Advances in Stroke 2017

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Brain Recovery and Rehabilitation

For stroke rehabilitation and recovery, 2017 was a year of reviews and research advances. Reviews included all aspects of poststroke rehabilitation and recovery. Cognitive rehabilitation for memory deficits was effective for memory improvements in the short term, but not in the long term.[1] Circuit class therapy could improve mobility after stroke in a clinically meaningful way, even after 12 months poststroke.[2] Electromechanical-assisted training for walking was most beneficial for subacute stroke survivors who were not ambulatory.[3] Repetitive task training was effective regardless of the amount of task practice, type of intervention, or time since stroke.[4] Physical activity training could positively affect poststroke cognition with small-to-moderate treatment effects that were apparent even in the chronic stroke phase.[5] In all cases, more research was required to improve the quality of the findings, and a review of poststroke fatigue reported that the overall quality of the research was poor.[6]

Discovery research provided more insight into basic aspects of stroke rehabilitation and recovery. Stradecki-Cohan et al[7] studied Sprague–Dawley rats subjected to 5 to 6 days of no (0 m/min), mild (6 m/min), moderate (10 m/min), or heavy (15–18 m/min) treadmill exercise 3 to 4 days poststroke and demonstrated that moderate exercise enhanced cognitive function for 1 week after exercise completion, independent of changes in physical fitness. Chang et al[8] demonstrated that the number of Met alleles in brain-derived neurotrophic factor genotypes and corticospinal tract (CST) functional integrity may be independent predictors of upper extremity motor outcome 3 months poststroke. Tu et al[9] found that concentrations of FABP4 (fatty acid–binding protein 4), an intracellular lipid chaperone involved in coordination of lipid transportation and atherogenesis, were a novel independent prognostic marker for poor functional outcome and mortality 3 months poststroke.

Imaging of the CST also played a role in poststroke functional prognosis. Schulz et al[10] found that different degrees of CST disruption differed in their dependency on structural premotor–motor connections for residual motor output using diffusion-weighted imaging and probabilistic tractography.

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Liu et al[11] reported that local diffusion homogeneity, a complementary marker for white matter alterations of the brain, in the ipsilesional CST paired with clinical assessment in acute stroke may accurately predict resolution of upper limb impairment within 12 weeks after subcortical infarction. Stinear et al[12] demonstrated that stroke survivors with functional CSTs recovered proportionally to their initial upper limb motor impairments, but those without functional CSTs did not recover proportionally and were impacted by greater CST damage. Furthermore, lower limb motor impairment resolved by ≈70% within 3 months after stroke and did not follow the proportionality rule.[13] Finally, Stinear et al[14] applied the Predict Recovery Potential algorithm, consisting of an assessment of paretic shoulder abduction and wrist extension strength, transcranial magnetic stimulation to assess the functional integrity of the ipsilesional lateral CST 5 to 7 days poststroke, and diffusion-weighted magnetic resonance imaging (MRI) to a cohort of acute stroke patients and found that it predicted the primary clinical outcome for 80% of recruited subjects. They reported reduced length of stay by 6 days in subjects for whom therapy content was modified based on the algorithm, when compared with a historical control.[14]

Clinical research continued to play a role in clarifying patterns of functional prognosis. Itaya et al[15] reported that living situation, type of stroke, Functional Independence Measure motor and cognitive scores on admission, and paresis predicted discharge to home after acute stroke with a sensitivity of 88.0% and a specificity of 68.7%. Scrutinio et al[16] developed a predictive models to assist clinicians in decision-making and planning rehabilitation care, including measures of time from stroke occurrence to rehabilitation admission, admission motor and cognitive Functional Independence Measure scores, and neglect; and age, male sex, time since stroke onset, and admission motor and cognitive Functional Independence Measure scores. MacIsaac et al[17] developed a short-form Barthel Index that condensed function to bladder control, transfer, and mobility items. Wang et al[18] developed a Functional Assessment of Stroke consisting of 29 items from 4 short-form tests of the Fugl-Meyer Assessment upper extremity, Fugl-Meyer Assessment lower extremity, Postural Assessment Scale for Stroke patients, and Barthel Index. Kapoor et al[19] reported that the modified Rankin Scale (mRS; modified Barthel index) was inadequate to measure overall stroke outcomes as more than half of stroke survivors with excellent functional recovery measured this way continued to have cognitive impairment and participation restrictions, and one third of patients continue to have depression 2 to 3 years poststroke.

Drug trials continued to have mixed results. A phase IIb double-blind, randomized, placebo-controlled trial of intravenous infusions of the monoclonal antibody GSK249320 within 72 hours of stroke demonstrated no improvement on gait velocity compared with placebo.[20] However, stroke survivors with persistent fatigue reported reduced fatigue and improved quality of life after taking modafinil 200 mg by mouth daily.[21]

Technology played a role in stroke rehabilitation. A preliminary study of the Fitbit One positioned on the nonparetic ankle accurately measured walking steps during inpatient rehabilitation physical therapy sessions.[22] A powered exoskeleton driven by a brain–computer interface, using neural activity from the unaffected cortical hemisphere, produced significant average increases in the Action Research Arm Test score, as well as improvements in grasp strength, Motricity Index, and the Canadian Occupational Performance Measure.[23]

Finally, 2 groups are attempting to facilitate or advocate for quality stroke rehabilitation and recovery research. First, the National Institutes of Health (NIH) instituted NIH StrokeNet, a network of centers that forms a foundation for stroke recovery and rehabilitation research. Several issues that the Working Group are addressing to improve the ability to complete meaningful clinical trials successfully include variable patterns of postacute stroke care delivery; challenges in recruiting and retaining subjects after discharge from the acute care setting; challenges in dealing with social and pragmatic factors in stroke rehabilitation research; the importance of concomitant activity and therapy during research participation; the competition among stroke rehabilitation and recovery research, other stroke trials, and healthcare business practices; the need to implement biomarkers; and standardization of outcomes measures.[24] The other group is an international roundtable of stroke rehabilitation and recovery research experts who are developing a conceptually rigorous framework for stroke rehabilitation and recovery research. They have defined the concepts of rehabilitation and recovery and made recommendations in the areas of basic science, biomarkers of stroke recovery, measurement in clinical trials, and intervention development and reporting.[25] Subsequently, they have defined the concept of sensorimotor recovery and measures consistent with this definition.[26]

Critical Care/Emergency Medicine

Novel Oral Anticoagulants and Intracranial Hemorrhage

With the increasing use of novel oral anticoagulants (NOACs) or direct oral anticoagulants, vascular neurologists and neurocritical care providers are more commonly encountering situations in which decisions need to be made about either starting or reversing these medications. The most common clinical indication for the NOACs is atrial fibrillation, and the most dreaded complication of NOACs is intracranial hemorrhage (ICH). This brief review will summarize the data on the safety and efficacy of the NOACs, with an emphasis on ICH, as well as the strategies to reverse the anticoagulation effects of the NOACs in those suffering bleeding complications.

NOACs and the Risk of ICH

The NOACs, including dabigatran (a direct thrombin inhibitor), apixaban and rivaroxaban (factor Xa inhibitors), and edoxaban (Xa and prothrombinase inhibitor), have at least equal efficacy, and to some extent a better safety profile, compared with vitamin K antagonists (VKAs), in patients with atrial fibrillation.[27–31] A meta-analysis of the randomized trials comparing 42 411 patients treated with NOACs and 29 272 treated with warfarin showed that NOACs significantly reduced stroke and systemic embolic events compared with warfarin (relative risk reduction [RR], 0.81; 95% confidence interval [CI], 0.73–0.91; $P<0.0001$), a result that was mainly driven by a reduction in ICH (RR, 0.49; 95% CI, 0.38–0.64; $P<0.0001$).[32] The relative reduction in ICH, including intracerebral hemorrhage, subarachnoid hemorrhage, subdural

hemorrhage, and epidural hemorrhage, observed with NOACs compared with warfarin was over 50% (RR, 0.48; 95% CI, 0.39–0.59; $P<0.0001$). All-cause mortality was also less in individuals taking NOACs (RR, 0.90; 95% CI, 0.85–0.95; $P=0.0003$), but there was an associated increase in gastrointestinal bleeding (RR, 1.25; 95% CI, 1.01–1.55; $P=0.04$).

More recent evidence from 28 high-quality real-world observational studies confirms the findings of the randomized controlled trials (RCTs) on the efficacy and safety of NOACs (dabigatran, rivaroxaban, and apixaban) in comparison to warfarin in patients with atrial fibrillation.[33] In particular, all 3 of these drugs were associated with a lower risk of ICH (apixaban hazard ratio [HR], 0.45; 95% CI, 0.31–0.63; dabigatran HR, 042; 95% CI, 0.37–0.49; rivaroxaban HR, 0.64; 95% CI, 0.47–0.86). Although the risk of ischemic stroke (IS) and systemic embolism was similar for all drugs, apixaban and dabigatran were both associated with lower mortality and apixaban was associated with fewer major and gastrointestinal hemorrhages.

On the basis of MarketScan data in the specific subgroup of patients with nonvalvular atrial fibrillation who have had a previous IS or transient ischemic attack, neither apixaban nor dabigatran reduced the combined primary end point of IS or ICH (HR, 0.70; 95% CI, 0.33–1.48 and HR, 0.53; 95% CI, 0.26–1.07), whereas rivaroxaban reduced the same combined end point (HR, 0.45; 95% CI, 0.29–0.72).[34] In these analyses, the rate of ICH was similar for the NOACs and warfarin. In a sample of Medicare beneficiaries, however, apixaban use was associated with the highest treatment persistence and lowest risk of any bleeding, compared with warfarin, rivaroxaban, and dabigatran.[35]

In summary, compared with VKAs, the NOACs, dabigatran, rivaroxaban, apixaban, and edoxaban, are at least as effective as VKAs to prevent IS and IS/systemic embolism in patients with atrial fibrillation. Importantly, ICH is reduced by roughly half.[32] Further, when compared with warfarin, NOACs have a more rapid onset of action, a shorter half-life, more predictable pharmacokinetics, less potential drug–drug interactions, and do not require routine monitoring.[36]

Current guidelines for antithrombotic therapy in nonvalvular atrial fibrillation, including the European Society of Cardiology and the American Heart Association/American College of Cardiology/Heart Rhythm Society, generally recommend NOACs in preference to or as an alternative to warfarin for stroke prevention,[37,38] and for patients who need to be anticoagulated despite a high risk for bleeding complications (as estimated by the HAS-BLED score [hypertension, abnormal renal or hepatic function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly (age >65 years), drug or alcohol abuse]), NOACs are felt to be a safer option than warfarin,[39] especially in light of the fact that the risk of major bleeding with apixaban in the AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) was as low as that seen with aspirin.[28]

Unfortunately, there are no direct comparisons of the 4 NOACs, and indirect comparisons between the RCTs are problematic as patients had different risk profiles (ie, different $CHADS_2$ or CHA_2DS_2-VASc scores [congestive heart failure, hypertension, age (≥75 years), diabetes, prior stroke or transient ischemic attack, vascular disease, age (65–74 years), sex category]). Individual assessment of the optimal drug choice and dose adjustments is required for each patient. The elderly with renal dysfunction and with prior strokes are at increased risk of both ischemic events and bleeding events; such individuals require a more nuanced approach to anticoagulant treatment.

