; p = 0.62)
  - <50% target dose s. ≥50% target dose
    - (HR, 0.95; 95% CI 0.87-1.03; p = 0.23)

β-Blockers - Strengths and Limitations

Strengths

- Elderly population
- Stratification of patients according to target dose

Limitations

- Observational data
- Excluded those without Medicare (high risk)
- Selection bias (self-selected for survival and adherence)
- Assessed medication refills only (patient adherence)
- Mortality cause not captured

β-Blockers - Conclusions

- Nearly 3 out of every 4 patients post-MI and ≥65 years remain on β-blockers 3 years post-MI
- No association between β-blocker use and long-term CV outcomes
    - Potentially self-selected to do well post-MI
    - Excluded all patients with re-infarction, highest risk for and benefit to use of B-blocker
- The role of prolonged β-blocker use, particularly in older adults, needs further investigation

Key Practice Changing Points

AUGUSTUS:

- Drop the ASA to minimize bleed risk: optimal time to discontinue not known
  - Discuss with the patient care team and the interventionalist on a patient by patient basis
- Apixaban lower bleed risk than VKA

PAUSE:

- Hold DOACs 1 day prior to elective surgery (minor procedure), up to 2 days for a major procedure
- Do not need to monitor drug levels for clinical correlation
- Likely do not need heparin

B-Blockade:

- Reassess need for B-blockade after 3 years in patients post-MI
- Determine need for agent on a patient by patient basis
- Still need more information to guide therapy

Critical Appraisal of Clinical Trials

- Does the study address a clinical question I care about?
- Are the results of this study valid?
- What were the results?
- Can I apply these results to my patients?

Comparison of Trials – Use Caution!

	AUGUSTUS	PAUSE	B-Blockade
Does the study address a clinical question I care about?	✓	✓	✓
Are the results of this study valid?	✓	✓	/
What were the results?	Apixaban + P2Y12	Simple regimen, no heparin	No difference to CV outcomes after 3 years
Can I apply these results to my patients?	✓	✓	✗

Honorable Mentions

Potentially practice-changing but yet to be (or newly) published...

Honorable Mentions from ESC

- ISAR-REACT 5
  - Prasugrel vs. ticagrelor for ACS
  - Composite death, MI or stroke was 30% higher in the ticagrelor arm
  - No difference in bleeding
- DAPA-HF
  - Dapagliflozin reduced HF events or CV death by 26% in patients with DM and without DM who had HFrEF
- PARAGON-HF
  - In patients with HFpEF, Entresto made no significant impact on outcomes
- THEMIS
  - Diabetic patients with CAD
  - No previous history of MI or stroke
  - Ticagrelor decreased primary endpoint CV death, MI and stroke - increased TIMI major bleeding
- POPULAR-AGE
  - Clopidogrel vs. ticagrelor or prasugrel among patients ≥70 years with NSTE-ACS
  - Lower bleeding with clopidogrel

Abbreviations

- RCT = randomized controlled trial
- AFib = atrial fibrillation
- ACS = acute coronary syndrome
- PCI = percutaneous coronary intervention
- VKA = vitamin K antagonist
- OAC = oral anticoagulation
- SCr = serum creatinine
- CrCl = creatinine clearance
- ICH = intracranial hemorrhage
- CABG = coronary artery bypass grafting
- INR = international normalized ratio
- CV = cardiovascular