Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

Summary—Transcatheter aortic valve implantation has been associated with a higher rate of cerebrovascular events (CVEs) compared with medical treatment or surgical aortic valve replacement. This multicenter study evaluated in a large cohort of consecutive patients (n=1061) the timing, predictors, and clinical impact of CVEs after transcatheter aortic valve implantation. The incidence of 30-day CVEs was 5.1% (stroke, 4.2%), with about half of these events occurring immediately or within the first few hours after the procedure. The predictors of acute (<24 hours) CVEs were mechanical factors such as further stretching of the valve prosthesis with balloon postdilation (odds ratio, 2.46; P=0.034) and valve dislodgment/embolization (odds ratio, 4.36; P=0.024), whereas subacute (1–30 days) CVEs were determined mainly by the occurrence of atrial arrhythmias (new-onset atrial fibrillation; odds ratio, 2.76; P=0.028). There were no differences in 30-day CVE rate between different types of valves (balloon expandable, self-expandable) or access routes (transfemoral, transapical). The rate of late (>30 days) CVEs was 3.3% (stroke, 2.1%) at a median follow-up of 12 months (3–23 months). The predictors of late CVEs were chronic atrial fibrillation (hazard ratio, 2.84; P=0.002), peripheral vascular disease (hazard ratio, 2.02; P=0.043), and prior cerebrovascular disease (hazard ratio, 2.04; P=0.047). The impact of CVEs on mortality was determined mainly by the severity of the event, and only the occurrence of major stroke was independently associated with an increased 30-day (hazard ratio, 7.43; P=0.001) and late cumulative (hazard ratio, 1.75; P=0.043) mortality. These results providing important insights for the implementation of preventive measures for CVEs after transcatheter aortic valve implantation.

Conclusions—In a large cohort of patients undergoing transcatheter aortic valve implantation, the rates of acute and subacute CVEs were 2.7% and 2.4%, respectively. While balloon postdilation and valve dislodgment/embolization were the predictors of acute CVEs, new-onset atrial fibrillation determined a higher risk for subacute events. Late events were determined mainly by a history of chronic atrial fibrillation and peripheral and cerebrovascular disease. The occurrence of major stroke was associated with increased early and late mortality. These results provide important insights for the implementation of preventive measures for CVEs after transcatheter aortic valve implantation.

Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)

Summary—Stroke is a feared complication of carotid endarterectomy (CEA) and carotid stenting (CAS). The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and European trials have shown that CAS is associated with a greater risk of stroke than CEA. CREST also showed that CAS was associated with a greater risk of myocardial infarction (MI) than CEA. The greater risk of MI numerically balanced the greater risk of stroke, so that the composite primary outcome (periprocedural stroke, MI, or death and ipsilateral stroke at up to 4 years) was similar for CEA and CAS. This result has invited criticism because of the differing directions of stroke and MI within the composite outcome. To understand further, we examined the strokes that occurred as a complication of the procedure. Stroke was still more common after CAS, but overall the risk of severe stroke was <1% and was similar for CEA and CAS. The delayed timing of some major strokes, particularly intracerebral hemorrhage that occurred a few days postoperatively, makes it plausible that these postoperative strokes are preventable, perhaps with careful attention to blood pressure control. Minor stroke occurred most commonly on the same day as CAS, which suggests that the technical aspects of the procedure could be improved to minimize stroke as a complication. Previously, we reported that MI, including biomarker-only MI, was associated with an increased risk in long-term mortality. Here we report that stroke, including minor stroke, was also associated with an increased risk in long-term mortality. Carotid intervention with CEA or CAS is safe. Periprocedural stroke incurred significant morbidity and mortality.

Conclusions—Stroke, particularly severe stroke, was uncommon after carotid intervention in CREST, but stroke was associated with significant morbidity and was independently associated with a nearly 3-fold increased future mortality. The delayed timing of major and hemorrhagic stroke after revascularization suggests that these strokes may be preventable.
Targeting Mannose-Binding Lectin Confers Long-Lasting Protection With a Surprisingly Wide Therapeutic Window in Cerebral Ischemia

Summary—Despite recent substantial progress in prevention and supportive care, stroke remains a leading cause of death and permanent disability worldwide. To date, thrombolysis with tissue plasminogen activator is the only available treatment and its narrow therapeutic window (3–4.5 hours) is one of the main obstacles to finding eligible patients. Thus, new approaches with a wider window of efficacy are needed. This study documents the pivotal role of mannose-binding lectin (MBL), a circulating protein that acts as the first step in activation of the lectin complement pathway in brain ischemic injury. The data show that MBL deposition on the ischemic endothelium represents a key pathogenetic event in brain damage. Importantly, strategies aimed at inhibiting MBL lead to neuroprotection with a time window of efficacy up to 24 to 30 hours postinjury, an extremely important factor in the attempt to translate experimental results into the clinical setting. Detailed analysis of the MBL gene in humans has revealed that a surprisingly high percentage of individuals (15% to 30% depending on the population considered) carries a genetic deficiency in MBL that leads to low circulating levels of MBL. Notably, this deficiency is associated with a better outcome after acute stroke in humans. Our data, providing a mechanistic insight into the role of MBL in brain ischemia and the demonstration that its inhibition is protective, strongly support the concept of MBL as a relevant therapeutic target in humans, one with a wide therapeutic window of application. Thus, we propose MBL as a novel therapeutic target for stroke.

