Stroke

INVITED TOPICAL REVIEW

Revolution in Stroke Treatment Over 50 Years and Predicting Stroke Care in 2050

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ABSTRACT: This article describes the remarkable progress over the past 50 years in acute stroke therapy, stroke prevention, and, to a lesser extent, stroke recovery, and forecasts advances in stroke care for 2050. Stroke has gone from an untreatable and unpreventable disease to a disease with effective medical and interventional treatments for acute ischemic and hemorrhagic stroke, many new medical, surgical, and interventional treatments for primary and secondary stroke prevention, and the beginnings of a revolution in our understanding of the neural code that portends a great future for stroke recovery. Progress in management of stroke risk factors has been mixed, with a major increase in obesity but a decrease in the prevalence of smoking, as well as better control of hypertension and hyperlipidemia in the United States and other high-income countries. The incidence rate of stroke in the US population studies has decreased, but with recent increases in younger segments of the population. Because age remains the most important risk factor for stroke, the burden of stroke is likely to continue to increase as the population ages. In 2050, we will use artificial intelligence to pull clinical trial data from multiple trials in the context of a patient's demographics, medical history, and biometric, imaging, and laboratory data to recommend the best treatment for that patient—true precision medicine. Making these precision treatments in the hospital, clinic, and home settings available to everyone, regardless of geographic, social, and economic situation, is one of our challenges of the next century. As we make greater progress in stroke prevention, acute treatment, and stroke recovery, we will need larger trials and more efficient trial designs. Large trials will require global efforts. The last 50 years have been about advances in stroke prevention and acute treatment. The next century will be about advances in recovery and rehabilitation after stroke and addressing current global disparities in access to proven therapies. Until we can mitigate mechanisms associated with aging, stroke will remain common and a tremendous societal and financial burden. We have made a significant dent in this burden over the past 50 years; the best is yet to come.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aging ■ hyperlipidemias ■ obesity ■ prevalence ■ smoking ■ tomography

Prior Feinberg award winners, including myself, were asked to participate in the Chinese Stroke Association Conference in July 2025. When I gave my original Feinberg lecture in 2003,[1] I reflected on the remarkable progress from 1975 to 2003 in acute stroke therapy and stroke prevention and the lack of any proven treatments for stroke recovery. At that time, I also predicted what stroke therapy would be like in 2025, including stroke recovery. As we are now in 2025, I thought that I would reprise my original Feinberg lecture and see what happened, what did not, and try to predict where we are headed in the next 25 years.

In my opinion, the beginning of modern neurology and modern stroke medicine was the invention of computed tomography of the head by Godfrey Hounsfield in October, 1971.[2] For my 2003 Feinberg presentation, I chose 1975 as a starting point to reflect the rapidly expanding use of computed tomography of the brain in the diagnosis and treatment of stroke and other neurological diseases and because some of the first trials of successful primary and secondary stroke prevention were reported about that time.[3–5] The past 50 years, which span my entire professional career, are truly a golden age in the advancement of acute treatment, prevention,

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and recovery from stroke. The question is where we are headed now.

ACUTE STROKE

History and Past Predictions

In 1975, when I was a sophomore at university, there was no scientifically proven treatment for acute stroke. In 1995, we demonstrated that rtPA (recombinant tissue-type plasminogen activator) improved outcome after acute ischemic stroke when given within 3 hours of onset.[6] This first scientifically proven treatment for ischemic stroke revolutionized our approach to acute stroke, but its incorporation into clinical practice was slow. During the next 10 years, changes in funding by the Center for Medicare and Medicaid in the United States for hospitalized patients with stroke treated with rtPA, the advent of certification for stroke care at hospitals, and the training and education of vascular neurologists and emergency physicians accelerated the implementation of thrombolytic therapy as the standard of care.[7,8] These observations reflect that decisions by governmental and other bodies can advance therapy as much as the clinical trials themselves. By 2003, we had also demonstrated the usefulness of stroke units,[9] the small benefit of aspirin in the acute setting,[10,11] the use of nimodipine for aneurysmal subarachnoid hemorrhage,[12] and the effectiveness of clipping and coiling of ruptured aneurysms[13] (Table 1). Intracerebral hemorrhage (ICH) remained the stroke subtype without a scientifically proven treatment.[14]

