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Ischemic Stroke Phenotyping System 2025: ISPS25

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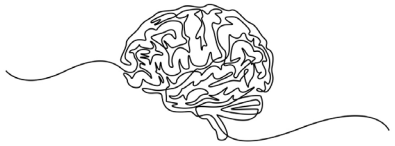


Rhode Island Stroke Symposium

Financial Relationship Disclosure(s)

Shadi Yaghi, MD, FAHA

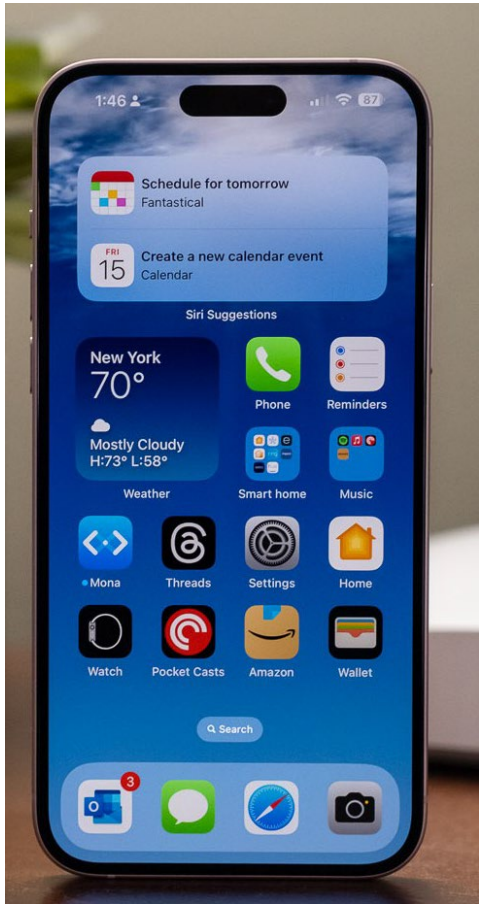
- Nothing to disclose

What year was the first smart phone launched?

1994

2000

2025



What year did the GPS system become fully operational?

1993

When was the first stroke subtyping system launched?

Classification of Subtype of Acute Ischemic Stroke

Definitions for Use in a Multicenter Clinical Trial

Harold P. Adams Jr., MD; Birgitte H. Bendixen, PhD, MD; L. Jaap Kappelle, MD;
José Biller, MD; Betsy B. Love, MD; David Lee Gordon, MD;
E. Eugene Marsh III, MD; and the TOAST Investigators

Background and Purpose: **The etiology of ischemic stroke affects prognosis, outcome, and management. Trials of therapies for patients with acute stroke should include measurements of responses as influenced by subtype of ischemic stroke. A system for categorization of subtypes of ischemic stroke mainly based on etiology has been developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST).**

Methods: **A classification of subtypes was prepared using clinical features and the results of ancillary diagnostic studies. "Possible" and "probable" diagnoses can be made based on the physician's certainty of diagnosis. The usefulness and interrater agreement of the classification were tested by two neurologists who had not participated in the writing of the criteria. The neurologists independently used the TOAST classification system in their bedside evaluation of 20 patients, first based only on clinical features and then after reviewing the results of diagnostic tests.**

Results: **The TOAST classification denotes five subtypes of ischemic stroke: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology. Using this rating system, interphysician agreement was very high. The two physicians disagreed in only one patient. They were both able to reach a specific etiologic diagnosis in 11 patients, whereas the cause of stroke was not determined in nine.**

Conclusions: **The TOAST stroke subtype classification system is easy to use and has good interobserver agreement. This system should allow investigators to report responses to treatment among important subgroups of patients with ischemic stroke. Clinical trials testing treatments for acute ischemic stroke should include similar methods to diagnose subtypes of stroke. (*Stroke* 1993;24:35–41)**

1993

And it is the most commonly used system

CNS Neurosci Ther. 2012 Jan 24;18(6):452–456. doi: 10.1111/j.1755-5949.2011.00292.x

Classifying Ischemic Stroke, from TOAST to CISS

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PMCID: PMC6493455 PMID: 22268862

Abstract

SUMMARY Ischemic stroke classification is critical in conducting basic research and clinical practice. A precise analysis of stroke subtypes requires the integration of clinical features, findings from diagnostic tests, and knowledge about potential etiologic factors by competent diagnostic investigators. We performed a literature review of the published stroke classification systems and examined each for its benefits and limitations in the evaluation of the stroke etiology. Two major approaches to etiologic classifications of ischemic stroke are currently being used: the causative and phenotypic subtyping. The most widely used causative system is the Trial of Org 10172 in acute stroke treatment (TOAST) classification.

3.3.1. TOAST classification **(Radu et al 2017)**

The TOAST classification is the most widely used system for establishing ischemic stroke etiology. It was implemented in 1993 by Adams et al. in order to be used in the Trial of Org 10172 in Acute Stroke Treatment [15]. Although this trial was negative [30], the TOAST classification was further used for a

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TOAST stroke subtype classification in clinical practice: implications for the Get With The Guidelines-Stroke nationwide registry

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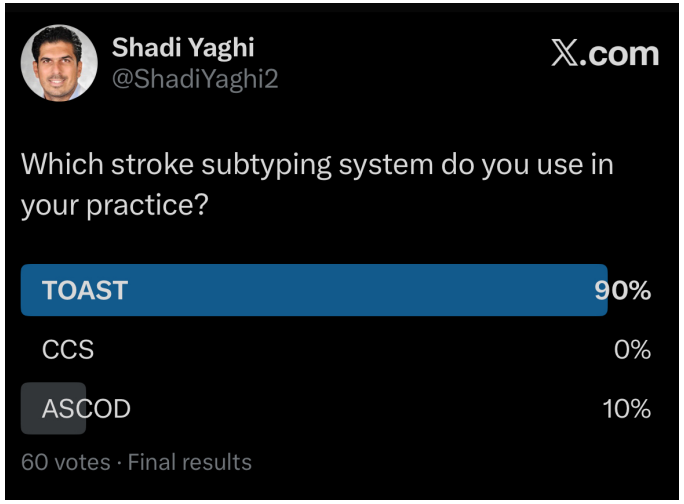
Introduction: The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) is the most commonly used ischemic stroke subtype classification system worldwide and a required field in the US National Get With The Guidelines-Stroke (GWTG-



Why do we need to subtype ischemic strokes?

- Standardized and generalizable approach to stroke
- Geared towards identification of the potential mechanism which may lead to changes in secondary prevention measures
- One size may NOT fit all when it comes to secondary prevention
- Improved patient/family understanding of the stroke and risk of recurrence, leading to improved adherence to secondary prevention measures

Current Classification Systems

- Trial of Org 10172 in Acute Stroke Treatment (TOAST)
- Causative Classification System for Ischemic Stroke (CCS)
- A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: Dissection (ASCOD)

TOAST (Adams et al, Stroke 1993)

- **Cardioembolism:** AF or flutter, recent MI, cardiac thrombus, infective or non-infective endocarditis, low ejection fraction, significant mitral valve disease, myxoma, patent foramen ovale, recent myocardial infarction, and prosthetic valve
- **Large Artery Atherosclerosis:** 50% stenosis or atherosclerotic occlusion of a corresponding artery
- **Small Vessel Disease:** <1.5 cm infarct on CT or MRI
- **Other Determined Etiology:** Non-atherosclerotic vasculopathies, hypercoagulable disorders, and hematological disorders.
- **Undetermined Etiology:** Two or more causes, undetermined cause, or incomplete evaluation

