

The NINDS Stroke Progress Review Group Final Analysis and Recommendations

Michael A. Moskowitz, James C. Grotta and Walter J. Koroshetz
on behalf of the National Institute of Neurological Disorders and Stroke

Stroke. 2013;44:2343-2350; originally published online July 2, 2013;

doi: 10.1161/STROKEAHA.113.001192

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2013 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/44/8/2343>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>

The NINDS Stroke Progress Review Group Final Analysis and Recommendations

Michael A. Moskowitz, MD; James C. Grotta, MD, on behalf of the Stroke Progress Review Group; Walter J. Koroshetz, MD, on behalf of the National Institute of Neurological Disorders and Stroke

As the nation's primary supporter of basic and clinical stroke research, the National Institute of Neurological Disorders and Stroke (NINDS) strives to pursue the most pressing and promising scientific opportunities. During the past decade, NINDS has led a stroke planning effort performed by the Stroke Progress Review Group (PRG), an external group of prominent stroke scientists, clinicians, and consumer advocates.¹ The third report of the Stroke PRG, summarized here, was posted in January 2012.² It is the product of ≈200 stroke experts working in 16 topic-related workgroups and provides a comprehensive view of stroke research advances, challenges, and scientific opportunities. The Stroke PRG reports serve to inform the research community and funding agencies, including the National Institutes of Health that invests more than \$300 million annually in stroke research. In 2012, the NINDS used the Stroke PRG report as the foundation for engaging the global stroke community in building consensus around the highest stroke research priorities.

Short summaries and 2 to 3 research priorities from each workgroup follow, and bulleted versions of the priorities are listed in Table 1. The topics are ordered loosely from basic to clinical research, although many of the recommendations are crosscutting and overlapping.

Transformative Research Methods for Stroke Research

Imaging

Neuroimaging is now being used for selection, monitoring, and testing of different therapeutic interventions. Identification of penumbral tissue using both MRI and computed tomographic techniques has markedly advanced. Functional imaging markers are also being developed, which could advance our knowledge of the underlying mechanisms of brain injuries and serve as surrogate outcomes for clinical trials. New molecular and cellular neuroimaging technologies are being used to define pathophysiological mechanisms. From a practical standpoint, the most cost-effective imaging workup for patients with both ischemic stroke and intracerebral hemorrhage, based on which modalities lead to treatment decisions that have been proven to affect outcomes, remains to be determined. Other

questions include the contribution of metabolic imaging (cerebral metabolic rate of oxygen [CMRO₂]) to multimodal acute stroke imaging, the development and usefulness of imaging markers of injury to large and small blood vessels, and the development of positron emission tomography ligands and other novel imaging techniques to allow imaging of synaptogenesis and other neuroplastic processes.

Three priorities going forward include the following:

Conducting serial imaging studies from acute to chronic time frames using multimodal imaging, cerebrovascular reserve studies, and computational modeling to better understand the impact of cerebral hemodynamics, collateral flow, oxygenation, and brain metabolism on tissue survival and function.

Conducting imaging-informed trial of late IV tissue-type plasminogen activator (t-PA) application. Conducting a randomized placebo-controlled trial of IV t-PA beyond 4.5 hours selected by penumbral mismatch imaging.

Creating an acute stroke imaging repository. This should include supporting infrastructure to enhance collaborative research to standardize and validate imaging protocols and processing methods.

Genetics

Significant progress has been made in understanding the role of genetics in stroke, as well as in identifying key challenges for the field going forward. For example, large consortia have been organized to identify risk loci for ischemic stroke, hemorrhage, and aneurysms, and much effort has gone into developing strategic approaches to mitigate confounds relating to harmonization of key measures and phenotypes across data sets. Such studies have proven essential to identify novel risk loci for intracranial hemorrhage, as well as to identify regions of interest contributing to the risk of aneurysm formation and ischemic stroke. There have been notable advances in the development of genetically engineered animal models expressing phenotypes relevant to stroke pathophysiology, such as mutations in Notch-3, peroxisome proliferator-activated receptor gamma (PPAR-γ), and collagen type IV, and in models of cavernous brain malformations. Critical opportunities confront the field of stroke genetics in studying under-represented

Received February 21, 2013; accepted June 4, 2013.

