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Preventing Recurrent Stroke in 2025: Clinical and Managed Care Perspectives

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The Future of Stroke Care: Exploring Unmet Needs in Secondary Prevention

Introduction

Stroke is the third most common cause of death and disability in the world.¹ Despite recommendations for antithrombotic therapy, stroke recurrence rates remain high.²⁻⁶ Missing from the management of a prevalent type of stroke called noncardioembolic ischemic stroke is a therapy that significantly lowers recurrent stroke and maintains a low risk of bleeding.²⁻⁷ Investigational factor XI (FXI) inhibitors may fill this gap by preventing thrombosis and sustaining bleeding risks that are lower than those of currently approved anticoagulants.^{8,9}

This article describes the clinical and economic impact of ischemic stroke, including the particular burden of recurrent stroke. Thereafter, it reviews the treatment landscape for recurrent stroke, including management guidelines, unmet needs, and data surrounding asundexian and milvexian, 2 FXI inhibitors under investigation in phase 3 trials.^{10,11} The article concludes with managed care considerations surrounding this costly neurological deficit.

Clinical Impact of Ischemic Stroke

Globally, approximately 1 in 4 people will experience a stroke in their lifetime.¹² In the United States, stroke is the fifth leading cause of death⁷ and a major cause of disability,¹ with as many as 76% of US stroke patients reporting a disablement.¹³ The prevalence of self-reported stroke in the US, standardized for age, has increased by 7.8% (95% CI, 4.9%-10.8%) from 2011-2013 to 2020-2022.¹⁴

Clinical Impact by Stroke Type

Stroke can be classified into hemorrhagic stroke, transient ischemic attack (TIA), and ischemic stroke. Hemorrhagic stroke includes intracerebral and subarachnoid hemorrhage, which make up 10% and 3% of strokes, respectively.⁷ A TIA is a brief episode of neurological dysfunction as a result of ischemia to the brain, spinal cord, or retina in which there is no infarct.¹⁵ Annually in the US, approximately 240,000 individuals experience a TIA.¹⁶

Ischemic strokes account for 87% of all strokes and contribute to substantial burden in the US that has grown recently.^{7,14} They are infarcts of the brain, spinal cord, or retina as a result of ischemia that result in neurological dysfunction.¹⁷ Each year in the US, 795,000 individuals experience ischemic stroke, and approximately 23% of these are recurrent.⁷ In 2022 in the US, 39.5 deaths per 100,000 people were due to ischemic stroke.¹⁸

Commonly, ischemic stroke is classified into cardioembolic, large artery atherosclerosis, small-vessel occlusion, stroke of other determined etiology, and embolic stroke of undetermined source (ESUS) subtypes.^{2,19} Whereas cardioembolic stroke occurs from an embolism originating in the heart, a noncardioembolic stroke may be embolic or thrombotic in nature.¹⁹ Noncardioembolic strokes account for 73% of ischemic strokes.²

Additional Impact of Recurrent Stroke

Recurrent strokes are associated with worse clinical outcomes and are costlier than index events.²⁰

Clinical Impact

Guideline recommendations seek to prevent recurrence of ischemic stroke. However, recurrence rates have remained elevated.²⁻⁶ Approximately 4.6% to 11.4% of patients who have had an ischemic stroke will have a recurrent stroke within 90 days.³⁻⁶ Approximately 16.8% of those who have had a TIA or minor ischemic stroke will have a recurrent event within 5 years.²¹

Mortality rates for recurrent stroke are also higher than those for index stroke.²⁰ In a 1991 sample of Medicare patients, 2-year survival rates for patients aged 65 to 69 years were lower after recurrent stroke vs after index stroke among men (51.1% vs 66.5%; $P < .001$) and women (53.5% vs 68.0%; $P < .001$).²² In a study of US managed care patients hospitalized for noncardioembolic ischemic stroke, the all-cause mortality rate was higher for 2180 patients after recurrent stroke than it was for 1808 patients after new stroke (86 vs 37 deaths/1000 patient-years).²⁰ Moreover, disability is a common sequela of stroke, and recurrent stroke is a predictor of increased disability.²³

Economic Impact

Stroke is a costly disease that results in hospitalizations associated with recurrent stroke and complications from the index stroke.^{24,25} Total economic costs of stroke are estimated to have been \$56.2 billion in the US in 2019-2020. Direct medical costs accounted for \$34.5 billion and are projected to rise to \$94.3 billion by 2035.⁷ Moreover, 13.8% of individuals discharged from certified primary stroke centers who survive an ischemic stroke are likely to experience a hospital readmission within 30 days.²⁴ Within the first year after an index stroke, some 40% (1052 of 2603) of Medicare patients discharged from Connecticut acute care hospitals in 1995 had at least 1 hospital readmission.²⁵ The indirect costs of caregiving after a stroke are also substantial. Patients with stroke-related health problems (SRHP) in 1993 had higher additional yearly costs due to caregiving that, adjusted for inflation, would total \$10,155 in 2024; those without SRHP would have expenditures totaling \$2108.²⁶

Although more recent studies are needed,²⁷ recurrent stroke has been shown to cost patients and the health care system 38% more than nonrecurrent stroke.²⁰ Average (SD) costs of primary and recurrent stroke in a managed care population including hospitalization, medical, and pharmacy costs in 2005 were \$40,670 (\$81,588) and \$51,760 (\$130,279), respectively.²⁰ Adjusting for inflation from January 2005 to August 2024, these costs were \$67,136 (\$134,681) for index vs \$85,442 (\$215,057) for recurrent stroke.^{20,28}

