



Beyond Platelets: The Next Chapter in Stroke Prevention

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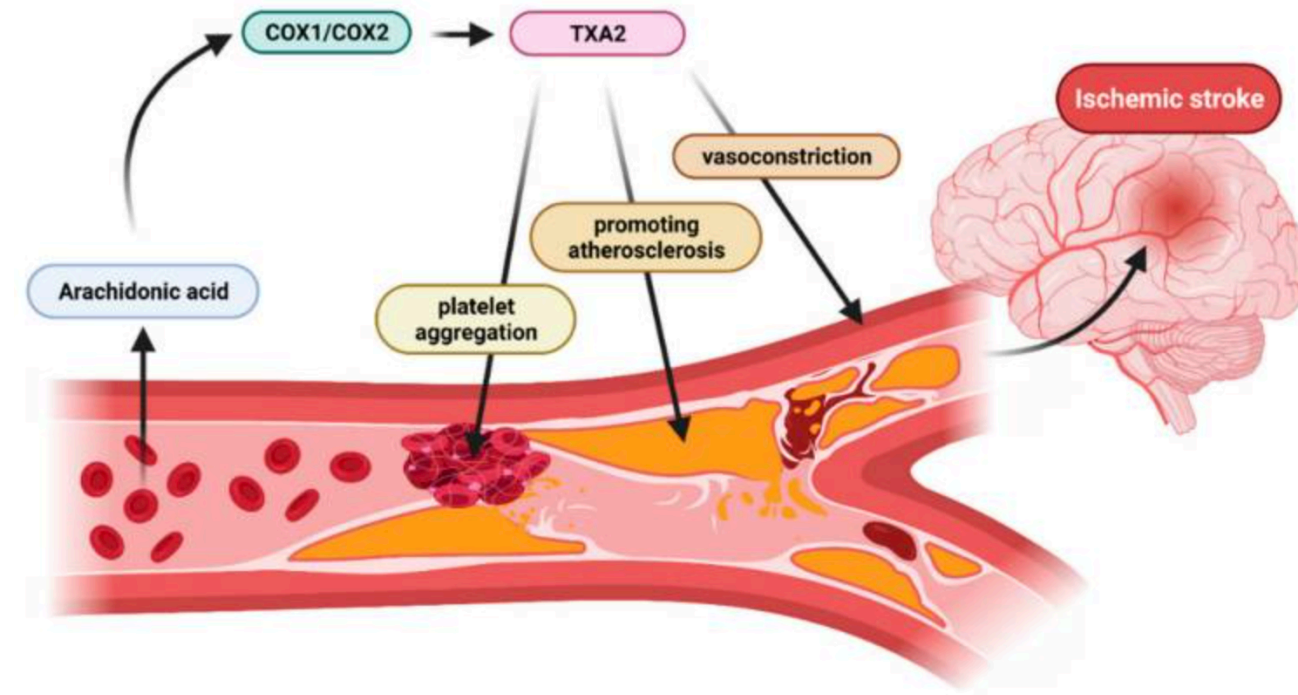
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Pathophysiology of Ischemic Stroke

PLATELET ACTIVATION AND AGGREGATION

- Endothelial damage exposes subendothelial matrix components like collagen and von Willebrand factor
- This process triggers platelet adhesion, activation and aggregation to form hemostatic plug



