

I Think, Therefore I AM

- Descartes

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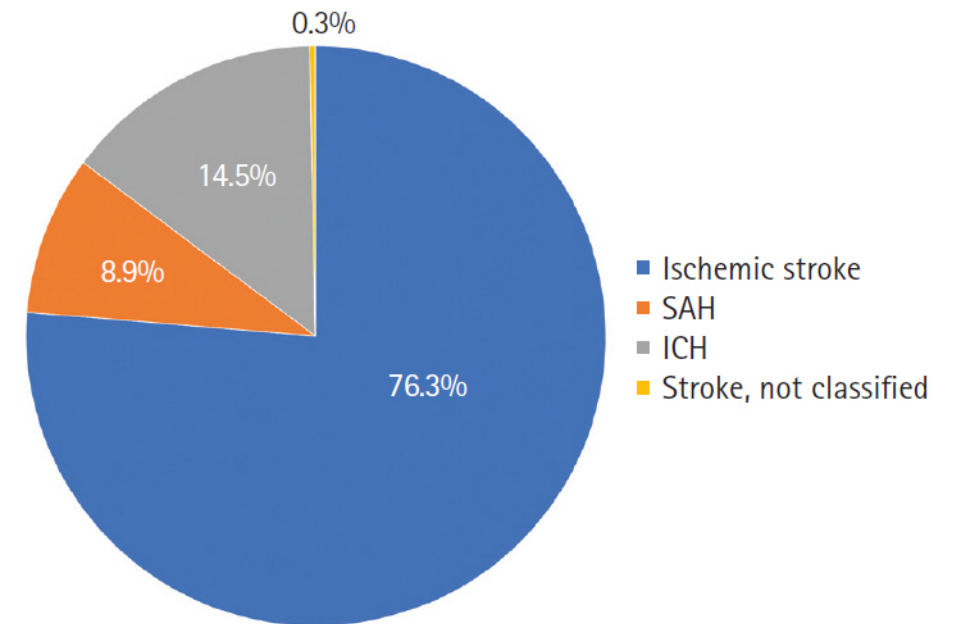
June 12, 2020

Stroke and Atrial Fibrillation

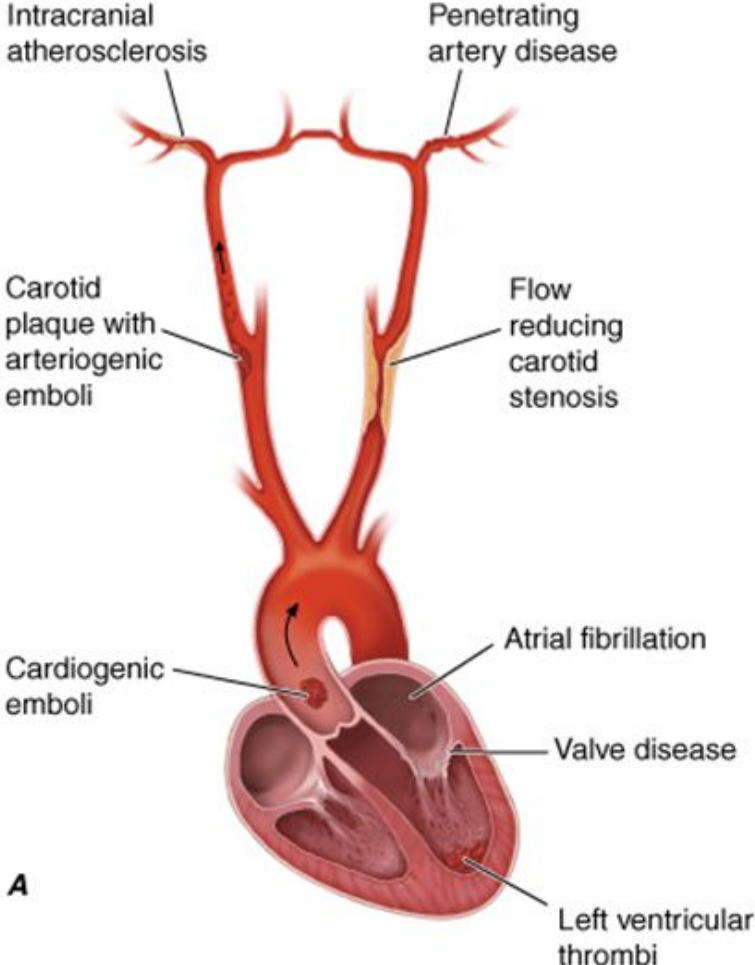
Stroke is defined as the sudden death of brain cells due to lack of oxygen

Causes of Stroke

- Ischemic (Blocked circulation)~80%
- Hemorrhagic (Bleeding)~10-20%
- Tumors
- Atherosclerosis
- Rare causes:
 - Hypercoagulable
 - Genetic
 - Blood vessel disease
 - Inflammatory/Infectious



Causes of Ischemic Stroke



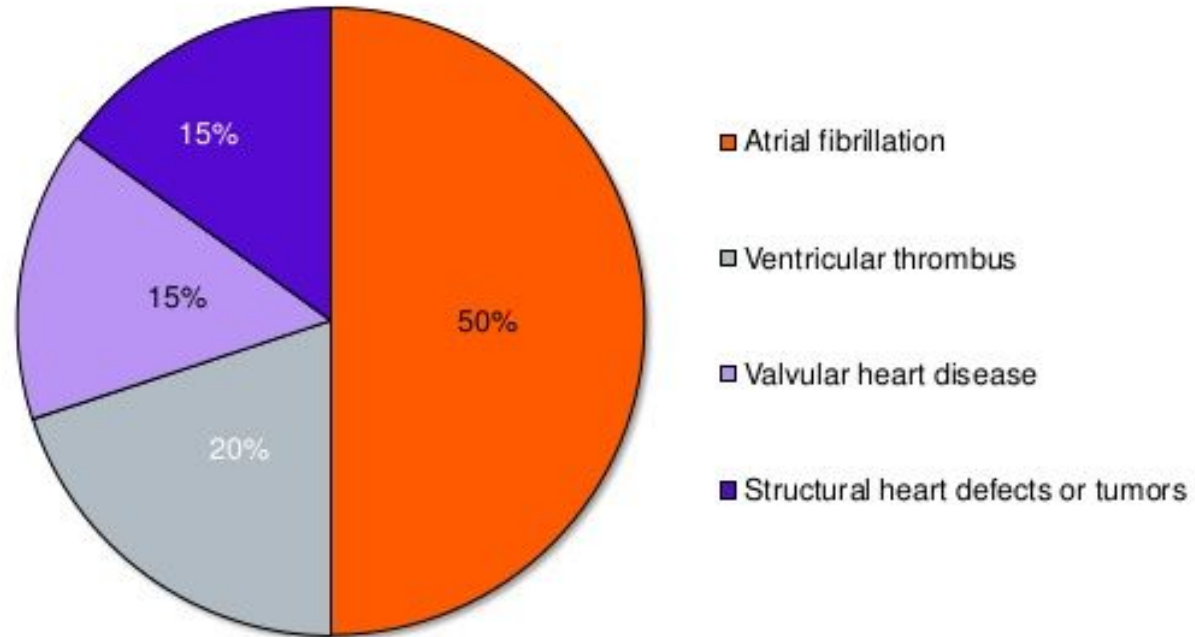
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>
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Causes of Hemorrhagic stroke