Risk Factors

Modifiable risk factors, most of which are behavioral and metabolic, are responsible for 90.5% of the global stroke

burden.²⁹ Those for recurrent stroke include diabetes, hypertension, hyperlipidemia, and smoking cessation.²

Nonmodifiable risk factors for recurrent stroke include a history of more than 1 stroke or TIA and male sex. In an analysis of data from 5390 participants who had had an ischemic stroke with ESUS within the previous 3 months, these factors, as well as renal impairment (creatinine clearance < 50 mL/min) and elevated CHA₂DS₂VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65-74 years, sex category) increased recurrent stroke risk after a median follow-up of 19 months (IQR, 13-27 months).³⁰

Recurrent stroke risk may vary based on risk factor management rather than on race. Robinson and colleagues studied 3816 patients who had an ischemic stroke and found after adjusting for age and sex that stroke recurrence rates were 34% higher in the Black population (95% CI, 10%-64%, $P = .003$). However, after adjusting for risk factors, Black race was not significantly associated with recurrent stroke (HR, 1.11; 95% CI, 0.90-1.36; $P = .32$).³¹

Prior TIA may confer greater risk of stroke than prior stroke. In the Framingham Heart Study, a longitudinal population-based cohort study spanning 3 generations and including more than 14,000 participants, stroke was 4.81 times (95% CI, 3.82-6.06; $P < .001$) more likely to occur in individuals who had had a TIA ($n/N = 130/435$) than in those who had had a prior stroke ($n/N = 165/2175$).³²

Sex and age (up to 90 years) constitute nonmodifiable factors influencing stroke mortality. In 2015, the percentage of deaths in the US from cerebrovascular disease (including hemorrhagic and ischemic stroke) was higher for women than for men across all age groups 20 years and older.³³ National Center for Health Statistics data from 2018 also demonstrate increased mortality in women 65 years and older compared with men, with the largest difference in those 85 years and older. These data also show that, as age increases each decade over 65 years, the rate of mortality more than doubles.³⁴

Treatment Landscape for Recurrent Stroke

The treatment landscape for recurrent stroke has focused on risk factor management and antithrombotic therapy with a concentration largely on antiplatelet therapy.

Guideline Recommendations

In 2021, the American Heart Association and American Stroke Association issued treatment guidelines for the prevention of stroke in patients who have already had a stroke or TIA.² These guidelines focus largely on management of vascular risk factors and on antithrombotic therapy. Based on existing literature, the guidelines recommend that treatment for prevention of stroke after an ischemic stroke be similar to treatment after TIA.²

Management of vascular risk factors including nutrition, physical activity, smoking cessation, substance use, hypertension, lipids, diabetes, obesity, and obstructive sleep apnea is critical to the prevention of recurrent stroke.² A summary of level 1 guideline recommendations for risk factor management can be found in the **Figure**.² Mitigation of vascular disease risk factors may involve many lifestyle changes at once. Thus, recommendations for behavioral changes include programs to help encourage behavioral change with proven techniques and an interdisciplinary team.²

Guideline-Recommended Antiplatelet Therapy

After ischemic stroke or TIA, antithrombotic therapy is recommended for all patients who do not have contraindications.² Patients with a recent, mild, noncardioembolic ischemic stroke (National Institutes of Health Stroke Scale score ≥ 3) or high-risk TIA (ABCD² score ≥ 4) should be started on dual antiplatelet therapy (DAPT) with aspirin and clopidogrel ideally within 12 to 24 hours of symptom onset and continued for at least 21 days and up to 90 days (**Table**).² After 90 days, single antiplatelet therapy (SAPT) is recommended, as it is for patients with non-high-risk TIA, noncardioembolic stroke after 24 hours from symptom onset, or moderate to severe noncardioembolic stroke.²

Alternative antiplatelet agents including ticagrelor, cilostazol, and dipyridamole are discussed in specific scenarios throughout the guidelines.² Ticagrelor is not recommended for use after ESUS but may be considered for patients with ipsilateral greater than 30% stenosis of a major intracranial artery in addition to aspirin as an alternative to clopidogrel. The choice to use clopidogrel or ticagrelor as part of DAPT is contingent on bleed risk, patient factors including medication adherence, and cost.² The role of cilostazol is unclear for small vessel disease; however, it may be used in addition to aspirin or clopidogrel in patients with stroke or TIA secondary to 50% to 99% stenosis of a major intracranial artery.² Extended-release dipyridamole is recommended generally for use in combination with aspirin as secondary prevention of ischemic stroke.²

For many ischemic stroke subtypes, specific management recommendations exist.² It is important to note that some of these subtypes have lower incidence and have not yet been studied as comprehensively as others, thus recommendations for antithrombotic management are not as clear.² When using antiplatelet therapy such as SAPT or DAPT, the risk of bleeding vs proven efficacy must be balanced.²

