REVIEW

Guidelines for the preventive treatment of ischaemic stroke and TIA (II). Recommendations according to aetiological sub-type


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KEYWORDS
Guidelines; Ischaemic stroke; Transient ischemic attack; Prevention

Abstract
Background and objective: To update the ad hoc Committee of the Cerebrovascular Diseases Study Group of The Spanish Neurological Society guidelines on prevention of ischemic stroke (IS) and Transient Ischaemic Attack (TIA).
Methods: We reviewed the available evidence on ischaemic stroke and TIA prevention according to aetiological subtype. Levels of evidence and recommendation levels are based on the classification of the Centre for Evidence-Based Medicine.
Results: In atherothrombotic IS, antiplatelet therapy and revascularization procedures in selected cases of ipsilateral carotid stenosis (70–99%) reduce the risk of recurrences. In cardioembolic IS (atrial fibrillation, valvular diseases, prosthetic valves and myocardial infarction with mural thrombus) prevention is based on the use of oral anticoagulants. Preventive therapies for uncommon causes of IS will depend on the aetiology. In the case of cerebral venous thrombosis oral anticoagulation is effective.

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Recommendations according to aetiological sub-type

Conclusions: We conclude with recommendations for clinical practice in prevention of IS according to the aetiological subtype presented by the patient.

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Guía para el tratamiento preventivo del ictus isquémico y AIT (II). Recomendaciones según subtipo etiológico

Resumen

Fundamento y objetivo: Actualizar las guías terapéuticas del Comité ad hoc del Grupo de Estudio de Enfermedades Cerebrovasculares de la SEN en el tratamiento preventivo de ictus isquémico (II) y ataque isquémico transitorio (AIT).

Métodos: Revisión de evidencias disponibles sobre la prevención del ictus isquémico y AIT en función del subtipo etiológico. Los niveles de evidencia y grados de recomendación se han basado en la clasificación del Centro de Medicina Basada en la Evidencia.

Resultados: En el II de origen aterotrombótico reducen el riesgo de recurrencias el tratamiento antiagregante y los procedimientos revascularizadores en casos seleccionados de estenosis carotidea ipsilateral (70-99%). La prevención de II de origen cardioembólico (fibrilación auricular, valopatías, prótesis valvulares y en infarto de miocardio con trombo mural) se basa en el uso de anticoagulantes orales. En el II de origen habitual, las terapias preventivas dependerán del subtipo etiológico; en la trombosis venosa cerebral la anticoagulación oral es eficaz.

Conclusiones: Se concluye con recomendaciones de práctica clínica en prevención de ictus isquémico y AIT adaptadas al subtipo etiológico de II que ha presentado el paciente.

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In Spain, cerebrovascular diseases (CVD) are the leading cause of death in women, the third most frequent in men,1 and the most common cause of disability. The measures we describe here are designed to prevent both first-ever ischaemic strokes (IS) and future episodes in patients who have already suffered a stroke. We will also consider measures aimed at reducing overall vascular risk in these patients.2 Due to the length of this article, we decided to publish it in 2 parts. The first part presented a review of the risk factors for ischaemic stroke3 and any modifications that would need to be made to prevent IS. In this second part, we will specify different preventive treatments according to the stroke subtype. Recommendations for each section are shown in tables for better readability. Levels of evidence and recommendation grades are based on the classification proposed by the Centre for Evidence Based Medicine at the University of Oxford4 (Table 1). To facilitate reading, we have included transient ischaemic attack (TIA) in our definition of ischaemic stroke. This practice coincides with current criteria. Therefore, all recommendations included in these clinical practice guidelines are directed at preventing focal cerebral ischaemia in general, without distinguishing between cerebral infarct and TIA.

Ischaemic stroke associated with large-vessel arteriosclerosis and small-vessel disease

(Table 2)

Risk factors (RF) should be modified. In addition, antiplatelet drugs are recommended along with carotid endarterectomy or percutaneous transluminal angioplasty in selected patients.

Antiplatelet drugs

Acetylsalicylic acid (ASA)

ASA reduces the absolute risk of stroke, acute myocardial infarction (AMI), or vascular death by 13% to 25% compared to placebo.5–7 This is a first-choice antiplatelet drug and the recommended dose is 100 to 300 mg/day.8,9

Clopidogrel

In patients with atherosclerotic disease (AMI, stroke, or peripheral artery disease), ASA is slightly more effective for reducing the risk of stroke, AMI, and vascular death (decrease in relative risk of 8.7%) with fewer digestive tract haemorrhages and the same risk of neutropenia.10 A sub-analysis in the CAPRIE study found that clopidogrel was no more effective than ASA in patients with a prior stroke.10 However, clopidogrel was more effective in the subgroup of patients with a history of symptomatic atherosclerosis (prior IS or AMI).11 These observations should be considered with care, given that the CAPRIE study was not designed for subgroup analysis. Clopidogrel dosed at 75 mg/day is considered a first-choice treatment, especially in patients with ASA intolerance.

