World Journal of Clinical Cases

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.12998/wjcc.v3.i5.418

World J Clin Cases 2015 May 16; 3(5): 418-429
ISSN 2307-8960 (online)

REVIEW

Cardiovascular risk factors for acute stroke: Risk profiles in the different subtypes of ischemic stroke

Adrià Arboix

Adrià Arboix, Unit of Cerebrovascular Diseases, Service of Neurology, Hospital Universitari del Sagrat Cor, University of Barcelona, E-08029 Barcelona, Catalonia, Spain
Author contributions: Arboix A designed the research, performed the PubMed bibliographic research, analyzed data and wrote the paper.
Conflict-of-interest: None to be declared.

Correspondence to: Adrià Arboix, MD, PhD, Unit of Cerebrovascular Division, Service of Neurology, Hospital Universitari del Sagrat Cor, University of Barcelona, C/Viladomat 288, E-08029 Barcelona, Catalonia, Spain. aarboix@hscor.com
Telephone: +34-93-4948940
Fax: +34-93-4948906
Received: August 6, 2014
Peer-review started: August 12, 2014
First decision: September 16, 2014
Revised: January 14, 2015
Accepted: February 10, 2015
Article in press: February 12, 2015
Published online: May 16, 2015

Abstract

Timely diagnosis and control of cardiovascular risk factors is a priority objective for adequate primary and secondary prevention of acute stroke. Hypertension, atrial fibrillation and diabetes mellitus are the most common risk factors for acute cerebrovascular events, although novel risk factors, such as sleep-disordered breathing, inflammatory markers or carotid intima-media thickness have been identified. However, the cardiovascular risk factors profile differs according to the different subtypes of ischemic stroke. Atrial fibrillation and ischemic heart disease are more frequent in patients with cardioembolic infarction, hypertension and diabetes in patients with lacunar stroke, and vascular peripheral disease, hypertension, diabetes, previous transient ischemic attack and chronic obstructive pulmonary disease in patients with atherothrombotic infarction. This review aims to present updated data on risk factors for acute ischemic stroke as well as to describe the usefulness of new and emerging vascular risk factors in stroke patients.

Key words: Cardiovascular risk factors; Hypertension; Atrial fibrillation; Diabetes mellitus; Ischemic stroke; Transient ischemic attack; Sleep apnea

Core tip: Prevention of acute stroke by controlling cardiovascular risk factors is a health care priority worldwide for a number of reasons, particularly due to the increasing occurrence of acute cardiovascular events in progressively older segments of the population, the high morbidity and mortality of some stroke subtypes and the economic burden associated to care of acute stroke patients. The frequency of the different cardiovascular risk factors is not equal for all subjects diagnosed of first-ever stroke. For this reason, it is necessary to know the most common profiles of vascular risk factors associated with each individual type of stroke in order to improve primary and secondary stroke prevention strategies. The role of new risk factors, such as sleep-disordered breathing or complex atheromatosis of the aortic arch merits further investigation.

Arboix A. Cardiovascular risk factors for acute stroke: Risk profiles in the different subtypes of ischemic stroke. *World J Clin Cases* 2015; 3(5): 418-429 Available from: URL: http://www.wjgnet.com/2307-8960/full/v3/i5/418.htm DOI: http://dx.doi.org/10.12998/wjcc.v3.i5.418

INTRODUCTION

Cerebrovascular diseases are the first cause of mortality in women and the second cause of death in men in industrialized countries[1-3]. Stroke is the main reason of functional disability. Neurological sequelae are present in 90% of stroke patients, one third of which will not be able to resume daily life activities at the same level than before stroke[1,2]. Cerebrovascular diseases are also an important cause of cognitive impairment and dementia[3]. The high frequency of stroke is illustrated by the cumulative incidence per 100000 persons-year that in Catalonia in 2002 and in the population over 24 years of age was of 218 new cases among males and 127 among females[4]. Therefore, to recognize cardiovascular risk factors and to treat them appropriately is the key to establish primary preventive strategies in non-stroke patients or secondary preventive measures to avoid recurrence in stroke victims.

The etiology of stroke is multifactorial, and therapeutic actions focused on vascular risk factors, particularly in secondary stroke prevention have been shown to reduce the risk of recurrent stroke, as well as the risk of any other coronary or peripheral vascular episode[4,5].

Risk factors for stroke are usually divided into non-modifiable (age, sex, ethnicity, low weight at birth, inherited diseases) and modifiable (hypertension, diabetes mellitus, heart diseases, smoking, dyslipidemia, alcohol abuse, obesity, metabolic syndrome, use of oral contraceptive drugs, hormone treatment in postmenopausal women, clinically silent carotid stenosis, peripheral artery disease, drug abuse, migraine, and other)[3-5].

NON-MODIFIABLE RISK FACTORS

Age, gender, ethnicity/race, low birth weight, family history of stroke and genetics/heredity[6]. In relation to age, in 2006, it was found that 93% of subjects who had suffered a stroke in Spain were older than 64 years of age[7]. Age is a continuous risk factor for the occurrence of stroke and dementia, with a two-fold increase in the incidence and prevalence rates for each successive 5 years after age 65 years. On the other hand, men show a higher incidence of cerebral vascular disease than women. With regard to ethnicity/race[8,9], it has been demonstrated that black patients have a higher incidence of stroke *vs* white patients. Intracranial atherosclerotic disease is more frequent in patients of Asian. Birth weight is inversely associated with coronary heart disease and stroke[9]. The underlying mechanisms of this association are poorly understood but might be related with genetic or nutritional factors[1].

Family history of stroke in a first-degree relative also increases the likelihood of suffering from an acute cerebrovascular event even after adjusting for other vascular risk factors. This increased risk may be due to different mechanisms, including inherited predisposition for stroke risk factors, genetic transmission of susceptibility to stroke, familial-related lifestyle, cultural and environmental factors, and interactions between genes and environmental factors[10].

Different genetic disorders have been associated with stroke. Rare monogenic disorders can cause stroke[11], such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), cerebral amyloid angiopathy, moyamoya syndrome, Fabry disease, Ehlers-Danlos syndrome type Ⅳ, Marfan syndrome, Sneddon syndrome, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) and coagulopathies. However, as with other complex traits, the genetic etiology of common stroke is likely to be polygenic and more related to genetic influences on well-documented risk factors, such as hypertension, dyslipidemia, cardiopathy or diabetes[12,13]. Cerebrovascular events have also been related to polymorphisms of genes that regulates clotting factors, angiotensin-converting enzyme, nitric oxygen synthetase and phosphodiesterase 4D among other[10].

A meta-analysis of genome-wide association studies (the METASTROKE collaboration) identified genetic variants specific to the different stroke subtypes[14]. This study highlights the importance of detailed stroke subtyping in order to maximize success of genetic studies in ischemic stroke and to establish whether different genetic pathophysiological mechanisms seem to be associated with different stroke subtypes.

MODIFIABLE RISK FACTORS

Modifiable risk factors for ischemic stroke are well known. Appropriate treatment of these risk factors has been associated with a reduction of stroke. This allows the implementation of measures for primary or secondary stroke prevention.

Hypertension

Hypertension together with age are leading risk factors for silent or symptomatic cerebrovascular disease[15-17]. High blood pressure multiplies the risk for stroke as much as 4-fold. Both factors are also related to the probability of suffering some degree of cognitive impairment[4]. The risk of cerebral hemorrhage in hypertensive patients is 3.9 times higher than in non-hypertensive individuals. In aneurysmal subarachnoid hemorrhage the relative risk is 2.8 higher[18-22]. The diagnosis and control of hypertension one of the main strategies for primary and secondary prevention of stroke[22-24]. The effect of chronic hypertension on cerebral vessels and tissue (microhemorhages, silent infarctions, white matter lesions and atrophy) also supports a physiopathological mechanism for the association between hypertension and cognitive

Table 1 Distribution by age groups of demographic and cardiovascular risk factors in 2704 consecutive patients with cerebral infarction collected from the "Sagrat Cor Hospital of Barcelona Stroke Registry"[7] *n* (%)

