PharmaNote

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Single Maintenance and Reliever Therapy (SMART) for Asthma Control

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About 300 million people had been diagnosed for asthma in 2004, with expectations to reach 400 million patients in 2025.[1] Unlike COPD, asthma is a reversible respiratory inflammation that is typically diagnosed and present in early ages. Pathology of asthma can be simply explained as hyperresponsiveness of the airway resulting in limited lung function and infiltration of neutrophils, eosinophils and lymphocytes.[1-2] Environmental factors, such as smoking, cold, allergens, viral infection, and exercise and stress can trigger symptoms of asthma.[2] The clinical presentation of asthma, which can present as wheezing, coughing, or shortness of breath is subjective and not specific to each individual with the diagnosis of asthma.[2] Spirometry is a common diagnostic testing to demonstrate obstruction and reversibility in patients aged of 5 and over by measuring forced expiratory volume in 1 second (FEV_1).[2] The concept of Single Maintenance and Reliever Therapy (SMART) has been studied over decades in European countries to demonstrate its efficacy and safety. Therefore, the objective of this article is to review and summarize the evidences of SMART therapy in asthma patients.

Severity of Asthma

Once asthma is diagnosed, its severity can be classified into two domains: impairment and risk. Impairment is symptoms and limitation assessment, while risk is either exacerbation or loss of lung function over time.[2] Altogether, asthma can be divided into intermittent or persistent based on impairment and risk assessment (**Table 1**).

IN THIS ISSUE

Current Management of Asthma

Even if reduction of lung function in asthma is reversible, the mainstay treatment goals are to reduce impairment (i.e., prevent chronic symptoms, maintain normal pulmonary function) and risk (i.e., prevent recurrence of exacerbation, minimize ED visits).[2] During asthma attack, the patient's airway is surrounded with inflammatory cells, cytokines and secretion, which can cause bronchoconstriction and limited airway. Therefore, there are many pharmacological options used in asthma targeting smooth muscle relaxation in the airway or inflammatory suppression. These options include beta2-agonist, anticholinergics, inhaled corticosteroids, leukotriene antagonists, mast-cell stabilizers, and IgE mediators. One of the most common controllers is inhaled corticosteroids (ICS), which reduces airway inflammation with broad inhibition of inflammatory processes including suppression of cytokines production and eosinophils as well as inflammatory mediators. Meanwhile, beta2-agonists, the most common bronchodilator, act on smooth muscle cells locally in the airway by increasing cAMP leading to its bronchodilation effect,[3-5] but 10-15% of beta2 receptors are also locates on cardiac muscle cells which leads to the tachycardia side effect.[2] As shown in **Table 2**,[3-6] the classification of beta2-agonists is based on their duration of action: short-acting and long-acting. The short-acting beta2-agonist (SABA), such as albuterol[3] and levoalbuterol[4] have fast onset and offset, while the long-acting beta2-agonits (LABA), such as formoterol[5] and salmeterol[6] have either slow or fast onset but long duration. Regardless its bronchodilation effect, the long-acting agents are not approved by FDA as rescue inhaler, but as a controller medication[5-6]. Thus, only short-acting (SABA) has been approved as rescue inhaler during asthma exacerbations. According to the NHLBI guideline of asthma,[2] stepwise therapy approach has been recommended based on severity and control (**Table 3**). Monotherapy of using SABA is only recommended in intermittent asthma. In contrast, in persistent asthma, controller in addition to rescue inhaler for exacerbation is the mainstay treatment. In addition to controlled asthma, the guideline[2] also strongly recommended SABA as reliever inhaler for every asthma patient. However, formoterol is an exceptional LABA which has fast onset comparable to albuterol and has longer duration. Some patients can experience fast onset of bronchodilator effect from formoterol, which may mislead them to understand that formoterol is reliever causing noncompliance issue.

In 2007, the cost of asthma was $56 billion in the United States, increasing 6% over 5 years period.[7] Majority of the cost were derived from medication and hospitalization costs.[7] To prevent re-admission to hospital or ED and decrease the cost, patients' compliance can play a major role in huge cost saving. Despite receiving the proper treatment, underuse or erratic use of medications can be harmful to patient's health. Patients might not receive its utmost benefits if they do not agree on or understand

Table 1 | Severity of asthma classification[2]

Component of severity		Intermittent	Mild	Persistent Moderate	Persistent Severe
Impairment	Symptoms	≤2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakening	None	1-2 times/month	3-4 times/month	> 1 time/week
	Number of SABA used (Not prevention of EIB)	≤2 days/week	> 2 days/week but not daily	Daily	Several times/ week
	Interference with normal activity	None	Minor	Some	Significant
Risk	Exacerbation[a] requiring oral steroids	0-1 per year	≥2 exacerbations/ 6months + oral steroids OR ≥4 wheezing/ year lasting >1 day + risk factors for persistent asthma		
Treatment		Step1	Step 2	Step 3 (consider short course of oral corticoster-oids)	Step 4-5 (consider short course of oral corticoster-oids)

[a]Exacerbation may be related to FEV_1 and its severity and interval should be taken into consideration.
EIB = exercise induce asthma; **SABA** = short acting beta2 agonist

the treatment plan. Besides patient factors, medication factors were also known to be associated with poor adherence in asthma, including difficulties with inhaler devices, medication cost, side effects, and distant pharmacy.[8] To improve patient's compliance, adjusting environmental and psychological complexity is one of the simplest strategy that providers can do to simplify the regimen as much as possible.[8] With the concept of using Single Maintenance and Reliever Therapy (SMART), the patient may be able to carry only one inhaler to minimize medications cost, improve patient compliance and minimize complexity.[9]

SMART Therapy

In 2005, the concept of using Single Maintenance and Reliever Therapy (SMART) has been first studied in European countries based on the assumption that the combination of fast onset LABA and ICS can be used as both controller and rescue inhaler, leading to improved compliance and lower cost.[9] As shown in **Table 2**, formoterol and budesonide (Symbicort®) is the combination of an ICS and LABA currently FDA approved for long-term asthma maintenance treatment in patients aged 12 and over.[10] However, even if it is not a common practice to use Symbicort® as rescue inhaler in the United State, some studies performed in European countries have demonstrated the efficacy and safety of this medication used in SMART therapy. The evidence of those studies will be summarized (**Table 4**) and discussed in the following section of this article.

