

Intracranial Stenosis and Cryptogenic Stroke

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Conflict of Interest Disclosure

Disclosure

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Overview

- **Intracranial cerebral artery disease**
- **Cervical artery dissection**
- **Cryptogenic stroke**

Intracranial Cerebral Artery Disease

Case

A 77 year old woman presents with 3 events of word-finding difficulty over a month and new right sided weakness.

**She has been taking aspirin, 81 mg.
Her BP is 157/79 and her LDL is 134.**

CTA head and neck reveals high grade left MCA stenosis.

Case

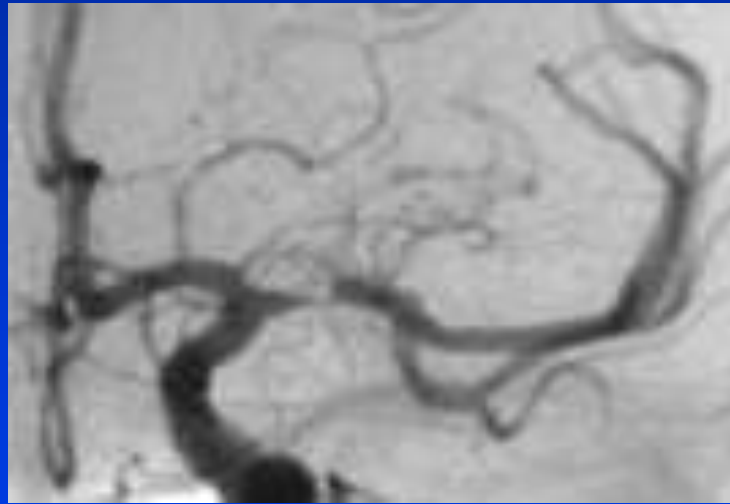
A 77 year old woman with high grade left MCA stenosis:

In addition to risk factor control, what should her management be?

- a) Switch to clopidogrel
- b) Add clopidogrel to the aspirin for 90 days
- c) Treat with a stent and dual antiplatelet agents

Intracranial Stenosis

- **May be the most common cause of stroke worldwide**



Stroke 2008; 39: 2396-2399

SAMMPRIS Randomized Trial

- **Stenting plus medical therapy vs medical therapy alone in symptomatic intracranial stenosis ($\geq 70\%$)**
- **Primary outcome: stroke or death within 30 days, or ischemic stroke in the territory of the qualifying artery beyond 30 days**

SAMMPRIS Intracranial Stenosis Stroke Study: Patient Characteristics

	Medical Group n=227	PTAS group n=224
Age	59.5	61.0
Men	64%	57%
Body mass index (kg/m ²)	30.7	30.3
History of hypertension	89%	89%
Diabetes	45%	47%
Ischemic heart disease	26%	21%
History of lipid disorder	89%	87%
Current tobacco smoker	30%	24%
Ethnicity - white	71%	71%

SAMMPRIS Randomized Trial:

