ORAL ANTIPLATELET THERAPY IN STROKE PREVENTION. MINIREVIEW

Michal Kral[a]*, Roman Herzig[a], Daniel Sanak[a], David Skoloudik[a], Ivanka Vlachova[a], Andrea Bartkova[a], Petr Hlustik[a], Michal Kovacik[b], Petr Kanovsky[a]

[a] *Stroke Center, Department of Neurology, Faculty of Medicine and Dentistry, Palacky University and University Hospital, Olomouc, Czech Republic*
[b] *Department of Neurology, Central Military Hospital, Ruzomberok, Slovakia*
E-mail: kral_michal@centrum.cz

Background. Antiplatelet therapy plays a crucial role in the primary and secondary prevention of noncardioembolic ischemic stroke / transient ischemic attacks (IS/TIA). Several antiplatelet agents are available. This review deals with the characteristics of particular antiplatelet agents as well as choice of antiplatelet treatment in various situations, based on the evidence and international recommendations.

Methods. PubMed and Stroke Trials Registry on-line databases and the European Stroke Organisation Guidelines for Management of IS/TIA 2008 and update of the recommendations of the American Heart Association / American Stroke Association Council 2008 on Stroke were used.

Results. Acetylsalicylic acid (ASA) is the only antiplatelet drug used in primary prevention, mainly to reduce the risk of myocardial infarction (MI), but also in women aged 45 years or more and in some patients with non-valvular atrial fibrillation to reduce risk of IS/TIA.

In the secondary prevention of noncardioembolic IS/TIA, ASA in combination with long release dipyridamole (DIP) and clopidogrel (CLOP) alone are considered first choice therapies. The choice of the particular antiplatelet agent should be individualized according to the patient risk factor profiles and treatment tolerance. ASA alone or triflusal can be used alternatively in patients who cannot be treated with either ASA+DIP or CLOP. The use of indobufen should be considered only in patients in need of temporary interruption of the antiplatelet therapy. Ticlopidine (TIC) should not be newly introduced into the treatment. Currently, insufficient data are available on the use of cilostazol in IS/TIA prevention.

ABBREVIATIONS

ADP	– Adenosindiphosphate
AF	– Atrial fibrillation
AHA/ASA	– American Heart Association/American Stroke Association
ASA	– Acetylsalicylic acid
cAMP	– Cyclic adenosine monophosphate
CAPRIE	– Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CARESS	– Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis
CATHARSIS	– Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis
CATS	– Canadian American Ticlopidine Study
CHARISMA	– Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CLOP	– Clopidogrel
COX-1	– Cyklooxygenase 1
COX-2	– Cyklooxygense 2
CREDO	– Clopidogrel for the Reduction of Events During Observation
CSPS	– Cilostazol Stroke Prevention Study
CSPSII	– Cilostazol Stroke Prevention Study II
CURE	– Clopidogrel in Unstable angina to prevent Recurrent Events
DIP	– Dipyridamole
ESO	– European Stroke Organisation
ESPRIT	– European / Australasian Stroke Prevention in Reversible Ischaemia Trial
ESPS 2	– Second European Stroke Prevention Study
EUSI	– European Stroke Initiative
IS	– Ischemic stroke
MATCH	– Management of Atherothrombosis with Clopidogrel in High-risk patients
MI	– Myocardial infarction
PCI-CURE	– Percutaneous Coronary Intervention – The Clopidogrel in Unstable angina to prevent Recurrent Events
PDE	– Phosphodiesterase
PGH2	– Prostaglandin H2
RRR	– Relative risk ratio
SINBA	– Studio Indobufene Nel Bypass Aortocoronarico
TACIP	– Triflusal Aspirin Cerebral Infarction Prevention
TAPIRSS	– Triflusal versus Aspirin for the Prevention of Infarction: A Randomized Stroke Study
TASS	– Ticlopidine Aspirin Stroke Study
TCD	– Transcranial Doppler
TIA	– Transient ischemic attack
TIC	– Ticlopidine
TISS	– Ticlopidine Indobufen Stroke Study
TRIF	– Triflusal
TXA2	– Tromboxan A2
UK-TIA	– United Kingdom TIA Study Group

INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality worldwide[1] and is the most important cause of morbidity and long-term disability in Europe, and demographic changes will result in the increase of both the incidence and the prevalence. It is also the second most common cause of dementia, the most frequent cause of epilepsy in the elderly, and a frequent cause of depression[2,3].

