Most Important Outcomes Research Papers on Stroke and Transient Ischemic Attack

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The following are highlights from the new series, Circulation: Cardiovascular Quality and Outcomes Topic Review. This series will summarize the most important manuscripts, as selected by the Editor, that have published in the Circulation portfolio. The objective of this new series is to provide our readership with a timely, comprehensive selection of important papers that are relevant to the quality and outcomes, and general cardiology audience. The studies included in this article represent the most significant research related to stroke and transient ischemic attack. (Circ Cardiovasc Qual Outcomes. 2014; 7:191-204.)

Each year in the United States, approximately 800 000 men and women are affected by stroke, which equates to one incident of stroke every 40 seconds.1 Stroke is the fourth leading cause of death nationally and is one of the foremost contributors to functional disability.2 The cost to the US healthcare system is substantial. Specifically, in 2010 medical treatment for stroke cost approximately $54 billion and is expected to exceed $1 trillion by 2050.3 The burden of stroke is not limited to US alone; mortality from stroke is responsible for -9% of all deaths worldwide and is the second most common cause of death following ischemic heart disease.4 While the overall risk of stroke has declined by 25% in the last decade,3 disability from stroke is now emerging as a major public health problem, particularly in the elderly, as we observe an increase in aging of the population. Accordingly, in this month’s topic review in Circulation: Cardiovascular Quality and Outcomes, we concentrate on contemporary issues around stroke and transient ischemic attack (TIA).

Significant knowledge and practice gaps continue to exist across the continuum of stroke care. First, risk factor modification for stroke remains suboptimal. The most important modifiable risk factor for prevention of stroke is hypertension (HTN), with the lowering of blood pressure associated with a more than 25% reduction in the relative risk (RR) of stroke.5,6 Modification of other risk factors such as diabetes, hypercholesterolemia, smoking cessation and atrial fibrillation (AF),8 have also been shown to reduce the incidence of stroke.9 However, appropriate identification of patients at risk and ensuring adherence to prevention strategies presents many challenges. For example, numerous patients with HTN are not on therapy and many of those who are treated have suboptimal blood pressure (BP) control.

Second, optimal antithrombotic therapy for stroke prevention in patients with AF remains challenging. Warfarin is the most commonly used and reduces RR of recurrent stroke in those with TIA/minor stroke by ~70%.10 However, warfarin can be difficult to dose and monitor and carries a significant risk of major bleeding. Novel anticoagulants have since been proposed over warfarin such as Dabigatran and Apixaban, which also reduce the risk of stroke in patients with AF.11,12 These medications provide many potential benefits as they do not require monitoring of INR, while offering similar efficacy in preventing ischemic events.

Lastly, guidelines established by the AHA/ASA advocate the initiation of fibrinolytic therapy for patients presenting within 3 hours of symptom onset and up to 4.5 hours for selected patients.13 Although fibrinolytic therapy is effective in reducing disability, it does not improve mortality.14 However, at present, only a fraction of patients receive fibrinolytic therapy on time and thus establishing systems to rapidly diagnose and treat eligible patients is a key challenge. Furthermore, novel rehabilitation programs for stroke have also recently showed promise; administering these programs, preferably within the first 24 hours, and, if possible, within a specialized stroke center is a key goal.15,16

Appropriately, in this topic review for Circulation: Cardiovascular Quality and Outcomes we have included papers that evaluate (1) stroke epidemiology, risk factors and outcomes, (2) therapeutic strategies for the treatment and prevention of stroke, and (3) health system interventions to improve stroke care.

Stroke Epidemiology, Risk Factors, and Outcomes

Stroke is one of the leading causes of disability and mortality worldwide and there is great variation in risk factors and outcomes in different populations.17,18 The epidemiology of stroke in the US has changed over time, and death attributable to stroke has declined7,19 due to changes in the landscape of risk factors and therapies and the implementation of guidelines and stroke systems of care.20,22 Despite these improvements, the disease burden is still substantial with close to 800 000 Americans suffering from stroke each year1 and many questions remain about the variation in risk factors and delivery of care.

Antithrombotic therapy has played a major role in the prevention of death and disability from stroke, and the last decade has seen the emergence of many new antithrombotic agents. On the other hand, thrombolytics are the mainstay for the acute treatment of stroke and we are now seeing the advent of promising newer endovascular procedures. With the evolution of therapies for prevention and treatment of stroke it is important to be able to identify both appropriate patients for the use of available treatments and those that may be harmed. There is a need to develop accurate measures for estimating risk, therapeutic efficacy, and outcomes. Better understanding
of these issues is critical to further reduce the burden of stroke and improve outcomes. The following section is a collection of contemporary articles addressing the epidemiology, risk factors and outcomes of acute ischemic stroke including variation in burden of stroke and its risk factors, predictive models for estimating risk of stroke and mortality.

**Temporal Trends in Patient Characteristics and Treatment With Intravenous Thrombolysis Among Acute Ischemic Stroke Patients at Get With the Guidelines–Stroke Hospitals.**

**Summary:** The time dependent nature of the benefit of tissue plasminogen activator tPA has led to considerable initiatives over the past decade by government agencies and professional societies alike, which has translated into increases in tPA usage. Accordingly, the authors utilized the Get With the Guidelines-Stroke registry (GWTG), consisting of 1,093,895 hospitalizations for ischemic stroke (2003-2011), in order to analyze temporal trends in tPA treatment. Overall, 22% of patients presented within 2 hours of onset and of whom 31% were eligible for tPA. Of the eligible cohort 67% received tPA within 3 hours. Over time tPA use within 3 hours increased from 4% to 7% in all ischemic stroke patients and from 43% to 77% in tPA eligible patients arriving within 2 hours (P<0.001). In multivariable analysis, each year the odds of an eligible patient to receive tPA increased by 1.37 (95% CI 1.35–1.41). The increase in tPA use was part due to expansion in selection of patients with an increase in the proportion of patients aged >85 years, nonwhite, female and those with milder strokes. Using a model term for years of participation in the GWTG–Stroke program the authors demonstrated that participation in the program also contributed to increased tPA usage (adjusted OR, 1.05; 95% CI, 1.02–1.07). Prevalence of AF, HTN, coronary artery disease (CAD), and smoking decreased over time, whereas diabetes mellitus and dyslipidemia increased. From a systems perspective, among patients presenting within 2 hours and receiving tPA within 3 hours door-to-image time reduced from a median of 24 minutes in 2003–2005 to 20 minutes in 2010–2011 and similarly door-to-needle time (median 81 versus 72 minutes) also improved. EMS utilization remained unchanged over the time period at ≥85% and no improvement was seen in last known well to hospital arrival times. tPA eligible and tPA-treated patients were more likely go have AF and less likely to have HTN and diabetes mellitus as compared with all ischemic stroke patients. Median National Institutes of Health Stroke Scale (NIHSS) score at presentation was also markedly higher in the tPA-eligible and tPA-treated groups.

**Conclusions:** The authors capture the time trend of tPA usage over the past decade in the US, a time, which has seen great advancement and innovation in the field of stroke care. There was marked improvement in rates of tPA therapy and time-based stroke care measures, though there remains substantial room for improvement. The authors acknowledge the limitations of an administrative database study lacking more clinical parameters. Also, a fourth of the patients did not have recorded NIHSS stroke severity. There is also the confounding aspect of hospital enrollment and change over time. 22

**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 economic development and industrialization can lead to major changes in healthcare and disease patterns. Here, the authors investigate trends in stroke epidemiology in Korea, which has undergone rapid growth over the past few decades, using the Korean Stroke Registry (KSR). The KSR is a multicenter, prospective, hospital-based stroke registry launched in 2002 involving 31 teaching hospitals nationwide which includes patients with stroke or transient ischemic attacks (TIA). This study included 46,098 patients registered in the KSR between January 2002 and November 2010. Mean age was 66.1±12.3 years, and 57.6% were men. The vast majority of patients had ischemic strokes (93.2%) and hypertension was the most common risk factor (63.5% of patients) followed by smoking (33.0%), diabetes (30.1%), and prior stroke (19.7%). Over the study period, age at stroke onset increased over time (0.237 per calendar year; p<0.01) but the proportion across genders did not significantly change (P=0.19). Further, time between symptom onset and admission has significantly decreased from 31.7 to 26.8 hours (p<0.01 for trend) and the proportion of patients admitted within 3 hours of symptom onset has increased from 20.2% to 28.6%. Overall all-cause mortality rates were 4% at 30 days, unchanged over time, and 12% at 1 year, which significantly declined over the study period (p<0.01). A subgroup of 36,191 patients with ischemic stroke underwent stroke subtype analysis, which showed that large artery atherosclerosis was most common at 36.1%, followed by small vessel occlusion (SVO) at 25.4% and cardioembolism (CE) at 17.1%. Over time, the proportion of SVO has decreased (RR 0.96 per year) while CE has increased (RR 1.06 per year).

