

# Antiplatelet therapy in secondary stroke prevention – state of the art

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## Abstract

Our objective is to provide the reader with an overview as well as an update on current antiplatelet therapy for secondary stroke prevention. Relevant journals were hand-searched by the authors to compile a broad but by far not comprehensive summary of innovative and clinically relevant studies. Aspirin, clopidogrel and the combination of dipyridamole plus aspirin are the cornerstone therapy in secondary prevention after non-cardio-embolic stroke or transient ischaemic attack. A head-to-head comparison showed no difference in the prevention of recurrent stroke between dipyridamole plus aspirin and clopidogrel. More potent antiplatelet drugs or the combination of aspirin and clopidogrel prevent more ischaemic events, but also lead to more bleeding complications. For secondary stroke prevention in patients with atrial fibrillation, oral anticoagulation is more effective than aspirin or the combination of aspirin and clopidogrel.

**Keywords:** ischaemic stroke • transient ischaemic attack • antiplatelet • anticoagulation • secondary prevention

## Introduction

Ischaemic stroke is the leading global cause of disability in the developed world, and the third leading cause of mortality [1]. Due to an increasing life expectancy, the rate of first stroke is still expected to rise despite of increasingly effective prevention strategies. About 75–85% of patients survive a first ischaemic stroke, but between 8% and 15% suffer a recurrent stroke in the first year. Risk of stroke recurrence or stroke following transient ischaemic attack (TIA) is highest in the first days following the cerebrovascular event and declines over time [2, 3]. Antithrombotic agents including antiplatelets have been established as a cornerstone in the treatment of both acute ischaemic stroke/TIA and in secondary stroke prevention. The latest meta-analysis by the Antithrombotic Trialist's Collaboration included 287 trials with 135,000 patients randomized to

antiplatelet therapy *versus* control and 77,000 patients randomized to different antiplatelet regimens [4]. Overall, antiplatelets reduced the relative risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke or vascular death) by about 25%. In those patients with a previous stroke or TIA ( $n = 23,020$ ), 36 serious events were prevented among 1000 patients treated for 2 years and the benefit substantially outweighed the absolute risks of major extracranial bleeding. Nevertheless, there are still controversies about the choice of antiplatelet agents or their combination in different stroke aetiologies, optimal dosing of aspirin as well as the time when to start and the duration of antiplatelet therapy for secondary stroke prevention.

In this review, we will discuss current best evidence of antiplatelet therapy in acute and long-term secondary stroke prevention.

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## Prevention of recurrent stroke using antiplatelets in patients with acute ischaemic stroke

### Aspirin

Acetylsalicylic acid, later on named aspirin, was originally developed 115 years ago for the treatment of joint pain and headache. Since aspirin is affordable, widely available, efficacious and reasonably safe, aspirin is still the most widely used antiplatelet agent in secondary stroke prevention. The antithrombotic treatment potential of aspirin is primarily related to the irreversible inhibition of the enzyme cyclooxygenase in platelets resulting in a decreased production of prostaglandins and thromboxane A<sub>2</sub>. Furthermore, aspirin reduces inflammation by the formation of nitric oxide radicals and protects endothelial cells from oxidative stress. Aspirin is the only antithrombotic agent that has been shown to be modestly effective when administered in the acute phase (first 48 hrs) in two large randomized trials. The IST (International Stroke Trial) randomized 19,435 patients within 48 hrs of symptom onset to receive aspirin (300 mg/day), subcutaneous heparin, both or placebo [5]. Patients allocated to heparin had significantly fewer recurrent ischaemic strokes within 14 days, but this was offset by a similar increase in haemorrhagic strokes. Thus, the difference in death or non-fatal recurrent stroke compared to placebo was not significant (11.7% *versus* 12.0%). Patients treated with aspirin had significantly fewer recurrent ischaemic strokes within 14 days with no significant excess of haemorrhagic strokes. The overall reduction in death or non-fatal recurrent stroke with aspirin (11.3%) compared with placebo (12.4%) was significant. The IST raised several methodological concerns, since it was conducted as an open study, anticoagulation monitoring was not available and not all patients received brain imaging to exclude brain haemorrhage before study entry.

