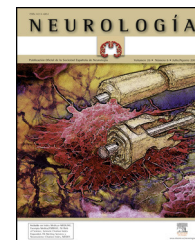




NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW

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

B. Fuentes (Secretary)^{*}, J. Gállego, A. Gil-Nuñez, A. Morales, F. Purroy, J. Roquer, T. Segura, J. Tejada, A. Lago, E. Díez-Tejedor (Coordinator) representing the ad hoc committee of the SEN Study Group for Cerebrovascular Diseases, M. Alonso de Lecñana, J. Álvarez-Sabin, J. Arenillas, S. Calleja, I. Casado, M. Castellanos, J. Castillo, A. Dávalos, F. Díaz-Otero, J.A. Egido, J.C. López-Fernández, M. Freijo, A. García Pastor, F. Gilo, P. Irimia, J. Maestre, J. Masjuan, J. Martí-Fàbregas, P. Martínez-Sánchez, E. Martínez-Vila, C. Molina, F. Nombela, M. Ribó, M. Rodríguez-Yañez, F. Rubio, J. Serena, P. Simal, J. Vivancos[◇]

Received 9 June 2011; accepted 29 June 2011
Available online 6 March 2014

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.

[☆] Please cite this article as: Fuentes B, Gállego J, Gil-Nuñez A, Morales A, Purroy F, Roquer J, et al. Guía para el tratamiento preventivo del ictus isquémico y AIT (II). Recomendaciones según subtipo etiológico. Neurología. 2014;29:168–183.

^{*} Corresponding author.

E-mail address: hplapazneuro@meditex.es (B. Fuentes).

[◇] Author affiliations and members of the committee are listed in the [Addendum](#).

PALABRAS CLAVE

Guía de práctica clínica;
Ictus isquémico;
Ataque isquémico transitorio;
Prevención

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

© 2011 Sociedad Española de Neurología. Published by Elsevier España, S.L. All rights reserved.

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 carotídea ipsilateral (70-99%). La prevención de II de origen cardioembólico (fibrilación auricular, valulopatías, prótesis valvulares y en infarto de miocardio con trombo mural) se basa en el uso de anticoagulantes orales. En el II de origen inusual, las terapias preventivas dependerán de la etiología; 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.

© 2011 Sociedad Española de Neurología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

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.

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

Source: Adapted from the Centre for Evidence Based Medicine (CEBM).¹

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.¹⁵

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.¹⁶ A recent Cochrane meta-analysis confirms that cilostazol was superior to ASA for preventing stroke recurrence in patients with IS.¹⁷

Other antiplatelet drugs under study

Sarpogrelate

Sarpogrelate's efficacy for secondary stroke prevention resembles that of ASA, and its haemorrhagic complication rate is lower.¹⁸

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.¹⁹ 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.²⁰ 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.^{21,22} 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%.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,²⁴ functional recovery,²⁵ or the potential development of cognitive impairment.²⁶

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.

