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Changes in Stroke Epidemiology, Prevention, and Treatment

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Stroke is arguably the most feared cardiovascular event among healthy subjects and those with cardiovascular disease. Recent studies document changes in the epidemiology of stroke, both within and beyond the United States, which will impact medical service needs. Advances in our treatments for primary and secondary prevention herald an exciting period of change, which promises to lower stroke rates.

Changing Epidemiology

In the United States, as with other industrialized countries, stroke rates, adjusted for age, declined over the last 30 years.^{1–3} However, the aging population implies that absolute numbers of stroke may stabilize or increase over the next 2 decades.⁴ These changes in population demographics and overall risk of disease will place demands on health services for both acute stroke care and long-term care associated with more severe loss of function. New risk scores can risk-stratify patients presenting with stroke and provide insights into the likelihood of long-term disability.⁵ The temporal changes will also impact future trials of stroke prevention, because lower rates of stroke in usual care groups will drive larger sample sizes for trials evaluating new therapies.⁶

The global perspective is quite different. Continuing industrialization of Asia and Africa is increasing unhealthy lifestyles, which promote stroke and other cardiovascular disease. As a result, the highest rates of stroke mortality and disability-adjusted life years lost occur in Asia, Russia, and Eastern Europe.⁷ Stroke is increasing rapidly in Eastern Europe and Central Asia compared with Western Europe³ and the United States.^{1,2} In China, rates of stroke and other cardiovascular disease are projected to increase dramatically due to combination of an aging population and the high prevalence of smoking and hypertension.⁸

The types of stroke are also changing in rapidly developing Asian countries such as China, with an increase in ischemic stroke and a decline in hemorrhagic stroke to approach patterns

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seen in industrialized countries.⁹ Risk factor management is extremely important for the primary and secondary prevention of stroke in Asia as it is Western countries. In a meta-analysis of several Japanese studies of patients with noncardiac sources of stroke, systolic and mean blood pressure were related to the risk of hemorrhagic and ischemic stroke¹⁰ and are prime targets for prevention programs.

Ischemic stroke is one manifestation of atherosclerosis, a disease that affects all major arteries in the body. It is not surprising that recent studies in industrialized communities show fairly high rates of asymptomatic coronary disease in patients with stroke¹¹ and the reverse relationship with higher risks of stroke soon after a myocardial infarct.¹² Thus, antiatherosclerosis medical therapies are critical not only for stroke prevention, but also for the prevention of all cardiovascular events.

New Perspectives on Prevention of Stroke

Many ischemic strokes are caused by embolism from the heart or more proximal arteries. Of the cardioembolic causes, left atrial thrombus due to atrial fibrillation is a common source of embolus causing stroke. Several new drugs offer the hope of better control of atrial fibrillation or anticoagulation to prevent thromboembolic stroke.

In a recent post hoc analysis of the ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular Hospitalization or death from any cause in patiENTs with Atrial fibrillation/atrial flutter trial), the multi-channel antiarrhythmic drug dronedarone lowered the risk of stroke.¹³ The authors were careful to point out that this was a post hoc analysis in a trial with a primary end point of hospitalization and death.¹⁴ Subjects had persistent or paroxysmal atrial fibrillation, and two thirds of patients were on anticoagulant therapy. The reasons for dronedarone's effect on stroke reduction are not clear. However, plausible mechanisms based on prior studies as well as the ATHENA study include the prevention of, or less frequent, atrial fibrillation, and lower blood pressure and a slower ventricular rate at rest and/or with exercise due to the drug's betablockade effect.¹³ Further studies are required to confirm this effect, but this analysis raises the possibility that antiarrhythmia treatment in atrial fibrillation, at least with this class of drug, may offer incremental reductions in the risk of stroke.

The second major advance in stroke prevention due to atrial fibrillation is the direct factor Xa inhibitors. This class of drug offers more stable anticoagulation without the need for frequent blood tests to assess whether patients are in the therapeutic range. In recent clinical trials, direct factor Xa inhibitors compared to standard warfarin therapy reduced the risk of hemorrhagic stroke and major bleeding without a difference in ischemic stroke.¹⁵⁻¹⁷ In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, Apixaban lowered the risks of all stroke or other systemic embolus by 21%, major bleeding by 31%, and death by 11%.¹⁵ The lower risk of hemorrhagic stroke and major bleeding is consistent with two other recent trials in atrial fibrillation comparing this class of drug to standard warfarin therapy using dabigatran¹⁷ and rivaroxapin.¹⁶ However, the downsides of the direct factor Xa inhibitors are their greater expense versus

generic warfarin and the fact that currently there is no rapid reversing agent in the event of life-threatening hemorrhage.