Stenting Plus Medical Therapy vs Medical Therapy Alone

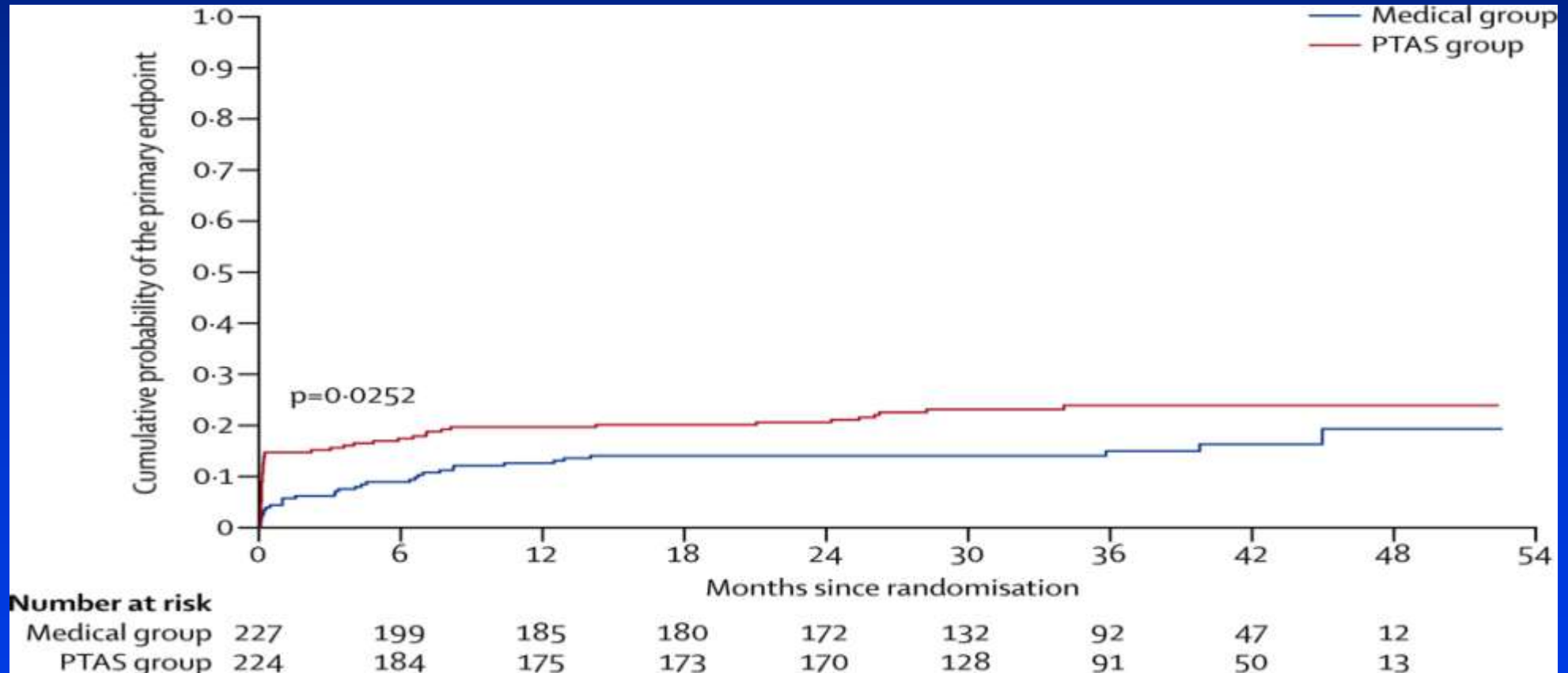
Enrollment halted for 30-day stroke or death rate after 451 patients enrolled (59%)

- Stenting + medical therapy: 14.7% (n=33)**
- Medical therapy alone: 5.8% (n=13) p=0.002**

Symptomatic Hemorrhages Within 30 Days

- Ten of 33 (**30.3%**) strokes in the PTAS group
- None of 12 (**0%**) strokes in the medical group

SAMMPRIS: Cumulative Probability of a Primary Endpoint by Treatment



Implementing Aggressive Medical Management

Antiplatelets

- Aspirin 325 mg per day for entire follow-up
- Clopidogrel 75 mg per day for 90 days

Aggressive risk factor management

- Systolic blood pressure <140 mm Hg
- Low density cholesterol <70 mg/dl

Lifestyle modification

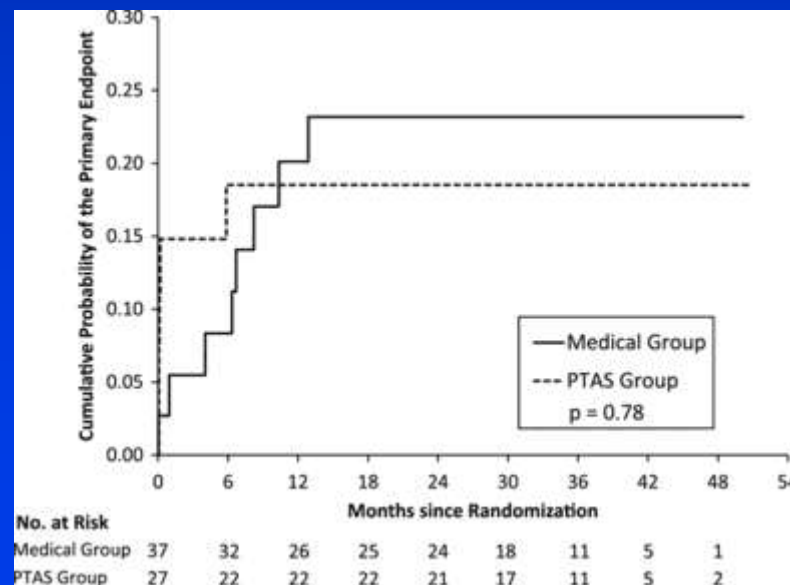
Can Subgroups of SAMMPRIS Benefit From Stenting?