CCS (Ay et al, Annals of Neurology 2005)

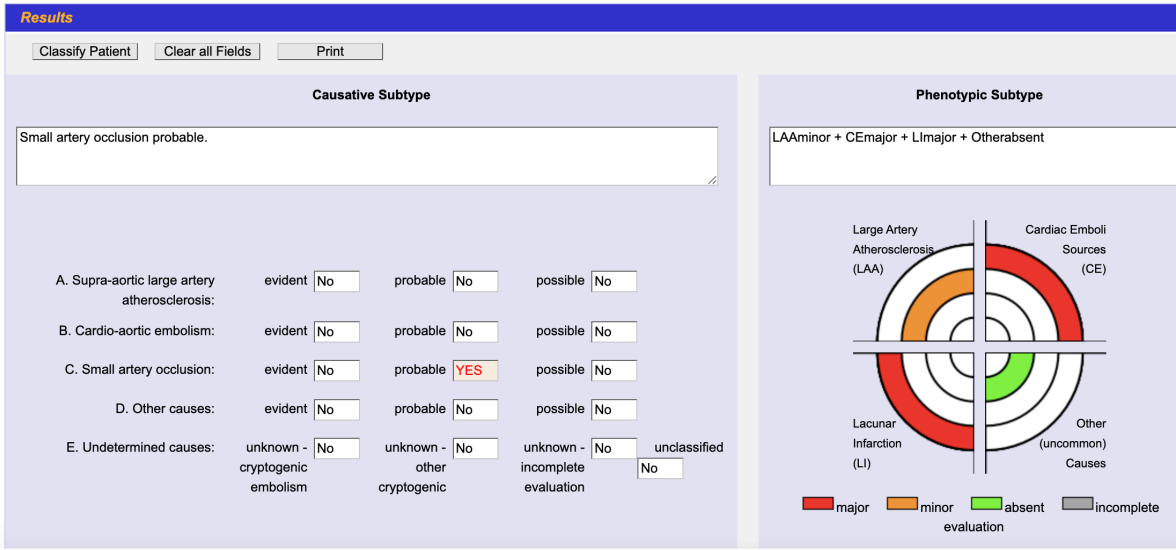
- **<u>Divides TOAST categories into buckets:</u>**

-Evident

- Probable
- Possible

- Includes less established mechanisms such as aortic arch disease, sub-stenotic atherosclerosis, left ventricular hypertrophy, and wall motion abnormalities

- Includes an online calculator with excellent agreement



ASCOD (Amarenco et al, Cereborvascular Diseases 2013)

- Classifies ischemic stroke patients based on the degree of likelihood of causal relationship with every potential mechanism (A = Atherosclerosis, S = Small Vessel Disease, C = Cardioembolism, O = Other, D = Dissection)

- E.g.: If a patient has an embolic infarct and AF as well evidence of severe white matter disease but no atherosclerosis, the ASOCD scoring would be A0S3C1D0.

  - 1 = Present and can be the cause
  - 2 = Present and the causal relationship is uncertain
  - 3 = Present and the causal relationship is unlikely
  - 0 = Absent
  - 9 = workup is insufficient

Limitations of the available systems

- Most of these do not specify the minimum diagnostic required and all do not account for the diagnostic evaluation when the cause is undetermined

- Some include less established mechanisms such as left ventricular hypertrophy and others discount mechanisms such as paroxysmal atrial fibrillation and cancer associated stroke

- Since these classification systems have been published, the field has gained more knowledge about newly reported mechanisms (e.g. carotid artery web), new treatments being effective (e.g. PFO closure), and new diagnostic testing (e.g. prolonged outpatient cardiac monitoring).

THE LANCET
Neurology

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Embolic strokes of undetermined source: the case for a new clinical construct

Dr Prof Robert G Hart, MD [a] · Prof Hans-Christoph Diener, MD [b] · Shelagh B Coutts, MD [c] · Prof J Donald Easton, MD [d] · Prof Christopher B Granger, MD [e] · Martin J O'Donnell, PhD [f] · et al.
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Embolic Stroke of Unknown Source

1. Ischemic stroke detected by CT or MRI that is not lacunar†

2. Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia

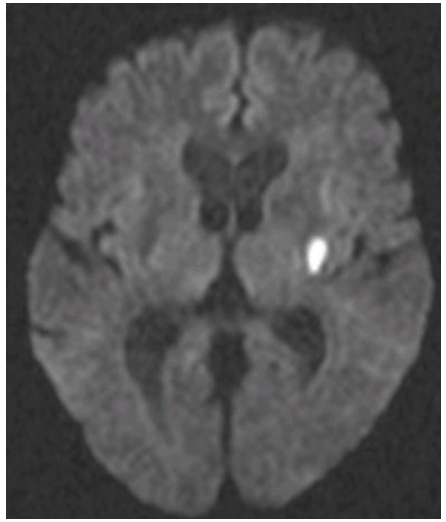
3. No major risk cardioembolic source of embolism‡

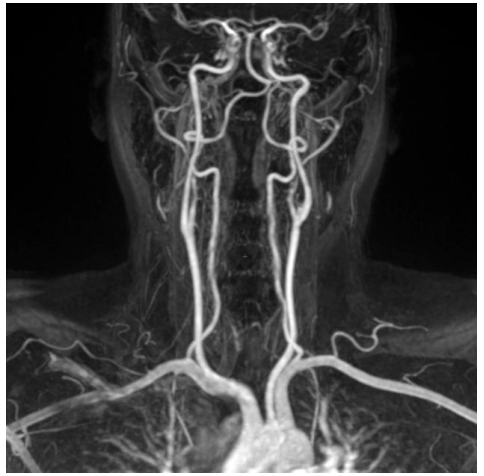
4. No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, and drug abuse)

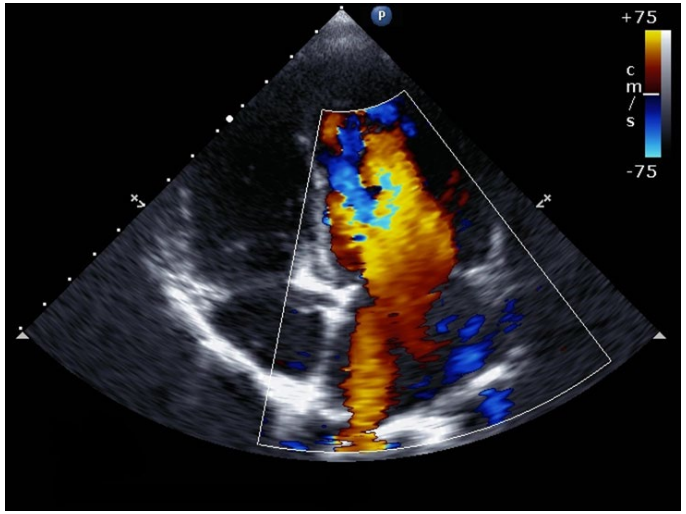
‡Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction <30%, valvular vegetations, or infective endocarditis.

