

# Atrial Fibrillation & Secondary Stroke Prevention: Therapeutics & Prolonged Cardiac Rhythm Monitoring



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## Objectives

- Atrial fibrillation (AF) and stroke risk
- Anticoagulation (AC)
  - Special populations
  - Timing of initiation after stroke
- Ischemic stroke (IS) despite AC
- Rhythm control & Factor XI/XIa inhibitors
- AF evaluation after IS
  - Prolonged cardiac rhythm monitoring
  - AF burden and IS risk
  - Atrial high-rate episodes
  - Wearables

# Atrial Fibrillation

- Global prevalence: ~59.7 million (2019)
- Lifetime risk ~33% (US,  $\geq 45$  y)
  - ↑ Caucasians
  - M > F

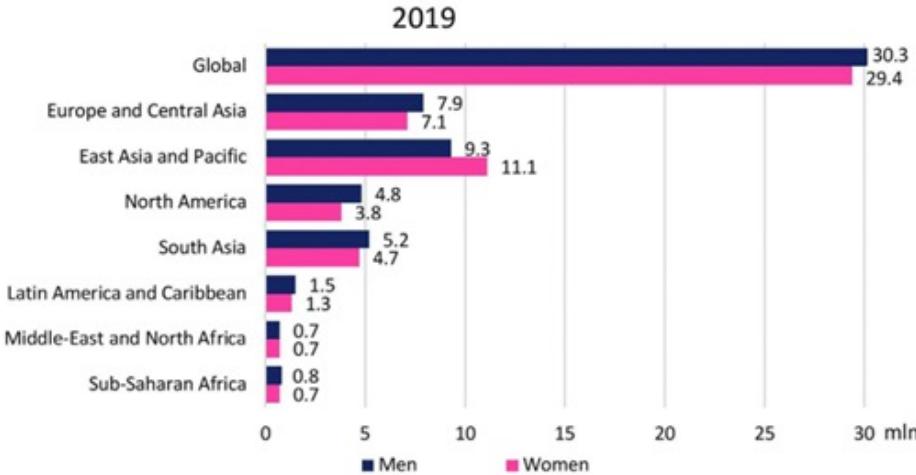
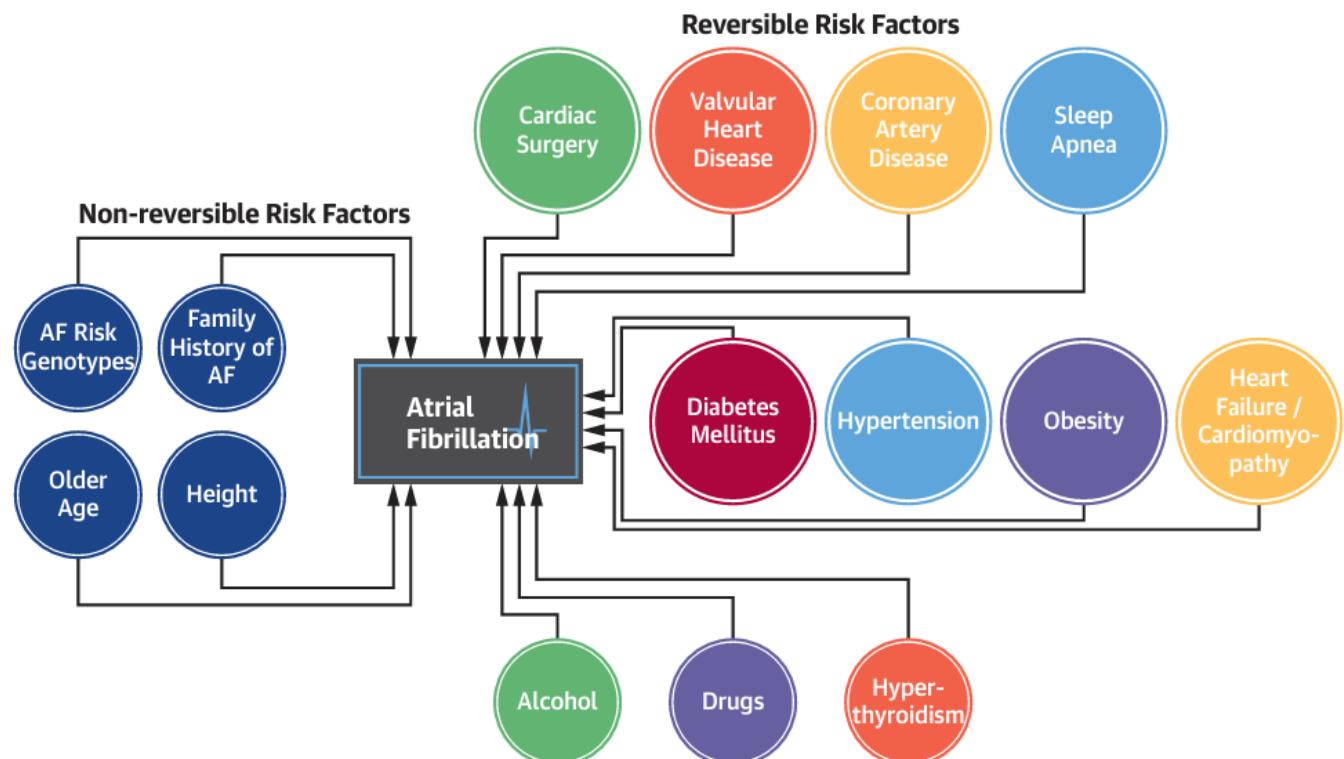
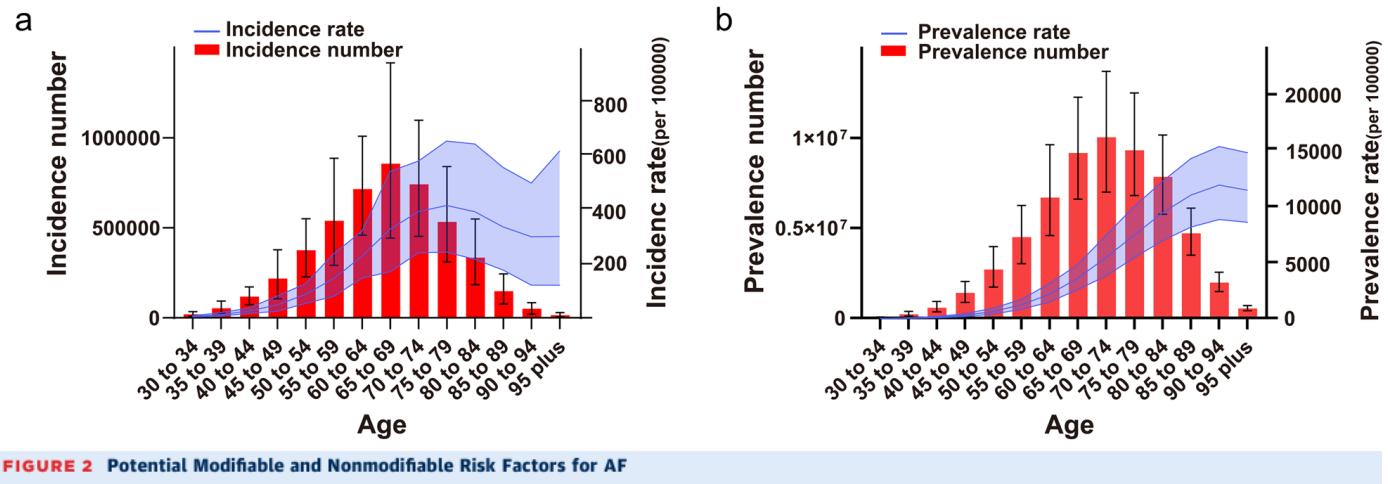


Fig. 2: Prevalence of atrial fibrillation/atrial flutter in both men and women.

Lancet Reg Health Eur. 2024 Feb 1;37:100786.

BMC Public Health. 2022 Nov 3;22(1):2015.

J Am Coll Cardiol. 2020 Apr 14;75(14):1689-1713.



# AF & Stroke Risk

- Non-valvular AF: ↑ 5x risk
  - AF w/ mitral stenosis: ↑ 20x
- 20-30% of IS
- Risk prediction models
  - CHA<sub>2</sub>DS<sub>2</sub>-VASc
    - \* female sex → risk modifier
    - ATRIA, GARFIELD
    - ML → c-index ~0.87

\*multimorbidity  
\*risk is dynamic

J Am Coll Cardiol. 2020 Apr 14;75(14):1689-1713.

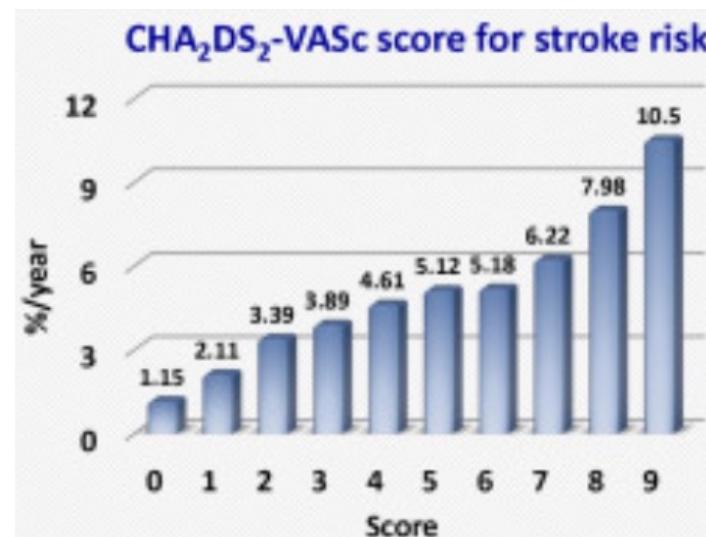
Thromb Haemost. 2022 Jan;122(1):142-150.

Thromb Haemost. 2019 Jul;119(7):1162-1170.

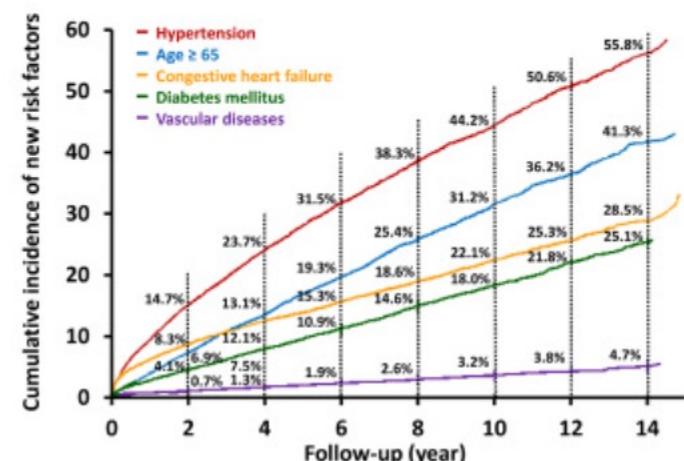
**TABLE 4 CHA<sub>2</sub>DS<sub>2</sub>-VASc Score for Prediction of Stroke in Atrial Fibrillation Patients**

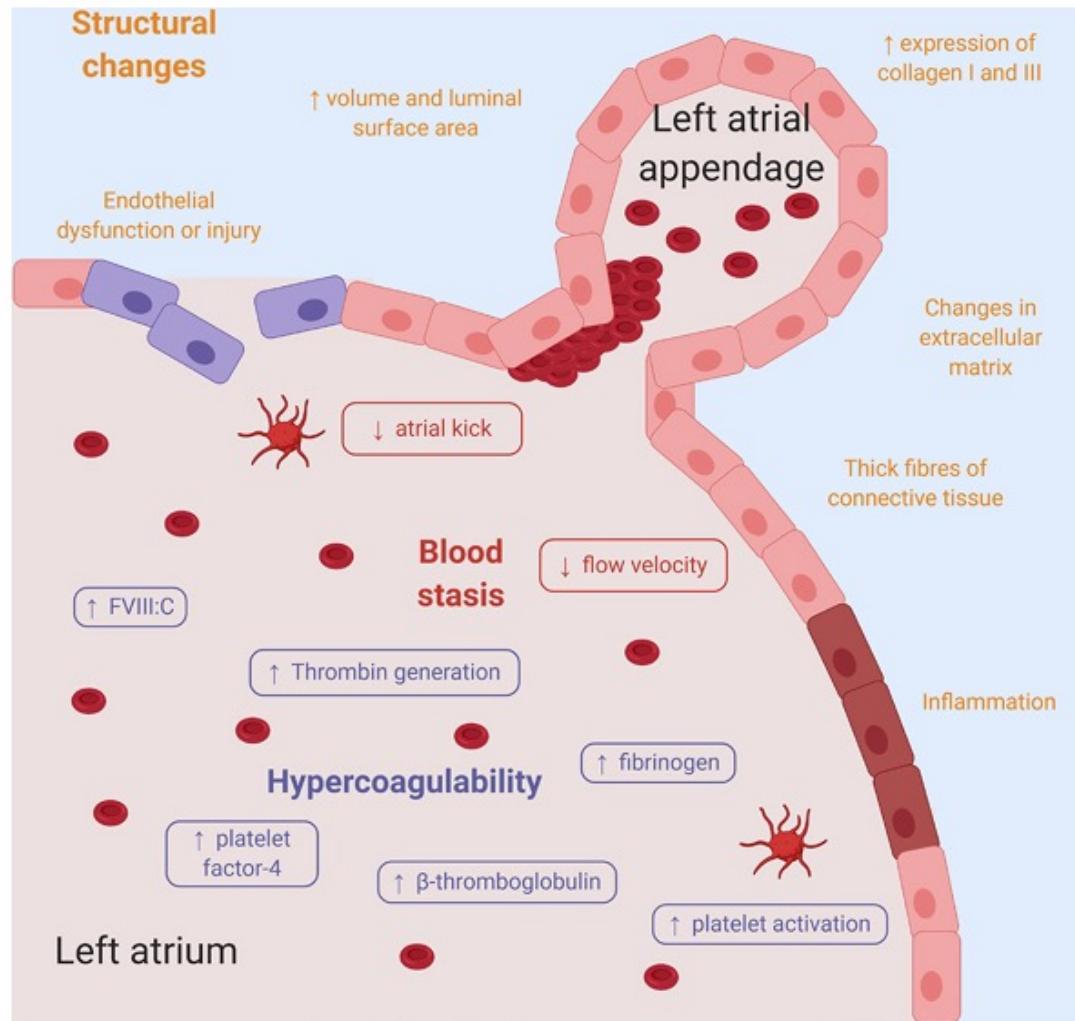
C	Congestive heart failure	1
H	Hypertension (>140/90 mm Hg)	1
A	Age ≥75 yrs	2
D	Diabetes mellitus	1
S <sub>2</sub>	Prior TIA or stroke	2
V	Vascular disease (MI, aortic plaque, and so on)	1
A	Age 65-74 yrs	1
Sc	Sex category (female = 1 point)	1

MI = myocardial infarction; TIA = transient ischemic attack.



Cumulative incidence of new stroke risk factors for patients with a baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 (M) or 1 (F)



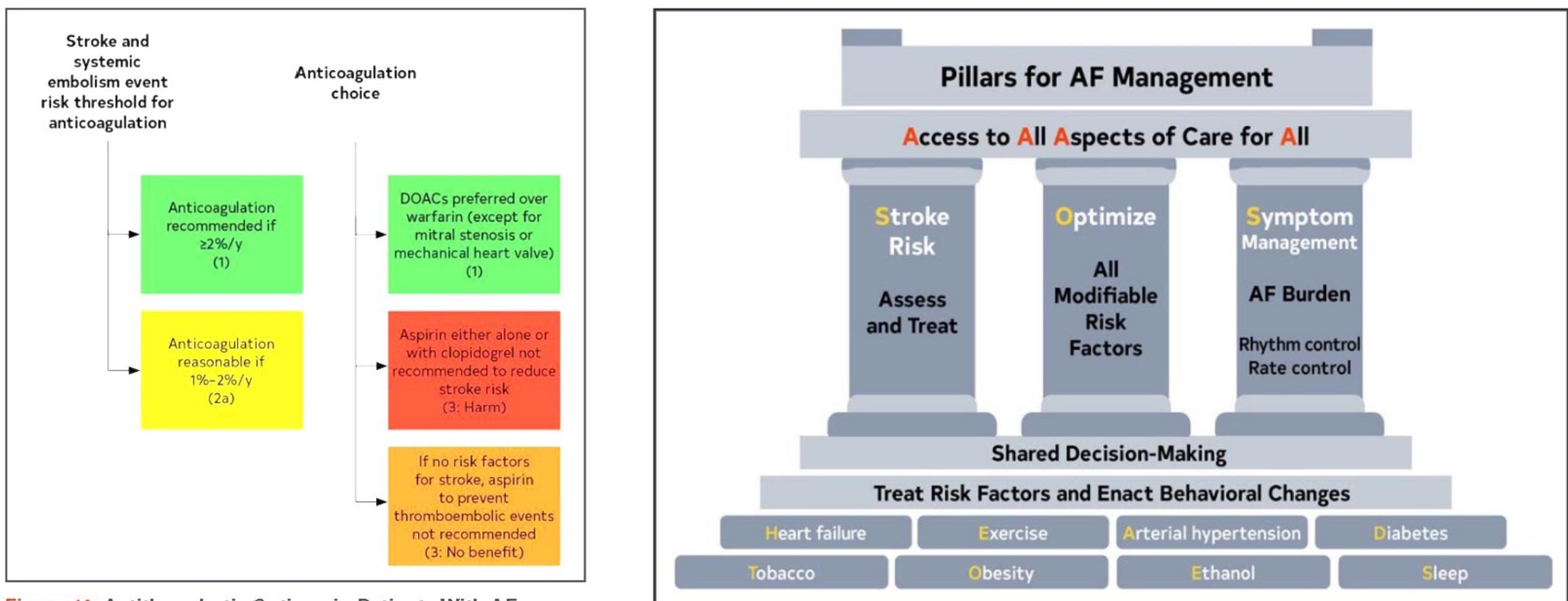


# Thromboembolism

- **Stasis**
- **Atrial structure (remodeling, dilation) & contraction**
- Hypercoagulability
- Endothelial dysfunction

**Figure 1** Effects of atrial fibrillation on the various elements of Virchow's triad (hypercoagulability, structural changes and blood stasis).

# AF Management



# Antiplatelets & Warfarin

- Aspirin → RRR ~22%  
\* SPAF-1
- Aspirin + Clopidogrel
  - ACTIVE A → RR 0.72
    - ARR: 0.9%
    - Major hemorrhage (DAPT): ~2%/yr
  - ACTIVE W → RR 0.69
    - Warfarin vs aspirin/clopidogrel
- Warfarin → RRR ~64%

Chest. 2018 Nov;154(5):1121-1201.  
Ann Intern Med. 2007 Jun 19;146(12):857-67.  
N Engl J Med. 2009 May 14;360(20):2066-78.  
Lancet. 2006 Jun 10;367(9526):1903-12.  
Stroke. 2006 Feb;37(2):447-51.

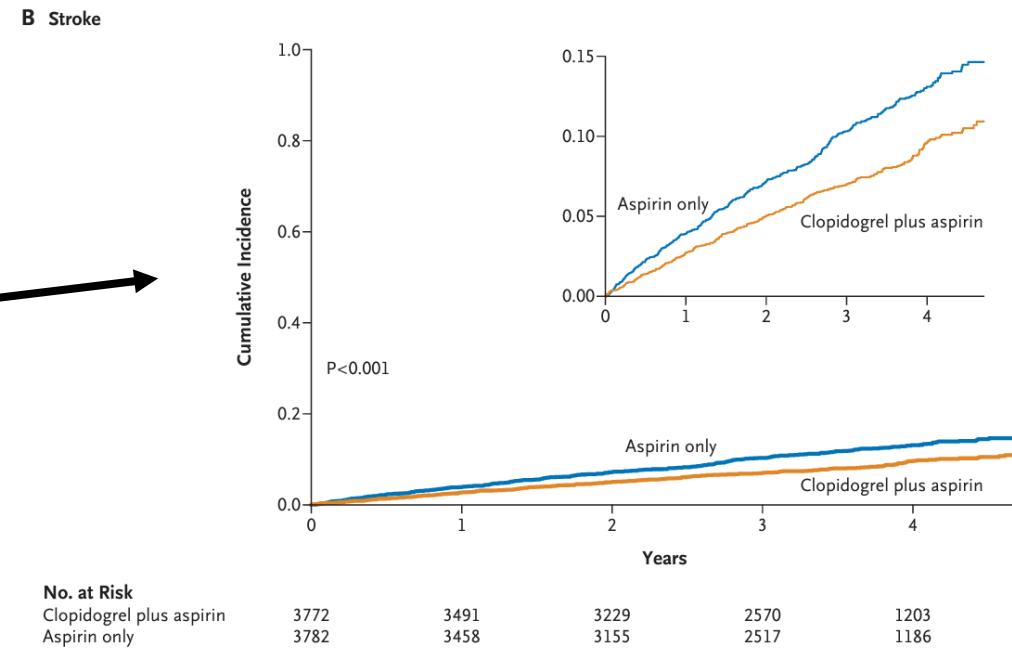
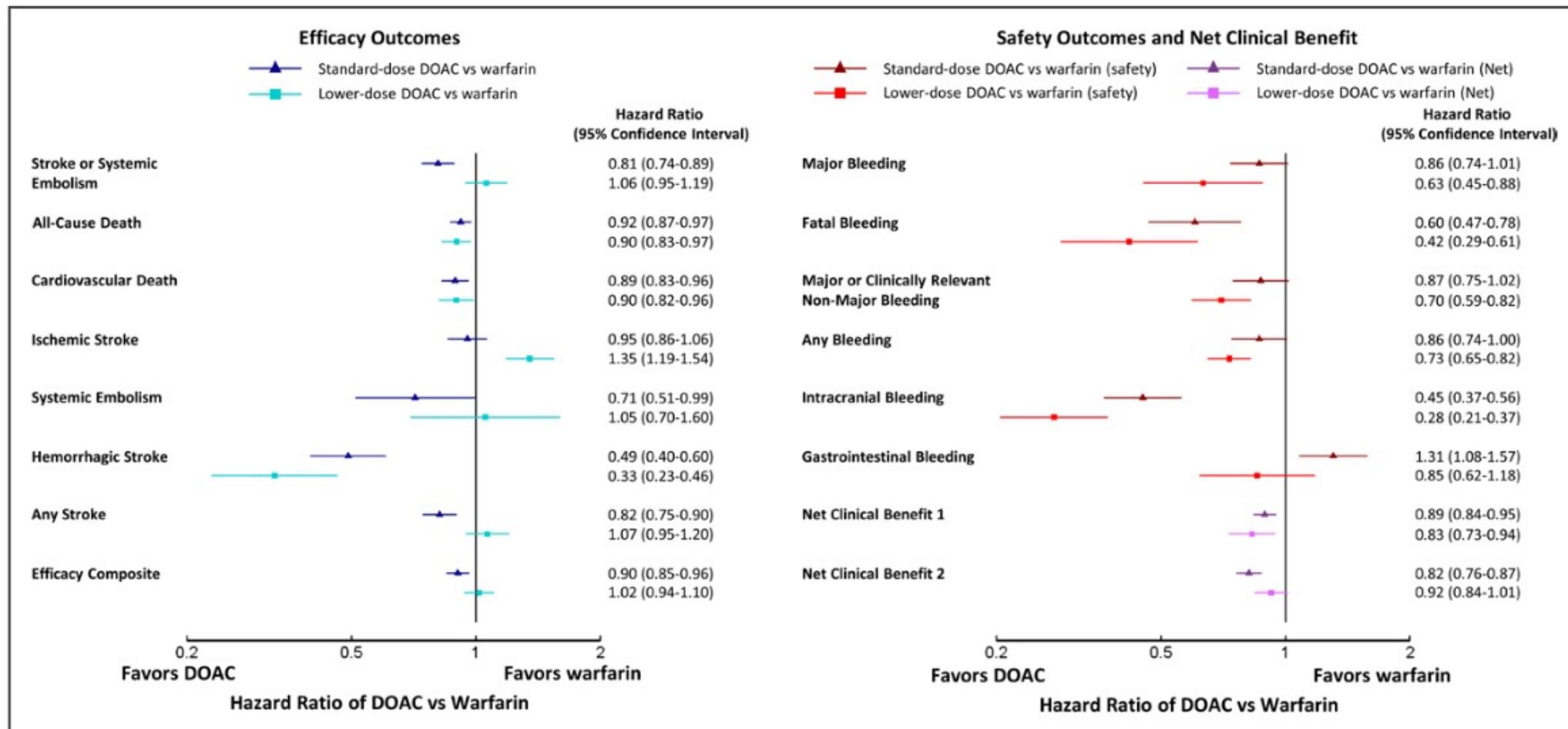


Figure 1. Cumulative Incidence of Trial Outcomes, According to Treatment Group.