**Conclusions:** Countries undergoing rapid periods of growth, as Korea have over the past 30 years, also experience unique changes in their health care systems and disease epidemiology. Stroke and TIA in Korea has seen an increase in the age of onset, an evolving distribution among the subtypes of stroke, and favorable trends suggesting decreased times to admission and improved outcomes. However, the results here may not be generalizable to other nations or to the general population of Korea, as it includes only neurology training hospitals. Nevertheless, it is important to understand and adapt care to the changing disease trends, particularly as rapidly developing countries undergo concurrent changes in disease epidemiology, such as the global rise of obesity in such nations. 23,24

**Added Predictive Ability of the CHADS2,VASc Risk Score for Stroke and Death in Patients With Atrial Fibrillation: The Prospective Danish Diet, Cancer, and Health Cohort Study**

**Summary:** The CHADS2 score (congestive heart failure, hypertension, age ≥75 years, diabetes and previous stroke) is the most widely used risk stratification tool for stroke in patients with atrial fibrillation (AF). However, this score does not include additional risk factors (vascular disease, female sex, ages 65–74 years). Therefore, the authors evaluated the added predictive ability of the CHADS2,VASc23 versus the CHADS2 risk score for stroke/death in non-anticoagulated patients with incident AF. Data was abstracted from 57,053 middle-aged Danish patients (50–64 years), enrolled in the Diet, Cancer and Health cohort (1993–1997), utilizing a prospective epidemiological study design. The final population included 1603 non-anticoagulated patients with AF (39% women), identified through ICD-8/10 codes. Stroke and death were established as primary and secondary outcomes respectively and time dependent ROC curves were used for further comparison of scoring systems (at 1 year and for entire follow up). The net reclassification improvement (NRI) method was employed to compare individual changes in risk assessment. The incidence rates of all cause stroke and death were higher at 1 year following AF (3.4 per 100 person years for stroke, 13.6 for death) than after long term follow up at 5.4 years (1.9 for stroke, 5.6 for death). Time dependent area under the ROC curves for both scoring tools was similar. The CHADS2,VASc score identified fewer patients as low risk, that is, more patients were classified as higher risk warranting anti-coagulation therapy. The NRI analysis revealed that a CHADS2,VASc score ≥2 is appropriately re-classified 32% of cases of AF as having a stroke at 5-year follow-up. The author’s estimate that for every 10 extra patients upgraded as moderate or high risk requiring treatment, at 5 years, using the CHADS2,VASc risk score, 1 patient would have had a stroke that might have been avoided with effective treatment.
Conclusions: This study suggests that the CHA\textsubscript{DS}VA\textsubscript{S} score is superior to the CHADS\textsubscript{2} score in identifying AF patients at risk of stroke as well as those at very low risk for stroke. Better prediction of stroke cases comes at the expense of more patients being designated as higher risk and potentially exposed to risks of anticoagulation therapy. Although clinically useful, this risk prediction tool does not take into account other important factors such as cognitive/functional decline and non-adherence to anticoagulant therapy. As with any administrative study, the limitations include its reliance on ICD codes to identify the components of the risk scores, perhaps resulting in incorrect calculation versus physician assessment.\textsuperscript{23}

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

Summary: Ischemic heart disease (IHD) and cerebrovascular disease are two of the leading causes of global mortality and have several well-established common risk factors. However, the extent of variation worldwide in the relative burdens of each form of vascular disease and the reasons for these variations are not well understood. Accordingly, the authors conducted an ecological study with publically available data to analyze IHD and stroke mortality, disability-adjusted life year (DALY) loss rates, and national rates of vascular disease risk factors. They found that, overall among 192 World Health Organization member countries, worldwide mortality rates and DALY loss rates from IHD exceeded those of stroke. However, stroke mortality rates were greater than IHD rates in 74 countries (38\%) (range: 12.7\% higher to 27.2\% lower than IHD) and stroke DALY loss rates exceeded IHD rates in 62 countries (32\%) (range: 6.2\% higher to 10.2\% lower than IHD). In addition, geographically, there was a disproportionately higher IHD burden in Australia, the Middle East, North America, and the majority of Europe in contrast to a higher stroke burden in Africa, South America, and China. Lower national income was associated with higher stroke relative mortality (p<0.001) and DALY loss rate (p<0.001). Even after adjustment for national income, mean serum cholesterol and diabetes mellitus prevalence were each associated with greater burdens of IHD.

Conclusion: This study portrays the substantial variation in global estimates of standard mortality and DALY loss rates for stroke and IHD. It also sheds light on the precarious state of low-income countries that face a larger burden of stroke and stroke mortality. It would be interesting to see whether these trends have changed using the new 2010 Global Burden of Disease data.\textsuperscript{28} This study is limited by heterogeneity in disease diagnosis, classification, and severity and data gathering between the countries. There is also the question of data reliability, especially for the lower income countries. Nevertheless, this study should serve as an impetus for stroke prevention and treatment efforts in low-income countries, with a particular focus in Africa, South America, and China, to maximize our ability to quell the ill effects of stroke.\textsuperscript{29}

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

Summary: The cumulative effect of advances in treatment for patients with acute ischemic stroke on recurrent stroke and vascular events is unknown. The authors therefore examined rates of recurrent stroke and vascular events among patients in secondary prevention trials of ischemic stroke that were conducted over the past 50 years. They performed a systematic search of all randomized, controlled trials of medical secondary stroke prevention published from 1960–2009. To promote homogeneity of populations across trials, the systematic review was restricted to studies with broad entry criteria enrolling diverse ischemic stroke patients. Studies focusing on single stroke mechanisms (atrial fibrillation, carotid stenosis, etc.) were excluded. Data from control arms was extracted to identify baseline characteristics and annual event rates for recurrent stroke, fatal stroke, and major vascular events over time. In total, the authors identified 59 trials containing more than 66000 subjects. Over the 5 decades of study, annual event rates for recurrent stroke, fatal stroke, and major vascular events declined by 1.00\%, 0.28\%, and 1.33\%, respectively. Lower blood pressure and increasing use of anti-thrombotic agents explained a significant percentage of these declines. In total, the annual rate of recurrent stroke declined from 8.71\% for trials launched in the 1960’s to 4.98\% for trials launched in the 2000’s. Over this period of time, annual rates for fatal stroke declined from 2.87\% to 0.36\% and annual rates for major vascular events fell from 10.91\% to 6.29\%. The sample size required for a trial to have an 80\% power to detect a 20\% reduction in recurrent stroke with a type 1 error of 5\% increased by a factor of 2.2 over this 50-year period.

Conclusion: Study findings importantly demonstrate that medical treatment for hypertension and platelet thrombosis have led to impressive declines in recurrent stroke and other vascular events over the past 50 years. Although the authors focus on the implications of this decline on sample size requirements in clinical trials, the larger point may be that further meaningful declines in absolute risk will be harder to achieve with additional pharmacotherapy. As the authors note, of the 6 trials in this systematic review that were initiated in the 2000s, none demonstrated improvement in even relative risk with the study intervention. Furthermore, findings highlight the pitfalls of using historical controls that may overestimate baseline risk and therefore suggest benefits to treatment that do not exist.\textsuperscript{30}

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: Results from The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)\textsuperscript{31,32} highlighted an increased risk of stroke among patients assigned to darbepoetin alfa treatment. Therefore, the authors aimed to identify the independent predictors of stroke (including any post-randomization factors) that may explain this relationship. Data was utilized from the TREAT registry with a total of 4038 patients with diabetes, chronic kidney disease (CKD) and anemia randomized to either darbepoetin alfa (n=2012, 58\% women) or placebo (n=2026, 56\% women) treatment. The authors employed a multivariate logistic regression model to identify baseline predictors of stroke. In addition, the authors conducted a nested case control analysis to determine if post-randomization blood pressure, hemoglobin level, platelet count, or treatment dose were responsible for the increased risk related to darbepoetin alfa (for both treatment groups). Precisely, for each treatment group, patients with stroke (case) were matched to 10 controls that had a similar rate of follow up (1:10 nearest neighbor propensity score matching). The results show that patients who received treatment with darbepoetin alfa had a 2-fold increased risk of stroke. Specifically, there were 154 cases of incident stroke (5\% darbepoetin vs 2.6\% placebo group, HR 1.9 95\% CI 1.4–2.7). The independent predictors of stroke included randomization to darbepoetin alfa (OR=2.1, 95\% CI 1.5–2.9), previous stroke (OR=2.0, 95\% CI 1.4–2.9), proteinuria, and recognized cardiovascular disease. In regards to patients receiving darbepoetin alfa, post randomization systolic/diastolic blood pressure, platelet count, hemoglobin level and darbepoetin alfa dose did not differ between those with/without stroke.