Pathophysiology of Ischemic Stroke

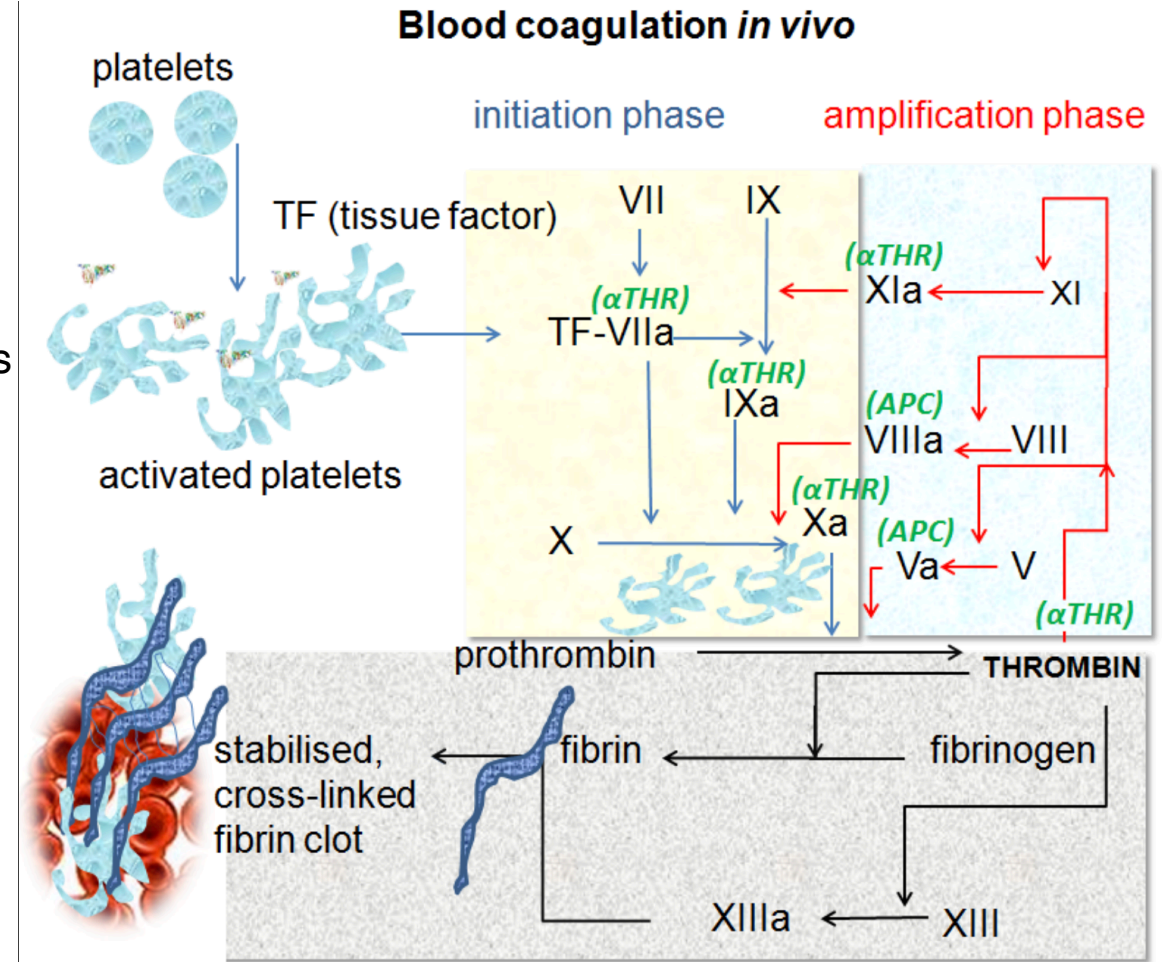
COAGULATION CASCADE

Thrombosis and Embolism

- Vessel Injury
- Platelet Activation
 - Signals like ADP and thromboxane recruit more platelets
- Clot growth