In 2003, my predictions for acute stroke therapy for 2025[1] were (1) whatever mechanical device or medication that opens the blocked artery as quickly as possible will be a successful treatment going forward. (2) We will use combined intravenous and intraarterial recanalization. (3) We would use wire devices that remove the clot by assuming a given shape after exiting the arterial catheter. At the time of that prediction, the first mechanical clot retrieval device was undergoing clinical testing (the Concentric retriever, which is shaped like a pig's tail after exiting the catheter). (4) Getting more patients to the hospital more rapidly represented the biggest opportunity to make a difference in acute stroke treatment, whatever the method of recanalization. (5) We would combine thrombolytic agents with other antithrombotic medications. (6) Neuroprotection, such as rapid hypothermia, would play a significant role during restoration of blood flow, as had been shown in cardiac resuscitation.

The Present

All these predictions proved to be pretty accurate except for neuroprotection, which has been a hard nut to crack and still has defied our best efforts. By 2025, we will have not only extended the evidence for rtPA out to 4 1/2 hours from onset of ischemic stroke,[15] but we will have demonstrated the efficacy of intravenous tenecteplase,[16] reteplase,[17] and prourokinase[18,19] for acute ischemic stroke. Evidence for the latter 2 intravenous medications is from recent trials in China, building on earlier trials. We also have proven the efficacy of thrombolytics beyond 4 1/2 hours with magnetic resonance imaging diffusion-flair mismatch[20] or perfusion imaging mismatch.[21] And our improvement in standardized care for patients in stroke care units and intensive care units has also led to improved outcomes.[9,22]

The largest advance since 2003 has been mechanical clot removal for ischemic stroke, first within 6 hours of onset and then out to 24 hours with appropriate imaging selection.[23–30] More recently, even basic noncontrast computed tomography scan examinations can provide data for decision making regarding endovascular therapy, and those patients with large areas of ischemic brain in brain imaging can still benefit.[31–36] Other important advances for ischemic stroke include delivery

Table 1. Advances in Acute Stroke Therapy

1975	2003	2025
None	rtPA out to 3 h	rtPA TNK, reteplase, prourokinase for acute ischemic stroke out to 4½ h
	Stroke units	Thrombolytics beyond 4½ hours with MRI mismatch or perfusion imaging
	Aspirin	Mechanical clot removal for ischemic stroke within 6 h of onset
	Nimodipine for aneurysmal SAH	Mechanical clot removal for ischemic stroke out to 24 h (imaging)
	Clipping-coiling aneurysms	Mobile stroke units
		EVT for large ischemic core strokes
		DAP after stroke (clopidogrel, ticagrelor)
		Blood pressure control after ICH (systolic 140 mm Hg target)
		Prothrombin complex concentrate, andexanet alpha, idarucizumab for reversal of anticoagulation-related ICH
		Minimally invasive removal of lobar hemorrhage within 24 h

DAP indicates dual antiplatelet therapy; EVT, endovascular therapy; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; rtPA, recombinant tissue-type plasminogen activator; SAH, subarachnoid hemorrhage; and TNK, tenecteplase.

of thrombolytic therapy via mobile stroke units[37,38] and dual antiplatelet use within 12 to 24 hours after ischemic stroke for 3 weeks in selected patients.[39–41] Blood pressure control after ICH with the systolic target of 140 mm of mercury improves outcome, evidenced by several large hospital and prehospital trials in China in the past several years.[42–45] Prothrombin complex concentrate, andexanet alpha, and idarucizumab stop or slow bleeding in patients with anticoagulation-related ICH.[46–48] Telemedicine has become part of the standard of care to assess and treat acute stroke patients quickly and remotely in many areas of the world.[49,50] Finally, minimally invasive removal of lobar ICH within 24 hours is the first scientifically proven surgical treatment for ICH.[51]