From the Neuroscience Center at Massachusetts General Hospital, Boston, MA (M.A.M.); Department of Neurology, University of Texas Medical School at Houston, TX (J.C.G.); and National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (W.J.K.).

Correspondence to: Walter J. Koroshetz, MD, National Institutes of Health, National Institute of Neurological Disorders and Stroke, Bldg 31, Room 8A52, 31 Center Dr MSC 2540, Bethesda, MD 20892. E-mail koroshetz@mail.nih.gov

(*Stroke*. 2013;44:2343-2350.)

© 2013 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.113.001192

and diverse populations and pediatric stroke. Gene discovery approaches are rapidly evolving, but logistical problems surround expensive and time-consuming sample collection and appropriate phenotyping.

Three priorities going forward include the following:

Performing large multicenter collaborations to recruit cases and controls with excellent and consistent characterization. New recruitment can effectively address the power or sample size demands of sequencing, and uniform clinical, risk factor, and radiographic phenotyping can address the heterogeneity of stroke.

Integrating genetic studies and pharmacogenomics into clinical trials.

Elucidating the mechanisms by which genetic factors modulate the risk and outcome of cerebrovascular disease and stroke using *in vivo* and *in vitro* modeling.

Omics

Stroke has benefited from rapid advances in omic technologies during the past few years, although the technologies and their application to stroke research are in their infancy. Early studies have shown that ischemic stroke subtypes can be differentiated by gene expression profiles in blood, a finding that may one day be useful for diagnosing and distinguishing between stroke phenotypes. Based on early work, plasma proteomics may become useful for identifying and screening for risk factors in human samples. Emerging challenges revolve around analysis and handling of very large data sets and access to clinical samples, with sufficient power to derive meaningful conclusions. The use of these technologies is rapidly moving from basic science studies to translational and clinical research, with the promise of applying them to clinical diagnosis and therapeutic monitoring.

Three priorities going forward include the following:

Facilitating access to and integration of genomic/transcriptomic, proteomic, metabolomic, and bioinformatics technology and enabling interaction and standardization of design, data analysis, and interpretation related to stroke.

Identifying molecular markers or profiles of stroke and stroke risk in patients. Creating methods and protocols for the collection of biological samples, with biospecimens sharing incorporated into current and future National Institutes of Health trials.

Recruiting geneticists and molecular biologists for collaboration with basic and clinical stroke researchers.

Primarily Basic, Mechanistic Research

Cerebrovascular Biology and Neurovascular Unit

The blood vessel wall and its component cells have been implicated in several mechanisms related to normal cerebrovascular regulation, as well as to stroke risk, acute stroke pathophysiology, and blood–brain barrier disruption. Pericytes have emerged as key players in neurovascular function, including capillary blood flow regulation, and in pathological states, such as the no-reflow phenomenon and loss of blood–brain barrier integrity after stroke. New technologies, such as optical

imaging, are now available to interrogate the blood vessel wall, and these tools are especially powerful for exploring critical interactions within the cerebrovascular bed using genetically manipulated animals. These and other tools can help to decipher critical cell targets that determine stroke risk and outcome by impacting inflammation, immune mechanisms, blood cells, and oxidative stress. We need to define cell-specific pathways and molecular mechanisms of disease, as well as the pathogenic interactions between cell types in large and small vessels.

Three priorities going forward include the following:

Defining cell-specific and molecular mechanisms of disease for all segments of the brain vascular bed, from large cerebral vessels outside the brain to intraparenchymal vessels in intimate contact with neurons and astrocytes, and assessing how activation, stroke risk factors, and injury alter such interactions and how damage to one cell type alters the homeostasis of the vessel wall, including function of the neurovascular unit (NVU) and the blood–brain barrier.

Elucidating the changes that occur during development and aging and investigating their sex specificity and the modifications induced by functional activation in the normal state after injury and during the repair processes.

Elucidating the signaling mechanisms governing the functional and trophic interactions among the cellular elements of the vasculature, as well as their relationships to neurons and perivascular cells in the developing adult and aging brain, and in both sexes. New and better tools, animal models, and efforts to train a new generation of investigators are critical.