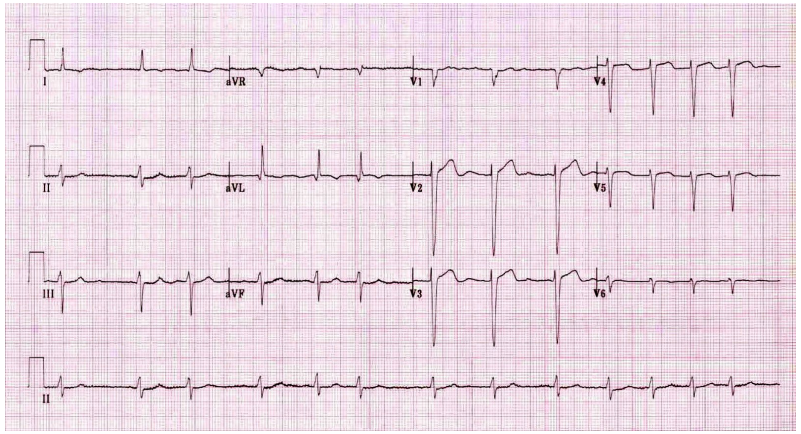
Workup required in ESUS

- Brain CT/MR
- 12-lead ECG
- Precordial echocardiogram
- Extra/intravascular imaging
- Cardiac monitoring for ≥24 hours



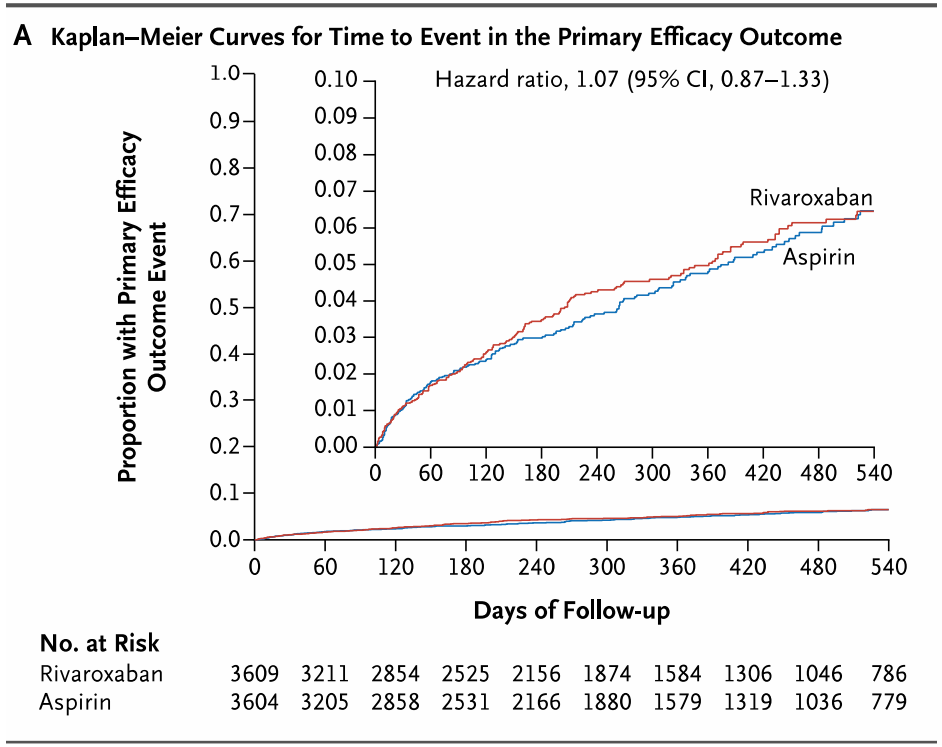


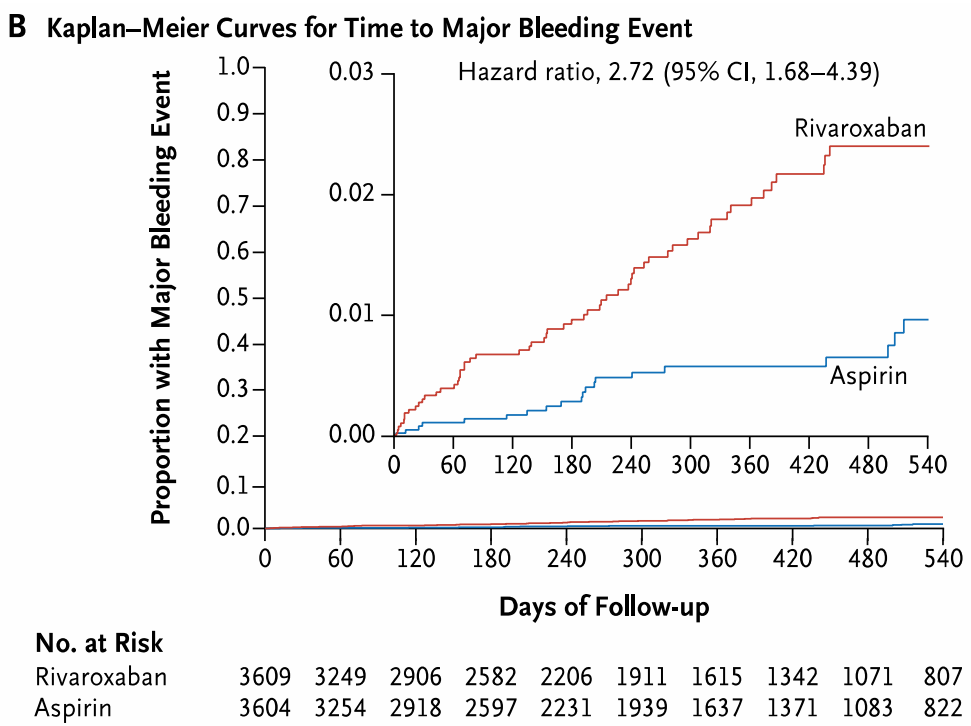




NAVIGATE-ESUS

- Randomized 7213 patients with ESUS to rivaroxaban 15 mg daily vs. aspirin 100 mg daily