Conclusions—Our data show an important role for MBL in the pathogenesis of brain ischemic injury and provide a strong support to the concept that MBL inhibition may be a relevant therapeutic target in humans, one with a wide therapeutic window of application.

Cerebral Embolization During Transcatheter Aortic Valve Implantation: A Transcatheter Doppler Study

Summary—Neurological events are currently considered one of the most pressing concerns with transcatheter aortic valve implantation (TAVI). A nearly 4-fold risk of such events within 30 days after the procedure was observed for nonoperable patients undergoing TAVI compared with patients treated with optimal medical therapy in cohort B of the Placement of AoRtic TranScatheterER valves (PARTNER) trial, and similar results were found when TAVI was compared with surgical aortic valve replacement in the high-risk population of cohort A. Moreover, a high load of clinically silent embolic lesions was documented on postprocedural cerebral diffusion-weighted MRI, which has raised additional safety concerns. In the present study, serial transtemporal Doppler monitoring was performed to elucidate the main source of procedural emboli. During TAVI, high-intensity transient signals were detected in all patients as a surrogate for microembolization. They predominately occurred during manipulation of the calcified native valve while positioning and implanting the stent valves, with no differences between the transfemoral and the transapical approach and only a trend toward a higher amount of high-intensity transient signals for the self-expandable prosthesis. Despite the omnipresence of high-intensity transient signals, however, only 2 (2.4%) neurological complications occurred within 30 days, and there were no late neurological events. However, these findings corroborate the importance of periprocedural embolization during TAVI and reinforce current calls for an increased focus on this issue, especially when TAVI indications are broadened toward younger, lower-risk patients. Future research is essential to better determine the “real” neurological risk of the TAVI procedure and to thoroughly investigate the feasibility, safety, and efficacy of upcoming strategies to reduce the risk for cerebral embolization, eg, use of less traumatic devices, omission of preparatory valvuloplasty, carotid compression during valve manipulation, or use of active cerebral protection devices.

Conclusions—Procedural high-intensity transient signals (HITS) were detected by transcranial Doppler in all patients. Although no difference was observed between the transfemoral and the transapical approach with the balloon-expandable ES stent valve, transfemoral TAVI with the self-expandable MCV prosthesis resulted in the greatest number of HITS, predominantly during implantation.
experience a dissection, and 17% have one or more aneurysms. A cerebrovascular event including transient ischemic attack, stroke, and/or amaurosis fugax occur in 1 of every 4 patients with FMD. The presence of a carotid bruit in a patient under 60 or an epigastric bruit in a patient with hypertension should alert the clinician to the possible diagnosis of FMD. Earlier diagnosis may prevent the consequences of poorly controlled hypertension, and allow for the identification of aneurysms and dissections and their appropriate treatment.

Conclusions—In this registry, FMD occurred primarily in middle-aged women, although it presents across the lifespan. Cerebrovascular FMD occurred as frequently as renal FMD. Although a significant proportion of FMD patients may present with a serious vascular event, many present with nonspecific symptoms and a subsequent delay in diagnosis.8

### Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes and a History of Stroke or Transient Ischemic Attack

**Summary**—Patients with acute coronary syndromes and a history of prior stroke are at a high risk of ischemic and bleeding events and constitute a treatment challenge. Therefore, novel and more potent antithrombotic agents need to be evaluated with regard to the balance between efficacy and safety, particularly in the most vulnerable patients. Ticagrelor provides faster, greater, and more consistent platelet inhibition than clopidogrel. The PLATelet inhibition and patient Outcomes (PLATO) trial showed that ticagrelor was superior to clopidogrel in a broad population of patients with acute coronary syndromes for the prevention of cardiovascular death, myocardial infarction, or stroke but with an increase in overall major bleeding events not associated with coronary artery bypass surgery. Among the 18624 patients randomized in the PLATO study, 1132 (6.2%) were reported as having a history of stroke or transient ischemic attack. These patients presented higher rates of the primary composite end point (myocardial infarction, CV death, and stroke) at 1 year compared with those patients without prior stroke or transient ischemic attack. The reduction of the primary composite outcome and total mortality at 1 year with ticagrelor versus clopidogrel was consistent with the overall trial results. The rates of overall PLATO-defined major bleeding events associated with coronary artery bypass graft surgery, as well as major bleeding events, were similar, and intracranial bleeding occurred infrequently in the randomized groups. In light of a favorable clinical net benefit and associated impact on mortality, the results of the present study suggest that treatment with ticagrelor should not be withheld in acute coronary syndrome patients with a history of ischemic stroke or transient ischemic attack for safety concerns if otherwise indicated.

