Antiplatelet agents in stroke prevention

Acute and long-term treatment strategies

R. Weber; C. Weimar; H.-C. Diener
Department of Neurology and Stroke Center, University Duisburg-Essen, Essen, Germany

Keywords
Ischaemic stroke, transient ischaemic attack, antiplatelet, primary prevention, secondary prevention, anticoagulation

Summary
In primary prevention, aspirin reduces the risk of stroke but not of myocardial infarction in women while in men only the risk of myocardial infarction but not stroke could be significantly reduced. Only aspirin has been shown to be safe and effective in large randomized trials in the first 48 hours after ischemic stroke. Aspirin/dipyridamole and clopidogrel both reduce the risk of a combined cardiovascular outcome in long-term secondary prevention compared to aspirin alone. More potent antiplatelet drugs or combination of aspirin and clopidogrel prevent more ischemic events, but also lead to more bleeding complications. No benefit of oral anticoagulants could be shown in patients with non-cardioembolic stroke. In patients with atrial fibrillation oral anticoagulation is more effective than aspirin in stroke prevention. The choice between oral anticoagulants and aspirin in these patients depends on age and the individual risk factor profile. Patients with symptomatic intracranial stenosis have a significantly decreased risk of a subsequent stroke in TIA patients result in a dramatic reduction of a subsequent stroke (50, 62). In the EXPRESS (Early use of EXisting PREventive Strategies for Stroke) study (62), the 90-day risk of a subsequent stroke in TIA patients behavior. At TIA patients with a recurrent stroke in the first year (37).

Risk of stroke recurrence or stroke following transient ischemic attack (TIA) is highest in the first seven days following the cerebrovascular event and declines over time (36, 53). Recent studies have demonstrated that urgent assessment and initiation of preventive treatment concepts including antiplatelet agents in TIA patients result in a dramatic reduction of a subsequent stroke (50, 62). In the EXPRESS (Early use of EXisting PREventive Strategies for Stroke) study (62), the 90-day risk of a subsequent stroke in TIA patients referred to a specialized TIA clinic with immediate preventive treatment could be decreased from 10.3% to 2.1%.

Antiplatelet agents have been established as a cornerstone in the treatment of both acute ischaemic stroke/TIA and in secondary stroke prevention.

This review will discuss the use of antiplatelet agents in the acute phase after an ischaemic stroke and their role in primary and secondary stroke prevention.

Antiplatelet agents

Acute stroke

To date, intravenously administered recombinant tissue plasminogen activator (rt-PA) remains the only proven causal therapy for acute cerebral ischaemia. Approved by auth-
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 (49). 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. The combination of aspirin (50 mg/day) and dipyridamole (400 mg/day) started within 24 hours of stroke onset is currently compared with aspirin alone (100 mg/day) in the randomised, multi-centre EARLY trial in 548 acute Germany stroke patients.

The intravenous use of the platelet glycoprotein IIIb/IIa inhibitor abciximab has been considered to be safe when administered within 24 hours after ischaemic stroke onset after two double-blind, placebo-controlled, randomized phase II trials had been carried out (1, 6). In the larger study with 400 patients, treatment with abciximab showed a nonsignificant trend in favourable outcome on the modified Rankin scale after three months, after adjustment for baseline variables (6). However, the international phase III AbESTT-II study (Abciximab in Emergency Treatment of Stroke Trial) had to be terminated prematurely after enrolment of 808 patients due to an increased bleeding rate (13). During the first five days of enrolment, 5.5% of patients who had received intravenously administered abciximab within five hours of onset of stroke had symptomatic or fatal intracranial haemorrhage versus 0.5% of placebo-treated patients (p = 0.002). Neither clopidogrel alone, nor ticlopidine or trifusal have been evaluated in randomized trials in patients with acute ischaemic stroke.