When and whether to resume anticoagulation after ICH is a common clinical dilemma.[40] The risk of thromboembolic events, based on a stratification scheme such as the CHA_2DS_2-VASc score, has to be balanced against the risk of ICH recurrence. Factors associated with the risk of ICH reoccurrence include increasing age, poor blood pressure (BP) control, lobar ICH location, the presence of microbleeds on susceptibility-weighted imaging, concurrent aspirin use, and the presence of apolipoprotein E ε2 or ε4 alleles and must be taken into account.[32,40]

NOAC Reversal

The most commonly encountered reason for reversing the anticoagulant effects of NOACs in the neurological intensive care unit is ICH. Hemorrhage enlargement after initial presentation with intracerebral hemorrhage is common and portends a poor outcome.[41] Further, patients who suffer an intracerebral hemorrhage while anticoagulated do worse than patients who are not anticoagulated.[42] Fortunately, the risk of ICH with NOACs is generally less than that with warfarin.[43] Nonetheless, individuals will still present with ICH while anticoagulated with an NOAC. It is thus prudent to understand the most expedient methods for reversing the biological effects of these drugs in the hopes of preventing intracerebral hemorrhage growth, especially in light of data that show rapid reversal of anticoagulation by VKAs is associated with a decrease in hemorrhage enlargement.[44,45]

Observational data suggest that the outcomes of intracerebral hemorrhage associated with the NOACs are similar to that in patient on VKAs—baseline intracerebral hemorrhage volume, the rates of hematoma expansion, 90-day mortality and functional outcome are similar.[46–48] The half-lives of the NOACs are much shorter than that of warfarin, but the risk of hemorrhage expansion occurs early after presentation and it is incumbent on the practitioner to reverse the anticoagulant effects of the NOAC as quickly as possible.

Dabigatran is a direct thrombin inhibitor and currently the only NOAC with a Food and Drug Administration–approved reversal agent, idarucizumab. Treatment with idarucizumab decreases dabigatran levels and normalizes laboratory measures of anticoagulation (including the diluted thrombin time and ecarin clotting time) almost immediately.[49] In a study of the safety and efficacy of idarucizumab for dabigatran reversal, 98 of 301 (32.6%) patients who presented with uncontrolled bleeding had an ICH. Data show that essentially all patients in this study had full reversal at 4 hours after administration of idarucizumab.[50] Thrombotic events occurred within 30 days after treatment in 14 of 301 (4.6%) patients who presented with bleeding complications and were treated with idarucizumab. As this was a single-arm trial, there are no data to prove that reversal of dabigatran with idarucizumab improves outcome from ICH, but with the approval/availability of idarucizumab, such a study could not be ethically done. Laboratory data suggest that prothrombin complex concentrate (PCC) does not adequately reverse the anticoagulation effects of

dabigatran, and PCC should not be given to patients who present with an ICH while on dabigatran.[51]

At present, there are no approved specific reversal agents for the oral factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban). PCCs are often used to reverse Xa inhibitors, and laboratory studies confirm rapid normalization of selected clotting parameters with 4 factor PCC.[52] Data to support the clinical efficacy of PCCs in patients who experience ICH while taking Xa inhibitors, however, are limited. In a multicenter observational study, the use of PCCs did not seem to prevent intracerebral hemorrhage growth or improve outcome.[53]

Andexanet alfa is a specific reversal agent designed to neutralize the anticoagulant effects of factor Xa inhibitors. In a trial of healthy older volunteers, andexanet reversed the anticoagulant effects of apixaban and rivaroxaban within minutes.[54] In a trial of 67 patients with acute major bleeding events within 18 hours after receiving a factor Xa inhibitor, andexanet reduced antifactor Xa activity and achieved effective hemostasis in 79% of patients by 12 hours after infusion.[55] ICH was the presenting bleeding complication in 28 of 67 (42%) patients, and thrombotic events occurred in 12 of 67 (18%) within 30 days of andexanet administration. As with the trial of idarucizumab for neutralization of the effects of dabigatran, this single-arm trial cannot address whether andexanet improves outcome from ICH in patients on apixaban or rivaroxaban. Additional clinical studies are ongoing.

Aripazine (also known as ciraparantag or PER977) is small molecule that binds to unfractionated and low–molecular weight heparins, fondaparinux, dabigatran, and Xa inhibitors. Aripazine has been shown to reverse the effects of edoxaban in healthy volunteers within 10 minutes.[56] Advanced phase clinical studies of aripazine are underway.

In summary, for patients who suffer an ICH while taking dabigatran, treatment with idarucizumab is indicated. For patients who suffer an ICH on apixaban, rivaroxaban, or edoxaban, the current recommendation is to administer PCCs. In the near future, however, it is possible that specific reversal agents will be available.

Emerging Therapies

Over the past 2 years, the results of large clinical trials provided data that have the potential to change clinical practice of stroke care. Some of the results can be seen as hypothesis generating and need to be confirmed by subsequent trials. Herein, we discuss the highlights of several relevant articles during the past 2 years that have influenced the field of emerging therapies for stroke.

Acute Stroke Recanalization Treatment

The ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study)[57] was a noninferiority trial assigning randomly 3310 thrombolysis-eligible patients to low-dose intravenous alteplase (0.6 mg/kg body weight) or to standard dose (0.9 mg/kg of body weight). The trial also included 935 patients who were randomly assigned to intensive or guideline-recommended BP management, the results of this BP substudy are yet to be published. The idea behind the trial was based on the data from Asian cohorts, and the low dose was considered to be noninferior compared with the standard dose on the efficacy and to have lower frequency of intracerebral hemorrhagic complications. Affordability of the low-dose treatment was another aspect driving the need for this trial. The noninferior design of the trial was recently addressed.[58] Treatment with the low-dose alteplase did not reach the prespecified noninferiority boundaries on the primary objective (3-month disability or death, mRS score of 2–6) despite the fact that two thirds of the patients were from Asia, where low-dose alteplase is frequently the treatment of choice because of a presumed high risk of ICH associated with the standard-dose treatment. The percentage of a good functional outcome (mRS score of 0–1) was 48.9% and 46.8% in the standard-dose and low-dose groups, respectively. This was true despite lower rate of major symptomatic ICHs in the low-dose group (1.0% versus 2.1%). Most probably, major hemorrhage occurred in patients with large infarctions and had no impact on the patients' outcome anyway. It would be of interest to have the data of low-dose alteplase in patients with white matter lesions. The trial may be seen as a hypothesis generating for a possible future trial testing low dose versus standard dose in patients on antiplatelet medication. Nonetheless, the trial provided no evidence that treatment of low-dose alteplase should replace the standard dose in acute stroke patients with different ethnical backgrounds and pre-medication.

The DAWN (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo).[59] The trial has clearly showed us that endovascular therapy compared with best medical treatment is associated with an improvement in clinical outcomes (>70% relative reduction in disability) and higher likelihood of functional independence in patients with a large vascular occlusion treated within 24 hours from last known well. It is important to note that the last time seen well does not equal to the first time seen unwell. The majority of patients qualified as wake-up strokes (more commonly in the intervention group) with an average time since last seen well of 13 hours and 5 hours from the time of first observation of stroke symptoms, which is similar to previous endovascular trials. On the other hand, it seems that recanalization treatment may be effective beyond generally accepted time delays from symptom onset as long as the infarct core is relatively small and there is substantial amount of the tissue to be saved. In fact, a clinical-core mismatch as defined by the DAWN trials seems a relevant selection criterion independent of the time of presentation. We still have limited understanding of the therapeutic benefits among patients with larger core infarcts (involving more than one third of the middle cerebral artery) or how to select patients when DAWN prespecified imaging criteria (RAPID automatic patient selection tool) is not available.

Advances in the Management of Hypertension in Acute Stroke

The ATACH-II (Antihypertensive Treatment of Acute Cerebral Hemorrhage II)[60] trial tested 2 different strategies of acute BP management in patients with intracerebral hemorrhage. One thousand patients were randomized to a systolic BP (SBP) target of 110 to 139 or 140 to 179 mm Hg; the trial was stopped because of futility data. There was a clear and early difference in BP values between groups; however, this did not translate into the 3-month functional outcome and mortality. There was no intergroup difference on early neurological deterioration. However, patients in the aggressive BP management had higher frequency

of renal adverse events, which could have been caused by renal hypoperfusion. There was only a trend for a smaller frequency of hematoma expansion in patients randomized to aggressive BP reduction. However, we need to point out that hematoma expansion was much less frequent than expected even in the conservatively treated patients. Of note, hematomas had a small baseline volume (median 10 mL). It appears from these results that hematoma expansion occurs despite early and aggressive BP management. The same held true for the INTERACT-II trial (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial), however, in that trial majority of the patients have not reached the target BP value within prespecified time window, which clearly differs from ATACH-II. It might be of interest to perform a trial similar to ATACH-II but with the BP management already in a prehospital setting. Such trial should analyze not only possible benefits of such an approach but also potential harms of aggressive BP lowering (at least cerebral and renal perfusion).

The SPRINT (Systolic Blood Pressure Intervention Trial)[61] involved 9361 hypertensive patients (mean age, 68 years) randomized to 2 SBP management groups (target <120 versus <140 mm Hg). The key inclusion criteria were an age ≥50 years, SBP of 130 to 180 mm Hg, and evidence of increased cardiovascular risk based on either a 10-year Framingham risk estimate of at least 15% or markers of vascular disease including chronic renal disease in approximately one third of participants. Of note, people with diabetes mellitus or stroke were specifically excluded. As take-home message, people at high cardiovascular risk in the intensive BP group had fewer cardiovascular events compared with the less intensive BP management group. It must be mentioned that the treatment effect was mostly caused by a reduction in heart failure and death. The annual stroke rate was rather low and similar in both groups (0.41%–0.47%), which is very likely related to a low estimated risk of stroke in the trial population. Participants in the more intensive BP arm had more frequently worsening of glomerular filtration rate and more commonly hypotension, syncope, and electrolyte abnormalities. These adverse events are of importance in elder patients, who have an increased risk of stroke. Of note, heart failure was the single most common event reduced in the aggressive BP management arm; however, the benefit of this reduction might not play as important role in stroke survivors. The SPRINT trial will affect the hypertension guidelines; however, we must remember that the trial excluded stroke patients and that beneficial and detrimental effects of aggressive BP management can have different pattern in stroke patients when compared with other patients with substantial cardiovascular risk.

Management of Patent Foramen Ovale

Two new clinical trials and extended follow-up of the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)[62] addressing the management of patent foramen ovale (PFO) for stroke prevention were published simultaneously. Recurrent stroke was significantly less frequent in the closure group compared with medical therapy in the RESPECT trial with extended follow-up (median, 5.9 years). These results were not dependent on age but were mostly seen in patients with atrial septum aneurysm and large shunts. Pulmonary embolism was 3.5-fold more likely in the closure group. The REDUCE trial[63] involved 664 patients with PFO and embolic-appearing cryptogenic stroke, who were randomized in a 2:1 ratio to closure with a GORE HELEX septal occluder/CARDIOFORM septal occluder or antiplatelet therapy. The median follow-up in the trial was 3.2 years, and the observed rate of recurrent stroke was 1.4% in the closure group compared with 5.4% in the antiplatelet group (P=0.002). No interaction across strata of age or shunt size was observed; however, there were no data on atrial septal aneurysm. The CLOSE trial (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence)[64] involved 663 young patients with PFO and presumed cryptogenic stroke. They either had atrial septal aneurysm or a large shunt and were randomized to either (1) aspirin, (2) oral anticoagulation (93% with a VKA), or (3) closure with any CE (European Conformity) approved device, the most common of which was St. Jude Amplatzer device (51%). Mean follow-up was 5.3 years, during which the patients in the closure group have not experienced stroke whatsoever, which was significantly different from 6% of patients treated with antiplatelets. Again, the benefit of closure over antiplatelet therapy was not related to patients' age, shunt size of even atrial septal aneurysm. There was no statistical comparison between the closure and anticoagulation (1.6% recurrent strokes: in 1 case an aneurysmal subarachnoid hemorrhage). No significant difference was detected between patients on anticoagulation and antiplatelet therapy, but an estimated 5-year risk was lower in the anticoagulant arm (1.5%) than in the antiplatelet arm (3.8%). PFO closure reduces the risk of recurrent stroke in cautiously selected young (<60 years) patients with assumed cryptogenic stroke after a thorough diagnostic workup. The absolute benefit seems to be modest and the annual risk of stroke recurrence to be low, but the cumulative lifetime risk needs to be considered especially in the young. Because there is a small risk of closure-related complications and closure itself is not an emergency procedure, one may allow time for counseling and weighing the pros and cons.

