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Medical Practice Variations
Health Services Research
10.1007/978-1-4899-7573-7_82-1

Medical Practice Variations in Stroke

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Abstract

Stroke is an important cause of mortality and morbidity worldwide. It is crucial to reduce practice variation in stroke care by following and adhering to best practice guidelines and quality improvement initiatives to provide consistent care. High compliance rates with these guidelines and standards will promise to improve clinical care and outcomes in stroke patients. Different aspects of practice variation in stroke care including variability in adherence to standards of evidence-based care and in the organization of stroke care are addressed. Finally, the impact of practice variation on stroke care, underlying causes, and different strategies to improve stroke care and how to minimize practice variations are emphasized.

Transient Ischemic Attack and Ischemic Stroke

Introduction: Transient Ischemic Attack and Subtypes of Ischemic Stroke

Stroke is an important cause of morbidity and mortality worldwide (Adamson et al. *2004*). This is the second most common cause of death worldwide and the fourth most common cause of death in the USA (Roger et al. *2012*). Transient ischemic attacks (TIAs) and ischemic strokes share similar mechanisms. TIA is defined as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 h, and there is no evidence of acute infarction on diffusion-weighted images on magnetic resonance imaging (MRI) brain. TIA is an important determinant of stroke. The 90-day risks of stroke after TIA can be as high as 10.5 % and the greatest stroke risk is in the first week after TIA. The classification of ischemic stroke is based on the underlying mechanism of the brain injury and the type and localization of the vascular lesion such as large-artery extracranial or intracranial infarction or small vessel ischemic disease. Other causes include embolism from a cardiac source or a main vessel, arterial dissection, hypercoagulable condition, sickle cell disease, or infarcts of undetermined cause (Adams et al. *1993*; Furie et al. *2011*). Age, sex, low birth weight, race/ethnicity, and genetic factors are important non-modifiable ischemic stroke risk factors, and hypertension, cigarette smoking, diabetes, hyperlipidemia, atrial fibrillation (AF), and carotid stenosis are important modifiable ischemic stroke risk factors (Goldstein et al. *2011*). In this section, we will discuss variations in some important aspects of TIA and acute ischemic stroke treatment including the use of thrombolytic therapy.

Variation in Hospitalization Rates in Patients with TIA

The short-term risk of stroke after TIA is as high as one-quarter to one-half of the strokes that occur within 3 months after TIA occurs within the first 2 days. Therefore, initial management decisions in a timely fashion are of critical importance in these patients. There is a significant variation in the hospitalization rates for TIA patients; in the Northwest USA 68 % of TIA patients are admitted to hospital for investigations and observation, but in the Western USA only 41 % of TIA patients are admitted. There are many clinical and nonclinical factors responsible for this variation which vary widely among practitioners, hospitals, and regions. These factors include age, comorbidities, socioeconomic and demographic characteristics, hospital type, and insurance status. Several studies have identified risk factors for stroke after TIA which can help making initial management decisions such as inpatient admission or outpatient workup in these patients. The risk stratification tools include ABCD2 score and patients with TIA score points for each of the following factors: age ≥60 years (1), blood pressure ≥140/90 mmHg on first evaluation (1), clinical symptoms of focal weakness with the spell (2) or speech impairment without weakness (1), duration ≥60 min (2) or 10–59 min (1), and diabetes (1). The score points are indicated in parentheses. The 2-day risk of stroke was 0 % for scores of 0 or 1, 1.3 % for 2 or 3, 4.1 % for 4 or 5, and 8.1 % for 6 or 7, but this score does not incorporate imaging findings (Coben et al. *2008*; Easton et al. *2009*). If these tools are used properly, it can help minimize variation in hospitalization rates in TIA patients.

Background, Guideline Recommendations, and Variations in Thrombolytic Therapy in Acute Ischemic Stroke

Introduction and Background. About 87 % of strokes are ischemic strokes (Roger et al. *2012*). Ischemic stroke occurs when blood flow to the brain is blocked by blood clots or fatty deposits called plaque in the blood vessel linings. Early restoration of blood flow in patient with acute ischemic stroke (AIS) by thrombolysis of the occlusive clots in the intracranial arteries improves functional outcome. Intravenous administration of recombinant tissue plasma activator (rtPA), alteplase, is the only approved thrombolytic therapy for patients with AIS and has become standard of care for treating ischemic stroke worldwide. This section summarizes the current evidence of thrombolytic therapy in AIS, guidelines for thrombolytic therapy in the management for AIS, and variation in the use of thrombolytic therapy for AIS.

The clinical efficacy of rtPA for AIS was established from the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial in 1995. A pooled analysis of NINDS, the European Cooperative Acute Stroke Study (ECASS), and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) demonstrated a greater benefit from intravenous rtPA administered within 3 h of stroke symptom onset and a diminishing small benefit for up to 4.5 h (Hacke et al. *2004*). The ECASS III trial showed safety and efficacy of rtPA when administered up to 4.5 h of onset of ischemic stroke symptom (Hacke et al. *2008*). A recent report using American Heart Association (AHA) Get With The Guidelines-Stroke (GWTG-Stroke) patient registry data suggested a significant increase in patients receiving rtPA between 3 and 4.5 h of symptom onset following the publication of ECASS III results (Minnerup et al. *2011*; Messe et al. *2012*).

Medical Variation and Underuse of Intravenous (IV) Thrombolytic Therapy

Different studies from the USA, Canada, and European and Asian countries highlight multiple factors which potentially can result in wide variation in the use of rtPA in acute stroke patients in spite of the fact that IV thrombolytic therapy has been widely recommended as a standard treatment for acute stroke patients in all practice guidelines. These variations seem to be related with transportation method; paramedic training; prehospital diagnostic accuracy and triage of patients; repatriation agreement with community hospitals; physician perception about thrombolytic therapy and concerns about bleeding complications with rtPA; patient factors such as age, sex, race, and severity of symptoms; and location of stroke as discussed below in further detail.

Analyzing 601,509 ischemic stroke admissions between 2003 and 2009 in 1,392 hospitals participating in the US GWTG-Stroke, Fonarow et al. found that 59.51 % of patients received IV rtPA treatment within 3 h of symptom onset. This subgroup of patients is among those who arrived at the emergency department within 2 h of symptom onset. Moreover, 35.6 % of patients had CT scan performed within 25 min of hospital arrival (Fonarow et al. *2010*). Among 12,686 acute ischemic stroke patients, identified from the Registry of the Canadian Stroke Network, presenting between 2003 and 2009 at the 11 stroke centers in Ontario, Canada, Saposnik et al. reported that 13.4 % received IV thrombolysis. Overall, mean time from symptom onset to rtPA was 160.5 ± 87 min, and 18.8 % received IV thrombolysis after 3 h. Patients receiving rtPA were more likely to be aphasic, had more severe strokes, and were more likely to arrive by ambulance compared to those who did not receive rtPA (Saposnik et al. *2012*). Sposato et al. investigated quality of ischemic stroke care in Argentinian National Stroke Registry (ReNACer). Examination of data for 1,991 patients admitted with ischemic stroke between 2004 and 2006 revealed only 1 % of patients receiving intravenous rtPA treatment in 74 participating academic and nonacademic institutions in ReNACer (Sposato et al. *2008*).

The safety of intravenous rtPA in terms of intracerebral bleeding has been of concern for ischemic stroke patients over 80 years of age. In a meta-analysis of six studies, Engelter et al. examined mortality, functional recovery, and occurrence of symptomatic intracerebral hemorrhage (ICH) after IV rtPA in <80-year-old and ≥80-year-old patients presenting with AIS. The results indicated less favorable outcome among IV rtPA-treated patients of ≥80 years compared to younger ones. The rtPA-treated stroke patients aged ≥80 years did not seem exceedingly prone to symptomatic ICH compared to younger cohort. It was concluded that IV rtPA for stroke patients aged 80 years and older is safe (Engelter et al. *2006*). Mateen et al. examined the benefits of IV rtPA for ischemic stroke among octogenarians in Canadian Activase for Stroke Effectiveness Study (CASES) national registry data. The investigators observed no significant difference in 90-day mortality, 30-day functional outcome, or rate of symptomatic ICH between patients ≥80 years old and those less than 80 years treated with intravenous rtPA when comparing population at similar baseline risk (Mateen et al. *2010*).

In a meta-analysis of 18 studies to examine the sex difference in the use of IV rtPA treatment for AIS, Reeves et al. found that women were less likely to receive thrombolysis treatment compared with men (Reeves et al. *2009*). In an analysis of 397,257 patients admitted with ischemic stroke to 1,181 hospitals participating in the GWTG-Stroke, Schwamm et al. found that black patients were less likely to receive IV rtPA relative to Hispanic or white patients (Schwamm et al. *2010*).

In their prospective study about the use of thrombolytic therapy in AIS patients in Asia, Suwanwela et al. found that only 2.1 % of these patients received rtPA (Suwanwela et al. *2006*). In Asian countries, rtPA therapy is underutilized, and key factors are lack of patient awareness, short therapeutic window for treatment and late patient arrival after symptom onset, unavailability of proper means of patient transfer to hospital by paramedics, and physician knowledge and concern about bleeding complications with rtPA therapy (Suwanwela et al. *2006*).

Anterior Versus Posterior Circulation Strokes. Approximately 5–10 % of all acute ischemic strokes occur in territory of posterior circulation. Analysis of prospectively collected data of 883 acute ischemic stroke patients (788 anterior circulation strokes (ACS), 95 posterior circulation stroke (PCS)) treated with IV rtPA at 3 Swiss stroke centers suggested lower risk of symptomatic ICH in patients with PCS compared with ACS, whereas favorable outcome and mortality were similar in both anterior and posterior circulation territory (Sarikaya et al. *2011*).

Intra-arterial (IA) Thrombolytic Therapy for AIS

The 2007 American Heart Association/American Stroke Association (AHA/ASA) treatment guidelines did not recommend IA thrombolysis over IV rtPA. It added the recommendation that the availability of IA thrombolysis should not preclude the IV administration of rtPA in otherwise eligible patients (Class III, level C) (Adams et al. *2007b*). The 2011 American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines recommended IA rtPA only in patients with AIS due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV rtPA. The expert panel suggested IA rtPA initiated within 6 h of symptom onset over no IA rtPA (Grade 2C) (Lansberg et al. *2012*). The variation in the use of IA rtPA in tertiary care centers is mostly related with different pre- and in-hospital factors such as delay in transfer from community hospitals and availability of neurointerventional resources. The delay in transfer from community hospitals can be related with multiple factors such as proper selection of patients for interventional procedures and time spent in imaging before transferring patients.

Prabhakaran et al. examined the barriers to IA rtPA therapy for ischemic stroke among 132 patients who were referred for possible IA therapy. Delay in hospital-to-hospital transfer was observed to be the most common reason for exclusion of AIS patients receiving interventional therapy. They

concluded that the likelihood of receiving IA therapy decreases rapidly by increasing transfer time (Prabhakaran et al. *2011*).
Nedeltchev et al. in their prospective study noticed that direct referral without prior imaging at community hospitals shortens the time until IA thrombolysis (Nedeltchev et al. *2003*).

Combined IV and IA Thrombolytic Therapy for AIS

The 2011 ACCP evidence-based clinical practice guidelines did not recommend combined IV/IA rtPA for AIS. The expert panel suggested IV rtPA over the combination IV/IA rtPA in patients with acute ischemic stroke (Lansberg et al. *2012*). The investigational Management of Stroke (IMS) II trial investigated the feasibility and safety of combined IV and IA approach to recanalization for ischemic stroke. The investigators reported combined thrombolysis (IV/IA) to be more beneficial in acute stroke patients. The 3-month mortality in IMS II subjects was 16 % compared to mortality of placebo 24 % and rtPA-treated subjects 21 % in the NINDS rtPA stroke trial. The rate of symptomatic ICH in IMS II subjects was not significantly different than that for the rtPA-treated subjects in the NINDS rtPA stroke trial. IMS II subjects also had significantly better outcome at 3 months than placebo-treated subjects or NINDS rtPA-treated subject (IMS II study *2007*). IMS III, a phase III, randomized, multicenter, open-label clinical trial, is comparing IV/IA approach to IV rtPA alone when initiated within 3 h of acute ischemic stroke onset. The trial result will provide confirmation about efficacy and safety of combined IV/IA rtPA treatment for AIS (Khatri et al. *2008*).
Mazighi el al. investigated the impact of combined IV/IA approach in patients 80 years of age and over. The combined IV/IA approach in patients ≥ 80 years of age was associated with lower 90-day favorable outcome, higher mortality, and asymptomatic hemorrhagic complication than in patients <80 years old. Among patients ≥ 80 years of age, patients treated by the IV/IA approach compared to IV-thrombolysis-treated patients had a higher rate of recanalization associated with increased early neurological improvement. Although there was a higher rate of asymptomatic ICH observed in the IV/IA group, no difference existed in symptomatic ICH rates and 90-day favorable outcome. The investigators concluded that a definite recommendation cannot be given, and an endovascular approach may cause more harm than positive effects in patients over 80 years and should not be considered outside an approved protocol (Mazighi et al. *2009*).

