Balkan Med J 2025;42:493-4

Factor XI/XIa Inhibitors: Promising Agents for the Secondary Prevention of Ischemic Stroke

Murat Mert Atmaca

Clinic of Neurology, University of Health Sciences Türkiye, Sultan II. Abdulhamid Han Training and Research Hospital, İstanbul, Türkiye

Globally, stroke remains the second leading cause of death among non-communicable diseases and the third leading cause of death and disability combined (as measured by disability-adjusted life-years lost).[1] Ischemic strokes (IS) constitute 85% of all strokes, while the remaining 15% are hemorrhagic strokes. The etiologic subtypes of IS include large artery atherosclerosis, cardioembolism, small artery occlusion, stroke of other determined cause, and embolic stroke of undetermined origin (ESUS). Despite current antithrombotic therapies, 25% of all IS patients experience recurrence within 5 years, with the annual IS recurrence rate ranging from 3% to 6%.[2] Moreover, stroke recurrence rates remain largely unchanged over time, despite the advances in secondary prevention strategies.[3] While intensifying antithrombotic therapy may further mitigate the incidence of thrombotic events, it substantially increases the risk of major and fatal bleeding, indicating that current antithrombotic strategies have reached their limit of effectiveness.[4] Furthermore, many patients at high-risk of bleeding are unable to receive optimal antithrombotic therapy.[5] The coagulation system comprises primarily two activation pathways: one for thrombin generation and the other for the common pathway. The extrinsic pathway is triggered by tissue factor (TF) released following vascular injury and involves FVII to activate the common pathway. The intrinsic pathway, also known as the contact activation pathway, consists of FXII and FXI and is typically activated by the negatively charged surfaces of activated cells. Targeting the extrinsic or common pathway impedes the hemostatic response following vascular injury. Indeed, hemostasis following vascular injury occurs when the released TF binds activated FVII (FVIIa), activating FX and generating thrombin. This initial thrombin is insufficient to propagate or sustain clot formation; however, thrombin activates FXI through an amplification loop, producing a secondary thrombin burst that enables the initial clot to expand and occlude the vessel. Inhibiting FXI/XIa may prevent thrombosis without disrupting hemostasis, representing a paradigm shift from warfarin and direct oral anticoagulants (DOACs).[4,6]

Patients with inherited FXI abnormalities offer valuable insight into the potential benefits of FXI/XIa inhibition. Those with elevated FXI levels experience more than double the risk of venous thromboembolic events (VTE), whereas FXI-deficient patients exhibit lower rates of IS and VTE compared with the general population, without an increased risk of spontaneous or major bleeding, despite prolonged activated partial thromboplastin time.[7] This favorable profile has driven the development of factor XI/XIa inhibitors.

DOACs and warfarin are employed for secondary prevention in cardioembolic IS. The fundamental principle of current anticoagulation practice is to minimize the risk of clinical thrombotic events, even at the expense of increased bleeding. While DOACs demonstrate a safer bleeding profile compared to warfarin, they are still associated with a 0.55% rate of intracranial hemorrhage (similar to aspirin) and a 2.41% rate of major hemorrhage (higher than aspirin).[8] Furthermore, 13% of atrial fibrillation (AF) patients hospitalized for stroke were deemed ineligible for anticoagulation due to elevated bleeding risk.[7] Factor XI/XIa inhibitors can potentially cause less bleeding than DOACs while offering comparable efficacy in patients with AF. However, the phase 3 OCEANIC-AF (NCT05643573) trial, which compared the factor XIa inhibitor asundexian with apixaban for stroke prevention in AF, was terminated early due to lack of efficacy. The phase 3 LIBREXIA-AF (NCT05757869) trial, evaluating another factor XIa inhibitor, milvexian, versus apixaban for the prevention of stroke and non-central nervous system systemic embolism in AF patients, is still ongoing. The phase 3 study, ANT-010 (LILAC-TIMI 76, NCT05712200), comparing the factor XI inhibitor abelacimab, a monoclonal antibody, with placebo for stroke prevention in patients with AF unsuitable for oral anticoagulation, is currently in progress. Whether these studies yield positive results remains to be observed, or they may reveal that bleeding is an unavoidable consequence of effective anticoagulation.

Non-cardioembolic IS accounts for approximately 75% of all IS, and as previously mentioned, stroke recurrence rates have remained

Corresponding author: Murat Mert Atmaca, Clinic of Neurology, University of Health Sciences Türkiye, Sultan II. Abdulhamid Han Training and Research Hospital, İstanbul, Türkiye

e-mail: drmuratmertatmaca@hotmail.com

Available Online Date: 31.10.2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025.160925

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: M.M.A. 0000-0003-2048-4930.

Cite this article as: Atmaca MM. Factor XI/XIa Inhibitors: Promising Agents for the Secondary Prevention of Ischemic Stroke. Balkan Med J.; 2025; 42(6):493-4.