Unmet Needs

Despite recommendations for antithrombotic therapy, stroke recurrence rates after noncardioembolic stroke

remain high. For 73% of ischemic strokes (noncardioembolic), therapy recommendations are SAPT or DAPT.² Direct oral anticoagulants (DOACs) are used for cardioembolic stroke where there is the assumption that the stroke was caused by atrial fibrillation.² However, DOACs are FDA approved to reduce the risk of stroke and systemic embolism in adults with nonvalvular atrial fibrillation (AF), not in patients with ischemic stroke without AF.³⁵⁻³⁷ DOAC use has been studied in patients with ESUS and is not recommended based on findings of increased bleeding.^{2,38,39} For instance, Hart et al found that, among 7212 patients with ESUS, those treated with rivaroxaban were 2.72 times more likely to experience major bleeding than those treated with aspirin (95% CI, 1.68-4.39; $P < .001$).³⁸ Similarly, Diener et al found the annualized rate of major bleeding in patients with ESUS was 1.7 among 2695 patients treated with dabigatran vs 1.4 in the same number of patients treated with aspirin (HR, 1.19; 95% CI, 0.85-1.55).³⁹ Patients treated with rivaroxaban and dabigatran were 51% (95% CI, 13%-100%; $P = .004$) and 73% (95% CI, 17%-154%) more likely to experience clinically relevant nonmajor bleeding than patients treated with aspirin, respectively.^{38,39} A therapy for noncardioembolic ischemic stroke that significantly lowers recurrent stroke and maintains a low risk of bleeding constitutes an unmet need.

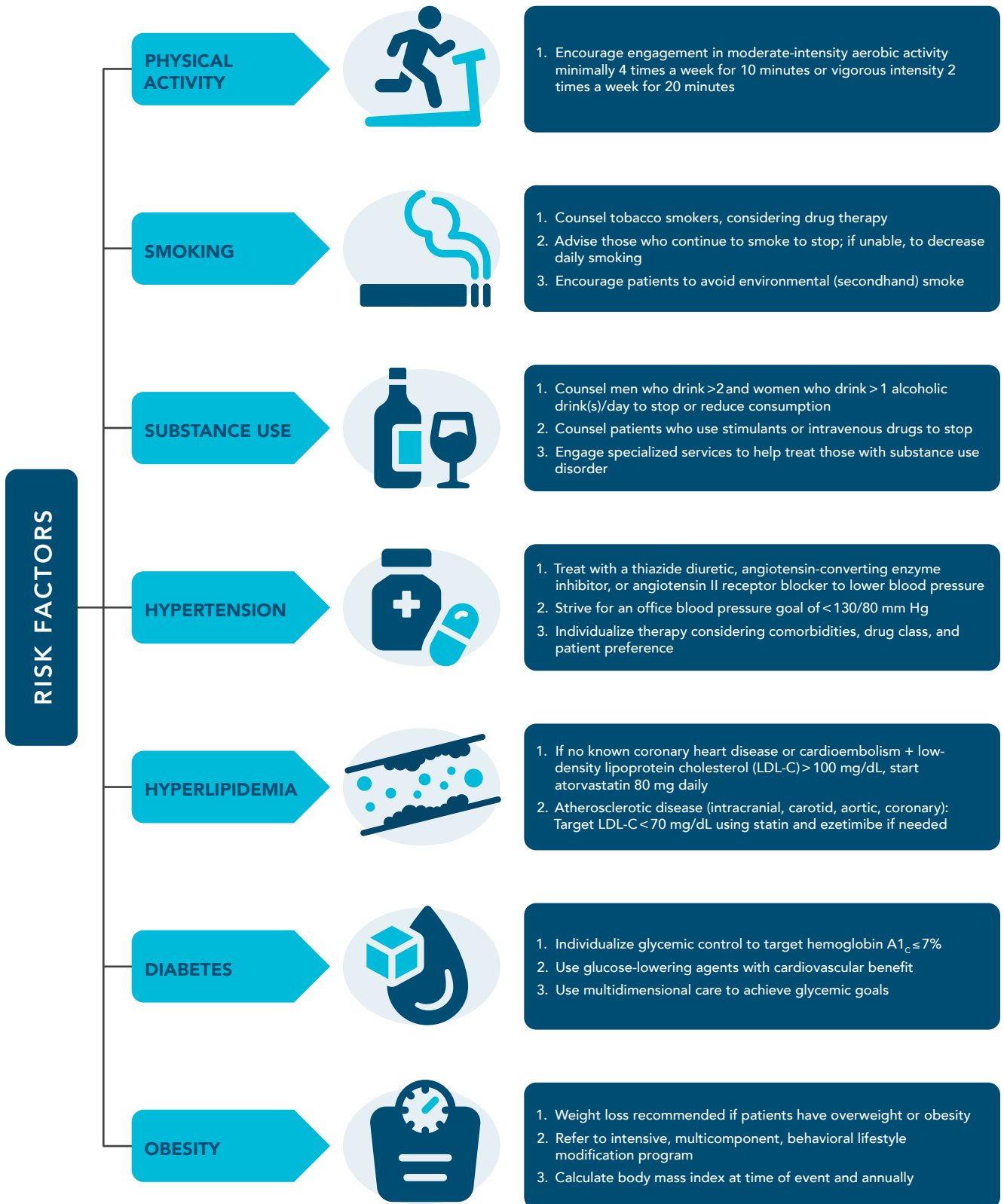
Agents Under Investigation: Factor XI Inhibitors