- Those previously on antithrombotic therapy had no benefit
- No assessed subgroup showed benefit

Stroke 2015;46:775-9; *Stroke* 2015, in press

What if on Both Clopidogrel and Aspirin?

- Of these 64, 37 randomized to AMM, 27 to PTAS
- The 2-year rates of the primary end point were 18.5% (95% CI, 8.2%–38.9%) in the PTAS group and 23.2% (95% CI, 12.3%–41.1%) in the AMM group
- Kaplan–Meier curves were not significantly different ($P=0.78$)



How About Those With Hypoperfusion Symptoms?

- 2-year event rates were not different with medical therapy vs stenting ($p=0.5780$)
- Of the 14% (31/227) patients that had hypoperfusion symptoms in the medical group, the 2-year probability of an outcome event was only 7%

Is a Balloon-Expandable Stent Better Than Self-Expanding?

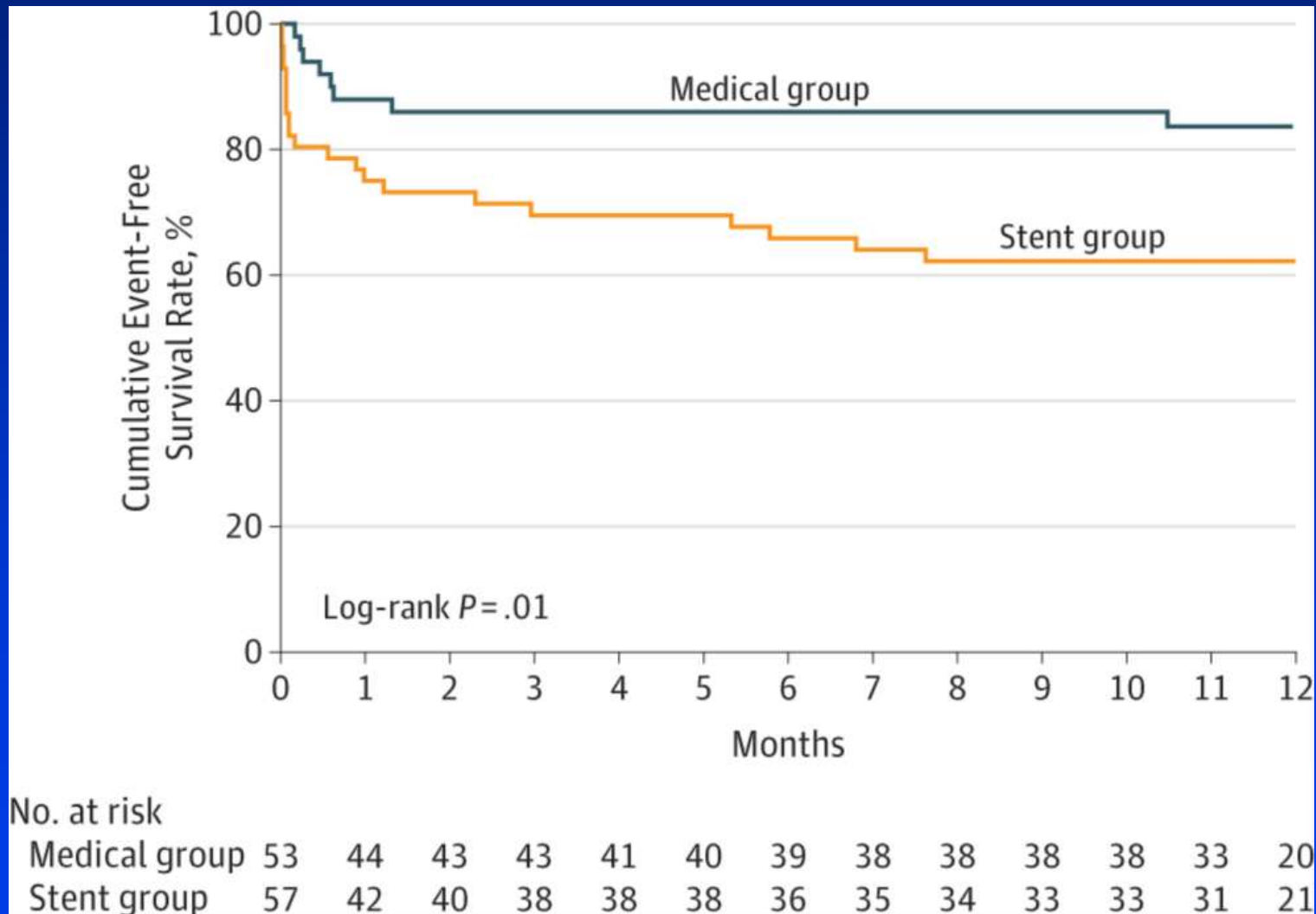
VISSIT trial

- Vitesse balloon-expandable stent plus medical therapy vs medical therapy alone in patients with symptomatic intracranial stenosis ($\geq 70\%$)
- Outcome: composite of stroke in the same territory within 12 months, or TIA in the same territory day 2 through month 12
- Enrollment halted for futility when 112 patients enrolled after SAMMPRIS prompted an early analysis

Symptomatic Hemorrhages Within 30 Days

- Five of 15 (**33.3%**) strokes in the PTAS group
- None of 3 (**0%**) strokes in the medical group

VISSIT: Kaplan-Meier Estimate of Event-Free Survival Rates



Future for Intracranial Stenosis?



Trial of transient ischemia of limb

- **Bilateral arm ischemic preconditioning (BAIPC)**
 - 5 brief cycles followed by reperfusion; twice daily over 300 consecutive days
 - Incidence of recurrent stroke and cerebral perfusion by SPECT in BAIPC group compared with controls

Results

- BAIPC group (n=38) had lower recurrent stroke risk and more reperfusion than controls (n=30) ($p < 0.01$)

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA



Clopidogrel plus aspirin: When OK

- Symptomatic high grade intracranial stenosis for 3 months as per SAMMPRIS
 - “For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable (Class IIb; Level of Evidence B). (New recommendation)”

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA



Clopidogrel plus aspirin: When OK

- Potential benefit in TIA and minor stroke when started within 24 hours as per the CHANCE trial
 - “...Might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (Class IIb; Level of Evidence B). (New recommendation)”
- POINT trial in US: both vs ASA alone within 12 hrs of high risk TIA or minor stroke and continued for 3 mos (SOCRATES trial: ticagrelor vs. aspirin within 24 hrs)

NEJM 2013; 269:11-19; *Stroke* 2014;45:2160-2236; ClinicalTrials.gov

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA



Clopidogrel plus aspirin: When not OK