Triflusal

In doses of 600 mg/day, triflusal has a similar efficacy to that of ASA with fewer haemorrhagic complications.12–14 It is also considered a first-choice treatment.
Table 1  Levels of evidence and grades of recommendation.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of study on which classification is based</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic review of randomised clinical trials (with homogeneity)</td>
<td>A B (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>1b</td>
<td>Randomised clinical trial with narrow confidence interval</td>
<td>A B (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review of cohort studies (with homogeneity)</td>
<td>B C (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low-quality randomised clinical trials, e.g. those with a follow-up level below 80%)</td>
<td>B C (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic reviews of case—control studies (with homogeneity)</td>
<td>B C (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>3b</td>
<td>Case-control studies</td>
<td>B C (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>4</td>
<td>Series of cases or cohort studies or low quality case-control studies</td>
<td>B C (extrapolation) D (inconclusive studies)</td>
</tr>
<tr>
<td>5</td>
<td>Experts’ opinion without explicit critical appraisal or based on physiology or pathophysiology.</td>
<td>B C (extrapolation) D (inconclusive studies)</td>
</tr>
</tbody>
</table>

Source: Adapted from the Centre for Evidence Based Medicine (CEBM).  

Dipyridamole
Although dipyridamole reduces stroke recurrence by 18% compared to placebo, it is not used in monotherapy because it has no effect on vascular death.  

Cilostazol
The Second Cilostazol Stroke Prevention Study (CSPS2), conducted in Asian patients with IS, showed that cilostazol (100 mg/12 h) was noninferior and could even be superior to ASA (81 mg/d) for preventing stroke recurrences due to being associated with a lower frequency of haemorrhagic complications. A recent Cochrane meta-analysis confirms that cilostazol was superior to ASA for preventing stroke recurrence in patients with IS.  

Other antiplatelet drugs under study
Sarpogrelate
Sarpogrelate’s efficacy for secondary stroke prevention resembles that of ASA, and its haemorrhagic complication rate is lower.  

SCH 530348
Follow-up on stroke patients was interrupted prematurely in the TRA-TIMI50 study as there was an increased risk of haemorrhage. The drug is still being investigated for patients with ischaemic heart disease or peripheral artery disease.  

Prasugrel
Compared to clopidogrel, prasugrel significantly reduced cardiovascular episodes in patients at moderate to high risk for acute coronary syndrome and treated with percutaneous coronary angioplasty. It is associated with a higher number of haemorrhagic complications; mortality was similar in both groups. This drug is not recommended in patients in early phases after stroke or TIA, and there have been no trials investigating its potential for secondary stroke prevention.  

Ticagrelor
Compared to clopidogrel, ticagrelor reduced the number of AMI and vascular deaths or deaths due to other causes among patients with acute coronary syndrome. While there were no differences in the overall number of major haemorrhagic complications, the percentage of fatal cerebral haemorrhages was lower. No studies have been conducted to specifically examine secondary stroke prevention with ticagrelor.  

Associations of antiplatelet drugs
ASA and dipyridamole
The ESPS2 and ESPRIT studies were the first to identify the combination of ASA and dipyridamole (ASA/DPR) as being superior to ASA for preventing vascular episodes. However, the validity of these results has been called into question due to methodology problems. A systematic review showed that the ASA/DPR combination, compared to ASA alone, decreased the risk of a new, non-fatal stroke by 23%. The PROFESS study compared clopidogrel 75 mg/d to ASA 25 mg/DPR 200 mg (extended release, administered twice daily). That study found that ASA/DPR was not superior to clopidogrel in the areas of secondary stroke prevention, functional recovery, or the potential development of cognitive impairment.  