Thrombo-Inflammation and Tissue Damage

- Recruiting immune cells
- Worsening Injury
- Repercussion Injury



Anti-platelet Therapy

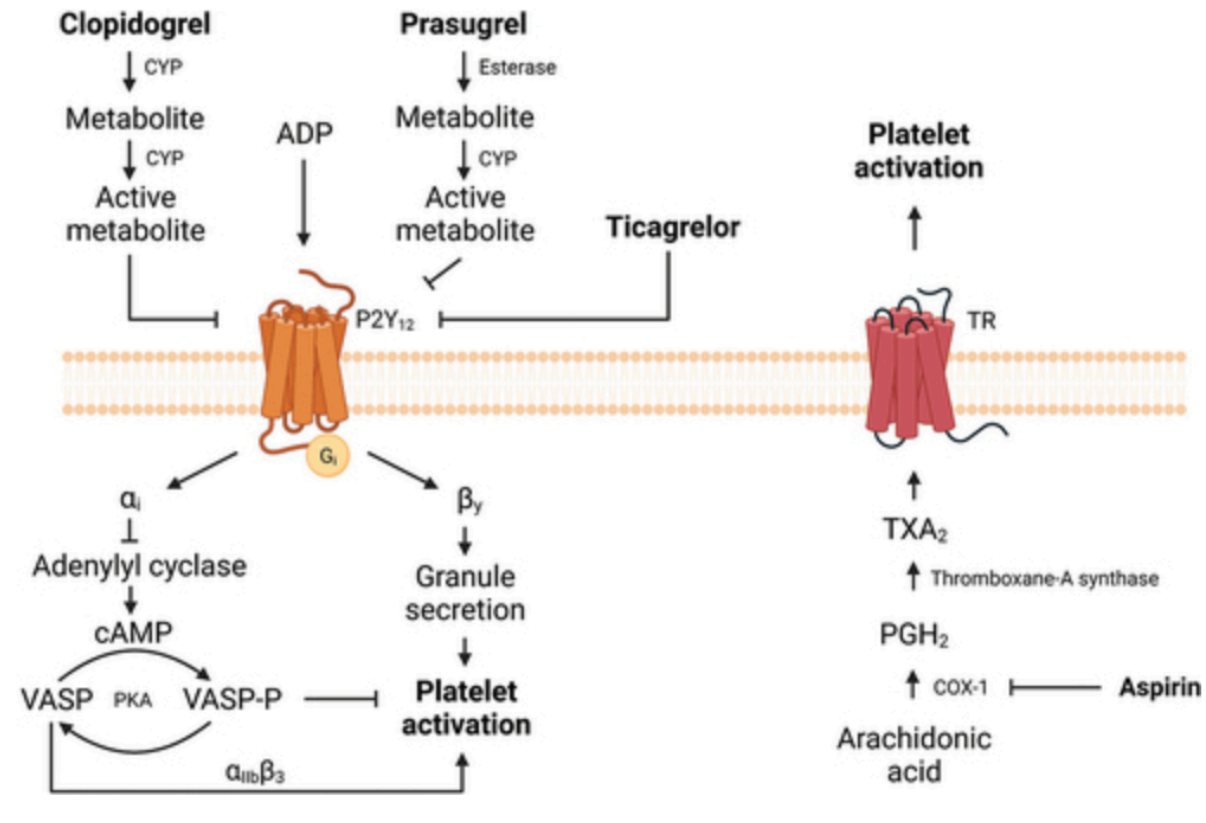
ASPIRIN AND P2Y₁₂ INHIBITORS

Aspirin

- Permanent COX-1 inhibitor
- Shuts down the production of **thromboxane A₂** which signals platelet activation and aggregation

P2Y₁₂ Inhibitors (Clopidogrel, Prasugrel, Ticagrelor, Cangrelor)

- Block adenosine diphosphate (ADP) from binding to P2Y₁₂ receptor on platelets
- Stop signaling pathway which prevents platelets from clumping together to form blood clots



Can we prevent ischemic stroke without causing more bleeding?

OCEANIC-STROKE TRIAL

ASUNDEXIAN FOR SECONDARY STROKE PREVENTION

- **Purpose**
 - Does adding to oral Factor Xla inhibitor asundexian (50mg once daily) to standard anti-platelet therapy significantly reduce the risk of recurrent ischemic stroke without increasing major bleeding compared to placebo
- **Study Design**
 - A global, double-blind, randomized, placebo-controlled Phase III trial
 - n= 12,327 patients within 72 hours of a non-cardioembolic ischemic stroke or high-risk transient ischemic attack

OCEANIC-STROKE TRIAL

EFFICACY

Ischemic stroke occurred in **6.2%** of the asundexian group versus **8.4%** in the placebo group (a 26% relative risk reduction; HR 0.74).