Coagulation, Hemostasis, and Endothelial Cell Interaction

The NVU has emerged as a key concept in understanding the pathology of cerebral ischemia and hemorrhage, hemostasis, inflammation, and integrity of the blood–brain barrier. Cerebral microvasculature, a component of the NVU, is now known to be dynamic and pluripotent in its acute and chronic response to focal ischemia and reperfusion. Further study of the microvasculature and NVU is likely to inform new therapeutic directions and explain current research limitations in ischemia, intracerebral hemorrhage, vascular dementia, and amyloid deposition disorders. The role of innate inflammation in the central nervous system (CNS) is gaining increased attention. A better understanding of CNS hemostasis will help identify new targets to more safely attenuate coagulation without impairing hemostasis. Understanding CNS-specific hemostatic mechanisms and their link to inflammation may help identify new modalities to prevent intracerebral hemorrhage and hematoma expansion, including for patients on anticoagulants.

Three priorities going forward include the following:

Further understanding the NVU components and their interrelatedness during focal ischemia. This includes how the NVU microvasculature differs from other microvascular beds, how the microvascular endothelium and astrocytes communicate with each other, the roles of the intervening extracellular matrix, and how these interactions are

modified by amyloid deposition, age, and other factors under normoxia and ischemia.

Studying innate inflammation under the conditions of health, focal ischemia, and hemorrhage, in particular, how the peripheral inflammatory network affects the CNS, the early roles of polymorphonuclear leukocytes, the role of complement components, and links between the contact pathway of coagulation and regulation of inflammation and vascular permeability.

Understanding how the brain and its vasculature regulate hemostasis uniquely, and the impact of hemostasis in responding to focal ischemia and hemorrhage. Understanding how the CNS microvasculature, development and maintenance of the permeability barrier, and various proteases, receptors, ligands, and inhibitors regulate CNS hemostasis. Continue work developing agents to prevent or reduce cerebral hemorrhage, reduce brain injury caused by clot-derived factors, and accelerate hematoma resolution. Increase understanding of the interaction between the inflammatory system and different proteases in the coagulation and fibrinolytic systems.

Neuro-Cerebrovascular Degeneration

Important progress has been made in understanding cross talk among neuronal, glial, and vascular elements of the NVU in brain injury and repair. There is an emerging consensus that a more accurate picture of events during stroke will be achieved by integrating this cellular model with an understanding of responses during and after brain injury in systemic tissue, body fluid (such as circulating blood elements), the immune system, and systemic blood vessels. There is also a growing body of evidence to suggest that cell–cell signaling within the NVU may have relevance to disorders other than stroke, such as vascular cognitive impairment and other causes of neurodegeneration. Several scientific opportunities exist, including consideration of the impact of subcellular elements, such as mitochondria and microRNAs on the NVU. These include consideration of regional differences that may exist, and especially the application of imaging and optogenetic tools to study the entire NVU simultaneously in transgenic and wild-type animals.

Three priorities going forward include the following:

Better understanding of how interactions in all elements of the NVU, along with systemic immune responses, underlie the transition from injury into repair after stroke.

Building better models (molecular, cellular, and animal) that capture pathophysiology, as it is influenced by altered neuro-cerebrovascular risk factors (age, sex, inflammation, and other disease states).

Better understanding of timing and dosing issues during stroke in models and how these timelines translate into humans. For example, if neuroprotection is observed within a 6-hour window in rodent stroke, how does that translate to stroke patients? What standards should apply in pre-clinical models before embarking on human studies?

Biology of Repair

Advances in the biology of brain repair have focused on molecular regeneration programs after stroke, as well as on

the therapeutic potential of cell-based strategies in the restorative process. It is becoming increasingly recognized that primary stem or progenitor cells stimulate astrocytes, microglia, and neurons to remodel compromised brain tissue after stroke, as well as secrete neurotrophic and other factors that enhance recovery. One or more of these responding endogenous cell populations together or individually become induced to amplify restorative processes, such as angiogenesis, neurogenesis, neurite outgrowth, and remyelination to promote neurological recovery. These molecular and macromolecular reparative programs play out in tissue adjacent to the stroke as well as in more remote brain regions communicated via long tracts (eg, corticorubral pathways). Because restorative mechanisms sustain for several weeks or longer after stroke, there is a relatively long window of opportunity for therapeutic intervention. One such intervention, behavioral experience, powerfully modulates neural and non-neural cellular responses after stroke, such as axonal sprouting, dendritic growth, and cell proliferative responses, and the net response may either positively or negatively impact recovery, as shown, for example, in animal models after compensatory learning in motor recovery.