	Recommendations	Level of evidence and recommendation grade
Antiplatelet drugs	- Treatment with antiplatelet drugs is recommended to prevent recurrence. - ASA (dosed at 50-300 mg/day) reduces the absolute risk of stroke, AML, or vascular death compared to placebo. It is considered a first-choice drug. - Clopidogrel (75 mg/day) is modestly more effective than ASA for reducing risk of stroke, AML, and vascular death in patients with atherosclerotic disease. It is considered a first-choice drug. - Triflusal 600 mg/day shows similar efficacy to ASA with fewer haemorrhagic complications, and it is considered a first-choice treatment. - The combination of ASA (25 mg) and dipyridamole (200 mg, delayed-release) taken twice daily reduces risk of stroke in a similar way to clopidogrel. - The combination of ASA and clopidogrel is not recommended for preventing stroke due to large-vessel atherosclerosis or small-vessel disease.	Level of evidence 1a; Recommendation grade A Level of evidence 1a; Recommendation grade A Level of evidence 1b; Recommendation grade A Level of evidence 1a; Recommendation grade A Level of evidence 1b; Recommendation grade A Level of evidence 1b; Recommendation grade A
Oral anticoagulant agents	- Oral anticoagulants are not recommended for prevention of stroke caused by large vessel atherosclerosis, small vessel disease, or intracranial artery stenosis, except in patients with antiplatelet drug intolerance or contraindications for antiplatelet therapy, or where emboligenic heart disease is also present.	Level of evidence 1a; Recommendation grade A
Carotid endarterectomy	- Carotid endarterectomy is recommended with ipsilateral carotid stenosis of 70% to 99% and an episode of TIA, amaurosis fugax, or cerebral ischaemia with minor sequelae in the preceding 6 months. Hospitals should have a surgical morbidity and mortality rate of less than 6%. - The procedure may be recommended in patients with 50% to 69% stenosis and men with risk factors and recent hemispheric symptoms. - This treatment is not appropriate for stenoses of less than 50%. - In cases of TIA or minor stroke, the procedure should be carried out within 2 weeks of the episode.	Level of evidence 1a; Recommendation grade A Level of evidence 1b; Recommendation grade A Level of evidence 1b; Recommendation grade A Level of evidence 1a; Recommendation grade A
Percutaneous transluminal carotid angioplasty	- Percutaneous transluminal angioplasty may be indicated as an alternative to carotid endarterectomy in symptomatic cases of carotid stenosis exceeding 50% (arteriography measurement) or $\geq 70\%$ (non-invasive measurement). It is especially feasible in patients in whom endarterectomy would be a high-risk or technically difficult procedure, those with restenosis following endarterectomy, stenosis after radiotherapy, or medical contraindications including severe coronary artery disease.	Level of evidence 1b; Recommendation grade A
Extra-intracranial anastomosis	- Extra-intracranial anastomosis is not recommended.	Level of evidence 1b; Recommendation grade B
Intracranial endovascular treatment	- Medical treatment, including antiplatelet drugs, statins, and modifying risk factors, is recommended for patients with symptomatic intracranial stenosis. Endovascular treatment is not recommended.	Level of evidence 2b; Recommendation grade B

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.²⁷ Additionally, the CHARISMA²⁸ 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/IIIa inhibitors. Data were insufficient in both cases to yield recommendations for stroke prevention.²⁹

Oral anticoagulant agents

The SPIRIT study³⁰ 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 WARSS³¹ 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.³² 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.³³

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.³⁴

Basilar artery stenosis

An analysis of the WASID study suggested that these patients might benefit from anticoagulant treatment even though differences were not significant.³⁵

Stroke recurrence despite antiplatelet treatment

Oral anticoagulants have not shown any benefits in these patients.³⁵

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 mark³⁶ and ECST shows 14% improvement at the 3-year mark.³⁷ For moderate cases of stenosis (50-69%), the benefit of carotid endarterectomy is less pronounced (4.5% reduction in absolute risk at 5 years)³⁸; there is no significant benefit for stenosis <50%.^{38,39} 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.⁴⁰ 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%.⁴¹⁻⁴³ 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.^{42,43} Medical treatment without endarterectomy is indicated in patients with carotid stenosis <50%.⁴¹⁻⁴³

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.⁴⁴ Technical advances include specific angioplasty balloons, stents, and most recently, distal protection devices. The SAPPHERE 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.⁴⁵ However, early interruption of the EVA-3S study due to high rates of 30-day mortality or stroke in the carotid angioplasty group,⁴⁶ 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.⁴⁷ 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.^{48,49} 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.⁵⁰ The ICSS study⁵¹ 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 study⁵² 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.⁵³ 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.^{48,54}

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.⁵⁵

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.^{42,55} 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.⁵⁶ In cases of cerebral 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.⁵⁵

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 $\geq 70\%$.³⁴ 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).⁵⁷ 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%.⁵⁸ 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%.⁵⁹ 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.⁶⁰ 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.⁶¹ 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.^{62–64}

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).⁶⁵ The number needed to treat (NNT) to avoid one stroke per year is 14 for warfarin and 50 for ASA.⁶⁶ While vitamin K antagonists (VKA) are effective, they pose significant problems in clinical practice and are consequentially 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.