The composite of cardiovascular death, myocardial infarction, or stroke occurred in **9.2%** (asundexian) versus **11.1%** (placebo)

Outcome	No. of Patients (%)	Asundexian (N = 6162) No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)§ %
Primary efficacy outcome			
Ischemic stroke	384 (6.2)	4.4 (4.0–4.9)	5.1 (4.6–5.7)
Secondary efficacy outcomes			
Any stroke	404 (6.6)	4.6 (4.2–5.1)	5.3 (4.8–5.9)
Death from cardiovascular causes, myocardial infarction, or stroke	568 (9.2)	6.6 (6.0–7.1)	7.3 (6.7–8.0)
Death from any cause, myocardial infarction, or stroke	649 (10.5)	7.5 (6.9–8.1)	8.3 (7.6–9.0)

OCEANIC-STROKE TRIAL

SAFETY

International Society on Thrombosis and Haemostasis (ISTH) major bleeding rates were **1.9%** for asundexian and **1.7%** for placebo, showing **no statistically significant increase** in major bleeding

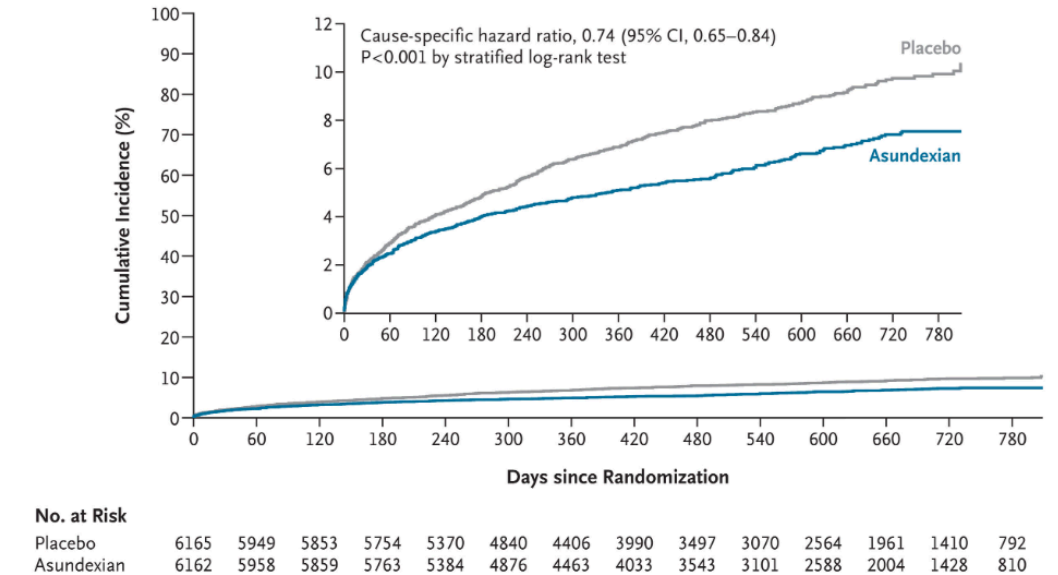
Outcome	Asundexian (N = 6124)		
	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)†
Primary safety outcome			
ISTH major bleeding	117 (1.9)	1.6 (1.4–2.0)	1.6 (1.3–1.9)
Secondary safety outcomes			
ISTH major or clinically relevant nonmajor bleeding	339 (5.5)	4.9 (4.4–5.4)	4.8 (4.3–5.4)
Clinically relevant nonmajor bleeding	231 (3.8)	3.3 (2.9–3.8)	3.3 (2.9–3.8)
Symptomatic intracranial hemorrhage, including intracerebral hemorrhage	41 (0.7)	0.6 (0.4–0.8)	0.5 (0.4–0.7)
Hemorrhagic stroke	13 (0.2)	0.2 (0.1–0.3)	0.2 (0.1–0.3)