Conclusion

Intravenous rtPA is an established therapy for AIS and has become standard of care for treating ischemic stroke worldwide. The national guidelines for acute stroke treatment recommend its use within 4.5 h of symptom onset. Attempts are being made to maximize IV rtPA treatment for ischemic stroke by establishing primary stroke centers (PSCs) and implementing stroke system of care, stroke registry, and legislative mandates. The variation in utilization of IV/IA thrombolytic therapy for acute ischemic stroke can be minimized by adherence with clinical standard guidelines and participation in stroke quality improvement programs and patient, paramedic, physician education, and citywide prehospital protocols.

Hemorrhagic Stroke

Introduction and Subtypes of Hemorrhagic Stroke, Variations in Management, and Related Key Medical Problems

Intracerebral hemorrhage is a medical emergency and an important cause of mortality and morbidity throughout the world. The important subtypes of hemorrhagic stroke include spontaneous intracerebral hemorrhage (SICH) and aneurysmal subarachnoid hemorrhage (aSAH). Hemorrhagic strokes account for about 13 % of all strokes (Adams et al. *2007a*; Morgenstern et al. *2010*; Steiner et al. *2011*). In each of the next two sections, a very brief overview of the major medical care areas and related variations of the hemorrhagic stroke subtypes followed by a discussion of medical care variations in hemorrhagic stroke subtypes is provided.

Spontaneous Intracerebral Hemorrhage

Many cases of SICH are related to the consequences of poorly controlled hypertension (Morgenstern et al. *2010*; Connolly et al. *2012*). In a study of 1,323 Japanese patients who experienced stroke, patients with blood pressures in the JNC 7 Stage 2 range and total cholesterol less than 160 mg/dl had a relative risk of hemorrhagic stroke of 14.8 as compared to a relative risk of 1.0 for patients with normal blood pressure based on JNC 7 criteria and total cholesterol of greater than 240 mg/dl (Suzuki et al. *2011*). In this study, a multivariable analysis revealed that the lower total cholesterol level (<160 mg/dl) and the higher BP increased the relative risk of hemorrhagic stroke. Similar to ischemic stroke, lifestyle factors such as increased body mass index (BMI), low levels of physical activity, smoking, and excessive alcohol intake are all associated with increased risk of hemorrhagic stroke (Zhang et al. *2011*).

Among stroke subtypes, patients with SICH are less likely to receive prophylactic therapy for deep vein thrombosis (DVT) than patients with ischemic stroke in a study of hospitals using Get With The Guidelines (GWTG) to monitor standard stroke care measures (Smith et al. *2009*). Arguably, organizations that have chosen special quality tracking programs such as GWTG to improve stroke care may have better outcomes than those that do not adhere to specialty guidelines. Prophylaxis against venous thromboembolism has been recommended for all stroke types (Skaf et al. *2005a*; Adams et al. *2007a*; Connolly et al. *2012*).

When seizures occur in SICH, special considerations must be taken. An Italian stroke registry study found that 6.3 % of stroke patients presented with symptomatic seizures (Zhang et al. *2011*). Patients with SICH are most likely to have seizures (OR 7.2, 95 % CI 3.5–14.9) followed by hemorrhagic transformation of ischemic stroke (OR 2.7, 95 % CI 0.8–9.6) (Zhang et al. *2011*). Prophylactic intervention to prevent seizures is not recommended according to the current guidelines including the recommendations by American Stroke Association (Morgenstern et al. *2010*).

Aneurysmal Subarachnoid Hemorrhage

Worldwide there is considerable variation in the incidence of aSAH with an overall worldwide incidence of 9 per 100,000 (de Rooij et al. *2007*). People in Japan (22.7/100,000) and Finland (19.7/100,000) had the highest likelihood of aSAH, whereas areas such as South and Central America had rates as low as 4.2/100,000 (de Rooij et al. *2007*). aSAH affects approximately 30,000 persons in the USA each year with devastating consequences (Zacharia et al. *2010*). Only 60 % of persons

affected by aSAH will reach functional independence, even with aggressive treatment (Zacharia et al. *2010*). Women are more likely than men to experience aSAH (CI 1.09–1.42) (de Rooij et al. *2007*; Eden et al. *2008*) with likelihood estimates for both sexes increasing with age (de Rooij et al. *2007*). Worldwide mortality from aSAH has decreased in the past four decades, especially in industrialized countries, but regional variation appears to exist (Connolly et al. *2012*). For example, the USA reports a mortality rate of 32 %, while Europe and Japan report mortality at 44 % and 27 %, respectively (Nieuwkamp et al. *2009*). It is difficult to discern the specifics of this variation due to the problems with understanding how prehospital deaths were accounted for in this study.

The use of systematic reliable and valid assessment scales in the care of patients with aSAH can reduce variability and improve communication among physicians and other providers (Degen et al. *2011*; Connolly et al. *2012*). The Hunt and Hess scale, modified Fisher scale, the World Federation of Neurological Surgeons scale, and the Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage scale are all used to quantify the status of patients with aSAH. In a small study ($n = 50$), the Hunt and Hess scale ($\kappa = 0.48$) had the lowest interrater reliability when compared with the World Federation of Neurological Surgeons ($\kappa = 0.60$) and the Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage scale ($\kappa = 0.68$) (Degen et al. *2011*) (κ = the weighted kappa value). Although the Hunt and Hess is one of the most frequently used tools by neurosurgeons (71 %) (Cavanagh and Gordon *2002*), like other scales such as the Glasgow Coma Scale, modified Fisher scale, and the World Federation of Neurological Surgeons scale, consistent standards for monitoring and determining patient outcomes in aSAH and clinical timing have not been determined (Cavanagh and Gordon *2002*). The World Federation of Neurological Surgeons scale was developed based on the Glasgow Coma Scale to overcome some of the reliability and variability issues seen in the Hunt and Hess.

Stabilization of the aneurysm is a primary goal in the treatment of aSAH. Both endovascular coiling and craniotomy with aneurysm clipping can be performed, but the decision of which treatment choice is best varies based on many patient-level factors such as patient's condition, aneurysm location and size, neurosurgical and endovascular specialty availability, and system-level factors such as size and experience level of the hospital as well as academic status of the facility (de Rooij et al. *2007*; Connolly et al. *2012*; Pope and Edlow *2012*).

Vasospasm and delayed cerebral ischemia contribute significantly to the mortality and disability associated with aSAH (Sanelli et al. *2011*). Determination of vasospasm can be achieved by transcranial Doppler (TCD) and digital subtraction angiography. TCD is a simple and reliable method to monitor emerging cases of vasospasm in aSAH (Woloszyn et al. *2012*). More recently, CT angiography and CT perfusion (CTP) have been added by some institutions (Sanelli et al. *2011*). CTP is mainly being used to see any delayed ischemia in these patients.

Effective fluid management has been a part of aSAH care for many years. Despite recent evidence to the contrary, the notion of triple-H therapy (hypertension, hypervolemia, and hemodilution) remains in practice (Connolly et al. *2012*). Euvolemia, avoiding dehydration diligently, is recommended and hemodilution is unnecessary (Bautista *2012*; Connolly et al. *2012*). The regulation of blood pressure in patients with aSAH is a difficult balance between prevention of re-bleeding and maintenance of cerebral perfusion (Kirkness et al. *2009*; Connolly et al. *2012*). Greater blood pressure variability rather than absolute blood pressure values was associated with poorer 6-month outcomes (Kirkness et al. *2009*).

Variations in the Management of Spontaneous Intracerebral Hemorrhage

Systems of care that facilitate stroke care have been shown to improve both diagnostic and outcomes measures in all stroke types. In a study of health organizations using Get With The Guidelines (GWTG) to monitor stroke outcomes, patients with SICH were much more likely to meet critical parameters of care that have been associated with better long-term outcomes. For example, patients with SICH that present to health-care organizations that use systems such as GWTG are more likely to have their CT scans completed within 25 min of emergency department arrival than those hospitals that do not use a tool to track quality elements of care (Smith et al. *2009*).

The INTERACT trial sought to explore how aggressive management of blood pressure affects outcomes in SICH (Anderson et al. *2010*). In over 400 patients sustaining SICH, patients with elevated systolic blood pressure (150–220 mmHg) were randomized to treatment groups of "guideline care" based on the 1999 American Heart Association guidelines or "aggressive care" that sought to reduce systolic blood pressure to 140 mmHg within 1 h of inclusion in the study. Patients who received care within the "aggressive care" group had decreased levels of expansion of his/her hematomas (Anderson et al. *2010*).

One interesting potential emerging therapy is the administration of platelets to patients with symptomatic ICH and with either low platelet counts or a history of antiplatelet therapy (Naidech et al. *2012*). In this study ($n = 45$), high-risk patients, those with low platelet counts or antiplatelet therapy, demonstrated smaller hemorrhage sizes on follow-up CT and better modified Rankin scores at 3 months (Naidech et al. *2012*). Elevated blood sugar on admission has been shown to significantly predict poorer functional outcomes after ICH in a sample of over 400 patients in a French study (Béjot et al. *2012*).

Systematic differences exist in rates of deep vein thrombosis (DVT), pulmonary embolism (PE), and venous thromboembolism (VTE) between hemorrhagic and ischemic strokes (Skaf et al. *2005b*). In a registry study of over 14 million stroke discharges in the USA, DVT occurred in 0.74 % of ischemic stroke patients compared to 1.37 % of hemorrhagic stroke patients. In ischemic stroke, 0.51 % of patients experienced PE compared to 0.68 % for hemorrhagic stroke. VTE occurred in 1.17 % of patients with ischemic stroke compared to 1.93 % for hemorrhagic stroke patients (Skaf et al. *2005b*). There is some evidence that the variation between the two types of stroke may be due to the aggressive use of early antithrombotic therapy in ischemic stroke compared to hemorrhagic stroke (Skaf et al. *2005a*; Adams et al. *2007a*) and the increased level of neurologic deficit and disability commonly seen in hemorrhagic stroke (Morgenstern et al. *2010*).

The use of neurosurgical techniques in SICH is a complex clinical decision and outcomes are generally poor. In the FAST trial, neurosurgery was generally associated with poor outcomes after 90 days (Steiner et al. *2011*). Less hematoma expansion is associated with lower mortality rates and variations exist among different hematoma locations. For example, deep gray matter SICH had more hematoma expansion than lobar SICH (Steiner et al. *2011*). Which patients are most likely to benefit from surgical evacuation of SICH is not clearly understood, but clinical decision-making is based on reducing the mass effect of the space occupying hematoma in the cranium. In 43 consecutive patients with SICH in Japan, patients who had their hematoma evacuated by endoscopic means had on average Glasgow Coma Scale score 3 points higher ($p < 0.05$) at day 7 than patients who had their hematoma evacuated by craniotomy (Nagasaka et al. *2011*). It appears that earlier intervention (between onset of symptoms and 72 h) is associated with better outcomes than delayed surgical intervention (Leung et al. *2010*; Steiner et al. *2011*).

In the evaluation of multiple international medical centers caring for patients with SICH, wide variation in the rate of surgical evacuation of SICH was seen. The median rate among 23 countries was 32 %, with the lowest rate seen in Hungary (2 %) and the highest in Lithuania (74 %) (Gregson and Mendelow *2003*). In this study, regression modeling was used to understand which factors were

significantly associated with the decision to provide surgical intervention including younger patient age, lower Glasgow Coma score, increased hematoma size, hematoma location, and country in which the person received care. All of the parameters except country can be categorized as patient-level indicators for surgery; however, country of care is a medical care variance issue that requires further investigation (Gregson and Mendelow *2003*). Researchers hypothesize that the variance in surgical intervention within individual countries is a function of access to care in rural areas as well as local variations in physician practice based on physician training (Gregson and Mendelow *2003*).

Variations in the Management of Aneurysmal Subarachnoid Hemorrhage

Although approximately 80 % of patients with aSAH complain of headache, there is considerable variability in the clinical presentation of patients with aSAH. Rapid diagnosis of aSAH is imperative as the misdiagnosis of aSAH can lead to a fourfold increase in mortality and disability (Connolly et al. *2012*). Misdiagnosis of aSAH is relatively common and approximately 5 % of aSAH cases are misdiagnosed (Vermeulen and Schull *2007*; Pope and Edlow *2012*). Patients with lower levels of acuity, patients who were less symptomatic, and those cared for at a nonteaching hospital were at higher risk for misdiagnosis (Vermeulen and Schull *2007*; Pope and Edlow *2012*).