- “The combination of aspirin and clopidogrel ...increases the risk of hemorrhage... and is **not recommended for routine long-term secondary prevention...**”

Contrast with Management of Carotid Artery Stenosis

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA



Symptomatic carotid stenosis:

- “For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%.”
- “For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%)...CEA is recommended depending on patient-specific factors...”
- “CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention...”

Guidelines for the Prevention of Stroke in Patients With Stroke and TIA



Asymptomatic carotid stenosis:

- “It is reasonable to consider performing **CEA** in asymptomatic patients who have $>70\%$ stenosis of the ICA if the risk of perioperative stroke, MI, and death is low ($<3\%$). However, its effectiveness compared with contemporary best medical management alone is not well established.
- Prophylactic **CAS** might be considered in highly selected patients with asymptomatic carotid stenosis ...but its effectiveness compared with medical therapy alone in this situation is not well established.”

Asymptomatic Carotid Stenosis: Risks Low on Current Medical Therapy?

Oxford Vascular Study of $\geq 50\%$ asymptomatic carotid stenosis

- 101 patients recruited consecutively from 2002-2009
- Intensive medical treatment
 - Usually aspirin+/-clopid x 30 days then Aggrenox, BP <130/80, statin
- Mean follow-up 3 years
- Average annual event rate **0.34%** for any ipsilateral ischemic stroke (1.78% for ipsilateral TIA)

Surgery/Intervention Versus Medical Management Trial

CREST 2 (NINDS) enrolling:

- Asymptomatic carotid artery stenosis
- Revascularization versus medical therapy

Cervical Artery Dissection

Case

A 42 year-old woman presents with left sided weakness for 10 minutes. Exam shows a right Horner's syndrome. CTA confirms extracranial right internal carotid artery dissection.

What is your recommended management?

- a) Daily aspirin
- b) Aspirin and clopidogrel for 90 days, then aspirin
- c) Anticoagulation
- d) Stent and dual antiplatelet agents

Dissection

CADISS open label feasibility trial

- Anticoagulant vs antiplatelet (agent chosen by physician) for prevention of ipsilateral stroke or death in patients with symptoms in past 7 days
- 90% had TIA or stroke; 10% had local symptoms

Results (n=250)

- No difference in prevention of stroke or death ($p=0.66$)
 - Only 2% had stroke recurrence by 3 months
 - One subarachnoid hemorrhage in anticoagulation group

CADISS Dissection Trial

Stroke recurrence rates low in dissection

- Rate was zero if didn't present with a stroke
- Occurred within first 10 days after randomization

Management now?

