KANSAS INITIATIVE FOR STROKE SURVIVAL

A PROJECT BY AND FOR KANSANS

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Cryptogenic stroke

"First Tuesdays" Lecture Series

Introduction and Goal of “First Tuesdays”

- Sabreena Slavin MD – Vascular Neurologist and Neurohospitalist at KU School of Medicine
- Didactic lecture series as part of the Kansas Initiative for Stroke Survival
- Updates in Practice and FAQ’s on Acute Stroke Care
- 30 minutes for didactics and questions/discussion.

Traditional terminology

- Stroke etiology per TOAST Criteria
  - Large-artery atherosclerosis
  - Cardioembolic stroke
  - Small vessel disease (lacunar)
  - Other cause (eg: hypercoagulability, vasculitis, etc)
  - “Cryptogenic cause”: about 1/3 of ischemic stroke

- Now switching terminology to **ESUS: Embolic source with undetermined source**
  - Up to 25% of ischemic stroke

Field et al, *Can J Cardiol* 2023

Possible mechanisms for ESUS

- Occult atrial fibrillation
- Atrial cardiopathy
- Paradoxical embolism (through cardiac shunt)
- Valvular abnormalities: endocarditis
- Cardiac failure with reduced ejection fraction
- Atherosclerotic plaque (with <50% stenosis)

Recommended workup

- Extracranial and intracranial vascular imaging (MRA or CTA or direct angiogram for both **head and neck**)
- Transthoracic echocardiogram (transesophageal echocardiogram in some cases)
- Cardiac rhythm monitoring for at least 24 hours: longer term monitoring preferred in clinical practice
- Other workup on case-by-case basis could include malignancy screening (solid tumor adenocarcinoma especially high risk) and hypercoagulable panel (antiphospholipid antibodies)

Table 1. Study characteristics and outcomes in first-generation ESUS trials

Study	N	Major inclusion criteria	Treatment arms	Duration of follow-up	Event rate of primary end point (DOAC vs ASA)	Event rate of safety endpoint (DOAC vs ASA)
NAVIGATE ESUS [3]	7213	ESUS within the past 6 months and aged 60 years or older, or age 50-59 years with 1 additional vascular risk factor	Rivaroxaban 15 mg daily vs ASA 100 mg daily	Median 11 months	Annualized rate of ischemic or hemorrhagic stroke or systemic embolism: 5.1% vs 4.8%; HR, 1.07 (95% CI 0.87-1.33)	Annualized rate of major bleeding (ISTH): 1.8% vs 0.7%; HR, 2.72 (95% CI 1.68-4.39)
RE-SPECT ESUS[4]	5390	ESUS within the past 6 months and aged 60 years or older, or within the past 3 months and age 18-59 years with $\geq$ 1 additional vascular risk factor	Dabigatran 150 mg BID (renal dose reduction to 100 mg permitted) vs ASA 100 mg daily	Median 19 months	Annualized rate of ischemic or hemorrhagic stroke: 4.1% vs 4.8%; HR, 0.85 (95% CI 0.69-1.03)	Annualized rate of major bleeding (ISTH): 1.7% vs 1.4%; HR, 1.19 (95% CI 0.85-1.66)
ATTICUS[14]	352	ESUS within $<$ 7 days and age $\geq$ 18 with $\geq$ 1 of the following: LA size $>$ 45 mm, spontaneous echocardiograph contrast in LA, atrial velocity $\leq$ 0.2 m/s, atrial high rate episodes, CHA_2DS_2-VASc score $\geq$ 4, PFO	Apixaban 5 mg BID (or appropriate dose reduction to 2.5 mg BID) vs ASA 100 mg daily	12 Months	Ischemic strokes or MRI ischemic lesions: 13.6% vs 16.1% ($P = 0.57$)	Annualized rate of major bleeding: 2/178 vs 1/174