Conclusions: This study demonstrates that darbepoetin alfa doubles the risk of stroke in patients with diabetes, non-dialysis CKD and anemia, and this risk in TREAT does not seem to be attributed to any baseline characteristic or to post-randomization blood pressure, hemoglobin, platelet count, or dose of treatment. This data confirms that measurement of these readily available follow-up parameters cannot be used to alleviate the risk of darbepoetin alfa related stroke.\textsuperscript{33}
Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation: Validation of the R2CHADS2 Index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K Antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (Anticoagulation and Risk factors In Atrial fibrillation) Study Cohorts

Summary: Current models for predicting stroke risk in patients with atrial fibrillation (AF) accounts for slightly over half of the attributable risk. To identify additional independent predictors for stroke and systemic embolism in patients with AF and to derive a new prediction model, investigators utilized the population from the ROCKET AF trial (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), and validated the model in an independent population from the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) cohort. In this trial, 14,264 patients with nonvalvular AF and creatinine clearance ≥60 mL/min were randomized to rivaroxaban or dose-adjusted warfarin. A Cox proportional hazards model was used to identify factors at randomization that were independently associated with the occurrence of stroke or systemic embolism. Over a median follow-up of 2 years, 4.0% of patients experienced primary end-point events, with reduced creatinine clearance representing a strong independent predictor, second only to prior stroke or transient ischemic attack. Thus investigators proposed a new model (R2CHADS2) in which creatinine clearance <60 mL/min is assigned 2 points, the same weight as a prior stroke or TIA. When tested in the ROCKET-AF cohort, the discriminatory ability of the R2CHADS2 model (C-index = 0.587) was modestly better than that of CHADS2 or CHA2DS2-VASc (C-statistics of 0.575 and 0.578, respectively) or that for CHADS2 in the ATRIA cohort (0.673 versus 0.672). When verified in ATRIA, the addition of renal function did not improve the discriminatory ability of the scores, as measured by c-index.

Conclusion: This study found the strength of association between creatinine clearance and stroke or systemic embolism to be second to that of previous stroke or transient ischemic attack. However, whether renal dysfunction merits equal weighting in risk stratification schemes is debatable, as its inclusion as proposed did not substantially improve the performance of the scores, as expressed using the c-statistic. It may be that only 21% of the subjects in the ROCKET-AF had moderate renal impairment at enrollment, and none had severe renal impairment. Nevertheless, this study underscores the importance of proper anticoagulation for patients with poor renal function.

Cardiac Biomarkers Are Associated With an Increased Risk of Stroke and Death in Patients With Atrial Fibrillation: a Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Substudy

Summary: Risk stratification tools such as the CHADS2 and CHA2DS2-VASc scores remain inadequate in prognosticating ischemic stroke and overall thromboembolic events in patients with AF. To understand additional markers of stroke risk, the authors described the association of elevations in troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) to stroke in patients with AF in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. The RE-LY trial was a prospective randomized trial comparing dabigatran and open-label warfarin over 12 months (n=6189), with biomarkers measured at time of randomization. Patients were stratified based on troponin I concentrations (<0.001 μg/L, n=2663; 0.010 to 0.019 μg/L, n=2006; 0.020 to 0.039 μg/L, n=1023; ≥0.040 μg/L, n=497) and NT-proBNP quartiles (<387; 387–800; 801 to 1402; >1402 ng/L). Outcomes were evaluated using Cox proportional hazards models, adjusting for cardiovascular risk factors and composite stroke risk via the CHADS2 and CHA2DS2-VASc risk scores. Stroke rates were independently related to levels of troponin I with 2.09%/year in the highest troponin I group, and 0.84%/year in the lowest (HR, 1.99 [95% CI, 1.17–3.39]; P=0.0040). Stroke risk was also independently related to levels of NT-proBNP with 2.30%/year versus 0.92% in the highest versus lowest quartiles (HR 2.40 [95% CI 1.41–4.07]; P=0.0014). The addition of these two biomarkers to CHADS2 and CHA2DS2-VASc scores slightly increased their performance (C-statistic for CHADS2, increased from 0.614 to 0.658, P=0.014; for CHA2DS2-VASc, from 0.618 to 0.654, P=0.0274). Addition of both biomarkers to cardiovascular risk factors in predicting systemic thromboembolic outcomes, including pulmonary embolism and myocardial infarction, significantly increased discriminatory abilities (C-statistic increased from 0.68 to 0.72; P<0.0001).

Conclusion: Elevations in troponin I and NT-proBNP were both independently related to increased risk of stroke and systemic embolism, mortality, and other cardiovascular events. Unfortunately, since RE-LY included only patients with non-valvular AF with at least one risk factor for stroke, results from this study may not apply to AF patients without any clinical stroke risk factors. The use of RE-LY imposes the additional constraint in the use of anticoagulation for every participant enrolled. Thus, these results do not allow conclusions to be drawn for selection of AF patients for oral anticoagulation in stroke prevention. Nonetheless, the consideration of biomarkers, already in common clinical use in addition to clinical findings represents prognostic gains for patients with AF.

Impact of Onset-to-Reperfusion Time on Stroke Mortality: a Collaborative Pooled Analysis

Summary: Endovascular treatment is a novel but invasive approach to the treatment of acute ischemic stroke. Successful reperfusion is associated with improved functional outcome and recovery. With increase in endovascular procedures, onset-to-reperfusion time (ORT) has emerged as a new goal and predictor of functional recovery. The authors study whether it is a predictor of all-cause mortality as well as 90 days. This study is a pooled analysis from 7 studies of patients with intracranial internal carotid (ICA) or middle cerebral artery (MCA) occlusion, treated with endovascular treatments, with achievement of partial or complete angiographic recanalization at 8 hours. Of the 480 patients, 360 had MCA infarcts. Overall 304 (63%) patients received intravenous TPA, 340 (71%) received intra-arterial TPA and 266 received mechanical revascularization (after intra-arterial therapy in 126 patients). Median age was 70 years, with 53% men and median National Institutes of Health Stroke Scale (NIHSS) stroke severity of 17. Median ORT in studies ranged from 225 to 323 minutes. Overall mortality was 20% and rate of intra-cerebral hemorrhage (ICH) was 27%. Mortality and ICH increased while functional outcomes (favorable= modified Rankin Scale score (mRS) 0–2; excellent=mRS 0–1) declined with increasing ORT. Adjusted odds ratio for each 30-minute time increase was 1.21 (95% confidence interval (CI), 1.09–1.34) for mortality, 0.79 (95% CI, 0.72–0.87) for favorable functional outcome, 0.78 (95% CI, 0.71–0.86) for excellent functional outcome, and 1.21 (95% CI, 1.10–1.33) for ICH. Effect size of ORT on mortality was larger in patients with ICA occlusion. Authors found no significant heterogeneity in the impact of ORT on outcomes between studies.