- High BP
- Aneurysms
- Trauma
- Tumors
- AV malformations

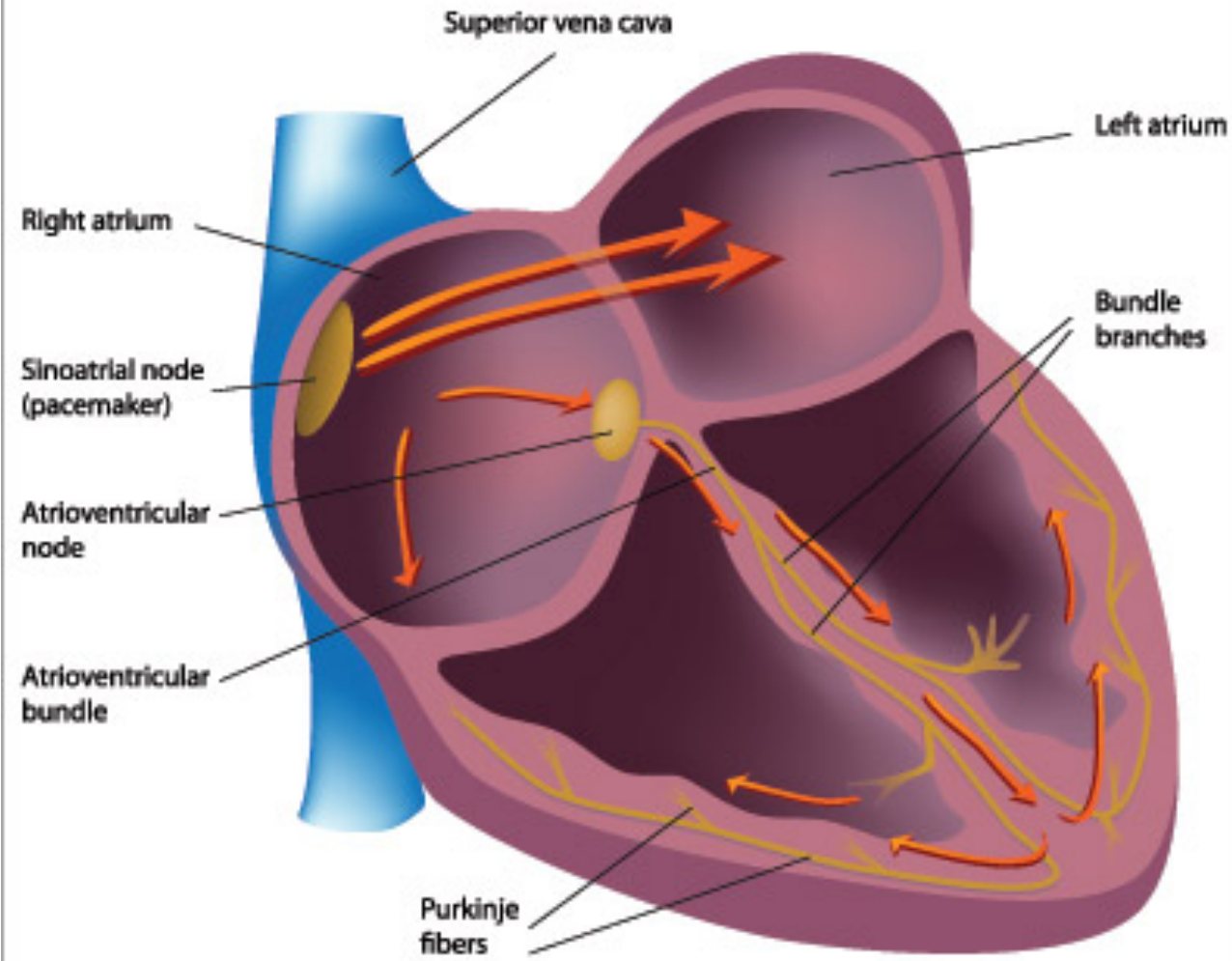
Ischemic Strokes

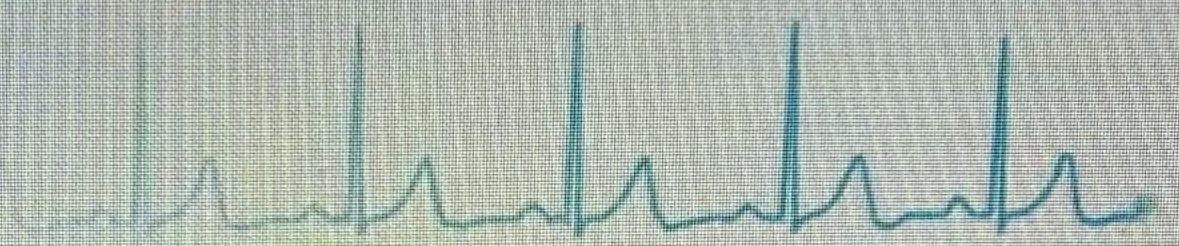
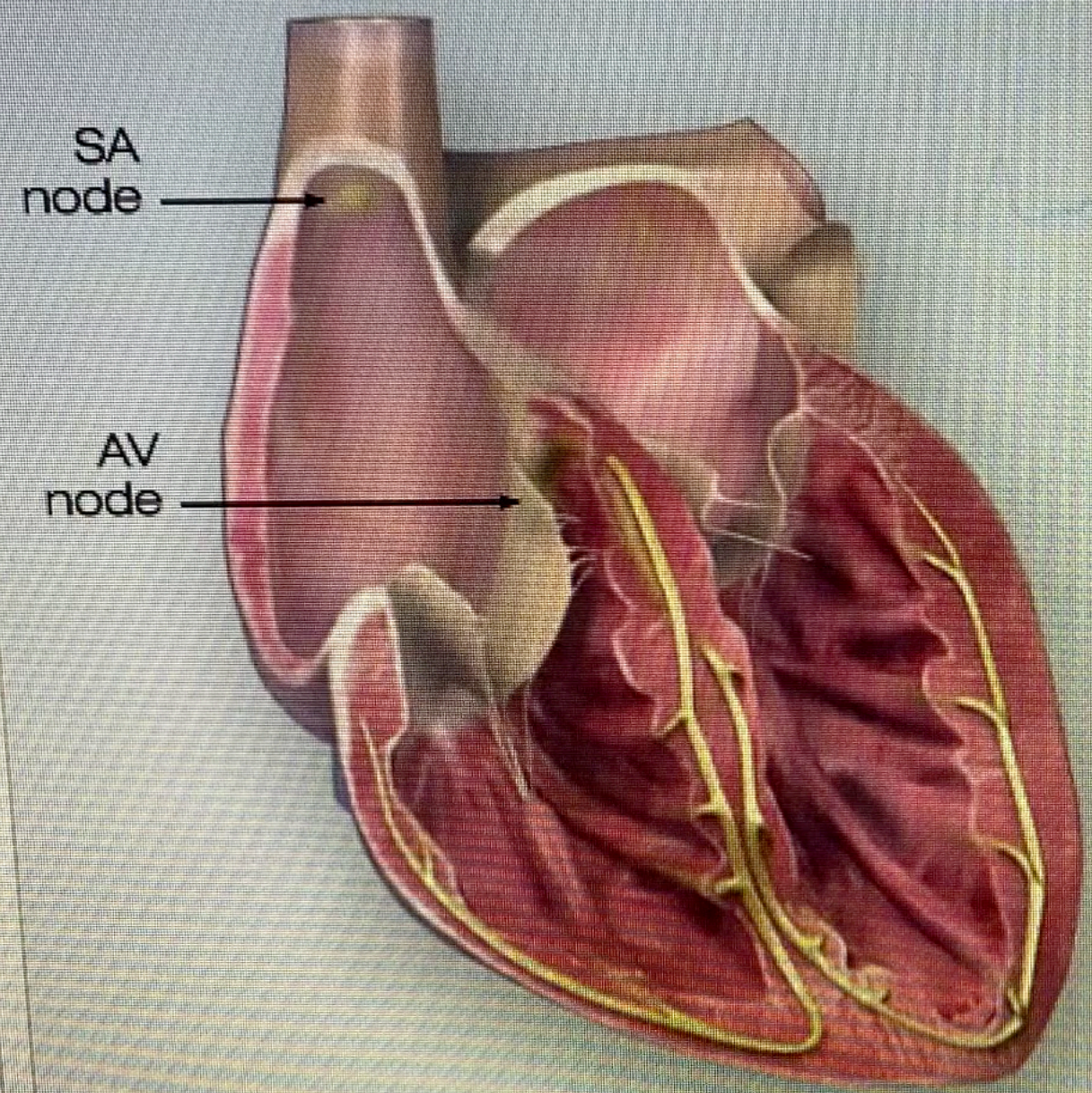
Cardiac Diseases Leading to Cardioembolic Events



1. Freeman WD, Aguilar MI. *Neurol Clin.* 2008;26:1129-1160.

The Cardiac Conduction System



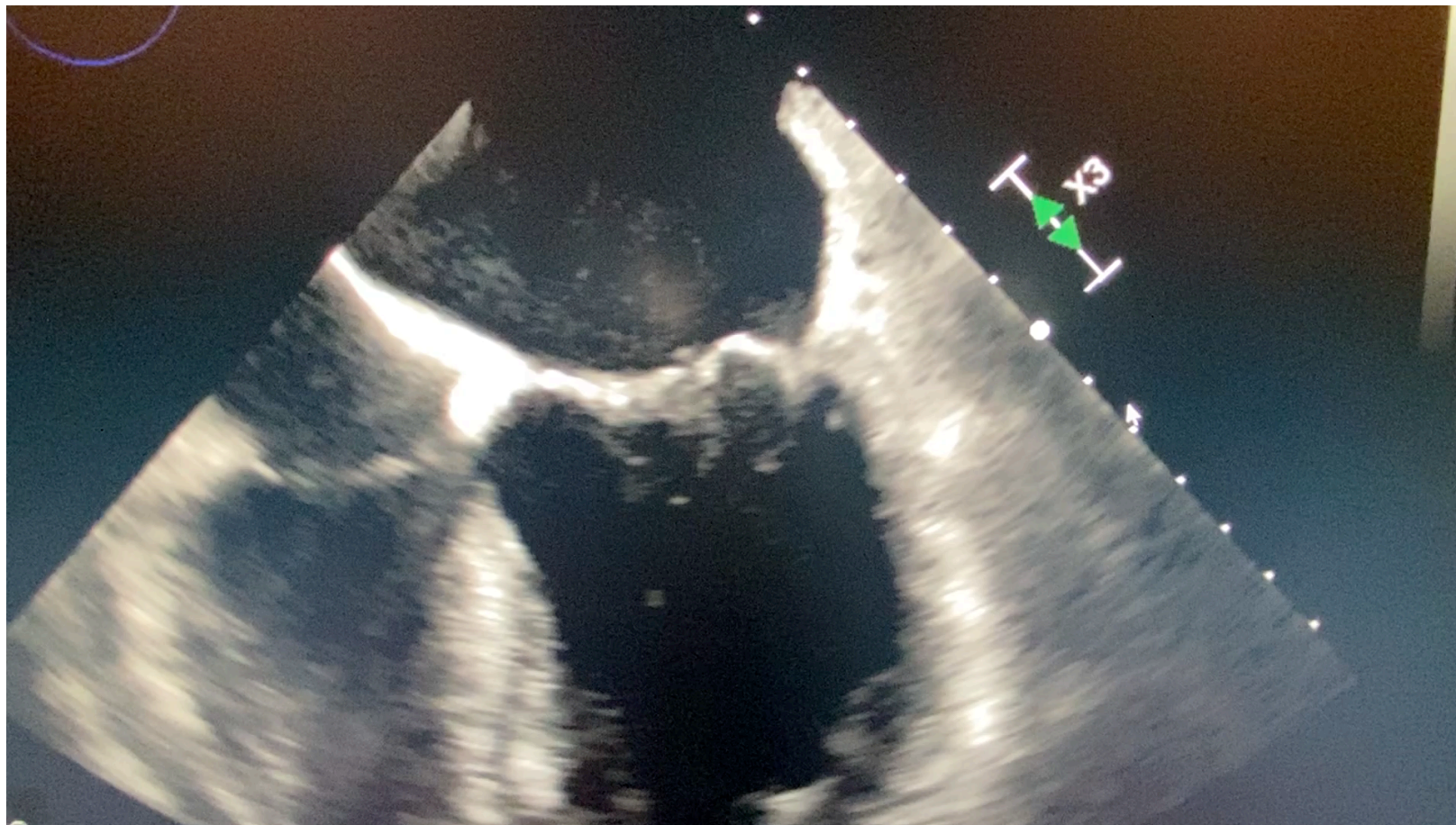


Normal Heartbeat

A normal "sinus rhythm" starts in the sinoatrial (SA) node and spreads down to the atrioventricular (AV) node as the atria contract and force blood into the ventricles. The ventricles then contract and pump blood out of the heart as electrical signals reach ventricular muscle cells.

