

UPDATE

Non-Coronary Arterial Disease (I)

Atherosclerosis As a Systemic Disease

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Atherosclerosis is a widespread, chronic progressive disease that mainly involves medium-sized arteries. Clinically, it can become apparent as ischemic heart disease, cerebrovascular disease, or peripheral arterial disease. In Spain, atherosclerosis is responsible for 124 000 deaths each year. Despite the trend towards a reduction in the aged-adjusted mortality rate for cardiovascular disease, the public health burden is expected to increase. The risk factors are the same for all affected vascular beds, regardless of location, and can be classified as either causal, conditional or predisposing. The presence of atherosclerosis in a particular vascular bed is frequently associated with disease in other vascular territories. Risk assessment tables, inflammatory markers, imaging, and the ankle-brachial index can help in identifying subclinical atherosclerosis. Given the systemic nature of the disease, treatment with statins, antiplatelet agents and angiotensin-converting enzyme inhibitors have consistently proven beneficial, irrespective of the vascular bed affected.

Key words: Atherosclerosis. Risk factors. Inflammation. Ankle-brachial index.

La aterosclerosis como enfermedad sistémica

La aterosclerosis es una enfermedad crónica, generalizada y progresiva que afecta sobre todo a las arterias de mediano tamaño. Clínicamente se manifiesta como cardiopatía isquémica, enfermedad cerebrovascular o enfermedad arterial periférica (EAP). En nuestro país es la causa de 124.000 muertes anuales. A pesar de la tendencia a la disminución de la tasa ajustada por edad de la mortalidad por las enfermedades cardiovasculares, el impacto sanitario de éstas se espera que aumente. Los factores de riesgo son los mismos para los distintos territorios vasculares y se pueden clasificar como causales, condicionales o predisponentes. La presencia de aterosclerosis en un territorio vascular se asocia con frecuencia con la afectación de otros territorios. Las tablas para la estimación del riesgo, los marcadores de inflamación, las pruebas de imagen y el índice tobillo-brazo pueden ser útiles para detectar la presencia de aterosclerosis subclínica. Dado que es una enfermedad sistémica, el tratamiento con estatinas, antiagregantes plaquetarios o inhibidores de la enzima de conversión de la angiotensina han demostrado consistentemente su beneficio, con independencia del lecho vascular afectado.

Palabras clave: Aterosclerosis. Factores de riesgo. Inflamación. Índice tobillo-brazo.

INTRODUCTION

Arteriosclerosis is a generic term that refers to the thickening and hardening of the arteries, regardless of their size. When it involves large and medium-sized arteries, it is referred to as atherosclerosis. Atherosclerosis is a chronic inflammatory process that affects the arteries of different vascular beds and is characterized by the

thickening of the intimal and medial layers, with loss of elasticity. The basic lesion is the atheromatous plaque, composed mainly of lipids, fibrous tissue and inflammatory cells, which goes through a number of stages of development.¹

Atherosclerosis complications generally results from the fissure, erosion or rupture of the plaque and the formation of a thrombus on its surface, a circumstance that facilitates its growth and the onset of ischemia or necrosis. This event is the cause of some of the clinical manifestations. This explains the use of the term atherothrombotic disease, in the attempt to include both processes in a single entity.

Atherosclerosis is a systemic disease that affects arteries at different sites simultaneously, but with differing degrees of progression. It tends to develop in the arteries that supply blood to the heart (the coronary arteries), to the

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ABBREVIATIONS

ABI: ankle-brachial index
 ACE: angiotensin-converting enzyme
 AMI: acute myocardial infarction
 AS: acute stroke
 CRP: C-reactive protein
 CVD: cardiovascular diseases
 HDL-C: high-density lipoprotein cholesterol
 IHD: ischemic heart disease
 LDL-C: low-density lipoprotein cholesterol
 NCEP: National Cholesterol Education Program
 PAD: peripheral arterial disease
 PAI-1: plasminogen activator inhibitor type 1
 RF: risk factor
 SAP: systolic arterial pressure
 TIA: transient ischemic attack

brain (the carotid, vertebral, and cerebral arteries) and the lower extremities (the iliac and femoral arteries). Thus, the presence of vascular involvement at a given site is associated with a higher risk of its development in other vascular beds.²

The clinical signs depend on the vascular bed affected. In the coronary arteries, it is signaled by the onset of acute coronary syndrome, acute myocardial infarction (AMI) or sudden death. In the brain, it presents clinically as acute stroke (AS) or a transient ischemic attack (TIA), and repeated episodes can result in multi-infarct dementia. In peripheral arteries, the clinical expression is intermittent

claudication or acute lower-limb ischemia. It can present in chronic form, due to arterial stenosis, as in stable angina or intermittent claudication, or acute form, due to the sudden rupture of the plaque and the formation of a thrombus, as occurs in acute coronary syndromes or ischemic stroke.

EPIDEMIOLOGICAL ASPECTS

Cardiovascular diseases (CVD) are the leading cause of death in Spain (Figure 1). In 2000, the last year for which data collected on a nationwide basis are available, CVD were responsible for 124 000 deaths (34.8% of all deaths; 29.4% of those in men and 36.1% of those in women).³ Among the CVD, ischemic heart disease (IHD) was the leading cause of death in men, followed by cerebrovascular disease, while in women, it was the other way around.⁴

With respect to the distribution according to the Spanish autonomous communities, the rate of mortality due to IHD is highest in the Canary Islands and the communities of Valencia, Murcia, and Andalusia, and lowest in the communities of Madrid, Navarre, and Castile and León. It follows a decreasing pattern, which goes from the island territories to the southern region of the peninsula, the Levante region (Alicante, Castellón, Murcia, and Valencia), the central region and the northern region.⁵ These differences in mortality among communities can not be fully explained by variations in the prevalence of the classical risk factors (RF) from one region to another. Thus, other aspects, such as socioeconomic level, dietary factors or physical activity may play an important role.