The Future

What will acute stroke therapy look like in 2050? I think that the diagnosis of acute stroke will begin at home with patient wearables, and treatments specific to ischemic and hemorrhagic stroke will begin before arrival at the hospital, because we will have new devices to differentiate between ischemic and hemorrhagic strokes, in addition to our current imaging devices in mobile stroke units. Wearables may be able to detect stroke as they currently detect atrial fibrillation, but they are certainly likely to be used even more so for stroke prevention and recovery.[52] However, for ischemic stroke, I think we will reach the limits of biology and time with regard to the reperfusion in about 15 to 20 years or less. Cardiology is already there. I also predict that we will see new drugs that complement or improve on thrombolytics, but the efficacy and safety of drugs will always be linked, as they are for thrombolytics. We will have better devices for clot removal that will enable clot removal most distally and more safely. The question is how small these devices can be. Finally, neuroprotection in the setting of reperfusion will remain a challenge, but hopefully one that we will have met. My guess is that hemodynamic approaches to neuroprotection may have the best opportunity for success.

We are going to need larger global trials to find much smaller benefits, as our success in acute stroke has dramatically increased. I think that we will have effective hemostatic treatment for spontaneous ICH and that early minimally invasive removal of ICH in the basal ganglia will also be efficacious for subgroups of patients. We are just starting to see pragmatic trials, which I think will maximize our critical care and management of subarachnoid hemorrhage as well as acute ischemic strokes. Artificial intelligence (AI) and telemedicine will play an even more important part in clinical decision-making worldwide and will help to deliver the best care to locations that currently lack expertise and resources. Finally, physiological time will remain the most important variable for success for all types of strokes.

STROKE PREVENTION

History and Past Predictions

In 1975, the only proven secondary prevention for ischemic stroke was aspirin based on a recently published trial (Table 2).[5] We also saw the first published trials demonstrating that antihypertensive therapy was an effective primary prevention method for stroke.[3,4] By 2003, we had added 3 other antiplatelet medications[53–55] and demonstrated warfarin's effectiveness in patients with atrial fibrillation for both primary and secondary stroke prevention.[56] We finally demonstrated that carotid endarterectomy, which had been used since the 1950s, when performed by surgeons with excellent track records of safety, was effective for both primary and secondary stroke prevention in appropriately selected patients.[57–60] Statins were effective for primary stroke prevention,[61,62] and we were beginning to accrue evidence for secondary stroke prevention as well. Transfusion in patients with sickle cell disease was shown to be an effective primary stroke prevention approach,[63] and epidemiological studies demonstrated that smoking cessation was effective for both primary and secondary stroke prevention.[64]

In 2003, my primary prediction for prevention in 2025 was that the reasons we had little progress in decreasing the incidence of stroke over the past several decades were our failure to alter our at-risk behaviors, the cost of therapies, and the aging of the brain vasculature and brain. Unless we could overcome these barriers, I thought that we would make little headway in achieving the goals of reducing the burden of stroke. I also predicted that we would have new therapies for genetic diseases, but that the costs may be prohibitive except for the very wealthy. Finally, since older age was the most important risk factor for stroke, unless we had a treatment to delay or halt aging, stroke would remain one of the great burdens of humanity and numerically even increase as the population continued to age.

The Present

What happened? In the United States, we are getting more obese (Figure 1).[65] On the contrary, the prevalence of cigarette smoking in the United States decreased over the past 25 years (Figure 2).[66] Unfortunately, this decrease is not reflected uniformly within the larger world population, where smoking remains an important cause of death in many countries for men and women.[67] We have also had improvements in the control of hypertension over the past 15 years (Figure 3)[68] although the percentage of controlled hypertension in the NHAHES survey has not changed much from 2013 to 2014 to 2021 to 2023.[69] Not surprising, given the improvement in hypertension control and smoking cessation, we have seen a decrease overall in the incidence rate stroke in the Greater Cincinnati/Northern Kentucky population over a

