

Dyslipidemia and Cardiovascular Risk: Lipid Ratios as Risk Factors for Cardiovascular Disease

Telmo Pereira

*College of Health Technologies, Polytechnic Institute of Coimbra
Portugal*

1. Introduction

There are extensive epidemiological data demonstrating that high blood cholesterol levels increase cardiovascular risk, and that this risk is dependent on the levels of the different blood cholesterol fractions. Moreover, the reduction of total blood cholesterol has been clearly related to a reduction in the risk of stroke, coronary disease and overall cardiovascular death. However, the traditional cholesterol measurements tend to be most accurate at predicting risk for those at the lower and higher ends of the risk spectrum. Recent data has shown LDL-Cholesterol/HDL-Cholesterol ratio and even Total-Cholesterol/HDL-Cholesterol ratio, to be accurate predictors of cardiovascular risk. In fact, changes in ratios have been shown to be better indicators of successful CHD risk reduction than changes in absolute levels of lipids or lipoproteins. In the Helsinki Study, the LDL-C/HDL-C ratio had more prognostic value than LDL-C or HDL-C alone (Manninen, Tenkanen, Koskinen *et al*, 1992). The ratio was especially accurate at predicting risk among those who also had elevated triglyceride levels. The PROSPER trial, a retrospective analysis of 6,000 patients, found that the ratio of LDL-C/HDL-C was the most powerful measure of cardiovascular disease risk in elderly people (Packard, Ford, Robertson *et al*, 2005). The PROCAM Study, which included almost 11,000 men aged 36 to 65 who were studied for 4 to 14 years, found a continuous and graded relationship between the LDL-C/HDL-C ratio and CVD mortality (Cullen, Schulte, Assmann *et al*, 1997). In addition, comparison of individual LDL-C/HDL-C ratios from subjects in the Framingham Study clearly indicates that these ratios are significantly more robust predictors of CVD than the individual levels of LDL-C or HDL-C (Kannel, 2005).

2. Theoretical framework

2.1 Cardiovascular risk – Generalities

Cardiovascular diseases are an unavoidable topic when discussing health related issues, particularly in developed societies. Cardiovascular disease is the leading cause of mortality in these countries (World Health Organization, 2002), assuming a progressively more important role in developing countries and even in less developed countries. In the latter, we may consider the presence of a *double-frontier* of health risk. These countries show

coexistence of important mortality indexes related to diseases whose prevalence is a demonstration to their stage of development (perinatal, nutritional and infectious health problems), with a more consistent presence of coronary disease, with increased percentage reaching 137% for males and 120% for females by the year 2010 (Yusuf, Reddy, Ounpuu *et al*, 2001).

In epidemiological terms, coronary heart disease and cerebrovascular disease represent the most significant expressions of cardiovascular disease, and were the main causes of mortality and morbidity worldwide, accounting for one third of total mortality in the year 2001 (American Heart Association, 2003). According to the World Health Organization, every year 16 million deaths occur from cardiovascular disease, and this number is expected to rise to 20 million in the first decade of the XXI century (World Health Organization, 2002). The singular importance of coronary heart disease is extraordinarily important and it is estimated that mortality by this disease had risen to 7.2 million individuals by the year 2001 (World Health Organization, 2002). However, in recent years, there has been a trend towards a decline in this disease in Western countries, with a concomitant increase in other lands, notably in Russia and Eastern European countries. In fact, in Western countries, the number of deaths from coronary per 100,000 inhabitants was 151 in 1972, dropping to 44 in 2004, in men aged 64 or less. Similar reductions were also observed in females (36 to 11 women per 100,000). Paradoxically, in Russia, there was a marked increase of this rate, from 169/100.000, in the year 1980, to 242/100.000 deaths, in the year 2005 (Allender, Scarborough, Black *et al*, 2008).

The onset of cardiovascular disease is consistently related to the presence of a group of cardiovascular risk factors, whose manipulation can be crucial to its prevention (see Table 1).

Reversible
Smoking
Arterial hypertension
Hyperlipidemia
Obesity
Sedentarism
Alcohol
Stress
Irreversible
Family history
Male gender
Age
Partially Reversible
Diabetes
Menopause

Table 1. Conventional cardiovascular risk factors.

Concerning reversible risk factors in which intervention could be decisive, we should highlight the relative importance of smoking, arterial hypertension and hypercholesterolaemia. Although the global fight against all reversible risk factors constitute a therapeutic imperative, the elimination of hypercholesterolemia would result in the single most important benefit against the incidence of coronary heart disease as well as other atherosclerotic vascular problems (Wilson, D'Augustine, Levy *et al*, 1998).