Clinical Trials

Patel M, et al[11] studied the efficacy of SMART therapy in a 24 -week randomized controlled trial, which included 303 participants with recent asthma exacerbation from four primary practices and one hospital in New Zealand. Exclusion criteria were a diagnosis of COPD or smoking ³ 10 pack/year. They compared the group of budesonide/formoterol 200/6 (units) two inhalations BID plus one extra actuation of budesonide/formoterol as needed (SMART) vs. budesonide/formoterol 200/6 two inhalations BID plus one or two salbutamol as needed (traditional group). The primary endpoint was the proportion of patients with at least one high-use episode of beta-agonist, while the secondary endpoints included number of days required high-use of beta-agonist and number of exacerbation. The results showed that SMART therapy did not significantly decrease number of patients with at least one high-use episode of beta2-agonist compared to the group using traditional (salbutamol) rescue inhaler (RR 1.24, 95% CI 0.99-1.56; p = 0.058). However, SMART group had significantly fewer days requiring SABA than traditional group (5.1 vs 8.9 days; p=0.01)[11] and significantly fewer number of exacerbations compared to traditional treatment (35 vs 66; p=0.004).

Hozawa S et al[12] conducted a randomized study measuring reduction of fractional exhaled nitric oxide (FeNO), which indicates airway inflammation, over 8 weeks. The study included a total of 30 participants aged 20 or over diagnosed with asthma, treated with moderate ICS for 12 weeks prior, FeNO > 35 ppb and required SABA use 2-6 times per week. The subjects were excluded if they had respiratory infections, positive tuberculosis, used beta-blocker, used oral corticosteroid in previous 8 weeks or had allergic rhinitis. All participants were randomly assigned to one of the two groups: the SMART arm given Symbicort® 160/4.5 (units) 2 inhalations BID plus as needed and the control given fluticasone/salmeterol 250/50 one inhalation BID plus procaterol as needed. The results showed that the SMART group had significant reductions in FeNO of -13.13 ppb vs - 8.20 ppb (p = 0.001) than control, respectively. However, pulmonary function test (PFT) were not statistically different between the groups with the FEV_1 at 8 weeks measured at 100% and 97.6% in SMART and control arms, respectively (p=0.397).

A multi-center open-labeled study in Asian population (SMARTASIA)[13] looked at the efficacy and safety of SMART therapy across Asia over 12-weeks. This study included 1,022 patients, aged over 18 with partially controlled and/or uncon-

Table 2 | Pharmacokinetics comparison of beta2-agonist agents[3-6]

	SABA		LABA	
Pharmacokinetics	**Albuterol**	**Levalbuterol**	**Formoterol**	**Salmeterol**
Onset (minutes)	5-15 minutes	4.5 -10 minutes	5-15 minutes	14 minutes
Duration (hours)	3-4 hours	3-6 hours	10 hours	12 hours
Excretion	Renal	Renal	Renal, Fecal	Renal, Fecal
Common available product	Ventolin®, Proair®, Proventil®	Xopenex HFA®	Symbicort® (budesonide and formoterol)	Advair® (fluticasone and salmeterol)

trolled persistent asthma previously on treatment for 4 weeks prior to the study. Patients were excluded if they had one of the following: COPD, previous treated with budesonide/formoterol, current use beta-blocker, on ICS within 30 days previous screening, or smoking > 10 packs/year. Those who were eligible underwent a 2-week run-in period with their existing asthma medications and then switched to Symbicort®160/4.5 units one inhalation twice daily plus as needed. The primary outcome was the difference in Asthma Control Questionnaire (ACQ-5) score from baseline. The findings showed that SMART strategy can clinically improve ACQ-5 score by 0.58 ± 0.93 (95% CI, 0.51-0.64, p < 0.0001) as well as improve in symptom-free days (23.89 ± 34.62% (95% CI, 21.56 to 26.21%). Not only was improvement found subjectively by participants, the study also found significant improvement in FEV_1 post-initiation (p<0.0001). About 1.5% of the patients in this study discontinued the medication because of adverse events with 19.8% of patients experiencing nasopharyngitis and upper respiratory tract infection. Serious adverse events were uncommon, two events of serious adverse events were associated with myocardial infraction, resulting in death; however, both deaths were not considered related to budesonide/formoterol.

Riemersma RA et al[14] conducted randomized controlled trial in 102 adult patients with mild-to-moderate stable asthma from 32 general primacy practices with 1 year follow-up. Eligible subjects were randomly assigned to either SMART group given budesonide/formoterol 80/4.5 (units) two inhalations once daily plus as needed or usual care group given treatment following Global Initiative for Asthma (GINA) guideline, including patients treated with Symbicort® as controller and SABA as needed. The primary outcome was improvement in hyperresponsive airway. The results showed that SMART did not have additional benefit over usual care, especially in bronchial hyperresponsiveness, and no difference in number of days with mild or severe exacerbation, 16.4 days/year vs. 16.8 days/year (p=0.08), respectively. Despite lack of significant improvement in percent predicted FEV_1 between these groups (p=0.58), SMART significantly improved the peak expiratory flow (PEF) in morning and evening (RR 23.1, 95% CI,11.0 to 35.2; P= 0.0003 and 16.5, 95% CI, 5.0 to 28.0; P=0.005, respectively). Additionally, with equivalent effectiveness, dose of steroid exposure was lower in SMART group compared with usual care (P<0.0001) in mild-moderate persistent asthma secondary to lower dose of budesonide/formoterol used in the study.