ASA and clopidogrel
The MATCH study examined the efficacy of the combination of ASA 75 mg/d and clopidogrel 75 mg/d (ASA/CLP),
Table 2 Recommendations. prevention of ischaemic stroke associated with large-vessel arteriosclerosis and small-vessel disease.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence and recommendation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antplatelet drugs</strong></td>
<td></td>
</tr>
<tr>
<td>- Treatment with antiplatelet drugs is recommended to prevent recurrence.</td>
<td>Level of evidence 1a; Recommendation grade A</td>
</tr>
<tr>
<td>- ASA (dosed at 50-300 mg/day) reduces the absolute risk of stroke, AMI, or</td>
<td>Level of evidence 1a;</td>
</tr>
<tr>
<td>vascular death compared to placebo. It is considered a first-choice drug.</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>- Clopidogrel (75 mg/day) is modestly more effective than ASA for reducing risk</td>
<td>Level of evidence 1b;</td>
</tr>
<tr>
<td>of stroke, AMI, and vascular death in patients with atherosclerotic disease.</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>It is considered a first-choice drug.</td>
<td></td>
</tr>
<tr>
<td>- Triflusal 600 mg/day shows similar efficacy to ASA with fewer haemorrhagic</td>
<td>Level of evidence 1a;</td>
</tr>
<tr>
<td>complications, and it is considered a first-choice treatment.</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>- The combination of ASA (25 mg) and dipyridamole (200 mg, delayed-release)</td>
<td>Level of evidence 1b;</td>
</tr>
<tr>
<td>taken twice daily reduces risk of stroke in a similar way to clopidogrel.</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>- The combination of ASA and clopidogrel is not recommended for preventing</td>
<td>Level of evidence 1b;</td>
</tr>
<tr>
<td>stroke due to large-vessel atherosclerosis or small-vessel disease.</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td><strong>Oral anticoagulant agents</strong></td>
<td></td>
</tr>
<tr>
<td>- Oral anticoagulants are not recommended for prevention of stroke caused by</td>
<td>Level of evidence 1a;</td>
</tr>
<tr>
<td>large vessel atherosclerosis, small vessel disease, or intracranial artery</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>stenosis, except in patients with antiplatelet drug intolerance or</td>
<td></td>
</tr>
<tr>
<td>contraindications for antiplatelet therapy, or where embolic heart disease is</td>
<td></td>
</tr>
<tr>
<td>also present.</td>
<td>Level of evidence 1a;</td>
</tr>
<tr>
<td>- Carotid endarterectomy is recommended with ipsilateral carotid stenosis</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>of 70% to 99% and an episode of TIA, amaurosis fugax, or cerebral ischaemia</td>
<td></td>
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<tr>
<td>with minor sequelae in the preceding 6 months. Hospitals should have a</td>
<td></td>
</tr>
<tr>
<td>surgical morbidity and mortality rate of less than 6%.</td>
<td>Level of evidence 1a;</td>
</tr>
<tr>
<td>- The procedure may be recommended in patients with 50% to 69% stenosis and</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>men with risk factors and recent hemispheric symptoms.</td>
<td></td>
</tr>
<tr>
<td>- This treatment is not appropriate for stenoses of less than 50%.</td>
<td>Level of evidence 1b;</td>
</tr>
<tr>
<td>- In cases of TIA or minor stroke, the procedure should be carried out within</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>2 weeks of the episode.</td>
<td>Level of evidence 1a;</td>
</tr>
<tr>
<td>- Percutaneous transluminal angioplasty may be indicated as an alternative</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>to carotid endarterectomy in symptomatic cases of carotid stenosis exceeding</td>
<td>Level of evidence 1b;</td>
</tr>
<tr>
<td>50% (arteriography measurement) or ≥ 70% (non-invasive measurement). It is</td>
<td>Recommendation grade A</td>
</tr>
<tr>
<td>especially feasible in patients in whom endarterectomy would be a high-risk</td>
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<tr>
<td>or technically difficult procedure, those with restenosis following</td>
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<tr>
<td>endarterectomy, stenosis after radiotherapy, or medical contraindications</td>
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<tr>
<td>including severe coronary artery disease.</td>
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<tr>
<td><strong>Extra-intracranial anastomosis</strong></td>
<td>Level of evidence 1b;</td>
</tr>
<tr>
<td>- Extra-intracranial anastomosis is not recommended.</td>
<td>Recommendation grade B</td>
</tr>
<tr>
<td><strong>Intracranial endovascular treatment</strong></td>
<td>Level of evidence 2b;</td>
</tr>
<tr>
<td>- Medical treatment, including antiplatelet drugs, statins, and modifying risk</td>
<td>Recommendation grade B</td>
</tr>
<tr>
<td>factors, is recommended for patients with symptomatic intracranial stenosis.</td>
<td></td>
</tr>
<tr>
<td>Endovascular treatment is not recommended.</td>
<td></td>
</tr>
</tbody>
</table>
compared to clopidogrel alone, in patients with a history of stroke or TIA. The combination was not superior to clopidogrel and it was associated with a significantly higher risk of haemorrhage. Additionally, the CHARISMA study in patients with clinically evident vascular disease or multiple RFs did not show ASA/CLP to have greater efficacy for stroke recurrence reduction than ASA monotherapy. One of the objectives of the study Secondary Prevention of Small Subcortical Strokes (SPS3), currently underway, is to evaluate the efficacy of ASA/CLP in reducing stroke recurrence in patients with small vessel disease.

Other combinations

Additional combinations of anti-platelet drugs have also been tested, including ASA/DPR/CLP and ASA/CLP with glycoprotein IIb/IIa inhibitors. Data were insufficient in both cases to yield recommendations for stroke prevention.

Oral anticoagulant agents

The SPIRIT study compared high-intensity oral anticoagulants (3.0-4.5 INR) to ASA (30 mg/d). It was terminated prematurely due to a high volume of haemorrhagic complications in the anticoagulant group. The WARSS study compared 325 mg/d ASA to warfarin adjusted for an INR target of 1.4 to 2.8 and had identified no differences at the 2-year point. The ESPRIT study concluded that medium-intensity oral anticoagulants (2-3 INR) were no more effective than ASA for secondary prevention of IS, and that any possible protective effect was cancelled out by the number of haemorrhagic complications. One systematic review showed that anticoagulants (INR of up to 2.6) displayed no advantages compared to antiplatelet treatment with regard to either risk of death by vascular causes or overall mortality. Furthermore, intensive anticoagulant treatment (3-4.5 INR) is associated with a significant increase in total mortality and severe haemorrhagic episodes.

Data from studies or specific cases of non-cardioembolic stroke appear below.

Stenosis of the intracranial arteries
The WASID study for symptomatic intracranial stenosis was interrupted prematurely since warfarin showed higher rates of haemorrhagic complications and no benefits compared to ASA dosed at 1300 mg/d.

Basilar artery stenosis
An analysis of the WASID study suggested that these patients might benefit from anticoagulant treatment even though differences were not significant.

Stroke recurrence despite antiplatelet treatment
Oral anticoagulants have not shown any benefits in these patients.