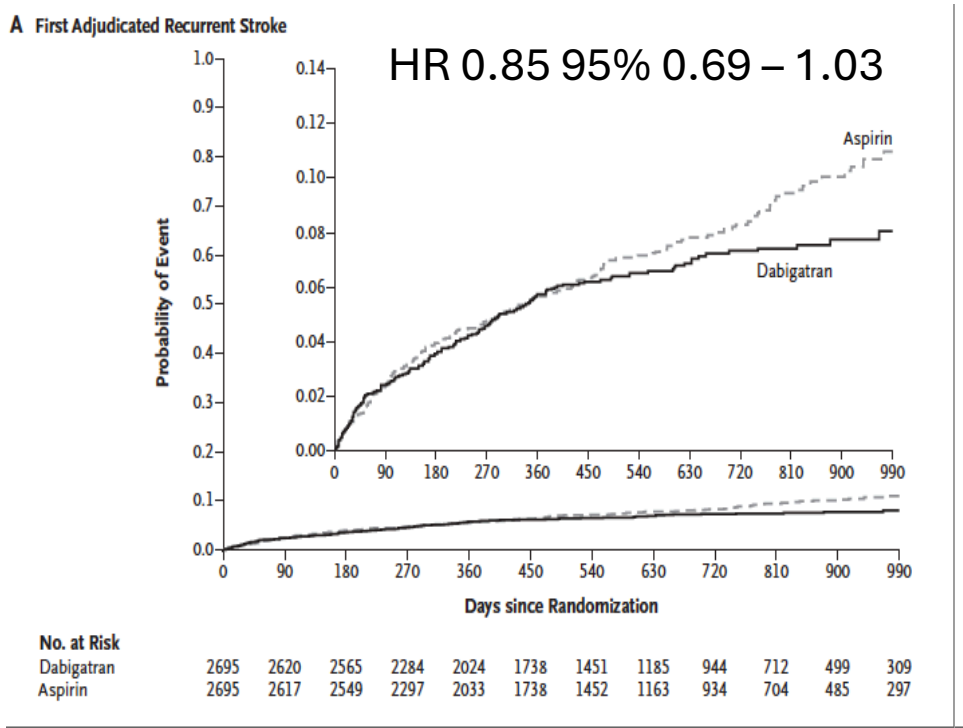


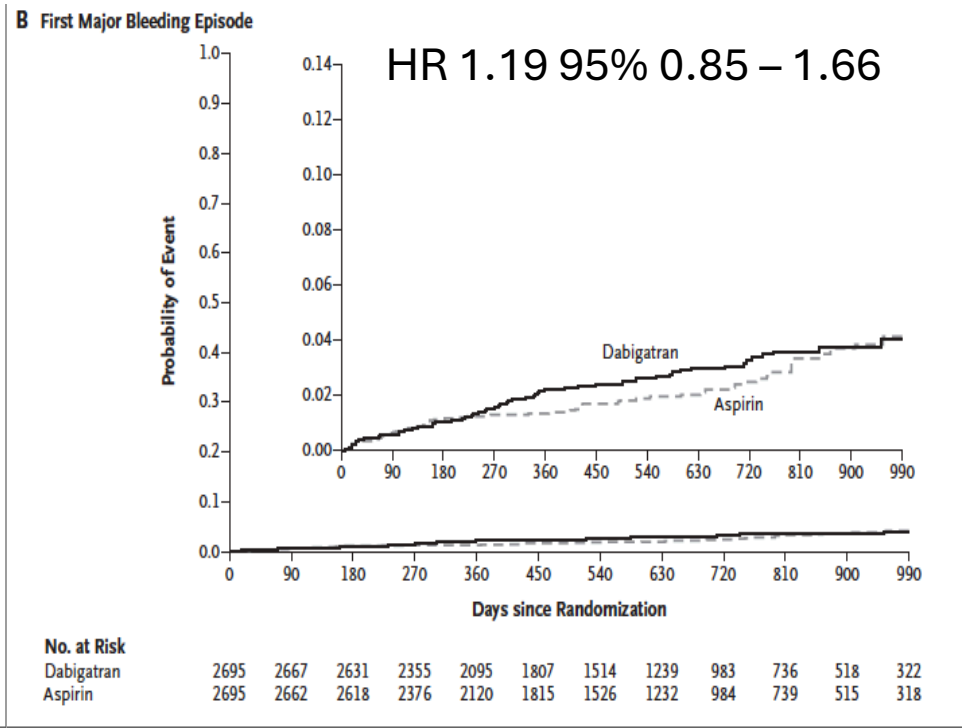


Hart et al, NEJM 2018

RESPECT-ESUS

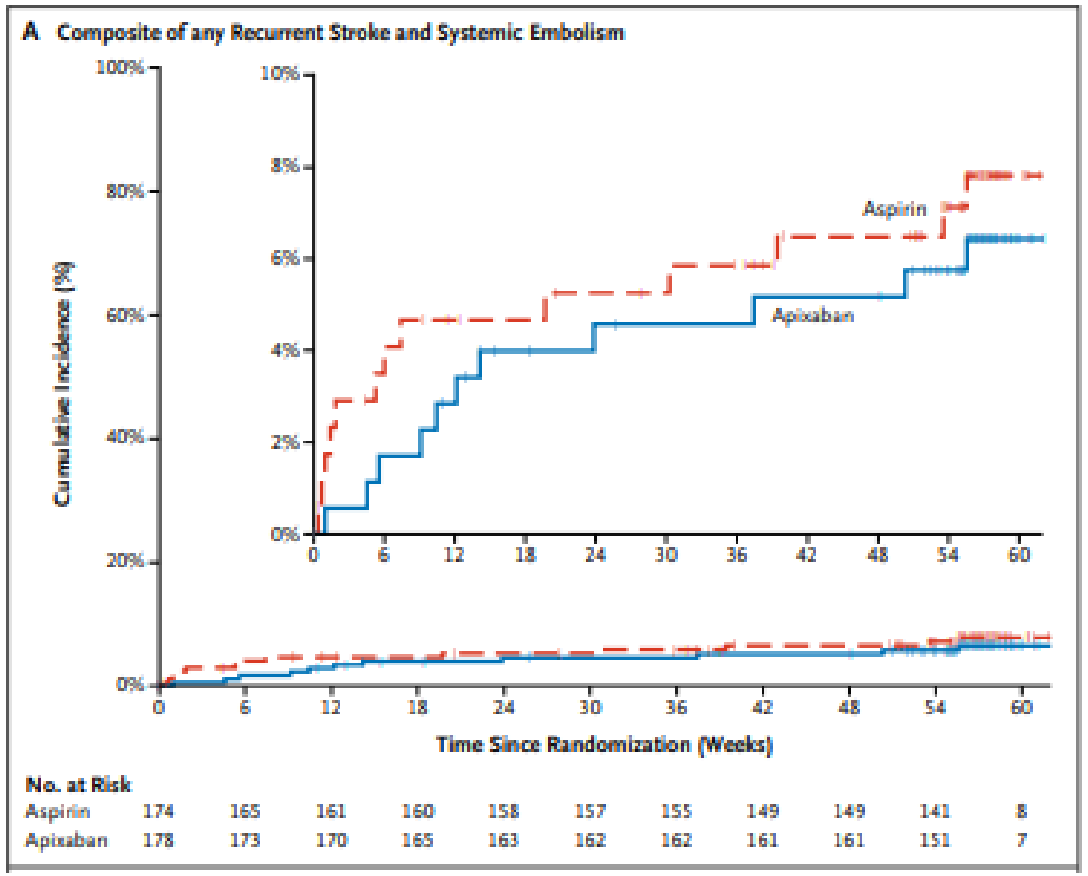
- Randomized 5390 patients with ESUS to aspirin 100 mg daily vs. dabigatran 150 mg BID or 100 mg BID (based on renal function)