In comparison with that of other countries, the age-adjusted rate of mortality due to coronary artery disease

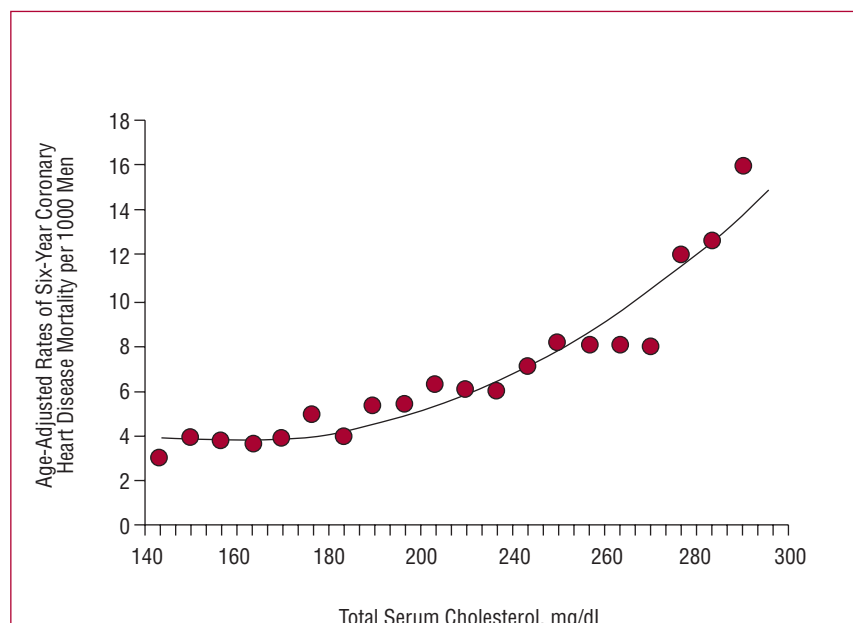


Figure 1. Proportional mortality found for all causes in both sexes (Spain, 2000). Taken from Llacer and Fernández-Cuenca.³

in Spain is similar to that of other Mediterranean countries, and clearly lower than those reported in central and northern Europe. With respect to the rates of mortality due to cerebrovascular disease throughout Europe, Spain shares a medium-to-low position with the rest of the Mediterranean countries.⁶ Since the mid-seventies, there has been a decrease in the age-adjusted mortality due to CVD in this country, mainly because of the lower rate of mortality due to cerebrovascular disease and, to a lesser extent, due to the decrease in mortality associated with IHD.⁷ This downward trend is observed in all the autonomous communities.

However, owing mainly to the aging of the population, the number of deaths due to IHD continues to rise. The rates of CVD-related in-hospital morbidity have not ceased to increase since the nineties, a decade in which this increase was especially accelerated. Thus, the impact of these diseases on public health and on society will continue to intensify over the coming years.⁷

CARDIOVASCULAR RISK FACTORS

These RF are considered to be those habits or biological characteristics that are useful for predicting the probability that an individual develop a CVD. The existence of a RF does not necessarily imply a cause-and-effect relationship with respect to the disease. The knowledge and detection of the RF plays an important role in the assessment of cardiovascular risk, a key element for intervention strategies to address these diseases. The presence of several RF in a given individual heightens the risk considerably. Although all the RF favor the development of atherothrombotic disease in the different vascular beds,

TABLE 1. Classification of the Cardiovascular Risk Factors*

| |
|--|
| Causal risk factors |
| Smoking |
| Hypertension |
| Increased total cholesterol (LDL-C) or low HDL-C |
| Diabetes |
| Advanced age |
| Conditional risk factors |
| Hypertriglyceridemia |
| Small dense LDL particles |
| Elevated serum homocysteine level |
| Elevated serum lipoprotein(a) |
| Prothrombotic factors (fibrinogen, PAI-1) |
| Inflammatory markers (C-reactive protein) |
| Predisposing risk factors |
| Obesity (body mass index >30) |
| Physical inactivity |
| Insulin resistance |
| Abdominal obesity (waist circumference >102 cm in men and >88 cm in women) |
| Family history of premature ischemic heart disease |
| Ethnic characteristics |
| Psychosocial factors |
| Socioeconomic factors |

*HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor type 1.

the predictive power of the RF differs from one territory to another. For example, the cholesterol level has a greater predictive power for the coronary territory, smoking for the peripheral vascular territory and hypertension for the cerebrovascular territory.