**Conclusions**—Patients with acute coronary syndrome with a prior history of ischemic stroke or transient ischemic attack (TIA) had higher rates of clinical outcomes than patients without prior stroke or TIA. However, the efficacy and bleeding results of ticagrelor in these high-risk patients were consistent with the overall trial population, with a favorable clinical net benefit and associated impact on mortality.7

### Long-Term Propensity Score–Matched Comparison of Percutaneous Closure of Patent Foramen Ovale With Medical Treatment After Paradoxical Embolism

**Summary**—The patent foramen ovale (PFO) is a recognized cause of stroke and systemic embolism, the mechanism being a venous clot that passes through the PFO and causes systemic ischemia. For about 20 years, PFOs have been closed percutaneously to prevent such events. The technique has matured and is now quite simple and safe. However, there is no evidence from randomized trials that this technique is safer than a conservative approach consisting of oral anticoagulation, platelet inhibitors, or a combination thereof. The data here represent the longest follow-up of 308 consecutive patients arbitrarily treated with PFO closure or medical therapy. In a propensity score–matched analysis, 103 patients with PFO closure were compared with 103 patients without PFO closure. At the mean follow-up of 10 years, a significant clinical event relatble to PFO occurred in 11% of patients with PFO closure and 21% of those without PFO closure (P=0.033). Transient ischemic attacks accounted for most of these events (5% and 14%, respectively). There were no complications with clinical sequelae in the PFO closure group. These data confirm other studies that PFO closure is safe; no late complications were found. The prevention of systemic ischemic events (particularly transient ischemic attacks) appears to be slightly superior to medical treatment.

**Conclusions**—In this long-term observational, propensity score–matched study, percutaneous PFO closure was more effective than medical treatment for the secondary prevention of recurrent cerebrovascular events among patients with PFO-related transient ischemic attack or stroke.8

### Downregulation of TMEM16A Calcium-Activated Chloride Channel Contributes to Cerebrovascular Remodeling During Hypertension by Promoting Basilar Smooth Muscle Cell Proliferation

**Summary**—During hypertension, cerebral arterioles undergo remodeling of the vascular walls, which contributes to the increased risk for stroke. Accumulating evidence suggests that chloride channels play an important role in regulation of cell cycle transition and cell proliferation and that the upregulation of volume-regulated chloride channel is involved in hypertension-induced cerebrovascular remodeling. Recently, TMEM16A was proposed to be the molecular candidate of the calcium-activated chloride channel (CaCC). TMEM16A has been found to be abundantly expressed and to mediate the calcium-activated chloride current in several types of vascular smooth muscle cells. However, the molecular identity of CaCC and its functions in cerebrovascular smooth muscle cells remain enigmatic. In present study, we demonstrate that TMEM16A is responsible for the CaCC in rat basilar smooth muscle cells. The activity of CaCC in basilar smooth muscle cells is remarkably reduced in hypertensive rats. Upregulation of CaMKII activity and downregulation of TMEM16A expression contribute to the attenuation of CaCC in hypertension. In addition, TMEM16A negatively regulates cell proliferation and cell cycle transition from the G1/S phase to the S phase through modulating cyclin D1 and cyclin E expression. These results provide evidence that the reduction of CaCC activity is an important contributor to hypertension-induced vascular smooth muscle cell proliferation and cerebrovascular remodeling, indicating that restoration of the TMEM16A CaCC activity could exert beneficial effects on hypertension-associated cardiovascular diseases such as stroke.

**Conclusions**—TMEM16A CaCC is a negative regulator of cell proliferation. Downregulation of CaCC may play an important role in hypertension-induced cerebrovascular remodeling, suggesting that modification of the activity of CaCC may be a novel therapeutic strategy for hypertension-associated cardiovascular diseases such as stroke.9
Migraine Mutations Increase Stroke Vulnerability by Facilitating Ischemic Depolarizations

Summary—Our study establishes a mechanism that links migraine and stroke, 2 highly prevalent and debilitating diseases. Migraine is a well-recognized stroke risk factor. Although its prevalence is on par with other stroke risk factors such as diabetes mellitus and hypertension, there has been little insight into the mechanism of the migraine-stroke association. Here, we present compelling evidence indicating that glutamatergic hyperexcitability associated with migraine mutations renders the brain more susceptible to ischemic depolarizations. As a result, the minimum critical level of blood flow required for tissue survival (ie, viability threshold) is elevated and infarction ensues, even in mildly ischemic tissues. This represents a paradigm shift in the search for a mechanism for increased stroke risk in migraineurs and differs radically from those previously postulated on the basis of clinical data alone. Our conclusions are based on optical and MRI and electrophysiological recordings in transgenic mouse models for familial hemiplegic migraine type 1, a monogenic migraine syndrome (mutations in Ca2.1 channels) that has been a model for common but genetically complex forms of migraine based on shared clinical features, glutamatergic mechanisms, and elevated stroke risk. Clinical implications include a shorter therapeutic window for acute stroke interventions in migraineurs because of accelerated loss of potentially salvageable penumbra. Furthermore, migraine prophylaxis may reduce stroke risk by suppressing cerebral hyperexcitability, and antithrombotic prophylaxis may be indicated in susceptible migraineurs because they are more likely to have infarcts if and when they develop cerebral ischemic events.