Table 2. Advances in Stroke Prevention

1975	2003	2025
Aspirin (s)	Aspirin and 3 other antiplatelet meds (s)	Aspirin and 5 other antiplatelet meds (s)
Antihypertensive Rx. (P)	Anti-hypertensive Rx. (P+s)	Statins (p+s), PCKS-9 inhibitors (p+s)
	Warfarin (p+s)	4 novel anticoagulants (p+s)
	Carotid endarterectomy (p+s)	Mediterranean diet/DASH diet
	Statins (p+s?)	Carotid stenting (p+s)
	Sickle cell–transfusion (p)	PFO closure devices (s)
	Smoking cessation (p+s–epidemiological)	Atrial appendage closure in atrial fibrillation (p+s)
		Enzyme replacement–Fabry, belzutifan for Von Hippel-Lindau
		Sickle cell–hydroxyurea, gene treatment, bone marrow transplant (P)
		GLP-1 RA in subpopulations (p)

GLP-1 RA indicates glucagon-like-peptide 1 receptor agonists; p, primary prevention; and s, secondary prevention.

similar period (Figure 4).[70] But this overall decrease has not been reflected in the younger population, in whom the incidence rates of stroke have numerically increased.[70]

Where are we in 2025 with regard to stroke prevention? As noted above, decreases in smoking, improved control of blood pressure, and treatment of cholesterol in the population have made the most impact. We also have aspirin and 5 other antiplatelet medications.[40,71,72] We know that the Mediterranean diet decreases the risk of recurrent stroke.[73] We have 4 novel anticoagulants for primary and secondary prevention, primarily in patients with atrial fibrillation.[74–77] We have more evidence that stenting is helpful in the setting of carotid artery disease,[78] although new data from CREST 2 in the upcoming months may qualify this observation, as our medical treatments for stroke prevention have improved.[79] Closure devices for a patent foramen ovale are efficacious for stroke prevention in selected patients,[80–83] and atrial appendage closure devices prevent stroke in patients with atrial fibrillation who cannot take anticoagulants.[84,85] PCSK-9 inhibitors have been an advance over statins for prevention of myocardial infarction and ischemic stroke, although they remain more expensive.[86–88] We have enzyme replacement and evolving therapies for Fabry disease[89] and other genetic diseases,[90] medical treatment for Von Hippel Lindau disease,[91] and gene treatment-cures for sickle cell disease.[92,93] The latest entrants for prevention have been GLP-1 (glucagon-like-peptide 1) and GIP receptor medications, which not only improve diabetic control and weight loss but also improve cardiovascular outcomes.[94–97]

The Future

My prediction for stroke prevention in 2050 is that behavioral lifestyle changes will remain the greatest challenge and opportunity for primary and secondary stroke prevention and brain health, as has been summarized by the American Heart Association Presidential Advisory in 2024 and Life's Essential Eight.[98] These include diet, sleep, exercise, weight control, blood pressure control, smoking cessation, and metabolic state (lipids, glucose control, inflammatory markers). The burden of stroke is

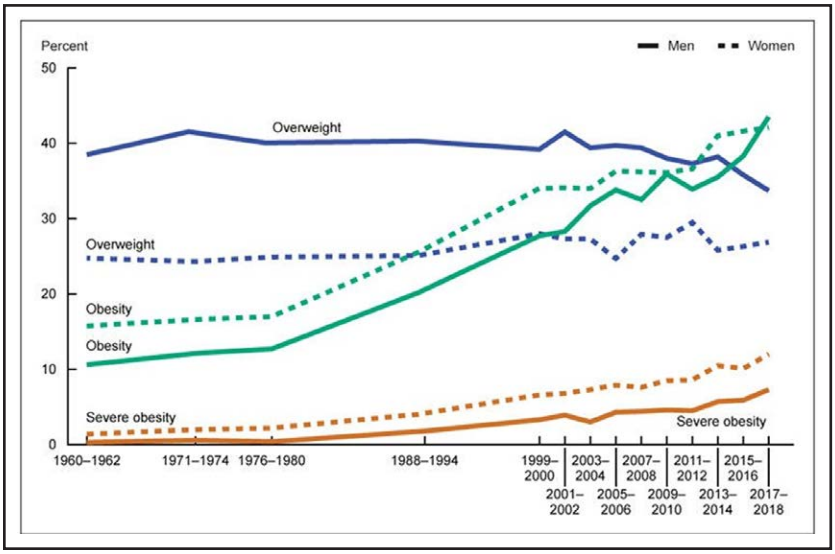

Figure 1. CDC report: January 29, 2021: regarding temporal trends in obesity.
Reprinted from Fryar et al.[65]