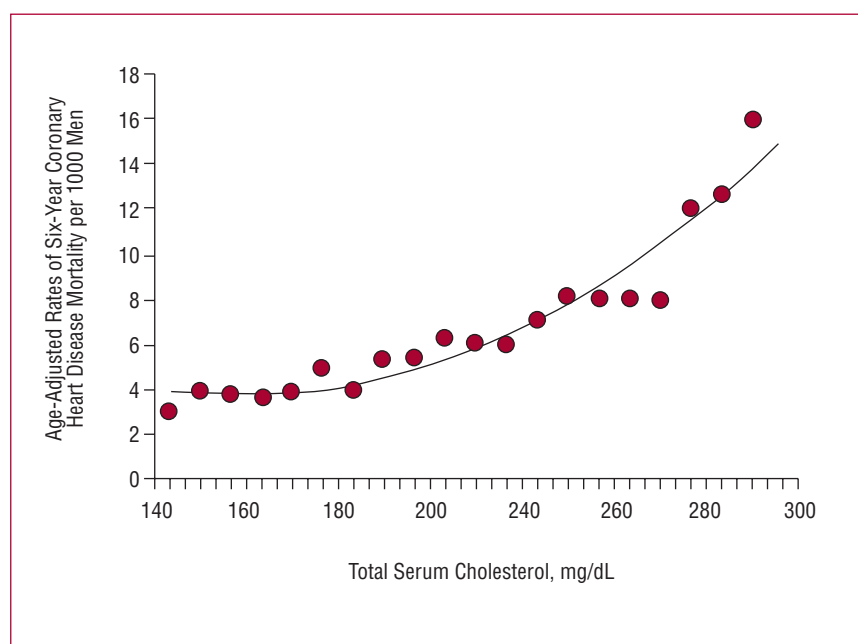


Figure 2. Relationship between total serum cholesterol and six-year mortality due to coronary heart disease in men aged 35 to 57 years (Multiple Risk Factor Intervention Trial [MRFIT] Study). Taken from Stamler et al.⁹

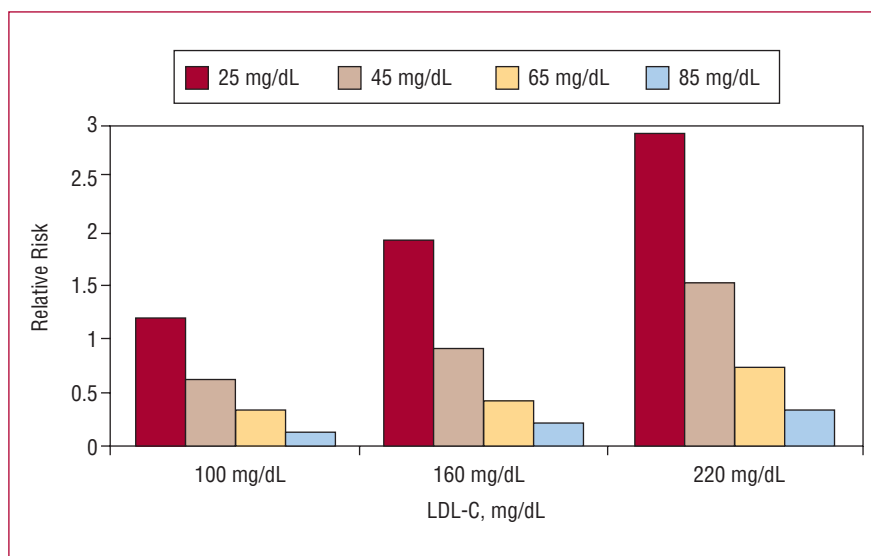


Figure 3. Risk of coronary heart disease for a given concentration of low-density lipoprotein cholesterol (LDL-C) in the presence of different levels of high-density lipoprotein cholesterol (HDL-C) (Framingham study). Taken from Kannel et al.¹⁰

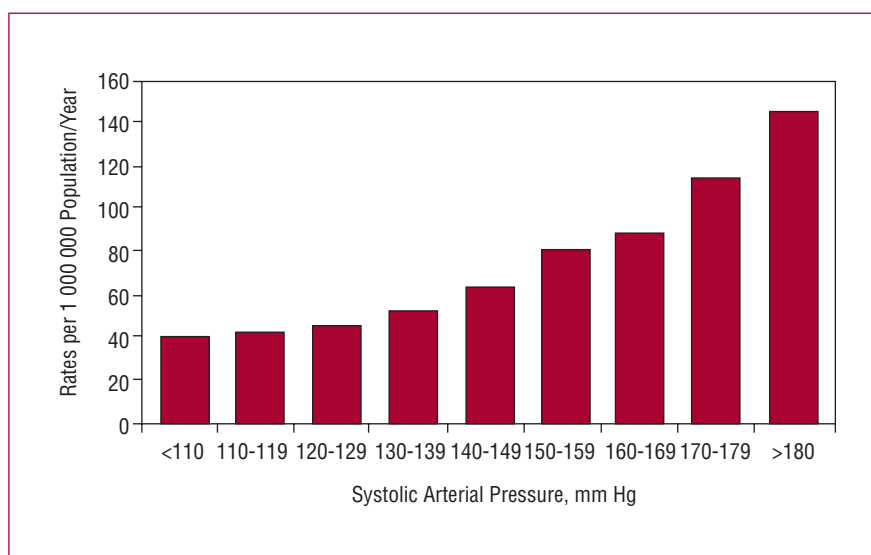


Figure 4. Relationship between systolic arterial pressure and total mortality after 11 years of follow-up (Multiple Risk Factor Intervention Trial [MRFIT] Study). Taken from Stamler et al.¹⁷

The RF can be divided into three groups: causal, conditional or predisposing⁸ (Table 1).

Causal RF are those that promote the development of arteriosclerosis and predispose to coronary artery disease; there is a large body of evidence to support their causal role, although the exact mechanisms have yet to be clearly explained. These RF act independently of one another, and their effects are additive.

Conditional RF are those associated with an increased risk of IHD, but for which a causal relationship has not been documented because their atherogenic potential is lower and/or because their prevalence among the population is not high enough.

Finally, predisposing RF are those that worsen the causal RF. Their association with coronary heart disease is complex since, one way or another, they all contribute to the causal RF. Some of the predisposing factors also

affect the conditional factors by increasing the risk in this way, although they can also act through unidentified causal mechanisms. Here, we comment briefly on the causal RF.