	Recommendations	Level of evidence and recommendation grade
Non-valvular atrial fibrillation	Primary prevention	
	- Oral anticoagulants are recommended for patients with non-valvular AF and a high risk of stroke (CHADS ≥ 2 or CHA ₂ DS ₂ -VASc ≥ 1).	Level of evidence 1a; Recommendation grade A
	- Treatment with ASA or oral anticoagulants may be indicated in patients with AF and a low to moderate risk level (CHADS 1 or CHA ₂ DS ₂ -VASc 1).	Level of evidence 1a; Recommendation grade A
	- Treatment with ASA or no treatment is recommended for patients with AF and a low risk level (CHADS 0 or CHA ₂ DS ₂ -VASc 0).	
	- Vitamin K antagonists, direct thrombin inhibitors (dabigatran) or factor X inhibitors (rivaroxaban, apixaban) are recommended for patients with an indication for oral anticoagulants.	Level of evidence 1a; Recommendation grade A
	- The combination of ASA and clopidogrel may be used in patients with contraindications for oral anticoagulants.	Level of evidence 1b; Recommendation grade A
	- The combination of ASA and warfarin is not recommended.	Level of evidence 1b; Recommendation grade B
Acute myocardial infarction (AMI)	- 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.	Level of evidence 1b; Recommendation grade A
	Secondary prevention	
	- Oral anticoagulants are recommended for patients with stroke and non-valvular AF (see 'primary prevention' section and main text).	Level of evidence 1b; Recommendation grade A
Cardiomyopathy with heart failure	- 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.	Level of evidence 1b; Recommendation grade B
	- Sustained treatment with oral anticoagulants after acute myocardial infarction reduces risk of stroke, but increases risk of major haemorrhagic complications.	Level of evidence 1b; Recommendation grade A
Rheumatic mitral stenosis	- 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.	Level of evidence 1b; Recommendation grade B
Mitral valve prolapse	- Oral anticoagulant treatment is recommended in patients with mitral stenosis who present AF or prior embolism even when they maintain sinus rhythm.	Level of evidence 2b; Recommendation grade C
	- 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.	Level of evidence 2b; Recommendation grade C
Valve replacements	- 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.	Level of evidence 2b; Recommendation grade B
	- For patients with biological valve replacements, oral anticoagulants are recommended during the first 3 months, followed by low-dose ASA as an antiplatelet drug.	Level of evidence 2b; Recommendation grade C
	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.	Level of evidence 2b; Recommendation grade B

Table 3 (Continued)

	Recommendations	Level of evidence and recommendation grade
Anomalies of the interatrial septum	- 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)	Level of evidence 2b; Recommendation grade C
	- 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.	Level of evidence 2b; Recommendation grade C
	- 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.	Level of evidence 2b; Recommendation grade C
	- 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.	Level of evidence 2b; Recommendation grade C
	- 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.	Level of evidence 1b; Recommendation grade A

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.⁶² As a result, only 10% to 18% of these patients have an appropriate INR.^{67,68} Risk of haemorrhage is another severe problem with VKA treatment. This risk can be reduced by treating AHT and monitoring INR.⁶² 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.⁶⁶ 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.⁶⁹ On the other hand, despite risk of haemorrhage, oral anticoagulants show clear benefits in patients over 85 and with AF.⁷⁰

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.⁷¹ 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.⁷² 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.⁷³ Dabigatran has been approved by the FDA and by Health

Canada, and it is pending approval in Europe. European and AHA guidelines^{63,74} 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 leukoaraiosis 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 study⁷⁵ 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^{76,77} 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 EAFT study⁶⁵ 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.⁷⁸ 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.⁷⁹

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.⁸⁰ 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.⁸¹ 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.⁸²

Antiarrhythmic agents

A post hoc analysis of the ATHENA⁸³ 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.⁸⁴ Doctors should maintain anticoagulant treatment after stabilising cardiac rhythm in patients with an elevated risk of cardioembolism (CHADS₂ $\geq$ 2).⁸⁵ 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.⁸⁶

Other drug treatments

Use of statins may prevent either appearance or recurrence of AF.⁸⁷ Use of ACE inhibitors or ARBs to block the renin-angiotensin system has been shown to reduce the risk of de novo AF.⁸⁸

