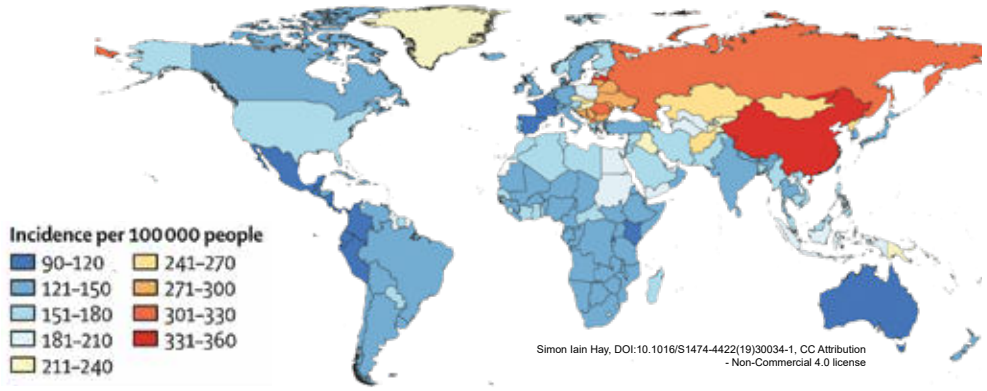
Advances in oral anticoagulation for stroke prevention

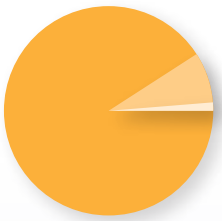
World Stroke Organization | World Stroke Academy

Age-standardised stroke incidence by country, for both sexes, 2016

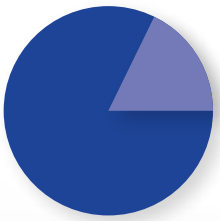


Antithrombotics for Stroke Prevention

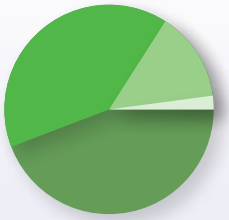
DOACs (rivaroxaban, apixaban, dabigatran, edoxaban) are the preferred oral anticoagulants for **non-valvular atrial fibrillation (AF).** VKAs are indicated in patients with AF related to prosthetic cardiac valves, rheumatic valve disease and severe mitral stenosis. Antiplatelet therapy preferred after non-cardioembolic stroke or TIA for ischemic stroke prevention.



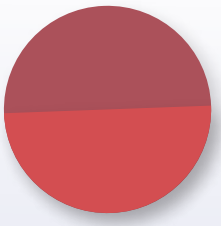
Stroke
- **88%** Ischemic Stroke
- **10%** Intracerebral Hemorrhage
- **2%** Subarachnoid Hemorrhage



Ischemic Stroke
- **77%** Non-Lacunar
- **23%** Lacunar (Majority due to small vessel disease)



Non-lacunar Stroke
- **45%** Cryptogenic
- **35%** Cardioembolic
- **17%** Large Artery
- **3%** Other

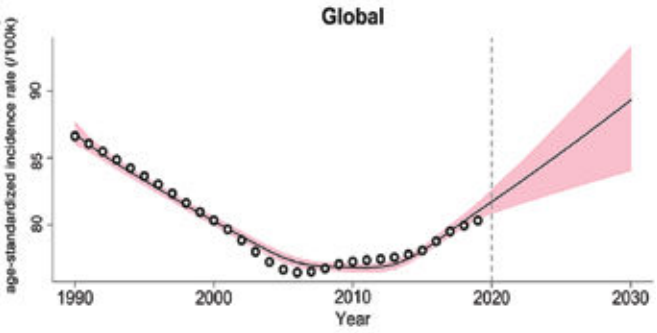


Cryptogenic Stroke
- **50%** ESUS
- **50%** Non-ESUS

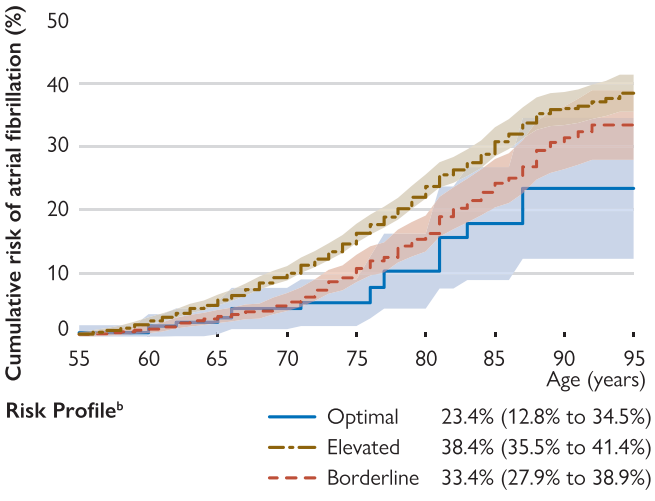
There is an unmet need for reducing ischemic stroke risk

Direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) are key therapies for preventing stroke and systemic embolism (SSE) in atrial fibrillation (AF). DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, directly inhibit clotting factors and offer comparable or superior efficacy to VKAs, with a lower risk of intracranial hemorrhage and no need for INR monitoring, though they are contraindicated in severe renal or hepatic impairment. VKAs, such as warfarin, require regular INR monitoring and have higher bleeding risks but remain effective for stroke prevention. In non-AF patients with ischemic stroke, antiplatelet therapy is the standard for secondary prevention. Single antiplatelet therapy (SAPT) with aspirin or clopidogrel reduces recurrent stroke risk, while dual antiplatelet therapy (DAPT), typically aspirin plus clopidogrel, is used short-term (21–90 days) in high-risk scenarios like minor ischemic stroke or TIA.

Projected increase ALL ischemic subtypes stroke with time

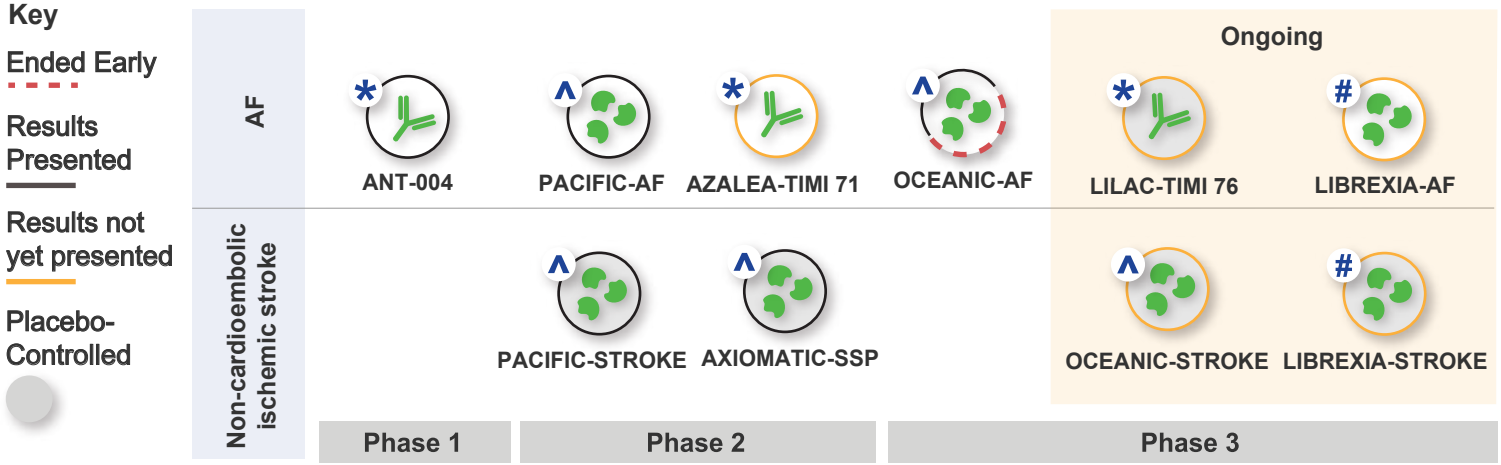


Lifetime risk of AF increases with increasing risk factor burden



Clinical trials targeting FXI/FXIa for stroke prevention

***Abelacimab, ^Asundexian, and #Milvexian** have been studied in phase 1 and phase 2 clinical trials in patients and have demonstrated promising preliminary results. Phase 3 trials of these drugs are currently underway.



* Abelacimab trials

ANT-004 was a phase 1 trial evaluating the safety and pharmacokinetics of Abelacimab in patients with AF. Patients were administered monthly subcutaneous doses of Abelacimab (120 mg and 180 mg), or placebo, for 3 months. The results demonstrated significant and sustained reduction in free Factor XI levels with no clinically relevant bleeding leading the way for this drug to be tested in phase 2 and 3 trials.

LILAC-TIMI 76 (NCT05712200) is a phase 3 randomized, placebo-controlled, double-blind trial to evaluate the safety and efficacy of Abelacimab relative to placebo in patients with AF who are unable to take currently available anticoagulation therapy. The trial is currently enrolling with expected completion in 2025.