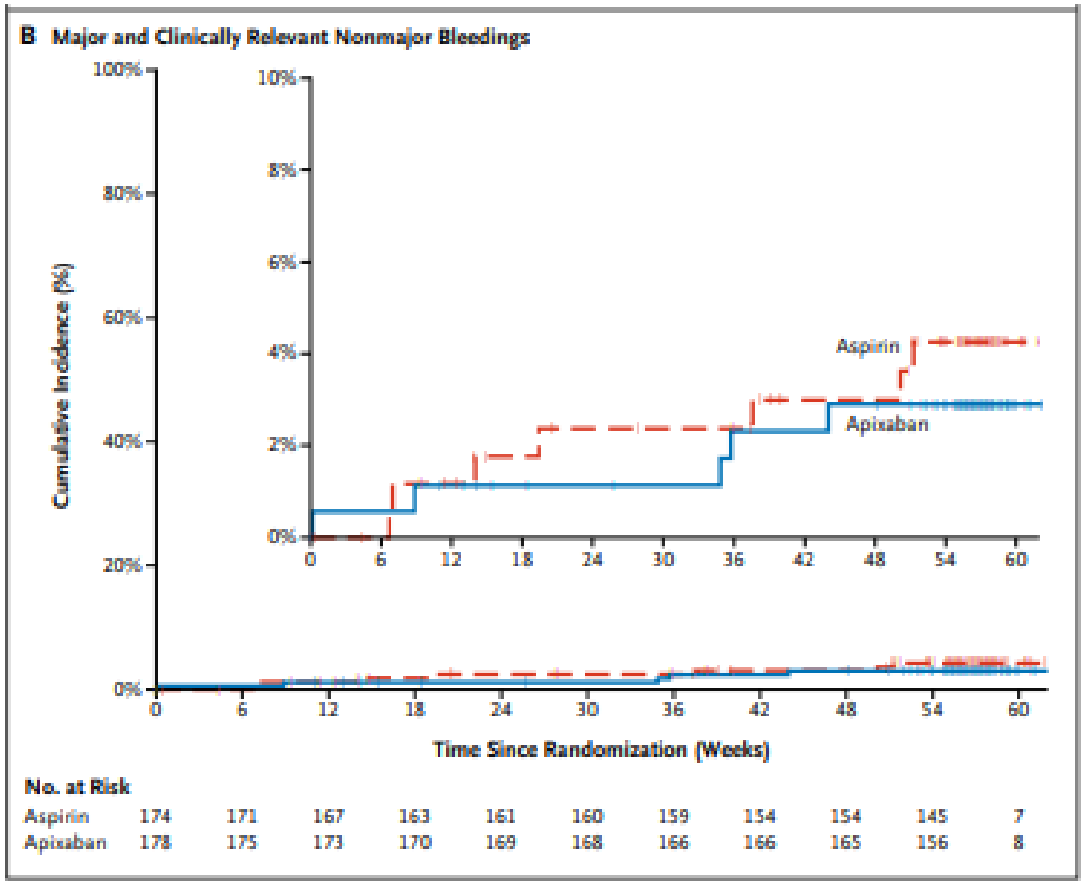




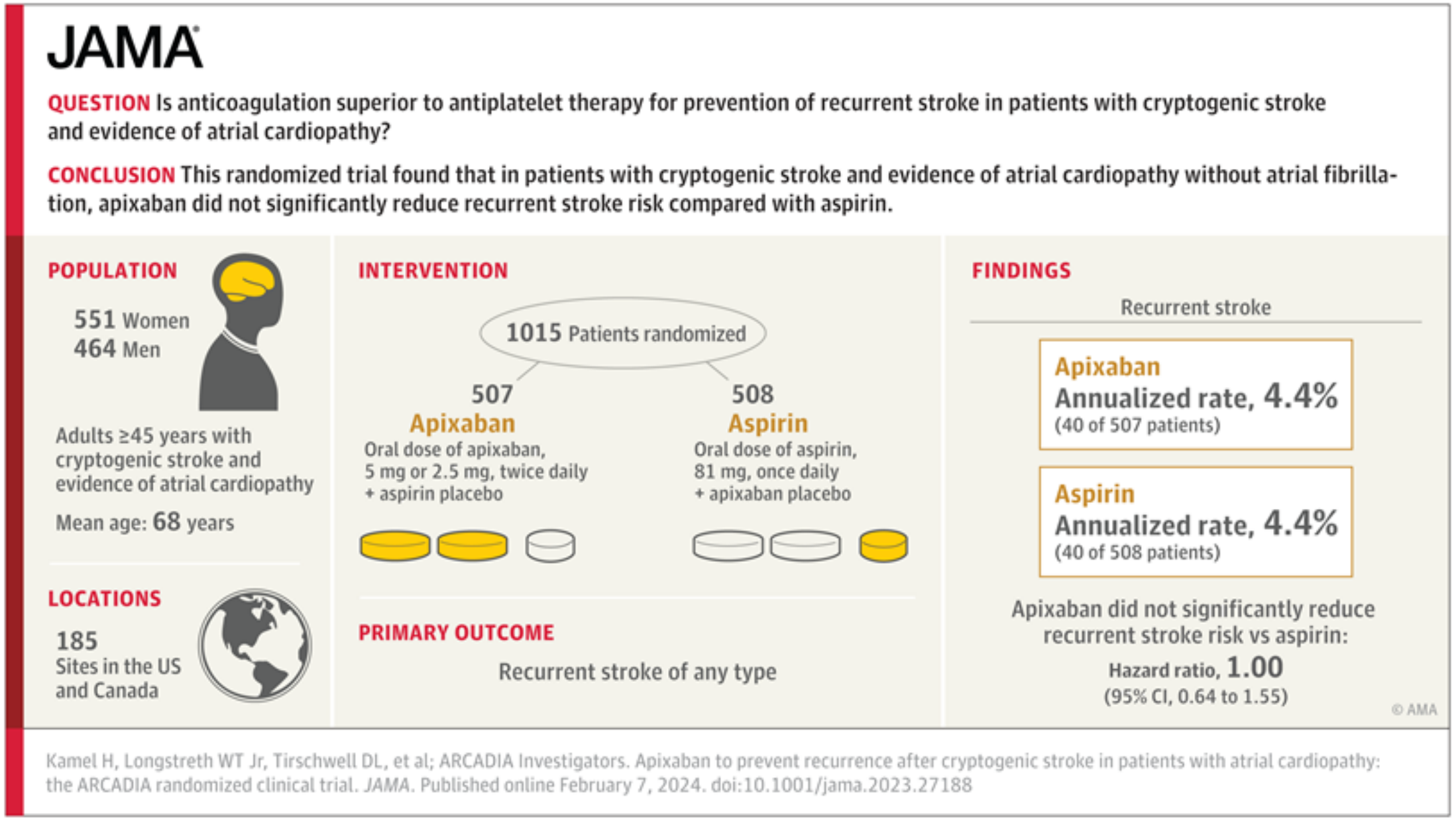
ATTICUS

- 352 patients with ESUS and cardioembolic risk factors, randomized to apixaban vs. aspirin