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.⁸⁹

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.⁴² A minimum of 3 months of oral anticoagulant treatment is recommended in anterior AMI with a thrombus detected by an imaging study.⁹⁰ 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.⁹¹

Cardiomyopathy with heart failure

In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH),⁹² 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 $\leq$ 35%.⁹³

Rheumatic mitral stenosis

Oral anticoagulant treatment is recommended in patients with mitral stenosis and AF or prior embolism, even when they maintain sinus rhythm.⁹⁴

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).⁹⁵ 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.⁹⁴ 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.⁹⁶

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.^{90,97} If doctors suspect paradoxical embolism due 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.^{98–100} PICSS, a sub-study of the WARSS clinical trial, observed no differences in recurrence rates among patients with cryptogenic stroke and PFO treated with either aspirin or oral anticoagulants.¹⁰¹ 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 study¹⁰² 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.¹⁰³

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.^{104–106} A prospective study showed a higher frequency of major haemorrhages with antithrombotic treatment (antiplatelet, 1%; anticoagulant, 2%) than of IS (0.3%).¹⁰⁴ 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.⁴² A systematic review of cases of carotid or vertebral artery dissection treated with angioplasty and stenting concluded that this technique is safe.¹⁰⁷ 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.¹⁰⁸ Although there are guidelines establishing general recommendations for acquired hypercoagulable states, there is no specific evidence regarding secondary stroke prevention.⁴² 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 that 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 1.4–2.8.¹⁰⁹ 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.⁴²

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.^{110,111} In a retrospective study, use of statins was independently associated with less stroke recurrence.¹¹² The Aortic Arch Related Cerebral Hazard Trial (ARCH), currently underway, compares warfarin to ASA/CLP combination therapy.¹¹³ 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.¹¹⁴

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.^{115,116} The decision to extend the treatment over the long term will depend on

Table 4 Recommendations for preventing ischaemic stroke of rare origin.

	Recommendations	Level of evidence and recommendation grade
Artery dissection	- Treatment with ASA over 3 to 6 months is recommended due to being as effective as oral coagulants while causing fewer complications.	Level of evidence 2a; Recommendation grade B
Atheromatous plaque in the aortic arch	- Oral anticoagulants (2.3 INR) or treatment with ASA may be considered to prevent stroke recurrence in patients with cerebral ischaemia and aortic arch atheroma ≥ 4 mm	Level of evidence 2b; Recommendation grade B
Cerebral/dural venous sinus thrombosis	- Use of statins in these patients may reduce risk of stroke recurrence. - Continuing treatment with oral coagulants is recommended during: - 3 months if the prothrombotic imbalance is transient. - 6 months for a low-risk case: protein C or S deficiency, heterozygosity for factor V Leiden or for the prothrombin G20210A mutation. - Indefinitely in a high-risk case: antithrombin deficit, homozygosity for factor V Leiden or the co-presence of 2 or more prothrombotic conditions, and in cases of 2 or more episodes of idiopathic venous thrombosis.	Level of evidence 2a; Recommendation grade B

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.

Coordinator: Exuperio Díez-Tejedor, Hospital Universitario La Paz, Madrid.