Data	< 65 yr (*n* = 386)	65-74 yr (*n* = 680)	⩾ 75-84 yr (*n* = 1068)	⩾ 85 yr (*n* = 570)
Gender				
Males	270 (69.9)	409 (60.1)	471 (44.1)	186 (32.6)
Females	116 (30.1)	271 (39.9)	597 (55.9)	384 (67.4)
Vascular risk factors				
Hypertension	186 (48.2)	415 (61)	624 (58.4)	276 (48.4)
Atrial fibrillation	38 (9.8)	157 (23.1)	366 (34.3)	246 (43.2)
Diabetes mellitus	90 (23.3)	187 (27.5)	252 (23.6)	103 (18.1)
Dyslipidemia	86 (22.3)	179 (26.3)	161 (15.1)	54 (9.5)
Previous cerebral infarction	42 (10.9)	130 (19.1)	194 (18.2)	102 (17.9)
Ischemic heart disease	37 (9.6)	128 (18.8)	185 (17.3)	85 (14.9)
Smoking (> 20 cigarettes/d)	34 (8.8)	85 (12.5)	132 (12.4)	66 (11.6)
COPD	112 (29)	88 (12.9)	50 (4.7)	10 (1.8)
Peripheral vascular disease	14 (3.6)	54 (7.9)	103 (9.6)	52 (9.1)
Heart valve disease	22 (5.7)	79 (11.6)	86 (8.1)	27 (4.7)
Congestive heart failure	26 (6.7)	46 (6.8)	69 (6.5)	33 (5.8)
Obesity (BMI ⩾ 30 kg/m^2)	7 (1.8)	16 (2.4)	54 (5.1)	71 (12.5)
Oral anticoagulants	20 (5.2)	42 (6.2)	44 (4.1)	12 (2.1)
Alcohol abuse (⩾ 80 g/d)	10 (2.6)	25 (3.7)	41 (3.8)	18 (3.2)
Previous cerebral hemorrhage	38 (9.8)	20 (2.9)	7 (0.7)	1 (0.2)

Data expressed as frequencies and percentages in parenthesis. COPD: Chronic obstructive pulmonary disease; BMI: Body mass index.

impairment[25-29]. As shown in Table 1, according to data of 2704 patients with first-ever ischemic stroke collected from the Sagrat Cor of Barcelona Stroke Registry, hypertension was the main risk factor in the different age groups[7].

Diabetes mellitus

Dyslipidemia, hypertension and obesity are atherogenic risk factors frequently found in type 2 diabetes patients[4,5]. Also, diabetes is an independent risk factor of ischemic stroke of atherothrombotic cause. The influence of diabetes upon increasing the stroke risk is higher in women than in men[30]. Diabetes is the main risk factor following hypertension of cerebral small vessel disease and has been identified as a significant independent variable of symptomatic recurrence in patients with first-ever cerebral infarction of the lacunar type[31,32]. The combination of hypercholesterolemia and hypertension increases the frequency of vascular complications in patients with diabetes.

Heart diseases

Heart diseases are the second cause of acute cerebrovascular events and are diagnosed in one third of patients with stroke[33,34]. Atrial fibrillation (AF) and atrial flutter are the most important and modifiable risk factor, frequently associated with cardioembolic stroke. Cardioembolic infarction is the most severe stroke subtype due to the very low percentage of symptom-free patients at hospital discharge, the non-negligible risk of early recurrent embolic events and the high mortality in the acute stroke phase (27% in the Sagrat Cor of Barcelona Stroke Registry)[33-36]. The prevalence of AF increases with age. It has been shown that 5% of subjects older than 70 years have AF (the mean age of patients with AF is 75 years), and about one fourth of acute strokes in very old patients (> 80 years) are also caused by AF[37,38]. Future embolism is also more frequent in patients with underlying comorbid heart diseases, such as AF and stenosis of the mitral valve. The risk of stroke is 3 to 4 times higher in the absence of organic heart disease or risk factors (lone atrial fibrillation). On the other hand, AF associated to hypertensive heart disease is the most common cardiogenic source of cerebral embolization in industrialized countries[33]. Similar rates of cardioembolism for paroxysmal and chronic AF have been reported, so that preventive therapy should not be different for patients with paroxysmal AF and those with chronic AF[33]. In patients without history of transient ischemic attack (TIA) or stroke, AF carries a risk of stroke of 2%-4% per year. Cardiac emboli arising from cardiac chambers are often large and hence especially likely to cause severe stroke, disability and death[33].

A number of cardiac conditions are potential sources of embolism, such as dilated myocardiopathy, heart valve disease (mechanical prosthetic valve, mitral rheumatic stenosis, infectious endocarditis, marantic endocarditis), left ventricular hypertrophy, atrial myxoma and congenital heart diseases (such as patent foramen ovale, atrial septal aneurysm and ventricular septal defects). Acute coronary syndromes are minor causes of cardioembolism. There is an inverse correlation between ejection fraction of the left ventricle and the incidence of ischemic stroke[33-39].

Cigarette smoking

Cigarette smoking is an independent predictor of cerebrovascular disease in both men and women[40]. Smokers have a relative risk of ischemic stroke of 1.92

times higher as compared to non-smokers. Smoking increases the risk of thrombus formation in narrow arterial vessels and contribute to enhance atherosclerotic plaque burden. Also, smoking increases blood viscosity, fibrinogen and platelet aggregation, and decreases high-density lipoprotein (HDL) cholesterol, which causes direct damage to endothelium and an increase in blood pressure[40-42]. A meta-analysis of 19 prospective studies has shown an association of smoking with dementia and cognitive decline[43]. Finally, there is growing acceptance that passive cigarette smoke increases the risk of stroke[44].

Dyslipidemia

Plasma lipids and lipoproteins [total colesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, HDL cholesterol and lipoprotein (a)] have an influence on the risk of cerebral infarction, but the relationships between dyslipidemia and stroke have not been consistently elucidated[9]. Data from prospective studies in male patients have shown that in the presence of total serum cholesterol values > 240 to 270 mg/dL, there is an increase in the rates of ischemic stroke[45].

In general, the risk of ischemic stroke in both genders is clearly related with dyslipidemia. In men, low HDL levels is a risk factor for cerebral ischemia but data in women are inconclusive. Because high levels of LDL are clearly related with a higher cardiovascular risk, adequate control of LDL cholesterol is recommended (*e.g.,* National Cholesterol Education Program Ⅲ guidelines) in subjects without history of cerebrovascular accident[46].

High triglyceride levels are a component of the metabolic syndrome. In a study of 11117 patients with coronary heart disease, cerebral infarctions were significantly associated with high serum levels of triglycerides and low levels of HDL cholesterol[9].

Alcohol abuse

Chronic heavy alcohol consumption (> 60 g/d) is associated with an increase in the relative risk of stroke [risk ratio (RR) of 1.69 in cerebral ischemia and RR = 2.18 in cerebral haemorrhage][44]. Ethanol is a direct neurotoxin and chronic ethanol abuse causes different neurodegenerative processes, including dementia[47,48]. However, light-to-moderate alcohol consumption (20-30 g/d, equivalent to 1 or 2 drinks per day) is associated with a lower risk of stroke, white matter disease and clinically silent cerebral infarcts[3,44].

Overweight and obesity: Adiposity

Obesity is defined as an increase above 25% of the theoretical body weight according to age and sex. The term "adiposity" refers to the amount of adipose (fat) tissue in the body, and can be considered more precise than "obesity" which is mainly one of the ways to measure adiposity. Adiposity is an energy imbalance between energy intake (calories) and energy expenditure (physical activity and metabolic processes); however, the ideal or normal threshold for adiposity has not been established. Increase in fat tissue is associated with a higher risk of insulin resistance, diabetes, hypertension, dyslipidemia, vascular diseases and other conditions. Persons with a body mass index (BMI) of < 18.5 kg/m^2 are classified as being underweight, between 18.5 and 25.9 kg/m^2 as healthy weight range, between 26 and 29.9 kg/m^2 as overweight and ⩾ 30 kg/m^2 as being obese[49]. Abdominal obesity is commonly measured by either the waist-to-hip ratio or waist circumference and appears to be a more sensitive measure of adiposity and vascular risk. Clinically, abdominal obesity is defined by a waist circumference > 102 cm in men and 88 in women[50]. Weight and abdominal fat reduction is associated with a lowering in blood pressure, and may thereby reduce the risk of stroke. Moreover, there is evidence linking the continuum of adiposity, hyperinsulinemia, and diabetes with dementia[51].

