Clinical Practice Guideline for Primary and Secondary Prevention of Stroke

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINES IN THE NHS.
MINISTRY OF HEALTHCARE AND CONSUMER AFFAIRS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO
Plan de Calidad para el Sistema Nacional de Salud
Generalitat de Catalunya
Departament de Salut

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MINISTRY OF HEALTH AND CONSUMER AFFAIRS







Generalitat de Catalunya
Departament de Salut

This clinical practice guideline (CPG) is an aid for decision-making in healthcare. It is not in any way an obliged requirement to adhere to every aspect of this CPG and it does not replace the clinical judgment of health care professionals.

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Presentation

Healthcare practice is becoming more and more complex due to multiple factors, the most relevant being the exponential increase of scientific information.

To ensure that clinical decisions are appropriate, efficient and safe, healthcare professionals must constantly update their knowledge, an objective that entails great dedication and effort.

In the year 2003, the National Health System's (NHS) Interterritorial Council created the HealthGuide project with the aim of improving evidence-based clinical decision-making by means of training activities and the configuration of a Clinical Practice Guidelines (CPG) register. Since then, the HealthGuide project has assessed dozens of CPGs in accordance with explicit criteria generated by its scientific committee, registered these CPGs and disseminated them throughout the Internet.

In early 2006, the Directorate General of the National Health System's Quality Agency elaborated the Quality Plan for the NHS, a plan that encompasses twelve strategies. The objective of this Plan is to increase cohesion of the NHS and aid in guaranteeing maximum quality healthcare to all citizens, regardless of their place of residence. As part of the plan, the development of eight CPGs on prevalent pathologies related with health strategies was assigned to different agencies and experts groups. This guide on stroke prevention is part of this assignment.

Additionally, the establishment of a common CPG development methodology for the NHS was assigned to CPG experts groups in our country, resulting in a collective effort of consensus and coordination amongst them. In 2007, the HealthGuide project was renovated and the Clinical Practice Guideline Library was created. This project thoroughly covers the development of CPGs and includes other services and products of evidence-based medicine. It also aims to favour the implementation and assessment of the use of CPGs in the NHS.

Stroke represents a significant health problem due to its high prevalence, the disability it entails, the decreased quality of life it generates and its enormous economic impact. Despite current scientific evidence, great variability in primary and secondary prevention strategies is still being reported. This guideline is the result of the work of a group of professionals involved in different fields and settings. They have all dedicated a great effort to developing these recommendations, which will surely help improve health care delivered both in primary and specialised levels of care. Scientific societies and patient associations directly involved in this health problem have collaborated in the review process of this guideline.

This guideline provides answers to many of the questions posed by the preventive approach to stroke, which are presented in the form of systematically developed recommendations that are based on the best available evidence. We hope all this work translates into higher quality health care of these patients and their families, as well as into a greater homogeneity of health care, which is the objective that motivates us.

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Spanish Society of Internal Medicine

Spanish Society of Primary Care Physicians SEMERGEN

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Spanish Society of Geriatrics and Gerontology

Spanish Society of Thrombosis and Hemostasia

Spanish Society of Hypertension

Spanish Society of Angiology and Vascular Surgery

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Declaration of Interests:

All working group members, as well as the people who have participated in the expert collaboration and external review, have completed the declaration of interests presented in annex 6.

The points of view or interests of the funding agencies have not influenced the development of this document.

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Key Questions

CARDIOVASCULAR RISK

1. What systems are available to assess vascular risk?

2. What population should vascular risk assessment be performed on and how often?

PRIMARY PREVENTION OF STROKE

3. What are the main risk factors of stroke?

4. Do lifestyle interventions reduce the risk of having an episode of stroke?

5. What strategies are available to reduce alcohol consumption or to stop smoking?

6. What strategies have been proven to be beneficial in reducing body weight in obese people?

7. What type of antihypertensive treatment is most beneficial for reducing the risk of having a stroke episode?

8. What are the target values for blood pressure?

9. What is the risk of having an episode of stroke in diabetic people?

10. What strategies can prevent the development of diabetes?

11. Do people with elevated plasma cholesterol levels or other dyslipemias have a higher risk of having an ischemic stroke or transient ischemic attack?

12. Do treatments aimed at reducing plasma cholesterol levels decrease the risk of having an ischemic stroke or transient ischemic attack?

13. What is the most adequate therapeutic approach in people who present metabolic syndrome criteria?

14. Do women who take oral contraceptives have a higher risk of having an ischemic or hemorrhagic stroke episode or cerebral venous thrombosis?

15. Does hormone therapy reduce the risk of stroke or other vascular episodes in postmenopausal women?

16. Does antithrombotic treatment reduce the risk of having an episode of stroke in patients with congenital or acquired thrombofilias?

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17. Is there any effective treatment to reduce the risk of stroke in patients with disorders such as elevated plasma homocysteine or lipoprotein A levels or who suffer migraine episodes or falciform cell disease?

18. In patients with certain embolic cardiopathies (atrial fibrillation, myocardial infarction, reduced ejection fraction, valve prostheses, mitral stenosis or mitral valve prolapse), does antithrombotic treatment (antiaggregant/anticoagulant) reduce the risk of having a stroke episode?

19. In patients with carotid artery stenosis, is surgical treatment effective at reducing the risk of having a first episode of stroke?

20. Does platelet antiaggregant treatment after the intervention offer additional benefits?

21. Is it reasonable to conduct screening of carotid artery stenosis in the general adult population?

22. Does platelet antiaggregant treatment reduce the risk of having a vascular or stroke episode in people with different levels of vascular risk?

23. What dose of antiaggregants has been shown to be effective at preventing vascular or stroke episodes?

24. What therapeutic options are available for pregnant patients who require antithrombotic treatment (antiaggregant/anticoagulant)?

25. What is the risk of bleeding in patients who receive anticoagulant treatment?

26. In patients with intact intracerebral aneurysm, does the intervention on the malformation (via surgery or via an endovascular approach) reduce the risk of having a subarachnoid hemorrhage?

SECONDARY PREVENTION OF STROKE

27. What is the risk of having a stroke in patients who have already had an ischemic stroke episode or a transient ischemic attack?

28. In patients with a history of prior stroke, do lifestyle interventions reduce the risk of new episodes?

29. In patients with a history of prior stroke, does hypertensive treatment reduce the risk of new episodes?

30. What are the target values for blood pressure?

31. In patients with a history of prior stroke, does hypolipemiant treatment reduce the risk of new episodes?

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32. What are the optimal doses of hypolipemiant treatment?

33. What are the target values for blood lipids?

34. In postmenopausal women with a history of stroke, does hormone therapy reduce the risk of new episodes?

35. In patients with congenital or acquired thrombofilias who have suffered a stroke episode, does antithrombotic treatment reduce the risk of new episodes?

36. In patients with a history of stroke and hyperhomocysteinemia, do vitamin complexes reduce the risk of new episodes?

37. In patients with certain cardiopathies (atrial fibrillation, cardiac valve prostheses, mitral stenosis, mitral valve prolapse, permeable foramen ovale) and a history of ischemic stroke or transient ischemic attack, does antithrombotic treatment (anticoagulant/antiaggregant) reduce the risk of new episodes?

38. In patients with carotid artery stenosis and a history of ischemic stroke or transient ischemic attack, does carotid endarterectomy versus endovascular techniques reduce the risk of new episodes?

39. Does antithrombotic treatment (antiaggregant/anticoagulant) following the intervention provide additional benefits?

40. In patients with a history of ischemic stroke or non-cardioembolic transient ischemic attack, does antithrombotic treatment reduce the risk of new episodes?

41. In patients with cerebral venous thrombosis, does anticoagulant treatment reduce the risk of new episodes?

42. What therapeutic approach should be adopted in a patient who presents intracerebral hemorrhage during treatment with antithrombotics?

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Summary of Recommendations

Assessment of evidence quality and grading of recommendations has been performed using the SIGN (Scottish Intercollegiate Guidelines Network) system (see annex 1). The following section includes the recommendations proposed in this guideline.

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Vascular risk

B	The calculation of vascular risk using one of the risk tables currently available (REGICOR or SCORE) is recommended as a complementary diagnostic tool in the clinical assessment of patients.
B	The SCORE table is recommended to calculate the risk of stroke.
✓	Vascular risk should be assessed at least once every five years after the age of 40.
✓	In patients with high vascular risk it should be assessed at least once a year.
✓	It is important that health care professionals be adequately trained for vascular risk calculation, and that such vascular risk calculation be integrated into the IT systems available at the medical consultation office.

PRIMARY PREVENTION OF STROKE

NON-modifiable risk factors

✓	Strict monitoring and follow-up of vascular risk factors is recommended in people with non-modifiable risk factors, especially elderly patients and those with a family history of stroke.

Lifestyle interventions: alcoholism

A	It is recommended to avoid alcohol consumption that exceeds two units per day.
A	Short informative interventions are recommended in people whose consumption could be considered harmful to health, with the objective of reducing consumption.
✓	It is important to detect alcohol consumption abuse as part of the routine clinical exam and at least every two years, especially in the case of problems that may be related to alcohol consumption abuse or before prescribing drugs that could interact with alcohol.
✓	It is recommended not to promote alcohol consumption in patients who do not drink.

Lifestyle interventions: tobacco smoking

✓	The anamnesis of any patient should explore the habit of smoking.
A	Professional counselling constitutes the main therapeutic option to stop smoking. Abstinence or smoking cessation should be recommended and exposure to second-hand smoke avoided.
A	Replacement treatment with nicotine, bupropion, nortriptyline* or varenicline is recommended as part of structured smoking cessation programmes aimed at increasing the percentage of smoking cessation.
✓	It is necessary to prioritise smoking cessation strategies in smokers or in populations at risk such as young people and disadvantaged social classes.

* This indication has not been approved for nortriptyline.

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Lifestyle interventions: use of illegal drugs

✓	In the routine anamnesis it is advisable to inquire about habitual or occasional use of illegal drugs.

Lifestyle interventions: sedentarism

B	It is recommended that all people perform at least moderately intense physical exercise, within their capabilities, for a minimum of 30 minutes a day.
B	A gradual increase in the intensity or frequency of physical exercise in people who are already moderately active is recommended.

Lifestyle interventions: dietary and nutritional factors

A	The reduction of total fat and especially saturated fat in the diet is recommended. These types of fat should contribute less than 30% and 10% respectively to daily calorie intake.
A	Consumption of fish at least once a week and consumption of at least three pieces of fruit daily are recommended.
A	The use of vitamin supplements to reduce vascular risk is not recommended.
A	Reduced salt intake is recommended, especially in people with high blood pressure.
✓	Salt intake under 6 g daily or, in hypertense patients, replacement with potassium salt, is recommended.
✓	It is advisable to eat a varied diet and promote the consumption of fresh vegetable products (legumes, whole cereals, fruit and vegetables), fish and unrefined virgin olive oil.

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Obesity

A	People with obesity or abdominal obesity are recommended to lose weight until appropriate weight is reached.
A	Diet modification and increased physical activity are recommended as the first therapeutic steps for weight reduction.
B	In addition to hygienic-dietary measures, the possibility of pharmacological treatment* over a limited period of time should be considered for people with obesity or abdominal obesity who do not respond to conservative measures.
B	In patients with morbid obesity, surgery is a therapeutic alternative that should be considered individually with each patient.

*** INFORMATION NOTE Spanish Agency of Medicines and Medical Devices (21st January 2010):**
Marketing authorisation for sibutramine has been suspended as the risks outweig the benefits.
More information available at:
http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2010/NI_2010-01_sibutramina_reductil.htm
(**Note:** website in spanish)

Hypertension (High blood pressure)

A	In patients with high blood pressure it is recommended to modify lifestyles with the aim of achieving smoking cessation, weight loss in obese patients, alcohol consumption moderation, regular physical exercise, reduced salt intake and increased consumption of fruits and vegetables, regardless of pharmacological treatment.
A	Thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers or calcium antagonists are recommended for the initial treatment of high blood pressure in the majority of situations and based on the characteristics of each patient.
B	Initial treatment with betablockers can be considered in young patients with non-complicated hypertension.
A	The maintenance of blood pressure levels under 140/90 mmHg is recommended.
B	The maintenance of blood pressure levels under 130/80 mmHg in diabetic patients is recommended.

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✓	In patients with blood pressure levels higher than 160/100 mmHg or in diabetic patients the combination of more than one antihypertensive treatments should be considered.
✓	In hypertense patients with diabetes the first treatment to consider should be with angiotensin converting enzyme inhibitors, angiotensin II antagonist monotherapy or in combination with another hypertensive drug.
✓	Combined antihypertensive drugs should have different but complementary mechanisms of action and be administered preferably at the minimal effective dose.

Diabetes mellitus

A	In people with altered basal glycaemia or impaired glucose tolerance, structured programmes aimed at encouraging physical activity and dietary changes are recommended.
B	In people with altered basal glycaemia or impaired glucose tolerance the use of alpha-glucosidase inhibitors or biguanides is not recommended with the aim of preventing diabetes mellitus.
A	In people with altered basal glycaemia or impaired glucose tolerance the use of thiazolidinediones (especially rosiglitazone) to prevent diabetes mellitus is not recommended.
D	Annual screening of diabetes by means of fasting morning glycaemia is recommended in the population at risk: hypertension, hyperlipemia, obesity, gestational diabetes, obstetric pathology (macrosomy, repeat abortions, malformations), altered basal glycaemia or impaired glucose tolerance at any age; and every three years in patients aged 45 years and older, within a structured vascular prevention programme.

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Dyslipemia

A	Statin treatment is recommended for adults without prior vascular disease and with high vascular risk.
A	Treatment with other drugs such as clofibrate, gemfibrozil, nicotinic acid or ion-exchange resins or their combination is not recommended for primary prevention of vascular disease.
✓	In patients with high blood cholesterol levels (>240 mg/dl of LDL cholesterol) treatment with statins should be considered.
✓	Treatment with statins should be jointly assessed with the patient after properly informing him/her of benefits and potential risks, taking associated pathologies and concomitant treatments into account. Additionally, at the beginning of treatment with statins, healthier lifestyle changes should be initiated.
✓	It is important to assess interactions between statins and other concomitant drugs metabolised preferably by cytochrome P450. If the risk of interaction is clinically relevant, treatment with pravastatin should be considered.

Metabolic syndrome

B	Individuals with metabolic syndrome should be identified and advised on lifestyle modifications with the aim of promoting a healthy diet and physical exercise to lose body weight.
✓	It is important to offer proper treatment for each component of the metabolic syndrome.
✓	It is important to carry out periodic follow-up of vascular risk.

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Use of oral contraceptives

B	The use of oral contraceptives is not recommended in women who smoke, suffer migraines or have a history of thromboemolic episodes; other birth control measures should be considered.
A	The use of oral contraceptives is not recommended in women with congenital thrombofilia; other birth control measures should be considered.

Hormone therapy

A	The use of hormone therapy (with estrogens alone or combined with progestagens) to prevent vascular disease in postmenopausal women is not recommended.

Thrombofilias

✓	After assessing the patient's age, risk of bleeding and presence of other vascular risk factors or associated pathologies, antithrombotic treatment can be initiated in patients with some type of congenital or acquired thrombofilia.

Others: hyperhomocysteinemia, elevated lipoprotein A, migraine, falciform cell disease

B	In patients with elevated plasma homocysteine levels and other vascular risk factors, vitamin B complex with folic acid should be considered.
C	In patients with elevated levels of lipoprotein A and other vascular risk factors, treatment with niacin should be considered.
B	The performance of periodic transfusions is recommended to reduce hemoglobin S to levels below 30% in patients with high risk falciform cell anemia, after assessing the risks and benefits with the patient.

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Embolic cardiopathies: atrial fibrillation

✓	All patients with atrial fibrillation should be individually assessed to establish a benefit-risk balance of antithrombotic treatment. It is advisable to assess the indication to administer anticoagulants at regular intervals.
A	In patients with paroxistic, persistent or permanent atrial fibrillation, who present HIGH thromboembolic risk, treatment with oral anticoagulants with an INR target range of 2 to 3 over an indefinite period of time is recommended for primary prevention of stroke of cardioembolic origin.
A	In patients with paroxistic, persistent or permanent atrial fibrillation, who present MODERATE thromboembolic risk, treatments with anticoagulants or antiaggregants are reasonable therapeutic options for the primary prevention of cardioembolic stroke.
A	In patients with paroxistic, persistent or permanent atrial fibrillation, who present LOW thromboembolic risk or formal contraindications to oral anticoagulants, antiaggregant treatment with aspirin (100-300 mg/d) is recommended for primary prevention of cardioembolic stroke.
B	The use of antiaggregants other than aspirin is recommended for patients with aspirin intolerance or related undesirable effects.
✓	In certain patients with MODERATE thromboembolic risk other factors, such as atrial size, presence of atrial blood clots or structural cardiac alterations, should be assessed when considering the benefits and risks of antithrombotic treatment.

Embolic cardiopathies: myocardial infarction

✓	In patients who have suffered a myocardial infarction it is important to manage vascular risk factors to reduce the risk of new episodes.
A	In patients who have suffered a myocardial infarction without increase of the ST segment, especially if they have undergone a percutaneous procedure with implantation of a pharmacoactive stent, double antiaggregation with aspirin (at the minimal effective dose) and

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	clopidogrel (75 mg/d) over twelve months is recommended.
B	In patients who have suffered a myocardial infarction with increase of the ST segment, regardless of whether they undergo acute reperfusion with fibrinolysis or a percutaneous procedure, double antiaggregation with aspirin (at the minimal effective dose) and clopidogrel (75 mg/d) over at least four weeks is recommended.
C	In patients who have suffered myocardial infarction with increase of the ST segment, it is reasonable to propose double antiaggregation treatment over a period of one year.
B	In patients who have suffered myocardial infarction with increase of the ST segment associated with dyskinesia or ventricular aneurysm, treatment with oral anticoagulants should be considered.

Embolic cardiopathies: dilated cardiomyopathy and other situations with reduced ejection fraction

B	In patients with ejection fraction below 30%, initiation of treatment with antiaggregants or anticoagulants should be considered. The selection of treatment should be individualised based on the presence of other vascular risk factors.

Embolic cardiopathies: valve prostheses

A	Indefinite anticoagulant treatment with an INR interval that depends on the type of valve and patient factors is recommended in patients who have a mechanical valve prosthesis.
B	In patients who have a mechanical valve prosthesis and high risk of thromboembolism (atrial fibrillation, hypercoagulability states, or dysfunction of the left ventricle), it is recommended to add antiaggregants (aspirin 100 mg/d) to anticoagulant treatment.
A	During the first three months after implantation of a biological prosthesis anticoagulant treatment is recommended with an INR target range of 2 to 3.

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B	Antiaggregant treatment (100-300 mg/d of aspirin or 600 mg/d of triflusal) is recommended in patients who have a biological valve and who have no risk factors for thromboembolism.
A	In patients who have a biological valve and risk factors for thromboembolism (atrial fibrillation, hypercoagulability states, or dysfunction of the left ventricle) treatment with anticoagulants is recommended with the objective of reaching an INR target range of 2 to 3 in aortic valves and an INR target range of 2.5 to 3.5 in mitral valves.

Embolic cardiopathies: mitral stenosis and mitral valve prolapse

✓	Patients with mitral stenosis or mitral valve prolapse should undergo periodic cardiac monitoring. Echocardiography is useful to detect patients with a high risk of complications.
A	Anticoagulant treatment with an INR target range of 2 to 3 is recommended in patients presenting mitral stenosis with a thrombus in the left atrium and in those who develop atrial fibrillation.
C	Treatment with antiaggregants (100-300 mg/d of aspirin) is recommended in patients with mitral valve prolapse only if they present high risk echocardiographic criteria.

Asymptomatic carotid artery stenosis

B	Surgical treatment (carotid endarterectomy) is recommended in asymptomatic patients with significant stenosis (>70%) of the carotid artery, if and when the surgical team confirms a perioperative morbimortality of less than 3%. The decision should be made together with the patient after informing him/her of the risks and benefits of the procedure and assessing factors such as age or comorbidities.
C	Surgical treatment (carotid endarterectomy) is not recommended in asymptomatic patients with mild carotid artery stenosis.
A	Antiaggregant treatment is recommended in all patients with carotid artery stenosis.

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B	The use of endovascular techniques with stent implantation should be individualised in patients with high surgical risk, in cases where there are technical difficulties for the performance of a carotid endarterectomy or within the context of a clinical trial.
A	Carotid stenosis screening programmes in the general population are not recommended.

Antiaggregant treatment in the primary prevention of stroke

A	Primary prevention of vascular episodes with antiaggregants is not recommended in the general population.
B	Treatment with aspirin at the minimal effective dose (100 mg/d) should be considered for certain patients, such as those with high vascular risk, once potential benefits and risks have been weighed.
✓	Clopidogrel, dipiridamol or triflusal can be considered alternatives for patients with hypersensitivity or intolerance to the adverse effects of aspirin.

Antithrombotic treatment in pregnant women

✓	In pregnant women in whom anticoagulation is indicated with the aim of reducing the risk of thrombotic phenomena, including stroke, the use of non-fractionated heparin or low molecular weight heparins throughout the pregnancy should be considered.
✓	In pregnant women who have one or more mechanical heart valves, with a high risk of embolic phenomena, the addition of aspirin (at the lowest dose possible) should be considered during the first two gestational trimesters.
✓	Antithrombotic treatment during pregnancy is a complex clinical situation that should be monitored by a multidisciplinary specialised team.

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Risk of bleeding with anticoagulant treatment

B	In patients in whom anticoagulant treatment is indicated, the assessment of bleeding risk using one of the existing indexes is recommended.
✓	Assessing benefits-risks before initiating anticoagulant treatment should include, additionally, the assessment of adherence to treatment, and the patient's values and preferences and family and personal environment.

Subarachnoid hemorrhage

✓	All patients with intact intracerebral aneurysm should be provided with adequate advice promoting healthier lifestyles, such as the cessation of smoking, alcohol consumption and use of any substance with sympatheticomimetic activity.
A	Patients with intact intracerebral aneurysm should maintain blood pressure values within the normal range.
B	In aneurysms whose size is equal to or bigger than 7 mm, intervention on the aneurysm sac (via surgery or an endovascular procedure) and individual assessment of the risks of each procedure, the patient's age, mass effect and localisation of the aneurysm should be considered.
B	Expectative attitude is recommended in people over the age of 65, without symptoms and with anterior circulation aneurysms of less than 7 mm in diameter.
✓	In case of adopting a conservative approach, changes in size or presentation of the aneurysm should be closely monitored.

SECONDARY PREVENTION OF ICTUS

Risk of a new episode of transient ischemic stroke or transient ischemic attack

✓	Therapeutic strategies in patients who have had a first episode of ischemic stroke or transient ischemic attack should be aggressive and aimed at reducing relapse risk and vascular risk in general.

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Lifestyle interventions

✓	The hospital discharge report should include the measures adopted for modification of lifestyles.
A	Patients who have suffered a stroke should avoid alcohol consumption of more than two units daily and be encouraged to quit smoking.
A	Alcohol consumption should not be encouraged in patients who do not drink. Patients who have suffered hemorrhagic stroke should avoid all kinds of alcohol.
B	Patients who have suffered a stroke are encouraged to exercise regularly within their capabilities and reduce body weight or abdominal obesity to normal levels.

Hypertension

✓	Blood pressure values of patients who have had an ischemic or hemorrhagic stroke should be closely monitored.
A	In patients with a history of stroke or transient ischemic attack and high or even normal blood pressure values it is recommended to initiate treatment with antihypertensive drugs, preferably with the combination of an angiotensin converting enzyme inhibitor and a diuretic (4 mg/d of perindopril and 2.5 mg/d of indapamide).
B	Depending on the patient's tolerance or concomitant pathologies, monotherapy treatment with diuretics, angiotensin converting enzyme inhibitors or angiotensin II antagonists should be considered.
B	Once a patient who has had an ischemic stroke or transient ischemic attack is stabilised, blood pressure values should be gradually decreased with the aim of maintaining levels below 130/80 mmHg, and preferably below 120/80 mmHg.
A	Lifestyle changes should be promoted, aside from pharmacological treatment.

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Dyslipemia

A	It is recommended to treat patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels.
B	Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology, regardless of their basal LDL-cholesterol levels.
✓	Treatment with statins should be jointly assessed with the patient after adequately informing him/her of the benefits and potential risks and taking associated pathologies and concomitant treatments into account. Aside from statin treatment, healthier lifestyles should be encouraged and adopted.
✓	These patients should maintain LDL-cholesterol levels below 100 mg/dl.
✓	The combination of statins with other hypolipemiant drugs to reach LDL-cholesterol target values should be avoided.

Hormone therapy

A	Hormone therapy (with estrogens alone or in combination with progestagens) for secondary prevention of vascular disease in postmenopausal women is not recommended.

Thrombofilias

B	In patients with hereditary thrombofilia and a history of thrombotic episodes long term treatment with anticoagulants is recommended.
B	In patients with previous ischemic stroke or transient ischemic attack, who have not presented any other alternative cause to the antiphospholipid

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	syndrome, long term treatment with anticoagulants is recommended.

Hyperhomocysteinemia

B	Folic acid and vitamin B complex supplements should be considered in patients with previous stroke or hyperhomocysteinemia with the aim of reducing elevated plasma homocysteine levels.

Embolic cardiopathies: atrial fibrillation

✓	All patients with atrial fibrillation should be individually assessed in order to establish an adequate benefit-risk balance of anticoagulant treatment.
A	Treatment with oral anticoagulants with an INR target range of 2 to 3 over an indefinite period of time is recommended in patients with paroxistic, persistent or permanent atrial fibrillation who have previously had a stroke and present no formal contraindications to treatment.
✓	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.
✓	Intensification of anticoagulation or addition of antiaggregant treatment (aspirin or triflusal) should be considered in patients with paroxistic, persistent or permanent atrial fibrillation, who receive correct doses of anticoagulant treatment and still present recurrent stroke or transient ischemic attack.

Embolic cardiopathies: heart valve prosthesis

A	In patients with one or more mechanical heart valve prostheses who suffer an ischemic stroke despite receiving proper anticoagulant treatment, the addition of low-dose aspirin (100 mg) or dipiridamol is recommended.
✓	The joint administration of clopidogrel or triflusal and an anticoagulant is a correct strategy in patients with contraindications to aspirin.

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Embolic cardiopathies: other cardiopathies

B	In patients with previous ischemic stroke or transient ischemic attack who present mitral stenosis, anticoagulant treatment with an INR target range of 2 to 3 is recommended, regardless of whether they present atrial fibrillation or not.
B	In patients with previous ischemic stroke or transient ischemic attack who present mitral valve prolapse, antiaggregant treatment (100-300 mg/d of aspirin) is recommended.
C	In patients with previous ischemic stroke or transient ischemic attack with mitral valve prolapse as the only cause, anticoagulant treatment with an INR target range of 2 to 3 should be considered only in cases of high risk of presenting cardioembolic phenomena.
B	In patients with previous ischemic stroke or transient ischemic attack who present permeable foramen ovale, treatment with antiaggregants (100-300 mg/d of aspirin) is recommended.
C	In patients with permeable foramen ovale and previous ischemic stroke or transient ischemic attack, treatment with anticoagulants should be considered if there is an increased risk of cardioembolic episodes (aneurysm of the atrial septum or associated with large interatrial communication).
✓	Surgical procedures with percutaneous closure of the permeable foramen ovale should only be considered in the context of a clinical trial and in cases of repeat strokes.

Symptomatic carotid artery stenosis

A	Carotid endarterectomy is recommended in patients with ischemic stroke of less than 6 months evolution and significant stenosis of the carotid artery (70% to 99%, NASCET values), if and when the surgical team confirms a perioperative morbimortality of less than 6%.
B	In patients with ischemic stroke of less than 6 months evolution and moderate carotid artery stenosis (50% to 69%, NASCET values), carotid endarterectomy should be considered depending on factors such as sex,

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	age and the presence of other comorbidities.
A	In patients with mild carotid artery stenosis (less than 50%, NASCET values) carotid endarterectomy is not recommended.
B	In patients with ischemic stroke or non-disabling transient ischemic attack and surgical indication, it is recommended to perform the intervention within the first two weeks after the episode.
A	In patients who are not candidates for intervention, treatment with antiaggregants is recommended after carotid endarterectomy, as well as intensive intervention on other vascular risk factors.
B	The use of endovascular techniques with stent implantation should be individualised in patients with high surgical risk, in cases where there are technical difficulties for the performance of a carotid endarterectomy or within the context of a clinical trial.

Antithrombotic treatment in the secondary prevention of stroke

A	In patients with non-cardioembolic ischemic stroke or transient ischemic attack, antiaggregation with aspirin (100-300 mg/d), combined aspirin and sustained release dipiridamol (50 and 400 mg/d), triflusal (600 mg/d) or clopidrogel (75 mg/d) is recommended.
A	Long term use of combined aspirin and clopidogrel is not recommended due to the increased risk of bleeding complications.
A	In patients with ischemic stroke or transient ischemic attack, the systematic use of anticoagulant treatment to prevent recurrent strokes is not recommended.
A	It is recommended to initiate treatment with aspirin within the first 48 hours of the clinical suspicion of ischemic stroke and after ruling out hemorrhagic stroke.
✓	In the case of presenting recurrent strokes despite adequate antiaggregant treatment, underlying causes should be carefully reviewed and the management of risk factors should be prioritised.

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Cerebral venous thrombosis

D	In patients who have suffered cerebral venous thrombosis, initial treatment with heparin and later with oral anticoagulants over a period of three to six months is recommended.
D	In patients with congenital or acquired thrombofilias and in patients over the age of 65 or with other factors that favour thrombotic phenomena, treatment with oral anticoagulants is recommended up to twelve months.

Antithrombotic treatment after intracerebral hemorrhage

B	Generalised introduction of anticoagulant or antiaggregant treatment is not recommended after an intracerebral hemorrhage.
✓	In patients who require anticoagulant treatment due to a previous condition, restoration of treatment should be individually assessed.
C	Anticoagulant treatment should be considered seven to ten days after an intracerebral hemorrhage only in patients with very high risk (>6.5% per year) of presenting ischemic stroke.
C	Treatment with low molecular weight heparins should be considered two days after an intracerebral hemorrhage with the aim of reducing the risk of deep venous thrombosis or pulmonary embolism.
C	Antiaggregant treatment is an alternative for patients who, after an intracerebral hemorrhage, present an indication for antithrombotic treatment and in whom anticoagulant treatment is not advisable.

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1. Introduction

Global magnitude of the problem

Cerebrovascular diseases or stroke, understood as circulatory brain disorders that momentarily or permanently alter the functioning of the brain, are one of the leading causes of morbimortality in the world. They are also a leading cause of permanent disability, which greatly impacts families and the community[1]. Cerebrovascular diseases or stroke are ranked third worldwide as the most frequent causes of death in developed countries, following coronary disease and cancer. They are also the most important cause of long-term morbidity and disability in Europe, leading to significant economic burden[2].

It is calculated that in 2007, 59 million people died worldwide and that cerebrovascular diseases were the cause of death in 10% of these cases and the cause of disability in many other millions of cases[3,4]. Hence, prevention is preferable to treatment[5]. The implementation of interventions that reduce hypertension, promote a healthier diet and encourage smoking cessation could avoid more deaths than all thrombolytic, antiaggregant and neuroprotective treatments combined[5].

Magnitude of the problem in our setting

There are few studies on the incidence of stroke in Spain and those that do exist present some limitations. Similarly to what has been observed in Europe[6], studies demonstrate geographic variability[7-10]. In a study conducted in Catalonia in the year 2002, the cerebrovascular mortality rate for every 100,000 inhabitants aged 24 years and older was 92 in men and 119 in women. Age-adjusted mortality rates were 58 (95% CI: 56 to 128) and 43 (95% CI: 41 to 44), respectively[11]. Accumulated incidence (fatal and non-fatal cases) per 100,000 inhabitants was 218 (95% CI: 214 to 221) in men and 127 (95% CI: 125 to 128) in women. Previous data derived from a study conducted in Segovia (150 new cases per 100,000 inhabitants) [12] reported somewhat lower incidences.

75% of strokes affect patients over the age of 65, which, due to the ageing population in our setting, predicts increased incidence and prevalence of this health problem in the upcoming years. According to data from the hospital morbidity survey, there has been a constant increase of the total number of patients admitted to hospital with the main diagnosis of cerebrovascular disease, reaching 114,498 cases in 2003. However, this increase does not seem to be explained solely by population growth[13].

The distribution of mortality due to cerebrovascular disease in the different autonomous communities during the period spanning from 1999-2002 shows that it was higher in women than in men. In contrast, age-standardised rates were similar for both sexes, although they were higher in women in Extremadura and Galicia. The highest mortality rates due to cerebrovascular disease, both in men and women, were reported in Andalusia and Murcia[14]. In both cerebrovascular diseases and ischemic cardiopathy, a pronounced North-South gradient is observed (Figure 1) [16]. In the southern part of Spain the mortality rate due to these diseases is greater than the country's total average, whereas the northern regions are below this average.

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However, Spain is one of the countries with the lowest mortality in both men and women when compared with northern European countries such as the Netherlands, Switzerland, Ireland, Iceland and Nordic countries[1].

Population strategies

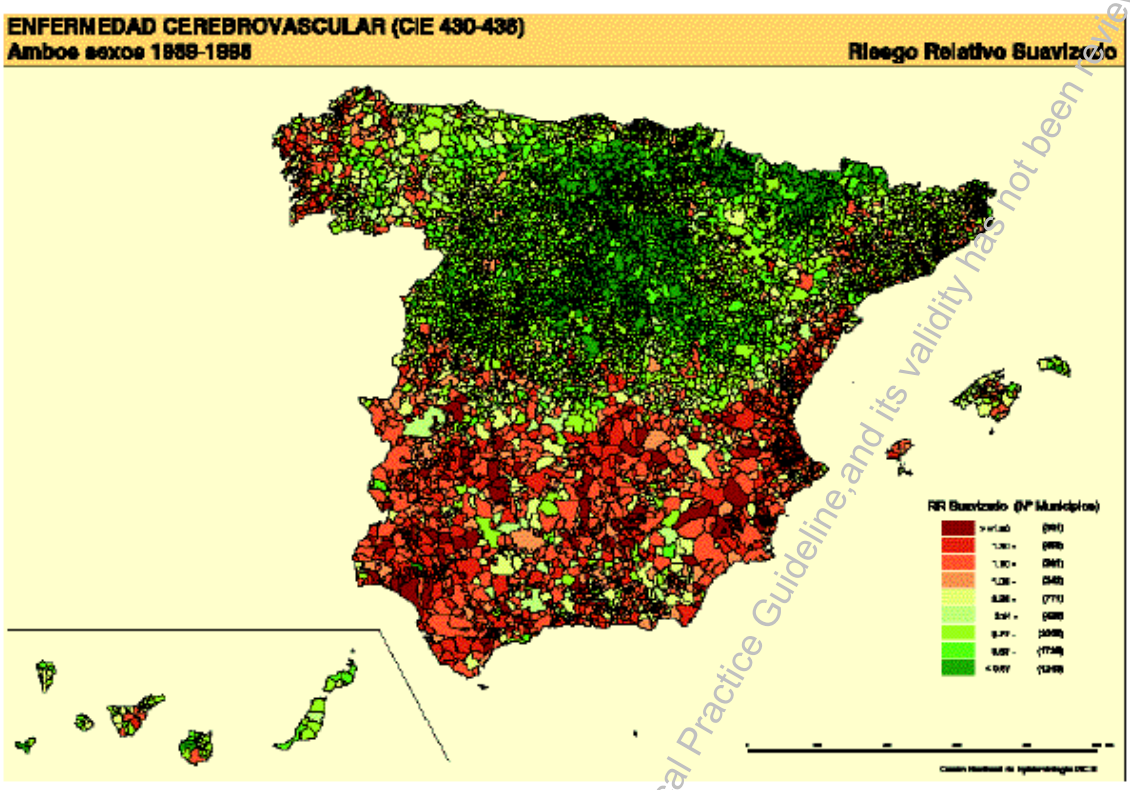
The most prevalent pathologies that entail a significant health care, family and social burden are receiving special attention from specialised international organisations in all countries. In developed countries, particularly in the case of chronic pathologies, they are affecting an increasing number of people over increasingly longer periods of time, and, if not properly prevented and treated, they can lead to significant losses in patient autonomy, resulting in a considerable burden for care givers[15].

The experience in several developed countries shows that by performing of a small number of interventions maintained over time it is possible to reduce the risk of death due to stroke. For example, during the 90s death rates due to stroke in our setting decreased 4% annually, as occurred in Australia, Germany, Italy or South Korea[3].

At present, the Ministry of Health and Consumer Affairs (MSC) has launched a campaign on healthy habits with the aim of promoting lifestyles and eating habits that favour citizens' health and well-being. The main objective of this campaign is to encourage healthy habits and lifestyles to prevent the development of vascular diseases. This campaign includes, amongst its main objectives: to increase society's awareness and mobilisation to generate a culture that works to prevent vascular diseases via the management of the main risk factors; to promote healthy lifestyles and manage risk factors with the aim of significantly reducing the incidence of vascular diseases in the general population, in healthy people as well as in those who have suffered some type of vascular disease; to increase awareness of the population with vascular disease and risk factors on the importance of becoming involved and being responsible for the management of their disease, following the recommendations and monitoring provided by health care professionals and follow-up of pharmacological treatment and, finally, promoting a culture of healthy habits: physical exercise, a low-fat, low-salt diet low and smoking cessation.

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Figure 1: Map of mortality due to cerebrovascular disease in Spain, 1989-1996[16]



Adapted from: López-Abente G, Ramis R, Pollán M, Aragonés N, Pérez-Gómez B, Gómez-Barroso D, *et al*. *Atlas municipal de mortalidad por cáncer en España*, 1989-1998. Madrid (Spain): Carlos III Institute of Health; 2006.

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2. Scope and Objectives

2.1. Justification

The existence of an updated clinical practice guideline (CPG) on the prevention of stroke can be a useful instrument to address the issues that emerge in health care delivery to healthy patients as well as to those who have previously had a stroke. One of the strategic lines to improve clinical practice (strategy 10) within the Quality National Plan for the National Health System (NHS) is to document and propose initiatives with the aim of decreasing the unjustified variability of clinical practice and to boost the development and use of CPGs linked to health strategies [14].

The MSC, in accordance with the World Health Organisation's (WHO) approach and with vascular prevention in general, proposes an integrated approach that combines prevention, diagnosis and treatment of ischemic cardiopathy with the corresponding measures for cancer, diabetes, cerebrovascular diseases and other chronic pathologies, given that many of them share the same risk factors such as smoking, unhealthy diet or physical inactivity, and require similar responses from the health care services of the NHS[14]. Within this guideline development programme, throughout the period between 2008 and 2009, two guidelines closely related with vascular prevention will be published: one on type 2 diabetes mellitus and one on prevention of child and adolescent obesity.

2.2. Scope

This CPG tackles primary and secondary prevention of stroke in adults. Acute episodes of stroke, both ischemic (transient ischemic attack [TIA] and brain stroke) and hemorrhagic, have been addressed. Primary prevention refers to strategies or interventions aimed at reducing the risk of having a stroke for the first time, and secondary prevention refers to strategies aimed at those people who have already had a stroke.

On the other hand, this CPG does not include recommendations for the diagnosis, treatment of acute stroke or the organisation of health care services. These aspects are the aim of other guidelines, both in our setting and at an international level (see annex 7).

2.3. Objectives

This guideline has been developed with the following objectives: to provide the professional with recommendations to improve the management of patients with risk of having a stroke or those who have already had one, both at primary and specialised care levels; to develop standards that can be used to assess professional practice, and aid patients in taking informed decisions. A CPG on primary and secondary prevention of stroke based on the best available evidence can benefit health care professionals by providing guidance in the best management for this situation and in the proper use of

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available health care resources, and also patients by providing them with homogeneous care and contrasted quality.
Patients as well as health care professionals, politicians, health care managers, health care services, and society in general, should have access to those tools that enable the contrast of health care quality and its efficiency, such as this CPG.

These recommendations have been developed by a multidisciplinary team composed of professionals involved in the management of this type of patients and who, prior to the development of the project, have completed and signed a declaration of interests (see annex 6).

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3. Methodology

The methodological manual for the development of the NHS's CPG includes a detailed description of the methodology employed to develop these guidelines and is freely available on the GuiaSalud website (http://www.guiasalud.es)[17].

The following steps have been followed:

- Creation of the guideline development group, comprised of primary (family and community medicine) and specialised (neurology, cardiology, internal medicine, geriatrics, haematology and pharmacology). These professionals were contacted through the different scientific societies related with CPG. In order to develop material for patients, a discussion group and interviews with patients has been created.

- Formulation of clinical questions following the PICO format: patient, intervention, comparison and outcomes.

- Bibliographic search that has prioritised the identification of systematic reviews (SRs) and other critical synthesis documents of scientific literature such as health technologies assessment reports. In order to do this, the first phase has included carrying out a search for other CPGs to determine what systematic reviews were considered to support their recommendations (the main CPGs used as secondary sources are included in annex 7). Subsequently, additional systematic reviews have been identified after the search date of selected CPGs. In this first phase the following electronic databases have been consulted:

    - TRIP Database
    - NHS National Library of Guidelines
    - AHRQ National Guideline Clearinghouse
    - Cochrane Database of Systematic Reviews (The Cochrane Library)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Health Technology Assessment Database
    - NHS Economic Evaluation Database (NHS EED)
    - MEDLINE (accessed through PubMed)
    - EMBASE (accessed through Ovid)

- Additionally, several technology assessment agencies such as the National Institute for Clinical Excellence (NICE), agencies that develop CPG such as SIGN and international societies such as the American Heart Association have been consulted.

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- In the second phase, a broader search has been performed for individual studies to update relevant systematic reviews in order to answer the questions of the CPG. The search has mainly attempted to identify randomised clinical trials (RCTs) and observational studies maintaining the original search strategy for relevant systematic reviews. When this strategy has not been available, a specific strategy for each of the questions has been designed and in each case filters validated for the identification of RCTs and observational studies have been added. In this phase the following databases have been consulted: The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (accessed through Ovid).

- No linguistic limits have been incorporated to the searches performed, but the studies considered have been mainly in Spanish, English and French. Searches until September 2007 have been performed, even though relevant studies have been identified in the most influential biomedical journals throughout the CPG development process.

- The search strategies corresponding to each section of the guideline are available at the Iberoamerican Cochrane Centre (tsc@cochrane.es).

- Quality assessment of the evidence and grading of recommendations has been performed using the system pertaining to the Scottish Intercollegiate Guidelines Network (SIGN) (see annex 1). Controversial recommendations or those lacking evidence have been resolved by means of simple consensus of the development group.

- The text has been reviewed by a multidisciplinary team of external reviewers that included patients. The final version of the guideline's text has been reviewed and approved by the group of authors.

- The CPG is to be updated every three years; however, its electronic version may be updated more frequently if necessary.

- The group of authors has participated in all stages of the process except in the search, quality assessment and synthesis of the literature, which were carried out by the authors from the Iberoamerican Cochrane Centre.

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4. Vascular Risk

Key Questions:

- What systems are available to assess vascular risk?
- In what population and how often should vascular risk be assessed?

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4.1. Importance of vascular risk

The etiology of stroke, myocardial infarction and peripheral arterial disease are multifactorial and the different SRs, mainly in secondary prevention, have demonstrated how several treatments not only prevent stroke but also other vascular episodes. Hence, the decision to initiate an intervention or preventive treatment should be guided by the estimation of the risk of developing one of these vascular episodes. Thus, preventive interventions do not only reduce the risk of having a stroke, but also the risk of myocardial infarction and peripheral arterial disease[18].

4.2. Vascular risk factors

Coronary disease and stroke share several risk factors, but the importance of each one of them in these conditions is not the same. In contrast to coronary disease, the most important risk factor of stroke is hypertension (HT) (relative risk [RR]>4), this factor being the only one consistently associated with all types of strokes. Other factors, as occurs in coronary disease, present more moderate associations (RR=2 to 4)[19].