A.1. Drafting committee

Exuperio Díez-Tejedor (Coord), Hospital Universitario La Paz, Madrid; Blanca Fuentes (Secretary), Hospital Universitario La Paz, Madrid; María Alonso de Leciñana, Hospital Universitario Ramón y Cajal, Madrid; José Álvarez-Sabin, Hospital Universitari Vall d'Hebron, Barcelona; Juan Arenillas, Hospital Universitario Clínico de Valladolid; Sergio Calleja, Hospital Universitario Central de Asturias, Oviedo; Ignacio Casado, Hospital San Pedro, Cáceres; Mar Castellanos, Hospital Josep Trueta, Girona; José Castillo, Hospital Clínico Universitario, Santiago de Compostela; Antonio Dávalos, Hospital Universitari Germans Trias i Pujol, Badalona; Fernando Díaz-Otero, Hospital Universitario Gregorio Marañón, Madrid; Exuperio Díez-Tejedor, Hospital Universitario La Paz, Madrid; José Antonio Egido, Hospital Clínico Universitario San Carlos, Madrid; Juan Carlos Fernández, Hospital Universitario Dr. Negrín, Las Palmas; Mar Freijo, Hospital Universitario de Basurto, Bilbao; Blanca Fuentes, Hospital Universitario La Paz, Madrid; Jaime Gállego, Hospital General de Navarra, Pamplona; Andrés García Pastor, Hospital Universitario Gregorio Marañón, Madrid; Antonio Gil-Núñez, Hospital Universitario Gregorio Marañón, Madrid; Francisco Gilo, Hospital Universitario La Princesa, Madrid; Pablo Irimia, Clínica Universitaria de Navarra, Pamplona; Aida Lago, Hospital Universitario La Fe, Valencia; José Maestre, Hospital Universitario Virgen de las Nieves, Granada; Jaime Masjuan, Hospital Universitario Ramón y Cajal, Madrid; Joan Martí-Fàbregas, Hospital de la Santa Creu i Sant Pau, Barcelona; Patricia Martínez-Sánchez, Hospital Universitario La Paz, Madrid; Eduardo Martínez-Vila, Clínica Universitaria de Navarra, Pamplona; Carlos Molina, Hospital Universitari Vall d'Hebron, Barcelona; Ana Morales, Hospital Universitario Virgen de la Arrixaca, Murcia; Florentino Nombela, Hospital Universitario La Princesa, Madrid; Francisco Purroy, Hospital Universitario Arnau de Vilanova, Lérida; Marc Ribó, Hospital Universitari Vall d'Hebron, Barcelona; Manuel Rodríguez-Yáñez, Hospital Clínico Universitario, Santiago de Compostela; Jaime Roquer, Hospital del Mar, Barcelona; Francisco Rubio,

Hospital Universitario de Bellvitge, Barcelona; Tomás Segura, Hospital Universitario de Albacete, Albacete; Joaquín Serena, Hospital Josep Trueta, Girona; Patricia Simal, Hospital Clínico Universitario San Carlos, Madrid; Javier Tejada, Hospital Universitario de León, León; José Vivancos, Hospital Universitario La Princesa, Madrid.

A.2. Review or institutional committee

José Álvarez-Sabín, Hospital Universitari Vall d'Hebron, Barcelona; José Castillo, Hospital Clínico Universitario, Santiago de Compostela; Exuperio Díez-Tejedor, Hospital Universitario La Paz, Madrid; Antonio Gil-Núñez, Hospital Universitario Gregorio Marañón, Madrid; José Larracochea, Hospital de Cruces, Bilbao; Eduardo Martínez-Vila, Clínica Universitaria de Navarra, Pamplona; Jaime Masjuan, Hospital Universitario Ramón y Cajal, Madrid; Jorge Matías-Guiu, Hospital Clínico Universitario San Carlos, Madrid; Francisco Rubio, Hospital de Bellvitge, Barcelona.