The Chinese Acute Stroke Trial randomized 21,106 patients within 48 hrs of onset of suspected acute ischaemic stroke to receive either aspirin (160 mg/day) or placebo for up to 4 weeks [6]. Treatment with aspirin resulted in a significant 14% relative reduction in mortality (3.3% *versus* 3.9%), significantly fewer recurrent ischaemic strokes (1.6% *versus* 2.1%) and non-significantly more haemorrhagic strokes (1.1% *versus* 0.9%). The prospectively planned combined analysis of these two large trials showed a modest but statistically significant benefit for aspirin over placebo, resulting in nine fewer deaths or non-fatal strokes per 1000 treated patients in the first few weeks.

### Aspirin plus dipyridamole

In the early treatment with aspirin plus extended release dipyridamole for transient ischemic attack or ischemic stroke with 24h of

symptom onset (EARLY) trial, aspirin monotherapy (100 mg/day) was compared with the combination of aspirin and extended-release dipyridamole (25 and 200 mg twice daily) in the acute post-ischaemic period [7]. A total of 543 patients presenting with either an ischaemic stroke within 24 hrs or a TIA in the previous 7 days were randomized to receive aspirin monotherapy or dual antiplatelet treatment for 7 days followed by the combination therapy. The primary end-point was functional outcome on day 90, assessed on the modified Rankin scale as recorded by a blinded telephone interview. At day 90, a total of 154 (56%) patients in combined group and 133 (52%) in the aspirin group showed no or only mild disability (difference 4.1%, 95% CI, -4.5 to 12.6). This trial showed that a functional end-point such as the modified Rankin scale is not a suitable end-point for secondary stroke prevention trials. The composite secondary vascular end-point (non-fatal stroke, TIA, non-fatal myocardial infarction and major bleeding complications) was also not significantly different between both treatment groups. Twenty-eight patients in the combined and 38 in aspirin group reached the composite end-point (hazard ratio 0.73, 95% CI, 0.44–1.19).

### Aspirin plus clopidogrel

Although the combination of clopidogrel and aspirin is used regularly in patients with acute coronary syndrome, this dual platelet inhibition has only been studied in a small safety trial in patients with acute ischaemic stroke [8]. The trial showed a trend for fewer stroke recurrences with the combination of clopidogrel plus aspirin but also a higher bleeding rate with combination therapy.

### Abciximab

The intravenous use of the platelet glycoprotein IIb/IIIa inhibitor abciximab has been considered to be safe when administered within 24 hrs after ischaemic stroke onset after two double-blind, placebo-controlled, randomized phase II trials had been carried out [9, 10]. However the international phase III study AbESTT-II (Abciximab in Emergency Treatment of Stroke Trial) had to be terminated prematurely after enrolment of 808 patients due to a significantly increased bleeding rate [11]. During the first 5 days of enrolment, 5.5% of patients who had received intravenously administered abciximab within 5 hrs of onset of stroke had symptomatic or fatal intracranial haemorrhage *versus* 0.5% of placebo-treated patients.

Neither clopidogrel alone, nor ticlopidine, cilostazol or triflusal have been evaluated in any randomized trial in patients with acute ischaemic stroke.

### Aspirin *versus* anticoagulation

A number of randomized trials in the 1980s and 1990s compared anticoagulants and antiplatelet agents in patients with acute

ischaemic stroke [12]. The anticoagulants tested were unfractionated heparin or low-molecular-weight heparin. Compared with aspirin, anticoagulants were associated with a small but significant increase in the number of deaths at the end of follow-up (OR 1.10, 95% CI, 1.01–1.29), a significantly increased risk of symptomatic intracranial haemorrhage (OR 2.35, 95% CI, 1.49–3.46), and a non-significantly increased risk of recurrent stroke of any type during treatment (OR 1.20, 95% CI, 0.99–1.46). Subgroup analyses could not identify any type, dose or route of administration of anticoagulants associated with any net benefit, or any benefit in patients with atrial fibrillation (AF). The results of a trial in Asian patients with acute ischaemic stroke attributable to large artery occlusive disease are consistent with those of the meta-analysis [13]. Despite this lack of evidence, some experts recommend full-dose heparin during the acute phase in selected patients, such as those with cardiac sources of embolism with high risk of re-embolism, arterial dissection or high-grade arterial stenosis prior to surgery [14].