We presented several well-designed and conducted trials, which have impacted clinical practice. There are emerging data on benefit of PFO closure in carefully selected patients with embolic-appearing cryptogenic stroke. There is a new hope for wake-up stroke patients with large-vessel occlusion (LVO) with small core and salvageable tissue. Low-dose alteplase did not find a place in stroke thrombolysis; however, its role in patients on antiplatelet medication could be tested in a new trial. There is still an equipoise on drastic lowering of the BP in ICH patients with a new trial possibly to come.

Genetics

The advent of the sequencing of the human genome is now 15 years old.[65,66] The technologies developed from this historic achievement have rapidly progressed, and implementation has led to numerous advances throughout the medical literature. In the last update in 2012, Meschia et al noted the high heritability of traits such as IS, large-vessel IS, and the importance of subtype specificity of findings to date.[66a] To maximize the power for discovery, generalizability, and clinical utility of genetic discoveries, investigators of the International Stroke Genetics Consortium have set up several large-scale partnerships.

Recent discoveries in IS genetics have emerged from 3 major consortia: Malik et al[67] reported on 12 genome-wide

association studies comprising 10 307 cases and 19 326 controls that were meta-analyzed as part of the METASTROKE consortium. Findings from the discovery phase were replicated in White (13 435 cases and 29 269 controls) and South Asian (2,385 cases and 5,193 controls) samples followed by a transethnic meta-analysis. The authors found 4 loci to reach genome-wide significance including a novel locus (*ABO)* for all IS along with replication of the *HDAC9* locus for large artery stroke, and *PITX2* and *ZFHX3* for cardioembolic stroke.[67] Variants at ABO have previously been shown to be associated with circulating levels of von Willebrand factor and factor VIII,[68] and the signal for ABO was strictly confined to large artery stroke and cardioembolic stroke,[67] thus emphasizing the role of thrombotic factors in these stroke subtypes.

The NINDS SiGN (National Institute of Neurological Disorders and Stroke Genetics Network) which includes data from an international collaboration on 16 851 cases and 32 473 stroke-free controls along with replication in 20 941 cases and 364 736 stroke-free controls identified a novel locus at 1p13.2 near *TSPAN2* that showed association with large artery stroke.[69] This study also confirmed prior genome-wide associations at *HDAC9*, *PITX2,* and *ZFHX3*. *TSPAN2* is expressed in arterial tissue and in whole blood cells, and *Tspan2*-deficient mice demonstrate increased neuroinflammation with activation of microglia and astrocytes, thus pointing to a possible role of Tspan2 in inflammation. The gene has also been associated with migraine although at a slightly different genetic locus.[70] The SiGN publication reclassified all strokes using the Causative Classification of Stroke system which is a web-based subtyping system to harmonize subtyping.[69] The Causative Classification of Stroke permits evaluation of not only subtype of IS, but subphenotypes such as intracranial versus extracranial disease, possible, probable and definite subtypes, and clinically specific syndromes.

The CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology; 18 population-based cohorts with 84 961 participants) recently reported on a novel locus on chromosome 6p25 near the *FOXF2* gene that reached genome-wide significance for all stroke (encompassing IS and hemorrhagic stroke [IS]) and replicated 7 of 8 known loci.[71] CHARGE included 4348 patients with incident stroke, and the findings were supported by the association with white matter hyperintensity burden and studies in animal models showing that deletion of *Foxf2* in mice is associated with infarction, reactive gliosis, and microhemorrhage. *Foxf2* has been shown to be required for brain pericyte differentiation and development of the blood–brain barrier and hence provides mechanistic insights.[72]

In HS, a meta-analysis including 1545 cases of spontaneous intracerebral hemorrhage (ICH) compared with 1481 controls identified a region on chromosome 1q22 with genome-wide association for nonlobar ICH, which was replicated in a cohort of 1194 cases and 2261 controls.[73] This finding is further supported by the association with white matter hyperintensity burden in CHARGE and a reported association with microbleeds.[74] In addition, Anderson et al[75] evaluated variants in the CETP (cholesteryl ester transfer protein) and found that variants associated with increased HDL (high-density lipoprotein) raised the risk of ICH. Hypercholesterolemia has a curious association with a decreased risk of intracerebral hemorrhage with low HDL and high HDL being associated with an increased risk. These findings augment the well-established role of apolipoprotein E alleles and risk of intracerebral hemorrhage.[76]

Novel discoveries continue to progress for Mendelian forms of stroke. In a targeted (candidate gene) approach, Rannikmäe et al[77] evaluated common genetic variants in genes previously shown to be associated with familial small-vessel disease (SVD; COL4A1, COL4A2, NOTCH3 [neurogenic locus notch homolog protein 3], HTRA1, TREX1, and CECR1) and examined these genes for association with both IS and intracerebral hemorrhages. Common variants at *COL4A2* were found to be associated with lacunar stroke and with deep ICH,[77] thus extending the involvement of *COL4A1* and *COL4A2* from rare familial forms of cerebral SVD[78,79] to sporadic SVD with allele frequencies as high as 41%. This approach furthers our understanding that cerebral SVD may manifest as white matter hyperintensity, small-vessel lacunar stroke, or deep intracerebral hemorrhage from a common underlying mechanism. Collagen 4A1 and 4A2 form heterotrimers, and mutations in either of these genes have been shown to interfere with proper formation of mature collagen molecules. Interestingly, analyses including exome sequencing in patients with pontine autosomal dominant microangiopathy with leukoencephalopathy revealed variants at a microRNA binding site within the 3′ untranslated region of the *COL4A*1 gene.[80] Variants at this site cause the upregulation of COL4A1 gene expression by disrupting miRNA29 binding—a mechanism separate from prior studies evaluating glycine variations.[80–82] Variants at *COL4A2* have further been associated with a combined phenotype of familial porencephaly and SVD.[83–85]

Further adding to the spectrum of Mendelian conditions associated with stroke, Bugiani et al[86] recently identified a rare variant within the CTSA (cathepsin A) that segregated with the disease in 2 families with adult-onset cerebral SVD and a common ancestor. This condition is now termed cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL).

Genetic risk scores are generated by the integration of ≥2 individual polymorphisms with an established association with a target phenotype such as hypertension. Each polymorphism may contribute a small amount of risk, and yet those with greater accumulation of these minor risks should theoretically have a higher risk of disease. In 2014, Malik et al[87] reported on gene risk scores for atrial fibrillation, coronary disease, hypertension, and SBP and other risk factors for stroke which associated with IS among participants in the METASTROKE collaboration with follow-up in the CHARGE Consortium. Falcone et al[88] reported on 39 SNPs (single-nucleotide polymorphisms) associated with BP levels, and although no single SNP was associated with ICH or pre-ICH hypertension, the BP risk score was associated with risk of ICH and in particular with deep ICH. These common and readily available gene risk scores may someday permit assessment well before stroke occurs on the most critical risk factors to seek and address in a patient population.

MR studies (Mendelian Randomization) refer to studies that use the genetic risk for a particular trait such as SBP or obesity. By extending from the risk scores described above for risk of disease, one can evaluate the scores through MR to

help in clarifying causal relationships between biomarkers or candidate risk factors and diseases such as stroke. A particular strength of MR is that it minimizes biases from reverse causation (eg, stroke may lead to behaviors that lower risk factors), confounding (eg, obesity may be associated with hypertension leading to an appearance of greater risk), and regression dilution bias (errors in measurement lead to a dilution or underestimation of true risk). Thus, a gene risk score for obesity, for example, can establish whether or not those at risk for obesity are at risk for stroke regardless of these biases. Dale et al[89] using data from the METASTROKE consortium recently undertook such an MR evaluation for adiposity and body fat distribution with coronary heart disease and IS and stroke subtypes. They were unable to identify a clear causal relationship with obesity and stroke or its subtypes, suggesting that the relationship may indeed be confounded by associated risk factors. But they did identify some evidence for waist:hip ratio with IS. This finding toward a risk of central obesity, rather than peripheral obesity, can help guide future studies in this line of research.

As illustrated by the development of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors and antisense oligonucleotides for lipid lowering,[90] genetics may provide a key opportunity to improve drug development efforts for stroke. Machuca-Parra et al[91] recently reported that systemic administration of an agonist NOTCH3 antibody prevents mural cell loss and modifies plasma proteins associated with Notch3 activity in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) C455R transgenic mice, thus extending targeted treatment paradigms to monogenic causes of stroke.

To summarize, major findings in stroke genetics have largely been subtype specific. The era of genome-wide association studies used a hypothesis-free approach, and the findings identified thus far were associations with genes that were unlikely to have been researched in the candidate gene era. The accumulation of numerous small risks likely determines the genetic association with stroke with 1 major and Mendelian inheritance stroke gene being unlikely. The accumulating evidence allows for the development of gene risk scores, new evidence for mechanisms and subtypes, and targets for potential treatment and prevention. The future may include translating these findings into clinical practice and development of novel therapeutics and expansion to different race/ethnicities, subtypes, and novel technologies.

Health Policy/Outcomes Research

Large-scale population-based studies and smaller hospital-based clinical studies have played a prominent role in providing comprehensive descriptions of the epidemiology of stroke. These studies have been largely focused on describing the patterns and clinical features of stroke according to the demographics and risk factors and determining the association between these factors and patient outcomes. More recently, stroke registries have been initiated to fill an important gap in our knowledge of how the quality of stroke care relates to patient outcomes, with the added aim of translating their findings into practice.

The expansion of quality-of-care–based stroke registries has been driven by the need to provide high-quality and effective acute stroke care. Indeed, in a recent review, Cadilhac et al[92] identified published reports from national-level stroke registries in 25 different countries. The main aims of these reports were to determine the impact of acute stroke therapies, such as thrombolysis, on patient outcomes and document the role of systems-level approaches to maximize adherence to quality-of-care indicators and to improve patient outcomes.[93,94] Although stroke registries have the common goal of improving the quality of stroke care and outcomes, there is substantial variability between them in terms of their structure, organization, and funding support.[92,95–98]

The development of nationally representative stroke registries has dovetailed with a broader recognition of the value of clinical patient registries.[99] Apart from measuring quality-of-care and patient outcomes, these national registries enable better monitoring of the safety and harm of specific products or services, as well as the assessment of clinical effectiveness and costs in a more representative sample of stroke patients than can be achieved with single or local hospital-based studies.