Represented here is a normal rhythm of 60 beats per minute.

On Echocardiography: Normal Rhythm

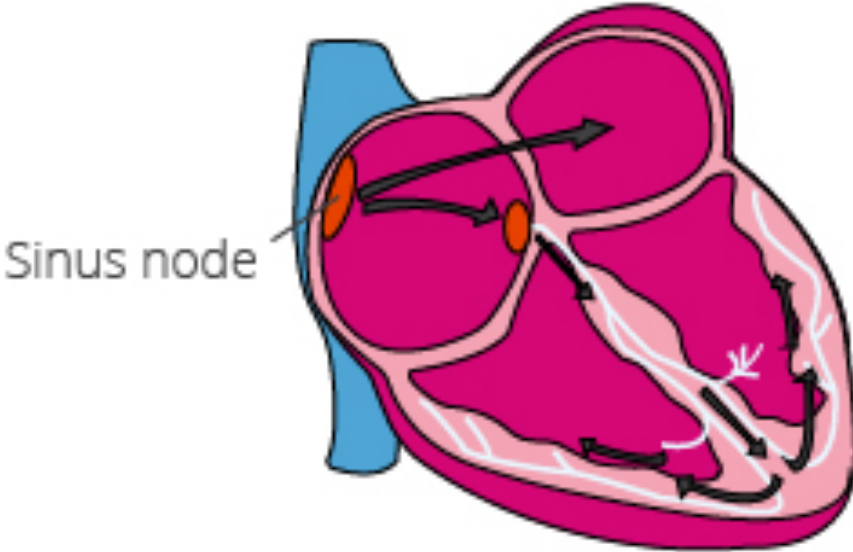


Left Atrial Appendage in Normal Rhythm

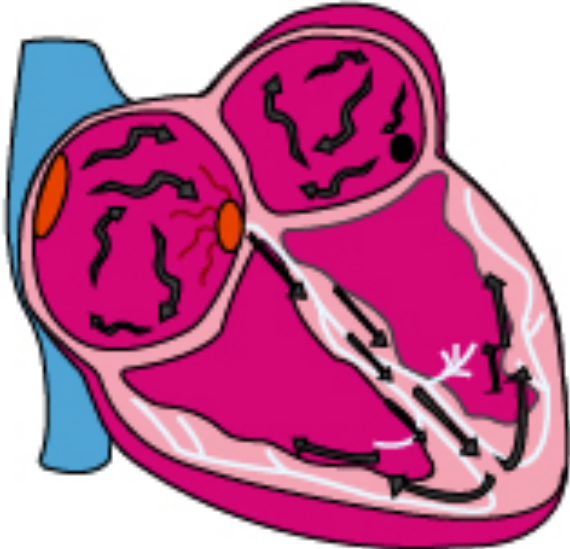


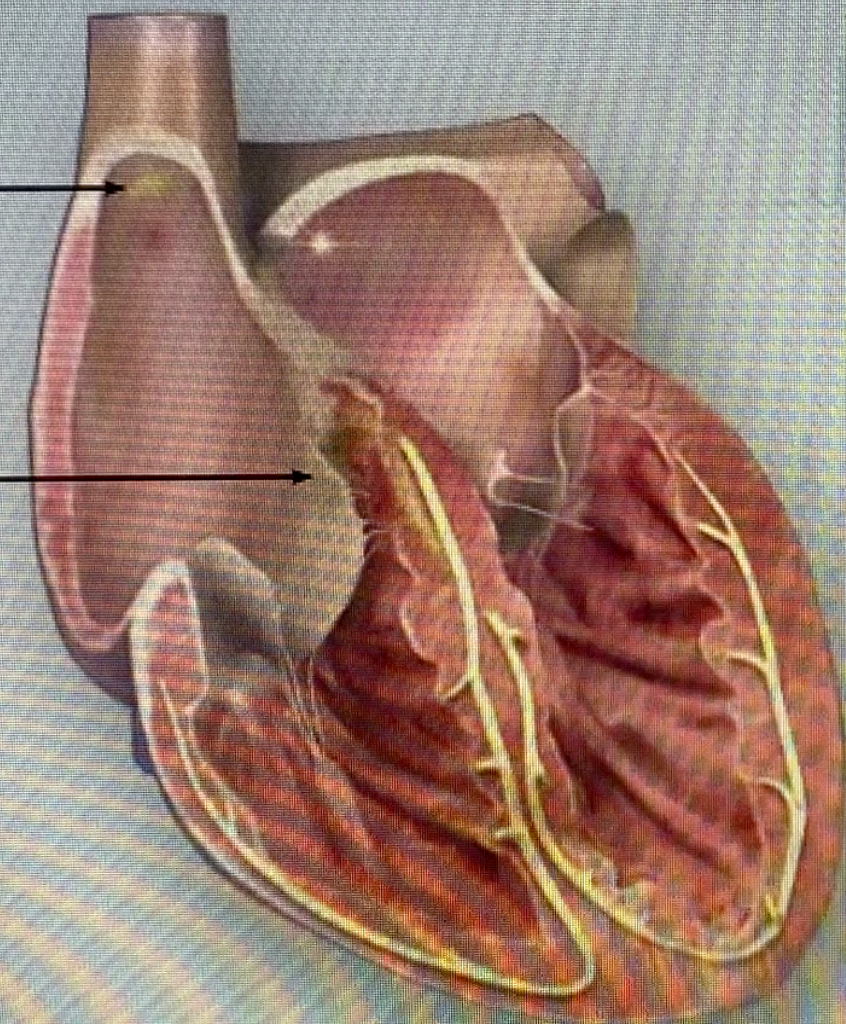
Atrial Fibrillation

Normal



Atrial Fibrillation





SA
node

AV
node



Normal Heartbeat



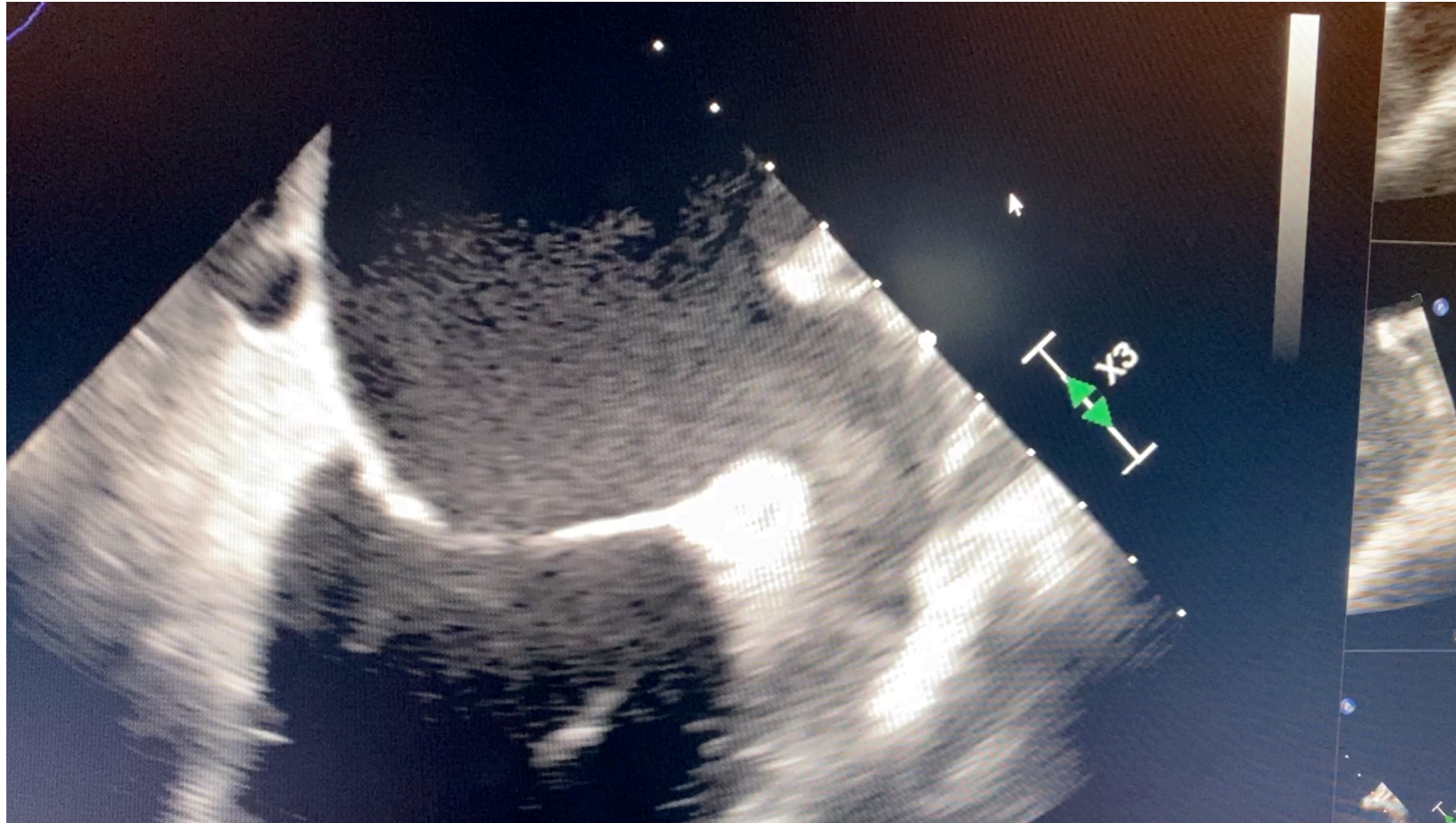
Atrial Fibrillation

Irregular electrical signals disrupt the normal conduction between the SA and AV nodes and cause the atria to quiver. This prevents them from effectively moving blood into the ventricles. It can lead to stroke or other heart-related complications.