Hypercholesterolemia

The association between serum cholesterol levels and the incidence of IHD has been demonstrated in experimental and epidemiological studies.^{9,10} The relationship between cholesterol and IHD is continuous, gradual and highly intense⁹ (Figure 2). The predictive value of the cholesterol level decreases with age, and actually is low from the sixth decade of life on. The risk attributed to hypercholesterolemia is due to low-density lipoprotein cholesterol (LDL-C). A number of intervention studies have demonstrated that the

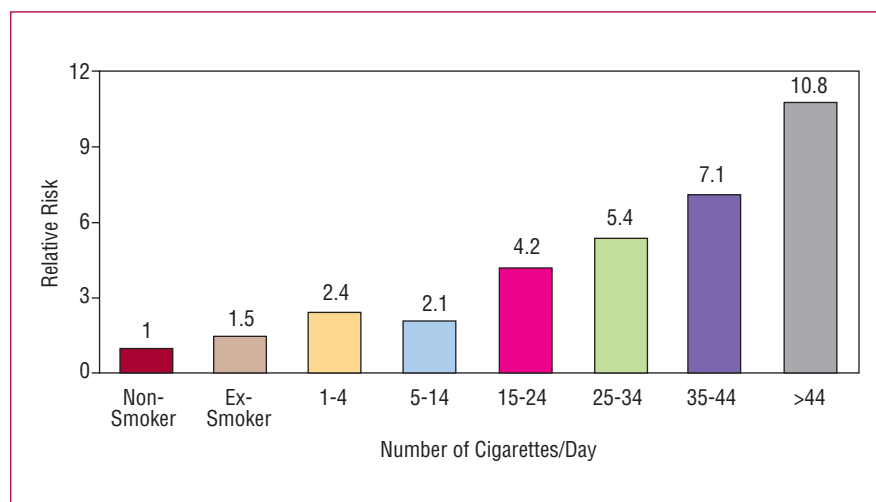


Figure 5. Relative risk of coronary events according to the number of cigarettes consumed. Taken from Willet et al.²²

lowering of LDL-C by means of hypolipidemic agents is accompanied by significant reductions in cardiovascular morbidity and mortality, both in primary and secondary care.¹¹ There is no clear correlation between the concentrations of cholesterol and the incidence of stroke, although treatment with statins reduces the risk of stroke in patients with IHD¹² or with a history of previous stroke.¹³ In all, 46.6% of the Spanish working population has a total cholesterol level over 200 mg/dL.¹⁴

An independent, inverse correlation between high-density lipoprotein cholesterol (HDL-C) and the risk of IHD has been observed in several epidemiological studies¹⁵ (Figure 3). The protection provided by HDL-C is independent of the LDL-C concentration. The National Cholesterol Education Program (NCEP) considers a HDL-C level below 40 mg/dL to be a RF, whereas concentrations over 60 mg/dL are reported to be a negative RF.¹⁶ A decrease in HDL-C of 1% is associated with an increase in the six-year risk of IHD of 3% to 4%. The HDL-C concentration correlates negatively with smoking, body weight and triglyceride concentration, and positively with fat and alcohol intake and physical exercise. Low HDL-C levels are found in 25.6% of the Spanish workforce.¹⁴

Hypertension

Hypertension is one of the major RF, independently of age, sex, or race. Arterial blood pressures, both systolic and diastolic, are correlated with the incidence of coronary heart disease and stroke. As the risk increases continuously within the pressure ranges, the risk in individuals with borderline hypertension is somewhat higher than that of normotensive individuals (Figure 4). Little is known about the role of hypertension in the atherothrombotic process. It has been postulated that the excessively high pressure would damage the endothelium and increase its

permeability. In addition, hypertension could stimulate the proliferation of smooth muscle cells or induce the rupture of the plaque. The presence of a lesion in the target organs (left ventricular hypertrophy and/or microalbuminuria) is accompanied by an increase in cardiovascular risk.

A number of clinical trials have demonstrated that a decrease in arterial blood pressure is associated with significant reductions in the rate of stroke and, to a lesser extent, in that of coronary events, circumstances that produce an overall decrease in cardiovascular mortality.¹⁸ Thus, reductions in diastolic arterial pressure of 5 mm Hg reduce the five-year incidence of stroke by 34%, that of IHD by 19% and that of cardiovascular mortality by 23%.¹⁹

Approximately 45% of the Spanish population has an arterial blood pressure over 140/90 or is being treated with antihypertensive drugs. This percentage increases to almost 70% among individuals over 60 years of age, nearly half of whom receive antihypertensive therapy, although the condition is controlled in only 10% of them.²⁰

Smoking

A number of epidemiological studies have clearly demonstrated that cigarette smoking increases the risk of IHD, stroke, peripheral arterial disease (PAD), and sudden death.²¹ There is a linear relationship between cigarette smoking and the risk of IHD, and the number of cigarettes that can be considered safe has not been defined²² (Figure 5). Low-nicotine cigarettes increase cardiovascular risk to the same extent as the regular type. The cardiovascular risk of pipe and cigar smokers is also increased, although to a somewhat lesser extent than that of cigarette smokers. The risk of coronary heart disease in passive smokers is between 10% and 30% higher.²³ Upon smoking cessation, the risk of coronary heart disease decreases by 50% during the first year and approaches

