TIA Management: Should TIA Patients be Admitted? Should TIA Patients Get Combination Antiplatelet Therapy?

The Neurohospitalist
2015, Vol. 5(3) 151-160
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DOI: 10.1177/1941874415580598
nhos.sagepub.com

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Abstract

Transient ischemic attack (TIA) has gained increasing attention over the last 2 decades with the realization that the condition is common, portends potentially serious consequences, and, when identified early, can be evaluated and treated to modify future risk. In this review, we examine the issues of whether all TIA patients need admission and whether such patients should receive short-term dual antiplatelet therapy. Not all patients require admission if evaluation and treatment are done promptly. There may be a role for dual antiplatelet therapy, but the results of further clinical trials will help provide better clarity on which patients are the best candidates for this treatment.

Keywords

transient ischemic attack, hospitalization, antiplatelet

Introduction

Transient ischemic attack (TIA) has gained increasing attention over the last 2 decades with the realization that the condition is common, portends potentially serious consequences, and, when identified early, can be evaluated and treated to modify future risk. Approximately 1 of every 8 strokes is heralded by a TIA.¹ In this review, we examine 2 common questions about TIAs: (1) Should all such patients be admitted to the hospital? and (2) Should all these patients receive short-term dual antiplatelet therapy?

Should TIA patients be Admitted?

The estimated incidence of TIA in the United States is 200 000 to 500 000 individuals per year, depending on the definitions used.² Given the volume of events, physicians and hospitals are often faced with the decision of admitting patients to the hospital or performing the evaluation and treatment in an observation or outpatient setting. The theoretical advantage of the former strategy is the ability to monitor for a second event and treat with thrombolysis, while the latter approach may improve patient satisfaction and improve hospital bed flow. Both methods can achieve rapid testing and treatment, but the latter may be less costly. Recent changes to admission payment schemes (ie, the “two-midnight rule”) have added further significance to the questions of how to best manage the patient with TIA.

Definition of TIA

In a 2009 scientific statement, the American Heart Association and the American Stroke Association defined TIAs as “brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.”² (pp. 2276-2277). Historical definitions have relied on clinical findings and their resolution for diagnosis. In 1958, the National Institutes of Health Committee on the Classification of Cerebrovascular Disease proposed the limitation of symptom duration as less than 24 hours,^{3,4} which was also suggested in a publication that same year by Fisher. However, with modern imaging techniques such as magnetic resonance imaging (MRI), as many as 30% to 50% of individuals with complete resolution of symptoms are found to have changes on diffusion-weighted MRI. In 2002, the concept of a tissue-based definition of TIA was introduced, which incorporated imaging into the definition, and reduced the time duration of TIA as defined in the 1950s.^{2,5} Currently, the diagnosis of TIA and stroke is heavily dependent upon

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imaging findings, which may supersede the practitioner's clinical impression.⁶ The notion of the "acute ischemic cerebrovascular syndrome" has also been proposed, intended as a more scientific approach to nomenclature, but has not yet gained wide acceptance.⁵

Risk of Stroke After TIA

Due to a better understanding of the consequences of TIAs, there is a greater emphasis on early diagnosis and intervention. In a period prior to rapid diagnosis and intervention, Johnston et al evaluated a cohort of 1707 patients with TIA for risk of stroke within 90 days as well as recurrent TIA, cardiovascular events, and death. Of those patients, 10.5% had a stroke, approximately half of whom presented within 2 days of the initial TIA. Additionally, 12.7% had recurrent TIAs, 2.6% had cardiovascular events, and 2.6% died. There were 5 factors that were found to be independently associated with stroke including age ≥ 60 , diabetes mellitus, TIA symptoms longer than 10 minutes, weakness, and speech disturbance.⁷

The ABCD2 score was later developed to stratify risk of stroke after TIA using easily available data, and it has been adopted by many centers as a clinical tool. The score is calculated by assigning 1 point for age older than 60, 1 point for blood pressure $\geq 140/90$, 2 points for clinical features of weakness, 1 point for speech impairment, up to 2 points for duration of TIA (1 point for 10-59 minutes and 2 points for >60 minutes), and 1 point for presence of diabetes. The ABCD2 score is more accurate compared to earlier clinical scoring systems including the ABCD and California scores. In the ABCD2 score, all components are independent risk factors for stroke at 2, 7, and 90 days.⁸ While stroke can occur at any ABCD2 score, Johnston and colleagues defined groups that correlated with low, moderate, and high risk of stroke at 2, 7, and 90 days. The low-risk group included patients with ABCD2 scores of 0 to 4, with a stroke risk of 1%, 1.2%, and 9.8% at 2, 7, and 90 days, respectively. The moderate-risk group included patients who scored 4 to 5 on ABCD2 for whom the stroke risk was 4.1%, 5.9%, and 9.8% at 2, 7, and 90 days, respectively. The high-risk group included ABCD2 scores of 5 or greater which conferred a stroke risk of 8.1%, 11.7%, and 17.8% at 2, 7, and 90 days, respectively.