Smokers

Unlike non-smokers, asthmatic smoker commonly has relatively poorer lung function and less reversibility with beta-agonist.[15] Therefore, these patients are more likely to have more days per week with symptoms and higher number with rescue inhaler use. Pilcher J et al[16] undertook subgroup analysis from a randomized trial of 303 high risk asthmatic adults comparing between smokers and former smokers. The primary outcome was number of participant with at least one severe exacerbation defined as using systemic steroids for at least 3 days or visit ED or hospitalized due to systemic steroids requirement. The results showed that SMART therapy in smokers is associated with fewer acute exacerbation compared to non-smokers (OR 0.45; 95%CI, 0.26-0.77; P=0.004), with no significance in composite systemic corticosteroids exposure (milligram of prednisone equivalent per year). Smoking status, however, was associated with higher number of days overusing rescue inhaler, defined as > 16 actuations of albuterol and > 8 additional actuations of budesonide/formoterol, compared with non-smokers (OR 3.78; 95% CI, 2.00-7.13; P<0.001). Interestingly, SMART therapy showed significantly lower number of days of zero actuation for maintenance therapy (number of non-adherence days) than standard treatment group (OR 0.73; 95%CI, 0.56-0.96, P=0.021) in this study.

EuroSMART study[15], a randomized, open-labeled, 6-month study, enrolled uncontrolled moderate-to-severe asthmatics to evaluate response to SMART in smokers and non-smokers. Participants enrolled in this study must not be older than 40 years and smoking history less than 10 pack/year for smokers. Former smokers or those with COPD were excluded. Overall, 886 smok-

Table 3 | Stepwise management in asthma[2]

	Preferred	Alternative
Step 1	SABA PRN	
Step 2	Low-dose ICS	Cromolyn, LTRA, nedocromil or theophyliine
Step 3	Low-dose ICS + LABA OR Medium-dose ICS	Lose-dose ICS + either LTRA, theophylline or zileuton
Step 4	Medium-dose ICS + LABA	Medium-dose ICS + either LTRA, theophylline or zileuton
Step 5	High-dose ICS + LABA	Omalizumab for allergies
Step 6	High-dose ICS + LABA + oral corticosteroid	Omalizumab for allergies

Adapted from NHLBL EPR-3, 2007.
ICS = inhaled corticosteroid; **LABA** = long-acting beta2-agonist; **LTRA** = leukotriene receptor antagonist; **SABA** = short-acting beta2-agonist

Table 4 | Summary of the evidence for SMART therapy vs usual care studies

Study / Author	Study design	N	Primary endpoint (SMART vs Usual Care)	Second endpoint (SMART vs. Usual Care)
Patel M et al[11]	24-week RCT	303	No significant benefit found in number of patients with at least one high-use episode of beta2-agonist (p=0.058)	Fewer days required SABA (p=0.01) Fewer number of exacerbations (p=0.004)
Hozawa S et al[12]	8-week RCT	30	Significant reductions in FeNO (p=0.001)	No significant difference in PFT (p=0.037)
SMARTASIA[13]	12-week RCT	1,022	Clinically improve ACQ-5 score (p<0.0001) Improved number of symptom-free days	Significant improvement in FEV_1 (p<0.0001)
Riemersma RA et al[14]	1-year RCT	102	No benefit in bronchial Hyperresponsiveness; No significant difference in number of moderate or severe exacerbation (p=0.08)	Significantly improve morning and evening PEF (p=0.0003 and p=0.005, respectively)
Smokers				
Pilcher J et al[16]	Subgroup analysis of 24-week RCT	303	Fewer number of acute exacerbation (p=0.004)	Higher number of overused rescue inhaler days in smoker (p<0.001)
EuroSMART[15]	6-month open-labeled uncontrolled trial	1,772	No significant difference in time to the first exacerbation	No significance in daily and night time symptoms
Pediatrics				
Bisgaard H et al[17]	1-year RCT	388	Significant lower rate of exacerbation (p<0.05) Prolonged time to first exacerbation (p<0.05)	Significant higher growth rate in SMART group

ers and 886 non-smokers were eligible and randomly assigned to one of the two groups: budesonide/fomorterol 160/4.5 one inhalation twice daily plus as needed (1 x 2) or budesonide/formoterol 160/4.5 two inhalations twice daily plus as needed (2 x 2). The primary outcome with 2x2 regimen showed significant reduction in rescue inhaler used (p=0.004). Unsurprisingly, the smokers who treated with 2x2 compared 1x2 showed significant reduction in exacerbation yearly rate of 9.6% and 19.5%, respectively (P=0.0121). The evidences showed that Symbicort® SMART had benefits and comparable safety in smokers; however, the evidences of such is inconclusive and needs more evidences.

Pediatrics

The concept of the SMART regimen has been extended to pediatrics. Bisgaard H et al[17] studied SMART in children aged 4 to 11 years with persistent asthma and at least one exacerbation in last 12 months. Eligible children from 41 centers in 12 countries were randomized in one of these groups: fixed-dose budesonide/formoterol 80/4.5 daily plus as needed (SMART), fixed-dose budesonide plus terbutaline as needed (BUD) and fixed-combination budesonide/formoterol plus terbutaline as needed (BUD/FORM). The results showed that the SMART significantly had lower rate of exacerbation (14%) compared with 38% in BUD and 26% in BUD/FORM (P<0.05) and prolonged time to first exacerbation (p<0.05). Risk of having an exacerbation simultaneously was 66% lower in SMART compared with fixed-dose combination and 51% lower compared with fixed-dose budesonide. Surprisingly, the safety outcome on growth rate showed that the patients receiving the SMART grew significant more than two other groups by 0.9 to 1.0 cm.