To determine whether improvements in the quality of care demonstrated in many of these registries have resulted in better patient outcomes,[96,100,101] patients must be followed up. All of the established stroke registries include the collection of outcomes, while the patient is still in hospital (ie, complications, deaths) or at discharge (eg, destination, functional status). Some of the registries, for example, the Swedish National Quality Registry for Stroke (RIKS-Stroke),[96] Australian Stroke Clinical Registry (AuSCR),[102] European Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST),[95] and the UK Sentinel Stroke National Audit Program (SSNAP)[103] also incorporate patient-reported outcome measures (PROM) collected after patients have left the hospital. PROM data are regarded as the gold standard patient outcome measures and typically include data on functional status (disability) and quality of life that are typically collected at 3 or 6 months after discharge. Collection of these data has been undertaken using a variety of methods including face-to-face interviews,[98] mailed questionnaires,[104] or telephone interviews with patients.[105] However, collection of PROMs represents considerable practical challenges in terms of the amount of resources (personnel time and costs) required of hospitals and registries.

Given the intensive resources required to track individual-level PROMs after discharge, data linkage to other routinely collected data provides an alternative approach to obtain data on longer-term outcomes. This approach is facilitated by the widespread availability of electronic health data, other large-scale administrative (billing) health data, vital records, and census data and should result in much greater efficiency for registries that are able to link to these data sources.[106] The success of this approach has been demonstrated within several registries including those in Sweden,[97] Canada,[101] the United States,[107] and Australia[108,109] with the linked data being used to ascertain a wide variety of outcomes including longer-term mortality, readmissions, return to home, follow-up physician visits, and medication use. However, practical challenges to this approach can often be daunting, especially when multiple agencies are involved.[108] Despite these difficulties, within the past 2 years, there has been a growing number of studies that

include linkage of stroke or cardiovascular registry data to other administrative, billing, or vital records data[110–114] or the cross-linkage of multiple clinical electronic health databases for research purposes.[115–118] These studies can provide the evidence needed to demonstrate that better quality of care is associated with reduced mortality, reduced readmissions, return to home, and other beneficial health outcomes.

However, informed consent processes within stroke registries can become major impediments to data linkage. These consent processes are highly variable and depend in part on the policies and preferences of local organizations and research oversight committees.[92,108] In some registries, consent must be obtained from patients before any data collection,[102,119] whereas in others, collection of in-hospital data has been approved with a waiver of consent.[100,120,121] In some registries—including those in Sweden, Ontario, Australia, and the United Kingdom—such waivers are combined with an opt-out function where individual patients can request that their data not be included in the registry.[104,119,121] The use of waiver and opt-out consent protocols help minimize the dropouts that can occur when written informed consent is required[119] and ensure a more generalizable sample of patients that occurs when only opt-in individual consent is required.

Over the past 20 years, the development of stroke registries and other community-based data systems around the world has provided the data necessary to promote substantial gains in the quality of care provided to patients with acute stroke. Ongoing registries have many benefits including the accrual of large sample sizes and the broad generalizability of stroke that they encompass in regions where the majority of people with stroke are hospitalized. A considerable number of opportunities exist for the continued development of stroke registries, especially in the area of data linkage, which is important for the assessment of quality-of-care processes on longer-term outcomes, such as rehospitalization and long-term service utilization. Further research is needed to develop efficient mechanisms to link registry data to complementary databases, as well as to create cost-efficient and sustainable systems to collect valid long-term PROM data. Development of these efficiencies may also help promote use of these approaches in low- to middle-income countries—where such data are currently lacking.

Continued development of the capacity and efficiencies in data linkage processes will increase the value of stroke registries by ensuring that they remain an efficient mechanism to track, improve, and evaluate the quality of stroke care and patient outcomes.[106]

Imaging

Thrombectomy is now the gold standard treatment for patients experiencing an acute brain infarction or cerebral ischemia caused by an LVO of the internal carotid artery or M1 segment of the middle cerebral artery when therapy can be initiated within 6 hours of onset.[122] Imaging selection can be limited to the absence of hemorrhage and a favorable Alberta Stroke Program Early CT Score (ASPECTS) on a noncontrast computed tomography (CT) in addition to an LVO documented by vessel imaging. However, prospective cohort studies report that ≈20% of patients presenting with acute stroke had experienced a wake-up or unknown onset stroke.[123] As a consequence, those patients typically do not meet the 6-hour window criteria to receive routine endovascular revascularization treatment, despite the likelihood that many may still have salvageable brain tissue.

For the past few decades, it has been postulated that advanced, multimodal brain imaging could be used to guide acute stroke treatment by identifying patients with small core infarcts and substantial volumes of ischemic penumbra, particularly in late time windows. Several experimental studies demonstrated that the presence of a mismatch (small ischemic core, large perfusion deficit) on multimodal imaging is a reliable surrogate for the presence of substantial ischemic penumbra.[124]

With the publication of the positive DAWN and DEFUSE-3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke), this year has witnessed a long-awaited breakthrough in advanced stroke imaging and acute stroke therapy: validation of the imaging selection hypothesis.[59,125]

Imaging Selection Criteria

Many approaches have been proposed to identify patients with favorable imaging profiles likely to benefit from acute reperfusion therapies. Central to all of these are the concept of a small region of core infarct and a large region of salvageable penumbral tissue (mismatch). The mismatch definitions used in various RCTs of thrombectomy have varied, but several have used the same thresholded parameters to outline the ischemic core and region of critical hypoperfusion.[59,125–128] Here, we focus on the definitions used in the current trials of imaging selection for thrombectomy beyond 6 hours.

These recent trials have relied on 2 parameters that offer the best estimation of the ischemic core: the Apparent Diffusion Coefficient on magnetic resonance diffusion-weighted imaging and relative cerebral blood flow on CT perfusion (CTP). Apparent Diffusion Coefficient and relative cerebral blood flow thresholds have been defined by their ability to predict the volume of final infarction after reperfusion.[129,130] After back-to-back direct comparison with gold standard techniques such as positron emission tomography scan or Xe CT, TMax with a delay longer than 6 s seems to be the more reliable parameter to outline critical hypoperfusion.[131,132]

In 2004, Dávalos et al[133] proposed the concept of a mismatch between a clinical deficit disproportionately severe relative to the initial infarct volume. An adaptation of its definition, using thresholded maps to assess the volume of ischemic core on CTP or diffusion-weighted imaging was developed as inclusion criteria for the DAWN trial (Table). The DEFUSE-3 trial used the definitions for target mismatch (TMM) developed and refined from previous DEFUSE-2 and CRISP study (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease).[134,135]

For these recent trials of thrombectomy beyond 6 hours, 2 different types of mismatch have been defined:

1. TMM:
   - maximal volume of the ischemic core, and
   - the ratio and the absolute difference critically hypoperfused region volume outlined by a TMax delay >6 s.
2. Clinical infarct mismatch:
   - maximal volume of the ischemic core, and
   - neurological deficit assessed by the National Institutes of Health Stroke Scale.

Table. DAWN and DEFUSE-3 Mismatch Definitions Are Summarized in the Table

DAWN clinical infarct mismatch[59]	DEFUSE-3 target mismatch[125]
Ischemic core (MR DWI or CTP rCBF)	Ischemic core (MR DWI or CTP rCBF)
	Critical hypoperfusion (CTP and PWI TMax >6 s)
Age ≥80 y; NIHSS ≥10; Ischemic core <21 mL	Ischemic core <70 mL
Age <80 y, NIHSS ≥10; Ischemic core <31 mL	Mismatch ratio ≥1.8
Age <80 y, NIHSS ≥20 an infarct; 31≤Ischemic core<51 mL	Mismatch volume ≥15 mL

CTP indicates computed tomographic perfusion; DAWN, DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DWI, diffusion-weighted imaging; MR, magnetic resonance; NIHSS, National Institutes of Health Stroke Scale; PWI, perfusion weighted imaging; and rCBF, relative cerebral blood flow.

Use of Multimodal Imaging Within 6 Hours From Onset

Of the positive trials demonstrating clinical benefit from thrombectomy for LVO within 6 hours of onset, many approaches to imaging selection were used. Common to each of these was demonstration of an LVO on vessel imaging and small core infarct regions (eg, ASPECTS score of ≥6). Two randomized trials conducted within 6 hours did use the presence of a TMM on CTP/MRI as an inclusion criterion.[126,127] One trial included measures to select patients with moderate-to-good collateral flow.[136] The percentage of increase in mRS score of 0 to 2 at 90 days was between 25% and 31% in RCTs using advanced imaging inclusion criteria versus 11% to 16% in those using noncontrast CT.[137] This finding suggests that the presence multimodal advanced imaging may identify the patients who will benefit the most from an emergent revascularization therapy within 6 hours after onset. However, other factors such as the exclusion of patients with cervical artery occlusion, a shorter delay from onset to revascularization by comparison with other trials might have also contributed to this difference.[138]

It is also possible that advanced imaging may be used to exclude those patients unlikely to benefit or even be harmed (malignant profile).[139] However, the trials that used advanced imaging did not enroll all patients regardless of their imaging profile and may have therefore excluded some patients who would have benefited from treatment. Further RCTs are needed to answer these questions. In the meantime, there are overwhelming data demonstrating that noncontrast CT and vessel imaging are sufficient to screen patients for thrombectomy within 6 hours of onset, and multimodal brain imaging is not currently recommended for the selection of patients within this timeframe.[122]

Wake Up, Unknown Onset, and >6 Hours Strokes

In November 2017, the results of the DAWN trial were published demonstrating clinical benefit in imaging-selected patients treated with stent retrievers 6 to 24 hours from onset. Imaging selection criteria required demonstration of a clinical infarct mismatch on CTP/MRI and an internal carotid artery/M1 occlusion. Good functional outcome (mRS score of 0–2) at 3 months was >3× higher in the thrombectomy arm (49%) compared with the rate observed in the standard care arm (13%).

In January 2018, the results of the DEFUSE-3 trial were presented.[125] This trial, using imaging selection for acute stroke patients presenting 6 to 16 hours after they were last known to be well, randomized patients to standard medical care plus thrombectomy (by any approved device) versus standard medical care alone. Imaging selection criteria required presence of a TMM on CTP/MRI. The rate of good functional outcome at 3 months was 2.6× higher in the thrombectomy arm (47%) compared with the standard care arm (17%). In addition, the 90-day mortality rate was almost 2× lower in the endovascular therapy group compared with the standard medical care group (14% versus 26%; P=0.05). Of note, 38% of the patients enrolled in DEFUSE-3 did not meet the inclusion criteria for DAWN, mostly because of an National Institutes of Health Stroke Scale score of <10, and did still benefit from endovascular treatment.

Altogether the rates of good functional outcome in these 2 trials of late thrombectomy therapy for imaging-selected patients, (49% and 47%) were in the range observed in the randomized trial performed within 6 hours and number to treat (2.8 and 2) the lowest observed in a randomized thrombectomy trial.[140]

Several additional points should be noted. There may be patients not meeting inclusion criteria for the DAWN/DEFUSE-3 trials who may still benefit from therapy beyond 6 hours. In both trials, the rate of good outcome for patients enrolled in the medical arm was particularly low with a rate of favorable outcome (mRS score of 0–2) of 13% and 17% at 3 months. Those findings were partially explained by the very low rate of thrombolysis (13% and 9%) in the control group of patients with a large penumbra that will progress into infarction in the absence of reperfusion. Finally, the median core volume assessed by the RAPID software in both trials were small (<10 mL).[59,125] Considering the low number to treat in both trials, this last result suggests that patients with larger core may still benefit from thrombectomy.