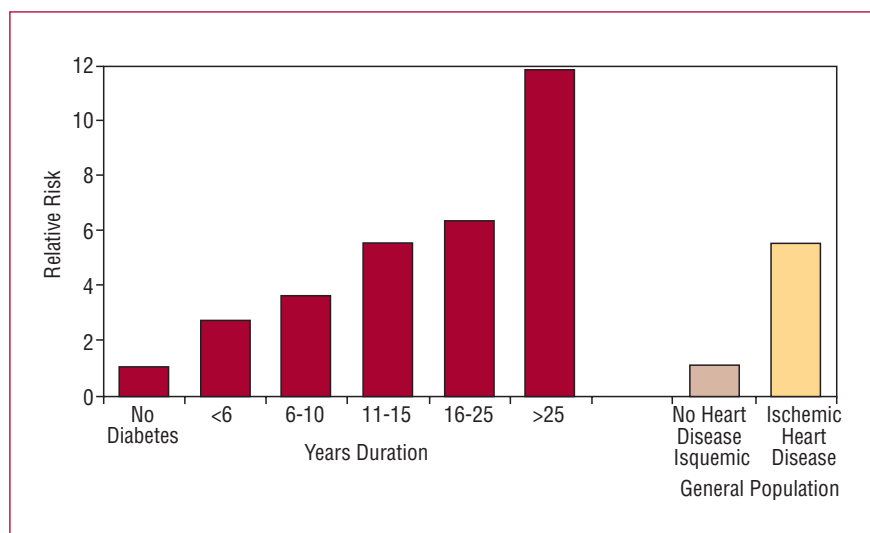


Figure 6. Risk of death due to coronary heart disease according to the duration of diabetes in years, as compared to the general population with and without ischemic heart disease. Taken from Hu et al.²⁵

that of nonsmokers in two years.²⁴ At the present time, approximately 36% of the Spanish population smokes.⁷ According to sexes, nearly half of the men and a fourth of the women are smokers. The considerable increase in the number of young women who smoke is worthy of note.

Smoking favors atherothrombosis through multiple mechanisms, including endothelial damage produced by circulating carbon monoxide, increased fibrinogen and factor VII, increased platelet adhesion and aggregability, increased LDL oxidation, and decreased HDL-C concentration.

Diabetes mellitus

Diabetes mellitus is associated with an elevated risk for IHD and PAD, regardless of whether or not the individual is insulin-dependent; this association is closer in women. Cardiovascular disease is the leading cause of death among diabetics. There is a direct relationship between the duration of diabetes in years and risk of IHD₂₅ (Figure 6). Type 2 diabetics present elevated cardiovascular risk which, on occasion, is similar to that of nondiabetic subjects who have experienced a coronary event.²⁶ For this reason, the major guidelines consider diabetics to be subjects at high cardiovascular risk who should receive the same treatment as patients who have a history of a previous cardiovascular event.¹⁶ Diabetes mellitus favors atherothrombosis through a number of mechanisms: an unfavorable lipid profile (high triglyceride levels, low HDL-C levels, small dense LDL particles), presence of modified LDL, hyperinsulinism, hypercoagulability and increased inflammatory markers. The overall prevalence of diabetes among the general population in Spain is approximately 6%, although it is as high as 17% among individuals over 60 years of age.⁷

Age

Age is the RF with the highest predictive value. The incidence of CVD increases with age, independently of sex and race. The development of CVD in individuals under 40 years of age is unusual. According to the recommendations of the NCEP, age over 45 years and over 55 years is considered to be a RF in men and women, respectively.¹⁶ The risk of IHD is approximately four-fold higher in men than in women with the same serum cholesterol concentration. The onset of IHD occurs between 10 and 15 years later in women as compared to men. Menopause considerably increases the incidence of IHD in women, but at no time does it reach the incidence in men.

ATHEROSCLEROSIS AS A SYSTEMIC DISEASE: FREQUENCY OF SIMULTANEOUS INVOLVEMENT OF DIFFERENT VASCULAR TERRITORIES

Atherosclerosis is a systemic disease that is not limited to a single arterial territory, since it is distributed throughout the whole organism. The presence of clinical signs in a given territory predisposes the individual to an increased risk of ischemic events in another territory. On the basis of the data obtained in the Framingham study, the life expectancy after acute myocardial infarction (AMI), AS or a diagnosis of PAD can be estimated to be 14, 9, and 16 years, respectively. In subjects with a history of previous AS who have a second AS or an AMI, the life expectancy is reduced to four years. When a patient diagnosed as having PAD has an AMI or AS, his or her life expectancy is reduced to 1.5 years. Finally, when patients who have had an AMI have a second AMI or an AS, their life expectancy is less than 5 months²⁷ (Figure 7). The incidence of multivessel involvement has been studied

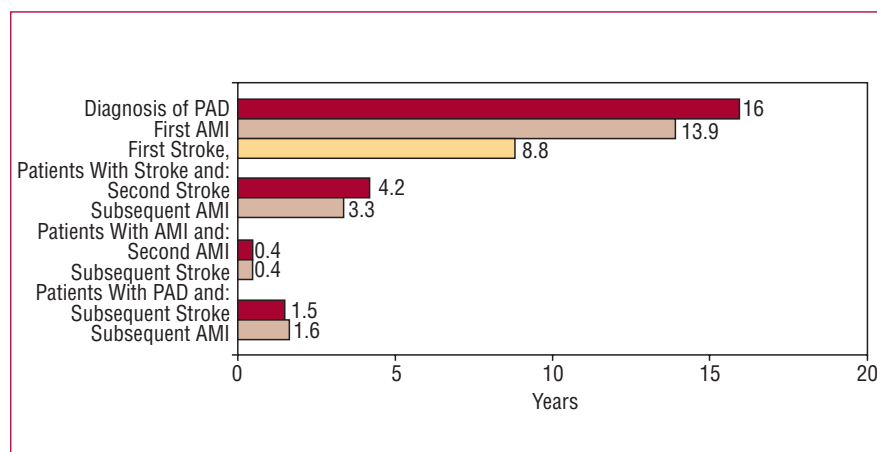


Figure 7. Life expectancy of patients with vascular disease according to the number of vascular territories involved and their location. AMI indicates acute myocardial infarction; PAD, peripheral arterial disease. Taken from Cupples et al.²⁷

according to the vascular territory that motivated the request for medical attention in both cross-sectional and prospective studies.