Three priorities going forward include the following:

Identifying critical restorative mechanisms at the molecular, cellular, tissue, and systemic levels and biomarkers to monitor recovery.

Defining and optimizing restorative therapies, including optimizing timing for cell-based, pharmacological, brain–machine interface, and brain stimulation approaches through mechanistic advances. For cell therapies, investigating and developing cell types, physical properties of grafted cells, associated material and scaffolds, and optimal noninvasive monitoring of graft or endogenous response.

Translating cell-based, pharmacological, brain stimulation and behavior manipulations with associated biomarkers and neuroimaging from animal models to clinical models. Identifying animal stroke models particularly useful for studying neural repair and animals carrying significant stroke risk factors. Optimizing behavioral and cognitive outcome indices of recovery.

Primarily Translational and Clinical Research

Acute Stroke Treatment

Although no therapy has been proven effective since intravenous t-PA, much has been accomplished. In particular, the use of t-PA in more patients has resulted from the establishment of primary stroke centers, demonstration of t-PA efficacy out to 4.5 hours from symptom onset, and the use of telemedicine. Still under investigation are endovascular techniques that have been shown to open arteries that cannot be cleared by IV t-PA and other methods to amplify t-PA. Although no neuroprotective therapies have been proven effective, approaches with pleiotropic effects, such as hypothermia and prehospital-administered magnesium, are also in the late stages of investigation. Stroke in children has received greater attention, and a consortium of collaborative investigators (the International Pediatric Stroke Study) has established a stroke registry and is mounting an analysis of acute stroke treatment in children.

Other consortia have facilitated research in acute stroke, including the Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) to identify promising new treatments and the Neurological Emergencies Treatment Trials (NETT) network to perform phase 3 stroke studies in emergency departments.

Three priorities going forward include the following:

Making reperfusion therapy swifter, safer, and surer.

New drugs and devices, alone and in combination, are needed to enable cerebral reperfusion interventions to achieve rapid, complete, and sustained vessel patency, with no risk of hemorrhage, in all patients harboring salvageable tissue.

Cerebral cytoprotection early and after reperfusion with potent, pleiotropic interventions and with optimal management of physiological parameters. Goals should be to stabilize the penumbra until reperfusion occurs and to block reperfusion injury in the postreperfusion period. In addition, evidence for optimal management of blood pressure, glucose, oxygen, and other physiological parameters is needed.

Acute stroke clinical trial networks: existing and new networks should be reviewed, refined, and fostered to drive rapid advances in acute stroke care by making translational treatment trials more inexpensive, efficient, and successful.

Neurovascular Protection Mechanisms

Since the last PRG report, new evidence has shown that peripheral tissues and organs, such as spleen and bone marrow, play a key role in stroke pathophysiology and impact secondary brain injury and recovery. In addition, the presence of potentially tissue-damaging peri-infarct depolarizations has been found in humans and in multiple animal species. These findings can contribute to the complex and challenging arena of neurovascular protection and help determine how best to translate key findings in an iterative way. Opportunities abound for investigative studies that (1) render animal models more relevant to the human condition, (2) achieve more coherent preclinical and clinical trial design, (3) accelerate the unduly long drug discovery process, (4) better match lesion age, size, location, and pathology to the experimental therapy, and (5) develop and validate disease biomarkers and surrogate end points in phase II studies before more extensive and expensive large clinical trials.

Two priorities going forward include the following:

Improving the cellular–animal–clinical trial translational interface.

Expanding our clinical trial repertoires to include approaches, such as specific pathology-focused, exclusive patient trials.

CNS Hemorrhage

Clinical trials have indicated that hemorrhage growth can be limited by hemostatic therapy and blood pressure reduction, but clinical benefit is still unproven. Efficacy studies of aggressive blood pressure reduction are underway, and better methods to identify patients at risk for hemorrhage growth

might make clinical trials aimed at preventing this phenomenon more informative. Open surgical evacuation of deep hemorrhages does not improve outcome, but studies are ongoing on stereotactic aspiration and open evacuation of lobar hematomas. Tissue protective therapy for prevention of secondary injury after brain bleeding primarily targets inflammation, spreading electric depolarization and ischemia. An endothelin receptor antagonist, clazosentan, can reduce angiographic vasospasm after subarachnoid hemorrhage, but clinical benefit remains unproven. Brain injury occurring early after the primary bleeding event may be important in patients with subarachnoid hemorrhage.