Conclusions

1. Within 6 hours after onset, selection of the patients based on favorable imaging patterns including TMM may be associated with a larger therapeutic effect than the one observed in patients selected with noncontrast CT, but for now there is no evidence to limit thrombectomy only to patients with a TMM. Benefit of thrombectomy in the subgroup of patients with a large ischemic core remains to be validated.
2. Patients experiencing an acute IS within 6 to 24 hours of last known normal with a demonstrable internal carotid artery/M1 occlusion and a clinical infarct mismatch based on DAWN criteria (up to 24 hours) or a TMM based on DEFUSE-3 criteria (up to 16 hours) should be treated with thrombectomy.

Interventional Radiology

Management of intracranial aneurysms is still challenging in 2017. A large series of 510 patients with untreated ruptured aneurysms reinforces the idea that treatment of ruptured aneurysms is mandatory to improve clinical outcome of patients.[141] In this series, the median survival time from symptom onset to death was 20 days. The 1-year mortality rate was 65% for

the whole group and 75% for good-grade patients admitted within a week.

The debate on indications for treatment of unruptured aneurysms is not close, and identification of factors helping in the decision-making process is important. Irregular aneurysm shape is considered in unruptured intracranial aneurysm treatment score (UIATS) as a factor associated with a higher risk of rupture.[142] In patients with multiple aneurysms and subarachnoid hemorrhage, irregular shape identifies ruptured aneurysms.[143] Importantly, in a series of 29 patients with angiograms before and after the rupture, the changes in aneurysm morphology observed after rupture is the compound effect of time with successive growth and formation of irregularities and the impact of the rupture per se.[144] Then postrupture morphology should not be considered an adequate surrogate for the prerupture morphology in the evaluation of rupture risk. An important emerging biomarker for the detection of unstable unruptured aneurysms associated with a higher risk of aneurysm rupture is aneurysm wall enhancement.[145,146]

Facing patients with unruptured (and also ruptured) aneurysms, it is important to manage risk factors associated with aneurysm growth and rupture. The 2 most important risk factors are smoking and hypertension. Two recent studies show that smoking intensity and duration are significantly associated with the risk of aneurysm rupture.[147,148] Smoking cessation is not associated with a reduced risk of rupture beyond that of reducing the cumulative dose.[148] A recent study shows that current alcohol consumption and intensity are significantly associated with intracranial aneurysm rupture.[149] This increased risk is not persisting in former alcohol users outlining the importance of alcohol cessation in patients with intracranial aneurysms.

On the endovascular techniques for intracranial aneurysms, there are still some controversies on the benefit of hydrocoils. In large and recurrent aneurysms, hydrogel coiling was not shown to be better than platinum.[150] However, GREAT study (German Randomized Endovascular Aneurysm Trial) that was randomly comparing bare and second-generation hydrogel coils shows that hydrogel coils are associated with reduction of the rate of unfavorable outcome events.[151] The benefit of the hydrogel coils is confirmed by the Gel-the-Neck registry.[152] Evaluation of new endovascular techniques for aneurysm treatment is continuing. Flow diversion represents an important development in the endovascular treatment of complex intracranial aneurysms, singularly large and giant aneurysms or wide-neck aneurysms. The 5-year results of the PUFS trial (Pipeline for Uncoilable or Failed Aneurysms) demonstrate the safety and high efficacy of flow diversion with Pipeline for the treatment of large and giant aneurysms of the intracranial internal carotid artery with high rate of complete occlusion (95.2%).[153] Flow disruption with intrasaccular devices is also an important advance in the management of wide-neck bifurcation aneurysms, and the recent analysis of the cumulated population of 3 good clinical practice studies dealing with this technique confirms the high safety and good efficacy of this technique at 1 year.[154]

The biggest news for the year was the DAWN trial results.[59] Patients were enrolled who were last seen normal between 6 and 24 hours from presentation. There needed to be a mismatch between clinical deficit and infarct volume. Patients were randomized to endovascular thrombectomy (EVT) using Trevo device plus standard of care versus standard of care alone. The study was stopped early with 206 patients enrolled because of the results of a prespecified interim analysis. The rate of functional independence at (mRS score of 0–2) 90 days was 49% in the thrombectomy group when compared with 13% in the control group. There was no significant difference in symptomatic ICH or mortality between the 2 arms.

This trial is a landmark study not only in the efficacy of EVT in the later time window but will have major implications on the organization of stroke care.

The ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness)[136] enrolled patients up to 12 hours from symptom onset. A total of 59 patients were randomized in the late time period. The results of these patients were also published recently.[155] The results from these 59 patients did not show any heterogeneity of treatment effect compared with the early patients. Interestingly, the good outcome rate in this study (mRS score of 0–2) were almost identical to the DAWN trial (48.5% versus 49%). The selection and inclusion criteria in ESCAPE were much more inclusive (any age, simpler imaging criteria ASPECTS >5; LVO and moderate-to-good collaterals on CTA [preferably multiphase]) and easier to implement in practice.

The ASTER trial (Contact Aspiration vs Stent Retriever for Successful Revascularization)[156] compared aspiration versus stent retrievers for EVT. The primary outcome was degree of revascularization (modified Treatment in Cerebral Infarction 2b-3 rates). The study found similar rates of reperfusion (85.4%; n=164) in the contact aspiration group versus 83.1% (n=157) in the stent retriever group; there were no significant differences between the 2 groups for the clinical efficacy outcomes (change in National Institutes of Health Stroke Scale score at 24 hours, mRS score at 90 days) and adverse events.

Since EVT became standard of care in 2015, one of the biggest practical issues is getting the correct patient to the correct hospital.[157] In addition, challenges of organization of stroke care and optimal organization of stroke call have been discussed.[158,159] Conditional probability models, based on time from onset to treatment and the decay in probability of good outcome for both alteplase and EVT over time, have been created to predict whether drip-and-ship or mothership transport is superior in patients with stroke because of LVO.[160,161] The decision to use drip-and-ship or mothership is sensitive to the distance of the patient from both non-EVT–capable and EVT-capable hospitals, the transport time between these 2 hospitals, and the treatment times (door to needle and door to groin puncture) at each hospital. Using 2-dimensional temporal-spatial diagrams, Holodinsky et al[160] have graphically displayed the model results in a variety of scenarios with varying distances between the EVT-capable and non-EVT–capable hospitals and at different hospital efficiencies, the results have also been mapped in the state of California, United States, and the provinces of Alberta and Ontario, Canada. These models show that with a 60-minute door-to-needle times at non-EVT–capable hospitals, drip-and-ship is only relevant when the travel time between the 2 hospitals is at least 45 minutes and the patient is in the immediate vicinity of the non-EVT–capable hospital or would travel past it en route to the EVT-capable hospital. However, as door to needle is reduced, the area where

drip-and-ship predicts best outcomes widens. Notably, these models were designed for patients with known LVO; ongoing work is addressing this assumption as it is expected the model results will also be sensitive to the probability of having an LVO based on paramedic field triage. The ongoing RACECAT trial (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion) in Barcelona, Spain (Unique identifier: NCT02795962, clinicaltrials.gov), is also addressing the question of transportation strategy for suspected LVO stroke patients. However, as context-specific factors have a large effect on decision-making, these results may not be generalizable to jurisdictions with different geographic or system-level constraints. However, empirical data from RACECAT may be combined with modeling strategies and be useful in predicting the best transport strategy in regions where the randomized comparisons are not feasible.

Population Studies

Several advances have been made using epidemiological research that has improved our understanding of stroke prevalence, incidence, and risk factors which we aim to summarize here.

Global Burden of Stroke

Sex Differences

Globally, ischemic heart disease and stroke are the biggest contributors to mortality, accounting for a combined 15 million deaths.[162] The GBD (Global Burden of Diseases, Injuries and Risk Factors) observed that the global burden of stroke has been increasing for both men and women, but the increases have been greater among men. There is a trend toward a decreased incidence of IS in women from 1990 to 2013, with no significant change detected for men. This is in some contrast to changes in the United States, where declines in all stroke and IS have been larger in men than women.[163] The GBD 2013 authors postulated that improved vascular risk factor control and better healthcare interventions were the most likely explanations for reductions in stroke incidence over this period seen for both sexes.

Age Differences

In a separate but related analysis, the GBD 2013 also looked at the age-specific patterns of incidence, prevalence, and mortality rates by country development. At age ≥50, IS incidence rates in developed countries were higher and demonstrated a steeper increase with age than that in developing countries; however, IS mortality rates were greater in developing countries but showed similar age-related increases in developed and developing countries. The GBD 2013 also found that the age-specific incidence and mortality rates of HS were greater in developing countries after the age of 39 years.[164]

Individual Risk Factors and Stroke

Hypertension and Stroke

Large-scale epidemiological studies have provided overwhelming evidence that high BP, in all age groups and in both the sexes, is associated with an increased risk stroke and vascular mortality (as well as with a range of other fatal and nonfatal vascular events).[165] The burden of stroke (as measured by disability-adjusted life years), is particularly large in low- and middle-income countries.[166] In low- and middle-income countries such as China, where the prevalence of hypertension is high and the awareness and management of hypertension is poor,[167] this is likely to contribute to the high burden stroke. A recent article from the China Kadoorie Biobank, a large-scale prospective cohort study of 0.5 million Chinese adults, found that about one third of Chinese adults in this population had hypertension. They also noted that the levels of diagnosis, treatment, and control were much lower than in Western populations and were associated with significant excess cardiovascular disease mortality (including stroke).[168] In contrast, in a pooled analysis of the REGARDS (Reasons for Geographic and Racial Differences in Stroke), MESA (Multi-Ethnic Study of Atherosclerosis), and JHS (Jackson Heart Study) that with the downward shifts in the entire BP distribution in the United States, over half (63.8%; 51.8%–75.8%) of stroke events are now occurring in individuals with BPs <140/90 mm Hg,[169] underscoring the importance of the new BP guidelines with lower thresholds for treatment.[170]

Diabetes Mellitus and Stroke

Although gains have been made over the past 2 decades in reducing the burden of stroke, the recent rise in rates of type II diabetes mellitus threatens to reverse these advances.[171] The Greater Cincinnati/Northern Kentucky stroke study found that diabetes mellitus was associated with increased IS incidence in all age groups, but this risk was strongest before the age of 55 years in Blacks and before the age of 65 years in Whites.[172] Diabetes mellitus seems related to both IS and HS, where The Emerging Risk Factors Collaboration showed that the adjusted HRs with diabetes mellitus were 2.27 (95% CI, 1.95–2.65) for IS, 1.56 (95% CI, 1.19–2.05) for HS, and 1.84 (95% CI, 1.59–2.13) for unclassified stroke.[173]