Metabolic syndrome

Metabolic syndrome is defined as te presence of three or more of the following: (1) abdominal obesity as determined by waist circumference > 102 cm and > 88 cm for women; (2) triglycerides ⩾ 150 mg/dL; (3) HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women; (4) systolic blood pressure ⩾ 130 mm Hg and diastolic blood pressure ⩾ 85 mmHg; and (5) fasting glucose ⩾ 110 mg/dL[52,53]. Hyperinsulinemia/insulin resistance is an important marker of the metabolic syndrome. The metabolic syndrome is a predictor of coronary heart disease, cardiovascular disease (which includes coronary heart disease and stroke) and all-cause mortality. Also, the risk of stroke is higher for patients presenting some of the diseases included in the metabolic syndrome[9].

Asymptomatic carotid stenosis

Approximately between 5% and 10% of men and women over 65 years had > 50% and 1% > 80% asymptomatic carotid stenosis[3], which has been also identified as a risk for stroke[9] and an important clinical feature of underlying ischemic heart disease.

Peripheral vascular disease

Epidemiological studies have shown that patients with intermittent claudication have a high risk of premature death due to ischemic heart disease and stroke. Also, individuals with peripheral vascular disease are at a higher stroke risk[9,54]. History of intermittent claudication, peripheral vascular disease or coronary heart disease in a patient with cerebral infarction indicates the presence of clinically generalized atherosclerosis, according to which the diagnosis of cerebral ischemia of atherothrombotic cause is highly probable.

Postmenopausal hormone therapy

Postmenopausal hormone therapy (estrogen with or without a progestin) should not be used for primary

prevention of ischemic stroke because, paradoxically, the risk of stroke is increased.

The increased risk for vascular outcomes should be taken into account when hormone replacement therapy is used for other indications[9,45].

Oral contraceptive use

The risk of stroke associated with low-dose oral contraceptives (containing low doses of estrogens) in women without additional risk factors (*e.g.,* cigarette smoking or history of thromboembolic episodes) appears low[45]. Women taking oral contraceptives older than 35 years, active smokers, with hypertension, diabetes, migraine headache or history of thromboembolism are at higher risk of stroke[9,45].

Drug abuse

Drug abuse (mainly heroin, cocaine, amphetamins) has been also identified as a risk factor for stroke through different mechanisms, including blood pressure, hematologic, hemostatic and vasculitic-type changes, as well as increased platelet aggregation and blood viscosity[3,9,45].

Migraine

Migraine has been marginally associated with stroke risk in young women but in persons over 60 years an association between stroke and migraine has not been documented[55]. The risk of stroke has been related to underlying pathophysiological mechanisms of migraine (with aura), such as reduced blood flow particularly in the posterior circulation[9]. In young adults, stroke and migraine may be linked by paradoxical embolism through a patent foramen ovale. Patients with migraine also show an increase in platelet–leukocyte aggregation and platelet activation, increasing the risk of emboli formation and suggesting a link at cellular level between stroke and migraine[55,56].

LESS WELL-DOCUMENTED VASCULAR RISK FACTORS

The causal role of these factors in stroke patients remains inconclusive and futher studies are needed to clarify the contribution of each of these factors to the overall stroke risk.

Increase of the apoB/apoA1 ratio

Plasma levels of apolipoprotein B (apoB) is an indicator of very-low density (VLDL) and LDL lipoproteins with proatherogenic properties because each VLDL and LDL particle contains a molecule of apoB. It seems that plasma concentration of apoB is the highest lipid predictor of ischemic heart disease. In patients with TIA, an increase in the apoB/apoA1 ratio would product stroke more strongly (HR = 2.9) than other lipid values, such as apoB (HR = 2.3), total cholesterol (HR = 1.8), LDL cholesterol (HR = 1.5), LDL/HDL ratio (HR = 1.3) and apoA1 (HR = 1.2)[9,45].

Sedentarism

A sedentary lifestyle is associated with an increase in the risk of stroke. Regular physical activity has well-established benefits for reducing the risk of cardiovascular disease, premature death and stroke[9]. The excellent review of Hankey[45] of potential new risk factors for ischemic stroke includes data of a meta-analysis of 23 studies and shows that subjects with high physical activity as compared to those with low physical activity had a lower stroke risk (RR = 0.79). Also, in another study, a reduction in the risk of stroke was reported in relation to moderate physical activity at leisure time (RR = 0.87) and active daily activity $\geqslant$ 30 min daily (cycling/walking to work). The protective effect of physical activity may be partly mediated through its role in reducing blood pressure and controlling other risk factors for cardiovascular disease, diabetes and increased body weight. It has been also related to a reduction of plasma fibrinogen and platelet activity, with increases of both tissue plasminogen activator and HDL cholesterol[3,45].

Insufficient daily fruit and vegetable intake

A meta-analysis of 17 cohort studies showed that risk of stroke decreased by 11% for each additional portion per day of fruit, by 5% for fruit and vegetables, and by 3% for vegetables[3,45]. A higher sodium intake increases the risk of stroke, whereas a higher consumption of potassium was associated with a reduction in the risk of stroke, probably due to the blood pressure lowering effect and mitigation of sodium effects on pressor responsiveness[9,45]. In Asian populations, diets characterized by consumption of cholesterol and saturated fats, as well as low consumption of animal-related proteins have been associated with an increased stroke[9,45].

Psychosocial stress

The risk of stroke is also increased in the presence of stressful live events, including depression[44].

Sleep-related breathing disorders

The presence of sleep apnea is also a risk factor for stroke. Sleep apnea may increase the risk of stroke by leading to or worsening hypertension or ischemic heart disease. Sleep apnea causes reductions in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, hypercoagulability, inflammation and paradoxical embolism in patients with patent foramen ovale. In patients with advanced sleep-disordered breathing, cardiac arrhythmias, atrioventricular block and atrial fibrillation appear when the oxyhemoglobin saturation falls to < 65%. Sleep apnea as a risk factor for

cerebrovascular events is usually underdiagnosed[57-59].

Inflammatory markers

There is increasing evidence of the relevance of inflammation as a physiopathological mechanism of atherothrombotic stroke.

Leukocyte and monocyte counts: In the CAPRIE trial (Clopidogrel *vs* Aspirin in Patients at Risk of Ischemic Events) patients with a history of peripheral arterial disease, stroke, or myocardial infarction or who had a leukocyte count in the highest quartile at baseline showed a higher adjusted risk of recurrent ischemic events compared with those in the lowest quartile (RR = 1.42)[45]. Monocyte count has been shown to be an independent predictor of future atherosclerotic plaque formation in the carotid artery in subjects without preexisting carotid atherosclerosis[3,60].

C-reactive protein: In apparently healthy individuals, high-sensitive C-reactive protein, acute-phase reactant and biological marker of inflammation, has been shown to be an independent risk factor for death of vascular cause, stroke and myocardial infarction[45].

Other biomarkers: An increase in the levels of other inflammatory biomarkers, among which, tumor necrosis factor (TNF) and interleukin 2 (IL-2) are also related to subclinical carotid disease[45]. Inflammatory cells in the atherosclerotic plaque are involved in the release of substances (matrix metallopeptidases) causing rupture of the plaque by instability of the fibrotic layer[45]. An increase of inflammatory mediators have been shown in atherosclerotic plaques in symptomatic as compared to asymptomatic patients[3,45].

Infection

It has been shown that recent infection (within 1 wk) can be a risk factor for stroke and coronary-related complications[3]. This may be partly related to generalized activation of circulating leukocytes, enhancing the tendency for thrombosis at the site of atherosclerotic plaque. Moreover, *Chlamydia pneumonia* DNA or *C. pneumonia* antigen, have been identified in 40% of atherosclerotic plaques[3,45].

Periodontal disease related to seeding of the bloodstream with Gram-negative organisms has been associated with carotid atherosclerosis and the risk of stroke[45]. However, antibiotic treatment has been unsuccessful in the prevention of severe cardiovascular events, at least in patients with established coronary heart disease.

Cytomegalovirus, herpes virus and *Mycoplasma pneumoniae* infection increase the risk of stroke by various mechanisms, particularly by increasing inflammatory mediators, facilitating the coagulation cascade and enhancing expression of adhesion molecules on vascular endothelial cells[3,45].

Helicobacter pylori have also been identified in human atherosclerotic plaque.

These data support the concept of "infectious burden", according to which prolonged exposure to multiple microorganisms during the life period may contribute to the development and activation of the atherosclerotic plaque[9,45].

Fibrinogen

In a meta-analysis of thres prospective studies, patient with fibrinogen concentrations above the median value showed an increased risk of stroke (HR = 1.34) in comparison with patients with serum fibrinogen values below the median, particularly in patients with non-lacunar syndromes (HR = 1.42)[45].