Table 6. Meta-analysis of the Efficacy of Antithrombotic Therapies for Stroke Prevention in Patients Who Have Atrial Fibrillation\*

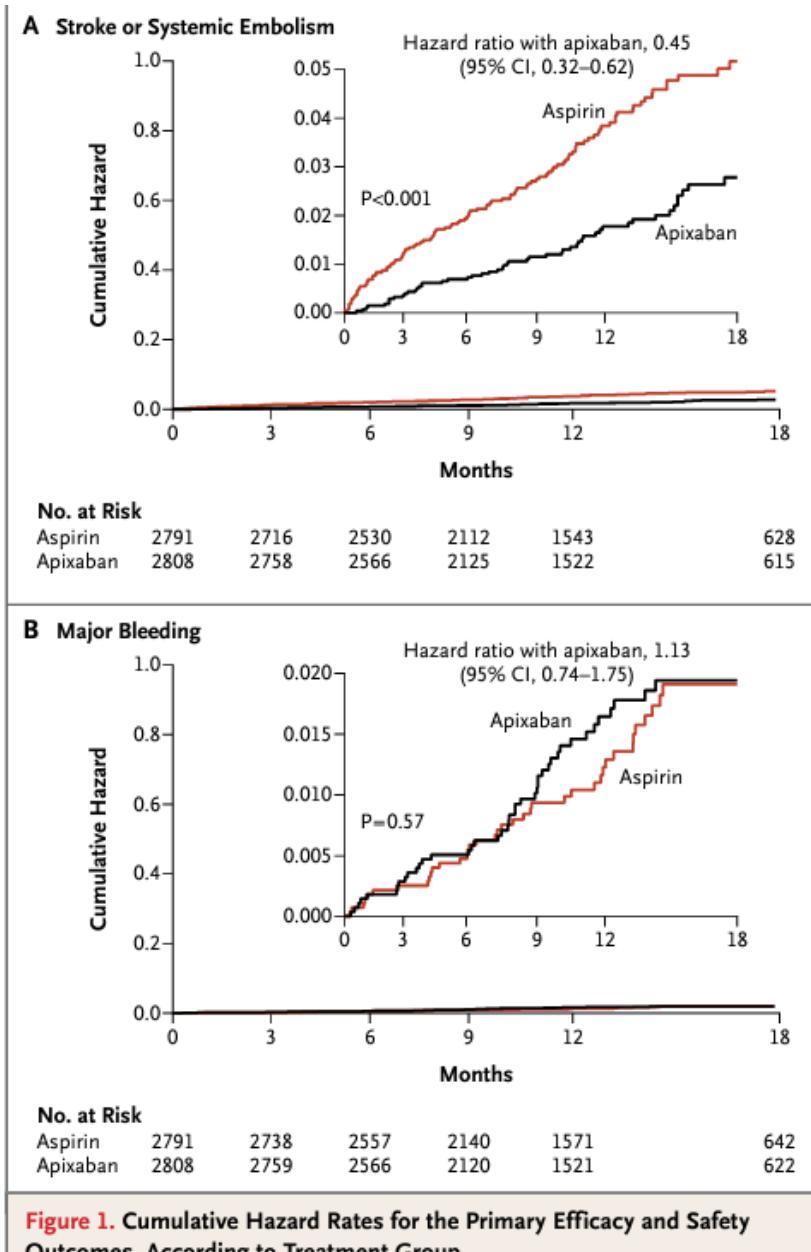
Comparison	Trials, n	Patients, n	Strokes, n	Relative Risk Reduction, %	Hypothetical NNT: Primary Prevention†	Hypothetical NNT: Secondary Prevention†
Adjusted-dose warfarin versus control	6	2900	186	64	40	14
Antiplatelet agents versus control	8	4876	488	22	111	34
Adjusted-dose warfarin versus antiplatelet agents	12	12 963	546	39	81	24

# Direct Oral Anticoagulants – Efficacy & Safety

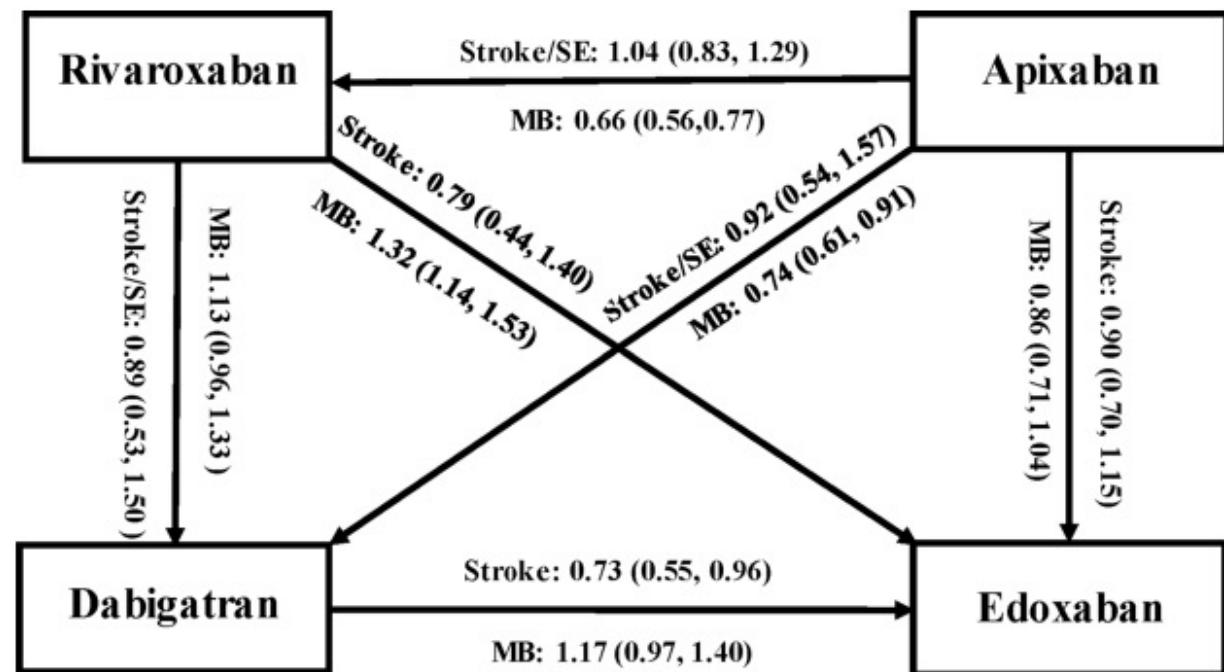


**Figure 1.** Comparison of standard-dose and lower-dose direct oral anticoagulants vs warfarin for efficacy, safety, and net clinical benefit outcomes.

# AVERROES



# Effectiveness



**Fig. 1** Indirect comparative effectiveness and safety amongst DOACs in patients with AF

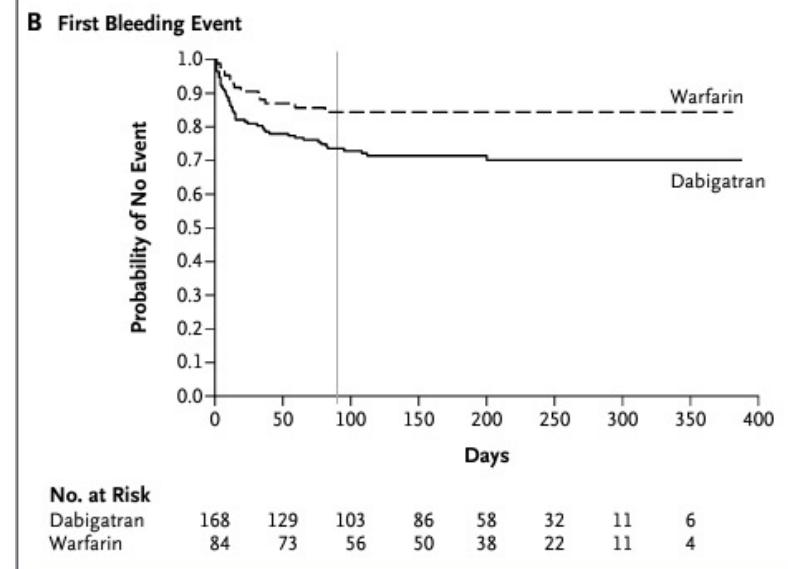
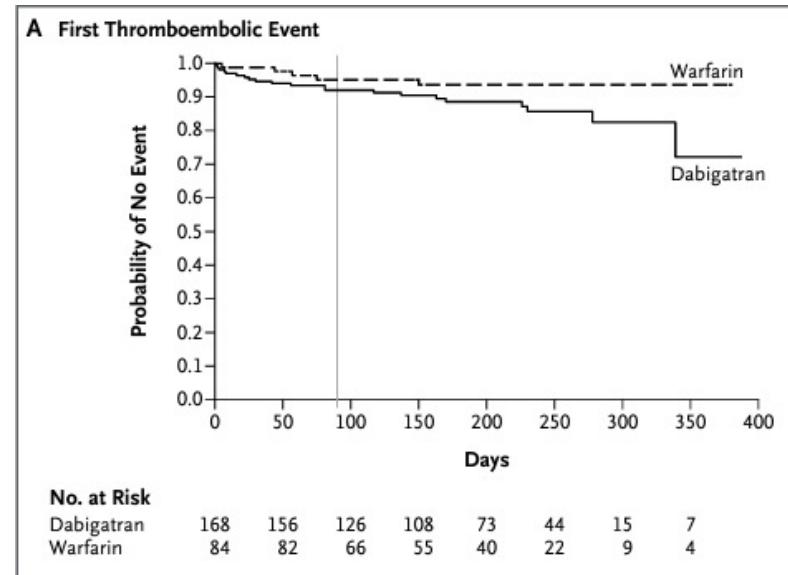
N Engl J Med. 2011 Mar 3;364(9):806-17.  
Eur J Epidemiol. 2021 Aug;36(8):793-812.

# Special Populations

- DOAC trials for AF – exclusions:
  - pregnancy
  - **mechanical heart valve**
  - moderate-severe MV stenosis
  - ESRD/dialysis



N Engl J Med. 2013 Sep 26;369(13):1206-14.  
NEJM Evid. 2023 Jul;2(7):EVIDoa2300067.  
Ann Biomed Eng. 2015 Apr;43(4):844-57.



**Figure 1. Kaplan-Meier Analysis of Event-free Survival.**

Panel A shows event-free survival from the first thromboembolic event (i.e., stroke, systemic embolism, transient ischemic attack, or myocardial infarction) or death ( $P=0.24$ ). Panel B shows event-free survival from the first bleeding event ( $P=0.01$ ). In each panel, the vertical line indicates the start of the RE-ALIGN extension trial (RE-ALIGN-EX) and the  $P$  value was calculated with the use of the Wald chi-square test.



## PROACT Xa

On-X Life  
Technologies

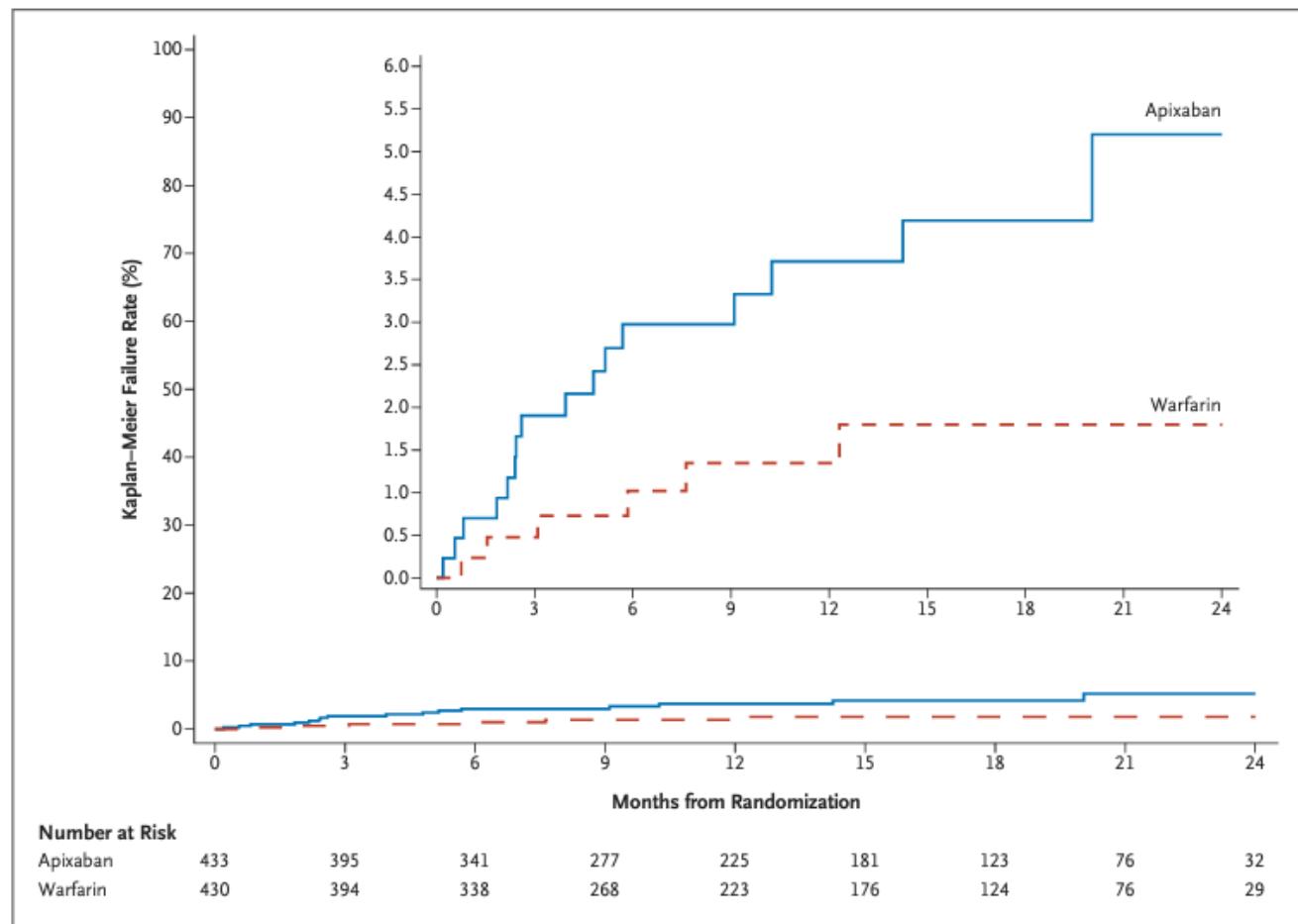
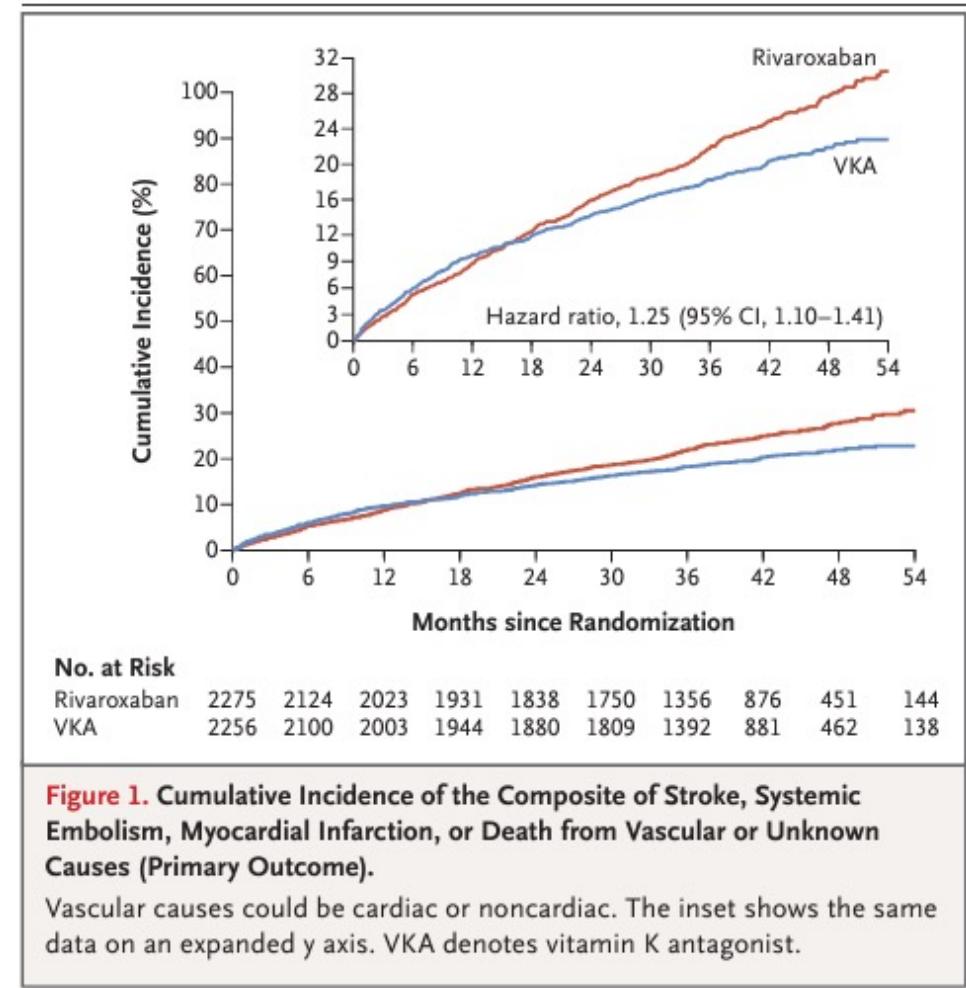


Figure 2. Cumulative Incidence of Valve Thrombosis or Valve-Related Thromboembolism.

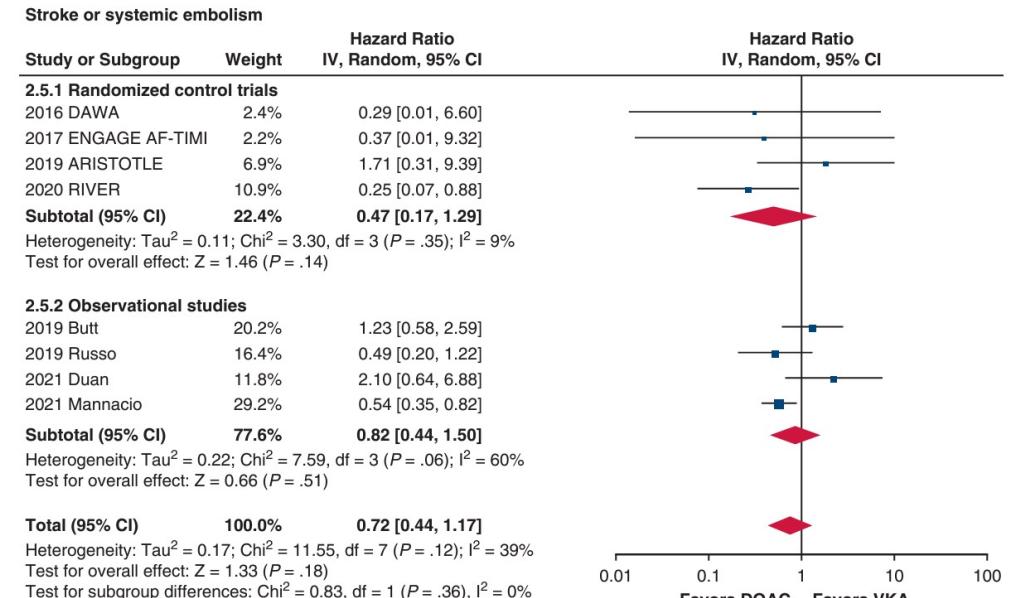
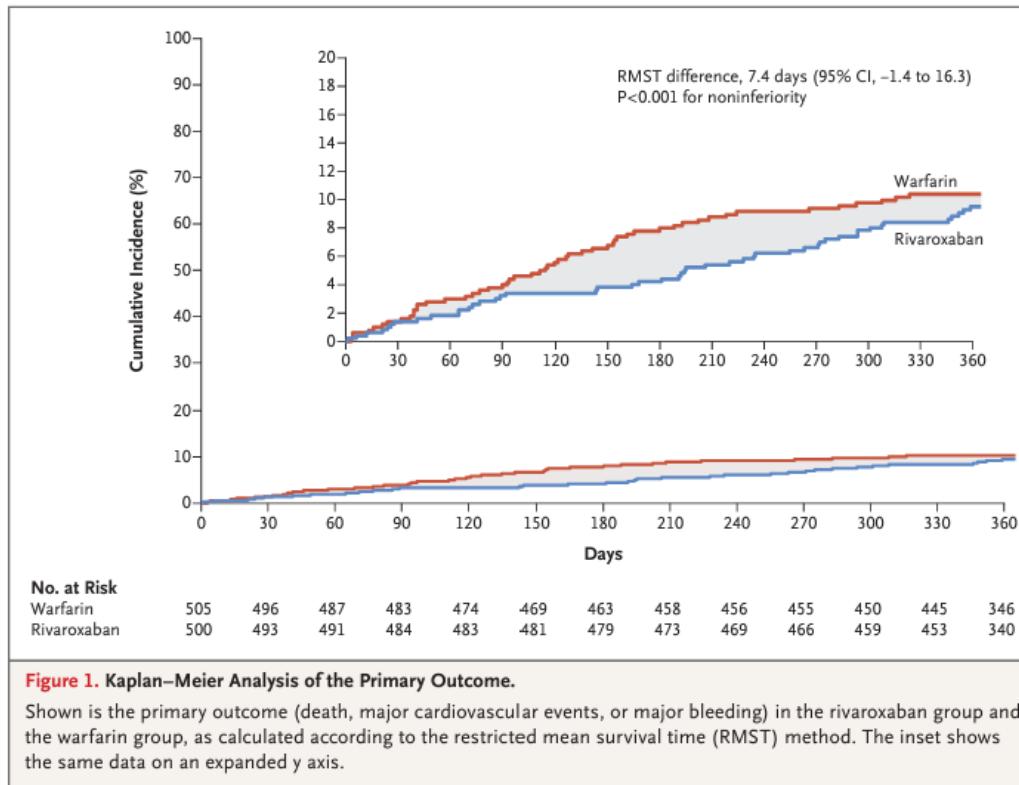
# Mitral Valve Stenosis

## INVICTUS

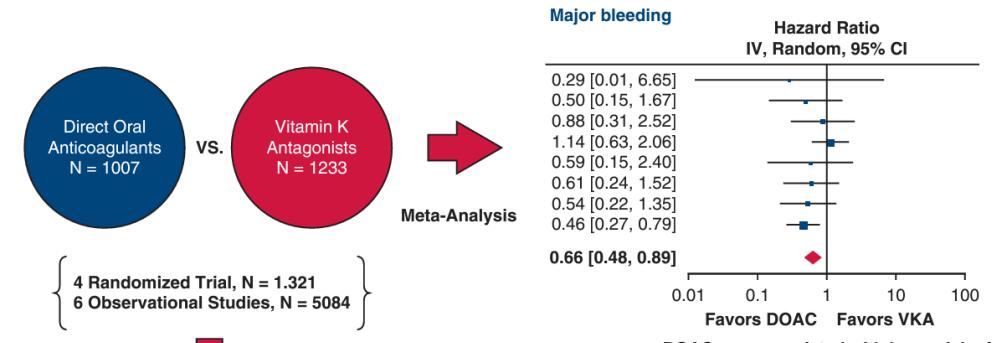


# Bioprosthetic Valves

## RIVER



**Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients with Atrial Fibrillation and Bioprosthetic Valves: A Meta-Analysis.**



CI = confidence interval, DOAC = direct oral anticoagulants, VKA = vitamin K antagonist, IV = inverse variance

J Thorac Cardiovasc Surg. 2023 Jun;165(6):2052-2059.e4.

Eur Heart J. 2022 Aug 1;43(29):2783-2797.

N Engl J Med. 2020 Nov 26;383(22):2117-2126.

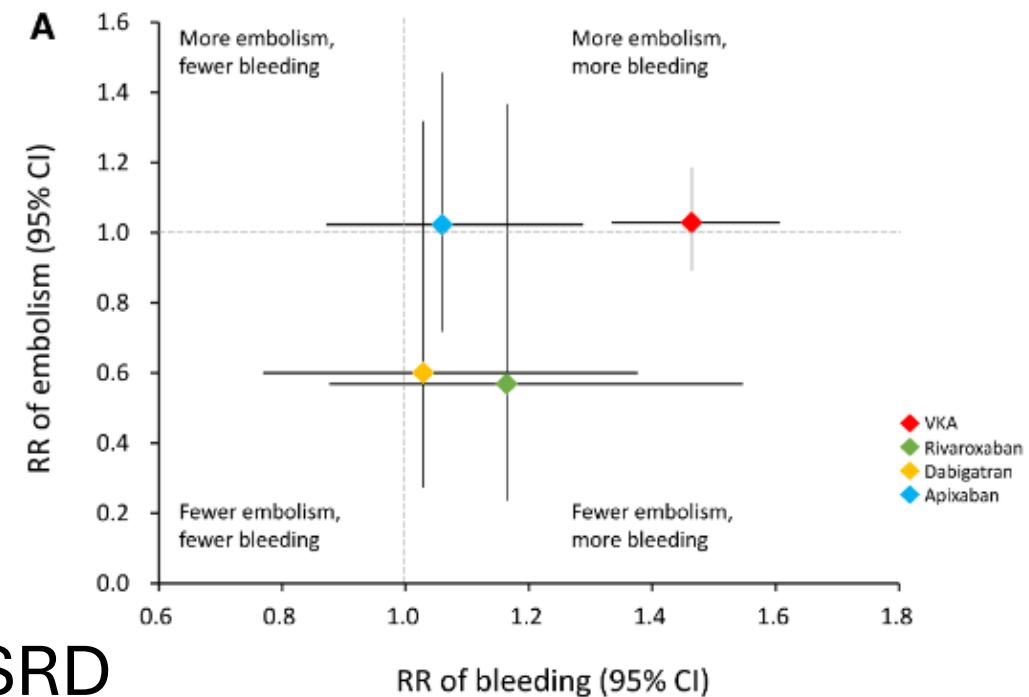
N Engl J Med. 2021 Dec 2;385(23):2150-2160.

