STROKE :

ANTIPLATELET RECOMMENDATION

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Stroke : Antiplatelet Recommendation

ANCC Accredited NCPD Hours: 2.5 hrs

Target Audience: RN/APRN

Need Assessment

Stroke is a leading cause of mortality and disability worldwide. ***Numerous studies have evaluated the safety and efficacy of dual antiplatelet therapy (DAPT) with clopidogrel, prasugrel or ticagrelor in combination with aspirin (ASA) to prevent secondary ischemic events including stroke and Transient ischaemic attack.*** Evidence-based recommendations should be provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy for cardioembolism and antiplatelet therapy for noncardioembolic stroke. Antiplatelet therapy is the cornerstone of secondary stroke prevention however; health care staff and practitioners should get more information about the clinical- and cost–effectiveness of these established therapies in real-world settings. A stipulated guideline should be followed for the easy administration, clear clarifications, data compilations and future researches.

Objectives

- Discuss stroke and its pathophysiology.
- Identify various types of antiplatelet drugs.
- Explain the mechanism of antiplatelets
- Describe the antiplatelet agents primary prevention of stroke.
- Explain the antiplatelet therapy in acute ischaemic stroke.
- Recognise the drug regime guidelines for secondary prevention of stroke.
- Describe the action of various antiplatelet drugs used for stroke management.
- Adapt to the Antiplatelet Agent Recommendations given by AHA
- Analyse the upcoming perspectives and novel researches in the discipline of 'Antiplatelet therapy in stroke'.

Goal

The goal of this article is to address antiplatelet drug therapy in stroke prevention and mechanisms of action of newer antiplatelet agents

Introduction

Stroke is one of the leading causes of disability and death. ***Ischemic stroke is a syndrome with heterogeneous mechanisms and multiple etiologies, rather than a singularly defined disease.***

Approximately one third of ischemic strokes are preceded by another cerebrovascular ischemic event. Stroke survivors are at high risk of vascular events - cerebrovascular and cardiovascular events, particularly during the first several months after the ischemic event. The use of antiplatelet agents remains the fundamental component of secondary stroke prevention. Based on the available data, antiplatelet agents should be used for patients with noncardioembolic stroke. The use of combination therapy (aspirin plus clopidogrel) has not been proven to be effective or safe to use for prevention of early stroke recurrence or in long-term treatment. There is no convincing evidence that any of the available antiplatelet agents are superior for a given stroke subtype. ***Currently, the uses of aspirin, clopidogrel, or aspirin combined with extended release dipyridamole are all valid alternatives after an ischemic stroke or transient ischemic attack.*** However, to maximize the effects of these agents, the treatment should be initiated as early as possible and be continued on a lifelong basis. [1, Rank 5]

Stroke

Of the 800,000 cerebrovascular events that happen annually in the United States, almost one third are recurrent. People who had an ischemic stroke or transient ischemic attack (TIA) are at significantly higher risk of stroke and other major ischemic events. Prospective studies have shown that the early risk of stroke post transient ischemic attack is much higher than previously thought—18% at 90 days. More importantly, most of the recurrent strokes happened within the first 2 days after the index event. After 1 year the risk falls at about 5% per year, with about 3% per year in the incidence of myocardial infarction (MI).

Secondary stroke prevention can be divided into early - prevention of early recurrence and long-term prevention - late recurrence. Elucidating the mechanism of stroke is crucial to select the most appropri-

" Stroke is the second leading cause of death worldwide. The global occurrence of stroke is fifteen million annually, and only 5 million of these patients achieve favorable functional recovery. The majority (~80%) of these strokes are ischemic. "

ate therapeutic strategy to prevent further events.

Commonly used antiplatelet drugs are aspirin, dipyridamole, and clopidogrel. Aspirin is an irreversible inhibitor of cyclooxygenase-1, which in turn inhibits the formation of thromboxane A2. Dipyridamole increases cyclic AMP by inhibiting platelet phosphodiesterase E5. Clopidogrel is a thienopyridine P2Y12 adenosine diphosphate receptor blocker. [5, Rank 5]

> **" Ischemic stroke is a heterogeneous syndrome that is comprised of the following categories according the underlying mechanism: atherothrombotic (30%), cardioembolic (20%), penetrating artery disease (25%), and cryptogenic (25%).**
>
> **Antiplatelet agents are the cornerstone for secondary prevention of ischemic events in patients with noncardioembolic disease. "**

Ischemic Stroke

Platelets are pivotal in the pathogenesis of atherothrombosis and the complex cascade of blood coagulation. Platelets are also involved in the initiation and progression of atherosclerosis. The arterial blood vessels are part of a high-flow and high-pressure system in which shear forces are present. Vascular injury exposes thrombogenic substances from the damaged vessel wall, which leads to platelet adhesion through the interaction of specific platelet cell-surface receptors (glycoprotein VI and Ib/V/XI) with collagen and von Willebrand factor (vWF). ***Platelet adhesion stimulates platelet activation by various intracellular signalling pathways, which result in inside/out activation of the platelet glycoprotein IIb/ IIIa receptors on the platelet surface and the release of mediators from the platelet, such as adenosine 5′-diphosphonate (ADP), thromboxane A2 (TXA2) and thrombin (factor II). Another major pathway of platelet activation involves the activation of the platelet protease-activator receptor (PAR) 1, which is also known as the thrombin receptor, by thrombin.*** Interactions among these various factors ensure redundancy in the pathways responsible for platelet activation. Simultaneously, the coagulation cascade results in local generation of fibrin, the main protein component of the thrombus. The recruitment and activation of adjacent platelets results in platelet aggregation and thrombus growth, a process mainly mediated by cross-linking of fibrinogen by the glycoprotein IIb/IIIa integrins. Thus, platelet and coagulation activation have been considered as 'inseparable, reciprocally self-amplifying processes. [33, Rank 3]

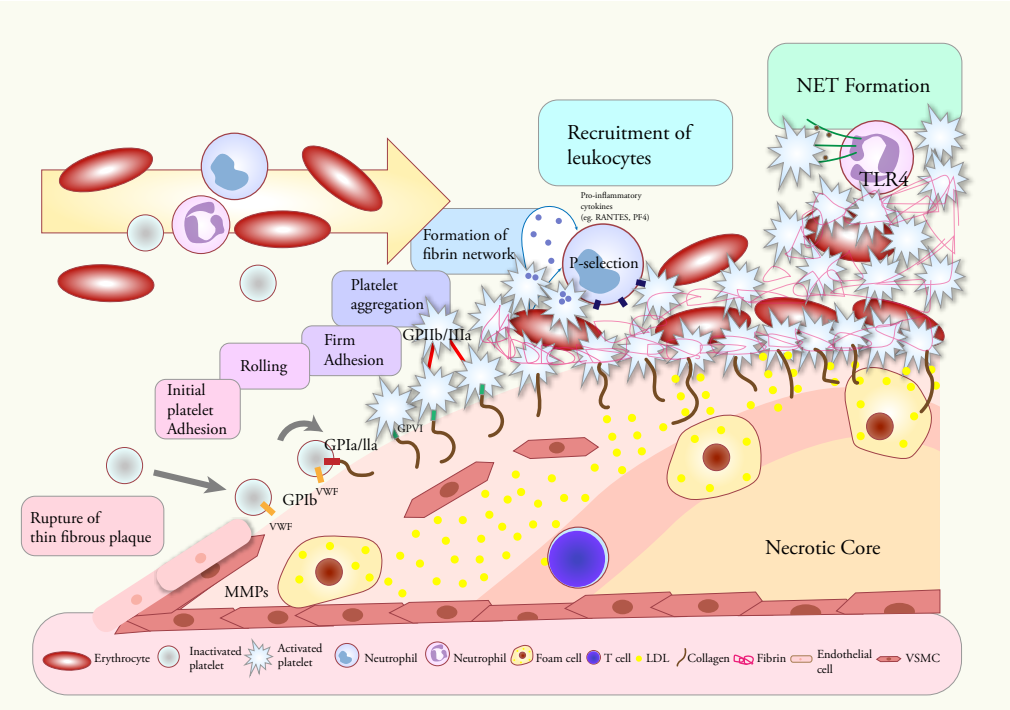

Figure 2: Professional Factors of Medical Errors

The primary target of available anti-platelet drugs is inhibition of platelet activation and aggregation. At present, there are no drugs in routine clinical use that block the early step in thrombus formation, namely the binding of platelets to collagen and vWF. However, several new drugs which target the interaction of platelets with the vWF are being developed. One of these, the nuclease resistant aptamer ARC1779 has been investigated in a randomized, double-blind and placebo-controlled dose-finding study trial in 47 healthy volunteers. ARC1779 produced dose- and concentration-dependent inhibition of vWF activity and was well tolerated with no observed bleeding complications. [34, Rank 2]

Ischaemic stroke is not a homogenous disease but is caused by various aetiologies: large artery atherosclerosis of the brain supplying extra- and intracranial blood vessels, cardiac embolism (mainly from atrial fibrillation) and cerebral microangiopathy of the small penetrating arteries.