Other biological factors

Hemocysteine: It has been consistently shown a positive and independent association between total plasma hemocysteine and atherosclerotic disease, risk of silent and symptomatic stroke and cognitive decline[45,61]. Also, *MTHFR TT* genotype confers a significantly greater mean hemocysteine levels and greater risk for stroke (OR = 1.26) than carriers of the *MTHFR CC* genotype. Although a standard definition of hyperhomocysteinemia is lacking, it seems that fasting plasma concentrations > 16 μmol/L may be considered indicative of hyperhomocysteinemia[3,55]. Ongoing randomized controlled clinical trials continue to assess the efficacy of homocysteine-lowering treatment for decreasing the risk of ischemic stroke.

Elevated lipoprotein (a): Lipoprotein (a) [Lp(a)] complex has proatherogenic and prothrombotic properties and has been shown to be a risk factor for coronary heart disease[45]. Lp(a) enhances arterial cholesterol deposition, thereby promoting atherogenesis[3,45]. There is an increasing evidence suggesting that high Lp(a) levels may induce cerebral ischemia but findings have not been completely consistent[45].

Lipoprotein-associated phospholipase A_2: High concentrations of Lp-PLA_2 are associated with an increased risk of cardiovascular events, independent of other risk factors, and potentially may increase the stroke risk[45].

Hypercoagulability: Venous thrombosis (but not cerebral infarction) is associated with thrombophilias (hereditary) or acquired hypercoagulable states[45]. Anti-phospholipid antibodies (aPL) is most frequently the cause of arterial thrombosis IgG and IgM anti-cardiolipin antibody and lupus anticoagulant are useful tests to detect aPL. Young women with cerebral infarction have a higher prevalence of aPL.

Therefore, primarily young women who have a history of thrombotic events and meet the laboratory criteria for antiphospholipid syndrome might benefit

from the administration of moderate-intensity warfarin or other antithrombotic therapies as primary or secondary prevention strategies[3,45]. On the other hand, a relationship between stroke and other hereditary hypercoagulable states (protein S or antithrombin Ⅲ, protein C deficiency, *etc.*) has not been reported in most case-control studies[45].

Albuminuria: An increased risk of stroke, death of vascular cause, myocardial infarction and renal dysfunction has been documented in patients with microalbuminuria or proteinuria (30-300 mg/d and > 1 g/d, respectively)[45].

Cystatin C: Cystatin C is a serum marker of renal function that has been shown to be a predictor of stroke, myocardial infarction and vascular death, even stronger in elderly subjects than is creatinine[3,45].

EMERGING VASCULAR RISK FACTORS

Asymptomatic vascular disease

Asymptomatic vascular disease is the first consequence of the impact of uncontrolled progression of cardiovascular risk factors on systemic or cerebral arteria vessels of the organism. Asymptomatic vascular disorders may be viewed as subclinical arterial markers related to cardiovascular risk factors, and are predictors of stroke, myocardial infarction and vascular death in the mid- and long-term. Mild carotid stenosis, carotid intima-media thickness and atheroma of the aortic arch, as well as carotid artery distensibility and endothelial reactivity of the brachial artery have been reported as potential causes of asymptomatic vascular disease[3,44].

Complex atheromatosis of the aortic arch is a risk factor of embolism. There is a significant relationship between atheromatous plaques in the aortic arch and cerebral ischemia, particularly in the presence of protruding plaques ⩾ 4 mm in thick. Morphologically complex plaques (aortic atherosclerotic debris) is considered a high risk embolic source (increased stroke risk by 1.7)[3,44,62-64].

Clinically silent cerebral ischemia

Modern neuroimaging techniques allow the detection of clinically silent cerebral ischemia in the form of white matter hyperintensities, cerebral infarcts, cerebral atrophy or microbleeds, which may be considered stroke risk factors[45]. Most lacunar infarctions are asymptomatic and magnetic resonance imaging (MRI) studies reveal the presence of lacunes in approximately 20%-28% of individuals older than 65 years. Silent lacunar infarction is a risk factor of new infarctions of the lacunar type and cognitive impairment[65-69]. Also, symptomatic progression of lacunar disease has been demonstrated given that at 3 years, between 10% and 50% of patients will show new silent lacunar infarcts in MRI studies. Progression of leukoaraiosis is documented in 40% of patients with lacunar infarct. Therefore, clinically silent small vessel cerebral disease is a stroke risk factor that should be taken into account given the independent role as significant predictor of both symptomatic vascular recurrence and cognitive impairment[70,71].

Other factors

Proteomic risk markers, history of TIA, previous cerebral infarction or primary intracerebral hemorrhage, chronic obstructive pulmonary disease (COPD), chronic liver disease and use of oral anticoagulants are other risk factor for stroke.

RISK FACTORS IN THE DIFFERENT ISCHEMIC STROKE SUBTYPES

Studies of data collected from hospital-based stroke registries have shown that the different etiological stroke subtypes present clearly differentiated cardiovascular risk profiles. In this respect, in the Sagrat-Cor of Barcelona Stroke Registry, clear differences between cerebral infarcts and spontaneous intracerebral hemorrhages were observed[72]. Main risk factors in patients with cerebral infarction are hypertension (54.1%), atrial fibrillation (29.3%) and diabetes (22.6%), whereas in patients with hemorrhagic stroke, the frequency of hypertension was higher (61.3) but the occurrence of atrial fibrillation (15.3%) and diabetes (14.7%) was lower[72] (Table 2). These differences were statistically significant and were consistent with data reported in other studies[73-78]. Also, it should be noted that risk factors in stroke patients present a characteristic profile according to the patient's age, with a high percentage of patients with atrial fibrillation and other heart conditions in the oldest old group (⩾ 85 years) (Table 1).

Moreover, each subtype of ischemic stroke exhibits a distinct vascular risk profile[7] (Table 3). When a logistic regression analysis was performed (Table 4)[7], the risk profile for the subtype of atherothrombotic infarction is characterized by the presence of peripheral vascular disease (OR = 2.28), which is a clear and well-known indicator of generalized atherosclerosis, together with hypertension (OR = 1.84) and diabetes mellitus (OR = 1.66), which are major risk factors traditionally related to cardiovascular and cerebrovascular morbidity of large artery atherosclerosis[36,79]. Other risk factors include history of TIA (OR = 1.50), which should be considered a true neurological emergency due to the early risk of subsequent neurological deterioration (cerebral ischemia)[80], COPD (OR = 1.40), -a clinical entity associated with cigarette smoking and recurrent infection episodes, which may cause an acquired subclinical hypercoagulable status-, previous cerebral infarction (OR = 1.40), the presence of which is associated with an increased risk of recurrent cerebral

Table 2 Comparison of demographic data, risk factors, neuroimaging findings and early outcome between stroke patients with intracerebral hemorrhage and cerebral infarctions ("Sagrat Cor Hospital of Barcelona Stroke Registry" period 1986-2004)[72] *n* (%)

Variable	Intracerebral hemorrhage (*n* = 380)	Cerebral infarction (*n* = 2082)
Age, yr, mean (SD)	72.51 (12.55)	74.97 (12.21)
Age, yr		
< 65	83 (21.8)	329 (15.8)
65-74	112 (29.5)	521 (25.0)
75-84	120 (31.6)	808 (38.8)
⩾ 85	65 (17.1)	424 (20.4)
Gender		
Males	199 (52.4)	987 (47.4)
Females	171 (47.6)	1095 (52.6)
Lacunar syndromes	36 (9.5)	554 (31.4)
Hypertension	233 (61.3)	1126 (54.1)
Diabetes mellitus	56 (14.7)	471 (22.6)
Atrial fibrillation	58 (15.3)	609 (29.3)
COPD	29 (7.6)	166 (8.0)
Magnetic resonance imaging	95 (25)	656 (31.5)
Respiratory events	45 (11.8)	183 (8.8)
Symptom-free at discharge	23 (6.1)	382 (18.3)
In-hospital mortality	107 (28.2)	249 (12.0)
Transfer to a convalescence/rehabilitation unit	64 (16.8)	243 (11.7)
Length of stay, median (IQR)	15 (8-26)	12 (8-20)

Data expressed as frequencies and percentages in parentheses unless otherwise stated. COPD: Chronic obstructive pulmonary disease; IQR: Interquartile range (25^{th}-75^{th} percentile).