The ABCD2 score does not take into account imaging that has become a routine component of evaluating patients with suspected TIA. In 2003, Douglas et al found that patients with a head computed tomography showing evidence of infarction had an increased short-term risk of stroke.⁹ Merwick et al further explored imaging as an independent risk factor for stroke with the proposal of 2 additional scores that accounted for both multiple TIAs and neuroimaging.¹⁰ Specifically, the age, blood pressure, clinical features, duration, diabetes, and dual TIA (Dual TIA defined as ≥ 2 TIA symptoms within 7 days) (ABCD3) score uses the same point assignments designated in the ABCD2 score, but adds 2 points for "dual TIA"

or earlier TIA within 7 days. The ABCD3-I score used the same scale as ABCD3 but also accounted for abnormal findings on imaging including carotid stenosis of at least 50% (2 points) and/or restricted diffusion on Diffusion weighted (MRI) image sequence (2 points). Kiyohara and colleagues confirmed the conclusions by Merwick et al and showed that both the ABCD3 and the ABCD3-I scores were superior to the original ABCD2 score.¹¹ The ABCD3-I score may also predict long-term outcome in patients with TIA, up to 3 years. While previous studies have shown that abnormal MRI is an independent predictor of recurrent stroke after TIA, this most recent study did not support this finding.^{11,12}

Daubail et al sought to further identify comorbidities that could be easily assessed on initial presentation that would reflect a high risk of recurrent TIA within 48 hours of the initial event.¹³ A prospective study evaluated 312 patients between 2011 and 2013 in a French hospital after a new diagnosis of TIA and found that the most common etiologies were atrial fibrillation (18.3%) and large artery atherosclerosis (10.6%). Patients with large artery disease experienced a statistically significant increase in recurrence of 12.1%, while those with atrial fibrillation had a 5.3% nonsignificant increased risk of recurrence. Average ABCD2 scores did not significantly differ between patients with and without a recurrent event. These findings support the idea of urgent evaluation of TIAs. Early vessel imaging may influence decisions about hospitalization and subsequent interventions.

Rothwell et al combined data from the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial and found that the benefit of carotid endarterectomy (CEA) was primarily dependent on the grade of stenosis with the best outcomes achieved if surgery is performed within 2 weeks of the initial event.¹⁴ An important caveat is that carotid revascularization done within the first 2 days of an event may be associated with a higher procedural risk of stroke or death.¹⁵ An analysis of the Swedish Vascular Registry found that the procedural risk of stroke was 11.5% between days 0 and 2 after stroke compared with a risk of approximately 4% from days 3 to 14. Therefore, the optimal timing for treatment of a symptomatic carotid artery may be between days 3 and 14.

Rapid Evaluation and Treatment

Urgent evaluation and management of TIA lowers the risk of subsequent stroke.^{13,16-18} In 2007, the Effect of urgent treatment of transient ischemic attack and minor stroke on early recurrent stroke study (EXPRESS) found an 80% decrease in the early risk of stroke after TIA with early evaluation and treatment.¹⁸ The study was a before and after design. In phase 1, patients received usual care. In phase 2, patients were referred for urgent evaluation and treatment. At 90 days, the risk of recurrent stroke decreased from 10.3% in phase 1 to 2.1% in phase 2, an approximate

Table 1. Comparison of Different Models of TIA Management.

Study	Year Published	Method of Evaluation	90-Day Stroke Recurrence Rates	Admission Rate
EXPRESS (phase II) ¹⁶	2007	ED followed by urgent clinic	2.14%	Not available
SOS-TIA ¹⁹	2007	ED followed by urgent clinic	1.69%	26%
Ottawa ¹⁷	2010	ED followed by urgent clinic	3.16%	1.6%
TWO ACES ²⁹	2011	Admission based on ABCD2 risk stratification	1.72%	30%
Monash ³⁰	2012	ED followed by urgent clinic	2.36%	0%

reduction of 80%. Median assessment from symptom onset decreased from 3 days to less than 1 day and, importantly, median time from symptom onset to first prescription decreased from 20 days to 1 day. In the SOS-TIA study, 1085 TIA patients were evaluated in a 24-hour, hospital-based clinic and provided immediate appropriate medical and surgical treatment.¹⁹ The 90-day stroke rate was 1.24%, which was 80% less than the predicted risk of 5.96% based on the ABCD2 score, a percentage reduction which was similar to that seen in EXPRESS. Of the patients, 5 had urgent carotid revascularization and another 5% received anticoagulation for atrial fibrillation. Nearly three-fourths of all patients were sent home the same day.