Conclusion: This study demonstrates a linear relationship of ORT with mortality and functional outcome, thus supporting its role as a goal for reperfusion therapy in acute ischemic stroke especially with the advent of endovascular therapies. The range of ORT though was narrow and the results may not apply to delayed ORT (>6 hours). Further, this pooled analysis study is limited by heterogeneity in selection for treatment and also center differences and may not be generalizable to all stroke centers with endovascular capability. The study though supports the usefulness of ORT as a predictor of...
outcome including mortality in acute ischemic stroke and a measure for comparative effectiveness studies in endovascular therapy.47

**IScore: a Risk Score to Predict Death Early After Hospitalization for an Acute Ischemic Stroke**

**Summary:** Predicting stroke mortality is important to identify patients at high risk for poor outcome, to discuss prognosis and aid treatment decisions, to anticipate supportive care services at discharge, and also help construct outcome based measures for profiling hospital performance. However, there are few validated risk score models for predicting mortality in acute ischemic stroke especially for both early (30 day) and late (1 year) time frames. The authors used the Registry of the Canadian Stroke Network to identify patients with acute ischemic stroke between 2003 and 2008. Of the 12,262 patients, 2/3rd were randomly selected for the derivation cohort and the rest served as the validation cohort. External validation was done in the Ontario stroke audit data which included community hospitals in contrast to the derivation cohort. Mortality rates in the derivation and internal validation cohorts were 12.2% and 12.6% respectively, at 30 days and 22.5% and 22.9% at 1 year. Independent predictors of 30-day and 1-year mortality were similar and included older age, male sex, stroke severity, non-lacunar subtype of stroke, serum glucose ≥135 mg/dL, history of atrial fibrillation, coronary artery disease, congestive heart failure, cancer, dementia, kidney disease on dialysis, and dependency prior to stroke. A risk score index stratified the risk of death and identified low- and high-risk individuals. The c statistic was 0.850 for 30-day mortality and 0.823 for 1-year mortality in the derivation cohort. Similar findings were observed in the internal validation dataset. In the external validation dataset the c-statistic was 0.790 for 30-day model and 0.782 for the 1-year model.

**Conclusion:** The IScore is non-cumbersome and has good predictive accuracy without needing stroke volume assessment. Its advantages over other scoring models46 include prediction over a wide range of mortality and inclusion of other important clinical co-morbidities. It cannot be extended to ambulatory settings and patients with hemorrhagic stroke. The risk model also requires re-calibration to use in other communities with different stroke patterns, racial mix etc. The score has been subsequently validated in other ischemic stroke populations in China49 and Korea40 supporting its generalizability to other populations.41

**Therapeutic Strategies for Prevention and Treatment of Stroke**

Therapeutic strategies for stroke are centered on prevention and treatment of stroke. Primary and secondary prevention of stroke includes lifestyle modification and measures to control risk factors such as hypertension, cholesterol, diabetes, and atrial fibrillation (AF). For example, blood pressure reduction in patients with hypertension leads to an estimated 25–30% reduction in the RR of stroke.53 Similarly, higher cholesterol levels are associated with an increased risk of ischemic stroke, and treatment with statins leads to a RR reduction of approximately 20%.54 Anticoagulation remains the mainstay of preventing risk of stroke and TIA in patients with AF. While warfarin is highly effective, the emergence of newer antithrombotic agents and left atrial appendage closure devices may offer alternative therapeutic strategies for stroke prevention in patients with AF without the need for regular monitoring. In contrast to prevention, however, treatment options for acute ischemic stroke remain limited. Tissue plasminogen activator (tPA) reduced disability from AIS, albeit at the expense of stroke prevention in patients with AF.46,47

**Prevalence of Inadequate Blood Pressure Control Among Veterans After Acute Ischemic Stroke Hospitalization: a Retrospective Cohort**

**Summary:** Blood pressure (BP) management after cerebrovascular events reduces the risk for recurrent strokes. Initiating such secondary prevention during hospitalization for the initial event has been shown to improve patient adherence. To describe post-stroke BP management among veterans after ischemic strokes, investigators analyzed BP control (<140/90 mmHg) at discharge and at 6 months following the event. Investigators used the Office of Quality and Performance Stroke Special Study to retrospectively examine 3987 veterans admitted with ischemic stroke to a Veterans Affairs Medical Center (VAMC) during 2007. BP control was analyzed as a binary outcome (controlled or uncontrolled) using logistic regression models with and without adjustments for demographical and clinical characteristics. Analysis at discharge excluded those who died, were hospice or comfort care only, or were missing discharge information (n=3640, n=3382 in adjusted analysis). The second outcome of BP control within 6 months post stroke was analyzed with further exclusion of those who died or readmitted within 30 days, were lost to follow-up, or did not have a BP recorded (n=2054, n=1915 adjusted analysis). The cohort was 62.7% white, 97.7% male, 46.9% ≥65; and 29% and 37% had a history of cerebrovascular or cardiovascular disease, respectively. BP control was not achieved in 43% of stroke patients at discharge. Black race (adjusted OR 0.77; 95% CI 0.42–0.63), diabetes (OR 0.73; CI 0.62–0.86), and history of hypertension (OR 0.51; CI 0.42–0.63) were associated with lower odds for controlled BP at discharge. Six-months after the initial event, nearly 33% remained uncontrolled; and only history of hypertension continued to have lower odds of BP control.

**Conclusion:** This study demonstrates deficiencies in the delivering of secondary prevention after stroke. This deficiency may have been enhanced at 6-month follow-up, since patients who are younger and healthier are less likely to seek outpatient follow-up, thus more likely excluded for missing follow-up BP measurement. Nonetheless, a notable portion of stroke patients had uncontrolled BP at discharge; and those with diabetes and other risk factors for recurrent strokes were more likely to have uncontrolled BP. These results call for better adherence to guidelines in initiating secondary prevention strategies while in-hospital, even at VAMCs, which are generally recognized to be the paragon of preventive care.46–52

**Risks and Benefits of Anticoagulation in Atrial Fibrillation: Insights From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry**

**Summary:** Evidence suggests that patients with atrial fibrillation (AF) at the highest risk of stroke derive the largest benefit from oral anticoagulation (OAC). However, those with the highest risk of stroke are also the least likely to receive OAC in clinical practice. This study assessed the association between stroke and bleeding risk on rates of OAC. In this study, the authors assessed the association between stroke and bleeding risk on rates of OAC among 10,098 patients (mean age was 73y; 58% male) with AF from 174 community-based outpatient practices enrolled in 2010–2011 in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). OAC was defined as warfarin or dabigatran use at study enrollment. Stroke and bleeding risk were calculated using the CHADS2 risk score53 and the anticoagulation and risk factors in AF (ATRIA) score54,55 respectively. Overall, 76% of patients received OAC (71% warfarin and 5% dabigatran). The use of OAC increased among those with higher CHADS2 scores (from 53% for CHADS2=0 to 80% for CHADS2≥2, p <0.001). OAC use fell slightly with increasing ATRIA
bleeding risk score (from 81% for ATRIA=3 to 73% for ATRIA≥5, p<0.001). Significant interaction was noted between ATRIA and CHADS$_2$ risk scores (p=0.021). Specifically, among those with low bleeding risk, OAC use increased significantly with increasing stroke risk. Among those with high bleeding risk, the use of OAC also increased with increasing stroke risk although the magnitude of the increase was significantly less.

**Conclusion:** Two important observations can be derived from this study. First, 76% of patients overall were on appropriate treatment with OAC, a significant improvement from prior observed cohorts. ORBIT-AF is a voluntary registry participant in this registry may not be representative of the general population which may explain the higher OAC rate. Second, the use of OAC therapy increased with increasing stroke risk (as measured by CHADS2 Score) but clearly clearly clinicians factor in the risk of bleeding in addition to the calculated risk of stroke in this decision with OAC use remaining lower in those with higher bleeding risk.55

**Comparative Efficacy and Safety of New Oral Anticoagulants in Patients With Atrial Fibrillation**

**Summary:** Several novel agents including Dabigatran, an oral thrombin inhibitor, and rivaroxaban and apixaban, oral factor Xa inhibitors, have been shown to be safe and effective in reducing the risk of stroke in patients with AF. However, all have compared to warfarin and there are no studies directly comparing these agents. Accordingly, the authors compare the efficacy and safety of the 3 new agents based on data from their published warfarin-controlled randomized trials. They included findings from 44,535 patients enrolled in 3 trials of the efficacy of dabigatran (Randomized Evaluation of Long-Term Anticoagulation Therapy [RELY]), apixaban (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]), and rivaroxaban (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF]). The control arm in each of these trials was warfarin but mean time in therapeutic range was higher in ARISTOTLE (62%) and RE-LY (64%) than in ROCKET-AF (55%). Other inclusion, exclusion criteria were similar except ROCKET-AF only included patients with CHADS2 score ≥2. The efficacy and safety of these 3 agents were compared using the method of indirect comparisons. The primary efficacy end point was stroke or systemic embolism; the safety end point was major hemorrhage. The results of the study showed found no statistically significant efficacy differences among the 3 drugs even among those at high risk (CHADS2 ≥3), although apixaban and dabigatran were numerically superior to rivaroxaban. Apixaban produced significantly fewer major hemorrhages events than dabigatran and rivaroxaban.