Dietary Factors and Stroke

Recent evidence from prospective studies of the association of dietary factors with stroke has highlighted 2 nutrients: long-chain omega-3 polyunsaturated fatty acids[174] and dietary fiber[175] that were inversely associated with stroke risk. A meta-analysis of prospective cohorts confirmed these findings and also identified that several foods (fruit, vegetables, fish, milk, eggs, tea, coffee, and nuts) are robustly inversely associated with risk of stroke.[176] Meta-analyses have also confirmed an inverse association between dietary potassium and stroke, and the World Health Organization has issued guidance on increasing potassium levels.[177] A recent Swedish study investigated adherence to the Dietary Approaches to Stop Hypertension (DASH) diet and found that it was inversely associated with the risk of IS, but not associated with intracerebral hemorrhage (ICH) or subarachnoid hemorrhage.[178] The authors suggested that the potential mechanisms for lower risk of IS could be that in addition to lowering BP, the DASH diets may lower antiatherosclerotic effects because these diets are rich in antioxidants from plant foods and low in saturated fatty acids and cholesterol.[178] A Danish study investigated the role of a Nordic diet (mainly including fish, apples and pears, cabbages, and root vegetables) in the prevention of stroke and found similar benefits for IS and nonsignificant benefits for HS.[179] A recent study from the Northern Manhattan study

investigated whether sodium to potassium ratio (Na:K) was associated with an increased risk of incident stroke in participants with no prior history of stroke. There was evidence that higher Na:K was associated with a 60% increased risk of IS after adjustment for important confounders.[180]

Stroke Risk Stratification

The ability to quantify the impact of potentially modifying risk factors for stroke in a variety of settings is extremely valuable. INTERSTROKE (Study of the Importance of Conventional and Emerging Risk Factors of Stroke in Different Regions and Ethnic Groups of the World) is a standardized international case–control study conducted in 32 countries that aimed to quantify the importance of potentially modifiable risk factors for stroke in different regions of the world.[181] The researchers observed regional variations in the importance of individual risk factors and that hypertension was more associated with ICH than with IS, whereas current smoking, diabetes mellitus, apolipoproteins, and cardiac causes were more associated with IS.[181] In the United States, the widely used Framingham Stroke Risk Function was updated, providing improved calibration and discrimination in stroke prediction (particularly in whites).[182] The REGARDS study reported an approach calculated from the response of 13 self-reported questions that provides risk stratification slightly better than that provided by the direct measures in the Framingham function.[183] A large-scale prospective Chinese study investigated the impact of low-risk lifestyle factors (defined as nonsmokers, moderate drinkers [alcohol consumption of <30 g/d], a median or higher level of physical activity, a diet rich in vegetables and fruits and limited in red meat, a body mass index of 18.5–23.9 kg/m^2, and a waist:hip ratio <0.90 for men and <0.85 for women) on IS. The report estimated that 39.1% (95% CI, 26.4%–50.4%) of the IS cases were attributable to poor adherence to a healthy lifestyle in this prospective study.[184]

Promise of Biorepositories

Emerging technologies have made it possible to simultaneously evaluate a large number of circulating proteins or metabolites as potential new stroke risk markers. There have been some replicated associations of certain proteins with IS,[185] but there is still uncertainty about the association of metabolites with stroke outcomes.[186] To date, previous studies of proteins and metabolites have focused on cardiovascular disease (with stroke a subcomponent) and have had a relatively small number of events.[187] The advent of large-scale population biorepositories that collect information on sociodemographic, lifestyle, environmental, physical measurement and blood, urine, and saliva samples, as well as a variety of chronic disease outcomes, should provide new exciting opportunities for stroke research.[188] Several such open-access biorepositories (to bona fide researchers—such as UK Biobank[189]) are now in existence from several continents and now have, or intend to have, detailed information on an unprecedented scale for analyses of not only classical risk factors but also emerging risk factors such as genomic, proteomic, metabolomics, and imaging data to investigate their relationship with stroke.[190] The REGARDS study has recently published associations of biomarkers (NT-proBNP [N-terminal pro-B-type natriuretic peptide],[191] Galectin-3[192]) with stroke outcomes. Collaborative projects using genetic data from biorepository consortia can provide high-quality, reliable, and valid estimates of associations between genotypes with stroke outcomes across multiple studies. For example, a pooled analysis of biorepositories (of European and US studies) investigated loss-of-function genetic variants in *PCSK9* gene that are associated with lower LDL-C (low-density lipoprotein cholesterol) levels. The findings were that in this population of blacks and whites *PCSK9* loss-of-function variants were associated with lower LDL-C and coronary heart disease incidence but were not associated with stroke risk.[193] Future research using large-scale biorepository data should provide sufficient statistical power to identify novel risk factors for stroke that could ultimately lead to new pathways and interventions to reduce morbidity and mortality from stroke.

Prevention and Health Services Delivery

Stroke-related mortality in the United States dropped over a period of 4 decades, but slowed over recent years and increased since 2013.[194] Importantly, 10 modifiable risk factors (hypertension, current smoking, physical inactivity, high apolipoprotein ApoB/ApoA1 ratio, poor diet, high waist:hip ratio, psychosocial factors, cardiac disease, excessive alcohol consumption, and diabetes mellitus) account for 90.7% of population attributable stroke risk worldwide.[181] Because much of the decline in stroke is attributed to improvements in prevention,[195] renewed reductions in death rates may be realized through enhancements in preventive strategies combined with more effective use of proven approaches addressing risk factors.

Hypertension is the single most important modifiable stroke risk factor.[196] Diet is a cornerstone of BP management, with adherence to the DASH diet reducing BP by 7 mm Hg in normotensive adults and 11.5 mm Hg in those with hypertension.[196] Data from the Cohort of Swedish Men and the Swedish Mammography Cohort, which included 74 404 men and women followed for a mean of 11.9 years, found that IS risk was inversely related to adherence to a modified DASH diet (*P* for trend=0.002; multivariable RR, 0.86; 95% CI, 0.78–0.94 for the highest versus lowest quartile of adherence) with a similar trend for intracerebral hemorrhage (RR, 0.81; 95% CI, 0.63–1.05).[178] Following a DASH-type diet should translate into a population-level reduction in stroke.

The HOPE (Heart Outcomes Prevention Evaluation)-3 investigators randomly assigned 12 705 participants who were at intermediate risk of major cardiovascular events (annual risk ≈1%) to a combination of an angiotensin-receptor blocker and thiazide diuretic, rosuvastatin 10 mg/d, both, or neither who were then followed for a median of 5.6 years.[197,198] There was a nonsignificant 20% reduction in fatal or nonfatal stroke among participants who received the antihypertensives that lowered BP by an average of 6/3 mm Hg (1.2% versus 1.5%; HR, 0.80; 95% CI, 0.59–1.08; *P*=0.14). The lack of clear benefit may be related to the study population's relatively low baseline BP (mean 138/81 mm Hg) and risk factor profile. In contrast, projections based on the application of BP targets from the SPRINT (; SBP goal <120 versus <140 mm Hg) to adults at high cardiovascular risk but without stroke, diabetes mellitus, or heart failure in the National Health and Nutrition Examination Survey cohort found that 107 500 deaths per year in the United States could be avoided with treatment to the

more intensive goal, albeit with an increase in serious adverse events.[199] A network meta-analysis of data from 17 trials that enrolled 55 163 patients with 204 103 patient-years of follow-up found a decrease in stroke with a SBP target of <120 versus <160 mm Hg (RR, 0.54; 95% CI, 0.29–1.00), with point estimates favoring lower compared with higher SBP targets (<120 or <130 mm Hg).[200] A SBP target of <130 mm Hg optimally balanced efficacy and safety.[200] These data influenced new BP guidelines that now eliminate the category of pre-hypertension with <120/80 mm Hg classified as normal and 120 to 129/<80 mm Hg as elevated.[201] Pharmacological treatment is recommended for patients with cardiovascular disease or an estimated 10-year atherosclerotic cardiovascular risk of ≥10% who have a BP ≥130/≥80 mm Hg.[201]

Analysis of the statin arm of the HOPE-3 trial found that treatment of men aged ≥55 years and women aged ≥65 years reduced stroke by 30% (1.6% versus 1.1%; HR, 0.070; 95% CI, 0.52–0.95),[198] as did the combination of the antihypertensive regimen and the statin (1.0% versus 1.7%; HR, 0.56; 95% CI, 0.36–0.87).[202] A secondary analysis from the primary prevention ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) focused on participants ≥65 years who had hypertension and at least 1 additional coronary heart disease risk factor or an LDL-C 120 to 189 mg/dL and fasting triglycerides <350 mg/dL.[203] Randomized treatment with open-label pravastatin 40 mg/d had no benefit compared with usual care, including no reduction in fatal or nonfatal stroke among those aged 65 to 74 years (HR, 1.03; 95% CI, 0.68–1.57; *P*=0.89) or those aged ≥75 years (HR, 1.09; 95% CI, 0.63–1.90; *P*=0.76).[203] On the basis of these data, the risk/benefit of lipid lowering as primary prevention in older patients remains unclear.

FAST (Face, Arm, Speech, Time) is the primary mnemonic promulgated as a means of educating the public about stroke symptoms and the need to activate emergency transport systems. FAST, however, may miss symptoms such as isolated visual field defects or gait impairments, which can lead to lasting functional deficits and are amenable to thrombolysis. Some educational programs use a modified mnemonic, BE-FAST (B, balance; E, eyes) to capture visual and gait-related symptoms, but supportive data are limited. An analysis of the records of 736 patients with IS found that 14.1% did not have FAST symptoms at presentation.[204] Of these, 42% had gait imbalance or leg weakness, 40% visual symptoms, and 70% either symptom. With their addition (ie, BE-FAST), the proportion of stroke patients potentially not identified was reduced to 4.4%. Further research is needed to determine the utility of BE-FAST in real-world use by the public and paramedics and the potential increase in identification of stroke mimics.

The advent of EVT for patients with emergent LVO (LVO) presents additional challenges for stroke care systems. A comprehensive literature review of prehospital care and triage of emergent LVO patients stresses the need for public recognition of those with acute IS, reviews tools for emergency medical service identification of emergent LVO patients (3-Item Stroke Scale, Los Angeles Motor Scale, Rapid Arterial Occlusion Evaluation scale, Cincinnati Prehospital Stroke Severity Scale, and the Vision, Aphasia, Neglect screening tool), provides criteria for transport prioritization, and discusses the potential utility of point-of-care thrombolysis using mobile stroke units.[205] A retrospective study in Berlin, Germany, compared the outcomes of patients with IS who received intravenous alteplase in a stroke emergency mobile (STEMO) vehicle (n=305) with usual care (patients treated within a hospital, n=353).[206] There was no significant difference in the proportions achieving a mRS score of 1 after 3 months (53% versus 47%, respectively, *P*=0.14; adjusted odds ratio, 1.40; 95% CI, 1.00–1.97; *P*=0.052). Larger trials are required to determine whether STEMO-based treatment improves the outcomes of patients treated with intravenous thrombolysis and the settings in which this approach is most cost-effective.

Translational Medicine

The demonstration of the efficacy of mechanical thrombectomy and its increasing widespread use has opened new opportunities for research on neuroprotection strategies, particularly in combination with revascularization therapies. Recent investigations are taking this approach from experimental studies to the clinic, as there may be room for further improvement and prevent neurological complications related to reperfusion injury. On the basis of positive experimental results, intra-arterial administration of the calcium channel blocker verapamil immediately after thrombectomy was investigated in the phase I SAVER-I clinical trial (Superselective Administration of Verapamil During Recanalization in Acute Ischemic Stroke) that showed safety and feasibility.[207] Oxidative stress remains as a putative target for stroke treatment, particularly when revascularization therapies are used. A study reported that the thrombolytic effect of r-tPA (recombinant tissue-type plasminogen activator) was attenuated by hydrogen peroxide, whereas the antioxidant edaravone enhanced r-tPA–mediated thrombolysis.[208] Also, the antioxidant uric acid was found to exert protective effects after ischemia/reperfusion in hyperglycemic mice.[209] Several lines of evidence show that NOX (nicotinamide adenine dinucleotide phosphate [NADPH] oxidase) is a critical target to reduce the generation of reactive oxygen species, particularly ischemia-induced type 4 NOX. Endothelial NOX4 was found to be involved in blood-brain barrier breakdown, whereas neuronal NOX4 causes neuronal autotoxicity.[210] Recent experimental studies have shown that intravenous N-acetylcysteine administration promotes lysis of arterial thrombi that are resistant to r-tPA and other agents.[211] Management of comorbidities may also improve outcomes. For instance, hyperglycemia primes the thromboinflammatory cascade leading to impaired reperfusion and exacerbated neurovascular damage,[212] thus emphasizing the need to maintain normoglycemia.