Patients With Acute Myocardial Infarction

Among patients who are admitted to the hospital with a diagnosis of AMI, there is a high prevalence of atherosclerotic involvement in other regions. Approximately 10% of these subjects report a previous history of intermittent claudication, and between 5% and 8% have had a stroke. These results vary according to age. In a study carried out in patients admitted to a coronary care unit with a diagnosis of AMI, 20.8% of the patients over 75 years of age had had a previous AMI versus only 10% of those under the age of 65.²⁸ In these two groups, 15.8% and 8.3%, respectively, reported a history of PAD and 6.9% and 1.7% had had an AS.²⁸

The relationship between coronary arteriosclerosis diagnosed by coronary angiography and the presence of atherosclerotic lesions in other vascular beds examined by means of ultrasound was also studied. The percentage of subjects with extracoronary atherosclerosis, according to whether or not they had had a positive coronary angiogram, was 81% versus 18% in aortic arch, 91% versus 32% in descending aorta, 72% versus 47% in femoral artery and 77% versus 42% in carotid artery, respectively.²⁹

Different prospective studies have evaluated the risk of developing clinical signs in another vascular territory according to the presence of previous evidence of coronary disease. After 24 years of follow-up, the Framingham study demonstrated that the risk of having an AS was three-fold higher in subjects who had been diagnosed as having coronary heart disease.³⁰ This risk remained two-fold higher after correcting for the classical RF. The risk of ischemic stroke was also higher, a fact that indicates that the relationship between coronary artery involvement and AS was not mediated only by the higher risk of embolism.

Patients With Acute Stroke

The prevalence of extracerebral vascular involvement in cases of cerebral infarction has been evaluated in a number of studies. In the Oxfordshire Community Stroke Project, 38% of the subjects who were admitted to the hospital with an AS had a previous history of IHD and 25% had PAD.³¹ In a study involving patients in Rochester, Minnesota, 21% of those with AS had been diagnosed in the past with angina and 15% had had an AMI.³² Cardiac involvement is more common in cases of acute embolic stroke (51% of the patients), less common in acute thrombotic stroke (22%) and is even rarer in cases of acute hemorrhagic stroke (9%).³³ In a study involving sex- and age-matched patients and controls carried out in Spain, the prevalence of IHD was 14.5% among patient versus 7.1% among controls, and that of symptomatic PAD was 7.9% versus 2.7%, respectively. These incidences rose to 14.2% and 6%, respectively, when the diagnosis was established by means of lower-extremity Doppler ultrasound.³⁴

Patients With Peripheral Arterial Disease

In the San Diego Artery Study, 29% of the men and 21.2% of the women with PAD also presented cardiovascular or cerebrovascular involvement, and this involvement was three times more frequent than that observed in the absence of PAD.³⁵ Individuals with PAD have a four-fold higher risk of coronary events and two to three-fold higher risk of stroke than those without PAD.³⁶ In the AIRVAG study, 21% of the subjects with PAD had asymptomatic involvement of some other vascular territory, diagnosed by carotid, cardiac or abdominal aortic ultrasound.³⁷ In prospective studies, the presence of PAD has an impact on the prognosis. Thus, the relative risk of mortality 10 years after the diagnosis of PAD was 3.1, 5.9 and 6.6 for total, cerebrovascular and cardiovascular mortality, respectively, in comparison with that of subjects in whom PAD was not present at the initiation of follow-up.³⁵

TABLE 2. Biomarkers of Atherothrombotic Disease*

| Inflammation | Thrombosis |
|--------------------|--|
| C-reactive protein | Fibrinogen |
| Interleukins | von Willebrand factor |
| CD40 ligand | Plasminogen activator inhibitor type 1 |
| Amyloid A protein | Fibrinopeptide A |
| Adhesión molecules | Prothrombin fragmento 1+2 |

*Taken from Viles-González et al.²

DIAGNOSTIC APPROACH TO ATHEROSCLEROTIC DISEASE

The diagnosis of atherosclerotic disease is relatively simple when clinical signs are present, but is much more problematical when the disease is in a subclinical phase. In these patients, early diagnosis is of great interest because the first acute episode is often fatal or leaves important sequelae. Thus, intensive intervention in subjects with advanced atherosclerotic disease, even when asymptomatic, could be especially effective. The tools available for the diagnosis of subclinical atherosclerosis are described here.

Risk Tables

Cardiovascular risk assessment is an indirect approximation to the determination of the atherosclerotic load. To calculate this risk, a number of tables and equations have been developed, based on cohort studies, in which the introduction of different parameters (age, sex, presence of RF) provides an estimation of the risk for the onset of a cardiovascular event in coming the years.

The tables most widely utilized for our patient population are those of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III),¹⁶ based on the Framingham equation as modified by Wilson, and the European tables designed for the Systematic COronary Risk Evaluation (SCORE) project.³⁸ The former estimates the 10-year risk of fatal infarction and considers a risk of more than 20% to be high. On the other hand, the European tables estimate the 10-year risk of vascular mortality and establish high risk at 5% or over. In general, the agreement between the two is limited and the percentage of subjects classified as high-risk is greater with the NCEP-ATP III guidelines, although with aging, especially from the age of 60 years on, many more individuals are included in the high-risk population and, thus, would be candidates for intensive therapy, when the SCORE project tables are employed.³⁹

While the tables have been an important advance for the calculation of cardiovascular risk and a great aid in the effective treatment of patients, they have certain

limitations. These include their low sensitivity, the failure to include some RF that could increase their predictive value (family history of early IHD, triglyceride levels, C-reactive protein [CRP], etc), the failure to take into account the possible intersubject variability of some RF over time, and the estimation of the short-term absolute risk, minimizing the risk in young people and magnifying the risk in older individuals.⁴⁰

Imaging Studies

Ultrasound, endothelial function tests, computed tomography, magnetic resonance, nuclear medicine studies, and electron beam computed tomography are tests that can provide valuable information on the atherosclerotic load of a patient. They will all be discussed in greater depth in another chapter of this series.