## 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

Aspirin is the most widely studied antiplatelet drug in secondary stroke prevention. 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 [15]. There is an ongoing debate about the dose of aspirin in secondary stroke prevention. Aspirin doses of less than 75 mg/day have been less widely assessed than doses of 75–100 mg/day [4]. However, there is no proven relationship between the dose of aspirin and its efficacy in secondary stroke prevention [16–18]. 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 [19], or 300 mg/day and 1200 mg/day [20]. In contrast, gastrointestinal side effects and bleeding complications are dose dependent and bleeding rates increase significantly beyond a daily aspirin dose of 150 mg [17, 21, 22]. An analysis of aspirin-treated

patients from the Dutch- and UK-TIA trials [19, 20] 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 [23, 24]. 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.

### 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) [25] and SPIRIT (Stroke Prevention in Reversible Ischemia Trial; target INR 3.0–4.5) [26] 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 2206 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 [27]. 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.

### 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 [28]. 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.

## Ticlopidine

Ticlopidine was compared to placebo in 1072 patients with recent ischaemic stroke [29]. 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 [30]. 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 [31]. 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 [32].

## 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) [33]. 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) [23]. 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%;  $P < 0.001$ ).

## 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 [34]. 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 [35]. 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 [36]. 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.

## Aspirin plus dipyridamole

The combination of low-dose aspirin and dipyridamole was first investigated in the randomized Second European stroke prevention (ESPS) 2 study with 6602 included patients with a TIA or ischaemic stroke [37]. Patients were randomized to receive aspirin alone (25 mg/twice a day), extended release dipyridamole (200 mg/twice a day), the combination of aspirin and extended release dipyridamole or placebo. For the primary end-point stroke, the combination therapy was superior to aspirin monotherapy (relative risk reduction 23%, absolute risk reduction 3%/2 years) and to placebo (relative risk reduction 37%, absolute risk reduction 5.8%/2 years). Aspirin monotherapy lowered the risk of stroke by 18% (absolute risk reduction 2.9%/2 years) and dipyridamole monotherapy by 16% (absolute risk reduction 2.6%/2 years) compared to placebo. Major bleeding complications were seen more frequently with aspirin and the combination aspirin and dipyridamole, whereas dipyridamole monotherapy had a similar bleeding rate compared with placebo. Cardiac events occurred in similar frequency in the groups treated with dipyridamole compared to aspirin [38]. The results of the ESPS-2 study could be replicated by the investigator-initiated ESPRIT trial [39]. A total of 2739 patients with presumed atherothrombotic TIA or minor stroke were randomized to aspirin (30–325 mg/day) or the combination of aspirin with dipyridamole (200 mg/ twice a day) and followed



for a mean period of 3.5 years. The primary end-point was the combination of stroke, myocardial infarction, major bleeding complications or vascular death. The event rate for the primary end-point was 16% with aspirin monotherapy and 13% with aspirin and dipyridamole resulting in a relative risk reduction of 20% (absolute risk reduction 1%/year).

A meta-analysis of all stroke prevention trials investigating aspirin monotherapy *versus* the combination aspirin plus dipyridamole in 7612 patients showed a relative risk reduction in favour of the combination therapy for a combined vascular end-point by 18% (95% CI, 9–26%) [40].

### 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 [41]. 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 [42]. 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.

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 [43] and dipyridamole might also induce migraine attacks in patients with a known migraine without aura [44]. 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 [45]. 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. How to treat this dipyridamole induced headache? 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 [46–48]. However, one has to keep in mind to add daily aspirin in this titration phase.