**Conclusions:** This study performed an indirect comparison of new anticoagulants based on existing trial data and suggests that dabigatran, apixaban, and rivaroxaban similar rates of stroke and systemic embolism, with a lower rate of major hemorrhage observed with apixaban. However, indirect comparisons usually but not always agree with the results of head to head randomized trials and they make several assumptions and is not a replacement for a well-designed randomized control trial. Nevertheless, until such a trial is performed this comparison provides some guidance for clinicians.56

**Percutaneous Left Atrial Appendage Closure for Stroke Prophylaxis in Patients With Atrial Fibrillation: 2.3-Year Follow-Up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) Trial**

**Summary:** Atrial fibrillation (AF) is strongly associated with risk for ischemic stroke, leading to the development of new approaches isolating the left atrial appendage (LAA) based on evidence suggesting it is the main site of thrombus formation.60,61 The PROTECT AF study sought to determine whether LAA closure with a Watchman filter device was noninferior to warfarin for stroke prevention in AF. Previous interim results demonstrated non-inferiority of LAA closure but few patients had been followed long-term.62 This is the final analysis of the trial cohort, consisting of 707 randomized patients (463 undergoing LAA closure; 244 in control arm) across 59 centers with nonvalvular AF and at least 1 risk factor (age ≥75, hypertension, heart failure, diabetes, or prior stroke/transient ischemic attack). The trial design has been previously published.63 Mean follow-up was 2.3±1.1 years and the primary efficacy endpoint was a composite of all stroke, systemic embolism, or cardiovascular death. Patients on warfarin maintained a therapeutic INR for 66% of the time. The event rate was 3.0% per year (95% CI: 2.15%-4.3%) in the intervention arm compared to 4.3% per year (95% CI: 2.6%-5.9%) in the control group (rate ratio 0.71; 95% CI: 0.44-1.30; probability of noninferiority >0.999; probability of superiority 0.88). Among the composite endpoints, the event rate for the intervention group was significantly lower in cardiovascular death and hemorrhagic stroke but higher, although not significantly different, in ischemic stroke (1.9% versus 1.4%). For safety, the primary annual adverse outcome rate was higher in the intervention group (5.5%; 95% CI: 4.2%-7.1%) versus the control group (3.6%; 95% CI: 2.2%-5.4%). The majority of adverse outcomes, particularly pericardial tamponade and procedure-related stroke, occurred proximate to the implantation procedure.

**Conclusions:** This final analysis of the PROTECT AF trial showed that closure of the LAA using the Watchman device was noninferior to continuing warfarin therapy for the primary endpoint of all stroke, systemic embolism, and cardiovascular death. However, the trial also showed higher rates of adverse outcomes in the intervention arm. Given the lack of superiority, higher adverse outcomes, greater cost, and lack of other studies of LAA devices showing benefit, it may be important to consider whether this approach is beneficial and if so, which patients would derive the most benefit. One important group not studied in this trial are patients in whom anticoagulation is contraindicated.64

**Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation**

**Summary:** Atrial fibrillation (AF) significantly increases the risk of stroke. In terms of management, it is currently unclear whether stroke rates differ between patients receiving prescriptions for rhythm or rate control. Routinely prescribed for patients with AF (1999–2007) utilizing linked administrative hospital discharge data and prescription drug claims databases, identified through ICD9/10 codes. The final cohort consisted of 16,325 patients receiving rhythm control (53% women) as well as 41,193 patients who received rate control therapy (56% women) (mean follow up of 2.8 years). Incidence rates for stroke/TIA were calculated as well as Kaplan-Meier curves and Cox proportional hazards models (with adjustment for important confounders). A propensity model was conducted to stratify by low, moderate and high-risk groups according to the CHADS$_2$ score. Patients on rate control therapy had a CHADS$_2$ score risk score of ≥2 as compared with those patients using rhythm control (58% vs. 67%), however treatment with antithrombotic drugs (i.e. warfarin, acetylsalicylic acid, clopidogrel) were comparable between groups (76% in rhythm control vs. 77% rate control). All cause stroke/TIA incidence was lower in patients with rhythm control as compared with rate control treatment (1.74 versus
Stepwise Screening of Atrial Fibrillation in a 75-Year-Old Population: Implications for Stroke Prevention

Summary: Screening for silent AF can be helpful in at-risk populations, as AF can be asymptomatic and thereby undiagnosed. However, it is unknown whether such routine screening could be helpful for stroke prevention through the initiation of oral anticoagulant (OAC) treatment. In this study, the authors explored the prevalence of previously undiagnosed asymptomatic AF requiring OAC using stepwise ECG screening in 848 75-76 year olds from Sweden and observed the rate of initiation of OAC. Specifically, the protocol was to perform a 12-lead ECG at registration, followed by intermittent handheld ECG recording over 2 weeks for patients in sinus rhythm with a CHADS2 score ≥2. 81 patients had known AF and 10 (1%) of the patients had previously undiagnosed silent AF on registration ECG; 35 out of 81 patients with known AF (43%) were not on OAC treatments. Of the 403 patients with ≥2 risk factors of stroke that underwent extended screening, 30 (7.4%) were diagnosed with paroxysmal AF. After screening, the total prevalence of AF among screened individuals was 14%, of which only 38% had OAC treatment. This resulted in 75 out of 848 screened patients (9%) being candidates for OAC treatment, with 57 of those (76%) subsequently starting treatment.

Conclusion: This study illustrates the potential of stepwise screening for AF in at-risk populations as a means for stroke prevention through the initiation of OAC treatment. Promisingly, a large share of candidates were yielded and the amount of OAC treatment on AF indication more than doubled among screened participants. However, there is no information about patient follow up to treat-ment; thus, it cannot be concluded that screening and the resulting start of OAC treatment serves as an actual preventative measure of stroke over time. Also, the cost-effectiveness of such a screening procedure needs to be ascertained. As acknowledged by the authors, given the homogenous study population, the results cannot be general-ized to other populations. In addition, there was only a 60% turn-out, albeit due to a weak invitation. Therefore, while screening for AF might be helpful for stroke prevention by identifying patients at an elevated risk, more studies are needed to prove its efficacy and cost-effectiveness.

Use of Antithrombotic Medications Among Elderly Ischemic Stroke Patients

Summary: Antithrombotic drugs such as aspirin and warfarin are recommended for the prevention stroke and venous thromboembo-lism (VTE) among hospitalized stroke patients. However, the use of antithrombotic agents among elderly patients is less well known. Accordingly, the authors sought to (a) assess the adherence to these medications among elderly patients hospitalized with an ischemic stroke, and (b) to determine the effects of increasing age (i.e. >65 years) and other patient characteristics on treatment. The authors utilized Medicare fee-for-service beneficiaries discharged with ischemic stroke (ICD 433.x1, 434.x1, 436) from the Medicare Health Care Quality Improvement Program’s National Stroke Project conducted between 1998–1999 and 2000–2001. Receipt of in-hospital pharmaco-logical deep vein thrombosis prophylaxis, antiplatelet medication, anticoagulants for AF, and antithrombotic medications at discharge were assessed in eligible patients, stratified by age (65 to 74, 75 to 84, and 85+ years). The final study cohort consisted of 31,554 patients among whom, 14.9% of those eligible received pharmacological VTE prophylaxis, 83.9% antiplatelet drugs, 82.8% anticoagulants for AF, and 74.2% were discharged on an antithrombotic medication. Crude rates of treatment decreased with age and were lowest for patients aged 85 years or older although when adjusted for baseline risk, lower rates were consistently observed only among those aged ≥85 years. Lower rates were also observed among patients discharged to a skilled nursing facility and with lower functional status.