- Transcatheter Aortic Valve Implantation + AF → edoxaban & apixaban ~ warfarin

# ESRD / Dialysis

- CKD → risk factor for stroke in AF
- Stage IV CKD (observational) → DOAC

→ apixaban or warfarin reasonable in ESRD



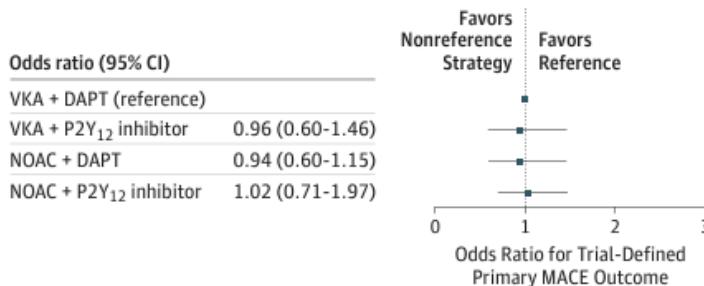
**Table 19.** Recommended Doses of Currently Approved DOACs According to Renal Function

DOAC	CrCl (mL/min)				
	>95	51-95	31-50	15-30	<15 or on dialysis
Apixaban	5 or 2.5 mg twice daily*				
Dabigatran	150 mg twice daily	150 mg twice daily	150 mg twice daily	75 mg twice daily	Contraindicated
Edoxaban	Contraindicated	60 mg once daily	30 mg once daily	30 mg once daily	Contraindicated
Rivaroxaban	20 mg once daily	20 mg once daily	15 mg once daily	15 mg once daily	15 mg once daily†

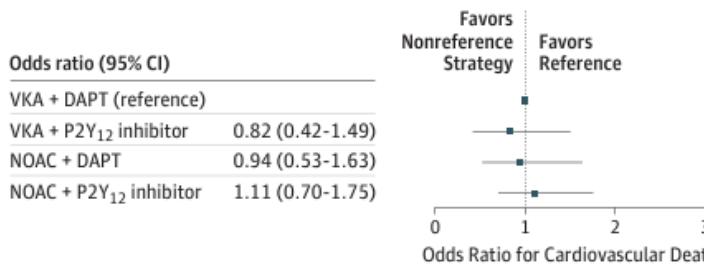
# Percutaneous Coronary Intervention

Figure 3. Forest Plots for Efficacy Outcomes

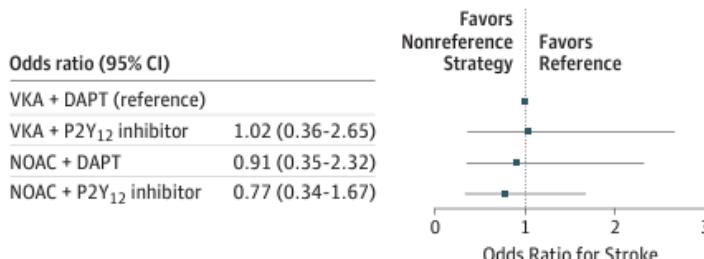
A Trial-defined primary MACE



C Cardiovascular death



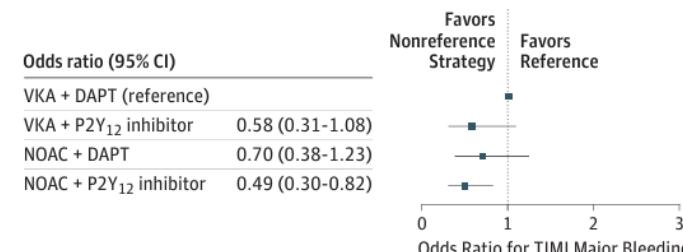
E Stroke



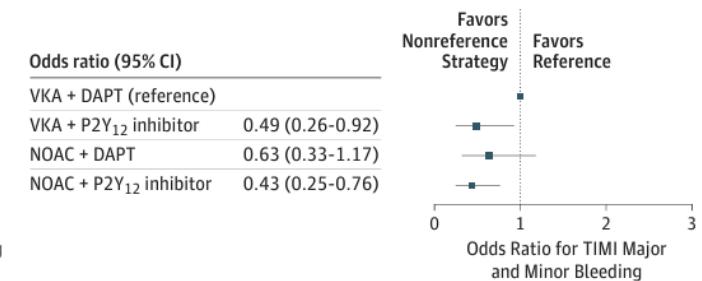
- DOAC + P2Y<sub>12</sub> inhibitor: ↓ risk of major hemorrhage & ICH

Figure 2. Forest Plots for Safety Outcomes

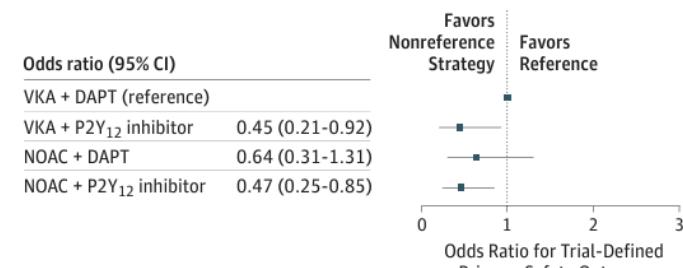
A TIMI major bleeding



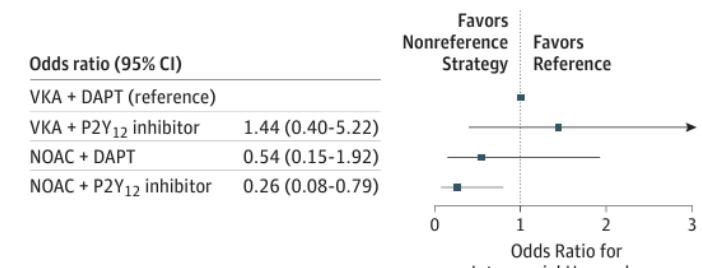
B TIMI major and minor bleeding



C Trial-defined primary safety outcome



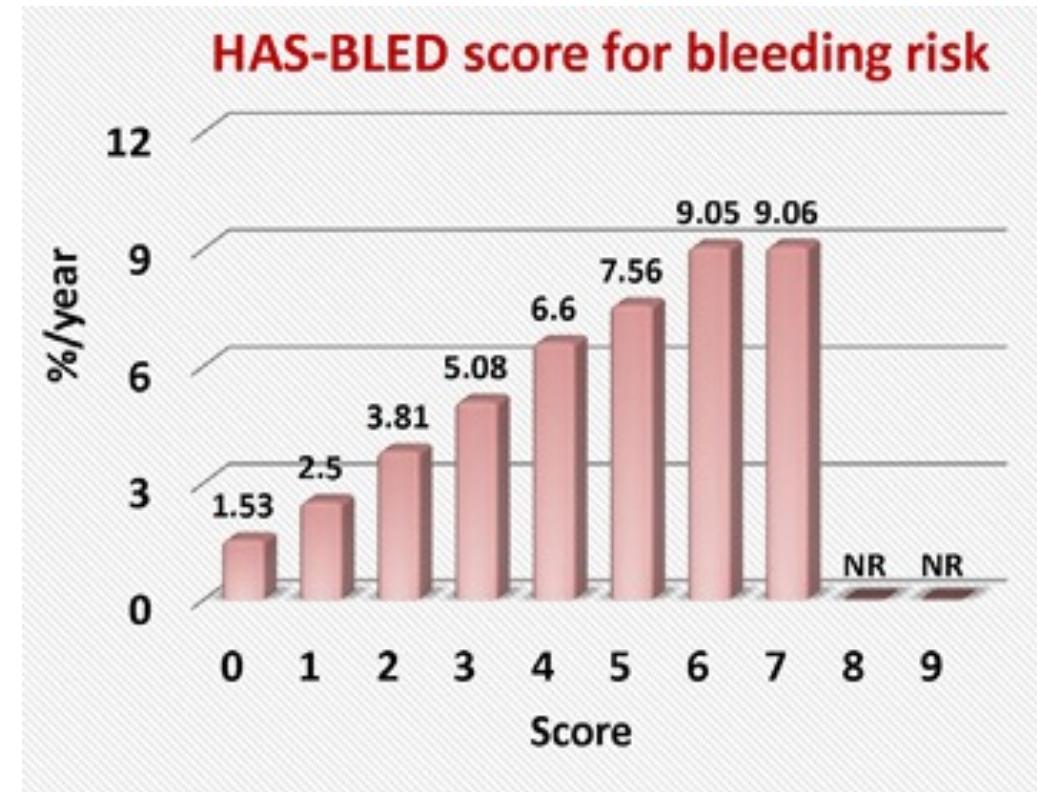
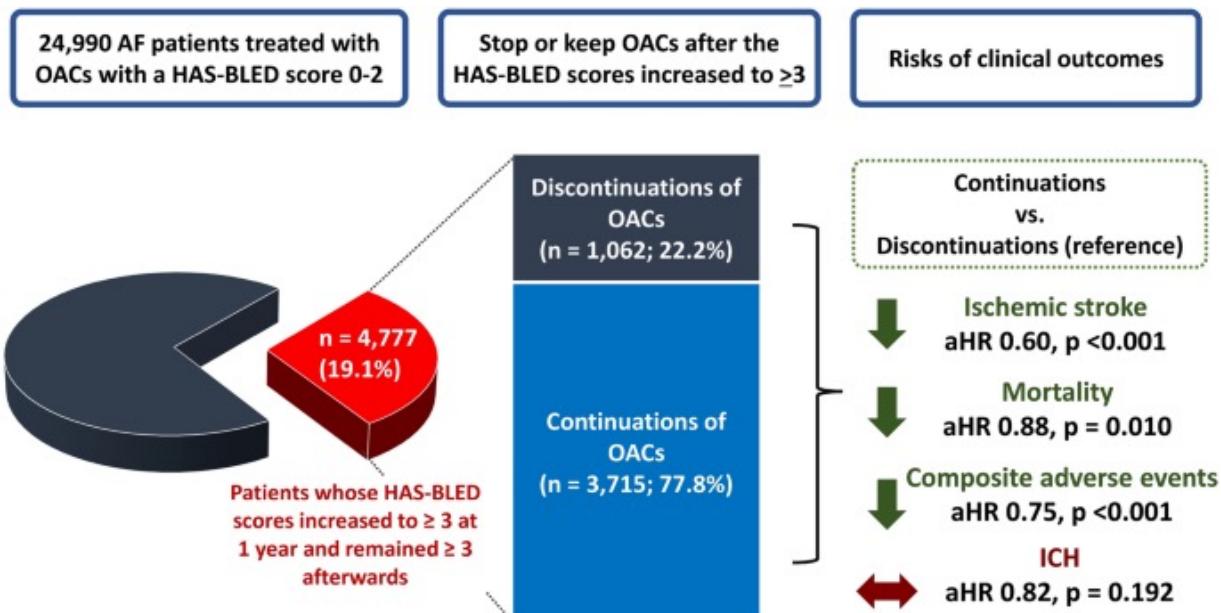
D Intracranial hemorrhage



# Bleeding Risk ≠ Avoid Anticoagulation

- Identify & correct modifiable risk factors
- HAS-BLED → c-index ~0.6-0.7
  - $\text{CHA}_2\text{DS}_2\text{-VASc}=1-2$  & HAS-BLED $\geq 3$  → OAC confers lower risk of ischemic stroke + ICH+ mortality

\* risk is dynamic



Lancet Reg Health Eur. 2024 Feb 1;37:100797.  
 Clin Res Cardiol. 2022 Jan;111(1):23-33.  
 Am J Med. 2020 Oct;133(10):1195-1202.e2.

Condition	Points
H – Hypertension	1
A – Ab(N) liver/renal	1 point each
S – Stroke	1
B – Bleeding	1
L – Labile INRs	1
E – Elderly (>65)	1
D – Drugs or ETOH	1 point each

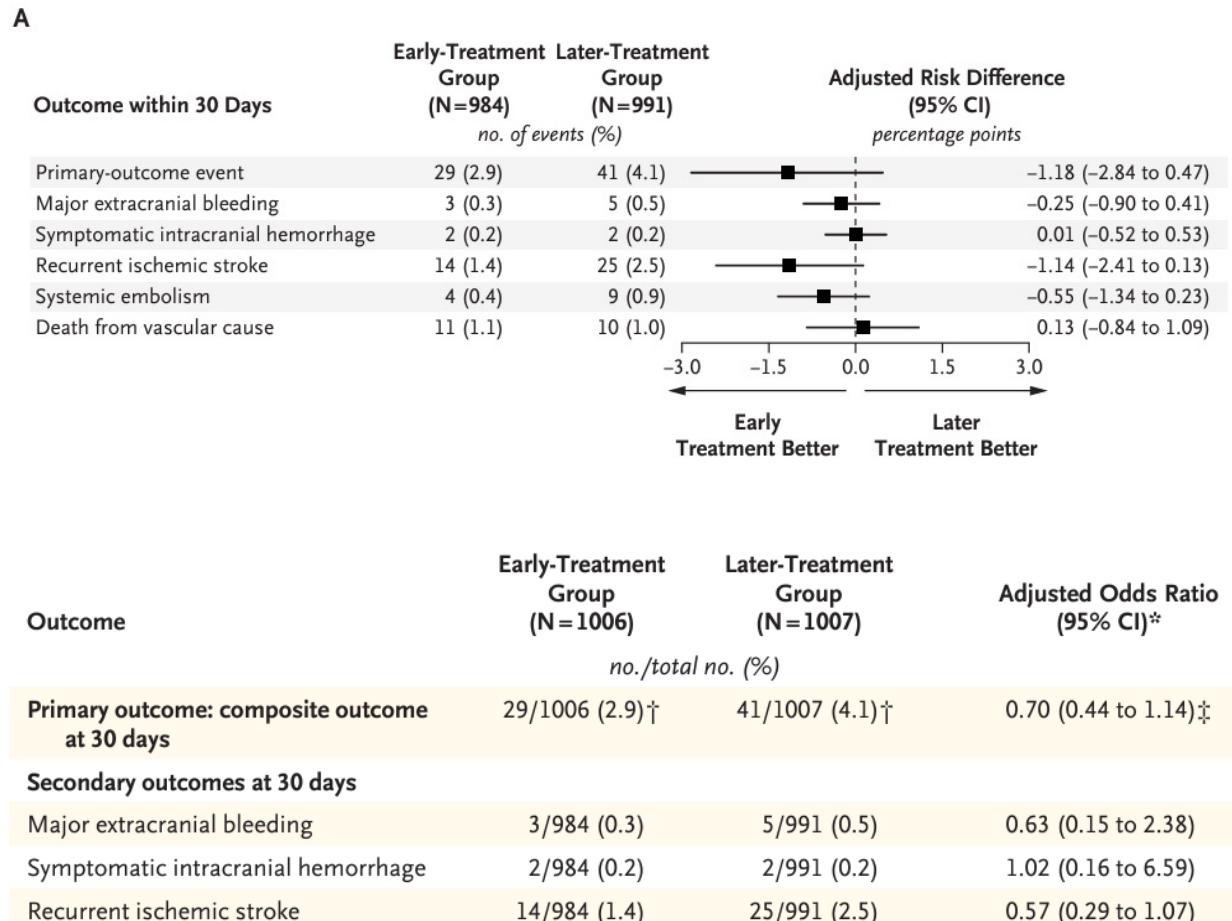
# Timing of AC After IS

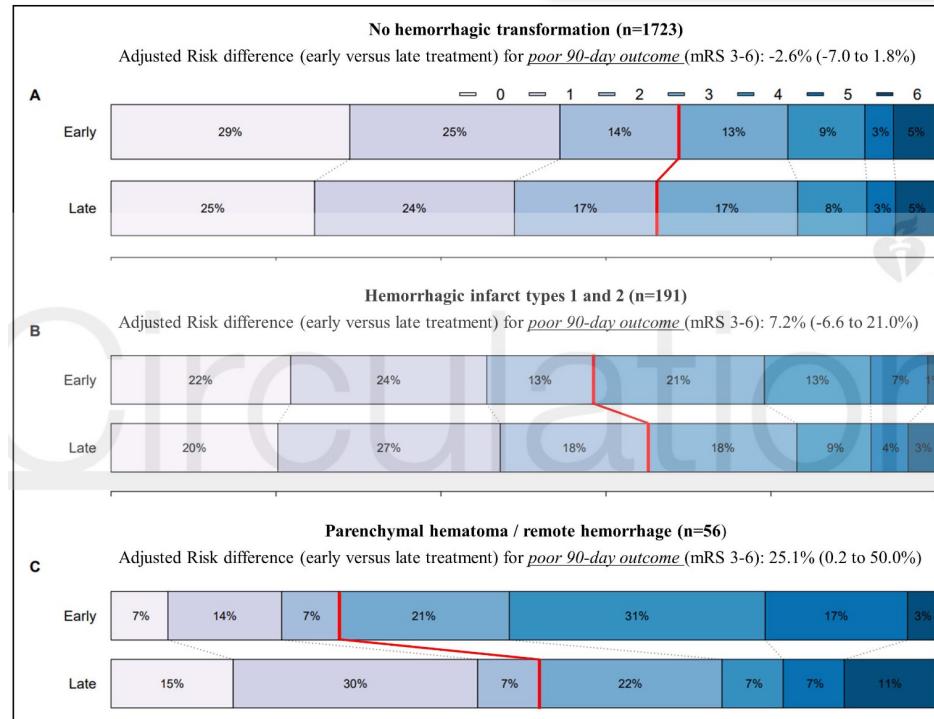
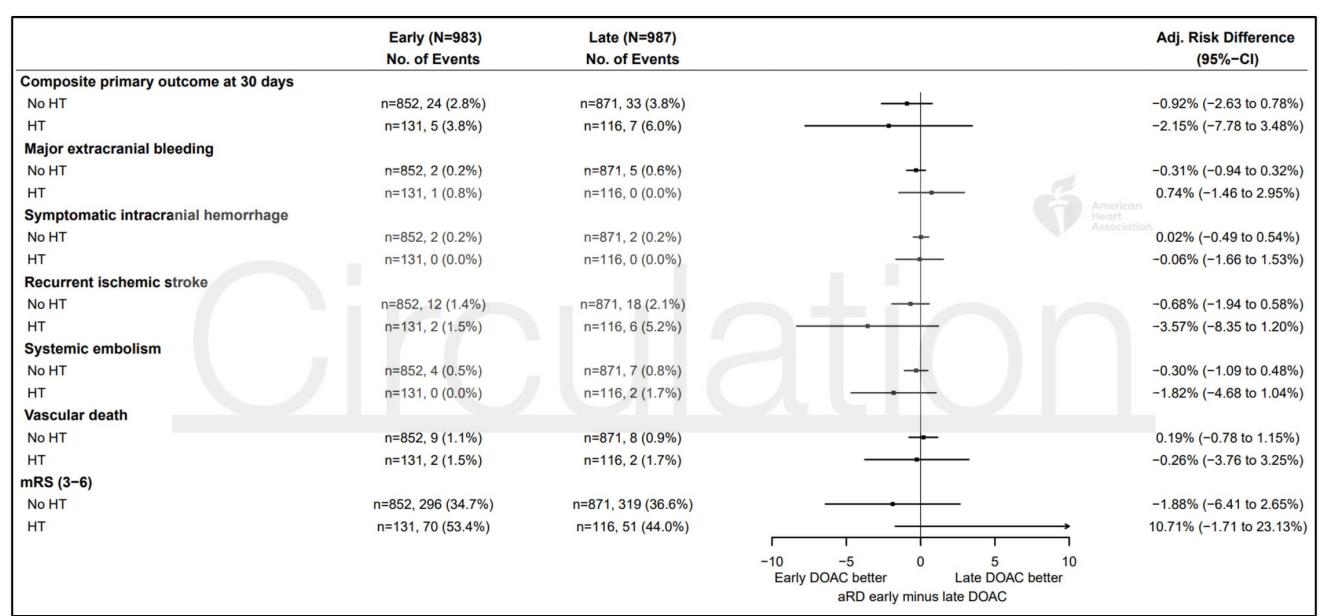
	TIMING (NCT02961348) <sup>54</sup>	ELAN (NCT03148457) <sup>16,55,56</sup>	OPTIMAS (NCT03759938) <sup>57</sup>	START (NCT03021928)
Status	Completed	Completed	Recruitment completed, awaiting results	Recruitment completed, results presented at the International Stroke Conference 2024 (Feb 7, 2024, Phoenix, AZ, USA), not yet published
Sample size	888 participants (planned 3000)	2013 participants	3648 participants	200 of 1500 planned participants (1000 patients with mild or moderate stroke and 500 with severe stroke)
Early start group	≤4 days after acute ischaemic stroke	<48 h after symptom onset (minor and moderate stroke) or at day 6 ( $\pm 1$ day) after symptom onset (major stroke)	≤4 days after acute ischaemic stroke	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke
Late start group	5–10 days after acute ischaemic stroke	Current recommendations (ie, minor stroke after day 3 [ $\pm 1$ day], moderate stroke after day 6 [ $\pm 1$ day], and major stroke after day 12 [ $\pm 2$ days])	7–14 days after acute ischaemic stroke	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke
Primary outcome	Composite outcome (recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality)	Composite outcome (major bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death)	Composite outcome at 90 days (recurrent symptomatic ischaemic stroke, symptomatic intracranial haemorrhage [including extradural, subdural, subarachnoid, and intracerebral haemorrhage and haemorrhagic transformation of the qualifying infarct], and systemic embolism)	Composite of any CNS haemorrhagic or other major haemorrhagic events and the ischaemic events of stroke or systemic embolism within 30 days of the index stroke
Time of assessment	90 days	30 days	90 days	30 days

- Small-moderate infarct → ≤48 hours
- Large infarct → 1-2 weeks

# Early vs Later AC for Stroke w/ AF (ELAN)

- Population:* acute IS + AF
- Intervention/Control:* early/late DOAC
  - Early: ≤48h minor/moderate, 6/7d major
  - Late: 3/4d minor, 6/7d moderate, 12/13/14d major
- $1^{\circ}$  *Outcome:* composite – recurrent IS, SE, sx ICH, major extracranial hemorrhage, vascular death @ 30d
- *Stroke severity:* median NIHSS 5 (IQR 2-12)
  - Minor (37%): ≤1.5cm
  - Moderate (40%): cortical superficial branch of MCA/ACA/PCA distribution
  - Major (23%): large volume in MCA/ACA/PCA distribution OR >1.5cm in brainstem/cerebellum





Early DOAC may worsen functional outcomes in IS with PH

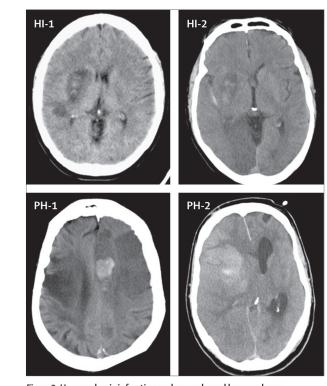
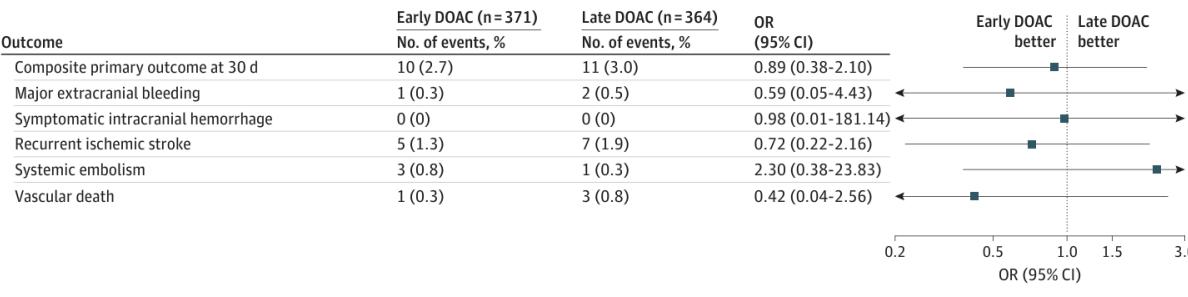


