Antiplatelet therapies for secondary stroke prevention: an update on clinical and cost-effectiveness

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Stroke exacts a huge toll physically, mentally and economically. Antiplatelet therapy is the cornerstone of secondary stroke prevention, and proven drugs available to successfully realize this therapeutic strategy for the long term include aspirin, dipyridamole plus aspirin and clopidogrel. However, government agencies, corporations, health plans and patients desire more information about the clinical and cost-effectiveness of these established therapies in real-world settings. This paper provides an update on evidence-based secondary stroke prevention with antiplatelet medications, discusses cost-related issues and offers perspective about the future.

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Stroke remains a global leading cause of death and long-term disability, highlighting the need for more effective treatment approaches [1,2]. The estimated economic impact of US\$73 billion in 2010 reflects the substantial mortality and morbidity of stroke [1]. Due to the limited options for acute stroke therapies, stroke prevention is an important therapeutic approach. Stroke prevention, particularly in patients who have already experienced stroke or transient ischemic attack (TIA), is critical for reducing the burden of disease on patients, their families and society since occurrence of a first stroke or TIA is the strongest predictor of a repeat event [3].

The majority of strokes are of ischemic origin (80–85%), often caused by large- or small-artery atherothrombosis, or cardioembolism [1,4]. Atherothrombotic disease is the primary cause of ischemic stroke. Indeed, as activated macrophages mature and narrow the aorticercerviocephalic arterial vasculature, they produce procoagulant tissue factor, which contributes to the development of thrombosis. Platelet aggregation and thrombosis are minimized through several pathophysiologic mechanisms. Many classes of antiplatelet medications may reduce stroke

risk because of these mechanisms. This paper reviews those various antiplatelet medications, their mechanisms of action, pivotal clinical trials and related costs.

Mechanisms, trial efficacy & clinical effectiveness

Aspirin

Aspirin is a common drug well known to patients and physicians for treatment of symptomatic vascular disease. Aspirin is effective in the prevention of recurrent vascular events among patients with established vascular disease as shown in the collaborative meta-analysis of randomized trials of antiplatelet therapy for the prevention of death, myocardial infarction and stroke in high-risk patients (ATC meta-analysis) published in 2002 [5].

The mechanism of aspirin is through irreversible inhibition of COX-1 and -2 enzymes and reduction of CRP that result in decreased formation of prostaglandin precursors and ultimately inhibit platelet aggregation. It is administered orally once a day at variable doses for prevention of stroke and myocardial infarctions. It has rapid absorption and lasts for approximately 46 h. While there remains some uncertainty about the

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dose of aspirin with the best risk benefit ratio, the ATC meta-analysis indicated that lower doses of aspirin are at least as effective as higher doses. In fact, doses as low as 30 mg a day were efficacious in preventing strokes and TIA in the Dutch TIA trial [6]. Furthermore, the UK-TIA study also reported favorable results in 2435 patients taking aspirin (300 mg or 1200 mg) versus placebo after experiencing a minor stroke with the odds of having a vascular event, including a major stroke about 15% lower in both of the aspirin groups versus the placebo group [7]. Lastly, a meta regression analysis of 11 randomized, placebo-controlled trials that included 5228 patients treated with aspirin also concluded that aspirin doses from 50 to 1500 mg/day uniformly decreased the risk of stroke by approximately 15% (risk ratio: 0.85; 95% CI: 0.77–0.94) [8]. Prevailing expert consensus guidelines recommend aspirin administration (325 mg) in the first 24–48 h after an acute stroke based on several lines of evidence including a Cochrane review of 12 trials involving 43,041 participants, which showed that aspirin was linked to a significant decrease in recurrent stroke (a relative risk ratio of 12% (95% CI: 3–21), adjusted risk ratio (ARR) of 0.5% and number needed to treat (NNT) of 200 (over 2–4 weeks) [9].