Stroke incidence rates vary in the Europe – from 2.0–2.5 per 1000 inhabitants in the Western Europe, with ischemic stroke (IS) representing about 85% of all stroke, to 3.0 – 5.0 per 1000 inhabitants in the Eastern Europe, with 70–85% ratio of IS[4]. When considering the etiology of IS, the atherotrombotic brain infarction represents almost 70%, emboligenic etiology about 30% and other causes about 1–2% of all IS[5-7].

Oral antiplatelet therapy currently plays an indispensable role both in the primary and secondary prevention of IS, in particular IS of atherothrombotic etiology. In this regard, its efficacy is at least fully comparable with oral anticoagulation therapy and it has markedly fewer side effects[8-11]. These days acetylsalicylic acid (ASA) is the most frequent antiplatelet drug used both in primary and secondary IS prevention. However, the effort to develop more efficient and safer antiplatelet drugs has been growing over the recent decades; thus ASA is being compared to the new generation of antiplatelet drugs. This paper reviews the various types of antiplatelet therapy used in stroke prevention.

ANTIPLATELET DRUGS

The list of antiplatelet drugs used in the stroke prevention is presented in Table 1 and the mechanisms of their action in Fig. 1.

Acetylsalicylic acid

ASA lowers platelet aggregation through the irreversible acetylation of cyklooxygenase 1 (COX-1) and cyklooxygenase 2 (COX-2), which catalyze conversion of arachidonic acid to prostaglandin H2 PGH2, representing the direct antecedent of eikosanoids (prostaglandin, tromboxan A2 and prostacyclin). ASA has a short biological half-time (15 to 20 min), and is a 50 to 170 times stronger inhibitor of COX-1 than COX-2. This results in the inhibition of COX-1 dependent production of tromboxan A2 (TXA2), which induces aggregation and vasoconstriction

Table 1. The list of antiplatelet drugs used in the stroke prevention.

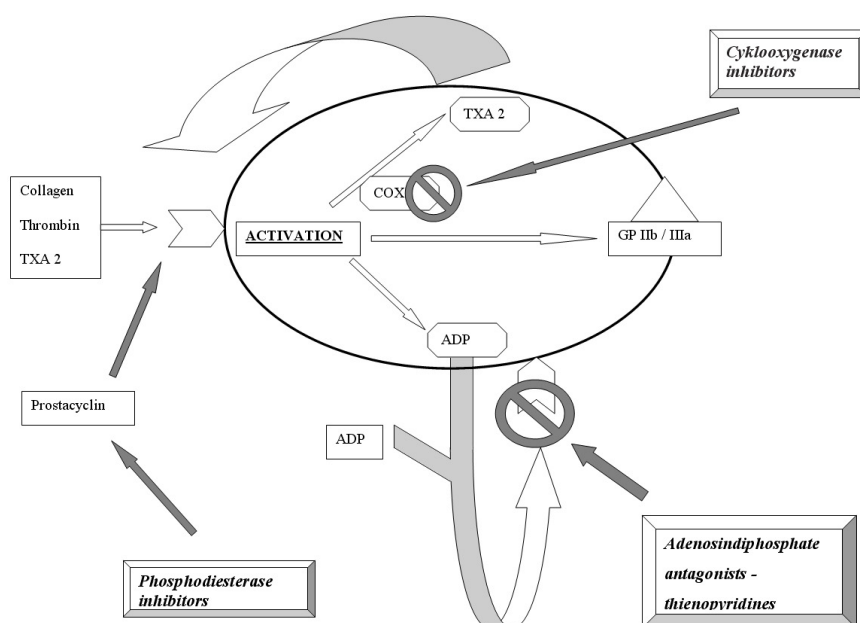| ORAL ANTIPLATELET AGENTS IN ISCHEMIC STROKE PREVENTION	
Cyklooxygenase (COX) inhibitors	acetylsalicylic acid, indobufen, triflusal
Phosphodiesterase (PDE) inhibitors	dipyridamole, cilostazol
Adenosindiphosphate (ADP) antagonists – thienopyridines	ticlopidine, clopidogrel