Table 3 Cardiovascular risk factors in 2704 consecutive patients with cerebral infarction collected from the "Sagrat Cor Hospital of Barcelona Stroke Registry" according to the different stroke subtypes[7] *n* (%)

Variables	Atherothrombotic (*n* = 770)	Lacunar (*n* = 773)	Cardioembolic (*n* = 763)	Undetermined cause (*n* = 324)	Unusual cause (*n* = 114)
Hypertension	509 (66.1)[b]	525 (71.6)[b]	377 (49.4)[b]	59 (18.2)[b]	31 (27.2)[b]
Atrial fibrillation	120 (15.6)[b]	81 (11.1)[b]	573 (75.1)[b]	25 (7.7)[b]	8 (7)[b]
Diabetes mellitus	242 (31.4)[b]	218 (29.7)[b]	142 (18.6)[d]	24 (7.4)[b]	6 (5.3)[b]
Dyslipidemia	164 (21.3)[b]	166 (22.6)[b]	88 (11.5)[b]	52 (16)[b]	10 (8.8)
Previous cerebral infarction	164 (21.3)[b]	117 (16)	146 (19.1)	31 (9.6)[b]	10 (8.8)[d]
Ischemic heart disease	150 (19.5)[a]	104 (14.2)	163 (21.4)[b]	14 (4.3)[b]	4 (3.5)[b]
History of transient ischemic attack	116 (15.1)[d]	80 (10.9)	73 (9.6)[a]	37 (11.4)	11 (9.6)
Smoking (> 20 cigarettes/d)	87 (11.3)[a]	86 (11.7)[b]	28 (3.7)[b]	41 (12.7)[b]	18 (6.9)
Chronic obstructive pulmonary disease	74 (9.6)	61 (8.3)	62 (8.1)	20 (6.2)	6 (5.3)
Peripheral vascular disease	100 (13)[d]	57 (7.8)	50 (6.6)	3 (0.9)[d]	4 (3.5)[d]
Heart valve disease	11 (1.4)[b]	21 (2.9)[b]	130 (17)[b]	6 (1.9)[d]	6 (5.3)
Congestive heart failure	43 (5.6)	24 (3.3)[d]	72 (9.4)[b]	8 (2.5)[d]	1 (0.9)[a]
Obesity (body mass index ⩾ 30 kg/m^2)	36 (4.7)	47 (6.4)[b]	17 (2.2)[d]	13 (4)	5 (4.4)
Oral anticoagulants	18 (2.3)[a]	7 (1)[b]	63 (8.3)[b]	2 (0.6)[b]	4 (3.5)
Alcohol abuse (> 80 g/d)	26 (3.4)[a]	21 (2.9)	5 (0.7)[a]	10 (3.1)	4 (3.5)
Chronic liver disease	17 (2.2)	15 (2.1)	15 (2)	10 (3.1)	0
Previous intracerebral hemorrhage	9 (1.2)	9 (1.2)	7 (0.9)	6 (1.9)	1 (0.9)

Data expressed as frequencies and percentages in parentheses. [a]$P < 0.05$; [b]$P < 0.001$; [d]$P < 0.01$.

infarcts, and ischemic heart disease (OR = 1.33), which is an epiphenomenon of clinically significant atherosclerosis and a potential cause of recurrent cerebral ischemia.

In lacunar infarction, the vascular profile includes hypertension (OR = 2.64) and diabetes mellitus (OR = 1.55). Both hypertension and diabetes are the main risk factors, a fact that is consistent with previous histopathological studies and data reported in main clinical series of patients published in the literature[25,81-87]. Obesity is also an independent risk factor associated with lacunar infarcts. The frequency of the different risk factors is different in patients with lacunar infarcts from those in patients with lacunar syndromes not due to lacunar infarction[88,89] (Table 5).

In cardioembolic ischemic stroke, cardiac sources of embolism including atrial fibrillation (OR = 20.01), valve heart disease (OR = 5.60) and ischemic heart disease (OR = 2.09) are the most prevalent heart conditions[89,90].

Table 4 Results of multivariate analysis: cardiovascular risk factors independently associated with the different subtypes of ischemic infarction in 2704 consecutive patients with cerebral infarction collected from the "Sagrat Cor Hospital of Barcelona Stroke Registry"[7]

	Odds ratio (95%CI)
Atherothrombotic infarction	
Peripheral vascular disease	2.28 (1.68-3.08)
Hypertension	1.84 (1.53-2.2)
Diabetes mellitus	1.66 (1.36-2.03)
Previous transient ischemic attack	1.50 (1.16-1.95)
Chronic obstructive pulmonary disease	1.41 (1.04-1.93)
Previous cerebral infarction	1.40 (1.12-1.76)
Ischemic heart disease	1.33 (1.06-1.68)
Atrial fibrillation	0.36 (0.28-0.45)
Heart valve disease	0.23 (0.12-0.43)
Lacunar infarction	
Hypertension	2.64 (2.19-3.20)
Diabetes mellitus	1.55 (1.23-1.90)
Obesity ($\geqslant$ 30 kg/m^2)	1.50 (1.01-2.25)
Oral anticoagulation	0.37 (0.16-0.82)
Heart valve disease	0.22 (0.17-0.28)
Cardioembolic	
Atrial fibrillation	20.01 (15.98-25.05)
Heart valve disease	5.60 (3.60-8.71)
Ischemic heart disease	2.09 (1.57-2.78)
Dyslipidemia	0.69 (0.50-0.94)
Diabetes mellitus	0.68 (0.52-0.89)
Hypertension	0.67 (0.54-0.85)
Previous transient ischemic attack	0.66 (0.46-0.95)
Smoking (> 20 cigarettes/d)	0.54 (0.34-0.88)
Obesity ($\geqslant$ 30 kg/m^2)	0.38 (0.20-0.73)
Undetermined cause	
Hypertension	0.12 (0.09-0.17)
Peripheral vascular disease	0.13 (0.04-0.41)
Atrial fibrillation	0.15 (0.10-0.23)
Diabetes mellitus	0.21 (0.13-0.32)
Ischemic heart disease	0.24 (0.13-0.42)
Heart valve disease	0.34 (0.14-0.80)
Previous cerebral infarction	0.61 (0.40-0.93)
Unusual cause	
Atrial fibrillation	0.15 (0.07-0.32)
Diabetes mellitus	0.17 (0.07-0.38)
Ischemic heart disease	0.21 (0.08-0.58)
Hypertension	0.27 (0.18-0.42)

In patients with cerebral infarctions of undetermined cause (or essential) and in patients with infarctions of unusual cause (haematological disorders, infections, vasculitis and other entities), classical cardiovascular risk factors are less frequent[91,92].

Finally, the role of emerging and less-well documented stroke risk factors as described above is still inconclusive but further characterization in well-designed clinical studies will add knowledge to develop more tailored primary and secondary preventive strategies in stroke.

ACKNOWLEDGMENTS

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance, Nuria Parra, MD and Maria José Sánchez for their assistance in the audio-core.

Table 5 Comparison of cardiovascular risk factors in lacunar infarction and in lacunar syndromes not due to lacunar infarcts[89] *n* (%)

Datos	Lacunar syndromes not due to lacunar infarction	Lacunar infarcts	*P* value
Total patients	146	733	
Male sex	82 (56.2)	423 (57.7)	0.73
Age, yr, mean ± SD	72.9 (12.6)	74.1 (10.2)	0.285
Age $\geqslant$ 85 yr	26 (17.8)	110 (15.0)	0.393
Risk factors			
Hypertension	107 (73.3)	525 (71.6)	0.683
Diabetes mellitus	31 (21.2)	218 (29.7)	0.037
Heart valve disease	10 (6.8)	21 (2.9)	0.017
Ischemic heart disease	23 (15.8)	104 (14.2)	0.623
Atrial fibrillation	44 (30.1)	81 (11.1)	0
Congestive heart failure	4 (2.7)	24 (3.3)	0.737
Previous transient ischemic attack	12 (8.2)	80 (10.9)	0.331
Previous cerebral infarction	16 (11)	117 (16)	0.123
Head traumatism	6 (4.1)	6 (0.8)	0.006
Peripheral vascular disease	17 (11.6)	57 (7.8)	0.124
Obesity (BMI $\geqslant$ 30 kg/m^2)	8 (5.5)	47 (6.4)	0.671
Alcohol abuse (> 80 g/d)	7 (4.8)	21 (2.9)	0.34
Smoking (> 20 cigarettes/d)	19 (13)	86 (11.7)	0.663
Dyslipidemia	29 (19.9)	166 (22.6)	0.46

Data expressed as frequencies and percentages in parentheses.