Figure 3: Haemorrhagic infarction and parenchymal haemorrhage

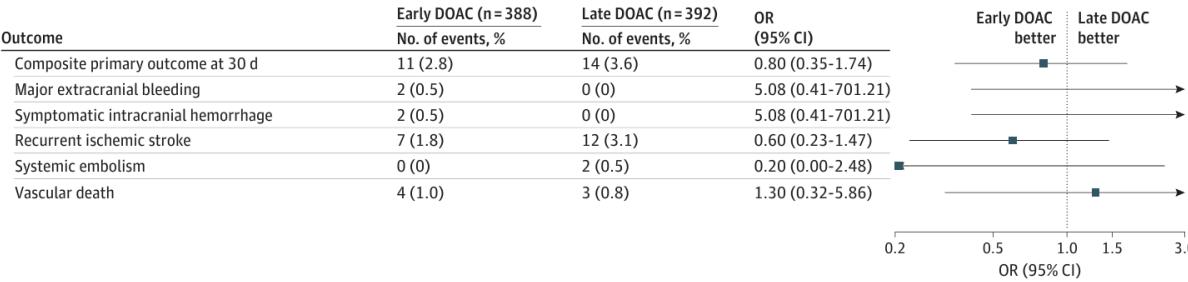
No treatment effect heterogeneity or elevation in sx ICH risk with early DOAC in subgroups: stroke severity, HT 1/2

Figure 2. Unadjusted Odds Ratios (ORs) of the Primary Composite Outcome and Secondary Outcomes at 30 Days

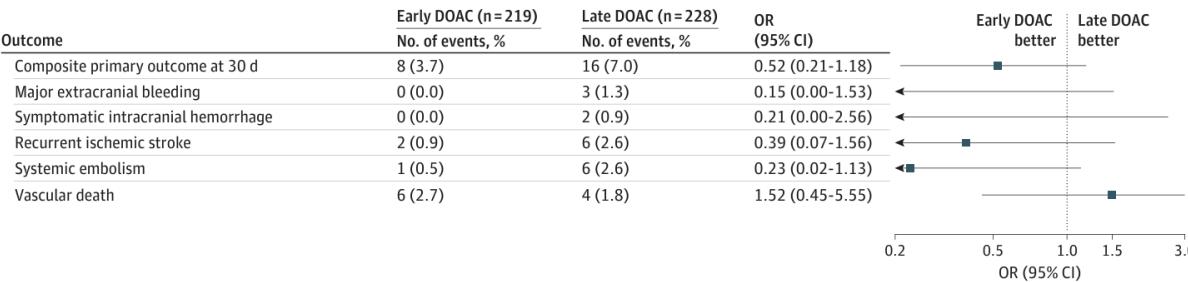
**A Minor stroke**



**B Moderate stroke**



**C Major stroke**



Hemorrhagic infarction - 1	Isolated petechial staining of infarcted tissue without mass effect
Hemorrhagic infarction - 2	Onfluent pachycephalic in infarcted tissue without mass effect
Parenchymal Hemorrhage - 1	Homogeneous high attenuation lesion with minimal mass effect occupying less than 30% of the infarcted area
Parenchymal Hemorrhage - 2	Lesion occupying more than 30% of the infarcted area with definite mass effect Possible extension of hemorrhage into the ventricular space, As well as any hemorrhage outside the infarcted area

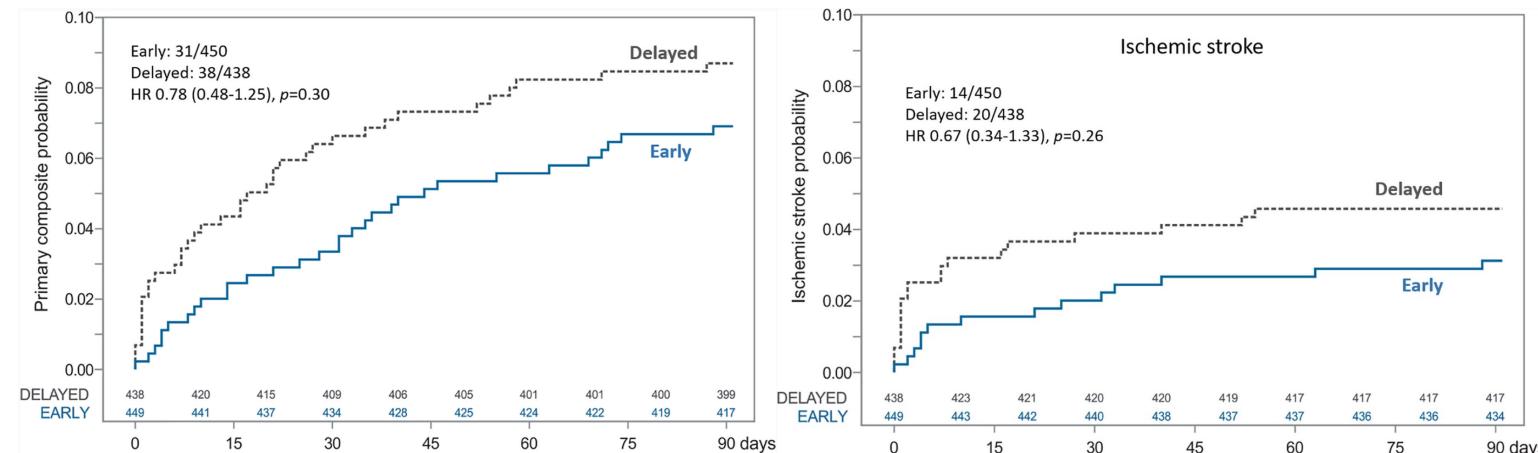
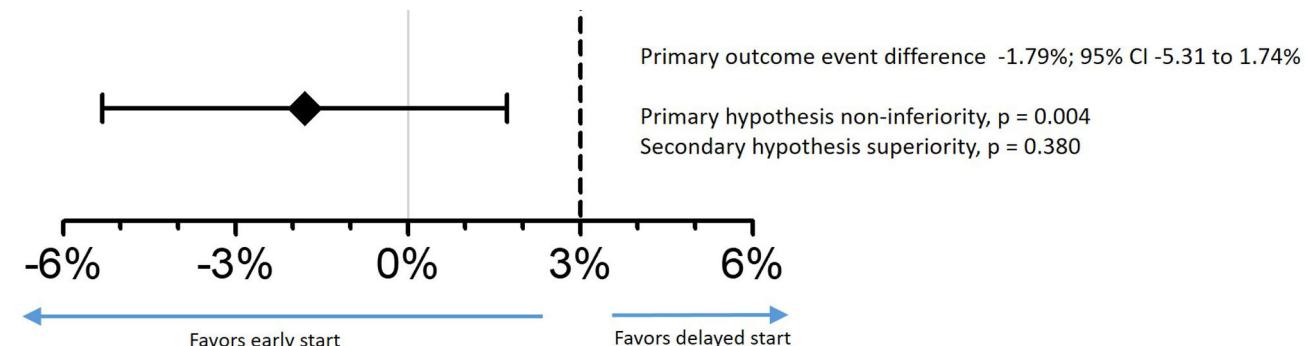
Circulation. 2024 May 16. PMID: 38753452.

JAMA Neurol. 2024 May 28. PMID: 38805207.

Lancet Neurol. 2013 Jul;12(7):689-705.

# Timing of OAC Therapy in Acute IS w/ AF (TIMING)

- *Population:* acute ischemic stroke + AF
- *Intervention/Control:* early/late DOAC
  - Early:  $\leq 72\text{h}$
  - Delayed: 5-10 days
- $1^\circ \text{ Outcome:}$  composite of recurrent IS, sx ICH, death @ 90d
- Non-inferiority margin: 3% → superiority
- Terminated early
- NIHSS: median 4 (IQR 2-9)



# IS despite AC

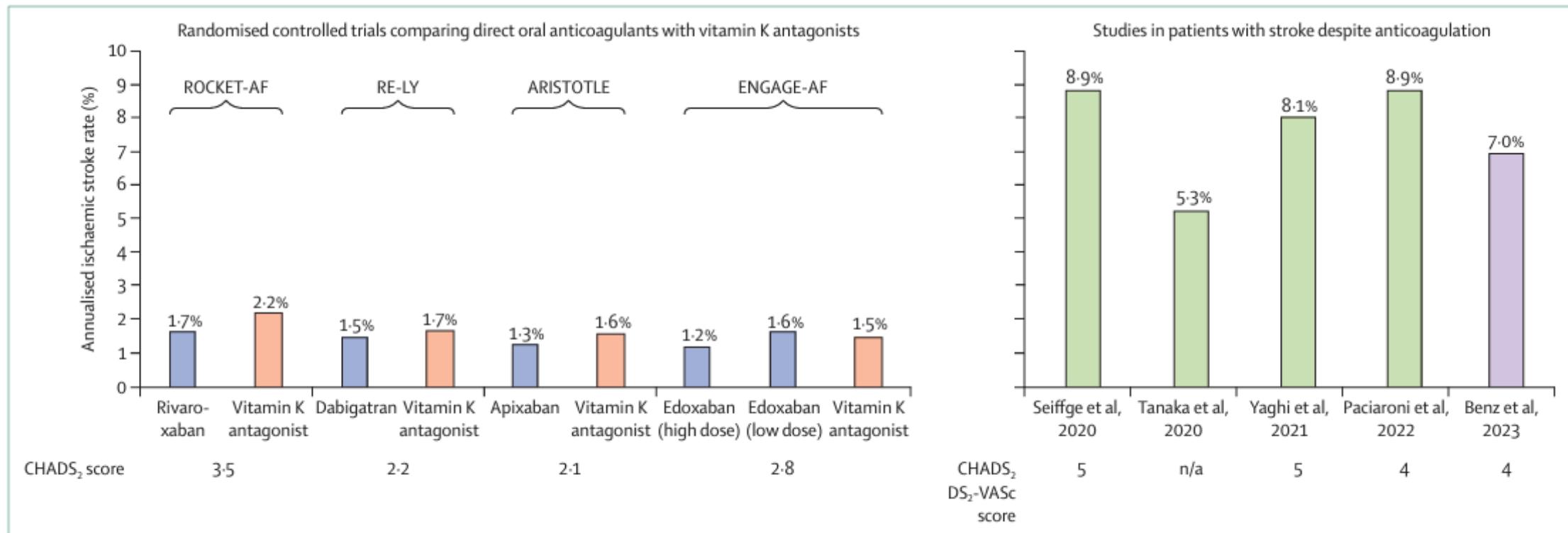
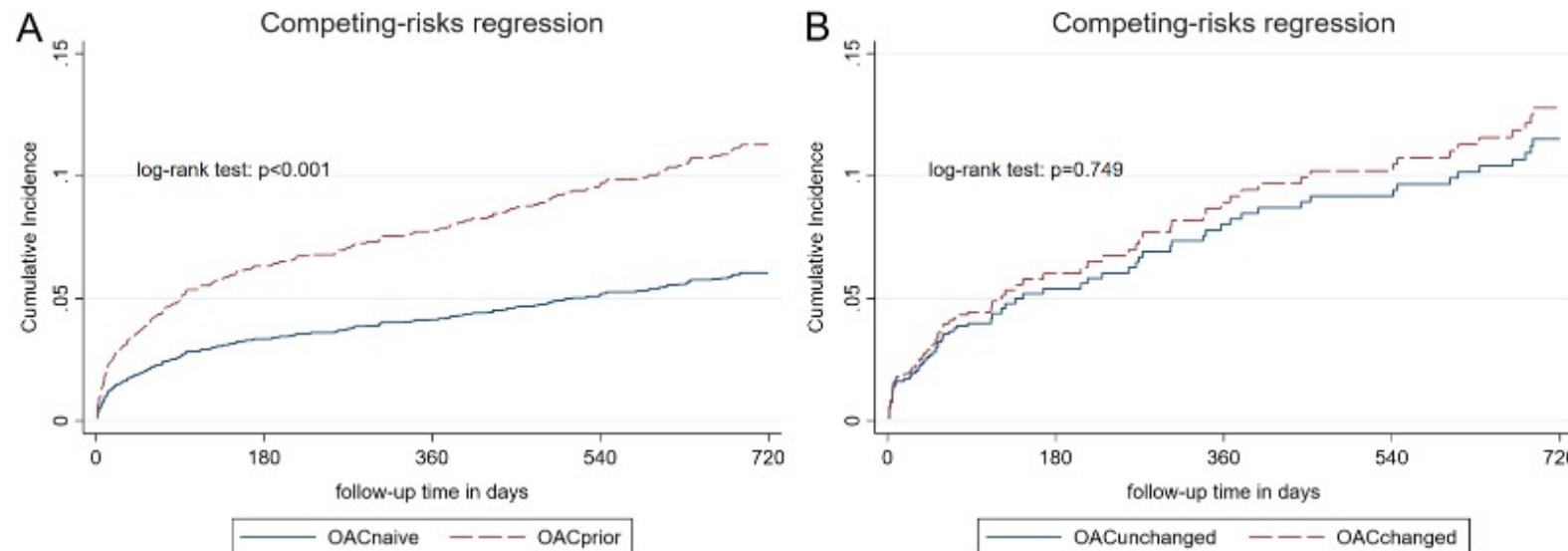


Figure: Annualised rates of ischaemic stroke events in randomised controlled trials comparing vitamin K antagonists (red bars) with different direct oral anticoagulants (blue bars) and in studies of patients with stroke despite anticoagulant therapy (green bars [observational studies] and violet [IPDMA of the RCTs RE-LY, ARISTOTLE, ROCKET-AF, ENGAGE-AF, and AVERROES])

- Non-adherence
- Alternative high-risk mechanism
- Inappropriate dosing
- Drug-drug interactions
  - CYP3A4 / P-glycoprotein efflux pump inducers: ↓ DOAC effect
    - Carbamazepine, phenytoin, primidone, phenobarbital
    - Rifampin
  - Drug-food interaction (rivaroxaban 15mg/20mg: bioavailability ↑ w/ food)

J Am Heart Assoc. 2020 Jul 7;9(13):e017559.  
Ann Neurol. 2020 Feb 12;87(5):677–87.



**FIGURE 2:** Cumulative incidence function curves for the main outcome of recurrent acute ischemic stroke. (A) Primary analysis of patients taking oral anticoagulation prior to the index event ( $\text{OAC}_{\text{prior}}$ , dashed line) compared to those not taking anticoagulants prior to the index event ( $\text{OAC}_{\text{naive}}$ , solid line). (B) Secondary analysis of patients that changed the type of anticoagulation ( $\text{OAC}_{\text{changed}}$ , dashed line) compared to those who continued the same type of anticoagulation ( $\text{OAC}_{\text{unchanged}}$ , solid line). [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]

B. Association of stroke etiology with the primary and secondary endpoint

Stroke etiology	Composite outcome						Recurrent ischemic stroke					
	unadjusted			adjusted†			unadjusted			adjusted†		
	OR [95%CI]	p value	N events/ total N in model	aOR [95%-CI]	p value	N events/ total N in model	OR [95%-CI]	p value	N events/ total N in model	aOR [95%-CI]	p value	N events/ total N in model
competing stroke mechanism	0.90 (0.69 to 1.16)	0.4	516/1906	1.18 (0.83 to 1.66)	0.363	473/1773	1.80 (1.07 to 3.02)	0.026	84/1842	1.83 (1.05 to 3.20)	0.034	77/1697
insufficient anticoagulation	1.02 (0.81 to 1.28)	0.891		0.93 (0.68 to 1.27)	0.648		0.91 (0.52 to 1.60)	0.751		0.99 (0.55 to 1.79)	0.968	
cardioembolism despite sufficient anticoagulation	(reference)			(reference)			(reference)			(reference)		

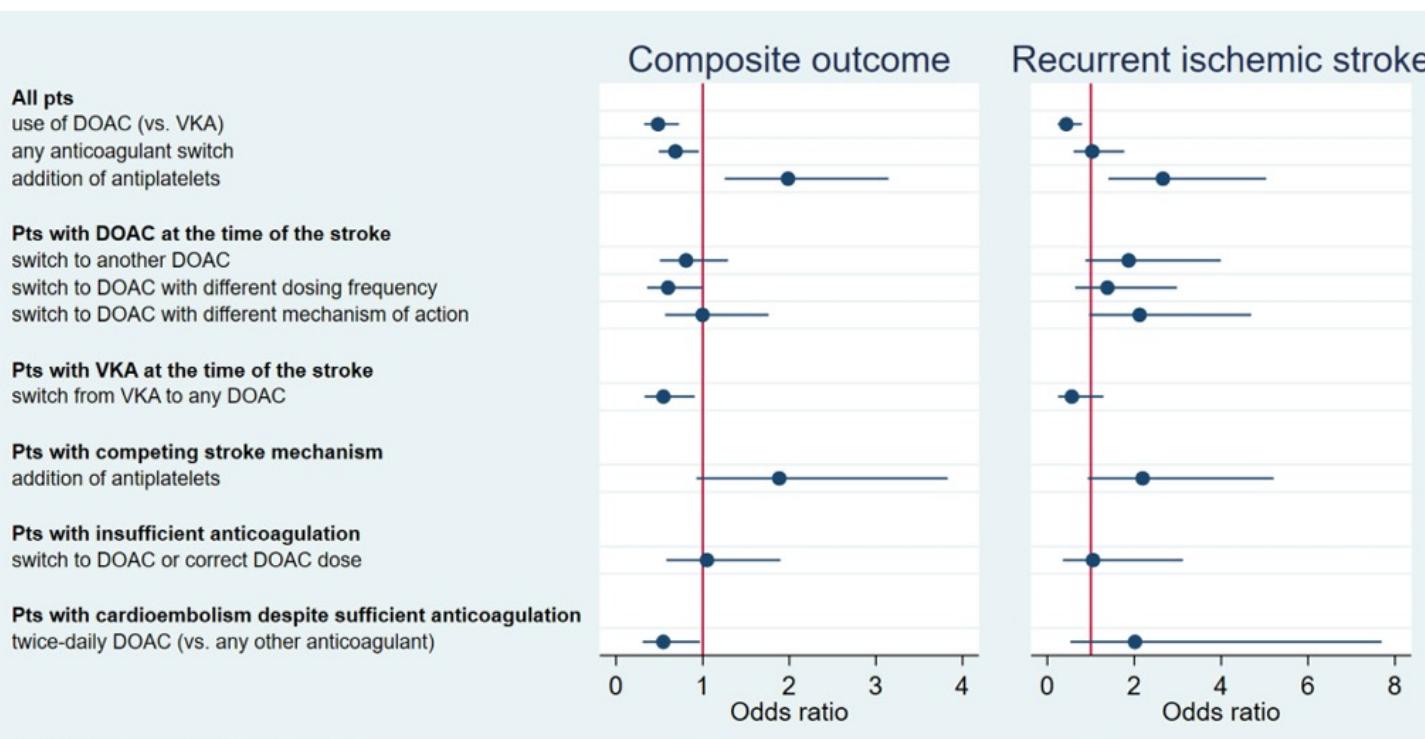
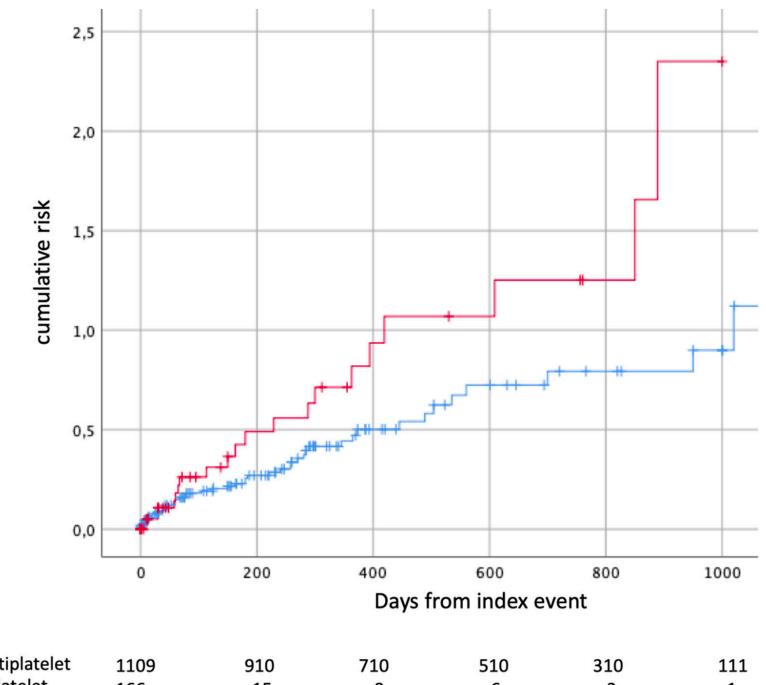


Figure 3 Association of preventive strategies after stroke despite anticoagulation with the primary and secondary endpoints from the adjusted models.



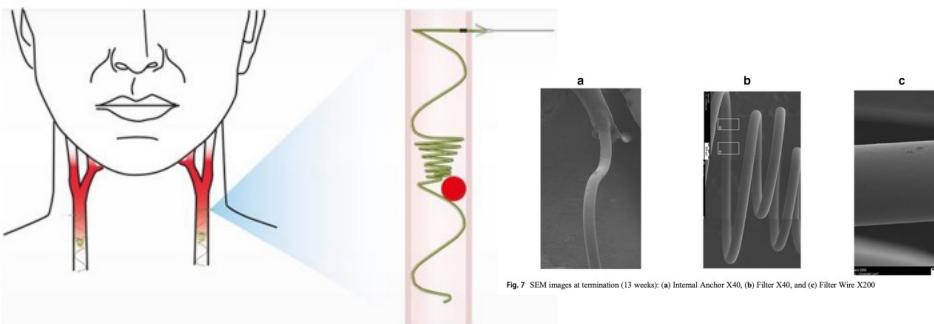
Hemorrhagic endpoint: intracranial bleeding and major extracranial bleeding (NOAC with or without antiplatelet therapy)  
OR 2.8 (95% 1.4-5.5)  
Log Rank (Mantel – Cox): p=0.04

# Part 1 - Key Messages

- Ensure comorbidities & symptom mgmt. addressed
- DOACs (apixaban) preferred
  - Exceptions: mechanical cardiac valves, mod-severe MV stenosis, rheumatic heart disease
- Concurrent AP tx indicated → DOAC + P2Y12 inhibitor
- Assess (and re-assess) bleeding risk
- Early DOAC for mild-moderate infarcts appears safe & efficacious
- Switching 1 DOAC to another has unclear benefit when IS occurs despite AC

# Novel Approaches

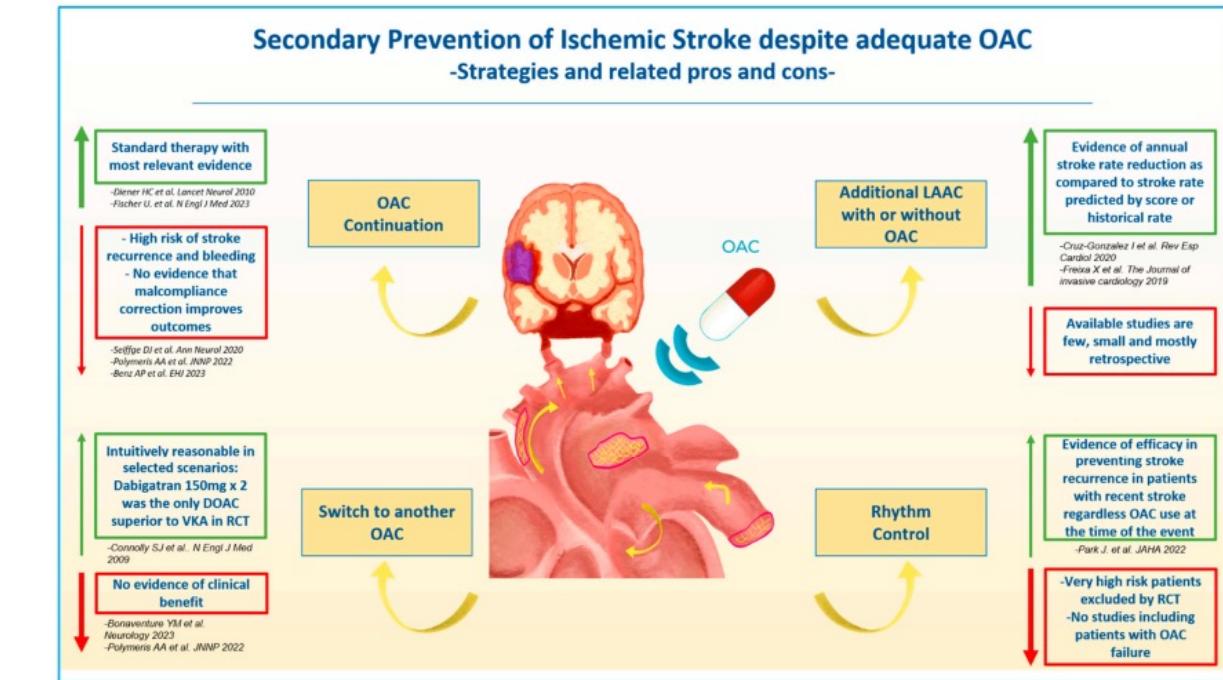
- Left atrial appendage occlusion
- Permanent CCA filters
- Early rhythm control
- Novel OACs



J Clin Med. 2023 Sep 5;12(18):5784.

Lancet Neurol. 2024 Apr;23(4):404-417.

Curr Cardiol Rep. 2020 Sep 10;22(11):144.