Clopidogrel

Another widely used antiplatelet drug is clopidogrel. This medication is administered once per day at 75 mg. clopidogrel works by irreversibly blocking the P2Y₁₂ component of ADP receptors on platelets that ultimately prevents the activation of GPIIb/IIIa receptor complexes. GPIIb/IIIa aids in platelet activation through its receptor site for fibrinogen and von Willebrand factors.

The CAPRIE trial demonstrated a relative risk reduction in the occurrence of a major vascular event and favorable safety profile when compared with aspirin [10]. With the advantage shown by clopidogrel over aspirin in CAPRIE, differing mechanisms of platelet inhibition elicited by aspirin and clopidogrel, synergistic antiplatelet activity in animal models, and results from the CURE trial among patients with a recent non-ST segment elevation acute coronary syndromes showing a benefit of aspirin plus clopidogrel versus aspirin alone on recurrent vascular events at 1 year (risk of stroke, MI and vascular death by 20%; $p < 0.001$), the effect of this dual antiplatelet combination among recent stroke patients needed to be assessed [10,11].

In the MATCH study, 7599 patients with a recent ischemic stroke or TIA were given add-on low-dose aspirin (75 mg) versus placebo against a backdrop of clopidogrel (75 mg) therapy. At 1 year, clopidogrel with aspirin was no better than clopidogrel alone for

the composite end point of ischemic stroke, MI, vascular death or rehospitalization for ischemic events (event rate: 15.7 vs 16.7%; 6.4% relative risk reduction; $p =$ not significant) [12]. In the CHARISMA study, 15,603 patients with established atherothrombotic disease or with atherothrombotic risk factors received clopidogrel plus aspirin therapy versus aspirin alone. There was no overall significant benefit associated with addition of clopidogrel to aspirin in reducing the composite primary end point of MI, stroke, or death [13]. In the SPS3 study, 3020 patients with recent symptomatic lacunar infarcts were randomly assigned to treatment with 75 mg of clopidogrel or placebo daily with both groups receiving 325 mg of aspirin daily. There was no reduction in the risk of recurrent stroke between the clopidogrel plus aspirin group (125 strokes; rate, 2.5% per year) versus aspirin alone (138 strokes, 2.7% per year; hazard ratio: 0.92; 95% CI: 0.72–1.16) at the end of a 3.4-year follow-up, while the risk of major bleeding almost doubled in the group receiving clopidogrel [14]. Kwok *et al.* conducted a meta-analysis of randomized controlled trials that reported risk of secondary stroke or death with antiplatelet treatment in patients with lacunar stroke. They found that that dual antiplatelet therapy (including dipyridamole/aspirin and clopidogrel/aspirin) did not demonstrate a clear benefit over monotherapy for patients with lacunar strokes [15].

Many patients despite compliance with clopidogrel therapy continue to have atherothrombotic events, and this has raised the issue of the variation of clopidogrel metabolism and the development of genetic testing. Clopidogrel is a prodrug that requires conversion into an active metabolite. Approximately 85% of absorbed is hydrolyzed into its inactive metabolite and 15% into the active metabolite. In some patients there is a gene mutation resulting in an aberrant splice leading to the production of truncated, nonfunctioning protein and ultimately nonfunctioning drug. In other ways clopidogrel can be over metabolized and lead to increased transcriptional activity and enhanced platelet response to treatment. This can lead to an increase in bleeding events [16]. It is becoming more widely used when patients fail clopidogrel with suspected compliance to do genetic testing and ultimately, if needed, change in antiplatelet therapy.