Serum Biomarkers of Atherosclerosis

In recent years, a number of serum markers have been proposed as predictors of atherosclerosis and its thrombotic complications² (Table 2). They include inflammatory markers, such as CRP and the interleukins, and thrombotic markers like fibrinogen and plasminogen activator inhibitor type 1 (PAI-1). Of these markers, that most widely studied is CRP.

C-reactive protein is an acute phase reactant that serves as an inflammatory marker. It is mainly produced in the liver in response to interleukin 6. Some authors have described several mechanisms (LDL oxidation, decreased nitric oxide production, tissue factor production, PAI-1 production, complement activation, etc) by which CRP could have a direct influence on vascular vulnerability. Should this be the case, CRP would not merely be a passive marker of the inflammatory process,⁴¹ although this issue is still a matter of debate.⁴²

The literature describes more than a dozen prospective studies, involving subjects in primary prevention programs, in which the CRP concentration is a robust predictor of future coronary events, stroke, PAD, congestive heart failure and cardiovascular mortality.⁴³ This relationship is independent of the traditional RF, although it loses power after adjustment for these factors. When high-sensitivity CRP is determined, values of less than 1 mg/L, from 1 to 3 mg/L and over 3 mg/L are considered to indicate low, medium and high cardiovascular risk, respectively,⁴⁴ although the cardiovascular risk gradient is continuous over the entire range of measurable values. The level of CRP may be a marker of subclinical atherosclerosis since its concentration correlates with the intima-media thickness⁴⁵ and with the degree of coronary artery calcification.⁴⁶ In patients in secondary prevention programs, CRP predicts the risk of a new event both in subjects with stable coronary artery disease and in those with acute coronary syndrome.⁴³ Moreover, treatment with statins reduces CRP, independently of the decrease

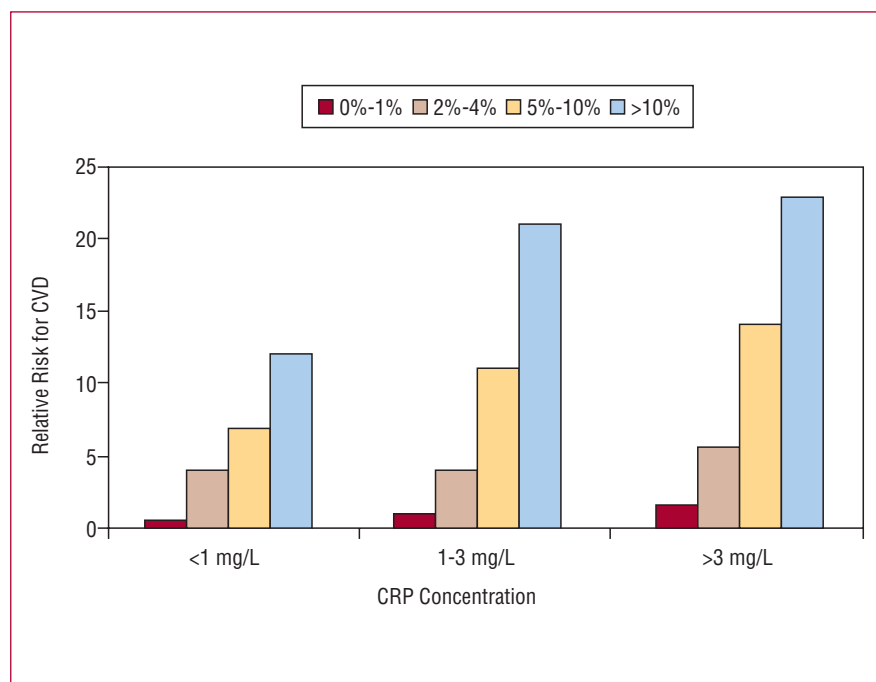


Figure 8. Adjusted relative risk of developing cardiovascular disease (CVD) according to the C-reactive protein (CRP) concentration, and the 10-year absolute risk of developing coronary heart disease, according to the Framingham algorithm applied to the Women's Health Study population. Taken from Lloyd-Jones et al.⁴⁸

in LDL-C, and the lower the CRP concentration achieved, the better the clinical outcome.⁴⁷ However, whether or not there is a correlation between the decrease in CRP and the clinical improvement, and whether this improvement is independent of the decrease in LDL-C, has yet to be determined.⁴⁸

Some authors consider that the CRP concentration could add information to coronary risk estimation when calculated using the Framingham algorithm, especially in individuals at intermediate risk⁴⁹ (Figure 8). However, in a recent critical review of this subject, given the slight improvement in risk discrimination that CRP contributes to the Framingham equation, its systematic utilization was not considered to be recommendable.⁴⁸

Ankle-Brachial Index

The ankle-brachial index (ABI) is a simple and highly reproducible test that is useful in the detection of PAD. It is the result of dividing the systolic arterial pressure (SAP) of each ankle (taking the highest value between the dorsal pedal and posterior tibial arteries) by the highest SAP value in either of the brachial arteries. This provides two ABI values, one for each lower limb, the lower of which is selected as definitive. An ABI of less than 0.9 presents a sensitivity of 95% and a specificity of 99% for the identification of obstruction of more than 50% in the vascular territory of the lower limbs, with respect to arteriography. Moreover, given that arteriosclerosis is a systemic disease that affects different vascular territories simultaneously, among subjects with a low ABI there is a high prevalence of coronary artery and cardiovascular disease, both symptomatic and asymptomatic.⁵⁰ The

prevalence of low ABI increases in relation to cardiovascular risk⁵¹ and the presence of diabetes⁵² or metabolic syndrome.⁵³