OCEANIC-STROKE TRIAL

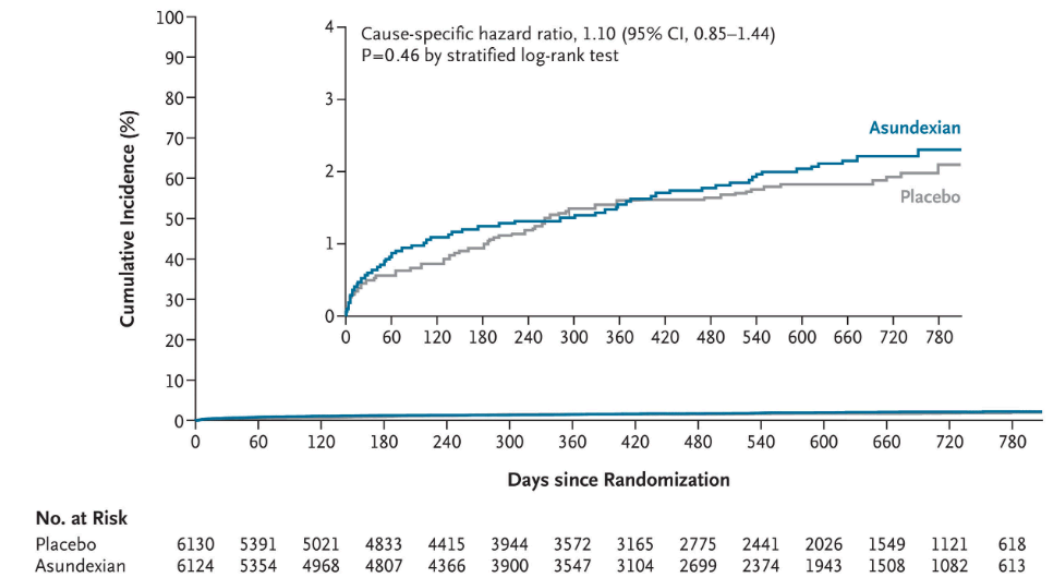
TAKEAWAYS

- The OCEANIC-STROKE Phase III trial demonstrated that adding the oral Factor XIa inhibitor asundexian to standard antiplatelet therapy **reduces recurrent ischemic stroke by 26% without increasing major bleeding risks.**
- Clinical implication:** this trial provides evidence for the safety and efficacy of initiating 50 mg of asundexian daily alongside anti-platelet regimens within 72 hours of a non-cardioembolic ischemic stroke or high-risk TIA

A Cumulative Incidence of Ischemic Stroke



B Cumulative Incidence of ISTH Major Bleeding



LIBREXIA-STROKE TRIAL

MILVEXIAN FOR SECONDARY STROKE PREVENTION

- **Purpose:** Does adding oral Factor Xla inhibitor milvexian (25mg twice daily) safely reduce the risk of recurrent ischemic stroke or high-risk transient ischemic attack when added to standard anti platelet therapy.
- **Study Design:** Ongoing Phase 3, randomized, double-blind, parallel-group, placebo controlled clinical trial
- **Participants:** Adults aged 40 and older experiencing an acute noncardioembolic ischemic stroke or high-risk TIA within 48 hours of symptom onset
- **Primary Endpoint:** Time to the first occurrence of a recurrent ischemic stroke.

Can we anticoagulate patients more safely?

LIBREXIA-AF TRIAL

MILVEXIAN VS APIXABAN FOR STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION OR ATRIAL FLUTTER

Purpose: Evaluate to safety and efficacy of milvexian (100mg twice daily) in stroke prevention compared to standard anticoagulant.

Design: Randomized, double-blind, parallel-group, active-controlled, event-driven trial.

Anticipated results: End of 2026.

LILAC-TIMI 76

ABELACIMAB FOR STROKE PREVENTION IN HIGH-RISK ATRIAL FIBRILLATION

Purpose: Measure efficacy in preventing ischemic stroke alongside rates of clinically relevant bleeding.

Design: international phase 3 clinical study with monthly injection of abelacimab (a Factor XI inhibitor) for patients aged 65 and older with atrial fibrillation deemed unsuitable for traditional anticoagulants.

Anticipated Results: End of 2026.

Can we avoid the need for anticoagulation?