unchanged, despite the use of secondary prevention. ESUS is identified as the etiological factor in approximately 17% of all IS cases and is linked to a significant stroke recurrence rate of 4% to 5% per year.[9] Given that approximately 90% of ESUS patients receive antiplatelet drugs, alternative antithrombotic strategies are necessary to lower the incidence of recurrent strokes. It has been postulated that oral anticoagulation may mitigate stroke recurrence risk in ESUS patients, a hypothesis that has been evaluated in two large randomized controlled trials: NAVIGATE ESUS (rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent embolic stroke of undetermined source) and RE-SPECT ESUS (dabigatran etexilate for secondary stroke prevention in patients with embolic stroke of undetermined source).[9,10] Both trials demonstrated that oral anticoagulation was not associated with lower stroke recurrence rates compared to aspirin. This lack of benefit may be attributed to the seven main embolic sources that may be etiologically implicated in ESUS: atrial cardiopathy, occult AF, left ventricular disease, atherosclerotic plaques, patent foramen ovale (PFO), valvular heart disease, and cancer.[11] In certain embolic sources (such as atrial cardiopathy, left ventricular disease, PFO, and cancer), the primary pathophysiological stimulus for thrombogenesis is assumed to be low blood flow, predisposing to red thrombus formation, which may respond more effectively to anticoagulants. Conversely, in other embolic sources, such as aortic arch, cervical, or intracranial atherosclerosis, plaque ulceration promotes white thrombus formation, which may be more responsive to aspirin.[12] In these two trials, where all potential sources of embolism were pooled, anticoagulation reduced stroke recurrence in patients with red thrombus-related mechanisms but failed to prevent stroke recurrence in those with white thrombus-related etiologies. Therefore, these ESUS studies may have yielded neutral results. A secondary analysis of the COMPASS trial (a randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease)[13] revealed that low-dose rivaroxaban plus aspirin was associated with large, significant reductions in cardioembolic strokes and ESUS among patients with systemic atherosclerosis.[14] In this study, even low-dose anticoagulation combined with antiplatelet therapy reduced the incidence of ESUS, indicating that simultaneously targeting both red and white thrombus sources may represent a promising strategy for stroke prevention. Factor XI/XIa inhibitors are ideal candidates to test the hypothesis that a combination of oral anticoagulation and aspirin could lower the risk of stroke recurrence in patients with ESUS associated with aortic arch, cervical, or intracranial atherosclerosis. Oral factor XIa inhibitors have been shown not to increase bleeding risk when added to dual antiplatelet therapy in milvexian and asundexian phase 2 trials[15,16], and are currently being evaluated against placebo in the ongoing phase 3 trials-LIBREXIA-STROKE (NCT05702034) and OCEANIC-STROKE (NCT05686070)-for prevention of stroke recurrence in patients with acute IS or high-risk transient IS, in addition to single or dual antiplatelet therapy. We eagerly await the results of these trials.

FXI inhibitors currently under clinical investigation can be classified into three categories: antisense oligonucleotides, monoclonal antibodies, and small-molecule inhibitors. Ongoing phase 3 trials-including ANT-007 (ASTER, NCT05171049) and ANT-008 (MAGNOLIA, NCT05171075), which compare the monoclonal antibody abelacimab with apixaban and dalteparin, respectively, for preventing VTE recurrence in patients with cancer-associated VTE; ANT-010 (LILAC-TIMI 76, NCT05712200) and LIBREXIA-ACS (NCT05754957), evaluating the small-molecule milvexian versus placebo in secondary prevention of acute myocardial infarction as an adjunct to standard of care (single or dual antiplatelet therapy); and LIBREXIA-STROKE (NCT05702034), LIBREXIA-AF (NCT05757869), and OCEANIC-STROKE (NCT05686070)[4]-may potentially usher in a paradigm shift in the secondary prevention of ischemic stroke.

REFERENCES

1. GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* 2024;23:973-1003. [CrossRef]
2. Amarenco P, Lavallee PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med.* 2016;374:1533-1542. [CrossRef]
3. Kolmos M, Christoffersen L, Kruuse C. Recurrent ischemic stroke - a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* 2021;30:105935. [CrossRef]
4. Engelen MM, Edom CV, Verstraete A, Verhamme P, Vanassche T. The current landscape of factor XI inhibitors. *Thromb Update.* 2024;15:100171. [CrossRef]
5. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med*. 2000;160:41-46. [CrossRef]
6. Heitmeier S, Visser M, Tersteegen A, et al. Pharmacological profile of asundexian, a novel, orally bioavailable inhibitor of factor XIa. *J Thromb Haemost.* 2022;20:1400-1411. Erratum in: *J Thromb Haemost.* 2022;20:2448. [CrossRef]
7. Hsu C, Hutt E, Bloomfield DM, Gailani D, weitz jı. factor XI, inhibition to uncouple thrombosis from hemostasis: jacc review Topic of the Week. *J Am Coll Cardiol*. 2021;78:625-631. [CrossRef]
8. Coyle M, Lynch A, Higgins M, et al. Risk of İntracranial hemorrhage associated with direct oral anticoagulation vs antiplatelet therapy: a systematic review and meta-analysis. *JAMA Netw Open*. 2024;7:e2449017. [CrossRef]
9. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med.* 2018;378:2191-2201. [CrossRef]
10. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med.* 2019;380:1906-1917. [CrossRef]
11. Ntaios G. Embolic Stroke of Undetermined source: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75:333-340. [CrossRef]
12. Kamel H, Merkler AE, Iadecola C, Gupta A, Navi BB. Tailoring the approach to embolic stroke of undetermined source: a review. *JAMA Neurol.* 2019;76:855-861. [CrossRef]
13. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med.* 2017;377:1319-1330. [CrossRef]
14. Perera KS, Ng KKH, Nayar S, et al. Association between low-dose rivaroxaban with or without aspirin and ischemic stroke subtypes: a secondary analysis of the COMPASS trial. *JAMA Neurol.* 2020;77:43-48. [CrossRef]
15. Sharma M, Molina CA, Toyoda K, et al. Safety and efficacy of factor XIa inhibition with milvexian for secondary stroke prevention (AXIOMATIC-SSP): a phase 2, international, randomised, double-blind, placebo-controlled, dose-finding trial. *Lancet Neurol.* 2024;23:46-59. [CrossRef]
16. Rao SV, Kirsch B, Bhatt DL, et al. A Multicenter, Phase 2, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Finding Trial of the Oral Factor XIa İnhibitor asundexian to prevent adverse cardiovascular outcomes after acute myocardial infarction. *Circulation.* 2022;146:1196-1206. [CrossRef]