There is substantial variability in patient outcome among patients with aSAH based on when, in the clinical course of events, the stabilization procedure is performed. Patients who have their aneurysms secured in the first 72 h post-hemorrhage have better outcomes than those with procedures performed later in their clinical course although the ideal timing of the procedure is not known. The International Subarachnoid Aneurysm Trial attempted to clarify this issue in a study of 2,106 patients who had coiling or clipping of their aSAH (Mees et al. *2012*). Risk for delayed cerebral ischemia was highest in patients who had their aneurysm securement delayed after day 10, but patient who had their securement between days 5 and 10 also had significantly higher delayed cerebral ischemia than those who were treated in the first 4 days (Mees et al. *2012*). Earlier aneurysm securement not only predicts decreased risk of delayed cerebral ischemia but also increases the likelihood of decreased disability after hospital stay (OR 0.77, 95 %CI 0.67–0.87). In a registry study of over 32,000 patients undergoing stabilization procedures for aSAH, earlier treatment (securement by day 3) was predicted by female gender ($p = 0.002$), coiling procedure ($p < 0.001$), and weekday admission ($p < 0.001$). Unfortunately, the mortality rate was also higher in the early treatment group than the delayed treatment group (OR 1.36 95 %, CI 1.12–1.66), highlighting the dynamic and complex nature of clinical decision-making in aSAH (Siddiq et al. *2012*). In any patient requiring securement of his/her aneurysm, the availability of post-procedure radiologic evaluation is necessary to detect re-bleeding and aneurysmal remnants (Connolly et al. *2012*). Institutions vary based on resources and structure in how they care for patients with aSAH. In general, most inpatients with aSAH are cared for in intensive care units (ICU). In a study regarding aSAH, patients were more likely to have longer length of hospital stay in hospitals that had neurointensive care units than those that used surgical or medical ICU (Meyer et al. *2011*). Patient length of stay for aSAH also varied based on whether or not the patient experienced evidence of cerebral vasospasm. Patients diagnosed with cerebral vasospasm had on average an ICU length of stay of greater than 10 days compared to 3–7 days for those patients without cerebral vasospasm (Meyer et al. *2011*).

Among hospitals that care for patients receiving treatment for aSAH, there is considerable variation in how vasospasm is clinically addressed. A survey of 167 physician respondents from the Neurocritical Care Society of North America was conducted to determine how triple-H therapy (HHH) was used for

prophylaxis and treatment of vasospasm in aSAH. Monitoring for cerebral vasospasm was accomplished through transcranial Doppler (TCD) in 88 % (*n* = 114) of the respondent hospitals. Respondents who used TCD most often (77 %) altered blood pressure and fluid management plans based on TCD. Of those respondents that did not use TCD, they most frequently monitored vasospasm using angiography (*n* = 36), single proton emission computed tomography (SPECT) (*n* = 3), and in addition clinical exam (*n* = 57). In patients with aSAH, fluid management has long been considered a cornerstone of patient management. Although medical societies such as the American Heart Association/American Stroke Association recommend that patients with aSAH receive care that maintains euvolemia and discourages prophylactic hypervolemia; however, considerable variation in care still occurs (Connolly et al. *2012*). In one study, prophylactic hypervolemia was used in 27 % of hospitals, and increased prevalence of prophylactic hypervolemia was seen in hospitals that did not have a dedicated neurointensive care unit (Meyer et al. *2011*). When assessing clinical reasoning for the use of prophylactic hypervolemia, various reasons were given: treated all patients regardless of grade (38 %), relied on Hunt and Hess score (22 %), used the Fisher grade (9 %), and increased the level of chronic comorbidities (4 %) (Meyer et al. *2011*).

Universally, all respondents stated that they would induce hypertension if there was TCD or clinical evidence of vasospasm (Meyer et al. *2011*). How blood pressure is monitored also varied between hospitals and practitioners. Mean arterial pressure (MAP) was used to guide blood pressure in 52 % of respondents where systolic blood pressure (SBP) was used in 49 %. There was also significant variation in the upper and lower limits for SBP and MAP in both prophylactic and therapeutic hypertension. For SBP the mean upper limit was 182 mmHg (SD = 20.6) for prophylactic hypertension and 209 mmHg (SD = 17.1) for therapeutic hypertension. The lower limit for SBP for prophylactic hypertension was 153 mmHg (SD = 17.9) and 169 mmHg (SD = 17.1) for therapeutic hypertension. When using MAP to monitor blood pressure, the upper limit was 118 (SD = 11.1) for prophylactic hypertension and 132 (SD = 18.4) for therapeutic hypertension. The lower limits for MAP were 102 (SD = 14.2) for prophylactic hypertension and 105 (SD = 19.1) for therapeutic hypertension (Meyer et al. *2011*).

When treating hypertension in aSAH, both nicardipine and labetalol have been identified as suitable agents to lower blood pressure during the acute phase of aSAH care (Varelas et al. *2010*; Woloszyn et al. *2012*). In two recent small studies, nicardipine demonstrated some benefit over labetalol by having decreased time to normalizing blood pressures and fewer treatment failures, thereby lowering blood pressure variability (Varelas et al. *2010*; Woloszyn et al. *2012*).

Clinically, prevention of post-aSAH vasospasm is addressed in a number of ways. Nimodipine, orally administered, has long been used in aSAH to decrease complications and can decrease the likelihood of cerebral ischemia but has the potential to cause hypotension (Bautista *2012*). Endovascular intervention may be necessary in refractory cases of cerebral vasospasm (Muroi et al. *2012*). A small study of 30 patients showed no appreciable differences between the administration of intra-arterial nimodipine and balloon angioplasty for cerebral vasospasm. Both groups had similar outcomes in mortality and disability measures (Aburto-Murrieta et al. *2012*). Intra-arterial nimodipine was also shown to be effective as a primary or adjunct therapy in reducing the effects of cerebral vasospasm in a small Swiss study (*n* = 10) (Dehdashti et al. *2011*). Newer therapies are being investigated that may show promise in aggressive treatment of cerebral vasospasm such as endothelin-1 antagonists, statin-type drugs, and magnesium sulfate (Muroi et al. *2012*).

Summary. In this section, we have briefly reviewed the types of hemorrhagic stroke and focused on the variations in medical care currently seen in practice. Some of the key areas of medical practice variability can be seen in Table 1. The most frequent elements of variation occur in the aSAH population. Further research is needed to explore the sources of variation in all types of hemorrhagic stroke.**Table 1**

Key elements of medical practice variability in hemorrhagic stroke

Variability type	Issue in medical practice variations in hemorrhagic stroke
Systems of care - multifactorial	1. In SICH, patients are less likely to receive DVT prophylaxis and have a higher rate of VTE than other stroke types (Smith et al. *2009*) 2. Variation in method, timing of radiologic follow-up, and type of imaging study in patients with hemorrhagic stroke. aSAH stabilization can be accomplished safely by either surgical clipping or endovascular coiling. The decision of which treatment choice is better varies based on patient-level factors such as patient's condition, aneurysm location and size, neurosurgical and endovascular specialty availability, and system-level factors such as size and experience level of the hospital (de Rooij et al. *2007*; Connolly et al. *2012*; Pope and Edlow *2012*) 3. There are multiple methods of vasospasm monitoring such as transcranial Doppler, CT angiography, digital subtraction angiography, and CT perfusion. There is wide variation on the timing of these imaging modalities to effectively evaluate vasospasm (Woloszyn et al. *2012*; Sanelli et al.)
Systems of care – physician	Variation exists in the implementation of blood pressure parameters and fluid management (such as triple-H therapy [a]) in both prophylaxis for vasospasm and treatment of vasospasm (Connolly et al. *2012*; Bautista *2012*; Kirkness et al. *2009*)
Systems of care – resources	In aSAH, patients receiving care in neurointensive care units vs. medical/surgical intensive care units have variable length of hospital stays, complications, and outcomes. Attention to the organization and processes of care can decrease variation in practice

aSAH aneurysmal subarachnoid hemorrhage, *CT* computerized tomography, *DVT* deep vein thrombosis, *SICH* spontaneous intracerebral hemorrhage, *VTE* venous thromboembolism

[a]Triple-H therapy – hypertension, hypervolemia, hemodilution

Miscellaneous Aspects of Acute Stroke Care

Variations in Organized Stroke Care and Stroke Units

In 2002, a task force sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) recommended calling for greater coordination for the various components and professionals involved in both prehospital and acute hospital stroke care so that stroke system should fundamentally be a single entity that is responsible for organizing the stroke system. Stroke units constitute a vital and central component of modern stroke services and part of this coordinated stroke care. According to the Stroke Unit Trialists' Collaboration, the basic characteristics of a stroke unit should include dedicated units, specially trained staff, multidisciplinary team care, procedures for diagnostic evaluation, acute monitoring, and acute treatment, early mobilization, and a very strong focus on rehabilitation (Langhorne and Pollock *2002*). The concept of "stroke units" has not been widely established in developing countries due to the lack of understanding and limited resources.

There are substantial challenges to the development of stroke units widely across the world, especially in low-income counties. However, the potential gains from such developments in stroke care are of substantial significance as shown by a study from Bangkok (Langhorne et al. *2012*). This study showed improvement in stroke care with organized acute stroke unit and stroke short-term ward. Suwanwela et al. prospectively collected data of acute stroke patients who were admitted after the setup of the stroke unit and stroke short-term ward in 2003 and compared with the data of those who were admitted in a general medical ward in 2001 (Suwanwela et al. *2007*). Patients in the stroke unit and the short-term ward had significantly less mortality than those in the general medical ward (8.9 and 2.1 %). Overall complications in the stroke unit and the short-term ward were 16.8 %, compared to 26 % of those admitted into the general medical ward. Significantly less brain edema, hemorrhagic infarction, urinary tract infection, pneumonia, and pressure sore were also observed. The length of hospital stay of the patients admitted in 2001 and 2003 was 11.26 and 8.09 days, respectively (Suwanwela et al. *2007*). This study showed that combination of organized acute stroke unit and short-term ward with early supported discharge reduced the mortality and complications of ischemic stroke patients during admission as well as the length of stay when compared to the general medical ward.

In Scandinavian countries, up to 60–70 % of stroke patients are managed in stroke units, while in other European countries like the UK, it reaches up to 30–36 % and in France or Italy <10 % (Fuentes and Diez-Tejedor *2009*). In Australia, only 19 % of 261 acute public hospitals participating in a cross-sectional survey claimed to have stroke units (Cadilhac et al. *2006*). In the Canadian Stroke Network report in 2004, only 18 % of acute stroke patients were admitted to stroke units (Kapral et al. *2004*). Zhu et al. showed a reduced length of stay and reduced in-hospital case fatality in a stroke unit compared to general neurology/medical wards. This was a retrospective study of two cohorts in the Foothills Medical Center in Calgary, Canada, using administrative databases, and authors compared a cohort of stroke patients managed on general neurology/medical wards before 2001 with a similar cohort of stroke patients managed on a stroke unit after 2003. The average length of stay for patients on a stroke unit (n = 2,461) was 15 days versus 19 days for patients managed on general neurology/medical wards (n = 1,567). The proportion of patients with length of stay >7 days on general neurology/medical wards was 53.8 % versus 44.4 % on the stroke unit (difference 9.4 %; p < 0.0001). The adjusted odds of a length of stay >7 days was reduced by 30 % (p < 0.0001) on a stroke unit compared to general neurology/medical wards. Overall, in this study in-hospital case fatality was reduced by 4.5 % with stroke unit care (Zhu et al. *2009*).

According to the Ontario Stroke Evaluation Report 2011 and 2012, 38.3 % of patients admitted to hospital with stroke or TIA spent some part of their hospital stay in a stroke unit – an improvement from 30.3 % in 2008/2009, 18.6 % in 2004/2005, and 2.7 % in 2002/2003 and one that was seen across all hospital types and in virtually all regions (p < 0.0001). The benchmark is 87.5 %, based on data from the 2010/2011 Ontario Stroke Audit. There was little difference in rates of admission to stroke units by sex: 38.6 % of women and 37.9 % of men were admitted. Stroke unit access was equivalent at regional and district stroke centers, whereas less than one in 10 patients (7.2 %) admitted to non-designated stroke centers received stroke unit care. Moreover, Ontario's age- and sex-adjusted in-hospital stroke/TIA mortality rate decreased from 15.8 % in 2003/2004 to 14.3 % in 2008/2009 (p = 0.0003), and care of stroke patients at stroke units helped to reduce complications, which seem to be having an effect in reducing the mortality rate (Hall, et al *2011*, *2012*). Therefore, there is a lot of data from randomized trials and observational studies from many different countries that allow us to implement stroke unit strategy more widely, both in developed and developing countries.

Variations in Stroke Patients Arriving by EMS at Acute Hospitals

It has become increasingly important for stroke patients to arrive at emergency department quickly as most of the acute stroke treatments are time sensitive including intravenous thrombolytic therapy and mechanical thrombectomy. The number of stroke patients arriving by ambulance to emergency department varies in different countries.