In conclusion, both clopidogrel and the combination aspirin/extended-release dipyridamole are more effective compared to aspirin (Table 1). 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 [49, 50]. On a 10-point scale, the ESRS predicts 1-year risk of recurrent stroke and combined cardiovascular events (Table 2). Patients with an ESRS  $\geq 3$  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 [51]. Because a prognostic score should also be easy to apply, the ESRS lends itself for use in daily clinical practice.

### The role of antiplatelets in cardioembolic stroke prevention

Oral anticoagulation (target INR 2.0–3.0) is the most efficient secondary stroke prevention therapy in stroke/TIA patients with non-valvular AF, irrespective of permanent, chronic or paroxysmal type of AF (Table 1). Aspirin (300 mg/day) was directly compared with warfarin and placebo for secondary stroke prevention only in the European Atrial Fibrillation Trial [52]. A total of 1007 patients with a recent TIA or minor ischaemic stroke and non-valvular AF were randomized and followed for a mean of 2.3 years. Oral anticoagulation reduced the risk of stroke from 12% to 4% per year (HR 0.34, 95% CI, 0.20–0.57) as compared to placebo and was also significantly more effective than aspirin (HR 0.60, 95% CI, 0.41–0.87). Furthermore, oral anticoagulation is recommended in most other cardiac conditions with an increased risk of systemic embolism, although randomized trials with antiplatelet agents in these indications are lacking. Oral anticoagulation also proved to be superior in patients with AF when compared with the combination of aspirin (75–100 mg per day recommended) and clopidogrel (75 mg per day) [53]. A total of 6706 patients were randomized in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial, 15% of which had a history of stroke or TIA. This trial had to be stopped prematurely because of superiority of oral anticoagulation therapy (annual risk

**Table 1** Relative risk reduction (RRR) and number needed-to treat (NNT)/year for recommended antithrombotic primary and secondary prevention of stroke and combined vascular end-point (stroke, myocardial infarction, vascular death)

Drug [Refs.]	Control group	Population	Stroke end-point RRR (NNT/year)	Combined end-point RRR (NNT/year)
Aspirin [64, 65]	Placebo	High cardiovascular risk	-	-23% (50–100)
Aspirin [66]	Placebo	AF	-29% (67)	-
Warfarin [66]	Placebo	AF	-59% (37)	-
Warfarin [67]	Aspirin	AF, high stroke risk*	-55% (35)	-
Warfarin [67]	Aspirin	AF, moderate stroke risk**	-45% (75)	-
Warfarin [67]	Aspirin	AF, low stroke risk***	-35% (>200)	-
Aspirin [66]	Placebo	Non-cardioembolic IS/TIA	-18% (75)	-13% (67)
Aspirin + dipyridamol [37, 68]	Placebo	Non-cardioembolic IS/TIA	-37% (35)	-34% <sup>#</sup>
Aspirin + dipyridamol [37, 68]	Aspirin	Non-cardioembolic IS/TIA	-23% (67)	-16% <sup>#</sup>
Clopidogrel [28]	Aspirin	Non-cardioembolic IS/TIA, myocardial infarction, peripheral arterial disease	-5.8% (650)	-8.7% (200)
Clopidogrel [28]	Aspirin	Non-cardioembolic IS/TIA	-8.0% (220)	-7.3% (180)
Aspirin [52, 66]	Placebo	IS/TIA, AF	-19% (40)	-18% (29)
Warfarin [52, 66]	Placebo	IS/TIA, AF	-68% (12)	-49% (11)

IS = ischaemic stroke, TIA = transient ischaemic attack, AF = atrial fibrillation.

\*High stroke risk = previous stroke or previous TIA or systolic blood pressure >160 mmHg or heart failure within the previous 3 months or left ventricular fractional shortening of ≤25% or women >75 years.

\*\*Moderate stroke risk = hypertension and no high risk features.

\*\*\*Low stroke risk = no hypertension and no high risk features.