In 2013, the Cochrane Library review[18] had included four studies both adults and children of 9,130 patients compared SMART therapy with traditional therapy (Symbicort® plus SABA). They found SMART showed lower number of hospitalization or ED visit for exacerbation (OR 0.72; CI 0.57-0.90)[2], and less oral steroids requirement (OR 0.75; CI 0.65-0.87). Interestingly, benefits on PEF, nocturnal awakening and quality of life remain controversial. The side effects of SMART were unclear.

Discussion

In 2011, Braido F et al[19] gathered the evidences from thirteen trials given 21,095 patients from availability data of SMART to explore the availability data of SMART towards the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) criteria. Based on these studies, Symbicort® SMART could have benefits on reduction of exacerbation rate and prolonged time to first severe exacerbation in both adults and children compared to traditional treatment; however, the data on pulmonary function test and spirometry are inconsistent across

the studies as well as the safety data in Symbicort® SMART. In contrast, the benefit of SMART reducing severe exacerbation in smokers remains controversial.

Upon patients' perspectives, the treatment that gives immediate relief is essential and favorable, while the treatment used during controlled period is concerned as unnecessary medication.[8] Despite sufficient treatment, asthmatic patients preferred simple treatment regimen as well as fewer drugs or inhalers.[8] Therefore, the SMART implied lower medication's cost and more simplicity of regimen which may possibly be a preferable treatment option as well as providing potential economic benefits. Wickstrom J et al[20] conducted a cost-effective study from five randomized controlled trials found that the SMART regimen had significant better clinical effectiveness, defined as number of severe exacerbation per patient per year as well as lower health-care cost than usual treatment. Meanwhile, the societal prospective including direct or indirect costs in the SMART regimen was least expensive across the studies, except for one study which studied compared three regimens: budesonide/formoterol plus terbutaline as needed, budesonide/formoterol plus formoterol as needed and budesonide/formoterol plus additional dose as needed. In the study, budesonide/formoterol as maintenance and reliever showed more effective, but also slightly more cost than the other two. However, since Symbicort® is not approved as rescue inhaler in the United States, most of the studies are done in European or Asian countries. Lack of cost-effectiveness data in the United State might limit generalizability and the results should be carefully interpreted on current evidences.

Conclusion

In conclusion, Single Maintenance and Reliever Therapy (SMART) has been shown to extend the time to first exacerbation and improve number of symptom-free days with comparable safety profile, although the benefit on pulmonary function was inconclusive in many studies. Based on current available evidence, the data on economic assessment showed significant direct cost reduction, but no cost saving in overall cost of treatment. Furthermore, most data analysis were done in European or Asian countries, where there are health-system and geographical differences. As of today, Symbicort SMART® has not been approved by FDA as rescue inhaler and none of the global or local guidelines have recommended the SMART regimen. Currently, a Clinical Study to Evaluate Symbicort Turbuhaler Used 'as needed' in Adults and Adolescents With Asthma (SYGMA trial)[21], a 52-week RCT phase III trial to evaluate efficacy and safety of budesonide/formoterol as needed in mild asthmatics is in process. The study is conducted in 18 countries in SYGMA trial 1 and 25 countries in SYGMA 2 trial accordingly. The primary outcomes include symptom-related parameters, such as rate of controlled symptom days and rate of exacerbation. The future results will demonstrate if Symbicort® SMART is superior than traditional recommendation.

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A Review of Antiplatelet Therapy in Secondary Stroke Prophylaxis

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Ischemic stroke generally involves the occlusion of a central artery due to atherosclerosis. Eventually, this occlusion could potentially lead to the subsequent formation of an emboli. Ischemic stroke is the most common subtype, occurring in about 88% of patients with stroke. Risk factors for ischemic stroke include age, sex, ethnicity, family history, and prior stroke/transient ischemic attack (TIA). According to the American Heart Association (AHA), approximately 795,000 people have a stroke in the United States each year. Ischemic stroke is the fifth most common cause of death in the United States and contributes to nearly 130,000 deaths each year, which translates to roughly one death for every 20 people in the United States.[1] According to the Centers of Disease Control and Prevention (CDC), African-American women are twice as likely to suffer strokes at a younger age than Caucasian women due to hypertension starting at a younger age and due to having higher rates of obesity and diabetes than other ethnicities.[2]

Since ischemic stroke can adversely affect the patients we treat, antiplatelet therapy for use in secondary prevention in non-cardiogenic stroke is pivotal. Current antiplatelet therapies include aspirin, clopidogrel, and aspirin/dipyridamole.[3] Recently, newer studies have examined the efficacy of other antiplatelet agents, such as ticagrelor and cilostazol in secondary stroke prophylaxis.[4,5] The purpose of this article is to review the current literature surrounding the efficacy of antiplatelet therapies in secondary stroke prevention and determine a hierarchy of these therapies in the prevention of noncardiogenic stroke.