	INTERCEPT (NCT05723926)	ELAPSE (NCT05976685)	LAAOS-4 (NCT05963698)
Intervention	Permanent bilateral carotid artery filter on top of DOAC therapy (plus antiplatelet therapy for 6 months)	Percutaneous left atrial appendage occlusion (any approved device) on top of DOAC therapy (plus antiplatelet therapy for 6 weeks)	Percutaneous left atrial appendage occlusion with device
Comparator	Standard DOAC therapy	Standard DOAC therapy	Local, standard medical care (any anticoagulation)
Sample size	2000 participants	482 participants (adaptive design)	4000 participants
Estimated percentage of patients with breakthrough strokes	66%	100%	Unknown (patients with breakthrough stroke are eligible among other patients at high risk of stroke)
Primary endpoint	Large vessel anterior circulation ischemic stroke	Composite of ischaemic stroke, systemic embolism, and cardiovascular death	Composite of ischaemic stroke and systemic embolism
Follow-up	44 months	Minimum 6 months, and maximum 48 months	4 years (estimated average)
Current status	Vanguard trial in preparation	First patient recruited in Q1/2024	First patient recruited in Q4/2023

DOAC=direct oral anticoagulant therapy.

**Table 3: Trials in patients with atrial fibrillation and stroke despite anticoagulation therapy**

# Rhythm Control

Rhythm control	
EAST-AFNET 4 (NCT01288352) <sup>66,67</sup>	
Trial characteristics	
Sample size	2789 participants
Intervention	Antiarrhythmic drugs or ablation
Comparator	No rhythm control
Anticoagulation	2517 (90%) participants
History of ischaemic stroke	328 (12%) participants
Outcomes	
Follow-up	5.1 years
Primary endpoint	Primary death from cardiovascular causes, stroke, or hospitalisation with worsening of heart failure or acute coronary syndrome 3.9 vs 5.0 events per 100 patient-years HR 0.79 (96% CI 0.66–0.94; p=0.005)
Stroke	0.6% (rhythm control) vs 0.9% (no rhythm control)
Mortality	1.0% (rhythm control) vs 1.3% (no rhythm control)

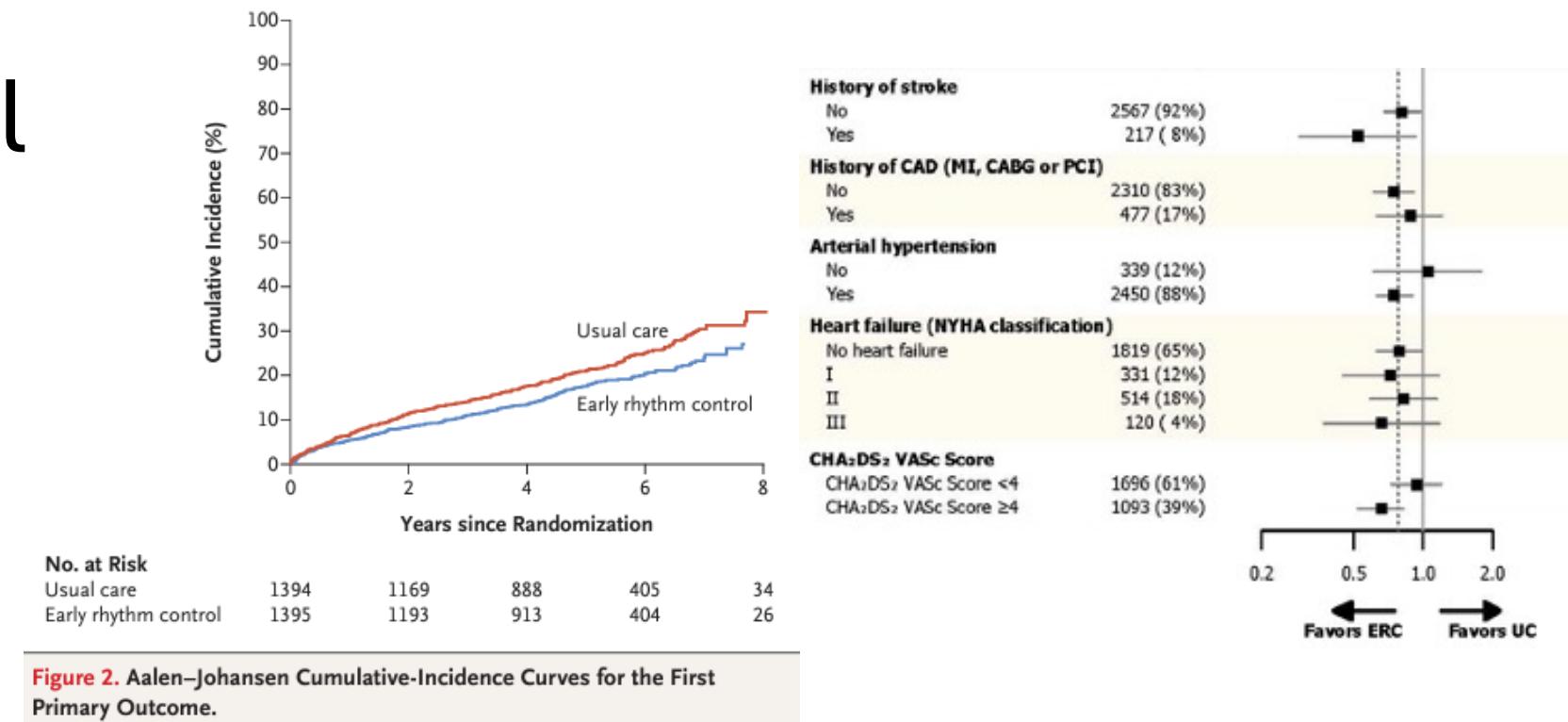


Table 2. Efficacy Outcomes.\*

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome — events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94)†
Components of first primary outcome — events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98)‡
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97)‡
Hospitalization with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02)‡
Hospitalization with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19)‡

Lancet Neurol. 2024 Apr;23(4):404-417.

N Engl J Med. 2020 Oct 1;383(14):1305-1316.

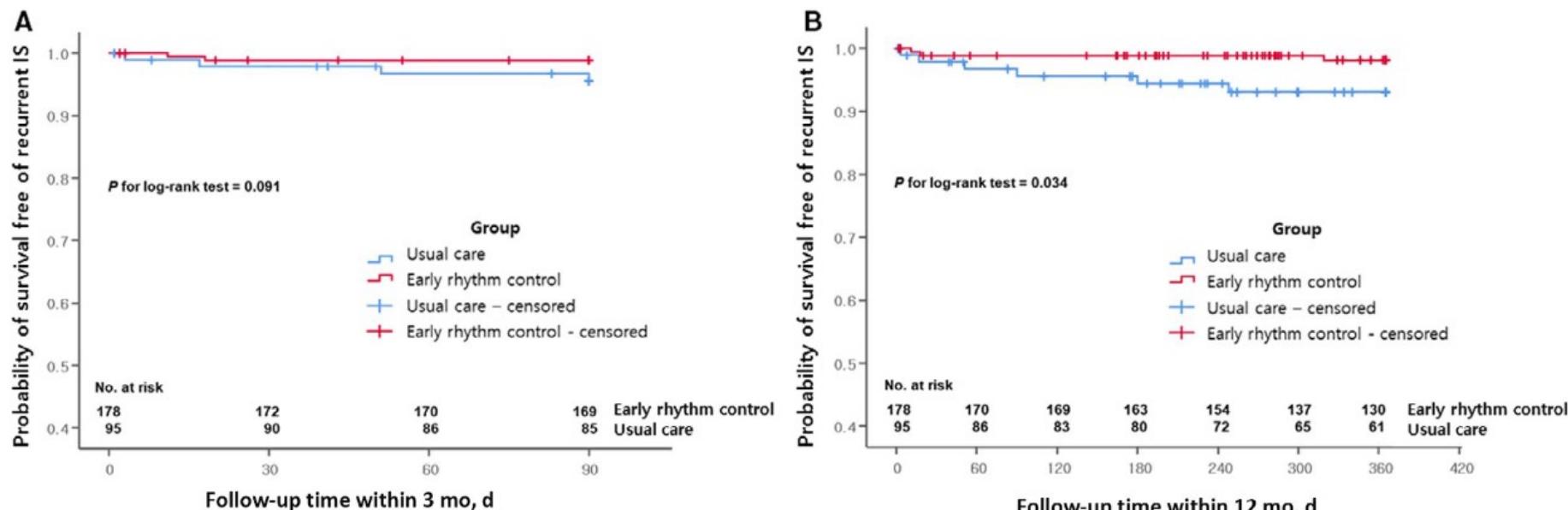
RAFAS (NCT02285387)<sup>16</sup>

#### Trial characteristics

Sample size	273 participants
Intervention	Antiarrhythmic drugs or ablation
Comparator	No rhythm control
Anticoagulation	255 (94%) participants
History of ischaemic stroke	273 (100%) participants

#### Outcomes

Follow-up	Outcome assessment for all participants at 12 months
Primary endpoint	Recurrent stroke at 3 months (2 [1.1%] vs 4 [4.2%]; HR, 0.257 [log-rank p=0.091]) and at 12 months (3 [1.7%] vs 6 [6.3%]; HR 0.251 [log-rank p=0.034])
Stroke	See primary endpoint
Mortality	Not reported



**Table 2. Primary and Secondary Clinical Outcomes**

	Early rhythm control (n=178)	Usual care (n=95)	HR	95% CI	P value
Primary outcome, n (%)*					
Recurrent stroke in 3 mo	2 (1.1)	4 (4.2)	0.257	0.047–1.405	0.117
Recurrent stroke in 12 mo	3 (1.7)	6 (6.3)	0.251	0.063–1.003	0.050
Secondary outcome, n (%)**					
Composite outcome in 3 mo	19 (10.7)	10 (10.5)	0.995	0.463–2.140	0.990
Composite outcome in 12 mo	25 (14.0)	16 (16.8)	0.808	0.431–1.513	0.505
Arrhythmia-related events in 3 mo	3 (1.7)	0	NA	NA	NA
Arrhythmia-related events in 12 mo	5 (2.8)	1 (1.1)	2.565	0.3–21.958	0.390
Sustained AF	60 (34.1)	59 (62.8)			<0.001
AF detection period in the consecutive Holter during 12 mo, mo	3.0 (1.0–9.0)	7.0 (1.0–12.0)			0.002
Stroke to NSR duration, d	13.0 (2.0–84.0)	2.0 (0.0–98.5)			0.083

# Direct Factor XI & Xla Inhibitors

- Factor XI → differential role in hemostasis & thrombosis

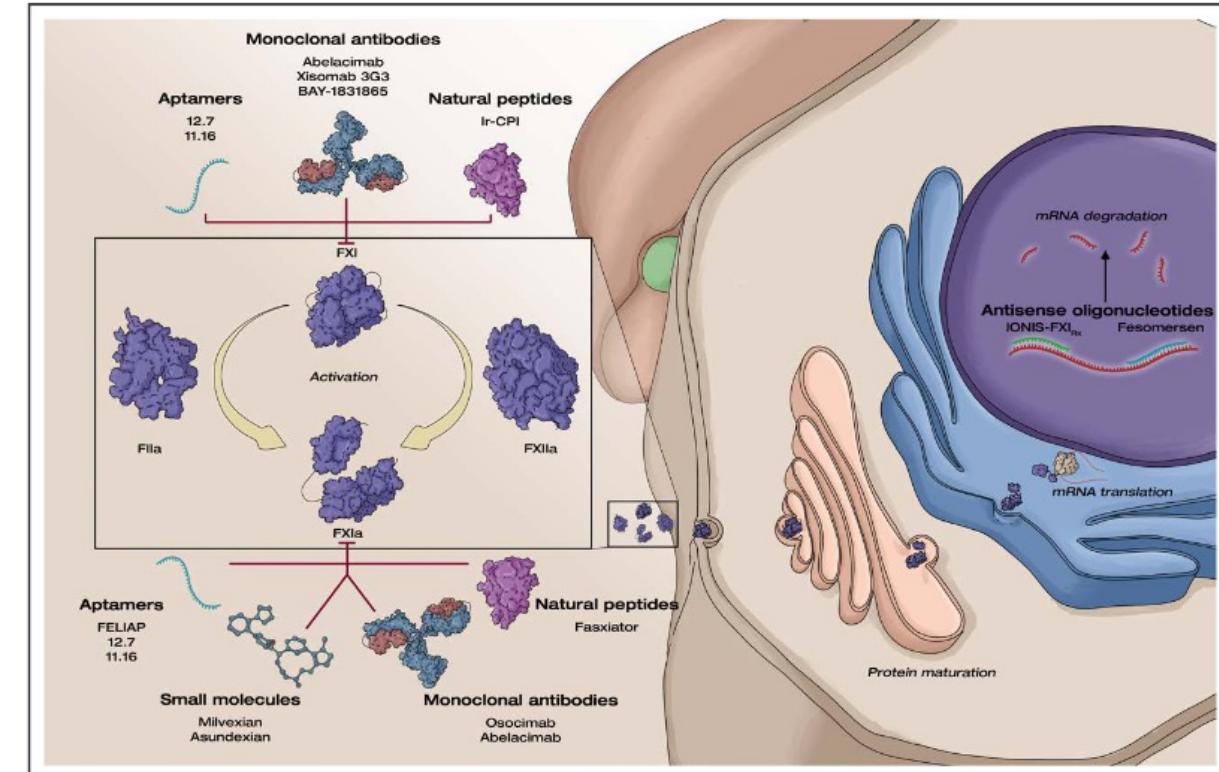
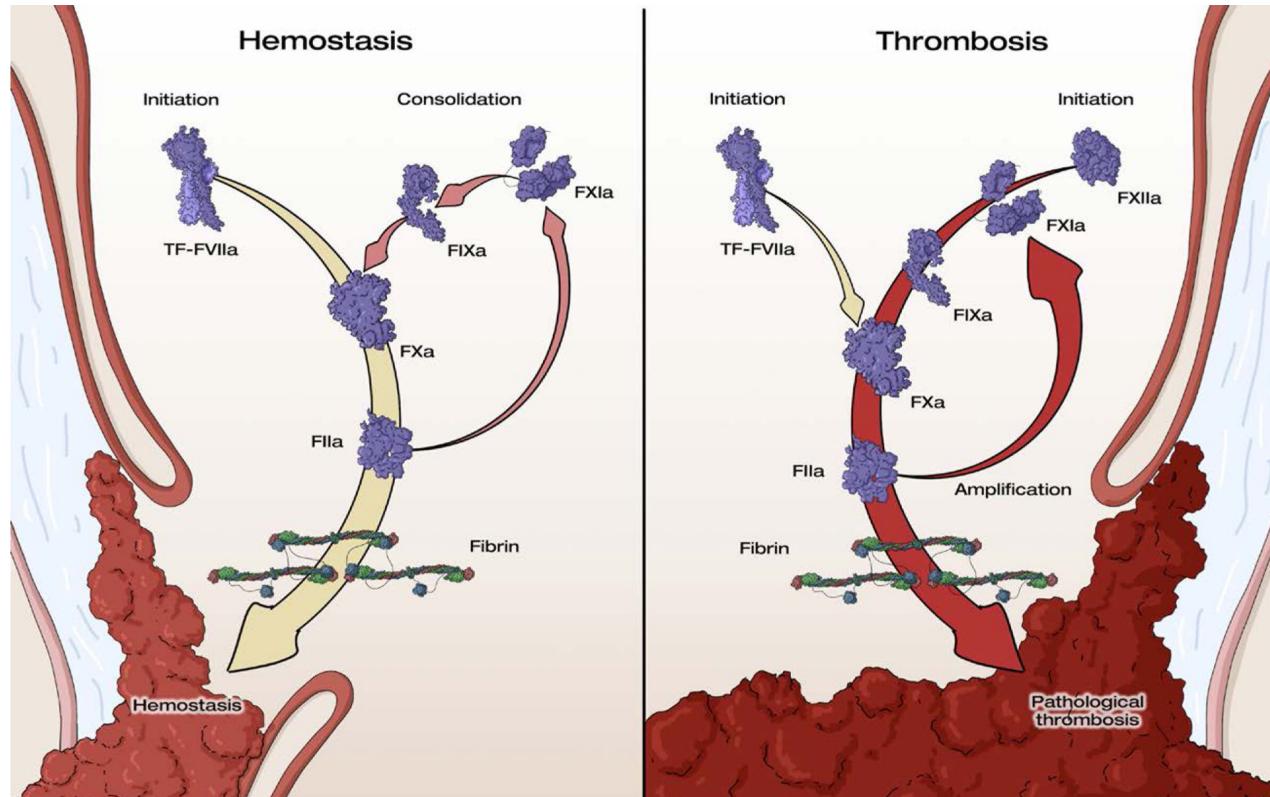
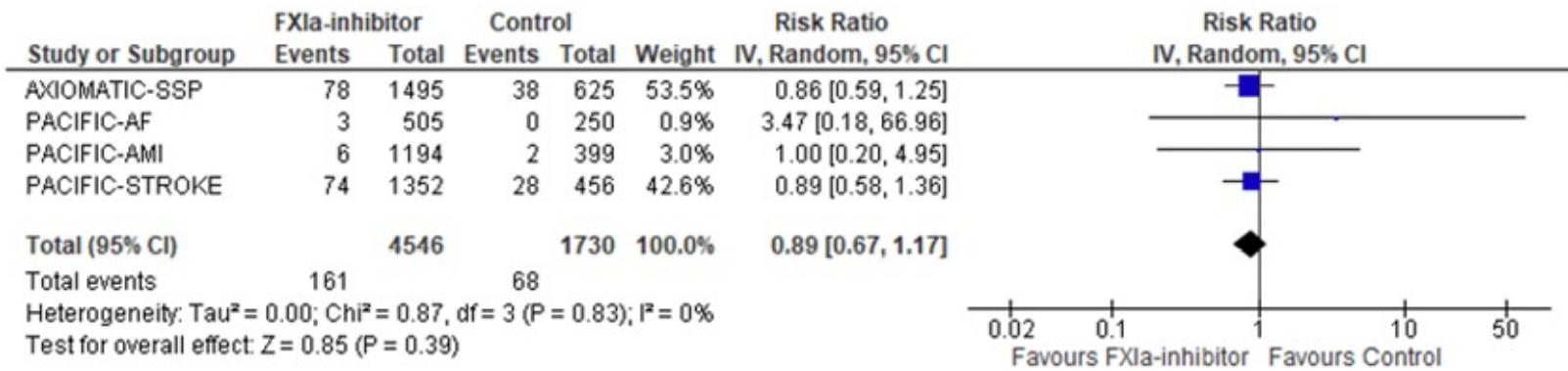
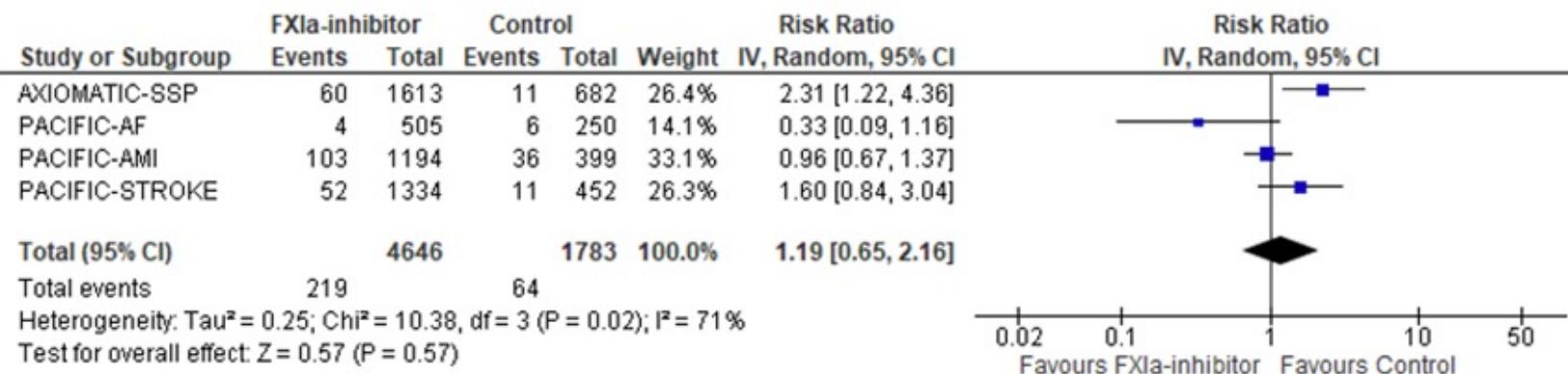


Figure 2. Classification and mechanism of action of FXI inhibitors.



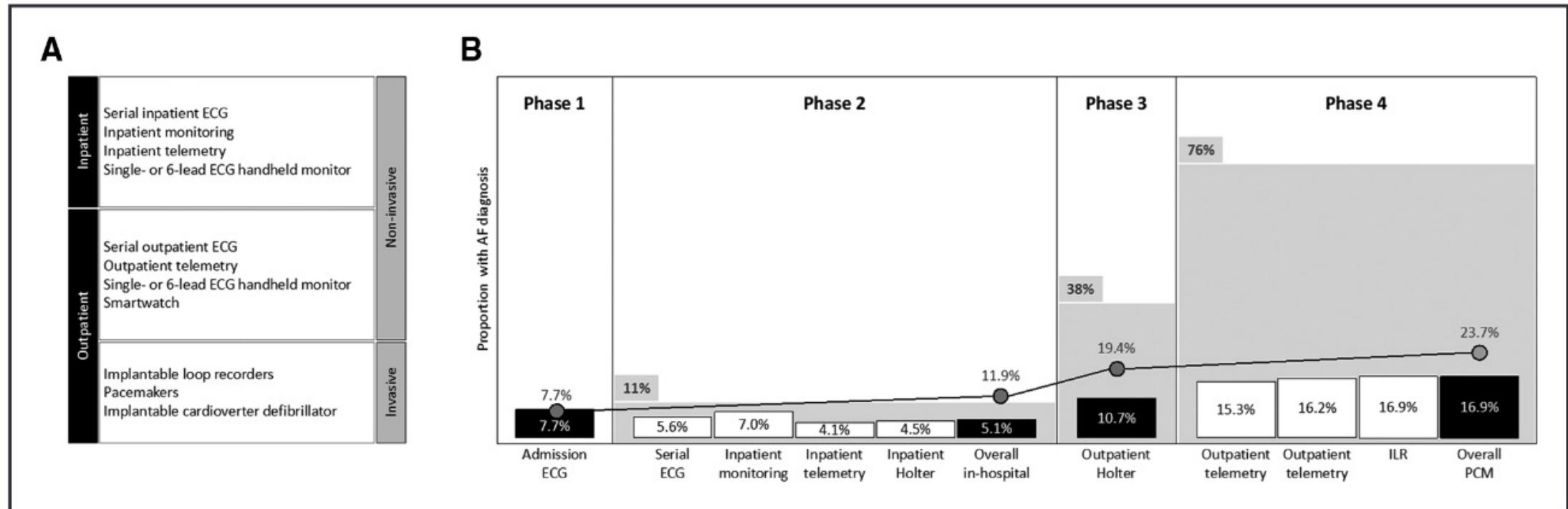
**Figure 3.** Forest plot presenting the association of factor XIa inhibitors compared to controls with symptomatic ischemic stroke.



**Figure 4.** Forest plot presenting the association of factor XIa inhibitors compared to controls with the composite of major bleeding and clinically relevant non-major bleeding.

- Phase 3 AF trials
  - OCEANIC-AF (asundexian) terminated → lack of efficacy
  - LIBREXIA-AF (milvexian) → active
  - LILAC-TIMI 76 (abelacimab) → active
    - Phase 2b: 67% ↓ risk of hemorrhage vs. rivaroxaban (N=1287)
    - Prior stroke excluded

# Cardiac Rhythm Evaluation – AF after IS



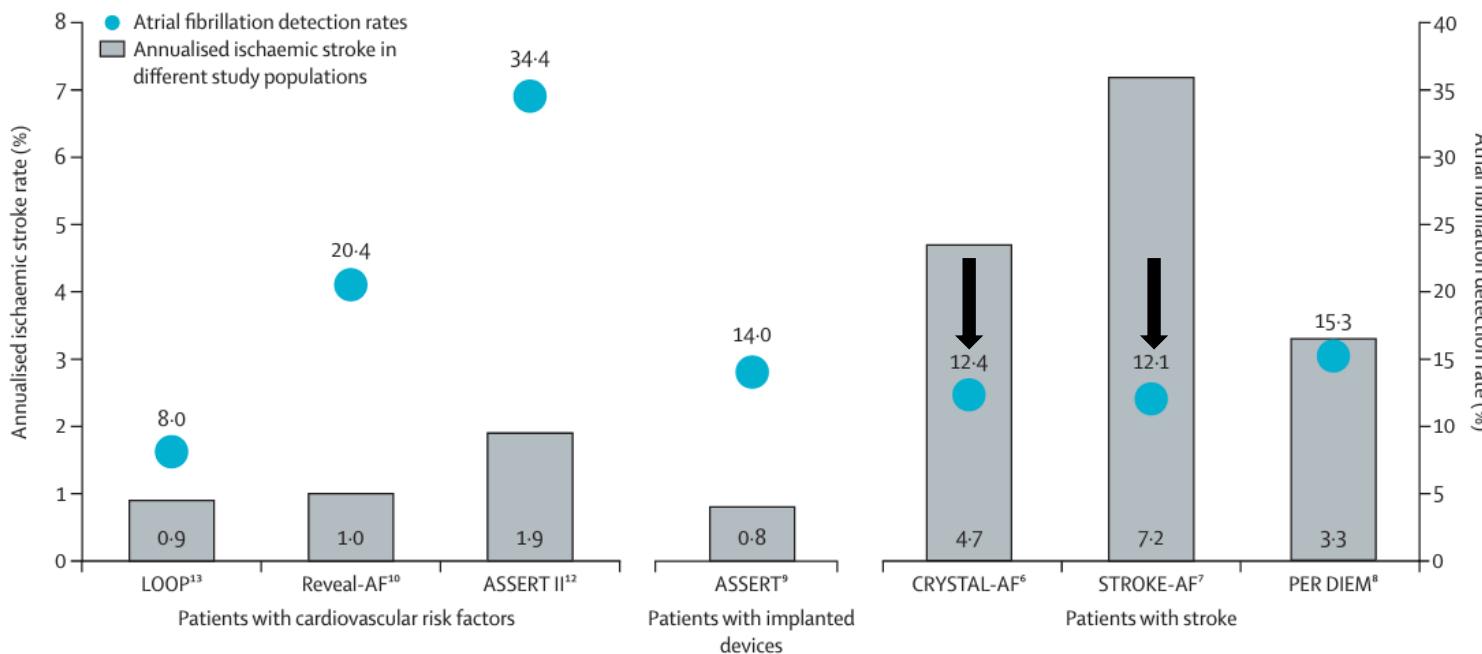
**Figure.** Available cardiac rhythm monitoring technologies and their incremental diagnostic yield.