Medications currently under investigation for recurrent stroke prevention include FXI inhibitors thought to prevent thrombus and to have a lower risk of bleeding compared with historically approved anticoagulants.^{8,9} The possibility of FXI inhibition as a therapeutic target arose from observational data demonstrating that individuals with FXI deficiency did not have statistically significant increased rates of spontaneous bleeding and may have decreased rates of ischemic stroke.^{40,41} However, high FXI levels may promote venous thrombosis.⁴² Thus, the mechanism for FXI inhibitors is thought to occur via contact activation of the coagulation cascade in which inhibition of FXI may minimally impair hemostasis while preventing thrombus.⁸ FXI inhibitors under investigation include asundexian and milvexian.^{10,43}

Asundexian

In the PACIFIC-Stroke phase 2 dose-finding trial (NCT04304508), 1808 participants with noncardioembolic ischemic stroke were randomly assigned to receive asundexian 10 mg, 20 mg, or 50 mg, or placebo with antiplatelet therapy and were followed for 26 to 52 weeks.⁴⁴ The primary outcome evaluated was covert infarct and recurrent symptomatic ischemic stroke up to 26 weeks, whereas the safety outcome of interest was major or clinically relevant nonmajor bleeding as defined by the

FIGURE. Summary of Level 1 Treatment Recommendations for Recurrent Stroke Risk Factor Management²



Icons-Studio - stock.adobe.com (treadmill, cigarette, alcohol, pills, blood sugar, scale icons); IconArt - stock.adobe.com (hyperlipidemia).

TABLE. Guideline-Recommended Antiplatelet Therapy for Noncardioembolic Stroke or TIA^{2,a}

	IS ^b			TIA ^c	
	Early IS		No early IS	High risk	No high risk
	NIHSS ≤ 3	NIHSS > 3			
Treatment for 0-90 days	DAPT ^d	SAPT	SAPT	DAPT ^d	SAPT
Treatment for > 90 Days	SAPT	SAPT	SAPT	SAPT	SAPT

DAPT, dual antiplatelet therapy; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale score; SAPT, single antiplatelet therapy; TIA, transient ischemic attack.

^aThese recommendations do not apply to patients receiving acute thrombolysis.

^bEarly IS is defined as less than 24 hours after symptom onset.

^cHigh-risk TIA is defined as an ACBD² score of at least 4.

^dDAPT is defined as aspirin plus clopidogrel.

International Society on Thrombosis and Haemostasis (ISTH) criteria.⁴⁴ Notably, there was no difference detected between the placebo group and asundexian group regarding reduction of the primary outcome.⁴⁴ Major or clinically relevant nonmajor bleeding occurred with no significant increase in those receiving asundexian vs placebo (HR, 1.57; 90% CI, 0.91-2.71).⁴⁴ Post hoc analysis demonstrated a numerical reduction in symptomatic ischemic stroke or TIA with asundexian 50 mg.⁴⁴

OCEANIC-STROKE (NCT05686070) is a phase 3 trial with estimated study completion of October 10, 2025, and a target enrollment of 12,300 participants.¹⁰ The trial is evaluating the efficacy and safety of asundexian dosed once daily vs placebo in addition to an antiplatelet for 3 to 31 months in patients aged at least 18 years who have had a recent noncardioembolic stroke, or TIA with systemic or cerebrovascular atherosclerosis or acute nonlacunar infarct.¹⁰ Primary outcomes that will be assessed include time to first occurrence of ischemic stroke and time to first occurrence of major ISTH bleed.¹⁰

Milvexian

AXIOMATIC-SSP (NCT03766581) was a phase 2 dose-finding trial in which 2366 participants 40 years or older with ischemic stroke or high-risk TIA were randomly assigned to receive milvexian 25 mg daily, 25 mg twice daily, 50 mg twice daily, 100 mg twice daily, 200 mg twice daily, or placebo. All patients received clopidogrel 75 mg daily for the first 21 days and aspirin 100 mg daily for the first 90 days.¹¹ The primary outcome evaluated was composite symptomatic ischemic stroke in the 90 days after randomization or new covert brain infarction; the safety outcome was major bleeding classified as type 3 and type 5 bleeding per the modified Bleeding Academic Research Consortium classification.¹¹ In terms of the primary outcome, a significant dose response was not

found.¹¹ However, there was a decreased number of symptomatic ischemic strokes in patients receiving all milvexian doses except for 200 mg twice daily compared with placebo.¹¹ Major bleeding rates did not vary among the different milvexian doses and there was not a substantial difference in number of bleeds in milvexian groups vs placebo.¹¹

LIBREXIA-STROKE (NCT05702034) is an ongoing phase 3 trial with estimated study completion of December 9, 2026, targeting an enrollment of 15,000 participants.⁴³ The LIBREXIA-STROKE trial is evaluating the efficacy and safety of milvexian dosed at 25 mg twice daily vs placebo in addition to SAPT or DAPT for up to 41 months in participants aged at least 40 years who have had an ischemic stroke or TIA.⁴³ The primary outcome that will be assessed includes time to first occurrence of ischemic stroke.⁴³

Managed Care and Access Considerations for Secondary Stroke Prevention

The direct and indirect expenses affiliated with primary and secondary stroke management are substantial.^{7,20,26} Despite progress, rates of initial and recurrent stroke remain elevated. Improved preventive care of initial and recurrent stroke may decrease patient and health care system expenditures. An analysis of investing in larger scale interventions to dissuade tobacco use, decrease sodium intake, and improve treatment of blood pressure, cholesterol, and stroke found a 10.9 benefit-to-cost ratio and predicted prevention of 13 million strokes within 15 years.⁴⁵

Stroke systems of care advocate for community education, primordial prevention, and primary prevention prior to a stroke.⁴⁶ Increasing community education and public awareness of stroke risk factors, providing tools to manage risk factors, and addressing health literacy and cultural context may be beneficial.⁴⁶ Primordial prevention programs as part of the stroke system of care

in geographical areas with higher recurrent stroke can be used to improve access to resources for successful lifestyle modification, better primary care, and social conditions.^{46,47} As part of primary and secondary prevention, health care professionals can encourage lifestyle modifications by using theoretical models of behavior change and leveraging members of the multidisciplinary team.²

As new medications are studied, ensuring access to those that are efficacious and cost-effective will be of the utmost importance.