AZALEA-TIMI 71 was a phase 2 randomized trial comparing the effect of two blinded doses of Abelacimab relative to rivaroxaban on the rate of major or clinically relevant non-major (CRNM) bleeding events in patients with AF who are at moderate-to-high risk of stroke (CHADSVASC2 ≥ 4). The trial was stopped prematurely in September 2023 due to significantly lower rate of bleeding with Abelacimab.

^ Asundexian trials

PACIFIC-AF was a Phase 2 study in patients with atrial fibrillation (AF), demonstrated a significant reduction in the primary safety endpoint of ISTH-defined major or clinically relevant non-major (CRNM) bleeding with Asundexian compared to Apixaban (HR 0.33, 90% CI 0.09–0.97). The 50 mg dose of Asundexian achieved >90% inhibition of Factor XIa activity.

OCEANIC-AF was a Phase 3 trial comparing Asundexian 50 mg to Apixaban in atrial fibrillation patients at stroke risk, was stopped early due to the inferior efficacy of Asundexian, as recommended by the Independent Data Monitoring Committee.

PACIFIC-STROKE was a Phase 2 study that evaluated asundexian in 1,808 patients with recent non-cardioembolic ischemic stroke. While it did not meet the primary efficacy outcome, the 50 mg dose showed potential to reduce recurrent strokes and TIAs, especially in atherosclerosis, without significantly increasing bleeding risk.

OCEANIC STROKE (NCT05686070) is a Phase 3 clinical trial designed to evaluate the efficacy and safety of Asundexian, an investigational oral Factor XIa inhibitor, in reducing the risk of recurrent ischemic stroke in patients who have recently experienced a non-cardioembolic ischemic stroke.

Milvexian

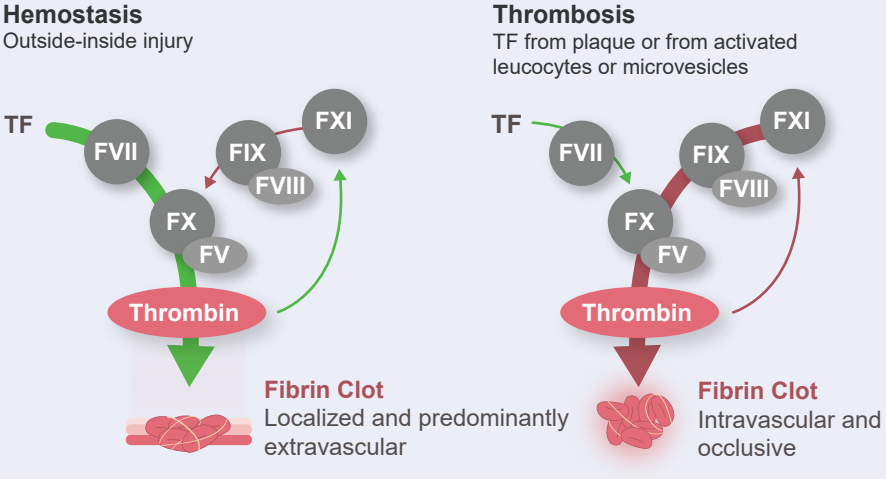
AXIOMATIC-SSP was a Phase 2 trial that evaluated milvexianin patients with acute non-cardioembolic ischemic stroke or high-risk TIA. While it did not significantly reduce ischemic events at 90 days, milvexian showed a favorable safety profile with no increase in major bleeding.

LIBREXIA-AF (NCT05757869) is a Phase 3 trial comparing the oral Factor XIa inhibitor Milvexian to apixaban for stroke prevention in atrial fibrillation patients.

LIBREXIA STROKE (NCT05702034) is a Phase 3 trial assessing Milvexian's efficacy in preventing recurrent strokes and ischemic events in patients after acute ischemic stroke or high-risk TIA.

Mechanism of action of FXI/FXIa inhibitors

When a FXI/FXIa inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi. The tissue factor (TF) pathway still produces thrombin, which allows beneficial blood clots to form to stop bleeding.



FXI/FXIa inhibitors are promising new options for stroke prevention, addressing the need for safer anticoagulation in atrial fibrillation (AF) and non-cardioembolic stroke. By inhibiting thrombin amplification, they prevent pathological clots while preserving normal hemostasis through the tissue factor pathway, which maintains normal hemostasis and allows beneficial clotting to stop bleeding. Phase 2 trials have demonstrated safety and potential efficacy, especially in non-AF patients. Completion of Phase III trials will confirm FXI/FXIa inhibition hypothesized for uncoupling hemostasis from thrombosis.

References:
1. DOI: 10.1093/eurheartj/ehaa612
2. DOI: 10.1093/eurheartj/ehw210
3. DOI: 10.1016/S0140-6736(13)62343-0

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