Fig. 1. The mechanisms of antiplatelet drugs used in the stroke prevention.

in megacaryocytes and in acaryote platelets. This effect lasts through the platelet lifetime, for 7 to 10 days, and it can be achieved by repeated ASA administration at a low dose of 30 – 160 mg daily. Despite the irreversible COX-1 inhibition in the platelets, no severe bleeding occurs as the platelet aggregation is also activated by other mechanisms – e.g. by the direct intracellular activation of Ca^{2+}, by high concentration of ADP and thrombin and by other mechanisms independent of TXA2 – by serotonin and by platelet aggregation factors.

The endothelial production of prostacyclin PGI2, which has the reverse effect to TXA2 (antiaggregation and vasodilatation), is dependent on the co-operation of COX-1 and COX-2. However, PGI2 production is affected only by intermediate (160–500 mg) and high (500–1500 mg) doses of ASA due to the different ASA selectivity to COX-1 and COX-2 and also due to the fact that PGI2 is produced by nuclear endothelial cells with the capacity to produce new COX.

Only a nonsignificant effect of ASA in the primary prevention of strokes in patients with type 2 diabetes mellitus was found by De Gaetano et al.[12]. In a separate study in healthy women aged 45 years or more, ASA reduced stroke (RR 0.83; 95% CI 0.69 – 0.99) and ischemic stroke (RR 0.76; 95% CI 0.63 – 0.93) but caused a nonsignificant increase in hemorrhagic stroke over 10 years; it did not reduce the risk of fatal or nonfatal myocardial infarction (MI), or cardiovascular death[13].

In a non-selected population, the antiplatelet effect of ASA in primary stroke prevention has not been confirmed[14-17].

At present, the recommended daily dose of ASA in secondary prevention is 50–325 mg daily[10,11], whereas the higher doses are not associated with any greater efficacy of the antiplatelet therapy but are associated with a higher incidence of side effects. For example, the incidence of IS or TIA was comparable for ASA doses of 300 and 1200 mg daily (22.1 versus 21.6%) in the United Kingdom TIA (UK-TIA) trial[18], and comparable results were also obtained for the ASA doses 30 and 283 mg daily (14.7 vs. 15.2%) in the Dutch TIA trial too[19].

Side effects represent ASA intolerance in patients with asthma, gout, chronic rhinitis, renal insufficiency, chronic or recurrent urticaria and gastroduodenal ulcers. The resistance to ASA treatment represents another limitation of this therapy. Currently, it is possible to assess the efficacy of ASA therapy using laboratory methods to verify platelet aggregability (mostly based on optical aggregometry and using arachidonic acid) but these methods have not been standardized and are not generally accepted.

ASA therapy is also associated primarily with the increased incidence of upper dyspectic syndrome, increased number of nonfatal extracranial hemorrhages (most often in the gastrointestinal tract – 0.3% without ASA and 0.5% annually on ASA therapy), and with the increased risk of intracranial hemorrhage (approximately 1 case per 1000 patients treated for a period of three years)[20,21].

Dipyridamole

The complex mechanism of the effects of dypiridamole (DIP), phosphodiesterase (PDE) type 5 inhibitor, is mainly associated with the metabolism of adenosine which has a powerful vasodilatory effect and also influences platelet aggregability and adhesivity. The normal effect is mediated by the blockade of adenosine uptake in erythrocytes, platelets and endothelial cells, leading to increased concentration of adenosine at the interface between the platelets and the blood vessel wall. Increase in the inhibitory effect of nitrogen dioxide on platelets in blood plasma and inhibition of cyclic adenosine monophosphate (cAMP) degradation being catalyzed by PDE, represent other mechanisms of the effect of DIP.

It has not been shown that DIP is more effective than ASA[22]. However because of the supposed additive effect of DIP, several trials assessing the effectiveness of combinations of DIP with other antiplatelet drugs (mostly with ASA, but also with sulphapyrazone) have been carried out. According to the metanalysis, there is no evidence that DIP reduces the risk of vascular death, though it may reduce the risk of further vascular events in patients with previous IS[23].