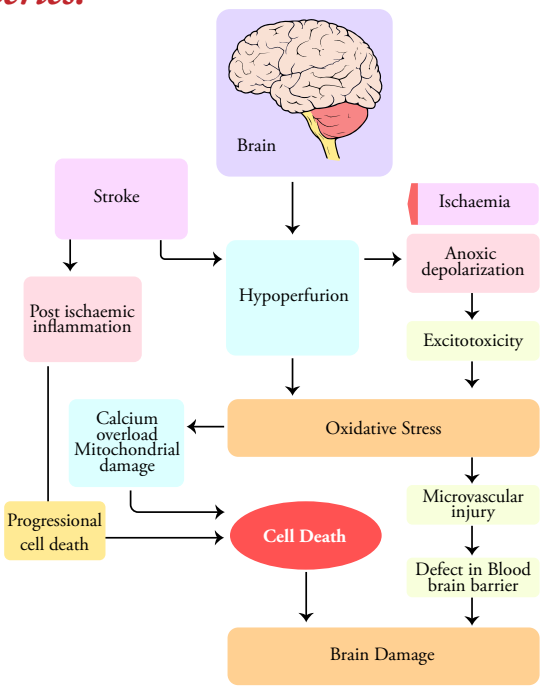

Figure 2: Pathophysiology of Stroke

- Ischemic stroke leads to hypo-perfusion of a brain area that initiates a complex series of events. ***Excitotoxicity, oxidative stress, microvascular injury, blood-brain barrier dysfunction and post-ischemic inflammation lead ultimately to cell death of neurons, glia and endothelial cells.*** The degree and duration of ischemia determine the extent of cerebral damage.
- Apart from the deleterious effect on brain cells, hypoxia also causes loss of structural integrity of brain tissue and blood vessels, partly through the release of proteases like matrix metalloproteases (MMP).
- Loss of vascular structural integrity results in the breakdown of the protective blood–brain barrier, manifesting as cerebral edema, along with secondary progression of brain injury.
- Brain ischemia also tends to activate the immune mechanism, which in some cases may be the cause for the exacerbation of damage and clinical deterioration of the patient

After all the cause of an ischaemic stroke remains unclear in up to 30% of ischaemic stroke patients or there are concurrent possible stroke mechanisms. In contrast, acute myocardial infarction is almost exclusively caused by large artery atherosclerosis due to atherosclerotic plaque rupture. Furthermore, endothelial cells of brain vessels are unique in that they express apical junctional complexes as part of the blood–brain barrier (BBB) which controls cerebral homeostasis.

The blood–brain barrier is altered after cerebral ischemia and reperfusion by oxidants, proteolytic enzymes, inflammation and therapeutic agents administered in acute stroke treatment such as recombinant tissue plasminogen activator. These changes result in an increased blood–brain barrier permeability which contributes to further brain damage, brain oedema formation and an increased risk of cerebral haemorrhage both in the acute and the chronic post-stroke phase. The increased bleeding risk has to be taken into account in the aged human brain when evaluating antiplatelet agents in secondary stroke prevention. [35, Rank 5]

Mechanism of Action of Current Antiplatelet

Antiplatelet agents that are currently approved by the Food and Drug Administration for secondary stroke prevention include aspirin, clopidogrel, and dipyridamole. These agents act at different sites of platelet aggregation pathway to inhibit platelet activation.

Aspirin is an irreversible cyclooxygenase (COX) inhibitor, which selectively

acetylates the hydroxyl group of the COX enzyme resulting in inhibition of conversion of arachidonate to prostaglandin G2/H2, and thromboxane A2. This leads to irreversible inhibition of platelet aggregation. [30, Rank 5]

Clopidogrel is a thienopyridine derivative that inhibits the binding of adenosine 5-diphosphate to glycoprotein IIb/IIIa preventing the binding of fibrinogen to this receptor.
[31, Rank 4]

> **" Dipyridamole is postulated to have multiple mechanisms of action, and primarily inhibits platelet phosphodiesterase resulting in an increase in intraplatelet cyclic adenosine monophosphate level, thereby potentiating the platelet-inhibitory actions of prostacyclin. Dipyridamole also acts by directly releasing eicosanoid from vascular endothelium, and it inhibits its cellular uptake and metabolism of adenosine, which again inhibits "**

Due to their different mechanisms of action, it is postulated that these antiplatelet agents may provide different degrees of vascular protection. In addition, combination therapy as compared to monotherapy may be more effective in reducing vascular events. This has led to multiple clinical trials studying the efficacy of these agents in ischemic stroke prevention. [32, Rank 3]

Antiplatelets can be classified based on the mechanism of action (as shown in Figure 3)

Figure 3: Antiplatelets: Action and Examples

Classification of Antiplatelets	
Class	**Name**
Cyclooxygenase inhibitor	Aspirin Indobufen
Adenosine diphosphate (ADP) antagonists- Thienopyridines	Ticlopidine Clopidogrel Prasugrel
Adenosine diphosphate (ADP) antagonists- Non Thienopyridines	Cangrelor Ticagrelor Elinogrel
Glycoprotein IIb/ IIIa inhibitors	Abciximab Tirofiban Eptifibatide Defibrotide
Phosphodiesterase inhibitors	Dipyridamole Cilostazol NT 702
Protease activated receptor inhibitors	SCH530348 E5555 Terutroban ARC 1779
Collagen platelet interaction inhibitor	Monoclonal antibodies Aptamers Peptide inhibitors

Table 1: Classification of Antiplatelet drugs

Mechanisms, Trial Efficacy and 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 [5].

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID). 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.

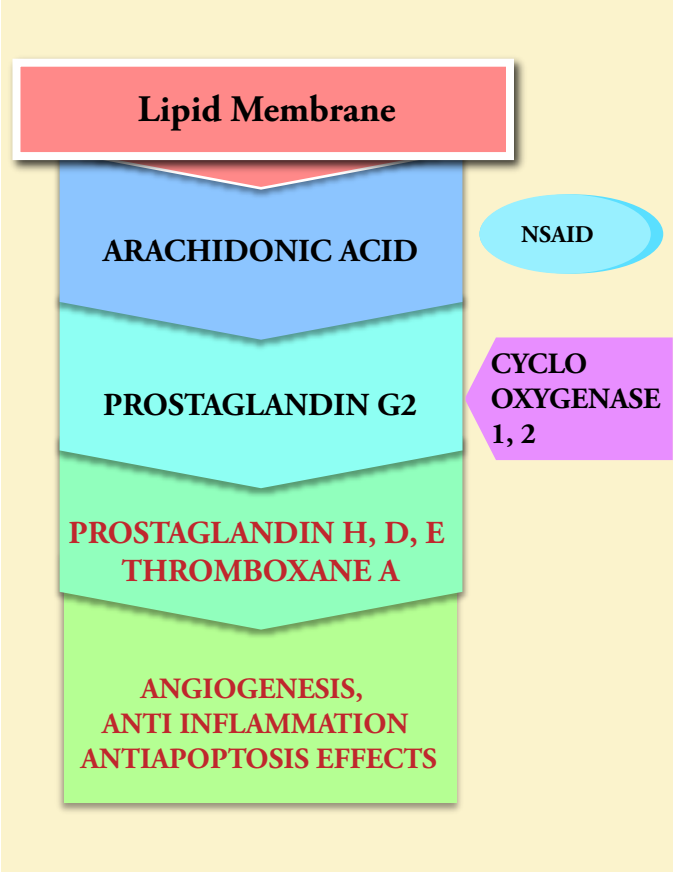

Figure 4: Action of NSAIDs

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 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 transient ischemic attack in the Dutch transient ischemic attack trial. 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. 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). 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) [17, rank 3]

Clopidogrel

Another widely used antiplatelet drug is clopidogrel. This medication is administered once per day at 75 mg. [18, Rank 3]

" Clopidogrel works by irreversibly blocking the P2Y12 component of Adenosisne Di Phosphate 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. 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. [19, Rank 4]

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). 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. 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. A meta-analysis of randomized controlled trials was conducted that reported risk of secondary stroke or death with antiplatelet treatment in patients with lacunar stroke. They found that that dual antiplatelet therapy (including dipyradamole/aspirin and clopidogrel/aspirin) did not demonstrate a clear benefit over monotherapy for patients with lacunar strokes. [20, Rank 3]

" 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. "

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. 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. 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. [21, Rank 4]

Antiplatelets for Stroke

Primary Prevention

Nine randomized controlled trials have investigated the effect of aspirin in primary prevention of cardiovascular events including ischaemic stroke. Meta-analyses of these trials have demonstrated a non-significant effect on all causes stroke. Any reduction in ischaemic stroke risk has not been shown to outweigh the consequent increased risk of gastrointestinal haemorrhage. As such, the role of antiplatelet agents in primary prevention of ischaemic stroke remains a controversial topic. Unfortunately, none of these trials examined primary prevention according to aetiological mechanism. [6, Rank 4]

Once an individual has had a stroke of one aetiological subtype, their recurrent stroke is more likely to be of the same cause as the index event given the complex interplay between environmental and polygenetic risk factors. For this reason, research could hypothesize that the primary prevention subgroup should give a more accurate estimate of the true effect size. However, the subgroup analysis of primary prevention contained data from only three small trials. Although concordant non-significant trends were observed using both fixed and random effects models, there was significant heterogeneity and the analyses were underpowered for discrimination of the true effect. [7, Rank 3]

The current US guidelines for stroke prevention are based on various classes and levels of evidence outlined jointly by the American College of Cardiology (ACC) and the AHA, which incorporate evidence from the ASA.