Vascular interventional procedures

Extracranial carotid artery stenosis

Carotid endarterectomy
Endarterectomy offers more advantages than medical treatment in cases of symptomatic carotid stenosis >70%. The NASCET study shows an improvement of 17% at the 2-year mark and ECST shows 14% improvement at the 3-year mark. For moderate cases of stenosis (50-69%), the benefit of carotid endarterectomy is less pronounced (4.5% reduction in absolute risk at 5 years); there is no significant benefit for stenosis <50%. In contrast, a meta-analysis that includes the ECST and NASCET studies points to higher benefits from endarterectomy in men, patients older than 75 years, and patients undergoing the procedure within 2 weeks of the stroke or TIA; it is less effective at later dates. It is currently indicated in patients with symptomatic carotid stenosis of 70% to 99% and an additional life expectancy of more than 5 years, provided that the hospital in question has a surgical morbidity and mortality rate of less than 6%. Endarterectomy may be considered in patients with symptomatic carotid stenosis of 50% to 69%, but certain variables may affect the risk-benefit balance: female sex (no clear benefit in clinical trials); initial manifestation as hemispheric IS (better results than in retinal ischaemia); or presence of a contralateral carotid occlusion, which is associated with a greater preoperative risk although benefits remain. Medical treatment without endarterectomy is indicted in patients with carotid stenosis <50%.

Percutaneous transluminal angioplasty
This technique has shown good results in patients with fibromuscular dysplasia, lesions due to radiotherapy, or restenosis following endarterectomy. It has been suggested as a treatment alternative for stenosing atherosclerosis. The CAVATAS study showed similar efficacy and safety results for percutaneous transluminal angioplasty and endarterectomy. Technical advances include specific angioplasty balloons, stents, and most recently, distal protection devices. The SAPPHIRE study of carotid angioplasty and stenting showed that the technique was superior to endarterectomy in patients with a high level of surgical risk and symptomatic or asymptomatic carotid stenosis. However, early interruption of the EVA-3S study due to high rates of 30-day mortality or stroke in the carotid angioplasty group, and the SPACE study’s failure to demonstrate that the technique was noninferior to carotid endarterectomy may constitute reasons to question carotid angioplasty as a safe alternative. However, long-term follow-up (2–4 years) has shown similar levels of reduction of ipsilateral IS for both techniques, although researchers stress the need to improve short-term safety results of carotid angioplasty and stenting. A meta-analysis indicates that endovascular treatment is associated with a modest increase in stroke and death rates 30 days after the procedure, with no significant intergroup differences in rates of incapacitating stroke or death at 30 days. On the other hand, surgical treatment is associated with a significant increase in cranial nerve palsy and AMI. The ICSS study found a 3.3% difference in absolute risk of stroke, death, or AMI at 120
days that pointed to endarterectomy as the superior technique. The CAVATAS study identified a higher incidence of non-perioperative stroke in patients with endovascular treatment (21.1%) than in those treated with endarterectomy (15.4%). This difference was observed even after the 2-year randomisation process, and it may be explained by the higher incidence of restenosis following angioplasty. Only a small group of patients in the CAVATAS study underwent stenting (22%). The true long-term incidence rate for post-stent restenosis is unknown. The CREST study, conducted in patients with high-grade stenosis, whether symptomatic (53%) or asymptomatic (47%), observed no significant differences regarding the study’s main objective. During the periprocedural period, however, there was a greater risk of non-disabling stroke with stenting, and a greater risk of AMI with endarterectomy. One important consideration is that over time (4 years), the rates of stroke recurrence were very low with both treatment options. This may be partially explained by the high percentage of asymptomatic patients in this group. Factors associated with a higher risk of periprocedural stroke or death with carotid angioplasty include male sex, age >70 years, prior stroke, and having experienced a stroke rather than a TIA.

In cases of symptomatic stenosis of the common carotid artery, the reasonable options are revascularisation by carotid angioplasty, direct arterial reconstruction, or extra-anatomic bypass grafting. However, available evidence is insufficient to make recommendations.

Extracranial vertebral artery stenosis; subclavian artery stenosis
Indications for revascularisation in cases of proximal vertebral artery stenosis are infrequent; generally speaking, the contralateral artery will supply the basilar artery sufficiently. In cases of stroke recurrence despite appropriate medical treatment, surgical or endovascular treatment may be considered. Evidence is insufficient to recommend one procedure over another. Surgical options include trans-subclavian vertebral endarterectomy, transposition of the vertebral artery to the ipsilateral common carotid artery, and reimplantation of the vertebral artery using a venous graft extension to the subclavian artery. The only randomised study on endovascular treatment in patients with vertebral artery stenosis was CAVATAS, which randomised 16 patients to receive either endovascular treatment and medical treatment, or medical treatment alone. In cases of cerebrovascular ischaemia in the posterior cerebral territory due to subclavian artery stenosis, doctors may consider the possibility of a carotid-subclavian extra-anatomic bypass for cases with low surgical risk. Percutaneous angioplasty and stenting should be considered in cases with an elevated risk of surgical complications.

Intracranial arterial stenosis
The WASID trial found a yearly risk of stroke of 11% despite the best medical treatment; this figure was 19% in the subgroup with stenosis > 70%. These patients present a high risk of recurrent ischaemia in the territory of the stenosed artery. This is also seen in the vertebrobasilar territory (12% at 1 year and 15% at 2 years). In 2005, the FDA approved the use of the Wingspan stent system, which is effective in 96.7 to 98.8% of all cases and has a 30-day complication rate of 6.1 to 9.6%. In one European registry, 25 to 30% of patients experienced restenosis (mostly asymptomatic), while 4.8% experienced an incapacitating stroke. The mortality rate was 2.2%. Researchers recently halted the SAMMPRIS study (Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis). The study compared angioplasty and the Wingspan stent system associated with medical treatment (modification of risk factors and ASA/CLP combination treatment) to medical treatment alone in patients with symptomatic intracranial stenosis > 70% and IS in the first 30 days. Recruitment was stopped after 451 patients, rather than the anticipated 764 since significant benefits were found for the medical treatment group, which yielded lower rates of stroke or death at 30 days (5.8% in the medical treatment group vs 14% in the Wingspan group).