SR of RCT 1+

Although numerous markers (biochemical, ankle-arm index, carotid intima-media thickness via ultrasound, coronary calcium index via computerised tomography) have recently been described, their use is yet unclear and their application would be aimed, in theory, at a more detailed assessment of people with moderate vascular risk[20, 21].

Observational studies 2+

4.3. Vascular risk calculation tables

Due to the multifactorial etiology of vascular disease, when the effect of a certain risk factor is estimated in an individual, other factors should be taken into account. An individual's vascular risk is calculated using equations of vascular risk, which establish excess risk in relation to the population's average.

The most widely used tables to calculate vascular risk in our setting are: the Framingham table, the REGICOR (Registre Gironí del Cor) table and the SCORE (*Systematic Coronary Risk Evaluation*)[22-24] table, which differentiate sex and age assessments as non-modifiable risk factors and,

Cohort studies 2+

additionally, incorporate blood pressure and cholesterol values, being a smoker or not, and, sometimes, the presence of diabetes.
Table 1 shows, for example, REGICOR's different estimations of coronary risk at 10 years in a 50-year old person taking into account the presence or absence of one or several risk factors and specific cholesterol, cholesterol HDL (high density lipoprotein) and blood pressure values.

Table 1. Impact of exposure to one or multiple risk factors on absolute coronary risk in a 50-year old man[35]

Cholesterol total (mg/dl)	Cholesterol HDL (mg/dl)	Diabetes	Blood pressure (mmHg)	Smoking	Coronary risk at 10 years
275	62	No	115/76	No	**3%**
210	50	No	170/94	No	**5%**
210	50	No	138/88	Yes	**5%**
230	34	No	152/94	Yes	**10%**
250	32	Yes	144/90	Yes	**19%**

*Risk calculated using the REGICOR table, valid for the Spanish population.

Adapted from: Department of Health of the Generalitat de Catalonia. *Llibre blanc. Consens sobre les activitats preventives a l'edat adulta dins l'atenció primària*. Barcelona: Directorate General for Public Health, 2005.

Cohort studies 2+

Framingham's tables have been used very frequently. Recently a new equation has been developed that includes the risk of stroke, although it overestimates risk in low-risk populations, and underestimates risk in higher risk populations [25, 26].

The REGICOR tables are the calibration of Framingham's equation in our setting. These tables estimate the risk of coronary morbimortality in individuals aged between 35 and 74 years, differentiate diabetic patients from those who are not and include the assessment of HDL cholesterol[27].

The SCORE tables include populations from different European regions and estimate the probability of vascular death in the population aged up to 65 years. These tables recommend a corrective factor for the calculation of risk in the diabetic population and include stroke in the estimation of vascular risk[24].

Table 2 shows the main differentiating characteristics of the REGICOR and SCORE tables. Annex 2 presents the SCORE tables for the low risk areas of Europe and REGICOR.

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Table 2. Comparison of the main differences between the REGICOR and SCORE tables[35]

	REGICOR	SCORE
Type of measure	Morbimortality	Mortality
Events included	Fatal or non-fatal or silent myocardial infarction, angina	Coronary death, cerebral vascular disease, peripheral arteriopathy, cardiac insufficiency, amongst others
Definition of high risk	>10%	>5%
Methodology	• Calibration of the equation based on a cohort study • Validated in our setting	• Equation based on a cohort study • Calibrated in our setting
Specific assessment of diabetic patients	Yes	No*

* The SCORE equation considers them to be high risk.

Adapted from: Department of Health of the Generalitat of Catalonia. *Llibre blanc. Consens sobre les activitats preventives a l'edat adulta dins l'atenció primària*. Barcelona: Directorate General of Public Health, 2005.

Cohort studies 2+

Different studies on the calibration, validation and comparative analysis of different tables demonstrate that all of them still provide inaccurate estimations[29-31]. Hence, these tables are at present a complementary diagnostic tool that should be considered jointly with the individual characteristics of each specific patient[18]. The subsequent decision to implement a preventive strategy and, even more importantly, if it is pharmacological, should consider the risk-benefit balance of this strategy and the patient's values and preferences.

The differences highlighted amongst the different tables of vascular risk estimation demonstrate that they do not identify the same profile of high-risk patients. Therefore, the same patient may or may not be a candidate for treatment depending on the risk calculation table used[32]. The economic impact of recommending the generalised use of one of the existing tables is a very relevant question but one that exceeds the scope of this guideline.

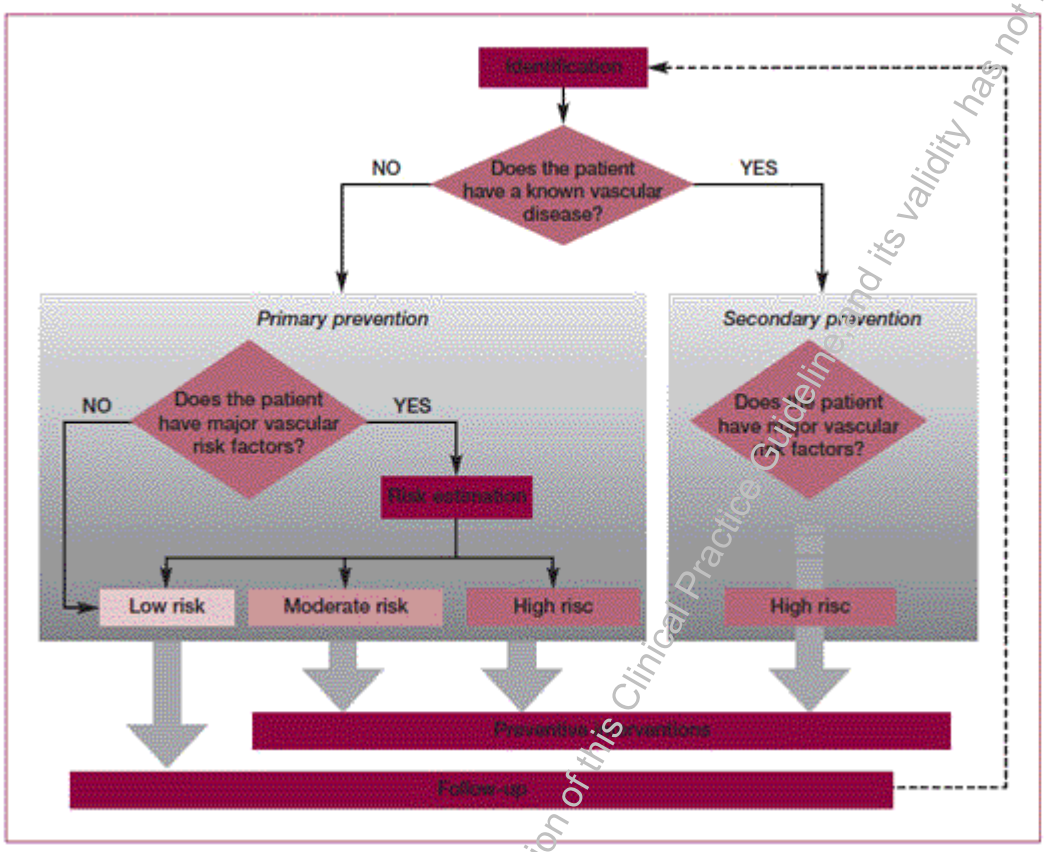
4.4. Vascular risk reduction strategies

The decision to initiate preventive strategies in the high-risk general population is still linked to a widespread debate regarding its real effectiveness and efficiency in relation to the cost and allocation of resources. Usually, high vascular risk is deemed to be an estimation higher than 5% of having a fatal vascular episode at 10 years according to SCORE tables or an estimation higher than 20% of having a coronary episode (fatal or not) at 10 years in the case of the REGICOR tables [24, 27].

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All these tables are for specific use in patients without known vascular disease. People with evidence of previous vascular disease present, regardless of the result obtained in the table, high vascular risk and should undergo more intensive preventive and therapeutic strategies [18]. Figure 2 shows an intervention algorithm proposal based on the estimation of vascular risk.

Figure 2. Intervention algorithm based on the estimation of vascular risk[14]



Adapted from: Ministry of Health and Consumer Affairs. Strategy for ischemic cardiopathy of the National Health System. Madrid: Ministry of Health and Consumer Affairs, Publications Centre, 2006.

RCT
SR of RCT
1+

Despite the previous information, there are no clinical trials that assess the efficacy of different preventive strategies on populations with different vascular risk. Additionally, a systematic review (SR) showed that the use of vascular risk tables does not reduce overall vascular risk[25]. However, in recent monitoring of patients with elevated plasma cholesterol levels that required hypolipemiant treatment, those who were informed on their level of vascular risk showed a more significant decrease of cholesterol values, and, essentially, of the risk profile[33].

It is important to calculate overall vascular risk in patients who so require it, a calculation that is not habitually performed at the present time. Specifically, a European study conducted in primary care reported that only 13% of the physicians consulted performed this calculation systematically on their patients, while 43% only does it occasionally[34].

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Summary of the Evidence

2+	There are different systems to assess vascular risk in the general population, although all of but all of them present certain limitations [22-32].
2+	Framingham's table overestimates vascular risk in our setting [25,26].
2+	The SCORE table evaluates vascular mortality and includes the risk of death due to stroke [24].
2+	The REGICOR table assesses the risk of coronary morbimortality validated in our setting [23].

Recommendations

B	The calculation of vascular risk using one of the available risk tables (REGICOR or SCORE) is recommended as a complementary diagnostic tool in the clinical assessment of patients.
B	The SCORE table is recommended to calculate the risk of stroke.
✓	Vascular risk should be assessed at least once every five years after the age of 40.
✓	In patients with high vascular risk, it should be assessed at least once every year.
✓	It is important that health care professionals be adequately trained for vascular risk calculation, and that such vascular risk calculation be integrated into the IT systems available at the medical consultation office.

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5. Etiologic classification of stroke

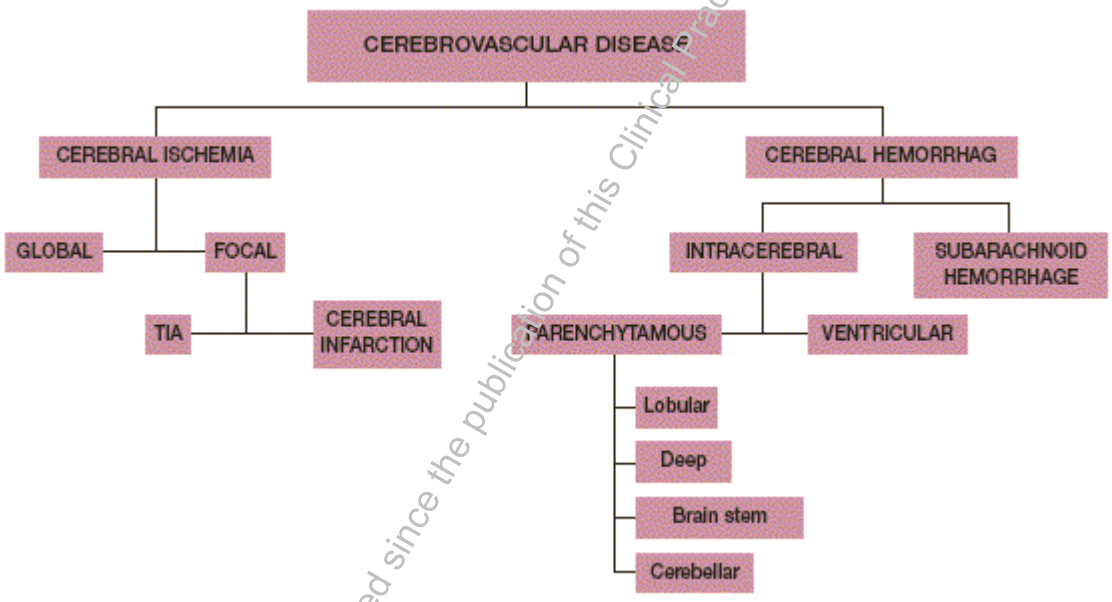
5.1. What is a stroke?

Cerebrovascular disease or stroke is caused by a circulatory brain disorder that transitorily or permanently disrupts the functioning of one or more parts of the brain[36]. There are several types of stroke, which, depending on the nature of the lesion produced, can cause cerebral ischemia or cerebral hemorrhage.

5.2. Types of stroke

Acute cerebrovascular disease is classified into two big groups: ischemic and hemorrhagic[36]. Ischemic cerebrovascular disease can be global or focal; the latter can be divided into two other big groups: TIA and cerebral infarction. Treatment and prevention (primary and secondary) strategies and prognosis depend on the cause and localisation of these attacks (Figure 3).

Figure 3: Clinical classification of strokes based on their nature [36]



Adapted from: Diez Tejedor E, Fuentes B, Gil Núñez AC, Gil Peralta A, Matías Guiu J, by the ad hoc committee of the SEN's (Spanish Society of Neurology) Study Group for Cerebrovascular Diseases. "Guía para el tratamiento preventivo de la isquemia cerebral". At: *Guía para el tratamiento y prevención del ictus*. Guidelines and procotocols of the SEN. In Díez Tejedor (ed.). Ed. ISBN: 84-8124-225-X. Barcelona: Prous Science, 2006: 133-183.

Depending on the nature of the lesion, the two main types of stroke are:

- **Established ischemic stroke or cerebral infarction:** occurs when cerebral ischemia lasts long enough to produce an area of tisular necrosis[36]. Sufficient duration is

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deemed to be when neurologic deficit lasts longer than 24 hours. There are several types of cerebral infarction depending on their mechanism of production and topographic localisation[36].

- **TIA:** brief episode of focal cerebral ischemia that is caused by an interruption of blood supply to an area that is supplied by the arterial system. It is reversible and there is no neurologic damage after it occurs. The definition of TIA has been recently modified: acknowledging the limitations of the classic definition ('focal brain dysfunction that lasts less than 24 hours'), the TIA Working Group redefines TIA as a brief episode of neurologic dysfunction, with clinical symptoms that last less than an hour and with no evidence of stroke in neuroimaging techniques.

- **Hemorrhagic stroke:** is the extravasation of blood within the brain as a result of a ruptured blood vessel. Depending on its localisation it can be cerebral (intraparenchymatous or ventricular) or subarachnoid.

Depending on the etiologic cause, the different subtypes of ischemic stroke are[36]:

- **Atherothrombotic ischemic stroke (TIA or cerebral infarction) due to large artery atherosclerosis:** it is generally a medium to large infarction, of cortical or subcortical topography and carotid or vertebrobasilar localisation, in which at least one of the following criteria are fulfilled:
  - Presence of atherosclerosis with stenosis: stenosis greater than or equal to 50% of the diameter of the vascular lumen or occlusion of an extracranial artery or a large calibre intracranial artery (middle cerebral artery, posterior cerebral artery or basilar stem), in absence of any another etiology causing the lesion.
  - Atherosclerosis without stenosis due to the presence of plaques or stenosis under 50% in the middle cerebral artery, cerebral posterior artery or basilar stem, in absence of any other etiology. At least two of the following cerebral vascular risk factors must coincide: person over the age of 50, HT, diabetes mellitus, smoking or hypercholesterolemia.

- **Cardioembolic ischemic stroke:** it is generally a moderate to severe intensity stroke, usually of cortical topography, for which there is evidence (in absence of an alternative etiology) of one of the following embolic cardiopathies: presence of a blood clot or intracardiac tumour, rheumatic mitral stenosis (MS), aortic or mitral prostheses, endocarditis, atrial fibrillation, sinus node disease, acute myocardial infarction in the previous three months with or without left ventricular aneurysm or extensive akinesia or presence of global cardiac hypokinesia or dyskinesia regardless of the underlying cardiopathy.
- **Small vessel arterial occlusive disease (lacunar stroke):** mild-intensity stroke (diameter less than 1.5 cm) of a brain penetrating artery that frequently causes a lacunar clinical syndrome (pure motor hemiparesia, pure sensory syndrome, sensorimotor syndrome, hemiparesia-ataxia or dysarthria – clumsy hand) in a patient with a history of HT or other vascular risk factors, in absence of another

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etiology that is causing it.

- **Uncommon ischemic stroke:** mild, moderate or severe intensity stroke, of cortical or subcortical localisation, in carotid or vertebrobasilar territory in a patient where atherothrombotic, cardioembolic or lacunar causes have been ruled out. It can be caused by systemic diseases (metabolic disturbances, coagulation disorders, connectivopathies, myeloproliferative syndrome or infectious processes) or by other causes such as cerebral venous thrombosis, migraine, septum aneurysm, arterial dissections, fibromuscular dysplasia, arteriovenous malformation, angeitis, or by an iatrogenic cause.
- **Undefined ischemic stroke:** moderate to severe intensity stroke, of cortical or subcortical localisation, in carotid or vertebrobasilar territory, where a comprehensive diagnostic study rules out atherothrombotic, cardioembolic, lacunar and uncommon subtypes. It can also be considered undetermined if there is more than one possible etiology or in cases in which an incomplete or insufficient study is carried out to rule out other causes.

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6. Primary prevention of stroke

Key questions:

- What are the main risk factors for having an episode of stroke?

6.1. Risk factors

This CPG presents the risk factors for having a stroke, including modifiable and non-modifiable factors, and provides recommendations for the main factors for which there are interventions available to reduce risk (Table 3). The recommendations presented are situated within the context of their specific impact on stroke, despite being closely linked with overall reduction of vascular risk.

Table 3. Modifiable risk factors of ischemic stroke[36]

Non-modifiable	Strong association	Weak association
– age – sex – race – low birth weight – hereditary factors	– hypertension – smoking – diabetes mellitus – atrial fibrillation – hypercholesterolemia – carotid artery stenosis – falciform cell disease – hormone therapy – alcoholism – left ventricular hypertrophy – hypercoagulability – previous ischemic stroke or TIA	– metabolic syndrome – drug use – oral contraceptives – migraine – hyperhomocysteinemia – elevated Lp(a) – inflammation and infection – obesity and body fat distribution – physical inactivity – dietary factors – certain embolic cardiopathies – others: obstructive sleep apnea syndrome, certain inflammatory conditions or infections

Adapted from: Diez Tejedor E, Fuentes B, Gil Núñez AC, Gil Peralta A, Matías Guiu J, by the ad hoc committee of the SEN's Study Group for Cerebrovascular Diseases. "Guía para el tratamiento preventivo de la isquemia cerebral". En: *Guía para el tratamiento y prevención del ictus*. Guidelines and protocols of the SEN. In Díez Tejedor (ed.). Ed. ISBN: 84-8124-225-X. Barcelona: Prous Science, 2006: 133-183.

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6.2. Non-modifiable risk factors

Primary prevention of stroke is aimed at interventions on modifiable vascular risk factors. Despite this, non-modifiable risk factors identify those subjects who have a higher risk of having a stroke and who may benefit from more rigorous management of modifiable factors.

6.2.1. Age

Age is the main non-modifiable risk factor of stroke. Although rates differ considerably, even within the same region, the incidence of stroke doubles approximately every ten years starting at 55 years of age[37-39]. After 75 years of age, specific vascular mortality rates per age group (decade) become the leading cause of death[40].

Observational studies 2++

6.2.2. Sex

Deaths due to vascular disease in Spain are more common in women than in men, even though the age- and type of disease-adjusted rate is higher in men. This trend is similar in other settings[40-42]. It may seem potentially paradoxical, but it has a well-known explanation: firstly, a higher vascular risk in men of the same age, and, secondly, vascular disease is much more frequent at older ages, and since women generally live longer than men, deaths due to stroke are more common in women[43].

Observational studies 2++/2+

6.2.3. Race

In several observational studies conducted in the United States it has been reported that people of African-American and Hispanic-American origin present higher stroke incidence and mortality[44-47]. Specifically, a study showed that the incidence of stroke in the black population was 38% higher than in the white population[48]. One of the explanations suggested to explain this phenomenon was the higher prevalence of risk factors such as hypertension or diabetes in the black population, although it is not likely that these factors explain the excess in disease load seen in certain races. In our setting, a case-control study did not show significant differences in the main risk factors amongst the Spanish and North European populations that had experienced a stroke, except for hypertension, which was more frequent in the Spanish population[49].

Observational studies 2++/2+

The race factor also seems to influence the response to treatment. Thus, the response to antiaggregants could be different between different races or ethnic groups[50]. Along the same lines, a SR showed different results in the prevention of vascular events with antihypertensive treatments in the black, white or Asian populations[51].

SR of RCT 1+

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6.2.4. Family history

The presence of a family history of stroke has been associated with a higher risk of stroke[52]. This could be due to the hereditary transmission of classic risk factors, the hereditary transmission of a greater vulnerability to these factors, and the sharing of certain environmental factors or lifestyles and the interaction amongst them all[53].

Observational studies 2++

A SR of 53 observational studies demonstrated that twins and people with a family history of stroke presented a higher risk of having a stroke depending on whether they were cohort or case-control studies (*odds ratio* [OR]: 1.30; confidence interval [CI]95%: 1.2 to 1.5 and OR: 1.76; 95% CI: 1.7 to 1.9 respectively) in comparison with the general population. Furthermore, homozygotic twins showed a more concordant history of stroke than heterozygotic twins. The majority of studies included in this review did not differentiate the types of stroke as ischemic or hemorrhagic, making it difficult to interpret the fact that such different pathological entities can share the same genetic basis. The review showed a relationship for ischemic stroke involving small and large vessels, but not for cardioembolic stroke[54].

SR of observational studies 2+

6.3. Modifiable risk factors

There are several risk factors for having a first episode of stroke. There is evidence on these factors indicating that adequate treatment can reduce their risk. These factors are, therefore, modifiable by means of therapeutic intervention. Stroke shares a fair amount of risk factors, to a greater or lesser degree of association, with coronary disease[55], differing in that, in the case of stroke, HT is the most important factor. Modifiable factors include smoking, diabetes, dyslipemia, obesity and physical inactivity. The degree of association of different modifiable risk factors with stroke and recommendations for its management are provided throughout the CPG.

Recently, increased risk of stroke has been attributed to certain conditions or markers, even though the evidence available is not yet conclusive. These include some inflammatory markers (leukocyte count, C-reactive protein or certain infections), fibrinogen, presence of microalbuminuria or plasma levels of cystatin-C[21, 56].

Observational studies 2+

Expert opinions 4

Summary of the Evidence

2++	Age is the main non-modifiable risk factor of stroke [37-40].
2++	Deaths due to vascular disease are higher in women, partly due to the fact that there are more elderly women [40-43].
2++/2+	Factors such as race have an uncertain relationship with stroke[44-49].

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2++	People with a family history of stroke have a higher chance of having a stroke[54].

Recommendations

✓	Strict monitoring and management of vascular risk factors is recommended in people with non-modifiable risk factors, especially in elderly patients and with a family history of stroke.

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6.4. Lifestyle Interventions

Key Questions:

- Do lifestyle interventions reduce the risk of having an episode of stroke?

The first steps of primary prevention of vascular disease should include the detection of certain lifestyle-related risk factors in an individual. The benefits of smoking cessation, a well-balanced diet and regular physical exercise provide undeniable benefits to vascular health. It is widely known that healthy life styles interrelatedly influence other pathologies[57]. Hence, interventions aimed at promoting healthy habits are potentially cost-effective. However, there is more uncertainty regarding how to influence individuals and populations using public health initiatives that address lifestyles in people with high vascular risk.

6.4.1. Alcoholism

Key Questions:

- Does alcohol consumption modify the risk of having a stroke?
- What strategies are available to reduce alcohol consumption in people who engage in excessive consumption?

SR of observational studies 2+

The association of stroke with alcohol consumption is a controversial issue[58]. Two SRs of observational studies that specifically analysed the risk of stroke for different levels of alcohol consumption and for different types of drink were located. Additionally, a further three SRs analysed alcohol consumption and its association with coronary risk[59-61]. Overall, the reviews show a "J"-shaped relationship for the risk of coronary morbimortality and alcohol consumption, which means smaller consumption could have a protective effect versus the harmful effect of greater consumption.

SR of observational studies 2+

In the specific case of stroke, a SR (19 cohort studies, 16 case-control studies) showed a non-linear relationship between a significantly increased risk of stroke and heavy drinking, and beneficial effects with light or moderate consumption[62]. Compared with abstainers, consumption of less than 12 g/d or <1 unit a day of alcohol was associated with reduced risk of total (RR:0.83; 95% CI:0.75 to 0.91) and ischemic (RR:0.80; 95% CI:0.67 to 0.96) stroke. In contrast, consumption of more than 60 g/d (>5 units a day) was associated with increased total risk of complete (RR:1.64; 95% CI:1.39 to 1.93), ischemic (RR:1.69; 95% CI:1.34 to 2.15) and hemorrhagic (RR:2.18; 95% CI: 1.48 to 3.20) stroke (Table 4). However, later cohort studies yielded inconsistent results[63-67].

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Table 4. Relative risk of stroke associated with alcohol consumption *[62]

Characteristics (number of studies)	Alcohol consumption	
	< 12 g/d	> 60 g/d
Total (35)	0.83 (0.75 to 0.91)	1.64 (1.39 to 1.93)
Ischemic (15)	0.80 (0.67 to 0.96)	1.69 (1.34 to 2.15)
Hemorrhagic (12)	0.79 (0.60 to 1.05	2.18 (1.48 to 3.20)
Men (27)	0.89 (0.79 to 1.01)	1.76 (1.57 to 1.98)
Women (16)	0.66 (0.61 to 0.71)	4.29 (1.30 to 15.14)

*** Values represent relative risk (RR) and the 95% confidence interval (CI).**

Adapted from: Reynolds K *et al*.,[62] Lewis B, Nolen JD, Kinney GL, Sathya B, He J. *Alcohol consumption and risk of stroke: a meta-analysis*. JAMA. 2003; 289(5):579-88.

SR of observational studies 2+

A SR (14 cohort studies, 12 case-control studies) assessed wine and beer consumption and its relationship with a combined variable of myocardial infarction, coronary disease and stroke (ischemic and hemorrhagic). Overall, risk reduction for wine consumers was 32% (RR: 0.68; 95% CI: 0.59 to 0.77) and 22% in the case of beer (RR: 0.78; 95% CI: 0.70 to 0.86). According to the results of four studies that analysed the risk of stroke, reduction was significant for wine consumers (RR: 0.43; 99% CI 0.24 to 0.78), but not for beer consumers (RR: 0.67; 99% CI 0.41 to 1.10) [68].

SR of observational studies 2+2+

A SR of observational studies showed that alcohol consumption greater than 150 g/d is associated with a two-fold increased risk of having a hemorrhagic stroke, especially in men. The effect in women was more inconsistent[69]. Alcohol consumption of <150 g/d was associated with a protective effect only in the analysis of case-control studies.

The reported protective effect of alcohol could be a result of potential study biases. A potential publication bias would favour the more frequent publication of positive studies, overestimating the beneficial potential of alcohol. Also, it is possible participants in the studies were classified as non-drinkers for presenting a greater number of comorbidities, which would involve a worse prognosis. Table 5 presents the corresponding values of units of alcohol and beverage volume to calculate the level of alcohol consumption using measure units.

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Table 5. Equivalent units of alcohol and beverage volume[75]

1 SDU:		
– 200 ml of beer – 100 ml of wine (small glass) – 50 ml of generous wine (sherry) – 50 ml of champagne (1 glass) – 25 ml of liquor (1 coffee with a shot of brandy)		
2 SDU:		
– 1 glass of cognac (50 ml) – 1 mixed drink (50 ml) – 1 vermouth(100 ml) – 1 whisky (50 ml)		
Type of Drink	**Volume**	**Number of Units**
Wine	1 glass (100 cc)	**1**
	1 l	**10**
Beer	1 glass (200 cc)	**1**
	1 l	**5**
Spirit drinks	1 glass (50 ml)	**2**
	1 coffee with a shot of brandy (25 ml)	**1**
	1 mixed drink (50 ml)	**2**
	1 l	**40**
Sherry, champagne, vermouth	1 glass (50 ml)	**1**
	1 vermouth (100 ml)	**2**
	1 l	**20**

SDU: standard drink unit, equivalent to 10 g of pure alcohol

Adapted from: Spanish Society of Family and Community Medicine; semFYC alcohol working group. *Recomendaciones semFYC: Alcohol*. Barcelona; 2000.

Strategies to modify alcohol consumption

SR of RCT 1++

Brief (5 to 20 minutes), informative interventions have proven to be effective at reducing alcohol consumption in people who engage in consumption that is considered high risk[70]. A recent SR (21 RCTs, 7,286 patients) of studies performed in primary care with patients who engaged in risky alcohol consumption showed that short interventions achieved significant reduction of consumption[71]. Other prior SRs yielded similar results[72, 73].

The specific nature of these disorders justifies the existence of a CPG that addresses in a detailed manner the treatment of patients with risky alcohol consumption and the management of the alcohol dependency syndrome[74].

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Summary of the Evidence

2+	High alcohol consumption increases the risk of vascular disease in general and stroke in particular, aside from having other harmful effects on health[62].
2+	The consumption of one or two units of alcohol per day does not seem to be a harmful factor; in fact, it could even be a protective factor in the development of vascular episodes, including stroke[62].
1++	Brief, informative interventions are effective at decreasing alcohol consumption[71].

Recommendations

A	It is recommended to avoid alcohol consumption greater than two units per day.
A	Brief, informative interventions are recommended in people who engage in consumption that could be considered harmful to health, with the aim of reducing this consumption.
✓	It is important to detect alcohol abuse as part of the routine clinical exam and at least every two years, especially when faced with problems that could be related with alcohol abuse or before prescribing drugs that could interact with alcohol.
✓	Alcohol consumption should not be encouraged in patients who do not drink.

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6.4.2. Tobacco smoking

Key Questions:

- Does smoking tobacco, actively or passively, increase the risk of having an episode of stroke?
- What interventions are available to quit smoking?

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There is a well-known association between tobacco smoking and lung, laryngeal, esophageal, bladder, kidney, pancreatic and cervical cancer, respiratory pathology (chronic obstructive pulmonary disease, asthma recurrences, amongst others), vascular pathology (ischemic cardiopathy, stroke, intermittent claudication, etc.) [55, 76], as well as with general mortality[77].

Observational studies 2++

Active smoking

A SR of observational studies showed that the risk of stroke in male and female smokers of any age was 50% higher than the risk in non-smokers[78]. Likewise, another SR of observational studies reported that smoking is consistently associated with a two- to three-fold higher risk of presenting hemorrhagic stroke, mainly a subarachnoid hemorrhage (SAH)[69]. On the other hand, an extensive international case-control study (Interheart) showed that the risk of coronary disease is linked to the smoking of any type of tobacco, even if smoking consists of 1 to 5 cigarettes a day[55].

SR of observational studies 2++

Case-control studies 2+

Smoking cessation considerably reduces the risk of developing different vascular diseases, including stroke, coronary disease, peripheral vascular disease and vascular death. Risk reduction is proportional to the duration of smoking cessation[79]. A SR reported a 36% mortality reduction in patients with a history of coronary disease who quit smoking[80].

SR of observational studies 2++

Passive smoking

Every day more information comes to light confirming the effects of tobacco on *passive smokers*[81]. A SR of cohort and case-control studies reported a 30% increased risk of coronary disease in non-smokers whose partners were smokers, in comparison with non-smokers whose partners did not smoke. These data point to a significant effect at relatively low exposure doses[76]. Later data on coronary disease and stroke corroborate the importance of this public health problem in other countries[82, 83]. Specifically in our country, exposure to environmental tobacco smoke in the work place and at home could account for 1,228 lung cancer-related deaths and 3,237 deaths due to coronary disease[84].

Observational studies 2++

Case series 3

Interventions to promote smoking cessation

Smoking reduction

It is advisable to attempt to reduce the damage caused by continuous tobacco smoking in smokers who cannot or do not want to quit smoking. Possible approaches to reduce exposure to tobacco toxins include decreasing the amount of tobacco smoked and to use less toxic products. Interventions assessed in controlled trials have tried mainly to reduce the number of cigarettes smoked[85]. A SR concluded that there is not sufficient data to support the long-term benefit of interventions designed to help smokers reduce tobacco smoking without quitting completely[85].

SR of RCT 1++

Smoking cessation

In several studies the efficacy of different strategies aimed at smoking cessation has been demonstrated. In a SR (39 RCTs, 31,000 patients) brief counselling proved to be moderately effective, and smoking cessation rates increased (OR: 1.74; 95% CI: 1.48 to 2.05). The most intensive interventions were slightly more effective than brief interventions[86].

SR of RCT 1++

In a SR, nicotine replacement treatment in any form of administration increased the percentage of abstinent people by more than 70% (OR: 1.77; 95% CI: 1.66 to 1.88) [87]. Another SR demonstrated that antidepressants (bupropion and nortriptyline) doubled the rate of abstinent people in the long-term, whereas serotonin reuptake inhibitors did not[88]. In all cases patients also followed a help programme to increase motivation. Results indicate that the mode of action of bupropion and nortriptyline is separate from their antidepressant effect and that they have similar efficacy to nicotine replacement. Adverse effects of both drugs are rarely serious and do not result in discontinuation of treatment.

SR of RCT 1++

More recently, a SR on varenicline (6 RCTs, 4,924 patients), a nicotine receptor agonist, has shown greater efficacy than placebo and bupropion in achieving smoking cessation at six months[89].

SR of RCT 1++

Population strategies

Due to the evidence available on the harmful effects of second-hand smoke, several countries have implemented legislation to prohibit smoking in bars or work places[90]. Different observational studies have assessed the impact of these prohibitions' strategies and have reported that workers' health has improved, presenting less respiratory symptoms, improved lung capacity and even lower coronary morbidity[90-95].

Observational studies 2+/2++

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Summary of the Evidence

2++	Tobacco smoking is associated with increased risk of vascular disease, stroke, respiratory pathology and several types of cancer[55,69,76-78].
2++	Increased vascular risk is also observed in passive smokers[76].
2++	Smoking cessation reduces the risk of developing vascular diseases, including stroke[80].
1++	Several pharmacological interventions aimed at achieving smoking cessation such as replacement treatment using nicotine, bupropion, nortriptyline* or varenicline have been proven effective[86-89].

* This indication is not approved for nortriptyline.

Recommendations

✓	The anamnesis of any patient should explore smoking.
A	Professional counselling embodies the essential therapeutic option to quit smoking. Smoking abstinence or cessation should be recommended and passive exposure to secondhand smoke avoided.
A	Replacement treatment using nicotine, bupropion, nortriptyline* or varenicline is recommended as part of structured smoking cessation programmes with the aim of increasing smoking cessation rates.
✓	It is necessary to prioritise smoking cessation strategies in smokers or in populations at risk such as young people and disadvantaged social classes.

* This indication is not approved for nortriptyline.

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6.4.3. Use of illegal drugs

Key Questions:

- Does the use of illegal drugs increase the risk of having an episode of stroke?

The common term of the word *drug* encompasses all those substances that present psychoactive effects and, more specifically, illegal drugs whose production or sale is prohibited by the law. The different administration routes and the characteristics of the person who takes drugs lead to wide variability as far as problems and risks derived from consumption[96].
In the population drug use patterns have varied considerably in the last decade and in Spain, for example, decreased use of heroin has been reported[97].

At the same time, the use of other drugs has been diversified and the use of new substances such as ecstasy (methylenedioxymethamphetamine [MDMA] or ketamine has been reported, while the use of other known drugs has been maintained (amphetamines, lysergic acid diethylamide [LSD], etc.) and cannabis and cocaine consumption have increased. In our setting one in every four young people reports habitual use of cannabis[98], while in the school population, cocaine consumption surveys of the last 30 days show an increase from 2.7% in 2002 to 3.4% in 2004[99].

The evidence that links the use of different drugs to vascular disease stems primarily from a series of cases that associate cocaine or crack use with ischemic stroke[99-107] or intracerebral hemorrhage (ICH)[108-111]. Likewise, marihuana, generally smoked, has been associated with ischemic stroke[112] and even with recurrent ischemic stroke[113, 114], and amphetamines and their structural derivatives such as MDMA (ecstasy, crystal, liquid crystal), with ischemic stroke[115-117], SAH[118, 119] and ICH[120, 121]. However, a cohort study of more than 65,000 participants did not show increased risk of death due to vascular causes in habitual marihuana users[122].

Observational studies 2+

Case series 3

Several case-control studies have associated cocaine or amphetamine consumption with stroke (OR: 7.0; 95% CI: 2.8 to 17.9) and vasospasm after a SAH, when comparing the results of non-users[123-125]. In a case-control study drug abuse of any kind produced a more than 6-fold higher risk of stroke[126]. In patients with vascular risk factors, cocaine consumption increases the chance of having a stroke even more[127]. However, other studies have associated cocaine consumption with acute myocardial infarction, but not with stroke[128].

Case-control studies 2+

The physiopathological mechanisms that mediate the vascular damage caused by different types of drugs have also been extensively studied. They are associated mainly with blood pressure, blood viscosity, platelet aggregation and vasospasm[129-131].

The therapeutic approach to patients with substance abuse-related disorders is complex. It encompasses treatment of intoxication and abstinence syndrome, as well as the pharmacological and psychological approach to

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dependency.

Summary of the Evidence

2+	Drug use increases the risk of stroke and other vascular diseases[100-128].

Recommendations

√	In the routine anamnesis it is advisable to ask about habitual or occasional use of illegal drugs.

6.4.4. Sedentarism

Key Questions:

- Does regular physical exercise reduce the risk of having an episode of stroke?

Sedentarism has been associated with vascular disease[55] and several locomotor, mental, endocrine and neoplastic disorders. The effects of physical exercise could be partly explained by their beneficial effect on the lipid profile, regardless of diet. The main effect seems to be increased HDL cholesterol, although it could also be decreased LDL cholesterol, total cholesterol and triglycerides[133]. The effect of exercise on systolic blood pressure (SBP) and diastolic blood pressure (DPB) is well-known, regardless of basal blood pressure or body weight values[134].

SR of observational studies 2+

A SR (24 cohorts, 7 case-control studies) showed that physical activity reduced the risk of stroke when compared to sedentarism. Physical activity reduced both ischemic and hemorrhagic strokes (RR: 0.78; 95% CI: 0.71 to 0.85) in people who exercised in their free time. As far as the studies that assessed the benefits of occupational physical exercise (generated by work), the reduction was not significant (RR: 0.74; 95% CI> 0.49 to 1.12). Moderate physical activity was sufficient to reduce the incidence of stroke[135]. Two previous SRs yielded similar results[136, 137].

SR of observational studies 2+

A recent SR (173,146 participants) showed an 11% reduction of vascular events, including stroke, in people who performed physical exercise on their way to work (mainly walking or riding a bicycle). The observed benefit was greater in women[138]. The relationship between physical exercise and the risk of SAH has not been consistent[69].

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Summary of the Evidence

2+	Physical exercise of any intensity is associated with decreased risk of vascular episodes, including stroke, in men and women[135-137].
2+	Physical exercise performed during free time and exercise performed in work-related activities is beneficial[138].

Recommendations

B	All people are encouraged to perform at least moderate physical exercise, within their capabilities, for at least 30 minutes a day.
B	It is recommended to encourage a gradual increase of intensity or frequency of physical exercise in people who are already moderately active.

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6.4.5. Dietary and nutritional factors

Key Questions:

- What type of diet is beneficial to reduce the risk of having an episode of stroke?

Dietary habits of developed societies have evolved towards eating patterns that include a higher content of animal fat in the total energetic intake, and fewer carbohydrates and vegetable fiber, a departure from the Mediterranean diet[139]. These changes in eating patterns, along with decreased physical activity, have been associated with a higher risk of developing chronic diseases such as obesity, certain types of cancer, type 2 diabetes, dental cavities, osteoporosis and vascular diseases[140].

A nutritional survey developed in our setting demonstrated that the standard diet lacks sufficient carbohydrates and has too many proteins and fats[140, 142]. 13% of the total energy derived from diet comes from saturated fatty acids, differing from the limit proposed by the Mediterranean diet, which is below 10%. Current CPG recommendations advise that fat accounts for less than 30% of total calories. Saturated and polyunsaturated fat should each contribute less than 10%, while monounsaturated fat should contribute approximately 15% to total daily calorie intake[57].

Fat

The three main types of lipids are saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids and are found in several types of food, making the study of health effects derived from a diet that is restrictive or rich in these subtypes complex.

Saturated fatty acids

SR of RCT 1++

Saturated fatty acids in diet are found mainly in animal products, cooking oils and fats (in Anglo-Saxon countries) and in industrially processed cooking products. A SR (27 RCTs, 18,196 patients) analysed the effects of reducing fats in diet on vascular morbimortality in male patients with different vascular risks. The review did not detect differences in overall mortality or vascular mortality but did report a reduction of vascular episodes (RR: 0.84; 95% CI: 0.72 to 0.99)[143].

RCT 1++

A recent clinical trial framed within the WHI initiative (Women's Health Initiative) performed on 48,835 postmenopausal women assessed the effect of reducing fat in diet, along with increased consumption of fruits, vegetables and legumes, on the development of breast and colorectal cancer. Additionally, as secondary objectives, effects on vascular disease were assessed. The contribution of fats to total daily calorie intake was greater than 30% in all participants. The study did not show significant differences between dietary intervention and standard diet in the incidence of vascular disease, stroke or coronary disease[144].

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Polyunsaturated fatty acids

Omega-6 and omega-3 fatty acids are the main components of polyunsaturated fatty acids, represented by linoleic acid (omega-6), which is found in vegetable oils, and eicosapentaenoic (EPA) and docosahexaenoic (DHA) (omega-3) acids, found in fish. The most recent SR (48 RCTs and 26 cohort studies) assessed the relationship between the consumption of omega-3 in food or in dietary supplements and vascular morbimortality in patients with different levels of vascular risk. The joint analysis of results did not show any effect of omega-3 consumption[145].

SR of RCT 1++

Additionally, a SR (9 cohort studies, 200,575 participants) in primary prevention of stroke demonstrated that the consumption of fish once a week reduces the risk of stroke by 18% (RR:0.82; 95% CI: 0.72 to 0.94). No differences were observed in the risk of hemorrhagic strokes[146].

SR of observational studies 2++

Fruits and vegetables

Fruits and vegetables provide vitamins and fiber. A SR (8 cohort studies, 257,551 participants) that assessed the effect of fruit and vegetable consumption in the primary prevention of stroke demonstrated that there was risk reduction if diet included three or more pieces of fruit per day (RR:0.89; 95% CI: 0.83 to 0.97). The benefit was greater in those who consumed five or more pieces of fruit per day (RR:0.74; 95% CI: 0.69 to 0.79)[147]. The effect was similar for ischemic and hemorrhagic strokes. Results were similar in a previous review[148].

SR of observational studies 2++

Vitamins

The group of tocopherols, specifically alpha-tocopherol, is the most common in the vitamin E family. It is a cell antioxidant[149]. A SR (7 RCTs, 106,625 participants) did not demonstrate a significant effect of vitamin E on vascular episodes or stroke (1,465 events; OR: 1.03; 95% CI: 0.93 to 1.14)[150].

SR of RCT 1++

Betacarotenes and retinoids are part of the vitamin A complex. Betacarotene supplements (1 RCT, 22,071 patients) have not proven to be superior to placebo at preventing vascular episodes[151]. In the CARET study (18,314 smoker patients or patients exposed to asbestos), the combination of carotenes and retinol was associated with an increase in vascular deaths to the limit of significance as compared to placebo[152]. More recently, an RCT (8,751 women with high vascular risk or a history of vascular disease) demonstrated that vitamin supplements (C, E and betacarotene) do not prevent vascular events[153].

RCT 1+

A recent SR (68 RCTs) assessed mortality outcomes in a wide spectrum of patients who received vitamins A, C, E or selenium as a primary or secondary prevention strategy of several health problems. In the analysis of high-quality RCTs (47 studies) vitamin supplements were associated with a significant increase of overall mortality (RR:1.05; 95% CI: 1.02 to 1.08)[154].

SR of RCT 1++

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Salt

The inclusion of sodium, especially in the form of sodium chloride, in diet influences blood pressure and blood pressure in turn impacts vascular episodes in general. A SR (28 RCTs, 2,954 patients) demonstrated that a moderate reduction of salt (6 g/d) significantly reduced blood pressure at one month follow-up in hypertense and normotense patients[155]. Another SR with 6 months follow-up also reported a reduction of blood pressure values in hypertense patients[156].