The antithrombotic agent is carefully selected based on the stroke and bleeding risks specific for each patient. The rate of major bleeding while taking anticoagulation therapy increases in patients with higher CHA2DS2-VASc scores. (VASc stands for vascular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma), and sex category (female gender) is also included in this scoring system.)

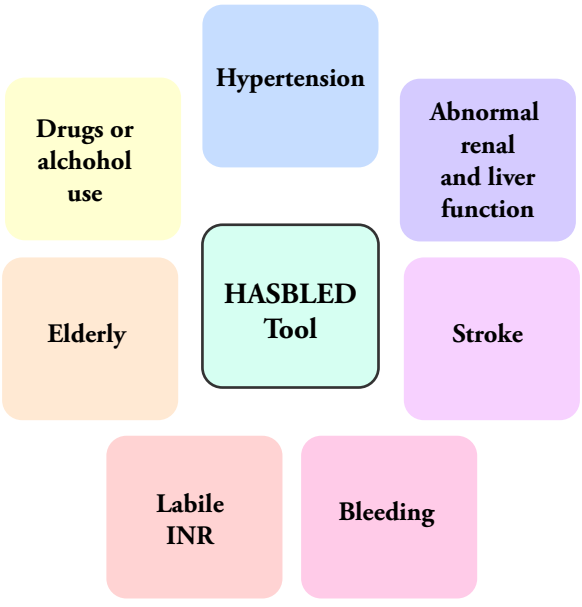

Figure 5: Components of HAS BLED scoring

Tools such as the HAS-BLED and HEMORR2HAGES schemes are used for appropriate selection of antithrombotic strategies in patients with atrial fibrillation with bleeding potential

HEMORR2HAGES TOOL
Hepatic or renal disease
Ethanol abuse
Malignancy
Older age [>75 years]
Reduced platelet count or function
Rebleeding risk [2 points]
Hypertension [uncontrolled]
Anemia
Genetic factors
Excessive fall risk
Stroke

Figure 6: Components of HEMORR2HAGES Tool

" Oral anticoagulation therapy has proven superior to aspirin therapy in patients with atrial fibrillation. However, this overall clinical benefit excluded patients at low stroke risk with a CHA2DS2-VASc score of 0 or 1. The US guidelines support omitting antithrombotic therapy in patients with atrial fibrillation and a CHA2DS2-VASc score of 0, but they also support aspirin or OAC therapy in patients with a CHA2DS2-VASc score of 1. "

Treatment for Acute Ischemic Stroke

Therapies aimed at restoring perfusion are the mainstay of acute stroke therapy. The goal of early reperfusion therapy is to minimize neurologic impairment, long-term disability, and stroke-related mortality. Reperfusion can be achieved through administration of thrombolytic agents such as recombinant tissue plasminogen activator (r-tPA) or by mechanical removal of blood clots. A second focus of acute stroke therapy is to prevent early recurrence of cerebrovascular events. This includes treatment with antiplatelet agents and anticoagulants.

In developing recommendations for the acute management of stroke, researchers

considered the following patient-important outcomes: mortality at 90 days and good functional outcome among survivors at 90 days. For recommendations related to IV thrombolytic therapy, they defined favorable functional outcome as a score of ≤ 1 out of a maximum of 5 on the modified Rankin Scale (mRS); this indicates full functional recovery with no symptoms or only minor symptoms that do not cause functional impairment. ***For recommendations dealing with endovascular stroke therapy, a favorable outcome was defined as mRS score ≤ 2, indicating functional independence for activities of daily living.*** Different definitions of favorable outcome were chosen because patients eligible for endovascular treatment, on average, have more severe strokes than the population of patients who are eligible for IV thrombolysis. Consequently, functional independence reflects a marked improvement from presenting symptoms for the average patient who is eligible for endovascular therapy, whereas full functional recovery reflects a marked improvement for the average patient who is eligible for IV thrombolysis. [14, Rank 3]

Aspirin in Acute Ischemic Stroke

Aspirin is an older agent that inhibits cyclooxygenase-1 (COX-1)-induced production of thromboxane A2and is commonly used for the prevention of recurrent stroke. Two large randomized controlled trials, IST (International Stroke Trial) and Chinese Acute Stroke Trial (CAST), contributed > 98% of the data to a Cochrane systematic review of four trials assessing the effect of early aspirin administration in patients with acute stroke. High-quality evidence shows that aspirin results in fewer deaths (nine per 1,000) and more patients with a good functional outcome (seven per 1,000) at 30 days after ischemic stroke. This occurs at the expense of a small increase in nonfatal major extracranial bleeding events (four per 1,000). The modest overall benefit of aspirin in terms of mortality and functional outcome is probably in large part due to a reduction in recurrent strokes (seven per 1,000) despite a small increase (two per 1,000) in symptomatic intracranial hemorrhages. [15, rank 1]

A combined analysis of 40 000 patients randomized in these 2 trials showed a highly significant decrease of 7 recurrent ischemic strokes per 1000 patients treated and a nominally significant reduction of 4 deaths without further stroke per 1000 patients treated. Overall, there was a net decrease of 9 per 1000 treated in the risk of further stroke or death in hospital. ***These data indicate strong benefit for acute initiation of aspirin after ischemic stroke but have been largely superceded by trials of***

dual antiplatelet therapy (DAPT) in the acute setting

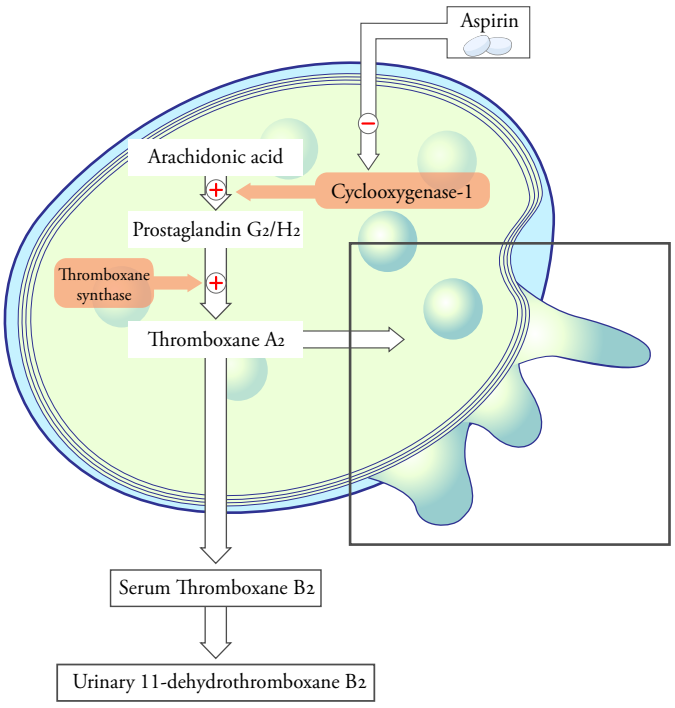

Figure 7: Antiplatelet effect of Aspirin

The optimal dose of initial aspirin therapy has not been studied in a head-to-head comparison. Eligible studies included in the meta-analysis used daily aspirin doses of 160 mg to 326 mg, and the meta-analysis found no heterogeneity in the effect on the different outcomes. Similarly, optimal timing of initiation of aspirin therapy has not been studied in randomized trials. ***In the included studies, the median time to initiating aspirin therapy varied from 19 to 24 h.*** Based on these data it is suggested to start aspirin at a dose of 160 to 326 mg per day, as early as possible after intracranial hemorrhage has been excluded and, ideally, within the first 48 h after symptom onset. To reduce bleeding complications, the aspirin dose may be reduced to secondary prevention dosing (75-100 mg/d) after 1 to 2 weeks of acute treatment.