This conclusion is based on the results of the Second European Stroke Prevention Study (ESPS 2), which investigated the safety and efficacy of low-dose ASA (50 mg daily), modified-release DIP (400 mg daily), and the two agents in combination for secondary IS prevention. Compared to placebo, stroke risk was reduced by 18% with ASA alone (p = 0.013), 16% with DIP alone (p = 0.039), and 37% with combination therapy (p < 0.001). Risk of stroke or death was reduced by 13% with ASA alone (p = 0.016), 15% with DIP alone (p = 0.015), and 24% with the combination (p < 0.001). The treatment had no statistically significant effect on the death rate alone. All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received ASA than placebo or DIP[22].

The superiority of the combination of ASA (30–325 mg, mean 75 mg daily) with extended-release DIP (200 mg twice daily) over ASA (30 – 325 mg, mean 75 mg daily) alone was also documented in the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) trial performed in patients with a history of TIA or minor IS of presumed arterial origin. The combination of ASA + DIP was associated with an absolute risk reduction of primary outcome event (the composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication, whichever happened first) 1.0% per year in this study24.

The efficacy of the combination of ASA (25 mg twice daily) with extended-release DIP (200 mg twice daily) in secondary stroke prevention was compared to clopidogrel (75 mg daily) in the Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) study. Recurrent stroke (as the study primary outcome event) occurred in 9.0% of patients assigned to ASA + extended-release DIP and in 8.8% of patients randomly assigned to clopidogrel. The occurrence of secondary outcome events, a

composite of vascular events (stroke, MI or death from vascular causes), was 13.1% in both subgroups. Major hemorrhagic event occurred in 4.1 versus 3.6% in the particular subgroups25.

Use of ASA (25 mg twice daily) with extended-release DIP (200 mg twice daily) is not associated with an increased risk of fatal extracranial bleeding but it is associated with an increased incidence of headache and dyspeptic syndrome. Provocation of anginous pain due to the steal phenomenon in patients with coronary stenosis is the most serious side effect of this drug. Thus, special attention is necessary during its administration in patients with unstable angina pectoris, recent MI, subvalvular aortic stenosis and haemodynamic instability (decompensated heart insufficiency). The potentiation of the hypotensive effect by the vasodilatation action of adenosine and the antagonistic effect against cholinesterase inhibitors, possibly causing the myasthenia gravis symptoms, are other possible side effects of this combination.

Ticlopidine

Ticlopidine (TIC) belongs to the group of thienopyridines, whose antiplatelet effect is based on the inhibition of adenosindiphosphate (ADP) and also on the blockage of the ADP mediated binding of fibrinogen membrane thrombocyte receptor, glycoprotein IIb/IIIa.

The Ticlopidine Aspirin Stroke Study (TASS) found only slightly higher efficacy of TIC 250 mg twice daily than ASA 1300 mg once daily in the secondary prevention of stroke. However, when compared to ASA, the use of TIC is associated with markedly more frequent side effects, such as diarrhea, gastro-intestinal intolerance, skin rash and haematological disorders but not with increased bleeding complications[26]. For example, within the TASS and Canadian American Ticlopidine Study (CATS, 250 mg of TIC twice daily), thrombocytopenia was observed in up to 2.4% and neutropenia in almost 2% of cases, out of which 1% represented a seriously impaired haemopoesis, although mostly regressing after the interruption of TIC administration[26,27]. Owing to these severe side effects and also the higher price, TIC serves as a second choice antiplatelet drug reserved for patients with ASA intolerance or with recurrent IS/TIA on already established ASA therapy. TIC administration was associated with necessary blood count check-ups, especially within the first three months. Currently, after the introduction of clopidogrel (CLOP), the use of TIC is limited. It should not be newly introduced in the therapy, but its use can be continued in already treated patients with no side effects of TIC therapy.

Clopidogrel

CLOP is also a thienopyridine with a similar mechanism of effect as TIC but its administration is associated with fewer side effects. Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study documented the superiority of CLOP 75 mg daily over ASA 325 mg daily in the secondary prevention of IS, with a 8.7% reduction of the risk of vascular (coronary and cerebral) events in patients treated with CLOP[28,29].