RCT 1+

Other recommendations

The Spanish adaptation of the *European Guide for Cardiovascular Prevention* includes dietary recommendations adjusted to our setting. Table 6 shows these recommendations[157].

Table 6. Dietary recommendations from the adaptation of the *European Guide for Cardiovascular Prevention in Clinical Practice*[157]

Diet should be varied and calorie intake appropriate to maintain an ideal weight.
Consumption of the following foods should be promoted: fresh vegetable products (legumes, whole cereals, fruits and vegetables), fish and olive oil.
Limited salt intake is a crucial element for the management of blood pressure. Thus, aside from recommending moderate addition of salt to food made at home, it is essential to recommend a diet based mainly on fresh foods with low sodium content. Fruits and vegetables are the main sources of potassium, and, at the same time, most contain calcium, which has a beneficial effect on blood pressure values.
The consumption of fresh vegetable products can have a positive effect on vascular prevention, due to the increased consumption of the fiber and several antioxidant substances they contain.
As far as vascular prevention, the type of fat consumed seems more important than the total quantity, whose upper limit could be situated around 30% and 35% of total calorie intake, if and when monounsaturated fatty acids are the most abundant. Given that it seems unlikely to be able to eliminate saturated fat from a nutritionally balanced diet, it is recommended to maintain the lowest possible consumption (<7% of total calorie intake), to try and eliminate or reduce to a minimum the consumption of hydrogenated fats and to stimulate the intake of monounsaturated fat, which is found in olive oil and essential fatty acids, particularly omega-3s, which is found in fish.
In summary, the Mediterranean diet, which is characterised by the abundance of fresh vegetable products (fruits, vegetables, cereals, potatoes, dried fruits, etc.), limited consumption of products containing refined sugars and red meats, the presence of olive oil as the main source of fat and the consumption of cheese, yogurt, chicken and fish in moderate amounts, constitutes a healthy eating pattern, and is considered ideal to prevent vascular diseases.

Adapted from: Brotons C, Royo-Bordonada MA, Álvarez-Sala L, Armario P, Artigao R, *et al.*, *Spanish Interdisciplinary Committee for Cardiovascular Prevention* (CEIPC). Adaptación Española de la Guía Europea de Prevención Cardiovascular. Rev Esp Salud Pública. 2004;78:435-438.

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Summary of the Evidence

1++	Maintained reduction of the contribution of fats to total daily calorie intake decreases vascular episodes[143-144].
1++	Interventions to increase the contribution of unsaturated fatty acids in diet do not reduce the risk of vascular diseases [145].
2++	Fish consumption more than once a week and consumption of three or more pieces of fruit daily reduce the risk of stroke[146].
1++	Vitamin dietary supplements do not show benefits in terms of mortality or vascular disease, and could even be harmful[150,153,154].
1+	Reduction of salt intake decreases blood pressure values[155-156].

Recommendations

A	It is recommended to reduce total fat and especially saturated fat in the diet. These should contribute less than 30% and 10% respectively to daily calorie intake.
A	Consumption of fish at least once a week and consumption of at least three pieces of fruit daily are recommended.
A	The use of vitamin supplements to reduce vascular risk is not recommended.
A	Reduced salt intake is recommended, especially in people with high blood pressure
✓	Salt intake under 6 g daily or, in hypertense patients, replacement with potassium salt, is recommended.
✓	It is advisable to eat a varied diet and promote the consumption of fresh vegetable products (legumes, whole cereals, fruit and vegetables), fish and unrefined virgin olive oil.

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6.5. Obesity

Key Questions:

- Does obesity or overweight increase the risk of having an episode of stroke?
- In people with obesity, does weight loss reduce the risk of having a stroke?
- In people with obesity, what strategies have proven to be effective at reducing body weight?

The WHO[158] defines obesity and overweight as an abnormal and excessive accumulation of fatty deposits that can be harmful to health. It also considers obesity to be the *epidemic of the XXI century* due to the dimensions it has acquired in the last decades and its impact on morbimortality, quality of life and health care expense[159].

An increasing prevalence of obesity has been observed in the past few decades. An observational study conducted in the adult population of northern Europe highlights an increase of prevalence during the period ranging from 1986 to 1993, from 4.6% to 11.4% in males and from 6.1% to 9.8% in women. Overweight also increased from 33.9% to 45.2% in males and from 19.6% to 29.1% in women[160]. In the years between 1987 and 2001, a similar trend was observed in our setting. The increase was reported in all age groups and educational levels, both in men and in women. Possible causes include diet as well as a lack of physical exercise[161].

The prevalence of obesity increases with age, even though it is becoming more frequent in adolescence[162, 163]. In the Spanish population aged between 25 and 60 years, obesity prevalence is 14.5%[164]. Because of what they entail at later stages of life, obesity prevalence rates in children and young adults (2-24 years) are even more worrisome: 13.9% present obesity and 26.3% overweight. During puberty (6-12 years) the prevalence of overweight reaches 16.1%[165]. **Observational studies 2+**

The body mass index (BMI) is the most well-know and widely used indicator to detect obesity in daily clinical practice. Based on this index, the WHO has proposed a widely accepted classification that differentiates low weight, normal weight, overweight and obesity. Hence, a person is considered obese if their BMI is greater than 30 kg/m^{2,} and overweight if their BMI ranges between 25 and just below 30 kg/m^2 [166].

6.5.1. Obesity and vascular risk

Obesity has a multifactorial origin, with a genetic predisposition component and the influence of environmental factors. It is a chronic disorder that entails increased morbimortality and is often associated with the main vascular risk factors, such as HT, diabetes or dyslipemia[167-169]. Obesity is associated with increased vascular morbimortality and overall mortality[167-173]. Likewise, childhood obesity has proven to be associated with higher **Observational studies 2++/ 2+**

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coronary disease risk in adulthood[174].

There is a significant amount of information indicating an association between BMI and increased risk of having an ischemic or hemorrhagic stroke[175-180]. However, there are other studies that do not confirm this relationship[181-186]. A SR also showed contradictory results for the risk of a SAH. A cohort study demonstrated that values lower than a BMI of 22 were associated with a significant reduction of risk of stroke, while two case-control studies reported a non-significant risk increase for low BMI values[69].

Observational studies 2++/ 2+

Abdominal obesity measured as a waist-hip index has also been associated with stroke[187]. A case-control study performed on a North American population reported that an increased waist-hip index was associated with a three-fold increased risk of stroke[188].

Case-control studies 2++

6.5.2. Weight reduction strategies

At present we do not have results pertaining to randomised and prospective studies that assess the impact of weight reduction on vascular morbimortality. A recent SR did not locate any RCTs or observational studies that assessed the relationship between weight reduction and decreased incidence of stroke[189].

SR of RCT 1+

A SR (6 RCTs, 361 patients) evaluated dietary interventions aimed at achieving weight loss and its effect on blood pressure versus no intervention[190]. Results showed that 6% to 9% body weight reductions were associated with moderate reduction of blood pressure. Other SRs that assessed multifactorial interventions that included diet, exercise, and behavioural and pharmacological treatment aimed at weight loss have proven to be beneficial in the lipid profile and blood pressure[191-193], as well as in reducing the incidence of diabetes[249].

SR of RCT 1+

A SR (43 RCTs, 3,476 participants) assessed the effectiveness of exercise to decrease weight in people with overweight or obesity. The results of this review recommend exercise as an intervention to lose weight, particularly in combination with dietary changes[194].

SR of RCT 1++

There are pharmacological treatments (mainly orlistat and sibutramine*) that together with lifestyle modification, modestly reduce body weight at two years follow-up (5-10%). In addition to weight loss, all of them have yielded positive results in other vascular risk factors such as blood pressure, dyslipidemia as well as diabetes or glucose intolerance[195]. Adverse effects are relatively frequent with these treatments. Sibutramine* has been associated with insomnia, nausea, dry mouth or dizziness. Even more worrisome is its relationship with increased blood pressure values which could lead to abandonment of treatment. Orlistat has been associated mainly with gastrointestinal adverse effects as well as with poor absorption of vitamins and certain treatments such as oral contraceptives. The

RCT 1+

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*** INFORMATION NOTE Spanish Agency of Medicines and Medical Devices (21st January 2010):**
Marketing authorisation for sibutramine has been suspended as the risks outweig the benefits.
More information available at:
http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2010/NI_2010-01_sibutramina_reductil.htm
(**Note:** website in spanish)

commercialisation of rimonabant has recently been suspended as a precautionary measure due to the report of severe psychiatric effects, including consummated suicide, in people who had been taking this drug. The much awaited results of the CRESCENDO trial to assess the efficacy and safety of rimonabant (CRESCENDO) [196] or the SCOUT trial[197] with sibutramine* will serve to confirm or rule out some of these issues. Initially these trials were designed with the objective of assessing vascular events and vascular-related deaths in patients with obesity or overweight.

Additionally, based on WHO criteria, patients with morbid obesity (BMI>40 kg/m^2) or with a BMI>35 kg/m^2 and associated comorbidities are candidates for surgery to treat obesity[166]. A SR showed that different types of intervention achieved 34.8 to 51.1 kg weight reduction at three years[198]. Mortality resulting from different procedures ranged between 0.1% and 1.1%, depending on the experience of the surgical team[199].

SR of RCT
1+

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(**Note:** website in spanish)

Summary of the Evidence

2++/ 2+	Obesity has a complex association with different vascular risk factor and entails a significant increase of vascular and general morbimortality.
2++/ 2+	General obesity as well as abdominal obesity are associated with an increased risk of stroke.
1++/1+	Weight reduction yields beneficial effects on vascular disease risk factors.
1+	Dietary interventions in overweight or obese people have been proven to be beneficial in weight reduction and management of other vascular risk factors.
1++	Physical exercise in overweight or obese people has proven to be beneficial in weight loss and management of other vascular risk factors, especially if it is associated with diet modification interventions.
1+	Pharmacological treatment, in addition to dietary interventions, has proven to be effective, given that is moderately reduces weight and improves other vascular risk factors. However, adverse effects are frequent with these treatments.
1+	Surgical procedures in patients with morbid obesity have resulted in substantial weight reduction. Surgery, depending on the technique and the

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	surgical team's experience, has a mortality rate ranging from 0.1% to 1.1%.

Recommendations

A	In people with obesity or abdominal obesity, it is recommended to reduce body weight until reaching satisfactory weight.
A	Diet modification and increased physical activity are recommended as the first therapeutic measure of weight reduction.
B	In addition to hygienic-dietary measures, the possibility of pharmacological treatment* over a limited period of time should be considered for people with obesity or abdominal obesity who do not respond to conservative measures.
B	In patients with morbid obesity surgery is the therapeutic alternative that should be individually considered in each patient.

*** INFORMATION NOTE Spanish Agency of Medicines and Medical Devices (21st January 2010):**
Marketing authorisation for sibutramine has been suspended as the risks outweig the benefits
More information available at:
http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2010/NI_2010-01_sibutramina_reductil.htm
(**Note:** website in spanish)

6.6. Hypertension

Key Questions:

- Does antihypertensive treatment reduce the risk of having an episode of stroke?
- What antihypertensive treatment has proven to be most beneficial for reducing the risk of having an episode of stroke?
- What are target blood pressure values?
- Do patients with diabetes benefit from a more strict management of blood pressure?

SR of RCT
1+

HT is an important risk factor, after age, for ischemic and hemorrhagic stroke. The hypertense population more frequently presents other vascular risk factors, such as overweight, sedentarism or excessive consumption of alcohol[200]. The risk of stroke is three to five times higher in patients with HT[19].

At present it has been determined that a person has HT when SBP is equal to or greater than 140 mmHg or DBP is equal to or greater than 90 mmHg. Throughout the years these limits have been corrected and reduced[201]. However, there is a linear increase of stroke risk with the increase of blood pressure values and at values greater than 115/75 mmHg[202].

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It is estimated that HT in Spain affects approximately 46.8% of the population between the ages of 35 and 64 years, according to a study that assessed the prevalence of HT in six European countries, Canada and the United States. The study reported a higher prevalence of HT in Europe and a similar pattern for stroke death rates[203]. This fact has already been observed in the MONICA international study, which confirmed a similar relationship between hypertension and incidence of stroke[204]. **Observational studies 2++/2+**

In our setting prevalence is around 30%-40% of the general adult population 68% in the population over the age of 60 years[205]. The benefits of treating blood pressure in terms of vascular risk reduction are undeniable. Despite there being no question about benefits, a study shows that, in people who have had a stroke, the implementation of recommendations provided by CPGs regarding treatment of vascular risk factors and therapeutic objectives is very poor[206]. In our setting, poor management of blood pressure values and the presence of left ventricular hypertrophy were significantly associated with stroke mortality[207, 208]. **Observational studies 2+**

6.6.1. Lifestyle interventions

Lifestyle modifications in hypertense patients that have proven to reduce blood pressure values are: smoking cessation, weight loss in obese patients, moderation of alcohol consumption, moderate physical exercise, reduced salt intake and increased consumption of fruits and vegetables[209]. These measures are also useful in the management of other vascular risk factors. **SR of RCT 1++**

A SR assessed the efficacy of educational interventions (with or without associated pharmacotherapy) in the management of vascular risk factors and mortality. There were no significant reductions of mortality, although moderate management of risk factors, such as blood pressure values, cholesterol or reduction of smoking, was achieved. The review concludes that these interventions show a poor impact in the population setting and that greater benefits are observed in hypertense people with higher vascular risk[210]. **SR of RCT 1++**

6.6.2. Pharmacological treatment

Numerous RCTs with placebo and antihypertensive treatment that included patients with one or more vascular risk factors have been conducted. The benefit of pharmacological treatment of blood pressure values in the reduction of vascular morbimortality is conclusive[211, 212] and has been consistent in young adults and elderly patients[213] both in men and in women,[214, 215] as well as in isolated systolic hypertension[216]. A recent SR has determined that the reduction of SBP values is the main factor responsible for decreased vascular episodes[217]. **SR of RCT 1++**

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A SR (29 RCTs, 162,341 patients) compared different treatments (angiotensin converting enzyme inhibitors [ACE INHIBITORS], diuretics, betablockers, calcium antagonists) with placebo ad with each other[226]. Some studies included patients with a history of vascular disorders, including stroke, yielding no differences between the different therapeutic groups in global reduction of vascular episodes. Angiotensin-II-receptor antagonists (ARA-II), ACE inhibitors and calcium antagonists reduced the risk of stroke when compared to placebo by 21%, 28% and 38%, respectively. There were no significant differences between ACE inhibitors, diuretics, betablockers or calcium antagonists in the reduction of risk of major vascular episodes. ARA-IIs reduced major vascular episodes by 10% versus control. Risk reduction of major vascular episodes was 15% higher in intensive treatments (DBP <80 mmHg objective) than in less intensive treatments. The same group analysed the efficacy of different antihypertensive treatment according to age in a SR (31 RCts, 190,606 patients), yielding no significant differences between patients under the age of 65 years and patients over the age of 65 years. Although the reduction of vascular events, relatively speaking, is lower in older patients, these have a high vascular risk, so benefits must be equated to those obtained in younger patients[218].

SR of RCT 1++

In a SR (42 RCTs, 192,478 patients) treatment with diuretics, even at low doses, compared to placebo, reduced the incidence of stroke by 29% (RR:0.71 95% CI: 0.63 to 0.81) amongst other vascular variables, as well as total mortality (RR:0.90 95% CI: 0.84 to 0.96)[211]. Although comparisons between different therapeutic groups were indirect, the SR concludes that ACE inhibitors, ARA-IIs, betablockers or calcium antagonists have not proven to be superior to diuretics at low doses.

SR of RCT 1++

A recent SR (13 RCTs, 91,561 patients) analysed the results of betablockers in the treatment of HT. In most of the studies atenolol was included as treatment and in some, patients with prior stroke[219]. Betablockers, versus placebo (4RCTs), reduced the risk of stroke (499 events; RR:0.80; 95% CI: 0.66 to 0.96). In contrast, when compared with other antihypertensive drugs (calcium antagonists and ARA-II), betablockers presented a greater number of stroke episodes. Furthermore, betablockers showed a tendency towards presenting more vascular events, which was significant in comparison with diuretics and calcium antagonists. In another SR (21 RCTs, 14,5811 patients) similar results were obtained for betablockers, indicating a protective effect when compared to placebo in patients under the age of 65 years, but not in older patients[220].

SR of RCT 1++

The VALUE trial, which was not included in previous reviews (15,245 patients) compared valsartan with amlodipine in patients with HT (half of them had ischemic cardiopathy) and did not find significant differences between both treatments in the prevention of coronary episodes or stroke. The trial emphasised the need to not delay the fulfillment of blood pressure target values[221]. More recently, the ASCOT-BPLA trial (19,257 patients) was prematurely ended given that it showed significant reduction of

RCT 1++

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mortality, vascular events and stroke in patient who received amlodipine treatment (with or without perindopril) compared with atenolol (with or without a thiazide diuretic) [222]. Amlodipine treatment reduced stroke episodes by 33% (749 events; hazard ratio (HR) 0.77; 95% CI: 0.66 to 0.89).

Safety of pharmacological treatment

Several national[223] and European[224] CPGs have addressed treatment of HT and the most indicated treatments or combined treatments in different clinical situations. There are clinical situations that can worsen and therefore require an antihypertensive treatment that is prescribed with caution or monitored more strictly. This is the case of ACEIs in pregnant women, in bilateral stenosis of the renal artery or in chronic renal insufficiency; betablockers in decompensated chronic heart insufficiency, severe bradycardia or advanced atrial-ventricular heart block; diuretics in gout, and calcium antagonists in congestive heart failure. These conditions, which often coexist in the same patient, should be taken into account when initiating a treatment for HT.

A SR analysed the frequency of treatment discontinuation due to adverse effects amongst the different antihypertensive treatment groups; rates were: ARA-II 3%; diuretics 3.1%; placebo 4.1%; betablockers 4.5%, ACE inhibitors 4.7% and calcium antagonists 6.7% (6.9% for dihydropiridines and 5.7% for non-dihydropiridines), even though there were no significant differences with placebo treatment. The most common adverse effects per therapeutic group were cough in ACE inhibitors, edema in calcium antagonists, headache in betablockers and metabolic effects in diuretics or ARA-II[225]. **SR of RCT 1+**

6.6.3. Diabetic patients

Available studies consistently indicate that vascular benefits do not differ in diabetic patients versus the general population. A SR (27 RCTs, 158,709 patients) analysed the vascular mortality and morbidity of different antihypertensive treatments in diabetic and non-diabetic populations. The treatments included were ACE inhibitors, calcium antagonists, ARA-II, betablockers and diuretics. Reduction of major vascular episodes was similar in both populations for all treatments. The majority of studies presented treatment as a primary prevention strategy. Similarly, the benefit of different treatments on the risk of having a stroke was similar, except for ARA-IIs, whose benefit was produced especially in non-diabetic patients[226]. **SR of RCT 1++**

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An analysis for the population with or without diabetes of the SHEP trial, whose data are not found in the previous SR demonstrate that in the long-term and in population over the age of 60 years with isolated systolic hypertension, diuretics were superior to placebo. The reduction of vascular mortality (HR 0.69; 95% CI: 0.53 to 0.85) and total mortality (RR:0.80; 95% CI: 0.68 to 0.95) was significant in patients with diabetes who received diuretic treatment versus placebo.[227]

RCT 1+

6.6.4. Blood pressure target values

In patients without high vascular risk, the HOT trial reported the highest benefit in reducing blood pressure values to 139/83 mmHg[228]. A SR of cohort studies demonstrated that the risk of stroke presents a consistent linear decrease until reaching blood pressure levels of 115/75 mmHg in men and women and for different types of stroke. Risk is reduced by approximately 30% for each 10 mmHg decrease of blood pressure values[229].

RCT 1+

SR of observational studies 2+

In regards to the diabetic population, different CPGs on diabetes or vascular prevention disagree on blood pressure target values and recommend values that range between 130-140 mmHg for SBP and 80-90 mmHg for DBP[223, 224, 230, 231]. This variability can be explained by the different assessment and interpretation of the limited evidence that exists on this issue.

Several trials have demonstrated that in patients with diabetes, stricter management of blood pressure compared with less strict management is accompanied by reduced vascular episodes or microvascular complications associated with diabetes[228, 232-235]. Specifically, a non prespecified analysis of patients with diabetes in the HOT trial reported benefits for the subgroup assigned to a target DBP below than 80 mmHg versus the subgroup assigned to a target DBP below than 90 mmHg. Although there were differences in total mortality, patients with a less strict DBP management target presented increased risk of vascular mortality (RR: 3.0; 95%CI:1.28 to 7.08)[228]. In spite of this, more recent reviews that address this issue conclude that the evidence regarding whether stricter management of blood pressure is more beneficial in the diabetic population than in the non-diabetic population is limited and inconclusive[226].

RCT 1+/2+

SR of RCT 1++

6.6.5. Hemorrhagic stroke

ICH is blood extravasation within the brain parenchyma generally caused by the non-traumatic rupture of a blood vessel. The rupture is caused by the fragility of the vascular wall, which is often secondary to HT or amyloid angiopathy. The main cause of SAH is a ruptured intracranial aneurysm. High blood pressure values are the most important risk factor of ICH for all age and sex groups, with an incidence of approximately 15 cases per 100,000 inhabitants[236]. Although less frequent than ischemic stroke, HIC-associated mortality is much greater.

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SAH, which is addressed more extensively in section 6.19, is caused by the extravasation of blood in the subarachnoid region and has a high morbimortality, despite accounting for only 1% and 7% of all strokes[238]. A SR of observational studies (3,936 patients) assessed the relationship of different factors with SAH risk[69]. High blood pressure values, alcohol consumption and smoking were consistently associated with a significantly higher risk of presenting a SAH.

SR of observational studies 2+

The vast majority of RCTs that have assessed several lifestyle interventions or pharmacological treatments have not separately assessed the efficacy on different types of stroke, so the efficacy of these measures as preventive strategy is, at best, controversial in hemorrhagic stroke. Very often studies that have assessed hemorrhagic strokes have not considered the two main types separately: ICH and SAH.

Specifically, the SHEP trial (4,736 patients) determined that isolated HT with a regimen based on thiazide diuretics in patients over the age of 60 years reduces the risk of stroke. Later, in an analysis of the different subtypes of stroke, antihypertensive treatment significantly reduced the risk of ischemic strokes versus placebo. The reduction of hemorrhagic strokes was not significant[239]. Results show the same trend in the PROGRESS study (6,105 patients). In this secondary prevention study (111 events), ACE inhibitor treatment (perindopril) significantly reduced the risk of recurrent hemorrhagic strokes by 50%, although the absolute risk difference was reduced by 1%[240].

RCT 1++

Summary of the Evidence

1++	HT is the most important risk factor for having a stroke, both ischemic and hemorrhagic[19].
1++	Lifestyle modifications in hypertense patients reduce blood pressure values and other vascular risk factors[209,210].
1++	Pharmacological treatment of hypertension reduces vascular and stroke morbimortality and is consistent in young and elderly people, in men and women, as well as in the treatment of isolated systolic hypertension[211-217].
1++	Diuretics, angiotensin converting enzyme inhibitors, angiotensin-II-receptor antagonists and calcium antagonists are effective in the primary prevention of stroke and other vascular episodes in hypertense patients. Betablockers have shown to be inferior, especially in the elderly[211,218-222,226].
1++ / 1+	Information regarding whether stricter management of blood pressure is more beneficial in the diabetic population than in the non-diabetic

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	population is inconclusive. In hypertense patients with diabetes mellitus, decreased DBP under 80 mmHg seems to reduce vascular morbimortality[228,232-235].
1++ / 1+	Treatment of HT with angiotensin converting enzyme inhibitors or a diuretic is effective at reducing the risk of hemorrhagic strokes[239-240].

Recommendations

A	In patients with high blood pressure it is recommended to modify lifestyles with the aim of achieving smoking cessation, weight loss in obese patients, alcohol consumption moderation, regular physical exercise, reduced salt intake and increased consumption of fruits and vegetables, regardless of pharmacological treatment.
A	It is recommended that the initial treatment of high blood pressure be with thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers or calcium antagonists in the majority of situations and based on the characteristics of each patient.
B	Initial treatment with betablockers can be considered in young patients with non-complicated hypertension.
A	It is recommended to maintain blood pressure levels below 140/90 mmHg.
B	In diabetic patients it is recommended to maintain blood pressure levels under 130/80 mmHg.
✓	In patients with blood pressure levels higher than 160/100 mmHg or in diabetic patients the combination of more than one antihypertensive treatments should be considered.
✓	In hypertense patients with diabetes the first treatment to consider should be with angiotensin converting enzyme inhibitors, angiotensin II antagonist in monotherapy or in combination with another hypertensive drug.
✓	Combined antihypertensive drugs should have different but complementary mechanisms of action and be administered preferably at the minimal effective dose.

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6.7. Diabetes mellitus

Key Questions:

- In diabetic patients, what is the risk of having an episode of stroke?
- What strategies can prevent the development of diabetes?

This guideline does not specifically address each and every intervention for the treatment of the diabetic patient. This issue is specifically and comprehensively tackled in the guideline on type 2 diabetes within the "Clinical Practice Guidelines Project of the Ministry of Health and Consumer Affairs" (CPG DM-II). This section only covers its prevention and screening based on the evidence located for diabetes[231].

Table 7. Diagnostic criteria for diabetes and prediabetes[231]

	Basal glycaemia*	2h- OGTT*	Random glycaemia*
Normal	<100 mg/dl	<140 mg/dl	-------
ABG	100-125 mg/dl	------	--------
IGT	------	>140 mg/dl	-------
DIABETES	126 mg/dl	≥200 mg/dl	≥200 mg/dl

*Venous plasma values.
** OGTT: Oral glucose tolerance test.

Adapted from: Working group of the *Clinical Practice Guidelines for type 2 diabetes. Guía de práctica clínica sobre la diabetes tipo 2*. Madrid: National Plan for the NHS of the MSC. OSTEBA. [In press 2008.]

6.7.1. Diabetes and vascular risk

Recently the WHO forecasted that by 2010 the number of diabetic people worldwide would reach 200 million, partly due to increased life expectancy and improvements in diagnosis, but also to lifestyle changes[241]. In our setting, overall prevalence of type 2 diabetes ranges from 6% to 10%, and reaches up to 24% in people over the age of 70[242]. On the other hand, half the people with diabetes present associated vascular risk factors, such as hypertension, dyslipemia and overweight[243].

Aside from a greater vulnerability to developing atherosclerosis, in diabetic men, the risk of stroke has a 2.5- to 4.1-fold increase, and in women it increases by 3.6 to 5.8 times; in contrast, with other risk factors, risk is two times higher. Diabetes as a risk factor is independent from stroke[244, 245]. **Observational studies 2+**

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In a SR of observational studies, patients with diabetes showed a tendency towards SAH risk reduction of approximately 30% in several case-control studies[69]. One possible explanation is that diabetic patients present a higher risk of death due to other causes and, hence, a lower risk of presenting ICH than controls[69].

SR of observational studies 2+

In people with altered basal glycaemia (ABG) the risk of developing diabetes is 4.7 times higher than in the general population and the risk of myocardial infarction, vascular episodes, vascular and total mortality is also slightly higher. Impaired glucose tolerance (IGT) presents an even higher risk of developing diabetes. This risk is six times higher than in people without blood glucose alterations and 12 times higher than in the case of people with ABG and IGT. In the case of IGT the risk of disease and vascular death and total mortality is also increased[246].

SR of observational studies 2+

6.7.2. Interventions to prevent the development of diabetes

Several SRs have assessed the efficacy of lifestyle changes and pharmacological treatment (mainly alpha-glucosidase inhibitors and biguanides) in patients with ABG or IGT[247-250]. Studies show that both diet and drugs are consistently effective, even though data on important variables for the patient (microvascular and macrovascular problems) are limited[251]. The DREAM study reported a reduction of diabetes incidence with rosiglitazone in people with altered plasma glucose levels[252]. The indication of hypoglyacemic drugs is not approved for use in prediabetic stages.

SR of RCT 1++

These treatments often entail adverse effects, including gastrointestinal effects such as diarrhea, and hypoglycaemia. More recently, based on the results of several SRs, the Spanish Drug and Health Products Agency issued a safety warning on the increased risk of coronary episodes and cardiac insufficiency with the use of rosiglitazone in comparison with other oral antidiabetics. There is not sufficient information on this issue for pioglitazone[253-257] At present the objective of the RECORD study, which is in the recruiting phase, is to assess the benefits of rosiglitazone in the prevention of vascular episodes[258].

SR of RCT 1++

6.7.3. Diabetes screening

No direct evidence was identified concerning the efficacy of diabetes mellitus screening in the general population[259]. However, some SRs consider screening in certain risk groups, such as people with HT, dyslipemia and, in some cases, people with obesity[259, 260]. Certain initiatives in our setting include healthy adults over the age of 45 in vascular prevention structured programmes, as well as people with first-degree relatives with diabetes, prior diagnosis of AGT or ABG or certain risk groups such as people of Asian or Central-American origin[231, 261, 262].

SR of RCT 1+

Expert opinions 4

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Summary of the Evidence

2+	Diabetes increases vascular and stroke risk[244-245].
1++	In people with altered plasma glucose, interventions that promote physical exercise and a proper diet reduce de risk of developing diabetes[247-251].
1++	In people with altered plasma glucose, several types of oral antidiabetics decrease the risk of developing diabetes, even though they are associated with adverse effects which, in the case of rosiglitazone, are serious[247-258].
–	There is no direct evidence on the efficacy of diabetes mellitus screening in the general poopulation[259-262].

Recommendations

A	In people with altered basal glycaemia or impaired glucose tolerance, structured programmes aimed at encouraging physical activity and dietary changes are recommended.
B	In people with altered basal glycaemia or impaired glucose tolerance the use of alpha-glucosidase inhibitors or biguanides is not recommended with the aim of preventing diabetes mellitus.
A	In people with altered basal glycaemia or impaired glucose tolerance the use of thiazolidinediones (especially rosiglitazone) is not recommended with the aim of preventing diabetes mellitus.
D	It is recommended to perform annual diabetes screening by means of fasting morning glycaemia in the population at risk: hypertension, hyperlipemia, obesity, gestational diabetes, obstetric pathology (macrosomy, repeat abortions, malformations), altered basal glycaemia or impaired glucose tolerance at any age; and every three years in patients aged 45 years and older, within a structured vascular prevention programme.

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6.8. Dyslipemia

Key Questions:

- Do people with high cholesterol plasma levels or other dyslipemias have a higher risk of presenting an episode of ischemic stroke or a transient ischemic attack?
- Do treatments aimed at reducing cholesterol plasma levels reduce the risk of having an episode of ischemic stroke or a transient ischemic attack?

According to data pertaining to our setting, more than 37% of the population between the ages of 18 and 74 years, especially people over the age of 45, have total blood cholesterol levels higher than 20mg/dl, [263]. Although high plasma cholesterol levels have a linear association with coronary mortality, there are differences between countries regarding the impact of the same blood lipid values on this variable. These differences are probably a result of other factors such as diet, which would explain why rates in southern Europe are lower than in Anglo-Saxon countries[264].

6.8.1. Association with stroke

Although the relationship between high cholesterol plasma levels and vascular risk is well-established, there is controversy regarding the association with the risk of having an episode of stroke[56, 265]. Recent data of a metaanalysis of individual data (61 prospective studies, 55,000 vascular deaths) show that total cholesterol is associated with mortality due to ischemic cardiopathy at middle and advanced ages. Specifically, it was observed that for every unit (mmol/l) of decreased plasma cholesterol, mortality due to ischemic cardiopathy was reduced by half, by a third and by a sixth in both sexes, in ages ranging between 40 and 49 years, 50 and 69 years and 70 and 89 years, respectively[266]

SR of observational studies 2++

In the case of SAH, results are inconsistent. A SR of observational studies found a negative association between hypercholesterolemia and the risk of presenting a SAH (40% reduction) in case-control studies. This association has not been confirmed in cohort studies[69].

SR of observational studies 2++

In spite of this, RCTs performed with HMG-CoA reductase inhibitors (statins) demonstrate that they reduce coronary and stroke episodes in patients of different ages[266]. This effect has been confirmed in available SRs where the stroke variable is usually secondary or part of a compound variable[267-273].

6.8.2. Effectiveness of statins

Several SRs have assessed the efficacy of statins in primary and secondary prevention of vascular disease. Many of the studies included in these reviews were carried out in patients without a history of coronary disease but with a history of other vascular episodes or high vascular risk.

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A prospective metaanalysis that resulted from an international collaboration (CTT [Cholesterol Treatment Trialists] Collaborators) included 14 RCTs and 90,056 patients (8,186 deaths, 14,348 major vascular events) and mean follow-up of 5 years. In this study, statins reduced the risk of death due to all causes by 12% for each 39 mg/dl (1.0 mmol/l) LDL cholesterol decrease (RR:0.88; 95%CI:0.84 to 0.91) and the risk of any major vascular episode (myocardial infarction, coronary death, revascularisation and stroke) by 21% (RR:0.79; 95%CI: 0.77 to 0.81). In studies that included patients without prior vascular disease, there was a 28% reduction for each 39 mg/dl decrease (RR:0.72; 95%CI:0.66 to 0.80). Benefits were reported regardless of plasma LDL cholesterol values at the beginning of treatment[274]. **SR of RCT 1++**

In the case of a stroke, fatal or not, risk was reduced by 17% (2,957 events; RR: 0.83; 95% CI: 0.78 to 0.88) for every unit (mmol/l) of decreased plasma LDL cholesterol, mainly due to the decreased number of ischemic strokes. Risk reduction was associated lineally with a decreased concentration of plasma cholesterol. The benefit was objectivizable after the first year of treatment. There was no effect on hemorrhagic stroke. In absolute terms, these results suggested that per each decreased 39 mg/dl (1 mmol/l) of LDL cholesterol in plasma, sustained over 5 years, five strokes were avoided (95% CI 1 to 8) per each 1.000 people without a past history of heart disease. Likewise, per each 1,000 people with a previous past history of heart disease, the absolute reduction in the number of previous heart conditions, would be eight (95% CI 4 to 12)[274]. **SR of RCT 1++**

A SR that specifically addressed statins and stroke prevention (42 RCTs, 121,285 patients) reported a significant reduction of the risk of stroke (RR: 0.84; 95% CI: 0.83 to 0.93) [275], as well as a reduction of mortality due to all causes, vascular death and non-hemorrhagic strokes (RR: 0.81; 95% CI:0.69 to 0.94). No significant differences were reported in the risk of hemorrhagic stroke or fatal strokes. **SR of RCT 1++**

A SR (7 RCTs, 42,848 patients) on the specific effect of statins on primary prevention (90% did not present a history of vascular disorders) demonstrated that the risk of major coronary episodes, cerebrovascular episodes and revascularisations (29.2% [95% CI: 16.7 to 39.8], 14.4% [95% CI: 2.8% to 24.6] and 33.8% [95% CI: 19.6 to 45.5], respectively) was reduced. Mean follow-up was 4.3 years. Coronary or total mortality reduction was not significant[276]. **SR of RCT 1++**

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Table 8. Reduction of death and stroke risk[274, 276]

Objective (Number of studies)	Total population	Relative Risk, RR (95% CI)	Absolute risk reduction	NNT
Primary prevention (6)	39,937	Death: 0.93 (95% CI; 0.86 to 1.01) Stroke: 0.86 (95% CI; 0.75 to 0.97)	- 0.37%	- 268*
Secondary prevention (14)	90,056	Death: 0.88 (95% CI; 0.84 to 0.91) Stroke: 0.83 (95% CI; 0.78 to 0.88)	1.2% 0.7%	143** 125**

For each 39mg/dl decrease of LDL cholesterol:
* Over mean 3.2-5.2 year follow-up.
** Over mean 5 year follow-up.

Adapted from: Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al.* CTT [Cholesterol Treatment Trialists] Collaborators. *Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins*. Lancet 2005;366(9493):1267-78 and de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Berman G, Forman S, Shear C, Domanski MJ, Sacks F, Rice MM, Wun CC, Pfeffer MA, Braunwald E. *Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial*. JAMA 2004;292(11):1307-16 and Ramsay SE, Whincup PH, Morris RW, Lennon LT, Wannamethee SG. *Is statin use in older men for primary prevention of cardiovascular disease justified? Evidence from a prospective population-based study*. Circulation 2009;119(1):28-35 and Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. *Standard or aggressive statin therapy in acute coronary syndromes: the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) study*. Am Heart J 2005;149(6):1043-9 and Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG. *Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial*. Lancet 2002;360(9346):1623-30 and Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. *Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial*. Lancet 2003;361(9364):1149-58 and Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, Hovingh GK, Kastelein JJ, Melamed S, Kondapally Seshasai SR, Amarenco P, Deedwania P, Hiatt WR, Laskey R, Pedersen TR, Waters DD, Wun CC, Ray KK. *Efficacy and safety of intensive statin therapy in asymptomatic individuals: a meta-analysis of randomized controlled trials*. Atherosclerosis 2012;220(1):155-63 and Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. *The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials*. Lancet 2012;380(9841):581-90 and Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. *Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force*. JAMA 2016;316(19):2008-2024 and Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. *Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials*. Lancet 2010;376(9753):1670-81 and Ramavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. *Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials*. Arch Intern Med. 2006;166(21):2307-13.

Table 9. Risk of stroke in statin trials[275]

Objective (Number of studies)	Total population	Mortality due to all causes RR (95% CI)	Stroke RR (95% CI)	Non-hemorrhagic strokes RR (95% CI)	Hemorrhagic strokes RR (95% CI)
Primary prevention (41)	121,285	0.88 (0.83 to 0.93)	0.84 (0.79 to 0.91)	0.81 (0.69 to 0.94)	0.94 (0.68 to 1.30)
Secondary prevention (1)	4,731	1.00 (0.82 to 1.21)	0.85 (0.73 to 0.99)	0.78 (0.66 to 0.94)	1.25 (1.06 to 1.47)

Adapted from: O'Regan C, Wu P, Arora P, Perri D, Mills EJ. *Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients*. Am J Med 2008;121(1):24-33.

A later RCT on primary prevention (MEGA study) that included a Japanese population reported that statins reduce the risk of having a first vascular episode (297 events; RR: 0.74 95% CI: 0.59 to 0.94) or a coronary episode (167 events; RR: 0.67 95% CI: 0.49 to 0.91), but did not demonstrate a decreased risk of stroke (102 events; RR: 0.83 95% CI: 0.57 to 1.21;)[277]. **RCT 1+**

Previous SRs have reported similar results[278-280]. A SR (65 RCTs, 200,000 patients) analysed the efficacy of different interventions aimed at decreasing blood lipids in patients with and without a history of coronary disease. The interventions included statins, fibrates, ion exchange resins, polyunsaturated fatty acids and different dietary strategies. The review showed that interventions aimed at reducing lipids were associated with a reduction of fatal episodes of stroke, when compared to placebo or habitual diet (RR: 0.89; 95% CI 0.83 to 0.96), especially in trials that used statins (RR: 0.82; 95% CI 0.76 to 0.90). Other interventions were not associated with a significant reduction of risk. There were no differences between interventions in general and statin treatment in particular in terms of the risk of hemorrhagic stroke. The benefit obtained in the prevention of fatal and **SR of RCT 1++**

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non-fatal strokes was equally significant in studies that used statins for patients with or without coronary disease (17 RCTs; RR:0.75; 95% CI:0.65 to 0.87 and 6 RCTs; RR:0.77; 95% CI 0.62 to 0.95, respectively). All interventions, except for diet treatment, significantly reduced myocardial infarctions (fatal or non-fatal). [278].

The results in a SR (26 RCTs, 90,000 patients) were similar and pointed in the same direction. This review compared different statins to placebo or habitual treatment. Treatment with statins reduced the risk of stroke by 21% (2,890 events; RR:0.79 95% CI: 0.73 to 0.85). No significant results were found for fatal stroke (487 events; RR: 0.91 95% CI: 0.76 to 1.10), or for hemorrhagic stroke (172 events; RR: 0.90 95% CI: 0.65 to 1.22)[279]. Finally, in a SR (14 RCTs, 54,160 men and 17,818 women) statins used as primary or secondary prevention of coronary disease did not show a significant reduction of the risk of stroke, even though only 3 RCTs in men and 2 RCTs in women were assessed. Other evaluated vascular episodes were reduced in a similar manner in men and women[281]. **SR of RCT 1+/1++**

6.8.3. Diabetic patients

Treatment with statins in the diabetic population has been associated with a reduction of vascular risk (including mortality due to all causes, fatal and non-fatal myocardial infarction). A recent SR of 14 RCTs (18,686 diabetics, 71,370 non-diabetics, 3,247 events) reported that for every mmol/l reduction of LDL cholesterol, mortality due to all causes was reduced by 9%, non-vascular by 13% and major vascular episodes by 21% (these effects were similar in the non-diabetic population) [282]. In diabetic patients a reduction of stroke risk (RR: 0.79; 95% CI: 0.67 to 0.93), myocardial infarction or coronary death and coronary revascularisation were also observed. After five years of treatment, the number of people with diabetes who had major vascular episodes dropped by 42 for every 1,000 people treated with statins. A previous SR yielded similar results[283]. **SR of RCT 1++**

A further SR also demonstrated that statins are as effective in diabetics as they are in non-diabetics[284]. Specifically, in primary prevention a reduction of major coronary events was confirmed in both diabetics (RR: 0.80; 95% CI: 0.71 to 0.90) and non-diabetics (RR: 0.77; 95% CI: 0.66 to 0.91). A later RCT in primary prevention (MEGA study) that compared diet treatment to diet plus pravastatin did not report significant differences between the diabetic and non-diabetic populations[277]. **SR of RCT 1++**

6.8.4. Elderly population

Although the relative benefit of statins in the elderly population is probably similar to that in the younger population, absolute benefit is probably greater due to the higher vascular risk presented by this population. However, available information stems primarily from populations with a history of vascular problems and trials usually exclude people over the age **SR of RCT 1+**

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of 80 and recruit very few people over the age of 75[285].

6.8.5. Relative efficacy of statins

No trials that evaluate the outcomes of relevant clinical variables and compare the efficacy of statins[275], nor studies that assess the relative or absolute benefits of treatment with statins aimed at reducing plasma LDL cholesterol values below certain levels, have been identified[291].

SR of RCT 1++

6.8.6. Safety of statins

Overall, statins have been shown to be safe in different SRs, with no evidence of increased risk of cancer or death due to a non-vascular cause[274, 286, 287]. A recent SR (86 RCTs and over 96,000 patients) analysed muscular adverse effects together with discontinuation due to treatment. Statins were associated with a slightly higher risk of discontinuation due to treatment when compared to placebo (OR: 0.88 95% CI: 0.84 to 0.93), and myositis (OR: 2.56 95% CI: 1.12 to 5.85), mainly for pravastatin and cerivastatin[288]. There was no evidence of a significant association with rhabdomyolysis in two SRs, and a very small increase of absolute risk at five years was reported[274, 288]. It is a well-known fact that RCTs often underestimate adverse effects; hence, in a SR that included cohort studies, the risk of rhabdomyolysis was 3.4 times higher than placebo, especially for statins that are metabolised by the CYP3A4 isoenzyme of the P450 cytochrome, and was especially high for cerivastatin. Elevated liver enzymes are more frequent than with placebo, especially at high doses[289]. Cerivastatin was withdrawn from the Spanish and other markets due to the risk of rhabdomyolysis when used in combination with gemfibrozil.

SR of RCT 1++

SR of observational studies 2++

Statin metabolism takes place for the most part in the liver cytochrome P450. Simvastin, lovastin and atorvastin are mainly metabolised by CYP3A4, whereas fluvastatin is metabolised by CYP2D9, such as cytochrome izoenzymes. Pravastatin is scarcely metabolised by the liver. This may lead to interactions with different drugs that share the same metabolic pathways[290].

Statin treatment in patients with higher vascular risk can lead to greater benefits, but in people with low risk, absolute benefit seems to be less and the risk of adverse effects is maintained[291].