Few studies have evaluated the combination of aspirin with other antiplatelet agents for acute ischemic stroke. The largest pilot study to date (N = 392) failed to demonstrate or exclude a beneficial or detrimental effect of the combination of aspirin with clopidogrel initiated within 24 h after symptom onset and continued for 90 days (7.1% recurrent stroke on combination vs 10.8% on aspirin alone; RR, 0.7; 95% CI, 0.3-1.2). This approach is currently being investigated in large-scale clinical trials. ***Aspirin may be used safely in combination with low doses of subcutaneous heparin for DVT prophylaxis but should not be given for the first 24 h after administration of r-tPA.*** [16, Rank 5]

ADP (Adenosine-diphosphate) receptor antagonists

Thienopyridine adenosine 5'-diphosphate (ADP) antagonists approved for antiplatelet activity in the United States include clopidogrel, ticlopidine, prasugrel, and ticagrelor.

The second-generation thienopyridine clopidogrel is a specific, irreversible antagonist of the platelet ADP P2Y12 receptor and initiates platelet aggregation. Furthermore ***it amplifies platelet response to other endogenous and exogenous stimu-***

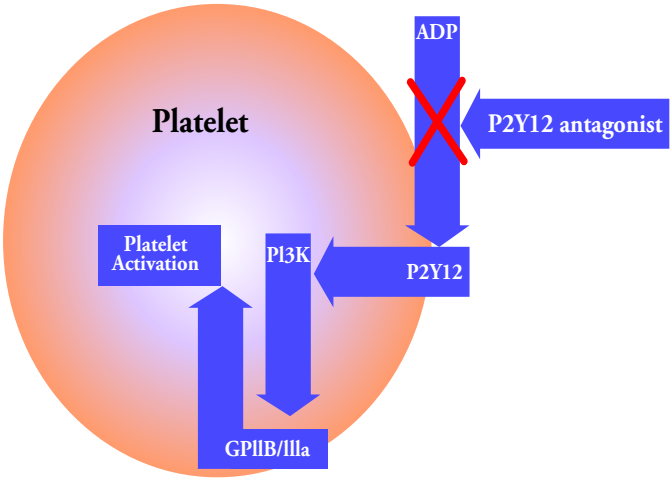

Figure 8: Action of ADP receptor antagonists

li such as Thromboxane A2 (TXA2) and thrombin. The prodrug clopidogrel is converted into the active metabolite by a two-step process that is mainly dependent from the hepatic cytochrome P450 (CYP) system. [36, Rank 3]

" Clopidogrel has been shown to be slightly more effective than aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial and to be equally effective compared with the combination of aspirin and dipyridamole in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial. "

Proton Pump Inhibitors

Platelet inhibitors are often prescribed together with Proton Pump Inhibitors, with the goal of reducing the risk of gastrointestinal tract bleeding. However, there have been concerns that many Proton Pump Inhibitors might diminish the antiplatelet effects of clopidogrel, possibly through inhibition of the CYP 2C19 isoenzyme and, therefore, the conversion of clopidogrel into its active metabolite. A retrospective cohort study in 8205 patients discharged on clopidogrel after an acute coronary syndrome did show that concomitant use of clopidogrel and Proton Pump Inhibitors (5244 patients) was associated with a higher risk of death or rehospitalization for acute coronary syndrome (adjusted hazard ratio 1.27; 95% CI, 1.10–1.46), but not for all-cause mortality (19.9% for patients taking clopidogrel and PPI versus 16.6% for patients taking clopidogrel alone; adjusted odds ratio 0.91, 95% CI, 0.80–1.05). Researchers assessed the association between concomitant use of clopidogrel or prasugrel and PPIs on in vitro platelet aggregation in the Prasugrel in comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction (PRINCIPLE-TIMI) 44 trial and clinical outcome in a post hoc analysis of the Trial to Assess Improvement in Therapeutic outcomes by optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial. In the PRINCIPLE-TIMI 44 trial, 201 patients undergo-

ing elective percutaneous coronary intervention were randomly assigned to prasugrel (60 mg loading dose, 10 mg daily maintenance dose) or high-dose clopidogrel (600 mg loading dose, 150 mg daily maintenance dose). Mean inhibition of platelet aggregation measured by light-transmission aggregometry was significantly lower for patients on a PPI than for those not on a PPI at 6 hrs after a 600 mg clopidogrel loading dose (23.2 ± 19.5%versus 35.2 ± 20.9%, P= 0.02), whereas a just non-significant difference was seen in patients after the 60 mg loading dose of prasugrel (69.6 ± 13.5% with PPI versus 76.7 ± 12.4% without PPI, P= 0.054). [37, Rank 1]

Antiplatelet Agents for Secondary Stroke

Prevention

Because platelets are key effector cells that contribute to the prothrombotic and proinflammatory milieu in stroke, antiplatelet agents are first-line treatment modalities for the prevention of recurrent stroke. These therapies include aspirin, dipyridamole, and clopidogrel, all of which reduce the risk of recurrent cerebrovascular and cardiovascular events, although there are several important differences with regards to their mechanisms of action and clinical efficacy. [8, Rank 3]

In summary, current guidelines support the use of any one of three therapeutic regimens (as shown in Figure 7)

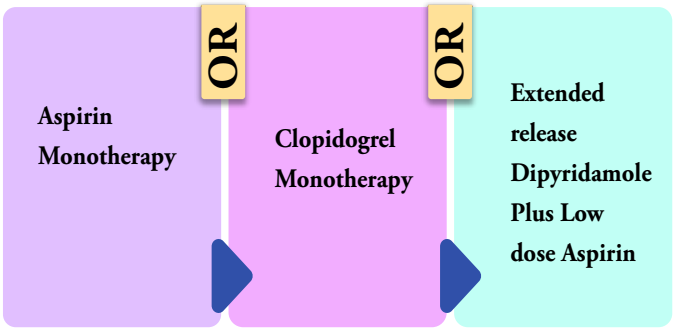

Figure 9: General Drug Guideline for Secondary Stroke prevention

Acceptable first-line antiplatelet therapeutic regimens for secondary stroke prevention include aspirin monotherapy, OR clopidogrel monotherapy OR Extended-release Dipyridamole Plus Low-dose Aspirin

In trials in patients with a history of stroke or transient ischemia attack (TIA), aspirin reduced the risk of subsequent stroke by 15–18% compared with placebo. Given this efficacy, its low cost and acceptable side-effect profile, aspirin as monotherapy (50–325 mg/ day) is recommended for the prevention of stroke in patients with a history of stroke or transient ischemia attack. Newer agents and combination therapy may be superior to aspirin monotherapy, although definitive data are still lacking and aspirin still retains a strong recommendation for use in patients with a history of stroke or transient ischemia attack. [9, Rank 3]

In ESPS2 (The Second European Stroke Prevention Study), patients treated with extended-release dipyridamole (200 mg twice a day) plus aspirin (50 mg daily) had a significant reduction in serious vascular events compared to aspirin alone. These findings were confirmed in the large (>6,000 patients) ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia) trial, and recent meta-analyses data support the higher efficacy of combination therapy over aspirin alone. Although the mechanisms to explain the apparent superiority of combination therapy over aspirin monotherapy are not entirely known, the 2008 ACCP guidelines do recommend dual therapy with extended-release dipyridamole plus aspirin over aspirin monotherapy alone for select patients.

Blockade of the adenosine di phosphate receptor dampens signaling events in platelets that promote platelet hyperactivity, including subsequent activation of the glycoprotein IIb, IIIa receptor with clopidogrel. [10, Rank 4]

" Clopidogrel requires activation in the liver by cytochrome P450 enzymes. The active metabolite of clopidogrel prevents platelet aggregation by specifically and irreversibly inhibiting the P2Y12subtype of adenosine di phosphate receptor on platelet membranes. "

CAPRIE was a large, randomized, controlled trial comparing clopidogrel (75 mg daily) to aspirin (325 mg daily) for the prevention of stroke, myocardial infarction, or vascular death. Overall, clopidogrel was more effective in reducing this composite endpoint. When analyzed by intention-to-treat analysis encompassing more than 19,000 patients, the annual risk of combined vascular complications in patients randomized to receive clopidogrel was lower compared to patients randomized to receive aspirin (5.32% vs. 5.83%, respectively; RRR of 8.7% in favor of clopidogrel, P = 0.043). Overall safety, including bleeding, appeared to be similar between clopidogrel and aspirin, although major bleeding was minimally higher in patients taking aspirin (1.55% vs. 1.38%). Clopidogrel has also been compared to combination therapy with extended-release dipyridamole plus aspirin. These recent data from the very large (>20,000 stroke patients) PROFESS trial suggest that aspirin plus extended-release dipyridamole and clopidogrel alone may have similar safety and efficacy profiles. ***Aspirin plus clopidogrel is generally not recommended for the intervention of secondary stroke.*** [11, Rank 2]

The antithrombotic properties of agents such as aspirin, dipyridamole, and

clopidogrel clearly play an important role in reducing the risk of recurrent stroke, as evident in the clinical studies cited earlier. However, inflammatory pathways also modulate the development of atherosclerosis and thromboembolic events, including stroke and transient ischaemic attack. ***Adherence of platelets to mononuclear phagocytes induces the synthesis of proinflammatory mediators, including MCP-1, IL-1, IL-8, and matrix metalloproteinases*** and these factors, among others, serve to promote atherosclerosis and enhance thrombus formation and subsequent embolization.