Conclusions—We propose that enhanced susceptibility to ischemic depolarizations akin to spreading depression predisposes migraineurs to infarction during mild ischemic events, thereby increasing the stroke risk.

Matrix Metalloproteinase-10 Effectively Reduces Infarct Size in Experimental Stroke by Enhancing Fibrinolysis via a Thrombin-Activatable Fibrinolysis Inhibitor–Mediated Mechanism

Summary—The majority of strokes, the third leading cause of death worldwide, are ischemic in nature. It is estimated that 1 of every 16 deaths is due to stroke, ranking as the No. 1 cause of adult disability with an estimated cost of $74 billion in 2010. With an aging population, these numbers are likely to rise. Intravenous fibrinolysis with recombinant tissue plasminogen activator (tPA) remains the only Food and Drug Administration–approved treatment for stroke patients presenting within 3 hours after onset, which can be extended to 4.5 hours in selected patients. Recombinant tPA, although effective in reducing disability, does not improve mortality. Indeed, most stroke centers use recombinant tPA in only ≈5% of stroke patients, the major adverse effect after recombinant tPA administration is intracerebral hemorrhage, seen in ≈6% to 7% of cases and thus remaining an important clinical issue. Because of the potential side effects of recombinant tPA, efforts are being made to improve recanalization after stroke by using new fibrinolytics or mechanical revascularization therapies. Fibrinolysis and matrix metalloproteinase–mediated proteolysis act in concert to degrade the occlusive fibrin clot. We have demonstrated that matrix metalloproteinase-10 reduces infarct size and favors fibrinolysis through a thrombin-activatable fibrinolysis inhibitor–mediated mechanism in an experimental stroke model in mice, with much lower effect on bleeding than tPA. This novel thrombolytic strategy can open new perspectives for the treatment of stroke, likely reducing the impact of this enormous economic and social burden provided that it can be translated to humans.

Conclusions—A novel profibrinolytic role for MMP-10 in experimental ischemic stroke is described, opening new pathways for innovative fibrinolytic strategies in arterial thrombosis.

Stroke in Patients With Type 2 Diabetes Mellitus, Chronic Kidney Disease, and Anemia Treated With Darbepoetin Alfa: The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) Experience

Summary—Although anemia has been associated with higher mortality and morbidity in subjects with diabetes mellitus and nondialysis chronic kidney disease, treatments with erythropoiesis-stimulating agents have not led to improvements in prognosis. In the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT), a concerning increase in the risk of darbepoetin alfa–related stroke was observed. We examined the role of baseline predictors and postrandomization factors that might explain this heightened risk of stroke with darbepoetin alfa. We found that in this cohort of patients with type 2 diabetes mellitus, nondialysis chronic kidney disease, and anemia, the risk of stroke related to darbepoetin alfa did not appear to be associated with any baseline characteristic. Despite extensive sensitivity analyses, this risk did not seem to be mediated by postrandomization factors previously implicated as mechanisms of erythropoiesis-stimulating agent–related adverse outcomes, including increase in hemoglobin level, blood pressure, or platelet number, and was not related to dose of darbepoetin alfa. Therefore, clinicians cannot rely on monitoring these readily available follow-up parameters to mitigate the risk of darbepoetin alfa–related stroke.

Conclusions—The 2-fold increase in stroke with darbepoetin alfa in TREAT could not be attributed to any baseline characteristic or to postrandomization blood pressure, hemoglobin, platelet count, or dose of treatment. These readily identifiable factors could not be used to mitigate the risk of darbepoetin alfa–related stroke.