It has been shown that patients whose first medical contact was with emergency medical services (EMS) arrived at the hospital faster than did patients whose first medical contact was with a personal physician (Barsan et al. *1993*). The use of EMS transport has also been associated with decreased in-hospital delay including time to physician evaluation in emergency department and door-to-CT time (Morris et al. *1999*).

Schroeder et al. showed that EMS use was associated with decreased prehospital and in-hospital delay (Schroeder et al. *2000*). The patients who used EMS had a median prehospital delay time of 2.85 h compared with 4.03 h for those who did not use EMS ($p = 0.002$). Moreover, older individuals were more likely to use EMS (odds ratio [OR] 1.21 for each 5-year increase, 95 % CI 1.14–1.29) (Schroeder et al. *2000*). The Institute for Clinical Evaluative Sciences (ICES) and Ontario Stroke Evaluation Report 2011 and 2012 showed that there was an increase in the proportion of stroke patients arriving at acute care hospitals by ambulance: from 52.8 % in 2003/2004 to 57.1 % in 2010/2011 ($p < 0.0001$). This is associated with an improvement in the proportion of stroke patients arriving at the emergency department in time to be considered for thrombolysis. There was an increase in the proportion of patients arriving by ambulance to designated stroke centers: at regional stroke centers, this ranged from 57.4 % in 2003/2004 to 66.4 % in 2010/2011 ($p = 0.0001$), and at district stroke centers, from 53.7 % in 2003/2004 to 63.6 % in 2010/2011 ($p = 0.0001$). There was also a reduction in the range of variation across LHINs. These improvements may reflect the positive impact of new stroke center designations, prehospital medical redirect protocols, and the provincial paramedic prompt card, all improvements occurring since 2003/2004. There was a reduction in variation in the proportion of adult patients arriving at the emergency department by ambulance across the LHINs from 16 % (41.3–57.2 %) in 2003/2004 to 9 % (49.5–59.1 %) in 2009/2010. To improve this situation further, a revised provincial EMS stroke prompt card was released, and EMS were encouraged to address local issues such as liaising with the regional stroke centers if needed (Hall et al *2011*, *2012*).

Secondary Stroke Prevention

Antiplatelet Medications

Background and Guideline Recommendations for the Use of Antiplatelet Medications in Ischemic Stroke

Antiplatelet medications are key pharmacologic therapies in recurrent stroke prevention. Antiplatelet medications are largely indicated to reduce the risk of recurrent stroke in patients with TIA or noncardioembolic ischemic stroke. There are some important differences between the antiplatelet medications for recurrent stroke prevention, and the data have shown that random assignment to any

antiplatelet therapy compared with control is associated with an 11 % reduction in the odds of stroke, myocardial infarction, or death attributable to vascular causes among patients with acute ischemic stroke and a 22 % reduction for long-term secondary prevention of stroke, myocardial infarction, or death attributable to vascular causes in patients with prior ischemic stroke or TIA (O'Donnell et al. *2008*).

The American Heart Association, American Stroke Association, and European Stroke Organisation recommend using either aspirin or clopidogrel monotherapy or the combination of aspirin and extended-release dipyridamole (ER-DP) as an initial management (Furie et al. *2011*). Cilostazol and triflusal may be used for recurrent stroke prevention in countries where these drugs have been approved by prevailing regulatory bodies. However, combination of these antiplatelet medications for secondary stroke prevention is not recommended (Furie et al. *2011*). When choosing which antiplatelet medication to administer, consideration should be given to patient characteristics and preference, relative effectiveness, safety, and cost. The combination of aspirin and extended-release dipyridamole, for example, may be more effective than aspirin alone for prevention of recurrent stroke (Diener et al. *1996*; Verro et al. *2008*; Furie et al. *2011*); however, in terms of cost, aspirin is by far the least expensive drug.

Race/Ethnicity, Sex Variations, and Antiplatelet Medications

The African American Antiplatelet Stroke Prevention Study (AAASPS) was a multicenter, randomized, double-blind, clinical trial to compare the effect of ticlopidine and aspirin in the prevention of recurrent stroke, myocardial infarction, and vascular death in African Americans with recent, noncardioembolic ischemic stroke. In this trial, ticlopidine (500 mg/day) and aspirin (650 mg/day) were the comparator agents (Gorelick et al. *1998*). The study was stopped for reasons of futility based on an interim statistical analysis; however, had the study continued to completion, there was an estimated 50 % likelihood that aspirin could have been superior to ticlopidine in the composite primary endpoint reduction. When balancing efficacy results and potential for serious adverse events, aspirin may be considered a better alternative than ticlopidine for aspirin-tolerant African-American patients for recurrent stroke prevention (Gorelick et al. *2003*).

Several study groups have examined race/ethnic disparities in administration of antiplatelet agents. For example, Stansbury et al. carried out a comprehensive literature review of ethnic variations in stroke epidemiology that showed that there were disparities in secondary pharmacological therapy and prevention for recurrent stroke (Stansbury et al. *2005*).

Niska et al. examined stroke prevention with antiplatelet agents by US nonfederal office physicians and hospital outpatient departments from 2005 to 2006 (Christian et al. *2003*). They used data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). This study provided nationally representative snapshot of antiplatelet therapy for secondary stroke prevention in outpatient settings. During this time period, there were about 15.4 million estimated outpatient visits by adult patients with a history of cerebrovascular disease who did not have bleeding contraindications to antiplatelet therapy and were not already anticoagulated. Antiplatelet medications were prescribed or continued at 31.1 % of those visits. This study showed that antiplatelet agents were more likely to be prescribed to patients with more comorbidities although this was significant only for patients with five or more comorbidities. Non-Hispanic black patients were significantly less likely to receive antiplatelet medications than non-Hispanic white patients. There was no significant influence in age in relation to receipt of antiplatelet agents. There was also no significant difference between men and women in prescriptions for antiplatelet agents (Christian et al. *2003*).

Lisabeth et al. studied the relationships between sex and race and antithrombotics prescribed at discharge in the Michigan Medicare population using retrospective medical record abstraction for the period January 1, 2001, to June 30, 2001. There were no significant differences in the use of aspirin, aspirin plus ER-DP, or clopidogrel at discharge by race or sex (Lisabeth et al. *2004*). A prospective cohort study from Germany found few sex differences in medical management after stroke or TIA (Muller-Nordhorn et al. *2006*). However, other studies have shown sex difference in the treatment of ischemic stroke. Holroyd-Leduc et al., however, showed that elderly men are more likely than elderly women to receive aspirin and ticlopidine after a stroke. They analyzed databases which contained information on 44,832 patients discharged from acute care hospitals with a diagnosis of acute stroke in Ontario between April 1993 and March 1996 (Holroyd-Leduc et al. *2000*).

Get With The Guidelines-Stroke Program and Antiplatelet Therapy

There may be an array of factors that predict utilization of medications for secondary stroke prevention after discharge from the hospital. These factors may include poor patient compliance, medication side effect profile, improper care transitions, poor patient–provider communication, and overall lack of patient resources and affordability of medications (Osterberg and Blaschke *2005*). Hospitals participating in the Get With The Guidelines-Stroke program may have superior job in making sure that patients are discharged with appropriate medications for secondary stroke prevention. This program focuses on adherence of hospitals to quality measures and has led to major changes in the care of hospitalized stroke patients during a 5-year comparison in a sample of 790 US hospitals (Schwamm et al. *2009*). It is important to be on proper medications for secondary stroke prevention as the risk of recurrent stroke is at least 15 % over 5 years and highest in the first 6 months (Hankey et al. *1998*).

Bushnell et al. analyzed the data of patients with ischemic stroke or TIA discharged from 106 hospitals participating in the American Heart Association Get With The Guidelines-Stroke (GWTG) program as a part of the Adherence eValuation After Ischemic Stroke Longitudinal (AVAIL) registry (Bushnell et al. *2011*). These patients were surveyed to determine the use of antithrombotics and other medications for secondary stroke prevention from discharge to 12 months. The recruitment period for this study was July 2006 through July 2008, and follow-up was completed in October 2009. The persistence for antiplatelet medication use was 87.1 %. Moreover, stroke patients participating in rehabilitation and other such therapy programs may have more changes in their medication regimen because rehabilitation includes frequent contact with health-care providers (Bushnell et al. *2011*). The AVAIL study also showed that there was no difference in medication persistence or outcomes between rural and urban dwellers after hospitalization for ischemic stroke or TIA (Rodriguez et al. *2011*).

Despite these results, there may be regional variations in administration of antiplatelet medications. Allen et al. studied GWTG-Stroke standards among 991,995 admissions in four US regions (South, Northeast, Midwest, and West). This study showed relatively high rates of adherence to stroke-related therapies in GWTG-Stroke hospitals; however, regional variations existed and over one-quarter of patients received suboptimal care. Most of the patients received antithrombotics and they varied from 95.6 % to 96.8 % (Allen et al. *2012*).

Carvalho et al. compared stroke treatment quality indicators from a private Brazilian tertiary hospital to those published by the GWTG-Stroke program in the USA (de Carvalho et al. *2012*). They reviewed a database of consecutive patients admitted with ischemic stroke or TIA from August 2008 to December 2010. Two performance measures used were antithrombotic medication use within 48 h of admission and discharge use of antithrombotics. These medications were administered in 98.2 % of

the eligible patients within 48 h, and all eligible patients were discharged using antithrombotic medications (de Carvalho et al. *2012*).
Hsieh et al. studied GWTG-Stroke standards using the Taiwan Stroke Registry, which involved 39 academic and community hospitals and observed that early and discharge use of antithrombotics was close to GWTG-Stroke standards (Hsieh et al. *2010*).
Another study by Sweileh et al. described the use of antiplatelet medications in ischemic stroke patients in a government hospital in Palestine (Sweileh et al. *2009*). They did not compare their standards with GWTG-Stroke. This study was carried out for only 5 months, October 2005 to March 2006, and 95 consecutive stroke patients were enrolled; monotherapy was prescribed for 61 stroke patients, and combination therapy (aspirin/clopidogrel) was prescribed for 17 patients (Sweileh et al. *2009*).
Summary. Variations may exist in the administration of antiplatelet medications for recurrent stroke prevention based on race/ethnicity and sex. Better organization of health-care services through implementation of such programs as GWTG-Stroke may help to reduce variation in guideline-based proper use of key preventives such as antiplatelet agents. A substantial proportion of stroke may be prevented with proper medication and lifestyle regimens. Reduction in disorganization of health-care services may lead to reduction in variation of key medical practices.

Antithrombotic Therapy for Atrial Fibrillation (AF)

Background and Guideline Recommendations for Stroke Prevention in AF

Atrial fibrillation is an important risk factor for stroke and systemic embolism with the occurrence of cerebral embolism being more common than that of systemic embolism. The overall prevalence of AF is 1–2 % in the general population in North America and Europe (Go et al. *2001*; Camm et al. *2010*). About 2.3 million adults in the USA have AF, and the prevalence is anticipated to rise to 5.6 million by 2050 (Go et al. *2001*). Stroke prevention is therefore a major issue when managing patients with AF.
In 1999, the American Heart Association recommended warfarin for the prevention of recurrent strokes among patients with AF or aspirin if warfarin was contraindicated (Wolf et al. *1999*). In 2001, the American Heart Association recommended antithrombotic therapy (either warfarin or aspirin) for high-risk patients with AF who had not had strokes previously (Goldstein et al. *2001*). This was based in part on a meta-analysis of 5 placebo-controlled trials that showed a 68 % reduction in the relative risk of thromboembolic strokes in patients with AF who were taking warfarin. In 2002, the American Heart Association published updated clinical guidelines for primary prevention of stroke. Warfarin was again recommended for patients with chronic AF, but aspirin (325 mg per day) was suggested for low-risk patients younger than 65 years of age (Pearson et al. *2002*).
In 2004, the American College of Chest Physicians published a set of antithrombotic therapy recommendations stratified by age and other risk factors. Either oral anticoagulants (OAC) or aspirin (325 mg per day) was recommended for patients with AF between 65 and 75 years old without other risk factors. For patients younger than 65 years without other risk factors, aspirin was recommended because the risks and clinical inconveniences of administration of OAC therapy seemed to outweigh the benefit of stroke prevention in that age group (Singer et al. *2004*).

In 2011, the American Heart Association and American Stroke Association recommended anticoagulation with warfarin for patients with ischemic stroke or TIA with a target international normalized ratio (INR) range of 2–3, and if a patient was unable to take an OAC, then aspirin alone was recommended (Furie et al. *2011*). In 2012, the American College of Chest Physicians published new guidelines according to which OAC including dabigatran 150 mg twice a day was the optimal choice for antithrombotic therapy for patients with AF and at high risk of stroke (i.e., CHADS2 score of ≥2). A more individualized decision approach at lower levels of stroke risk was suggested, and in addition, patient preferences for treatment were to be considered (You et al. *2012*).