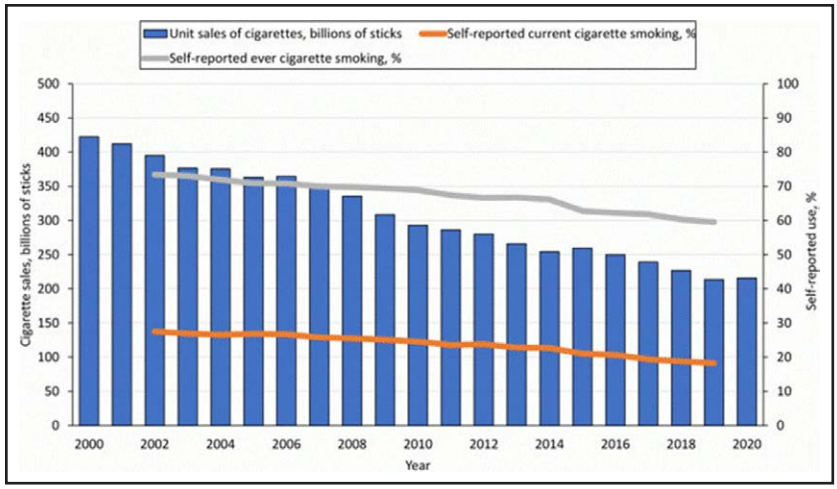

Figure 2. CDC report: July 2022: temporal trends in cigarette sales and self-reported smoking.
Reprinted from Nkosi et al.[66]

likely to remain disproportionately higher among ethnic minorities, immigrants, and indigenous populations, as well as persons with low levels of education, lower income, and lacking health insurance, unless more concerted efforts are directed to address these ongoing disparities. Weight control medications will be integral to primary and secondary stroke prevention and cardiovascular health as much as lipid medications. Biomarkers will provide greater precision for the use of antithrombotic drugs and devices. Additional precision medicines to treat genetic diseases, such as CADASIL, will be available but costly. But again, unless we have treatments that slow aging, the overall stroke burden will only decrease a little.

STROKE RECOVERY

History and Past Predictions

In both 1975 and 2003, there were no scientifically proven treatments for stroke recovery (Table 3). My prediction in 2003 was that growth factors, stimulant medications, stem and stromal cells, and new methods of physical therapy, such as modified constraint or robotic therapy, may play a role.[1] The listing of so many options for the future reflected the plethora of ideas, but the lack of great science provided a clear path forward. The second prediction was that the use of biomedical interfaces between neurons and silicon circuitry powering electric mechanical devices was likely to play an increasingly larger role than originally thought to be feasible, and that a totally paralyzed individual may be able to direct an electromechanical device such as a wheelchair via implants in the brain. My last prediction was that we would not be able to grow and insert new cortical neurons in the brain of the same paralyzed individual, which could traverse the white matter, internal capsule, brainstem, and spinal cord and synapse with appropriate targets to improve the outcome. In other words, science will not advance enough in the next 25 years.