- Didn't provide definitive answer on whether antiplatelet or anticoagulation is better
- Perhaps at least those that present with symptoms other than stroke or after 10 days are lower risk and can be treated with an antiplatelet agent

Cryptogenic Stroke

Cryptogenic Stroke Questions

Excluding atrial fibrillation

- How to monitor
- What is a significant finding

Cryptogenic stroke and Embolic Stroke of Unknown Source (ESUS)

- Definitions
- Potential causes and treatment approaches

How Should We Monitor for AF in Cryptogenic Stroke?

30-day event monitor vs second 24-hr monitor

- Patients aged 55 years or older
- Stroke in previous 6 mos; had had 24 hrs monitoring
- AF occurred in 16.1% with 30-day monitor vs 3.2%

6-month insertable monitor vs M.D. discretion

- Patients aged 40 years or older
- Stroke in previous 3 mos; had had 24 hrs monitoring
- AF occurred in 8.9% vs 1.4% (by 12 mos 12.4% vs 2.0%)

Monitoring For AF – Zio Patch

Stanford group reviewed manufacturer's data of monitoring with indication of TIA or stroke

- 1,171 monitoring reports analyzed – retrospective
- Median monitor wear time was 13.0 days
- Median analyzable time relative to wear time 98.7%

Atrial fibrillation

- Present in 5% of all reports
- Mean duration to first AF episode was 1.5 days
- 14.3% occurred after the first 48 hours

Frontiers in Neurology; published 12 January 2015

Case

You monitor a 75 year old woman with a cryptogenic stroke and treated hypertension and find a run of probable atrial fibrillation lasting for nearly 30 seconds.

Your management approach is:

- a) Put her on daily aspirin
- b) Put her on clopidogrel and aspirin
- c) Put her on an anticoagulant

What Duration of AF is Significant?

- Thirty seconds likely too short
- If >6 minutes, associated with stroke risk but new questions about mechanism

Atrial Fibrillation of Short Duration

Clinical and imaging features in AF <30 seconds compared to those with AF or no AF

- Retrospective study of 611 consecutive stroke patients monitored for 24 hours
- Non-sustained AF in 21%
- Non-sustained AF intermediary phenotype between AF and no AF by clinical, lab and echo features
- Lesion patterns in cryptogenic stroke with non-sustained AF resembled those without any AF

Atrial Fibrillation of Short Duration

Table 2. Prevalence of Nonsustained AF Among Noncardioembolic Stroke Subtypes

Large artery atherosclerosis (n=123)	31%
Small artery occlusion (n=37)	38%
Other causes (n=59)	22%
Cryptogenic causes (n=125)	32%
Unclassified causes (n=37)	24%

“The prevalence of [AF <30 sec] was similar among cryptogenic and non-cryptogenic stroke patients.”

Atrial Fibrillation of >6 Minutes: ASSERT Trial

Study of patients with pacemaker or defibrillator and no clinical atrial fibrillation

- **2580 patients aged ≥ 65 years with hypertension**
- **Monitored 2.5 years (initial check at 3 months)**
- **Atrial arrhythmias seen in 34.7% by 2.5 years**
- **Those with atrial tachyarrhythmias compared to those without had an increased risk of stroke or systemic embolism by a factor of 2.5 ($p=0.05$)**