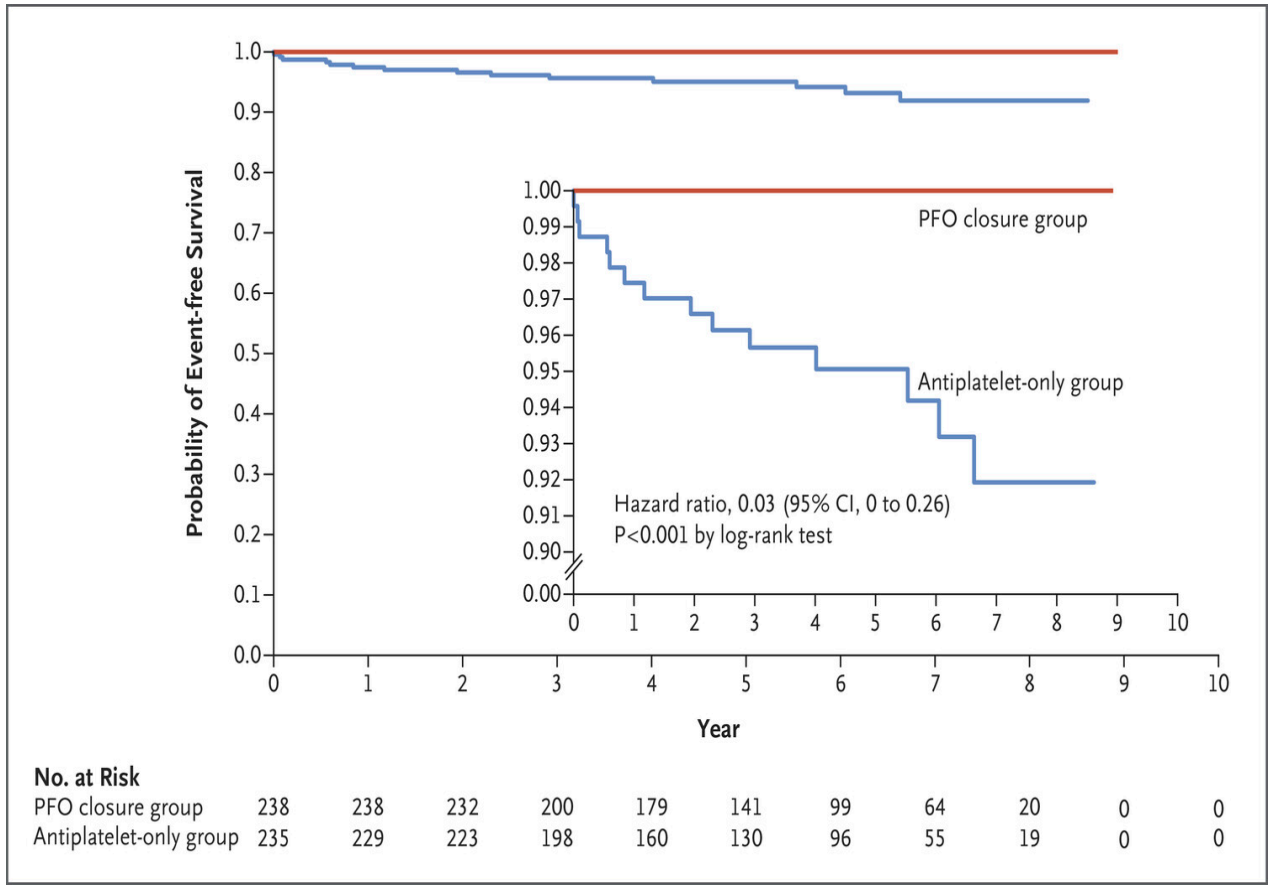


ARCADIA – atrial cardiopathy – negative trial



Positive trials in ESUS subgroups
1. PFO and improved selection

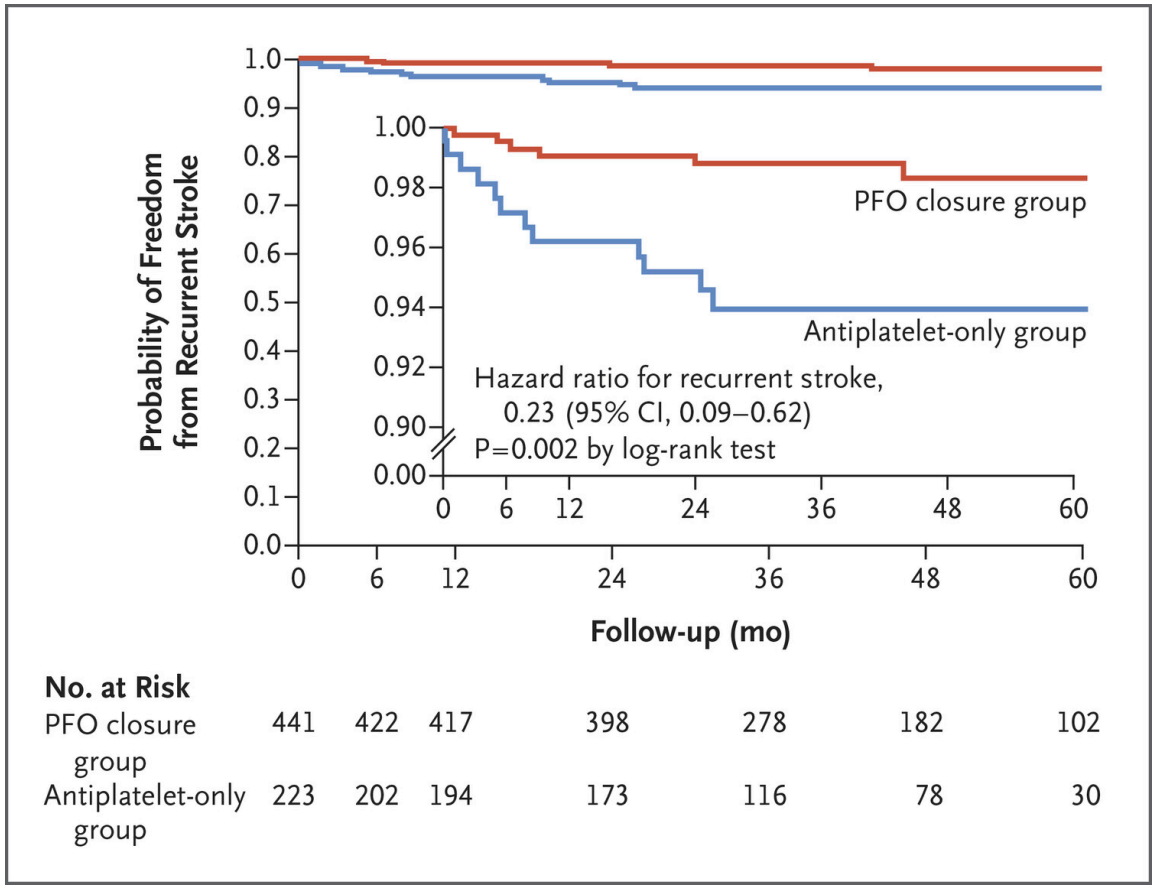
CLOSE trial



No. at Risk

PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