Hospitalization

While most studies agree on the need for urgent evaluation in the setting of TIA, there are no clear guidelines on hospitalization. The ABCD2 score is accurate in predicting severe stroke but less accurate in predicting any subsequent stroke.²⁰ Further, when admission decisions are based on ABCD2 score alone, there are high-risk patients missed without vascular evaluation and cardiac monitoring, also supporting that urgent evaluation is necessary regardless of score.^{21,22} The ABCD3-I score is more accurate in predicting risk of stroke after TIA and may have predictive out to 3 years after TIA.¹¹ Nevertheless, these tools were not developed to determine the need for hospitalization nor have they been adequately studied for that purpose. Indeed, both the EXPRESS and the SOS-TIA studies were conducted in the context of outpatient urgent evaluations.

Cucchiara and Kasner suggest that hospitalization is the optimal management after TIA for rapid assessment to determine etiology and possible interventions to preserve cerebral perfusion including CEA, anticoagulation, and statin therapy.^{23,24} Overall, practitioners widely recognize the condition of TIA as needing urgent assessment and close monitoring as evidenced by the steady increase in admission rates since 2000.²⁵ However, Amarenco argues that any setting where the patients can be evaluated in an efficient manner and triaged accordingly is the best setting, in or out of hospital.²⁶

Several studies have demonstrated that clinics with extended patient access and specialized TIA clinics affiliated with stroke centers provide management resources that decrease

overall risk of recurrent TIA or stroke.^{17,19,27,28} Additional data have supported that expedited outpatient assessment in the emergency department can also significantly decrease risk of recurrent events as well as need for hospitalization.^{29,30} In these latter studies, 90-day recurrence has ranged between 1.7% and 3.2% (Table 1). Molina and Selim agree that most patients with TIA can be effectively evaluated in a well-organized outpatient or emergency department setting, however, suggest that there are a select group of high-risk patients such as those with occlusive vascular lesions who should be admitted for close observation and intervention.³¹ Joshi and colleagues examined hospitalization compared to same-day clinic and concluded that hospitalization was only beneficial for a very small group of patients in terms of access to tissue plasminogen activator (tPA) but otherwise may not be cost-effective or globally beneficial based on limited hospital resources.³²

In our practice, we evaluate most patients with TIA in a dedicated TIA unit, located in the emergency department. Figure 1 shows the algorithm that is followed for triage, evaluation, and management of these patients. Using that strategy, we only admit about 20% of all patients with TIA and have observed a 90-day risk of stroke of about 2%. Patients are primarily admitted if symptomatic internal carotid stenosis and atrial fibrillation are identified. The ABCD2 score is used only for entry into clinical trials.

Economic Considerations

Analysis of hospitalization after TIA has previously assumed benefit associated with access to tPA in the setting of recurrent symptoms. Nguyen-Huynh and Johnson proposed that hospitalization could be cost-effective for patients with a risk of stroke >5% in the first 24 hours based on the access to tPA.³³ However, many assumptions were made in this model including only admitting patients eligible for tPA. Many prior studies have shown that there is a significantly increased short-term risk of stroke after TIA, with up to 50% of eventual strokes occurring within 48 hours.^{7,33} After TIA, patients are often eligible to receive tPA. With a high risk of stroke after TIA, hospitalization may provide an opportunity for timely intervention that is superior than if the patient was discharged home. There was an overall cost benefit of US\$55 044 per quality-adjusted life year (QALY). Joshi and colleagues found that hospitalization is only cost-effective in a very select group

Figure 1. Probability of survival free of ischemic or hemorrhagic stroke in the CHANCE trial. Reprinted with permission from Wang et al, the New England Journal of Medicine.³⁹

of patients at very high risk of stroke who might benefit from tPA. The cost-effectiveness of tPA assumed in this study was extrapolated from a prior study by Fagan and colleagues showing an increase in QALYs of 0.564 per patient treated with tPA.³⁴ The major limitations to this analysis was that a hypothetical TIA cohort was used; no actual observational information was available on how many hospitalized TIA patients progress on to stroke.³² In an analysis of hospitalization resource use and costs, Luengo-Fernandez and colleagues found that the increased hospital costs after TIA or stroke were primarily due to the initial hospitalization, further supporting that the initial hospitalization of patients after TIA should be targeted to very high-risk patients.³⁵ Martinez-Martinez et al provided additional evidence that patients evaluated in TIA clinics receive efficient care at about one-fifth the cost of hospitalization.²⁸ In this study, there was a 77.8% decrease in hospitalization as well as a savings of US\$1537.90 per patient managed in the TIA clinic instead of the hospital. Therefore, with the establishment of organized community services including TIA clinics and specialized TIA observational units, most patients can expect the same benefit in decreasing risk of stroke at a significantly decreased cost. Additionally, patients may experience a greater degree of satisfaction with not being hospitalized but this latter measure requires further study.