6.8.7. Other treatments

At present there is not sufficient evidence to determine that other treatments such as clofibrate, gemfibrozil, nicotinic acid or ion exchange resins are beneficial for the primary prevention of vascular episodes or other clinical variables of interest. Although these treatments have proven to reduce, to a greater or lesser extent, cholesterol values and, in some cases, have shown an effect on combined clinical variables, the effect has not been consistent and no effect has been separately evidenced for each of the components of

CPG 1++

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vascular disease[291].

More recently, ezetimib, associated with a high-dose statin, has not shown to reduce a subrogated variable, such as the carotid artery's intima-media thickness, in patients with familial hypercholesterolemia, despite decreasing blood LDL cholesterol values. [292].

RCT 1++

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Summary of the Evidence

1++	In patients with high vascular risk, treatment with statins reduces the risk of having an ischemic stroke and other vascular episodes in populations with or without a history of vascular disease [274-285] .
1++	The beneficial effects of statins are observed in men and women, in diabetic patients and in the elderly population [274-285].
	There are no trials that compare the relative efficacy of available statins [275].
1++/2++	Statins have been associated with increased liver enzymes and muscular adverse effects, that were severe after combination with fibrates [288, 289].
1++	There is insufficient evidence on vascular benefits, including stroke, of other hypolipemiant drugs [291].

Recommendations

A	It is recommended to treat adults without prior vascular disease and with high vascular risk with statins.
A	Treatment with other drugs such as clofibrate, gemfibrozil, nicotinic acid or ion-exchange resins or their combination is not recommended for primary prevention of vascular disease.
✓	In patients with high blood cholesterol levels (>240 mg/dl de colesterol LDL) treatment with statins should be considered.
✓	Treatment with statins should be jointly assessed with the patient after properly informing him/her of benefits and potential risks, taking associated

	pathologies and concomitant treatments into account. Additionally, at the beginning of treatment with statins, healthier lifestyle changes should be inititiated.
✓	It is important to assess interactions between statins and other concomitant drugs metabolised preferably by cytochrome P450. If the risk of interaction is clinically relevant, treatment with pravastatin should be considered.

6.9. Metabolic syndrome

Key Questions:

- Do people with metabolic syndrome criteria have a higher risk of having an episode of stroke?
- What is the most appropriate therapeutic approach for people who present metabolic syndrome criteria?

The metabolic syndrome is a combination of risk factors in an individual that predispose the individual to develop diabetes mellitus and present increased vascular risk. The main components for its diagnosis are abdominal obesity, atherogenic dyslipemia (increased triglycerides and decreased HDL cholesterol), high blood pressure and increased fasting glycaemia or diabetes mellitus. The central physiopathological mechanism could be phenomena of resistance to insulin.

There are several different definitions of the metabolic syndrome. The most widely endorsed criteria are the 2006 modified ATP-III (Adult Treatment Programme) criteria, and the 2005 IDF (International Diabetes Federation) criteria. The prevalence of the metabolic syndrome in the population presents differing values depending on the definition used for its calculation, although all values point to increased prevalence in the past few decades in men and women. In our setting prevalence is estimated to be approximately 25% in men and 20% in women[293-295].

Observational studies 2+

A recent SR showed that the risk of vascular disease and death was 78% higher in patients with metabolic syndrome (RR: 1.78; 95% CI: 1.58 to 2.00). Risk was higher in women than in men and subjects without prior coronary disease. The main source of variability stemmed from the different criteria used to define the metabolic syndrome[296]. A previous SR reported very similar results in three studies that assessed the risk of stroke: risk was 76% higher in patients with metabolic syndrome [297].

SR of observational studies 2++

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Following the publication of these SRs, several observational studies, most of them prospective cohorts, that assess the risk of stroke, amongst other variables, in patients with metabolic syndrome based on ATP II criteria have been identified. They all consistently point to a significant risk of ischemic stroke and stroke in general[298, 299].

Observational studies 2+/2++

Patients with metabolic syndrome have higher vascular risk and benefit from more aggressive strategies. Although there is no information of clinical trials that evaluate a global approach to the metabolic syndrome and its relation to stroke, the therapeutic approach of its components has proven to be beneficial in the prevention of vascular disease and stroke in numerous clinical trials. Lifestyle modifications aimed at weight loss in patients with obesity and at diabetes prevention have also proven to be effective [294].

SR of RCT 1++

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Summary of the Evidence

2++	The metabolic syndrome, in any of its definitions, is associated with an increased risk of stroke [296-299].
1++	Even though there is no evidence on the global approach to the metabolic syndrome, interventions for each of its components have proven to be beneficial in preventing vascular disease and stroke [294].

Recommendations

B	Individuals with metabolic syndrome should be identified and provided with advice regarding lifestyle modifications with the aim of promoting a healthy diet and physical exercise to reduce body weight.
✓	It is important to provide proper treatment for each component of the metabolic syndrome.
✓	It is important to carry out periodic follow-up of vascular risk.

6.10. Use of oral contraceptives

Key Questions:

- Do women who take oral contraceptives have a higher risk of having an episode of ischemic stroke, hemorrhagic stroke or cerebral venous thrombosis?
- Does risk differ depending on the type of contraceptive or the woman's individual characteristics?

The association of stroke and venous thromboembolic disease due to the use of oral contraceptives is a controversial issue, despite the development of the so-called *first generation* contraceptives that have high doses of estrogen (>50 µg). The development of second and third generation contraceptives with lower estrogen doses has continued to generate debate[300].

A recent SR of observational studies (4 cohort and 16 case-control studies) analysed the risk of stroke associated with oral contraceptives and showed a significant increase of risk (OR: 1.79; 95% CI: 1.62 to 1.97). However, case-control studies showed this relationship. The analysis for the type of stroke indicates that contraceptives seem to increase the risk of ischemic stroke but not hemorrhagic stroke, although results were equally variable[301]. In a similar fashion, a SR of observational studies analysed the risk of vascular episodes (myocardial infarction or stroke) associated with the use of second and third generation contraceptives. Results indicated increased risk for both variables, although it was slightly more pronounced for strokes (OR: 2.12; 95% CI: 1.56 to 2.86) in six case-control studies. Risk was similar for both second and third generation contraceptives[302].

SR of observational studies 2-

Both reviews, despite certain methodological limitations, showed a similar result as a previous SR of 16 observational studies and a significant increase of risk (OR: 2.75; 95% CI: 2.24 to 3.38). Risk was lower with second and third generation contraceptives, even though the risk increase persisted, and was higher in smokers. Attributable risk in absolute terms would be relatively low, given that it would only increase by 4 additional cases per 100,000 people[303].

SR of observational studies 2++

A SR of observational studies (one cohort study and seven case-control studies) did not show an association between the use of contraceptives and stroke[69]. Although the studies that were analysed were very similar to a prior SR[304], this SR also demonstrated a significant increase of risk of SAH in women who take oral contraceptives (RR: 1.42; 95% CI: 1.12 to 1.80), especially those containing higher estrogen doses.

SR of observational studies 2+

There are situations that can increase the risk of vascular episodes in women who take contraceptives, such as certain conditions that present a higher risk

SR of observational studies

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of thrombosis. Certain congenital thrombofilias such factor V Leiden, patients with prothombrin 20210 mutation, methylenenetrahydrofolate reductase enzyme (MTHFR) mutation or hyperhomocysteinemia have been associated with an increased risk of presenting cerebral venous thrombosis in two SRs[305, 306].

Observational studies 2+

Observational studies that appeared after these SRs reported an overall increased risk of ischemic stroke, hemorrhagic stroke and cerebral venous thrombosis[306-309].

Observational studies 2++/2+

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Summary of the Evidence

2++	Oral contraceptives increase the risk of stroke, especially ischemic stroke, even though absolute risk is low. Risk seems to be related with estrogen doses, and is higher for high dose or first generation contraceptives and for smokers[69,302-304].
2++	The risk of cerebral venous thrombosis and thrombosis in other areas is particularly high in women who present congenital thrombofilia and who take oral contraceptives[305,306].

Recommendations

B	In women who smoke, have migraines or a past history of thromboembolic episodes, the use of oral contraceptives is not recommended and other contraceptives measures should be assessed.
A	In women with congenital thrombofilia oral contraceptives are not recommended and other contraceptive measures should be assessed.

6.11. Hormone therapy

Key Questions:

- Does hormone therapy reduce the risk of stroke or other vascular episodes in postmenopausal women?

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Over the past two decades, based on the results of observational studies, hormone therapy (HT) was widely used in postmenopausal patients to prevent vascular disease, osteoporosis and dementia[310]. The first publications of the Women Health Initiative (WHI) study questioned previous results and showed a potential harmful effect of HT on the prevention of vascular episodes[311]. The WHI initiative (161,809 participants) consists in a series of clinical trials aimed at ascertaining the risks and benefits of certain strategies such as a low-fat diet, vitamin D supplements or the use of HT on vascular disease, breast and colorectal cancer and the risk of fractures in postmenopausal women between the ages of 50 and 79 years.

SR of RCT 1++

A SR studied the risk of vascular disease and stroke in postmenopausal women who received HT (estrogens alone or in combination with progestagens) as primary or secondary prevention. In primary prevention, two RCTs (16,830 patients) did not find a protective effect of HT (alone or in combination) for total mortality (RR: 1.00; 95% CI: 0.98 to 1.21) or vascular death (RR: 1.16; 95% CI: 0.70 to 1.92)[312]. On the contrary, HT was associated with increased thromboembolic episodes, including stroke (RR: 1.44; 95% CI: 1.10 to 1.89), pulmonary thromboembolism (RR: 2.15; 95% CI: 1.41 to 3.28) and non-fatal myocardial infarction (RR: 1.32; 95% CI: 1.02 to 1.71). Results in primary and secondary prevention are very similar for estrogens alone (3 RCTs, 1,903 participants) as well as in combination with progestagens (6 RCTs, 22,380 participants). In both cases the risk of stroke increased, even though it is significant only in combined therapy. Taking all these studies into consideration, HT does not provide a protective effect for vascular mortality, non-fatal myocardial infarction or stroke; on the contrary, it increases the risk of venous and pulmonary thrombosis.

RCT 1++

A recent publication of the WHI trial shows the results of 27,347 women between the ages of 50 and 79 years who received HT (alone or in combination) or placebo. The study did not show reduced coronary disease or overall mortality. Furthermore, the risk of stroke was 32% higher in patients who received HT (alone or in combination) (566 events; HR 1.32; 95% CI: 1.12 to 1.56), similar for any age or period of time after menopause. Annual incidence of stroke was 0.38% for HT and 0.29% for placebo, conferring an excess of absolute risk of 9.3 events for every 100,000 people and year. In the case of coronary disease, risk was significantly higher for women 20 or more years after menopause (HR: 1.28; 95% CI: 1.03 to 1.58), mainly for combined HT. HT was not beneficial for combined risk, including variables such as breast cancer, colorectal cancer, endometrial cancer, hip fracture or overall mortality[313].

On the other hand, the WISDOM study, which randomised a total of 5,692 postmenopausal women who received HT (alone or in combination) versus placebo, was prematurely interrupted after the publication of the WHI study results, which included 26% of the total forecasted sample. The objectives were to assess the efficacy of HT for vascular disease, osteoporotic fractures and breast cancer. This study's published results showed a significantly increased risk of having a vascular and venous thromboembolism episode. In the specific case of stroke, differences were not significant (33 events; HR 0.73; 95% CI: 0.37 to 1.46)[314]. **RCT 1+**

In a SR of observational studies HT was not consistently associated with a higher risk of SAH[69]. **SR of RCT 2+**

Summary of the Evidence

1++	HT (with estrogens alone or in combination with progestagens) increases the risk of stroke and other vascular episodes such as venous thromboembolism [312-314].
1++	The risk seems to increase in relation with duration of treatment [313].

Recommendations

A	Hormone therapy (with estrogens alone or in combination with progestagens) to prevent vascular disease is not recommended in postmenopausal women.

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6.12. Thrombofilias

Key Questions:

- Does antithrombotic treatment reduce the risk of having an episode of stroke in patients with congenital or acquired thrombofilias?

6.12.1. Congenital thrombofilia

Thrombofilia is a condition characterised by congenital or acquired defects or anomalies of several components of the haemostatic mechanism that favour the formation, onset or persistence of blood clots[315].

SR of observational studies 2++/2-

A SR of case-control studies related several congenital thrombofilias with the risk of having a first stroke in the child population. Amongst them, only protein C deficit and MTHFR enzyme mutation showed a significant association[316]. A previous SR of case-control and cohort studies, which had a high risk of bias, showed increased risk of ischemic stroke, for certain congenital thrombofilias, in a population that included children and adults [317].

RCT 1+

Observational studies 2+

No studies have reported a clear association between factor V Leiden and ischemic stroke. Several studies have carried out a subgroup analysis for this type of patients, amongst which the Physicians' Health Study[318], the Cardiovascular Health Study[319], the Stroke Prevention in Atrial Fibrillation III[320] or the Copenhagen City Heart Study[321] should be highlighted; all of them provided a limited number of patients to the analysis. The latter included a joint analysis of data from previous studies that did not show association between factor V Leiden and stroke in adults, although in children the association was significant[321]. Studies and SRs have yielded discordant results; higher risk is reported only if it is associated with the use of oral contraceptives, hypertension or diabetes[322].

Case-control studies 2+

The study of cases and controls of the Physicians' Health Study RCT did not show a significant relationship between prothrombin G20210A mutation and stroke[323].

SR of observational studies 2++

Also, a recent SR analysed the association between different congenital thrombofilias and the risk of cerebral venous thrombosis[305]. The association was significant for patients with factor V Leiden (OR: 3.38; 95% CI: 2.27 to 5.05), patients with prothrombin 20210 mutation (OR: 9.27; 95% CI: 5.85 to 14.67) and patients with MTHFR enzyme mutation (OR: 4.07; 95% CI: 2.54 to 6.52). In patients with factor V Leiden, G20210A mutation of the prothrombin gene or hyperhomocysteinemia who take oral contraceptives, the risk of presenting cerebral thrombosis is much higher[306]. No studies

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relating cerebral venous thrombosis and other causes of congenital thrombofilia were located.

6.12.2. Acquired thrombofilia

The antiphospholipid syndrome (APS) is a clinical condition characteristed by recurrent thrombosis and plasma presence of antiphospholipid antibodies (APA) from the cell membrane (the most characteristic being anti-cardiolipin antibodies and lupic anticoagulants). It has a multifactorial origin. Association has been determined between these antibodies and the risk of thrombosis and obstetric morbidity[315].

Several retrospective studies have analysed the relationship between the presence of antibodies against cardiolipin and stroke. Specifically, in a retrospective study of 360 patients with APS the probability of developing stroke or TIA was 4.4%[324]. The presence of antibodies against cardiolipin was associated with a 1.5- to 2.2-fold higher risk of having a stroke[325] in male patients, while a cohort study reported this relationship in women[326]. **Observational studies 2++/2+**

However, there is controversy due to the lack of clinical trials on the role of antithrombotic prophylaxis in patients with APS without prior thrombosis[327, 328]. Therefore, it would be necessary to conduct studies that address issues on primary and secondary prevention in this type of patients[327, 329]. **Expert opinions 4**

Summary of the Evidence

1+/2+	The majority of studies have not demonstrated an association between different hereditary thrombofilias and ischemic stroke. Only factor V Leiden has been associated with ischemic stroke in children [316-323].
2++	Some congenital thrombofilias have been significantly associated with the development of cerebral venous thrombosis; the risk is greater in women who use oral contraceptives [305,306].
2++	The presence of anti-cardiolipin antibodies has been associated with the development of ischemic stroke, especially in women [324-326].
–	There are no studies that assess the efficacy of antithrombotic treatment in patients with congenital or acquired thrombofilias [327, 328].

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Recommendations

✓	In patients with some type of congenital or acquired thrombofilia, after assessing the patient's age, the risk of bleeding and the presence of other vascular risk factors or associated pathologies, the initiation of antithrombotic treatment can be considered.

6.13. Other related factors and conditions

Key Questions:

- Is there any effective treatment for reducing the risk of stroke in patients with high plasma homocysteine or lipoprotein A levels, migraine episodes or falciform cell disease?

6.13.1. Hyperhomocysteinemia

Several observational studies indicate an association between hyperhomocysteinemia and vascular disease[330-332] or stroke[333, 334]. The relationship between homocysteine plasma levels and vascular risk seems to be linear[335]. A cut-off point has not been established, but usually plasma levels greater than 16 mmol/l are considered hyperhomocysteinemia.

Observational studies

2++/2+

Several clinical trials have assessed the efficacy of folic acid or vitamin B supplements in patients who generally presented high vascular risk and elevated plasma homocysteine levels. Although all patients showed reductions, to a greater or lesser extent, of homocysteine plasma levels, levels at the time of inclusion varied and were sometimes under 16 mmol/l.

A SR (12 RCTs, 16,958 patients) did not show reduced risk of vascular diseases, coronary disease, stroke or death in patients who received folic acid supplements versus those who received placebo. The risk of stroke was reduced, but the difference was not significant (RR: 0.86; 95% CI: 0.71 to 1.04)[336].

SR of RCT

1++

A more recent SR (8 RCTs, 16,841 patients) assessed the impact of folic acid supplements, with or without vitamin B complex vitamins, in the prevention of stroke in patients with different vascular risk factors. The objectives were the same, but fewer studies were included; the SR reported an 18% reduced risk of stroke for folic acid supplements (RR: 0.82; 95% CI: 0.68 to 1.00). In trials without prior history of stroke (7 RCTs), there was a 25% reduction (RR: 0.75; 95% CI: 0.62 to 0.90), while for interventions that lasted over 36 months (4 RCTs), reduction was 29% (RR: 0.71; 95% CI: 0.57 to 0.87)[337].

SR of RCT

1++

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6.13.2. Lipoprotein A increase

Lp(a) is a lipoprotein complex with properties that contribute to thrombogenesis, antifibrinolysis and atheromatosis. This lipoprotein complex has a structure similar to low density lipoproteins (LDL), so certain lipoproteins such as type B apolipoprotein join together and transport cholesterol to tissues and arteries. High Lp(a) levels have been associated with an increased risk of coronary disease[338].

SR of observational studies 2+

A SR of observational studies indicated an increased risk of stroke in people with higher Lp(a) values versus people with normal values (1,645 events; RR: 1.22; 95% CI: 1.04 to 1.43). Case-control studies reported that patients with stroke had higher levels of Lp(a). The studies used different techniques to measure Lp(a) levels and, although a 30mg/dl value is proposed as the upper limit of normality, it has not yet been validated[339].

SR of observational studies 2++

Niacin treatment can decrease Lp(a) levels, but there are no randomised clinical trials that show that this treatment reduces the incidence of stroke or other vascular diseases[340].

RCT 1+

6.13.3. Migraine

The relationship between migraine, especially if preceded by aura, and the risk of stroke is complex. Both conditions seem to share certain vascular alterations[341-343].

A SR (11 case-control studies and three cohort studies) evaluated the risk of ischemic stroke in patients with migraine. The review indicated increased risk of ischemic stroke in people who presented migraine crisis (RR: 2.16; 95% CI: 1.89 to 2.48); in the case of migraines preceded by aura the risk was higher (RR: 2.27; 95% CI: 1.61 to 3.19). The joint analysis of three case-control studies evidenced especially significant increased risk in those patients who also took oral contraceptives (RR: 8.72; 95% CI: 5.05 to 15.05)[344]. Later observational studies generally yield similar results[345-348].

SR of observational studies 2++

Observational studies 2+

6.13.4. Falciform cell disease

Falciform cell disease is a public health problem in many African countries[349]. Stroke is one of the most important and devastating complications it entails, given that up to 11% of children with this disease have an episode of stroke[350, 351]. In Europe, the number of patients who have this disease is continuously growing due to emigration, which should result in improved provision of health care services for this population[352]. Most complications deriving from falciform cell disease occur before adulthood. However, due to increased life expectancy, the number of older patients is increasing.

Recurrent stroke is a frequent complication which, without a specific intervention, affects between 4.9% and 6% of patients, especially those who are carriers of SS hemoglobin[353]. Approximately 10% to 23% of patients in chronic transfusion regimen will have another episode of stroke[354].

Observational studies 2+

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The STOP RCT assessed the efficacy and safety of a chronic hematite transfusion programme for primary and secondary prevention of stroke in children. Chronic transfusions, with the aim of maintaining the percentage of hemoglobin S under 30%, reduced the risk of stroke by 92%, versus no intervention. Only one stroke was reported in the group that received transfusion and 11 in the non-intervention group over an approximate 21 months follow-up. Regular transfusions were associated with long-term complications, especially hemosiderosis and alloimmunisation, which should be part of the benefit-risk balance when considering long-term transfusion programmes[355].

RCT 1++

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Summary of the Evidence

2++	High homocysteine and Lp(a) plasma levels have been associated with an increased risk of vascular disease and stroke [339].
1++	Evidence on whether the administration of folic acid supplements in patients with high plasma homocysteine levels and vascular risk factors reduces stroke risk is inconclusive [336,337].
1+	Although niacin can reduce plasma Lp(a) levels, there is no evidence of its benefit on relevant clinical variables [340].
2++	Patients who present migraine episodes, especially if preceded by aura, have an increased risk of stroke [344-348].
2+	Stroke is a frequent complication of falciform cell disease [353, 354].
1+	In children, treatment with periodic transfusions reduces the risk of having a first stroke [355].

Recommendations

B	Folic acid in vitamin B complex supplements should be considered in patients with elevated plasma homocysteine levels and other vascular risk factors.
C	Treatment with niacin should be considered in patients with elevated lipoprotein A levels and other vascular risk factors.

B	Periodic transfusions are recommended to reduce hemoglobin S to values below 30% in patients with high-risk falciform cell anemia, after assessing risks and benefits with the patient.

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6.14. Embolic cardiopathies

Key Questions:

- In patients with atrial fibrillation, what is the risk of having an episode of stroke?
- In patients with atrial fibrillation, does antithrombotic treatment (antiaggregant/anticoagulant) reduce the risk of stroke?
- In patients who have had a myocardial infarction or reduced ejection fraction, does antithrombotic treatment (antiaggregant/anticoagulant) reduce the risk of stroke?
- In patients who have a mechanical or biological valve prosthesis, does anticoagulant treatment alone or in combination with an antiaggregant reduce the risk of stroke?
- In patients with mitral stenosis or mitral valve prolapse, does anticoagulant or antiaggregant treatment reduce the risk of stroke?

Embolic cardiopathies are a group of heterogeneous conditions that present high risk of systemic thrombolembolisms. This guide covers the main aspects of preventing the outcome of these conditions using antithrombotic treatment. This guide does not aim to comprehensively address the detailed management of each of these conditions, since there are CPGs that provide specific recommendations for atrial fibrillation[356-358], ischemic cardiopathy[359, 360] or heart valve diseases[361].

6.14.1. Atrial fibrillation

Atrial fibrillation of a non-valvular origin is a common cardiac arrhythmia in the elderly population and the leading cause of stroke of cardioembolic origin. The risk of stroke in patients with atrial fibrillation increases with age and is up to five times higher when compared to people without this condition [362]. Age, hypertension, cardiac insufficiency, diabetes or prior ischemic stroke or TIA are independent factors that significantly increase the risk of stroke in patients with atrial fibrillation[363-365].

The classification of atrial fibrillation based on its presentation as recurrent episodes (paroxistic atrial fibrillation) or as permanent or persistent atrial fibrillation is important when determining treatment to restitute sinus rhythm or treatment to prevent new episodes of stroke. Large observational studies have not differentiated these types, leading to the conclusion that both present similar risk of embolic complications[366].

Risk of stroke

The risk of stroke in patients with atrial fibrillation is not homogeneous and different factors contribute differently. These factors have been used in several models for the estimation and stratification of stroke risk[367]. Of all available models, the $CHADS_2$ is the most well-known and widely used and has been validated[364]. $CHADS_2$ criteria consider the risk of stroke according

Observational studies 2++

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to the additional presence of several factors and propose certain treatment recommendations (Table 10). On the other hand, the risk of hemorrhage should be assessed based on the presence of factors such as elderly age, hypertension or others, the use of antiaggregants, anticoagulants or non-steroid antiinflammatories, hypertension or multiple treatments[368].

Table 10. $CHADS_2$ risk table[364]

	Level of risk	Treatment recommendations
0	Low	Aspirin 75-325 mg/d
1	Low to moderate	Anticoagulation (2.0 to 3.0 INR) or aspirin 75-325 mg/d
≥2	Moderate, high or very high	Anticoagulation (2.0 to 3.0 INR)

- **1 point: elderly age (>75 years), hypertension, cardiac insufficiency, diabetes.**
- **2 points: prior stroke.**

Adapted from: Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. *Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation*. JAMA. 2001; 285:2864-70.

Bleeding risk stratification systems

In a recent analysis, the incidence of Severe bleeding in people over the age of 80 years was 13.1 for every 100 people and year and 4.7 in people under the age of 80 years[369]. However, the role of models for bleeding risk estimation in patients with atrial fibrillation is yet uncertain[370].

Observational studies 2++

There are several models to estimate the risk of Severe bleeding in patients who receive anticoagulant treatment[371-373]. The ORBI index has been validated in an elderly population with a history of atrial fibrillation[371]. The most recent proposal derived from a cohort of over 26,000 patients, many of them over the age of 80, that includes eight variables for risk stratification (age >70 years, gender, history of bleeding or recent bleeding, drug or alcohol abuse, diabetes, anemia and antiaggregant treatment). However, it excludes international normalised ratio (INR) values to calculate risk. This model presents bleeding risks at 90 days that range from 0.9% to 5.4% amongst low- and high-risk groups, respectively. [373].

Despite the existence of reference documents for the clinical management of patients with atrial fibrillation, anticoagulants continue to be underused. In some cases this is a result of the doctor's lack of knowledge concerning the evidence or the difficulty to apply risk stratification indexes and the inappropriate information provided to the patient on the benefits and risks of treatment[374].

Expert opinions 4

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In any case, it is essential to establish an adequate balance between the benefits of treatment for reducing the risk of recurrent episodes of stroke or TIA and the risks of a Severe hemorrhagic episode for each patient using available models[374].

Expert opinions 4

Antithrombotic treatment

Two SRs assessed the efficacy and safety of oral antiaggregants and anticoagulants in patients with chronic atrial fibrillation of a non-valvular origin to prevent a first episode of stroke[375, 376]. More recently another SR compared these two strategies in the same group of patients[377].

SR of RCT 1++

A SR (3 RCTs, 1,965 patients) did not indicate differences between antiaggregant treatment (all of them using aspirin) and placebo in the reduction of stroke, ischemic strokes, vascular mortality or overall mortality. Ischemic strokes were significantly reduced when a trial in which warfarin at low doses was applied to patients treated with antiaggregants was included (OR: 0.72; 95% CI: 0.52 to 0.99). Antiaggregants were not associated with increased major hemorrhage or intracerebral hemorrhage, even though the total number of events that were analysed was very limited[375].

SR of RCT 1++

The same author demonstrated in a SR (5 RCTs, 2,313 patients) that anticoagulants adjusted to an INR of 2.0 to 3.0 were associated with a significant reduction of stroke (OR: 0.39; 95% CI: 0.26 to 0.59), ischemic strokes (OR: 0.34; 95% CI: 0.23 to 0.52), incapacitating strokes (OR: 0.47; 95% CI: 0.28 to 0.80) and overall mortality (OR: 0.69; 95% CI: 0.50 to 0.94) when compared to placebo. Major bleeding or intracerebral hemorrhages did not differ in both groups, although the number of events was limited [376]. In a more recent SR (8 RCTs, 9,598 patients) oral anticoagulants were associated with a significant reduction of stroke (OR: 0.68; 95% CI: 0.54 to 0.85), ischemic strokes (OR: 0.53; 95% CI: 0.41 to 0.68) and systemic embolisms (OR: 0.48; 95% CI: 0.25 to 0.90) versus antiaggregant treatment. The risk of intracerebral hemorrhages was doubled with the use of anticoagulants when compared to treatment with antiaggregants (OR: 1.98; 95% CI: 1.20 to 3.28) [377].

SR of RCT 1++

Outcomes were similar in a SR (29 RCTs, 28,044 patients) in primary and secondary prevention, where oral anticoagulants proved to be superior to placebo and to antiaggregants in the prevention of stroke in patients with atrial fibrillation. Adjusted anticoagulant doses reduced the risk of stroke when compared to placebo (64% relative effect and 2.7% absolute effect, for a total of 186 events) and to antiaggregant treatment (37% relative effect and 0.9% absolute effect for a total of 462 events). Antiaggregants in general were associated with a modest but significant reduction of stroke risk. Patients treated with adjusted anticoagulant doses presented twice as many severe intracranial and extracranial hemorrhages, even though absolute risk increase was 0.2%[378]. Other prior SRs yielded similar results[379-381].

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A study included in the previous review, which specifically compared anticoagulant treatment with the combination of clopidogrel and aspirin, was interrupted earlier than expected as a result of the superiority demonstrated by anticoagulant treatment (165 events). The combination of aspirin and clopidogrel showed a greater risk of suffering a combined variable (stroke, non-cerebral systemic embolism, myocardial infarction or vascular death) (399 events; RR: 1.44; 95% CI: 1.18-1.76)[382]. Additionally, the NASPEAF trial assessed the efficacy of combining anticoagulant treatment and triflusal (600 mg/d) in 1,209 patients with high- or moderate-risk atrial fibrillation (fibrillation of a non-valvular origin or without prior embolism). Combined treatment reduced the risk of vascular events (vascular death, TIA, non-fatal stroke or systemic embolism) by 67% in the group of moderate risk (HR 0.33; 95% CI: 0.12 to 0.91) when compared to anticoagulant treatment alone. Combined treatment managed to reduce the intensity of anticoagulation[383]. **RCT 1+**

A recent multicentre study compared warfarin (INR: 2.0 to 3.0) to aspirin (75 mg/d) for the primary prevention of embolic episodes in elderly patients in primary care (> 75 years). Anticoagulant treatment reduced the risk of the combined variable of embolic episodes (stroke, intracerebral hemorrhage or arterial embolism) by 52% (72 events; RR: 0.48; 95% CI: 0.28 to 0.80) versus aspirin for the absolute risk reduction (ARR), which was 2%. Benefit was even greater for ischemic strokes (RR: 0.30; 95% CI: 0.13 to 0.63). Furthermore, the risk of intracerebral hemorrhage, any type of hemorrhaging or mortality due to any cause, was similar in both interventions. This study on elderly population confirms that anticoagulation is superior to antiaggregation[384]. **RCT 1+**

Lastly, other options such as ximelagatran were withdrawn from the market in 2006 due to hepatoxicity and more recently an open RCT that assessed treatment with penta-saccharides (idraparinux) versus anticoagulation in patients with atrial fibrillation had to be prematurely interrupted due to an excess of intracranial hemorrhaging when compared to isolated anticoagulation[385]. **RCT 1+**

Patient perceptions

The prescription of an anticoagulant treatment should consider the values and preferences of patients. In a European survey administered to patients with atrial fibrillation who received anticoagulant treatment it was reported that only 7% of patients knew about the objective of treatment and 38% did not know than an INR below or above the recommended range was associated to health risks. The study throws light on the poor knowledge patients have on the risks and benefits of anticoagulant treatment[386]. **Case series 3**

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Additionally, in this type of patient, preferences vary considerably and often differ from those of physicians and from CPG recommendations[387]. These differences could be a result of patients' greater tolerance to suffering severe bleeding and a lesser tolerance to an increased risk of stroke[388].

Expert opinions 4

Home self-management of anticoagulant treatment

Several SRs show that patient self-management is as safe as routine follow-up in primary care or in the hospital and that it significantly reduces the risk of thromboembolic episodes and death[389, 393]. Self-management is limited to patients who are able to carry it out and are provided with specific training. This therapeutic option is currently not funded by our health care system. Cost-effectiveness studies conducted in other countries yield inconsistent results, even though they indicate that this therapeutic option is cost-effective in the mid-long term[393-395].

SR of RCT 1++

Summary of the Evidence

2++	Atrial fibrillation is a stroke risk factor especially in patients over the age of 75 years, HT, cardiac insufficiency (or ejection fraction under 30%), diabetes or a history of ischemic stroke or transient ischemic attack[364].
2++	In patients with atrial fibrillation without additional risk factors (age, hypertension, cardiac insufficiency or prior stroke) the probability of presenting a stroke is approximately 2% annually [364].
1++	In patients with non-valvular atrial fibrillation, anticoagulant treatment (2 to 3 INR) is more effective than antiaggregant treatment for the prevention of stroke and has a higher frequency of severe hemorrhagic episodes[378-381].
1+	Combined antiaggregant and anticoagulant treatment has not demonstrated greater efficacy and presents greater hemorrhagic risk[382, 383].
1++	Home self-management of anticoagulant treatment significantly reduces the risk of thromboembolic episodes and the risk of death[389-393].

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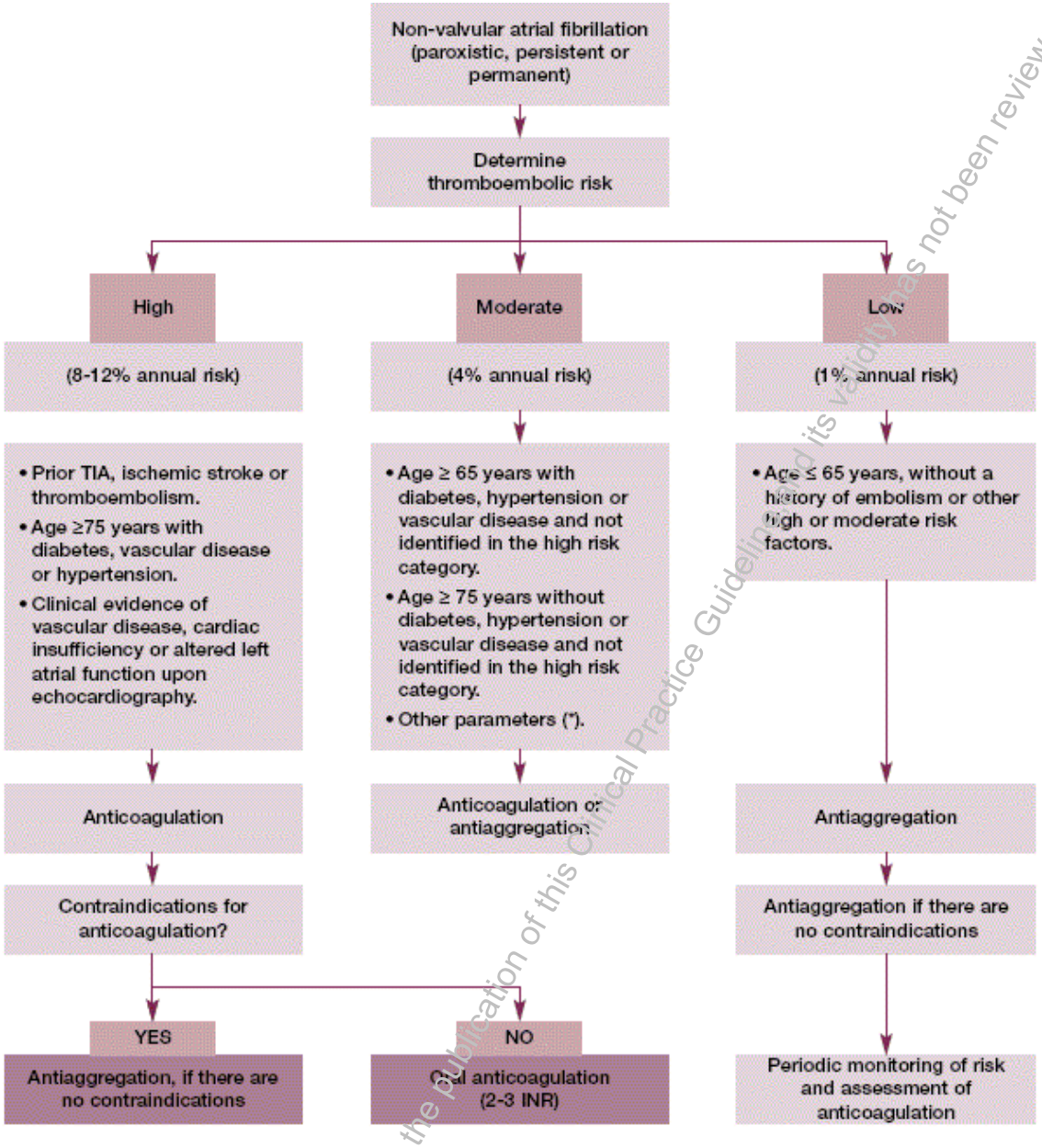
Recommendations

✓	All patients with atrial fibrillation should be individually assessed to establish a benefit-risk balance of antithrombotic treatment. It is advisable to assess the indication to administer anticoagulants at regular intervals.
A	In patients with paroxistic, persistent or permanent atrial fibrillation, who present HIGH thromboembolic risk, treatment with oral anticoagulants with an INR target range of 2 to 3 over an indefinite period of time is recommended for primary prevention of stroke of cardioembolic origin.
A	In patients with paroxistic, persistent or permanent atrial fibrillation, who present MODERATE thromboembolic risk, treatments with anticoagulants or antiaggregants are reasonable therapeutic options for the primary prevention of stroke of cardioembolic origin.
A	In patients with paroxistic, persistent or permanent atrial fibrillation, who present LOW thromboembolic risk or with formal contraindications to oral anticoagulants, antiaggregant treatment with aspirin (100-300 mg/d) is recommended for primary prevention of stroke of cardioembolic origin.
B	The use of antiaggregants other than aspirin is recommended for patients with aspirin intolerance or related undesirable effects.
✓	In certain patients with MODERATE thromboembolic risk other factors, such as atrial size, presence of atrial blood clots or structural cardiac alterations, should be assessed when considering the benefits and risks of antithrombotic treatment.

See Figure 4 for the definition of high, moderate and low risk populations.

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Figure 4. Algorithm of antithrombotic treatment management in patients with non-valvular atrial fibrillation[367]



Adapted from: Lip GY, Boos C. *Antithrombotic therapy for atrial fibrillation*. Heart 2006;92:155-61.
* Certain patients classified as presenting moderate risk, with any of the following parameters obtained by echocardiography, such as increased size of the left atrium, the presence of dense contrast medium in the atrium or the presence of an altered cardiac structure with no ventricular dysfunction, should be considered for treatment with oral anticoagulants.

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6.14.2 Myocardial infarction

The main diagnostic entities of acute coronary syndrome (unstable angina and acute myocardial infarction) are defined by plasma concentration of myocardial necrosis markers[396]. At present the initial treatment of acute coronary syndrome entails aggressive antiaggregation, anticoagulation and percutaneous angioplasty strategies with the aim of minimising the area of necrosis and reducing the incidence of subsequent ischemic episodes. Assessment of the efficacy of antiaggregant and anticoagulant treatments in the

prevention of vascular episodes in acute coronary syndrome was carried out before the generalised application of these treatments, so the resulting net benefit in the current clinical context is unknown.

Stroke is a complication in 0.75% to 1.2% cases of acute myocardial infarctions[397-399]. Several predisposing factors contribute to having an embolic stroke after a myocardial infarction, such as age, hypertension, atrial fibrillation, prior stroke or reduced ejection fraction[397, 400, 401]. Myocardial infarctions in any localisation can cause the formation of thrombi. Specifically, extensive anterior infarctions with dyskinesia are frequently associated with the formation of intramural thrombus[402]. Detachment of all or part of the thrombus of the left heart cavities can cause embolic stroke[397].

Observational studies 2+

Case series 3

Antiaggregant treatment

A SR showed that in patients with recent myocardial infarction (15 RCTs, 19,302 patients) antiaggregant treatment during the first month reduced vascular episodes (including stroke) by 30% versus placebo (2,377 events). For stroke in particular, relative reduction was 38% and absolute reduction was 3% (118 events). Estimated annual risk of extracranial hemorrhaging due to antiaggregant treatment was one case for every 1,000 treated patients. In most trials the antiaggregant was aspirin alone or in combination with dipiridamol. Antiaggregants also demonstrated significant reduction of vascular episodes in patients with unstable angina (56%, 535 events) and after angioplasty (53%, 132 events[403].

SR of RCT 1++

Long-term treatment with aspirin (325 mg/d) was as effective as clopidogrel (75 mg/d) at reducing vascular episodes (myocardial infarction, stroke or vascular death) after a myocardial infarction or stroke in patients with a history of atherothrombosis. Clopidogrel was superior to aspirin only in patients with a history of peripheral arterial disease[404].

RCT 1++

Long-term results of the CURE trial showed that the combination of aspirin (75-325 mg) and clopidogrel (75 mg) is more effective than aspirin alone during the first 30 days of acute coronary syndrome without increased ST segment, according to a variable composed of vascular death, non-fatal myocardial infarction and stroke (RR: 0.79; 95% CI: 0.70 to 0.95). The benefit is similar in the period spanning from 30 days to 12 months after the acute episode. Combined treatment was associated to a significant increase of major hemorrhagic episodes during the first 30 days (1.54% for aspirin and 2.01% for combined treatment) and up to 12 months (1.18% versus 1.75% respectively) [405]. If the patient undergoes a percutaneous intervention with the implantation of a pharmacoactive stent, the stent produces reepitelisation delay, which is why increasing the duration of double antiaggregation is recommended[406].

RCT 1++

Combined treatment with clopidogrel and aspirin after an acute coronary syndrome and increased ST segment reduced mortality and vascular

RCT 1+

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morbidity in the short term (1 month) in two RCTs[407, 408]. In the first study (COMMIT-CCS-2) 45,852 patients were assessed. Half of them received fibrinolysis and significant reduction of the combined variable consisting of of death, reinfarction or stroke (10.1% for aspirin and 9.2% for combined treatment) was reported. The benefit was similar for both groups, for those who received fibrinolysis and those who did not[407]. In the second study (CLARITY-TIMI) in which 3,491 patients received fibrinolysis, combined treatment was more effective than aspirin alone for a combined variable (myocardial infarction or death) prior to an angiography (between 2 to 8 days) and in patients who received a subsequent percutaneous intervention. There were no significant differences between treatments in terms of the risk of hemorrhaging[408].

Anticoagulant treatment

A SR (16 RCTs, 10,056 patients with coronary disease) showed a reduction of overall mortality (1,541 events; OR: 0.78; 95% CI: 0.69 to 0.87), reinfarctions (1,313 events; OR: 0.58; 95% CI: 0.52 to 0.66) and strokes (OR: 0.52; 95% CI: 0.40 to 0.67) in patients treated with anticoagulants (2.8 to 4.8 INR) versus control treatment. Treatment also led to a significant increase of major bleedings (4.6% versus 0.7%) (214 events; OR: 6.0; 95% CI: 4.4 to 8.2). Less intensive anticoagulant treatment (2 to 3 INR) demonstrated more modest benefits; the reduction of new cases of myocardial infarction was significant. Major bleeding was also more frequent in the group that received anticoagulation (3.5% versus 0%). In comparison to an antiaggregant (aspirin), anticoagulant treatment showed similar efficacy for the reduction of mortality, myocardial infarctions or stroke, but was associated with a higher risk of major bleeding (3.7% versus 1%). Similarly, anticoagulants (INR >2) combined with aspirin proved to be superior to aspirin alone in the reduction of mortality, myocardial infarctions and strokes (39 events; OR: 0.44; 95% CI: 0.23 to 0.83), even though the combination was also associated with increased major bleeding (3.3% versus 1.7%)[409]. **SR of RCT 1++**

In two later trials in patients with acute coronary syndrome, anticoagulants (2.8 to 4.2 INR) were superior to aspirin (80-160 mg) in the reduction of stroke, while the combination of aspirin and an anticoagulant (2 to 2.5 INR) proved to be more effective than aspirin alone, but caused an increased number of hemorrhages[410, 411]. **RCT 1+**

A recent SR that included 10 RCTs and 5,938 patients with acute coronary syndrome showed that anticoagulant treatment combined with aspirin reduced myocardial infarctions (1.9% absolute effect and 44% relative effect) in comparison to aspirin alone, even though no benefits in terms of overall mortality were obtained. Major bleeding was more frequent in the combined treatment[412]. **SR of RCT 1++**

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Other treatments

There are other treatments for acute coronary syndrome, such as betablockers, ACEIs, ARA-IIs, aldosterone antagonists, statins or fibrates. They have all demonstrated their efficacy at reducing the different components of vascular morbimortality after an acute coronary episode. Only statins and fibrates have demonstrated a reduced incidence of stroke after an acute coronary episode[413]. The effect of hypolipemiant treatment is extensively covered in section 6.8 of this guideline. Other treatments are considered part of the treatment of acute coronary syndrome and are thus beyond this guide's scope.