Conclusions

Ischemic stroke is prevalent in the US and carries a high risk of mortality, morbidity, and recurrence; it is associated with long-term disability and economic cost. Recurrent strokes are associated with worse clinical outcomes and pose greater financial burdens for patients, caregivers, and health care organizations compared with index stroke. Although current treatment guidelines focus on managing or preventing vascular disease risk factors and optimizing antiplatelet therapy for noncardioembolic stroke, the risk of recurrent stroke remains. FXI inhibitors are a novel therapeutic option to both promote hemostasis and prevent thrombosis. Asundexian and milvexian are 2 agents undergoing clinical trials that may help prevent ischemic stroke and may pose decreased risk of bleeding. There is room to improve the risk of recurrent strokes through increased community awareness, primordial prevention, primary prevention of risk factors, access to resources, adherence to medications, and development of additional medication therapies. ♦

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Clinical Insights Into Recurrent Stroke

A Q&A With Andrew Russman, DO



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AJMC®: In your experience, what are the most significant long-term clinical effects of a recurrent stroke?

RUSSMAN: Recurrent strokes tend to have more severe long-term clinical effects than initial strokes and impact physical, cognitive, and emotional health. Physically, they often lead to increased disability that requires more intensive rehabilitation as brain damage compounds. This can worsen mobility and functional independence, while cognitive decline—including vascular dementia—becomes more likely. Emotional health can also decline; recurrent strokes often exacerbate depression and anxiety. Unfortunately, mental-health care often is neglected in favor of physical rehabilitation, although both are crucial for comprehensive recovery. Additionally, recurrent strokes can lead to complications such as obstructive sleep apnea, swallowing dysfunction, and reduced social engagement, all of which further diminish quality of life.

AJMC: How do the challenges of preventing recurrent stroke shape your clinical approach?

RUSSMAN: Prevention presents several challenges. The management of risk factors drives prophylaxis. While factors like age and genetics cannot be changed, key risks such as hypertension, high cholesterol, diabetes, smoking, and atrial fibrillation (AF) are critical targets for intervention. Hypertension is the most important modifiable factor due to its prevalence and the significant risk reduction achieved through control. Managing diabetes, cholesterol, and AF can substantially lower the likelihood of a recurrent stroke as well.

Two major challenges in preventing recurrent stroke are treatment adherence and cost management. Newer therapies such as PCSK9 inhibitors for hyperlipidemia and diabetes medications like semaglutide reduce stroke risk, but they often have high costs and complex insurance preauthorization processes. To shape our clinical approach, we balance the best evidence-based treatments with affordability.

Balancing stroke prevention and the risk of bleeding presents another challenge as we select antithrombotic therapies, whether antiplatelet agents or anticoagulants. For this, tailoring treatment to each patient is essential.

AJMC: How do the American Heart Association/American Stroke Association (AHA/ASA) guidelines¹ influence your treatment strategies?

RUSSMAN: The AHA/ASA guidelines provide a strong foundation for secondary stroke prevention, particularly in addressing noncardioembolic strokes. They are heavily evidence based and offer clear recommendations for managing risk factors like hypertension, hyperlipidemia, diabetes, smoking, and AF. For noncardioembolic strokes, especially those caused by large artery atherosclerosis, the guidelines support revascularization procedures such as carotid artery stenting or endarterectomy for patients with severe symptomatic carotid stenosis. However, there are gaps in evidence for other conditions like vertebral artery stenosis for which clear treatment protocols are still lacking. In areas

where evidence is limited, treatment decisions often rely on clinical judgment.

Regarding antiplatelet therapy for secondary prevention, short-term dual antiplatelet therapy (DAPT) has been shown to benefit most patients with noncardioembolic stroke. The current evidence suggests that a 21- to 30-day course of DAPT (typically aspirin and clopidogrel or ticagrelor) strikes a balance between reducing ischemic stroke risk and minimizing bleeding complications. Beyond this period, continuing DAPT offers little additional benefit, with single-agent aspirin being sufficient for most patients.

While the guidelines provide a robust framework for secondary stroke prevention, real-world practice often involves balancing evidence-based treatments with individual patient needs, especially in areas where evidence is scarce.

I'm particularly excited about the development of new antithrombotic therapies such as factor XI inhibitors and the growing emphasis on understanding optimal treatment intervals and agents for individual patients.

AJMC: In the current treatment landscape, what are the most pressing unmet needs in preventing recurrent strokes?

RUSSMAN: One of the most pressing needs is understanding underlying stroke etiology. Without a clear understanding of the cause, we often apply a generic approach to risk reduction, which may not be most effective for all patients. For instance, patients with small-vessel disease may benefit more from aggressive risk factor modification than from other therapies like dual antiplatelet treatment.

