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Early Secondary Prevention in Transient Ischemic Attack (TIA) and Minor Stroke

Dominic Tse [1,2] · Michael D. Hill [1,2] · Shelagh B. Coutts [1,2]

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Abstract

Purpose of Review The purpose of this study was to review recent literature on the early secondary prevention in transient ischemic attack (TIA) and minor stroke.

Recent Findings The result of Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events and the secondary analysis of Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) have shown that treatment with clopidogrel and aspirin for 21 days reduced the risk of recurrent stroke with no significant increase in bleeding risk. Triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole resulted in a significant increase in major (including fatal) bleeding with no significant reduction in the recurrent stroke or TIA.

Summary The early treatment of patients with TIA or minor stroke with clopidogrel and aspirin for 21 days was effective in reducing the risk of recurrent stroke with no significant increase in bleeding risk. Most stroke guidelines have been updated to reflect this recommendation.

Keywords Transient ischemic attack · Minor stroke · Secondary stroke prevention · Antiplatelet therapy · Clopidogrel · Aspirin

Introduction

Transient ischemic attack (TIA) is classically and clinically defined as focal neurological symptoms of presumed vascular origin lasting less than 24 h. Yet, 30–50% of TIAs have evidence of new infarction on diffusion-weighted magnetic resonance imaging (MRI) [1]. A newer tissue-based, rather than time-based definition, was proposed in 2002: "transient ischemic attack (TIA): a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" [2]. The corollary is that the diagnosis is minor ischemic stroke if there is evidence of infarction on MRI, even if symptoms have resolved within 24 h of onset. This definition has been embraced in academic centers in high-income countries where MR imaging is available and routinely used, but not where the technology is unavailable.

In contrast, there is no consensus on the definition of minor stroke. Many groups have adopted the arbitrary cutoff of the National Institutes of Health Stroke Scale (NIHSS) ≤ 5 or ≤ 3 as the definition. Recent observational studies have explored stroke outcomes according to various definitions [3, 4]. The definitions NIHSS ≤ 3 and scoring ≤ 1 on each NIHSS item with a normal level of consciousness had the best short- and medium-term outcomes and were proposed to be the best-suited definition of minor stroke [4]. A more impactful definition of a minor stroke might be a composite of the presenting clinical symptoms, the potential functional impact, and the risk of early neurological deterioration [5]. The reality is that ischemic stroke syndromes have a continuous range from mild and transient to severe and even fatal. TIA and minor stroke are at the mild end of the spectrum of stroke severity.

This article is part of the Topical Collection on *Stroke*

✉ Shelagh B. Coutts
scoutts@ucalgary.ca

Dominic Tse
dmytse@gmail.com

Michael D. Hill
michael.hill@ucalgary.ca

[1] Calgary Stroke Program, Department of Clinical Neuroscience, Foothills Medical Centre, 1403 29th St NW, C1242, Calgary, AB T2N 2T9, Canada

[2] Cummings School of Medicine, University of Calgary, Calgary, AB, Canada

Epidemiology of TIA

The crude annual incidence of TIA ranged between 29 and 61 per 100,000 people per year in western countries [6]. Population studies from Belgium (1984–1999) [7]; Oxfordshire, UK (1981–2004) [8]; Victoria, Australia (2001–2011) [9]; and Canada (2003–2013) [10] have reported a decreasing trend in the incidence of TIA. Possible explanations for the decreasing trend include the implementation of stroke strategies and guidelines as well as the improvement of cardiovascular risk management. An alternative consideration is the changing definition of TIA. Remuneration of stroke diagnoses for hospitals in some jurisdictions is greater than for TIA and this provides an incentive to use MR imaging to make a definitive diagnosis of and to code for stroke using an imaging-based definition. This ascertainment bias may account for the apparent decline in TIA.

Early Recurrent Stroke after TIA or Minor Stroke

The 90-day stroke risk following a TIA was estimated at 10% [11]. The reported stroke risk after TIA varied significantly largely due to differences in study methodology [12]. A systematic review and meta-analysis of studies with methodology involving active ascertainment of stroke outcomes demonstrated a higher early risk of stroke following TIA of 17.3% at 90 days [13]. A 1-year follow-up study showed that recurrent strokes occurred in 1.5% patients within 2 days after the initial TIA or minor stroke, in 2.1% patients within 7 days, in 2.8% patients within 30 days, and in 3.7% patients within 90 days. In a follow-up of the 1-year study, the risk of recurrent TIA or stroke was similar between the first year and the second through to the fifth year [14].