References

1. Instituto Nacional de Estadística. Defunciones según causa de muerte 2006. [accessed 29.7.11]. Available in: <http://www.ine.es/prensa/np490.pdf>
2. Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Stroke*. 2003;34:2310–22.
3. Fuentes B, Gallego J, Gil-Núñez A, Morales A, Purroy F, Roquer J, et al. Guía para el tratamiento preventivo del ictus isquémico y AIT (I). Actuación sobre los factores de riesgo y estilo de vida. *Neurología*. 2011, doi:10.1016/j.nrl.2011.06.0023.
4. Centre for Evidence Based Medicine. [accessed 29.7.11]. Available in: <http://www.cebm.net/>
5. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81–106.
6. Algra A, van Gijn J. Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin. *J Neurol Neurosurg Psychiatry*. 1999;66:255.
7. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
8. Algra A, van Gijn J. Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia. *J Neurol Neurosurg Psychiatry*. 1996;60:197–9.
9. Johnson ES, Lanes SF, Wentworth 3rd CE, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose–response effect of aspirin on stroke. *Arch Intern Med*. 1999;159:1248–53.
10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–39.
11. Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events Investigators. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. *Stroke*. 2004;35:528–32.
12. Matias-Guiu J, Ferro JM, Álvarez-Sabín J, Torres F, Jiménez MD, Lago A, et al. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction: the TACIP Study: a randomized, double-blind, multicenter trial. *Stroke*. 2003;34:840–8.
13. Culebras A, Rotta-Escalante R, Vila J, Dominguez R, Abiusi G, Famulari A, et al. Triflusal vs aspirin for prevention of cerebral infarction: a randomized stroke study. *Neurology*. 2004;62:1073–80.
14. Costa J, Ferro JM, Matias-Guiu J, Álvarez-Sabín J, Torres F. Triflusal for preventing serious vascular events in people at high risk. *Cochrane Database Syst Rev*. 2005:CD004296.
15. De Schryver ELLM, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Systematic Reviews*. 2007;(3):CD001820.
16. Shinohara Y, Katayama Y, Uchiyama S, Yamaguchi T, Handa S, Matsuo K, et al. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol*. 2010;9:959–68.
17. Kamal AK, Naqvi I, Husain MR, Khealani BA. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Cochrane Database Syst Rev*. 2011:CD008076.
18. Shinohara Y, Nishimaru K, Sawada T, Terashi A, Handa S, Hirai S, et al. Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS): a randomized, double-blind, aspirin-controlled trial. *Stroke*. 2008;39:1827–33.
19. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–15.
20. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–57.
21. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A, European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143(1–2):1–13.
22. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A, ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367:1665–73.
23. Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke*. 2008;39:1358–63.
24. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–51.
25. Bath PM, Cotton D, Martin RH, Palesch Y, Yusuf S, Sacco R, et al. Effect of combined aspirin and extended-release dipyridamole versus clopidogrel on functional outcome and recurrence in acute, mild ischemic stroke: PROfESS subgroup analysis. *Stroke*. 2010;41:732–8.
26. Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PROfESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol*. 2008;7:875–84.
27. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with

- clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–7.
28. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–17.
 29. Geeganage C, Wilcox R, Bath PM. Triple antiplatelet therapy for preventing vascular events: a systematic review and meta-analysis. *BMC Med*. 2010;8:36.
 30. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol*. 1997;42:857–65.
 31. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345:1444–51.
 32. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A, ESPRIT Study Group. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol*. 2007;6:115–24.
 33. Algra A, De Schryver EL, van Gijn J, Kappelle LJ, Koudstaal PJ. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. *Cochrane Database Syst Rev*. 2006;3:CD001342.
 34. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352:1305–16.
 35. Kasner SE, Lynn MJ, Chimowitz MI, Frankel MR, Howlett-Smith H, Hertzberg VS, et al. Warfarin vs aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. *Neurology*. 2006;67:1275–8.
 36. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–53.
 37. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet*. 1991;337:1235–43.
 38. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–25.
 39. Endarterectomy for moderate symptomatic carotid stenosis: interim results from the MRC European Carotid Surgery Trial. *Lancet*. 1996;347:1591–3.
 40. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–24.
 41. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507.
 42. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2011;42:227–76.
 43. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, et al. Carotid endarterectomy – an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2005;65:794–801.
 44. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357:1729–37.
 45. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358:1572–9.
 46. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355:1660–71.
 47. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, et al., SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006;368:1239–47.
 48. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7:885–92.
 49. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol*. 2008;7:893–902.
 50. Wiesmann M, Schopf V, Jansen O, Bruckmann H. Stent-protected angioplasty versus carotid endarterectomy in patients with carotid artery stenosis: meta-analysis of randomized trial data. *Eur Radiol*. 2008;18:2956–66.
 51. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, et al., International Carotid Stenting Study investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985–97.
 52. Ederle J, Bonati LH, Dobson J, Featherstone RL, Gaines PA, Beard JD, et al. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol*. 2009;8:898–907.
 53. Brott TG, Hobson 2nd RW, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.
 54. Stingele R, Berger J, Alfke K, Eckstein HH, Fraedrich G, Allenberg J, et al. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. *Lancet Neurol*. 2008;7:216–22.
 55. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AAAS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS AT guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular

- Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Stroke*. 2011;42:e420–63.
56. Coward LJ, McCabe DJ, Ederle J, Featherstone RL, Clifton A, Brown MM, CAVATAS Investigators. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Stroke*. 2007;38:1526–30.
 57. Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation*. 2006;113:555–63.
 58. Fiorella D, Levy EI, Turk AS, Albuquerque FC, Niemann DB, Aagaard-Kienitz B, et al. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. *Stroke*. 2007;38:881–7.
 59. Kurre W, Berkefeld J, Brassel F, Bruning R, Eckert B, Kamek S, et al. In-hospital complication rates after stent treatment of 388 symptomatic intracranial stenoses: results from the INTRASTENT multicentric registry. *Stroke*. 2010;41:494–8.
 60. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med*. 1985;313:1191–200.
 61. Fluri F, Engelster S, Lyrer P. Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease. *Cochrane Database Syst Rev*. 2010:CD005953.
 62. Gil Nunez A. Advances in the prevention of cerebral ischaemia due to atrial fibrillation. *Neurologia*. 2010;25:401–8.
 63. Camm AJ, Kirchhof P, Lip GY, Schotten U, et al., European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–429.
 64. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes 3rd NA, et al. ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123:1144–50.
 65. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342:1255–62.
 66. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–67.
 67. Samsa GP, Matchar DB, Goldstein LB, Bonito AJ, Lux LJ, Witter DM, et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. *Arch Intern Med*. 2000;160:967–73.
 68. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke*. 2009;40:235–40.
 69. Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–100.
 70. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009;151:297–305.
 71. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–51.
 72. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RELY trial. *Lancet Neurol*. 2010;9:1157–63.
 73. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:1–11.
 74. Wann LS, Curtis AB, Ellenbogen KA, Estes M, Ezekowitz MD, Jackman WM, et al. Tracy CM. 2011 ACCF/AHA/HRS Focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice Guidelines. *Circulation*. 2011;123:104–23.
 75. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al., CB the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–17.
 76. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J*. 2010;159:340–7.
 77. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al., ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–91.
 78. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al., ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360(May):2066–78.
 79. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al., ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–12.
 80. Gorelick PB. Combining aspirin with oral anticoagulant therapy: is this a safe and effective practice in patients with atrial fibrillation? *Stroke*. 2007;38:1652–4.
 81. Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol*. 2004;44:1557–66.
 82. Bover R, Pérez-Gómez F, Maluenda MP, Asenjo S, Pérez-Saldana R, Igea A, et al., Long-term follow-up of atrial fibrillation patients in the NASPEAF study. Prospective evaluation of different antiplatelet treatments. *Rev Esp Cardiol*. 2009;62:992–1000.
 83. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668–78.
 84. Connolly SJ, Crijns HJ, Torp-Pedersen C, van Eickels M, Gaudin C, Page RL, et al. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation*. 2009;120:1174–80.
 85. Natale A, Raviele A, Arentz T, Calkins H, Chen SA, Haissaguerre M, et al. Venice Chart international consensus document on atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2007;18:560–80.