**Primary stroke prevention**

Only aspirin and clopidogrel plus aspirin have been evaluated for primary prevention of cardiovascular events including stroke in randomised trials. Six large prospective trials have been conducted with different aspirin doses (75, 100, 300 mg/day, 100 and 325 mg/ every other day) (2, 7, 25, 42, 48, 61). A meta-analysis of these trials comprising 47 293 patients treated with aspirin and 45 580 control patients assessed the following end points: total coronary heart disease, nonfatal myocardial infarction, total cardiovascular events, stroke, cardiovascular mortality, and all-cause mortality (16). Aspirin significantly reduced

- coronary heart disease (OR 0.77, 95% CI 0.70–0.86),
- nonfatal myocardial infarction (OR 0.76, 95% CI 0.67–0.85) and
- total cardiovascular events (OR 0.85; 95% CI 0.79–0.92),

but not stroke (OR 0.94, 95% CI 0.84–1.06), cardiovascular mortality (OR 0.89, 95% CI 0.72–1.10) and all-cause mortality (OR 0.94, 95% CI 0.87–1.00).

However, a second metaanalysis stratified by sex did find a significant reduction in women for overall stroke (OR 0.83, 95% CI 0.70–0.97) and ischaemic stroke (OR 0.76, 95% CI 0.63–0.93) (17).

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and ischaemic Stabilization, Management, and Avoidance) trial was a combined primary and secondary prevention study and compared the combination of clopidogrel (75 mg/day) and aspirin (75 to 162 mg per day) with aspirin monotherapy in 15 603 patients with either clinically evident cardiovascular disease or multiple cardiovascular risk factors (19). While there was no significant difference in the primary efficacy end point (a composite of myocardial infarction, stroke, or death from cardiovascular causes), the combination of clopidogrel and aspirin was less effective compared to aspirin alone in the subgroup of patients with multiple vascular risk factors due to an increased rate of death from cardiovascular causes.

In patients with non-valvular atrial fibrillation (AF) a metaanalysis of eight randomised trials showed that antiplatelet agents significantly reduced the rate of stroke by 22% (RR 0.78, 95% CI 0.65–0.94) (45).

Current guidelines recommend using antiplatelet agents in patients with AF who are at low risk for development of stroke according to the CHADS2 score or who have contraindications against oral anticoagulation with vitamin K antagonists (35). Nevertheless, vitamin K antagonists confer the most effective prevention in AF patients older than 75 years who have at least one ad-
ditional cardiovascular risk factor (arterial hypertension, chronic heart failure, diabetes mellitus, prior ischaemic stroke or TIA). Warfarin (target international normalised ratio (INR) 2.0–3.0) is clearly more effective than antiplatelet agents at reducing stroke (RR versus placebo 0.36, 95% CI 0.26–0.51) (45). Because both risk of stroke and incidence of AF increases with age, stroke prevention in elderly people with AF is of major importance. Older patients were significantly under-represented in the aforementioned trials and there were special concerns about increased bleeding risk, especially intracranial haemorrhage in patients aged 75 years and older.

These considerations resulted in the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trial comparing aspirin (75 mg/day) and warfarin (INR target 2.0–3.0) in 973 AF patients ≥75 years (54). Over a mean follow-up period of 2.7 years, warfarin significantly reduced the risk of the primary combined endpoint (fatal or disabling stroke, intracranial haemorrhage, clinically significant arterial embolism) (RR 0.48, 95% CI 0.28–0.80, p = 0.003). Thus, age alone should not be regarded as a contraindication to oral anticoagulation, unless there are clear contraindications against or patients will not to take oral anticoagulants.

Oral anticoagulation with warfarin is also superior to dual antiplatelet inhibition with clopidogrel and aspirin in patients with AF. The ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial randomised 6706 patients with AF and an increased risk of stroke to receive either oral anticoagulation therapy (target INR ratio of 2.0–3.0) or clopidogrel (75 mg/day) plus aspirin (75–100 mg/day) (22). Primary outcome was first occurrence of stroke, non-cerebral systemic embolism, myocardial infarction, or vascular death. The trial was stopped prematurely after a median follow-up duration of 1.28 years due to superiority of warfarin on interim analysis (RR 1.44, 95% CI 1.18–1.76; p = 0.0003).