Extra-intracranial arterial anastomosis
Approximately 10% of patients with non-disabling stroke present occlusion or stenosis of the internal carotid artery or middle cerebral artery. Effects of this condition might be reduced by anastomosing the superficial temporal branch of the external carotid artery to an extra-intracranial bypass, although the only completed clinical trial yielded negative results. Regardless of the effectiveness this technique has displayed in selected patients with giant aneurysm of the internal carotid artery, or moyamoya disease in young patients, there are currently no indications for extra-intracranial anastomosis as a means of preventing stroke. Results from the clinical trial Carotid Occlusion Surgery Study, presented at ISC 2011, did not show surgery to be an effective means of preventing stroke recurrence at 2 years because of the low recurrence rate in the non-surgical group.

Ischaemic stroke of cardioembolic origin (Table 3)
Nonvalvular atrial fibrillation
Current treatment follows 2 strategies: prevention of thromboembolism using antithrombotic agents, and treatment of the FA itself, including stabilising both heart rate and rhythm. Furthermore, new non-pharmacological treatments are being developed to decrease risk of stroke in patients with non-valvular AF.

Oral anticoagulant agents
The European Atrial Fibrillation Trial (EAFT) in stroke patients with non-valvular AF showed a 66% decrease in the IS recurrence rate in the warfarin group, vs a 15% decrease in the ASA group (300 mg). The number needed to treat (NNT) to avoid one stroke per year is 14 for warfarin and 50 for ASA. While vitamin K antagonists (VKA) are effective, they pose significant problems in clinical practice and are consequently often underused. Vitamin K antagonists may also be dosed incorrectly due to their delayed action and metabolism, narrow therapeutic range, the
### Table 3 Recommendations for preventing ischaemic stroke of cardioembolic origin.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence and recommendation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-valvular atrial fibrillation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
</tr>
<tr>
<td>- Oral anticoagulants are recommended for patients with non-valvular AF and a high risk of stroke (CHADS ≥ 2 or CHA2DS2-VASC ≥ 1).</td>
<td>Level of evidence 1a; Recommendation grade A</td>
</tr>
<tr>
<td>- Treatment with ASA or oral anticoagulants may be indicated in patients with AF and a low to moderate risk level (CHADS 1 or CHA2DS2-VASC 0).</td>
<td>Level of evidence 1a; Recommendation grade A</td>
</tr>
<tr>
<td>- Treatment with ASA or no treatment is recommended for patients with AF and a low risk level (CHADS 0 or CHA2DS2-VASC 0).</td>
<td>Level of evidence 1a; Recommendation grade A</td>
</tr>
<tr>
<td>- Vitamin K antagonists, direct thrombin inhibitors (dabigatran) or factor X inhibitors (rivaroxaban, apixaban) are recommended for patients with an indication for oral anticoagulants.</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
<tr>
<td>- The combination of ASA and clopidogrel may be used in patients with contraindications for oral anticoagulants.</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
<tr>
<td>- The combination of ASA and warfarin is not recommended.</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
<tr>
<td>- Percutaneous left atrial appendage closure may be an alternative to using warfarin to prevent stroke in patients in whom oral anticoagulants are strictly contraindicated. The procedure is associated with higher rates of complications, and should therefore be limited to patients with low complication rates and hospitals with experience.</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
</tr>
<tr>
<td>- Oral anticoagulants are recommended for patients with stroke and non-valvular AF (see ‘primary prevention’ section and main text).</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
<tr>
<td><strong>Acute myocardial infarction (AMI)</strong></td>
<td></td>
</tr>
<tr>
<td>- Anticoagulant treatment over 3 months, beginning with heparin followed by oral anticoagulants, is recommended for cases of anterior AMI and thrombus detected by imaging techniques.</td>
<td>Level of evidence 1b; Recommendation grade B</td>
</tr>
<tr>
<td>- Sustained treatment with oral anticoagulants after acute myocardial infarction reduces risk of stroke, but increases risk of major haemorrhagic complications.</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
<tr>
<td><strong>Cardiomyopathy with heart failure</strong></td>
<td></td>
</tr>
<tr>
<td>- In patients with stroke and heart failure, warfarin treatment is superior to ASA or clopidogrel for reducing risk of stroke, although statistical power is limited.</td>
<td>Level of evidence 1b; Recommendation grade B</td>
</tr>
<tr>
<td><strong>Rheumatic mitral stenosis</strong></td>
<td></td>
</tr>
<tr>
<td>- Oral anticoagulant treatment is recommended in patients with mitral stenosis who present AF or prior embolism even when they maintain sinus rhythm.</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td><strong>Mitral valve prolapse</strong></td>
<td></td>
</tr>
<tr>
<td>- An aetiological study to rule out other possible causes of stroke is crucial in stroke patients with mitral valve prolapse. If no other causes are identified, treatment with antiplatelet drugs is recommended, following general indications for preventing recurrences of stroke of undetermined origin.</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td><strong>Valve replacements</strong></td>
<td></td>
</tr>
<tr>
<td>- Oral anticoagulant treatment with warfarin (2.5-3.5 INR) is superior to antiplatelet drugs for reducing thromboembolic complications in patients with mechanical valve replacements.</td>
<td>Level of evidence 2b; Recommendation grade B</td>
</tr>
<tr>
<td>- For patients with biological valve replacements, oral anticoagulants are recommended during the first 3 months, followed by low-dose ASA as an antiplatelet drug.</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td>- Associating ASA 100 g/day with an oral anticoagulant delivers better reduction of the risk of embolism in patients with mechanical valve replacements and stroke recurrence despite appropriate anticoagulant treatment. However, this does significantly increase risk of haemorrhage.</td>
<td>Level of evidence 2b; Recommendation grade B</td>
</tr>
</tbody>
</table>
Recommendations according to aetiological sub-type