86. Bertaglia E, Tondo C, De Simone A, Zoppo F, Mantica M, Turco P, et al. Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience. *Europace*. 2010;12:181–7.
87. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation a meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2008;51:828–35.
88. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study. *Ann Intern Med*. 2010;152:78–84.
89. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534–42.
90. Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, et al. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133 6 Suppl.: 776S–814S.
91. Haq SA, Heitner JF, Sacchi TJ, Brenner SJ. Long-term effect of chronic oral anticoagulation with warfarin after acute myocardial infarction. *Am J Med*. 2010;123:250–8.
92. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation*. 2009;119:1616–24.
93. Pullicino P, Thompson JL, Barton B, Levin B, Graham S, Freudenberger RS, et al. Warfarin versus aspirin in patients with reduced cardiac ejection fraction (WARCEF): rationale, objectives, and design. *J Card Fail*. 2006;12: 39–46.
94. Bonow RO, Carabello BA, Chatterjee K, De Leon Jr AC, Faxon DP, Freed MD, et al. Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2008;2008:e1–142.
95. Mok CK, Boey J, Wang R, Chan TK, Cheung KL, Lee PK, et al. Warfarin versus dipyridamole-aspirin and pentoxifylline-aspirin for the prevention of prosthetic heart valve thromboembolism: a prospective randomized clinical trial. *Circulation*. 1985;72:1059–63.
96. Little SH, Massel DR. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev*. 2003;CD003464.
97. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol*. 2007;49:797–802.
98. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology*. 2000;55:1172–9.
99. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med*. 2001;345:1740–6.
100. Serena J, Marti-Fabregas J, Santamarina E, Rodriguez JJ, Perez-Ayuso MJ, Masjuan J, et al. Recurrent stroke and massive right-to-left shunt: results from the prospective Spanish multicenter (CODICIA) study. *Stroke*. 2008;39: 3131–6.
101. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105:2625–31.
102. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al., Study Design of the CLOSURE I Trial: a prospective, Multicenter, Randomized, Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex Septal Closure System Versus Best Medical Therapy in Patients with Stroke or Transient Ischemic attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale. *Stroke*. 2010;41: 2872–83.
103. O'Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC, American Heart Association. Percutaneous device closure of patent foramen ovale for secondary stroke prevention: a call for completion of randomized clinical trials: a science advisory from the American Heart Association/American Stroke Association and the American College of Cardiology Foundation. *Circulation*. 2009;119:2743–7.
104. Georgiadis D, Arnold M, von Buedingen HC, Valko P, Sarikaya H, Rousson V, et al. Aspirin vs anticoagulation in carotid artery dissection: a study of 298 patients. *Neurology*. 2009;72: 1810–5.
105. Lyrer P, Engelster S. Antithrombotic drugs for carotid artery dissection. *Stroke*. 2004;35:613–4.
106. Menon R, Kerry S, Norris JW, Markus HS. Treatment of cervical artery dissection: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2008;79: 1122–7.
107. Pham MH, Rahme RJ, Arnaout O, Hurley MC, Bernstein RA, Batjer HH, et al. Endovascular stenting of extracranial carotid and vertebral artery dissections: a systematic review of the literature. *Neurosurgery*. 2011;68: 856–66.
108. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348:1425–34.
109. Levine SR, Brey RL, Tilley BC, Thompson JL, Sacco RL, Sciacca RR, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA*. 2004;291:576–84.
110. Kronzon I, Tunick PA. Aortic atherosclerotic disease and stroke. *Circulation*. 2006;114:63–75.
111. Di Tullio MR, Russo C, Jin Z, Sacco RL, Mohr JP, Homma S, et al. Aortic arch plaques and risk of recurrent stroke and death. *Circulation*. 2009;119:2376–82.
112. Tunick PA, Nayar AC, Goodkin GM, Mirchandani S, Francescone S, Rosenzweig BP, et al. Effect of treatment on the incidence of stroke and other emboli in 519 patients with severe thoracic aortic plaque. *Am J Cardiol*. 2002;90: 1320–5.
113. Macleod MR, Amarenco P, Davis SM, Donnan GA. Atheroma of the aortic arch: an important and poorly recognised factor in the aetiology of stroke. *Lancet Neurol*. 2004;3: 408–14.
114. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey Jr DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55:e27–129.

115. Stam J, de Bruijn SF, deVeber G. Anticoagulation for cerebral sinus thrombosis. *Cochrane Database Syst Rev.* 2002;(4). Art. No.: CD002005.
116. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest.* 2008;133 6 Suppl.:454S–545S.
117. Einhaupl K, Stam J, Bousser MG, De Bruijn SF, Ferro JM, Martinelli I, et al. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. *Eur J Neurol.* 2010;17:1229–35.
118. Saposnik G, Barinagarrementeria F, Brown Jr RD, Bushnell CD, Cucchiara B, Cushman M, et al., American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42:1158–92.

Additional References

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011 Sep 15;365(11):981-92.

Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, Hoh BL, Hourihane JM, Levy EI, Alexandrov AV, Harrigan MR, Chiu D, Klucznik RP, Clark JM, McDougall CG, Johnson MD, Pride GL Jr, Torbey MT, Zaidat OO, Rumboldt Z, Cloft HJ; SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* 2011 Sep 15;365(11):993-1003.