Should TIA Patients Get Combination Antiplatelet Therapy?

A long-standing question regarding the initial antiplatelet management of patients with TIA or minor stroke has been whether to use combination therapy versus a single agent. A theoretical advantage to dual antiplatelet therapy includes enhanced platelet inhibition during a period when a ruptured plaque may promote clot formation within a vessel. Indeed,

trials of patients with acute ST-segment elevation myocardial infarction (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28 trial (CLARITY-TIMI 28)³⁶ and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)³⁷ and acute non-ST-segment elevation acute coronary syndrome (CURE³⁸) have convincingly shown benefit in patients with primary cardiac disease. A theoretical disadvantage to dual antiplatelet treatment includes an increased risk of intracranial and major bleeding. Until recently, there was little evidence to support dual antiplatelet therapy in the short term for TIA and minor stroke patients; however, the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events trial (CHANCE) suggested that short-term combination treatment may be appropriate for some patients.³⁹ Nevertheless, there continues to be an ongoing debate about whether these results are generalizable to all patients.

Dual Antiplatelet Therapy in Secondary Stroke Prevention Trials

The Management of Atherothrombosis with Clopidogrel in High-risk patients trial (MATCH) compared aspirin plus clopidogrel versus clopidogrel alone in patients with ischemic stroke or TIA in the previous 3 months.⁴⁰ Participants received aspirin 75 mg or placebo in addition to clopidogrel and were treated for 18 months. The primary end point was ischemic stroke, myocardial infarction, vascular death, or rehospitalization for ischemia. The primary outcome measure occurred in 15.7% of the monotherapy group patients and 16.7% of the dual antiplatelet therapy patients which was not statistically significant, however included strokes due to both large and small vessel diseases. Stroke occurred at an equal rate of 9% of patients in both groups. Life-threatening bleeding occurred in 2.6% of dual antiplatelet therapy group patients and 1.3% of dual antiplatelet therapy group patients, which was statistically significant. Dual antiplatelet therapy may be more likely to show benefit in the setting of large vessel strokes. Therefore, without stratifying for large or small vessel disease, positive effects among patients with large-vessel disease may have been missed. Symptomatic intracranial hemorrhage was increased by 4 per 1000 treated with dual antiplatelet therapy. However, the Kaplan-Meier survival curve diverged between the two groups only after 90 days, suggesting that dual antiplatelet therapy may not significantly increase risk of bleeding when limited to 3 months.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study compared aspirin alone versus aspirin and clopidogrel in patients with multiple atherothrombotic risk factors, coronary artery disease, cerebrovascular disease, or peripheral arterial disease at any time in the past.⁴¹ This study randomly assigned 15 603 patients, 37% of whom had stroke or TIA, to aspirin 75 to 162 mg plus clopidogrel 75 mg daily or aspirin 75 to 162 mg daily plus placebo. The primary outcome measure was

myocardial infarction, stroke, or death from cardiovascular causes. Patients were followed for a median of 28 months. The primary outcome measure occurred in 6.8% of patients treated with dual antiplatelet therapy and 7.3% of patients treated with monotherapy, which was not statistically significant. Severe bleeding occurred in 1.7% of patients treated with dual antiplatelet therapy and 1.3% of patients treated with monotherapy, which was not statistically significant. The occurrence of intracranial hemorrhage, 0.3%, was the same in both groups.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial compared the combination of aspirin 325 mg daily and clopidogrel 75 mg daily with aspirin 325 mg daily and placebo in patients with lacunar infarction in the prior 6 months.⁴² Patients were treated for a mean of 3.4 years. The primary end point was any recurrent stroke, which included ischemic and hemorrhagic events. The event rates were 2.5% per year versus 2.7% per year, respectively, a result which was not statistically significant. Ischemic strokes occurred at a rate of 2.0% per year among patients taking dual antiplatelet therapy and 2.4% per year among patients taking monotherapy, also not statistically significant. Major hemorrhage was significantly increased among patients taking dual antiplatelet treatment (2.1% per year vs 1.1% per year) as was all-cause mortality (2.1% per year vs 1.4% per year). Gastrointestinal bleeding was the major driver behind the increased occurrence of major hemorrhage.