Table 3 (Continued)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence and recommendation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomalies of the interatrial septum</td>
<td></td>
</tr>
<tr>
<td>- Preventive treatment is not indicated for asymptomatic patients with patent foramen ovale; risk of stroke in a patient with PFO resembles that in the general population (primary prevention)</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td>- If there is suspicion of paradoxical embolism due to deep vein thrombosis in a stroke patient with PFO, anticoagulant treatment should be administered for at least 3 months.</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td>- In other cases, treatment will depend on risk of recurrence estimated based on the co-presence of PFO and other anomalies associated with elevated risk of recurrence.</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td>- For lack of results from clinical trials on stroke prevention in patients with PFO, antiplatelet treatment is considered appropriate for stroke patients with isolated PFO. Oral anticoagulants are suitable for patients with high-risk PFO or stroke recurrence despite treatment.</td>
<td>Level of evidence 2b; Recommendation grade C</td>
</tr>
<tr>
<td>- Percutaneous closure of a PFO is no better than medical treatment as a means of preventing stroke, and it is associated with more serious complications. The procedure is not recommended.</td>
<td>Level of evidence 1b; Recommendation grade A</td>
</tr>
</tbody>
</table>

considerable variation in their metabolism process and numerous interactions with foods and other drugs, the presence of genetic polymorphisms that affect the dosing requirements, and the need for regular coagulation monitoring and frequent dose adjustments, which generates additional costs. As a result, only 10% to 18% of these patients have an appropriate INR. Risk of haemorrhage is another severe problem with VKA treatment. This risk can be reduced by treating AHT and monitoring INR. If the range is appropriate (2-3 INR), the risk of cerebral haemorrhage is 0.5% per year with a NNT of 200; this is acceptable when compared to the NNT of 14 for avoiding a stroke. We recommend using the HAS-BLED scale of risk of severe haemorrhage to assess the risk-benefit balance of oral anticoagulants. Patients with scores ≥ 3 are considered to be at high risk. On the other hand, despite risk of haemorrhage, oral anticoagulants show clear benefits in patients over 85 and with AF.

New anticoagulants are currently available (thrombin and factor X inhibitors) that provide the added advantage of not requiring INR level monitoring. Dabigatran dosed at 100 mg/12 h has shown similar efficacy to warfarin treatment for stroke reduction. It is associated with a lower frequency of major haemorrhages; at doses of 150 mg/12 h, it is more effective than warfarin for stroke reduction with similar haemorrhage rates. Dabigatran is easy to administer, as it has set doses and does not require monitoring. Analysis of the subgroup with IS showed efficacy results for dabigatran that were similar to those for the total group, but tending towards superiority over warfarin. Both dabigatran dosages also showed a significantly lower risk of intracranial haemorrhage and haemorrhagic stroke. In a cost-effectiveness study in patients older than 65 years with a CHADS2 score ≥ 2, dabigatran proved itself to be an alternative to warfarin based on prices in the USA. Dabigatran has been approved by the FDA and by Health Canada, and it is pending approval in Europe. European and AHA guidelines place dabigatran on par with VKAs for stroke prevention in patients with AF. Doses of 110 mg/12 h are indicated in patients with a lower risk of cardioembolism or a higher risk of haemorrhage (very advanced age, poorly managed AHT, prior cerebral haemorrhage, neuroimaging evidence of leukoaraisosis or cerebral microhaemorrhage, or HAS-BLED score ≥ 3). Doses of 150 mg/12 h are indicated for patients with a higher risk of cardioembolism or INR below the therapeutic range despite VKA treatment, or where there are other VKA-related problems. For secondary prevention of cardioembolic stroke, 150 mg/12 h is an appropriate dose in patients with a HAS-BLED score < 3 or stroke recurrence despite correct treatment with VKAs. The dose of 110 mg/12 h is recommended for HAS-BLED scores ≥ 3. The AVERROES study in patients with AF and a VKA contraindication showed a significant impact by apixaban compared to ASA on the annual stroke or systemic embolism rate (1.6% vs 3.6%). Haemorrhage rates were similar for both treatments. The ROCKET AF study demonstrated that rivaroxaban dosed at 20 mg every 24 hours is noninferior to warfarin as a means of preventing stroke and peripheral embolism without increasing risk of haemorrhage. Analysis of the treated population found significant differences (1.71% vs 2.16%) with rivaroxaban appearing to be superior. Other anticoagulants currently being developed include edoxaban and betrixaban.

