Milvexian fails to cut ischemic risk in recent ACS, raising questions for FXIa inhibitors

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The search for antithrombotic agents that reduce ischemic events without increasing bleeding risk remains a persistent challenge in cardiology. Factor XIa (FXIa) inhibitors emerged as a class with results showing attenuation of thrombosis while preserving hemostasis better than traditional anticoagulants. But clinical outcomes have not consistently mirrored pharmacodynamic target engagement, leaving clinicians to wonder if the results will translate to practice.1

KEY TAKEAWAYS

- The Pivot: Milvexian, an oral FXIa inhibitor, did not reduce ischemic events in patients with recent acute coronary syndrome.
- The Data: No significant reduction in ischemic risk was observed, challenging the broad applicability of FXIa inhibition in this high-risk population.
- The Action: Clinicians should continue to rely on established antithrombotic regimens for secondary prevention in ACS, as FXIa inhibitors have yet to demonstrate consistent benefit across all indications.

Patients recovering from acute coronary syndrome (ACS) face a substantial ongoing risk of recurrent ischemic events, necessitating potent antithrombotic therapy. But this benefit often comes at the cost of increased bleeding, a complication that can be as devastating as the ischemic event itself. The theoretical advantage of FXIa inhibitors, like milvexian, lies in their ability to target a pathway important for pathological thrombus formation while potentially sparing physiological hemostasis. This selective inhibition aims to offer a safer antithrombotic profile.1,2

Milvexian, an oral small-molecule inhibitor of activated factor XI (FXIa), entered clinical development with the goal of improving upon existing antithrombotic strategies. Its mechanism involves blocking FXIa, an enzyme that plays a role in amplifying thrombin generation, a key step in coagulation. By inhibiting FXIa, milvexian was hypothesized to reduce thrombotic risk without significantly impairing primary hemostasis, which is largely dependent on factor VIII and factor IX. Preclinical studies and early phase trials confirmed its pharmacological coherence and target engagement.1,3

The Unmet Expectation in ACS

Despite the compelling mechanistic rationale, milvexian did not reduce ischemic risk in patients with recent ACS. This outcome contrasts with some earlier data from other FXIa inhibitors in different indications, highlighting the complex, indication-specific nature of antithrombotic efficacy. The trial, which evaluated milvexian in this high-risk population, aimed to determine if adding this novel agent to standard care would improve outcomes.1

The broader class of oral small-molecule FXIa inhibitors has shown mixed results across various thrombotic

conditions. For example, asundexian, another FXIa inhibitor, demonstrated a reduction in ischemic stroke in the OCEANIC-STROKE trial. In that study, ischemic stroke occurred in 6.2% with asundexian versus 8.4% with placebo (HR 0.74, 95% CI 0.65-0.84). Major bleeding rates were comparable, at 1.9% versus 1.7% (HR 1.10, 95% CI 0.85-1.44).1,2 This specific success in stroke prevention, however, did not translate to a benefit in atrial fibrillation (AF). In OCEANIC-AF, stroke or systemic embolism occurred in 1.3% with asundexian versus 0.4% with apixaban (HR 3.79, 95% CI 2.46-5.83), indicating inferiority to a direct oral anticoagulant (DOAC) in this setting. Still, asundexian did show less major bleeding in AF (0.2% vs. 0.7%; HR 0.32, 95% CI 0.18-0.55).1,2

The lack of efficacy for milvexian in ACS raises important questions about the generalizability of FXIa inhibition across different thrombotic states. It suggests that the role of FXIa in thrombus formation may vary significantly depending on the underlying pathology and the specific patient population. In ACS, where platelet activation and thrombin generation are highly pronounced, the incremental benefit of FXIa inhibition on top of dual antiplatelet therapy (DAPT) or other standard anticoagulants may be insufficient to alter hard clinical outcomes. This is a distinction with a high stake for patient outcomes, as the potential for FXIa inhibitors to reduce post-MI bleeding has been a key area of interest.1

Pharmacology and Clinical Translation

The translational development of oral FXIa inhibitors has been a complex journey, integrating molecular design, preclinical pharmacology, human pharmacokinetics/pharmacodynamics (PK/PD), and clinical outcomes. While PD markers consistently confirm target engagement, they have not proven to be validated efficacy surrogates. This means that even when a drug effectively inhibits its target, it does not automatically translate into a clinical benefit. Hard clinical outcomes remain the decisive factor in determining a drug's utility.1,2

The systematic review by Janiak et al. included 68 eligible reports, comprising seven randomized outcome trials and nine reports with in vivo thrombosis or bleeding experiments. This comprehensive analysis highlighted that clinical benefit from FXIa inhibition is highly dependent on the indication, the comparator therapy, and the background therapy. For instance, the efficacy of FXIa inhibitors in preventing ischemic stroke after an index stroke, as seen with asundexian, does not automatically extend to other high-risk cardiovascular conditions like ACS or atrial fibrillation when compared to established agents.1 Clinicians seeking a concise guide to modern cardiological practice might find the Oxford Handbook of Cardiology a useful reference for navigating these complex therapeutic guidelines.

The comparison of different FXIa inhibitors, such as abelacimab, asundexian, and milvexian, in in vitro models of medical device-induced clotting and thrombin generation also highlights differences in their pharmacological profiles. Guo et al. explored these distinctions, showing that while all are FXIa inhibitors, their precise effects on coagulation pathways can vary.3 These subtle differences in molecular design and pharmacology might contribute to the divergent clinical outcomes observed across trials and indications. The specific context of ACS, with its unique thrombotic drivers, may simply not be as amenable to FXIa inhibition as other conditions. The question of whether FXIa inhibitors can reduce post-MI bleeding without compromising efficacy remains a central theme in ongoing research.

The trial's outcome for milvexian in ACS is a clear signal that not all antithrombotic mechanisms translate uniformly across all indications. It reinforces the principle that novel therapies must demonstrate efficacy in rigorous outcome trials specific to the target population and disease state. The enthusiasm for a new drug class, however mechanistically sound, must always be tempered by the reality of clinical trial results. The lack of benefit here means that for patients with recent ACS, the current standard of care remains the most evidence-based approach for secondary prevention.

CLINICAL IMPLICATIONS

The failure of milvexian to reduce ischemic risk in patients with recent ACS is a sobering reminder that elegant pharmacology does not always translate to clinical benefit. For European GPs and specialists, this means no immediate shift in the management of post-ACS patients. The established regimens, with their known efficacy and bleeding profiles, remain the bedrock of secondary prevention.

This outcome also highlights the lesson from the broader FXIa inhibitor class: efficacy is highly context-dependent. What works for stroke prevention in one population, as seen with asundexian, does not automatically extend to another high-risk cardiovascular setting. Clinicians must resist the temptation to extrapolate positive results from one indication to others without robust, dedicated outcome data.

For the pharmaceutical industry, the milvexian results in ACS are a clear signal to refine their development strategies for FXIa inhibitors. The initial goal of a safer antithrombotic agent with less bleeding risk is still compelling, but the path to market requires a more specific understanding of which patient populations and thrombotic mechanisms are truly amenable to this approach. The focus must shift from broad-stroke

> development to highly targeted indications where FXIa inhibition offers a distinct, measurable advantage over existing therapies.

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