REFERENCES

1 **Catalan Society of Neurology.** Official Guidelines for diagnosis and treatment. In: Cerebrovascular Diseases. 2nd ed. Barcelona: Societat Catalana de Neurologia, 2011: 159-240
2 **Kalaria RN**. Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. *Stroke* 2012; **43**: 2526-2534 [PMID: 22879100 DOI: 10.1161/STROKEAHA.112.655803]
3 **Allen CL**, Bayraktutan U. Risk factors for ischaemic stroke. *Int J Stroke* 2008; **3**: 105-116 [PMID: 18706004 DOI: 10.1111/j.1747-4949.2008.00187.x]
4 **Marrugat J**, Arboix A, García-Eroles L, Salas T, Vila J, Castell C, Tresserras R, Elosua R. [The estimated incidence and case fatality rate of ischemic and hemorrhagic cerebrovascular disease in 2002 in Catalonia]. *Rev Esp Cardiol* 2007; **60**: 573-580 [PMID: 17580045]
5 **The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee.** Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25**: 457-507 [PMID: 18477843 DOI: 10.1159/000131083]
6 **Goff DC**, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PW. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **63**: 2935-2959 [PMID: 24239921 DOI: 10.1161/01.cir.0000437741.48606.98]
7 **Arboix A**, García-Eroles L, Comes E, Oliveres M, Targa C, Balcells M, Pujadas R, Massons J. Importance of cardiovascular risk profile for in-hospital mortality due to cerebral infarction. *Rev Esp Cardiol* 2008; **61**: 1020-1029 [PMID: 18817678]
8 **Furie KL**, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-

Smoller S, Turan TN, Wentworth D. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011; **42**: 227-276 [PMID: 20966421 DOI: 10.1161/STR.0b013e3181f7d043]

9 **Goldstein LB**, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, Degraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006; **37**: 1583-1633 [PMID: 16675728 DOI: 10.1161/01.STR.0000223048.70103.F1]

10 **Dichgans M.** Genetics of ischaemic stroke. *Lancet Neurol* 2007; **6**: 149-161 [PMID: 17239802 DOI: 10.1016/S1474-4422(07)70028-5]

11 **del Río-Espínola A**, Mendióroz M, Domingues-Montanari S, Pozo-Rosich P, Solé E, Fernández-Morales J, Fernández-Cadenas I, Montaner J. CADASIL management or what to do when there is little one can do. *Expert Rev Neurother* 2009; **9**: 197-210 [PMID: 19210195 DOI: 10.1586/14737175.9.2.197]

12 **Lubitz SA**, Yi BA, Ellinor PT. Genetics of atrial fibrillation. *Heart Fail Clin* 2010; **6**: 239-247 [PMID: 20347792 DOI: 10.1016/j.hfc.2009.12.004]

13 **Andersen KK**, Andersen ZJ, Olsen TS. Age- and gender-specific prevalence of cardiovascular risk factors in 40,102 patients with first-ever ischemic stroke: a Nationwide Danish Study. *Stroke* 2010; **41**: 2768-2774 [PMID: 20966413 DOI: 10.1161/STROKEAHA.110.595785]

14 **Traylor M**, Farrall M, Holliday EG, Sudlow C, Hopewell JC, Cheng YC, Fornage M, Ikram MA, Malik R, Bevan S, Thorsteinsdottir U, Nalls MA, Longstreth W, Wiggins KL, Yadav S, Parati EA, Destefano AL, Worrall BB, Kittner SJ, Khan MS, Reiner AP, Helgadottir A, Achterberg S, Fernandez-Cadenas I, Abboud S, Schmidt R, Walters M, Chen WM, Ringelstein EB, O'Donnell M, Ho WK, Pera J, Lemmens R, Norrving B, Higgins P, Benn M, Sale M, Kuhlenbäumer G, Doney AS, Vicente AM, Delavaran H, Algra A, Davies G, Oliveira SA, Palmer CN, Deary I, Schmidt H, Pandolfo M, Montaner J, Carty C, de Bakker PI, Kostulas K, Ferro JM, van Zuydam NR, Valdimarsson E, Nordestgaard BG, Lindgren A, Thijs V, Slowik A, Saleheen D, Paré G, Berger K, Thorleifsson G, Hofman A, Mosley TH, Mitchell BD, Furie K, Clarke R, Levi C, Seshadri S, Gschwendtner A, Boncoraglio GB, Sharma P, Bis JC, Gretarsdottir S, Psaty BM, Rothwell PM, Rosand J, Meschia JF, Stefansson K, Dichgans M, Markus HS. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. *Lancet Neurol* 2012; **11**: 951-962 [PMID: 23041239 DOI: 10.1016/S1474-4422(12)70234-X]

15 **McGuinness B**, Todd S, Passmore AP, Bullock R. Systematic review: Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *J Neurol Neurosurg Psychiatry* 2008; **79**: 4-5 [PMID: 18079296]

16 **Mancia G**, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, Grassi G, Sega R. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007; **49**: 1265-1270 [PMID: 17452502 DOI: 10.1161/HYPERTENSIONAHA.107.088708]

17 **Mancia G**. Prognostic value of long-term blood pressure variability: the evidence is growing. *Hypertension* 2011; **57**: 141-143 [PMID: 21199992 DOI: 10.1161/HYPERTENSIONAHA.110.165852]

18 **Eguchi K**, Hoshide S, Schwartz JE, Shimada K, Kario K. Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. *Am J Hypertens* 2012; **25**: 962-968 [PMID: 22739805 DOI: 10.1038/ajh.2012.75]

19 **Johansson JK**, Niiranen TJ, Puukka PJ, Jula AM. Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study. *Hypertension* 2012; **59**: 212-218 [PMID: 22215704 DOI: 10.1161/HYPERTENSIONAHA.111.178657]

20 **Shimbo D**, Newman JD, Aragaki AK, LaMonte MJ, Bavry AA, Allison M, Manson JE, Wassertheil-Smoller S. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertension* 2012; **60**: 625-630 [PMID: 22753206 DOI: 10.1161/HYPERTENSIONAHA.112.193094]

21 **Suchy-Dicey AM**, Wallace ER, Mitchell SV, Aguilar M, Gottesman RF, Rice K, Kronmal R, Psaty BM, Longstreth WT. Blood pressure variability and the risk of all-cause mortality, incident myocardial infarction, and incident stroke in the cardiovascular health study. *Am J Hypertens* 2013; **26**: 1210-1217 [PMID: 23744496 DOI: 10.1093/ajh/hpt092]

22 **Kang J**, Ko Y, Park JH, Kim WJ, Jang MS, Yang MH, Lee J, Lee J, Han MK, Gorelick PB, Bae HJ. Effect of blood pressure on 3-month functional outcome in the subacute stage of ischemic stroke. *Neurology* 2012; **79**: 2018-2024 [PMID: 23054228 DOI: 10.1212/WNL.0b013e3182749eb8]

23 **Brickman AM**, Reitz C, Luchsinger JA, Manly JJ, Schupf N, Muraskin J, DeCarli C, Brown TR, Mayeux R. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010; **67**: 564-569 [PMID: 20457955 DOI: 10.1001/archneurol.2010.70]

24 **Pelegrí A,** Arboix A. Blood pressure variability and cerebrovascular disease. *World J Hypertens* 2013; **3**: 27-31 [DOI: 10.5494/wjh.v3.i4.27]

25 **Arboix A**, Martí-Vilalta JL. Lacunar stroke. *Expert Rev Neurother* 2009; **9**: 179-196 [PMID: 19210194 DOI: 10.1586/14737175.9.2.179]

26 **Edwards JD**, Jacova C, Sepehry AA, Pratt B, Benavente OR. A quantitative systematic review of domain-specific cognitive impairment in lacunar stroke. *Neurology* 2013; **80**: 315-322 [PMID: 23319476 DOI: 10.1212/WNL.0b013e31827deb85]

27 **Grau-Olivares M**, Arboix A, Bartrés-Faz D, Junqué C. Neuropsychological abnormalities associated with lacunar infarction. *J Neurol Sci* 2007; **257**: 160-165 [PMID: 17316693]

28 **Duering M**, Righart R, Csanadi E, Jouvent E, Hervé D, Chabriat H, Dichgans M. Incident subcortical infarcts induce focal thinning in connected cortical regions. *Neurology* 2012; **79**: 2025-2028 [PMID: 23054230 DOI: 10.1212/WNL.0b013e3182749f39]