Current Guidelines

As summarized in **Table 1**, the 2014 AHA/ASA guidelines currently recommends the use of aspirin 50 to 325 mg daily for monotherapy or extended-release aspirin/dipyridamole 25/200 mg (Aggrenox®) twice daily as the initial therapy for the secondary prevention of ischemic stroke or TIA. The guidelines also state that aspirin 50 to 100 mg has equal efficacy to aspirin 325 mg in the setting of secondary prevention in ischemic stroke and is safer than the 325 mg in regards to major bleeds. Although clopidogrel 75 mg daily is not recommended as one of the initial therapies for the secondary prevention of ischemic stroke or TIA, it is considered a reasonable alternative to the two aforementioned therapies, especially if a patient has an allergy to aspirin. These three therapy options, on average, reduce the relative risk of stroke, MI, or death by approximately 22%. The use of dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel could be considered for up to 21 days following a stroke. The use of DAPT after 21 days is not recommended due to the risk of hemorrhage when compared with the use of either aspirin or clopidogrel monotherapy.[4]

Current Therapeutic Options

Aspirin

The most common agent used for the secondary prevention of ischemic stroke is aspirin. Aspirin irreversibly inhibits COX-1 and COX-2; however, the antiplatelet effects for aspirin occur through inhibition of COX-1. Platelet aggregation occurs via thromboxane A2 synthesis, which occurs via activation of COX-1. The onset of action occurs within 1 hour and the duration of the antiplatelet effects lasts the entire lifespan of platelets, which is approximately 10 days. Aspirin has a half-life of about 15-20 minutes in adults and is metabolized through hepatic conjugation in the liver. Bleeding risk with aspirin is increased when it is combined with other antithrombotics, such as warfarin, apixaban, and enoxaparin, as well as other NSAIDS. Certain herbals, such as garlic, celery, and ginger, have antiplatelet effects and can enhance the antiplatelet effects of aspirin, so any type of bleeding should be closely monitored when herbal medications are used in conjunction with aspirin.[6]

To determine which dose of aspirin has the most optimal effect in treating patients for secondary prevention of ischemic stroke, a metaregression analysis[7] evaluated the dose-response effect of aspirin on secondary stroke prevention. The analysis included randomized, placebo controlled trials to determine whether the aspirin dose-response relationship for the risk of a recurrent stroke in patients with a previous history of TIA or ischemic stroke. Eleven randomized trials with a total of 5,228 patients who recently had a TIA or stroke were included in the aspirin group for the metaregression analysis while 4,401 patients were randomized to placebo. The results of the metaregression analysis showed that the slope of the aspirin dose-response was virtually flat from an aspirin dose of 50 mg to 1500 mg ($p=0.49$) and that these range of doses decreased the risk of stroke by approximately 15% when compared with patients on placebo (RR 0.85, 95% CI 0.77-0.94). As a result, this metaregression analysis was able to conclude that aspirin 50 mg has the same efficacy as aspirin 1500 mg in reducing the reoccurrence of stroke in patients with a previous history of TIA or ischemic stroke.

Initiation of aspirin after a patient has had an episode of TIA or ischemic stroke is pivotal. In 2016, a pooled analysis evaluated 12 randomized trials that involved over 15,000 patients to compare the risk of stroke reoccurrence among patients taking aspirin with those patients taking placebo at time intervals of ≤6 weeks, 6 to 12 weeks, and ≥12 weeks.[8] Trials for this meta-analysis were eligible if patients with TIA or ischemic stroke were randomized to receive aspirin at any strength or a placebo/anticoagulant in the secondary prevention of stroke or other vascular events. This trial sought to include individual patient data on the severity of stroke at entry and on time to first recurrent stroke during the trial period. The results of the study showed that aspirin reduced the 6-week risk of stroke reoccurrence by 60% when compared with placebo (0.99% in the aspirin group vs 2.4% in the placebo group;

Table 1 | Current Antiplatelet Therapies Used for the Secondary Prevention of Ischemic Stroke[6,9,15,18,19]

Medication	Usual dose	Mechanism of Action	Metabolism	Clinical Pearls	Guideline Recommendations
Aspirin	81 mg daily	Inhibits cyclooxygenase-1 and 2	UGT1A6, CYP2C9, NAT2	Chronic NSAID use can compromise antiplatelet effects Monitor for GI ulceration	First line option: 50-325 mg daily 50-100 mg has equal efficacy as 325 mg daily
Clopidogrel (Plavix®)	75 mg daily	Inhibits $P2Y_{12}$ component of ADP receptors	CYP2C19 (Primary) CYP3A4	Prodrug requiring CYP 2C19 activation to active metabolite CYP2C19 inhibitors may reduce efficacy	Alternative to either aspirin or aspirin/ dipyridamole, especially if patient has a true allergy to aspirin
Aspirin/ dipyridamole (Aggrenox®)	25 mg/200 mg daily	Dipyridamole: Inhibits uptake of adenosine into platelets	Dipyridamole: Hepatic to glucuronide conjugate	39% of patients have experienced headaches	First line option for the secondary prevention of ischemic stroke
Ticagrelor (Brilinta®)	90 mg twice daily	Inhibits $P2Y_{12}$ component of ADP receptors	CYP3A4 CYP3A5	Monitor closely for dyspnea, bradyarrhythmia (including ventricular pauses), and CYP 3A4 interactions	Not mentioned in the 2014 AHA/ASA guidelines
Cilostazol (Pletal®)	100 mg daily	Inhibits platelet phosphodiesterase III	CYP 3A4 CYP 2C19 CYP 1A2 CYP 2D6	CYP 3A4 and CYP 2C19 interactions Administer before or 2 hours after meals Contraindicated in heart failure	Not mentioned in the 2014 AHA/ASA guidelines

HR=0.42, p <0.0001). Aspirin also prevented fatal ischemic stroke by about 70% (36/8452 (0.00426%) of the aspirin group had a fatal stroke while 110/7326 (0.015%) had a fatal stroke in the placebo group, HR=0.07, CI: 0.02-0.31, p=0.0004, with the greatest benefit in patients who recently had a TIA/ minor stroke. The results of these studies were independent of patient-related characteristics such as gender, age, race, or etiology of TIA or stroke. There were further reductions in preventing occurrence of stroke from weeks 6 to 12; however, further reductions were not seen after week 12 (OR=0.97, p=0.67). Although the results of patients taking aspirin at an interval of 6 to 12 weeks showed that there was a reduction in reoccurrence of stroke when compared with patients who took a placebo/anticoagulant, the results for this portion of the meta-analysis were statistically insignificant. One limitation is that the trials in this meta-analysis recruited very few patients in the first few days after a TIA/stroke.