The ACTIVE A trial included those patients with AF and a high risk for stroke who were not suitable for participation in ACTIVE W, i.e. patients with a specific risk of bleeding, a physician’s judgment that vitamin K antagonists were inappropriate, and the patient’s will not to take oral anticoagulation (23). A total of 7554 patients were randomised to aspirin alone (75–100 mg/day) or the combination of aspirin and clopidogrel (75 mg/day). After a median follow-up of 3.6 years, the primary outcome (composite of stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes) was significantly reduced in patients receiving clopidogrel and aspirin (RR 0.89; 95% CI 0.81–0.98; p = 0.01). The difference was primarily due to a reduction in the rate of stroke. Occurred in 296 patients receiving aspirin/clopidogrel (2.4% per year) and 408 patients receiving aspirin (3.3% per year. RR 0.72; 95% CI 0.62–0.83; p < 0.001).

However, major bleedings occurred significantly more often in patients receiving clopidogrel and aspirin (2.0% per year versus 1.3% per year in patients with aspirin alone. RR 1.57; 95% CI 1.29–1.92; p < 0.001). Overall, 28 strokes can be prevented if 1000 patients are treated with the combination therapy for three years at the price of 20 major bleedings.

Oral anticoagulation is the therapy of choice in patients with AF who are at high risk for stroke and every effort should be undertaken to ensure that all eligible patients receive anticoagulation – irrespective of age. The combination aspirin/clopidogrel is more effective than aspirin alone in preventing strokes in AF patients who are at high risk for stroke and are not suitable for oral anticoagulation, but bleeding risk also has to be considered very carefully in every single patient.

Secondary stroke prevention

Antiplatelet drugs are effective in secondary stroke prevention after TIA or ischaemic stroke. The latest report from the Antithrombotic Trialist’s Collaboration from 2002 included a metaanalysis of 287 trials with 135000 patients randomised to antiplatelet therapy versus control and 77000 patients randomised to different antiplatelet regimens (4). Overall, antiplatelet agents reduced the risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) by about 25% (relative percentage). In those patients with a previous stroke or TIA, 36 serious events were prevented among 1000 patients treated for two years and the benefit substantially outweighed the absolute risks of major extracranial bleeding.

Nevertheless, there are still controversies about the choice of the antiplatelet agent in different stroke aetiologies, optimal dose (for aspirin), as well as time and duration of prescription.

Non-cardioembolic stroke: aspirin, clopidogrel and dipyridamole

Aspirin is the most widely studied antiplatelet drug in secondary stroke prevention. A meta-analysis of eleven randomised 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 endpoint of stroke, myocardial infarction and vascular death (15). There is no relationship between the dose of aspirin and its efficacy in secondary stroke prevention (4, 20, 60). Studies directly comparing the effects of aspirin failed to show differences in stroke recurrence between 30 mg/day and 283 mg/day (5), or 300 mg/day and 1200 mg/day (33). However, gastrointestinal side effects and bleeding complications are dose dependent and bleeding rates increase significantly beyond a daily aspirin dose of 150 mg (20, 67, 72). Therefore, the recommended dose of aspirin in patients with TIA or ischaemic stroke is below 150 mg/day (28).

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 ratio 2.0–3.0) (4) and SPIRIT (Stroke Prevention in Reversible Ischaemia Trial; target INR ratio 3.0–4.5) (11) 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 so-called light anticoagulation (target INR ratio 1.4–2.8) with aspirin (325 mg/day) in 2206 patients with non-cardioembolic stroke over a follow-up of two years proved to be equivalent with respect to prevention of recurrent ischaemic stroke, rate of major haemorrhage and death (57). 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.

The thienopyridine derivative clopidogrel was first investigated for secondary stroke prevention in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial (10). Clopidogrel monotherapy (75 mg/day) was compared to aspirin (325 mg/day) in 19,185 patients with stroke, myocardial infarction or peripheral arterial disease. After a mean follow-up period of 1.9 years, the combined primary endpoint (stroke, myocardial infarction and vascular death) was significantly reduced by 8.7% (95% CI 0.3–16.5) under clopidogrel with an ARR of 0.51% per year. Thus, clopidogrel was slightly more effective than aspirin in preventing the composite endpoint of vascular events. The risks of gastrointestinal bleeds (1.99% versus 2.66%) and gastrointestinal side effects (15% 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.

The combination therapy of aspirin and clopidogrel has been investigated in two large randomised trials for secondary stroke prevention, the aforementioned CHARISMA trial (19) and the MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischaemic stroke) trial (30). MATCH compared the combination of clopidogrel (75 mg/day) and aspirin (75 mg/day) with clopidogrel monotherapy in 7,599 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 endpoint 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). Similar to MATCH, the CHARISMA trial failed to show a benefit for combination therapy in the overall study population and displayed a higher bleeding rate under the combination therapy (19).