Modulation of inflammation to improve stroke outcome is under intense investigation. Following studies in experimental brain ischemia showing benefits of blocking leukocyte-endothelium adhesion, Natalizumab, an antibody against integrin α4 and already studied in multiple sclerosis, was studied in a randomized, placebo-controlled, double-blind phase 2 trial in acute IS patients (ACTION [The Awareness, Care, and Treatment In Obesity Management Study]).[213] Although Natalizumab did not reduce infarct growth, it improved functional outcomes. Brain cell–associated suppression of tumorigenicity 2 (ST2), a molecule belonging to the IL (interleukin)-1 receptor family that inhibits IL-33 signaling, seems to limit inflammation and exert protective effects in experimental stroke.[214]

More attention has been paid to brain hemorrhage in laboratory studies. Patients treated with oral anticoagulants have a higher risk of significant brain hemorrhage after IS. In warfarin-treated mice, 12/15-lipoxygenase inhibition or deficiency reduced hemorrhagic transformation.[215] Inflammation may also be a realistic target in intracerebral hemorrhage (ICH). After the observation in stroke patients that tPA treatment led to sustained suppression of regulatory T cells in the blood, tPA-induced hemorrhagic transformation in ischemic mice could be prevented by treatment with regulatory T cells.[216] The expression of the endogenous anti-inflammatory factor A20 was increased in peripheral blood mononuclear cells of ICH patients and was negatively related to functional outcome. In experimental studies, A20 reduced ICH-induced inflammation and exerted beneficial effects.[217] The innate immune receptor toll-like receptor 4 that mediates inflammatory signaling was involved in hemorrhagic transformation after delayed tPA administration in a thromboembolic stroke model.[218] TGF (transforming growth factor)-β1 was found to modulate microglia-mediated neuroinflammation after ICH and promote functional recovery in mice, and early increases in plasma TGF-β1 concentrations in ICH patients were associated with better outcomes at 90 days.[219]

Interestingly, several lines of evidence support sex differences in the immune responses to stroke. Female mice displayed higher numbers of immune regulatory cells and smaller infarcts after transient middle cerebral artery occlusion than male mice.[220] Female mice showed smaller lesions induced by permanent ischemia after inhibition or deficiency of pannexin-1, a mediator of apoptotic and inflammatory cascades in neurons, whereas male mice were unresponsive.[221] In female mice, multiparity has been shown to reduce brain inflammation and improve outcomes after cerebral ischemia.[222] These and other findings support the need to investigate neuromodulatory strategies in animals of both sexes and emphasize the importance of studying stroke outcomes in a sex-dependent manner.

Experimental findings have identified different molecules that may be useful as biomarkers for stroke severity and prognosis. Inflammatory molecules might also have prognostic value. Soluble ST2 (in contrast to cell-associated ST2) was independently associated with poor outcome and hemorrhagic transformation.[223] Higher serum levels of MMP-9 (matrix metalloproteinase-9)[224] were associated with increased risk of mortality and major disability. Current investigation surrounding blood levels of extracellular microparticles (ie, vesicles of different sizes released by cells) indicates that the number of vesicles increases in the serum of acute stroke patients and these vesicles have proinflammatory properties.[225] Plasma levels of $CD14^+$ microparticles were also significantly correlated with stroke severity.[226] In patients with atherosclerotic cerebrovascular disease, endothelial-derived exosomes contained more prothrombotic and proinflammatory molecules including vWF (von Willebrand Factor),[227] an important regulator of thrombosis. Yet another study showed that plasma levels of ADAMST13, the enzyme that cleaves vWF, were significantly decreased in stroke patients.[228] High levels of oxidized LDL were associated with the high risk of death and poor functional outcome within 1 year after stroke onset, especially in large artery atherosclerosis and small artery strokes.[229] In patients with SVD, elevated peripheral blood lipid peroxidation markers may be related to hypertensive injury to the deep subcortical white matter.[230]

The PSD-95 (postsynaptic density protein 95) which binds nNOS (neuronal nitric oxide synthase) allows the formation of the nNOS/PSD-95/NMDA (N-methyl-D-aspartate) receptor complex. It is considered a putative target to minimize the deleterious effects of NMDA receptor activation. A recent study showed that an inhibitor of this complex, Tat-N-dimer, crosses the blood-brain barrier, reaches the neurons, and reduces overall neuronal excitability and the amplitude of the spreading depolarization wave.[231] The NA-1 (Tat-NR2B9c) peptide inhibits this signaling and was protective when given intravenously 60 minutes after the onset of middle cerebral artery occlusion,[232] although protection was lost if given after 5 hours.[233] Besides acute effects of PSD-95 blockade, new experimental evidence supports beneficial effects on functional recovery of drugs that induce nNOS/PSD-95 dissociation as they reduced excessive tonic inhibition caused by astrocyte-mediated γ-aminobutyric acid release in the peri-infarct cortex.[234]

Improving rehabilitation strategies through new technologies and old targets is another area of investigation. Spalletti et al[235] used a robotic platform with repeatable exercises in combination with a plasticity-stimulating strategy based on reversible inactivation of the contralesional cortex in a stroke model and found enhanced motor recovery and reduced transcallosal inhibition. Studies in stroke patients using brain–computer interface–assisted motor imagery and transcranial direct current stimulation intervention indicate that transcranial direct current stimulation facilitates neuroplasticity and may improve rehabilitation.[236] Rodent studies showed that stimulation of the mesencephalic locomotor region improved gait recovery after experimental stroke.[237] Blood-brain barrier disruption, while known to have a negative impact acutely, may also negatively impact long-term recovery. Recent studies showed that the presence of fibrinogen in the brain environment inhibits remyelination and suggest that targeting fibrinogen may have regenerative potential.[238] Although complement is thought to exacerbate ischemic brain damage, daily treatment of mice with complement component 3A has also been related to regeneration and repair. Complement component 3A treatment increased synaptic density and GAP43 (growth associated protein 43) expression and promoted motor recovery.[239]

Recent studies have moved the laboratory phenomenon of remote ischemic preconditioning to the treatment of patients with SVD. Fourteen SDV patients received 5 cycles of limb ischemia for 5 minutes twice daily for 1 year (remote ischemic preconditioning) and were compared with a control group of 16 SVD patients.[240] Remote ischemic preconditioning reduced white matter hyperintensities, improved serum lipid profiles, and improved visuospatial and executive ability. The authors concluded that remote ischemic preconditioning may slow cognition decline in SVD patients.

Investigation of large-scale data using genomics, epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics tools is rapidly advancing in the field. Novel genes identified in human genetic studies in patients with cerebrovascular diseases can be investigated in genetic models to obtain molecular and functional information that may lead to the development of druggable targets for therapeutic

purposes. Several genome-wide association studies have already been identified in relation to stroke subtypes. A large genome-wide meta-analysis in 4203 SVD patients compared with 50 728 controls found a novel genetic variant on chromosome 16q24.2 associated with SVD.[241] This variant seems to be related to subtle changes in gene expression and DNA methylation, but further studies are still needed. Meta-analyses of genomic data of 21 500 cases and 40 600 controls found association of a locus in COL4A2 with SVD and deep ICH suggesting common pathophysiologic mechanisms.[77] In a genome-wide association study, Sennblad et al[242] identified novel regulators of plasma factor XI levels, microRNAs, miR-145 and miR-181, and others. Genome-wide transcriptional profiling has allowed the identification of transcriptional signatures in peripheral blood associated with stroke subtypes. miRNAs are emerging as critical regulators of gene expression, and several specific miRNAs have been identified in experimental and clinical stroke. Using RNAseq of human blood samples, a set of circulating microRNAs (miR-125a-5p, miR-125b-5p, and miR-143-3p) was found associated with acute IS.[243] The miRNA profile in the peripheral blood mononuclear cells of IS patients compared with controls showed the upregulation of certain miRNAs (hsa-miR-4656, -432, and -503) and one downregulated miRNA (hsa-miR-874), and these changes were related to immune system dysfunction.[244]

Finally, there is growing concern on the need to improve experimental designs and increase value in translational stroke research. We refer the interested readers to relevant papers published in 2017 on this topic.[245–248]

Vascular Cognitive Impairment

Declining Age-Specific Prevalence of Dementia

Tucked into the unrelentingly ominous projections for future burden of dementia is a promising nugget. Although aging of the population will continue to produce increasing numbers of dementia diagnoses, occurrence of dementia for each age group may be falling. Recent analyses from several population-based studies used different methods to examine age-adjusted dementia prevalence or incidence[249–251] in cohorts enrolled over the 1970s to 2010s and found reductions in age-adjusted dementia of ≈30% to 40%. As these declines in dementia coincide with reductions in stroke incidence, it is tempting to ascribe improvement to decreases in the vascular contribution to dementia. This connection between reduced dementia and stroke remains unproven, however, as the dementia trend seemed independent of stroke risk factor control in multivariable analysis.[249] Even the existence of decreasing age-specific dementia is not consistent across all studies.[252,253] If trends toward reduced age-specific dementia are confirmed, they would provide hope that this threat might be mitigated by improving vascular health.

Emerging Diffusion Tensor Imaging Methods as Candidate Biomarkers for Vascular Cognitive Impairment

Biomarker identification and validation has been highlighted as a high-priority goal for vascular cognitive impairment (VCI).[254] Among the various neuroimaging biomarkers of cerebral SVD-related VCI, those based on MRI diffusion tensor imaging seem promising. One recent approach is to create a histogram of diffusion tensor imaging–measured mean diffusivity in a skeleton of white matter tracts and use peak width of the skeletonized mean diffusivity as a measure of white matter microstructural damage. In a validation study across independent data sets of 57 individuals with CADASIL, 444 with sporadic SVD, and 105 with SVD presenting to a memory clinic, peak width of the skeletonized mean diffusivity calculated by an automated algorithm accounted for a substantial proportion of intersubject variation in processing speed.[255] Peak width of the skeletonized mean diffusivity in longitudinally imaged CADASIL patients increased significantly over an 18-month interval, suggesting that this marker might be useful for clinical trials. A different analytic approach is structural network reconstruction, yielding measures of brain connectivity such as global efficiency, defined as the inverse of the shortest path length between every pair of brain regions (or nodes) weighted by diffusion tensor imaging–measured fractional anisotropy. In an analysis of 38 nondemented individuals with probable cerebral amyloid angiopathy (CAA), the global efficiency parameter also explained a large proportion of intersubject variation in processing speed and executive functioning.[256] Global efficiency decreased in 33 CAA patients reimaged after 16 months and the decline correlated with worsening executive function,[257] again suggesting possible applications for interventional trials.

The importance of biomarker identification and validation for VCI research has motivated creation of several multicenter collaborations, such as the US MarkVCID consortium (markvcid.org) and European SVDS@targets network (svds-at-target.eu).