A low ABI is associated with a greater risk of total mortality,⁵⁴ with a higher incidence of cardiovascular mortality,⁵⁵ coronary complications⁵⁴⁻⁵⁶ and stroke.^{55,56} The predictive value of the ABI is observed in patients in both primary and secondary prevention programs, as well as in diabetics,⁵⁷ even after adjusting for RF.⁵⁶ Moreover, the presence of a low ABI significantly improves risk prediction based on classical RF.⁵⁵

It has recently been reported that subjects with an ABI over 1.4 or having incompressible arteries, who are usually excluded from the studies of this measurement, exhibit a risk of cardiovascular mortality similar to that of individuals with a low ABI^{58,59} (Figure 9). Thus, a low ABI, an ABI over 1.4 and incompressible arteries are associated high cardiovascular risk and are considered to be indicative of disease.

The determination of the ABI is a highly useful tool for cardiovascular risk stratification since it identifies individuals with subclinical arteriosclerosis and high cardiovascular risk. The determination of the ABI would be especially recommendable in subjects over 60 years of age with intermediate cardiovascular risk (between 10% and 20% according to the Framingham study or between 3% and 4% according to the SCORE project), given that results indicative of disease would change their risk classification and make it necessary to intensify the treatment of the RF.⁶⁰ It would also be advisable in diabetics over the age of 50 years, given the high cardiovascular risk and the high prevalence of PAD in this patient population.⁶¹

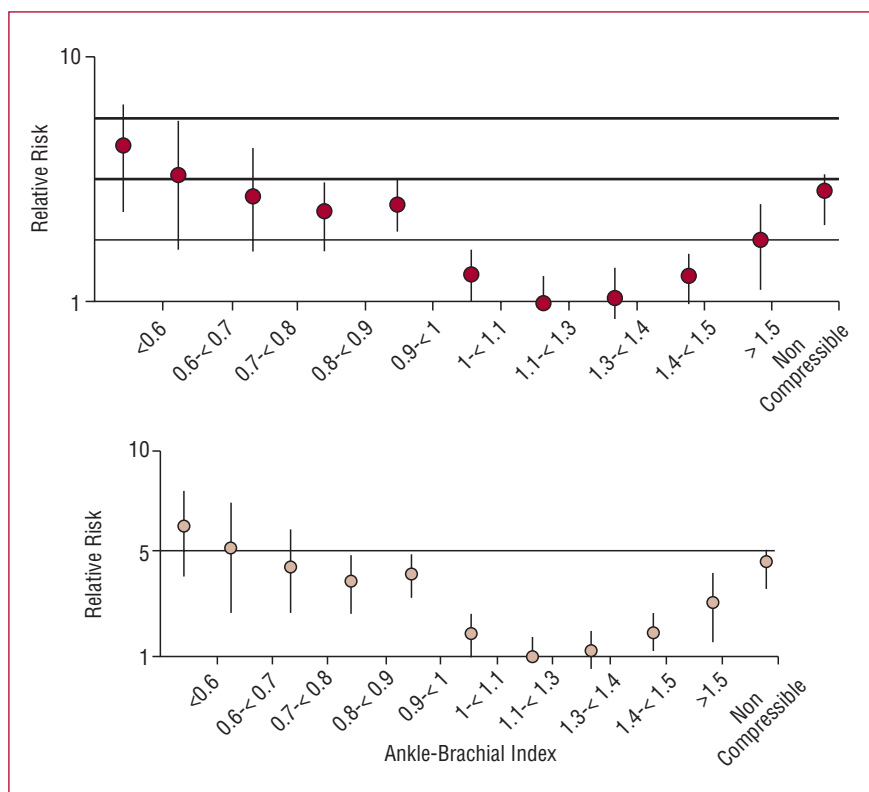


Figure 9. Adjusted relative risk of death according to the ankle-brachial index in the cohort of the Strong Heart Study after 8.3 years of follow-up. Taken from Resnick et al.⁵⁹

THE SAME DISEASE, THE SAME TREATMENT

As we mentioned above, atherosclerosis is a single disease located at different sites and with differing presentations. Thus, it is logical to think that the treatments that prove to be useful in atherothrombotic disease would be effective regardless of the vascular bed involved.

In the Heart Protection Study, more than 20 000 patients with cardiovascular disease, diabetes or hypertension were randomized to receive simvastatin (40 mg/day) or placebo over a five-year period. Treatment with simvastatin significantly reduced the risk of coronary heart disease, stroke and PAD by about 20%, regardless of the baseline LDL-C concentrations.¹²

With respect to antiplatelet therapy, in the Antithrombotic Trialists' Collaboration, a metaanalysis involving more than 135 000 patients receiving antiplatelet therapy and 75 000 controls, the reduction of the risk of new vascular events was similar in subjects with coronary heart disease, stroke or PAD. The relative risk was reduced by approximately 20% in every case.⁶²

Finally, with respect to angiotensin-converting enzyme (ACE) inhibitors, in the Heart Outcomes Prevention Evaluation (HOPE) study, with the participation of 10 000 patients with vascular disease or diabetics with at least one RF, treatment with ramipril (10 mg/day) for five years reduced the relative risk of a new vascular event by 20.9% in patients with previous AMI, by 25.9% in those who had had a stroke and by 22% in patients with PAD.⁶³

Thus, a number of drugs (statins, antiplatelet agents, ACE inhibitors) that act against atherothrombotic disease at different sites are equally effective, regardless of the vascular territory involved.

In conclusion, atherosclerosis is a slowly progressive systemic disease that, despite the involvement of different territories and the differing presentations, has the same pathogenesis, RF, diagnostic approach and treatment.

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