According to the same study, CLOP is associated with fewer side effects than TIC and, compared to ASA, the incidence of skin rash and diarrhoea is about one third lower and also the occurrence of gastrointestinal bleeding and upper-type dyspepsia is significantly lower for CLOP. The absence of risk of haemopoesis inhibition, mainly neutropenia, represents the most significant advantage of CLOP over TIC and also the main reason why CLOP is replacing TIC in the therapy.

As mentioned, the PRoFESS study found the same efficacy for CLOP (75 mg daily) as the combination of ASA (25 mg twice daily) and extended-release DIP (200 mg twice daily) in the secondary prevention of stroke. However, CLOP was better tolerated in this study, with fewer adverse events, such as headache, nausea, vomiting, diarrhea and dizziness, associated with fewer treatment discontinuations[25].

Combination clopidogrel + acetylsalicylic acid

Although it was presumed, that the different mechanism of the effect of CLOP and ASA will contribute to the additive effect of their combined therapy, clinical trials have not confirmed these expectations. For example, in the Clopidogrel in Unstable angina to prevent Recurrent Events study (CURE) study, this dual antiplatelet therapy (75 mg daily of CLOP and 75 to 325 mg daily of ASA) was associated with the decreased relative and absolute risk of non-fatal MI, stroke and vascular death (20% relative risk reduction) and with higher bleeding risk (38% relative excess) than ASA (75 to 325 mg daily) alone[30].

The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study tested the antiplatelet effect of CLOP 75 mg + ASA 75 mg daily versus CLOP 75 mg daily alone in patients with the history of IS (within the last 3 months) and with the presence of at least one vascular risk factor. Dual antiplatelet therapy was associated with a nonsignificant decrease in relative risk of MI, fatal stroke and rehospitalizations due to acute stroke. However, this reduction was more than outweighted by a significant increase of the risk of life threatening intracerebral haemorrhages in the same study[31]. Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study compared ASA 75 – 162 mg + CLOP 75 mg daily versus ASA 75 – 162 mg and it failed to confirm that CLOP + ASA were more effective than ASA alone in reducing the rate of MI, stroke, or death from cardiovascular causes[32]. Based upon the results of the these studies and also according to the European Stroke Organization 2008 guidelines, the combined use of CLOP and ASA (each 75 mg a day) is indicated only in the case of the coincidental occurrence of IS/TIA with non-Q-wave MI or with unstable angina pectoris[10].

Percutaneous transluminal angioplasty of cervical or intracranial arteries with stenting represents the next indication for the temporary use of the dual antiplatelet therapy with CLOP and ASA, as comfirmed in several studies, such as Percutaneous Coronary Intervention – The Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) (ref.[33]) and Clopidogrel for the

Reduction of Events During Observation (CREDO) (ref.[34]). The superiority of the CLOP + ASA combined antipletelet therapy in comparison to the combination of ASA with heparin after carotid artery stenting was reported by McKevitt et al.[35]. The neurological complication rate in the 24-hour heparin group was 25% versus 0% in the CLOP group (p = 0.02) and the 30-day 50 – 100% stenosis rates were 26% in the heparin versus 5% in the CLOP group (p = 0.10) in this study. However, the study was terminated prematurely due to the unacceptable number of bleeding complications in the heparin group (bleeding complications occurred in 17% of the heparin and 9% of the CLOP group) (ref.[35]).

The dual antiplatelet therapy with CLOP + ASA is not recommended for the secondary prevention of IS/TIA with the above mentioned exceptions[10,11], although this therapy was associated with a significant decrease in number of asymptomatic microembolic events, as assessed by transcranial Doppler (TCD) examination, found in patients with carotid stenosis $\geq 50\%$, who experienced an IS/TIA in the ipsilateral carotid territory within the last 3 months, in the CARESS study[36], and also with a significant reduction of the number of such events detected by TCD within 3 hours after carotid endarterectomy, as reported by Payne et al.[37].