Variation in Administration of Oral Anticoagulant Therapy

The use of anticoagulant therapy varies markedly between countries and according to those managed in community settings versus hospitals (Lip et al. *2012*). Oral anticoagulation therapy is frequently underused in patients with AF in daily practice as seen in many observational studies, and this varies from 30 to 60 % (Stafford and Singer *1998*; Go et al. *1999*). Therefore, there remains a missed opportunity to prevent stroke and other thromboembolic complications from AF because many individuals may fail to have the condition diagnosed and/or fail to receive treatment with warfarin or other newer anticoagulants such as dabigatran, rivaroxaban, or apixaban. Furthermore, antithrombotic therapy use in patients with AF differs significantly from guideline recommendations (Furie et al. *2011*; You et al. *2012*) despite the fact that potential benefits of warfarin therapy in high-risk populations have been clearly demonstrated (Lip and Boos *2006*). It is obvious that the decision to prescribe anticoagulants in these patients has to be balanced against the risk of complication from therapy. However, these risks are often difficult to quantify in the individual patient, and older patients who are likely to gain the most benefit are generally considered to be at higher risk of complications.

It has been shown that when warfarin therapy is recommended, it may be substituted with aspirin (Burgess et al. *2007*). Aspirin is low cost to the patient and is much easier to prescribe since it does not require INR monitoring and aspirin is used in a fixed dose. Also, it is considered safer than warfarin in regard to bleeding complications although bleeding risk is small with either therapy. Moreover, a significant percentage of patients already take aspirin for ischemic heart disease, and in these patients aspirin would be indicated and providers may be concerned about adding warfarin to aspirin for fear of an increased bleeding risk (Burgess et al. *2007*). However, warfarin is superior to aspirin in preventing stroke in patients with AF as per the current guidelines (Furie et al. *2011*; You et al. *2012*).

What Are the Secular Trends or Variation in the Use of OAC Therapy in AF?

There are several studies that have examined the secular trend and variation in the use of OAC therapy in AF during the 1990s and early 2000s. In one study, using the National Ambulatory Medical Care Survey (NAMCS) data set profiling physician office-based practices, anticoagulant use in patients with AF increased from 13 % in 1989 to 40 % in 1993, but did not change thereafter and through 1996 (Stafford and Singer *1998*).

In a second study, NAMCS-only study, approximately 47 % of patients with AF were prescribed anticoagulants during 1999–2000 (Fang et al. *2004*). In another study using the National Disease and Therapeutic Index data set, warfarin use in patients with AF increased to 51 % in 2002 (Stafford and

Radley *2003*). Niska et al., using the NAMCS from 2001 to 2006, showed that warfarin was prescribed during more than half (52.2 %) of visits of patients with AF, but there were disparities among race, sex, and region (Niska and Han *2009*). Underutilization of warfarin has been mentioned in the primary care setting. Sudlow et al. noted that only 23 % of patients with AF were using anticoagulants (Sudlow et al. *1998*). Go and Wang et al. from the USA showed that differing uptake of anticoagulation after AF was diagnosed. Go and colleagues noted that nearly 55 % of their cohort with nonvalvular AF and in whom there was no contraindication to warfarin received warfarin (Go et al. *2003*). Wang et al., in a community-based survey, noted that 705 of 861 patients with AF were not treated with warfarin; however, it is not clear from this study how many of the patients had contraindications to anticoagulation administration (Wang et al. *2003*).

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study found that only 62 % of patients with AF who from chart review were thought to be ideal candidates for warfarin received the drug (Go et al. *1999*). A review of health-care claims for about four million members of a managed care organization showed that 61 % of patients with AF were candidates for warfarin, but only 39 % received warfarin therapy (Darkow et al. *2005*).

Burgess et al., in a study about the use of antithrombotics in patients presenting with stroke and AF, assessed the frequency and appropriateness of antithrombotic therapy in patients admitted to Capital and Coast District Health Board hospitals in Wellington, New Zealand (Burgess et al. *2007*). The study was a retrospective case series of 219 patients (mean age 77.2 years) admitted between January 1999 and December 31, 2001, with a diagnosis of stroke and AF. One hundred and fifty patients were known to have had AF prior to admission. Of those patients with known AF, only 43 were on treatment consistent with guideline recommendations. Warfarin was administered in 144 of the entire cohort, but only 39 were taking it. Fifty-three patients were receiving aspirin although warfarin was the recommended treatment. Fifty-four patients with known AF were not on any antithrombotic treatment. Factors significantly associated with the use of antithrombotic treatment were history of AF ($p = 0.0004$), valvular heart disease ($p = 0.02$), venous thromboembolism ($p = 0.04$), risk of thromboembolism ($p = 0.003$), and presentation with a nonischemic infarct ($p = 0.008$) (Burgess et al. *2007*). Antithrombotic treatment for an unselected group of patients, admitted with a stroke and AF, was found to be underused in spite of guidelines favoring OAC. Underuse was particularly marked with warfarin where only 43 patients (19.6 %) were taking the drug prior to admission. According to guidance available at the time, warfarin would have been indicated in 144 patients (Burgess et al. *2007*).

The use of warfarin was low in community-based cohorts in some countries such as China (0.5–2.7 %) (Zhou and Hu *2008*) than other countries such as Japan (70.1 %) (Uchiyama et al. *2010*). Moreover, aspirin was used more commonly than warfarin; however, warfarin use was greater in hospital-based cohorts than community-based cohorts in these studies. Concern over warfarin use has been common in many Asian countries as brain hemorrhage rates have traditionally been high, and in some of the countries, adequacy of monitoring for warfarin may be lacking or cost may be prohibitive.

Reasons for Variation of Administration of OAC in AF

Several factors can underlie the poor implementation of administration of OAC such as lack of stroke risk stratification and poor adherence to or lack of knowledge of antithrombotic treatment guidelines. This seems to be multifactorial challenge including unawareness among clinicians about guidelines, various risk stratification criteria including the CHADS2 score, poor appreciation of the risk–benefit ratio, and overestimation of bleeding risks. Sex, geographic region, the presence of embolic risk

factors, and the number of visits within the last 12 months may be associated with the use of warfarin. Warfarin is considered to be associated with a high risk of bleeding and requires regular monitoring, and the elderly have other risks such as that of falls or dementia that place them at risk of bleeding complications (Burgess et al. *2007*).

Stroke subtype is another factor to consider when contemplating antithrombotic therapy administration in patients with stroke and AF as not all ischemic strokes that occur in patients with AF are cardioembolic. It has been estimated that one-third of strokes occurring in patients are due to small vessel disease or have an atherosclerotic basis (Evans et al. *2000*). In these patients antiplatelet therapy may be preferred as there is no difference in mortality or stroke recurrence whether these patients are treated with warfarin or aspirin (Evans et al. *2001*). Given the fact that there is a growing aged population in many developed countries, these factors need to be considered before using OAC (Burgess et al. *2007*).

A study which used a nationwide stroke database in Sweden showed that there were variations between hospitals and regions in using OAC in stroke patients according to age, sex, functional impairments, and comorbidities. The reasons that primary care physicians provided for not using warfarin in some studies include past history of bleeding, noncompliance, cognitive difficulties, frailty, and patient choice (Burgess et al. *2007*). Sometimes, lack of availability of a "warfarin clinic" or a monitoring center for anticoagulation plays a role in the lack of administration of this drug. Use of warfarin is labor-intensive and time-consuming for a general practitioner, and also they may be concerned about regular monitoring of INR in these patients. However, even if physicians prescribe anticoagulants, there might be a significant dropout rate. Evans et al. noted in a sample of 288 patients that 74 stopped taking warfarin, 25 because of bleeding complications and 37 for reasons such as choice, compliance, or logistics (Evans et al. *2000*). Similar findings were reported from the much larger AFFIRM study where 33.6 % of the trial participants discontinued warfarin use for some period during the trial. The major reason for withdrawal was maintenance of sinus rhythm, but bleeding was the second most common reason for stopping warfarin in this study (DiMarco et al. *2005*). Please see Table 2 for a summary of factors predicting variation in practice pattern of anticoagulation use in patients with AF.

Table 2

Factors predicting variation in practice pattern of anticoagulation use in patients with atrial fibrillation (*AF*)

Variability type	Issues in variation in practice pattern of anticoagulation in patients with AF
Systems of care – physician	Lack of stroke risk factor stratification, poor adherence to guidelines, poor appreciation of risk–benefit ratio, and overestimation of bleeding risks result in not prescribing anticoagulation in patients with AF. Educating practitioners about guidelines and addressing concerns such as anticoagulation-related hemorrhages (Burgess et al. *2007*; Go et al. *1999*; Furie et al. *2011*; Israel et al. *2004*; You et al. *2012*; Stafford and Singer *1998*)
Systems of care – multifactorial	There are gender and racial variations when deciding about anticoagulation in patients with AF (Lichtman et al. *2011*; Meschia et al. *2010*; Niska and Han *2009*)
Systems of care – resources	Lack of availability of warfarin clinic is an important factor many patients with AF are not taking warfarin. Warfarin clinics and availability of pharmacists who help to adjust the dose of warfarin based on INR can make a significant difference in the management of these patients (Gardiner et al. *2005*)

Patient adherence and related factors	Noncompliance is an important factor many patients with AF are not on anticoagulation (Burgess et al. *2007*; Meschia et al. *2010*). Proper patient education especially addressing any concern about bleeding complications can address this problem. Therefore, patient education about awareness of AF and its clinical implications is important (Evans et al. *2000*; DiMarco et al. *2005*)

AF atrial fibrillation, *INR* international normalized ratio

Means to Improve Administration Rates of OAC and Reduce Variability in AF

Means to improve the use and compliance with warfarin have included home follow-up after initiation of warfarin in the hospital setting. Jackson et al. compared usual care (general practitioner only) with a project pharmacist who visited patients at home and adjusted the dose of warfarin accordingly (Jackson et al. *2004*). Using this program, the pharmacist arm of the study achieved a significantly greater proportion of patients with a therapeutic INR early in treatment and with less bleeding events (Jackson et al. *2004*). Therefore, the presence of a lead pharmacist on the team is very promising, because they are familiar with drug interactions and the difficulties with using warfarin. They are also likely to maintain the INR in the therapeutic range and therefore may be more likely to prevent bleeding complications.

Other options to make warfarin use more attractive relate to self-monitoring of the INR. Gardiner and colleagues showed that self-testing of INR in AF patients was effective and acceptable (Gardiner et al. *2005*). This study involved 84 patients who were self-selected from 800 who were invited to take part. However, the average age of the study patients was less than the average age of other patients seen in a warfarin clinic. Moreover, this study was open and not controlled (Gardiner et al. *2005*).

Another study by Murray and colleagues was a randomized controlled trial involving 608 patients (Murray et al. *2004*). They invited 2,586 patients for this study. Three hundred and twenty seven patients were randomized to self-management, but of these 26 % were unable to complete training. Factors that were associated with success in training and continuing in the trial were younger age and more education (Murray et al. *2004*). Therefore, having a pharmacist on the team and a "warfarin clinic" which can provide a central control of anticoagulation seems to be a good method to increase the use of warfarin.

The prevalence of warfarin use is influenced by patient preferences; however, it could be modified by counseling on the benefits and risks of anticoagulation and explaining to patients current guideline recommendations and how warfarin may help and with proper administration prevent complications (Niska and Han *2009*). Awareness and understanding of the presence of AF may be poor in stroke and TIA patients. The West Birmingham Atrial Fibrillation Project found that only 49 % of patients with AF could identify their cardiologic condition, and only about half of the patients with AF knew that AF is a risk for thromboembolism (Lane et al. *2006*). Greater awareness of AF and its clinical implications might lead to greater utilization of warfarin, which might in turn lead to greater stroke reduction. However, some physicians and patients accept the reduced efficacy of aspirin compared to warfarin in spite of a high risk of stroke in the presence of AF. Those patients at high risk for stroke who receive only aspirin may be concerned about bleeding complications associated with anticoagulation or the inconvenience of monitoring the INR on a regular basis.

In one study, the average patient with AF who had been on warfarin was willing to take it if it reduced the 2-year risk of stroke by approximately 2 % annually. Even with an estimated 5 % annual risk of stroke, only 1 out of 64 patients in that study would have opted against warfarin if they had the proper

information (Man-Son-Hing et al. *1996*). Another study examined how elderly patients were willing to accept the risk of either anticoagulation side effects or stroke after being informed of the risks of anticoagulation. Only 61 % of the total group wanted to be treated with warfarin, although the guidelines would have recommended that nearly all of them should have been anticoagulated (Protheroe et al. *2000*). These findings further emphasize the importance of a patient-centered approach in the decision of whether warfarin will or will not be administered in patients with AF.