29 **Smith EE**, Arboix A. Focal cortical thinning is caused by remote subcortical infarcts: spooky action at a distance. *Neurology* 2012; **79**: 2016-2017 [PMID: 23054231 DOI: 10.1212/WNL.0b013e3182749f6e]

30 **Arboix A**, Milian M, Oliveres M, García-Eroles L, Massons J. Impact of female gender on prognosis in type 2 diabetic patients with ischemic stroke. *Eur Neurol* 2006; **56**: 6-12 [PMID: 16804310]

31 **Megherbi SE**, Milan C, Minier D, Couvreur G, Osseby GV, Tilling K, Di Carlo A, Inzitari D, Wolfe CD, Moreau T, Giroud M. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke* 2003; **34**: 688-694 [PMID: 12624292 DOI: 10.1161/01.STR.0000057975.15221.40]

32 **Arboix A**, Font A, Garro C, García-Eroles L, Comes E, Massons J. Recurrent lacunar infarction following a previous lacunar stroke: a clinical study of 122 patients. *J Neurol Neurosurg Psychiatry* 2007; **78**: 1392-1394 [PMID: 17615167 DOI: 10.1136/jnnp.2007.119776]

33 **Arboix A**, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010; **6**: 150-161 [PMID: 21804774 DOI: 10.2174/157340310791658730]

34 **Khoo CW**, Lip GY. Clinical outcomes of acute stroke patients with atrial fibrillation. *Expert Rev Cardiovasc Ther* 2009; **7**: 371-374 [PMID: 19379061 DOI: 10.1586/erc.09.11]

35 **Arboix A**, García-Eroles L, Massons JB, Oliveres M, Pujades R, Targa C. Atrial fibrillation and stroke: clinical presentation of

cardioembolic versus atherothrombotic infarction. *Int J Cardiol* 2000; **73**: 33-42 [PMID: 10748308]
36 **Arboix A**, Oliveres M, Massons J, Pujades R, Garcia-Eroles L. Early differentiation of cardioembolic from atherothrombotic cerebral infarction: a multivariate analysis. *Eur J Neurol* 1999; **6**: 677-683 [PMID: 10529755]
37 **Kishore A**, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* 2014; **45**: 520-526 [PMID: 24385275 DOI: 10.1161/STROKEAHA.113.003433]
38 **Arboix A**, García-Eroles L, Massons J, Oliveres M, Targa C. Lacunar infarcts in patients aged 85 years and older. *Acta Neurol Scand* 2000; **101**: 25-29 [PMID: 10660148 DOI: 10.1034/j.1600-0404.2000.00005.x]
39 **Serena J**, Jiménez-Nieto M, Silva Y, Castellanos M. Patent foramen ovale in cerebral infarction. *Curr Cardiol Rev* 2010; **6**: 162-174 [PMID: 21804775 DOI: 10.2174/157340310791658794]
40 **Burns DM**. Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis* 2003; **46**: 11-29 [PMID: 12920698]
41 **Underner M,** Paquereau J, Meurice JC. [Cigarette smoking and sleep disturbance]. *French Rev Mal Respir* 2006; **23** (3 Suppl): 6S67–6S77 [PMID: 16820750]
42 **Lavie L**, Lavie P. Smoking interacts with sleep apnea to increase cardiovascular risk. *Sleep Med* 2008; **9**: 247-253 [PMID: 17513169]
43 **Anstey KJ**, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol* 2007; **166**: 367-378 [PMID: 17573335 DOI: 10.1093/aje/kwm116]
44 **Belvis R,** Martí-Vilalta JL. Factores de riesgo. Prevención. En: Enfermedades vasculares cerebrales. In: Martí-Vilalta JL, editor. Barcelona: Mayo S.A., 2012: 55-73
45 **Hankey GJ**. Potential new risk factors for ischemic stroke: what is their potential? *Stroke* 2006; **37**: 2181-2188 [PMID: 16809576 DOI: 10.1161/01.STR.0000229883.72010.e4]
46 **National Institutes of Health.** Adult Treatment Panel III: Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Bethesda, MD: National Institutes of Health, 2002
47 **Peters R**, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing* 2008; **37**: 505-512 [PMID: 18487267 DOI: 10.1093/ageing/afn095]
48 **Ruitenberg A**, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, Breteler MM. Alcohol consumption and risk of dementia: the Rotterdam Study. *Lancet* 2002; **359**: 281-286 [PMID: 11830193 DOI: 10.1016/S0140-6736(02)07493-7]
49 **Luchsinger JA**, Mayeux R. Adiposity and Alzheimer's disease. *Curr Alzheimer Res* 2007; **4**: 127-134 [PMID: 17430235 DOI: 10.2174/156720507780362100]
50 **Gustafson D.** Adiposity indices and dementia. *Lancet Neurol* 2006; **5**: 713-720 [PIMD: 16857578 DOI: 10.1016/S1474-4422(06)70526-9]
51 **Beydoun MA,** Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev* 2008; **9**: 204-218 [PIMD: 18331422 DOI: 10.1111/j.1467-789X.2008.00473.x]
52 **Arenillas JF,** Moro MA, Dávalos A. The metabolic syndrome and stroke. Potential treatment approaches. *Stroke* 2007; **38**: 2196-2203 [PIMD: 17540972 DOI: 10.1161/STROKEAHA.106.480004]
53 **Segura B**, Jurado MA, Freixenet N, Bargalló N, Junqué C, Arboix A. White matter fractional anisotropy is related to processing speed in metabolic syndrome patients: a case-control study. *BMC Neurol* 2010; **10**: 64 [PMID: 20663196 DOI: 10.1186/1471-2377-10-64]
54 **Arboix A**, Tarruella M, García-Eroles L, Oliveres M, Miquel C, Balcells M, Targa C. Ischemic stroke in patients with intermittent claudication: a clinical study of 142 cases. *Vasc Med* 2004; **9**: 13-17 [PMID: 15230483 DOI: 10.1191/1358863x04vm523oa]
55 **Whisnant JP**. Modeling of risk factors for ischemic stroke. The Willis Lecture. *Stroke* 1997; **28**: 1840-1844 [PMID: 9303034 DOI: 10.1161/01.STR.28.9.1840]
56 **Arboix A**, Massons J, García-Eroles L, Oliveres M, Balcells M, Targa C. Migrainous cerebral infarction in the Sagrat Cor Hospital of Barcelona stroke registry. *Cephalalgia* 2003; **23**: 389-394 [PMID: 12780770 DOI: 10.1046/j.1468-2982.2003.00534.x]
57 **Parra O**, Arboix A, Montserrat JM, Quintó L, Bechich S, García-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J* 2004; **24**: 267-272 [PMID: 15332396 DOI: 10.1183/09031936.04.00061503]
58 **Bonnin-Vilaplana M**, Arboix A, Parra O, García-Eroles L, Montserrat JM, Massons J. Sleep-related breathing disorders in acute lacunar stroke. *J Neurol* 2009; **256**: 2036-2042 [PMID: 19629569 DOI: 10.1007/s00415-009-5236-x]
59 **Somers VK**, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008; **118**: 1080-1111 [PMID: 18725495 DOI: 10.1161/CIRCULATIONAHA.107.189375]
60 **Grau AJ**, Boddy AW, Dukovic DA, Buggle F, Lichy C, Brandt T, Hacke W. Leukocyte count as an independent predictor of recurrent ischemic events. *Stroke* 2004; **35**: 1147-1152 [PMID: 15017013 DOI: 10.1161/01.STR.0000124122.71702.64]
61 **Wright CB**, Lee HS, Paik MC, Stabler SP, Allen RH, Sacco RL. Total homocysteine and cognition in a tri-ethnic cohort: the Northern Manhattan Study. *Neurology* 2004; **63**: 254-260 [PMID: 15277617]
62 **Capmany RP**, Ibañez MO, Pesquer XJ. Complex atheromatosis of the aortic arch in cerebral infarction. *Curr Cardiol Rev* 2010; **6**: 184-193 [PMID: 21804777 DOI: 10.2174/157340310791658712]
63 **Zavala JA**, Amarrenco P, Davis SM, Jones EF, Young D, Macleod MR, Horky LL, Donnan GA. Aortic arch atheroma. *Int J Stroke* 2006; **1**: 74-80 [PMID: 18706048 DOI: 10.1111/j.1747-4949.2006.00026.x]
64 **Di Tullio MR,** Homma S. Atherosclerotic disease of the proximal aorta. In: Mohr JP, Wolf PhA, Grotta JC, Moskowitz MA, Mayberg MR, von Kummer R, editor. Stroke. Pathophysiology, diagnosis and management. 5th ed. Philadelphia PA: Elsevier, 2011: 741-757
65 **Gorelick PB**, Bowler JV. Advances in vascular cognitive impairment. *Stroke* 2010; **41**: e93-e98 [PMID: 20075354 DOI: 10.1161/STROKEAHA.109.569921]
66 **Grau-Olivares M**, Bartrés-Faz D, Arboix A, Soliva JC, Rovira M, Targa C, Junqué C. Mild cognitive impairment after lacunar infarction: voxel-based morphometry and neuropsychological assessment. *Cerebrovasc Dis* 2007; **23**: 353-361 [PMID: 17268166 DOI: 10.1159/000099134]
67 **Arboix A,** Blanco-Rojas L. Cognitive impairment in ischaemic lacunar stroke. *Eur Neurol Rev* 2013; **8**: 144-148
68 **Blanco-Rojas L**, Arboix A, Canovas D, Grau-Olivares M, Oliva Morera JC, Parra O. Cognitive profile in patients with a first-ever lacunar infarct with and without silent lacunes: a comparative study. *BMC Neurol* 2013; **13**: 203 [PMID: 24341857 DOI: 10.1186/1471-2377-13-203]
69 **Jokinen H**, Gouw AA, Madureira S, Ylikoski R, van Straaten EC, van der Flier WM, Barkhof F, Scheltens P, Fazekas F, Schmidt R, Verdelho A, Ferro JM, Pantoni L, Inzitari D, Erkinjuntti T. Incident lacunes influence cognitive decline: the LADIS study. *Neurology* 2011; **76**: 1872-1878 [PMID: 21543730 DOI: 10.1212/WNL.0b013e31821d752f]
70 **Moran C**, Phan TG, Srikanth VK. Cerebral small vessel disease: a review of clinical, radiological, and histopathological phenotypes. *Int J Stroke* 2012; **7**: 36-46 [PMID: 22111922 DOI: 10.1111/j.1747-4949.2011.00725.x]
71 **Wardlaw JM**, Doubal F, Armitage P, Chappell F, Carpenter T, Muñoz Maniega S, Farrall A, Sudlow C, Dennis M, Dhillon B. Lacunar stroke is associated with diffuse blood-brain barrier