Because ***inflammation mediates atherosclerosis progression, plaque rupture, and thromboembolism,*** agents that inhibit these processes and, in parallel, reduce inflammation may enhance clinical efficacy. For example, in vitro investigations have demonstrated that dipyridamole, at a concentration similar to peak plasma concentrations achieved with administration in vivo to patients, inhibits inflammatory gene expression in platelet–monocyte aggregates.

> **" Dipyridamole inhibits phosphodiesterase activity and increases extracellular adenosine levels, is associated with greater stroke risk reduction when used in combination with low-dose aspirin. "**

Dipyridamole attenuated nuclear translocation of NF-κB and delayed IL-8 synthesis in platelet–monocyte aggregates. In addition, dipyridamole blocked the synthesis of MCP-1 and decreased translation of MMP-9 mRNA into protein. [12, Rank 3]

Clopidogrel, through inhibiting ADP-mediated platelet aggregation, indirectly influences inflammatory events elicited by platelet–leukocyte aggregates. In isolated human platelets, clopidogrel reduced P-selectin expression and circulating platelet–leukocyte aggregates. In addition, the active metabolite of clopidogrel reduces platelet–leukocyte aggregate formation and immunoreactive tissue factor exposure on platelet and leukocyte surfaces.

Emerging data suggests that combination therapy with extended-release dipyridamole plus aspirin may be superior to aspirin alone. Pleiotropic effects of current therapies, although incompletely understood, may provide additional risk reduction and, once better understood, may help us improve on standard therapies and develop new drugs with improved clinical benefit. [13, Rank 2]

The class of thienopyridines irreversibly inhibits the platelet ADP P2Y12 receptor. The first- and second-generation thienopyridines, ticlopidine and clopidogrel have been investigated in secondary stroke pre-

vention trials, and found to be more effective compared with aspirin.

Prasurgel

Similar to clopidogrel, the third-generation oral thienopyridine prasugrel is also a prodrug that is metabolized by the CYP system to form its active metabolite (R-138727). However, ***prasugrel achieves greater and more consistent platelet inhibition than clopidogrel.*** This difference might partly be caused by a distinct and more efficient conversion of prasugrel into its active metabolite by a two-step biotransformation. Prasugrel has been widely studied in patients with coronary heart disease, but so far there is no distinct randomized trial available in secondary stroke prevention. The TRITON-TIMI 38 trial compared prasugrel (60 mg loading dose and a 10 mg daily maintenance dose) to clopidogrel (300 mg loading dose and a 75 mg daily maintenance dose) in 13,608 patients with scheduled percutaneous coronary intervention. Treatment with prasugrel resulted in a significant reduction of the primary combined vascular end-point (9.9% in patients treated with prasugrel versus 12.1% in patients receiving clopidogrel; hazard ratio 0.81; 95% CI, 0.73 -0.90). However, major bleeding was significantly more frequently observed in patients receiving clopidogrel (2.4% versus 1.8%; hazard ratio 1.32; 95% CI, 1.03–1.68). A post hoc analysis from the TRITON-TIMI 38 trial in 518 patients with a history of ischaemic stroke or TIA revealed a lack of efficacy and an increased risk of major bleeding in this subgroup of patients. However, this post hoc subgroup analysis comprised only 3.8% of the entire study population. Based on these results, prasugrel cannot be recommended for use in secondary stroke prevention.

Beside the thienopyridines, there are two reversible non-thienopyridine ADP receptor antagonists, ticagrelor and cangrelor, which are currently under clinical investigation in patients with acute coronary syndromes. [37, Rank 4]

Prasurgel is more efficiently metabolized compared with clopidogrel and thus producing a higher and more predictable level of inhibition and is also irreversible. Prasurgel 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. 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. [22, Rank 3]

Combining Aspirin and Clopidogrel ??

To date there are three antiplatelet regimens which are recommended for secondary prevention by guidelines and most widely used in patients with non-cardioembolic stroke: aspirin monotherapy, clopidogrel monotherapy and the combination of aspirin and dipyridamole.

A systemic review about the bleeding risk of antiplatelet therapies for secondary stroke prevention which included 13 randomized trials with a follow-up of ≥1 year found a significantly higher total and major bleeding rate with the combination of aspirin and clopidogrel both for total bleeding and major bleeding. Total bleeding rates were 4.8% with aspirin (≤325 mg/day), 2.9% with clopidogrel monotherapy, 3.6% with aspirin plus dipyridamole, 10.1% with aspirin and clopidogrel and 16.8% with oral anticoagulation. Major bleeding occurred at mean rates of 1% with aspirin monotherapy, 0.85% with clopidogrel monotherapy, 0.93% with aspirin plus dipyridamole, 1.7% with aspirin plus clopidogrel and 2.5% with anticoagulation. [2, Rank 4]

> **" The combination of aspirin and clopidogrel is recommended for up to 9 months in stroke patients who were treated with stenting of the internal carotid artery or an intracranial brain artery but it is not recommended for long-term secondary stroke prevention. "**

PCI-CURE trial

Favorable results of combination aspirin and clopidogrel for prevention of vascular events in patients with percutaneous coronary intervention in the PCI-CURE (a substudy of the CURE) and acute MI in the CURE and CREDO trials prompted an interest in investigating this combination in patients with prior cerebrovascular disease.

However, ***there is an ongoing debate, whether the combination of aspirin and clopidogrel should be used in the acute post-stroke and early prevention time period*** (e.g. the first 3 months after the stroke event), where the risk of stroke recurrence is highest. These considerations were partly derived from the observation that there was no early increase in life-threatening bleeding and, more specifically, in primary intracranial haemorrhage in the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial.

MATCH Trial

The MATCH trial compared clopidogrel 75 mg per day alone to clopidogrel 75 mg per day plus aspirin 75 mg per day in 7,599 patients with a recent ischemic stroke or transient ischaemic attack. About 70% of the participants were diabetics. Patients assigned to combination therapy had a non-significant reduction of primary outcome of 6% (P=0.24). There was an excess of non-central nervous system life-threatening hemorrhages among those receiving combination therapy (absolute increase of 0.5% per year; P<0.05). In short, MATCH did not show a benefit of adding aspirin to clopidogrel in this cohort.

Furthermore, ***more than 50% of the patients in the MATCH trial were classified as having lacunar strokes due to small vessel disease, which might not be of pure atherothrombotic origin. Additionally, an increased bleeding rate has been noted in this patient group.***

FASTER trial

The combination of aspirin and clopidogrel has been investigated in several smaller randomized trials in the early phase after a transient ischemic attack or stroke. The placebo-controlled Fast assessment of Stroke and Transient Ischemic attack to prevent Early Recurrence (FASTER) trial was designed as 2 × 2 factorial study to assess, whether clopidogrel (300 mg loading dose followed by 75 mg/day) and simvastatin, if started within 24 hrs of symptom onset and continued for 90 days, would reduce the risk of stroke after a transient ischaemic attack or minor stroke. All patients also received aspirin at a dose of 81 mg/day. The trial had to be stopped prematurely due to a slow recruitment rate after 392 patients had been randomized. The primary outcome of total stroke (ischaemic and haemorrhagic) within 90 days occurred in 14 (7.1%) patients on clopidogrel and aspirin compared with 21 (10.8%) patients on aspirin monotherapy (risk ratio 0.7, 95% CI, 0.3–1.2). There were 33 ischaemic and 2 haemorrhagic strokes, both of them in patients treated with clopidogrel and aspirin. [3, Rank 3]

Patients with symptomatic carotid or intracranial stenosis are at particular high risk of early recurrent stroke and the combination of aspirin and clopidogrel was assessed in this patient group in two smaller randomized trials. In both studies the detection of microembolic signals (MES) on transcranial Doppler ultrasound was used as surrogate parameter of efficacy. This surrogate parameter has just been shown to be useful in predicting subsequent ipsilateral ischaemic strokes in 467 patients with asymptomatic carotid stenosis [35, Rank 4].