<sup>#</sup>Odds reduction.

of stroke, non-CNS systemic embolus, myocardial infarction or vascular death of 3.93% under warfarin *versus* 5.60% under aspirin and clopidogrel; relative risk 1.44, 95% CI, 1.18–1.76) [56]. The ACTIVE A trial compared clopidogrel (75 mg/day) plus aspirin (recommended dose 75–100 mg/day) with aspirin monotherapy in 7554 patients with AF who were at increased risk for stroke and for whom therapy with a vitamin K antagonist was considered inappropriate by the treating physician (50%), unsuitable due to an increased bleeding risk (23%) or the patient's preference not to take warfarin (27%) [54]. After a median follow-up of 3.6 years, the same primary vascular end-point had occurred in 832 patients receiving clopidogrel and aspirin (6.8% per year) and in 924 patients receiving aspirin monotherapy (7.6% per year; RR with clopidogrel and aspirin 0.89, 95% CI, 0.81–0.98). The difference was primarily due to a reduction in the rate of stroke with clopidogrel and aspirin. Stroke occurred in 296 patients receiving clopidogrel plus aspirin (2.4% per year) and 408 patients receiving only aspirin (3.3% per year; RR 0.72; 95% CI, 0.62–0.83). However, major bleeding complications were significantly more frequent and occurred in 251 patients with clopidogrel plus aspirin (2.0% per year) *versus* 162 patients with aspirin monotherapy

(1.3% per year) (RR 1.57, 95% CI, 1.29–1.92). These data suggest that treating 1000 patients with AF for 1 year with clopidogrel plus aspirin prevents eight major vascular events (including two fatal and three disabling strokes) but causes seven major haemorrhages (one fatal) compared with aspirin monotherapy.

In stroke patients with AF and concomitant stable coronary disease, the combination of oral anticoagulation and aspirin was associated with an incremental rate of major bleeding of 1.6% per year [55]. In the Stroke Prophylaxis using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials the combination of aspirin with warfarin did not reduce vascular end-points but also increased the risk of major bleeds significantly [56].

## Antiplatelets in patients with symptomatic intracranial stenosis

The WASID (warfarin-aspirin symptomatic intracranial disease) trial compared oral anticoagulation with warfarin (target INR

**Table 2** Essen stroke risk score (ESRS)

Risk factors	Points
Age 65–75 years	1
Age >75 years	2
Arterial hypertension	1
Diabetes mellitus	1
Previous MI	1
Other cardiovascular disease (except MI and AF)	1
Peripheral artery disease	1
Current smoker	1
Previous TIA or ischaemic stroke in addition to qualifying event	1
Maximum ESRS score	10

Patients with an ESRS score  $\geq 3$  have a recurrent annual stroke risk > 4% and are considered to be at high risk.

MI = myocardial infarction, TIA = transient ischaemic attack, AF = atrial fibrillation.

2.0–3.0) and high dose of aspirin (1300 mg/day) in 569 patients with symptomatic, angiographically proven intracranial stenosis 50–99% [57]. 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 [58]. 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.

The completed TOSS-II is a double-blind trial in Asia comparing aspirin (75–150 mg per day) in combination with cilostazol (100 mg twice a day) with a combination of aspirin and clopidogrel (75 mg per day) in patients with significant middle cerebral artery or basilar artery stenosis (NCT00130039). Preliminary results show a lower progression of symptomatic intracranial stenosis under cilostazol (10.0%) *versus* clopidogrel (15.5%) over 7 months. Another ongoing trial is the open-label cilostazol–aspirin therapy against recurrent

stroke with intracranial artery stenosis in Japan, comparing open-label aspirin and cilostazol with aspirin alone in patients with symptomatic 50–99% stenosis of the supraclinoid internal carotid artery, middle cerebral artery or basilar artery (NCT00333164).

## 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 [59, 60]. 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 [61]. 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) [62]. In the absence of any published data from randomized trials comparing medical therapy and percutaneous device closure in ischaemic stroke patients with PFO, aspirin (300 mg/day) is currently recommended by secondary stroke prevention guidelines as first line treatment [63]. The preliminary results of the randomized CLOSURE I trial which compared treatment by device closure of PFO 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 (NCT00201461).

## Disclosures

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Prof. Dr. H.-C. Diener has no ownership interest and does not own stocks of any pharmaceutical company.

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