Antiplatelet drugs
The EAFIT study showed that oral anticoagulants were clearly superior to ASA 300 mg for secondary stroke prevention. The ACTIVE-A study showed that 2 antiplatelet drugs used in combination (ASA 75-100 mg/CLP 75 mg) in patients with a contraindication for VKAs achieved a 28% reduction in risk of stroke compared to ASA alone (75-100 mg). However, there was a significant increase in risk of major
haemorrhagic complications. In contrast, the ACTIVE W study found oral anticoagulants to be superior to the ASA 75-100 mg/CLP 75 mg combination for reducing stroke, systemic embolism, AMI, and vascular death.

Combining oral anticoagulants and antiplatelet drugs
In cases of embolism recurrence despite appropriate anticoagulant treatment, empirical treatment calls for associating these drugs with ASA. Nevertheless, studies have found no differences in stroke or systemic embolism reduction through treatment with warfarin and ASA compared to warfarin alone, whereas the combination is associated with a significant increase in haemorrhagic complications. On the other hand, a significant reduction in the risk of death of vascular causes, TIA, non-fatal stroke, and systemic embolism has been observed with the combination of triflusal 600 mg/day and moderate-intensity anticoagulants, without a significant increase in haemorrhagic complications. A long-term analysis of one patient subgroup found that the combination of triflusal 600 mg/day and an oral anticoagulant was superior to anticoagulant only.

Antiarrhythmic agents
A post hoc analysis of the ATHENA study in patients with persistent or paroxysmal AF found that dronedarone reduced risk of stroke by 36% regardless of presence or absence of antithrombotic treatment. Doctors should maintain anticoagulant treatment after stabilising cardiac rhythm in patients with an elevated risk of cardioembolism (CHADS2 ≥ 2). After cardiac ablation, the AF recurrence rate is 13% at 2 years, 21.8% at 3 years, 35% at 4 years, 46.8% at 5 years, and 54.6% at 6 years. Even patients who do not experience recurrence in the first year cannot be considered cured; follow-up studies show that 40% will experience recurrence.

Other drug treatments
Use of statins may prevent either appearance or recurrence of AF. Use of ACE inhibitors or ARBs to block the renin-angiotensin system has been shown to reduce the risk of de novo AF.

Non-pharmacological treatments
In most patients with non-valvular AF, thrombi are located in the left atrial appendage. As a result, one possible approach would be excising that structure in selected patients with absolute contraindications to oral anticoagulants. In the PROTECT AF study, percutaneous closure of the atrial appendage was noninferior to warfarin for stroke prevention, although it yielded a higher rate of periprocedural complications.

Other causes of cardioembolism
Evidence regarding risk and recommendations for preventing stroke due to other cardioembolic causes are not as clear as in non-valvular AF or in other specific situations.

Acute myocardial infarction (AMI)
Early onset of heparin treatment followed by oral anticoagulants decreased the risk of IS from 3% to 1% and yielded a > 50% reduction in thrombus formation. A minimum of 3 months of oral anticoagulant treatment is recommended in anterior AMI with a thrombus detected by an imaging study. A meta-analysis comparing oral anticoagulants associated with ASA or used in monotherapy, ASA alone, or placebo found that while warfarin did not reduce mortality or reinfarction rates, it did decrease risk of stroke while also increasing risk of major haemorrhage.

Cardiomyopathy with heart failure
In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH), warfarin was associated with a significantly lower stroke rate (0.6%) than ASA dosed at 162 mg/day or clopidogrel at 75 mg/day (2.3%). However, the study’s statistical power is insufficient to establish which treatment is better. Another study, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF), is currently underway in patients with LVEF ≤ 35%.

Rheumatic mitral stenosis
Oral anticoagulant treatment is recommended in patients with mitral stenosis and AF or prior embolism, even when they maintain sinus rhythm.

Mitral valve prolapse
There are no available clinical trials in patients with stroke and mitral valve prolapse. Stroke patients with mitral valve prolapse will require an aetiological study to rule out other possible causes of stroke. If no other causes are identified, antiplatelet treatment is recommended according to general indications for preventing recurrences of stroke of undetermined origin. Oral anticoagulants should be prescribed when patients experience recurrence despite ASA treatment, evidence of prior systemic embolism, or associated AF.

Valve replacements
The indication for antithrombotic treatment depends on the type of replacement and associated RFs. As a means of reducing thromboembolic complications, warfarin has been shown to be superior to 2 different antiplatelet regimens (ASA dosed at 650 or 990 mg/day + dipyridamole 150-225 mg/day or ASA 650 mg/day + pentoxifylline 800 mg/day). Oral anticoagulants are indicated for mechanical valves; however, even when INR levels are appropriate (2.5–3.5), there is still a yearly risk of thromboembolism of 1-2%. Valves in the mitral position are at more risk than those in the aortic position. INR should therefore remain between 2.5 and 3.5 for mechanical valves in the mitral position, but lower, between 2.0 and 3.0, for bivalvular or Medtronic Hall valves in the aortic position, provided that the factors mentioned above are not present.
For biological valves, oral anticoagulants are recommended during the first 3 months after surgery, which is when emboli are most likely to appear (before the valve is completely endothelialised). Subsequently, doctors may consider long-term antiplatelet therapy with low-dose ASA (75-100 mg), provided that the patient does not have associated RFs such as AF, history of thromboembolism, left ventricular dysfunction, or a hypercoagulable state. Oral anticoagulants are recommended in these cases. Associating low doses of ASA (100 mg/day) or dipyridamole with an oral anticoagulant is more effective for reducing risk of embolism in patients with mechanical valve replacements and stroke recurrence despite appropriate anticoagulant treatment. However, this does significantly increase risk of haemorrhage.