Field et al, *Can J Cardiol* 2023

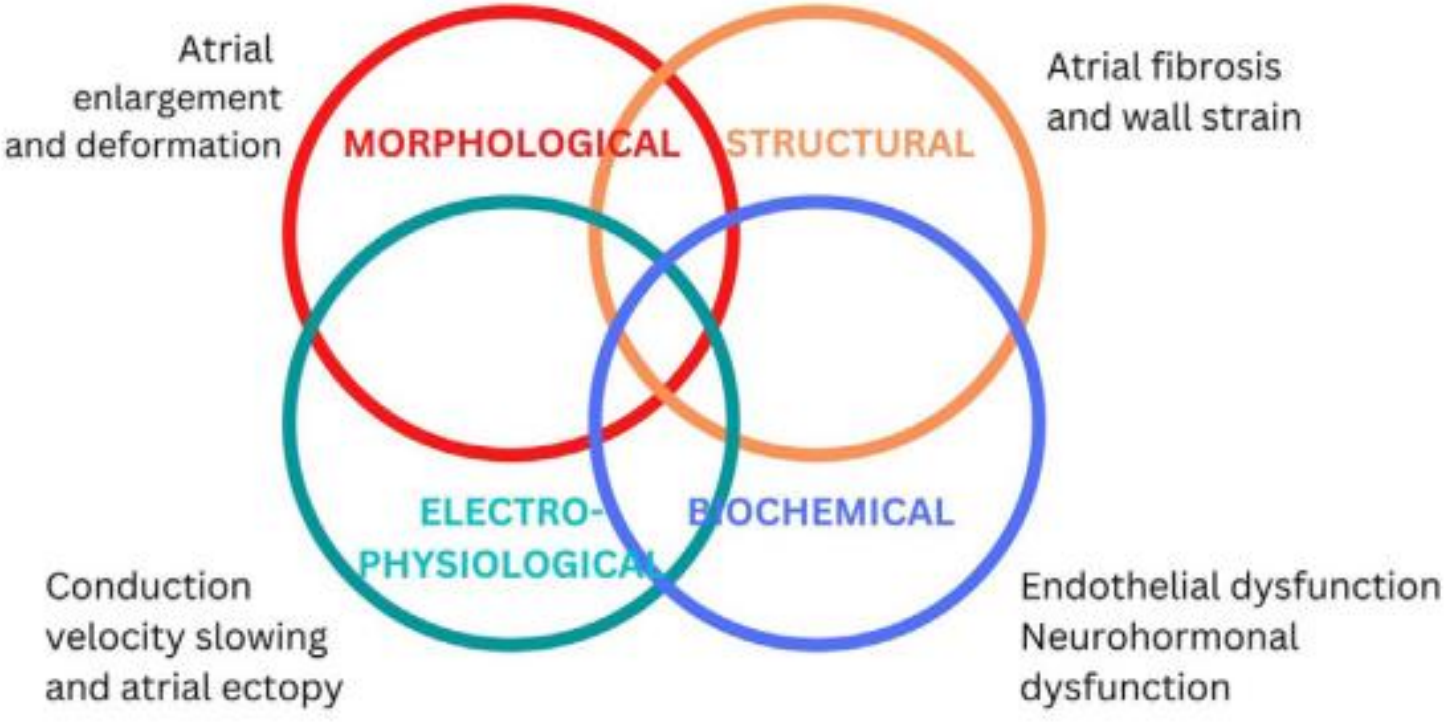


Figure 1. Features of atrial cardiopathy.

Field et al, *Can J Cardiol* 2023

ARCADIA trial

- Multicenter RCT enrolling patients to randomize to Apixaban 5 mg bid vs Aspirin 81 mg daily
- Patients need at least one of these three
  - P-wave terminal force >5000 µV*ms in ECG lead V1
  - Serum NT-proBMP >250pg/mL
  - Left atrial diameter index ≥ 3 cm/m^2

Kamel et al, *ESOC 2023 Abstract*

ARCADIA results

- No differences between Apixaban and aspirin for endpoint of recurrence in all stroke or ischemic stroke/secondary embolism.
- Apixaban had statistically similar rates of symptomatic hemorrhage compared with aspirin (0% in Apixaban group vs 1.1% in aspirin group)
- All-cause mortality was slightly higher in Apixaban group but not statistically significant (1.8% Apixaban vs 1.2% aspirin)

Kamel et al, *ESOC 2023 Abstract*

Longer term monitoring for atrial fibrillation

- EMBRACE: Randomized cryptogenic stroke patients to 30 days of external cardiac monitoring vs 24 hour Holter: 16.1% detected Afib in extended monitoring vs 3.2% in control group.
- CRYSTAL-AF: Randomized cryptogenic stroke patients to implantable loop recorder vs additional ECGs: 8.9% in ILR group vs 1.4% in control group.
- PER-DIEM: Randomized to ILR for 12 months vs external cardiac monitoring for 30 days: 15.3% in ILR group vs 4.7% in external group had Afib detected.