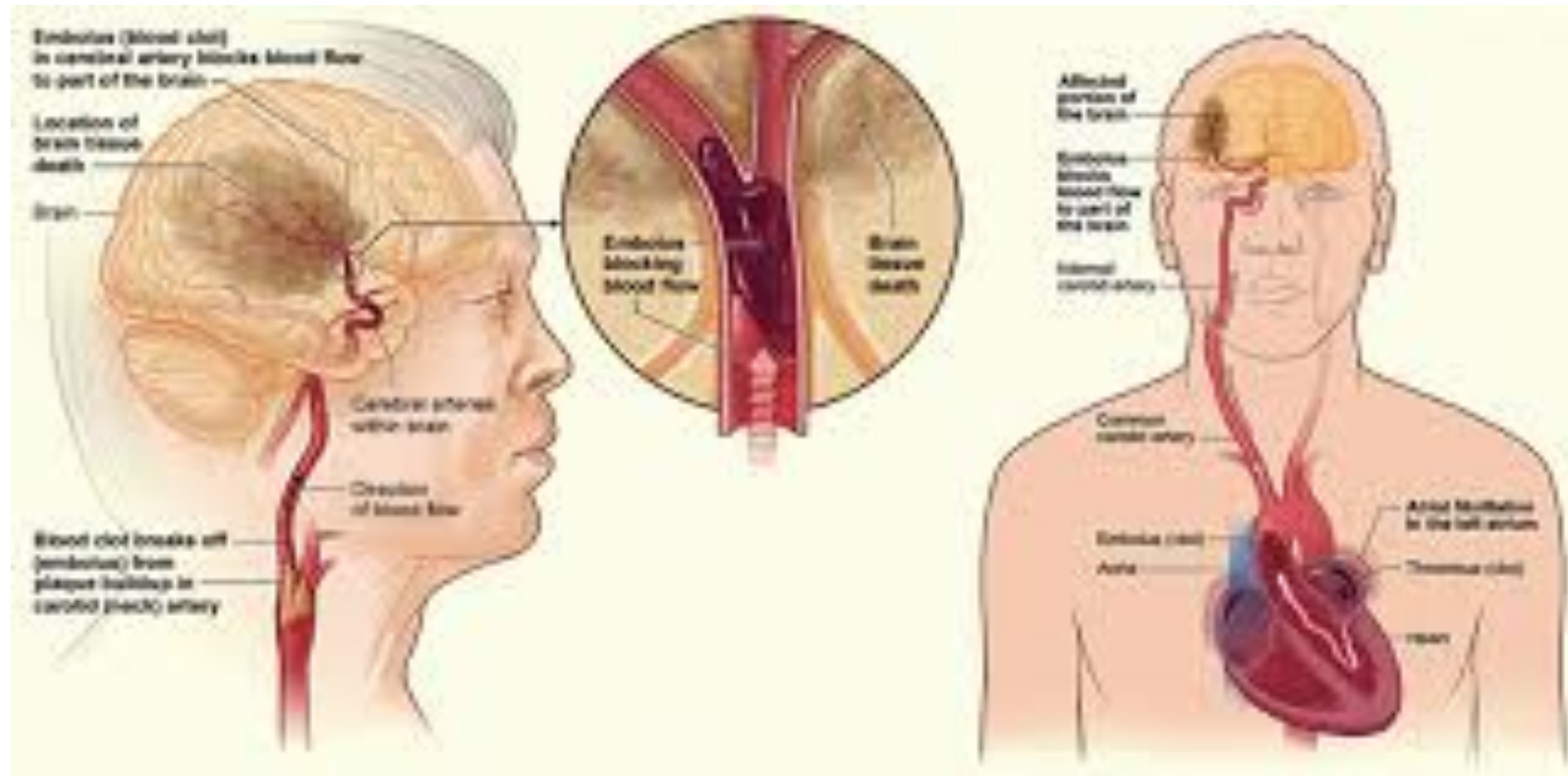
“Smoke” in a patient with Atrial Fibrillation



Thrombus in the Left Atrial Appendage in Atrial Fibrillation

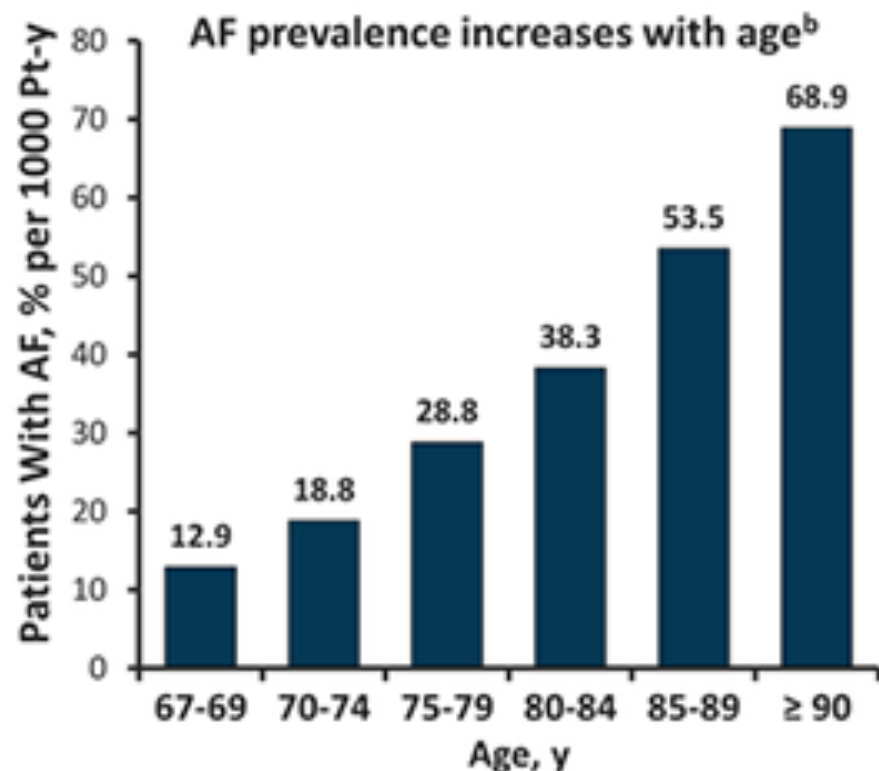


Mechanism of Stroke in Atrial Fibrillation



The Burden Of Atrial Fibrillation

- Most common sustained arrhythmia
 - Estimated prevalence: 2.3% to 3.4%^a
- Rare in people age < 40 years but prevalence increases with age^a
 - Incidence approximately doubles with each decade of life after age 55
 - Expected to affect 1 in 4 people over the age of 40