The predicted barriers to successful stroke recovery in 2003 were the extent of initial injury from stroke, the brain plasticity of a given patient (younger is better), and understanding the neural code.[1] We needed to

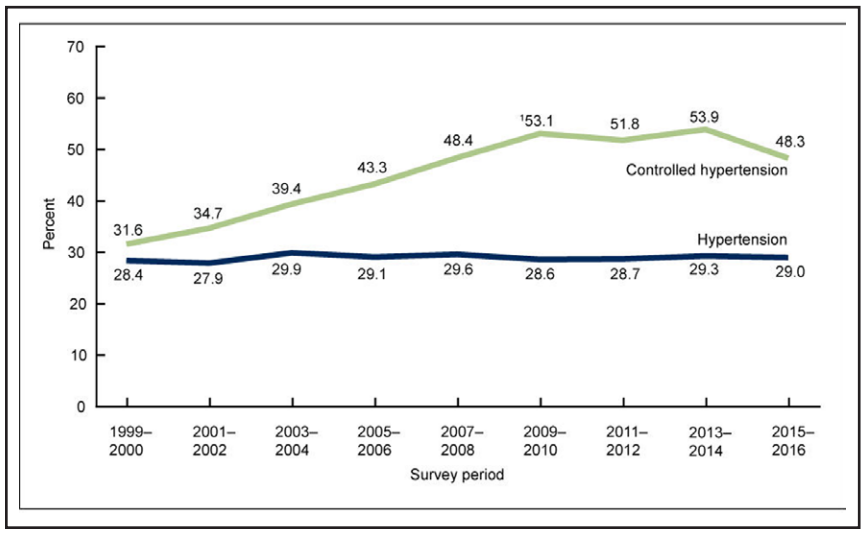

Figure 3. Age-adjusted trends in hypertension and controlled hypertension among adults aged 18 years and over: United States, 1999–2016.
Reprinted from Fryar et al.[68]

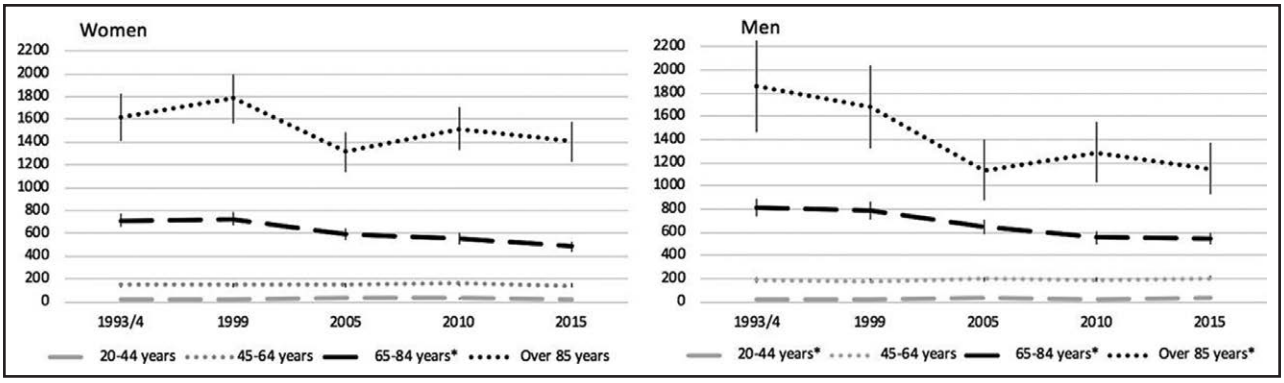

Figure 4. Temporal trends in stroke incidence rates in men and women–Greater Cincinnati Northern Kentucky.
Reprinted from Madsen et al.[70]

understand better how the brain is organized, and how the cells communicate with each other, since we wanted to coax the brain of a 75-year-old patient with stroke to act like the brain of a 2-year-old with minimal side effects.

The Present

In 2025, we now have modified constraint therapy[99] and vagal nerve stimulation combined with modified constraint therapy[100] as proven scientific treatments. Major advances in cochlear[101,102] and retinal implants[103,104] have dramatically improved the function of individuals, and these connections with extensions of the brain have shown the power of technologies to improve outcomes. Even more impressive is the AI revolution in understanding the neural code. Patients without the ability to move or to speak have been able with AI-driven brain-device interface to train their brains to move devices, to write words on the screen, and even to speak.[105–107] We have also developed techniques for decoding what the brain is visualizing. These advances will continue to accelerate.[108] However, one of the major barriers to progress in stroke recovery has been the predominance of small single-center randomized trials of a given therapeutic approach rather than larger multicenter trials.[109] We are currently in transition and sharing expertise from the investigators specializing in larger trials of acute and prevention therapies of stroke with investigators who best understand the science and delivery of poststroke therapy is helping to accelerate this transition.