- Range 24 hours – 3 years
- RCTs → designed/powerd to detect Δ AF rates (not IS rates)

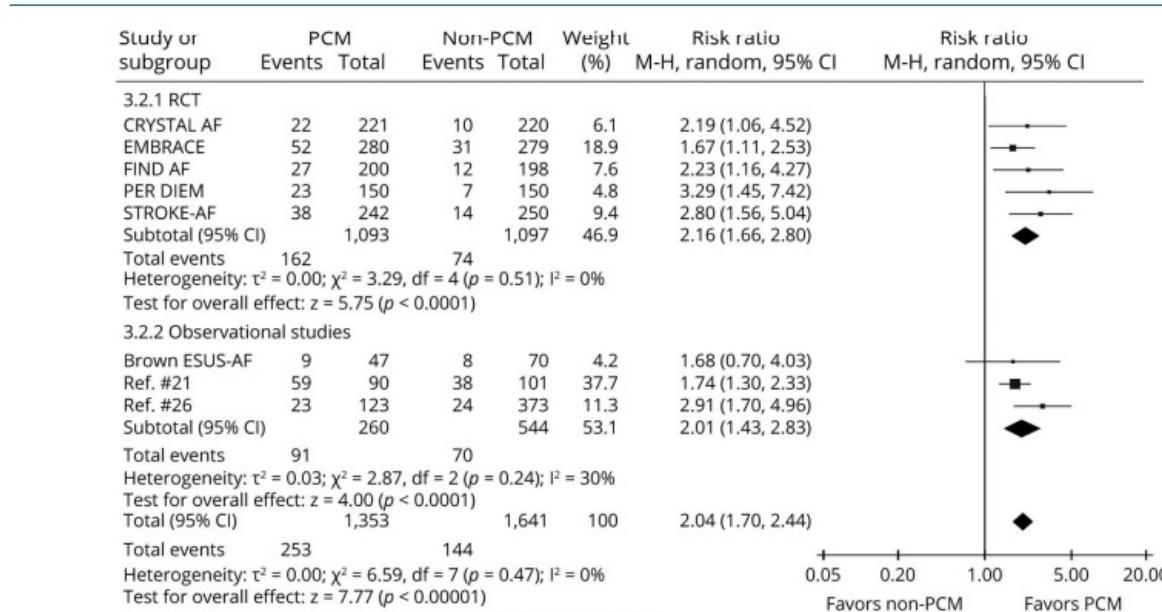
**Table. Rate of AF Detection in Clinical Trials of Prolonged (14 Days or More) Cardiac Monitoring in Patients With Recent Ischemic Stroke**

Cryptogenic ←  
~50% Cryptogenic ←  
66% Cryptogenic ←  
cSVD or LAA stroke ←

Trial	Intervention	Duration of long-term monitor (d)	Required AF duration	AF rate (%)	Ischemic events (no.)
CRYSTAL-AF	ICM	180	>30 s	8.9	11
	24-h holter or telemetry	--	>30 s	1.4	18
EMBRACE	30-d event recorder	30	>30 s	16.1	NR
	24-h holter	--	>30 s	3.2	NR
Find-AF <sub>RANDOMIZED</sub>	10-d holter repeated thrice	30	>30 s	14	5
	24-h holter	--	>30 s	5	9
PER-DIEM	ICM	180	>120 s	15.3	5
	External loop recorder	30	>120 s	4.7	8
STROKE-AF	ICM	365	>120 s	12.1	16
	Usual care	--	>30 s	1.8	23

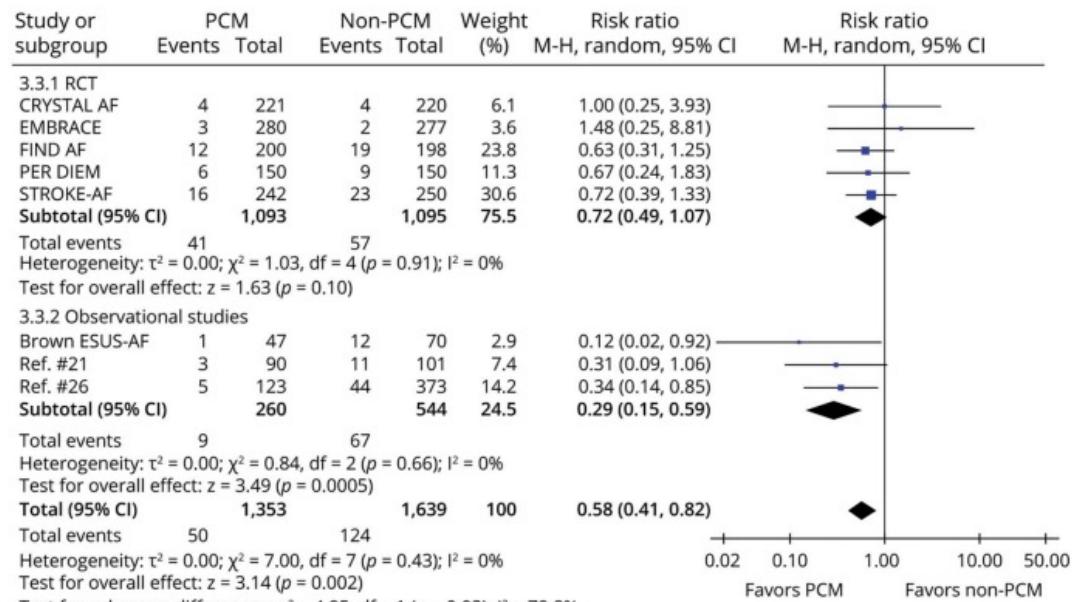


**Figure 3** Forest Plot Presenting the Differences Between Prolonged and Conventional (Nonprolonged) Cardiac Rhythm Monitoring in the Probability of Anticoagulant Initiation, Stratified by Study Type



M-H = Mantel-Haenszel; PCM = prolonged cardiac rhythm monitoring; RCT = randomized controlled trial.

**Figure 4** Forest Plot Presenting the Differences Between Prolonged and Conventional (Nonprolonged) Cardiac Rhythm Monitoring in the Risk of Recurrent Stroke During Follow-Up, Stratified by Study Type



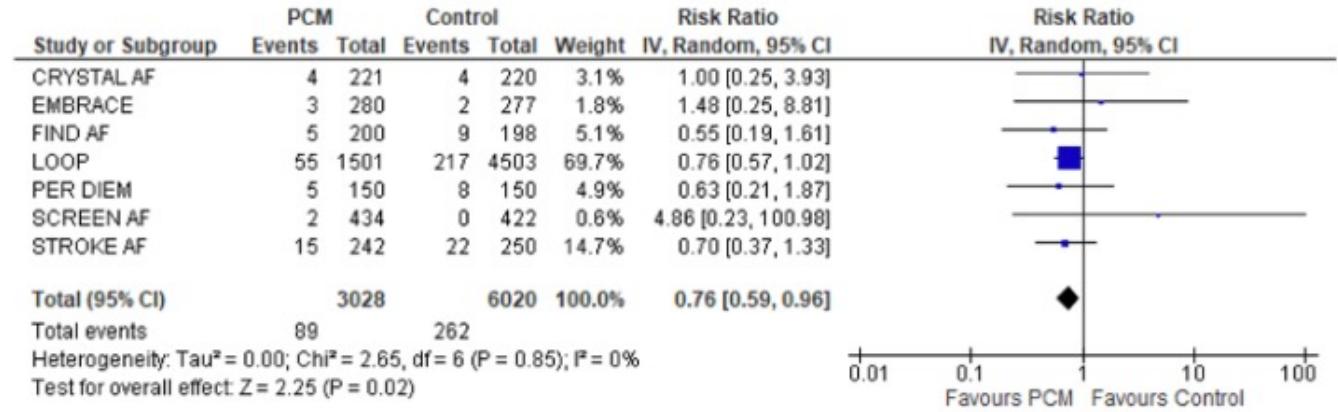
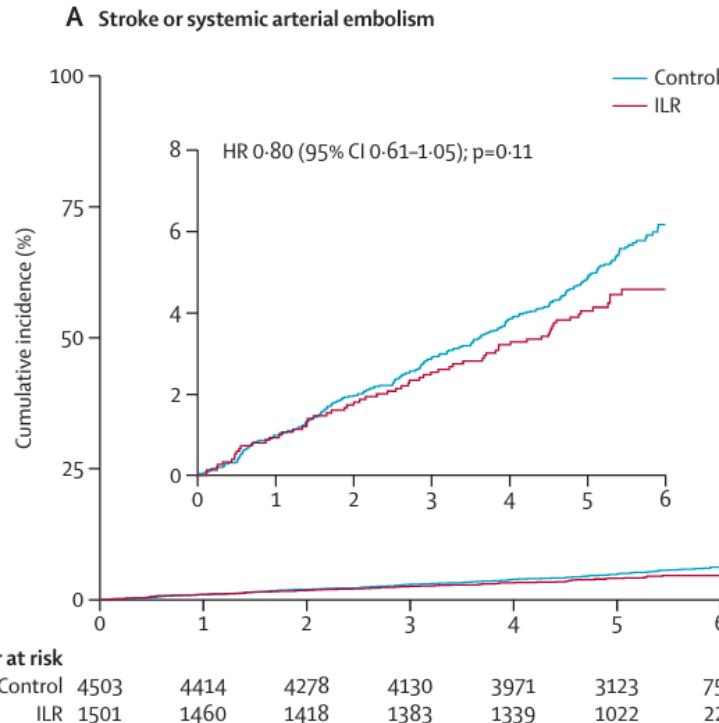
\*Unpublished data from Brown ESUS-AF, CRYSTAL AF, and EMBRACE. M-H = Mantel-Haenszel; PCM = prolonged cardiac rhythm monitoring; RCT = randomized controlled trial.

## Prolonged cardiac rhythm monitoring in stroke populations:

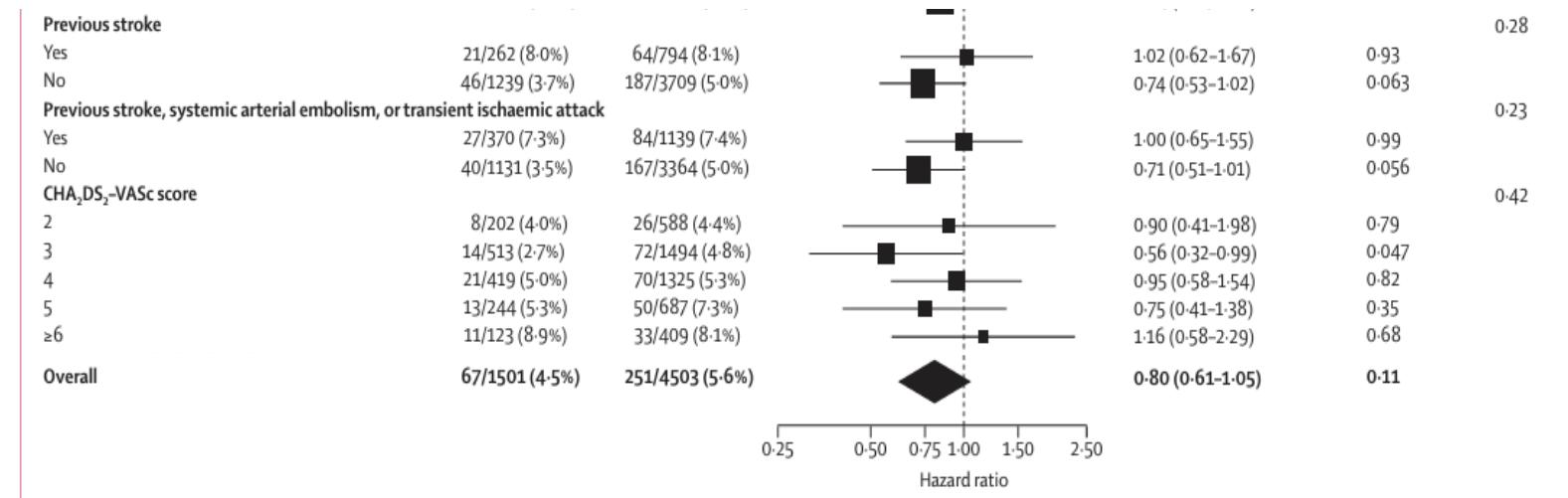
- Increased AC initiation
- Unclear effect on recurrent stroke risk
- AF burden often low

# LOOP Study

- Population: 70-90 y + HTN / DM / prior stroke / HF
  - Intervention/Control: ILR / usual care
  - 1° Outcome: stroke / systemic embolism
- \* CHA<sub>2</sub>DS<sub>2</sub>-VASc: median 4 (IQR 3-4)
- \* Prior stroke/TIA/SE: ~25%
- \* AF detection: ILR ~32%, usual care ~12%



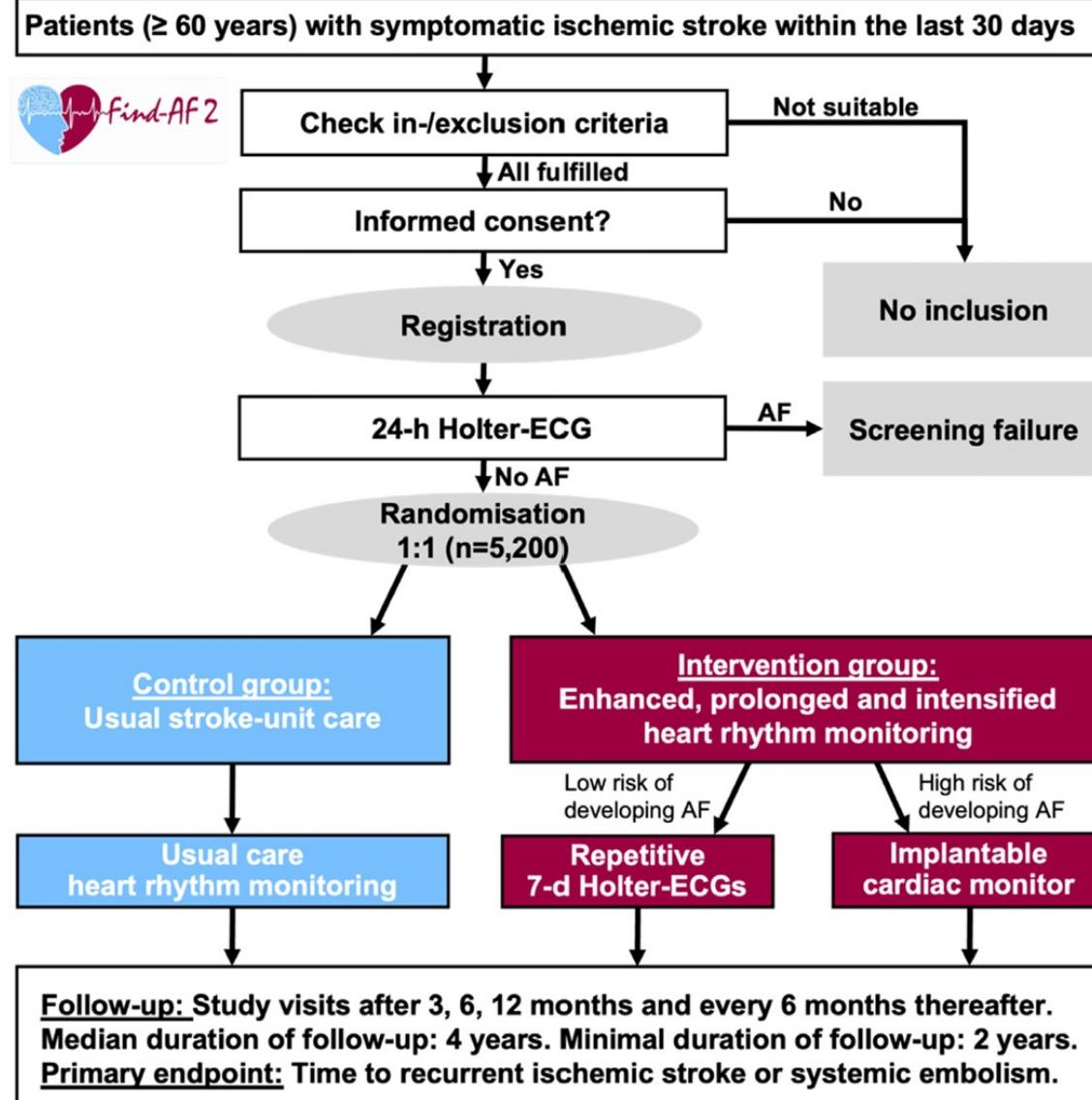
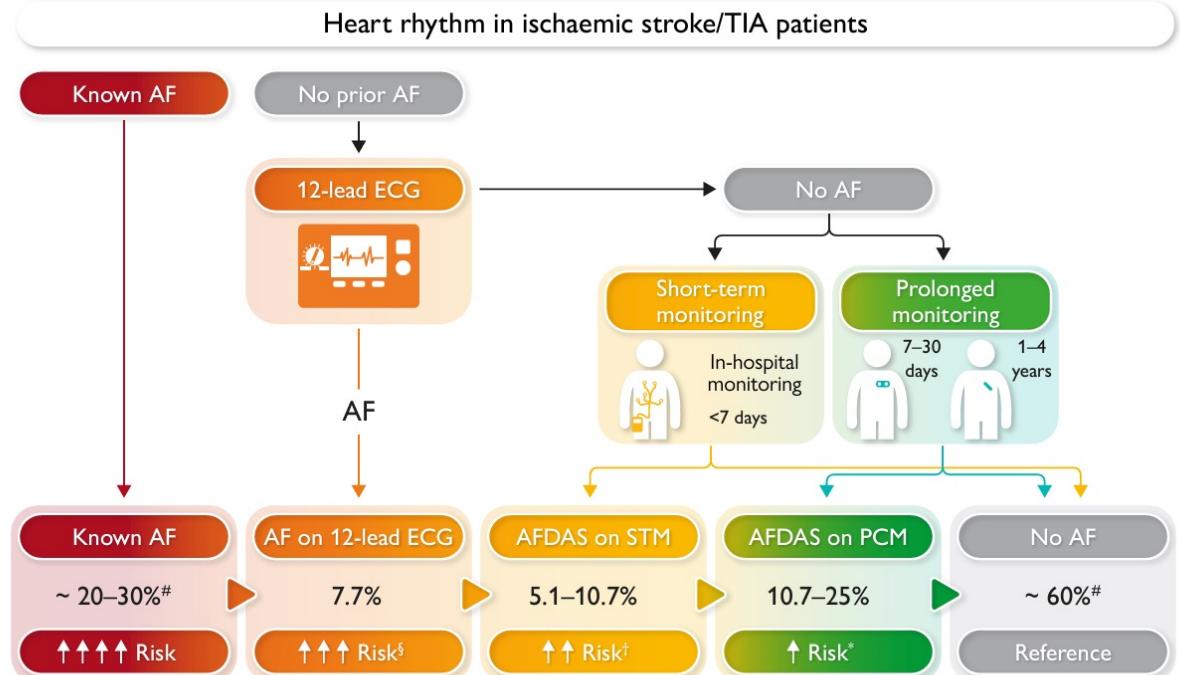
**Figure 2.** Forest plot presenting the association of prolonged cardiac monitoring (PCM) with occurrence of ischemic stroke compared to controls.



**Figure 3:** Frequency of the primary outcome grouped by randomisation arm and hazard ratios in prespecified subgroups

Lancet. 2021 Oct 23;398(10310):1507-1516.  
Eur Stroke J. 2023 Mar;8(1):106-116.

### Graphical Abstract

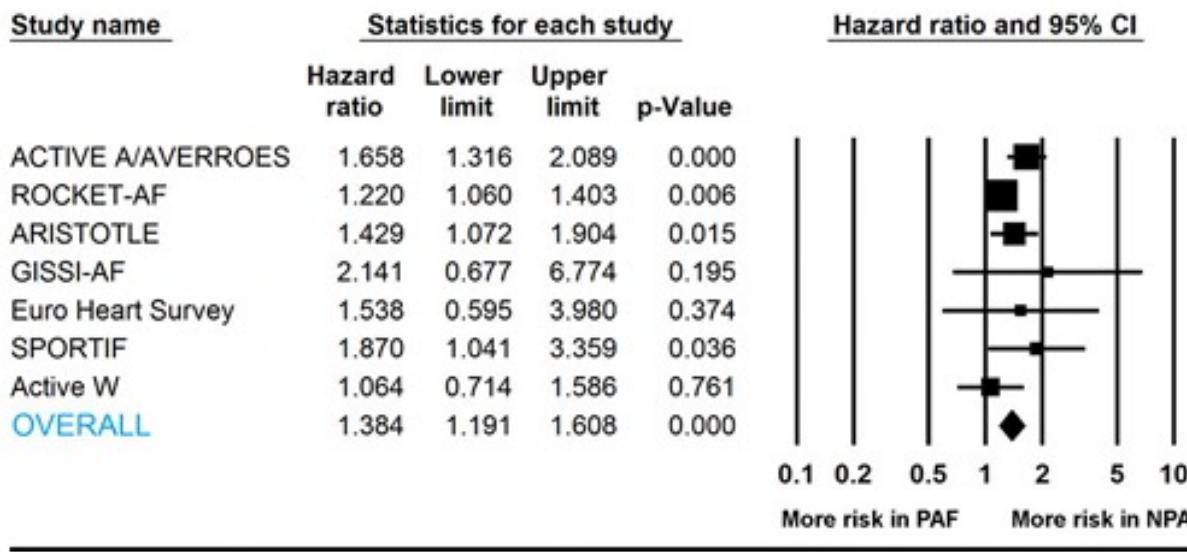


# AF Burden & IS Risk

- IS risk ↑ permanent > paroxysmal AF

B

## Stroke or Systemic Embolism (adjusted)



Eur Heart J. 2016 May 21;37(20):1591-602.

Eur Heart J. 2017 May 1;38(17):1339-1344.

Eur Heart J. 2014 Feb;35(8):508-16.

Circulation. 2016 Oct 18;134(16):1130-1140.

Circulation. 2019 Nov 12;140(20):1639-1646.