Other (ADP) receptor antagonists

Other receptor antagonists include prasugrel and ticagrelor. These fall under platelet aggregation inhibition through ADP receptor inhibition. Both are similar to ticlopidine and clopidogrel. Prasugrel is more efficiently metabolized compared with clopidogrel and thus producing a higher and more predictable level of inhibition and is also irreversible [17]. Prasugrel was

compared with clopidogrel in the TRITON-TIMI 38 trial in patients with moderate to high risk acute coronary syndromes presumed to receive percutaneous coronary intervention after diagnostic angiography [18,19]. The primary end point in this study was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in which this was significantly reduced by prasugrel. Although, this study demonstrated that the major risk of bleeding was increased as well as life-threatening bleeding and fatal bleeding. There was also no clinical benefit or possibly harm with prasugrel in patients who qualified for prior stroke or TIA at baseline [11,17].

Cilostazol

Cilostazol is an inhibitor of phosphodiesterase III leading to cyclic AMP increase and irreversible inhibition of platelets. Its onset of action can take up to 2–4 weeks, or as long as 12 weeks for some patients, and its half-life is approximately 11–13 h. The recommended dosing is 100 mg administered twice per day for patients with TIA or noncardioembolic stroke. This drug is typically used for treatment of intermittent claudication, but has an unlabeled use for post coronary artery stenting after myocardial infarction and for transient ischemic attack.

Among patients with noncardioembolic ischemic stroke, the second CSPS 2 study examined the non-inferiority of cilostazol versus aspirin for prevention of stroke [20]. Patients (aged 20–79 years) who had had a stroke or TIA within the previous 26 weeks were administered cilostazol (100 mg twice daily; $n = 1379$) or aspirin (81 mg once daily; $n = 1378$) for 1–5 years. Stroke occurred at annual rates of 2.76% ($n = 82$) in the cilostazol group and 3.71% ($n = 119$) in the aspirin group (hazard ratio: 0.743; 95% CI: 0.564–0.981; $p = 0.0357$). Hemorrhagic complications were lower in the cilostazol arm of the study (0.77%; $n = 23$) than in the aspirin arm (1.78%; $n = 57$; 0.458, 0.296–0.711; $p = 0.0004$). Also, the CASISP trial examined the efficacy and safety of cilostazol versus aspirin for the long-term prevention of the recurrence of ischemic stroke. In CASISP, patients with an ischemic stroke in the preceding 6 months were administered cilostazol ($n = 360$) or aspirin ($n = 360$). The primary end point (ischemic stroke, hemorrhagic stroke or subarachnoid hemorrhage) was reported in 12 patients in the cilostazol group and in 20 patients in the aspirin group (estimated hazard ratio 0.62 [95% CI: 0.30–1.26; $p = 0.185$]). Cerebral hemorrhage events were more common in the aspirin group than in the cilostazol group (7 vs 1, $p = 0.034$) [21]. Since studies of cilostazol have largely been conducted among men of Asian race, and the drug carries the side effect of possible

leukopenia, the medication is not currently used in the USA for recurrent stroke prevention.

Aspirin plus dipyridamole

The aspirin/extended release dipyridamole drug combination (ASA+ER-DP) is a dual medication regimen composed of 25 mg of aspirin and 200 mg of extended release dipyridamole administered twice per day. Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes. The half-life is approximately 10–12 h and time to peak is 2–2.5 h.

A secondary stroke prevention trial, ESPS-2, used dipyridamole and acetylsalicylic acid (ASA) to help determine how effective dipyridamole and aspirin are alone, if the combination of treatments is superior to each individual agent, and if doses lower than 50 mg of aspirin eliminate the propensity to induce bleeding. Ultimately, the 24-month stroke rate was 13.2% in dipyridamole alone, 12.9% in aspirin alone, 9.9% in ASA+ER-DP and 15.8% in placebo. Stroke risk was significantly reduced by 37% with ASA+ER-DP compared with 18.1% with aspirin alone and 16.3% with dipyridamole alone. The relative risk reduction was 22% in this study [22].