Improved Detection Methods for Cortical Microinfarcts

Cerebral microinfarcts are estimated to number in the hundreds or thousands in brains with advanced SVD and may mediate a substantial proportion of SVD-related VCI,[258] Two MRI-based methods have been identified to detect a subset of microinfarcts during life: diffusion-weighted imaging and high-resolution structural imaging. Punctate diffusion-weighted imaging hyperintense lesions suggestive of acute cerebral microinfarction occur commonly in patients with SVD or leukoaraiosis[259] but are detectable only within a 1- to 2-week window. High-resolution structural MRI using 7T[260] and more recently 3T[261] magnets can detect microinfarcts durably over time, though only the subset of larger lesions located in cerebral cortex. Criteria for visually detecting and rating cortical microinfarcts have recently been proposed,[258] emphasizing the characteristic T2-weighted hyperintensity, T1-weighted hypointensity, and T2*-weighted isointensity of the durable lesions and their visibility in at least 2 imaging planes. Important microinfarct mimics include juxtacortical enlarged perivascular spaces, vascular flow-voids, and cortical microbleeds.

Genetic Alterations From Monogenic Diseases in Sporadic Cerebral SVD

Recent studies have identified variants of genes implicated in monogenic hereditary cerebral SVD as risk factors for sporadic

SVD. Studies have reported an association between common variants of NOTCH3, the causative gene in CADASIL, and risk of age-related white matter lesions in sporadic patients with hypertension[262] and a modest association of common NOTCH3 variants in 269 White probands with small-vessel stroke.[263] Another study, however, could not confirm associations between common NOTCH3 variants and lacunar stroke or white matter hyperintensity volumes.[264] A meta-analysis pooled genotype data from a large cohort of stroke patients to determine possible associations with common variants in 6 familial SVD genes: COL4A1, COL4A2, NOTCH3, HTRA1, TREX1, and CECR1.[265] A locus in COL4A2 was found to be associated with both lacunar IS and deep intracerebral hemorrhage (ICH), whereas an HTRA1 variant was associated with lacunar IS and, to a lesser extent, deep (ICH). These data support the possibility that there may be shared genetic determinants and common pathophysiologic mechanisms between hereditary and sporadic cerebral SVD.

Another intriguing possibility is that heterozygous mutations in recessive forms of monogenic SVD may manifest clinically. All affected members in an apparently autosomal dominant SVD family were found to be heterozygous carriers of an HTRA1 variant predicted to be pathogenic.[266] The same study also found deleterious HTRA1 variants in 10 of 201 unrelated probands with familial SVD of previously unknown cause. Similar findings emerged from another study of 142 NOTCH3-negative patients and 160 healthy age-matched controls, in which 5 different HTRA1 heterozygous mutations were detected in 9 patients from 5 unrelated families.[267]

Diagnosis of CAA-Related Inflammation

CAA is a well-recognized cause of ICH and contributor to VCI, but remains largely untreatable. A treatable subset of CAA patients are those who present with vascular inflammation[268] or vasculitis[269] because of an autoimmune response to the vascular amyloid. Patients with CAA-related inflammation (CAA-ri) typically present with headaches, subacute cognitive decline, or seizures and neuroimaging evidence of vasogenic edema. As patients often improve clinically and radiographically with immunosuppression, CAA-ri is an important diagnosis to make in practice, ideally without brain biopsy. A key clue to the pathogenesis of CAA-ri was demonstration of autoantibodies to β-amyloid in cerebrospinal fluid during the disease's active phase,[270] but assays for anti-β-amyloid antibodies are not available as a clinical test. As a potential alternative diagnostic approach, clinicoradiological criteria for CAA-ri were recently proposed and validated in a small group of individuals with pathologically confirmed CAA-ri.[271] The criteria define probable CAA-ri by MRI demonstration of unifocal or multifocal white matter hyperintensities that are asymmetrical and extend to immediately subcortical white matter along with characteristic CAA-related lobar ICH, microbleeds, or cortical superficial siderosis. The validation analysis of probable CAA-ri showed high interrater reliability, 82% sensitivity and 97% specificity. High specificity is particularly relevant to clinical application of the criteria, as it suggests that individuals meeting these criteria might be treated without confirmatory brain biopsy.

Vascular Neurosurgery

This section summarizes new information on surgically relevant diseases or interventions which have emerged in the vascular neurosurgery arena within the last year.

In the realm of ICH, the results of the randomized CLEAR III trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage, Phase III) were published, examining the effect of intraventricular thrombolytic (alteplase) administration after the placement of ventriculostomy for primary intraventricular hemorrhage associated with small volume (<30 cc) ICH.[272] A benefit in the primary end point of mRS score of ≤3 at 180 days was not realized. However, the odds of mortality was reduced by 50%, although this was achieved with a higher relative proportion of bed-ridden patients (ie, mRS score of 5). Secondary analysis revealed a beneficial association between extent of clot clearance and also suggested the potential for functional benefit in patients with larger IVH volume (>20 cc). For patients with primary acute ICH, several multicenter prospective trials are underway, including decompressive craniectomy,[273] and several studies focused on minimally invasive clot evacuation, such as the MISTIE III trial (Minimally Invasive Surgery Plus rt-PA for ICH Evacuation Phase III) evaluating stereotactic clot aspiration and r-tPA administration,[274] endoscopic clot evacuation,[275] and use of a keyhole craniotomy approach.[276]

In the realm of brain vascular malformations, new guidelines addressing the management of arteriovenous malformations (AVMs) and cavernous malformations (CMs) were published.

A CM guidelines document was produced by a multi-disciplinary writing group convened by the Angioma Alliance[277] and focused on 5 topic areas: epidemiology/natural history, genetic testing/counseling, diagnostic criteria/radiology standards, neurosurgical considerations, and neurological considerations. On the basis of the guidelines, as regards neurosurgical management, surgical resection was not routinely recommended for asymptomatic CMs. Early surgery was recommended for CMs causing epilepsy and for symptomatic CMs dependent on anticipated mortality and morbidity. Given the higher risks associated with surgery for brain stem lesions, but in acknowledgment of their more aggressive natural history, surgical resection was recommended to be considered after a second symptomatic hemorrhage. The recent publication of the largest series of brain stem CMs published to date examined outcomes in 397 patients in a single-center retrospective review and found that early intervention (within 6 weeks of hemorrhage) offers the most benefit[278] in cases where surgery is performed.

The American Heart Association/American Stroke Association published a scientific statement on the management of brain AVMs, which reviewed the current state of the literature, including surgical, endovascular and stereotactic radiosurgical treatment, and management of ruptured and unruptured AVMs.[279] The statement reviewed the risks and efficacy of each treatment modality, which can be briefly summarized as follows: surgical resection is curative and surgical risk is well predicted by surgical outcome grading scales, specifically the Spetzler-Martin and related scales; radiosurgery is effective in obliteration of AVMs in 70% to 80% of cases overall, and radiosurgical outcome scales can help to

characterize risks of adverse radiation effects and obliteration outcomes; and endovascular embolization can be used as a presurgical or radiosurgical adjunct, to target high-risk angiographic features, for palliation of high-flow symptoms, or for curative purposes in selected cases. The risk of incident hemorrhage is quoted as ≈1% annually, and recurrent hemorrhage as ≈5%, and treatment decisions should weigh relative risks and benefits of different interventional strategies.

Several recently published studies continue to address management of unruptured brain AVMs, in the context of the results of the ARUBA trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformation), the randomized trial comparing interventional therapy and medical management which concluded that conservative management was superior to treatment.[280] ARUBA combined heterogeneous treatments, that is, microsurgery, radiosurgery, and embolization, into its interventional arm, and was criticized for its high rate of adverse events compared with prior cohorts treated with microsurgery or radiosurgery alone, and for its short follow-up. A recent multicenter stereotactic radiosurgery database review of 509 patients meeting ARUBA eligibility criteria estimated the need for 15 to 20 years of follow-up to adequately ascertain the potential benefits of radiosurgery, in contrast to the 2.8-year average follow-up in ARUBA.[281] Results of the subgroup of 232 patients with Spetzler-Martin I and II AVMs compared favorably with results from ARUBA; the results also highlighted the importance of radiosurgical dose (>20 Gy margin dose) to optimize obliteration and outcomes.[282] An additional single-center review of 233 ARUBA-eligible AVMs treated with radiosurgery similarly determined favorable outcomes compared with the natural history cohort of ARUBA when extrapolated to the longer follow-up of 8.4 years form this series.[283] A single-center review examining outcomes of microsurgical treatment identified 155 ARUBA-eligible patients and found less disabling deficits than reported in ARUBA.[284] Similarly, a single-center review of 105 ARUBA-eligible patients treated with microsurgery and radiosurgery reported a lower overall risk of stroke and death than observed in ARUBA.[285] Collectively, these studies suggest that selected patients with unruptured brain AVMs still require consideration for treatment. Along these lines, a European consensus conference statement on behalf of European Societies of Neurosurgery, Interventional Therapy and Radiosurgery[286] warns that the results of ARUBA cannot be applied equally to all unruptured brain AVMs and for all treatment modalities. The consensus statement recommends consideration of treatment-related morbidity and life expectancy as the main factors in decision-making.

On surgical management of carotid disease, currently CREST-2 (Carotid Revascularization for Primary Prevention of Stroke) is underway, enrolling patients with asymptomatic carotid disease into 2 concurrent randomized trials of intensive medical management versus carotid revascularization, with one trial examining carotid endarterectomy and the other, carotid stenting.[287] The study has currently enrolled over 850 patients of the ≈2500 planned enrollment at over 100 centers across North America. Ongoing studies are also examining aspects of aneurysmal subarachnoid hemorrhage management. The multicenter ULTRA study (Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage) in the Netherlands is currently randomizing patients within 24 hours of ictus to standard treatment versus tranexamic acid as a potential intervention to reduce rebleeding and improve outcomes.[288] An international multicenter phase 3 study examining administration of intraventricular sustained-release nimodipine after subarachnoid hemorrhage is also underway,[289] following initial promising data related to the reduction of delayed cerebral ischemia from a small phase 1/2a study.[290] Intraoperative tools for visualization of vascular anatomy during aneurysm and neurovascular surgery continue to evolve, with recent introduction of fluorescein video angiography as a potential alternative or adjunct to the now widely used intraoperative indocyanine green video angiography[291]; both modalities allow for direct vessel imaging through the operating microscope at the time of surgery after intravenous injection of the requisite dye and have largely, though not completely, supplanted the need for intraoperative catheter angiography.[292]

Recent publications have again highlighted the importance of the volume–outcome relationship in treatment of cerebrovascular surgical disease. Analysis of data from the nationwide inpatient sample, the largest inpatient database representing ≈20% of inpatient admissions to nonfederal US hospitals, demonstrated that patients with vascular malformations treated at high-volume centers and by high-volume surgeons had lower morbidity and mortality, respectively.[293] Similarly, an analysis of the nationwide inpatient sample data for patients undergoing extracranial-intracranial bypass surgery for various indications from 2001 to 2014 demonstrated better outcomes at high-volume centers,[294] replicating results from a similar analysis of the prior decade.[295] These studies further bolster the sizeable existing literature showing high-volume hospitals to be associated with improved outcomes in aneurysm treatment and further highlight the need to regionalize cerebrovascular surgical care to high-volume centers.

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KEY WORDS: alleles ■ cognition ■ gait ■ quality of life ■ white matter