Another critical need is better access to advanced diagnostic tools, particularly for identifying AF in patients with recurrent strokes of unknown cause. Cardiac rhythm monitoring, including the use of implantable loop recorders, has shown that up to 30% of these patients may have undiagnosed AF after 3 years of monitoring. However, there are challenges in securing payer support for these tools despite their proven value in guiding the most effective anticoagulant therapy.

There's also a need for more efficient screening tools such as patch-based monitors to identify AF and other conditions early. This early identification allows clinicians to apply guideline-driven therapies that significantly reduce stroke risk.

Finally, addressing social determinants of health is crucial. Many patients face barriers to accessing advanced therapies due to cost, which can affect their ability to manage risk factors and recover fully after a stroke. The affordability and support for newer, more effective therapies remain significant gaps in stroke prevention efforts.

AJMC: What future research or developments in stroke prevention are you most excited about, and how do you anticipate that they will impact clinical practice?

RUSSMAN: I'm particularly excited about the development of new antithrombotic therapies such as factor XI inhibitors and the growing emphasis on understanding optimal treatment intervals and agents for individual patients. A one-size-fits-all approach to stroke prevention is inadequate, especially when we know that stroke recurrence risk is highest in the first 90 days after an initial event. This calls for more tailored treatment strategies based on each patient's specific etiology and risk profile over time.

Precision medicine is the future of stroke prevention. By applying the right antithrombotic therapy to the right patient for the right duration, we can reduce the risk of stroke recurrence while minimizing adverse effects like increased bleeding. Rather than using a generic approach, precision medicine considers individual factors—like genetic predispositions that affect a patient's response to certain medications such as anticoagulants and antiplatelet agents. This could be further enhanced by artificial intelligence (AI) models, which can help clinicians analyze vast amounts of data to make more precise treatment decisions.

Beyond antithrombotic therapy, there's potential for innovation in other areas like optimal blood pressure and lipid management. For example, combining statins with PCSK9 inhibitors or using antihyperglycemic agents that reduce stroke and heart attack risk can be personalized to each patient's needs. Coupling these medical advancements with effective strategies for smoking cessation and addressing social determinants of health will further enhance stroke prevention.

AJMC: You mentioned factor XI inhibitors. What potential do you see for these agents in the treatment landscape, and how might they change current practices?

RUSSMAN: Current antithrombotic therapies, such as direct oral anticoagulants like apixaban, are quite effective; they balance ischemic risk reduction with a lower risk of

bleeding complications. Apixaban has become a market leader due to its efficacy and safety profile, especially for conditions like AF. Any new therapy, including emerging factor XI inhibitors, will need to demonstrate a comparable or superior balance of efficacy and safety to challenge apixaban and other established treatments. The bar is high, and it remains unclear whether factor XI inhibitors will outperform apixaban in AF.

That said, factor XI inhibitors show significant promise in other areas, particularly noncardioembolic stroke. If they prove to be both effective in reducing stroke risk and safer with lower bleeding risks, they could reshape stroke prevention strategies. However, the key will be identifying which patients will benefit most and for how long. This aligns with the growing shift toward precision medicine.

While there's enthusiasm for these new therapies, cost and affordability will also play a significant role in their adoption. To fully integrate factor XI inhibitors or other novel treatments into clinical practice, we'll need robust clinical trial data demonstrating long-term benefits and safety. Additionally, emerging tools like AI could enhance our ability to tailor therapies to individual patients.

AJMC: How do you involve patients in the decision-making process regarding stroke prevention therapy, particularly when discussing treatment risks and benefits?

RUSSMAN: Involving patients starts with a thorough understanding of their stroke's etiology. As clinicians, we need to investigate and explain the diagnostic approach, which includes MRI, vessel imaging, laboratory tests, and cardiac monitoring. Effective stroke prevention relies on understanding the underlying cause, which can lead to more targeted and effective treatment.

For patients with recurrent strokes and unknown etiology, we need to discuss the benefits and risks of further investigation. For example, if AF is suspected, we might recommend a surface monitor or an implantable loop recorder. It's essential to clearly communicate that while these investigations have minimal risks, they can significantly impact treatment outcomes. Identifying AF and initiating anticoagulant therapy can drastically reduce the risk of subsequent strokes from around 7% to 10% annually to 1.5% to 2%.

Engaging patients involves addressing their specific concerns and explaining how tailored treatments can alleviate their worries. For instance, if patients are hesitant about medication adherence, exploring their underlying concerns—such as affordability, adverse effects, or lifestyle impacts—can help in addressing those issues effectively. Discussing the importance of self-care in

the context of caregiving responsibilities can also be a powerful motivator.

Addressing social determinants of health is also crucial. This includes helping patients navigate issues like transportation, medication affordability, and access to support services. Ensuring that patients are aware of financial assistance programs or insurance adjustments can improve adherence and overall outcomes.

AJMC: What key takeaways or advice would you offer to health care professionals and managed care organizations focused on optimizing secondary stroke prevention?

RUSSMAN: I'd offer 5 key takeaways. First, health care professionals should prioritize understanding and applying clinical practice guidelines. It's not just about using the latest medications—it also involves effectively using proven strategies to reduce stroke risk.

Second, smoking cessation is a critical component of secondary stroke prevention. It significantly reduces risk but requires time and commitment from health care providers to discuss and implement effective quit strategies. Managed care organizations should support these efforts by providing robust smoking cessation programs through medication or other strategies.