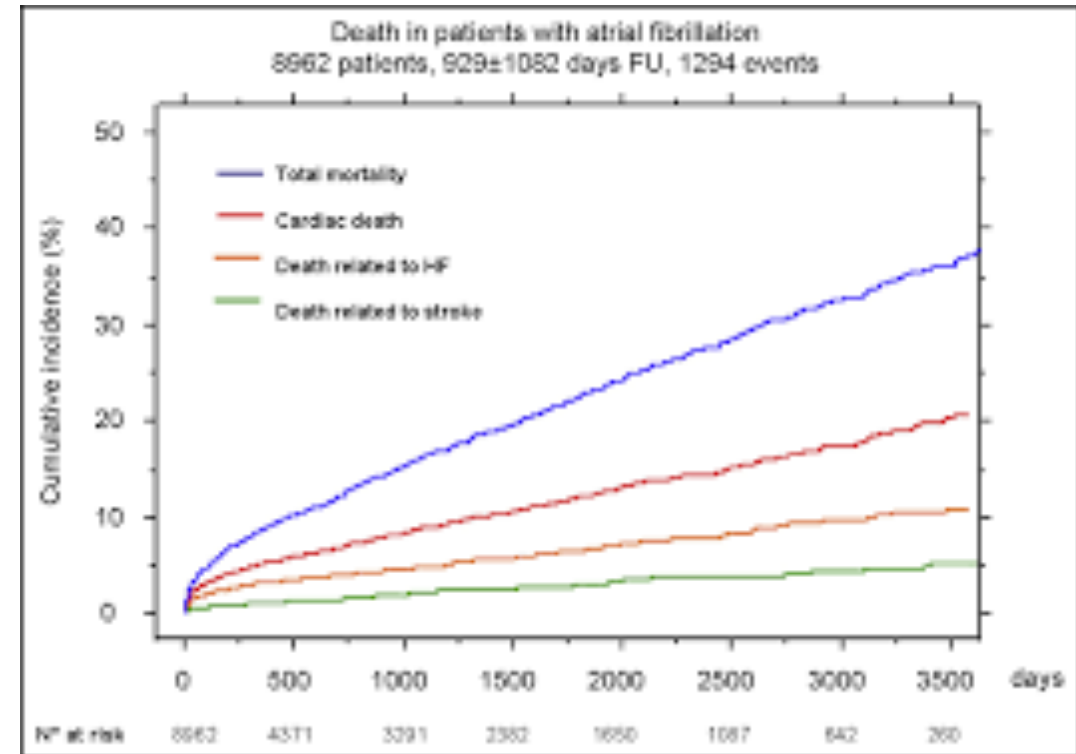


Incidence of AF in the Medicare 5% Sample in 2007

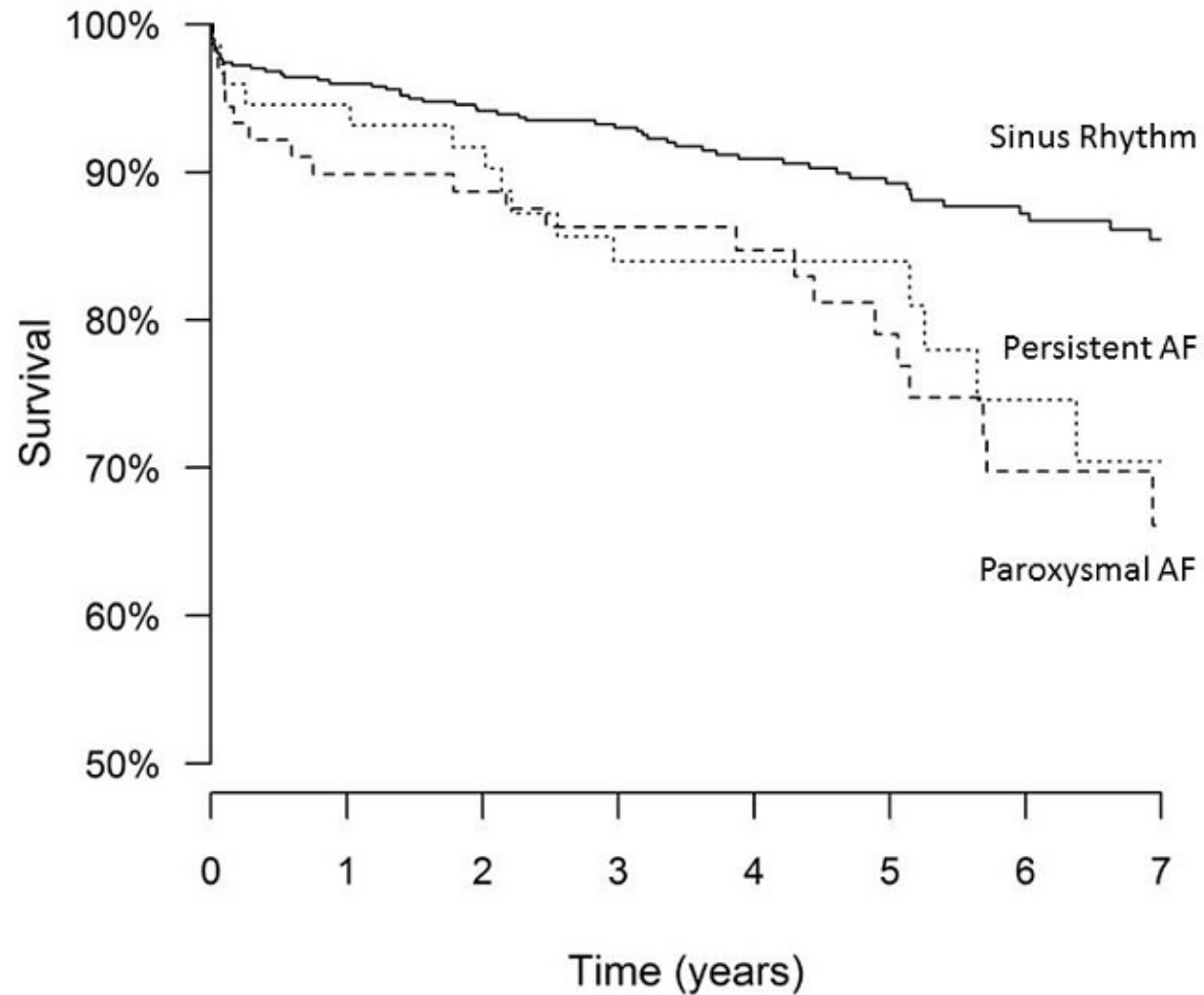
a. Ball J, et al. *Int J Cardiol.* 2013;167:1807-1824; b. Piccini JP, et al. *Circ Cardiovasc Qual Outcomes.* 2012;5:85-93.

Effect of Atrial Fibrillation

- Without anticoagulation, ischemic stroke risk rate is ~5-10%/ year
- 15% of all strokes occur in patients with Atrial Fibrillation ~75,000/year
- Total mortality rate is doubled in patients with Afib vs NSR



Rate vs Rhythm Control

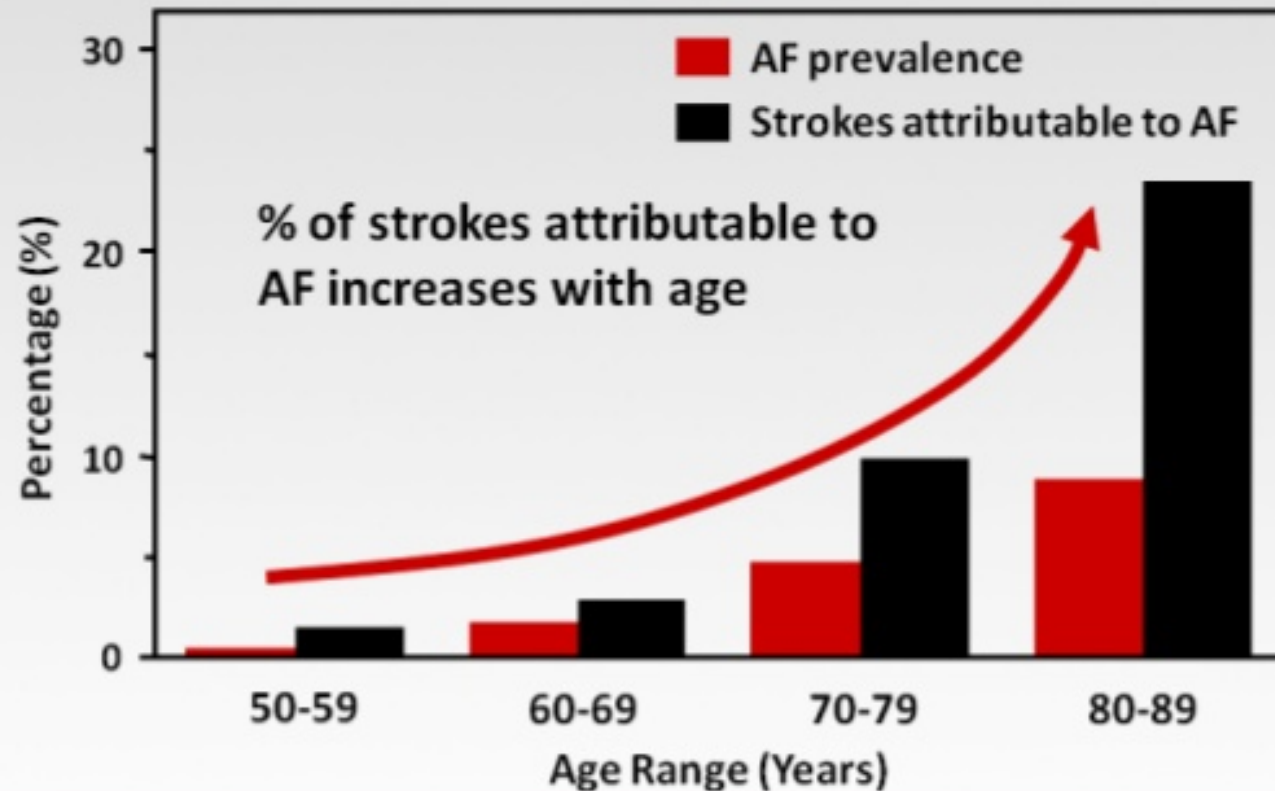


Atrial Fibrillation and Stroke Risk Factors

- Major Risk Factors: Score 2
 - Previous stroke
 - TIA
 - Age >75 years
- Other Risk Factors: Score 1
 - CHF
 - Hypertension
 - Diabetes
 - Female gender
 - Age 65-75 years
 - Vascular disease

Af and incidence of stroke increase with age: the Framingham Heart Study

8



Prevalence expected to increase 2.5-fold by 2050

KNOW YOUR STROKE RISK

CHA2DS2-VASc Risk	Score	CHA2DS2-VASc Score	Adjusted stroke rate (% / year)
		0	0
CHF or LVEF <40%	1	1	1.3
Hypertension	1	2	2.2
Age > 75	2	3	3.2
Diabetes	1	4	4
Stroke / TIA / Thromboembolism	2	5	6.7
Vascular Disease	1	6	9.8
Age 65-74	1	7	9.6
Female	1	8	6.7
		9	15.2

*CHF = congestive heart failure; TIA - transient ischemic attack;
LVEF = left ventricular ejection fraction.*

