

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 stroke³⁶

Non-modifiable	Strong association	Weak association
<ul style="list-style-type: none"> – age – sex – race – low birth weight – hereditary factors 	<ul style="list-style-type: none"> – 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 	<ul style="list-style-type: none"> – 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: Díez 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.

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 age³⁷⁻³⁹. After 75 years of age, specific vascular mortality rates per age group (decade) become the leading cause of death⁴⁰.

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 settings⁴⁰⁻⁴². 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 women⁴³.

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 mortality⁴⁴⁻⁴⁷. Specifically, a study showed that the incidence of stroke in the black population was 38% higher than in the white population⁴⁸. 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 population⁴⁹.

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 groups⁵⁰. Along the same lines, a SR showed different results in the prevention of vascular events with antihypertensive treatments in the black, white or Asian populations⁵¹.

SR of RCT
1+

6.2.4. Family history

The presence of a family history of stroke has been associated with a higher risk of stroke⁵². 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 all⁵³.

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 stroke⁵⁴.

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 disease⁵⁵, 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 .

2++	People with a family history of stroke have a higher chance of having a stroke ⁵⁴ .
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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 pathologies⁵⁷. 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?

The association of stroke with alcohol consumption is a controversial issue⁵⁸. 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 risk⁵⁹⁻⁶¹. 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 consumption⁶². 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 results⁶³⁻⁶⁷.

**SR of
observational
studies
2+**

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.

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+**

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 inconsistent⁶⁹. Alcohol consumption of <150 g/d was associated with a protective effect only in the analysis of case-control studies.

**SR of
observational
studies
2+2+**

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.

Table 5. Equivalent units of alcohol and beverage volume⁷⁵

1 SDU:		
<ul style="list-style-type: none"> - 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:		
<ul style="list-style-type: none"> - 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

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 risk⁷⁰. 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 consumption⁷¹. Other prior SRs yielded similar results^{72, 73}.

**SR of RCT
1++**

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 syndrome⁷⁴.

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 on 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.

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?

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 mortality⁷⁷.

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-smokers⁷⁸. 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 day⁵⁵.

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 cessation⁷⁹. A SR reported a 36% mortality reduction in patients with a history of coronary disease who quit smoking⁸⁰.

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 doses⁷⁶. 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 disease⁸⁴.

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 smoked⁸⁵. 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 completely⁸⁵.

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 interventions⁸⁶.

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 not⁸⁸. 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 months⁸⁹.

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 places⁹⁰. 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 morbidity⁹⁰⁻⁹⁵.

Observational studies
2+/2++

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.

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 consumption⁹⁶.

In the population drug use patterns have varied considerably in the last decade and in Spain, for example, decreased use of heroin has been reported⁹⁷.

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 cannabis⁹⁸, 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 2004⁹⁹.

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 stroke⁹⁹⁻¹⁰⁷ or intracerebral hemorrhage (ICH)¹⁰⁸⁻¹¹¹. Likewise, marihuana, generally smoked, has been associated with ischemic stroke¹¹² and even with recurrent ischemic stroke^{113, 114}, and amphetamines and their structural derivatives such as MDMA (ecstasy, crystal, liquid crystal), with ischemic stroke¹¹⁵⁻¹¹⁷, 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 users¹²².

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-users¹²³⁻¹²⁵. In a case-control study drug abuse of any kind produced a more than 6-fold higher risk of stroke¹²⁶. In patients with vascular risk factors, cocaine consumption increases the chance of having a stroke even more¹²⁷. However, other studies have associated cocaine consumption with acute myocardial infarction, but not with stroke¹²⁸.

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 vasospasm¹²⁹⁻¹³¹.

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

dependency.

Summary of the Evidence

2+	Drug use increases the risk of stroke and other vascular diseases ¹⁰⁰⁻¹²⁸ .
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Recommendations

√	In the routine anamnesis it is advisable to ask about habitual or occasional use of illegal drugs.
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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 disease⁵⁵ 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 triglycerides¹³³. 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 values¹³⁴.

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 stroke¹³⁵. 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 women¹³⁸. The relationship between physical exercise and the risk of SAH has not been consistent⁶⁹.

**SR of
observational
studies
2+**

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.

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 diet¹³⁹. 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 diseases¹⁴⁰.