CHAMPION-AF

DEVICE-BASED LEFT ATRIAL APPENDAGE CLOSURE (WATCHMAN FLX) VS NOAC

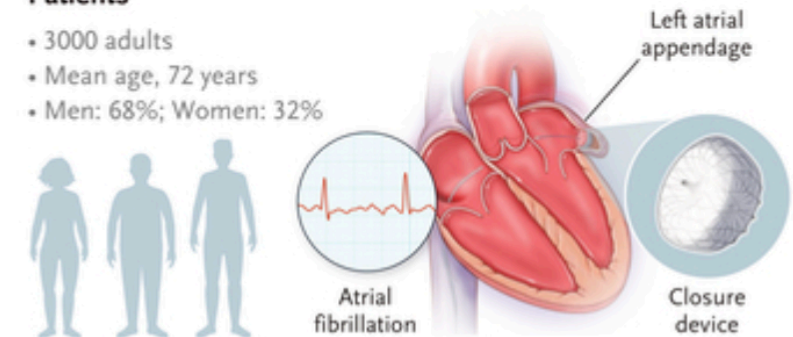
Purpose: compare device-based left atrial appendage closure using the Watchman FLX device to non-vitamin K antagonist oral anticoagulant (NOAC) therapy for preventing stroke, systemic embolism, and cardiovascular death.

Design: A prospective, randomized, global, multicenter investigation comparing LAAC (Watchman FLX) against NOACs in 3,000 patients with non-valvular atrial fibrillation.