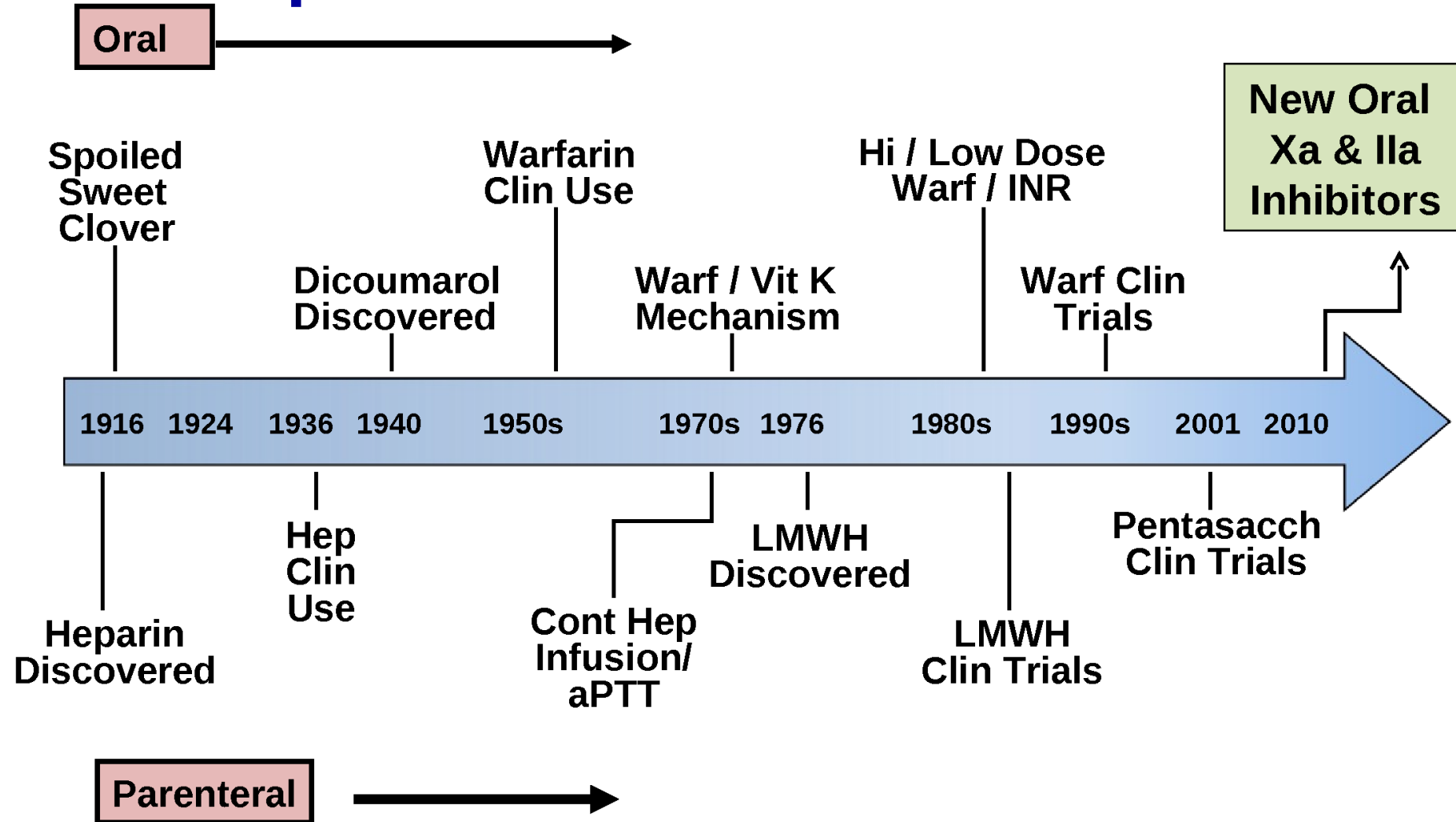
Risk of Stroke with Different CHA2DS2VaSc scores

Table 1: CHA2DS2-VASc Score and Annual Stroke Rates

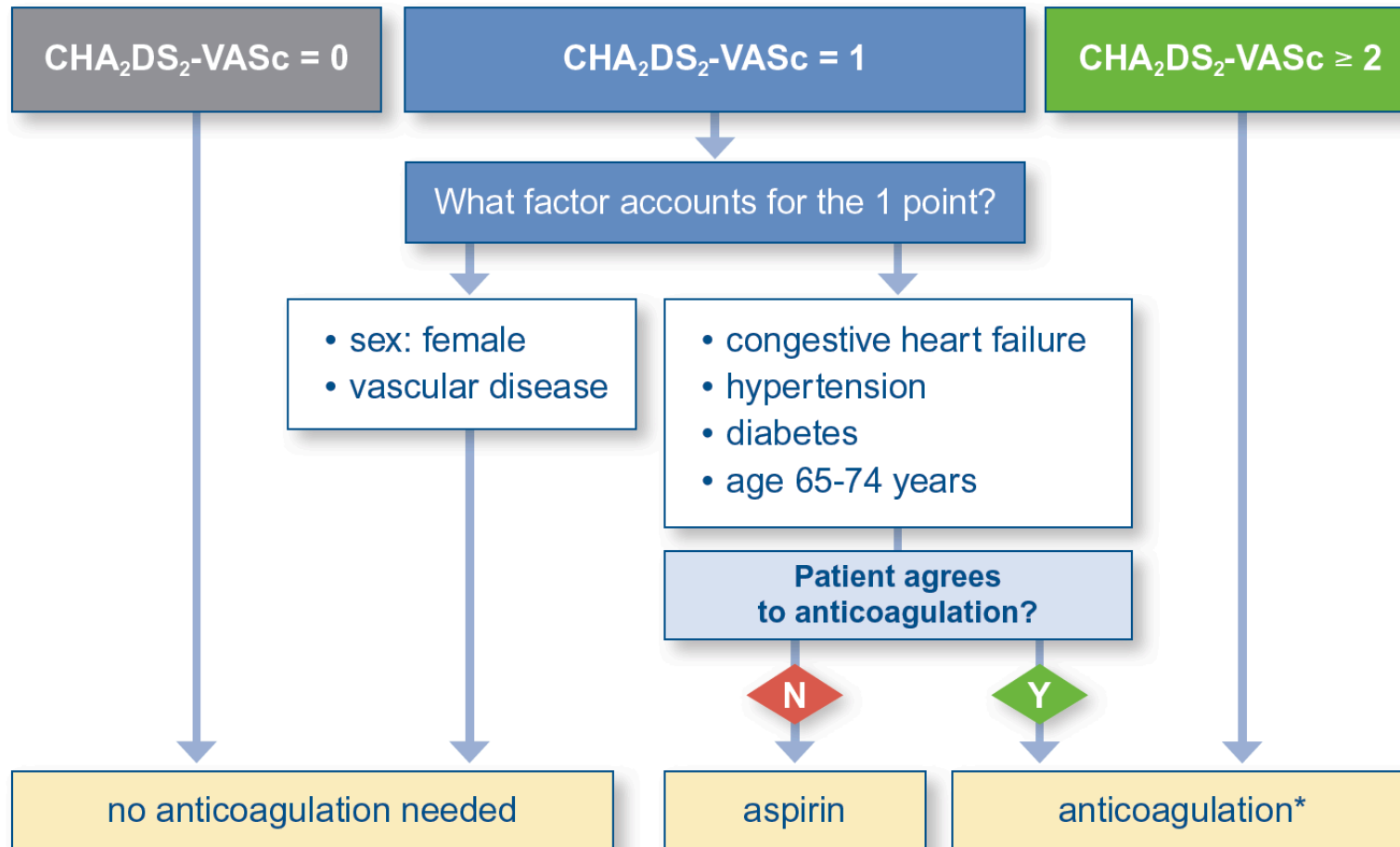
CHA2DS2-VASC Score	Adjusted Annual Stroke Rate
0	0 %
1	1.3 %
2	2.2 %
3	3.2 %
4	4.0 %
5	6.7 %
6	9.8 %
7	9.6 %
8	6.7 %
9	15.2 %

Modified from the European Society of Cardiology guidelines for the management of atrial fibrillation.²⁴

Anticoagulants – Highlights in Development



Guidelines for Anticoagulation 2019



*DOAC preferred over warfarin, unless unaffordable or contraindicated.

Risk of Bleeding with OACs

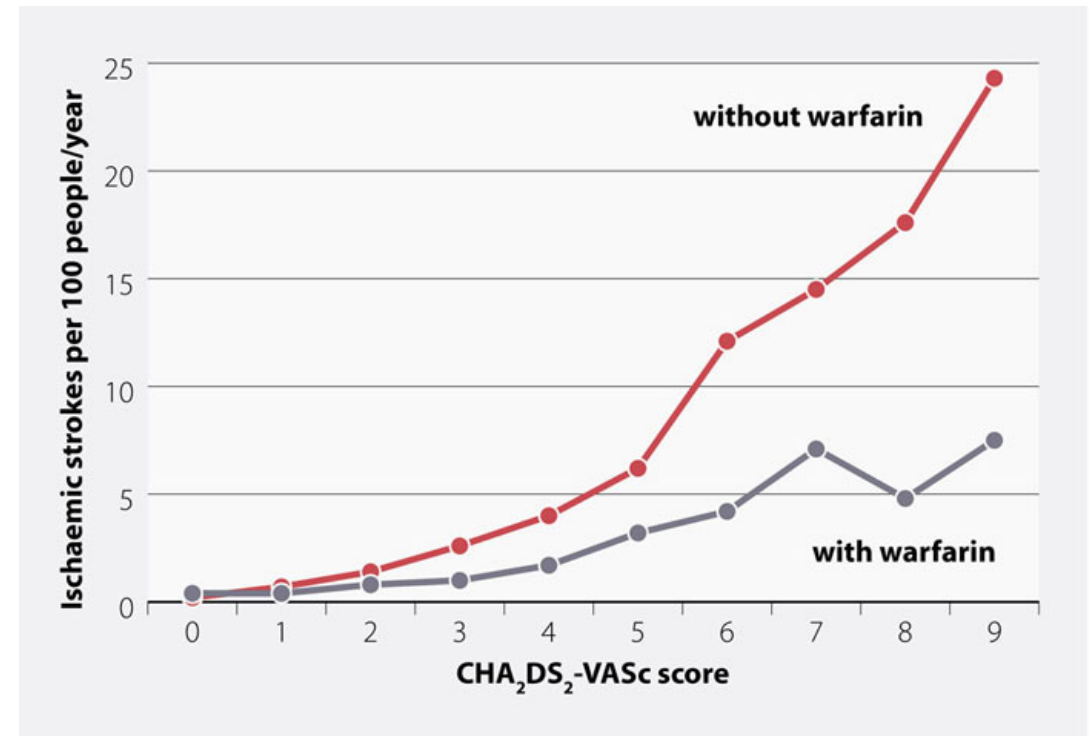
HAS-BLED Criteria	Score	Total Score	Bleeds per 100 patient years
Hypertension	1	0	1.13
Abnormal renal or liver function (1 point each)	1 or 2	1	1.02
Stroke	1	2	1.88
Bleeding	1	3	3.74
Labile INRs	1	4	8.7
Elderly (> 65 years)	1	5	12.5
Drugs or alcohol (1 point each)	1 or 2		

Decision for Oral Anticoagulation

- Shared Decision Making between Physician and Patient
 - Risk of embolism
 - Risk of bleeding
 - Medical/ nonmedical comorbidities: CAD, stents, Pregnancy, Valvular Heart Disease, Cancer, Kidney or liver Disease
 - Beliefs/ Ease of Use
 - Cost of Drugs

Effect of Warfarin/ Coumadin

- Difficulty controlling INRs
- Difficulty and cost of INR checks
- Dietary restrictions
- Affected by many drugs
- Easy to reverse
- Well studied in Valvular heart disease: Mitral stenosis, Mechanical Heart Valves
- Pregnancy



Novel Oral Anticoagulants

RIVAROXABAN (XARELTO; BAYER)

Usual dose: 20mg od with food. **Bioavailability:** 66% (without food), almost 100% (with food). **Peak plasma level:** 2–4 hrs. **Half-life:** 5–9 hrs (young), 11–13 hrs (elderly). **Renal excretion:** 35%. **Liver metabolism:** yes.