CARESS trial

The clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial randomized 107 patients with ≥50% carotid stenosis who had experienced an ipsilateral TIA or stroke within the last 3 months and detection of MES to receive clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo in addition to 75 mg aspirin/day. The primary end-point was the proportion of patients who were MES+ on a 1 hr recording performed 7 days after initiation of the combination therapy. In CARESS, dual antiplatelet therapy resulted in a significantly reduced proportion of MES+ patients on day 7 (43.8%versus 72.7%, relative risk reduction 39.8%; 95% CI, 13.8–58.0). [4, Rank 2]

CHARISMA study

The CHARISMA study compared aspirin alone (75–162 mg/d) to aspirin plus clopidogrel (75 mg/d) in 15,603 patients with symptomatic vascular disease (80%, including prior stroke, MI, or peripheral vascular disease) or multiple vascular risk factors (asymptomatic). The overall results showed no significant difference in primary outcome in both groups (RR, 0.93; 95% CI, 0.83–1.05; P=0.22). There was a trend in favor of combination therapy in the symptomatic patients (RR, 0.88; 95% CI, 0.77–0.998; P=0.046) and a 20% reduction in nonfatal stroke (RR, 0.80; 95% CI, 0.65–0.997; P=0.05) among all participants. Compared with MATCH, which demonstrated an increase in intracerebral hemorrhage (ICH), CHARISMA did not show this same safety concern. CHARISMA reported no differences in ICH (26 vs. 27; P = not significant) or in major bleeding (130 vs. 104; P=0.09), although moderate bleeding was increased in the combination group (P<0.001) [35, Rank 2]

Combination of Aspirin and 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. [25, Rank 3]

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. 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 were 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. [26, Rank 3]

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. It seemed that patients were more likely to discontinue ASA+ER-DP due to secondary side effects when compared with clopidogrel. [27, Rank 4]

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. [23, Rank 4]

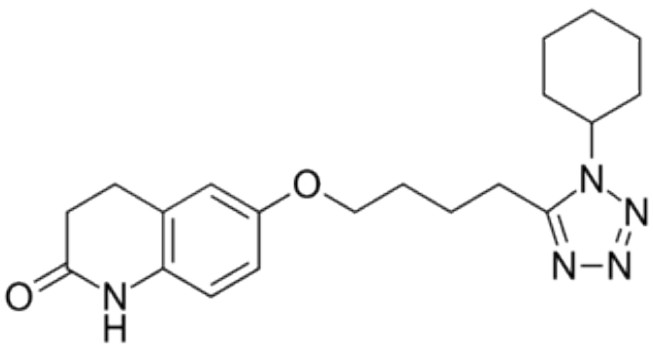

Figure 10: Structure of Cilostazol

Cilostazol acts on different pathophysiological pathways. Cilostazol also prevented the progression of symptomatic intracranial atherosclerotic stenosis of the middle cerebral artery when added to aspirin 100 mg/day in a randomized, double-blind and placebo controlled study [51].

> **" Cilostazol is a selective antagonist of the phosphodiesterase type 3 enzyme which prevents the inactivation of the intracellular second messenger cyclic adenosine monophosphate and irreversibly inhibits platelet aggregation. In addition, cilostazol promotes arterial vasodilation, suppressed smooth muscle cell proliferation and intimal hyperplasia in animal models. "**

Cilostazol has been studied in several Asian trials in the setting of percutaneous coronary intervention and secondary stroke prevention to find an antiplatelet agent which is able to substantially reduce the risk of aspirin-related cerebral haemorrhage. ***Cilostazol was first investigated in a randomized placebo-controlled trial in 1095 Japanese patients with ischaemic stroke.*** The primary end-point was the recurrence of cerebral infarction and was significantly reduced under treatment with cilostazol (3.37%/year versus 5.78%/year, relative risk reduction 41.7%, 95% CI, 9.2–62.5). The rate of intracranial haemorrhage was not significantly different in both treatment arms (four under cilostazol and six under placebo). [24, Rank 5]

Compared with standard-dose aspirin (100 mg/day), random assignment to cilostazol (100 mg bid) showed no significant difference in the rate of stroke recurrence (including ischaemic and haemorrhagic stroke and sub-arachnoid haemorrhage) in a pilot trial with 720 enrolled Chinese patients. There were 11 ischaemic and 6 haemorrhagic strokes in the cilostazol group versus 15 ischaemic and 5 haemorrhagic strokes in the aspirin group (hazard ration 0.62, 95% CI, 0.30–1.26) during a follow-up period of little more than 1 year. All six patients with symptomatic haemorrhage had previous cerebral microbleeds detected on magnetic resonance imaging in the area where the haematoma was located.

The results of another double-blind randomized trial with cilostazol were presented on the European Stroke Conference 2010 in Barcelona. The Cilostazol Stroke Prevention Study II enrolled 2672 Japanese stroke patients with a non-cardioembolic stroke to receive either aspirin (81 mg/day) or cilostazol (100 mg bid) for a median follow-up of 2.5 years (NCT00234065). The primary end-point ischaemic or haem-

orrhagic stroke was statistically significant reduced under cilostazol (2.57% in patients treated with cilostazol versus 3.71% in patients treated with aspirin, relative risk reduction 25.7%). This difference was primarily caused by the markedly reduced rate of haemorrhagic strokes (31 versus 10).

Thus, cilostazol appears to be a safer antiplatelet agent in comparison with aspirin. However, there is a need for larger phase III trials comparing cilostazol with clopidogrel and the combination of aspirin and dipyridamole and in other ethnic groups. [38, Rank 1]

Sarpogrelate

The antiplatelet agent sarpogrelate is a selective inhibitor of the 5-hydroxytryptamine receptor which is involved in platelet aggregation and vasoconstriction.

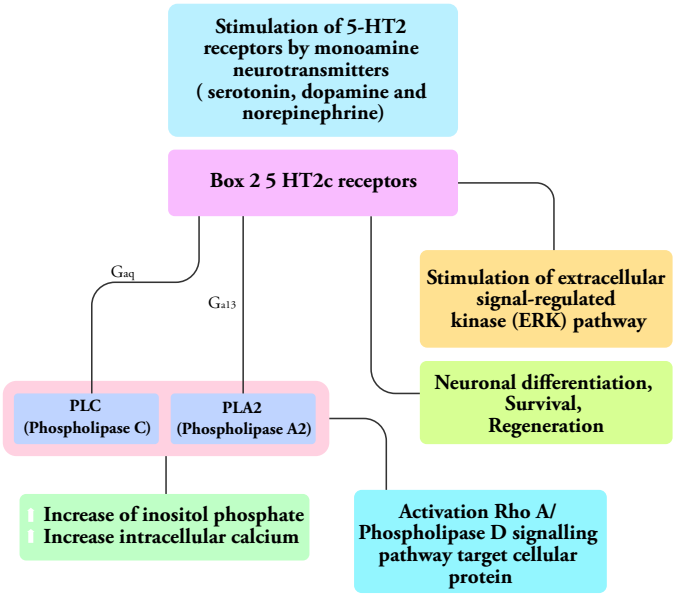

Figure 11 : Action of Sarpogrelate

Sarpogrelate has been used in Asian patients with peripheral artery disease and was also compared to aspirin in secondary stroke prevention. The S-ACCESS trial randomly assigned 1510 Japanese patients with a recent ischaemic stroke (1 week to 6 months after onset) to receive either sarpogrelate (100 mg three times daily) or aspirin (81 mg/day) for a mean follow-up of 1.59 years. ***The primary efficacy end-point was recurrence of cerebral infarction.*** Sarpogrelate was not able to show non-inferiority to aspirin in the prevention of recurrence of cerebral infarction with 72 ischaemic strokes occurring in the sarpogrelate group and 58 in the aspirin group (hazard ratio 1.25, 95% CI, 0.89–1.77). The overall bleeding rate was significantly lower in patients treated with sarpogrelate (11.9% versus 17.3%). To date, sarpogrelate has not been investigated in other ethnic stroke populations. [39, Rank 2]

Terutroban

Terutroban (S18886) is a Thromboxane A2 receptor antagonist binding to membrane-bound G-coupled receptors. These receptors are found on the surface of platelets but also on macrophages, monocytes, vascular endothelial cells and smooth muscle cells. Unlike aspirin, terutroban inhibit both Thromboxane A2 and eicosanoids such as isoprostanes and prostanoids which are generated non-enzymatically.

Thromboxane A2 and eicosanoids may be also generated by activated monocytes and macrophages in inflammatory atherosclerotic lesions and terutroban have been shown to prevent atherosclerosis by reducing inflammation and proliferation in the vessel wall of rabbits. Furthermore, ***the administration of terutroban resulted in a significantly improved vasodilation in peripheral arteries*** in a small double-blind, placebo-controlled trial with 20 randomized patients. Based on these multiple modes of action, terutroban was compared with aspirin in a large secondary prevention trial.

The PERFORM trial randomized 19,119 patients aged ≥55 years with a recent ischaemic stroke (≤3 months) or TIA (≤8 days) to terutroban (30 mg/day) or aspirin (100 mg/day). The primary efficacy end-point is a composite of ischaemic stroke, myocardial infarction or other vascular death. However, this trial has been stopped prematurely in November 2009 because interim efficacy analyses suggested that continuation of the trial would be futile. [40, Rank 5]

PAR-1 antagonists

Vorapaxar (brand name Zontivity, formerly known as SCH 530348) 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. 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. Also, there was no clear benefit within clinically relevant groups defined by the type and timing of prior ischemic stroke or background antiplatelet therapy. [28, Rank 4]

Thrombin is a key factor in thrombus formation. In addition to generating fibrin, thrombin is also a very potent stimulus for platelet activation via binding to the PAR1 receptor on the surface of platelets.