A nutritional survey developed in our setting demonstrated that the standard diet lacks sufficient carbohydrates and has too many proteins and fats^{141, 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 intake⁵⁷.

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

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.

**SR of 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 disease¹⁴⁴.

**RCT
1++**

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 consumption¹⁴⁵.

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 strokes¹⁴⁶.

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 review¹⁴⁸.

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 antioxidant¹⁴⁹. 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 episodes¹⁵¹. 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 placebo¹⁵². 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 events¹⁵³.

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++

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 patients¹⁵⁵. Another SR with 6 months follow-up also reported a reduction of blood pressure values in hypertense patients¹⁵⁶.

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 recommendations¹⁵⁷.

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.

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.

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 WHO¹⁵⁸ 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 expense¹⁵⁹.

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 women¹⁶⁰. 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 exercise¹⁶¹.

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/m², and overweight if their BMI ranges between 25 and just below 30 kg/m²¹⁶⁶.

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 dyslipemia¹⁶⁷⁻¹⁶⁹. Obesity is associated with increased vascular morbimortality and overall mortality¹⁶⁷⁻¹⁷³. Likewise, childhood obesity has proven to be associated with higher

Observational studies
2++/ 2+

coronary disease risk in adulthood¹⁷⁴.

There is a significant amount of information indicating an association between BMI and increased risk of having an ischemic or hemorrhagic stroke¹⁷⁵⁻¹⁸⁰. However, there are other studies that do not confirm this relationship¹⁸¹⁻¹⁸⁶. 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 values⁶⁹.

Observational studies
2++/ 2+

Abdominal obesity measured as a waist-hip index has also been associated with stroke¹⁸⁷. 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 stroke¹⁸⁸.

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 stroke¹⁸⁹.

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 intervention¹⁹⁰. 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 pressure¹⁹¹⁻¹⁹³, as well as in reducing the incidence of diabetes²⁴⁹.

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 changes¹⁹⁴.

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 intolerance¹⁹⁵. 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+

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 trial¹⁹⁷ 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/m²) or with a BMI>35 kg/m² and associated comorbidities are candidates for surgery to treat obesity¹⁶⁶. A SR showed that different types of intervention achieved 34.8 to 51.1 kg weight reduction at three years¹⁹⁸. Mortality resulting from different procedures ranged between 0.1% and 1.1%, depending on the experience of the surgical team¹⁹⁹.

SR of RCT
1+

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

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

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?

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 alcohol²⁰⁰. The risk of stroke is three to five times higher in patients with HT¹⁹.

**SR of RCT
1+**

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 reduced²⁰¹. However, there is a linear increase of stroke risk with the increase of blood pressure values and at values greater than 115/75 mmHg²⁰².

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 rates²⁰³. This fact has already been observed in the MONICA international study, which confirmed a similar relationship between hypertension and incidence of stroke²⁰⁴.

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 years²⁰⁵. 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 poor²⁰⁶. 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 vegetables²⁰⁹. 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 risk²¹⁰.

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 patients²¹³ both in men and in women,^{214, 215} as well as in isolated systolic hypertension²¹⁶. A recent SR has determined that the reduction of SBP values is the main factor responsible for decreased vascular episodes²¹⁷.

SR of RCT
1++

A SR (29 RCTs, 162,341 patients) compared different treatments (angiotensin converting enzyme inhibitors [ACE INHIBITORS], diuretics, betablockers, calcium antagonists) with placebo and with each other²²⁶. 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 patients²¹⁸.

**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 stroke²¹⁹. 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 patients²²⁰.

**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 values²²¹. More recently, the ASCOT-BPLA trial (19,257 patients) was prematurely ended given that it showed significant reduction of

**RCT
1++**

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 national²²³ and European²²⁴ 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-II²²⁵.

**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 patients²²⁶.

**SR of RCT
1++**

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 mmHg²²⁸. 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 values²²⁹.

**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 inconclusive²²⁶.

**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 inhabitants²³⁶. Although less frequent than ischemic stroke, ICH-associated mortality is much greater.

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 strokes²³⁸. A SR of observational studies (3,936 patients) assessed the relationship of different factors with SAH risk⁶⁹. 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 significant²³⁹. 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

	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.

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 diabetes²³¹.