Anticoagulation With the Oral Direct Thrombin Inhibitor Dabigatran Does Not Enlarge Hematoma Volume in Experimental Intracerebral Hemorrhage

Summary—The direct thrombin inhibitor dabigatran was recently approved for long-term prophylaxis of thrombembolic events in patients with atrial fibrillation. For this indication, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial revealed a favorable benefit–risk profile for dabigatran compared with that of the gold standard, warfarin. Intracerebral hemorrhage (ICH) is the most feared complication of long-term anticoagulation. Whereas warfarin pretreatment leads to largely increased hematoma volumes and higher mortality rates compared to those of ICH occurring in nonanticoagulated patients, no such data are available for dabigatran anticoagulation. In 2 animal models of ICH, we found no differences in terms of hematoma volume between dabigatran-treated mice and controls, whereas warfarin anticoagulation dramatically worsened ICH volume. On a molecular level, warfarin vastly reduced activity levels of coagulation factors II, VII, IX, and X, but dabigatran reversibly inhibited the active site of factor II only, still allowing sufficient coagulation induction to prevent extensive hematoma enlargement. If
conformed in humans, our findings may represent a significant safety advantage of dabigatran anticoagulation over that of warfarin. Further study is warranted to determine if rapid anticoagulation reversal (eg, by means of prothrombin complex concentrates) is not necessary for ICH occurring during dabigatran treatment.

Conclusions—In contrast with warfarin, pretreatment with dabigatran did not increase hematoma volume in 2 different experimental models of ICH. In terms of safety, this observation may represent a potential advantage of anticoagulation with dabigatran over warfarin.

Global Variation in the Relative Burden of Stroke and Ischemic Heart Disease

Summary—Stroke and ischemic heart disease account for a substantial and growing share of overall mortality and disease burden worldwide. However, despite having overlapping risk factors and disease mechanisms, there may be significant variation in the relative burden of disease from stroke compared with ischemic heart disease worldwide. In the present study, we used data from the World Health Organization Burden of Disease Program to develop a comprehensive overview of the geographic patterns of variation in burdens of stroke and heart disease. We found that there is substantial global variation in the relative burden of stroke versus ischemic heart disease; mortality and disease burdens from stroke and ischemic heart disease do not track uniformly with each other. There was disproportionately greater stroke burden in China, Africa, and South America, whereas ischemic heart disease burden was greater in the Middle East, North America, Australia, and much of Europe. Lower-income countries have a higher relative stroke burden overall, which may be related in part to associations with vascular risk factor profiles. These data suggest that a better understanding of the reasons for this variation may be helpful to develop targeted national interventions.

Conclusions—There is substantial global variation in the relative burden of stroke compared with ischemic heart disease. The disproportionate burden from stroke for many lower-income countries suggests that distinct interventions may be required.

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Summary—Each year, in the United States alone, atrial fibrillation causes >50000 strokes and $12 billion in medical expenditure. Thus, safe and cost-effective stroke prevention is critical to the atrial fibrillation population. Dabigatran etexilate was developed with the hope that it would be as effective as warfarin, but safer and easier to administer. The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) found that dabigatran 150 mg twice daily was superior to warfarin in the prevention of ischemic stroke. On the basis of results from RE-LY, the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE), and other trials, we developed a decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies. Dabigatran 150 mg (twice daily) was cost-effective in atrial fibrillation populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk atrial fibrillation populations unless international normalized ratio control was poor.

Conclusions—Dabigatran 150 mg (twice daily) was cost-effective in AF populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk AF populations unless international normalized ratio control was poor.

Declining Stroke and Vascular Event Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years and Consequences for Current Trial Design

Summary—Formal analysis of secondary stroke prevention trials over the last 5 decades confirms that vascular event rates in control arms have declined substantially. Annual recurrent stroke rates in control arms fell from 8.71% in trials launched in the 1960s to 6.10% in the 1970s, 5.41% in the 1980s, 4.04% in the 1990s, and 4.98% in the 2000s. Annual event rates for fatal stroke decreased from 2.87±1.04% in the 1960s to 0.36±0.14% in the 2000s, and those for major vascular events declined from 10.91±1.29% in the 1960s to 6.29±0.68% in the 2000s. Multivariate analysis suggests that increasing antithrombotic use and lower blood pressures were the most important drivers of vascular event rate reduction. The sample size required for adequately powered trials more than doubled during the study period. If a continued linear decline is assumed, the annual recurrent stroke rate in trial control arms in the coming decade is projected to be 2.25%, and control group sample size requirements would increase to 15 983 patients for a trial designed to detect a 20% relative risk reduction in the frequency of recurrent stroke, with 2 years of follow-up, 80% power, and 5% α error. The introduction into clinical practice of successive waves of therapies with proven efficacy in stroke prevention has been notably successful, resulting in a substantial decline in the rate of recurrent vascular events in the control arms of secondary stroke prevention trials. Consequently, trials of new therapies are more arduous, requiring ever larger sample sizes to confirm treatment efficacy, and clinical investigators must cope with the paradox of progress.

Conclusions—Recurrent stroke and vascular event rates have declined substantially over the last 5 decades, with improved blood pressure control and more frequent use of antiplatelet therapy as the leading causes. Considerably larger sample sizes are now needed to demonstrate incremental improvements in medical secondary prevention.