Conclusion: This study suggests substantial underuse of antithrombotic medications among eligible hospitalized stroke patients. In particular, it insinuates a remarkably low rate of VTE prophylaxis despite the well-known risk of VTE among stroke patients. However, increasing age is associated with increased “frailty,” cognitive and functional impairment, polypharmacy, psychological distress, and social isolation, all of which contribute to an age-related risk for morbidity and mortality that must be balanced against the disease-specific risk from stroke. This may explain the declining use of anti-thrombotic medica-tions with increasing age. Furthermore, this data was from 1998–2002 and may not reflect current practice. More recent data suggests substantial improvements in these quality measures have occurred generally among hospitalized stroke patients. Nevertheless, this study suggests room for improvement in the use of antithrombotic therapy, and thereby stroke outcomes, among elderly patients.

Cost-Effectiveness of Apixaban Compared With Aspirin for Stroke Prevention in Atrial Fibrillation Among Patients Unsuitable for Warfarin

Summary: Atrial fibrillation is the most common cardiac arrhythmia in the United States. Many patients with this condition have either failed or are unable to tolerate therapy with a vitamin-K antagonist. The authors of this study therefore compared the cost-effectiveness of treatment of atrial fibrillation with aspirin compared with apixaban in patients deemed inappropriate for warfarin. Using data from the Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin-K Antagonist Treatment (AVERROES) trial, the authors constructed a Markov model to evaluate the costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness of apixaban versus aspirin. The base case was assumed to be a 70-year-old patient with a CHADS, score of 2 and a low risk of bleeding. As per data from AVERROES, the risk of major bleeding with apixaban was deemed equal to aspirin. Analyses were performed for both 1-year and 10-year follow-up. Total costs per patient were $1649 higher for apixaban in the 1-year model and $5834 lower for apixaban in the 10-year model. QALYs were the same between the 2 agents at 1 year and 0.36 higher for apixaban at 10 years, thereby making apixaban the inferior strategy at 1-year (more expensive) and the dominant strategy at 10 years (both cheaper and associated with higher quality-of-life). Conclusions in the 10-year model were sensitive to baseline stroke rate, relative risk of stroke between treatment arms, cost of stroke, and other variables.

Conclusion: Cost effectiveness analysis is particularly important when evaluating treatment for AF, as more than 2.7 million Americans currently have the condition and more than 12 million are expected to have AF by 2050. Unfortunately, findings from this paper are significantly limited by the fact that both assumptions and results were
derived from 1 randomized trial that was stopped early and surprisingly found that major bleeding rates were similar between aspirin and apixaban. Findings are further limited to patients with a CHADS² score of 2 and low bleeding risk who constitute only a minority of persons with AF who are unable to tolerate warfarin therapy. Findings should therefore be applied to other persons with atrial fibrillation who are unable to tolerate warfarin with great caution.46

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Summary: While there have been studies on alternatives to warfarin for stroke prophylaxis in patients with AF, there have been few studies on the cost-effectiveness of such alternatives. The authors developed a Markov decision-analysis model to assess the cost-effectiveness of dabigatran at 110 mg and 150 mg twice daily dosages based on the results of various trials and, using a cost-effectiveness threshold of $50,000 per quality-adjusted life-year (QALY), ran it on a hypothetical cohort of 70-year-old patients with AF. They noted that for patients with the lowest stroke rate (CHADS² score = 0) aspirin was cost-effective; with moderate stroke rate (CHADS² score = 1 or 2) warfarin was cost-effective unless quality of international normalized ratio was poor or risk of hemorrhage was high; and with high stroke risk (CHADS² ≥ 3) dabigatran 150 mg (twice daily; estimated at US $9 per day) was cost-effective unless there was a good international normalized ratio control.

Conclusion: The cost-effectiveness of a given therapy for stroke prophylaxis in AF patients was found to depend on stroke risk for patients with average risk of a major hemorrhage (~3%/year). In general, aspirin was the most cost-effective for patients with the lowest stroke rate, warfarin for those with a moderate stroke rate, and dabigatran 150 mg (twice daily) for patients with a high stroke rate. Dabigatran at the 110 mg dose and dual therapy (clopidogrel and aspirin) were not cost-effective for any risk category. One limitation of this study was that the efficacies of dabigatran were based on single trial – the Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY). In addition, as noted by Avorn,75 the analysis is heavily dependent on drug cost estimates, particularly the utilization of unreliable average wholesale prices of drugs. To fully understand the cost-effectiveness of dabigatran, we need both better estimates of the costs of treatment and more experience with the drug to understand its true effectiveness.47

Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation

Summary: The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial reported better outcomes with the use of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation.46

The present study addressed whether, the apparent efficacy and safety of apixaban in ARISTOTLE varies according to the quality of International Normalized Ratio (INR) control in the warfarin group. In a post-hoc analysis of ARISTOTLE data (n=18,201), centers were classified into quartiles based on their patients’ average percentage of time in therapeutic INR range (cTTR). Hazard ratios for apixaban compared to warfarin were measured independently in each cTTR quartile. The hazard ratio for the primary outcome (SSE) was 0.73 (95% CI 0.53 – 1.00) in the lowest cTTR quartile, compared with 0.88 (0.57 – 1.35) in the highest cTTR quartile. In addition, hazard ratios for major bleeding were 0.50 [0.36 – 0.70] and 0.75 [0.58 – 0.97] in the lowest and highest cTTR quartiles, respectively. For mortality, the hazard ratios were similar in both the lowest and highest cTTR quartiles (0.91). There was no significant interaction between treatment effect and cTTR quartile (p > 0.05 for all outcomes).

Conclusions: This study finds no statistically significant differences in the benefits of apixaban across hospitals with varying quality of INR control. However, the observed differences across quartiles may be clinically meaningful. Specifically, the effect size (expressed as 1 minus hazard ratio) for SSE/bleeding increased more than 2-fold from the highest to lowest cTTR quartiles. Due to wide confidence intervals, no firm conclusions can be drawn from this study regarding the relative benefits of apixaban across settings with varying quality of INR control.77

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: The European Cooperative Acute Stroke Study III (ECASS-III) trial showed a benefit of tissue plasminogen activator (tPA) between 3–4.5 hours of symptom onset in acute ischemic stroke (AIS).70 This prompted the American Heart Association/American Stroke Association (AHA/ASA) to expand the time window for tPA eligibility from <3 to <4.5 hours.73 This study investigated how the ECASS-III findings influenced clinical practice in 1711 hospitals in the Get With the Guidelines (GTW) Stroke Registry. The authors identified 217,692 patients with AIS with an onset-to-door time of ≤ 4.5 hours who met eligibility criteria for tPA. The authors find a significant increase in tPA use between 3–4.5 hours after publication of ECASS-III. In particular, among patients presenting within 3.5 hours of symptom onset, the rate of tPA use within 4.5 hours increased from 19% to 35% after ECASS-III. This rate did not increase in the first three months after ECASS-III was published in September 08, but did increase by 7.25% points in the three months after publication of the AHA/ASA advisory in May 09.

Conclusions: This study shows a significant increase in tPA usage between 3–4.5 hours of symptom onset that is temporally related to the ECASS-III trial. While this rapid response is encouraging, it is striking that even after ECASS-III nearly two thirds of eligible patients presenting within 3.5 hours fail to receive tPA within the recommended 4.5 hour window. This suggests that there remain significant opportunities for quality improvement in AIS. The finding that tPA use increased significantly only after the release of the AHA/ASA advisory – and not immediately after ECASS-III publication - illustrates the importance of expert guidelines in translating evidence into widespread practice. As hospitals participating in the GWTG registry are more likely to be academic hospitals with an interest in quality improvement, it is unclear whether these findings extend to the broader hospital population.79

Health Systems Interventions to Improve Stroke Care

Over the last decade several health system innovations have contributed to the improvement in stroke outcomes. First, the recommendation to develop centers for excellence in stroke care led to the establishment of primary and comprehensive stroke centers that consolidate the care of stroke patients by providing specialized stroke units, standardized stroke protocols, and advanced neuroimaging and acute treatment capabilities.80,81 Evidence suggests that patients treated at stroke centers have lower mortality, greater functional recovery, and a lower risk of subsequent stroke compared to non-specialized centers.82 Second, tissue plasminogen activator (tPA), and more recently endovascular therapy, have emerged as viable treatment options for acute ischemic stroke (AIS). tPA, when given very early in the course of AIS, reduces stroke disability. The relatively short therapeutic window for treatment led to the development of systems to rapidly perform neuroimaging and to safely administer TPA therapy. While endovascular therapy has not shown a mortality benefit over tPA for AIS, it may improve outcomes for those who fail or have a contraindication to tPA. Despite these innovations, only a small fraction of patients...
receive tPA therapy, and gaining rapid access to endovascular therapy remains challenging. Lastly, reporting hospital performance and outcomes is widely recognized as a key strategy to improve the quality of care. Evidence suggests that performance measurement by initiatives such as the Get-with-the-guidelines (GWTG) Stroke initiative, along with other quality improvement efforts, have contributed to marked improvement in the adherence to guideline recommendations and may ultimately contribute to improvement in patient outcomes.