Risk stratification is important in determining patients at higher risk of stroke following a TIA. The $ABCD^2$ score (age, blood pressure, clinical features, duration of symptoms, and diabetes) has been promoted to identify patients at high risk for imminent stroke. However, it has inadequate discriminative value for clinical use with studies showing its insufficient sensitivity and specificity in predicting stroke risk [15, 16]. In contrast, DWI positivity or the presence of a symptomatic intracranial or extracranial severe arterial stenosis of occlusion on CT/CTA has been shown to be highly predictive of recurrent stroke [17].

Patients who had a TIA can follow a malignant course. Up to 15% of patients with TIA or minor stroke become disabled (modified Rankin Scale (mRS) ≥ 2) at 90-day follow-up. CT/CTA-positive metric defined as acute ischemic change seen on CT or intracranial or extracranial vessel occlusion or stenosis ipsilateral to the clinically relevant ischemic brain tissue, was predictive of disability [18]. Furthermore, a 1-year TIA follow-up study in Alberta showed a combined risk of stroke, MI, or death of 21.8% (95% confidence interval (CI) 20.0–23.6) [19].

In Calgary, the early risk of stroke was shown to be significantly lower in patients who received rapid TIA assessment and treatment (4.7%) as compared with standard care (9.7%) ($P = 0.05$) [20]. With early initiation of treatments after TIA, an 80% reduction in the early stroke risk has been reported [21].

Early Secondary Prevention

While there are numerous well-established early secondary preventative measures including carotid revascularization for symptomatic carotid artery stenosis, anticoagulation for atrial fibrillation, blood pressure management, and statin therapy, this review will focus on recent findings regarding antiplatelet therapy.

Dual Antiplatelet Therapy

The efficacy of antiplatelet agents including aspirin, dipyridamole, cilostazol, and clopidogrel in the secondary prevention of stroke and TIA has been well established. Over the last two decades, the focus had been on reducing the ischemic stroke risk even further with dual antiplatelet therapy while minimizing the risk of hemorrhage.

Management of atherothrombosis with clopidogrel in high-risk patients (MATCH) [22] was a randomized, double-blinded, placebo-controlled trial of 7599 patients comparing the efficacy and safety of aspirin with placebo in patients already receiving clopidogrel. Patients were eligible if they had a TIA or recent ischemic stroke in the previous 3 months. The duration of treatment and follow-up was 18 months. The combination of aspirin and clopidogrel was associated with a non-significant difference in reducing major vascular events including ischemic stroke, myocardial infarction, vascular death, or re-hospitalization for acute ischemic event (relative risk reduction 7.1%, 95% CI −8.5 to 20.4; $P = 0.353$). The risk of life-threatening or major bleeding was increased in the clopidogrel-aspirin group.

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) [23] was a randomized, double-blinded, placebo-controlled trial of 15,603 patients investigating the efficacy and safety of clopidogrel and aspirin as compared with aspirin in patients at high risk for a cardiovascular event. Patients were eligible if they had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease during the previous 5 years, or documented symptomatic peripheral arterial disease. Patients remained on the randomized medications indefinitely and were followed for a median of 28 months. The combination of clopidogrel and aspirin did not reduce the rate

of myocardial infarction, stroke, or vascular death compared to aspirin alone (relative risk 0.93, 95% CI 0.83–1.05; $P = 0.22$). The rate of severe bleeding did not differ between the two groups.

The negative results of MATCH and CHARISMA could be attributed to several important factors in the trial design. First, as mentioned previously, the risk of recurrent stroke after TIA or minor stroke is highest in the first few days. Neither MATCH nor CHARISMA aimed to enroll patients during the period of high early risk. Indeed, in the MATCH trial, the only subgroup with suggested benefit in the post hoc secondary analyses was the group enrolled within 7 days of their event. Second, the treatment effect was reduced with the exclusion of patients with symptomatic carotid disease. Third, patients of all stroke severity were included in the studies. The wide selection criteria could have diluted the beneficial effect of the clopidogrel-aspirin therapy.

Fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER) was a randomized trial with a 2 × 2 factorial design that randomly assigned patients with TIA or minor stroke within 24 h of symptom onset to clopidogrel or placebo and simvastatin or placebo [24]. All patients received aspirin. Three hundred ninety-two patients were enrolled before the trial was stopped due to slow recruitment. The combination of clopidogrel and aspirin did not significantly reduce the risk of stroke (ischemic and hemorrhagic) compared with aspirin alone (risk ratio 0.7, 95% CI 0.3–1.2; $P = 0.19$). There were more symptomatic hemorrhages on combination therapy compared to aspirin alone (risk difference 3%, 95% CI 0.6–5.4; $P = 0.03$). The major limitation of this trial was the lack of statistical power owing to the early termination of the study. However, a meta-analysis including the patients in FASTER and the few patients in MATCH and CHARISMA showed evidence of benefit for dual antiplatelet therapy with a 34% relative risk reduction (RR 0.66, 95% CI 0.43–1.00) [24].

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) [25••] was a randomized, double-blinded, placebo-controlled trial of 5170 patients in China comparing the safety and efficacy of clopidogrel-aspirin therapy for 21 days versus aspirin alone in patients with non-disabling ischemic stroke or TIA. Patients in the group receiving clopidogrel were given a 300 mg loading dose of clopidogrel followed by a daily dose of 75 mg. The daily aspirin dose was 75 mg. The study drug was commenced within 24 h of symptom onset. Clopidogrel-aspirin therapy reduced the risk of recurrent stroke (ischemic and hemorrhagic) by 32% (hazard ratio (HR) 0.68, 95% CI 0.57–0.81; $P < 0.001$). Bleeding events (severe, moderate, and mild) were similar between the two groups (HR 1.41, 95% CI 0.95–2.10; $P = 0.09$). At 1-year follow-up, the clopidogrel-aspirin group continued to have a lower risk of stroke (HR 0.78, 95% CI 0.65–0.93; $P = 0.006$) [26]. There was no significant difference in moderate-severe hemorrhages between the two groups (HR 0.67, 95% CI 0.24–1.87; $P = 0.44$).

Generalizability of the results was a perceived limitation of the trial. First, the trial was conducted entirely in China and therefore thought to be applicable to Asian patients only. Second, China has a higher incidence of large-artery intracranial atherosclerosis in comparison to other developed countries. However, this was largely incorrect because the result was highly concordant with FASTER, with an identical effect size and subsequently confirmed by the next trial.

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) [27••] was a randomized, double-blinded, placebo-controlled, multicenter, international trial of 4881 patients comparing the safety and efficacy of clopidogrel-aspirin therapy for 90 days versus aspirin alone in patients with non-disabling ischemic stroke or TIA. Patients in the group receiving clopidogrel were given a 600 mg loading dose of clopidogrel followed by a daily dose of 75 mg. The daily aspirin dose ranged between 50 and 325 mg. Patients were randomized within 12 h of symptom onset. The trial was terminated early because the data and safety monitoring board had determined that clopidogrel-aspirin therapy was associated with both a lower risk of major ischemic events including ischemic stroke, myocardial infarction, or ischemic vascular death (HR 0.75, 95% CI 0.59–0.95; $P = 0.02$) and a higher risk of major hemorrhage than aspirin alone at 90 days (HR 2.32, 95% CI 1.10–4.87; $P = 0.02$). The higher risk of major hemorrhage was likely related to the longer duration of clopidogrel-aspirin therapy.

The similarities and differences between the trial designs of CHANCE and POINT have been summarized in Table 1. The POINT trial confirms earlier estimates of the effect size of both CHANCE and FASTER, arguing that ethnicity and stroke mechanism are not relevant concerns in the use of dual antiplatelet therapy for early secondary stroke prevention.

Optimal Duration of Clopidogrel-Aspirin Therapy

A pre-specified secondary analysis of POINT assessing the time course of risk versus benefit for clopidogrel-aspirin therapy was presented at the World Stroke Congress in 2018. The rate of primary efficacy events was highest over the first 21 days, occurring in 5.6% within 0–21 days, and 0.9% within 22–90 days in the aspirin group versus 3.6% within 0–21 days and 1.4% within 22–90 days in the clopidogrel-aspirin group. The rate of major hemorrhage remained fairly constant in both groups during the 90 days, occurring in 0.2% within 0–21 days and 0.2% within 22–90 days in the aspirin group versus in 0.4% within 0–21 days and 0.5% within 22–90 days in the clopidogrel-aspirin group [28•]. The results of