Summary of the Evidence

1++	Antiaggregant treatment *versus* placebo reduces the incidence of stroke after myocardial infarction [403].
1+	Treatment over 6 or 12 months with combined clopidogrel (75 mg/d) and aspirin (75-325 mg/d) has been proven to be more effective than aspirin alone at reducing vascular episodes after myocardial infarction without increased ST segment [405].
1+	Short-term treatment with clopidogrel and aspirin has proven to be more effective than aspirin alone at reducing the risk of a vascular episode after myocardial infarction with increased ST segment [407, 408].
1++	Anticoagulant treatment has proven to be more effective than aspirin at reducing the incidence of stroke after myocardial infarction. Combined anticoagulant and aspirin treatment was superior to aspirin alone, even though it was associated to a higher risk of bleeding [409-412].

Recommendations

✓	In patients who have suffered a myocardial infarction it is important to manage vascular risk factors to reduce the risk of new episodes.
A	In patients who have suffered a myocardial infarction without increased ST segment, especially if they have received percutaneous intervention with implantation of a pharmacoactive stent, double antiaggregation with aspirin (at the minimal effective dose) and clopidogrel (75 mg/d) over twelve months is recommended.

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B	In patients who have suffered a myocardial infarction with increase of the ST segment, regardless of whether they receive acute reperfusion with fibrinolysis or percutaneous intervention, double antiaggregation with aspirin (at the minimal effective dose) and clopidogrel (75 mg/d) over at least four weeks is recommended.
C	In patients who have suffered myocardial infarction with increase of the ST segment, it is reasonable to propose double antiaggregation treatment over a period of one year.
B	In patients who have suffered myocardial infarction with increase of the ST segment associated with dyskinesia or ventricular aneurysm treatment with oral anticoagulants should be considered.

6.14.3. Dilated cardiomyopathy and other situations with reduced ejection fraction

Patients with cardiac insufficiency have an increased risk of thromboembolic episodes due to blood stasis in the ventricles. This risk is relatively low (1% to 3% per year) even in patients with a very reduced ejection fraction and echocardiographic evidence of intracameral thrombi[414, 415].

Cohort studies 1++/2+

An RCT (297 patients) openly assessed treatment with aspirin (300 mg/d), warfarin (with a 2.5 INR goal) or no treatment, with no differences in a main combined variable comprised of death, non-fatal myocardial infarction and non-fatal stroke. There were no differences between warfarin and aspirin (52 events; HR 1.21; 95% CI: 0.70 to 2.09). There were only two episodes of stroke in the non-treatment group, two in the aspirin group and none in the anticoagulant treatment group. Severe hemorrhagic episodes were more frequent in the treatment with anticoagulants (four) when compared to aspirin (one)[416, 417].

RCT 1+

There are three post-hoc retrospective analyses of cohort studies that assessed the efficacy of antithrombotic treatment in patients with cardiac insufficiency[401, 414, 418]. In the V-HeFT-I study the incidence of thromboembolism in patients with and without antiaggregant treatment (aspirin, dipiridamol or both) was 0.5% and 2.7%, respectively, with no significant differences reported[414]. In the V-HeFT II study there were no differences regarding thrombotic episodes in patients treated or not treated with antiaggregants (1.6% versus 2.1% respectively)[418]. Although no direct comparisons were made between different antithrombotic treatments, the incidence of thromboembolic episodes for anticoagulants in both studies was

Cohort studies 2+

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2.1% and 4.9% per year in the V-HeFT I and II studies respectively[414].

In a later analysis of the SAVE study for patients with ventricular dysfunction due to prior myocardial infarction, antiaggregant treatment reduced the risk of stroke by 56% (RR: 0.44; 95% CI: 0.29 to 0.65) when compared to no treatment. For anticoagulants there was an 81% reduction (RR: 0.19; 95% CI: 0.13 to 0.27), versus no treatment[401]. **Observational studies 2+**

The WATCH RCT, which aimed to assess the best anticoagulant or antiaggregant treatment in patients with cardiac insufficiency, was ended prematurely due to a low recruitment rate[419].

Summary of the Evidence

2++	Patients with left ventricle ejection fraction under 30% present a higher risk of stroke [414, 415].
1+	Both antiaggregants and anticoagulants have been proven to reduce the risk of stroke in patients with cardiac insufficiency [414, 416-418].
1+	There is no evidence on the superiority of anticoagulants versus antiaggregants in the primary prevention of stroke in patients with cardiac insufficiency [401].

Recommendations

B	Antiaggregant or anticoagulant treatment should be considered in patients with ejection fraction below 30%. The selection of treatment should be individualised based on the presence of other vascular risk factors.

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6.14.4. Valve prostheses

Patients who have undergone surgery for the implantation of a prosthetic heart valve represent an important part of the total number of patients with valvular disease. The selection of the prosthetic valve (mainly mechanical or biological) should be individualised, acknowledging the complications of surgery and the subsequent management of these patients. Factors that should be assessed include:

- Life expectancy
- Presence of mechanical prostheses in other heart valves
- Absolute contraindications for anticoagulation
- Structural deterioration of the prosthesis
- Women in fertile age
- Quality of life.

Most complications derived from the implantation of a prosthetic heart valve derive from the risk of thromboembolism and the risk of bleeding associated with anticoagulant treatment. Therefore, anticoagulant treatment should be prescribed to patients with a mechanical prosthetic heart valve, while those with a biological heart valve the prescription of anticoagulant treatment will depend on each patient's risk factors.

Anticoagulant treatment

The limited number of patients included in the studies, short follow-up and the limitations for its application limit the generalisation of the limited available evidence. Management of anticoagulant treatment is based primarily on observational studies, individual case series, expert opinions and the weighing of the risk of thrombosis for each type of valve and the risk of severe bleeding derived from the intensity of anticoagulant treatment.

All patients with a mechanical prosthetic heart valve require oral anticoagulant treatment for life. Depending on the type of mechanical valve and the patient´s risk factors, the working group for the management of vascular disease of the European Society of Cardiology has recently proposed the mean INR values that are acceptable in each case (Table 11)[361].

Table 11. Mean INR values for mechanical prosthetic heart valves

Risk of thrombogenicity	Patient risk factors	
	No risk factors	One or more risk factors
Low	2.5	3.0
Moderate	3.0	3.5
High	3.5	4.0

The risk of thrombogenicity derived from prostheses is classified as low, moderate or high, in the following manner:

- **Low:** Carbometrics (in the aortic position), Medtronic Hall, St Jude Medical (without Silzone).
- **Moderate:** Björk-Shiley, other types of double disk prostheses, new types of prostheses until more information is available.
- **High:** Lillehei-Kaster, Omniscience, Starr-Edwards.

Risk factors derived from the patients include: mitral, tricuspid or pulmonary valve replacement, prior thromboembolic

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episode, atrial fibrillation, diameter of the left atrium >50 mm, spontaneous echocontrast in the left atrium, MS of any degree, left ventricle ejection fraction <35% and hypercoagulability state.

*Adapted from: Vahanian A, *Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. ESC Committee for Practice guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007;28(2):230-68.*.[361]

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The risk of thromboembolic episodes is especially high in the month following the valve replacement procedure[420]. Although there is no consensus on when anticoagulant treatment should begin, non-fractionated heparin and anticoagulant treatments are usually initiated within the first 24-48 hours of the valve replacement procedure and heparin is interrupted once INR target values have been achieved. The first three months after replacement of a biological valve prosthesis entail an increased risk of thromboembolic episodes, which is why anticoagulant treatment is recommended during this time.

Observational studies

Expert opinion 2+/4

Several observational studies have assessed the results of anticoagulant or antiaggregant treatment after the implantation of a biological valve, yielding inconsistent results. Treatment with anticoagulants was determined to be beneficial, mainly for aortic prostheses [421]. Other studies have not reported differences between anticoagulants and antiaggregants[422-424]. Biological prostheses, after the first three months since the intervention, present a low risk of thromboembolism and anticoagulant treatment does not provide an additional benefit[423, 425].

Observational studies 2+

Antiaggregant treatment

Treatment with antiaggregants is beneficial in patients with vascular disease[403] and, in combination with anticoagulant treatment, in patients with valve prostheses and vascular disease[426]. The risk of Severe hemorrhagic episodes is higher in the combination of anticoagulants and antiaggregants[403, 426]. However, an RCT showed that triflusal (600 mg) had similar efficacy as anticoagulant treatment in the prevention of thromboembolic episodes after the implantation of an aortic biological valvular prosthesis[427]. The possible benefit in patients with valve prostheses without known vascular disease is yet unknown.

SR of RCT 1++

RCT 1+

Patients with a history of prior thromboembolism, atrial fibrillation, hypercoagulability states or left ventricle dysfunction present a special risk of systemic thromboembolism[428]. These factors should be acknowledged when considering combined anticoagulant and antiaggregant treatment.

Cohort studies 2+

In a recent study in patients without thromboembolism risk factors, no differences were found between patients treated with antiaggregants and patients who did not receive treatment in new episodes of ischemic stroke or other embolic episodes over a one year follow-up, after the implantation of an aortic biological valve[429].

Non-randomised CT 2+

Summary of the Evidence

2+/4	Mechanical heart valve prostheses present a high risk of thrombosis [420].
2+/4	Biological valve prostheses present a lower risk of thrombosis, except in the first three months after their implantation, when there is moderate risk of thrombosis [423].

Recommendations

A	Indefinite anticoagulant treatment with an INR interval that depends on the type of valve and patient factors is recommended in patients who have a mechanical valvular prosthesis.
B	In patients who have a mechanical valvular prosthesis with high risk of thromboembolism (atrial fibrillation, hypercoagulability states, or dysfunction of the left ventricle), it is recommended to add antiaggregants (aspirin 100 mg/d) to anticoagulant treatment.
A	During the first three months after the implantation of a biological prosthesis, anticoagulant treatment is recommended with an INR target range of 2 to 3.
B	Antiaggregant treatment (100-300 mg/d of aspirin or 600 mg/d of triflusal) is recommended in patients who have a biological valve and who have no risk factors for thromboembolism.
A	In patients who have a biological valve and present thromboembolism risk factors (atrial fibrillation, hypercoagulability states, or dysfunction of the left ventricle) treatment with anticoagulants is recommended with the objective of reaching an INR target range of 2 to 3 in aortic valves and an INR target range of 2.5 to 3.5 in mitral valves.

6.14.5. Other valvulopathies

Some valvulopathies such as MS or mitral valve prolapse (MVP) lead to an increased risk of embolic strokes due to the frequent coexistence of atrial fibrillation. This section briefly describes available evidence on the prevention of thromboembolic episodes and stroke, but does not address the benefits derived from pharmacological treatments or

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surgical procedures in terms of survival or improvement of other pathologies frequently associated with heart valve disease, despite the fact that the treatment of these conditions indirectly reduces the risk of having an embolic episode.

Mitral stenosis

MS has a primarily inflammatory nature due to a rheumatic condition, but also due to calcification of the mitral ring in elderly people, although it may also be congenital.

Systemic embolisms occur with relative frequency (10%-20%) in individuals with MS. The greatest embolism risk corresponds to patients who have developed atrial fibrillation[430, 431]. There are no randomised studies that assess the efficacy of anticoagulant treatment in the prevention of embolic episodes specifically in patients with MS. Observational studies have reported reduced incidence of embolic episodes in patients who follow anticoagulant treatment versus those who were not treated with anticoagulants, even though primary and secondary prevention strategies were combined in patients with previous embolisms[432, 433].

Observational studies 3

Case series 2+

Observational studies have determined that elderly age, a smaller mitral valve area or increased left atrium size increase the risk of embolic phenomena[434, 435]. More recently, results of a cohort analysis of the SPAF II trial more consistently associated left atrium size and left ventricle dysfunction with embolic phenomena[436]. More precise imaging techniques, especially echocardiography, could identify those patients with a higher risk of thromboembolism and maximise the benefit of antithrombotic treatment[437, 438]. In standard clinical practice, the decision to initiate treatment with anticoagulants to prevent thromboembolic episodes, including stroke, in a patient with MS in sinus rhythm is based on the overall assessment of other factors associated with the convenience of initiating anticoagulant treatment.

Observational studies 2++/2+

Patients with MS who have developed atrial fibrillation are considered at high risk of presenting embolic episodes. Anticoagulant treatment has proven to be beneficial in patients with high risk atrial fibrillation, even though trials have excluded valvular pathology[439].

Cohort studies 2++

Mitral valve prolapse

MVP is a frequent cardiopathy that, depending on the diagnostic criteria applied, is observed in 2.5% of the population[440]. MVP is often a result of a congenital defect of the mesenchymal type, which explains why patients with the Marfan syndrome and other connectivopathies can present this valvulopathy[441]. There are familial MVP forms that are hereditarily transmitted, of gradual evolution and often benign. Sudden death is an uncommon outcome[443].

Case series 3

The presence of mitral regurgitation (moderate or severe), increased mitral valve thickness (>5 mm) or left atrium size greater than 50 mm, measured by echocardiography, were associated with increased vascular mortality and complications related with MVP, such as stroke[444, 445]. Based on these data,

Observational studies 2+

More data have been published since the publication of this Clinical Practice Guideline and its validity has not been reviewed

antiaggregant treatment has been considered in patients who present high risk echocardiographic criteria[446].

Patients with MVP often develop atrial fibrillation. The management of these patients should not differ from the recommendations provided on primary prevention of patients with atrial fibrillation[444].

Expert opinions 4

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Summary of the Evidence

3	MS due to rheumatic fever is a frequent cause of systemic embolism and stroke [430-438].
2++	Patients with MS and left atrium size greater than 50 mm, older patients, with reduced mitral area, presence of thrombus in the left atrium and those who develop atrial fibrillation, have a higher risk of presenting thrombotic phenomena [434-436].
3	Mitral valve prolapse is a relatively common valvular cardiopathy with a very variable clinical spectrum [440-443].
2+	Patients with mitral valve prolapse with mitral regurgitation (moderate or severe) or increased thickness of the mitral valve (>5 mm) measured by echocardiography, present greater vascular morbimortality [445].

Recommendations

✓	Patients with mitral stenosis or mitral valve prolapse should undergo periodic cardiologic monitoring. Echocardiography is useful to detect patients with a high risk of complications.
A	Anticoagulant treatment with an INR target range of 2 to 3 is recommended in patients with mitral stenosis with a blood clot in the left atrium and in those who develop atrial fibrillation.
C	Treatment with antiaggregants (100-300 mg/d of aspirin) is recommended in patients presenting mitral valve prolapse only if they present high risk echocardiographic criteria.

6.15. Asymptomatic carotid artery stenosis

Key Questions:

- Is surgical treatment effective at reducing the risk of having a first episode of stroke in patients with carotid artery stenosis?
- What degree of carotid stenosis benefits most from these interventions?
- What additional benefits does platelet antiaggregant treatment provide after the intervention?
- Is it reasonable to carry out carotid artery stenosis screening in the general adult population?

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Cohort studies 2+

The main pathology of the supraaortic trunks is atherosclerotic stenosis or occlusion of the carotid artery. This lesion affects mainly the carotid stem at the bifurcation, involving both the external carotid artery and the internal carotid artery. At long-term, 16.6% of patients can suffer from an ipsilateral stroke[447]. The neurological symptoms are mainly attributable to a brain embolic mechanism (emboligenous theory) with detachment of a portion of the atheroma plaque and acute interruption of focal cerebral flow. Symptoms can also be a result of decreased blood flow to the brain due to occlusion or poor compensation caused by collateral circulation (hemodynamic theory) [448].

Observational studies 2+

It is estimated that the prevalence of carotid artery stenosis increases with age and affects 0.5% of people under the age of 50 and up to 10% of people over the age of 80 without prior symptoms[449]. The risk of stroke ranges between 2% and 3% annually, and up to 5% annually for more severe stenosis. There are factors such as accelerated occlusion progression, high LDL cholesterol levels and the presence of coronary disease which increase the likelihood of having a stroke[450]. Despite the high incidence of this pathology in people over the age of 80, diagnosis and treatment rates are lower when compared to younger patients[451].

Case series 3

6.15.1. Carotid endarterectomy

The efficacy and safety of carotid endarterectomy (CEA) has been assessed in several studies that include patients without prior ischemic stroke or TIA but with a greater or lesser degree of stenosis detected via imaging techniques. The clinical application of the results of these trials requires that morbimortality results of the surgical team itself be taken into account and the understanding that the performance of most of these trials was prior to the appearance and generalised use of treatments that have been proven to reduce the risk of stroke in patients with high vascular risk.

SR of RCT

A SR (3 RCTs, 5,223 patients) reported a significant benefit of CEA when

compared to medical treatment (usually with antiaggregants), in those cases with a significant degree of stenosis. Risk reduction for the combined variable composed of death or perioperative stroke or any following stroke was 31% (414 events; RR: 0.69; 95% CI: 0.57 to 0.83), while reduction of death or perioperative stroke or subsequent ipsilateral strokes was 29% (252 events; RR: 0.71; 95% CI: 0.55 to 0.90). However, absolute risk attributable to CEA during the first month (death or stroke) was 2.9% and absolute reduction during the first three years was approximately 1% annually. A subgroup analysis determined that the benefit was greater in men and young patients. The review's trials included asymptomatic patients with a degree of stenosis higher than 60% based on both criteria: North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST)[452]. **1++**

Different surgical teams can obtain different results depending on their experience, and these results should be weighed in the risk-benefit balance. As a result, it has been suggested that only centres of excellence that can confirm morbimortality values below 3% should perform the procedure with the aim of maximising its outcome[453]. **CPG 1++**

Endarterectomy safety

Certain aspects derived from the technique or the patient can determine variable perioperative risks.

A SR of 62 studies with different designs and methodological quality assess perioperative risk in patients with and without previous symptoms. Perioperative risk in women was 31% higher than in men (1,252 events; OR: 1.31; 95% CI: 1.17 to 1.47); the absolute difference was 1%. Short-term risk of death after a CEA was higher in patients over the age of 70, but there were no differences for the risk of stroke after the intervention[454]. A prior SR (103 studies with different designs and methodological quality) reported that the short-term risk of CEA was significantly lower in patients without prior ischemic stroke or TIA[455]. **SR of observational studies 2+**

Antiaggregant treatment after endarterectomy

Treatment with antiaggregants in patients who underwent a CEA (with or without previous symptoms) was assessed in a SR (6 RCTs, 907 patients) that showed that antiaggregants reduce the risk of stroke (61 events; OR: 0.58; 95% CI: 0.34 to 0.98) when compared to placebo or no treatment[456]. These results point in a similar direction as the *Antithrombotic Trialists' Collaboration* study that jointly analysed trials conducted in other patients with high vascular risk[403]. **SR of RCT 1++**

6.15.2. Endovascular treatments

Endovascular treatments with implantation of a carotid artery stent (CAS) are technologies still under development that are performed under local anesthesia. The

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constant evolution of material and methods used for distal occlusion makes it difficult to assess their long-term efficacy[457, 458].

A recent SR (7 RCTs, 2,979 patients) assessed the efficacy and safety of endovascular treatments and CEA in patients with carotid artery stenosis with or without previous symptoms[459]. Results at 30 days were significantly favourable to CEA and endovascular treatments showed an increase of the combined variable of death or any stroke (OR: 1.39; 95% CI: 1.05 to 1.84), of ipsilateral ischemic stroke (OR: 1.48; 95% CI: 1.05 to 2.07) or any type of stroke (OR: 1.50; 95% CI: 1.05 to 2.16). The risk of death or stroke at 6 months was also favourable to CEA, but not at one year. CEA was also associated with a lower risk of surgical failure. The review includes the EVA 3S trial which was prematurely interrupted for safety reasons when a high rate of stroke or death after endovascular treatment was reported[460]. In a similar manner, long-term results (three years follow-up) of the SAPHIRE study did not report differences in the risk of death in the case of CEA or the endovascular procedure with distal protection system. The study included patients who were deemed to present high surgical risk, with and without previous symptoms[461].

SR of RCT 1+

6.15.3. Carotid artery stenosis screening

A recent SR performed by the USPTF (U. S. Preventive Services Task Force) reported that the sensitivity and specificity of a Doppler ultrasound on the supraaortic trunks is 94% and 92% respectively. Ultrasound screening in the general population, without the confirmation of angiographic ultrasound results, could result in the performance of procedures in people without surgical indication or without severe stenosis. Angiography confirmation is not risk-free and can cause ischemic strokes. There is insufficient evidence to suggest stratification of the population in the risk category[462].

SR of RCT 1++

Summary of the Evidence

1++	In patients without a history of ischemic stroke or transient ischemic attack and with a significant degree of carotid artery stenosis, CEA has been shown to be beneficial. The studies have been performed in specific centres with a low perioperative morbimortality rate[452].
1++/2+	It has been demonstrated that the benefit of CEA is greater in men and young patients[452].
1++	Antiaggregant treatment after CEA reduces the risk of stroke [456].
1+	In most patients, CEA has yielded better results than endovascular

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	procedures [459-461].
1++	Population screening programmes for the detection of asymptomatic carotid artery stenosis have not been proven beneficial [462].

Recommendations

B	Surgical treatment (carotid endarterectomy) is recommended in asymptomatic patients with significant stenosis (>70%) of the carotid artery, if and when the surgical team confirms a perioperative morbimortality of less than 3%. The decision must be made together with the patient, after informing him/her of the risks and benefits of the intervention and assessing factors such as age or comorbidities.
C	Surgical treatment (carotid endarterectomy) is not recommended in asymptomatic patients with mild carotid artery stenosis.
A	Antiaggregant treatment is recommended in all patients with carotid artery stenosis.
B	The use of endovascular techniques with stent implantation should be individualised in patients with high surgical risk, in cases where there are technical difficulties for the performance of a carotid endarterectomy or within the context of a clinical trial.
A	Carotid stenosis screening programmes in the general population are not recommended.

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6.16. Antiaggregant treatment in the primary prevention of stroke

Key Questions:

- Does treatment with platelet antiaggregants reduce the risk of a vascular episode or stroke in people presenting different levels of vascular risk?
- What doses are effective at preventing vascular episodes or stroke?
- Is platelet antiaggregant treatment beneficial for the reduction of stroke risk in patients with diabetes?

Six big trials have been performed that assess the efficacy of aspirin for the primary prevention of vascular disease.

A SR (6 RCTs, 92,873 people without prior vascular disease) showed that aspirin (75-500 mg/d), compared to placebo, reduces the risk of coronary disease (fatal and non-fatal myocardial infarction) by 33% (OR: 0.77; 95% CI: 0.70 to 0.86) non-fatal myocardial infarction by 25% (OR: 0.75; 95% CI: 0.67 to 0.85). Aspirin did not reduce the risk of stroke or overall mortality[463]. Other previous SRs reported very similar results. Later, the WHI study reported a significant reduction of stroke, especially ischemic, in women without vascular history[464-466]. **SR of RCT RCT 1+**

A SR (5 RCTs, 53,035 patients) showed that aspirin (75-500 mg/d) increases the risk of Severe gastrointestinal bleeding and hemorrhagic stroke when compared to placebo, even though the number of events in both cases was limited. Specifically, for every 1,000 people with moderate coronary risk (5% at 5 years), aspirin treatment would prevent between 6 and 20 episodes, but could cause up to 2 hemorrhagic strokes and 2 to 4 Severe gastrointestinal bleeding. In the case of people with low coronary risk (1% at 5 years) 1 to 4 episodes could be avoided, causing a similar excess of hemorrhagic episodes[465]. Another SR indicates that for coronary risk greater than 15% at 10 years, the benefits of treatment with aspirin would outweigh the risks[467]. **SR of RCT 1+**

A case-control study assessed the risk of digestive bleeding for different antiaggregants. Aspirin and ticlopidin showed a significant association (OR: 4.0; 95% CI: 3.2 to 4.9 and OR: 3.1; 95% CI: 1.8 to 5.1 respectively), while clopidogrel, dipiridamol and triflusal do not[468]. **Case-control studies 2++**

6.16.1 Dose and antiaggregants for enteric protection

A recent SR determined that there is no data available to recommend long-term aspirin treatment at doses higher than 75-81 mg/d for the prevention of vascular diseases. Higher doses such as those usually prescribed do not prevent vascular episodes more effectively; instead, they are associated with a higher risk of gastrointestinal bleeding[469]. **SR of RCT 1++**

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Enteric coated antiaggregants have not been shown to reduce severe bleeding complications and entail greater treatment cost[470-472].

SR of RCT 1++

Observational studies 2++

6.16.2. Gender differences

In a SR (6 RCTs, 51,342 women and 44,114 men), a 50-500 mg/d dose of aspirin was associated with a significantly reduced risk of vascular episodes in men (OR: 0.86; 95% CI: 0.78 to 0.94) as well as women (OR: 0.88; 95% CI: 0.79 to 0.99) when compared to control or placebo treatment. In the specific case of stroke, a 17% reduction was reported in women (OR: 0.83; 95% CI: 0.70 to 0.97), while in men no benefit was reported. In contrast, the risk of myocardial infarction was reduced in men (OR: 0.68; 95% CI: 0.54 to 0.86) but not in women. There were no gender differences in terms of adverse effects[473]. These results indicated that antiaggregation with aspirin could have a differential effect on both sexes (Table 12).

SR of RCT 1++

Table 12. Vascular risk reduction of aspirin versus placebo in men and women (primary prevention) [473]

	Women		Men	
Vascular episodes	**Absolute risk**	**Hazard ratio (95% CI)**	**Absolute risk**	**Hazard ratio**
Total*	- 0.3%	0.88 (0.79-0.99)	- 0.35%	0.86 (0.78-0.94)
Myocardial infarction	-	NS	- 0.85%	0.68 (0.54-0.86)
Ischemic stroke	- 0.23%	0.83 (0.70-0.97)	-	NS
Hemorrhagic stroke	-	NS	+ 0.12%	1.69 (1.04-2.73)
Severe bleeding	+ 0.25%	1.68 (1.13-2.52)	+ 0.32%	1.71 (1.35-2.20)
Mortality due to all causes	-	NS	-	NS
Vascular mortality	-	NS	-	NS

* Vascular mortality, non-fatal myocardial infarction and non-fatal stroke. NS: not significant.

Adapted from: Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. *Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials*. JAMA. 2006; 295(3):306-13.

6.16.3. Diabetic patients

The efficacy of antiaggregation for the primary prevention of vascular episodes in the diabetic population is a controversial issue. There are few specific studies with diabetic patients and most data pertains to studies conducted in primary care, which include some diabetic patients.

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The PPP trial (Primary Prevention Project), which included 1,031 patients with type 2 diabetes, assessed the efficacy of aspirin (100 mg/d) and vitamin E (300 mg/d) versus placebo. The trial ended prematurely when greater efficacy was demonstrated for the combination of aspirin and vitamin E in patients with vascular risk factors. The subgroup analysis for diabetic patients did not show significant differences in vascular episodes[474]. The only specific study that assessed the efficacy of aspirin in patients with diabetes is the ETDRS study, which included 3,711 patients, half of them presenting a history of vascular complications. In these patients treatment with aspirin over 7 years did not reduce the incidence of myocardial infarction, stroke or vascular death[475].

RCT 1+

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Summary of the Evidence

1++	In the primary prevention of vascular disease, aspirin reduces the risk of coronary disease, even though it does not reduce the risk of stroke or overall mortality [463-467].
1++	An aspirin dose of 75-81 mg/d is sufficient for vascular prevention, while higher dose is associated with a similar protective effect with a higher risk of gastrointestinal bleeding [469].
1++	Aspirin could have a different effect in men and women. This effect, a reduction of myocardial infarctions in men and stroke in women, remains uncertain [473].

Recommendations

A	Primary prevention of vascular episodes with antiaggregants is not recommended in the general population.
B	In certain patients, such as those with high vascular risk, treatment with aspirin at the minimal effective dose (100 mg/d) should be considered once potential benefits and risks have been assessed.
✓	In patients with hypersensibility or intolerance to aspirin's adverse effects, clopidogrel, dipiridamol or triflusal should be considered as alternatives.

6.17. Antithrombotic treatment in pregnant women

Key Questions:

- What therapeutic options are available for pregnant patients who require antithrombotic treatment (antiaggregant/anticoagulant)?

The therapeutic management of antithrombotic treatment during pregnancy is beyond this CPG's scope; there are current publications that address specific clinical situations during pregnancy such as prophylaxis of deep venous thrombosis, certain thrombofilias or women who have mechanical heart valves[476]. It should be highlighted that some of the recommendations provided include situations for which the use of anticoagulants or antiaggregants is not approved in our country.

Treatment with antithrombotics during pregnancy is complex. One of the clinical situations is the prevention of embolic phenomena in patients who have mechanical prosthetic heart valves. Due to the lack of clinical trial data, recommendations for the use of antithrombotics during pregnancy are based on indirect results of studies that excluded this population or on case series.

Available therapeutic options include non-fractionated heparin and low molecular weight heparins. Neither one of them crosses the placenta barrier and are not believed to have the potential to cause teratogeny or fetal bleeding, even though there is a risk of causing bleeding problems in the utero-placental attachment area. Due to its high molecular weight, non-fractionated heparin is not excreted with breastmilk. On the contrary, there is little information on the possibility of low molecular weight heparin being eliminated with breast milk. In our country non-fractionated heparin has the indication of use for prophylaxis in pregnant women with heart valves. However, it presents other risks such as maternal bleeding and development of osteoporosis.

Coumarine derivative anticoagulants cross the placenta barrier, causing fetal bleeding, which is especially relevant during labour, and present some teratogenic potential. It is, hence, a medical-legal problem, given that coumarine anticoagulants are contraindicated during pregnancy. According to the Food and Drugs Administration (FDA) classification for the use of drugs during pregnancy,coumarine derivatives are classified in the X category, indicating that studies on animals and humans demonstrate fetal abnormalities, or that adverse effect data indicate evidence of fetal risk.

The use of antiaggregants, such as aspirin, during pregnancy entails the risk of causing miscarriages and congenital malformations. It may be considered during the first and second month of gestation and at the minimal effective dose, but after the third trimester of pregnancy its administration is contraindicated.

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Summary of the Evidence

–	Treatment with antithrombotics during pregnancy is a complex clinical situation for which there are a limited number of therapeutic alternatives.
–	In pregnant women with heart valves, non-fractionated heparins have demonstrated to be safe for the fetus and are indicated as prophylaptic treatment for thrombotic episodes.
–	Coumarine derivatives have some teratogenic potential.

Recommendations

✔	In pregnant women in whom anticoagulation is indicated with the aim of reducing the risk of thrombotic episodes, including stroke, the use of non-fractionated heparin or low molecular weight heparins should be considered throughout the entire pregnancy.
✔	In pregnant women who have one or more mechanical heart valves, with a high risk of embolic phenomena, aspirin (at the minimal effective dose) should be considered during the first two trimesters of gestation.
✔	Treatment with antithrombotics during pregnancy is a complex clinical situation that should be monitored by a specialised multidisciplinary team.

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6.18. Risk of bleeding with anticoagulant treatment

Key Questions:

- What is the risk of bleeding in patients who receive anticoagulant treatment?

The main complication of anticoagulant treatment is the risk of bleeding. A joint analysis of results of 5 RCTs showed that the risk of severe bleeding in patients who received anticoagulants was 1.3% per year, versus 1% per year for the control. For ICH risk, risk was 0.3% and 0.1% per year for anticoagulant treatment and control, respectively[477]. However, in standard clinical practice, the risk of bleeding could be greater than that established by clinical trials, especially in older patients[369].

SR of RCT 1+

Observational studies 2++

The assessment of bleeding risk in a patient is an essential part of weighing benefits and risks when indicating an anticoagulant treatment. There are several validated models available that are useful for a more systematic assessment.

A bleeding risk calculation model (Outpatient Bleeding Risk Index) identified four factors that were associated with an increased risk of presenting a Severe hemorrhagic event: age older than 65 years, a history of prior digestive bleeding, prior stroke and one or more of the following situations (recent myocardial infarction, hematocrit under 30%, creatinine greater than 1.5 mg/dl or diabetes mellitus). According to a cohort study for the validation of this index, the risk of bleeding at 48 months was 53% in high risk patients (three or four factors), 12% in patients with one or two risk factors and 3% in patients without risk factors[478]. Other studies have validated this index[479-481].

Observational studies 2+

Another model included age, sex and the presence of malignant pathology to estimate the risk of bleeding, even though the study included patients who received anticoagulant treatment for venous thromboembolism and the risk was estimated at three months of treatment[482]. A cohort of patients with atrial fibrillation led to the creation of a model that included eight variables: age 70 years or older, sex, previous bleeding episode, bleeding episode during hospitalisation, alcohol or drug abuse, diabetes, anemia and antiaggregant treatment[483].

Observational studies 2+

The most recent proposal (HestenosismitralORR2HAGES Index) in patients with atrial fibrillation includes the majority of factors of previous proposals and suggests assigning a score depending on the presence or absence of these factors (Tables 13 and 14). Hence, the risk of having a Severe hemorrhagic episode (that requires hospitalisation) is estimated to be 1.9 per 100 patients/year in patients with no risk factors and up to 12.3 episodes per

Observational studies 2+

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100 patients/year if a patient has a score equal to or greater than 5[484].
These proposals should not replace clinical judgement and should be jointly assessed with functional and cognitive state, adherence to treatment, and the patient's values and preferences and family and personal environment. The objective of these models is to facilitate decision-making, helping to weigh benefits and risks of anticoagulant treatment, as well as determining the intensity or duration of treatment and frequency of anticoagulation intensity monitoring.

Table 13. HEMORR2HAGES Index score[484]

Previous hemorrhagic episode	2
Liver or kidney disease	1
Alcohol abuse	1
Malignant pathology	1
Age > 75 years	1
Low platelet count or altered platelet function	1
Hypertension (uncontrolled)	1
Anemia	1
Genetic factors	1
Significant relapse risk	1
Stroke	1

Adapted from: Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, *et al*. *Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF)*. Am Heart J 2006; 151:713-9.

Table 14: Risk of severe hemorrhages based on the HEMORR2HAGES index score [484]

0 points	1 point	2 points	3 points	4 points	5 or more points
1.9*	2.5	5.3	8.4	10.4	12.3

*Risk per 100 patients and year.

Adapted from: Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, *et al*. *Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF)*. Am Heart J 2006; 151:713-9.

Summary of the Evidence

1+/2++	The risk of bleeding is the main complication of anticoagulant treatment and frequently results in treatment discontinuation [369, 477].
2+	There are several models that assess the risk of having a hemorrhagic episode in patients who receive anticoagulant treatment [478-484].

Recommendations

B	In patients with anticoagulant treatment indication, it is recommended to

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	assess hemorrhagic risk using one of the indexes available.
✔	Before initiating anticoagulant treatment, the benefits and risks of treatment should be weighed, including the assessment of adherence to treatment and the patient's values, preferences and family and personal environment.

6.19. Subarachnoid hemorrhage

Key Questions :

- What is the risk of spontaneous rupture in patients with intact intracerebral aneurysm?
- In patients with intact intracerebral aneurysm, does the procedure on the malformation (via surgery or via an endovascular approach) reduce the risk of presenting subarachnoid hemorrhage?

SR of observational studies

Observational studies 2+

SAH accounts for a relatively small percentage of all strokes (between 1% and 7%). However, its impact on overall morbimortality is very high, given that it affects people who are relatively young; it has a very poor prognosis[238]. The incidence non-traumatic SAH ranges from 6-25 cases per 100,000 inhabitants. The highest rates correspond to studies performed in Finland and Japan[485-488]. A SR (3,936 patients) explored the relationship of several factors and the risk of SAH. High blood pressure values (RR: 2.5; 95% CI: 2.0 to 3.1), alcohol consumption (>150 mg/d) (RR: 2.1; 95% CI: 1.5 to 2.8) and smoking (RR: 2.2; 95% CI: 1.3 to 3.6) were consistently associated with a significantly higher risk of SAH[69].

The main cause of SAH is a ruptured intracranial aneurysm (80%), while the remaining 20% corresponds to arteriovenous malformations, tumours, blood dyscrasias, central nervous system infections, use of drugs or to an unknown cause[489]. Although it has been suggested that there could be a genetic component, most SAHs are caused by lifestyle-related risk factors. The estimated prevalence of aneurysm pathology in the population ranges between 1% and 6%, with a mean annual rupture risk of 0.7%. 10% to 30% of cases are multiple[490].

Intracranial aneurysms are a result of weakness in an artery's vascular wall and interaction with hemodynamic factors such as HT, which can lead to growth and rupture of the aneurysm[491, 492]. When an intracranial aneurysm is located, therapeutic strategies should be aimed at preventing hemorrhage due to aneurysm rupture. Currently available options are the management of risk factors associated with hemorrhagic stroke and a surgical approach to the aneurysm sac.

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6.19.1. Perform surgery or wait?

A SR that included 4,705 patients with intact aneurysms reported that certain patient characteristics, such as age older than 60 years or female gender, were associated with an increased risk of a ruptured aneurysm (RR: 2.0; 95% CI: 1.1 to 3.7 and RR: 1.6; 95% CI: 1.1 to 2.4 respectively)[493]. The aneurysm's characteristics, posterior localisation or size larger than 5 mm were associated with a significantly higher rupture risk (RR: 2.5; 95% CI: 1.6 to 4.1 and RR: 2.3; 95% CI: 1.0 to 5.2 respectively).

SR of observational studies 2+

There are no trials comparing any type of procedure performed on the aneurysm sac versus expectative attitude and it is unlikely that this type of studies will be designed in the future. Because of this, the available evidence is based on data yielded by the few observational studies that are described in the natural history of this pathology. Other factors to be taken into account when the time comes to decide between one or the other option are, for instance, the presence of neurological symptoms in the absence of bleeding, generally due to pressure or the mass effect; the patient's age which determines prognosis following surgery or the reference values of the patients whom upon diagnosis may experience a deterioration in their quality of life.

The ISUIA cohort study (International Study of Unruptured Intracranial Aneurysms) has been the most relevant up until now. The study described the natural history of unruptured intracranial aneurysms and the risk related to the surgical procedure or endovascular procedure in a cohort of 4,060 patients[494]. The natural course, with no operation, in people with an unruptured aneurysm shows that the risk of rupture at 5 years for an anterior circulation aneurysm is 0% (for those with a size < 7 mm), 2.6% (7 to 12 mm), 14.5% (13 to 24 mm) and 40% (> 25 mm). The risk of rupture is different for posteriorly located aneurysms, being at 5 years 2.5% (for those with a size< 7 mm), 14.5% (7 to 12 mm), 18.4% (13 to 24 mm) and 50% (> 25 mm).

Cohort studies 2++

Surgery versus endovascular procedures

The risks in patients who underwent a surgical or endovascular procedure were also high. 6% of patients who underwent surgery presented a rupture aneurysm, 4% cerebral hemorrhage and 11% had a stroke during the procedure. The complications of endovascular treatment were cerebral hemorrhage (2%) and stroke (5%) during the procedure. In patients with intact aneurysm who underwent surgery, the main risk factors for poor clinical evolution after surgery were age older than 50 years (RR: 2.4; 95% CI: 1.7 to 3.3), diameter larger than 12 mm (RR: 2.6; 95% CI: 1.8 to 3.8), posterior localisation (RR: 1.6; 95% CI: 1.1 to 2.4) and prior ischemic stroke (RR: 1.9; 95% CI: 1.1 to 3.02).

Cohort studies 2++

In patients who underwent endovascular treatment, aneurysm diameter greater than 12 mm (RR: 2.4; 95% CI: 1.0 to 5.9) and posterior localisation (RR: 2.25; 95% CI: 1.1 to 4.4) were factors associated with poor clinical evolution after the procedure[494].

Cohort studies 2+

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Complications after the endovascular procedure or surgery have been reported by case series or retrospective cohort studies. A recent cohort of individuals treated for intact intracerebral aneurysm (2,535 patients) reported a lower rate of complications related with the endovascular procedure (6.6%) when compared to surgical procedure (13.2%), as well as lower mortality (0.9% versus 2.5% respectively)[495].

Summary of the Evidence

2++	High blood pressure values, alcohol consumption and smoking have been associated with an increased risk of SAH [69].
2++	The main cause SAH is a ruptured intracranial aneurysm. Rupture risk increases with aneurysm size[493].
2++/2+	The endovascular procedure presents a lower rate of complications than the surgical procedure[494, 495].
2++	Factors associated with poor prognosis after the intervention are age, female gender, intervention on a large aneurysm and posterior localisation[494].

Recommendations

✓	All patients with intact intracerebral aneurysm should be provided with adequate advice promoting healthier lifestyles, such as the cessation of smoking, alcohol consumption and use of any substance with sympatheticomimetic activity.
A	Patients with intact intracerebral aneurysm should maintain blood pressure values within the normal range.
B	In aneurysms whose size is equal to or bigger than 7 mm, a procedure on the aneurysm sack (via surgery or an endovascular procedure) and individual assessment of the risks of each intervention, the patient's age, mass effect and localisation of the aneurysm should be be taken into account.
B	Expectative attitude is recommended in people over the age of 65, without symptoms and with anterior circulation aneurysms of less than 7 mm in

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	diameter.
✓	In case of adopting a conservative approach, changes in size or presentation of the aneurysm should be closely monitored.

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7. Secondary prevention of stroke

This section, which covers aspects relating to secondary prevention, aims to provide a set of recommendations for the management and monitoring of risk factors or underlying conditions in patients who have already had a stroke.

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7.1. Risk of a new episode of ischemic stroke or transient ischemic attack

Key Questions:

- What is the risk of having a stroke in people who have already an episode of ischemic stroke of TIA?

One of the main concerns regarding a patient who has had a stroke or TIA is the possibility that they may have another cerebral vascular episode. Different studies have shown that this increased risk includes both coronary disease and death due to a vascular cause[496, 497].

SR of observational studies 2++

20% to 30% of patients who have had a stroke die within the first few months following the episode. Amongst those who overcome the first episode, more than a third present some kind of disability at one year, making the dependent on a carer[498, 499] Although the majority of early deaths are directly associated with the episode itself, mortality in the first year has also been associated with other vascular episodes and complications relating to mobilisation deficit such as infections or traumatisms[500, 501].

Observational studies RCT 1+/2+

After an ischemic stroke, the risk of recurrence within the first year is approximately 10% and after the first year the average annual risk is 5%. The risk of presenting coronary disease is estimated to be 6% during the first year and later an annual 4.6% after a first episode of stroke[497]. Hence, the risk of vascular relapse during the first year after an ischemic stroke or TIA is usually cardiovascular. The risk of having an ischemic stroke is especially high after a TIA. A SR showed that 3.5% of patients had a stroke within the first two days of aTIA, 8% within the first month and up to 9.2% within the first 90 days. These percentages could be reduced if an active assessment of episodes was carried out after the TIA[496, 502, 503].

SR of observational studies 2+

Observational studies 2++

7.1.1. Risk calculation models

In response to these alarming numbers, scales based on clinical characteristics have been proposed to stratify the risk of stroke recurrence in individuals who have had a prior TIA. The most important are: the California scale[504], the ABCD scale[505] and the $ABCD_{2\ scale}$[506]. These scales have been validated in several studies[506-510], but validation studies in the Spanish population have been negative[511, 512].

Observational studies 2++

These tables establish that the risk of presenting an ischemic stroke after a TIA, according to results of the $ABCD_2$ scale, is 18% after the first 90 days following a TIA (Table 15).

Table 15. Risk of stroke within 2, 7 and 90 days after a TIA ($ABCD_2$ risk table) * [506]

Risk score	2 days	7 days	90 days
Low risk (0-3)	1%	1.2%	3.1%
Moderate risk (4-5)	4.1%	5.9%	9.8%
High risk (6-7)	8.1%	12%	18%

Adapted from: Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, *et al*. *Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack*. Lancet. 2007; 369:283-92.