dysfunction. *Ann Neurol* 2009; **65**: 194-202 [PMID: 19260033 DOI: 10.1002/ana.21549]
72 **Arboix A**, Massons J, García-Eroles L, Grau-Olivares M, Targa C, Comes E, Oliveres M. [Trends in risk factors, clinical characteristics and prognosis in primary intracerebral haemorrhage (1986-2004)]. *Med Clin* (Barc) 2014; **142**: 1-6 [PMID: 23768852 DOI: 10.1016/j.medcli.2013.03.017]
73 **Arboix A**, Comes E, García-Eroles L, Massons J, Oliveres M, Balcells M, Targa C. Site of bleeding and early outcome in primary intracerebral hemorrhage. *Acta Neurol Scand* 2002; **105**: 282-288 [PMID: 11939940]
74 **Arboix A**, Vall-Llosera A, García-Eroles L, Massons J, Oliveres M, Targa C. Clinical features and functional outcome of intracerebral hemorrhage in patients aged 85 and older. *J Am Geriatr Soc* 2002; **50**: 449-454 [PMID: 11943039 DOI: 10.1046/j.1532-5415.2002.50109.x]
75 **Morgenstern LB**, Hemphill JC, Anderson C, Becker K, Broderick JP, Connolly ES, Greenberg SM, Huang JN, MacDonald RL, Messé SR, Mitchell PH, Selim M, Tamargo RJ. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; **41**: 2108-2129 [PMID: 20651276 DOI: 10.1161/STR.0b013e3181ec611b]
76 **Kase CS**, Kurth T. Prevention of intracerebral hemorrhage recurrence. *Continuum* (Minneap Minn) 2011; **17**: 1304-1317 [PMID: 22810032 DOI: 10.1212/01.CON.0000410037.64971.e3]
77 **Rosenow F**, Hojer C, Meyer-Lohmann C, Hilgers RD, Mühlhofer H, Kleindienst A, Owega A, Köning W, Heiss WD. Spontaneous intracerebral hemorrhage. Prognostic factors in 896 cases. *Acta Neurol Scand* 1997; **96**: 174-182 [PMID: 9300072]
78 **Stein M**, Misselwitz B, Hamann GF, Scharbrodt W, Schummer DI, Oertel MF. Intracerebral hemorrhage in the very old: future demographic trends of an aging population. *Stroke* 2012; **43**: 1126-1128 [PMID: 22282880 DOI: 10.1161/STROKEAHA.111.644716]
79 **Jauch EC**, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 870-947 [PMID: 23370205 DOI: 10.1161/STR.0b013e318284056a]
80 **Arboix A**, Cabeza N, García-Eroles L, Massons J, Oliveres M, Targa C, Balcells M. Relevance of transient ischemic attack to early neurological recovery after nonlacunar ischemic stroke. *Cerebrovasc Dis* 2004; **18**: 304-311 [PMID: 15331877]
81 **Arboix A**, Blanco-Rojas L, Martí-Vilalta JL. Advancements in understanding the mechanisms of symptomatic lacunar ischemic stroke: translation of knowledge to prevention strategies. *Expert Rev Neurother* 2014; **14**: 261-276 [PMID: 24490992 DOI: 10.1586/14737175.2014.884926]
82 **Fisher CM.** Lacunar infarcts. A review. *Cerebrovasc Dis* 1991; **1**: 311-320 [DOI: 10.1159/000108861]
83 **Arboix A**, Padilla I, Massons J, García-Eroles L, Comes E, Targa C. Clinical study of 222 patients with pure motor stroke. *J Neurol Neurosurg Psychiatry* 2001; **71**: 239-242 [PMID: 11459902 DOI: 10.1136/jnnp.71.2.239]
84 **Arboix A**, Martí-Vilalta JL, García JH. Clinical study of 227 patients with lacunar infarcts. *Stroke* 1990; **21**: 842-847 [PMID: 2349585 DOI: 10.1161/01.STR.21.6.842]
85 **Benavente OR**, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012; **367**: 817-825 [PMID: 22931315 DOI: 10.1056/NEJMoa1204133]
86 **Micheli S**, Agnelli G, Palmerini F, Caso V, Venti M, Alberti A, Biagini S, Paciaroni M. Need for extensive diagnostic work-up for patients with lacunar stroke. *J Neurol* 2008; **255**: 637-642 [PMID: 18283395 DOI: 10.1007/s00415-008-0762-5]
87 **Arboix A**, García-Plata C, García-Eroles L, Massons J, Comes E, Oliveres M, Targa C. Clinical study of 99 patients with pure sensory stroke. *J Neurol* 2005; **252**: 156-162 [PMID: 15729520]
88 **Arboix A,** Martí-Vilalta JL. Lacunar syndromes not due to lacunar infarcts. *Cerebrovasc Dis* 1992; **2**: 287-292 [DOI: 10.1159/000109029]
89 **Arboix A**, Massons J, García-Eroles L, Targa C, Comes E, Parra O. Clinical predictors of lacunar syndrome not due to lacunar infarction. *BMC Neurol* 2010; **10**: 31 [PMID: 20482763 DOI: 10.1186/1471-2377-10-31]
90 **Arboix A**, García-Eroles L, Massons J, Oliveres M. Predictive clinical factors of in-hospital mortality in 231 consecutive patients with cardioembolic cerebral infarction. *Cerebrovasc Dis* 1998; **8**: 8-13 [PMID: 9645975]
91 **Arboix A**, Bechich S, Oliveres M, García-Eroles L, Massons J, Targa C. Ischemic stroke of unusual cause: clinical features, etiology and outcome. *Eur J Neurol* 2001; **8**: 133-139 [PMID: 11430270 DOI: 10.1046/j.1468-1331.2001.00180.x]
92 **Arboix A**, Morcillo C, García-Eroles L, Oliveres M, Massons J, Targa C. Different vascular risk factor profiles in ischemic stroke subtypes: a study from the "Sagrat Cor Hospital of Barcelona Stroke Registry". *Acta Neurol Scand* 2000; **102**: 264-270 [PMID: 11071113 DOI: 10.1034/j.1600-0404.2000.102004264.x]

P- Reviewer: Jorge V, Wan YL **S- Editor**: Tian YL **L- Editor**: A
E- Editor: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com