Another study, ESPRIT, compared ASA+ER-DP with just aspirin alone. In total, 13% of study patients demonstrated events such as death from vascular causes, nonfatal stroke, nonfatal myocardial infarction or major bleeding in dual therapy as compared with aspirin monotherapy [23]. This trial also demonstrated that dual therapy is superior at preventing vascular events as compared with aspirin alone. Unfortunately, the permanent discontinuation of ASA+ER-DP happened more frequently due to the secondary side effects, most commonly headaches. Gastrointestinal bleeding was more common in the aspirin groups than the placebo or dipyridamole monotherapy groups. Ultimately ASA+ER-DP was proven to be a promising medication in preventing secondary stroke with dual antiplatelet components. Although, patients and practitioners need to keep in mind that side effects can affect compliance and ultimately efficacy.

The PROFESS trial compared ASA+ER-DP to clopidogrel and demonstrated that there was no significant difference in recurrent stroke risk. Major hemorrhagic events occurred more frequently in patients on ASA+ER-DP but there was no difference in the frequency of death [24]. It seemed that patients were more likely to discontinue ASA+ER-DP due to secondary side effects when compared with clopidogrel.

PAR-1 antagonists

Vorapaxar is an agent that antagonizes thrombin-mediated activation of the PAR-1 on platelets. The

oral dosing is usually 2.08 mg once daily in combination with aspirin and/or clopidogrel. Vorapaxar reduced the global risk of cardiovascular death, MI or stroke by 13% while increasing the risk of moderate or severe bleeding [16]. Vorapaxar's most robust benefit tends to be seen among myocardial infarction patients with or without prior history of stroke and low risk of bleeding. In fact, a post-hoc analysis of the main study among patients with prior ischemic strokes demonstrated that vorapaxar did not reduce the rate of major cardiovascular events but rather increased the risk of major bleeding including intracerebral hemorrhage [25]. Also, there was no clear benefit within clinically relevant groups defined by the type and timing of prior ischemic stroke or background antiplatelet therapy.

Other key systematic reviews & meta-analyses

Wong *et al.* evaluated the efficacy and safety of dual versus single antiplatelet therapy in the secondary prevention of stroke [26]. They included 14 randomized, controlled trials including 9012 patients with therapy initiated within 3 days after an acute non-cardioembolic ischemic stroke or TIA. They found that dual antiplatelet therapy significantly reduced risk of stroke recurrence (risk ratio: 0.69; 95% CI: 0.60–0.80; $p < 0.001$) and the composite outcome of stroke, TIA, acute coronary syndrome, and all death (risk ratio: 0.71; 95% CI: 0.63–0.81; $p < 0.001$) when compared with monotherapy. Risk of major bleeding was increased with dual therapy, but not significantly (risk ratio: 1.35; 95% CI: 0.70–2.59; $p = 0.37$). All of the studies reviewed comprised aspirin in combination with dipyridamole or clopidogrel (except for one study which administered cilostazol). Seven of the included studies were double-blind.

Lee and colleagues evaluated the risk-benefit profile of long-term (greater than 1 year) dual versus mono antiplatelet therapy among patients with ischemic stroke [27]. The seven studies that were included in the analysis were randomized studies ($n = 39,574$) that mainly examined recurrent stroke and intracranial hemorrhage (ICH) as outcome measures. Risk of recurrent stroke risk did not differ between patients receiving dual therapy versus those receiving aspirin alone (relative risk: 0.89; 95% CI: 0.78–1.01) or clopidogrel (relative risk: 1.01; 95% CI: 0.93–1.08). The risk for ICH also did not differ between the groups. Those patients that received dual therapy had a relative risk of 0.99 (95% CI: 0.70–1.42) versus those taking aspirin alone; while the relative risk of ICH in patients taking dual therapy versus clopidogrel was greater (relative risk: 1.46; 95% CI: 1.17–1.82) [28].