Clopidogrel (Plavix®)

Clopidogrel is a prodrug that requires hepatic activation to transform into the active thiol metabolite. Clopidogrel can go through two pathways: the first pathway, which occurs 85% of the time, involves carboxylesterase 1 (CES-1) transforming the prodrug of clopidogrel into an inactive metabolite that is excreted through the feces and urine. The second pathway, which occurs 15% of the time, involves CYP enzymes, transforming the prodrug of clopidogrel into an intermediate metabolite known as 2-oxo-clopidogrel. The intermediate metabolite of clopidogrel in this pathway is further metabolized by CYP enzymes, especially CYP2C19, into the active thiol metabolite of clopiogrel that irreversibly binds to the P2Y12 receptor on platelets to exert its antiplatelet effects. The duration of action for clopidogrel is 5 days and the half-life is 6 hours, with the half-life of the active metabolite being 30 minutes.[9] Since clopidogrel primarily uses CYP2C19 to transform its prodrug into an active metabolite, CYP2C19 inhibitors, such as azole antifungals, can prevent the prodrug from converting to its active metabolites. This prevention can lead to increased CV outcomes as a result. Extreme caution should be used when initiating clopidogrel in the setting of CYP2C19 inhibitors.

The CAPRIE study was a randomized, double-blind trial,

which examined the use of clopidogrel 75 mg daily against aspirin 325 mg daily in secondary prevention of stroke, myocardial infarction (MI), and CV death in patients who recently had a recent CV event, such as a stroke or MI.[10] The study included patients who had a recent CV event, defined as an ischemic stroke ≥1 week and ≤ 6 months before randomization, neurological signs ≥1 week from the stoke onset, and an MI ≤ 35 days before randomization with other signs of heart irregularities, such as new Q waves and R waves in V1. Nine-thousand five-hundred ninety-nine patients were randomized to the clopidogrel group while 9,586 patients were randomized to the aspirin group, with a mean follow up period of 1.9 years. The primary outcome of ischemic stroke, MI, or CV death (event rate/year) for the clopidogrel group was 5.32%, while the aspirin group was 5.83% (RR 0.91, p=0.043). The clopidogrel group had a greater incidence of rash (6% vs 4.6%, p <0.05) and significantly greater incidence of diarrhea (4.5% vs 0.23%, P <0.05) when compared with aspirin. The aspirin group, in contrast, had a greater incidence of gastrointestinal (GI) complaints (17.6% vs 15.0%, p<0.05) and had a slightly greater incidence of GI bleeding (2.7% vs 2.0%, P <0.05). The clopidogrel group had a greater incidence of any bleeding when compared with aspirin (9.3% vs 1.4%) but was not statistically significant in this study. Although this study concluded that clopidogrel 75 mg daily is more effective than aspirin 325 mg daily at preventing CV events, this study was not designed to determine if clopidogrel was non-inferior to superior to aspirin among secondary prevention of ischemic strokes in patients with previous strokes and included other primary endpoints, such as MI and CV death.

Dual Antiplatelet Therapy (Aspirin plus Clopidogrel)

The use of dual antiplatelet therapy using aspirin and clopidogrel for secondary prevention of ischemic stroke has been studied and continues to be studied. One trial entitled "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" compared the efficacy of DAPT therapy with clopidogrel in patients who have had a stroke /TIA in the past 3 months and who had ≥ 1 CV risk, such as diabetes mellitus, MI, angina, or symptomatic PAD. Patients were randomized to either a treatment group of aspirin 75 mg and clopidogrel 75 mg or clopidogrel 75 mg plus placebo. The primary outcomes of this study was the first occurrence of ischemic stroke, MI, CV death, or hospitalization for acute ischemic event. After a mean follow-up of 18 months, the primary outcome occurred in 16% of the aspirin/clopidogrel group compared with 17% in the clopidogrel group (p=0.244). Life-threatening bleeds were higher in the aspirin/clopidogrel group (2.6%) when compared with the clopidogrel group (1.3%). Majority of the patients in the study had lacunar CVAs, therefore the results of the study may not be entirely generalizable for patients with other types of ischemic stroke.[11]

Another study entiled "The Secondary Prevention of Small Subcortical Strokes" (SPS3) study[12] was a multicenter, randomized, controlled trial with similarities to the MATCH study; majority of enrolled patients had lacunar strokes. Patients were randomized to receive enteric-coated aspirin 325 mg and clopidogrel 75 mg or clopidogrel 75 mg and placebo. The primary outcome for this study was the incidence of stroke with a follow up period of mean 3.4 years, but the study had to be stopped 10 months before the planned end date. Similar to the MATCH trial, the aspirin/clopidogrel group did not show any significant difference in further reducing recurrent ischemic strokes (2.7% vs 2.5%/yr, respectively; p=0.48). Additionally, the aspirin/clopidogrel group was shown to have increased risk of bleeding compared to the clopidogrel group (2.1%/yr vs 1.1%/yr, respectively; p=<0.001). A potential limitation of this study was that the aspirin dose of 325 mg may be considered too high according to the 2014 AHA/ASA Secondary Stroke Prevention Guidelines. Additionally, the mean age of the patients in the study was 63, which is lower than mean age of the patients in other ischemic stroke trials.