Glutathione Peroxidase-3 Deficiency Promotes Platelet-Dependent Thrombosis In Vivo

Summary—The identification of genetic risk factors for thrombotic stroke is a field in its infancy. This study presents a unique mouse model of thrombotic risk in which the extracellular antioxidant enzyme, glutathione peroxidase-3 (GPx-3), is eliminated by targeted gene disruption. This enzyme, the most important antioxidant enzyme in plasma and the extracellular space, eliminates peroxides from those compartments. This model was developed because earlier work from our group showed that a deficiency of this enzyme in plasma is an independent risk factor for thrombotic stroke in young individuals. Here, we show that mice deficient in glutathione peroxidase-3 have heightened platelet activation in the basal state, and, with provocation, have an increased propensity to thrombosis in the pulmonary and cerebral circulations. Furthermore, thrombotic strokes in glutathione peroxidase-3–deficient mice are much more severe than in wild-type mice; the size and severity of these strokes can be attenuated by inhibiting platelets and reactive oxygen species pharmacologically. These results demonstrate the importance of this key antioxidant enzyme in modulating platelet activation and thrombotic responses, and, together with prior genetic epidemiological studies from our group and others, suggest that glutathione peroxidase-3 is a potential marker of and therapeutic target for thrombotic stroke.

Conclusions—These findings demonstrate that GPx-3 deficiency results in a prothrombotic state and vascular dysfunction that promotes platelet-dependent arterial thrombosis. These data illustrate the
importance of this plasma antioxidant enzyme in regulating platelet activity, endothelial function, platelet-dependent thrombosis, and vascular thrombolic propensity.17

Iscore: A Risk Score to Predict Death Early After Hospitalization for an Acute Ischemic Stroke

Summary—Stroke is a leading cause of death and adult disability. The ability to estimate prognosis in acute stroke patients directly affects treatment decisions for patients. It may also guide supportive care plan and facilitate patient and/or family counseling or discussions pertaining to end-of-life decisions. At the population level, prognostic estimations may assist policymakers in conducting fair comparisons when evaluating stroke fatality among different facilities for hospital outcomes and performance assessment. Clinicians usually rely on their own personal experience or average mortality reported in clinical trials, which do not account for valuable information available at the time of the hospital presentation. Unfortunately, few risk scores are available that include simple and relevant clinical variables, including stroke severity on admission. In this large cohort study, we created and validated a risk score model to predict 30-day and 1-year mortality early after hospitalization for patients with an acute ischemic stroke. Our model was designed to include clinical variables easily obtained in the early hours of hospital presentation and is independent of specialized laboratory tests or imaging evaluations. Additionally, this model allows estimating death at small centers and at community hospitals with limited resources. Predictors of mortality included older age, male sex, severe stroke, nonlacunar stroke subtype, glucose ≥7.5 mmol/L (135 mg/dL), history of atrial fibrillation, coronary artery disease, congestive heart failure, cancer, kidney disease on dialysis, and dependency before the stroke. Our risk score helps to estimate 30-day and 1-year mortality in individuals presenting with an acute ischemic stroke. Examples are provided in the text. An online Web-based tool (http://www.sorcan.ca/iscore) is available to estimate mortality by adding individual patient characteristics.

Conclusions—Among patients with ischemic stroke, factors identifiable within hours of hospital presentation predicted mortality risk at 30 days and 1 year. The predictive score may assist clinicians in estimating stroke mortality risk and policymakers in providing a quantitative tool to compare facilities.18

Timeliness of Tissue-Type Plasminogen Activator Therapy in Acute Ischemic Stroke: Patient Characteristics, Hospital Factors, and Outcomes Associated With Door-to-Needle Times Within 60 Minutes

Summary—Tissue-type plasminogen activator (tPA) is a proven intervention for acute ischemic stroke patients. The benefits of intravenous tPA in acute ischemic stroke are time dependent, and guidelines recommend an arrival to treatment initiation (door-to-needle) time of ≤60 minutes. Despite the proven benefits, guidelines recommendations, and explicit goals for timely administration of tPA, the frequency, patient and hospital characteristics, temporal trends, and outcomes of ischemic stroke with door-to-needle times ≤60 minutes have not been well studied. Data from 25,504 acute ischemic stroke patients treated with tPA within 3 hours of symptom onset from 2003 to 2009 in 1082 hospitals participating in the Get With the Guidelines–Stroke Program were analyzed to determine frequency, patient and hospital characteristics, and temporal trends in patients treated with door-to-needle times ≤60 minutes. Only 26.6% of tPA-treated patients had a door-to-needle time ≤60 minutes. Patient factors most strongly associated with door-to-needle time ≤60 minutes were younger age, male gender, white race, and no prior stroke. Hospital factors associated with ≤60-minute door-to-needle times included greater annual volumes of tPA-treated stroke patients. The proportion of patients with door-to-needle times ≤60 minutes varied widely by hospital and increased modestly from 19.5% in 2003 to 29.1% in 2009. Despite similar stroke severity, in-hospital mortality was lower and symptomatic intracranial hemorrhage was less frequent for patients with door-to-needle times ≤60 minutes compared with patients with door-to-needle times >60 minutes. These findings support the need for a targeted initiative to improve the timeliness of reperfusion in acute ischemic stroke.