- Predictors of AF burden

- Age
- Left atrial enlargement
- Natriuretic peptides
- Frequent PACs

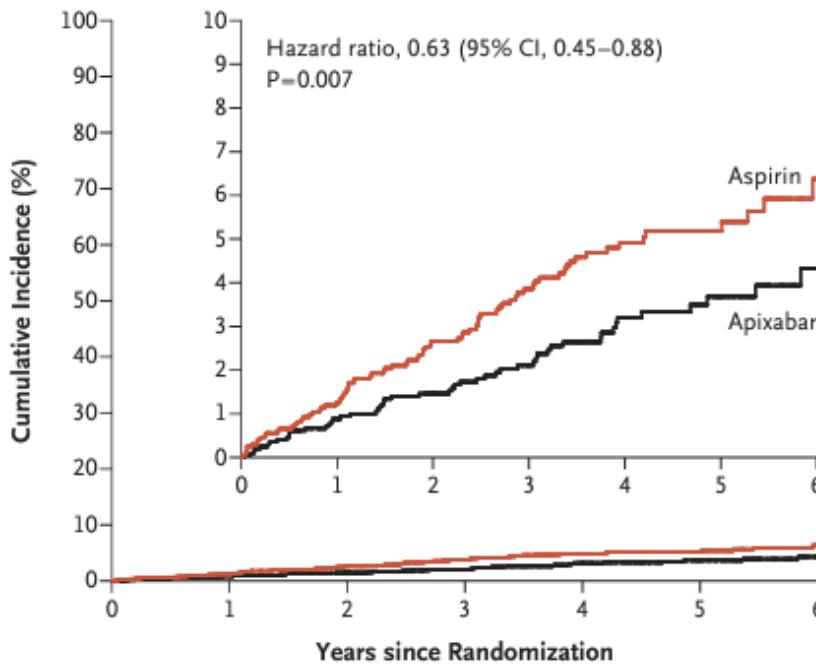
- Burden of paroxysmal AF ~ IS risk

- ASSERT (post-hoc analysis) → 24h
- SOS-AF project → 1h
- RATE study → 20s
- CHA<sub>2</sub>DS<sub>2</sub>-VASC X AF Burden interaction

Maximum Daily AF Duration	CHA <sub>2</sub> DS <sub>2</sub> -VASC Score				
	0 n=2922 (13.4%)	1 n=2151 (9.9%)	2 n=4554 (20.9%)	3-4 n=7164 (32.9%)	≥5 n=4977 (22.9%)
No AF n=16815 (77.2%)	<b>0.33%</b> 40 events	<b>0.62%</b> 46 events	<b>0.70%</b> 95 events	<b>0.83%</b> 139 events	<b>1.79%</b> 157 events
AF 6 min–23.5 h n=3381 (15.5%)	<b>0.52%</b> 11 events	<b>0.32%</b> 4 events	<b>0.62%</b> 17 events	<b>1.28%</b> 42 events	<b>2.21%</b> 36 events
AF >23.5 h n=1572 (7.2%)	<b>0.86%</b> 4 events	<b>0.50%</b> 3 events	<b>1.52%</b> 19 events	<b>1.77%</b> 28 events	<b>1.68%</b> 13 events

# ARTESIA

- Population:* 6m ≤ AF ≤ 24h detected by PM, defibrillator, cardiac monitor + CHA<sub>2</sub>DS<sub>2</sub>-VASC ≥ 3, age ≥ 55y
- Intervention/Control:* apixaban / ASA
  - AF > 24h or clinical AF → study drug d/c'ed & AC initiated
- 1° Outcome:* stroke / systemic embolism



No. at Risk							
Aspirin	1997	1777	1539	1120	780	468	200
Apixaban	2015	1786	1558	1157	820	474	214

Figure 1. Stroke or Systemic Embolism (Primary Efficacy Outcome).

Table 2. Clinical Outcomes (Intention-to-Treat Population).\*

Outcome	Apixaban (N = 2015)		Aspirin (N = 1997)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	%/patient-yr	no. of patients with event	%/patient-yr		
Stroke or systemic embolism	55	0.78	86	1.24	0.63 (0.45–0.88)	0.007
Stroke	55	0.78	84	1.21	0.64 (0.46–0.90)	
Ischemic or unknown type†	45	0.64	71	1.02	0.62 (0.43–0.91)	
Hemorrhagic	10	0.14	13	0.18	0.76 (0.33–1.73)	
Severity according to score on modified Rankin scale‡						
0–2	31	0.44	45	0.65	0.68 (0.43–1.07)	
3–6	19	0.27	37	0.53	0.51 (0.29–0.88)	
Missing data	5	0.07	2	0.03	2.48 (0.48–12.80)	
Systemic embolism	0		2	0.03	NA	
Stroke, TIA, or systemic embolism§	82	1.17	107	1.56	0.75 (0.56–1.00)	
Stroke, systemic embolism, or death from cardiovascular causes	148	2.10	171	2.47	0.85 (0.68–1.06)	
Stroke, myocardial infarction, systemic embolism, or death	419	6.01	418	6.10	0.98 (0.86–1.12)	
Myocardial infarction	37	0.52	41	0.59	0.89 (0.57–1.40)	
Death	362	5.06	341	4.82	1.04 (0.90–1.21)	
Death from cardiovascular causes	105	1.47	108	1.53	0.96 (0.73–1.25)	
Major bleeding¶	106	1.53	78	1.12	1.36 (1.01–1.82)	0.04
Fatal bleeding	10	0.14	14	0.20	0.70 (0.31–1.57)	
Symptomatic intracranial hemorrhage	17	0.24	23	0.33	0.73 (0.39–1.36)	
Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)	
Transfusion performed	35	0.49	31	0.44	1.11 (0.68–1.80)	

\* CHA<sub>2</sub>DS<sub>2</sub>-VASC: mean ~4 ( $\geq 4$ : 61%)

\* Prior stroke/TIA/SE: 9%

# NOAH-AFNET 6

- Population: AHREs  $\geq 6$  m (implanted cardiac devices) + age  $\geq 65$  y + additional stroke risk factor
  - No AF
- Intervention/Control: edoxaban / placebo
- 1° Outcome: composite – stroke, SE, CV death

\* CHA<sub>2</sub>DS<sub>2</sub>-VASc: median 4 (IQR 3-5)

- Prior stroke/TIA: 10%
- AHREs duration: median 2.8 h (IQR 0.8-9.4)
- ASA indication: ~54%

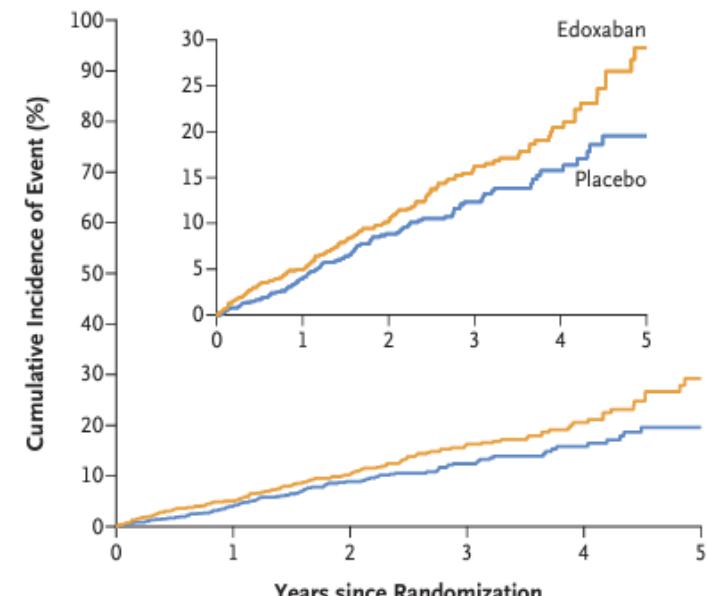
**Table 2. Efficacy Outcomes.\***

Outcome	Edoxaban (N=1270)	Placebo (N=1266)	Adjusted Hazard Ratio (95% CI)
<i>no. of patients with event/patient-yr (% per patient-yr)</i>			
Primary composite efficacy outcome†	83/2557 (3.2)	101/2495 (4.0)	0.81 (0.60 to 1.08)‡
Ischemic stroke	22/2573 (0.9)	27/2519 (1.1)	0.79 (0.45 to 1.39)

**A Stroke, Systemic Embolism, or Death from Cardiovascular Causes**



**B Major Bleeding or Death from Any Cause**



**No. at Risk (no. of events)**

Edoxaban	1270 (37)	873 (20)	559 (19)	327 (3)	148 (4)	42
Placebo	1266 (44)	822 (30)	534 (16)	329 (7)	137 (1)	50

**No. at Risk (no. of events)**

Edoxaban	1270 (57)	866 (41)	551 (30)	324 (11)	145 (10)	44
Placebo	1266 (42)	829 (36)	538 (17)	332 (9)	138 (5)	49

**Table. Comparison of DOAC vs No Anticoagulation in Randomized Clinical Trials**

Characteristic	AVERROES <sup>7,8</sup>	NOAH-AFNET 6 <sup>2</sup>	ARTESIA <sup>3</sup>
Mean age, y	70	78	77
AF classification	Paroxysmal (27%) Persistent (20%) Permanent (52%)	>6 min Atrial high-rate event	6 min to 24 h of Subclinical AF
CHA <sub>2</sub> DS <sub>2</sub> Vasc score	3.2 <sup>a</sup>	4 <sup>b</sup>	3.9 <sup>a</sup>
Treatment arm	Apixaban	Edoxaban	Apixaban
Control arm	Aspirin	Placebo	Aspirin
Annualized risk of stroke or systemic embolism without DOAC, %	3.7% <sup>c</sup>	1.07% <sup>c</sup>	1.02% <sup>c</sup>
Annualized risk of stroke or systemic embolism with DOAC, %	1.6% <sup>c</sup>	0.86% <sup>c</sup>	0.64% <sup>c</sup>
No. needed to treat	48	476	263
Annualized risk of major bleeding without DOAC, %	3.8% <sup>c</sup>	1.00% <sup>c</sup>	0.94% <sup>d</sup>
Annualized risk of major bleeding on DOAC, %	4.5% <sup>c</sup>	2.09% <sup>c</sup>	1.71% <sup>d</sup>
No. needed to harm	143	92	130

# Wearables

- Photoplethysmography
- Single-lead ECG

→ Require EKG & clinical confirmation

- Limitations / Sources of Error
  - Motion
  - Skin contact
  - Discrimination b/w similar dysrhythmias
  - Longer episodes for detection when inactive

**TABLE 2** Summary of the 3 Largest Mass Population-Based AF Screening Studies

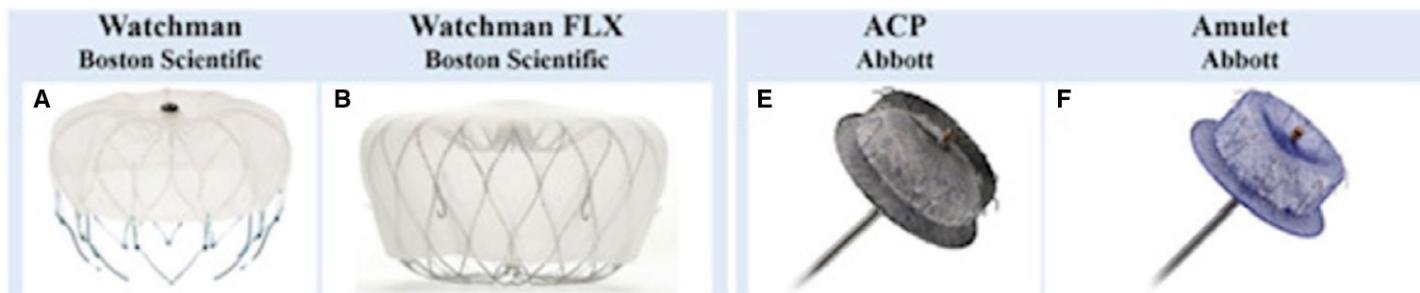
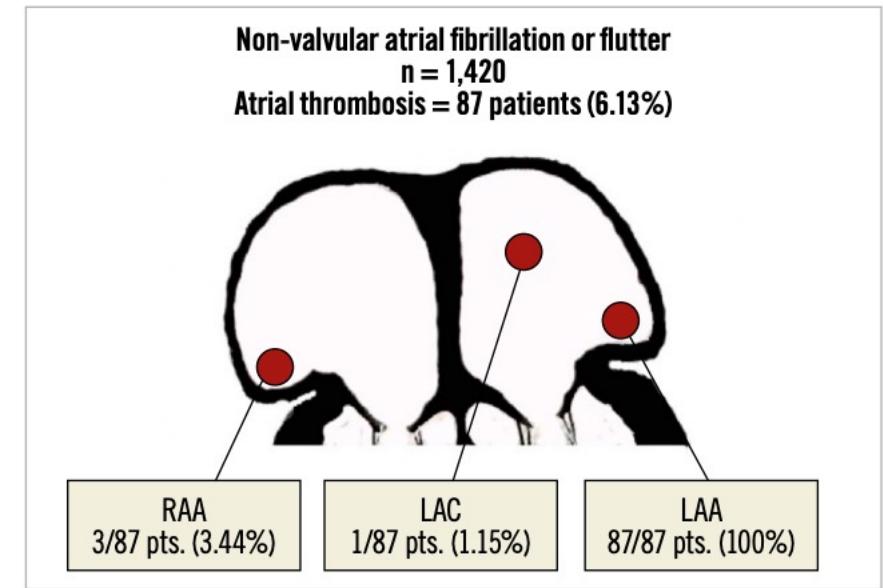
	Huawei Heart Study (N = 187,912)	Apple Heart Study (N = 419,297)	Fitbit Heart Study (N = 455,699)
Algorithm accuracy			
Passive PPG PPV	91.6%	84%	98% PPV for the algorithm during ECG patch wear among 1,057 participants who had previously received an IHRD notification and then wore and returned an ECG patch monitor
User experience			
Active measurement	PPG recorded by bands or watches analyzed by smartphones	ECG recorded and analyzed by Apple Watch	PPG-based algorithm for detecting undiagnosed AF from a range of wrist-worn devices
Period measurement	Based on PPG Periodic measurement results given; the proportion of irregular rhythms analyzed	Based on PPG Periodic measurement results not given	Overlapping 5-min pulse windows (tachograms)
Period measurement frequency	Every 10 min	Every 2 h for baseline mode; irregular tachogram initiates a cascade of more frequent mode (every 16 mins)	Every 5 min
Closed-loop service			
Follow-up mode	Follow-up by mAFA platform, combined with clinical care AF management	Video visit with study doctor by app and mail ECG ePatch	Eligible participants with an IHRD, defined as 11 consecutive irregular tachograms, invited to schedule a telehealth visit and mailed a 1-week ambulatory ECG patch monitor
Diagnosis method for AF	Confirmed with medical history, physical examination, ECG, or 24-h Holter monitor by health care providers	By the results of ePatch	Ambulatory ECG patch monitor
Follow-up	62%	Only 44% of participants initiated contact with a telehealth doctor when prompted by the app, and among those receiving ePatches only 21% were returned and analyzed	Of participants who received IHRD notifications, 1,671 (35.3%) completed a telehealth visit
Percentage of confirmed AF by doctors or ePatch	87%	34%	32.2%

# Key Messages: Prolonged Cardiac Rhythm Monitoring for Secondary Stroke Prevention

- AF detected after stroke is common but confers lower risk
- Prolonged monitoring increases AF detection, but unclear if it reduces recurrent stroke risk
- AF burden is a determinant of IS risk
- Burden of subclinical, device-detected AF to confer net clinical benefit w/ AC (reduction in stroke risk > hemorrhage risk) is not clear (but likely small)
- AF begets AF (AHREs → subclinical AF → clinical AF)
- Wearables will likely supplant current rhythm monitoring approaches

# Left Atrial Appendage Occlusion (LAAO)

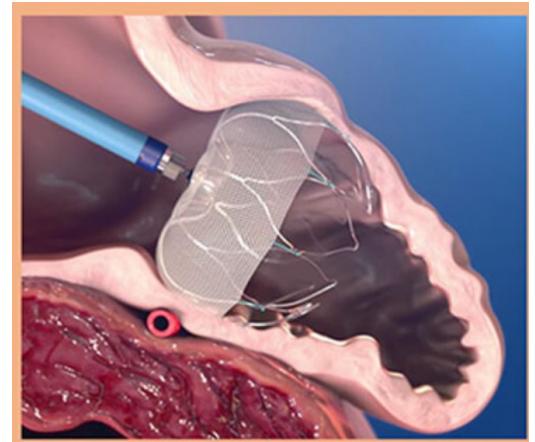
- 80-90% thrombi → LA appendage (NVAF)
  - TEE, surgery, autopsy
  - Cardioversion: TEE
  - Acute stroke: cardiac CT
- 50-60% in valvular (rheumatic) AF



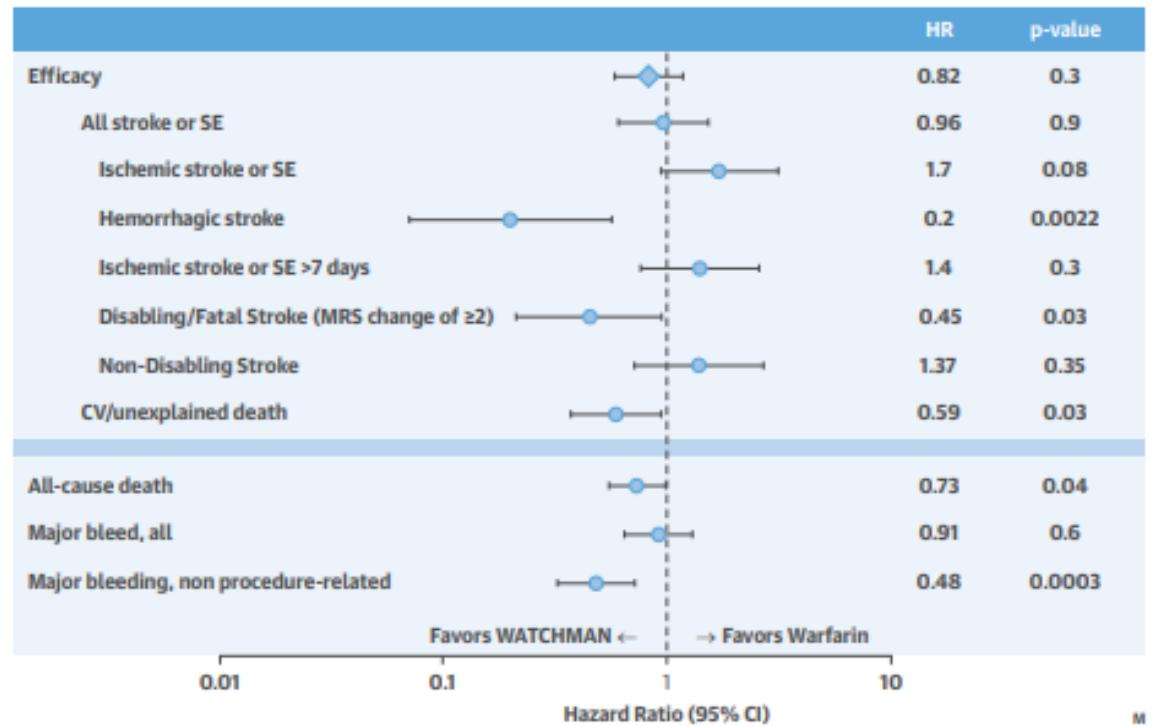
**Figure 2.** The localisation of atrial thrombi in the population study is represented in the schema.

Ann Thorac Surg. 1996 Feb;61(2):755-9.  
EuroIntervention. 2019 Jun 12;15(3):e225-e230.  
J Am Heart Assoc. 2021 Nov 2;10(21):e022274.  
Eur Stroke J. 2023 Mar;8(1):168-174.

# Percutaneous LAAO & Warfarin



- PROTECT AF (N=707)
  - Non-inferiority, open-label
  - *Population:* nonvalvular AF eligible for AC, CHADS<sub>2</sub>≥1
  - *Intervention/Control:* LAAO-Watchman / warfarin (2:1)
    - LAAO → warfarin x 45 d, then DAPT x 6 m, then ASA alone
    - *Outcome:* composite (stroke, SE, CVD death)
- PREVAIL (N=407)
  - FDA mandated confirmatory study



# Percutaneous LAAO & DOACs

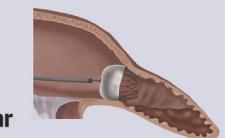
- PRAGUE-17 (N=402)
  - Non-inferiority, open-label
  - *Population:* nonvalvular AF +
    - major hemorrhage, cardioembolic event i/s/o OAC, &/or CHADS<sub>2</sub>VASc≥3 + HAS-BLED>2
  - *Intervention/Control:* LAAO-Watchman/Amulet or DOAC
    - DOAC → ~96% apixaban
  - *Outcome:* composite (stroke, TIA, SE, CVD death, hemorrhage, complications)

## CENTRAL ILLUSTRATION: A Summary Slide of Primary and Secondary Endpoints

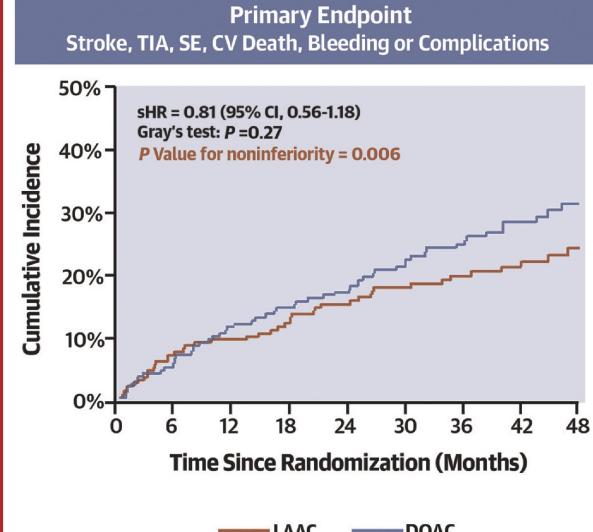
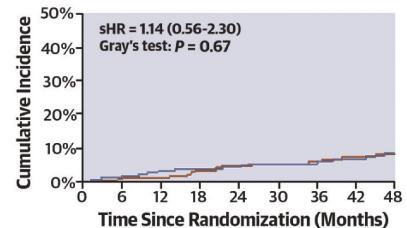
### PRAGUE-17 Trial: Long-Term (4-Year) Follow-Up



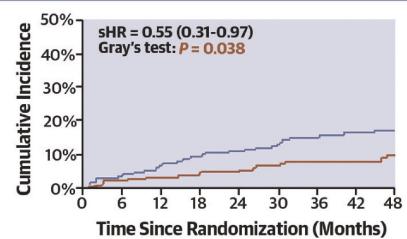
- 402 High-risk AF pts → Randomized
  - CHA<sub>2</sub>DS<sub>2</sub>-VASc = 4.7 ± 1.5
  - HAS-BLED = 3.1 ± 0.9
- Median Follow-up: 3.5 years (IQR 2.6-4.3), 1,354 pt-year



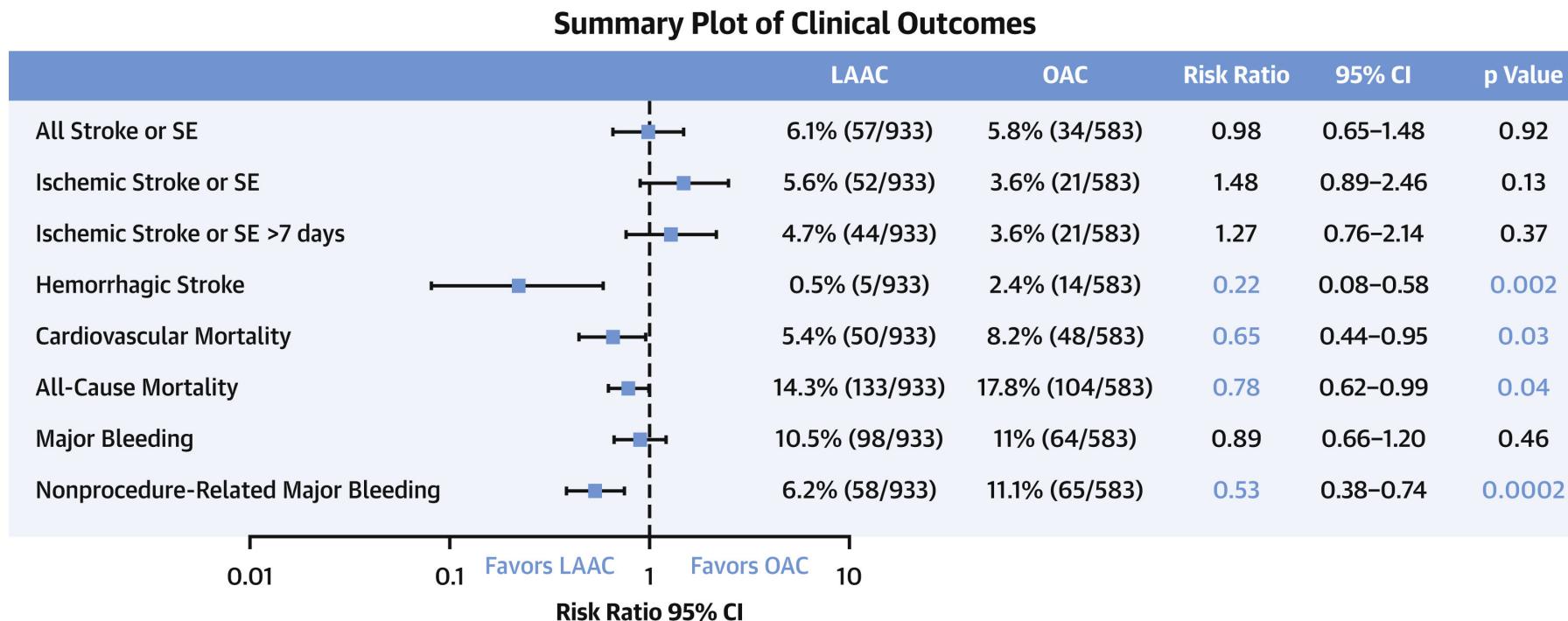
### Stroke or TIA



### Non-Procedural Clinically Relevant Bleeding



# Percutaneous LAAO

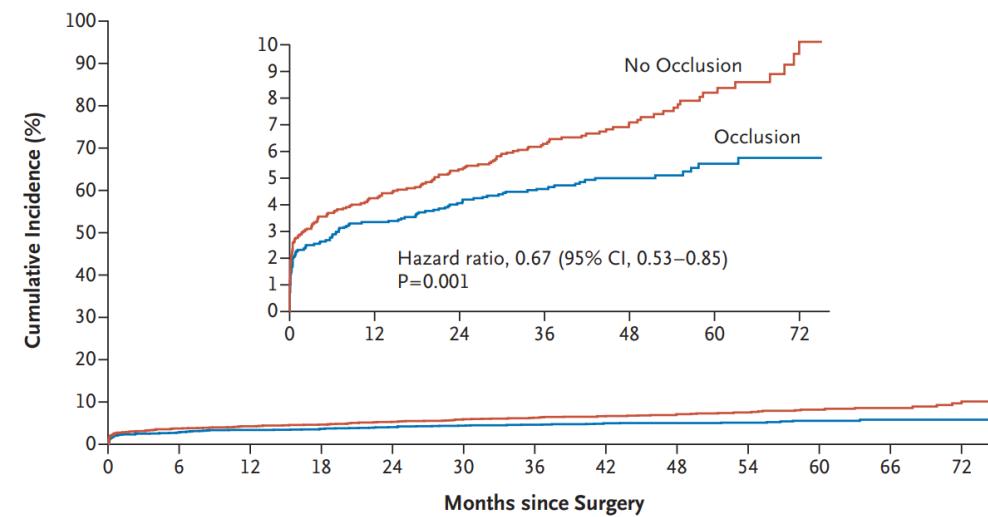
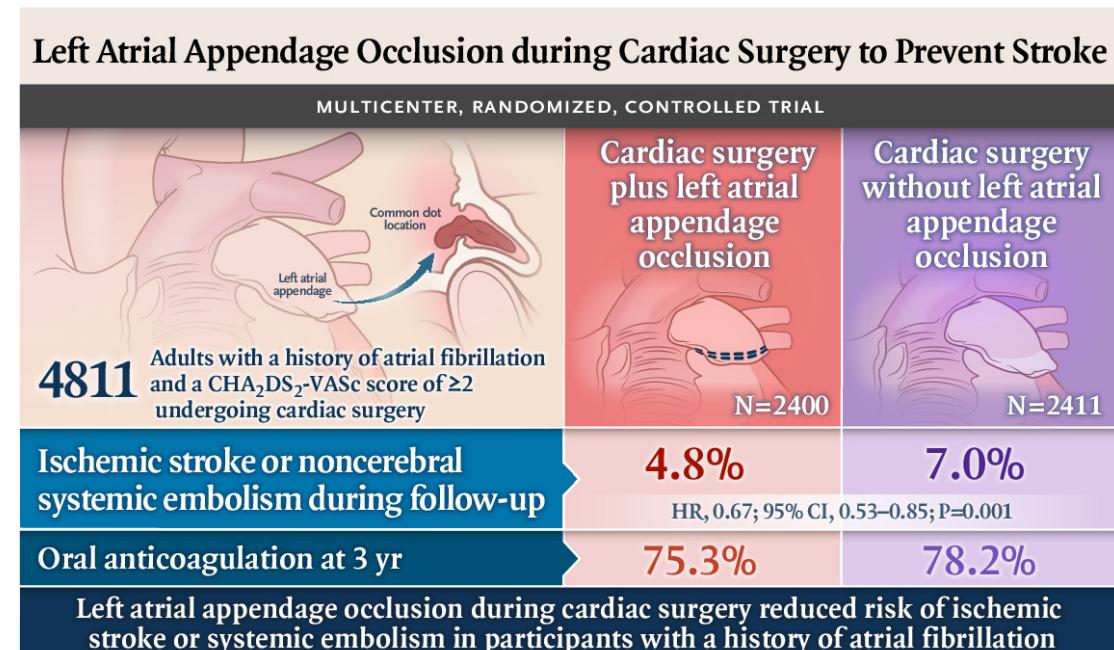