On the basis of these studies, guidelines for secondary stroke prevention advise against the long-term combination of clopidogrel and aspirin for secondary stroke prevention.⁴³

Multiple studies suggest conflicting evidence about the overall risk benefit of dual antiplatelet therapy for the prevention of recurrent stroke.⁴⁴ Lee and colleagues conducted a meta-analysis of 39 574 patients over 7 randomized control trials and found no difference in risk among patients taking dual antiplatelet therapy versus aspirin or clopidogrel monotherapy. There were also no significant differences in risk of hemorrhage between aspirin monotherapy and dual antiplatelets; however, this same dual antiplatelet group was more likely to have bleeding complications when compared to clopidogrel alone.⁴⁵

The discussion of dual antiplatelet therapy usually implies the combination of aspirin and clopidogrel. However, other combinations that have been tested in clinical trials for long-term stroke prevention including dipyridamole with aspirin. The European Stroke Prevention Study 2 (ESPS-2)⁴⁶ and European/Australasian Stroke Prevention in Reversible Ischemia (ESPRIT)⁴⁷ trials both compared aspirin monotherapy with the combination of aspirin and dipyridamole. In both trials, dual antiplatelet therapy was superior to aspirin alone. The ESPRIT trial randomized 1376 patients to aspirin 30 to 325 mg daily plus dipyridamole 200 mg twice daily or placebo within 6 months of a TIA or stroke. The primary outcome measure was stroke, myocardial infarction, vascular deaths, or major bleeding complication. During a mean

follow-up of 3.5 years, patients were more likely to reach the primary outcome with aspirin alone than with aspirin plus dipyridamole (16% vs 13%).^{47,48} Many clinicians assumed, by transitive logic, that because aspirin and clopidogrel monotherapy were approximately similar in stroke prevention as demonstrated in the Clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE)⁴⁹ trials that the combination of aspirin and dipyridamole would be similar to clopidogrel monotherapy. However, this assumption proved to be false. In the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, 20 332 patients were randomized to 25 mg aspirin with 200 mg dipyridamole or 75 mg daily clopidogrel. There was no significant difference in rate of stroke, MI, or death between groups, but there was an increased risk of hemorrhage among patients taking dual antiplatelet therapy versus clopidogrel alone.⁵⁰

Usman et al combined data across studies to assess risk of hemorrhage in secondary stroke prevention trials using antiplatelets. Annualized rates of any hemorrhage were 4.8% with aspirin alone, 3.6% with aspirin plus dipyridamole, 2.9% with clopidogrel alone, 10.1% with aspirin plus clopidogrel, and 16.8% with anticoagulation. Annualized major hemorrhage rates were 1% with aspirin alone, 0.93% with aspirin plus dipyridamole, 0.85% with clopidogrel alone, 1.7% with aspirin plus clopidogrel, and 2.5% with anticoagulation. While clopidogrel alone has the lowest risk of bleeding, combined with aspirin it had the second greatest after anticoagulation. Aspirin combined with any second antiplatelet increased the risk of bleeding with a limited benefit when taken together with other agents.⁵¹

Dual Antiplatelet Therapy in Acute TIA and Stroke Trials

The first study to compare dual antiplatelet therapy with monotherapy in the TIA and acute minor stroke and TIA setting was the Fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER) trial.⁵² A total of 392 patients were randomly assigned to aspirin plus clopidogrel or aspirin plus placebo. The primary outcome measure was all stroke (ischemic and hemorrhagic) at 90 days. The trial was stopped early due to slow enrollment. The rate of stroke was 7.1% in the dual antiplatelet therapy group and 10.8% in the monotherapy group, with a *P* value of .19. Two patients in the dual antiplatelet group had an intracranial hemorrhage compared to none in the monotherapy group.

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial randomized 107 patients with (1) 50% of greater carotid stenosis, (2) a TIA within the previous 3 months, and (3) 1 or more microembolic signals on transcranial Doppler during a 1-hour recording to aspirin plus placebo or aspirin plus clopidogrel for 7 days.⁵³ The primary outcome measure was the proportion of patients who continued to have microembolic signals at day 7. In all, 43.8% of the dual antiplatelet therapy patients compared with 72.7%

Figure 2. Algorithm for the triage, evaluation, and management of patients with transient ischemic attack (TIA).

of monotherapy patients had microemboli at day 7 ($P = .0046$). Microembolic signals were reduced by 61.6% on day 2 and by 61.4% on day 7. Four recurrent strokes and 7 TIAs occurred in the monotherapy group compared with 4 TIAs in the dual antiplatelet group. There were no episodes of major bleeding.