A recent multicenter, randomized, placebo-controlled trial entitled "Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack" (CHANCE) study[13] evaluated the use of aspirin/clopidogrel therapy against aspirin monotherapy in Chinese patients. Patients of Chinese descent generally have a much higher risk of stroke compared to patients in the United States due to undertreated modifiable risk factors, such as diabetes and hypertension, and polymorphisms in the CYP 2C19 genes that may affect clopidogrel metabolism. As a result, the results from these studies may not be generalizable to the population in the United States. Unlike the patients in the MATCH and SPS3 trials, patients were included in the study if they had an acute episode of ischemic stroke or TIA. Patients were randomized to either aspirin 75 mg/clopidogrel 75 mg or aspirin 75 mg during the first 21 days, followed by transitioning the aspirin/clopidogrel group to clopidogrel monotherapy. At the 90-day mark, the aspirin/clopidogrel group showed a 3.5% absolute and 30% relative reduction in the prevention of stroke compared with the aspirin monotherapy group (8.2% vs. 11.7%, respectively; p<0.001). The primary safety outcome of major bleeding was similar for both groups (2.3% vs 1.6%, respectively; p=0.09). As a result, this study concluded that DAPT therapy with aspirin and clopidogrel for the first 21 days following an ischemic stroke/TIA reduced the incidence of stroke in the first 90 days and did not increase the rate of bleeding when compared with aspirin monotherapy.

The "Platelet –Oriented Inhibition in New TIA and Minor Ischemic Stroke" (POINT) study is currently ongoing to evaluate the use of DAPT therapy following ischemic strokes in the United States.[14] The aim of this trial is to determine whether DAPT taken < 12 hours after TIA or minor ischemic stroke symptom onset is more effective in preventing major ischemic vascular events at 90 days compared with aspirin monotherapy alone. This trial is a prospective, doubled-blinded, multicentered trial. The patients in this study has to have had a very recent episode of TIA or minor ischemic stroke and were randomized to clopidogrel 600 mg loading dose followed by 75 mg/day or matching placebo. All patients will receive open-label aspirin 50-325 mg/day, with a dose of 162 mg daily for 5 days followed by 81 mg daily strongly recommended. The primary outcome for this study will be the composite of new ischemic vascular events: ischemic stroke, myocardial infarction or ischemic vascular death, by 90 days. The trial is expected to be completed around 2018 at the earliest. The results of this study should hopefully provide additional clarity regarding DAPT therapy in reducing major ischemic vascular events compared to aspirin alone

Aspirin/Dipyridamole (Aggrenox®)

Dipyridamole inhibits the uptake of adenosine in platelets, leading to an accumulation of adenosine and vasodilation through the stimulation of adenosine receptors on smooth muscles. This increases the synthesis of cAMP, which has the ability to inhibit platelet function. Dipyridamole also works by inhibiting phosphodiesterases, thereby increasing cAMP. Aspirin/dipyridamole

has a biphasic half-life: alpha half-life is approximately 1 hour, and beta-half-life is 12 hours. The most common side effect of aspirin/dipyridamole is headache, which has been reported in 39% of patients.[15] Headaches were also the most common reason for discontinuation from the ESPRIT and PRoFESS trials, especially among women and non-smokers.

The Aspirin plus dipyridamole versus aspirin alone after cerebral ischemia of arterial origin (ESPRIT): Randomized controlled trial study was an open-label, randomized, controlled trial in 2006, which compared aspirin 30 to 325 mg and dipyridamole 200 mg twice daily with aspirin 30 to 325 mg daily in patients with TIAs or minor ischemic stroke.[16] Dipyridamole was prescribed as either a fixed dose combination of aspirin and dipyridamole or as a free combination. This study randomized 2,739 patients in a 1:1 ratio (1,363 patients in the aspirin/dipyridamole group and 1,376 patients in the aspirin group) to determine whether the combination of aspirin/dipyriadamole reduced the CV outcomes in patients who have had TIAs or minor ischemic stroke compared to just aspirin alone. Primary outcome was the composite of vascular mortality, non-fatal stroke, non-fatal MI or non-fatal major bleeding. Overall, the authors found that aspirin plus dipyridamole was associated with fewer rates of the primary outcome when compared with the aspirin group (12.7% vs 15.7%, respectively; HR 0.80, 95% CI 0.66-0.98, NNT=33). Of note, this study was not blinded so this could have led to bias, such as confirmation bias.

The "Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke" (PRoFESS) study [17] was a multicentered, double-blind, randomized, placebo-controlled trial that compared the efficacy of aspirin 25 mg/dipyridamole 200 mg twice daily against the efficacy of clopidogrel 75 mg daily in preventing recurrent stroke in patients with a recent ischemic stroke (90 to 120 days after a previous noncardiogenic stroke). After a mean follow up of 2.5 years, no significant difference was found between aspirin/dipyridamole and clopidogrel in preventing recurrent stroke (9% vs 8.8%, respectively; HR 1.01, 95% CI 0.92-1.11). The clopidogrel arm originally included the use of aspirin as well, but as the study went on, aspirin plus clopidogrel was changed to just clopidogrel alone when the MATCH trial demonstrated an increased risk of bleeding with the combination of clopidogrel and aspirin. The inclusion of aspirin in the clopidogrel arm at the beginning of the trial may have influenced the primary outcome of this trial as aspirin can interfere with the influence of clopidogrel monotherapy.