Data from the phase II trial which enrolled 1030 patients aged ≥45 years who were undergoing non-urgent percutaneous coronary intervention did suggest a low bleeding rate. The primary end-point (incidence of clinically significant major or minor bleeding) was seen in 2–4% of patients treated with three different doses of SCH 530348, which was not statistically different from the bleeding rate of 3% in placebo patients.

> **" Vorapaxar is a selective and competitive antagonist of the platelet PAR1 receptor but is not affecting the formation of fibrin and it could have the potential for a favourable balance of antithrombotic efficacy and risk of bleeding."**

SCH 530348 is currently evaluated in the randomized placebo-controlled phase III Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis trial. This trial started in 2007 and plans to enrol about 27,000 patients with established myocardial infarction, ischaemic stroke of presumed thrombotic aetiology (time period ≥2 weeks and ≤12 months after the stroke) or peripheral artery disease. ***The primary end-point is a composite of cardiovascular death, myocardial infarction, stroke or coronary revascularization.*** Among the first 12,000 randomized trial approximately 16% had an ischaemic stroke as qualifying event. Trial completion is expected in 36 to 44 months from first enrolment. [37, Rank 3]

Long Term Secondary Stroke Prevention in Non-Cardioembolic Stroke

Ischaemic stroke is a heterogeneous disease caused by different pathologies. ***The identification of a cardioembolic source of stroke is of utmost importance since antithrombotic treatment differs from that in patients with non-cardioembolic stroke.*** The efficacy of antiplatelet therapy beyond 4 years after the initial cerebrovascular event has not been studied in randomized trials. Theoretically, treatment should continue lifelong, unless contraindications emerge.

Aspirin versus anticoagulation

Oral anticoagulation was as effective as aspirin (30–325 mg/day) in the prevention of recurrent ischaemic stroke in the ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial; target INR 2.0–3.0) and SPIRIT (Stroke Prevention in Reversible Ischemia Trial; target INR 3.0–4.5) trial in patients with non-cardioembolic stroke, but caused significantly more severe haemorrhagic complications in both trials. In the Warfarin versus Aspirin Recurrent Stroke Study (WARSS), the comparison of 'light' anticoagulation (target INR 1.4–2.8) with aspirin (325 mg/day) in 2200 patients with non-cardioembolic stroke over a follow-up of 2 years was equivalent with respect to prevention of recurrent ischaemic stroke, rate of major haemorrhage and death. However, given the limitations associated with oral anticoagulation (i.e. need for INR testing and dose adjustment, interaction with other drugs and food ingredients), ***aspirin is clearly preferred for***

secondary stroke prevention in patients with non-cardioembolic stroke. [25, Rank 1]

Aspirin

A meta-analysis of 11 randomized and placebo-controlled trials investigating aspirin monotherapy in secondary stroke prevention found a relative risk reduction of 13% (95% CI, 6–19%) for the combined end-point of stroke, myocardial infarction and vascular death.

Studies directly comparing the effects of aspirin in secondary stroke prevention failed to show any differences in stroke recurrence between doses of 30 mg/day and 283 mg/day, or 300 mg/day and 1200 mg/day. In contrast, gastrointestinal side effects and bleeding complications are dose dependent and bleeding rates increase significantly beyond a daily aspirin dose of 150 mg. An analysis of aspirin-treated patients from the Dutch- and UK-TIA trials found higher gastrointestinal bleeding rates among patients treated with higher aspirin doses. Observational data from the blockade of the GP IIb/IIIa receptor to avoid vascular occlusion (BRAVO) and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trials demonstrated an increased risk of bleeding with higher doses of aspirin. Most guidelines suggest lower doses of aspirin (i.e. 100 mg/day) given the higher rate of side effects associated with such a high dose of aspirin. [29, Rank 4]

Clopidogrel

The second-generation thienopyridine derivative clopidogrel was first investigated for secondary stroke prevention in the CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events) trial. Clopidogrel monotherapy (75 mg/day) was compared to aspirin (325 mg/day) in 19,185 patients with recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease. After a mean follow-up period of 1.9 years, the combined primary end-point (stroke, myocardial infarction and vascular death) was significantly reduced by 8.7% (95% CI, 0.3–16.5) under clopidogrel with an ARR of 0.5% per year. Clopidogrel was slightly more effective than aspirin in preventing the composite end-point of vascular events. The risks of gastrointestinal bleeds (2.0% versus 2.7%) and gastrointestinal side effects (15.0% versus 17.6%) were lower with clopidogrel than with aspirin. For the subgroup of patients with ischaemic stroke as the qualifying event, the relative risk reduction was 7.3% which was not statistically significant although the CAPRIE trial was not designed to specifically address this subgroup of patients. The highest benefit of clopidogrel over aspirin was seen in patients with peripheral arterial disease. [23, rank 2]

Ticlopidine

Ticlopidine was compared to placebo

in 1072 patients with recent ischaemic stroke. There was a 23% relative risk reduction of the composite vascular end-point with 3.5% absolute risk reduction over 2 years of follow-up. However, ticlopidine doubled the risk of major bleeding, increased the risk of severe neutropenia and was associated with an increased risk of thrombotic thrombocytopenic purpura, affecting about 1 in 5000 patients primarily during the first 3 months of treatment. Among 3069 patients with a recent ischaemic stroke, random assignment to ticlopidine (250 mg daily twice daily) compared with aspirin (650 mg twice daily) did not significantly reduce serious vascular events compared with aspirin (25.6% versus 24.2%, OR 0.93, 95% CI, 0.79–1.09) during up to 3 years of follow-up. Likewise, the African American Antiplatelet Stroke Prevention Study found no statistically significant difference between ticlopidine and aspirin in the prevention of recurrent stroke, myocardial infarction, or vascular death during a 2-year follow-up in 1809 African American patients with recent non-cardioembolic stroke. [20, rank 3]

Triflusal

Triflusal is a drug of the salicylate family but it is not a derivative of acetylsalicylic acid. It has been compared with aspirin in four randomized trials among patients with ischaemic stroke or TIA. A meta-analysis with a total of 2944 included patients showed no significant difference between triflusal and aspirin in the risk of serious vascular events (OR 1.02, 95% CI, 0.83–1.26). However, triflusal was associated with a lower risk of haemorrhagic complications, both minor (OR 1.60, 95% CI, 1.31–1.95) and major haemorrhages (OR 2.34, 95% CI, 1.58–3.46).

Lotrafiban

The oral glycoprotein IIb/IIIa inhibitor lotrafiban was compared with aspirin (75–325 mg/day) in the randomized BRAVO trial in 9190 patients with cardiovascular disease (41% of which had cerebrovascular disease at the time of entry). There was no significant difference in the primary end-point (composite end-point of all-cause mortality, myocardial infarction, stroke, recurrent ischemia requiring hospitalization and urgent revascularization), but serious bleeding complications were significantly more frequent in the lotrafiban arm (8.0% versus 2.8%; $P < 0.001$). [33, Rank 3]

Aspirin plus clopidogrel

Given the only modest effect of single antiplatelet therapy, the combination of aspirin and clopidogrel has been also investigated in long-term secondary stroke prevention. The management of atherothrombosis with clopidogrel in high-risk patients with recent TIA or ischaemic stroke (MATCH)

trial compared the combination of clopidogrel (75 mg/day) and aspirin (75 mg/day) with clopidogrel monotherapy in 7599 high risk patients with recent ischaemic stroke or TIA and at least one additional vascular risk factor. It failed to show superiority of combination antiplatelet therapy for the combined end-point of stroke, myocardial infarction, vascular death and hospitalization due to a vascular event. Instead, the combination resulted in a significant increase of life-threatening bleeding complications (absolute risk increase 1.3%, 95% CI, 0.6–1.9). The clopidogrel for high atherothrombotic risk and ischaemic stabilization, management and avoidance (CHARISMA) trial was a combined primary and secondary prevention study and compared the combination of clopidogrel (75 mg/day) and aspirin (75–162 mg/day) with aspirin monotherapy in 15,603 patients with either clinically evident cardiovascular disease or multiple cardiovascular risk factors. Similar to MATCH, CHARISMA failed to show a benefit for combination therapy in the overall study population and displayed a higher bleeding rate under the combination therapy. Patients with prior myocardial infarction, ischaemic stroke or symptomatic peripheral artery disease appeared to derive significant benefit from dual antiplatelet therapy with aspirin and clopidogrel. Again, one has to keep in mind that these data were derived from a post hoc analysis and CHARISMA was not designed to address this question with adequate statistical power. Therefore, only TIA/ischaemic stroke patients with a clear cardiac indication, such as an acute coronary syndrome or recently placed stent should receive the combination of clopidogrel and aspirin for a limited time. [26, Rank 3]