Table 1 Trial designs of CHANCE and POINT

	Wang (2013), CHANCE	Johnston (2018), POINT
Study countries	China	North America, Europe, Australia, New Zealand
Study population	Minor stroke (NIHSS ≤3) or TIA ($ABCD^2 \geq 4$)	
Timing of randomization (from symptom onset)	Within 24 h	Within 12 h
Intervention	Clopidogrel plus aspirin Clopidogrel: 300 mg loading dose on day 1, followed by 75 mg per day from days 2 to 90 Aspirin: dose ranged from 75 mg to 300 mg on day 1, followed by 75 mg per day from days 2 to 21	Clopidogrel plus aspirin Clopidogrel: 600 mg loading dose on day 1, followed by 75 mg per day from days 2 to 90 Aspirin: dose ranged from 50 mg to 325 mg per day from days 1 to 90
Control	Aspirin only: dose ranged from 75 mg to 300 mg on day 1, followed by 75 mg per day from days 2 to 21	Aspirin only: ranged from 50 mg to 325 mg per day from days 1 to 90
Duration of intervention	21 days	90 days
Follow-up	90 days	90 days
Primary efficacy endpoint	New stroke (ischemic or hemorrhagic)	Composite of ischemic stroke, MI, vascular death
Primary safety endpoint	Moderate-to-severe bleeding events (GUSTO)	Major hemorrhage

CHANCE and the secondary analysis of POINT suggest that the optimal duration of clopidogrel-aspirin therapy is 21–28 days.

Triple Antiplatelet Therapy and Phosphodiesterase Inhibitors

Triple Antiplatelets for Reducing Dependency after Ischemic Stroke (TARDIS) [29] was an international, multicenter, randomized, open-label, blinded-endpoint trial comparing the safety and efficacy of triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with ischemic stroke or TIA. Participants were randomized within 48 h of symptom onset and continued the assigned therapy for 30 days. The primary efficacy outcome was recurrent stroke or TIA over 90 days. Three thousand ninety-six participants were randomized with 1556 in the triple antiplatelet therapy arm. The trial was stopped early on the recommendation of the data monitoring committee based on three observations: triple antiplatelet therapy was not associated with a significant reduction in the primary outcome (adjusted common odds ratio (cOR) 0.90, 95% CI 0.67–1.20; $P = 0.47$), significant increase in major (including fatal) bleeding (adjusted cOR 2.54, 95% CI 2.05–3.16; $P < 0.0001$), and that the trial was highly unlikely to demonstrate a significant difference in the primary outcome based a conditional power analysis.

The phosphodiesterase inhibitor dipyridamole has also been used for long-term antiplatelet effect in stroke prevention with mixed results [30–33]. It has not been evaluated acutely. Similarly, the recently presented Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) reported a lower a risk of ischemic stroke recurrence in high-risk stroke patients receiving a combination of cilostazol with aspirin or clopidogrel (HR 0.49, 95% CI 0.31–0.76; $P = 0.001$) and a similar risk of major bleeding than those who received aspirin or clopidogrel alone (HR 0.66, 95% CI 0.27–1.60; $P = 0.354$) [34]. Very few patients were enrolled acutely. Therefore, the role of acute use of these agents remains uncertain.

Updated International Guidelines

Since the publication of the CHANCE and POINT trials, North American stroke guidelines on the secondary prevention of stroke and TIA had been updated. The 2018 American Heart Association (AHA)/American Stroke Association (ASA) Guidelines for the Early Management of Patients With Acute Ischemic Stroke recommended the use of dual antiplatelet therapy (aspirin and clopidogrel) for 21 days in patients presenting with minor stroke (class of recommendation (COR) IIa, level of evidence (LOE) B–R) [35].

The Canadian Stroke Best Practice Recommendations for Acute Stroke Management updated in 2018 recommended the combination of clopidogrel and ASA for a duration of 21–30 days followed by antiplatelet monotherapy (such as ASA or clopidogrel alone) in very high-risk TIA patients ($ABCD^2$ score > 4) or minor stroke of noncardioembolic origin (NIHSS 0–3) (evidence level A) [36]. The European Stroke Organization (ESO) secondary prevention and TIA management guidelines are currently in development and will be published in 2019.