The Future

Increased intensity of various physical, occupational, and speech therapies will enhance recovery in selected children and adults. The AI revolution in understanding the neural code will accelerate and will connect the disconnected brain and related organs with machines and the digital web to enhance daily function, but will be limited by cost. Recovery approaches will be limited by the initial damage and the physiological age of the recovering brain. Implanting new brain cells to replace damaged brain tissue that make new connections throughout the nervous system to enhance function may still require science beyond 2050.

Table 3. Advances in Stroke Recovery and Rehabilitation

1975	2002	2025
None	None	Modified constraint therapy
		Vagal nerve stimulation combined with constraint therapy

FINAL THOUGHTS ABOUT THE FUTURE OF STROKE

My primary prediction once again quotes a very old comic strip character, Pogo, we have met the enemy, and he is (still) us. Changing our individual and societal behaviors will remain the biggest challenge but the greatest opportunity to decrease the burden of stroke, even though it is not an easy path for many. This opportunity is as much a social and governmental responsibility as an individual one, where governmental bodies and societal support can provide incentives and guardrails for decreasing smoking, improving diet, and making medications for the treatment of blood pressure, hyperlipidemia, and weight control affordable in all world populations. In addition, governments around the world have decision-making powers that impact the future environmental risks of stroke, such as air pollution[110] and microplastics in blood vessels[111] and the brain. These large and important issues require a sense of urgency and will to change the future for our children and grandchildren.

In 2050, we will have many new tools, medications, and devices to prevent and treat strokes. Clinical trials give us an overall effect of treatment in a defined population, but some people in the trial cohort benefit tremendously, whereas others do not at all, and some may be harmed. We will use AI to pull all the available clinical trial data from multiple trials in the context of an individual patient's demographics, medical history, and

biometric, imaging, and laboratory data to recommend the best treatment for that specific patient—true precision medicine.[112,113] As our treatments have become more successful, larger clinical trials are needed to demonstrate smaller benefits. Large trials usually require global efforts. Again, the collaboration among clinical trialists in different countries is already great, but governmental barriers to joint funding, data sharing, and legal concerns hinder progress. And some treatments will be quite expensive and not available to much of the world's population. Making these precision treatments in the hospital, clinic, and home settings available to everyone, regardless of geographic, social, and economic situation, is one of our great challenges of the next century.

As we make greater progress in stroke prevention and acute treatment, we will need much larger trials and more efficient trial designs, such as platform trials, to find smaller benefits.[114] Very large trials will require global efforts. We will also need trials that test treatments which are incorporated into the standard workflow for clinical care as much as possible—what we currently refer to as pragmatic trials.[114] The primary barriers to global trials are not scientific disagreements or a lack of collaboration among clinical researchers, but are predominantly political, societal, and financial. We must continue to work to address these barriers, in addition to advancing science, if we truly are to have an impact.

The last 50 years have been about advances in stroke prevention and acute treatment. But these advances have occurred primarily in developed countries with more economic resources, and these advances need to be implemented worldwide. I believe that the next century will be about advances in recovery and rehabilitation after stroke and addressing current global disparities in stroke incidence, outcomes, and access to proven therapies. And until we better understand the mechanisms of aging and develop methods to limit its negative consequences, stroke will remain common and a tremendous societal and financial burden. We have made a significant dent in the burden of stroke over the past 50 years, and the best is yet to come.

ARTICLE INFORMATION

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Sources of Funding

None.

Disclosures

Dr Broderick reports compensation from Kroger Prescription Plans Inc for consultant services; grants from Genentech for role on TIMELESS Trial; compensation from F. Hoffmann-La Roche for consultant services; study medication and grant support from Novo Nordisk for National Institute of Neurological Disorders and Stroke funded FASTEST Trial; compensation from Brainsgate for consultant services; and compensation from Basking Bioscience for consultant services.

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