The following summaries review systems of care for stroke, including quality measurement, cost-effectiveness of telestroke centers, and rapid access to endovascular therapy.

Patterns of Emergency Medical Services Use and Its Association With Timely Stroke Treatment: Findings From Get With the Guidelines-Stroke

Summary: It is well known that “time is brain” in acute stroke, as it is important for patients with stroke to arrive at the hospital as quickly after symptom onset as possible to reduce neurological damage. However, current rates of Emergency Medical Service (EMS) use and its association with timely stroke treatment is unknown. Therefore, the authors used the Get With the Guidelines-Stroke database to analyze data from 204,591 patients with ischemic and hemorrhagic stroke. 63.7% of patients arrived at the hospital by EMS. The patients most likely to use EMSs were those with severe stroke, those with Medicaid and Medicare insurance, and older patients. However, patients living in rural communities and of minority race and ethnicity were less likely to use EMSs. EMS transport was found to have many benefits, as it was independently associated with earlier arrival (onset-to-door time, ≤3 hours; adjusted odds ratio, 2.00; 95% confidence interval, 1.93–2.08), prompter evaluation (more patients with door-to-imaging time, ≤25 minutes; odds ratio, 1.89; 95% confidence interval, 1.78–2.00), more rapid treatment (more patients with door-to-needle time, ≤60 minutes; odds ratio, 1.44; 95% confidence interval, 1.28–1.63), and more eligible patients to be treated with tissue-type plasminogen activator if onset is ≤2 hours (67% versus 44%; odds ratio, 1.47; 95% confidence interval, 1.33–1.64).

Conclusion: Despite the positive association between EMS use and reduced time to hospital presentation and rapid evaluation and treatment of stroke, over one-third of stroke patients did not use EMSs. Therefore, interventions are needed to increase EMS activation, with a particular focus on young and minority patients. Some limitations of this study were its lack of information on patient income and educational levels and on patients’ place of residence. Further studies are warranted to better understand the populations that are more likely to underuse EMSs to ultimately improve outcomes for patients with stroke.

Cost-Effectiveness of Hub-and-Spoke Telestroke Networks for the Management of Acute Ischemic Stroke From the Hospitals’ Perspectives

Summary: The use of telemedicine in the treatment of stroke – commonly referred to as telestroke – has been shown to increase appropriate use of intravenous thrombolysis and improve clinical outcomes in centers that lack specialist capacity. While telestroke is cost-effective from a societal perspective, high upfront costs borne by individual hospitals may limit their uptake. To address this barrier, the authors analyzed the cost-effectiveness of telestroke networks from the perspective of both a tertiary referral hospital (“hub”) and referring (“spoke”) hospitals. The authors modeled a hypothetical telestroke network consisting of one hub hospital and seven spoke hospitals. They calculated costs and benefits over a five-year period, deriving model assumptions from the Georgia Health Sciences University and Mayo Clinic telestroke networks. Effectiveness was measured in terms of the incremental numbers of eligible patients treated with advanced therapies (intravenous or endovascular thrombolysis) and the number of home discharges. Cost savings for each hospital was calculated as reimbursements minus costs due to telestroke setup, maintenance, and acute ischemic stroke (AIS) treatment. Telestroke led to 65 more patients treated with advanced therapies and 6.11 more home discharges annually. While the hub incurred a positive annual cost of $405,121, each spoke hospital had $109,080 in annual cost savings, resulting in network-wide net savings of $358,435.

Conclusions: This study suggests that telestroke networks not only improve patient outcomes, but may also result in a net profit for hospitals. However, an important finding is that financial benefits may not be realized equally, with hub hospitals potentially bearing a substantial cost burden. The hub realizes cost savings only when there are frequent spoke-to-hub transfers of high-reimbursement AIS patients – a scenario which is clinically sub-optimal. The authors suggest that spoke-to-hub transfer payments could be arranged to allow all hospitals to share cost savings equally. While the benefit of telestroke to patients is clear, this study shows that financial considerations are important in promoting the establishment of telestroke networks.

Does the Inclusion of Stroke Severity in a 30-Day Mortality Model Change Standardized Mortality Rates at Veterans Affairs Hospitals?

Summary: As the Centers for Medicare and Medicaid Services (CMS) was developing a 30-day hospital-level acute ischemic stroke mortality measure, many expressed concerns over adequate risk adjustment without the inclusion of stroke severity. Therefore, this study sought to determine whether inclusion of the National Institutes of Health Stroke Scale (NIHSS), a validated measure of stroke severity, would affect 30-day mortality rates and comparisons across hospitals in the Veterans Health Administration (VHA). Utilizing national data from a 2007 comprehensive review of VHA ischemic stroke care quality, the authors identified 2563 veterans across 64 VA hospitals who were admitted with a principle discharge diagnosis of ischemic stroke. For consistency with the proposed CMS measures at that time, hospitals with < 25 stroke patients and patients transferred from outside hospitals were excluded. The hospital-level median age was 67.6 (range 61.5–75.4) with a median NIHSS of 3.8 (0.8–6.8) and median proportion of males of 98% (88–100%). The risk-adjusted mortality rate (RSMR) across the VHA based on the CMS model was 5.40% (95% CI: 2.52–9.92%). After addition of the NIHSS (grouped into 7 categories based on score), the RSMR remained similar at 5.42% (2.52%–9.92%). The RSMR interquartile range remained consistent at 5.1%–5.6% with and without the NIHSS. Hospital-level RSMRs plotted with and without the NIHSS across hospitals showed overlapping 95% CIs, with no hospital significantly above or below the mean-unadjusted mortality rate.

Conclusions: The addition of the NIHSS score as a measure of stroke severity into risk adjustment model produced little effect on hospital-level RSMRs or comparisons across hospitals. Based on this study, all VA hospitals would receive the same rating regardless of model, with no distinction of high-performing or underperforming hospitals. However, the limited sample in this study and the lower mortality rates and decreased variation among VA hospitals compared with other Medicare hospitals suggest that results may be more discriminatory for hospitals outside the VHA.

Are Quality Improvements in the Get With the Guidelines: Stroke Program Related to Better Care or Better Data Documentation?

Summary: Reporting performance is a key strategy for improving quality, reducing cost, and increasing healthcare value. Increasing compliance with stroke performance measures has been shown in prior studies. However, it is uncertain whether this is due...
to improvement in care or due to better data documentation. Accordingly, the authors examined trends in the documentation of eligibility criteria, treatment contraindications, and missing data for 7 accepted performance measures of in-hospital stroke care: intravenous recombinant tissue plasminogen activator therapy, early anti-thrombotics, deep vein thrombosis prophylaxis, anticoagulants for atrial fibrillation/flutter, discharge anti-thrombotics, lipid therapy, and smoking cessation). They assessed the association between trends in documentation of eligibility criteria, treatment contraindications, and missing data with increased performance measure compliance. The final cohort included 569,883 ischemic stroke admissions from 1028 Get with the Guidelines (GWTG)-Stroke hospitals between 2003–2009 with yearly change analyzed for evaluation of trends using descriptive statistics. The study results revealed a significant increase in the proportion of eligible participants treated across the study period for all 7-performance measures (as documented in prior studies). However, these increases occurred without significant changes in the proportion of patients with contraindications or missing data. Anticoagulation therapy for AF/flutter was the only exception where the increase measure compliance occurred in conjunction with a decline in the proportion of patients with contraindications.