Table 7. Diagnostic criteria for diabetes and prediabetes²³¹

	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 changes²⁴¹. 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 70²⁴². On the other hand, half the people with diabetes present associated vascular risk factors, such as hypertension, dyslipemia and overweight²⁴³.

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+

In a SR of observational studies, patients with diabetes showed a tendency towards SAH risk reduction of approximately 30% in several case-control studies⁶⁹. 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 controls⁶⁹.

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 increased²⁴⁶.

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 IGT²⁴⁷⁻²⁵⁰. Studies show that both diet and drugs are consistently effective, even though data on important variables for the patient (microvascular and macrovascular problems) are limited²⁵¹. The DREAM study reported a reduction of diabetes incidence with rosiglitazone in people with altered plasma glucose levels²⁵². The indication of hypoglycemic 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 pioglitazone²⁵³⁻²⁵⁷. 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 episodes²⁵⁸.

SR of RCT
1++

6.7.3. Diabetes screening

No direct evidence was identified concerning the efficacy of diabetes mellitus screening in the general population²⁵⁹. 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

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 the 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 population 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.

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 countries²⁶⁴.

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, respectively²⁶⁶.

**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 studies⁶⁹.

**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 ages²⁶⁶. This effect has been confirmed in available SRs where the stroke variable is usually secondary or part of a compound variable²⁶⁷⁻²⁷³.

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.

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 treatment²⁷⁴.

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 significant²⁷⁶.

SR of RCT
1++

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 Thavendiranathan 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 trials²⁷⁵

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 results²⁷⁸⁻²⁸⁰. 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++**

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 women²⁸¹.

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 results²⁸³.

SR of RCT
1++

A further SR also demonstrated that statins are as effective in diabetics as they are in non-diabetics²⁸⁴. 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 populations²⁷⁷.

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+

of 80 and recruit very few people over the age of 75²⁸⁵.

6.8.5. Relative efficacy of statins

No trials that evaluate the outcomes of relevant clinical variables and compare the efficacy of statins²⁷⁵, 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 identified²⁹¹. **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 cerivastatin²⁸⁸. 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 doses²⁸⁹. 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. Simvastatin, lovastatin and atorvastatin are mainly metabolised by CYP3A4, whereas fluvastatin is metabolised by CYP2D9, such as cytochrome isoenzymes. Pravastatin is scarcely metabolised by the liver. This may lead to interactions with different drugs that share the same metabolic pathways²⁹⁰.

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 maintained²⁹¹.

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++**

vascular disease²⁹¹.

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++**

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 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.

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 women²⁹³⁻²⁹⁵.

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 syndrome²⁹⁶. A previous SR reported very similar results in three studies that assessed the risk of stroke: risk was 76% higher in patients with metabolic syndrome²⁹⁷.

SR of observational studies
2++

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 effective²⁹⁴.

SR of RCT
1++

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 debate³⁰⁰.

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 variable³⁰¹. 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 contraceptives³⁰².

**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 people³⁰³.

**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 stroke⁶⁹. Although the studies that were analysed were very similar to a prior SR³⁰⁴, 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**

of thrombosis. Certain congenital thrombophilias such factor V Leiden, patients with prothombrin 20210 mutation, methylenetrahydrofolate 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 thrombosis³⁰⁶⁻³⁰⁹. **Observational studies 2++/2+**

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 thrombophilia 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 contraceptive measures should be assessed.
A	In women with congenital thrombophilia 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?

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 dementia³¹⁰. 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 episodes³¹¹. 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.

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.

SR of 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 mortality³¹³.

RCT
1++

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 SAH⁶⁹.

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. Thrombophilias

Key Questions:

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

6.12.1. Congenital thrombophilia

Thrombophilia 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 clots³¹⁵.

A SR of case-control studies related several congenital thrombophilias 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 association³¹⁶. 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 thrombophilias, in a population that included children and adults³¹⁷.

**SR of
observational
studies
2++/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 Study³¹⁸, the Cardiovascular Health Study³¹⁹, the Stroke Prevention in Atrial Fibrillation III³²⁰ or the Copenhagen City Heart Study³²¹ 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 significant³²¹. Studies and SRs have yielded discordant results; higher risk is reported only if it is associated with the use of oral contraceptives, hypertension or diabetes³²².

**RCT
1+

Observational
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 stroke³²³.