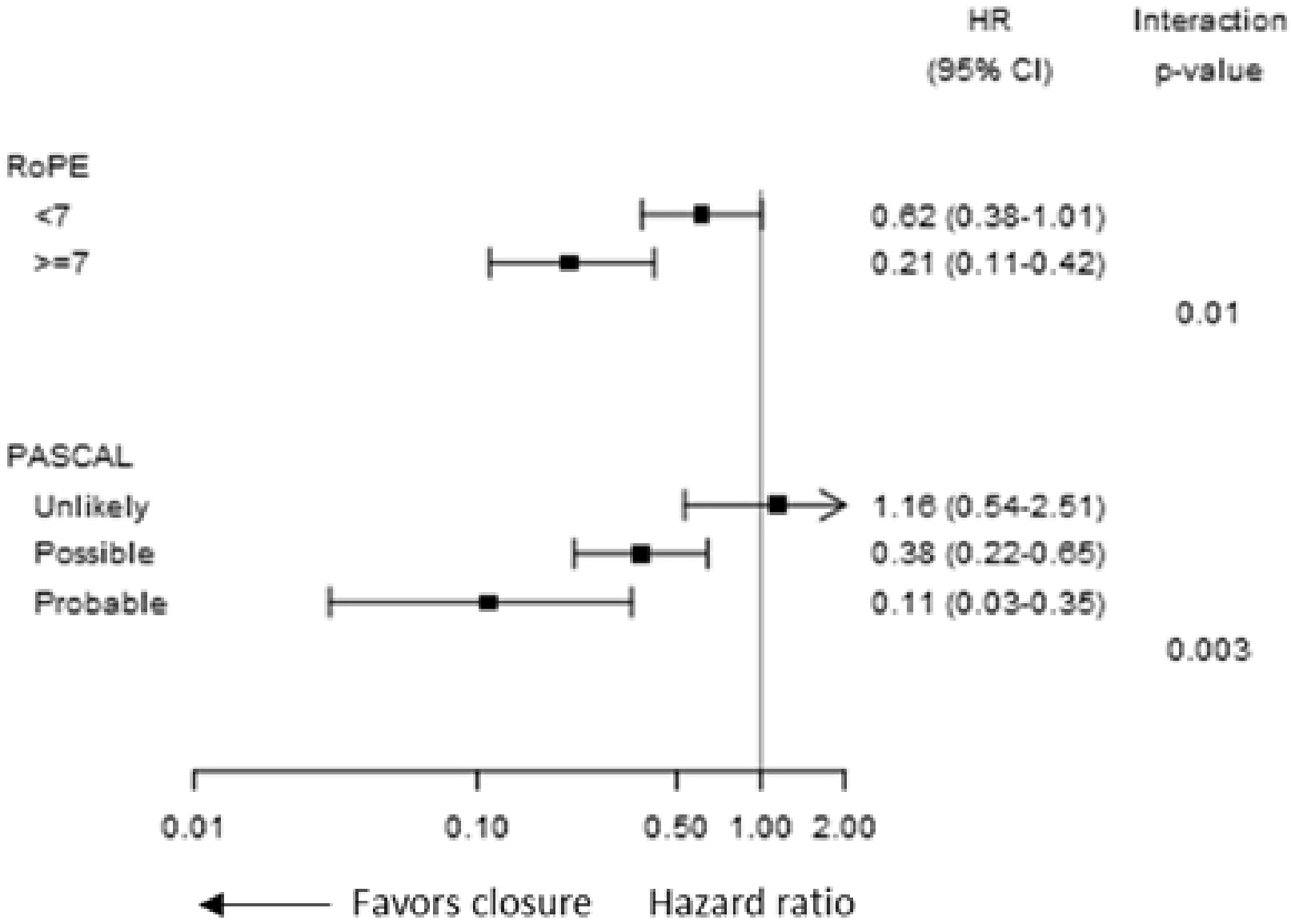
GORE REDUCE trial



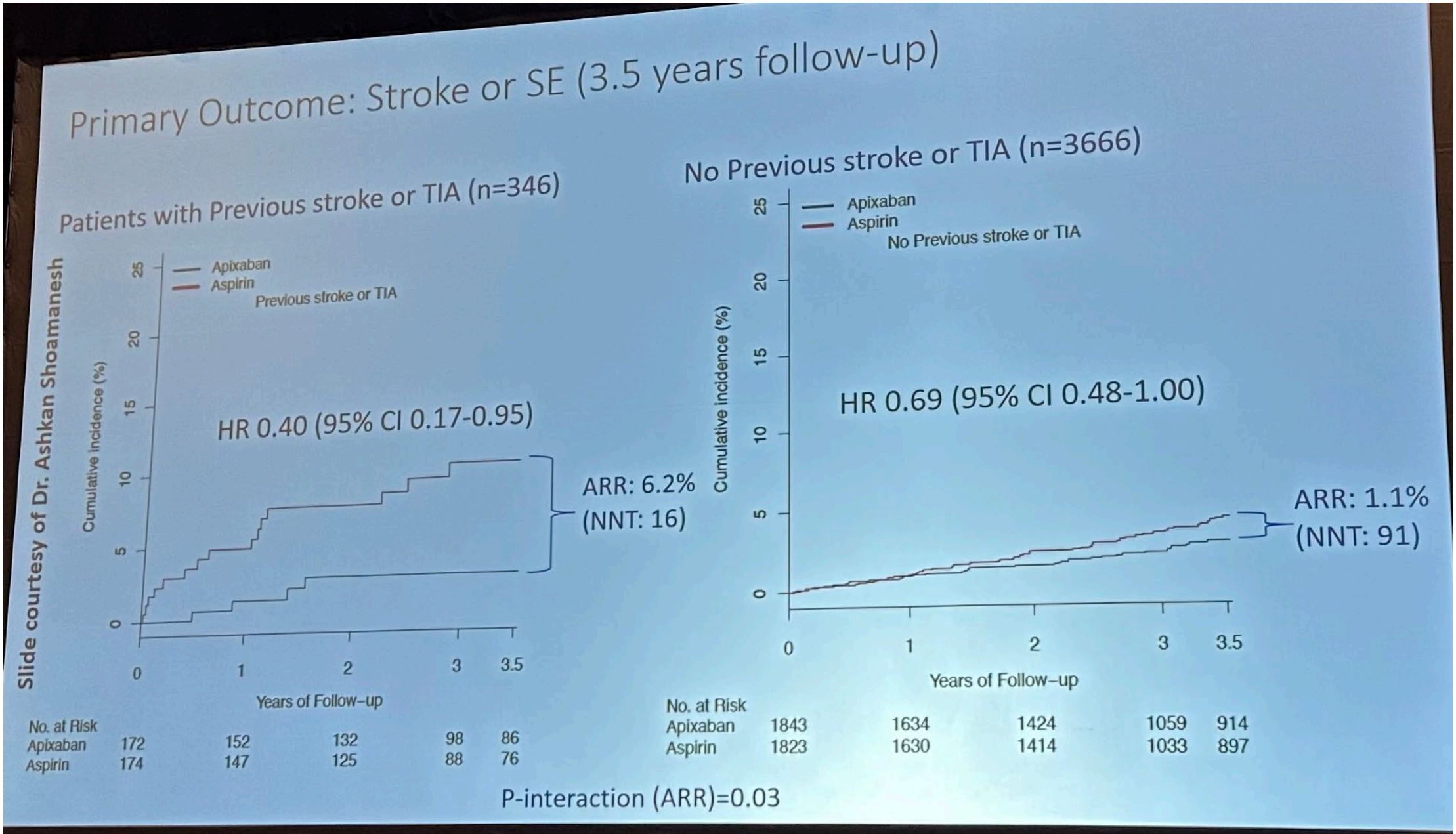
No. at Risk

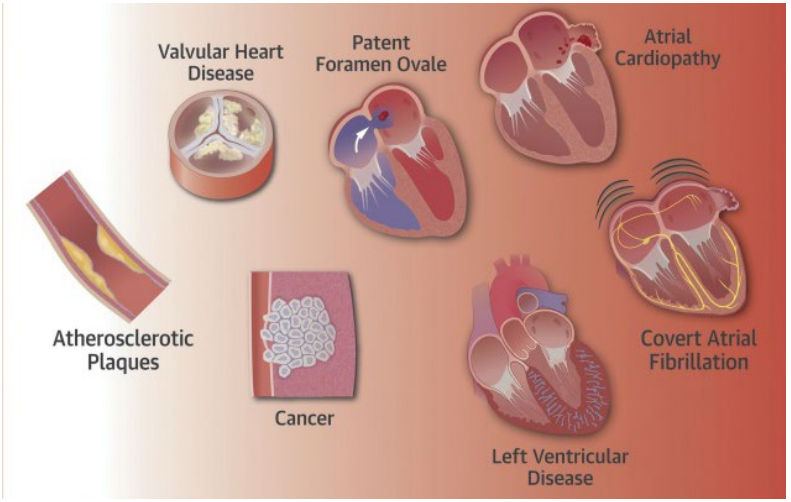
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

PASCAL scoring system (Kent et al JAMA 2021)