* $ABCD_2$ tables present a total score range of 0 to 7 points for the following independent risk components or predictors:
Age >60 years (1 point)
Blood pressure (SBP>140 mmHg or DBP >90 mmHg) (1 point)
Clinical features [focal weakness (2 points) or impaired speech without focal weakness (1 point)]
Duration of symptoms: ≥60 minutes (2 points); <60 minutes (1 point)
Diabetes mellitus (1 point)

Observational studies 2+/3

However, the percentage of patients who, following a stroke, receive some type of treatment for secondary prevention is not satisfactory. Several studies reflect the infrautilisation of antithrombotic treatment despite extensive evidence in favour of these treatments. After the first nine months following a stroke, approximately only half of patients receive aspirin or some other antiaggregant. Similarly, data from our setting indicate that only 50.6% of patients with atrial fibrillation receive anticoagulant treatment[513]. These studies evidence the hesitance regarding the use of anticoagulants, especially in elderly patients. Although it is true that the trials include a certain population, recent studies had demonstrated the benefit of anticoagulant treatment in elderly patients[497, 514-516].

Observational studies 2+

Similarly, up to 20% of hypertense patients who have had a stroke do not receive antihypertensive treatment. Furthermore, only 40% of patients who receive antihypertensive treatment manage to maintain blood pressure values below 140/90 mmHg[497, 516, 517]. The situation with the use of hypolipemiant treatments is similar; only 40% of patients with high blood cholesterol levels receive pharmacological treatment and 8.7% of patients over the age of 80[497].

Summary of the Evidence

2++	The risk of having a recurrent ischemic stroke or a new vascular event is especially high within the first year of having had a transient ischemic attack[496].

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2++	There are scales, which have not been validated in our setting, to calculate the risk of recurrence after a transient ischemic attack[506].

Recommendations

✓	Therapeutic strategies in patients who have had a first episode of ischemic stroke or transient ischemic attack should be aggressive and aimed at reducing recurrence and overall vascular risk.

7.2. Lifestyle interventions

Key Questions:

- Do lifestyle interventions reduce the risk of new episodes of stroke in patients with a history of stroke?

Evidence regarding lifestyle interventions derives mainly from studies conducted in primary care. These studies are available in sections 6.4 and 6.5 of this guideline. Some of the studies performed in populations with vascular pathology are described below.

There is consistent evidence that chronic consumption of alcohol is a risk factor for any type of stroke, aside from having harmful effects on other pathologies and health in general.

Cohort studies 2++/2+

Two RCT nested cohort studies that included patients with a history of vascular disease were identified. In the cohort of patients with left ventricular hypertrophy of the LIFE it was demonstrated that consumption of one to seven units of alcohol per day reduces the risk of myocardial infarction, while consumption of more than 8 units per day is associated with a non-significant tendency to present more strokes, when compared to non-drinkers[518]. A second cohort of the SAVE study included patients with left ventricular dysfunction after myocardial infarction. Consumption of one to ten units of alcohol per day did not alter the risk of ventricular dysfunction progression when compared to non-drinkers[519]. However, alcohol consumption is significantly related with the risk of a first episode of stroke, both ischemic and hemorrhagic[62]. In order to reduce consumption, brief (5 to 20 minutes) informative interventions have been proven to be effective[70].

SR of observational studies 2++

Smoking cessation reduces vascular risk. This reduction is proportional to the duration of smoking cessation[79, 520].There are no RCTs that address the efficacy of different smoking cessation measures in patients who have

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previously had a stroke. However, in people with prior coronary disease, a SR of observational studies that last at least 2 years reported a 36% reduction of overall mortality amongst people who quit smoking versus smokers[80, 521].It has been observed that two to four years after quitting smoking the risk of stroke is reduced by 27%, and patients who continue to smoke present higher mortality (RR: 2.27) versus non-smokers or ex-smokers[522, 523].

Patients who have had a stroke often present severe physical impairment. Additionally, neurological deficits result in a gradual physical deterioration. In this situation, programmes to promote physical exercise are especially difficult. No studies have been identified that assess benefits, in terms of reducing the risk of a repeat stroke or other vascular episodes, in patients with prior stroke or TIA. Several studies have reported that aerobic exercise programmes improve the mobility, balance and resistance to exercise of these patients[524]. These programmes are considered part of the stroke patient's rehabilitation and have been addressed in other guidelines of our setting[525].

Obesity, and especially abdominal obesity, are associated with the risk of having a stroke[526]. Even though there are no randomised and prospective studies that assess the impact of weight reduction in vascular morbimortality or stroke in primary or secondary prevention, several studies have determined that weight reduction improves blood pressure, the lipid profile and glucose values, factors that are closely associated with vascular disease[190-193, 249].

Observational studies 2++

SR of RCT 1++/1+

Summary of the Evidence

2+	In non-gestating men and women with a history of vascular disorders, consumption of small amounts of alcohol has not been determined to be harmful, and could even be a protective factor on the development of vascular episodes[518, 519].
2++	In patients with a history of vascular disorders, smoking cessation reduces vascular risk. This reduction is proportional to the duration of smoking cessation[79, 80, 520-523].
1++/1+	In people with obesity or overweight, weight reduction improves several risk factors related with vascular disease[190-193, 249].

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Recommendations

✓	The hospital discharge report should include the measures adopted regarding lifestyle modification.
A	Patients who have suffered a stroke should avoid alcohol consumption of more than two units daily and be encouraged to quit smoking.
A	Alcohol consumption should not be encouraged in patients who do not drink. Patients who have suffered hemorrhagic stroke should avoid all kinds of alcohol consumption.
B	Patients who have suffered a stroke are encouraged to exercise regularly within their capabilities and reduce body weight or abdominal obesity to normal levels.

7.3. Hypertension

Key Questions:

- In patients with a history of an episode of stroke, does antihypertensive treatment reduce the risk of new episodes?
- What are the target blood pressure values?

HT is the most important risk factor, after age, for ischemic and hemorrhagic stroke. Amongst modifiable risk factors, HT is the most prevalent, and is present in almost half of the population with risk factors[200]. The number of trials designed to directly assess if treatment of blood pressure reduces the incidence of new stroke or other vascular episodes is limited[527]. Most information has been extracted from trials that evidence the importance of treating HT in the prevention of vascular episodes[229].

On the other hand, there is a lack of information on antihypertensive treatment in the acute phase of an ischemic stroke that may present high blood pressure values. Normally a cautious strategy is recommended, given that the time when treatment was initiated is unknown. In this phase, a sharp decrease of blood pressure values could reduce cerebral perfusion and thus increase the area of infarction. Special care should be taken with patients presenting bilateral obstruction of the carotid artery greater than 70%, where a sudden reduction of blood pressure entails a special risk of stroke recurrence[528].

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There are CPGs that extensively address treatment in the acute phase of an ischemic stroke or TIA[529]. In any case, antihypertensive treatment should be aimed at gradually reducing blood pressure values and the indication for any treatment should be performed taking each patient's tolerance and concomitant pathology into consideration.

7.3.1. Risk of a new episode with treatment

A SR of 7 RCTs and 15,527 patients with a history of stroke (ischemic, TIA or hemorrhagic), with and without HT, demonstrated that antihypertensive treatment reduces the risk of having a new episode of stroke by 24% (OR: 0.76; 95% CI: 0.63 to 0.92), a myocardial infarction by 21% and vascular episodes by 21%, even though it does not significantly reduce overall mortality or mortality due to stroke. The benefits reported were mainly a result of SBP management[530]. **SR of RCT 1++**

The results of this SR showed that ACEIs reduce the risk of myocardial infarction (OR: 0.74; 95% CI: 0.56 to 0.98), while diuretics reduce the risk of a new stroke (OR: 0.68; 95% CI: 0.50 to 0.92) and vascular episodes (OR: 0.75; 95% CI: 0.63 to 0.90). Betablockers (atenolol) were not shown to be superior to placebo in individual studies or in the joint analysis of results. They were also a significant source of heterogeneity in the results[530]. Data for the combination of a diuretic and an ACEI were obtained from one RCT, the PROGRESS trial[500].

The PROGRESS study, included in the previous version, randomised 6,105 patients with a history of ischemic stroke or TIA with and without HT to three groups that received perindopril (4 mg/d) alone, in combination with indapamide (2.5 mg/d) or placebo. The study had a four year follow-up[500]. The most significant benefits were reported in the group that combined perindopril and indapamide, with a 43% reduction of the risk of having a new episode of stroke (405 events; RR: 0.57; 95% CI: 0.46 to 0.70), a 76% reduction of risk of hemorrhagic strokes and a 40% reduction of risk of vascular episodes. Combined treatment demonstrated a greater reduction of blood pressure values. **RCT 1++**

A subsequent analysis of the PROGRESS study for different types of stroke indicated that treatment with an ACEI (perindopril) reduced the risk of recurrent hemorrhagic stroke by 50%; absolute reduction was 1% (111 events) [240]. **RCT 1+**

The MOSES trial, a RCT conducted after these studies that included 1,045 patients with HT and a history of stroke determined that antihypertensive treatment with eprosartan (600 mg/d), an ARA-II, results in a 25% stroke risk reduction when compared to a calcium antagonist (nitrendipine) (236 events; incidence density ratio [IDR] 0.75; 95% CI: 0.58 to 0.97) and a 21% vascular episode risk reduction. However, the study had an open design, amongst other methodological limitations[531]. **RCT 1 -**

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Different types of antihypertensive treatments reduce blood pressure values. In contrast, benefits in primary or secondary prevention of vascular episodes, including stroke, differ considerably. One possible explanation for this effect is that the renin-angiotensin system has been associated with arteriogenesis and proliferation of the vascular smooth muscle[532]. Thus, ACEIs and ARA-IIs could have additional benefits aside from the reduction of blood pressure values[527].

Lifestyle modifications in patients with HT that have been determined to reduce blood pressure values are smoking cessation, weight loss in patients with obesity, alcohol consumption moderation, regular physical activity, reduced salt intake and increased consumption of fruits and vegetables[209]. These measures are also useful in the management of other vascular risk factors.

SR of RCT 1++

7.3.2. Blood pressure target values

A SR of cohort studies demonstrated that the risk of stroke decreases lineally and consistently with blood pressure until 115/75 mmHg levels in men and women and for different types of stroke. Risk is reduced by about 30% for every 10mmHg decrease of blood pressure values[229].

SR of cohort studies 2++

With the aim of maximising vascular benefits, more intensive treatment with antihypertensives has been suggested for patients with high vascular risk. In patients with a history of stroke, a later analysis of the PROGRESS study reported a gradual benefit in the recurrence of stroke by managing SBP values up to 120 mmHG[533]. Although the benefit obtained with decreased BP values is lineal, some more recent international and national CPGs suggest values below 140/90 mmHg [201, 202], 130/80 mmHg [36, 534, 535] or even 120/80 mmHg [536] as the target values in secondary prevention. Other CPGs, on the other hand, emphasise the need to initiate treatment in those hypertense or even normotense patients who have had a stroke or who present some vascular risk, but do not establish target values in their recommendations [223, 537].

RCT 1++

Despite the benefits of antihypertensive treatment, a study performed in our setting determined that in people who had had a stroke, the implementation of the recommendations provided by CPGs and the therapeutic objectives of the treatment of vascular risk factors, including HT, were very poor[206].

Summary of the Evidence

1++	In patients who have had a stroke or transient ischemic attack, antihypertensive treatment reduces the risk of recurrence or other vascular episodes. The benefit is mainly a result of SBP reduction [530].
1++	The greatest benefits are obtained with the combination of angiotensin converting enzyme inhibitor and a diuretic (4 mg/d of perindopril in

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	combination with 2.5 mg/d of indapamide) [500].
1++	Diuretic monotherapy treatment reduces the risk of having a new stroke and other vascular episodes. Angiotensin converting enzyme inhibitor monotherapy reduces the risk of myocardial infarction. Betablockers have been shown to be beneficial in the secondary prevention of stroke [530].
1-	Treatment with angiotensin II antagonists (eprosartan) could be beneficial in reducing the risk of a recurrent stroke [531].
1++	Antihypertensive treatment is beneficial in patients with blood pressure values within established normal limits [500].
1++	In hypertense patients, lifestyle modifications reduce blood pressure values and other vascular risk factors [209].

Recommendations

✓	Blood pressure values of patients who have had an ischemic or hemorrhagic stroke should be closely monitored.
A	In patients with a history of stroke or transient ischemic attack and high or even normal blood pressure values, it is recommended to initiate treatment with antihypertensive drugs, preferably with the combination of an angiotensin converting enzyme inhibitor and a diuretic (4 mg/d of perindopril and 2.5 mg/d of indapamide).
B	Depending on the patient's tolerance or concomitant pathologies, monotherapy with diuretics, angiotensin converting enzyme inhibitors or angiotensin II antagonists should be considered.
B	Once a patient who has had an ischemic stroke or transient ischemic attack is stabilised, blood pressure values should be gradually decreased with the aim of maintaining levels under 130/80 mmHg, and preferably under 120/80 mmHg.
A	Lifestyle changes should be promoted, aside from pharmacological treatment.

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7.4. Dyslipemia

Key Questions:

- In patients with a history of an episode of stroke, does hypolipemiant treatment reduce the risk of new episodes?
- What is the optimal dose of hypolipemiant treatment?
- What are the target blood lipid values?

SR of RCT 1++

A SR of patients' individual data, the result of an international collaboration (CTT [Cholesterol Treatment Trialists] Collaborators), included 14 RCTs and 90,056 patients and a mean 5 year follow-up, with a total of 8,186 deaths and 14,348 major vascular episodes. This study demonstrated that statins reduced the risk of death due to all causes by 12% for every 39 mg/dl (1.0 mmol/l) reduction of LDL cholesterol (RR: 0.88; 95% CI: 0.84 to 0.91) and the risk of a major vascular episode by 21% (myocardial infarction, coronary death, revascularisation and stroke) (RR: 0.79; 95% CI: 0.77 to 0.81).

Specifically, in the case of fatal and non-fatal strokes (2,957 events), there was a 17% risk reduction (RR: 0.83; 95% CI: 0.78 to 0.88), so for every 39 mg/dl reduction of LDL cholesterol (maintained over five years) there were 8 (95% CI: 4 to 12) episodes less per 1,000 treated patients. The benefit was objectivisable from the first year of treatment.

In this same study, statin treatment reduced the incidence of major vascular episodes at five years by 20% for every 39 mg/dl reduction of LDL cholesterol. This benefit was independent from the initial lipid profile and other characteristics such as the presence of a history of vascular disorders. Absolute benefit for each 39 mg/dl reduction of LDL cholesterol (maintained over 5 years) was 48 (95% CI: 39 to 57) major vascular episodes less per 1,000 patients with a history of coronary disease[274]. Prior reviews report similar results pointing in the same direction[273, 278-280].

RCT 1+

A later clinical trial (SPARCL) (4,731 patients, 575 events) assessed the efficacy and safety of atorvastatin (80 mg/d) compared to placebo in patients who had had a recent stroke or TIA (one to six months before) and without prior coronary disease. In these patients, atorvastatin reduced the overall incidence of stroke by 16% (HR 0.84; 95% CI: 0.71 to 0.99; ARR 2.2%), as well as death due to stroke (HR 0.57; 95% CI: 0.35 to 0.95), even though increased hemorrhagic stroke (HR 1.66; 95% CI: 1.08 to 2.55) and increased blood liver enzyme levels were reported. The number of patients who needed to be treated to prevent stroke was 46 (NNT 46; 95% CI: 24 to 243). In regards to hemorrhagic strokes, the number of events was limited (55 in atorvastatin and 33 in placebo), but the percentage of patients included with hemorrhagic stroke was also limited[538].

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With the aim of assessing the possible increased risk of hemorrhagic strokes, a recent SR jointly analysed two RCTs (8,011 patients) that showed results for this event: the SPARCL trial in atorvastatin and the HPS (Heart Protection Study) in simvastatin. Results were consistent and showed a significantly increased risk (120 events; RR: 1.73; 95% CI: 1.19 to 2.50)[539].

SR of RCT 1+

7.4.1. High doses versus low doses

A SR (27,548 patients, 2,385 events) that compared the efficacy of standard dose statins to high dose statins in secondary prevention (patients with a history of coronary disease) reported that high doses result in a greater decrease of an outcome variable comprised of coronary death or myocardial infarction (OR: 0.84; 95% CI: 0.77 to 0.91)[540]. Higher doses were also more effective at reducing the risk of presenting a variable consisting of coronary death or any vascular episode (OR: 0.84; 95% CI: 0.80 to 0.89). Specifically, high dose statins significantly decreased the risk of stroke (697 events; OR: 0.82 95% CI: 0.71 to 0.96). No significant differences were reported in overall or vascular mortality. A later SR yielded similar results in this population and highlights the absence of evidence to establish LDL cholesterol target values, indicate the use of combinations to reach these objectives or the use of more intense regimens in patients without coronary disease[541].

SR of RCT 1++

7.4.2. Elderly patients

A SR jointly assessed the results of 9 RCTs that included a total of 19,569 elderly patients (65 to 82 years) with a history of coronary disease. Statins, compared to placebo, reduced mortality (overall and coronary), myocardial infarction, the need for revascularisation and stroke. In the specific case of stroke, risk was reduced by 25% (RR: 0.75 95% CI: 0.56 to 0.94). The number of patients who needed to be treated to avoid one death was 28[542].

SR of RCT 1++

7.4.3. Target values

Despite the fact that many institutions that develop health recommendations include LDL cholesterol values as potential thresholds to obtain benefit, there is very little information available. Specifically, a review on this issue did not identify studies that showed the relationship between LDL cholesterol levels and vascular risk in patients with values below 130 mg/dl[543]. However, the main international and national institutions agree in recommending values below 100 mg/dl and in some cases even below 70 mg/dl. Even so, the long-term safety and impact of these intensive strategies on available resources remains unknown and therefore, more recent guidelines recommend treatment with statins, reflecting their reservations about establishing target values [291, 544, 545]. These CPGs also highlight that there is no evidence concerning the cost-effectiveness in relevant clinical variables of the combination of a statin with other hypolipemiant drugs to achieve LDL cholesterol target values[291].

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Summary of the Evidence

1++	In patients with a history of vascular disorders (including stroke) statin treatment reduces the risk of recurrence and new vascular episodes. Coronary episode risk is decreased more than stroke risk [238, 273, 274, 278-280].
1++	In patients with a history of ischemic stroke or transient ischemic attack, without prior coronary disease, high dose statin treatment reduces the risk of recurrence and other vascular episodes. However, adverse effects are more frequent at higher doses [540, 541].
	There is no direct evidence regarding what the target LDL cholesterol levels in secondary prevention are [543].

Recommendations

A	It is recommended that patients with ischemic stroke or prior atherothrombotic transient ischemic attack be treated with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels.
B	Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior atherothrombotic transient ischemic attack, regardless of their basal LDL-cholesterol levels.
✓	Treatment with statins should be jointly assessed with the patient after adequately informing him/her of the benefits and potential risks and taking associated pathologies and concomitant treatments into account. Aside from statin treatment, healthier lifestyles should be adopted.
✓	These patients should maintain LDL-cholesterol levels below 100 mg/dl.
✓	The combination of statins with other hypolipemiant drugs to reach LDL-cholesterol target values should be avoided.

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7.5. Hormone Therapy

Key Questions:

- In postmenopausal women with a history of stroke, does hormone therapy reduce the risk of new episodes?

HT had been widely used in postmenopausal women to prevent vascular diseases, osteoporosis and dementia up until the publication of the WHI study, which demonstrated that the risks outweighed the benefits[311] Evidence supporting this notion is consistent with results that appeared after the WHI[313] and WISDOM[314] studies. In secondary prevention, however, evidence is more limited.

RCT 1++/1+

A SR in postmenopausal women (7 RCTs, 32,000 women) reported that HT does not modify the risk of death due to any cause, coronary DEATH or non-fatal myocardial infarction. In 5 of these RCTs, the women had a history of vascular disease[546]. The SR evidenced increased risk of stroke in the case of estrogens alone or in combination with progestagens (831 events; RR: 1.29; 95% CI: 1.13 to 1.48). In the only RCT that included women with a history of stroke or TIA, HT was not associated with a differential risk of recurrence versus placebo[547].

SR of RCT RCT 1++

Summary of the Evidence

1++	HT treatment (with estrogens alone or in combination with progestagens) increases the risk of stroke in women with prior vascular disease [546, 547].

Recommendations

A	Hormone therapy (with estrogens alone or in combination with progestagens) is not recommended as secondary prevention of vascular disease in postmenopausal women.

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7.6. Thrombofilias

Key Questions:

- In patients with congenital or acquired thrombofilias who have had an episode of stroke, does antithrombotic treatment reduce the risk of new episodes?

7.6.1. Congenital thrombofilia

Several studies with different designs (RCTs, cohort and case-control studies) have evaluated the relationship between different congenital thrombofilias and the risk of stroke, yielding inconsistent results. The relationship with ischemic stroke is weak in adults. In patients with associated pathology and in children it is stronger. The relationship is more consistent for the risk of cerebral venous thrombosis, especially in women who take oral contraceptives. Evidence supporting this relationship does not differ from the evidence described in section 6.12 of primary prevention.

RCT 1+

Observational studies 2++

The issue concerning whether these congenital alterations can increase the risk of recurrent strokes is controversial. In this sense, the POLARIS study, currently in the recruitment phase, aims to study the relationship between different genetic polymorphisms (including factor V Leiden and prothrombin G20210A mutation) and the recurrence of thrombotic episodes, including strokes and TIAs.

7.6.2. Acquired thrombofilia

APS is a clinical condition characterised by recurrent thrombosis and the presence in plasma of antibodies against cell membrane phospholipids. In observational studies the presence of APS has been associated with the first episodes of thrombotic episodes and even stroke, even though the evidence is not yet consistent. The issue of whether APS has a role in recurrent strokes remains controversial. However, in several prospective studies, patients with ischemic stroke and APS presented a higher probability of recurrence[322].

Observational studies 2++

In patients with a history of vascular disease, the prospective observational cohort APASS (Antiphospholipid Antibodies and Stroke Study)[548] nested in the WARSS[549] trial, which was stratified according to the presence or absence of APAs, showed that the presence of APAs in patients with ischemic strokes does not entail an increased risk of occlusive vascular episodes at two years follow-up or a different response to aspirin or warfarin.

Cohort studies 2++

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Summary of the Evidence

1+/2+	There is controversy regarding whether different congenital thrombofilias can increase the risk of having recurrent strokes [305, 306, 316, 323].
2++	No relationship has been found between the presence of antiphospholipid antibodies and recurrence of stroke or other occlusive vascular episodes [322].
2++	The presence of antiphospholipid antibodies does not seem to increase the risk of recurrent strokes or to reach a different prognosis depending on the antithrombotic treatment prescribed after an ischemic stroke [348].

Recommendations

B	In patients with hereditary thrombofilia and a history of thrombotic episodes, long-term anticoagulant treatment is recommended.
B	In patients with previous ischemic stroke or transient ischemic attack, who have not presented any other alternative cause to the antiphospholipid syndrome, long term treatment with anticoagulants is recommended.

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7.7. Hyperhomocysteinemia

Key Questions:

- In patients with a history of stroke and hyperhomocysteinemia, do vitamin complexes reduce the risk of new episodes?

Different observational studies evidence the association between hyperhomocysteinemia, especially the form linked to the genetic alteration of the MTHFR enzyme, and vascular disease[330-332], including stroke[334]. **Observational studies 2++/2+**

Two SRs assessed the efficacy of folic acid supplements in patients with or without prior vascular disease according to plasma homocysteine levels, which were not high in all patients. The reviews yielded inconsistent results[336, 337]. The first review in a population with a history of vascular disease (12 RCTs, 16,958 patients) concluded that the risk of vascular disease, coronary disease, stroke or death in patients who received folic acid supplements or placebo is similar (RR: 0.86; 95% CI: 0.71 to 1.04)[336]. **SR of RCT 1+**

In another SR (8 RCTs, 16,841 patients) which assessed folic acid supplements, with or without B complex vitamins, an 18% stroke risk reduction was reported (RR: 0.82; 95% CI: 0.68 to 1.00) in favour of supplements versus control. The effect was obtained mainly in trials that lasted longer than 36 months, were conducted in countries that fortify cereals with folic acid and included patients without a prior history of stroke[337]. **SR of RCT 1+**

The VISP study (3,680 patients), the only one that has been conducted in population with a history of non-cardioembolic stroke and increased plasma homocysteine levels, assessed the effect of treatment with high and low vitamin doses (B6, B12 and folate)[550]. Although homocysteine values were lower by the end of follow-up in the group that received high doses of vitamins, it did not translate into decreased incidence of new episodes of stroke or other vascular outcomes or mortality. Additionally, a gradient between the different outcomes and basal homocysteine levels was evidenced and some authors determine that there is a probable benefit in patients with higher levels and/or a more pronounced decrease of homocysteine levels[551]. **RCT 1++**

The VITATOPS study, which aims to assess the effect of vitamin B6, B12 and folate supplements in the secondary prevention of stroke, is currently in the recruitment phase[552]. This study will contribute to a collaborative metaanalysis with 52,000 patients which will help to throw light on the effectiveness of this therapeutic option[553].

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Summary of the Evidence

2++	Elevated plasma homocysteine levels are associated with an increased risk of vascular disease and stroke. There is no evidence on whether the reduction of homocysteine levels reduces the risk of stroke recurrence [330-332, 334].
1++/1+	In patients with elevated plasma homocysteine levels and a history of stroke, complex B vitamins and/or folic acid do not seem to reduce the risk of stroke recurrence or other vascular episodes [336, 337, 550].

Recommendations

B	In patients with prior stroke or hyperhomocysteinemia, folic acid and vitamin B complex supplements should be considered with the aim of reducing elevated plasma homocysteine levels.

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7.8. Emboligenous cardiopathies

Key Questions:

- In patients with atrial fibrillation and a history of ischemic stroke or TIA, does antithrombotic treatment reduce the risk of new episodes?
- In patients with a prosthetic heart valve who are under adequate antithrombotic treatment and who present an ischemic stroke or TIA, what is the most adequate therapeutic strategy?
- In patients with certain cardiopathies such as MS, mitral valve prolapse of permeable foramen ovale and a history of an episode of ischemic stroke or TIA, does antithrombotic treatment or surgery reduce the risk of having new episodes?

7.8.1. Atrial fibrillation

Non-rheumatic atrial fibrillation is a frequent heart rhythm alteration that can be found in 17% of patients with prior stroke[554-558]. Annual mortality rate in these patients is 5%[559].

Antithrombotics.

Two SRs that assessed the efficacy of anticoagulant treatment versus placebo and antiaggregants for the prevention of recurrent stroke in patients with atrial fibrillation were identified[561, 562].

The first SR jointly analysed the results of two RCTs. Anticoagulant treatment reduced the risk of a new episode of stroke (74 events; OR: 0.36; 95% CI: 0.22 to 0.58) compared to placebo, even though the number of events was limited. Overall vascular events were reduced by 45% in patients treated with anticoagulants. The review showed a significantly increased risk of Severe extracranial hemorrhages for anticoagulant treatment (2.5 to 4 INR) versus the control group (2.8% and 0.7% respectively) according to the data derived from one study[561]. **SR of RCT 1++**

In the second SR, which also included two RCTs, anticoagulants were superior to antiaggregants in the prevention of recurrent strokes (OR: 0.49; 95% CI: 0.33 to 0.72) and new vascular episodes (OR: 0.67; 95% CI: 0.5 to 0.91). Severe extracranial hemorrhages were more frequent in patients taking anticoagulants, even though the absolute difference was extremely small[562]. **SR of RCT 1++**

Results were similar to those yielded by another SR (29 RCTs, 28,044 patients) that included studies on primary and secondary prevention of vascular episodes. Oral anticoagulants were superior to placebo and antiaggregants at preventing stroke in patients with atrial fibrillation[378]. Furthermore, a recent multicentre study performed on 973 patients without a **SR of RCT RCT 1++**

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history of stroke reported that the benefit of anticoagulant treatment can be applied to elderly patients[384].

The efficacy of anticoagulant treatment to prevent thromboembolic episodes in patients with atrial fibrillation has been consistently evidenced in several RCTs, even when compared to antiaggregant treatment. The optimal intensity of anticoagulant treatment for the secondary prevention of stroke lies between 2 and 3 INR[563, 564]. Efficacy is reduced for INR values below 2. Anticoagulant treatments have a narrow therapeutic margin and present frequent interactions with other drugs and with certain types of food, requiring frequent monitoring and dose adjustments. All this could contribute to infrautilisation of anticoagulant treatment or use of infratherapeutic doses, which could result in inadequate protection of high risk patients.

RCT 1++

No studies have been identified that assess possible therapeutic strategies in patients with atrial fibrillation who suffer a stroke, even when receiving treatment with optimal anticoagulation intensity. The additional benefit of intensifying anticoagulant treatment or adding an antiaggregant to this treatment is therefore unknown. However, the NASPEAF trial assessed the efficacy of combined treatment with anticoagulants and triflusal (600 mg/d) in 1,209 patients with high risk (valvular origin with or without prior embolism) or moderate risk atrial fibrillation. Combined treatment reduced the risk of vascular events (vascular death, TIA, non-fatal stroke or systemic embolism) in 67% of patients with moderate risk (HR 0.33; 95% CI: 0.12 to 0.91) and in 49% of high risk patients (HR 0.51; 95% CI: 0.27 to 0.96), compared to anticoagulant treatment alone. Combined treatment reduced the intensity of anticoagulation. The number of severe bleeding episodes was similar in high risk patients, but the total number of events was limited[383].

RCT 1+

Patient perceptions

Patients taking anticoagulants generally do not have enough information on the objectives and risks of this treatment (section 6.18)[367]. In a significant portion of patients anticoagulation self-management programmes lead to reduced thromboembolic episodes and risk of death[389-392].

Bleeding risk stratification systems

There are several models to estimate the risk of severe bleeding in patients who receive anticoagulant treatment[371-373], but all of them present limitations. It is essential to establish a balance between the benefits of anticoagulant treatment in reducing the risk of having a new episode of ischemic stroke or TIA and the risks of a severe bleeding episode. This risk should be evaluated in each patient using one of the currently available models (section 6.14.1)[374].

Observational studies 2++

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Summary of the Evidence

2++	Atrial fibrillation is a risk factor for stroke, especially in elderly patients who have had a prior ischemic stroke [364].
1++	In patients with paroxistic, persistent or permanent atrial fibrillation and a history of stroke, anticoagulant treatment (2 to 3 INR target range) is more effective than antiaggregants at preventing new episodes [378, 562].
1++	Anticoagulants present more hemorrhagic adverse effects than antiaggregants and require strict and periodic follow-up of treatment [378, 562].
	There are no studies that assess possible therapeutic strategies for patients with atrial fibrillation who have a stroke even when receiving treatment with optimal anticoagulation intensity.

Recommendations

✓	All patients with atrial fibrillation should be individually assessed in order to establish an adequate benefit-risk balance of anticoagulant treatment.
A	Treatment with oral anticoagulants with an INR target range of 2 to 3 for an indefinite period of time is recommended in patients with paroxistic, persistent or permanent atrial fibrillation who have previously suffered a stroke and who present no formal contraindications to treatment.
✓	In cases where anticoagulant treatment is contraindicated, treatment with aspirin (300 mg/d) is an appropriate alternative.
✓	Intensification of anticoagulation or combination with antiaggregant treatment (aspirin or triflusal) should be considered in patients with paroxistic, persistent or permanent atrial fibrillation, who receive correct doses of anticoagulant treatment and still present stroke or recurrent transient ischemic attack.

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7.8.2. Valve prostheses

There are several types of mechanical prosthetic heart valves. All of them require indefinite anticoagulant treatment. In section 6.14.4 of this guideline recommendations are provided to determine the required intensity of anticoagulant treatment depending on the type of mechanical valve and patient risk factors, following the recommendations formulated by the working group for vascular disease management of the European Society of Cardiology [565].

Even with anticoagulant treatment, the risk of presenting a thromboembolic episode in these patients ranges between 1% and 2% annually[425, 566]. Most of the evidence is indirect, deriving from trials that have assessed the combination of an antiaggregant and anticoagulant treatment, resulting in decreased incidence of thrombotic episodes but also an increased risk of bleeding.

SR of RCT 1++

A SR (11 RCTs, 2,428 patients) reported that combining antiaggregant treatment and anticoagulant treatment reduces the risk of thromboembolic episodes by 61% (156 events; OR: 0.39; 95% CI: 0.28 to 0.56) and overall mortality by 45% (173 events; OR: 0.55; 95% CI: 0.40 to 0.77) when compared to anticoagulant treatment alone. Both aspirin at low doses (100 mg) and dipiridamol yield similar results. The risk of major hemorrhagic episodes significantly increased by 66% (151 events; OR: 1.66; 95% CI: 1.18 to 2.34)[426].

Summary of the Evidence

1++	In patients with a mechanical heart valve prosthesis who have an ischemic stroke despite receiving anticoagulant treatment with an INR objective within the recommended range for each type of valve, combined treatment with aspirin at low doses (100 mg) or dipiridamol reduces overall mortality and the risk of thrombotic episodes, even though it also increases the risk of hemorrhagic episodes[426].

Recommendations

A	In patients with one or more mechanical prosthetic heart valves who have an ischemic stroke while receiving adequate anticoagulant treatment, it is recommended to add aspirin at low doses (100 mg) or dipiridamol.
✓	In patients with contraindications to aspirin, the joint administration of clopidogrel or triflusal and an anticoagulant is a correct strategy.

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7.8.3. Other cardiopathies

This guideline does not aim to provide detailed information on the therapeutic management of very specific conditions such as certain cardiopathies that are often found amongst the causes of stroke.

Mitral stenosis

MS due mainly to rheumatic fever is a frequent cause of recurrent systemic embolism. The highest risk corresponds to those patients who have developed atrial fibrillation[430, 431].

Observational studies 2+

There are not RCTs that assess the efficacy of anticoagulant treatment to reduce the risk of embolic episode recurrence in patients with MS. Several observational studies have reported reduced incidence of embolic episodes in patients who followed anticoagulant treatment, even though patients with and without prior embolic episodes were combined and in many cases they also had atrial fibrillation[432, 433, 567, 568].

Observational studies 2+

When considering antithrombotic treatment, its benefit should always be weighed with the risk of a hemorrhagic stroke. Taking the frequency and permanent sequelae of thromboembolic phenomena into account, the benefits of antithrombotic treatment are superior to the complications derived from hemorrhagic episodes, so in standard practice anticoagulant treatment would be indicated for most patients[569].

Expert opinions 4

Patients with MS who have developed atrial fibrillation should be considered at high risk of presenting recurrent embolic phenomena. Data extracted from large cohort studies have demonstrated the benefit of anticoagulant treatment in patients with atrial fibrillation and prior thrombotic episodes, even though patients with valvular atrial fibrillation were specifically excluded[570].

Cohort studies 2++

Mitral valve prolapse

MVP is a common cardiopathy, with a generally benign prognosis, even though the possibility that it may cause recurrent thromboembolic phenomena continues to be a much discussed issue[440, 442]. The presence of mitral regurgitation (moderate or severe), increased mitral valve thickness (>5mm) or left ventricle size (> 50 mm) measured by echocardiography are associated with a higher risk of vascular mortality and MVP-related complications[444, 445]. Patients with a thrombus in the left atrium or atrial fibrillation also have a higher risk of recurrent embolic phenomena.

Observational studies 2+

There are no randomised studies that compare the efficacy of different antithrombotic treatments in patients with ischemic stroke or TIA who present this type of valvulopathy. The benefits of antithrombotic treatment should be extrapolated from studies on secondary prevention, serving as a basis for the formulation of recommendations.

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Permeable foramen ovale

The persistence of a permeable foramen ovale is frequent in the general population. In echocardiographic studies it has been reported in 25.6% of the studied population. The septal aneurysm is less frequent and can affect up to 2% of the general population[571]. The possibility that the presence of a permeable foramen ovale may cause stroke is a much discussed issue: its importance is increasingly evident, especially in young patients. A SR of case-control studies showed that patients who had had a stroke presented more permeable foramen ovale and septal aneurysm findings (OR: 3.1; 95% CI: 2.3 to 4.2 and OR: 6.1; 95% CI: 2.5 to 15.2 respectively) [572]. Later, a case-control study determined the presence of atrial septal aneurysm to be an independent risk factor of stroke[573].

SR of case-control studies 2++/

Case-control studies 2+

A SR that included three cohort studies (one of them nested in the WARSS randomised study) did not find increased incidence of recurrent strokes or death (OR: 0.95; 95% CI: 0.62 to 1.44) in patients with permeable foramen ovale and with a history of stroke or TIA[574]. In all these studies, participants received antithrombotic treatment with antiaggregants or anticoagulants. There is insufficient data to estimate the risk for septal aneurysms given that patients who presented a permeable foramen ovale with or without septal aneurysm were combined.

SR of cohort studies 2++/2+

In regards to stroke recurrence, results yielded by different studies differ. One cohort study of 581 participants reported an increased risk of stroke recurrence in patients with permeable foramen (3.8% annually) versus patients without this defect (1.1% annually)[575]. In a previous cohort study of 160 participants, patients with or without permeable foramen showed a similar risk of stroke or TIA recurrence and only those patients with a greater degree of interatrial communication presented higher stroke recurrence[576].

Cohort studies 2++/2+

No differences were found between anticoagulant treatment and antiaggregant treatment in terms of stroke recurrence or death in a subgroup of patients of the WARSS trial[549] who participated in a prospective cohort[577], even though patients treated with anticoagulants presented more mild bleeding complications.

Cohort studies 1-

One therapeutic option consists of the percutaneous closure of the interatrial defect. There are no RCTs that compare medical treatment and surgical treatment. One SR (16 case series) that included 895 patients with medical treatment (antithrombotic) and 1,355 patients with surgical treatment showed that the surgical option can decrease the risk of recurrent episodes. The incidence of recurrent strokes or TIAs at one year for antithrombotic treatment varied between 3.8% and 12%, while in the case of surgical procedure it ranged between 0% and 4.9% even though it was associated to a higher incidence of complications[578].

SR of case series 3

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Summary of the Evidence

3	Mitral stenosis due to a rheumatic condition is a frequent cause of recurrent ischemic stroke [430-438].
2+/4	In patients with mitral stenosis who have already had a stroke, the benefits of anticoagulant treatment are superior to the risks derived from suffering a hemorrhagic episode [432, 433, 567, 568, 570].
2+	Mitral valve prolapse can cause recurrent ischemic stroke or transient ischemic attack. Certain conditions such as the presence of mitral regurgitation, increased mitral valve thickness or presence of a thrombus in the left atrium or atrial fibrillation comprise a group that is especially at risk [440, 442, 444, 445].
2++	Persistent foramen ovale and the presence of an atrial septal aneurysm have been associated with an increased incidence of stroke, even though the effect on the risk of recurrence is unclear [571-574].
1-	In patients with persistent foramen ovale, the benefits of anticoagulant or antiaggregant treatment are similar [577].
3	One possible therapeutic option is the percutaneous closure of the interatrial defect [578].

Recommendations

B	In patients with previous ischemic stroke or transient ischemic attack who present mitral stenosis anticoagulant treatment with an INR target range of 2 to 3 is recommended, regardless of whether they present atrial fibrillation or not.
B	In patients with previous ischemic stroke or transient ischemic attack who present mitral valve prolapse, antiaggregant treatment (100-300 mg/d of aspirin) is recommended.
C	In patients with previous ischemic stroke or transient ischemic attack who

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	present mitral valve prolapse as the only cause, anticoagulant treatment with an INR target range of 2 to 3 should be considered only in cases of high risk of presenting cardioembolic phenomena.
B	In patients with previous ischemic stroke or transient ischemic attack who present permeable foramen ovale, treatment with antiaggregants (100-300 mg/d of aspirin) is recommended.
C	In patients with permeable foramen ovale and previous ischemic stroke or transient ischemic attack, treatment with anticoagulants should be considered if there is an increased risk of cardioembolic episodes (atrial septal aneurysm or associated with large interatrial communication).
✓	Surgical procedure via percutaneous closure of the permeable foramen ovale should only be considered in the context of a clinical trial and in cases of repeat strokes.

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7.9. Symptomatic carotid artery stenosis

Key Questions:

- In patients with carotid artery stenosis and a history of an episode of ischemic stroke or TIA, does carotid endarterectomy reduce the risk of new episodes compared to endovascular techniques?
- What degree of carotid stenosis benefits most from the performance of these interventions?
- Does antithrombotic treatment (antiaggregant/anticoagulant) after the intervention provide additional benefits?

7.9.1. Carotid endarterectomy

The main pathology of supraaortic trunks is stenosis or atherosclerotic occlusion of the carotid artery at the bifurcation level. This arteriopathy can evolve without symptoms, but can cause about 30% of ischemic strokes[448]. There are some specific anatomic features of the carotid lesion that play an essential role in the rupture of the plaque and its distant embolisation such as ulceration of the atheromatous plaque or that embolisation causes the formation of a thrombus[579].

The benefits of CEA in patients with prior ischemic stroke or TIA and different degrees of carotid artery stenosis have been assessed in three big clinical trials: the NASCET[580], ECST [581] and the Veterans Affairs Cooperative Study Program (VACSP)[582].

The NASCET and ECST trials assessed the degree of carotid artery stenosis using imaging techniques and obtained differential results in regards to the percentage of occlusion. Table 16 shows the corresponding values for both proposals.

Table 16. Corresponding ECST and NASCET values for assessment of carotid artery stenosis[583]

ECST	30%	50%	58%	70%	82%	99%	100%
NASCET	-17%	17%	30%	50%	70%	99%	100%

Adapted from: Cina CS, Clase CM, Haynes RB. *Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database of Systematic Reviews*. 1999, Issue 3. Art. No.: CD001081.

It is important to note that the performance of these trials and the potential benefits documented for CEA were prior to the appearance and generalised use of treatments that have been proven to reduce the risk of stroke in patients with prior vascular disease, such as the combination of aspirin and dipiridamol, statins and the generalisation of recommendations on the strict monitoring of blood pressure values. At present there is uncertainty regarding the real absolute benefit of CEA in patients with a more intensive medical treatment for vascular disease.

A SR jointly analysed the results of the NASCET and ECST studies (5,950 patients), even though it did not include the results from the VASCP study, **SR of RCT 1++**

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which ended prematurely after the NASCET study results came out[583]. The benefit of CEA was associated with the degree of stenosis, so the intervention resulted in an overall reduction of the risk of disabling stroke and death in patients with moderate or severe stenosis (NASCET >50%; ECST >70%). Net benefit was moderate for patients with moderate stenosis (NASCET 50 to 69%; ECST 70 to 82%), while lesser degrees of stenosis were harmed by CEA. Table 17 presents a summary of the review's main results.

Table 17. Main results of the SR according to degree of stenosis[583]

% of stenosis		Disabling stroke or death		Disabling stroke or death (30 days)	
ECST	NASCET	RRR (95% CI)*	ARR (95% CI)**	RR (95% CI)***	ARR (95% CI)
82-99	70-99	48% (27 to 63)	6.7% (3.2 to 10)	3.52 (1.11 to 11.13)	2% (1 to 3)
70-81	50-69	27% (5 to 44)	4.7% (0.8 to 8.7)		
<70	<50	20% (0 to 44)	2.2% (0 to 4.4)	2.16 (1.36 to 3.44)	1% (1 to 2)

Adapted from: Cina CS, Clase CM, Haynes RB. *Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database of Systematic Reviews*. 1999, Issue 3. Art. No.: CD001081.

*RRR (95% CI): Relative risk reduction and its 95% confidence interval.
**ARR (95% CI): Absolute risk reduction and its 95% confidence interval.
***RR (95% CI): Relative risk and its 95% confidence interval.

A subgroup analysis of this review reported that the greatest benefits of surgery are achieved if the procedure is performed sometime within two weeks and 3 months after a non-disabling ischemic stroke or TIA. The benefit decreases if the procedure is performed more than six months after the acute episode[583]. Results obtained from later SRs indicate that in these patients there are no data to support delayed surgical procedure [584, 585].