**Conclusion:** This study provides reassuring evidence that the improvements in performance seen in the GWTG-Stroke hospital performance measures, and documented in other studies, are indeed real and reflect better treatment of eligible stroke patients. These findings reiterate the observation that measuring and reporting performance is a key strategy for improving quality of care for hospitalized stroke patients. However, it remains uncertain as to whether collecting and reporting on performance measures improves stroke outcomes. In this context, routine measuring and reporting of outcomes of stroke patients may further enhance patient care.84

**“Picture to Puncture”: a Novel Time Metric to Enhance Outcomes in Patients Transferred for Endovascular Reperfusion in Acute Ischemic Stroke**

**Summary:** Endovascular intervention for acute ischemic stroke (AIS) is only available at highly specialized stroke centers and is useful in patients who have failed thrombolysis or where thrombolysis is contra-indicated. However, delays in acute transfer of eligible patients may negate the benefit of endovascular therapy. Accordingly, the authors sought to identify transfer delays and to assess the impact of such delays on patient outcome by performing a retrospective evaluation of patients treated with endovascular therapy from 2010 to at a single center. Specifically, they compared the time delay to treatment divided into components (time to presentation, imaging time, and endovascular procedure time). They defined “picture-to-puncture” time as the time from initial computed tomography to groin puncture for the endovascular procedure. The primary outcome was good functional status as defined by 90-day modified Rankin Scale scores of 0 to 2. Patients were analyzed by transfer status (transferred from outside hospitals vs. locally treated patients for analysis) as well by the “picture-to-puncture” time. A total of 193 patients were analyzed (mean age 65.8±14.5 y, median National Institutes of Health Stroke Scale score of 19). Of these patients, 68% were transferred. Transferred patients had longer median picture-to-puncture times (205 vs. 89 minutes, P<0.001) and had less favorable Alberta Stroke Program Early CT Scores on pre-procedural computed tomographic imaging (Scores ≥7; 50% vs. 76%; P<0.001) and significantly worse clinical outcomes (29% versus 51%; P=0.003). Picture-to-puncture times were independently associated with good outcomes (OR 0.994; 95% CI 0.990–0.999).

**Conclusion:** Endovascular treatment of AIS is an emerging therapeutic strategy. This study suggests patients transferred to specialized centers for endovascular therapy have longer time to treatments and have worse outcomes. These findings support the need for strategies to reduce transfer delays and the use of the picture-to-puncture time as a quality measure to monitor transfer delays. It is important to note that endovascular therapy does not improve clinical outcomes compared to thrombolysis in AIS as shown by a recent meta-analysis of five randomized clinical trials.85 Therefore, if eligible, thrombolysis at the presenting hospital is the preferred therapeutic strategy with transfer for endovascular therapy only indicated for patients who have a failed response and among those with a contra-indication to lytic therapy.86

**Estimating and Reporting on the Quality of Inpatient Stroke Care by Veterans Health Administration Medical Centers**

**Summary:** Inpatient quality assessment may suffer from estimation error when quality measures are based on small numbers of observations per facility. To address this concern with regard to the reporting of stroke care quality at Veterans Health Administration Medical Centers, the authors applied multilevel modeling and empirical Bayes (EB) estimation to construct novel quality measures for stroke care. The authors included 3812 veterans who were admitted to 106 Veterans Health Administration Medical Centers with a principal discharge diagnosis of ischemic stroke in 2007. Centers with less than 12 hospitalizations for stroke over the study period were excluded due to concern for unreliable estimates. At included centers, the median number of stroke hospitalizations was 34 (range 12–105). Stroke quality was measured with 13 evidence-based quality indicators. Patients could pass or fail each indicator, and facility-level pass rates and confidence intervals were calculated for each using multilevel modeling and EB estimation. Compared with observed rates of facility performance, EB-estimated rates showed less variability across centers; hospitals with small numbers of observations or extremely high or low rates were most likely to be affected. 8 of 13 potential quality indicators were considered useful for performance reporting, as they could be calculated for the large majority of hospitals, demonstrated significant variation across facilities, had room for improvement, and identified sites with performance significantly above or below both the national average and an 85% pass-rate standard.

**Conclusion:** In using an approach with similarities to that used by the Centers for Medicare & Medicaid Services to evaluate hospita mortality and readmission performance, the authors have developed tools to more confidently assess adherence to process measures for stroke care. The multi-level modeling and empirical Bayes estimation techniques used in this study intentionally decrease the likelihood that hospitals with small stroke volumes are incorrectly labeled as having poor performance for stroke care. However, this approach also increases the likelihood that some facilities with poor quality may be undetected and that others with good quality will be unrewarded. Ultimately, the methodology used should be guided by the clinical or policy question and the manner in which the data will be used.87

**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) treatment given within 3 hours improves neurologic recovery. Guidelines suggest a door-to-needle time of ≤60 minutes to ensure rapid receipt of tPA.5 The authors analyzed the Get-With-the Guidelines-Stroke registry to determine how often this target is achieved and the implications for stroke outcomes. Among the 25 504 ischemic stroke patients treated with tPA within 3 hours of symptom onset from 2003 to 2009 (19.6% of all stroke patients), a door-to-needle time of ≤60 minutes was achieved in 26.6% patients. Patient characteristics strongly predicting a door-to-needle time ≤60 minutes included younger age, male gender, white race, no prior stroke, higher stroke severity, on-hours
arrival and longer onset to arrival time. Hospitals with greater annual volume of tPA-treated stroke patients were associated with higher odds of ≤60 minute door-to-needle time. Proportion of patients with door-to-needle time ≤60 minutes varied widely by hospital (0% to 79.2%) and increased overall from 19.5% in 2003 to 29.1% in 2009. In patients with door-to-needle times ≤60 minutes, in-hospital mortality was lower (adjusted odds ratio, 0.78; 95% CI, 0.69–0.90) and symptomatic intracranial hemorrhage was less frequent (4.7% versus 5.6%) compared with patients with door-to-needle times >60 minutes, despite similar stroke severity.

Conclusion: Only a minority of patients were treated with tPA within the recommended 60 min. The proportion of patients treated within 60 minutes varied across hospitals, with high volume hospitals performing better. There was an improvement in overall performance over time. Disparity in rates of achieving door-to-needle time for females, black race and elderly patients was concerning and warrants attention. Target time may not be achievable in patients with complex presentations and unstable clinical status. Limitations of the study include those typically associated with a registry based study, including bias in hospital participation in the registry and lack of in-depth information on clinical and hospital factors. Nonetheless, the study provides national level data for introspection and identifies the wide gap in meeting door-to-needle time supporting the cause for a national effort101 to reduce door-to-needle times.101

Emergency Medical Service Hospital Prenotification Is Associated With Improved Evaluation and Treatment of Acute Ischemic Stroke.

Summary: With the time dependent nature of tPA efficacy, every minute is critical, and EMS pre-notification can potentially reduce treatment time by improving triage and hospital preparedness. In the Get With The Guidelines- Stroke registry based study, 371625 patients were transported by EMS for whom information regarding pre-notification was available. Two-thirds of the patients had hospital pre-notification. Among eligible patients arriving within 2 hours of symptom onset, patients with EMS pre-notification were more likely to be treated with tPA within 3 hours (82.8% versus 79.2%, P<0.0001). They also had briefer onset to arrival times (113 minutes versus 150 minutes), door-to-imaging times (26 minutes versus 31 minutes), door-to-needle times (78 minutes versus 80 minutes), and onset-to-needle times (141 minutes versus 145 minutes). After adjustment for confounders EMS pre-notification remained independently associated with earlier imaging, earlier tPA administration and more eligible patients treated with tPA. EMS was more likely to pre-notify hospitals for patients who were younger, white, male, higher NIHSS scores or with a history of AF. Patients with a history of previous stroke/TIA, diabetes, peripheral vascular disease, HTN, dyslipidemia, or heart failure were less likely to have EMS pre-notification. The notified hospitals tended to be centers with higher annual stroke volume and tPA administration.

Conclusion: Although substantial focus is needed on community education to identify symptoms of stroke, EMS pre-notification is an important cog in reduction of pre hospital delay. The data lacks information about the extent of pre-hospital assessment, which would be useful. Nonetheless, the study illustrates the effective reduction in assessment and treatment times with hospital pre-notification. Concerted efforts are required to bridge the gap in utilization or pre-notification for stroke.100

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Disclosures

None.

References