Indobufen

Indobufen, belonging to the group of non-steroid antiphlogistic drugs, reversibly inhibits the thrombocyte, resulting in decreased production of thromboxan B2. Its effect is similar to that of ASA, but is only short-term with regard to the reversibility of the COX blockade. In the past, the clinical effects of indobufen 200 mg twice daily were compared to ASA 300 or 325mg + DIP 75 mg 3 times daily after the implantation of the aorto-coronary bypass in a Studio Indobufene Nel Bypass Aortocoronarico (SINBA) study, in which the indobufen as effective as ASA+DIP in the prevention of early and late occlusion of the saphenous grafts[38].

In the Ticlopidine Indobufen Stroke Study (TISS), the effect of indobufen (200 mg daily) was markedly worse than TIC (250 mg daily) in the secondary stroke prevention. TIC effect was significantly better than indobufen in the composite of fatal and non fatal events (49.6% relative risk reduction in TIC), or death alone (54.4% relative risk reduction in TIC) in this study[39].

Presently, due to the lack of clinical studies, no data are available supporting the administration of indobufen as an alternative treatment to ASA. Indobufen administration is also not justified in patients with a history of gastric ulcer due to the same mechanism of effect and the same ulcerogenic potential of indobufen and ASA. Thus, a short-term antiplatelet treatment of patients in risk (for example before a planned surgery) remains the only indication of indobufen administration thanks to its reversible antiplatelet effect.

Triflusal

Triflusal (TRIF) is a fluorinated salicylate agent, with a chemical structure very similar to ASA, which was de-

veloped more than 20 years ago in Spain, and currently is registered in Italy, Portugal, Greece, some countries in Asia and in the majority of countries of Latin America.

TRIF irreversibly inhibits COX-1 and reduces thromboxane B2 production, but to a lesser degree compared to ASA.

The effect of TRIF was assessed by two clinical studies – Triflusal versus Aspirin for the Prevention of Infarction: A Randomized Stroke (TAPIRSS) (ref.[40]), a multicentric pilot study, including 431 patients, and Triflusal Aspirin Cerebral Infarction Prevention (TACIP) (ref.[41]), including 2113 patients. In both studies, the effect of TRIF 600 mg a day and ASA 325 mg a day was compared. The combined incidence of cardiovascular death, non-fatal stroke or non-fatal MI was not significantly different in the TACIP study (13.1% in TRIF vs. 12.4% in ASA). However, a significant decrease in total incidence of extra- and intracranial hemorrhages was observed in the TACIP study (16.4% in TRIF vs. 24.5% in ASA) (ref.[41]).

Similar findings were also observed in the TAPIRSS study – no differences were found in the primary endpoint that combined the incidence of vascular death, cerebral ischemic infarction, nonfatal MI, or major hemorrhage (13.9% in ASA vs. 12.7% in TRIF). In a post hoc analysis, the overall incidence of major and minor hemorrhagic events was significantly lower in TRIF group (2.8%) than the ASA group (8.3%) (ref.[40]). TRIF is being used in the above mentioned countries, especially in Spain, as an alternative to ASA in cases of ASA intolerance.

Cilostazol

Cilostazol is an antiplatelet agent that inhibits (like dipyridamole) PDE in platelets and vascular endothelium. However, cilostazol inhibits type 3 PDE, which is specific for cyclic adenosine monophosphate. Cilostazol as well as dipyridamole are known to have both antiplatelet and a vasodilating effect as an essential effect of PDE inhibitors. It is being used as a general anti-thrombotic agent and in the stroke prevention in some Asian countries. In the US and in some EU countries, cilostazol is approved only for the treatment of peripheral artery disease.

In the Cilostazol Stroke Prevention Study (CSPS), a randomized double-blind, placebo-controlled trial involving more than 1000 Japanese patients, cilostazol (100 mg twice daily) was found to significantly reduce the risk of secondary stroke by 41.7% when compared to placebo. The greatest risk reduction (43.4% in cilostazol versus placebo) was found in patients who initially presented with lacunar infarction, suggesting that cilostazol has a specific effect against small-vessel disease. These clinical benefits were not associated with adverse events[42]. The clinical implications of the CSPS results are limited due to the fact that patients were also not randomized to the ASA (a standard antiplatelet treatment at the time of the study). Thus, direct comparison of the cilostazol and ASA effect was not made.