Cost-effectiveness

Taking the cost of stroke management and of medications for secondary prevention of stroke into account can be just as important as side effects and treatment efficacy. If a patient cannot afford the medication, then they are less likely to invest in the medication and their health. Estimated costs of stroke related treatment include physician/professional visits, hospitalization and nursing home/home healthcare [29]. On average, aspirin costs approximately US\$12.75 for 81 mg over the counter, but can range from US\$3 up to US\$16 at various drug stores. Clopidogrel is by far the most expensive, but over the years has become more widely available and affordable. The average cost of antiplatelet medications in the USA in the year 2011 was: aspirin (81 mg) = US\$1/month, clopidogrel (75 mg) = US\$254/month, aspirin plus dipyridamole (25 mg/200 mg) = US\$247/month, prasugrel (10 mg) = US\$222/month and ticlopidine (250 mg) = US\$64/month [30,31].

Several studies have looked at the cost-effectiveness when comparing medications and their ability to reduce secondary strokes, aspirin and aspirin plus dipyridamole are both cost effective when compared with placebos [3]. Other analyses have indicated that aspirin plus dipyridamole offers a cost effective alternative to aspirin alone [23]. Aspirin plus dipyridamole has a cost-per-stroke averted ratio of US\$28,472 (therapies are thought to be cost effective if the cost-per-health effect ratio is less than US\$50,000). Other studies demonstrated that even dipyridamole alone is cost effective for patients who are intolerant to aspirin [12]. Although some analyses have indicated that the cost-effectiveness of aspirin and aspirin plus dipyridamole is similar, it also indicates that patients would see better clinical outcomes if they are willing to pay more for dual therapy treatments [32]. Surprisingly, clopidogrel was not found to be cost effective when compared with aspirin alone, even in the second year of therapy [33]. Many of these studies compared clopidogrel when a cheaper generic drug was not widely available to physicians and/or patients. So when the cheaper generic form of clopidogrel emerged on the market, a reanalysis of cost-effectiveness was performed and clopidogrel was shown to be the most cost effective when comparing aspirin plus dipyridamole and aspirin alone [27].

In addition to associated costs and primary efficacy of treatment, the risk of side effects must also be considered when determining the best medications for treatment. Side effects such as intracranial hemorrhage or gastrointestinal hemorrhage are associated with a higher risk of death and incurs a greater loss of health over a lifetime [27]. As such, it may be assumed that there will be a higher healthcare cost and decreased

cost-effectiveness when side effects are considered. clopidogrel has a lower risk of gastrointestinal bleeding and aspirin has a subsequent higher risk of this complication [34]. Given this information, it may be efficacious to use clopidogrel for certain patients who have failed aspirin treatments, especially now that it is generic, even though prior studies (before clopidogrel became generic) deemed clopidogrel to not be cost effective [35].

Conclusion

Stroke is a major cost within our healthcare system today, an expense, which is expected to substantially soar over the next 20 years [29]. Patients with prior stroke are at significant risk of experiencing a recurrent event, and a subsequent stroke carries a high risk of death and disability. Moreover, ongoing cross-risk after ischemic stroke for ischemic complications in other vascular beds including coronary and peripheral, reinforces the importance of long-term control of the underlying atherothrombotic disease process [36], and underscores the notion that clinical and cost-effectiveness of these therapeutic agents after stroke need to be viewed in the light of broader clinical consequences beyond just recurrent stroke. Also, realizing that risk factor modification is likely far more important than secondary prevention of stroke.

Due to the key role of platelets in atherosclerotic plaque development and progression, antiplatelet therapy with aspirin, clopidogrel, the combination of aspirin plus clopidogrel, and the combination of aspirin plus ER dipyridamole have been shown in numerous clinical trials to be both effective and safe in the secondary prevention of adverse events in patients with cerebrovascular disease. Based on these trial data, antiplatelet therapy is a critical component of secondary stroke prevention guidelines and the aforementioned drugs are all recommended as first-line treatment options after an index ischemic stroke or TIA [3]. However, dual antiplatelet therapy remains a controversial issue, and at the very least data thus far, suggests that such a regimen needs to be initiated very early, of relatively short duration, and only in a very select group of patients. Indeed, the best therapy should be individualized to the patient, taking into account the underlying pathophysiologic mechanism and co-morbidities. However, to optimize sustained antiplatelet therapy use, clinicians should not only be aware of any potential adverse effects and cost limitations their patients might experience, but also be willing to openly discuss these issues and their possible solutions with patients.