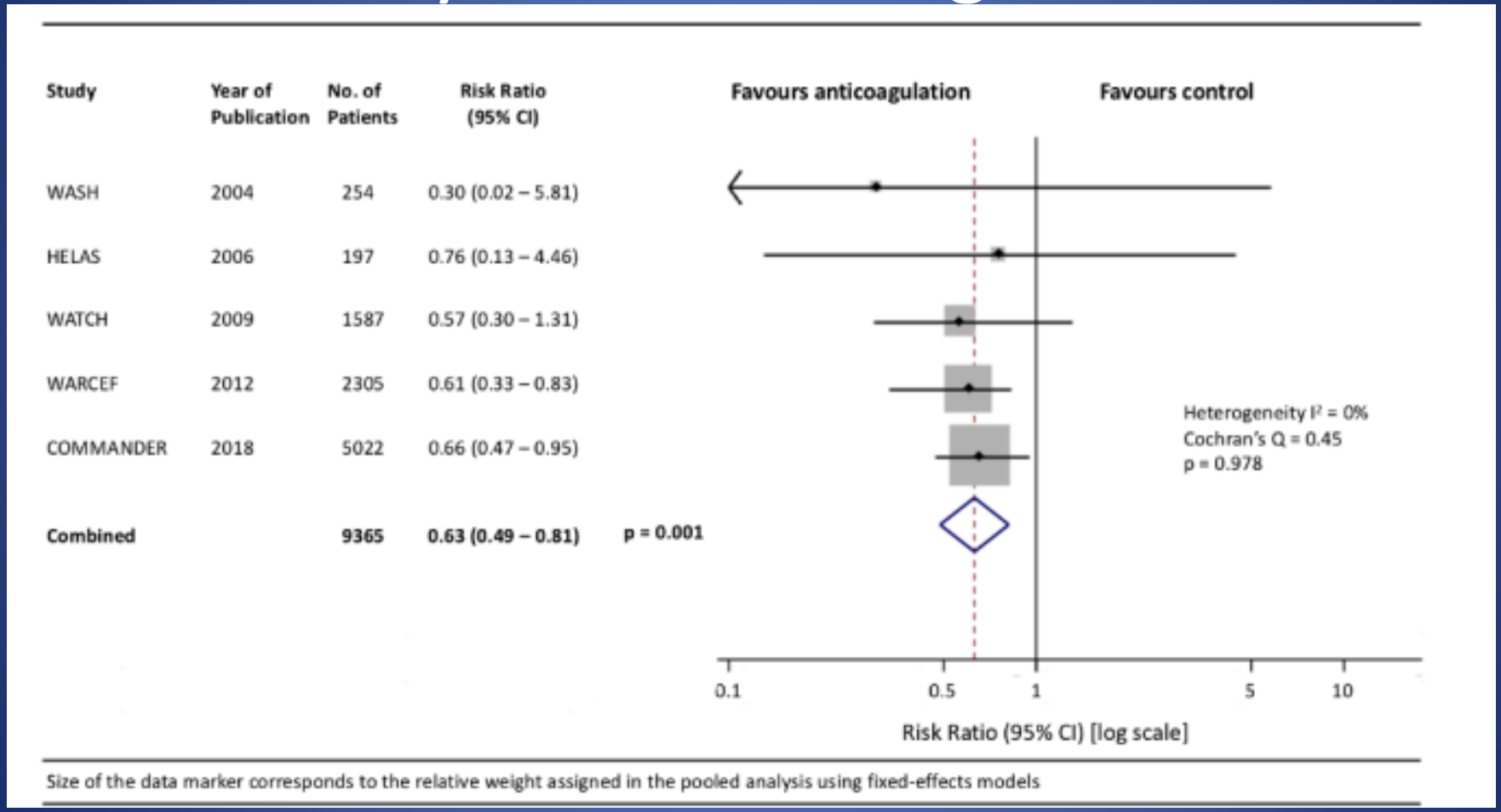
EMRBACE: Gladstone et al, *NEJM* 2014
CRYSTAL-AFSanna et al, *NEJM* 2014
PER-DIEM: Buck et al, *JAMA* 2021