Summary of the Evidence

1++	In patients with a history of ischemic stroke or transient ischemic attack and with a moderate-to-severe degree of carotid artery stenosis (>50% of NASCET values), CEA has been beneficial, especially if performed at an early stage [583].
1++	Treatment with antiaggregants after a CEA results in reduced risk of stroke [456].
1+	CEA has obtained better results than endovascular procedures in the majority of patients [459-461].

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Recommendations

A	Carotid endarterectomy is recommended in patients with ischemic stroke of at least 6 months evolution and significant stenosis of the carotid artery (70% to 99%, NASCET values), if and when the surgical team confirms a perioperative morbimortality of less than 6%.
B	In patients with ischemic stroke of less than 6 months evolution and moderate carotid artery stenosis (50% to 69%, NASCET values), carotid endarterectomy should be considered depending on factors such as sex, age and the presence of other comorbidities.
A	In patients with mild carotid artery stenosis (less than 50%, NASCET values), carotid endarterectomy is not recommended.
B	In patients with ischemic stroke or non-disabling transient ischemic attack and surgical indication, it is recommended to perform the procedure within the first two weeks following the episode.
A	In patients who are not candidates for intervention, treatment with antiaggregants is recommended after carotid endarterectomy, as well as intensive intervention on other vascular risk factors.
B	The use of endovascular techniques with stent implantation is not routinely recommended. Indications should be individualised in patients with high surgical risk if there are technical difficulties for performing carotid endarterectomy or within the context of a clinical trial.

Note: The information regarding the safety of CEA, antiaggregant treatment after the procedure and endovascular treatment do not differ from what has been presented in the section on asymptomatic carotid artery stenosis. The evidence presented in the aforementioned section should be used for the synthesis of the evidence and the elaboration of the following recommendations.

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7.10. Antithrombotic treatment in the secondary prevention of stroke

Key Questions:

- In patients with a history of an episode of non-cardioembolic ischemic stroke or TIA, does antiaggregant treatment reduce the risk of new episodes?
- Does the combination of two antiaggregant treatments provide an additional benefit versus treatment with only one antiaggregant?
- Has anticoagulant treatment been proven to be superior to antiaggregant treatment?

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7.10.1. Antiaggregant treatment

SR of RCT 1++

Antiaggregants have proven to reduce the risk of vascular episodes such as myocardial infarction, stroke or vascular death in patients with high vascular risk in a SR (287 RCTs). Specifically, in patients with a history of ischemic stroke or TIA, antiaggregants showed a 25% reduction for new episodes of stroke and a 20% increase for hemorrhagic strokes. Absolute difference favoured antiaggregant treatment, with a subsequent 2.7% reduction of any stroke. Absolute reduction of vascular episodes was 3.6% (Table 18). Most evidence was for the use of aspirin. 75 mg to 150 mg per day aspirin doses were as effective as higher doses and presented fewer adverse effects, even though the risk of severe bleeding was similar. The review concludes that there is insufficient evidence to determine that any other antiaggregant treatment is superior to aspirin, even though most studies were small[403].

Table 18. Estimators of relative and absolute risk of antiaggregants versus control in the prevention of vascular episodes in patients with high vascular risk[403]

	Relative effect (number of events)	Absolute effect
Overall vascular episodes	-22 % (17,207 events)	-2.5%
Vascular episodes in patients with prior stroke/TIA	-22% (4,509 events)	-3.6%
Ischemic strokes in patients with prior stroke/TIA	-25% (1,780 events)	-2.4%
Hemorrhagic strokes in patients with prior stroke/TIA	+20% (115 events)	+0.08%
Any stroke in patients with prior stroke/TIA	-23% (2,807 events)	-2.7%

Adapted from: 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.

RCT 1++

The direct comparison of clopidogrel and aspirin was carried out in the CAPRIE trial, which included over 19,000 patients. In this RCT clopidogrel (75 mg/d) reduced the risk for a combined variable comprised of ischemic stroke, myocardial infarction and vascular death versus aspirin (325 mg/d) in

a population with prior vascular disease. The absolute difference of risk was 0.5% annually. There were no differences between both treatments in the subgroup of patients with a history of stroke and the differences were mainly due to patients with peripheral arteriopathy. The incidence of adverse effects was similar, while gastrointestinal tolerance could be better for clopidogrel[586].

Tioclipidin is an active ingredient structurally similar to clopidogrel which has not been proven superior to aspirin and presents frequent adverse effects such as diarrhea (12%), skin rash or, less frequently, neutropenia (2%, severe neutropenia <1%)[403, 587, 588]. **RCT 1+**

Two RCTs specifically assessed the efficacy of triflusal in the secondary prevention of stroke [589, 590]. The TACIP trial, which included 2,113 patients with prior ischemic stroke or TIA, did not show differences for a combined variable comprised of vascular episodes (including stroke) between triflusal (600 mg/d) and aspirin (325 mg/d). Results for non-fatal strokes were also similar. The overall incidence of hemorrhagic episodes was significantly higher for aspirin (25.2% versus 16.7%)[589]. Additionally, results of a previous trial (TAPIRSS) were similar[590]. A recent SR (4 RCTs, 2,994 patients) did not show differences between treatment with triflusal and aspirin (>300 mg/d) for the secondary prevention of vascular episodes, including stroke and TIA (596 events). In patients with prior ischemic stroke or TIA, triflusal was superior to aspirin in reducing recurrence of fatal episodes (253 events). The risk of hemorrhagic episodes, including severe ones, was lower for triflusal, with a 1.7% absolute reduction[591]. **RCT 1++** **SR of RCT 1+**

The benefit of introducing aspirin treatment (160 to 300 mg/d) is produced immediately (within the first 48 hours) after the clinical suspicion of ischemic stroke, according to the joint analysis of two big RCTs in which 40,000 patients participated. The relative reduction of recurrent strokes was 30%. 1.5% of patients treated with aspirin and 2.3% of the control group had a recurrent ischemic stroke (777 events), which corresponds to a 0.7% absolute reduction. In contrast, the risk of having hemorrhagic strokes or hemorrhagic transformation of the stroke was 1% and 0.8% for aspirin and the control group, respectively. With all this, aspirin reduced the risk of having any type of stroke or death in the hospital in 9 out of every 1,000 patients. It should be noted that in most patients hemorrhagic stroke was ruled out by means of neuroimaging before continuing treatment. Benefits were observed within the first four weeks, which was the maximum duration of the studies included[592]. **RCT 1+**

Combinations

The strategy of adding an antiaggregant that acts on platelet aggregation via a different route could yield an additional benefit. Two SRs have assessed the combination of aspirin at different doses and dipiridamol in patients with a history of vascular disorders. The most recent SR (6 RCTs and 7,648 patients) only included secondary prevention studies. The dose of aspirin **SR of RCT 1++**

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(30-1,300 mg/d) and dipiridamol (150-400 mg/d) varied, as well as the immediate- or sustained-release pharmaceutical presentation. The combination of aspirin and dipiridamol, when compared to aspirin, reduces the risk of a new episode of non-fatal stroke by 23% (675 events; RR: 0.77; 95% CI: 0.67 to 0.89). Only the studies that used sustained release dipiridamol (2 RCTs) were associated with a significant benefit for the prevention of new strokes (549 events) or other vascular episodes (934 events)[593].

Another SR, without the results of the ESPRIT study, determined that the combination of dipiridamol and aspirin significantly reduces 10% of vascular episodes in a combined variable[594]. **SR of RCT 1++**

The ESPRIT study demonstrated that treatment with sustained release dipiridamol (400 mg/d) and aspirin, compared to aspirin alone, reduced a variable comprised of vascular-related death, stroke or non-fatal myocardial infarction and major hemorrhagic episode by 20% (389 events; HR 0.80; 95% CI: 0.66 to 0.98) in patients with a presumably arterial ischemic stroke or TIA. Headache was a frequent cause (26%) of dipiridamol treatment discontinuation[595]. Additionally, the ESPRIT trial compared the efficacy of anticoagulant treatment (2 to 3 INR) versus aspirin (30-325 mg/d) in 1,068 patients with a history of ischemic stroke or TIA. The trial ended early after results confirmed the efficacy of combined dipiridamol and aspirin. Anticoagulant treatment was not superior to aspirin at reducing the risk of vascular episodes or at the secondary prevention of new episodes of ischemic stroke and was associated with a higher risk of severe bleeding[596]. **RCT 1+**

The combination of aspirin and clopidogrel was assessed in two big studies (CHARISMA and MATCH) in high vascular risk patients or patients with established vascular disease[597, 598]. Combined treatment was not more effective than aspirin or clopidogrel monotherapy and was associated with an increased risk of severe bleeding. Only one fourth of patients had a history of stroke. A later analysis of the CHARISMA study indicated a reduction of the variable comprised of vascular death, myocardial infarction and stroke in patients with an established vascular disease (763 events; HR 0.83; 95% CI: 0.72 to 0.96)[599]. **RCT 1++**

The efficacy and safety of long-term clopidogrel treatment compared to the combination of aspirin and dipiridamol is being assessed in the ProFESS trial (Prevention Regimen for Effectively Avoiding Second Strokes Trial)[600].

Bleeding risk

A case-control study analysed the risk of digestive bleeding for different antiaggregants. Aspirin and ticlopidin increased the risk of bleeding (OR: 4.0; 95% CI: 3.2 to 4.9 and OR: 3.1; 95% CI: 1.8 and 5.1 respectively), while clopidogrel, dipiridamol and triflusal did not show this association[468]. **Case-control studies 2++**

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7.10.2. Anticoagulant treatment

SR of RCT 1+

A SR (5 RCTs, 4,076 patients) that compared the efficacy of anticoagulant treatment, at different intensities, to antiaggregation in patients with a history of non-cardioembolic stroke, did not report differences in the risk of presenting a new episode. No differences were found between anticoagulants (INR up to 2.6) and antiaggregants in terms of deaths due to vascular causes or overall mortality. However, intense anticoagulant treatment (3 to 4.5 INR) was associated with a significant increase of overall mortality and severe bleeding episodes (RR: 9.0; 95% CI: 3.9 to 2.1)[601].

Summary of the Evidence

1++	In patients with high vascular risk, antiaggregants (aspirin, clopidogrel and triflusal) reduce the risk of vascular episodes such as stroke, myocardial infarction and vascular death [403].
1+	The combination of aspirin and sustained release dipiridamol results in increased efficacy versus aspirin monotherapy for the prevention of recurrent stroke or other vascular episodes [592].
1++	The combination of aspirin and clopidogrel is not more effective than monotherapy for the prevention of recurrent stroke and is associated with increased severe bleeding [586].
1++	Antiaggregant treatment with triflusal has similar efficacy to aspirin for the secondary prevention of vascular episodes, with fewer bleeding adverse effects [589, 590].
1+	Aspirin treatment within the first 48 hours of determining the clinical suspicion of ischemic stroke has been beneficial [592].
1++	Anticoagulant treatment is not more effective than antiaggregants at reducing the recurrence of non-cardioembolic stroke and is associated with an increased risk of bleeding episodes [601].

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Recommendations

A	In patients with non-cardioembolic ischemic stroke or transient ischemic attack, platelet antiaggregation with aspirin (100-300 mg/d), combination of aspirin and sustained release dipiridamol (50 and 400 mg/d), triflusal (600 mg/d) or clopidogrel (75 mg/d) are recommended.
A	Long term use of combined aspirin and clopidogrel is not recommended due to the increased risk of bleeding complications.
A	In patients with ischemic stroke or transient ischemic attack, the systematic use of anticoagulant treatment to prevent recurrent strokes is not recommended.
A	It is recommended to initiate treatment with aspirin within the first 48 hours of the clinical suspicion of ischemic stroke and after ruling out hemorrhagic stroke.
✓	In the case of presenting recurrent strokes despite adequate antiaggregant treatment, underlying causes should be carefully reviewed and the management of risk factors prioritised.

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7.11. Cerebral venous thrombosis

Key Questions:

- In patients with cerebral venous thrombosis, does anticoagulant treatment reduce the risk of new episodes?
- What is the optimal duration of anticoagulant treatment?

Cerebral venous thrombosis is an uncommon cause of stroke. Its incidence in adults is unclear, given that there are no population-based epidemiological studies that address this issue. Its most frequent presentation is in young adults, especially women in a ratio of 3 men per each 10 affected women[602]. In children, incidence is estimated to be between 6 and 7 cases per one million, half of them newborns[603]. Diagnosis is often difficult to make or delayed due to the wide spectrum of clinical signs and symptoms that include headache, focal neurologic deficits, convulsions, mental status disorders, intracranial hypertension or papiledema, amongst others. Although the main diagnosis is based on neuroimaging, often it shows non-specific lesions[604].

Observational studies 2+

There are several factors that have been associated with a greater incidence of cerebral venous thrombosis, such as certain congenital or acquired thrombofilias (congenital mutations of the coagulation factor V Leiden), pregnancy and the postnatal period, use of oral contraceptives and certain infections in areas close to the brain sinuses, even though in the majority of cases is has a multifactorial etiology and it is possible to identify more than one factor[306].

Observational studies 2+

The objective of the initial treatment is to achieve recanalization of the sinus or thrombosed vein and also to prevent recurrence or future episodes of thrombosis in other territories. Treatment with anticoagulants is also controversial because cerebral venous thrombosis can spontaneously result in hemorrhagic stroke[605]. Three RCTs have been located that assess non-fractioned and low molecular weight heparin treatment after the diagnosis of cerebral venous and sinus thrombosis[606-608]. One SR showed the combined results of two of them for a total of 79 patients[609]. There were no differences between heparin treatment and placebo in terms of death or dependence at three months, even though the number of events was very limited. Seven deaths were reported in the group that received placebo and two in the active treatment group. Neither study properly assessed new thromboembolism cases. In spite of this, two probable cases were reported, both in the control group.

RCT 1++/1+

No randomised studies that assess the efficacy of oral anticoagulant treatment have been identified, while two SRs of observational studies did not yield conclusive evidence for the use of thrombolysis[610, 611].

SR of observational studies 2+

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The ISCVT observational study showed the results in 624 patients with cerebral vein and sinus thrombosis with a 16-month follow-up. 2.2% of patients had a new episode of cerebral vein thrombosis, while 4.3% of patients had another type of thromboembolic episode. More than half the patients with new episodes did not follow anticoagulant treatment. Mean duration of anticoagulant treatment was 7.7 months. This study proposed mental status disorder (a certain degree of coma) and the presence of thrombosis in other deep vein territories as poor prognostic factors[605].

Cohort studies 2+

The optimal duration of anticoagulant treatment is unknown. In patients older than 65 years, the probability of thrombotic episodes is greater, worsening prognosis[612].

Other guidelines have addressed diagnosis and treatment of patients with cerebral vein and sinus thrombosis is detail[613].

Summary of the Evidence

2+	Cerebral venous thrombosis may occasionally cause recurrent ischemic and hemorrhagic strokes [602-604].
1++/1+	Anticoagulant treatment, first with heparin and later with oral anticoagulants, seems beneficial, but the evidence is very limited [606-608].

Recommendations

D	In patients who have had cerebral venous thrombosis, initial treatment with heparin and later with oral anticoagulants over a period of three to six months is recommended.
D	In patients with congenital or acquired thrombofilias and in patients over the age of 65 or with other factors that favour thrombotic phenomena, treatment with oral anticoagulants up to twelve months is recommended.

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7.12. Antithrombotic treatment after intracerebral hemorrhage

Key Questions:

- What therapeutic approach should be adopted in a patient who presents intracerebral hemorrhage during treatment with antithrombotics?

The use of antithrombotics (antiaggregants or anticoagulants) in patients who have had an ICH is a complex clinical situation. Most of the evidence has been extracted from case series of patients who were receiving anticoagulant treatment due to a mechanical heart valve prosthesis or for the treatment of atrial fibrillation and had an ICH during this time. The detailed management of this situation has been addressed in other CPGs[237].

Anticoagulant treatment, still within a 3 to 2 INR therapeutic target range, entails a two-fold increased risk of presenting ICH. The incidence of this complication is estimated to be approximately 0.3% annually[365, 614]. Similarly, treatment with antiaggregants can increase the risk of ICH up to 80%[615]. Table 19 shows the incidences of ICH in different clinical conditions[616].

RCT

SR of RCT
1++

Table 19. ICH absolute risks [616]

General population (mean age: 70 years)	0.15%/year
Aspirin (any dose)	
Atrial fibrillation	0.2%/year
Cerebrovascular disease	0.3%/year
Aspirin plus clopidogrel	
Atrial fibrillation	0.3%/year
Cerebrovascular disease	0.4%/year
Anticoagulation (INR 2.5)	
Atrial fibrillation	0.3%-0.6%/year
Cerebrovascular disease	0.4%-1.0%/year
Anticoagulation (INR 2.5) plus aspirin	0.5%-1.0%/year

Adapted from: Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke. 2005;36:1588-93.

There are situations in which the risk of presenting ICH during treatment with anticoagulants increases, such as elderly age (generally >75 years), high blood pressure (SBP >160 mmHg), prior strokes or anticoagulation intensity[617-619].

Observational studies
2++/2+

7.12.1. Use of anticoagulants

Although there is no data on the efficacy and safety of interrupting anticoagulant treatment, in standard clinical practice, in a patient with ICH or SAH, anticoagulant treatment is interrupted with the aim of normalising INR values as soon as possible, aside from initiating treatment with heparin inhibitors or vitamin K.[237]

Expert opinions
4

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Several case series have described the clinical evolution after stopping anticoagulant treatment. The risk of having an ischemic stroke or other embolic episode during the period of anticoagulant treatment discontinuation (between 10 and 20 days) is, in theory, relatively low. Hence, in a case series with 28 patients who had mechanical heart valve prostheses, no embolic episodes were reported after a period of two weeks without anticoagulant treatment[620]. In another case series of 141 patients with ICH, the risk of presenting an ischemic stroke depended on the indication of anticoagulation. In patients with a heart valve prosthesis, risk was 2.9% and, finally, 4.8% in patients with a history of ischemic stroke or TIA[621].

Case series 3

A decision analysis assessed the approach that should be adopted after ICH in patients who presented indication for anticoagulant treatment, specifically atrial fibrillation. The study concludes that anticoagulant treatment cannot be recommended after an ICH unless there is a risk of ischemic stroke higher than 6.5% in one year. Aspirin is preferable in cases in which the risk of ischemic stroke is lower than 6.5% annually[622]. Results would be applicable in those cases in which ICH has been caused by a prior anticoagulant treatment as well as other causes.

Observational studies 2+

7.12.2. Use of antiaggregants

A SR (9 RCTs, 2,043 patients) that assessed the safety of antiaggregant treatment after suffering ICH or SAH demonstrated that antiaggregant treatment does not increase the risk of a new episode. However, the study presents certain limitations. In the trials included to estimate the risk of recurrence of a SAH, patients underwent mostly surgical treatment of an aneurysm. Additionally, the fact that antiaggregant treatment was interrupted in half of the patients after diagnosis of ICH should be taken into[623].

SR of RCT 1-

7.12.3. Use of low molecular weight heparins

Deep venous thrombosis and pulmonary embolisms are a cause of morbimortality in patients who have had an ICH. To avoid this complication, one of the therapeutic options available is low molecular weight heparins, but the risk of bleeding should be acknowledged. A RCT performed in a limited number of patients showed that the introduction of low molecular weight heparins after the first two days of an ICH significantly reduced thrombotic complication versus a later administration. Re-bleeding did not increase in either group[624].

RCT 1-

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Summary of the Evidence

2+	The risk of presenting intracerebral hemorrhaging during anticoagulant treatment is superior in certain clinical situations such as elderly age, high blood pressure, prior stroke or anticoagulation intensity [617-619].
2+	The risk of initiating anticoagulant treatment after intracerebral hemorrhaging outweighs, overall, the benefit in patients who do not present a very high risk of embolic ischemic episodes [620-622].
4	The decision to initiate or resume anticoagulant treatment should be individualised acknowledging the risk of a new intracerebral hemorrhage [237].

Recommendations

B	Generalised introduction of anticoagulant or antiaggregant treatment is not recommended after an intracerebral hemorrhage.
√	In patients who require anticoagulant treatment due to a previous condition, restoration of treatment should be individually assessed.
C	Anticoagulant treatment should be considered seven to ten days after an intracerebral hemorrhage only in patients with very high risk (>6.5% annually) of presenting ischemic stroke.
C	Treatment with low molecular weight heparins should be considered two days after intracerebral hemorrhage with the aim of reducing the risk of deep venous thrombosis or pulmonary embolism.
C	In patients who, after intracerebral hemorrhage, present indication for antithrombotic treatment and in those for whom anticoagulant treatment is not advisable, treatment with antiaggregants is an alternative.

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8. Dissemination and implementation

Guideline formats, dissemination and implementation

The CPG consists of two versions, the complete version and the summarised version, as well as the section containing information for patients. All versions are available in HTML format and PDF format at the GuiaSalud (HealthGuide) website (www.guiasalud.es). The summarised version is printed in paper and contains the CD-ROM with the complete version.

- Dissemination and implementation strategies are as follows:
- Official presentation of the guideline by the health care authorities.
- Individualised delivery of copies to professionals and potential users.
- Distribution of the guideline amongst patients.
- Dissemination of the guideline in electronic format in the websites of the health services and societies involved in the project.
- Presentation of the guideline in scientific activities (conferences, congresses, meetings).
- Publication of the guideline in medical journals.

Proposed indicators

Below is a list and description of the indicators proposed by the authors of this guideline. Their objective has not been to design a comprehensive and detailed assessment that entails the use of all proposed indicators. Those in charge of evaluating the impact of the CPG and the health care of patients should choose the most appropriate information sources and the most convenient timeframe that each indicator refers to.

Primary prevention of stroke

- Proportion of patients over the age of 40 in whom vascular risk has been assessed and recorded in the medical chart for the five previous years.
- Proportion of patients over the age of 40 in whom blood pressure values were determined and recorded in the medical chart for the two previous years
- Proportion of patients over the age of 45 in whom blood cholesterol values have been determined and recorded in the medical chart for the five previous years.
- Proportion of adult patients whose body weight has been determined and recorded in the medical chart for the five previous years.
- Proportion of patients who are smokers who are provided with counselling to quit smoking.
- Proportion of patients with high vascular risk who are prescribed treatment with statins as a vascular risk prevention strategy.

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Secondary prevention of stroke

- Proportion of patients who have had an ischemic stroke or a TIA who receive antiaggregant treatment.
- Proportion of patients who have had an ischemic stroke or atherothrombotic TIA who receive statin treatment.
- Proportion of patients with atrial fibrillation and who have had an ischemic stroke or TIA who receive anticoagulant treatment.
- Proportion of patients who are smokers who have had an ischemic stroke or TIA and have quit smoking.
- Proportion of patients who have had an ischemic stroke or TIA who undergo a carotid artery imaging study.

Other shared indicators of vascular disease proposed by the National Health System (Quality Plan) are presented in Annex 8.

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9. Recommendations for future research

Primary Prevention

Validation of the SCORE tables in our setting.

Studies in primary care that assess the efficacy of brief interventions at reducing alcohol consumption in populations at risk.

Studies that assess the effect of the Law on Tobacco in our country.

Studies that assess clinical variables of the benefit of different strategies to achieve smoking cessation.

Long-term studies that assess the minimal effective dose of treatment with antiaggregants.

Studies that assess the benefits of antiaggregant treatment, such as primary prevention of vascular events, in the diabetic population.

Studies that assess the comparative efficacy of different statins.

Studies that compare high dose statins to standard dose statins in patients with high vascular risk.

Secondary prevention

Studies that assess the maintenance of lifestyle changes after having a stroke.

Studies that assess the benefits of double antiaggregation treatment in patients who present recurrent stroke or very high vascular risk.

Studies that assess resistance to antiaggregant treatment in patients with good management of risk factors and recurrent stroke.

Studies that assess the comparative efficacy of different statins.

Studies that assess different doses of statins based on specific target values.

Studies that assess the benefits of bypass surgery in certain cases of caro
tid artery stenosis.

Studies that assess the long-term safety of more aggressive (high doses) strategies with statins.

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Annexes

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Annex 1. Levels of evidence and grades of recommendation

Levels of evidence

1++	High quality meta-analysis, systematic reviews of clinical trials or high-quality clinical trials with low risk of bias.
1+	Well conducted meta-analysis, systematic reviews of clinical trials, or well conducted clinical trials with low risk of bias.
1-	Meta-analysis, systematic reviews of clinical trials, or clinical trials with high risk of bias.
2++	High quality systematic reviews of cohort or case-control studies Cohort or case-control studies with very low risk of bias and high probability of establishing a causal relationship.
2+	Well conducted cohort or case-control studies with low risk of bias and moderate probability of establishing a causal relationship.
2-	Cohort or case-control studies with high risk of bias and significant risk of non-causal relationship.
3	Non-analytic studies such as case reports, case series or descriptive studies.
4	Expert opinion.

Grades of recommendation

A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the guide's target population, or a body of evidence composed of studies classified as 1+ with high consistency amongst them.

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B	Body of evidence composed of studies classified 2++, directly applicable to the guide's target population and that have been shown to have high consistency amongst them, or evidence extrapolated from studies classified as 1++ or 1+.
C	Body of evidence composed of studies classified as 2+ directly applicable to the guide's target population and that have shown to have high consistency amongst them; or evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 evidence or evidence extrapolated from studies classified as 2+.

Good clinical practice

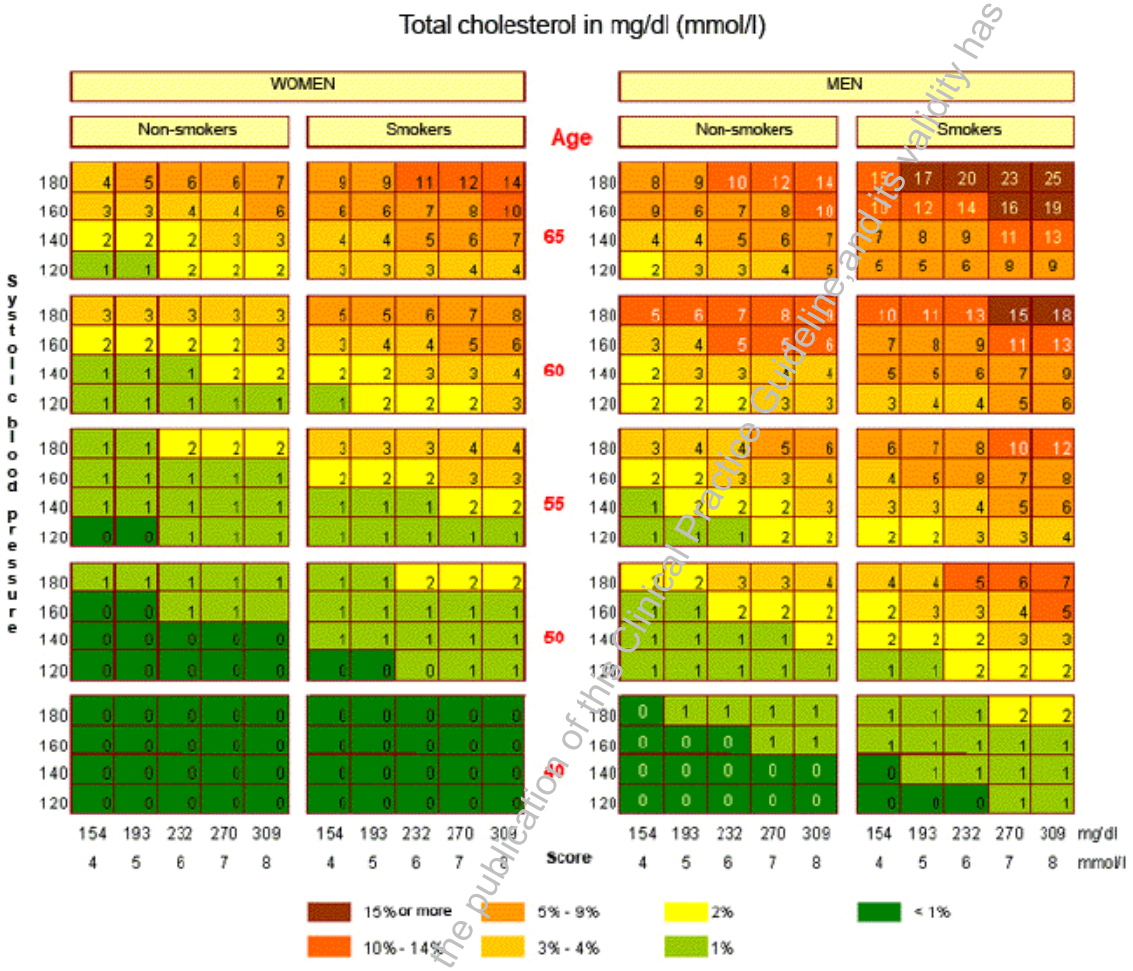
√ *	Recommended practice based on clinical experience and the consensus of the elaborating team.

* Occasionally the working group becomes aware that there is an important practical aspect it wishes to emphasise and for which there probably is no supporting evidence available.

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Annex 2. Vascular risk calculation tables (SCORE and REGICOR)*

SCORE table for risk of fatal cardiovascular disease at 10 years in low-risk European regions according to sex, age, BP, total cholesterol and tobacco smoking.

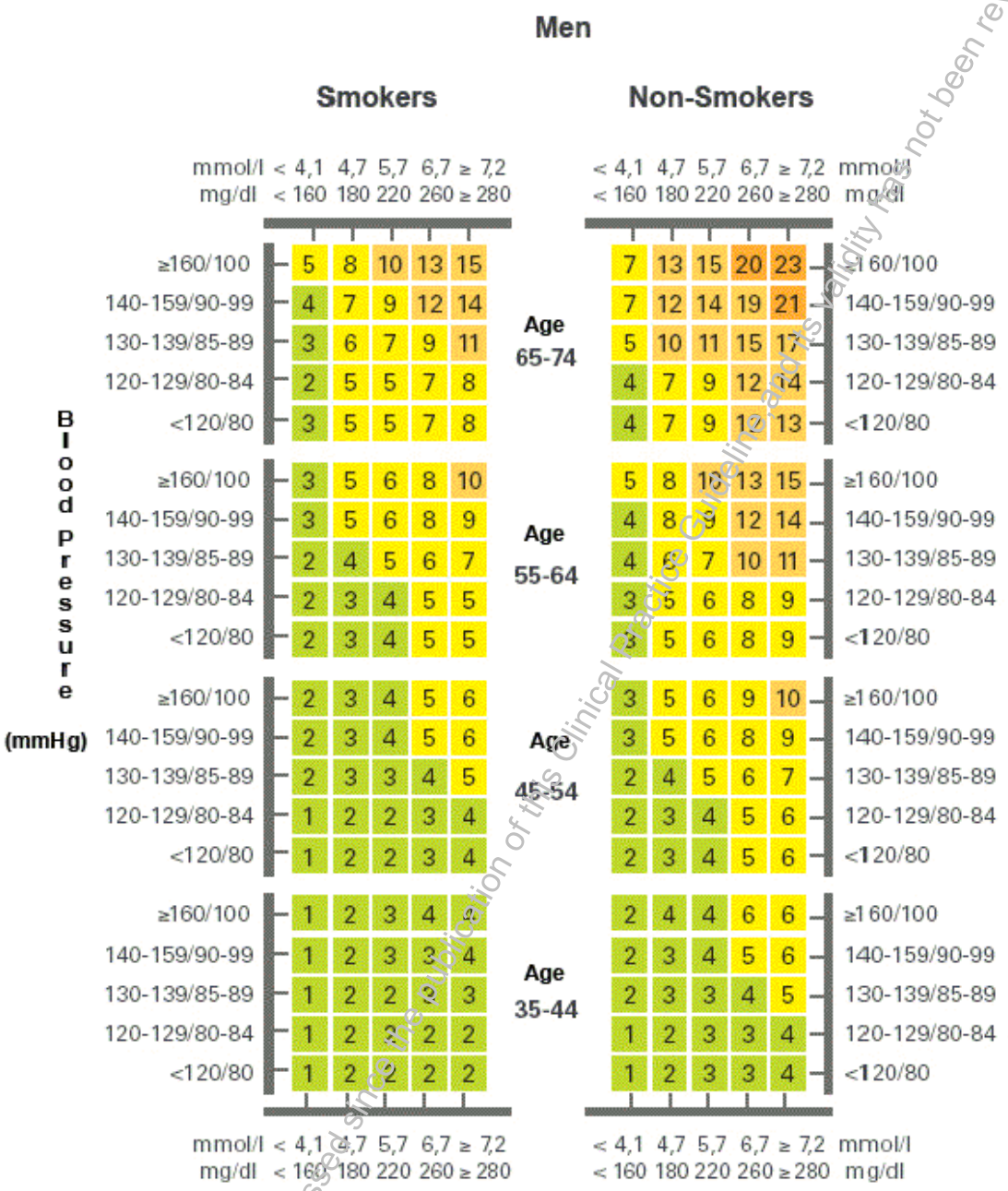


Percentage of risk of cardiovascular death at 10 years in low-risk European regions. Version with total cholesterol

Reproduced from the original version of the *European guidelines on cardiovascular disease prevention in clinical practice*. Summarised version (European Heart Journal 2007;28:2375-414) and complete text [(European Journal of Cardiovascular Prevention and Rehabilitation 2007;14(suppl 2):S1-S113),(Rev Esp Cardiol. 2008;61(1):e1-e49)]. Reproduced with permission from the European Society of Cardiology. © 2007 ESC.

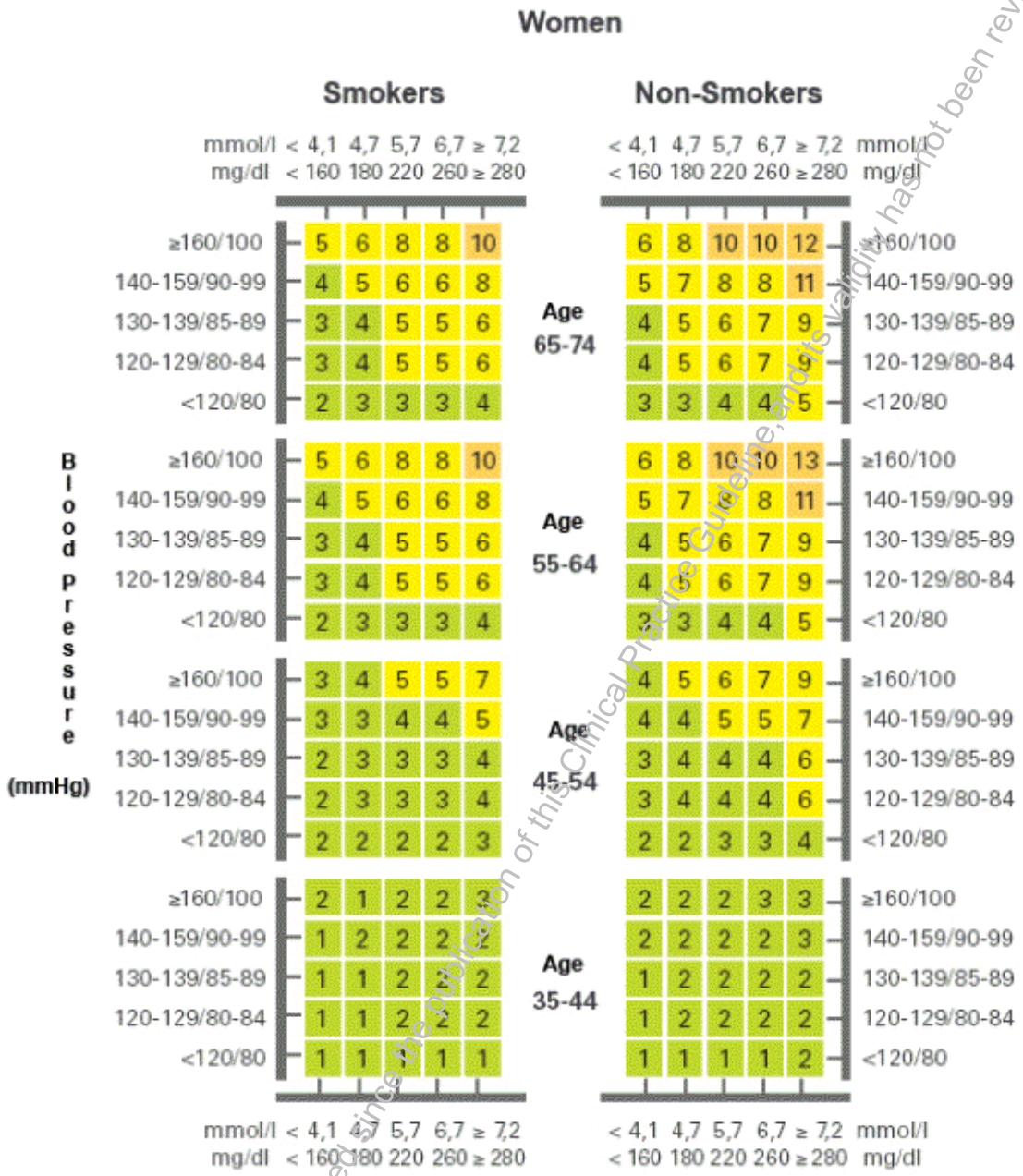
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REGICOR table for risk of coronary disease (fatal or non-fatal) in men at 10 years according to age, systolic blood pressure (SBP), total cholesterol and tobacco smoking.



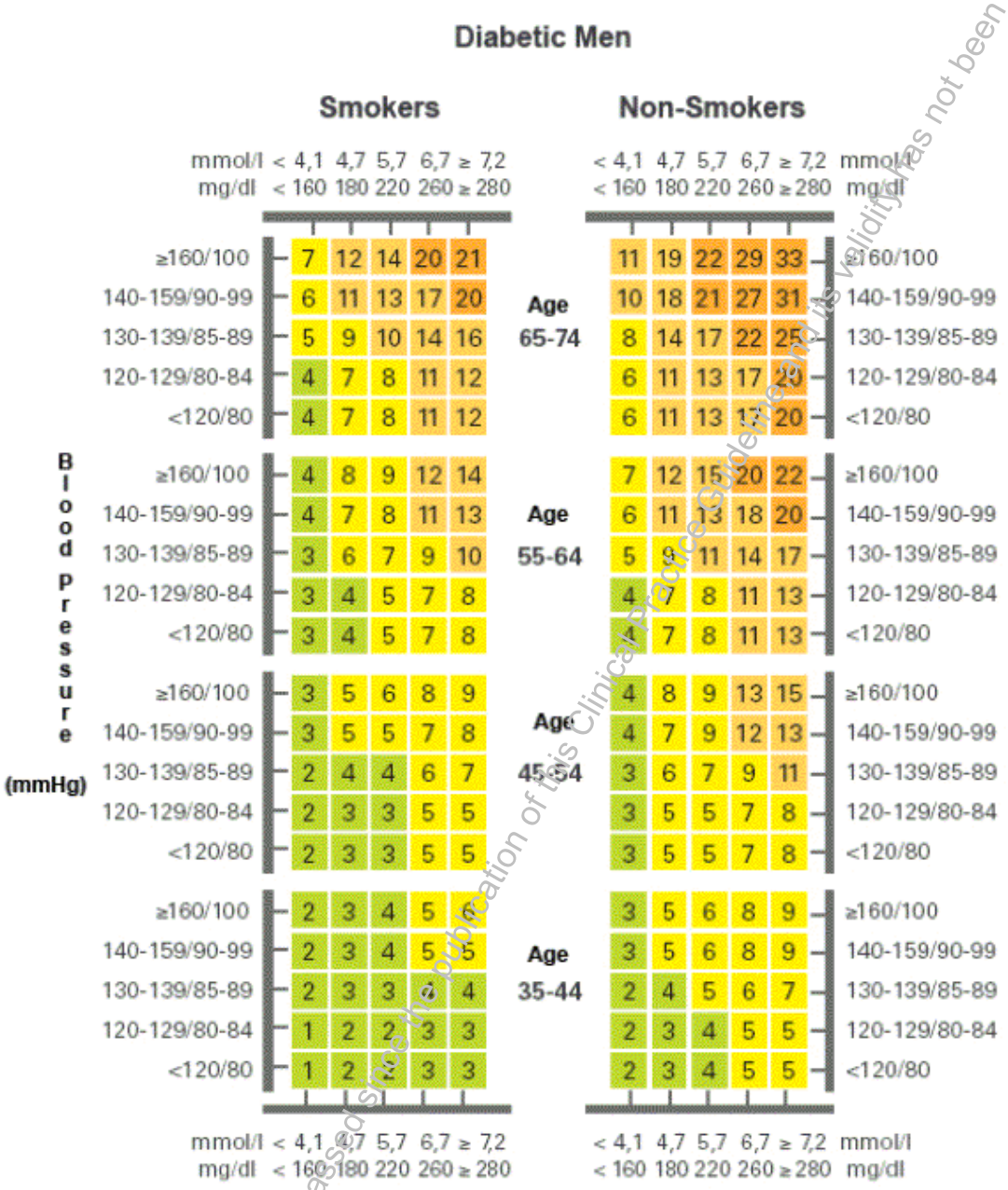
More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

REGICOR table for risk of coronary disease (fatal or non-fatal) in women at 10 years according to age, SBP, total cholesterol and tobacco smoking.



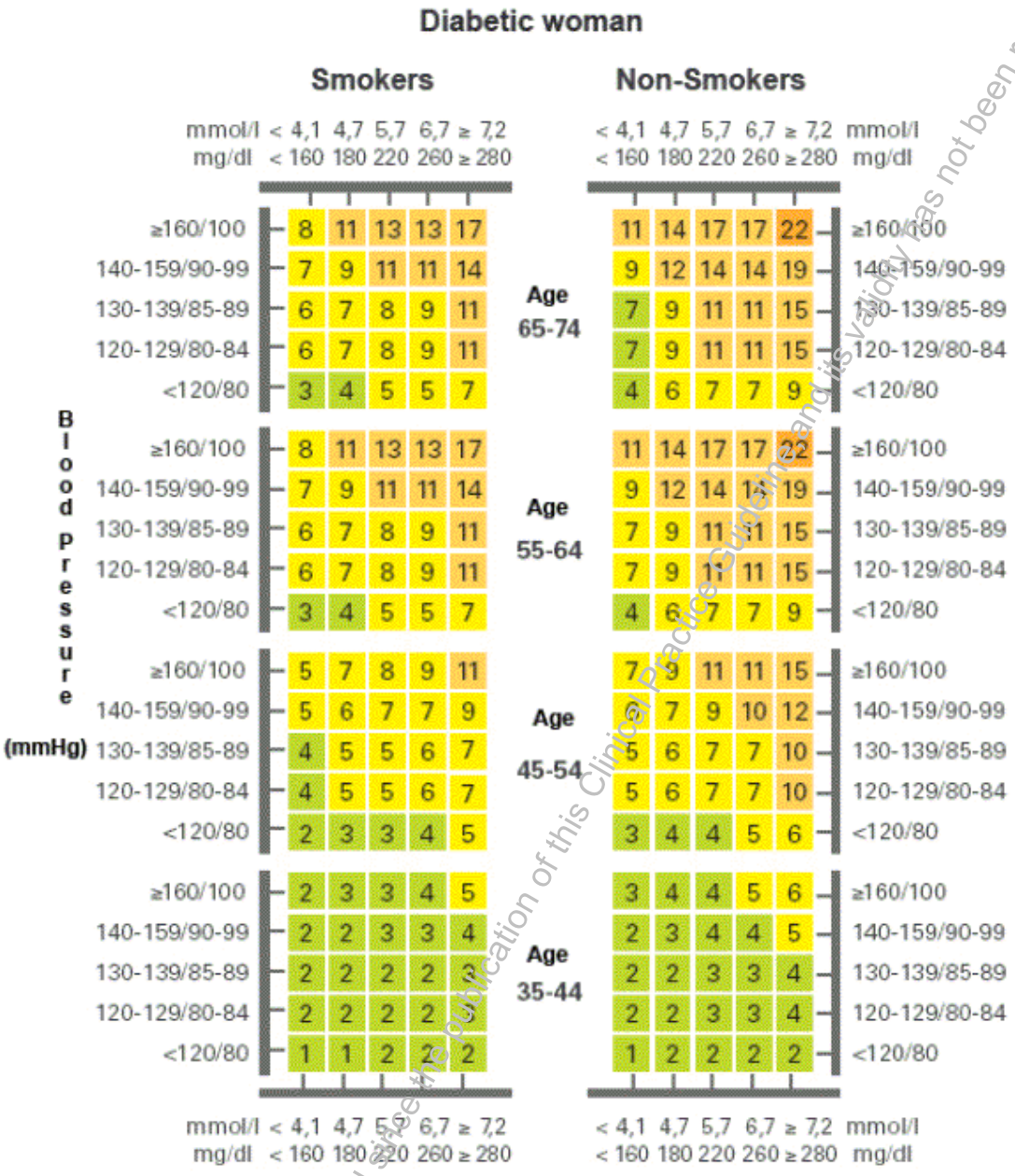
More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

REGICOR table for risk of coronary disease (fatal or non-fatal) in diabetic men at 10 years according to age, SBP, total cholesterol and tobacco smoking.