Conclusions—Fewer than one-third of patients treated with intravenous tPA had door-to-needle times ≤60 minutes, with only modest improvement over the past 6.5 years. These findings support the need for a targeted initiative to improve the timeliness of reperfusion in acute ischemic stroke.19

Secular Trends in Ischemic Stroke Characteristics in a Rapidly Developed Country: Results From the Korean Stroke Registry Study (Secular Trends in Korean Stroke)

Summary—Rapid industrial and societal changes can lead to dynamic changes in risk factors, stroke phenotypes, and treatment. Korea has achieved a remarkably high level of economic growth in a short period of time. The ages of patients with stroke are steadily increasing over time. Cardioembolic stroke continues to increase; extracranial artery stenosis is on the rise. Arriving at the hospital within 3 hours and reperfusion therapy are increasing. Age-adjusted all-cause mortality at 1 year is decreasing.

Conclusions—During the first decade of 21st century, stroke characteristics in Korea changed, likely because of increased lifespan, westernized lifestyle, and improved public awareness. Stroke experts need to cope with these distinguishing trends to establish a better strategy for prevention and acute therapy.20

Associations Between Incident Ischemic Stroke Events and Stroke and Cardiovascular Disease-Related Genome-Wide Association Studies Single Nucleotide Polymorphisms in the Population Architecture Using Genomics and Epidemiology Study

Summary—Recent genome-wide association studies (GWAS) have identified a number of genetic variants associated with stroke and cardiovascular disease (CVD). However, data regarding GWAS variant replication in independent samples and across different ancestry/ethnicity groups are lacking, but are important for prioritizing genetic variants for translational research and for furthering our understanding of population differences in complex diseases such as stroke. We sought to replicate previously identified single nucleotide polymorphisms (SNPs) associated with ischemic stroke in GWAS and meta-analyses using a large, well-characterized, multi-ethnic population. In addition, we tested whether SNPs previously associated with CVD risk factors also were associated with ischemic stroke. In spite of reasonable power, we did not replicate several of the previous stroke findings in European-descent individuals, but did identify associations in African-Americans for 2 SNPs in the AIM1 and HPS1 genes. In exploratory analyses investigating CVD risk factor SNPs, we identified additional lipids and body mass index SNPs, which may be associated with stroke in diverse United States ancestral groups, including African-Americans.
and American Indians who are at high risk of stroke. Our findings highlight the importance of replication and consideration of power in genetic studies, and support the investigation of non–European-descent populations for identifying genetic factors associated with complex disease.

Conclusions—Our analyses showing lack of replication in spite of reasonable power for many stroke SNPs and differing results by ancestry highlight the need to follow up on GWAS findings and conduct genetic association studies in diverse populations. We found modest IS associations with BMI and lipids SNPs, though these findings require confirmation.21

The Acute Effects of Changes to AV Delay on BP and Stroke Volume: Potential Implications for Design of Pacemaker Optimization Protocols

Summary—Optimization of the AV and VV delay settings of cardiac resynchronization devices is increasingly being performed clinically to maximize their potential therapeutic benefit. There is no universally accepted method for performing such optimization, although noninvasive blood pressure measurement is rapidly gaining recognition as a potential guide. Previous studies have shown, however, that the initial blood pressure increment obtained on optimization decays somewhat over the initial minutes after the transition in pacemaker settings. This decline could represent a (detrimental) decrease in cardiac output, or be the result of (desirable) compensatory changes in peripheral vascular tone. This study demonstrates that the cardiac output improvement is maintained after AV delay optimization, and that the reduction in blood pressure readings is secondary to compensatory vasodilatation. This differential pattern of response in pressure and flow to changes in pacemaker AV delay is important for understanding the physiological characteristics and critical for improving the design of quantitative pacemaker optimization protocols. This study also investigates the suitability of both noninvasive blood pressure and conventional Doppler echocardiography as markers to guide pacemaker optimization. It is important to develop optimization protocols that deliver reliable, reproducible, optimum delay settings, and understanding the relative temporal behavior of signal and noise, in pressure and flow, is critical to this understanding. Noninvasive blood pressure is easier to measure and interpret (by nonskilled operators), with significantly less noise, and the earliest phase (before vascular compensation) has the greatest signal information content.