Three priorities going forward include the following:

Understanding hemostasis and coagulation within the CNS and how it affects the NVU, including electric disturbances, cellular signaling, microvascular dysfunction, tissue inflammation, and matrix biology. More relevant models of acute hemorrhage-induced brain injury are needed.

Advanced imaging, physiological monitoring, and tissue/molecular/biomarker analysis and genetic profiling are needed to better define the time window, mechanisms, and clinical impact of potentially modifiable primary and secondary injury pathways during the acute phase of bleeding.

Further studying surgical hematoma evacuation, including image-guided minimally invasive interventions.

Vascular Cognitive Impairment

Advances in transgenic technology, neuroimaging, genetics, and the biology of amyloid angiopathy have reinforced the growing appreciation that cerebrovascular disease is a major contributor to the risk of cognitive impairment and dementia. In human brain, neuroimaging has provided key biomarkers for vascular cognitive impairment (VCI; eg, presence of cerebral microbleeds, microinfarcts, β -amyloid deposition, lacunar infarcts, white matter lesions), although establishing the precise causal link between small-vessel–related brain lesions and VCI remains a major challenge for future investigation. New and better characterized transgenic mouse models are needed to ensure progress, and genetically engineered mice have already provided invaluable clues to pathophysiology. Determining how each mutation and its associated vascular phenotype contributes to disease phenotype in rodents remains a major challenge. On the translational side, it is possible that disease progression can be diminished by using available drug and nutritional strategies that reduce stroke risk, although it will be a challenge to demonstrate that such strategies actually reduce VCI risk in long-term clinical trials.

Three priorities going forward include the following:

Developing animal models that mimic the full range of tissue damage of human VCI in the setting of common vascular risk factors. Developing noninvasive tools for detecting the key molecular and cellular pathways among relevant cell types.

Incorporating novel human biomarkers such as β -amyloid imaging into studies of VCI and small-vessel–related neuroimaging markers into studies of Alzheimer

disease, with a focus on unraveling the links among small-vessel pathology, neurodegenerative disease, and neurological impairment.

Developing large-scale clinical trials of dementia-free but high-risk subjects for intensive vascular risk factor modification.

Recovery and Rehabilitation

Advances in recovery and rehabilitation have reinforced the notion that function can be restored through interventions many months after stroke. Although the biological basis for this recovery is poorly understood, research into the science of brain plasticity and repair is the key to maximizing the impact of this emerging field in both adult and pediatric brain. Many strategies are now at an early stage of development, including drugs and biological therapies, MR and electric brain stimulation, robotic technologies, activity-based therapies, and brain-computer interface approaches. Although early results for each approach show promise, the field awaits clinical trials on larger and more homogeneous patient populations and more uniform outcome measures. Also needed are advances in imaging and the development of other biomarkers that can inform us about the impact of specific treatments at the tissue level and predict the likelihood of recovery.

Three priorities going forward include the following:

Developing methods to measure clinical brain plasticity that are valid, reliable, affordable, and accessible and correspond to functional recovery and determining how these markers can be best used to guide and individualize rehabilitation and restorative therapies.

Understanding the neuroscientific basis of experience-dependent poststroke plasticity and distinguish which experiences and what level of experience will maximize outcomes during recovery from stroke.

Developing and implementing a range of new restorative therapies in humans, including mechanisms, organization, and clinical trial design to best translate them from bench to bedside using strategies, such as specialized programs for recovery.

Prevention of First and Recurrent Stroke

Advances in stroke prevention include several major clinical trials clarifying appropriate antiplatelet use and the role of stenting in carotid and intracranial atherosclerosis, as well as safer and more effective anticoagulants for stroke prevention in patients with atrial fibrillation. Establishment of NeuroNEXT and stroke prevention/intervention centers for research on stroke disparities also address PRG priorities. Other exciting opportunities and areas for prevention research include population-based primary stroke prevention, perinatal stroke prevention, personalized stroke prevention, plaque hemorrhage and rupture, and technology as a tool to enhance patient and physician adherence.