Third, health care systems need to support smoking cessation and other preventive measures by creating infrastructure and programs that enable providers to deliver effective care. Managed care organizations should facilitate access to these resources and build strong relationships with smoking cessation programs.

Fourth, managed care organizations should negotiate rates that reflect the benefits of secondary prevention strategies. Effective interventions, even if initially costly, can lead to long-term savings by reducing downstream health care expenditures. Ensuring that these strategies are affordable for patients is crucial.

Fifth and finally, health care professionals and managed care organizations should use available data and guidelines to inform prevention strategies. This will help to ensure that interventions are not only personalized but also cost-effective and aligned with the latest evidence.

By integrating these practices, health care professionals and managed care organizations can enhance stroke prevention efforts and ultimately improve patient outcomes and reduce overall health care costs. ♦

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Optimizing Secondary Stroke Prevention in the Hospital and Throughout Managed Care

A Q&A With *Alpesh N. Amin, MD, MBA*



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AJMC®: How commonly do you see patients or treat patients for recurrent stroke in the hospital setting?

AMIN: In the hospital setting, approximately 15% to 30% of patients experience a recurrent stroke within 2 years; the survivability rate for ischemic stroke is around 80% to 85%. However, the frequency of encountering recurrent stroke cases can vary significantly; it is influenced by factors such as the patient's follow-up care in the ambulatory setting and specific risk factors like hypertension and atrial fibrillation. Adherence to treatment and lifestyle choices also plays a crucial role in determining the likelihood of recurrence. Patients with factors that put them at higher risk are more likely to present with recurrent strokes that require hospital management, whereas those at lower risk typically transition to prevention-based outpatient care.

AJMC: Do you find that patients are seen less frequently in the inpatient setting than in outpatient care?

AMIN: Yes. We primarily encounter patients during acute events when they present through the emergency department (ED). These patients are assessed for stability over 24 to 48 hours, particularly if there are no complications like bleeding or ongoing symptoms. Most patients are admitted to the hospital for further care, although, in rare cases, some may be placed under observation status. Therefore, our interactions with these patients in the inpatient setting are generally limited to acute situations rather than ongoing management.

AJMC: How might inpatient treatment for stroke and recurrent stroke differ from outpatient treatment?

AMIN: There are several key differences. In the inpatient setting, acute management is critical; it requires careful monitoring of the patient's blood pressure and overall stability, and may require the administration of thrombolytics that would not be provided in outpatient care. Diagnostic testing such as CTs, MRIs, and angiograms is generally more accessible in the hospital, facilitating prompt assessment and intervention. In addition, inpatient care often involves a multidisciplinary team including hospitalists, neurologists, pharmacists, nurses, and rehabilitation specialists, which enhances the comprehensive care approach during acute episodes. Preventive measures such as initiation of anticoagulants or antiplatelet agents—some of which can be administered intravenously—are also prioritized in the hospital. Furthermore, the inpatient phase emphasizes the transition and continuity of care, including short-term rehabilitation for functional recovery. In contrast, outpatient care focuses on chronic management that addresses long-term issues like diabetes, hypertension, and lifestyle modifications along with extensive patient education and family support to ensure a solid care network. Overall, while both settings require patient education and multidisciplinary involvement, the inpatient approach is more acute and immediate, while outpatient care emphasizes ongoing management and rehabilitation.

AJMC: The American Heart Association/American Stroke Association (AHA/ASA) guidelines provide a foundation for secondary stroke prevention.¹

What specific challenges to implementing these guidelines arise in the hospital setting?

AMIN: Implementing the AHA/ASA guidelines for secondary stroke prevention presents several challenges not only in hospitals but across the entire health care system. Effective patient care involves multiple touch-points including the ED, hospital floors, intensive care unit (ICU), and various outpatient settings like rehabilitation and primary care. This interconnectedness highlights the critical need for coordinated care, which the guidelines emphasize but which often faces hurdles. Communication gaps frequently arise, particularly when electronic medical records (EMRs) differ between hospitals and outpatient facilities and complicate information sharing. Resource limitations further complicate care transitions, especially for patients not enrolled in well-structured managed care programs. For these individuals, care pathways may be inconsistent, hindering access to medications and services essential for recovery. Additionally, patient-level challenges such as medication adherence and lifestyle modifications pose significant barriers as many patients struggle to change long-standing habits. The guidelines also call for the elimination of social and economic barriers, which can be deeply entrenched. Furthermore, health literacy and cultural sensitivities present ongoing challenges in patient education. While the AHA/ASA guidelines provide valuable recommendations, their successful implementation is impeded by these multifaceted challenges within the health care continuum.

AJMC: How might hospitals implement standardized pathways or protocols for stroke patients to ensure adherence to secondary prevention guidelines, and how can they effectively manage transitions to subsequent care?

AMIN: Standardized pathways play a crucial role in ensuring effective multidisciplinary communication and meeting the needs of stroke patients. By adopting these pathways, hospitals can shift from a reactive to a proactive approach in patient care to clarify the roles and responsibilities of the entire health care team that includes physical therapy, nutrition, medication management, and nursing care. This proactive framework aids in planning follow-up care and patient disposition and aligns expectations for both patients and their families. Well-developed pathways can also include standardized educational materials tailored to different literacy levels, ensuring that both the health care team and patients receive consistent information. Integrating these pathways into EMR systems allows for better organization and prompts for the health

care team about upcoming tasks. Additionally, initiating the discharge planning process upon admission helps to maintain a clear line of sight for patient transitions. Pathways facilitate data monitoring by enabling the collection of relevant information throughout a patient's journey from hospitalization to outpatient care especially when using a closed EMR system. These data can be leveraged to refine pathways and improve patient outcomes, ensuring adherence to appropriate medications and follow-up care. Furthermore, standardized pathways assist in managing transitions across various care settings, including the ICU, outpatient clinics, and rehabilitation facilities, to provide a structured approach to continuity of care.