However, 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 (18). Again, one has to keep in mind, that this data was 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 at least three months.

The combination of low-dose aspirin and dipyridamole was first investigated in the randomised ESPS-2 (Second European stroke prevention) study with 6,602 included patients with a TIA or ischaemic stroke (31). Patients were randomised 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 (RRR) 23%, absolute risk reduction (ARR) 3%) and to placebo (RRR 37%, ARR 5.8%). Aspirin monotherapy lowered the risk of stroke by 18% (ARR 2.9%) and dipyridamole monotherapy by 16% (ARR 2.6%) 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 (32).

The results of the ESPS-2 study could be replicated by the investigator-initiated ESPRIT (European-Australasian Stroke Prevention in Reversible Ischaemia Trial) study (41). ESPRIT randomised 2,739 patients with presumed atherothrombotic TIA or minor stroke to aspirin (30 to 325 mg/day) or the combination of aspirin with dipyridamole (200 mg/ twice a day) and followed them for a mean period of 3.5 years. The primary endpoint was the combination of stroke, myocardial infarction, major bleeding complications, or vascular death. The event rate for the primary endpoint was 16% with aspirin monotherapy and 13% with aspirin and dipyridamole resulting in a RRR of 20% (ARR 1%/year). Of note, 34% of patients in the combination arm (versus 13% in the aspirin monotherapy arm) terminated the trial prematurely mostly because of headache as adverse event. The clinical relevant side effect of tension-type like headache in patients treated with dipyridamole can be reduced by slow titration and administration of dipyridamole only once daily before bed time during the first 7–14 days of intake (26). In case of titration starting with a single dose of aspirin plus dipyridamole we would recommend to add 50 mg of aspirin until the BID dosing is achieved.

A metaanalysis of all stroke prevention trials investigating aspirin monotherapy versus the combination aspirin/dipyridamole in 7,612 patients showed a RRR in favour of the combination therapy for a combined vascular endpoint by 18% (95% CI 9%-26%) (40).

Direct comparisons of the combination aspirin/extended-release dipyridamole and clopidogrel estimated a relative risk reduction of 16% (95% CI 3–27%) in favour of aspirin/dipyridamole (66). However, 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 endpoints in the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial (63). A total of 20,332 patients were followed for a mean of 2.5 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 haemorrhage (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 a benefit of one treatment regimen over the other.
The efficacy of antiplatelet therapy beyond four years after the initial event has not been studied in randomised trials. Theoretically, treatment should continue lifelong, unless contraindications emerge.

**Stratification by risk**

Both clopidogrel and the combination aspirin/extended-release dipyridamole are more effective compared to aspirin (►Tab. 1). In case of economic restraints, 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 (69, 70). On a 10-point scale, the ESRS predicts 1-year risk of recurrent stroke and combined cardiovascular events (►Tab. 2). Patients with an ESRS ≥ 3 have a recurrent annual stroke risk > 4% and thus should be considered as high risk in secondary stroke prevention.

**Patients with intracranial stenosis**

Aspirin is the only antiplatelet agent which has been studied in a randomised prospective trial in the subgroup of patients with a TIA/minor ischaemic stroke due to an intracranial arterial stenosis. The WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) study compared oral anticoagulation with warfarin (target INR 2.0–3.0) and high dose aspirin (1300 mg/day) in 569 patients with symptomatic, angiographically proven intracranial stenosis 50%-99% (21). Although there was no difference in the primary endpoint 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 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. Current guidelines suggest lower doses of aspirin (i.e. 100 mg/day in the German guidelines (28) 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.