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS) trial, which compared best medical therapy alone versus best medical therapy with stenting for large vessel atherosclerosis, included treatment with aspirin and

clopidogrel for 90 days. In addition, statin use was titrated to a low-density lipoprotein <70 mg/dL. There was no monotherapy arm in the study. Best medical therapy alone was superior to the combination of best medical therapy and stenting for the primary end points including stroke and death.⁵⁴

The CHANCE trial randomized 5170 patients within 24 hours of TIA or minor stroke to aspirin 75 mg daily and clopidogrel 75 mg daily or aspirin 75 mg daily and placebo. In the group assigned dual antiplatelet therapy, the combination was used for 21 days after which clopidogrel monotherapy was used until day 90. Patients assigned to both aspirin and clopidogrel were significantly less likely to have a stroke compared to those taking aspirin alone (8.2% vs. 11.7%) in the first 90 days of treatment without any significant difference in risk of hemorrhage.³⁹ In addition, the separation of event curves was within the first few days and then remained parallel for the next 90 days (Figure 2) suggesting that dual antiplatelet therapy may not need to be continued beyond the first week. In contrast to treatment patterns in North America, only 35% of patients were taking an antihypertensive medication and only 42% were taking a lipid-lowering drug at 90 days. It is unclear whether higher rates of treatments with the agents might have mitigated the results observed in the CHANCE trial. In addition, the study was conducted in China, a population that is known to have a higher rate of intracranial atherosclerosis. Large vessel atherosclerosis may be a target population for whom dual antiplatelet therapy is specifically helpful. For these reasons, the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, which is similar in design to CHANCE, continues in the United States.⁵⁵ Notable differences in trial design between the 2 studies include (1) a shorter time window in POINT (12-hour window vs 24-hour window in CHANCE), (2) a higher loading dose of clopidogrel in POINT (600 mg versus 300 mg), and (3) continuation of dual antiplatelet therapy until day 90 in POINT (compared with 21 days in CHANCE). Unfortunately, neither trial is collecting data systematically on intracranial atherosclerosis.

Due to concerns about the limited use of antihypertensives and statins in the CHANCE trial potentially limiting the generalizability of the results, we continue to use monotherapy outside a clinical trial. At our center, eligible patients are enrolled in the POINT trial, including those with intracranial atherosclerosis. If the POINT trial confirms the results of the CHANCE trial, our practice will change as will, likely, national guidelines.

Future Directions

If the CHANCE results are reproduced in the POINT trial, short-term (ie, <3 months) dual antiplatelet treatment with aspirin and clopidogrel will become routine in the treatment of patients with TIA and minor stroke. Other opportunities for study in the setting of acute stroke and TIA include cilostazol, ticagrelor, and the novel oral anticoagulants.

Cilostazol showed superiority in secondary stroke prevention studies when compared with placebo (Cilostazol for prevention of secondary stroke trial (CSPS))⁵⁶ and aspirin (Cilostazol for prevention of secondary stroke 2 (CSPS-2)).⁵⁷ In CSPS-2, the annual rate of stroke was 2.76% with cilostazol and 3.71% with aspirin. In addition, major hemorrhage occurred less frequently with cilostazol (0.77% vs 1.78% over a mean of 29 months). Because these studies were conducted in Japan, the medication, which is available for use in the United States for treatment of peripheral arterial disease, was not approved by the Food and Drug Administration for the treatment of stroke.

Ticagrelor, an inhibitor of adenosine diphosphate receptors, has been tested and shown to be of benefit in acute coronary syndrome.⁵⁸ In the Platelet Inhibition and Patient Outcomes trial (PLATO) study, ticagrelor reduced the risk of myocardial infarction by 1.1% and death by 1.4% at 12 months, compared with clopidogrel. Overall major bleeding rates were similar (approximately 11%), but ticagrelor was associated with a higher rate of fatal intracranial hemorrhage in this population (0.1% vs 0.01%). It is currently being tested in an acute TIA and minor stroke study called SOCRATES.⁵⁹ Patients are randomly assigned within 24 hours of ictus to aspirin 100 mg daily (after a loading dose of 300 mg) or ticagrelor 180 mg daily. The primary outcome measure is stroke, myocardial infarction, or death at 90 days.