Patent foramen ovale (PFO) and atrial septal aneurysm (ASA)

Preventive treatment is not indicated for asymptomatic patients with patent foramen ovale; risk of stroke in a patient with PFO resembles that in the general population. If doctors suspect paradoxical embolism does to deep vein thrombosis in a stroke patient with PFO, anticoagulant treatment should be administered for at least 3 months. In other cases, treatment will depend on the risk of recurrence, which is estimated based on co-presence of PFO and other anomalies that are associated with an increased yearly risk of recurrence. Such anomalies include hypercoagulable state or co-presence of an ASA; the significance of the latter is more debatable. A PICSS, a sub-study of the WASSS clinical trial, observed no differences in recurrence rates among patients with cryptogenic stroke and PFO treated with either aspirin or oral anticoagulants.

For lack of results from clinical trials on stroke prevention in patients with PFO, antiplatelet treatment is considered appropriate for stroke patients with isolated PFO. Oral anticoagulants are suitable for patients with high-risk PFO or stroke recurrence despite treatment. Results from the CLOSURE-I study show that percutaneous closure of PFO is nonsuperior to medical treatment for stroke prevention, and that its complication rate is higher. The RESPECT and REDUCE trials are still underway, and at present, percutaneous closure of PFO is not recommended except in clinical trials.

Infarcts of rare causes (Table 4)

In this section, we consider only the main aetiologies implicated in IS of rare causes in our setting. These include artery dissection, prothrombotic states, atheromatous plaque in the aortic arch, and lastly, thrombosis of dural sinuses.

Artery dissection

There is no evidence regarding treatment of carotid or extracranial vertebral dissection; analysis of studies performed with either ASA or oral anticoagulants does not reveal significant differences between these regimens. A prospective study showed a higher frequency of major haemorrhages with antithrombotic treatment (antiplatelet, 1%; anticoagulant, 2%) than of IS (0.3%). As efficacy is similar, it would be reasonable to use the drug with the lowest haemorrhagic risk, that is, the antiplatelet drug. Doctors believe that maintaining treatment during 3 to 6 months is appropriate, although no studies support this. A systematic review of cases of carotid or vertebral artery dissection treated with angioplasty and stenting concluded that this technique is safe. However, no conclusions can be drawn regarding its efficacy, since there are no studies comparing this option to medical treatment.

Prothrombotic states

Deep vein thrombosis is an indication for short- or long-term anticoagulation therapy, depending on the clinical and haematological circumstances. Although there are guidelines establishing general recommendations for acquired hypercoagulable states, there is no specific evidence regarding secondary stroke prevention. Oral anticoagulants are recommended in cases of protein C, S, and antithrombin III deficiency, especially in high-risk situations and for secondary prevention. For secondary prevention in patients with lupus anticoagulant, anticoagulant treatment is indicated, although there are no appropriately designed studies that assess the efficacy of this treatment compared to antiplatelet treatment. The APASS study revealed that the presence of antiphospholipid antibodies was not associated with an increased risk of stroke recurrence or with a different response to treatment with ASA 325 mg/day or warfarin with an INR of 1.4-2.8. Based on these data, aspirin and low-intensity anticoagulation may be considered preventive treatments in patients with antiphospholipid antibody positivity after a first ischaemic stroke. Oral anticoagulants for an INR of 2-3 are recommended for cases of antiphospholipid syndrome.

Atheromatous plaque in the aortic arch

Atheromatous plaque in the aortic arch is associated with an elevated risk of stroke recurrence and death, especially if plaques measure ≥ 4 mm or they are complex (presence of ulceration or mobile components) despite treatment with ASA or oral anticoagulants. In a retrospective study, use of statins was independently associated with less stroke recurrence. The Aortic Arch Related Cerebral Hazard Trial (ARCH), currently underway, compares warfarin to ASA/CLP combination therapy. Oral anticoagulants or ASA treatment may be considered to prevent recurrent stroke in patients with ASA and atheromatous plaque in the aortic arch measuring 4 mm or larger.

Cerebral/dural venous sinus thrombosis

Treatment with oral anticoagulants should be maintained for at least 3 months to avoid rethrombosis following the early-phase anticoagulant treatment. The decision to extend the treatment over the long term will depend on
whether or not a prothrombotic risk factor is detected. If this risk factor is transient, anticoagulants may be discontinued after 3 months. For lower-risk situations, such as protein C or S deficiency, or heterozygosity for factor V Leiden or for the prothrombin G20210A mutation, anticoagulants may be maintained during 6 months. In contrast, for high-risk situations such as antithrombin deficiency, homozygosity for factor V Leiden, or co-presence of 2 or more prothrombotic conditions, long-term anticoagulation is recommended. This is also true in cases of multiple episodes of idiopathic venous thrombosis.117,118

### Ischaemic stroke of undetermined origin

In cryptogenic IS, antiplatelet drugs are recommended as the primary treatment method. Some authors recommend anticoagulants when strokes recur despite treatment with antiplatelet drugs. In cases of IS of undetermined aetiology due to an incomplete work-up, missing data must be obtained so as to start the most suitable treatment. For IS of several possible aetiologies, treatment should be tailored to the cause with the highest risk of recurrence and act on all causes where possible.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### Addendum

Ad hoc committee of the SEN Study Group for Cerebrovascular Diseases formed to draw up clinical practice guidelines for stroke.

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A.2. Review or institutional committee

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Recommendations according to aetiological sub-type


Additional References