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Patients

- 3000 adults
- Mean age, 72 years
- Men: 68%; Women: 32%



Device-Based Left Atrial Appendage Closure



N=1499

Non-Vitamin K Antagonist Oral Anticoagulants



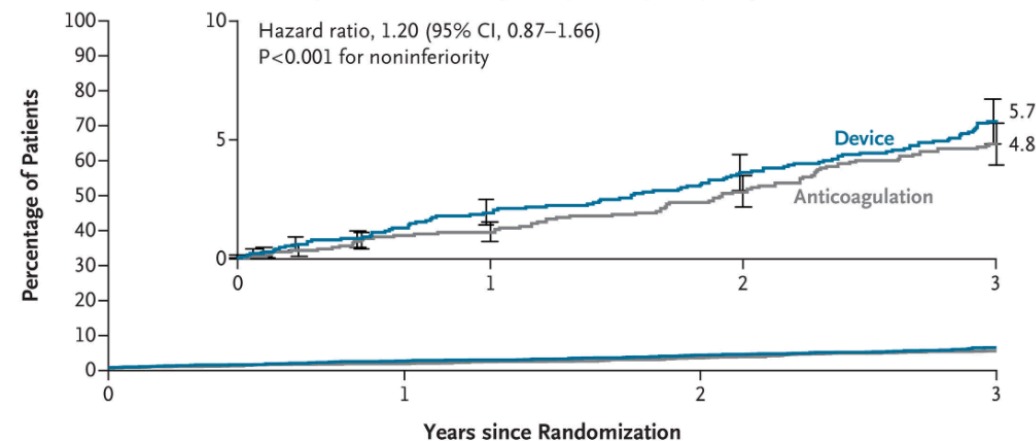
N=1501

CHAMPION-AF

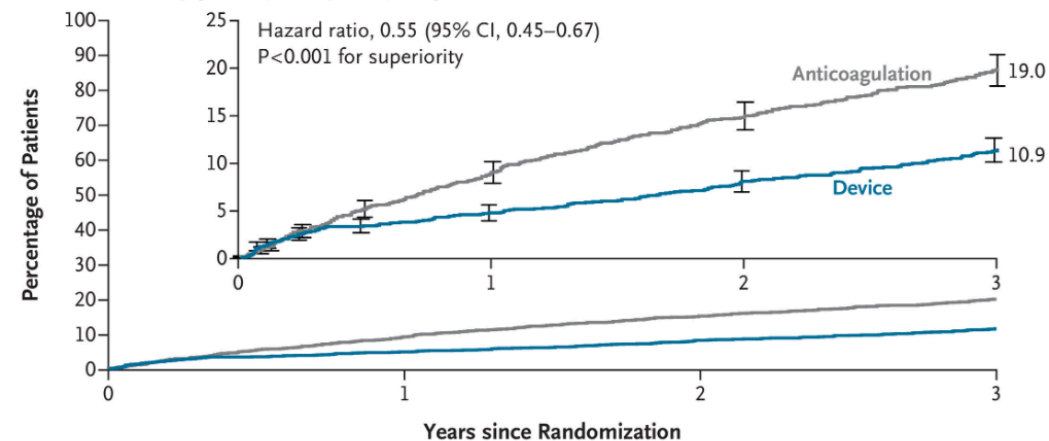
RESULTS

- **Primary Efficacy Endpoint:** A composite of cardiovascular death, ischemic stroke, hemorrhagic stroke, and systemic embolism
 - 5.7 (device group) vs 4.8 (anticoagulation group); 95% confidence CI, -0.8 to 2.6; $p < 0.001$ for non inferiority
 - **Met non-inferiority criteria**
- **Primary Safety Endpoint:** Non-procedure-related major bleeding and clinically relevant non-major bleeding.
 - 10.9 (device group) vs 19.0 (anticoagulation group); 95% CI, 0.45 to 0.67); $p < 0.001$ for superiority
 - **Showed superiority for the device group at 3 years**

A Death from Cardiovascular Cause, Stroke, or Systemic Embolism (primary efficacy end point)



B Non-Procedure-Related Bleeding (primary safety end point)



CHAMPION-AF

CLINICAL TAKEAWAY

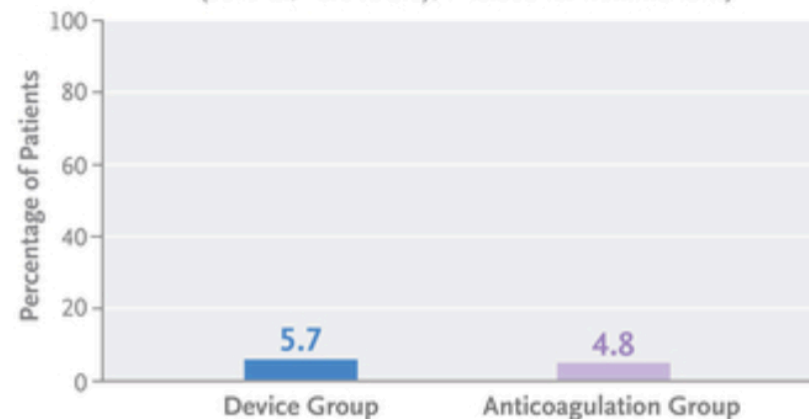
Superior Long-Term Safety: The device group achieved a **45% relative risk reduction** in long-term, non-procedural major and clinically relevant non-major bleeding (10.9% for LAAC vs. 19.0% for DOACs).

Real-World Compliance Factor: In CHAMPION-AF, DOAC adherence was over 90%. In a real-world stroke clinic, roughly 40% of AF patients are non-compliant with blood thinners. This makes the "one-time mechanical fix" highly attractive for patients with documented adherence issues

Takeaway: the CHAMPION-AF trial positions Left Atrial Appendage Closure (LAAC) with the Watchman FLX as a viable **first-line alternative** to direct oral anticoagulants (DOACs) for stroke prevention.

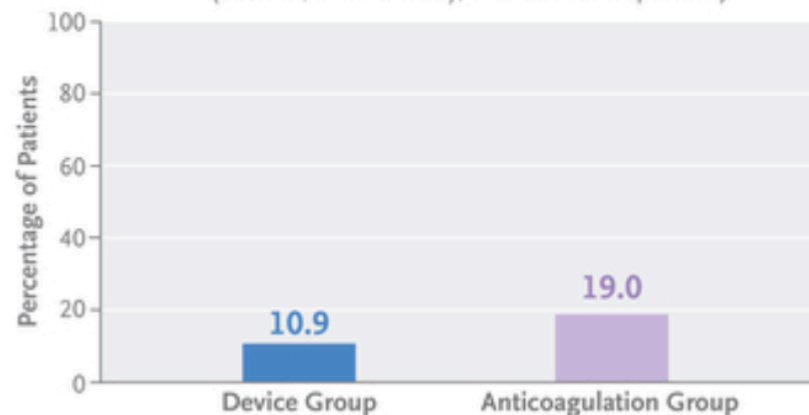
Cardiovascular Death, Stroke, or Embolism