The complexity of establishing and monitoring anticoagulation is an issue for both physicians and patients as mentioned above. In contrast to aspirin, warfarin therapy may involve frequent laboratory follow-up and the need to contact patients to adjust their doses to achieve the goal INR. Many physicians consider that a decision to anticoagulate a patient is not without risk as an adverse outcome and bleeding complications are possible even when guidelines are followed. A survey of internists showed a significant association between their risk aversion styles and how frequently they would prescribe warfarin in various AF scenarios. Internists who would more regret not anticoagulating a patient who went on to have an ischemic stroke chose warfarin more frequently than those who would more regret anticoagulating a patient who then had a hemorrhagic stroke (Niska and Han *2009*). Interestingly, the perceived risks of anticoagulation were 10–30 times higher than the actual risks documented in the literature. This perception was also associated with not prescribing warfarin (Niska and Han *2009*). Thus, not only is a patient-centered approach important, but also a physician-centered approach is needed to make a decision about administration of OAC in patients with AF.

It has been shown that blacks are less likely to be aware of AF and less likely to be treated with warfarin than whites. These findings are consistent with other studies demonstrating that blacks are less likely to achieve quality of care goals for stroke risk factors. Meschia et al. in their study about racial disparities in awareness and treatment of AF found that blacks were about one-third as likely to be aware that they had AF as whites in a US national biracial sample of adult men and women (Meschia et al. *2010*). All the study individuals had EKGs for the confirmation of the diagnosis of AF. The study findings suggest that lower awareness of AF and reduced likelihood of treatment among blacks may place blacks at higher risk of a stroke event, which in turn could contribute to the higher stroke mortality among blacks. The reasons for the racial discrepancy are not clear. Many of the study participants may be undiagnosed, as often AF itself is not symptomatic. Alternatively, these patients may have been diagnosed with the condition, but simply did not remember or understand the condition. Whether the participant had or lacked insurance coverage was not an independent predictor of awareness of AF, and whether the participant had or lacked access to health care was not an independent predictor of awareness of AF (Meschia et al. *2010*). Among those who were aware that they had AF and who had confirmation of the diagnosis of AF, blacks were about one-quarter as likely to be treated with warfarin as whites (Meschia et al. *2010*). Risk of stroke as stratified by the CHADS2 score was not a predictor of warfarin use. The fact that risk of future stroke did not significantly alter the likelihood of warfarin use would seem to reflect lack of awareness of physicians about guidelines for the treatment of AF (Meschia et al. *2010*). Evidence-based guidelines on the use of warfarin and antithrombotic medications in nonvalvular AF suggest consideration of risk of stroke (CHADS2 score) be part of the decision process regarding long-term anticoagulation (You et al. *2012*). Therefore, CHADS2 score not being a predictor of warfarin use highlights an evidence–practice gap. Therefore, efforts focused on practitioner awareness and education about AF as a significant stroke risk factor might be warranted. Moreover, future investigations for better understanding of the determinants of racial disparities in stroke and the impact of improved diagnosis and treatment of AF on race-related stroke outcomes will be of public health importance.

In addition, Meschia et al. found that women with documented AF, who were also aware of their condition, had about a third of the chance as men of being treated with aspirin (Meschia et al. *2010*).

The reasons for this undertreatment with antithrombotics are not clear as sometimes the decision to administer OAC is often complex and physicians are sometimes concerned about hemorrhagic complications especially in patients with poorly controlled hypertension. Niska et al. also showed that warfarin was prescribed less to women and to nonwhite patients than their counterparts (Niska and Han *2009*). Mahmud et al. in an Irish national study showed underutilization and missed opportunities of prescription of anticoagulation in women with AF aged 75 years or older (Mahmud et al. *2007*). Patients with first detected or paroxysmal AF had a lower chance of receiving OAC compared with patients with persistent or permanent AF (Nieuwlaat et al. *2006*). This might relate to the fact that a low AF burden is thought to be associated with a low risk for stroke which might not be true. Because perceived AF burden is lower in paroxysmal AF patients, historically these patients had a lower chance of receiving OAC than patients with chronic (persistent/permanent) AF. More recently, it has been shown that patients with paroxysmal AF are at about as high a risk of stroke as those with permanent AF. Therefore, OAC should be considered irrespective of AF burden (Nieuwlaat et al. *2008*). An important factor complicating this issue is that the physicians' perception of AF burden mostly underestimates the true AF burden, as many patients suffer from asymptomatic recurrences (Israel et al. *2004*).

It has been observed that when AF was the only reason for the qualifying admission or visit, OAC was prescribed more often (Nieuwlaat et al. *2006*). This could be due to less distraction by other medical problems or management of AF by a specialized physician who is more aware of the importance of OAC. The availability of an OAC monitoring outpatient clinic also played a significant role in the decision-making process. The ability for safe INR monitoring is important for OAC prescription, which is not easy to arrange in all patients and also may not be available in all countries because of restrictions in infrastructure. A prior major bleed was a factor against prescribing any antithrombotic drugs in these patients when admitted to the hospital (Nieuwlaat et al. *2006*).

There is underutilization of these therapies in eligible elderly patients hospitalized with ischemic stroke, particularly among the oldest patients. Lichtman et al. analyzed the data including Medicare free-for-service beneficiaries discharged with ischemic stroke randomly selected among eligible ischemic stroke patients more than 85 years of age. In this group, 78 % received antiplatelet medications, 76 % received anticoagulants for AF, and 70 % received antithrombotics at discharge (Lichtman et al. *2011*). Decreased mobility and admission from a skilled nursing facility were associated with lower receipt of each therapy (Lichtman et al. *2011*). Race/ethnicity was associated with the rates of anticoagulant use for AF, and antithrombotic use at discharge, but these associations were inconsistent across race/ethnic groups and treatments (Lichtman et al. *2011*). The analyses from the National Stroke Project data show that antithrombotics prescribed at discharge for patients with acute stroke or TIA and warfarin for patients with AF are underutilized in patients age 65 years or older (Jencks et al. *2003*). Lichtman et al. also showed that the underutilization of therapies is even more pronounced for the very elderly and differs by other patient characteristics including admission location and level of functional dependence (Lichtman et al. *2011*).

Patient's age may influence physicians' decisions to prescribe warfarin. It is independent of other demographic and clinical factors. Lichtman et al. in their study noted that the rates of treatment decreased with age and were lowest for patients aged 85 years or older (Lichtman et al. *2011*). One explanation for this age difference may be physicians' concern to avoid hemorrhagic stroke, the risk for which increases with age. Although the risk of major anticoagulant-associated bleeding is higher in the very elderly, the risks do not offset the benefits for most high-risk patients with AF if anticoagulants are carefully administered.

Moreover, one-fourth of eligible patients did not receive antithrombotic medications at discharge (Lichtman et al. *2011*). This rate was somewhat higher than the 16–17 % reported in two other studies

of Medicare patients in Michigan during the same time period (Lisabeth et al. *2004*; Jacobs et al. *2005*). It may be associated with local variations in stroke care that are not clear and very obvious within a single geographic location. For example, Volpato et al. found no difference in the prescription of antithrombotic therapy at discharge among elderly stroke patients in Italian clinical centers, but did find lower utilization rates with decreased functional independence (Volpato et al. *2004*).

A Canadian study reported similar rates of antithrombotics at discharge across all elderly age groups (<59, 60–69, 70–79, and >80), but only included patients admitted to designated stroke centers in Ontario which may represent a higher level of care than in non-stroke center facilities (Saposnik et al. *2009*). The data from a California Acute Stroke Pilot Registry (CASPR) did not show any age difference (>80 vs. <80) in optimal utilization of antithrombotic therapy (Ovbiagele et al. *2006b*). In this study optimal therapy was defined as receipt at discharge of at least one medication from the class of antiplatelet or anticoagulant drugs or a valid contraindication to treatment. There was wide variation in the rates of actual and optimal treatment across the 11 CASPR hospitals. Higher compliance rates would also be expected among committed hospitals that were aware they were being monitored for these therapies, including those participating in quality improvement programs such as the Get With The Guidelines-Stroke program (GWTG-Stroke program) (Ovbiagele et al. *2006b*; LaBresh et al. *2008*). The underutilization of antithrombotic drugs among elderly stroke patients, particularly the very elderly, suggests that there may be an opportunity to improve their secondary preventive stroke care. Future work will need to determine the effectiveness of performance improvement activities such as primary stroke center certification, the GWTG-Stroke program, and other similar efforts in the elderly population. Please see Tables 2 and 4 for a summary of means to improve use of anticoagulation in patients with AF.

Newer Classes of OAC and Variation in Administration

The available data about the medical practice variation in the use of new OACs such as dabigatran, rivaroxaban, and apixaban is very limited at this point in time. Briefly, dabigatran has been tested in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. RE-LY, a randomized open-label study, demonstrated that at a dose of 150 mg twice daily, dabigatran was superior to warfarin in relation to lowering the primary outcome cluster of stroke or systemic embolism, rates of major hemorrhage were similar, but intracranial bleeding rate was substantially lower (Diener et al. *2010*).

Rivaroxaban was compared with warfarin in patients with AF and previous stroke or TIA (ROCKET AF trial). Rivaroxaban was non-inferior (but not superior) to warfarin for prevention of stroke or systemic embolism and similar to dabigatran and apixaban; there was no evidence that the relative efficacy or safety of rivaroxaban compared with warfarin was different between patients who did or did not have a history of previous stroke or TIA (Hankey et al. *2012*). Also, apixaban was superior to warfarin in the reduction of stroke and systemic embolism (Granger et al. *2011*). These results support the use of dabigatran and rivaroxaban for prevention of recurrent stroke in patients with AF. Apixaban has a still pending approval from the US FDA.

These new OACs should further improve stroke prevention in AF and will hopefully help to overcome hurdles caused by warfarin’s limitations. Some of the issues such as monitoring while taking these medications, reversal of anticoagulant effects, and perioperative management are areas which require further investigation and clarification that will help us to enhance our ability to safely and effectively use these new OAC (Ahmad and Lip *2012*).

Lipid-Lowering Therapies

Background and Guideline Recommendations for Lipid-Lowering Therapies in Ischemic Stroke

There is convincing evidence that statin use reduces the risk of having a first or recurrent ischemic stroke (Amarenco and Labreuche *2009*). Even young patients with a first ischemic stroke of undetermined etiology who used a statin medication poststroke have lower rates of new vascular events in long-term follow-up (Putaala et al. *2011*). Furthermore, there are recent studies which suggest that statin use around the time of stroke hospitalization may reduce mortality and improve functional outcome (Flint et al. *2012*; Milionis et al. *2009*). It is also shown that statin withdrawal at the time of ischemic stroke may worsen poststroke outcomes (Flint et al. *2012*). It is possible that statin therapy has neuroprotective effects in addition to its lipid-lowering effect, which may explain a protective role in the acute stroke setting (Cimino et al. *2007*).

American Heart Association and American Stroke Association 2011 guidelines recommend statin therapy with intensive lipid-lowering effects to reduce the risk of stroke and cardiovascular events among patients with evidence of atherosclerosis and an LDL-C level ≥100 mg/dL (Furie et al. *2011*). These guidelines also recommend reduction of at least 50 % in LDL-C or a target LDL-C level of <70 mg/dL to obtain maximum benefit (Furie et al. *2011*). For patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease, it is recommended to manage the cholesterol level according to the National Cholesterol Education Program (NCEP III) guidelines (Furie et al. *2011*). European Stroke Organisation 2008–2009 guidelines, as AHA/ASA guidelines, also recommend using statin medications in patients with noncardioembolic stroke. Similar recommendations were mentioned in the consensus statement by the Working Group on Stroke and Lipids Management in Asia (Hankey et al. *2010*). Moreover, stroke guidelines from many of the Asian countries have recommended consideration of statin therapy for recurrent stroke prevention in patients with previous stroke or TIA. The population attributable risk of ischemic stroke due to nonoptimal blood cholesterol concentration has been estimated to be as high as 45 % in Asian-Pacific countries (Woodward et al. *2008*). Therefore, many Asian countries' stroke guidelines recommend an LDL target of <100 mg/dl, and some such as those from the Philippines, Thailand, and China recommend a more aggressive target of less than 70 or 80 mg/dL for high-risk patients, similar to the US National Cholesterol Education Program Adult Treatment Panel III guidelines (Hankey et al. *2010*).

In spite of convincing data about the protective role of statins in primary and secondary stroke prevention, there is underutilization of statin medications worldwide.

Variation in Administration of Lipid-Lowering Therapies

Moreover, many stroke and TIA patients are not being treated with a lipid-lowering therapy on discharge from the hospital or other acute or rehabilitative setting. In their study, based on the data from a statewide stroke registry, Mullard et al. showed that only 12.9 % of patients with stroke or TIA and previously not on lipid-lowering therapy received a lipid-lowering therapy (Mullard et al. *2006*). They found that lipid-lowering therapy administration peaked among 50–69-year-olds and then

declined with increasing age. Women were significantly less likely to receive in-hospital lipid testing, but there was no association between gender and lipid-lowering therapy at discharge (Mullard et al. *2006*).