**Patients with a patent foramen ovale**

A patent foramen ovale (PFO) is present in about 25% of the general population, and can be found in up to 40% of young patients with otherwise cryptogenic stroke (39, 56, 58). In

---

### Tab. 1

<table>
<thead>
<tr>
<th>Drug (reference)</th>
<th>Control group</th>
<th>Population</th>
<th>Stroke RRR (NNT/year)</th>
<th>Combined RRR (NNT/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (25, 59)</td>
<td>Placebo</td>
<td>High cardiovascular risk</td>
<td>-</td>
<td>-23% (50–100)</td>
</tr>
<tr>
<td>Aspirin (27, 31)</td>
<td>Placebo</td>
<td>Non cardioembolic IS/TIA</td>
<td>-18% (75)</td>
<td>-13% (67)</td>
</tr>
<tr>
<td>Aspirin + dipyridamol (31, 51)</td>
<td>Placebo</td>
<td>Non cardioembolic IS/TIA</td>
<td>-37% (35)</td>
<td>-34%#</td>
</tr>
<tr>
<td>Aspirin + dipyridamol (31, 51)</td>
<td>Aspirin</td>
<td>Non cardioembolic IS/TIA</td>
<td>-23% (67)</td>
<td>-16%#</td>
</tr>
<tr>
<td>Clopidogrel (10)</td>
<td>Aspirin</td>
<td>Non cardioembolic IS/TIA, myocardial infarction, peripheral arterial disease</td>
<td>-5.8% (650)</td>
<td>-8.7% (200)</td>
</tr>
<tr>
<td>Clopidogrel (10)</td>
<td>Aspirin</td>
<td>Non cardioembolic IS/TIA</td>
<td>-8.0% (220)</td>
<td>-7.3% (180)</td>
</tr>
<tr>
<td>Aspirin + dipyridamol (63)</td>
<td>Clopidogrel</td>
<td>Non cardioembolic IS/TIA</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Aspirin (43)</td>
<td>Placebo</td>
<td>Atrial fibrillation</td>
<td>-29% (67)</td>
<td>-</td>
</tr>
<tr>
<td>Warfarin (44)</td>
<td>Placebo</td>
<td>Atrial fibrillation</td>
<td>-59% (37)</td>
<td>-</td>
</tr>
<tr>
<td>Warfarin (44)</td>
<td>Aspirin</td>
<td>Atrial fibrillation, high stroke risk*</td>
<td>-55% (35)</td>
<td>-</td>
</tr>
<tr>
<td>Warfarin (44)</td>
<td>Aspirin</td>
<td>Atrial fibrillation, moderate stroke risk**</td>
<td>-45% (75)</td>
<td>-</td>
</tr>
<tr>
<td>Warfarin (44)</td>
<td>Aspirin</td>
<td>Atrial fibrillation, low stroke risk*</td>
<td>-35% (&gt;200)</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin (12, 43)</td>
<td>Placebo</td>
<td>IS/TIA, atrial fibrillation</td>
<td>-19% (40)</td>
<td>-18% (29)</td>
</tr>
<tr>
<td>Warfarin (12, 43)</td>
<td>Placebo</td>
<td>IS/TIA, atrial fibrillation</td>
<td>-68% (12)</td>
<td>-49% (11)</td>
</tr>
</tbody>
</table>

IS: Ischaemic stroke; TIA: Transient Ischemic Attack; n.s.: Non Significant; # odds reduction; **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; ***High stroke risk: previous stroke or TIA or systolic blood pressure >160 mmHg or heart failure within the previous 3 years.
young 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 four years of follow-up (35). 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 ratio of 1.4–2.8) versus aspirin (325 mg/day) (46). In the absence of any data from ongoing randomised trials comparing medical therapy and percutaneous device closure in ischaemic stroke patients with PFO, aspirin (300 mg/day) is currently recommended as first line treatment (28, 29).

**Cardioembolic stroke**

Oral anticoagulation (target INR ratio 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 (Tab. 1). Aspirin (300 mg/day) was compared with warfarin and placebo in EAFT (European Atrial Fibrillation Trial) (12). A total of 1007 patients with a recent TIA or minor ischaemic stroke and non-valvular AF were randomised 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) compared to placebo and was also significantly more effective than aspirin (HR 0.60, 95% CI 0.41–0.87). Oral anticoagulation is also recommended in most other cardiac conditions with an increased risk of systemic embolism, although randomised trials with antiplatelet agents in these indications are lacking (8, 29).

As mentioned, oral anticoagulation proved to be superior in the subgroup of stroke patients with atrial fibrillation (15% of the subjects included in the ACTIVE W study had a history of stroke or TIA) when compared with dual antiplatelet therapy (22).