**Case-control
studies
2+**

Also, a recent SR analysed the association between different congenital thrombophilias and the risk of cerebral venous thrombosis³⁰⁵. 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 higher³⁰⁶. No studies

**SR of
observational
studies
2++**

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

6.12.2. Acquired thrombophilia

The antiphospholipid syndrome (APS) is a clinical condition characterized 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 morbidity³¹⁵.

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 stroke³²⁵ in male patients, while a cohort study reported this relationship in women³²⁶.

Observations
1 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 thrombophilias and ischemic stroke. Only factor V Leiden has been associated with ischemic stroke in children ³¹⁶⁻³²³ .
2++	Some congenital thrombophilias 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 thrombophilias ^{327, 328} .

Recommendations

✓	In patients with some type of congenital or acquired thrombophilia, 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.
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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 disease³³⁰⁻³³² or stroke^{333, 334}. The relationship between homocysteine plasma levels and vascular risk seems to be linear³³⁵. 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++

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 disease³³⁸.

**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 validated³³⁹.

**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 diseases³⁴⁰.

**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 alterations³⁴¹⁻³⁴³.

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 results³⁴⁵⁻³⁴⁸.

**SR of
observational
studies
2++**

**Observational
studies
1
2+**

6.13.4. Falciform cell disease

Falciform cell disease is a public health problem in many African countries³⁴⁹. 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 population³⁵². 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 hemoglobin³⁵³. Approximately 10% to 23% of patients in chronic transfusion regimen will have another episode of stroke³⁵⁴.

**Observational
studies
1
2+**

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 programmes³⁵⁵.

RCT
1++

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 thromboembolisms. 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 fibrillation³⁵⁶⁻³⁵⁸, ischemic cardiopathy^{359,360} or heart valve diseases³⁶¹.

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 condition³⁶². 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 fibrillation³⁶³⁻³⁶⁵.

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 reconstitute 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 complications³⁶⁶.

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 risk³⁶⁷. Of all available models, the CHADS₂ is the most well-known and widely used and has been validated³⁶⁴. CHADS₂ criteria consider the risk of stroke according

Observational studies
2++

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 treatments³⁶⁸.

Table 10. CHADS₂ risk table³⁶⁴

	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 years³⁶⁹. However, the role of models for bleeding risk estimation in patients with atrial fibrillation is yet uncertain³⁷⁰.

There are several models to estimate the risk of Severe bleeding in patients who receive anticoagulant treatment³⁷¹⁻³⁷³. The ORBI index has been validated in an elderly population with a history of atrial fibrillation³⁷¹. 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 treatment³⁷⁴.

Observational studies
2++

Expert opinions
4

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 models³⁷⁴.

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 patients³⁷⁷.

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 limited³⁷⁵.

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 limited³⁷⁶. 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 results³⁷⁹⁻³⁸¹.

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 anticoagulation³⁸³.

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 antiaggregation³⁸⁴.

RCT
1+

Lastly, other options such as ximelagatran were withdrawn from the market in 2006 due to hepatotoxicity and more recently an open RCT that assessed treatment with penta-saccharides (idaraparinux) versus anticoagulation in patients with atrial fibrillation had to be prematurely interrupted due to an excess of intracranial hemorrhaging when compared to isolated anticoagulation³⁸⁵.

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 treatment³⁸⁶.

Case series
3

Additionally, in this type of patient, preferences vary considerably and often differ from those of physicians and from CPG recommendations³⁸⁷. These differences could be a result of patients' greater tolerance to suffering severe bleeding and a lesser tolerance to an increased risk of stroke³⁸⁸.