Suggested risk increased by AF duration

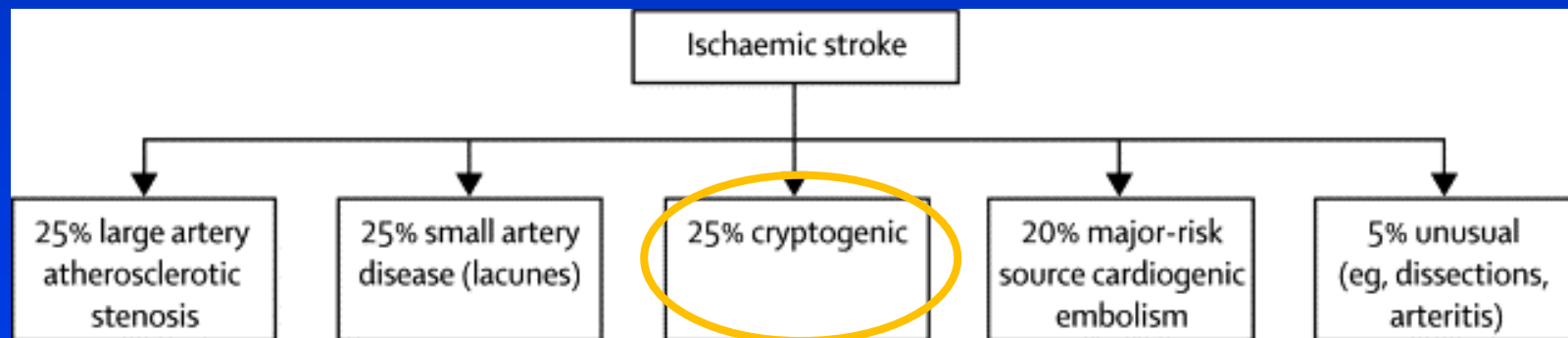
Atrial Fibrillation of >6 Minutes: Temporal Relationship to Stroke?

Analysis of ASSERT study

- 51 of the 2580 patients had stroke or systemic embolism
 - Half (51%) had subclinical AF
 - Only 4 patients (8%) had subclinical AF in the 30 days prior to the embolic event ; only one at time of stroke
 - Eight (16%) had AF only after the stroke
- While subclinical AF is associated with stroke, any causal relationship may be indirect

What is a Cryptogenic Stroke?

- Stroke for which the cause is not found
 - Excludes strokes presumed due to small vessel disease, arterial stenosis of >50%, major or medium risk cardioembolic or other causes
- Accounts for 25% of ischemic strokes



What is an Embolic Stroke of Undetermined Source (ESUS)?

- A subset of cryptogenic strokes
- Don't have a major-risk cardioembolic source but can have medium-risk cardiac source and be ESUS
 - The excluded major risk cardioembolic sources are AF and left ventricular thrombi

ESUS: Causes Most Likely Embolic

- Some potential causes have sufficiently low inherent risk of thromboembolism that causal role of stroke at patient level is unclear

Cardiac

- PFO, valvular disease, LV dysfunction
- Rhythm abnormalities: brief AF, sick sinus, etc.

Arterial

- Cerebral artery non-stenotic plaque with ulceration or aortic arch atherosclerotic plaque

Treatment Trials in Embolic Stroke of Undetermined Source (ESUS)

NAVIGATE ESUS

- Rivaroxaban (Bayer) versus aspirin, 100 mg
- No atrial fibrillation on cardiac monitoring for ≥ 24 hrs

RE-SPECT ESUS

- Dabigatran (Boehringer) versus aspirin, 100 mg
- No atrial fibrillation on cardiac monitoring for ≥ 24 hrs

Treatment Trials in Embolic Stroke of Undetermined Source (ESUS)

NAVIGATE ESUS

- Excludes patients with history of AF, AF on ECG or episode of AF lasting **6 minutes or longer** detected after \geq 24-hour cardiac monitoring

Didn't We Already Have a Trial of Anticoagulation vs Aspirin?

WARSS trial

- Warfarin (INR 1.4-2.8) vs aspirin, 325 mg daily, for prevention of recurrent ischemic stroke or death
- Excluded those with high grade carotid stenosis or inferred cardioembolic stroke

Results (n=2206)

- No difference in prevention of recurrent events or rate of major hemorrhage

Cause of stroke was cryptogenic in only 26%

Lacunar strokes in 56%

NEJM 2001;345:1444-51

Subgroup Analysis From WARSS

Cryptogenic strokes in WARSS

- Post-hoc analyses
- Those without hypertension, or with posterior circulation strokes sparing the brainstem, had better outcomes on warfarin compared to aspirin
- Authors raise the possibility that these might represent occult embolic strokes

Thank you!

No More Bridging Patients on Warfarin?

Randomized trial of dalteparin vs placebo after perioperative interruption of warfarin in AF

- 1884 patients enrolled
- Required CHADS2 of ≥ 1 but 77% were CHADS ≥ 2
- Only 9.4% had had a previous stroke

Results

- Arterial thromboembolism 0.4% in no-bridging and 0.3% in bridging group ($p=0.01$ for non-inferiority)

Major bleeding 1.3% in no-bridging vs 3.2% in bridging group ($p=0.005$ for superiority)