Availability of proven antiplatelet medications for secondary stroke prevention and the costs associated with them continue to evolve. Long term costs of

these medications for both patients and their carers are not well defined and impact on quality of life has hitherto not been properly established. These are two key areas that warrant future investigation. Nonetheless, several new classes of antiplatelet agents continue to be tested for superior efficacy to standard care in clinical trials. In addition, costs and reimbursement levels of the various antiplatelet treatment options are changing: established drugs like clopidogrel which were once expensive, are now generic, thereby enhancing their accessibility for patients with affordability problems and resistance to the effects of aspirin. Of note, emerging data suggest that eliminating co-payments for relatively cheap, frequently prescribed drugs for preventing vascular events led to better medication adherence and lowered the occurrence of subsequent vascular events, while greatly decreasing costs for patients and not boosting the insurer's healthcare costs [37].

Finally, when fully implemented, the US Affordable Care Act (ACA) is expected to broaden private and public insurance coverage to an additional 32 million Americans (95% of the non-elderly population) by 2019 [37]. The ACA emphasizes the provision of evidence-based clinical preventive services and especially requires that most private health plans and Medicare provide first-dollar coverage of evidence-based preventive services. These efforts could potentially have a substantive and positive impact on the timely and sustained use of antiplatelet drugs for secondary stroke prevention, thereby possibly lessening the clinical and financial toll of stroke on individuals and society.

Future perspective

Although stroke has declined from the third to the fifth leading cause of death in the USA, the burden of stroke remains significant especially since it remains the leading cause of adult disability [2]. As such, efforts aimed at preventing stroke occurrence will remain a top priority, and exploring avenues to further mitigate the thrombotic causal underpinnings of stroke by using more potent and precise drug regimens will be a major area of emphasis. Already, ongoing trials are examining the roles of brief courses of dual antiplatelet therapy with POINT [38], triple therapies with TARDIS [39], or novel antiplatelet agents with the SOCRATES [40] in the early setting after a minor ischemic stroke or TIA. Interest continues to rise in evaluating the differential impact of pharmacogenomics in the treatment of patients with symptomatic vascular disease [41]. Concerns about how to pay for these expected therapeutic advancements will inevitably arise, and so it will be helpful for providers, policy makers and payers, to have corresponding information about the cost-effectiveness of these future treatments in real world settings.

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Executive summary**Role in secondary stroke prevention**

- Symptomatic atherothrombosis leads to the majority of ischemic strokes, thereby making optimal use of antiplatelet drugs, a premier therapeutic goal in secondary stroke prevention.

First-line drug options

- Aspirin, clopidogrel, and aspirin/extended release dipyridamole drug combination remain the first-line antiplatelet drug options following the occurrence of an index ischemic stroke or transient ischemic attack.

Role of dual antiplatelet treatment

- Adding clopidogrel to aspirin is not routinely recommended for long-term secondary stroke prevention.
- When therapy is initiated within 3 days after an acute noncardioembolic ischemic stroke or transient ischemic attack, dual antiplatelet therapy may significantly reduce risk of stroke recurrence when compared with monotherapy.
- Dual antiplatelet therapy does not seem to be efficacious for long-term stroke prevention among patients with lacunar strokes.

Impact of cost on adherence & outcomes

- As a policy strategy, eliminating co-payments for commonly used medications for preventing cardiovascular events might lead to enhanced medication adherence and reduced the rate of vascular events.

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