Ovbiagele et al. analyzed GWTG-Stroke data from 2005 to 2007 and found that discharge statin prescription among hospitalized patients with stroke increased over time. Among 173,284 patients with ischemic stroke and TIA, overall discharge statin treatment was 83.5 %, and it increased over the 2-year study period from 75.7 % to 84.8 % ($p < 0.001$) (Ovbiagele et al. *2010b*). In another study Ovbiagele et al. abstracted data from the Vitamin Intervention for Stroke Prevention (VISP) study database from the USA and Canada to incorporate into algorithms for initiating statin therapy according to the National Cholesterol Education Program (NCEP) guidelines for high-risk individuals (Ovbiagele et al. *2006c*). The authors found that almost half of the high vascular risk subjects were not prescribed a statin even though they had LDL concentration above the ATP target for treatment initiation. When they applied the more aggressive LDL target goals recommended in the ATP III guidelines, they found an even higher rate of potential undertreatment among high-risk patients. They directly compared dyslipidemia management in a high-risk population in the USA and Canada. Statin treatment was more prevalent in the USA than Canada; however, the percentage of high-risk patients above the LDL concentration initiation threshold for statin treatment and below the LDL concentration upper goal appeared to be similar to the USA and Canada (Ovbiagele et al. *2006c*).

Ovbiagele et al. also analyzed California Acute Stroke Prototype Registry (CASPR) from November 2002 to January 2003 and found that only half the patients hospitalized for ischemic stroke or TIA had LDL levels tested. Overall, 48.4 % of the CASPR cohort received lipid-lowering medication at discharge (Ovbiagele et al. *2006a*).

Underuse of lipid testing and that of antilipid therapy in stroke and TIA patients admitted to hospital can be explained by a series of factors. Overall appreciation of importance of high cholesterol as a stroke risk factor seems to correlate with testing lipids and treating these patients with lipid-lowering therapy. There might be concern about the risk of ICH in patients treated with statins. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial revealed that among patients with recent symptomatic cerebrovascular disease and no established history of known coronary artery disease, the incidence of cardiovascular events was significantly fewer in those who received intensive statin treatment compared with placebo, but the benefit was slightly offset by a higher incidence of hemorrhagic strokes in the high-dose statin treatment arm (Amarenco et al. *2006*). A recent meta-analysis of 31 randomized controlled trials of statin therapy has shown that active statin therapy was not associated with significant increase in ICH and again a significant reduction in all stroke and all-cause mortality was observed with statin therapy (McKinney and Kostis *2012*). Therefore, ICH related with statin therapy is of less concern and should not be a reason for not prescribing statin medication in inpatient and outpatient setting. A study by Ovbiagele et al. has shown that discharge statin prescription among hospitalized patients with ICH has modestly risen overtime. They analyzed the GWTG-Stroke data between 2005 and 2007 (Ovbiagele et al. *2010a*). There may be some patient factors, including noncompliance or side effects from statin medications, contributing to underuse of statins in patients with stroke and TIA. However, in order to reduce the burden of vascular diseases including stroke, diagnosis of dyslipidemia and treatment with lipid-lowering therapy should be improved at the time of acute stroke and also in outpatient settings.

Treatment of Carotid Stenosis

Background and Current Clinical Guideline Recommendations

Atherosclerosis is an important underlying cause of ischemic stroke and TIA – about 20–30 % of cerebral infarctions are estimated to be due to atherothrombosis of either extracranial or intracranial vessels (Rothwell *2000*). Based on observational cohort studies, estimates of the absolute risk of stroke associated with moderate to severe stenosis of the carotid arteries vary from 0.3 % to 3 % per year depending on the populations studied and medical treatments provided (Brott et al. *2010*).

Indications for surgical treatment of carotid artery stenosis are determined by the patient's underling stroke risk which are a function of both the degree of narrowing of the vessel and whether the patient has a history of stroke or stroke-like symptoms that can be related to the same (ipsilateral) side of the affected vessel (referred to as symptomatic patients). Population-based studies suggest that between 5 % and 10 % of elderly persons have moderate carotid artery stenosis (defined as >50–69 % narrowing) and an estimated 1 % have severe carotid artery stenosis (defined as >70 % narrowing).

Carotid endarterectomy (CEA) refers to the surgical removal of atherothrombotic material from the affected carotid artery. Studies show that CEA requires a substantial amount of surgical expertise and that outcomes and complications are directly linked to the experience of the surgeon. Several trials (e.g., NASCET, ECST) have demonstrated the benefit of this procedure compared to standard medical therapy in symptomatic patients with severe (>70 %) stenosis (Rothwell *2000*). Carotid endarterectomy is recommended in such patient populations (Class I, level of evidence A) providing that the perioperative morbidity and mortality is less than 6 % (Brott et al. *2011*). Indications for CEA in symptomatic patients with moderate stenosis (50–69 %) are less clear cut and depend on the presence of patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms (Class I, level of evidence B) (Brott et al. *2011*).

Although trials such as the Asymptomatic Carotid Surgery Trial (ACST) and Asymptomatic Carotid Artery Study (ACAS) have shown clinically important risk reductions from the prophylactic use of CEA among asymptomatic patients (Rothwell *2000*), the absolute benefits are smaller and so ensuring a positive benefit/risk ratio of CEA is even more dependent on the rate of periprocedural complications (i.e., stroke, death) in this patient population. Currently, prophylactic CEA is only recommended in asymptomatic patients with greater than 70 % stenosis if the complication rate of the surgeon is known to be less than 3 % (Class IIa, level of evidence A) (Brott et al. *2011*).

Carotid artery stenting (CAS) involves the use of balloon angioplasty followed by placement of a stent to maintain vessel patency. CAS has been proposed as an alternative to CEA especially in patients who have contraindications to surgery (e.g., anesthesia risk, unfavorable vessel anatomy). Similar to CEA, studies show that CAS requires a substantial amount of expertise and that perioperative outcomes and complications are directly linked to the experience of the operator. Several initial trials directly compared the efficacy of CAS to CEA in a range of both symptomatic and asymptomatic clinical populations (e.g., SAPPHIRE, EVA-3S, SPACE) (Yadav et al. *2004*; Mas et al. *2006*; Ringleb et al. *2006*). All of these trials faced difficulties associated with slow enrollment or concerns over the experience of the CAS operators. Overall, CEA was associated with lower perioperative complications of death and stroke compared to CAS, but longer-term reductions in stroke risk and mortality were generally similar between the 2 procedures (Brott et al. *2011*). Two more recent CEA versus CAS trials (one in Europe [ICSS] and one in the USA [CREST]) have unfortunately not resolved the debate over the relative merits of the two interventions. Thus, while the long-term results in CREST were similar, the choice between CAS and CEA depends in large part to the relative weighting given to the increased stroke risk in the CAS group relative to the increased MI risk in the CEA group. In summary, there remains ongoing debate about the relative benefits and risks of CEA versus CAS for the treatment of carotid artery stenosis. Currently, CAS may be recommended

as an alternative to CEA in low- or average-risk symptomatic patients with less than 70 % stenosis if the short-term complication rate of stenting is <6 % (Class I, level of evidence B) (Brott et al. *2011*). Prophylactic use of CAS in asymptomatic patients may be considered in patients with less than 70 % stenosis (Class IIb, level of evidence B), but its effectiveness compared to modern-day aggressive medical therapy is increasingly uncertain (Brott et al. *2011*).

Variation in CEA and CAS Utilization, Timing, and Outcomes

Given the shifting evidence base demonstrating the relative efficacy and safety of CEA and CAS over the years, it is not surprising that substantial variation exists in the use of these procedures. Dramatic geographic variations in CEA utilization rates were first recognized and publicized by the Dartmouth Atlas group. Birkmeyer and colleagues examined 11 common surgical procedures in fee-for-service (FFS) Medicare data from 1995 and found that CEA utilization rates had one of the highest variation profiles with differences of over 10-fold across 306 US hospital referral regions (Birkmeyer et al. *1998*). Wennberg and colleagues examined perioperative mortality rates among FFS Medicare patients undergoing CEA during 1992 and 1993 and found that the rates were substantially higher than those that had been reported in the recent NASCET and ACAS trials (Wennberg et al. *1998*). This study also found that 30-day mortality was inversely proportional to hospital case volumes suggesting that quality was substantially better at high-volume centers.

The utilization of CEA at any point in time appears to be readily responsive to the prevailing evidence operating at that time. For example, Tu and colleagues examined secular trends in annual CEA rates in California, New York, and Ontario between 1983 and 1995, finding that rates of CEA fell by 50 % or more in all three regions between 1984 and 1989 following publication of studies demonstrating high rates of CEA complications (Tu et al. *1998*). However, following the release of the NASCET and ACAS RCTs in the 1990s which showed benefit for CEA, the rates of CEA increased dramatically particularly in the two US states. However, the study failed to show any evidence that patients were being selectively referred to centers with low mortality rates, and so similar to the report by Wennberg et al. (*1998*), this study also raised troubling questions about whether the benefits of CEA as demonstrated in the clinical trials could be translated to the general population.

Subsequent studies have continued to show high regional variation in CEA use in the USA (Magner et al. *2009*), Canada (Feasby et al. *2001*), and Scotland (Benade et al. *2003*). Feasby et al. concluded that the marked regional variation in rates was likely a reflection of differing views on the appropriateness of CEA particularly among asymptomatic patients, as well as inconsistencies in clinical guidelines (Feasby et al. *2001*).

Recent studies have now been published demonstrating regional variations in both CAS and CEA. Goodney and colleagues examined geographic variation in CAS and CEA performed in US Medicare beneficiaries in 306 hospital referral regions between 1998 and 2007 (Goodney et al. *2010*). Overall, the rate of carotid revascularization fell slightly over the decade from 3.8 procedures per 1,000 in 1998 to 3.1 procedures in 2007. However, there was a dramatic shift in the type of procedures performed – the rate of CEA decreased from 3.6 to 2.5 procedures per 1,000 beneficiaries, while CAS rates increased more than fourfold, from 0.1 to 0.6 CAS procedures per 1,000 beneficiaries. Because there was very little correlation between regional rates of CAS and CEA ($r = 0.06$), the authors concluded that CAS was being performed as a substitute for CEA rather than being performed in addition to CEA. Similar conclusions regarding the decline of CEA rates and concomitant increase in CAS rates among FFS Medicare, as well as the substantial regional variation in procedure rates, have also been reported by Patel and colleagues (Patel et al. *2010*).

The wide variation in utilization rates of both CEA and CAS along with the shifting secular patterns has led to obvious concerns about the appropriateness of these procedures.

Most of the studies that have examined appropriateness in detail have identified areas of concern. A Canadian study applied RAND/UCLA Appropriateness Method to data on all CEAs performed in four Canadian provinces between January 2000 and December 2001 (Kennedy et al. *2004*). They found that only half of the 3,167 CEAs were performed for appropriate indications (with a range across provinces of 46–78 %). Overall, 10.3 % of procedures were deemed inappropriate and appropriateness was affected by both the type of surgical specialist and case volume (Kennedy et al. *2004*). Higher rates of appropriate CEA were found when procedures were performed by neurosurgeon compared with all other surgeons (74.4 % vs. 49.4 %). Interestingly, appropriateness was inversely related to case volume – the proportion of appropriate CEAs was higher in operators who did less than 31 procedures over the 2-year period compared with surgeons who did more (70.1 % vs. 49.5 %) and was higher in hospitals who did fewer than 135 procedures per year versus those that did more (63.4 % vs. 49.1 %). The authors interpreted the findings as indicating a combination of both overuse and underuse and suggested that greater emphasis be put on preoperative assessment to reduce the one in 10 CEAs procedures that were inappropriate (Kennedy et al. *2004*).

A similar RAND-based appropriateness study was done using data from all CEAs performed in New York State in elderly patients between January 1998 and June 1999 (Halm et al. *2007*). Among the 9,588 patients, 93.6 % had severe carotid stenosis (>70 %) but nearly three-quarters were asymptomatic. The rate of appropriate CEAs was a lot higher in this study (87.1 %) compared to the Canadian study by Kennedy, although the rate of inappropriate procedures was similar (8.6 %). The study also found that the rate of inappropriate CEAs was substantially lower following publication of the NASCET and ACAS RCTs (32 % before vs. 8.6 % after). Although the increasing rates of appropriate CEAs were positive, finding the shift to a greater proportion of asymptomatic patients was concerning to the authors because of the much smaller net benefit of CEA in this population.