Interactions: Use with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics or HIV protease inhibitors, is not recommended. Co-administration with dronedarone and strong CYP3A4 inducers should be avoided.



DABIGATRAN ETEXILATE (PRADAXA; BOEHRINGER INGELHEIM)

Usual dose: 150mg bid. **Bioavailability:** 3–7%. **Peak plasma level:** 2hrs. **Half-life:** 12–17hrs. **Renal excretion:** 80%. **Liver metabolism:** no.

Interactions: Use with strong P-gp inhibitors ketoconazole, cyclosporine, itraconazole and dronedarone is contraindicated. Use with P-gp inhibitor verapamil requires dose reduction. Use with P-gp inducers should be avoided.



APIXABAN

(ELIQUIS; BRISTOL-MYERS SQUIBB-PFIZER)

Usual dose: 5mg bid. **Bioavailability:** 50%. **Peak plasma level:** 1–4 hrs. **Half-life:** 12 hrs. **Renal excretion:** 27%. **Liver metabolism:** yes.

Interactions: Use with strong inhibitors of CYP3A4 or P-glycoprotein (P-gp) is not recommended. Use with strong inducers of CYP3A4 and P-gp requires caution.



EDOxabAN (LIXIANA; DAIICHI SANKYO UK)

Usual dose: 60 mg od. **Bioavailability:** 62%. **Peak plasma level:** 1–2 hrs. **Half-life:** 10–14 hrs. **Renal excretion:** 50%. **Liver metabolism:** minimal.

Interactions: Use with the P-gp inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole requires dose reduction to 30mg once daily. Use with caution concomitantly with P-gp inducers (e.g. rifampicin).

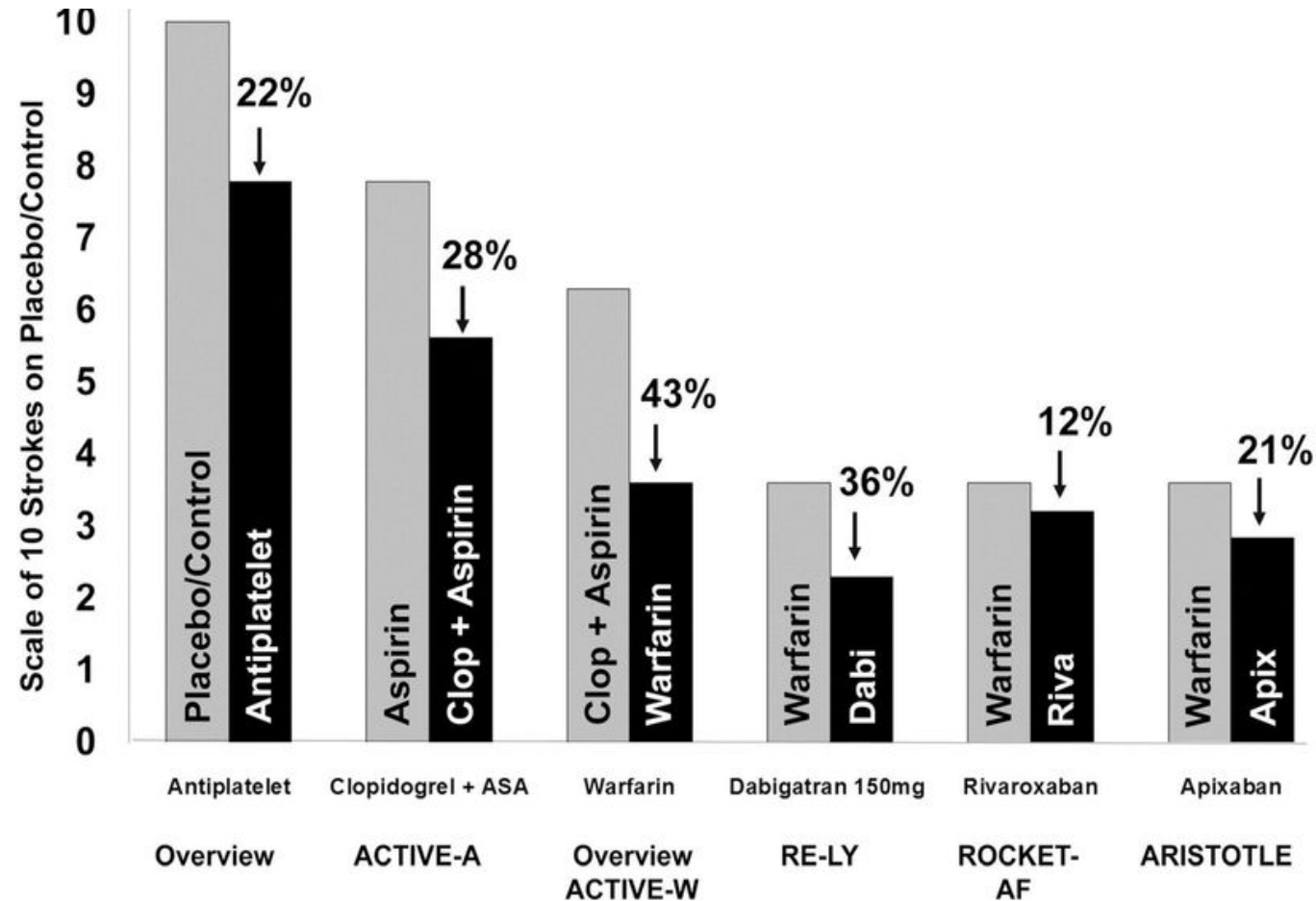
DSC
L30

DSC
L60

Direct Oral Anticoagulants

- Directly inhibit coagulation factors – Thrombin – Factor Xa
- No routine monitoring
- Very Little dose adjustments
- Short half lives
- No food interactions
- Few drug interactions
- No reversal for factor Xa inhibitors – Praxbind (idarucizumab) available for Pradaxa
- Approved for NVAF