**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 term³⁹³⁻³⁹⁵.

**SR of RCT
1++**

Summary of the Evidence

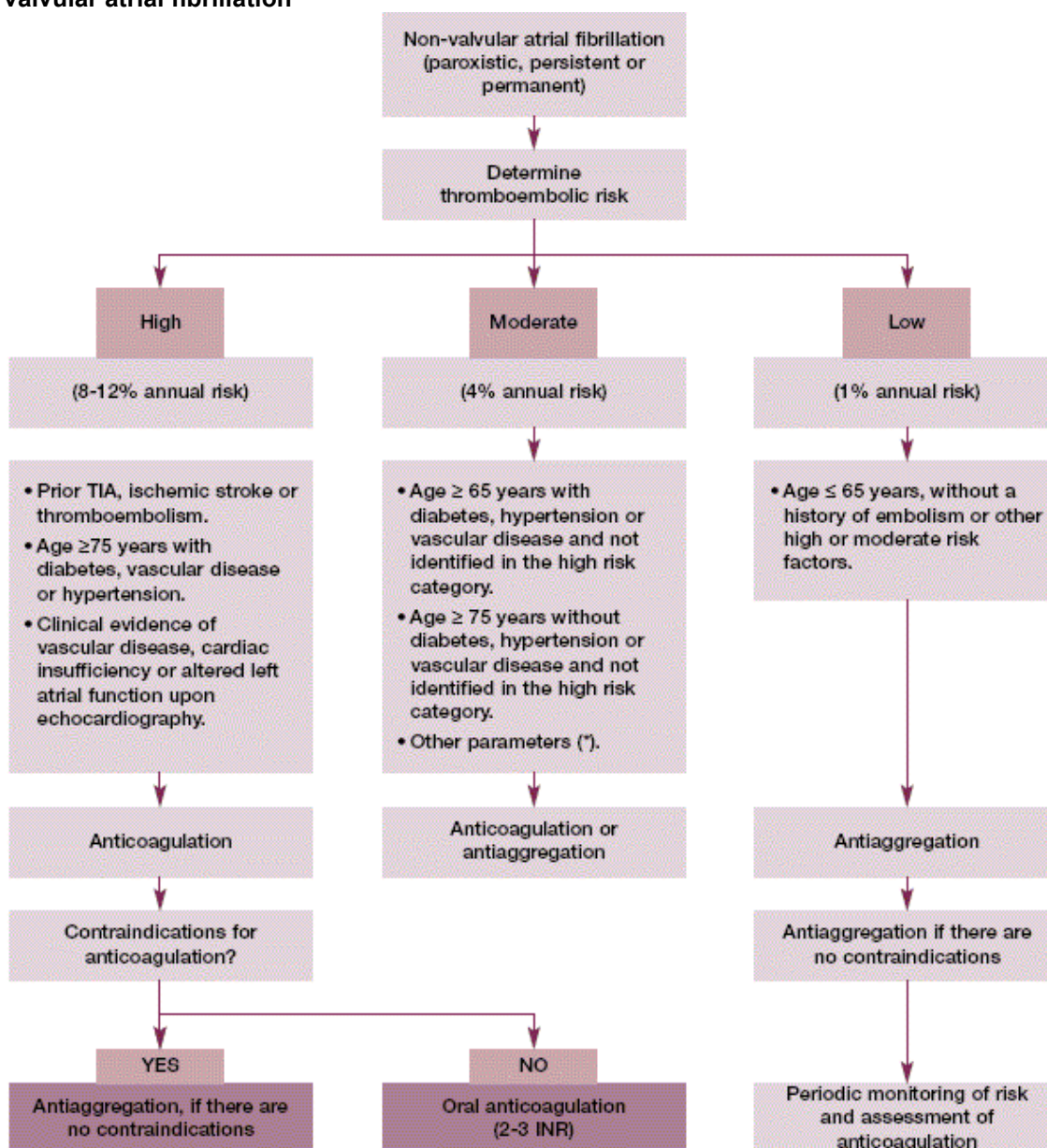
2++	Atrial fibrillation is a stroke risk factor especially in patients over the age of 75 years, HT, cardiac insufficiency (or ejection fraction under 30%), diabetes or a history of ischemic stroke or transient ischemic attack ³⁶⁴ .
2++	In patients with atrial fibrillation without additional risk factors (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 .

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 paroxysmic, 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 paroxysmic, 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 paroxysmic, 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.

Figure 4. Algorithm of antithrombotic treatment management in patients with non-valvular atrial fibrillation³⁶⁷



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.

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 markers³⁹⁶. 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 infarctions³⁹⁷⁻³⁹⁹. 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 thrombus⁴⁰². Detachment of all or part of the thrombus of the left heart cavities can cause embolic stroke³⁹⁷.

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 dipyridamol. 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 disease⁴⁰⁴.

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 recommended⁴⁰⁶.

RCT
1++

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

RCT
1+

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 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 not⁴⁰⁷. 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 hemorrhaging⁴⁰⁸.

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 treatment⁴¹².