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REGICOR table for risk of coronary disease (fatal or non-fatal) in diabetic women at 10 years according to age, SBP, total cholesterol and tobacco smoking.



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Annex 3. Information for patients

3.1. Information for people who have not had a stroke

3.1.1. Regarding circulatory or vascular disorders:

1. Frequency

The two main components of vascular disease are ischemic heart disease and cerebrovascular disease.

Vascular diseases are the leading cause of death in the Spanish population. In 2005, vascular diseases caused over 120,000 deaths in Spain. Since 1975, there has been a gradual decrease of vascular-related deaths, partly due to improved health care for these patients, despite the progressive ageing of the population. In Spain, as in most Mediterranean countries, mortality due to vascular disease is relatively low when compared to English-speaking countries and northern-central European countries.

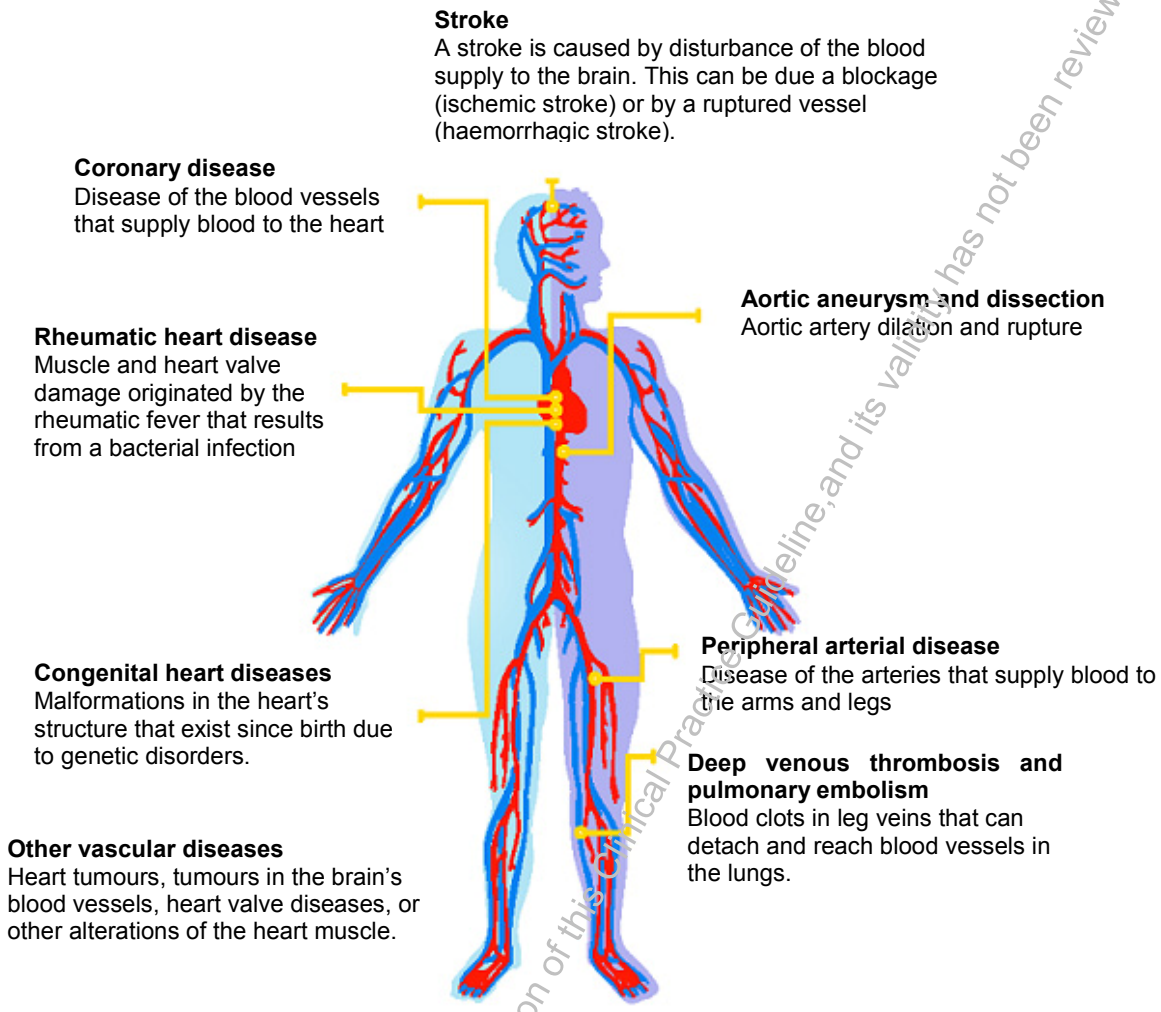
2. Types of vascular disease

The term *vascular disease* refers to diseases that affect the blood vessels (arteries and veins) and hence, can affect any part of the body. The part that is most affected is the heart, which can lead to ischemic disease of the heart and brain and, therefore, to cerebrovascular disease (Figure 1).

Hypertension is the main factor that can trigger vascular disease affecting the brain, while atherosclerosis is the main trigger of vascular heart disease and consists of a persistent disorder characterized by the hardening of the arteries. The causes, mechanisms and treatment and prevention of both conditions are very similar.

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Figure 1. Types of vascular disease



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3. Vascular risk factors

Certain circumstances or medical problems can increase the risk of developing a vascular disease, cerebrovascular accident or stroke. These are risk factors. Some of these factors respond to treatment and others do not. Understanding risk factors can help you prevent a stroke and other vascular pathologies, given that many of them can be treated by means of lifestyle modifications, drugs or surgery.

You should be aware of the fact that having one or more risk factors does not necessarily mean you will develop any of these diseases. Also, that NOT having any risk factors does NOT mean you will never develop any of these diseases.

Some of the most well-known risk factors are:

Non-modifiable factors:

- **Age:** risk increases with age.
- **Sex:** it is more frequent in men than in women.
- **Race:** African-Americans present a higher risk than Caucasians.
- **Hereditary transmission:** risk is higher in people with a family history of vascular disorders.
- **Prior vascular disease:** greatly increases the risk of having another vascular disease.

Contributing factors:

- **Excessive alcohol consumption:** risk increases due to increased blood pressure. More than two units per day in men and more than one in women are considered excessive.

1 unit:	2 units:
200 ml of beer (one glass) 100 ml of wine (one small glass) 50 ml of generous wine (sherry) 50 ml of champagne (one glass) 1 vermouth (100 ml) 25 ml of liquor (1 coffee with a shot of brandy)	1 glass of cognac (50 ml) 1 mixed drink (50 ml) 1 whisky (50 ml)

- **Smoking:** risk increases as a result of active exposure (smoker) and passive exposure (passive smoker). It also increases the risk of other severe diseases such as lung cancer.
- **Use of illegal drugs:** the use of intravenous drugs, cocaine, amphetamines or marihuana increase risk.
- **Physical inactivity:** it is more and more common in our setting. Regular physical exercise decreases blood pressure and cholesterol, and therefore reduces risk.
- **Obesity:** if weight is greater than recommended values, there is an increase of risk.

Modifiable or treatable factors:

- **High blood pressure:** it is the most important factor and is often undetected.
- **Diabetes:** blood glucose levels are high, favouring damage of blood vessels throughout the body, including the brain.
- **Cholesterol levels:** high blood fat levels favour accumulation of fatty deposits in the arteries (atheromatosis) and the risk of vascular diseases.

Often, one person may present several risk factors at the same time; the appearance of one risk factor often favours the development of others and the chances of developing

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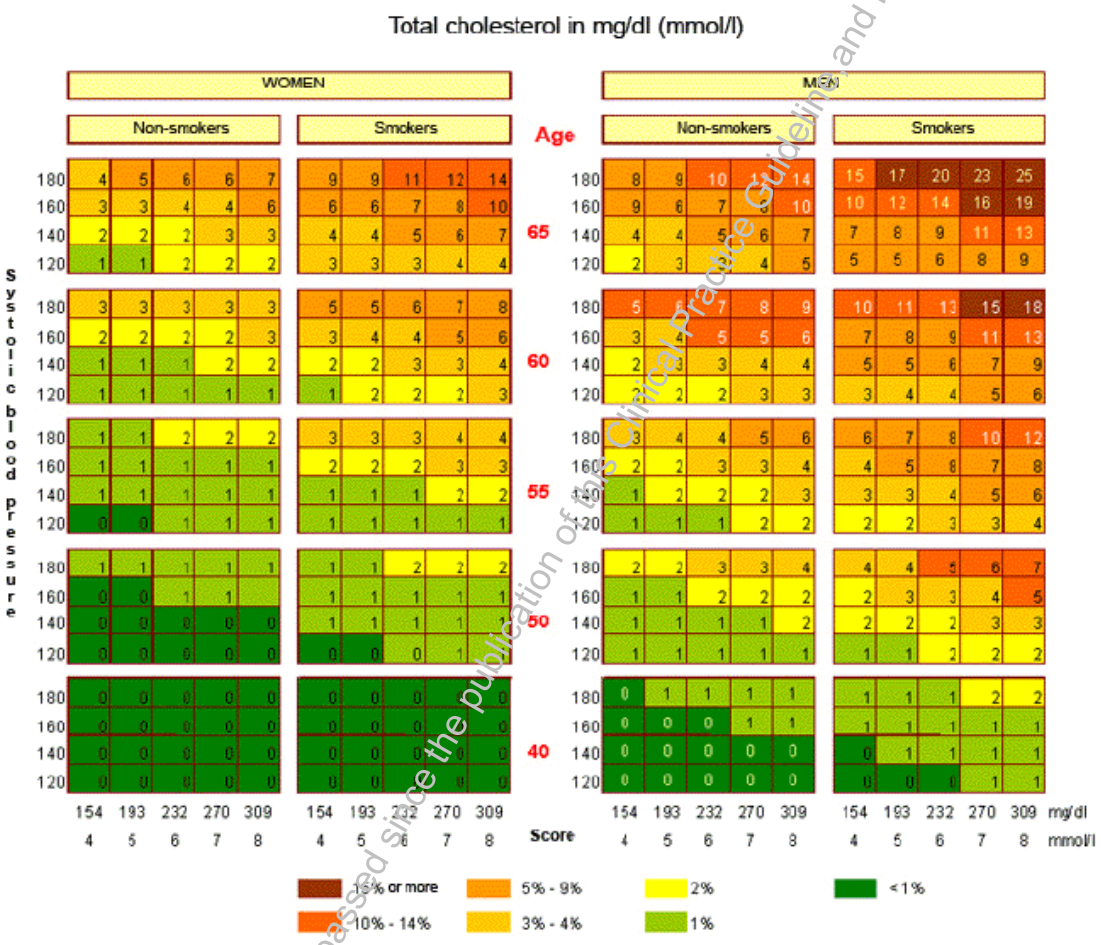
a vascular disease are multiplied.

It is very important to understand these factors, given that certain simple lifestyle modification measures are effective as prevention methods.

4. How can I find out what my vascular risk is?

In order to know your vascular risk, or how likely it is that in the next ten years you will develop one of these diseases, physicians use tables that predict such probability with certain precision, based on age, sex, smoking habit, blood pressure and blood cholesterol levels (Table 1).

Table 1. Sample vascular risk calculation table for non-diabetic men and women

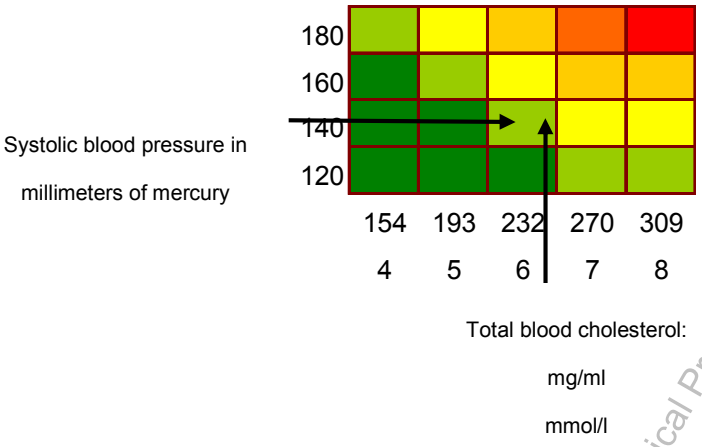


Percentage of risk of cardiovascular death at 10 years in low-risk European regions. Version with total cholesterol.

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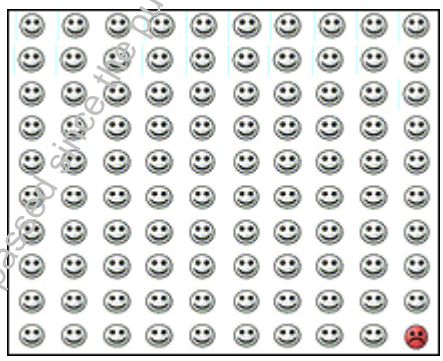
Although the exact calculation of risk should be performed by the physician, the table provides approximate values of greater or lesser risk by means of a colour code.

- You must first select the adequate column depending on whether you are a man or a woman, a smoker or a non-smoker.
- Secondly, you must select the adequate row based on your age (40 to 49; 50 to 54; 55 to 59; 60 to 64; over 65).
- Finally, using the adequate square, cross the corresponding values of your blood pressure (maximum or systolic) and total blood cholesterol levels and you will obtain a small coloured square. Each colour represents a higher or lower risk according to the legend.



You will obtain a code of colours that correspond to the risk (approximate) of developing one of these diseases within the next ten years.

The  box corresponds to a 1% risk. This means that in your same situation at least 1 in every 100 people will develop one of these diseases within the next 10 years (see Figure below).



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3.1.2 Regarding stroke

1. What is a stroke?

Strokes (cerebrovascular accidents or apoplexies) are caused by disorders affecting blood supply to the brain that transitorily or permanently disrupt the functioning of one or more parts of the brain.

2. Types of stroke:

Blood supply to the brain can be altered for several reasons:

Insufficient blood supply to the arteries that nourish the brain:
- TIA: no sequelae
- Cerebral infarction: with sequelae

Ruptured brain artery:
- Cerebral hemorrhage

Clogged brain vein:
- Cerebral venous thrombosis

Stroke requires immediate intervention to perform diagnosis and treatment.

3. How can stroke be prevented?

Initiating a plan to prevent stroke or treatment does NOT mean you will never have a stroke.

If your physician has identified one or more of the previously listed risk factors it is reasonable that he/she advises you to adopt a healthier lifestyle.

The following aspects are equally valid for ALL people:

Follow a healthy diet:
- Reduce animal-fat in your diet.
- Eat fish regularly.
- Eat fruit and vegetables regularly.
- Reduce salt intake.

Exercise regularly: any physical activity, for example walking or riding to work, during your free time or as a sport, is beneficial. If you already exercise, increase duration or frequency.

Avoid smoking: if you smoke, quit smoking. Secondhand smoke is also harmful. There are treatments to help you quit smoking.

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Regarding alcohol: if you do not usually drink alcohol, do not start drinking. If you habitually drink alcohol, try to moderate your consumption. Do not drink more than two units per day if you are a male or one if you are a female.

Reduce and maintain your body weight: if you are overweight or obese, you should lose weight and maintain it. Your physician will advise you on the best way to lose weight.

Do not take drugs: you must avoid the habitual or occasional use of any drug.

There are a series of disorders that often do not present symptoms, but people who experience them have a higher risk of having a cerebral infarction or other vascular diseases than people who do not have these disorders. In order to correct or treat these disorders there are treatments that have been shown to be beneficial.

There disorders are:

Hypertension: Normal blood pressure values are below 120/80 mmHg. If your blood pressure is usually above these values, the risk of having a stroke increases. To reduce blood pressure values, the first step is to transform certain lifestyle aspects into healthier ones. The advice previously listed will help you reduce blood pressure.

If these lifestyle or habit changes do not help to decrease blood pressure values, there are drugs available that have been proven to reduce blood pressure and, hence, the risk of stroke. Your physician will indicate which drugs are the most appropriate in your case. The objective is for your blood pressure to remain below 140/90 mmHg.

Dyslipemia: altered blood cholesterol or triglycerides values increase the risk of having a stroke. As with hypertension, healthier lifestyles are beneficial.

There are drugs that have been proven beneficial and that reduce the risk of stroke. Your physician will indicate what drugs are the most appropriate in your case.

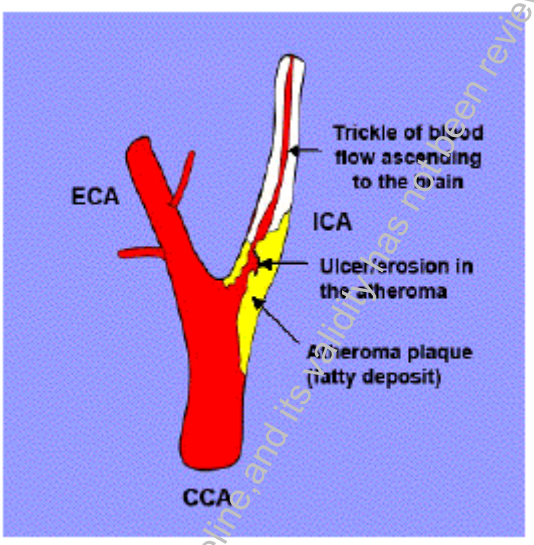
Diabetes: increased blood glucose values extensively damage blood vessels throughout the body. If you have diabetes or any other of the previously described disorders, your risk is even higher. You should attempt to maintain blood glucose values within normal levels for as long as possible. To do so, you should follow a specific diet, and, if necessary, be treated with certain drugs or insulin. Blood pressure or cholesterol and triglycerides monitoring should be stricter if you have diabetes.

Obstruction of the carotid arteries: the accumulation of fatty deposits in the carotid artery (the main artery connecting the heart and brain) can obstruct this very important source of blood supply (Figure 2). It is a frequent cause of stroke.

Depending on the degree of obstruction you have, your physician may recommend treatment with aspirin or a similar drug or even suggest a surgical procedure.

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Figure 2. Accumulation of fatty deposits in the carotid arter



ECA: *external carotid artery*
ICA: *internal carotid artery*
CCA*: common carotid artery*

4. Treatment with aspirin:

If your risk of having a vascular disease is high, your physician may suggest additional treatment with aspirin, regardless of the measures previously suggested. Aspirin prevents the formation of blood clots and has beneficial effects on blood vessels.

However, aspirin can also cause severe undesired effects, such as intestinal bleeding. For this reason aspirin treatment should only be initiated if it is indicated by your physician. There are other similar drugs available in case you have aspirin intolerance.

5. Can cerebral hemorrhages be prevented?

The main causes of cerebral hemorrhaging are:

Hypertension: increases the risk of ruptured brain arteries and, hence, the risk of cerebral hemorrhages. In order to reduce blood pressure values, the first recommended step is to modify unhealthy lifestyles and adopt healthier habits. If blood pressure values are not reduced, there are drugs that have been proven to reduce blood pressure values and the risk of having a cerebral hemorrhage.

Aneurysms: they are small dilations of brain arteries that can burst and cause cerebral hemorrhaging. To avoid rupture, surgery is sometimes an option.

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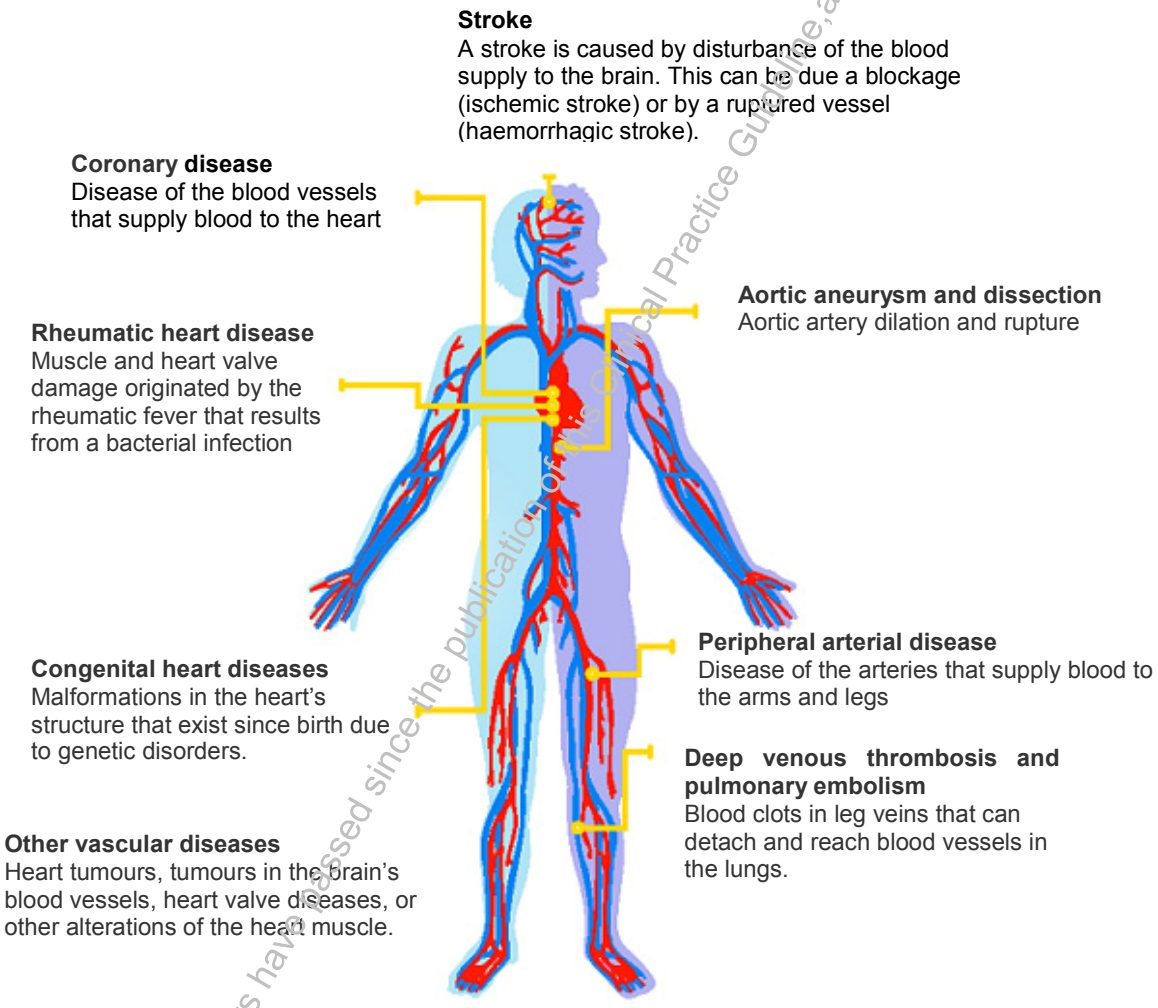
3.2. Information for people who have had a stroke

3.2.1 Regarding stroke:

1. What is a stroke?

Strokes (cerebrovascular accidents or apoplexies) are caused by a circulatory brain disorder that transitorily or permanently disrupts the functioning of one or more parts of the brain. Therefore, they are a vascular disease that affects blood vessels (arteries and veins) in the brain. Hypertension is the most frequent cause of vascular disease of the brain. Vascular diseases can affect other parts, the most important being the heart (Figure 1).

Figure 1. Types of vascular disease



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2. Types of stroke:

Blood supply to the brain can be altered for several reasons:

Insufficient blood supply to the arteries that nourish the brain:

- TIA: no sequelae
- Cerebral infarction: with sequelae

Ruptured brain artery:

- Cerebral hemorrhage

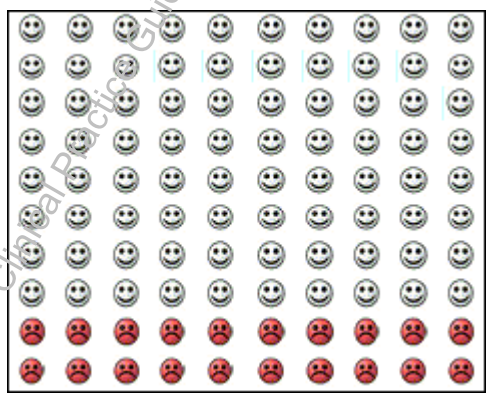
Clogged brain vein:

- Cerebral venous thrombosis

Stroke requires immediate intervention to perform diagnosis and treatment.

3. How to prevent episode recurrence

If you have already had a stroke or any other vascular disease, you are at high risk of having another stroke or other episodes affecting the heart or blood vessels (arteries and veins) of the body. This risk is higher than 20% at 10 years. This means that in your same situation, at least 20 in every 100 people will have another episode within the next 10 years.



Lifestyle modifications

If you have already had a stroke or other vascular disease, you should know that:

- If you are a smoker, **you should quit smoking**. There are treatments available to help you quit smoking. Secondhand smoke is also harmful.
- If you usually do not drink alcohol, do not start drinking. **You should not drink** more than two units per day if you are a male and one unit per day if you are a female.
- You should eat a **healthy diet**, reduce animal fat, increase the consumption of fish, fruits and vegetables and reduce salt intake.
- You should **exercise regularly** within your capabilities.
- If you are overweight or obese, you should **lose weight** and maintain it.

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Hypertension: normal blood pressure values should be below 120/80 mmHg. If your blood pressure is usually above these values, you should take medication with the aim of maintaining blood pressure below 130/80 mmHg. Your physician will indicate which treatment is the most appropriate in your case and regularly monitor your blood pressure values. If you have had a cerebral hemorrhage, blood pressure monitoring is more important than other factors.

Dyslipemia: if you have had a stroke, you should know that there are drugs commonly known as statins that are beneficial for preventing recurrence. If you have high cholesterol, your physician should regularly monitor blood cholesterol values and other fats. Statins are also useful at reducing cholesterol levels.

Other treatments: There are the so-called *antiaggregant treatments* that prevent the formation of blood clots and have beneficial effects on blood vessels. The most well-known antiaggregant is aspirin, but there are others that are also beneficial. All of them can lead to severe adverse effects, such as intestinal bleeding, to a greater or lesser extent. Your physician will indicate which treatment is the most appropriate in your case. If you have had a cerebral hemorrhage, these treatments are not beneficial, and may even me harmful.

4. Have you already had another circulatory disorder?

If you have already had a cerebral infarction, it may be a result of other circulatory disorders that must be properly treated. You may present an increased risk of cerebral infarction if you have any of the following diseases:

Atrial fibrillation: it is a form of cardiac arrhythmia.

Acute myocardial infarction: an area of the heart muscle has been permanently damaged.

Cardiac insufficiency: the heart muscle is not able to pump with sufficient efficiency.

Valve prostheses: if you have undergone a surgical procedure to insert an artificial prosthesis in one or more heart valves.

Many of these situations require specific treatment, consisting of anticoagulants, to prevent the formation of blood clots that can result in cerebral infarction if their propagation occurs towards the direction of the heart, but that may also affect other parts of the body.

5. Where can I get more information?

There are several online portals that provide very useful information aimed specifically at patients and the general public. They can be found listed below:

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- The Spanish Neurology Society's section containing information aimed at the general public:
  http://www.sen.es/publico/index.htm

- The Spanish Neurology Society's Study Group on Cerebrovascular Diseases' section containing information aimed at patients:
  http://www.ictussen.org/
  ("Patients section")

- The Spanish Foundation of Neurological Diseases portal:
  http://www.feeneurologia.com/pacientes.php

- The Heart Foundation portal, promoted by the Spanish Cardiology Society:
  http://www.fundaciondelcorazon.com/index_ie.html ("Patients" section)

- The Hypertense Club portal, promoted by the Spanish Society Against Hypertension:
  http://www.seh-lelha.org/club/clubhto.htm

- Portal to learn about nutrition tables and establish nutritional programmes provided by the Spanish Hypertension Society and the Spanish League Against Hypertension:
  http://www.seh-lelha.org/alimento.htm

- Fisterra patient portal:
  http://www.fisterra.com/Salud/index.asp

- Stroke/Vascular Disease Foundation
  http://www.fundacioictus.com

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Annex 4. Abbreviations

%: percentage

ABS: altered basal glycaemi

ACEI: angiotensin converting enzyme inhibitors

APA: antiphospholipid antibodies

APS: antiphospholipid syndrome

ARA II: angiotensin-receptor II antagonists

ARR: absolute risk reduction

BMI: body mass index

CAS: carotid artery stent

CEA: carotid endarterectomy

CI: confidence interval

cm^2: square centimeter

cm^3: cubic centimeter

CPG: Clinical Practice Guideline

DARE: Database of Abstracts of Reviews of Effects

DBP: diastolic blood pressure

ECST: European Carotid Surgery Trial

FDA: Food and Drug Administration

g/d: grams per day

h: hour

HDL: high density lipoproteins

HR: *hazard ratio*

HT: hormone therapy

HT: hypertension

ICD: International Classification of Diseases

ICH: intracerebral hemorrhage

IDR: *incidence density ratio*

IGT: impaired glucose tolerance

INR: international normalised ratio

kg/m^2: kilograms per square meter

LDL: low density lipoproteins

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Lp(a): lipoprotein A

LSD: lysergic acid diethylamide

MDMA: methylenedioxymetamphetamine

mg/dl: Milligrams per decilitre

mg: milligrams

ml: millilitre

mm: millimeters

mmHg: millimeters of mercury

mmol/l: millimoles per litre

MS: mitral stenosis

MSC: Ministry of Health and Consumer Affairs

MTHFR: methylenetetrahydrofolate reductase

MVP: mitral valve prolapse

NASCET: North American Symptomatic Carotid Endarterectomy Trial

NHS: National Health System

NICE: National Institute for Clinical Excellence

NNT: number needed to treat

OR: odds ratio (relative opportunity)

RCT: randomised clinical trial

REGICOR: Registre Gironí del COR

RR: relative risk

RRR: relative risk reduction

SAH: subarachnoid hemorrhage

SAU: standard alcohol units

SBP: systolic blood pressure

SCORE: Systematic Coronary Risk Evaluation

SIGN: Scottish Intercollegiate Guidelines Network

SR: systematic review

TIA: transient ischemic attack

WHO: World Health Organisation

µg: micrograms

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Annex 5. Glossary

Cochrane Library: Database on effectiveness developed by the Cochrane Collaboration, that includes the organisation's original systematic reviews and others.

Randomised clinical trial: It is a study design in which subjects are randomly assigned to two groups: an experimental group, which receives the treatment that is being tested, and a comparison or control group, which receives standard treatment or placebo. There is follow-up of both groups to observe differences in outcomes. This is how treatment efficacy is assessed.

Cohort study: It is a follow-up study of one or more cohorts of individuals who present different degrees of exposure to a risk factor, and in whom the onset of the disease or condition that is being studied is measured.

Case-control study: Study that identifies people with a disease (cases), for example lung cancer, and compares them to a disease-free group (control). The relationship of one or several factors, such as tobacco, with the disease is examined, by comparing the frequency of exposure to this or these factors in cases and controls.

Embase: Dutch European database, developed by Excerpta Medica, with clinical medicine and pharmacology content.

Heterogeneity: See *Homogeneity*.

Homogeneity: Means 'similarity'. Some studies are deemed to be more homogeneous if their results do not vary between themselves more than what could be expected at random. The opposite of *homogeneity* is *heterogeneity*.

Confidence interval: Interval in which the true magnitude of the effect is found, even if it is never exactly determined, with a prefixed degree of safety or confidence. This term is often referred to as 95% confidence interval or 95% confidence limits. It means that the true value would be found within that interval in 95% of cases.

Medline: Predominantly clinical database developed by the United States' National Library of Medicine.

Metaanalysis: Statistical technique that makes it possible to integrate results from different studies (diagnostic tests, clinical trials, cohort studies, etc.) into one estimator, granting more weight to results from bigger studies.

NICE: Part of the NHS (British National Health Service). Its role is to provide physicians, patients and the public in general with the best available evidence, primarily in the form of clinical guidelines.

NNT/NNH: Treatment efficacy measure that consists of the number of people who need to be treated (NNT) with a specific treatment to produce, or avoid, an additional

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event. The number needed to harm (NNH) is defined in the same way to assess undesirable effects.

Odds Ratio (OR): Treatment efficacy measure. If it is equal to 1, treatment effect is no different from control effect. If the OR is greater or lesser than 1, treatment effect is greater or lesser than the control effect. The effect that is being measured may be an adverse effect (for example, death, disability) or a desirable effect (for example, quitting smoking).

Systematic review (SR): Review of the evidence for a topic that has been systematically identified, assessed and summarised in accordance with predetermined criteria. It may or may not include metaanalysis.

Relative risk (RR): It is the coefficient between the events rate in the treatment group and in the control group. Its value can be interpreted in the same way as the OR.

SIGN: Multidisciplinary Scottish agency that develops evidence-based clinical practice guidelines and methodological documents for their design.

Terms relating to methodological aspects are based on the CASPe glossary (programme of critical reading skills in Spain), at http://www.redcaspe.org/homecasp.asp.

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Annex 6. Declaration of interests

The declaration of interests of the authors and reviewers has been carried out by means of a predefined form included in the methodological manual of the NHS.[17]

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Annex 7. Main clinical practice guidelines used and other useful resources

Main documents of interest

In order to develop the clinical practice guideline on primary and secondary prevention of stroke some published guidelines addressing this issue and vascular prevention have been taken into account as secondary reference sources. Some of these documents have inspired and served as a model for certain sections due to their rigour and clarity. The following list provides the main documents and the link to their full text which, because of their quality or recent publication, can be an important consultation source for the users of this guideline.

Clinical practice guidelines on stroke

Title: Management of patients with stroke: assessment, investigation, immediate management and secondary prevention. SIGN
Link: http://www.sign.ac.uk/guidelines/published/index.html

Title: Guia de pràctica clínica (GPC) sobre l'ictus. [2007 Update]
Link: http://www.gencat.net/salut/depsan/units/aatrm/pdf/gp07ictusca.pdf

Title: Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults. 2007 Update. A Guideline from the American Heart Association / America stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group.
Link: http://www.americanheart.org/presenter.jhtml?identifier_4431

Title: Guidelines for the Early Management of Adults with Ischemic Stroke: A Guideline from the American Heart Association / America stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups.
Link: http://stroke.ahajournals.org/cgi/content/full/38/5/1655

Title: Primary Prevention of Ischemic Stroke: A Guideline from the American Heart Association / America stroke Association Stroke Council.
Links: http://stroke.ahajournals.org/cgi/content/full/37/6/1583
http://circ.ahajournals.org/cgi/content/full/113/24/e873

Title: Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack: A Statement for Healthcare Professionals from the American Heart Association / America stroke Association Council on Stroke.
Link: http://stroke.ahajournals.org/cgi/content/full/37/2/577

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Title: Guía para el tratamiento y prevención del ictus. Ad hoc committee of the Study Group for Cerebrovascular Diseases. Spanish Society of Neurology (2006).
Link: http://www.sen.es/profesionales/ictus.htm

Title: National Clinical Guidelines for Stroke. Royal College of Physicians (2004).
Link: http://www.rcplondon.ac.uk

Clinical practice guidelines on the prevention of vascular disease

Title: Scottish Intercollegiate Guidelines Network (SIGN). Risk Estimation and the Prevention of Cardiovascular Disease. A National Clinical Guideline (2007).
Link: http://www.sign.ac.uk/pdf/sign97.pdf
This guide is part of a group of five guidelines addressing related topics (SIGN 93 to 97).

Title: Prevention of Cardiovascular Disease. Guidelines for Assessment and Management of Cardiovascular Risk. World Health Organisation (2007).
Link: http://www.who.int/cardiovascular diseases/en

Title: European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Fourth Joint Task Force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice (2007).
Link:
http://www.eas-society.org

Clinical practice guidelines on related aspects

Title: Liquid modification: cardiovascular risk assessment and the modification of blood liquids for the primary and secondary prevention of cardiovascular disease. NICE Clinical Guideline 67 (2008).
Link: http://www.nice.org.uk

Title: Clinical Guidelines and Evidence Review for Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners (2007).
Link: http://www.nice.org.uk

Title: Scottish Intercollegiate Guidelines Network (SIGN). Acute Coronary Syndromes. A National Clinical Guideline. SIGN 93 (2007).
Link: http://www.sign.ac.uk/pdf/sign93.pdf

Title: Guidelines for the Diagnosis and Treatment of non-ST-Segment Elevation Acute Coronary Syndromes. The Task Force for the Diagnosis and Treatment of non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology.

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Link: http://eurheartj.oxfordjournals.org

Title: Guidelines on the Management of Valvular Heart Disease. The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology.
Link: http://eurheartj.oxfordjournals.org

Title: Guidelines on Diabetes, Prediabetes, and Cardiovascular Diseases: Full Text. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD).
Link: http://eurheartj.oxfordjournals.org

Title: Guidelines for the Management of Arterial Hypertension. The Task Force on the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (2007).
Links: http://www. escardio.org
http://www. eshonline.org

Title: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction.
Links: http://www. acc.org
http://www. americanheart.org

Title: ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation (2006).
Links: http://www. acc.org
http://www. americanheart.org
http://www. escardio.org

Title: Atrial Fibrillation. National Clinical Guideline for Management in Primary and Secondary Care.
Link: http://www.rcplondon.ac.uk

Title: ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease (2006).
Link: http://www.acc.org/clinical/guidelines/valvular/index.pdf

Title: National Institute for Health and Clinical Excellence. Statins for the Prevention of Cardiovascular Events.
Link: http://www.nice.org.uk/TA094

Title: Recomendaciones PAPPS. Programa de Actividades Preventivas y de Promoción de la Salud.
Link: http://www.papps.org/recomendaciones/01_recomendaciones.pdf

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Related resources

World Health Organisation: "The Atlas of Heart Disease and Stroke"

The WHO published this document in 2004 together with the Center for Disease Control and Prevention (CDC) of the United Stated. It addresses the burden of heart diseases and stroke at a worldwide scale and in each country using easy-to-understand maps and graphics. It also provides statistics for the main risk factors with comparative figures for different countries.
Link: http://www.who.int/cardiovascular_diseases/resources/atlas/en/

Carlos III Health Institute, National Center of Epidemiology

Provides a database of mortality and morbidity related to cardiovascular diseases in the hospital and out-hospital setting.
Link: http://www.isciii.es

National Institute of Statistics

Offers the possibility of consulting health surveys and statistics and of downloading the data file classified according to different characteristics.
Link: http://www.ine.es

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Annex 8. Proposed assessment indicators

Key Questions:

- What indicators are used to monitor quality of primary and secondary prevention of stroke?

It is important to determine if the fulfillment of the most important recommendations leads to the desired objectives. In order to do this, the assessment of the most relevant process and clinical outcome indicators is suggested. Many of the indicators included in the ischemic cardiopathy strategy of the National Health System (National Quality Plan) are the same as in vascular disease. Therefore, most of the following proposed indicators are the same as those included in the aforementioned Plan. Additionally, the working group has proposed others.

Detection of vascular risk factors

Formula:	a × 100 / b, where: **a** = Number of people over the age of 14 identified in primary care as presenting one or more vascular risk factors. **b** = Total number of people over the age of 14 attended in primary care.
Definition/ clarifications:	For this assessment, risk factors that are considered major have been included, such as diabetes mellitus, hypercholesterolemia, HT, obesity and tobacco smoking, and the presence of first degree family history of early coronary disease.
Disaggregation:	By risk factor detected, autonomous communities, age and sex groups.
Sources of information:	Intervention programmes and/or portfolio of primary care services in the autonomous communities (local regional governments).

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Assessment of vascular risk

Formula:	a × 100 / b, where: **a** = Number of people over the age of 40 whose primary care clinical history indicates that screening activities for one or more vascular risk factors were performed, and assessment and stratification of their level of vascular risk were carried out. **b** = Total number of people over the age of 40 without a known vascular disease with one or more identified vascular risk factors that are included in the primary care clinical history.
Definition/clarifications:	For this assessment, risk factors that are considered major have been included, such as diabetes mellitus, hypercholesterolemia, HT, obesity and tobacco smoking, and the presence of first degree family history of early coronary disease. In order to calculate vascular risk, the quantitative model consensuated by the scientific societies should be used.
Disaggregation:	By autonomous communities, age and sex groups
Sources of information:	Intervention programmes and/or portfolio of primary care services in the autonomous communities (local regional governments).

Incidence of ischemic stroke

Formula:	a × 100.000 / b, where: **a** = Number of patients who have been discharged with the main diagnosis of ischemic stroke in one year. **b** = Population that year.
Definitions/clarifications:	All discharges with main diagnosis coded using the International Classification of Diseases (ICD) (code 434 of the current ICD9-CM version) will be counted. Of the total number of discharges, re-admittances will be excluded.
Disaggregation:	By autonomous communities, age and sex groups.

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Sources of information:	Notification in the hospital discharge. Population projections by the NSI (National Statistics Institute).

Rates of mortality due to stroke

Formula:	a × 100,000 / b, where: **a** = Number of people who have died from stroke in one year. **b** = Population that year.
Definition/ clarifications:	Gross and adjusted rates will be calculated.
Disaggregation:	By autonomous community and sex.
Sources of information:	Death statistics by the NSI (National Statistics Institute). Population projections by the NSI.

Rate of potential years of life lost from stroke

Formula:	a × 1000 / b, where: **a** = Number of years of life lost due to deaths from stroke before 65 years of age and before 75 years of age, in a given year. **b** = Population aged between 0 and 64 years and between 0 and 74 years, respectively, in that year.
Definition/ clarifications:	Gross and adjusted rates will be calculated.
Disaggregation:	By autonomous community and sex.
Sources of information:	Death statistics by the NSI (National Statistics Institute). . Population projections by the NSI.

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Prevalence of smokers in people over the age of 15

Formula:	a × 100 / b, where: **a** = Number of people over the age of 15 who have participated in the survey and have reported to smoke tobacco on a daily basis in the interview. **b** = Total number of people over the age of 15 who have participated in the survey.
Definition/ clarifications:	A person is considered a smoker if he/she smokes tobacco daily, regardless of the quantity smoked.
Disaggregation:	By autonomous community, sex and age groups.
Source of information:	National Health Survey.

Prevalence of obesity

Formula:	a × 100 / b, where **a** = Number of people included in the survey, with a BMI equal to or greater than 30 kg/m^2. **b** = Total number of people included in the survey.
Definition/clarifications:	BMI is calculated using height and weight data expressed in the following way: • In the case of adults, using the standard formula (weight in kg / square of height in meters). • In the case of minors under the age of 18, the cutoff points established for age and sex subgroups published by Cole TJ, et al BMJ 2000; 320: 1-6, are used.
Disaggregation:	By autonomous community, sex and age groups.
Source of information:	National Health Survey.

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Prevalence of obesity

Formula:	a × 100 / b, where **a** = Number of people who exercise included in the survey **b** = Total number of people included in the survey.
Definition/clarifications:	In individuals aged or less, physical exercise in their spare time is assessed. This same criterion is used in unoccupied adults. All other individuals are assessed both in terms of the time they exercise in their spare time as well as the degree of the physical effort employed while al work.
Disaggregation:	By autonomous community, sex and age groups.
Source of information:	National Health Survey.

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