2. Device detected AF (ARTESIA)





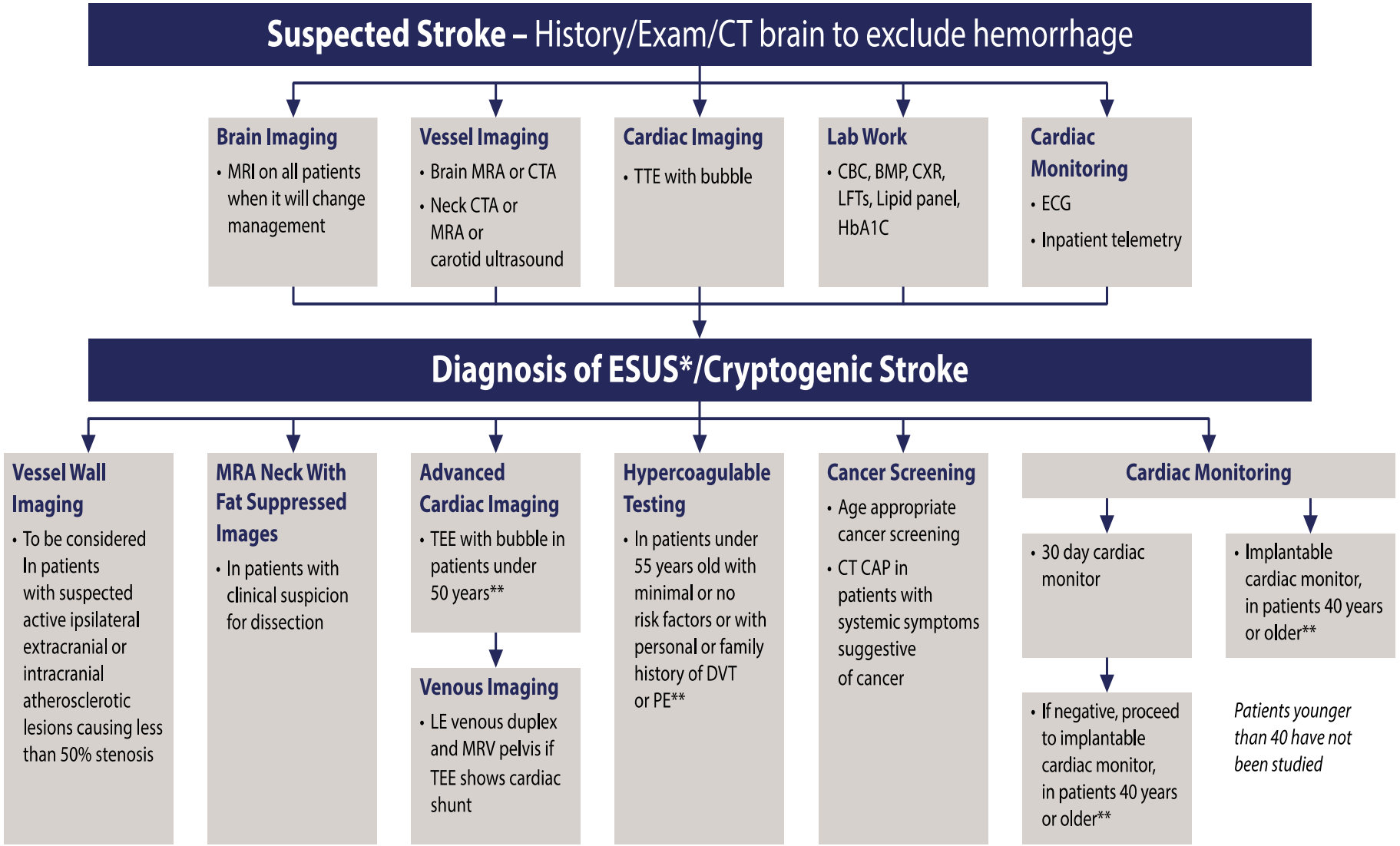
Based on the current definition of ESUS and the workup required, we should NOT treat ESUS as one entity

One size does not fit all

Perform a comprehensive initial evaluation and carefully review initial diagnostic tests

- Look for sub-stenotic high risk atherosclerotic lesions
- Look for non-atherosclerotic vascular lesions such as carotid artery web
- Look for intermediate risk cardiac sources such as left ventricular compaction

EXPAND DIAGNOSTIC EVALUATION



Ischemic stroke standard workup

Rule out

- SVD
- LVD
- High risk cardioembolism (AF, mechanical valve, EF < 30%)
- Other causes: hypercoagulability, dissection, drugs

ESUS (25%)

Advanced workup

Rule out

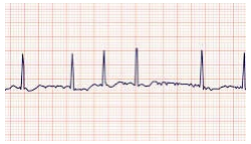
- PFO with PASCAL definite, probable, or possible
- Ipsilateral carotid web
- Ipsilateral cervical artery dissection (not seen on CTA or regular MRA)
- Device detected AF (especially high burden detected early on)
- Cardiac myxoma or fibroelastoma (not seen on TTE)
- High risk atherosclerotic plaque (diagnosed on high resolution MRI)
- APLS (confirmed on repeat testing)
- Occult cancer (in those with B symptoms)

ESUS 2.0 (5%)

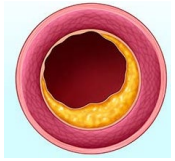
We need an updated classification system

- Include newly established mechanisms such as carotid artery web and cancer associated ischemic stroke
- Specify a minimum diagnostic evaluation required as a first pass and second pass
- Incorporate newly developed tools (e.g. PASCAL) and diagnostic testing (e.g. prolonged outpatient cardiac monitoring)
- Reclassify ischemic strokes in the ESUS bucket after careful review of initial diagnostic tests or after a second pass diagnostic evaluation

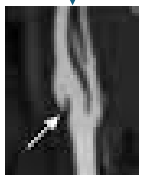
ESUS



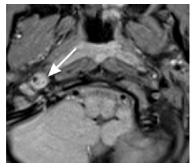
DOAC



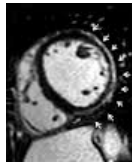
DAPT vs. SAPT



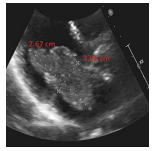
Anti-thrombotic +/- revascularization



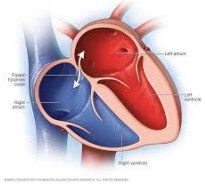
Anticoagulation in high-risk patients with low bleeding risk, otherwise antiplatelets



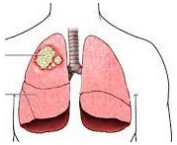
Antiplatelets, clinical trials needed to test DOACs



Surgery



Antithrombotics PFO closure if PASCAL possible or probable



Consider LMWH or DOAC

ANTIPHOSPHOLIPID SYNDROME

Warfarin

Multiprong approach for secondary prevention

- Secondary stroke prevention requires a multipronged approach factoring in all elements that could contribute to a recurrent stroke is important regardless of the etiology of the initial stroke.

- For example, aggressive blood pressure control is associated with a lower risk of hemorrhagic stroke in patients with lacunar stroke, vascular events in patients symptomatic intracranial atherosclerosis, as well as ischemic stroke in patients with atrial fibrillation.

- Furthermore, while most of recurrent ischemic strokes have a similar mechanism as the index ischemic stroke, some may be of different mechanism.

- In the Stroke-AF trial, at nearly 20% of recurrent strokes were attributed to cardioembolism or stroke of undetermined etiology.

Consideration of stroke triggers

- Infection or Inflammation, temporally associated with ischemic stroke

- Whether infection or inflammation constitutes an ischemic stroke mechanism in certain patients who have an otherwise undetermined cause is an open question.

- Whether stroke in the setting of acute infection or inflammation should be targeted by use of anti-inflammatory drugs remains uncertain and more research is needed to address this issue.

Stroke

SPECIAL REPORT

Proposal for the Ischemic Stroke Phenotyping System 2025: ISPS25

Shadi Yaghi, MD; Michelle C. Johansen, MD, PhD; Malik Ghannam, MD; Scott E. Kasner, MD; Nishita Singh, MD; Luciano A. Sposato, MD; James E. Siegler, MD; Nicole B. Sur, MD; Farhan Khan, MD; Hooman Kamel, MD; Mitchell S.V. Elkind, MD; Karen Furie, MD