In contrast, anticoagulation may not offer additional protection from recurrent stroke from artery-to-artery embolus. In a substudy of the Warfarin Aspirin Recurrent Stroke Study (WARSS), patients with a cryptogenic stroke and aortic arch atheroma identified by transesophageal echocardiography were randomly allocated to warfarin or aspirin treatment.¹⁸ Although large aortic arch atheroma and complex plaques were associated with a higher risk of stroke over the subsequent 2 years, warfarin did not reduce the risk of stroke beyond aspirin therapy.¹⁸

Lowering blood cholesterol in patients at elevated cardiovascular risk remains a significant strategy in stroke prevention. In addition to several older studies showing lower risks of stroke with HMG-CoA reductase inhibitors (statins),¹⁹ the JUPITER study reiterated this finding in a primary prevention population at elevated risk.²⁰

Thrombolytic Treatment of Stroke

Acute ischemic stroke requires early presentation, early diagnosis, and early thrombolytic therapy to prevent stroke complications. Although the adoption of thrombolytic therapy in acute stroke is less rapid than the early days of thrombolysis for myocardial infarction, improvements are occurring. In the AHA Get With The Guidelines (GWTG) – Stroke Program, over three quarters of patients presented to hospital more than 3 hours after the onset of symptoms and beyond the therapeutic window for intravenous thrombolytic therapy.²¹ Among those presenting within 3 hours, 20% of patients had thrombolytic therapy within 60 minutes of presentation to one of over 1 200 hospitals participating in the program.²¹ More rapid thrombolysis within 60 minutes was associated with less mortality and less hemorrhagic stroke than delayed thrombolysis.²¹ Although rates of thrombolysis within 60 minutes improved slowly over the time course of the study, more work is required to increase the presentation to hospital sooner, recognize acute ischemic stroke, and initiate timely thrombolytic therapy.

These changes may be happening, at least in centers participating with the GWTG-Stroke Program. Another report from the same quality improvement program examined changes in treatment over the time of the program. Over the 5-year period, participants in the GWTG-Stroke program reported increased use of thrombolytics at the acute presentation, antiplatelet agents, deep vein thrombosis prophylaxis, anticoagulation for atrial fibrillation, advice to stop smoking, and lipid-lowering therapy.²² This illustrates the potential for quality improvement programs to stimulate the adoption of secondary prevention measures for ischemic stroke.

Interventional Treatment for Stroke Prevention

In the last year, 2 key studies inform us on the value of endovascular treatments for stroke prevention. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) compared carotid artery stenting with surgical carotid endarterectomy for extracranial internal carotid artery stenosis.²³ This is the largest randomized trial comparing these 2

revascularization strategies in patients with symptomatic and asymptomatic carotid stenosis and at average risk for surgical complications. In the main analysis, the primary end point of any procedural stroke or myocardial infarction, or death, and subsequent ipsilateral stroke was no different between the 2 treatment groups.²³ Subgroup analyses identified a slightly higher risk of periprocedural myocardial infarction with surgery and a slightly higher periprocedural risk of stroke with stenting. Although quality of life indices were lower for patients having a periprocedural stroke,²³ a subsequent analysis showed that periprocedural myocardial infarction was associated with a higher risk of death during follow-up.²⁴ These findings suggest that periprocedural myocardial infarction, even if identified by biomarkers of myocardial necrosis alone, is important to avoid and likely to influence the mode of revascularization.²⁵

More recently, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMPPRIS) study addressed the value of intracranial carotid artery stenting versus intensive medical therapy in patients with intracranial disease and a recent transient ischemic attack or stroke.²⁶ This study was stopped early because of a high rate of nonfatal stroke and death in the stented group that was more than double the rate in the intensive medical therapy group.

The contrast between intracranial stenting and extracranial carotid artery stenting or surgery is worth noting. Anatomically, the intracranial arteries are smaller, have a more tortuous path, and have numerous small penetrating brain arteries compared with the extracranial arteries. These features increase the chance of hemorrhage from guidewire perforation or infarction from occluding penetrating arteries by balloons or stents. These differences are likely the key reason why the 30-day stroke and death rates were 2 to 3 times higher in SAMPPRIS compared with rates in symptomatic patients in the CREST trial.

Although extracranial carotid stenting is now an acceptable treatment compared with surgical endarterectomy, the SAMPPRIS trial does highlight the need to compare stent and surgical revascularization with intensive modern medical therapy, particularly with asymptomatic disease.²⁵

Conclusions

Over the last few years, changing demographics and risk factors for atherosclerosis continue to change age-adjusted and overall stroke rates. Ischemic stroke is increasing in Eastern Europe, China, and other nations witnessing rapid economic changes and the widespread adoption of unhealthy lifestyles. Novel anticoagulants offer greater convenience than warfarin for stroke prevention due to atrial fibrillation, but antiplatelet therapy and intensive lowering of atherosclerosis risk factors remain key components of stroke prevention from artery-to-artery embolus and intracranial disease. Extracranial internal carotid artery stenting and surgical endarterectomy offer similar outcomes in suitable patients at high risk of stroke and low periprocedural/perioperative risk.

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