Clopidogrel Nonresponsiveness

Clopidogrel belongs to the class of thienopyridines, which are prodrugs. It requires metabolism to its active by hepatic cytochrome p450 (CYP) isoenzymes to exert its antiplatelet activity. Polymorphisms of the *CYP2C19* gene are strong predictors of clopidogrel nonresponsiveness. The prevalence of *CYP2C19* loss-of-function variants is high in East Asian populations [37]. As part of the prespecified genetic substudy of CHANCE, three single-nucleotide polymorphisms (SNPs) for *CYP2C19* including *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*17* were genotyped in 2933 participants [38]. Among the participants, 58.8% were *CYP2C19* loss-of-function carriers. Clopidogrel-aspirin reduced the rate of recurrent stroke in the noncarriers but not in the loss-of-function carriers (HR 0.51, 95% CI 0.35–0.75; $P = 0.02$). Bleeding risk did not differ between the noncarriers and loss-of-function carriers (HR 0.92, 95% CI 0.39–2.17; $P = 0.86$). These findings appear to support the potential for *CYP2C19* genotyping when considering treatment with clopidogrel-aspirin in patients with TIA or minor stroke. Genotyping analyses of the POINT participants are underway.

Other $P2Y_{12}$ Receptor Antagonists

Ticagrelor or prasugrel might be useful alternatives for clopidogrel non-responders.

Ticagrelor

Ticagrelor belongs to the class of cyclopentyltriazolopyrimidines and is a reversibly binding, oral $P2Y_{12}$ receptor antagonist. Unlike clopidogrel, ticagrelor is orally active without the need for metabolic activation [39]. Other advantages of ticagrelor over clopidogrel include faster onset and more consistent platelet inhibition.

Ticagrelor was evaluated in the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial [40]. Although ticagrelor was not superior to aspirin in reducing the rate of stroke, MI, or death at 90 days (HR 0.89, 95% CI 0.78–1/01; $P = 0.07$), it was superior to aspirin in reducing ischemic stroke (HR 0.87, 95% CI 0.76–1.00; $P = 0.046$). There was no significant difference in the rate of major bleeding (HR 0.83, 95% CI 0.52–1.34); $P = 0.45$). In a prespecified subgroup analysis of SOCRATES, ticagrelor was superior to aspirin at preventing stroke, MI, or death at 90 days in patients with ipsilateral atherosclerotic stenosis (HR 0.68, 95% CI 0.53–0.88; $P = 0.03$) [41].

Prasugrel

Prasugrel is another oral $P2Y_{12}$ receptor antagonist with platelet inhibition not affected by the *CYP2C19* genetic polymorphism. PRAsugrel and clopidogrel in Japanese patients with ischemic STROke (PRASTRO)-I was a phase 3 randomized, double-blinded, non-inferiority trial of 3753 patients comparing the safety and efficacy of prasugrel versus clopidogrel in patients who had a non-cardioembolic stroke in the previous 1–26 weeks. Although prasugrel was not shown to be non-inferior to clopidogrel for the prevention of ischemic stroke, MI and vascular death (RR 1.05, 95% CI 0.79–1.44), prasugrel showed similar efficacy to clopidogrel in terms of number of events. The incidence of bleeding events was not significantly different between the treatment groups (RR 0.77, 95% CI 0.41–1.42) [42].

Conclusions

Based on the results of CHANCE and the secondary analysis of POINT, the early treatment of patients with TIA or minor stroke with clopidogrel and aspirin for 21 days was effective in reducing the risk of recurrent stroke with no significant increase in bleeding risk.

Compliance with Ethical Standards

Conflict of Interest Dominic Tse declares no potential conflicts of interest. Shelagh Coutts received research/grant support from the Canadian Institutes of Health Research (CRH-112319), the Heart and Stroke Foundation of Canada (G-16-00012585), and Genome Canada (143TIA-Penn). Michael D. Hill reports payment for serving as a stroke outcome event adjudicator for a panel of clinical trials from Merck; reports non-financial support for a drug received as in-kind support for a clinical trial—TEMPO-1 trial, 2013–2016 from Hoffmann-La Roche Canada Ltd.; reports grant to the University of Calgary support the ESCAPE trial 2012–2014 from Covidien (Medtronic); reports grant to the University of Calgary support the TEMPO-2 trial 2016-present; Advisory board for the COLUMBUS registry from Boehringer-Ingleheim; reports grant to the University of Calgary to support the UNMASK-EVT study 2017–present from Stryker Inc.; reports grant to the University of Calgary for the HERMES collaboration 2016-present from Medtronic LLC; reports grant to the University of Calgary to support the ESCAPE-NA1 study 2017-present from NoNO Inc., outside the submitted work. In addition, Dr. Hill has a patent Systems and Methods

for Assisting in Decision-Making and Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software, is also a director of the Canadian Federation of Neurological Sciences, a not-for-profit group and has received grant support from Alberta Innovates Health Solutions, CIHR, Heart & Stroke Foundation of Canada, and National Institutes of Neurological Disorders and Stroke.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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