Balancing recurrent non-cardioembolic stroke prevention with bleeding risk is a complex challenge.... Fortunately, newer... agents are being developed to minimize bleeding risks while optimizing thrombosis management.

AJMC: What roles do value-based care models play in improving stroke outcomes while managing costs?

AMIN: Value-based care models offer a framework for aligning the interests of all stakeholders in stroke care, emphasizing that *value* extends beyond profit and cost savings. One common definition of value is the equation: Value equals quality times service, divided by cost. This means that improvements in quality and service enhance value, even if cost reductions are not immediately evident. Therefore, understanding this definition is crucial for all parties involved. Value-based care fosters alignment in thought, action, and interaction that potentially leads to exponential gains in outcomes. To achieve this alignment, incentivization plays a significant role alongside the necessary investments in systems and resources to meet desired outcomes. In stroke care, value-based programs encourage data-driven approaches that prioritize patient-centered and coordinated care, ultimately improving quality. For example, our institution was among the pioneers in establishing a comprehensive stroke program,

focusing on high-quality coordinated care and preventive measures. While measuring cost can be complex, sophisticated systems can begin to assess these aspects over time. Additionally, value-based programs promote collaboration among providers, managed care organizations, community resources, and ambulatory care settings, thereby creating a comprehensive support network for stroke patients. Overall, these programs represent an opportunity to transform stroke care delivery through enhanced collaboration and a commitment to achieving better patient outcomes.

AJMC: How do you balance recurrent, noncardioembolic stroke prevention with bleeding risk? Are there particular cases in which the current therapies fall short?

AMIN: Balancing recurrent noncardioembolic stroke prevention with bleeding risk is a complex challenge, as many risk factors contribute to both thrombosis and bleeding. This overlap necessitates careful evaluation of the patient's overall risk profile. Typically, the emphasis has favored managing thrombosis over addressing bleeding risk. In discussions with patients and health care providers, a common sentiment emerges: many would favor a bleed vs a stroke. This is because bleeds can usually be stabilized, whereas stroke complications are often permanent. Fortunately, newer anticoagulants and antiplatelet agents are being developed to minimize bleeding risks while optimizing thrombosis management. The focus is often on significant bleeding events like subdural or epidural hemorrhages, but these are generally linked to specific risk factors such as falls or concurrent use of other medications that increase bleeding risk. Ultimately, a comprehensive assessment of all contributing factors is essential for effective management in stroke prevention.

AJMC: Do data analytics currently play a role in your practice, and would you like them to have a bigger role?

AMIN: Data analytics do play a role in my practice, although I see opportunities for much greater integration. Currently, we use existing analytics, but I envision a future where predictive analytics continuously guide patient care, particularly as we manage conditions over the long term. By leveraging data specific to each patient's risk factors and lifestyle, we can make more personalized recommendations. I would like to see analytics empower patients, enabling them to track their progress toward health goals and identify areas needing more focus. While we are starting to gather data through wearables, EMRs, and insurance information, we must enhance our approach to use this data effectively for real-time improvements in patient care.

AJMC: How do you envision artificial intelligence (AI) transforming the landscape of health care delivery and patient management in the future?

AMIN: AI is poised to play a significant role in health care as it continues to evolve. As machine learning and AI technology advance, the tools we develop will become increasingly sophisticated and precise, allowing us to act on data more effectively. For instance, in industries like banking, we've transitioned from paper to nearly fully electronic systems, where advanced tools help manage finances seamlessly. Similarly, in aviation, pilots now spend less time navigating and more time monitoring data from AI-driven systems. This evolution indicates that AI has the potential to enhance decision-making and patient treatment in health care. As we adopt these advanced technologies, we can expect improvements in patient management and outcomes.

AJMC: What are the top strategies that you would recommend managed care organizations implement to effectively reduce the risk of recurrent strokes?

AMIN: I recommend focusing on 3 key strategies for managed care organizations to reduce the risk of recurrent strokes: education, engagement, and empowerment—what I like to call *The 3 Es*. First, patient education is critical; we need to ensure that patients and their support systems fully understand stroke risk factors, symptoms, and necessary lifestyle changes. This knowledge is foundational for effective management. Next, engagement is about getting patients to recognize the importance of adhering to their treatment plans and making lifestyle adjustments. We want them to understand the *why* behind these changes, which can significantly impact their willingness to follow through. Finally, empowerment involves providing patients with data and tools that enable them to take ownership of their health. When patients receive feedback on their progress, they become more active participants in their care, fostering a sense of partnership in the health care process. Additionally, I suggest implementing a comprehensive care coordination program that brings together a multidisciplinary team to eliminate communication gaps and facilitate seamless transitions between care settings. Also, we should leverage advanced data analytics for real-time monitoring and interventions, which can help identify risks and optimize treatment plans. Together, these strategies can create a more effective framework for stroke prevention and significantly improve patient outcomes. ♦

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