Can We Set a New Standard of Care for Secondary Stroke Prevention?

Evaluating Current Gaps and Future Goals

Key Clinical Summaries From PeerVoice Talks on Stroke

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In this video IME activity, expert Mike Sharma, MD, MSc, FRCPC explores unmet needs and future directions in secondary stroke prevention. Watch at the URL below, or you may review the key clinical summaries of the most salient science presented as part of the activity.

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Access an expert talk and personal story in the online activity at the URL below:

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Learning Objectives

- Identify ongoing unmet needs in secondary stroke prevention, based on the efficacy and safety of currently available antithrombotic strategies
- Explain the rationale and potential role for inhibitors of factor XI and factor XIa in secondary stroke prevention
- Evaluate existing data and the design of ongoing clinical trials for factor XIa inhibitors in secondary stroke prevention

Content developed in concert with the faculty.

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Secondary Stroke Prevention Today: Key Challenges and Gaps

Burden of Stroke: A Growing Global Challenge[1,2]

- Stroke is a major global health issue, with approximately 12 million cases annually.
- The incidence is expected to double within 20 years, significantly increasing societal and economic burdens.
- The financial cost of stroke in 2021 was nearly $1 trillion and this is projected to double by 2050.
- Beyond the economic impact, stroke leads to profound disability and loss of independence.
- Survivors of a stroke or a transient ischaemic attack (TIA) have a much higher risk of experiencing another stroke.

Secondary Stroke Prevention Strategies[3-5]

- When treating a patient who has experienced a stroke, several factors need to be considered and a holistic approach to care should be adopted.
- Antihypertensive therapy should be initiated 48 hours post-stroke (unless blood pressure is critically high) and is typically administered in the evening for gradual lowering.
- For patients with a mild noncardioembolic stroke, the standard of care for preventing a stroke recurrence is antithrombotic therapy: Dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel/ticagrelor for 21 days, followed by long-term aspirin monotherapy. This is based on the results of several key clinical trials:
  - CHANCE and POINT: These studies support short-term DAPT for early stroke prevention. However, approximately 5% to 8% of patients experienced a recurrent stroke.
  - THALES: This study showed that ticagrelor offered potential advantages but similar outcomes to clopidogrel, with incidence of recurrent stroke in 5% of patients.
  - INSPIRES: This study indicated that DAPT can be started up to 72 hours post-stroke in atherosclerotic patients.

Lifestyle Modifications for Stroke Prevention[3]

- Smoking cessation: Smoking doubles the risk of recurrent stroke.
- Exercise: 30 min/day of moderate intensity exercise is recommended. Physically demanding jobs do not replace structured aerobic activity.
- Diet: Encourage 5–10 servings of fruits and vegetables daily. Patients benefit from structured dietary and lifestyle changes to regain control over health.

Challenges in Long-Term Stroke Prevention[6,7]

- Despite best efforts, residual stroke risk remains even with treatment adherence.
- Additional challenges are medication adherence and the difficulty some patients have in implementing and/or sustaining lifestyle changes.
- Recurrent stroke is devastating as risk of disability quadruples with a second event.
- Cognitive decline affects 50% of stroke/TIA survivors, impacting memory, executive function, and emotional well-being.

Unmet Needs in Stroke Prevention[7]

- Aspirin monotherapy has remained unchanged for the last 50 years, with only modest efficacy.
- New and more effective long-term antithrombotic strategies are urgently needed.

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Beyond Standard Care: Optimising Stroke Prevention With New Therapies

Unmet Needs in Stroke Prevention[1]

- Despite standard antiplatelet therapy, many patients experience recurrent stroke resulting in devastating disability.
- New strategies aim to improve stroke prevention beyond aspirin while minimising bleeding risk.

The COMPASS Trial[2]

- The COMPASS trial included over 27,300 patients and compared the factor Xa inhibitor rivaroxaban alone vs aspirin alone vs low-dose rivaroxaban plus aspirin in combination.
- The combination of antiplatelet therapy with a factor Xa inhibitor was potentially a more effective antithrombotic strategy for the prevention of major vascular events in patients with atherosclerosis.
- The results showed that combination therapy reduced stroke risk by almost 50%. Although there was no increase in intracerebral haemorrhage, higher gastrointestinal bleeding risk did limit widespread adoption.

Targeting Factor XI: A Novel Strategy for Stroke Prevention[3-6]

- In the coagulation cascade, factor XI plays a role in thrombosis but is not essential for haemostasis.
- Reducing factor XI activity may prevent pathological clotting without increasing bleeding risk.
- Genetic studies have shown that factor XI deficiency reduces ischaemic stroke risk without increasing intracerebral haemorrhage.
- Higher factor XI levels correlate with increased stroke risk, reinforcing the therapeutic potential.

PACIFIC-Stroke Trial: Asundexian (10 mg, 20 mg, 50 mg) Plus Aspirin vs Placebo[7]

- This was a prospective, randomised, double-blind, placebo-controlled, phase 2, dose-ranging study.
- It included patients with ischaemic stroke within 48 hours.
- The primary efficacy endpoint was the combined incidence of MRI infarcts and clinical stroke, which showed no difference between treatment and control groups. However, the ischaemic stroke risk was reduced at the asundexian 50 mg dose.
- The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding. No significant increase in major bleeding was observed.

AXIOMATIC-SSP Trial: Milvexian (25 mg QD, 25 mg BID, 50 mg BID, 100 mg BID; 200 mg BID) Plus Aspirin vs Placebo[8]

- Similar to PACIFIC-Stroke, this was also a prospective, randomised, double-blind, placebo-controlled, phase 2, dose-ranging study.
- It included patients with ischaemic stroke or high-risk TIA within 48 hours and atherosclerosis.
- The primary efficacy endpoint and findings were similar to that of the PACIFIC-Stroke study.
- A reduction in ischaemic stroke at most doses of milvexian was observed (with the exception of the 100 mg dose), with no clear dose-dependent increase in bleeding (a secondary endpoint).
- Similar to PACIFIC-Stroke, there was no effect on MRI-defined infarcts.

Ongoing Phase 3 Trials With Factor XIa Inhibitors for Prevention of Noncardioembolic Secondary Stroke[9,10]

- Both PACIFIC-Stroke and AXIOMATIC-SSP suggested clinical stroke reduction without significant bleeding, justifying further research.
- OCEANIC-Stroke (NCT05686070): Asundexian 50 mg QD plus antiplatelet therapy.
- LIBREXIA-STROKE (NCT05702034): Milvexian 25 mg BID plus antiplatelet therapy.

Future Outlook in Noncardioembolic Stroke Prevention[1]

- Factor XI inhibitors present a promising alternative for noncardioembolic stroke prevention.
- Unlike traditional antithrombotics, they may provide stroke risk reduction without excess bleeding.
- Results from large phase 3 trials will determine if this approach redefines secondary prevention of noncardioembolic stroke.

Reference(s):

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