Two recent studies by Nallamothu and colleagues using FFS Medicare data collected between 2005 and 2007 have provided important information that addresses the appropriateness of CAS as currently practiced in the USA (Nallamothu et al. *2011a*, *b*). In the first study, the authors examined the association between CAS outcomes and two measures of operator experience: annual volume and experience at the time of the procedure among new operators who first performed carotid stenting following the national coverage decision by CMS (Nallamothu et al. *2011b*). Almost 25,000 procedures were performed by 2,339 operators, and of these, almost half were performed by 1792 new operators who first performed carotid stenting after the CMS coverage decision. Of particular note, the median annual operator volume among Medicare beneficiaries was only 3 per year (IQR 1.4–6.5) and only 11.6 % of operators performed 12 or more procedures per year during the study. Overall, 30-day mortality was 1.9 %, but mortality was strongly associated with the operator volume, decreasing from 2.5 % in low-volume operators (<6 per year) to 1.4 % in high-volume operators (>24 procedures per year) (Nallamothu et al. *2011b*). These data illustrate the widely known principle that mortality and outcomes are directly influenced by operator experience.

Nallamothu et al. examined the same dataset (FFS Medicare data collected between 2005 and 2007) to determine how physician specialty relates to CAS utilization rates and outcomes (Nallamothu et al. *2011a*). Cardiologists made up approximately one-third of the CAS operators but were responsible for more than half of all CAS procedures. Importantly, the characteristics of the patients treated by cardiologists were different from those treated by other specialties – they had higher rates of invasive cardiac procedures and lower rates of acute stroke or TIA in the 180 days prior to the CAS procedure. These findings are a concern because RCT data suggest that the risk–benefit equation of CAS is likely to be less than favorable if a patient population is dominated by asymptomatic patients who have

higher cardiac comorbidities. The study also found that population-based utilization rates were significantly higher in hospital referral regions (HRRs) where cardiologists performed more of the procedures indicating that the involvement of cardiologist contributed to greater regional variation in CAS utilization rates (Nallamothu et al. *2011a*).

These recent findings related to the utilization of CAS have many parallels to the early studies that examined the utilization of CEA. These CEA studies also found that there was significant regional utilization in CEA procedures and that the patients undergoing CEA procedures in real-life practice had significantly poorer outcomes compared to those reported in the RCTs. The CAS data presented by Nallamothu and colleagues suggest that there are significant problems with the current utilization of CAS in practice and that the potential benefits of CAS demonstrated by the RCTs are unlikely to be reproduced.

According to the Ontario Stroke Evaluation Report 2011, the time to a carotid intervention (carotid stenting or carotid endarterectomy) within 6 months of an initial stroke among adults decreased dramatically between 2003/2004 and 2010/2011. The median wait time was 51 days in 2003/2004, dropping to 18 days in 2010/2011 ($p \leq 0.0001$). In some Local Health Integration Networks (LHINs), patients waited less than 7 days in 2010/2011. This dramatic improvement may be associated with the implementation of stroke prevention clinics and increased awareness of surgical best practices. In 2010/2011, regional stroke centers continued to have the shortest wait times for carotid intervention with a median time of 10 days. District stroke centers had a median wait time of 22 days compared to 26 days at non-designated centers. The higher rate at district stroke centers is unexpected and should be monitored closely.

Poststroke Rehabilitation and Practice Variation

Background and Variations in Systems of Care in Poststroke Rehabilitation

In the aftermath of acute stroke, returning the person to maximal functional capacity is the goal of rehabilitation therapy. After assurance of hemodynamic stability, early assessment and identification of rehabilitation needs are critical to both regaining function and preventing complications related to stroke. Early mobilization decreases the risk of immobility-related complications since complications of immobility such as deep vein thrombosis, pulmonary embolism, and pneumonia are related to over half of the poststroke-related deaths in the first 30 days (Bernhardt et al. *2004*). In this section, the essential elements of stroke rehabilitation as well as variations in medical care that occur in stroke rehabilitation are discussed and also summarized in Table 3.**Table 3**

Key issues in medical practice variability in poststroke rehabilitation

Variability type	Issue in poststroke rehabilitation
Systems of care – multifactorial	Settings in which stroke rehabilitation is accomplished vary greatly from country to country (McNaughton et al. *2005*; Bernhardt et al. *2008*, *2009*; Indredavik *2009*; Good et al. *2011*). Regional variance exists in access to assistive devices in the USA and other countries. Moreover, reimbursement types may also drive the setting in which rehabilitation care is given. In the USA, there is a considerable financial pressure to provide rehabilitation services

	in less costly environment (McNaughton et al. *2005*; Good et al. *2011*). However, it has been seen that early initiation of rehabilitation improves outcomes; therefore, organized rehabilitation care and implementation of best practices for screening stroke patients are needed (Horn et al. *2005*; Maulden et al. *2005*)
Patient adherence and related factors	Variability in adherence by patients and caregivers is common in poststroke rehabilitation. There are many other factors involved in this such as poststroke fatigue, depression, lack of motivation, and other musculoskeletal issues (Jurkiewicz et al. *2011*; Cully et al. *2005*; DeJong et al. *2005*)

USA United States

Some studies have demonstrated variations in rehabilitation outcomes based on variations in practice patterns between different countries. In a study of rehabilitation facilities in New Zealand and the USA, patients in the US rehabilitation facilities had better functioning at discharge than their counterparts in New Zealand as measured by the Functional Independence Measure (FIM). The US rehabilitation facilities demonstrated better outcomes even though the US patients had more severe stroke symptoms and shorter rehabilitation length of stay (18.6d vs. 30.0d, $p < 0.001$). Patients in the USA received more intensive physical and occupational therapy, as measured in therapy hours per day, and US patients were less likely to be discharged to an institutional setting (13.2 % vs. 21.5 %; $p = 0.006$) (McNaughton et al. *2005*). Two major system issues were identified that may contribute to the variation seen in the study between the US and New Zealand stroke rehabilitation care. Firstly, dedicated stroke units are rare in New Zealand. Dedicated stroke units have been associated with improved outcomes in stroke care in the USA, Australia, and Europe (McNaughton et al. *2005*; Bernhardt et al. *2008*, *2009*; Indredavik *2009*; Good et al. *2011*).

Secondly, New Zealand operates under a nationalized health system which differs from the US system. In the US system, there is considerable financial pressure to provide rehabilitation care in less costly environments, and only 25–30% of stroke patients qualify for the intensive rehabilitation that was described in the US/New Zealand comparison study (McNaughton et al. *2005*; Good et al. *2011*).

The Institute for Clinical Evaluative Sciences (ICES) and Ontario Stroke Evaluation Report 2011 showed that the proportion of stroke patients discharged from acute inpatient hospitalization and admitted to inpatient rehabilitation increased from 27.8 % in 2003/2004 to 30.7 % in 2009/2010 (Hall et al *2011*). Patients admitted to non-designated centers for inpatient acute stroke care were less likely to be discharged to inpatient rehabilitation than those admitted to designated stroke centers. The benchmark for this was 41 %. Over the 7-year study period, the proportion of severely disabled stroke patients admitted to inpatient rehabilitation facilities decreased and the proportion of patients with mild stroke admitted to these facilities was unchanged. In 2003/2004, severely disabled stroke patients represented 37.6 % of inpatients and mildly disabled patients, 21.9 %. In 2009/2010, severely disabled stroke patients represented 31.9 % of inpatients despite a reasonable length of stay of 2 months. The median time from stroke onset to admission to an inpatient rehabilitation facility was 13 days in 2003/2004, decreasing to 11 days in 2009/2010. The marked regional variation in wait times for rehabilitation admission decreased over the 7 years: from an 18-day difference between LHINs with the shortest and longest wait times in 2003/2004 to a six-day difference in 2009/2010. In 2009/2010, 43.9 % of patients were discharged home with services following inpatient rehabilitation, a minimal change from 43.2 % in 2003/2004. There was also minimal change in the discharge Functional Independence Measurement (FIM) over the same time period. In 2003/2004, the discharge FIM was 106 compared to 107 in 2009/2010.

There was wide institutional variation in the mean change in FIM scores and length of stay. Specialized rehabilitation centers had lower rates of functional improvement (changes in FIM) per day

compared to general rehabilitation centers. It is generally agreed that the target FIM score for admission to stroke rehabilitation is 40–80 as per ICES 2011 report (Hall et al. *2011*). A provincial median admission FIM score of 78 (average score, 76) suggested that a notable proportion of patients in the severe group (those with an FIM score of less than 60) did not have access to inpatient rehabilitation. This also suggested that patients with mild disability were going to inpatient rehabilitation due to a lack of outpatient services and/or pressures on inpatient rehabilitation centers to reduce length of stay. There was modest variation in admission median FIM scores assigned on admission to inpatient rehabilitation across the LHINs in 2009/2010, ranging from 72 to 83. The proportion of patients going to long-term care facilities following inpatient rehabilitation decreased from 13.5 % in 2003/2004 to 9.6 % in 2009/2010.

The mean number of rehabilitation services offered by Community Care Access Centres (CCACs) to patients discharged with an acute stroke hospitalization in 2007/2008 did not change from the previous year: four visits for physical therapy, three for occupational therapy, three for speech–language pathology, and three for social work over a 60-day period. There was little variation in service intensity across the LHINs, ranging from an average of 2.8 to 4.9 physical therapy visits per stroke client in 2008/2009. The median time to first CCAC rehabilitation visit from stroke onset was 27 days. CCAC service intensity was low and likely inadequate to achieve functional changes in those who had difficulty living independently (Hall, et al. *2011*).

Variations in Timing of Poststroke Rehabilitation

The timing of initiation of rehabilitation can also influence the ultimate outcomes of stroke rehabilitation. In a study of six inpatient rehabilitation hospitals in the USA, earlier initiation of stroke rehabilitation is associated with better FIM scores and decreased length of stay regardless of the severity of stroke (Horn et al. *2005*; Maulden et al. *2005*). Although stroke outcomes have been shown to be improved by dedicated stroke units, there can be substantial variability even among those units. One study comparing stroke units in Norway and Australia demonstrated that among patients with similar baseline characteristics, stroke patients in Australia hospitals had 21 % more time at bed rest than those in Norway (Bernhardt et al. *2008*).

Early rehabilitation interventions have clearly been associated with improved care outcomes. Approximately 10 % of US patients hospitalized in institutions participating in Get With The Guidelines (GWTG)-Stroke program did not receive rehabilitation evaluations while receiving inpatient care (Bettger et al. *2013*). Among patients in the GWTG database (n = 616, 9182), those that did not receive rehabilitation evaluations were more likely older, had multiple comorbidities, were at increased risk for complications, and were more likely to be readmitted within 30 days (Bettger et al. *2013*). Since GWTG organizations were more likely to have organized systems of stroke care, the 10 % rate of defects in care for rehabilitation outcomes is likely lower than hospitals without organized systems of stroke care.

Variation in Adherence to Poststroke Rehabilitation Care

Variation in adherence to rehabilitation care standards can affect patient outcomes such as functional independence and the ability to safely remain in their home. Provider and caregiver adherence to stroke education standards and secondary prevention measures (statin medication and hypertension treatment) are associated with patient's increased ability to discharge home as well as better FIM scores (Hubbard et al. *2012*). Variance in adherence to rehabilitation treatment and guidelines is also

sensitive to patient-level factors. In a small study, fatigue, lack of motivation, and musculoskeletal issues were most closely associated with poor adherence to home rehabilitation programs (Jurkiewicz et al. *2011*). Although routine use of antidepressants poststroke is not recommended (Hackett and Anderson *2005*; Hackett et al. *2005*, *2008*), the failure to adequately manage affective disorders such as depression can have negative consequences regarding the patient's participation in therapy modalities (Cully et al. *2005*; DeJong et al. *2005*).

Conclusion

In this book chapter, we have discussed different variations in stroke care including acute stroke treatments, stroke prevention, and rehabilitation. Different aspects of these practice variations including underlying causes and impacts on patient care in clinical practice and possible strategies to improve stroke care and minimize these variations have also been addressed in respective sections of this chapter and summarized in Table 4.**Table 4**
Key means to reduce practice variations in stroke care

Variability type	Suggestions to reduce practice variations in stroke care
Systems of care – health-care providers	Educating practitioners about practice guidelines such as the American Heart Association/American Stroke Association, Canadian Stroke Association, European Stroke Organisation, and regional guidelines in different countries
Systems of care – multifactorial	To improve access to best practice stroke prevention and care, including access to designated stroke facilities
Systems of care – EMS	Revision of EMS stroke prompt card and better access of suspected stroke patients to time-sensitive therapies at stroke centers and telestroke sites
Systems of care – institutions	1. Participate/implement GWTG-Stroke program 2. Organized stroke care including designated stroke centers, stroke units for inpatient stroke care, and TIA clinics 3. Organized rehab care and implementation of best practices for screening and management of poststroke problems such as dysphagia 4. Stroke prevention clinic, improving and expanding accessibility of patients to stroke prevention clinics
Adherence – patient	Patient education and awareness of stroke risk factors, signs and symptoms, and its clinical implications

EMS emergency medical services, *GWTG* Get With The Guidelines, *TIA* transient ischemic attack

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