SR of RCT
1++

Other treatments

There are other treatments for acute coronary syndrome, such as betablockers, ACEIs, ARA-IIIs, 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 episode⁴¹³. 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 <i>versus</i> 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.

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, dipyridamol or both) was 0.5% and 2.7%, respectively, with no significant differences reported⁴¹⁴. 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+

2.1% and 4.9% per year in the V-HeFT I and II studies respectively⁴¹⁴.

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 treatment⁴⁰¹.

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 rate⁴¹⁹.

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

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

The risk of thromboembolic episodes is especially high in the month following the valve replacement procedure⁴²⁰. 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 prostheses⁴²¹. Other studies have not reported differences between anticoagulants and antiaggregants⁴²²⁻⁴²⁴. 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 disease⁴⁰³ and, in combination with anticoagulant treatment, in patients with valve prostheses and vascular disease⁴²⁶. 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 prosthesis⁴²⁷. 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 thromboembolism⁴²⁸. 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 valve⁴²⁹.

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

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 phenomena⁴³⁶. 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 pathology⁴³⁹.

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 population⁴⁴⁰. 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 valvulopathy⁴⁴¹. There are familial MVP forms that are hereditarily transmitted, of gradual evolution and often benign. Sudden death is an uncommon outcome⁴⁴³.

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+

antiaggregant treatment has been considered in patients who present high risk echocardiographic criteria⁴⁴⁶.

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 fibrillation⁴⁴⁴.

**Expert
opinions**
4

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?

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 stroke⁴⁴⁷. 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.

Cohort 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 symptoms⁴⁴⁹. 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 stroke⁴⁵⁰. Despite the high incidence of this pathology in people over the age of 80, diagnosis and treatment rates are lower when compared to younger patients⁴⁵¹.

Observational studies
2+

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.

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

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 outcome⁴⁵³.

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 intervention⁴⁵⁴. 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 TIA⁴⁵⁵.

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 treatment⁴⁵⁶. These results point in a similar direction as the *Antithrombotic Trialists' Collaboration* study that jointly analysed trials conducted in other patients with high vascular risk⁴⁰³.

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

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 symptoms⁴⁵⁹. 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 reported⁴⁶⁰. 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 symptoms⁴⁶¹.

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 category⁴⁶².

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

	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.

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 mortality⁴⁶³. Other previous SRs reported very similar results. Later, the WHI study reported a significant reduction of stroke, especially ischemic, in women without vascular history⁴⁶⁴⁻⁴⁶⁶.

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 episodes⁴⁶⁵. Another SR indicates that for coronary risk greater than 15% at 10 years, the benefits of treatment with aspirin would outweigh the risks⁴⁶⁷.

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, dipyridamol and triflusal do not⁴⁶⁸.

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 bleeding⁴⁶⁹.

SR of RCT
1++

Enteric coated antiaggregants have not been shown to reduce severe bleeding complications and entail greater treatment cost⁴⁷⁰⁻⁴⁷². **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 effects⁴⁷³. 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

Vascular episodes	Women		Men	
	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.

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 episodes⁴⁷⁴. 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 death⁴⁷⁵.

RCT
1+

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 hypersensitivity or intolerance to aspirin's adverse effects, clopidogrel, dipyridamol 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 thrombophilias or women who have mechanical heart valves⁴⁷⁶. 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.

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 prophylactic 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.

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, respectively⁴⁷⁷. However, in standard clinical practice, the risk of bleeding could be greater than that established by clinical trials, especially in older patients³⁶⁹.

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 factors⁴⁷⁸. Other studies have validated this index⁴⁷⁹⁻⁴⁸¹.

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 treatment⁴⁸². 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 treatment⁴⁸³.

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+

100 patients/year if a patient has a score equal to or greater than 5⁴⁸⁴.

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 score⁴⁸⁴

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 score⁴⁸⁴

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?

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 prognosis²³⁸. The incidence non-traumatic SAH ranges from 6-25 cases per 100,000 inhabitants. The highest rates correspond to studies performed in Finland and Japan⁴⁸⁵⁻⁴⁸⁸. 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 SAH⁶⁹.

**SR of
observational
studies**

**Observational
studies
2+**

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 cause⁴⁸⁹. 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 multiple⁴⁹⁰.

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.

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 patients⁴⁹⁴. 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 procedure⁴⁹⁴.

Cohort
studies
2+

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 sympathicomimetic 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 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

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