Apixaban,^{60,61} dabigatran,⁶² edoxaban,⁶³ and rivaroxaban⁶⁴ have all been compared with warfarin for stroke prevention in patients with atrial fibrillation. In the Apixaban versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, warfarin was compared with aspirin in patients with atrial fibrillation deemed “unsuitable” for anticoagulation with warfarin. A total of 5599 patients were randomly assigned to apixaban 5 mg twice daily or aspirin 81 to 324 mg daily. Of all patients, 40% had previously failed treatment with warfarin. The primary outcome was stroke or system embolism, which occurred at a rate of 1.6% per year with apixaban and 3.7% per year with aspirin. Major bleeding occurred at a rate of 1.4% per year in the apixaban group and 1.2% per year in the aspirin group, which was not statistically significantly different. Rates of intracranial hemorrhage were the same (0.4% per year). In a subgroup analysis of the 764 patients who entered the study with TIA or stroke, the annualized rate of stroke or systemic embolism was 2.4% per year with apixaban and 9.2% per year with aspirin.⁶⁵ The major bleeding rate was 4.1% per year with apixaban and 2.9% per year with aspirin. Intracranial bleeding occurred at a rate of 1.2% per year with apixaban and 1.6% per year with aspirin. Of note, none of the patients were randomized within the first few days after TIA or minor stroke.

There are now trials being planned comparing apixaban, dabigatran, and rivaroxaban for secondary stroke prevention in patients with cryptogenic atrial fibrillation. In the future,

some of these agents may be considered for acute treatment provided there is an acceptable balance of benefit in terms of ischemic event reduction and risk in terms of major bleeding.

Conclusion

Significant advances have been made over the last 2 decades with respect to the evaluation and treatment of patients who experience TIA. Initial management has changed from casual observation to urgent evaluation and treatment. This has been associated with a decrease in the occurrence of stroke at centers that have adopted this approach. Not all patients necessarily require admission so long as decisive treatment is initiated promptly. There are many alternative approaches including urgent TIA clinics and observation units within the emergency department. These latter approaches may reduce admissions by as much as 80% without exposing patients to harm.

The optimal antiplatelet therapy in the days after TIA and minor stroke is still undergoing evaluation. Aspirin is of proven benefit, and, for some, dual antiplatelet therapy may provide additional risk reduction. With newer antithrombotic drugs being approved, it is likely that additional studies of patients with TIA will occur in the near future.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

- Hackam DG, Kapral MK, Wang JT, Fang J, Hachinski V. Most stroke patients do not get a warning: a population-based cohort study. *Neurology*. 2009;73(13):1074-1076.
- Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276-2293.
- National Institute of Neurological Disease and Blindness PHS. A classification and outline of cerebrovascular diseases. *Neurology*. 1958;8(5):395-434.
- Fisher CM. Intermittent cerebral ischemia. In: Wright IS, Millikan CH, eds. *Cerebral Vascular Disease*. New York: Grune & Stratton; 1958:81-97.
- Kidwell CS, Warach S. Acute ischemic cerebrovascular syndrome: diagnostic criteria. *Stroke*. 2003;34(12):2995-2998.
- Chalela JA, Kidwell CS, Nentwich LM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet*. 2007;369(9558):293-298.
- Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284(22):2901-2906.
- Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558):283-292.
- Douglas VC, Johnston CM, Elkins J, Sidney S, Gress DR, Johnston SC. Head computed tomography findings predict short-term risk after transient ischemic attack. *Stroke*. 2003;34(12):2894-2898.
- Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet Neurol*. 2010;9(11):1060-1069.
- Kiyohara T, Kamouchi M, Kumai Y, et al. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. *Stroke*. 2014;45(2):418-425.
- Giles MF, Albers GW, Amarenco P, et al. Addition of brain infarction to the ABCD2 score (ABCD2I) a collaborative analysis of unpublished data on 4574 patients. *Stroke*. 2010;41(9):1907-1913.
- Daubail B, Durier J, Jacquin A, et al. Factors associated with early recurrence at the first evaluation of patients with transient ischemic attack. *J Clin Neurosci*. 2014;21(11):1940-1944.
- Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363(9413):915-924.
- Stromberg S, Gelin J, Osterberg T, Bergstrom GM, Karlstrom L, Osterberg K. Very urgent carotid endarterectomy confers increased procedural risk. *Stroke*. 2012;43(5):1331-1335.
- Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370(9596):1432-1442.
- Wasserman J, Perry J, Dowlatsahi D, et al. Stratified, urgent care for transient ischemic attack results in low stroke rates. *Stroke*. 2010;41(11):2601-2605.
- Johnston SC, Nguyen-Huynh MN, Schwarz ME, et al. National Stroke Association guidelines for the management of transient ischemic attacks. *Ann Neurol*. 2006;60(3):301-313.
- Lavallée P, Mesequer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet Neurol*. 2007;6(11):953-960.