Three priorities going forward include the following:

Implementation research: improving implementation of existing, proven stroke prevention interventions by (1) identifying barriers to implementation from the perspective of the patient, healthcare providers, and the healthcare system; (2) studying methods to overcome these

barriers, including through technologies, systems-based interventions, and incentives; and (3) evaluating the effectiveness of innovative initial and recurrent stroke prevention interventions, especially in underserved populations and minority racial and ethnic groups.

Risk factor assessment and risk prediction: tracking the prevalence and impact of stroke risk factors in the United States and developing and examining the effectiveness of quantitative risk factor assessment tools that can identify stroke-prone individuals who need aggressive risk factor management and recurrent stroke prevention interventions, with particular emphasis on underserved populations and minority racial and ethnic groups.

Innovative prevention strategies: identifying and evaluating innovative stroke prevention treatments and strategies, with particular attention to dietary, lifestyle, and population-directed interventions that are inexpensive and cost-effective.

Epidemiology, Trials, and Implementation

Epidemiology and Risk Factors

A great deal of progress has been made in stroke epidemiology since the last PRG analysis. The first priority of the previous PRG was to establish common data elements, which was accomplished through an NINDS project. In addition, epidemiological data are being linked to administrative (Medicare) data. The second priority, elucidating temporal trends in stroke incidence, was addressed in publications from the Framingham Heart Study, the Greater Cincinnati-Northern Kentucky Stroke Study, the Brain Attack Surveillance in Corpus Christi (BASIC) study, and Reasons for Geographic and Racial Differences in Stroke (REGARDS), a large study examining important stroke disparities in the United States. Increased epidemiological training, the third priority, was addressed in ≥ 6 NINDS T32 programs, 19 K23s, 2 K24s, 4 KO2s, and 1 F31, as well as through SPOTRIAS and R25s. In addition, other epidemiological studies have focused on stroke geography, stroke in women (including hormone replacement therapy), pediatric stroke, disparities in stroke care, stroke in Hispanics and blacks, novel risk factors, vascular cognitive impairment, stroke genetics, and translational epidemiology.

Three priorities going forward include the following:

Improving the understanding of stroke disparities to reach a depth sufficient to guide interventions. Epidemiological studies need to focus on specific gaps in our understanding of risks, determinants, and outcomes of stroke in special populations, including women, racial and ethnic subgroups, and children, as well as geographically distinct populations.

Evaluating the usefulness of health information technology as a tool for epidemiological research. We need to evaluate the validity and effectiveness of large administrative data sets and electronic medical records in providing added value to stroke epidemiology and surveillance.

Translating knowledge from epidemiological studies into improved health. Information gained from epidemiological studies needs to be translated into improved health by informing evidence-based practice recommendations and clinical care, translating findings into