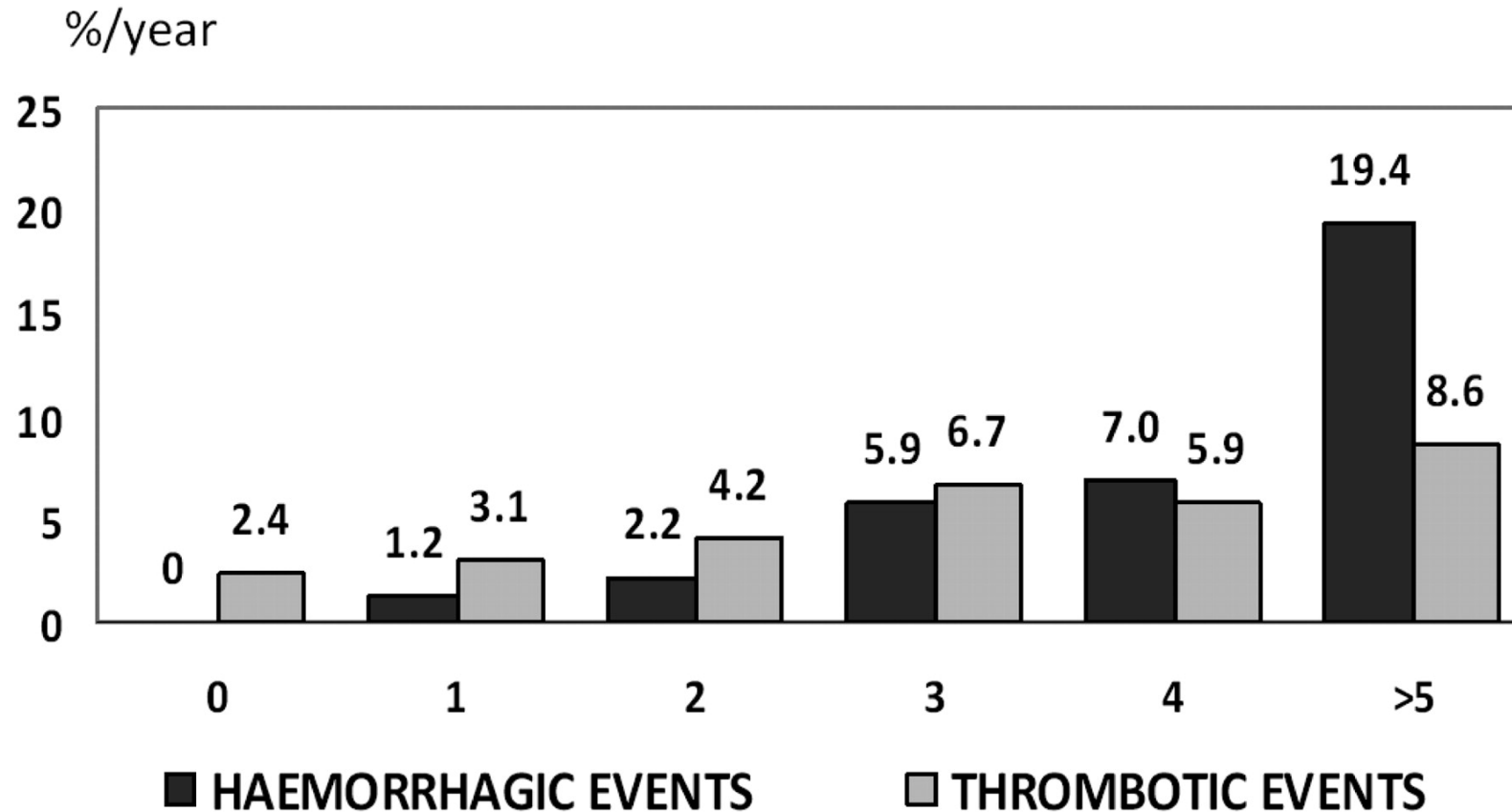
Effects of DOACs on stroke prevention



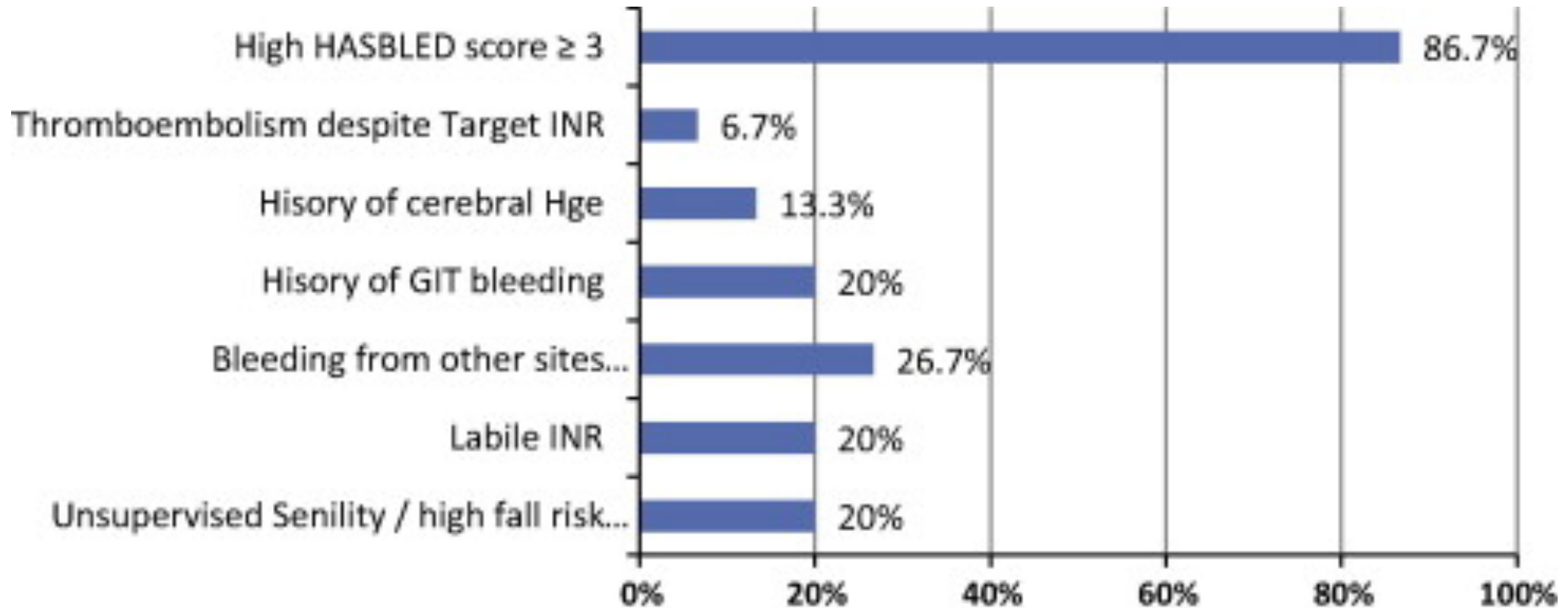
Christopher B. Granger, and Luciana V. Armaganijan
Circulation. 2012;125:159-164



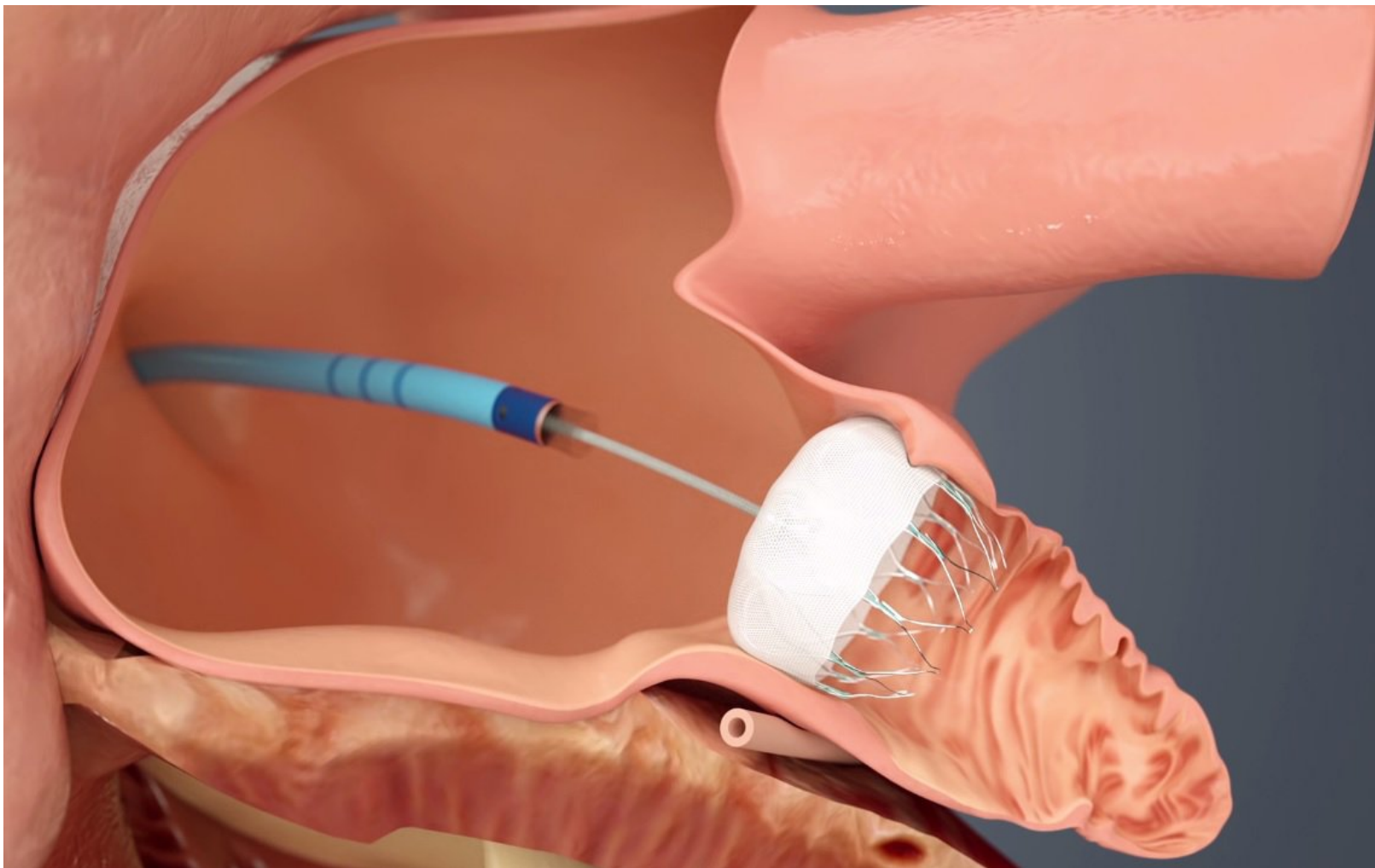
Risk of Bleeding vs Stroke based on CHA2DS2VaSc



Indications for the Watchman device



Watchman Device



Outcomes of Left Atrial Appendage Closure

WATCHMAN LAA closure effective and safe
in routine clinical practice

BACKGROUND

LAA dominant source for thrombo-embolism in non-valvular AF
Mechanical closure alternative to anticoagulation?



ROUTINE PRACTICE

47 sites outside US
1020 patients treated with
WATCHMAN LAA closure

72% unsuitable for OAC
Mean CHA₂DS₂-VASc = **4.5**
Mean HAS-BLED = **2.3**

30% prior stroke/TIA
15% prior hemorrhagic stroke
31% prior major bleed

RESULTS

WATCHMAN LAA Closure effective
and safe for stroke prevention.
After 2 years follow-up:



-83% Ischemic stroke

-46% Major bleeding

Atrial Fibrillation: JACC Council Perspectives

April 2020

- Lifestyle/risk modification studies that have included weight loss and exercise in obese AF patients (LEGACY, CARDIOFIT, ARREST-AF) have demonstrated significant reductions in AF burden.
- Detection of subclinical AF lasting >5 minutes in patients with an implanted device are associated with a risk of silent ischemic brain lesions.
- patients with a history of AF can remain at risk of thromboembolic events even when AF is successfully suppressed by medications or ablation.

- In the most recent US and European guidelines, a DOAC is preferred over warfarin in the absence of a contraindication, and aspirin is no longer recommended for stroke prevention in low-risk patients.
- Left atrial appendage (LAA) closure not only reduces the risk of thromboembolic events but also may reduce AF burden.

Thank you