Patent foramen ovale

- Transesophageal echocardiograms obtained for younger patients or those with stroke in multiple vascular distributions
- ROPE score: Uses history of HTN, DM, previous stroke/TIA, smoking, cortical stroke on imaging, and age to determine risk that stroke is due to PFO
- High risk features: larger shunt or association with atrial septal aneurysm
- Recommendation is to close those with high risk

Messe et al, *Neurology* 2020

Heart failure and stroke risk meta-analysis of anticoagulation



Beggs et al, *Heart* 2019

COMMANDER-HF

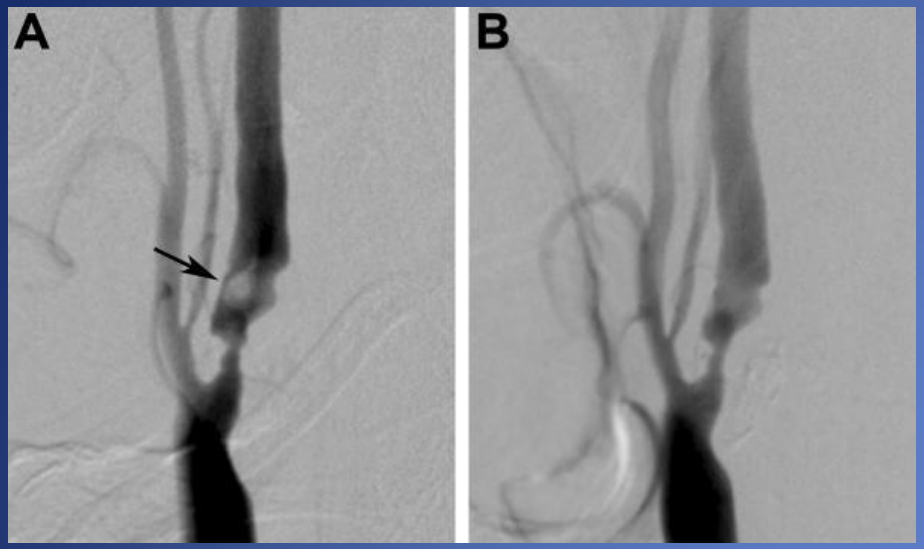
- Randomized patients with EF less than 40% and coronary artery disease who did not have atrial fibrillation to Rivaroxaban 2.5 mg bid vs placebo in addition to standard of care.
- No differences in all-cause mortality or fatal/critical bleeding
- Post-hoc analysis showed that there was a reduction in ischemic stroke for Rivaroxaban group: HR 0.64 (95% CI 0.43-0.95)

Zannad et al, *NEJM* 2018; Greenberg et al, *JAMA Cardiology* 2019

Atherosclerotic embolism

- More risk of atherosclerotic disease as mechanism of stroke other than significant stenosis (>50%):
  - Total carotid plaque area
  - Intraluminal thrombus
  - Intraplaque hemorrhage (high resolution MRI/vessel wall imaging can detect)
  - Higher soft plaque thickness

- Carotid webs are likely underdetected and present a unique stroke mechanism



Vellimana et al, *J Neurosurg 2013*

Wojcik et al, *Ochsner J* 2018

Key points

- Beyond “basic” workup: consider advanced cardiac imaging, long term cardiac monitoring, and advanced vessel imaging for select patients to diagnose ESUS or cryptogenic stroke.
- May often place patients with possible cardioembolic mechanism without definite cause on empiric anticoagulation if they have a second event on antiplatelet (no evidence for this)

Questions?

- Call for help anytime!
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