Difference, 0.9 percentage points
(95% CI, -0.8 to 2.6); $P < 0.001$ for noninferiority



Non-Procedure-Related Bleeding

Hazard ratio, 0.55
(95% CI, 0.45 to 0.67); $P < 0.001$ for superiority



CATALYST TRIAL

DEVICE-BASED LEFT ATRIAL APPENDAGE CLOSURE (AMPLATZER AMULET) VS NOAC

Purpose: evaluate whether left atrial appendage occlusion (LAAO) using Abbott's Amplatzer Amulet Occluder is a safe and effective alternative to non-vitamin K oral anticoagulants (NOACs) for stroke prevention in patients with atrial fibrillation (AF).

Design: global, randomized clinical trial enrolling up to 2,650 patient with non-valvular atrial fibrillation at elevated risk of stroke with 1:1 randomization across more than 120 global sites with patient follow-up extending through 5 years

Core Endpoints

- **Thromboembolic Safety:** Assessing non-inferiority regarding a composite of ischemic stroke, systemic embolism, and cardiovascular death through 2 years.
- **Bleeding Reductions:** Evaluating superiority regarding major or clinically relevant non-procedural bleeding events compared to lifelong pharmaceutical anticoagulation

Estimated results: January 2029

What alternative mechanisms for stroke prevention are currently being investigated

Glycoprotein VI Inhibition

ACTIMIS

- Phase 1b (dose escalation) and Phase 2a (dose confirmation) enrolling 106 patients
- Tested glenzocimab, a novel drug blocking glycoprotein VI
- Demonstrated decreased symptomatic intracranial hemorrhage, lower 90 day all-cause mortality and better functional outcomes in the glenzocimab vs placebo group

ACTISAVE

- Phase 2/3 confirmatory study designed to prove the clinical efficacy of glenzocimab
- Failed to show a statically significant benefit in improving stroke outcomes o

Neuroprotectants

INCRETINS AS ADJUVANTS TO ENDOVASCULAR THROMBECTOMY

GALLOP 2

- A multicenter, randomized clinical study evaluating the GLP-1 receptor agonist semaglutide as a neuroprotective adjuvant therapy for acute large vessel occlusion (LVO) stroke patients treated with endovascular thrombectomy (EVT) without prior intravenous thrombolysis.
- **Patient Population:** Patients experiencing acute anterior circulation large vessel occlusion stroke undergoing mechanical thrombectomy without intravenous thrombolysis. [1]
- **Intervention:** Subcutaneous injection of semaglutide administered prior to or during EVT and followed by a repeat dose on day 7, compared against standard reperfusion care alone.
- **Preliminary data:** Initial findings from GALLOP-2 were announced at the European Stroke Organisation Conference (ESOC) in May 2026, pointing to semaglutide as a promising adjunctive cytoprotective strategy in stroke care

TOPAZ

- **Intervention:** Subcutaneous injection of tirzepatide administered in two doses—one prior to the EVT procedure and a second dose 7 days post-procedure for patients undergoing EVT for anterior-circulation large vessel obstruction.
- Primary outcome: 90 day functional outcome measured by proportion of patients achieving mRS score 0-1
- Rationale & Mechanism
 - **Incretin Neuroprotection:** Preclinical and translational studies suggest that dual GIP/GLP-1 receptor agonists like tirzepatide exhibit pleiotropic protective effects beyond glycemic control.
 - **Blood-Brain Barrier (BBB):** Experimental models indicate that tirzepatide helps mitigate stroke-induced BBB disruption, reduce permeability, and restore tight-junction proteins like Claudin-1, leading to reduced tissue damage and improved neurological recovery

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