- Risks → device-related thrombus (2-5%), residual leak
- Post-procedural antithrombotics
  - 45d DOAC + AP → ASA alone (WATCHMAN FLX)
  - 6m DAPT → ASA alone (AC contraindication)

# Surgical LAAO

- LAAOS-III (N=4811)
  - *Population:* AF + CHADS<sub>2</sub>VASc≥2 undergoing cardiac surgery
  - *Intervention/Control:* surgical LAAO / no LAAO
  - *Outcome:* Ischemic stroke / SE
- Mean CHADS<sub>2</sub>VASc ~4
- ~77% OAC (3 y)

N Engl J Med. 2021 Jun 3;384(22):2081-2091.



No. at Risk												
No Occlusion	2391	2134	2081	2030	1981	1897	1607	1291	1016	751	540	348
Occlusion	2379	2163	2105	2059	2020	1948	1642	1322	1046	781	550	349

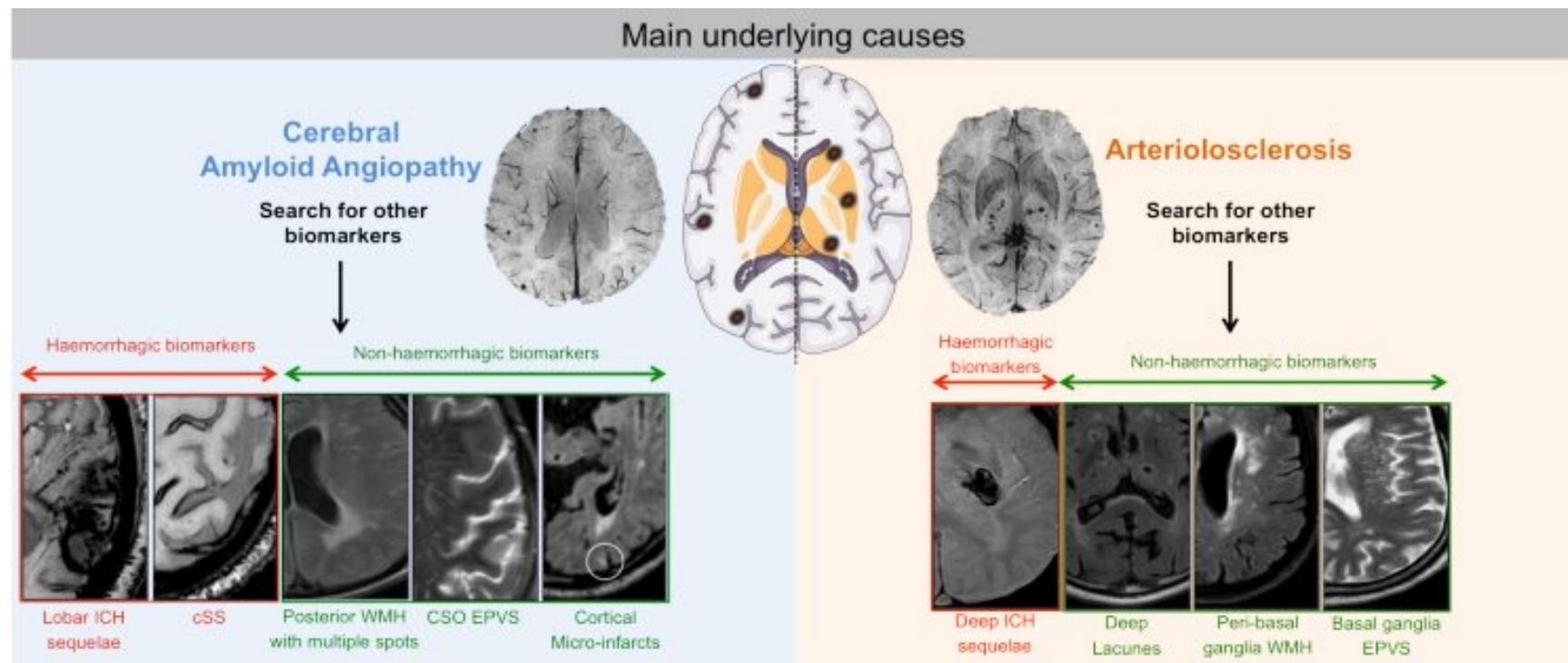
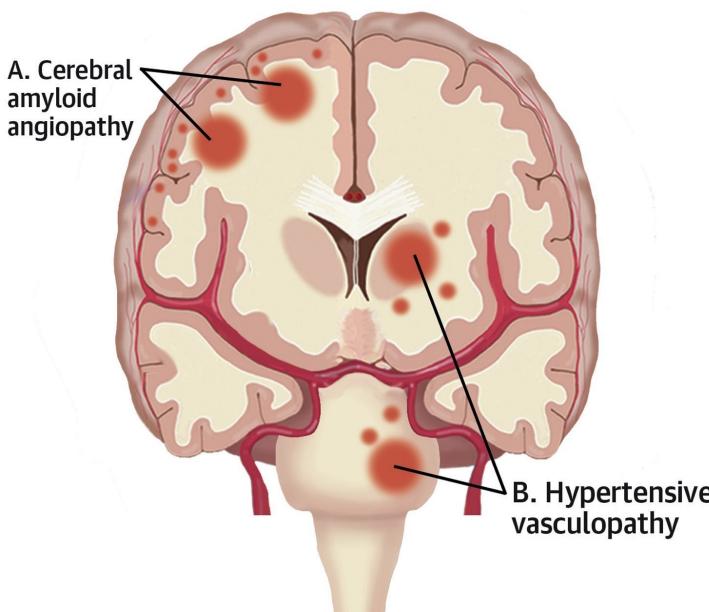
Figure 1. Cumulative Incidence of Stroke or Systemic Arterial Embolism.

Left atrial appendage occlusion (LAAO)				
	PROTECT-AF (NCT00129545) <sup>11</sup>	PREVAIL (NCT01182441) <sup>19</sup>	PRAGUE-17 (NCT02426944) <sup>20,21</sup>	LAOO5-III (NCT01561651) <sup>22</sup>
<b>Trial characteristics</b>				
Sample size	707 participants	407 participants	404 participants	4770 participants
Intervention	Percutaneous LAAO	Percutaneous LAAO	Percutaneous LAAO	Surgical LAAO
Comparator	Warfarin	Warfarin	DOAC	No LAAO
Anticoagulation	Warfarin 50% (control group)	Warfarin 50% (control group)	DOAC 50% (control group)	82% (64% VKA, 18% DOAC)
History of ischaemic stroke	131 (18%) participants	111 (28%) participants	129 (35%) participants	9% of participants
<b>Outcomes</b>				
Follow-up	3.8 years, mean	1.5 years, mean	3.5 years, median	3.8 years, mean
Primary endpoint	Stroke, systemic embolism, and cardiovascular or unexplained death 8.4% (LAAO) vs 13.9% (warfarin), RR 0.60; 95% CI 0.41-1.05	Stroke, systemic embolism, and cardiovascular or unexplained death 0.064 (LAAO) vs 0.063 (warfarin), RR 1.07; 95% CI 0.57-1.89	Stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or complications related to procedure or device 10.99% (LAAO) vs 13.42% (NOAC), HR 0.84; 95% CI 0.53-1.31; p=0.44	Ischemic stroke or systemic embolism 4.8% (LAAO) vs 7.0% (OAC), HR 0.67; 95% CI 0.53-0.85
Stroke	1.4 (LAAO) vs 1.1 (warfarin) events per 100 patient-years	1.9% (LAAO) vs 0.7% (warfarin)	1.9% (LAAO) vs 1.8% (DOAC)	4.6% (LAAO) vs 6.9 (no LAAO)
Mortality	Cardiovascular or unexplained death 1.0 (LAAO) vs 2.4 per 100 years (warfarin)	Cardiovascular or unexplained death 2.6% (LAAO) vs 2.2% (warfarin)	All cause mortality 7.0% (LAAO) vs 7.8% (DOAC)	All cause mortality 22.6% (LAAO) vs 22.5% (no LAAO)

# AF antithrombotic management after ICH

- (Annual) Recurrence Risk

- CAA: ~9%
- HTN: <2%
- Mixed: ~5%



J Am Coll Cardiol. 2020 Apr 21;75(15):1819-1831.  
J Neurol Neurosurg Psychiatry. 2021 Feb 9:jnnp-2020-323951.  
Neurology. 2018 Jan 9;90(2):e119-e126.

# Aspirin

- RESTART (N=537)
  - *Population:* ICH taking antithrombotic
  - *Intervention/Control:* start / avoid AP
  - *Outcome:* recurrent sx ICH
- AF → ~25%
- AP start → median 76 d

J Neurol Sci. 2018 Jan 15;384:133-138.  
Lancet. 2019 Jun 29;393(10191):2613-2623.

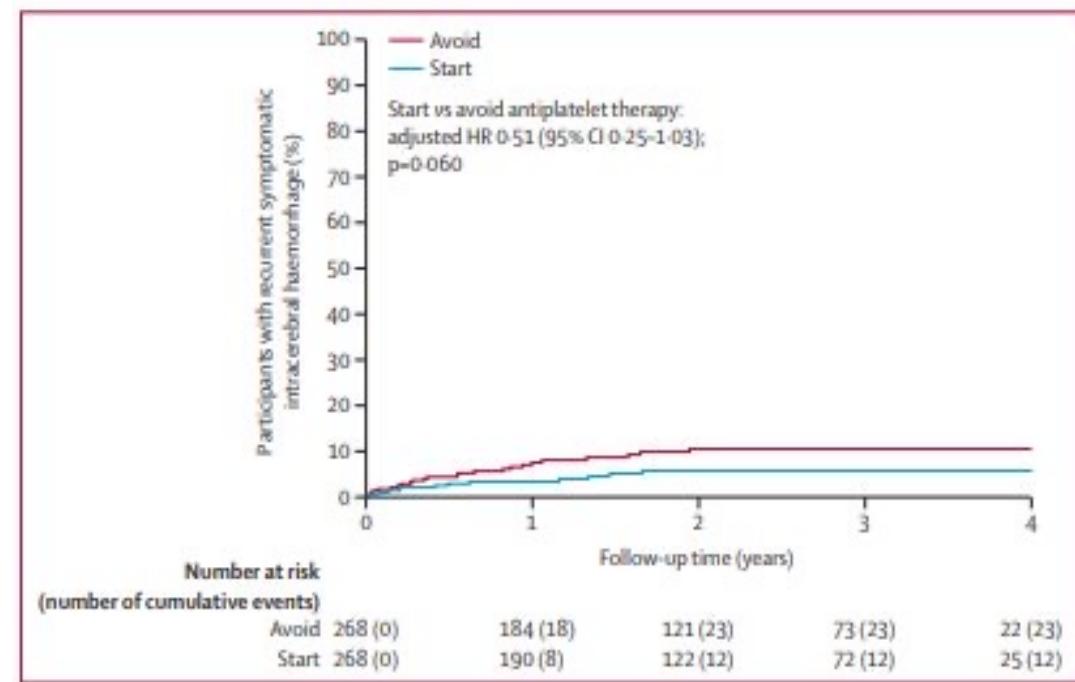
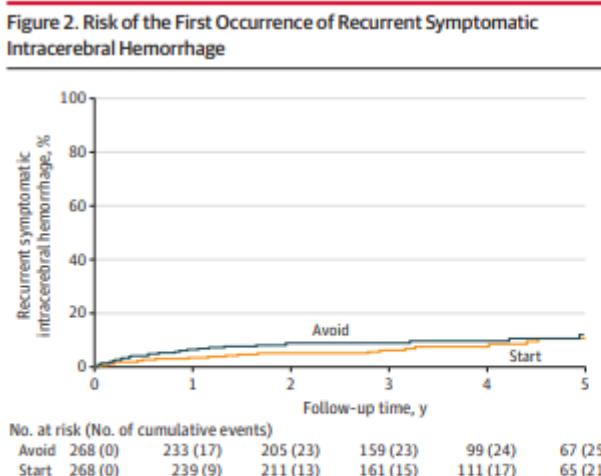
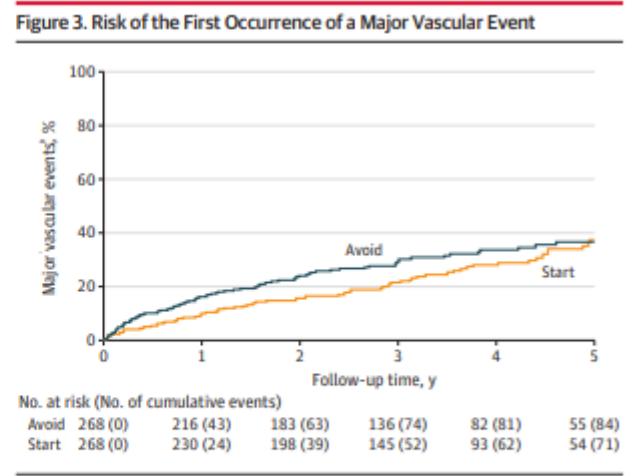


Figure 2: Kaplan-Meier plot of the first occurrence of recurrent symptomatic intracerebral haemorrhage



Numbers at risk refer to survivors undergoing follow-up at the start of each year according to treatment allocation. Plot was censored at 5 years. Cumulative events indicate the participants in follow-up with a first event.



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# Anticoagulation

- CHADS2VASc > estimated risk of ICH recurrence?
- Uncertain benefit of AC resumption (stroke/CVD death)
  - Timing → ~8 weeks

**Table 3.** Ongoing Post-ICH Stroke Prevention Trials in Patients With Nonvalvular Atrial Fibrillation

Trial Name	Intervention vs comparator	Projected n	Country(ies)
ASPIRE	Apixaban vs aspirin	700	United States
ENRICH AF	Edoxaban vs aspirin	1200	Canada+20 countries
PRESTIGE AF	Anticoagulant vs antiplatelet vs none	654	United Kingdom, Austria, France, Italy, Germany, Spain

Stroke. 2017 Feb;48(2):314-320.  
 Lancet Neurol. 2023 Dec;22(12):1140-1149.  
 Stroke. 2024 Jan;55(1):214-225.

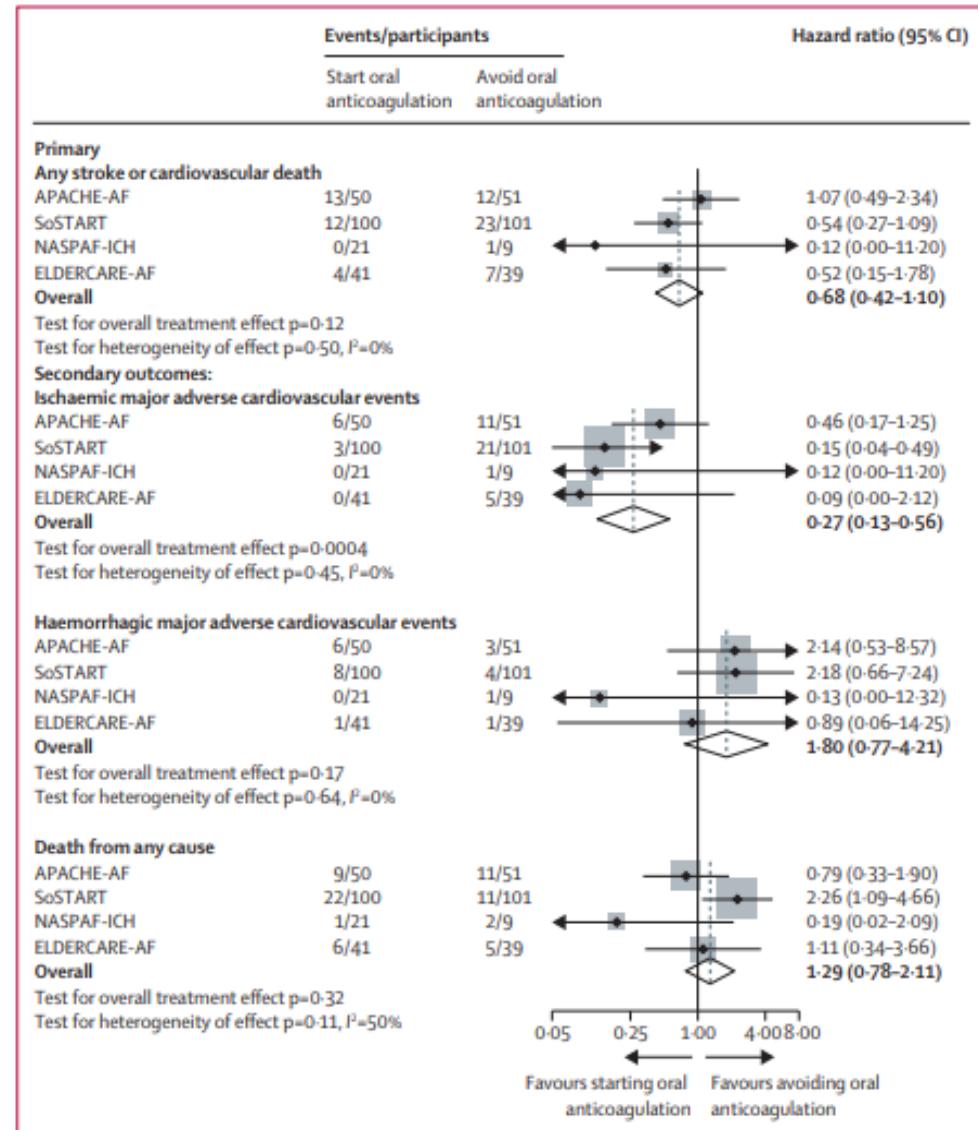
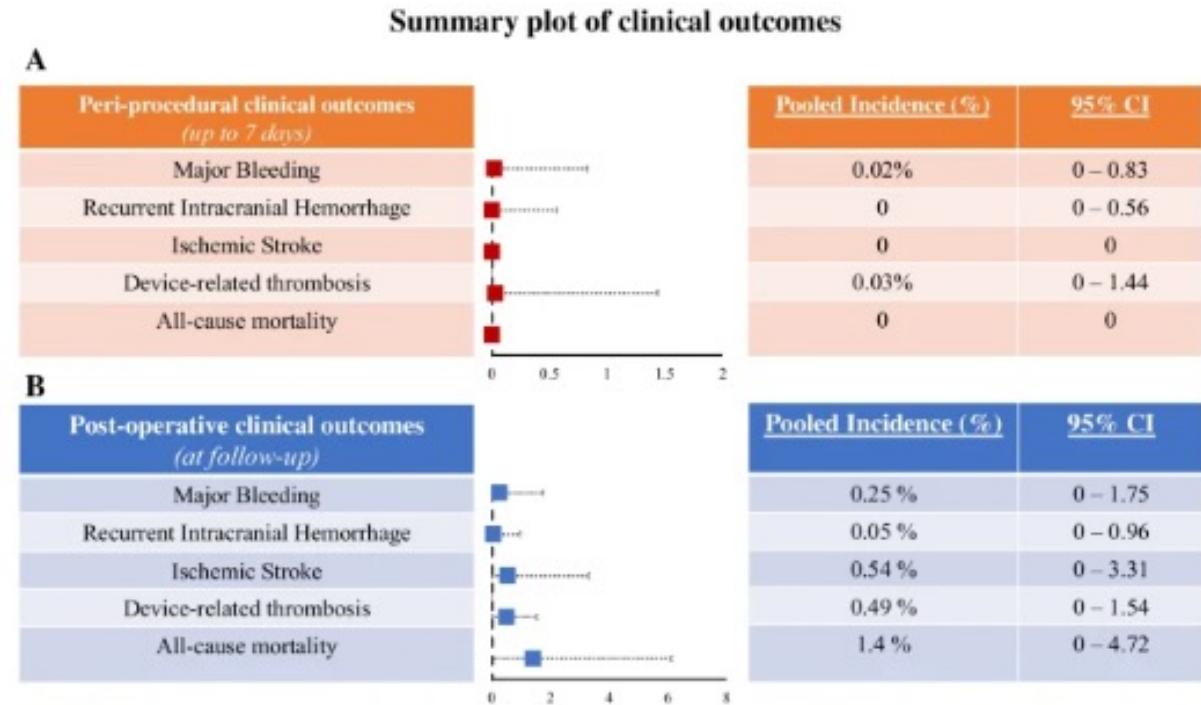


Figure 2: Effect of starting versus avoiding oral anticoagulation for atrial fibrillation after intracranial haemorrhage on primary and secondary outcomes, using individual participant data from four trials

# Percutaneous LAAO

- Observational studies
  - Retrospective
  - N = small
- Low event rates after LAAO



**Table 3. Ongoing Post-ICH Stroke Prevention Trials in Patients With Nonvalvular Atrial Fibrillation**

Trial Name	Intervention vs comparator	Projected n	Country(ies)
CLEARANCE trial	WATCHMAN FLX vs DOAC	550	Germany
STROKECLOSE	Amulet vs DOAC	750	Denmark
A <sub>3</sub> ICH	DOAC vs LAAC vs ASA/none	300	France

EuroIntervention. 2017 Jun 20;13(3):371-378.

J Interv Card Electrophysiol. 2020 Nov;59(2):415-421.

Transl Stroke Res. 2021 Apr;12(2):259-265.

J Interv Card Electrophysiol. 2022 Sep;64(3):551-556.

# Key Messages – LAAO & Antithrombotic Mgmt After ICH

- LAAO reasonable consideration when hemorrhage risk is unacceptably high, BUT:
  - Benefit : Risk (in comparison to DOAC) not established in stroke populations
  - LAAO + DOAC superior to DOAC alone in ischemic stroke despite AC?
- Optimal antithrombotic mgmt. after ICH in AF populations is uncertain
  - Enroll into ASPIRE whenever possible
  - ASA resumption safe