Aspirin plus dipyridamole versus clopidogrel

A direct head-to-head comparison of the combination aspirin (25 mg/twice a day) and extended-release dipyridamole (200 mg/twice a day) with clopidogrel (75 mg/day) did not show any significant difference in efficacy across major end-points in the PRoFESS (prevention regimen for effectively avoiding second strokes) trial. A total of 20,332 patients were followed for a median of 2.4 years. Recurrent stroke occurred in 9.0% of patients receiving aspirin/ extended-release dipyridamole and in 8.8% receiving clopidogrel. Aspirin/extended-release dipyridamole resulted in significantly more intracranial haemorrhages (1.4%versus 1.0%) and a higher dropout rate due to headache compared with clopidogrel (5.9%versus 0.9%). There was no subgroup of patients who had any benefit of one treatment regimen over the other. Treatment with combined aspirin and extended release dipyridamole versus clopidogrel in 1360 patients with acute, mild ischaemic

stroke recruited within 72 hrs did not differ in terms of effects on functional outcome, recurrence, death, bleeding or serious adverse events. Non-significant trends to reduced recurrence (OR = 0.56; 95% CI, 0.26–1.18) and vascular events (OR = 0.71; 95% CI, 0.36–1.37) were present with aspirin and extended release dipyridamole. [17, Rank 4]

An important adverse event of treatment with dipyridamole is headache. Similar to the PRoFESS trial, headache was also significantly increased in both the ESPS-2 and the ESPRIT. A total of 34% of patients in the aspirin/dipyridamole arm of ESPRIT (versus 13% in the aspirin monotherapy arm) terminated the trial prematurely mostly because of headache. The pathophysiology of this dipyridamole associated headache is not exactly known but there are similarities with migraine headache and dipyridamole might also induce migraine attacks in patients with a known migraine without aura. There are several reports about a mechanism of action of dipyridamole on the vascular system. Dipyridamole inhibits the reuptake of adenosine by red blood cells, platelets and the vascular endothelium, thereby increasing the extracellular level of adenosine. Adenosine activates the enzyme adenylate cyclase which results in an increase of cyclic adenosine monophosphate and subsequently in vasodilation. Furthermore, dipyridamole inhibits the enzyme phosphodiesterase which results in an increase of cyclic GMP by endothelium derived vasodilation factors (e.g. nitric oxide). The vasodilation might be responsible for the observed higher headache rate. Several smaller randomized trials that used an initial titration phase (initial 14 days) with a lower dose of dipyridamole showed a reduction in the rate of associated headaches. However, one has to keep in mind to add daily aspirin in this titration phase.

In conclusion, ***clopidogrel and the combination aspirin/ extended-release dipyridamole are more effective compared to aspirin.*** Patients at high risk should preferably receive a more potent secondary prevention therapy to derive the greatest benefit in terms of absolute risk reduction. To this aim, several risk stratification scores have been validated. The Essen stroke risk score (ESRS) was developed from the data subset of 6431 cerebrovascular patients from the CAPRIE trial and subsequently validated in patients with acute ischaemic stroke as well as stable cerebrovascular outpatients. On a 10-point scale, the ESRS predicts 1-year risk of recurrent stroke and combined cardiovascular events. Patients with an ESRS ≥3 have a recurrent annual stroke risk >4% and thus should be considered as high risk in secondary stroke prevention, while low-dose aspirin (85–150 mg/day) is recommended in

patients with a lower risk of recurrent stroke. A prospective comparison of four long-term prognostic scores in acute stroke patients yielded similar accuracies of the individual predictions. Because a prognostic score should also be easy to apply, the ESRS lends itself for use in daily clinical practice. [15, Rank 5]

Antiplatelets in Patients with Symptomatic Intracranial Stenosis

The WASID (warfarin-aspirin symptomatic intracranial disease) trial compared oral anticoagulation with warfarin (target INR 2.0–3.0) and high dose of aspirin (1300 mg/day) in 569 patients with symptomatic, angiographically proven intracranial stenosis 50–99%. Although there was no difference in the primary end-point of ischaemic stroke, brain haemorrhage or death from vascular causes other than stroke, the study was prematurely stopped after a mean follow-up of 1.8 years due to a significantly elevated rate of death and major bleeding complications in the anticoagulation arm. ***Thus, aspirin is currently recommended as treatment of choice in secondary stroke prevention in patients with a symptomatic intracranial arterial stenosis.*** Most guidelines suggest lower doses of aspirin (e.g. 100 mg/day) given the higher rate of side effects associated with such a high dose of aspirin. Nevertheless, it remains to be determined if patients with intracranial stenosis benefit from lower doses of aspirin.

Cilostazol has been reported to reduce restenosis rate after coronary angioplasty and stenting. The Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis (TOSS) was performed to investigate the effect of cilostazol on the progression of intracranial arterial stenosis. There was no stroke recurrence in either the cilostazol or placebo group, but there was one death and two coronary events in each group. Progression of symptomatic intracranial arterial stenosis in the cilostazol group was significantly lower than that in the placebo group.

In patients with peripheral arterial disease, the addition of cilostazol to a therapy with aspirin and/or clopidogrel did not increase bleeding times, compared with either agent alone. In another study of patients with peripheral arterial disease, the incidence of hemorrhagic events was comparable in subjects receiving cilostazol and in those receiving placebo. In a meta-analysis of randomized controlled trials in patients with a drug-eluting stent, the incidence of hemorrhagic events in the group receiving triple antiplatelet therapy (cilostazol plus aspirin and clopidogrel) was similar to that in the group receiving dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. Thus, the addition of cilostazol may

enhance the preventive effects of classical antiplatelet agents (aspirin, clopidogrel) in high-risk Ischemic Stroke patients, without increasing hemorrhagic risk. [14, Rank 3]

Antiplatelet Agent Recommendations by AHA

1	For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events	Class I; Level of Evidence A
2	Aspirin (50–325 mg/d) monotherapy Aspirin (50–325 mg/d) monotherapy Combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily as initial therapy after TIA or ischemic stroke for prevention of future stroke	Class I; Level of Evidence B
3	Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole also in patients who are allergic to aspirin	Class IIa; Level of Evidence B
4	The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics	Class I; Level of Evidence C
5	The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 21 days	Class IIb; Level of Evidence B
6	The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA	Class III; Level of Evidence A
7	For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin	Class IIb; Level of Evidence C
8	For patients with a history of ischemic stroke or TIA, AF, and CAD, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events	Class IIb; Level of Evidence C
9	Unstable angina and coronary artery stenting represent special circumstances in which management may warrant DAPT/VKA therapy	New recommendation

Table 2: AHA guidelines on Anti platetherapy for Stroke

Special cases

Antiplatelets in Stroke Patients with Patent Foramen Ovale

Patent foramen ovale ***(PFO) is present in about 25% of the general population,*** and can be found in up to 40% of younger patients with otherwise cryptogenic stroke. In younger stroke patients (18–55 years of age) with cryptogenic stroke and PFO only, the overall risk of stroke recurrence under antiplatelet therapy with aspirin (300 mg/day) was 2.3% over 4 years of follow-up. Although not sufficiently powered, the PICSS (Patent foramen ovale In Cryptogenic Stroke Study) study in 203 cryptogenic stroke patients with PFO did not find any evidence for superiority of oral anticoagulation (target INR of 1.4–2.8) versus aspirin (325 mg/day). In the absence of any published data from randomized trials comparing medical therapy and percutaneous device closure in ischaemic stroke patients with Patent foramen ovale, aspirin (300 mg/day) is currently recommended by secondary stroke prevention guidelines as first line treatment. The preliminary results of the randomized CLOSURE I trial which compared treatment by device closure of Patent foramen ovale and best medical therapy (aspirin 325 mg/day and/or warfarin) did not show superiority of the percutaneous intervention in the prevention of recurrent strokes and TIAs. [10, Rank 4]

Upcoming 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. 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, triple therapies with TARDIS, or novel antiplatelet agents with the SOCRATES 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. 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. [29, Rank 5]

Conclusion

Stroke is a common and often devastating event characterized by a widespread, systemic, inflammatory, and thrombotic milieu. Platelets and leukocytes (including monocytes and macrophages) mediate atherothrombosis through a series of processes. These key effector cells modulate cellular activation and adhesion (both to one another and to endothelial cells), the release of cytokines, and the synthesis and release of other factors that promote the progression of atherosclerosis and the development of an acute thromboembolic event. Current therapies to reduce secondary stroke target different pathways in platelets. Select agents, in addition to their direct inhibition of platelet function, also modulate inflammatory responses of other cells. Inhibition of dysregulated inflammation may translate to improved clinical efficacy, but further data are clearly needed to understand the complexities of secondary stroke and to optimize current treatments. [40, Rank 5]

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