In stroke patients with atrial fibrillation and concomitant stable coronary disease, oral anticoagulation should not be combined with aspirin due to an increased bleeding risk (34).

Tab. 2. Essen Stroke Risk Score (ESRS): Patients with an ESRS ≥ 3 have a recurrent annual stroke risk > 4% and are considered to be at high risk.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65–75 years</td>
<td>1</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>2</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1</td>
</tr>
<tr>
<td>Other cardiovascular disease (except MI and AF)</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1</td>
</tr>
<tr>
<td>Previous TIA or ischaemic stroke in addition to qualifying event</td>
<td>1</td>
</tr>
<tr>
<td>Maximum ESRS score</td>
<td>10</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; MI: myocardial infarction; TIA: transient ischemic attack

**Other antiplatelet agents in secondary stroke prevention**

Aspirin, the combination of dipyridamole and aspirin and clopidogrel are most widely used as antiplatelet agents for secondary prevention. The quest for a safe and more potent antiplatelet agent has not been successful to date, as shown in the following section.

Triflusal is an antiplatelet agent structurally related to the salicylate group of compounds. In a metaanalysis comparing triflusal and aspirin, four randomised trials with 2944 TIA/stroke patients were included. Triflusal reduced stroke recurrence with similar efficacy to aspirin (OR 1.04, 95% CI 0.87–1.23) with aspirin showing significantly more bleeding complications (minor haemorrhages OR 1.60, 95% CI 1.31–1.95; major haemorrhages OR 2.34, 95% CI 1.58–3.46) (24). However, triflusal has not been approved by the European Medicines Agency and is only available in Portugal and Spain.

The oral glycoprotein IIb/IIIa inhibitor lotrafiban was compared with aspirin (75–325 mg/day) in the randomised BRAVO (Blockade of the GP IIb/IIIa Receptor to Avoid Vascular Occlusion) trial in 9190 patients with cardiovascular disease (41% of which had cerebrovascular disease at the time of entry) (67). There was no significant difference in the primary end point (composite endpoint of all-cause mortality, myocardial infarction, stroke, recurrent ischaemia 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).

Two randomised phase II trials with new antiplatelet agents have been recently published in Asian stroke patients. Cilostazol, a phosphodiesterase-3-inhibitor, was compared with aspirin for long-term secondary stroke prevention in 720 Chinese stroke patients (47). In this pilot study, non-significantly lower rates of ischaemic and significantly lower rates of haemorrhagic stroke were observed in the cilostazol arm after 12–18 months. Sarpogrelate, a selective inhibitor of the 5-hydroxytryptamine receptor, was tested against aspirin (81 mg/day) in 1510 Japanese patients with a recent ischaemic stroke (65). Although bleeding rates were significantly reduced in patients treated with sarpogrelate for a mean follow-up of 1.51 years, sarpogrelate was not able to show noninferiority in aspirin in the prevention of recurrence of cerebral infarction.

The two thienopyridine derivatives prasugrel and clopidogrel have been compared only in patients with acute coronary syndrome to date (71). A post-hoc analysis in 518 patients with a history of ischaemic stroke or TIA revealed a lack of efficacy (primary composite endpoint of cardiovascular death, myocardial infarction or stroke) and an increased bleeding risk in this subgroup of patients (64). However, this post-hoc subgroup analysis comprised only 3.8% of the entire study population.

**Bleeding risk**

The use of antiplatelet drugs for stroke prevention always has to balance the benefit (prevention of ischaemic strokes or vascular events) against the bleeding risk. In patients with coronary heart disease, gastrointestinal bleeds are most common. These can be treated in most cases. In contrast, patients with stroke have a considerable risk of intracranial bleeds with a poor prognosis. Usman et al. performed a review of bleeding rates across all trials using antiplatelets or oral anticoagulation for secondary stroke prevention.
(68). They found a similar bleeding rate for aspirin (<325 mg), clopidogrel and aspirin plus dipyridamole. The combination of aspirin plus clopidogrel and oral anticoagulation were associated with an increased bleeding risk. The common observation is that more potent antiplatelet drugs will prevent more ischaemic events, but also lead to more bleeding complications. This has recently been shown for prasugrel in acute coronary syndrome (71).

References