Conclusions—Improving AV delay immediately increases BP, but the effect begins to decay within a few seconds. Reassuringly, this is because of compensatory vasodilatation rather than reduction in cardiac function. Pacemaker optimization will never be reliable unless there is an adequate signal/noise ratio. Using BP rather than Doppler minimizes noise. The early phase (before vascular compensation) has the richest signal lode.22

Relevance of Electric Remodeling in Human Atrial Fibrillation: Results of the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial Mechanisms of Atrial Fibrillation Study

Summary—Changes in the electrophysiological (EP) properties of the atria have been shown to facilitate the development of atrial fibrillation (AF) in several experimental animal models. This process, termed electric remodeling, includes changes, such as shortening of the atrial refractory period and slowing of conduction velocity. However, long-term human studies have not been performed; thus, the relevance of these data to human AF is uncertain. The most common risk factors for clinical AF are advancing age and hypertension. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial enrolled 2580 patients ≥ 65 years of age with a history of hypertension, but no prior AF, who were receiving a dual-chamber pacemaker. The primary goal of the study was to determine the incidence of pacemaker-detected AF and to determine its association with stroke. However, as all patients had pacemakers capable of performing noninvasive EP testing, a sub-study was performed to examine changes in atrial EP properties over 2 years, comparing patients who developed AF against those who did not. Of the 485 patients in this substudy, 100 developed AF. Patients who developed AF had longer P-wave durations and were more likely to have AF induced during EP testing; however, their atrial effective refractory periods and corrected sinus node recovery times were similar to those who did not develop AF. Patients who developed AF did not have any significant changes in their EP parameters over 2 years of follow-up; however, the atrial rate during longer episodes of AF was significantly faster compared with the shorter episodes of AF.

Conclusions—Prolonged P-wave duration, but not differences in atrial effective refractory periods, was associated with the development of atrial tachyarrhythmias in pacemaker patients.23

Use of Tissue-Type Plasminogen Activator Before and After Publication of the European Cooperative Acute Stroke Study III in Get With The Guidelines-Stroke

Summary—Intravenous tissue-type plasminogen activator given within 3 hours of the onset of acute ischemic stroke improves the likelihood of good outcome, but only a small percentage of patients with acute ischemic stroke are able to receive this medication because of the narrow inclusion criteria and limited time window. In September 2008, the European Cooperative Acute Stroke Study III randomized controlled trial demonstrated that intravenous tissue-type plasminogen activator given 3 to 4.5 hours after onset of acute ischemic stroke provides a more modest, but still clinically meaningful improvement in outcome. Among hospitals participating in Get With The Guidelines-Stroke program, the use of intravenous tissue-type plasminogen activator has significantly increased since publication of the European Cooperative Acute Stroke Study III in both the traditional 3-hour time window and the expanded 3- to 4.5-hour window without negatively influencing treatment times or clinical outcomes. The increased use appeared to be temporally related to both European Cooperative Acute Stroke Study III trial results and publication of the American Heart Association/American Stroke Association science advisory supporting tissue-type plasminogen activator use in the expanded time window, highlighting the importance of practice guidelines and quality care initiatives in facilitating the integration of new information into clinical practice. Despite the improvement in tissue-type plasminogen activator treatment rates observed, there remain further opportunities to improve treatment of patients with acute ischemic stroke arriving at the hospital within 4.5 hours of symptom onset.

Conclusions—Following publication of ECASS III, there has been a significant increase in the use of tPA between 3 and 4.5 hours without
adversely affecting treatment of patients in the <3-hour window. However, there remains substantial opportunity to further improve treatment rates in the later time window.

**Familial Effects on Ischemic Stroke: The Role of Sibling Kinship, Sex, and Age of Onset**

**Summary**—Although strong familial inheritance of stroke risk had been previously demonstrated in prior family and twin studies, where a stronger genetic effect over environmental ones had been suggested, few had addressed potential effects of sex, age at onset, or sibling kinship on familial risk of ischemic stroke, and the possibility of interactions among these factors had not been studied. Using a very large nationwide population-based matched cohort study based on exposure status of sibling pairs, the relative risks of ischemic stroke comparing exposed study participants (individuals having a sibling with ischemic stroke) with unexposed study participants (individuals having a sibling without ischemic stroke) were estimated, taking the aforementioned factors and socioeconomic status into account. The risk for ischemic stroke was 60% higher in individuals having a sibling with prior stroke, and this risk was stronger for those with affected full siblings compared with those with affected half siblings. Having a sibling with early ischemic stroke doubled the risk of early ischemic stroke; however, no sex differences in the familial inheritance of ischemic stroke were observed in our population. Knowledge of ischemic stroke history within families may help to identify those at increased risk of ischemic stroke. It is important for public awareness of ischemic stroke in the general population and may be relevant for practicing clinicians when advising patients with affected first-degree relatives.

**Conclusions**—There was a 60% increased risk for ischemic stroke in individuals having a sibling with prior stroke. The familial effect was even higher for full-sibling relations. Familial effects were observed in both male and female individuals, and no differential effects depending on sex of the either of the siblings were found.

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Circulation. 2013;128:e162-e170
doi: 10.1161/CIRCULATIONAHA.113.005571
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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