20. Asimos AW, Johnson AM, Rosamond WD, et al. A multicenter evaluation of the ABCD2 score's accuracy for predicting early ischemic stroke in admitted patients with TIA. *Ann Emerg Med.* 2010;55(2):201-210.
21. Amarenco P, Labreuche J, Lavallée PC, et al. Does ABCD2 score below 4 allow more time to evaluate patients with a transient ischemic attack? *Stroke.* 2009;40(9):3091-3095.
22. Amarenco P, Labreuche J, Lavallée PC. Patients with transient ischemic attack with ABCD2 <4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD2 ≥4. *Stroke.* 2012;43(3):863-865.
23. Cucchiara BL, Kasner S. All patients should be admitted to the hospital after a transient ischemic attack. *Stroke.* 2012;43(5):1446-1447.
24. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355(6):549-559.
25. Durrani-Tariq S, Eskin B, Allegra JR. Admission rates of ED patients with transient ischemic attack have increased since 2000. *Am J Emerg Med.* 2013;31(9):1349-1351.
26. Amarenco P. Not all patients should be admitted to the hospital for observation after a transient ischemic attack. *Stroke.* 2012;43(5):1448-1449.
27. Lavallée P, Amarenco P. TIA clinic: a major advance in management of transient ischemic attacks. *Front Neurol Neurosci.* 2014;33:30-40.
28. Martinez-Martinez MM, Martínez-Sánchez P, Fuentes B, et al. Transient ischaemic attacks clinics provide equivalent and more efficient care than early in-hospital assessment. *Eur J Neurol.* 2013;20(2):338-343.
29. Olivot JM, Wolford C, Castle J, et al. Two ACES: transient ischemic attack work-up as outpatient assessment of clinical evaluation and safety. *Stroke.* 2011;42(7):1839-1843.
30. Sanders LM, Srikanth VK, Jolley DJ, et al. Monash transient ischemic attack triaging treatment: safety of a transient ischemic attack mechanism-based outpatient model of care. *Stroke.* 2012;43(11):2936-2941.
31. Molina CA, Selim MM. Hospital admission after transient ischemic attack: unmasking wolves in sheep's clothing. *Stroke.* 2012;43(5):1450-1451.
32. Joshi JK, Ouyang B, Prabhakaran S. Should TIA patients be hospitalized or referred to a same-day clinic? A decision analysis. *Neurology.* 2011;77(24):2082-2088.
33. Nguyen-Huynh MN, Johnston SC. Is hospitalization after TIA cost-effective on the basis of treatment with tPA? *Neurology.* 2005;65(11):1799-1801.
34. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology.* 1998;50(4):883-890.
35. Luengo-Fernandez R, Silver LE, Gutnikov SA, Gray AM, Rothwell PM. Hospitalization resource use and costs before and after TIA and Stroke: results from a population-based cohort study (OXVASC). *Value Health.* 2013;16(2):280-287.
36. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med.* 2005;352(12):1179-1189.
37. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005;366(9497):1607-1621.
38. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345(7):494-502.
39. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* 2013;369(1):11-19.
40. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364(9431):331-337.
41. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354(16):1706-1717.
42. SPS3 Investigators; Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med.* 2012;367(9):817-825.
43. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(7):2160-2236.
44. Hong KS. Dual antiplatelet therapy after noncardioembolic ischemic stroke or transient ischemic attack: pros and cons. *J Clin Neurol.* 2014;10(3):189-196.
45. Lee M, Saver J, Hong KS, Rao NM, Wu YL, Ovbiagele B. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: a systematic review and meta-analysis. *Ann Intern Med.* 2013;159(7):463-470.
46. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study. 2. dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996;143(1-2):1-13.
47. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet.* 2006;367(9523):1665-1673.
48. Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke.* 2008;39(4):1358-1363.
49. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348(9038):1329-1339.
50. Sacco RL, Diener HC, Yusuf S, et al; PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med.* 2008;359(12):1238-1251.

51. Usman MH, Notaro LA, Nagarakanti R, et al. Combination antiplatelet therapy for secondary stroke prevention: enhanced efficacy or double trouble? *Am J Cardiol*. 2009;103(8):1107-1112.
52. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *The Lancet*. 2007;6(11):961-969.
53. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation*. 2005;111(17):2233-2240.
54. Chimowitz MI, Lynn MJ, Derdeyn CP, et al; SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011 Sep 15; 365(11):993-1003.
55. Jauch EC, Saver J, Adams HP Jr, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947.
56. Gotoh F, Tohgi H, Hirai S, et al. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. *J Stroke Cerebrovasc Dis*. 2000; 9(4):147-157.
57. Shinohara Y, Katayama Y, Uchiyama S, et al. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9(10):959-968.
58. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
59. SOCRATES trial. Web site. <http://www.clinicaltrials.gov/show/NCT01994720>. Accessed September 1, 2014.
60. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011; 365(11):981-992.
61. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817.
62. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
63. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.
64. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365(10):883-891.
65. Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol*. 2012;11(3): 225-231.