Ticagrelor (Brilinta®)

Ticagrelor is a reversible inhibitor of the P2Y12 component of the ADP receptor and is metabolized primarily by CYP3A4 and minorly by CYP3A5 and is a P-gp substrate. It has a half-life of 7 hours while its active metabolite has a half-life of 9 hours. The duration of inhibition of platelet aggregation is at least 8 hours and CYP3A4 interactions should be closely monitored. Side effects of ticagrelor include hemorrhage, dyspnea, nausea, and ECG abnormalities (including ventricular pause).[18]

A recent trial in 2016 entitled the "Ticagrelor versus aspirin in acute stroke or transient ischemic attack" (SOCRATES) study was a multicenter, randomized, double-blinded, double-dummy, parallel-group trial that examined whether ticagrelor was superior to aspirin in preventing short-term recurrent stroke, MI, or death in patients with an acute stroke or TIA.[4] The inclusion criteria for this trial included patients who were age ≥ 40, could undergo randomization within 24 hours of symptoms onset, and had either an acute ischemic stroke with an National Institute of Health (NIH) stroke scale score of 5 or lower, or had a high risk of TIA with ABCD2 stroke of 4 or greater or had symptomatic intracranial or extracranial arterial stenosis. In this trial, 13,199 patients who fit the inclusion criteria were randomized to receive either a ticagrelor 180 mg loading dose followed by ticagrelor 90 mg twice daily or aspirin 300 mg load followed by aspirin 100 mg daily. These patients (6,589 in the ticagrelor group and 6,610 in the aspirin group) were spread out of 674 sites in 33 countries and were enrolled from January 2014 through October 2015, with a follow-up duration of 90 days. At the end of the 90 day follow up, the ticagrelor group had a marginal 1% reduction in the primary endpoint of stroke, MI, or death, driven primarily by a reduction in ischemic stroke (6.7% vs 7.5%; HR 0.89, 95% CI 0.78-1.01, p=0.07). The secondary outcomes of major bleeding was similar for both groups (0.5% in the ticagrelor group vs 0.6% in the aspirin group; HR 0.83, 95% CI 0.52-1.34, p=NS). The authors for this trial concluded that ticagrelor was not superior to aspirin in patients with acute stroke or TIA at 90 days with similar bleeding rates. Ticagrelor did have a greater incidence of dyspnea (6.2%) compared to aspirin (1.4%) which led to more discontinuation in the ticagrelor group. Limitations of this study include excluding a population of patients that were at a high risk for stroke reoccurrence, including patients with high-grade carotid intracranial stenosis or who were undergoing thrombolysis or thrombectomy. The follow-up time of 90 days may also be too short to determine long-term benefits of ticagrelor.

Cilostazol (Pletal®)

Cilostazol inhibits phosphodiesrerase III, which leads to an increased concentration of cAMP. Elevated levels of cAMP reduces platelet aggregation and leads to vasodilation. Cilostazol is metabolized through two major CYP enzymes, 2C19 and 3A4, and two minor CYP enzymes, 2D6 and 1A2. It has an elimination half-life of 11 to 13 hours and should be administered 2 hours before or after meals since taking cilostazol with a meal high in fat can increase peak concentration by 90% and overall exposure by 25%. Cilostazol is contraindicated in patients with any severity of heart failure since phosphodieseterase inhibitors have decreased survival rates in patients with class III-IV heart failure. Medications with CYP 2C19 interactions, such as fluconazole and omeprazole, and CYP 3A4, such as diltiazem, erythromycin, and ketoconazole, should have their dose reduced or should be avoided. Cilostazol 100 mg twice daily is the recommended dose and frequency generally used for the secondary prevention of stroke.[19]

A meta-analysis completed by Peng-Peng Niu et al., examined the comparative efficacy and safety of different antiplatelet regimens in patients with prior ischemic stroke or TIA in the long term secondary prevention (≥ 3 months) of ischemic stroke by examining a total of 36 randomized controlled trials.[5] The results showed that cilostazol was significantly more effective than low-dose aspirin 75 mg to 162 mg daily (OR 0.69; 95% CI 0.55-0.86) and clopidogrel 75 mg daily (OR 0.77; 95% CI 0.6-0.98) in the long-term prevention of non-cardiogenic ischemic stroke or TIA. Cilostazol also had a significantly lower bleeding risk compared to both low-dose aspirin and aspirin 50 mg/dipyridamole 400 mg combination. Although the results from this meta-analysis appeared promising, these results may not be clinically significant to patients in the United States since the sample size and number of events for patients in the cilostazol group were too small. Between four small trials, there were only 2,461 patients included in the cilostazol group, with less than 200 serious vascular events. These results also may not be generalizable to the population in

the United States since the cilostazol studies only included patients of Asian descent. Before cilostzol can be considered as a viable option for secondary prevention in ischemic stroke and TIA, larger, randomized, head-to-head trials are needed to show its efficacy against the currently recommended antiplatelet therapies. These studies should also include a diverse cohort of patients in order to ensure generalizability to varying patient populations.

Conclusion

Low-dose aspirin and aspirin/dipyridamole combination are currently recommended as first line options for secondary prevention of ischemic stroke and TIA. Aspirin/dipyridamole has been shown to reduce cardiovascular outcomes when compared with aspirin alone; however, its use may be limited due to increased cost and high prevalence of headaches. Clopidogrel has also been shown to reduce outcomes compared aspirin monotherapy, and is currently recommended as an alternative option in patients with an aspirin allergy. Ticagrelor in the SOCRATES trial did not show any significant difference in preventing MI, death, or recurrent stroke when compared with aspirin alone. It was also not tolerated as well as aspirin due to dyspnea. According to the CHANCE trial, DAPT therapy with aspirin and clopidogrel within 24 hours of symptom onset reduces the 90-day stroke incidence without increasing bleeding risks, when compared to aspirin monotherapy. The POINT trial is currently underway to evaluate the use of DAPT in the United States and may provide more clarity for the use of DAPT in patients with an acute ischemic stroke. Cilostazol has uncertain efficacy in preventing secondary stroke in non-Asian populations and larger, randomized trials may help determine its generalizability to more diverse populations.

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