Table. Summary of Stroke Progress Review Group Workgroup Research Priorities

	Priorities
Imaging	<p>Conduct poststroke (acute and chronic) imaging studies to understand cerebral hemodynamics, collateral flow, oxygenation, and brain metabolism effects on tissue.</p> <p>Use imaging in a trial of late IV t-PA administration (4.5 h).</p> <p>Create an acute stroke imaging repository, including infrastructure for standardization.</p>
Genetics	<p>Improve power/sample size and elucidate stroke heterogeneity in clinical trials through large multicenter collaborative recruitment efforts.</p> <p>Integrate genetic studies and pharmacogenetics into clinical trials.</p> <p>Elucidate mechanisms of genetic factors for stroke risk and outcomes.</p>
Omics	<p>Facilitate access to and integration of omics and bioinformatics technology and data.</p> <p>Identify molecular markers or profiles of stroke risk. Enable biospecimen collection and sharing.</p> <p>Foster collaboration between geneticists/molecular biologists and stroke researchers.</p>
Cerebrovascular biology and neurovascular unit	<p>Define cell-specific and molecular mechanisms of disease in the brain vascular bed, including changes caused by stroke risk factors and injury.</p> <p>Elucidate changes during development and aging and after injury.</p> <p>Elucidate cell-to-cell signaling mechanisms within the vasculature and with neurons and perivascular cells.</p>
Coagulation, hemostasis, and endothelial cell interaction	<p>Understand the unique responses of the neurovascular unit components during focal ischemia.</p> <p>Study the effects of innate immune activation on the CNS.</p> <p>Understand how homeostasis in the brain is regulated through permeability barriers and cellular/molecular mechanisms.</p>
Neuro-cerebrovascular degeneration	<p>Understand how the NVU and immune responses mediate transition from injury to repair after stroke.</p> <p>Build better molecular/cellular/animal models for specific stroke risk factors.</p> <p>Understand how timing and dosing in stroke models translate to human timing and dosing.</p>
Biology of repair	<p>Identify restorative molecular/cellular/tissue/systemic mechanisms and corresponding biomarkers of recovery.</p> <p>Define and optimize restorative therapies, including cell-based, pharmacological, and brain-machine interface or stimulation approaches.</p> <p>Identifying animal models for repair, translating repair interventions to humans, and optimizing behavioral and cognitive indices of recovery.</p>
Acute stroke treatment	<p>Make reperfusion therapy swifter, safer, and surer through new drugs and devices.</p> <p>Improve cerebral cytoprotection early and after reperfusion; stabilize the penumbra before reperfusion and block reperfusion injury.</p> <p>Improve acute stroke clinical trial networks, making trials more inexpensive, efficient, and successful.</p>
Neurovascular protection mechanisms	<p>Improve cellular–animal–clinical trial translation interface.</p> <p>Conduct clinical trials that focus on very specific pathology.</p>
CNS hemorrhage	<p>Understand homeostasis and coagulation in the CNS. Improve relevance of animal models of hemorrhage-induced brain injury.</p> <p>Enhance imaging, physiological monitoring, biomarker analysis, and genetic profiling to define time frame, mechanisms, and clinical impact of primary and secondary hemorrhagic injury.</p> <p>Further study of hematoma evacuation, including minimally invasive interventions.</p>
Vascular cognitive impairment	<p>Develop relevant VCI animal models with common vascular risk factors. Develop noninvasive tools for relevant molecular/cellular pathways.</p> <p>Examine the links among small-vessel pathology, neurodegenerative disease, and neurological impairment.</p> <p>Develop large-scale clinical trials of vascular risk factor modification in high-risk subjects.</p>
Recovery and rehabilitation	<p>Develop valid, reliable, affordable, and accessible measures of clinical brain plasticity and functional recovery. Determine use of these markers in guiding interventions.</p> <p>Understand the basis of and maximize benefit of experience-dependent poststroke plasticity.</p> <p>Develop and implement new restorative therapies in humans.</p>

(Continued)

Table. Continued

	Priorities
Prevention of first and recurrent stroke	<p>Improve implementation of stroke prevention interventions by identifying and overcoming barriers and evaluating effectiveness, especially in underserved populations.</p> <p>Track prevalence and impact of risk factors and develop risk factor assessment tools.</p> <p>Identify and evaluate innovative dietary/lifestyle/population stroke prevention treatments and strategies.</p>
Epidemiology and risk factors	<p>Understand stroke risk, determinants, and outcomes in women, racial and ethnic subgroups, children, and geographically distinct populations.</p> <p>Evaluate the validity and effectiveness of electronic medical records for stroke epidemiology.</p> <p>Translate epidemiology knowledge into improved health.</p>
Clinical trials	<p>Improve clinical trial efficiency through improved infrastructure, reimbursement from Centers for Medicare and Medicaid Services for experimental therapies within trials, international collaboration, and coordination of trials.</p> <p>Improve trial design, conduct, and outcome assessment; validate outcome measures; consider innovative statistical approaches and trial designs.</p> <p>Conduct clinical trials to advance evidence-based therapies and for conditions without proven therapies. (A list of examples follows in main text.)</p>
Health services implementation	<p>Evaluate strategies to improve identification, treatment, and control of vascular risk factors. Strategies should include environmental changes, medication compliance, and lifestyle changes.</p> <p>Identify and address barriers to widespread use of hypothermia postcardiac arrest.</p> <p>Identify and uniformly implement strategies to improve patient access to comprehensive rehabilitation services that enhance outcomes poststroke.</p>

CNS indicates central nervous system; NVU, neurovascular unit; t-PA, tissue-type plasminogen activator; and VCI, vascular cognitive impairment.

behavioral interventions, and providing the fundamental preliminary data needed for randomized clinical trials.