This direct comparison of the efficacy and safety of cilostazol (100 mg twice daily) and ASA (81 mg once daily) in the secondary stroke prevention is the aim of the CSPS II study. Subject recruitment is already finished, but

the final results are not yet available. Cilostazol-Aspirin THerapy Against Recurrent Stroke with Intracranial artery Stenosis (CATHARSIS) study is another ongoing study, evaluating the effect of ASA 100 mg daily plus cilostazol 200 mg daily and ASA 100mg daily alone on the progression of intracranial arterial stenosis in 200 chronic stroke patients with 50–99% stenosis; the patients should be followed for up 2 years. Thus, further data are needed to assess the cilostazol efficacy in the stroke prevention in comparison to ASA, especially in a multi ethnic population.

ANTIPLATELET THERAPY IN THE PRIMARY AND SECONDARY PREVENTION OF ISCHEMIC STROKE / TRANSIENT ISCHEMIC ATTACK

Primary prevention

According to the European Stroke Organisation (ESO) Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008(ref.[10]), low dose ASA is recommended in women aged 45 years or more who are not at increased risk for intracerebral haemorrhage and who have good gastrointestinal tolerance; however, its effect is very small. It is also recommended that low-dose ASA may be considered in men for the primary prevention of MI; however, it does not reduce the risk of ischaemic stroke. ASA may be recommended for patients with non-valvular AF who are younger than 65 years and free of vascular risk factors. Unless contraindicated, either ASA or an oral anticoagulant (international normalized ratio, INR, 2.0–3.0) is recommended for patients with non-valvular AF who are aged 65 – 75 years and free of vascular risk factors. Low-dose ASA is recommended also for patients with asymptomatic ICA stenosis > 50% to reduce their risk of vascular events. Other antiplatelet drugs than ASA have not been studied in asymptomatic subjects and therefore cannot be recommended for primary stroke prevention.

Secondary prevention

According to the ESO 2008 guidelines[10], an appropriate antithrombotic therapy should be given to prevent IS recurrence and further vascular events. It is recommended that patients not requiring anticoagulation should receive antiplatelet therapy. Where possible, combined ASA and DIP, or CLOP alone, should be given. Alternatively, ASA alone, or TRIF alone, may be used.

The combination of ASA and CLOP is not recommended in patients with recent ischaemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting); treatment CLOP 75 mg and ASA 75 mg daily should be given for up to 9 months after the event[10]. In patients with cardioembolic stroke it is recommended that combined low-dose ASA and DIP should be given if oral anticoagulation is contraindicated. It is recommended that patients who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors.

Also the updated American Heart Association/American Stroke Association (AHA/ASA) 2008 recommendations for the prevention of stroke in patients with stroke and transient ischemic attack[11] are very similar to the ESO 2008 guidelines. ASA (50 to 325 mg/d) monotherapy, the combination of ASA and extended-release DIP, and CLOP monotherapy are all acceptable options for initial therapy. The combination of ASA and extended-release DIP is recommended over ASA alone. CLOP may be considered over ASA alone on the basis of direct-comparison trials. Combination therapy of ASA and CLOP is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (i.e., coronary stent or acute coronary syndrome). For patients who have an ischemic cerebrovascular event while taking ASA, there is no evidence that increasing the dose of ASA provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well studied in patients who have had an event while receiving aspirin.

CONCLUSION

ASA is the only antiplatelet drug used in the primary prevention, mainly to reduce the risk of MI, but also in women aged 45 years or more and some patients with non-valvular AF to reduce the risk of IS/TIA. In the secondary prevention of noncardioembolic IS/TIA, ASA in combination with long release DIP and CLOP alone are considered the first choice therapy. The choice of the particular antiplatelet agent should be individualized according to the patient risk factor profiles and treatment tolerance. Combinations of ASA and CLOP can be used only in specific cases, ASA alone, or TRIF can be used alternatively in patients who cannot use ASA + DIP or CLOP alone. The use of indobufen should be considered only in patients in need of fast interruption of the antiplatelet therapy.

TIC should not be newly introduced in the therapy, but its use can be continued in already treated patients with no side effects of TIC therapy. There are insufficient data available for the use of cilostazol in IS/TIA prevention.

Conflict of Interest: There are no conflicts of interest associated with this manuscript, financial or otherwise.

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