Clinical Trials

Several recently completed clinical trials have suggested that future research in prevention should include aggressive treatment of vascular risk factors. They also raise the question of whether the results of prevention trials conducted more than a decade ago are still valid in the modern era of statins and newer antihypertensive medications. In addition, advances in clinical trial methodology and infrastructure will make future trials more efficient. Finally, Centers for Medicare and Medicaid Services reimbursement policies have had a major effect on trial recruitment and need to be coordinated with research efforts.

Three priorities going forward include the following:

Improving efficiency of clinical trials. This includes infrastructure to facilitate timely and efficient completion of trials (creation of networks, National Institutes of Health-sponsored institutional review boards, resources for study monitoring), reimbursement by Centers for Medicare and Medicaid Services for promising but unproven therapies within phase 2 and 3 trials (but non-payment outside of such trials), international collaboration, and minimization of overlapping and concurrent competing trials.

Improving trial design, conduct, and outcome assessment. Outcome variables need to be validated and used across all studies. Training tools for new coordinators and investigators should build on past successful trials, and innovative statistical approaches and trial designs should be considered.

Conducting clinical trials that advance current evidence-based therapies or for those conditions without proven therapies. Examples would include the following:

- a. Acute ischemic stroke: treatments beyond IV t-PA or selecting patients beyond 4.5 hours
- b. Acute intracerebral hemorrhage (medical and surgical)
- c. Ruptured aneurysms
- d. Aggressive medical therapy versus interventional treatment of asymptomatic carotid stenosis
- e. New antithrombotic agents in patients without a cardioembolic source who fail to respond to antiplatelets
- f. Behavior change/primary stroke prevention
- g. Neurorecovery therapies

Health Services Implementation

The effective implementation of stroke-related advances in medical science has the potential to rapidly improve the delivery of care and patient outcomes. Stroke systems of care, including stroke centers, provide the infrastructure for implementing advances in stroke care. On average, patients who receive care at primary stroke centers have better outcomes, and preferential routing of patients to stroke centers by emergency medical services can ensure that stroke patients have access to the highest level of stroke care as quickly as possible. Telemedicine and related technologies can extend expertise from stroke centers to underserved areas. Several tools, such as the American Heart Association’s Get With the Guidelines, are effective for improving processes and measuring the extent to which evidence-based therapies are implemented. New programs that pay for performance may accelerate the adoption and implementation of best practices for hospitals, physician groups, and individual practitioners,

but outcome measures and reimbursement should be appropriately adjusted for stroke severity and medical complexity to reflect the quality of care accurately. More research is needed on health services implementation in general.

Three priorities going forward include the following:

Evaluating strategies to improve the identification, treatment, and control of vascular risk factors across the spectrum of care to reduce initial and recurrent stroke rates and health-care costs. These strategies should include environmental changes and development of effective interventions for improving medication compliance and lifestyle changes. Research programs are needed to determine the causes and remedies for suboptimal risk factor control, including limited access to outpatient care, lack of standardized outpatient performance measures, poor medication adherence, and difficulty in instituting lifestyle changes.

Identifying and addressing barriers to the widespread use of hypothermia to treat postcardiac arrest patients. Hypothermia is a class I level I recommendation and has the potential to improve outcomes and reduce the long-term use of expensive health care and related resources.

Identifying strategies and uniformly applying them to improve patient access to comprehensive rehabilitation

services that have been shown to enhance outcomes and quality of life after stroke.

Acknowledgments

The authors acknowledge Dr Riju Srimal, Dr Katherine Pahigiannis, and Katherine Saylor of the National Institute of Neurological Disorders and Stroke for their indispensable support of the Progress Review Group (PRG) planning effort and for their contributions to the PRG report and this summary.

Disclosures

Dr Grotta receives grant support from Haemonetics and is a consultant for Lundbeck. The other authors have no conflicts to report.

References

1. National Institute of Neurological Disorders and Stroke. Stroke Progress Review Group. <http://www.ninds.nih.gov/strokeprg>. Accessed February 21, 2013.
2. National Institute of Neurological Disorders and Stroke. Final Report of the Stroke Progress Review Group—January 2012. http://www.ninds.nih.gov/find_people/groups/stroke_prg/01-2012-stroke-prg-report.htm. Accessed February 21, 2013.

KEY WORDS: planning ■ priorities ■ recommendations