Regarding arterial hypertension, it always presents itself as a major risk factor, given its very high incidence and prevalence. Despite all the research carried out and considering all the remarkable therapeutic advances, the control of blood pressure levels only provides a reduction of about 40% in mortality from cerebrovascular disease and a more modest 20% reduction in mortality from coronary heart disease (Kaplan, 2002).

Diabetes is another important risk factor, with the particularity of becoming the major epidemic of this century given its substantial and consistent epidemiological growth. The high cardiovascular risk that diabetes provides is well illustrated by the prognostic similarity between a diabetic patient without clinical manifestations of coronary heart disease and a patient with a history of acute coronary events (Hafnner, Lethe, Ronnema *et al*, 1988).

Obesity is undoubtedly a major risk factor for cardiovascular disease (Higgins, Kannel, Garrison *et al*, 1988), now becoming a public health problem, given the alarming increase of its prevalence in industrialized countries. The pathogenic mechanisms involved in this situation are complex and not just related to the metabolic overload involved, but also determined by its close associations with arterial hypertension, type 2 diabetes, dyslipidemia, and inflammation (Higgins, Kannel, Garrison *et al*, 1988).

Smoking is consensually assumed as a relevant contributor to cardiovascular disease, both in the active as well as the passive form. Some studies indicate that smokers have a reduced life expectancy of about ten years (although this number is dose-dependent) and that this habit cancels the natural cardioprotection in women (Silva, 2000). In fact, the differences in cardiovascular risk amongst men and women are well known, largely documented by the classic time lag between genders, with a higher risk in males until the fifth decade of life, with a progressive increase in women of cardiovascular risk until the eighth decade of life, when the risk is similar in men and women. The explanation for this is closely linked to the production and subsequent estrogen deficiency (as a consequence of menopause) seen in different phases of a woman's life. But other factors must not be overlooked. For instance, if we consider only the lipid profile changes induced by menopause, on average a 10% increase in LDL-cholesterol, an 8% reduction in HDL-cholesterol and an elevation in triglycerides are expected. Nonetheless, these changes can be normalized by hormonal replacement therapy (Stampfer, Colditz, Willet *et al*, 1991). Oral contraception, by contrast, tends to cause an adverse impact on lipid profile. At present, the worrying rate of young women with acute coronary events, a situation rarely seen before, has directed special attention to factors that could be blamed for this surprising finding. The association of hormonal contraception with smoking has emerged as very common in this population, likely to concur not only for atherogenic metabolic features but also for potentially thrombotic coagulation disorders (Mosca, Grundy, Judelson *et al*, 1999).

The cardiovascular impact of alcoholic intake must also be considered. The cardiovascular impact of this behaviour is closely related to the amount of alcohol consumed. A moderate intake may confer some cardiovascular protection, particularly by raising HDL-cholesterol and reducing platelet aggregation, yet it may lead to a higher incidence of arterial hypertension and cerebrovascular disease. Patterns of high alcoholic consumption are an unusually hazardous behaviour, particularly for the heart, greatly increasing the risk of sudden death (Silva, 2000).

2.2 Cardiovascular risk – Dislipidemia

Lipids are a very heterogeneous group of compounds, and their influence on metabolism goes far beyond the misdeeds attributed to him. Lipids constitute an important source of energy storage, represented by triglycerides, and assume a great importance in the constitution of the brain (17% of its dry weight), the formation of hormones, lipoproteins, bile acids, vitamins, and in the structure of cell membranes. Cholesterol and Triglycerides are transported between various components of the organism by specific proteins called apoproteins. These constitute the protein fraction of lipoproteins whose lipid component includes phospholipids, cholesterol and Triglycerides. Lipoproteins are usually divided into six classes according to their composition, size, density and function: Quilomicra, VLDL (very low density lipoproteins), IDL (intermediate density lipoprotein), LDL (low density lipoprotein), HDL (high density lipoprotein) and Lipoprotein (a). The interaction of lipoproteins with a high number of enzymes, transport proteins and receptors, constitutes a complex metabolism where equilibrium is determined by intrinsic and extrinsic factors, and its unbalance leads to the pathophysiological cascade of atherosclerosis, with its well known clinical consequences (Silva, 2000). In very one-dimensional terms, fat from the diet is transported to the intestinal wall and integrated into large lipoprotein particles rich in triglycerides - the Quilomicra - which, when secreted by the lymphatic system eventually reach the bloodstream. The liver, in its turn, synthesizes other lipoproteins with high content of triglycerides, the VLDL. The extracellular lipoprotein-lipase degrades triglycerides of Quilomicra and VLDL into free fatty acids, which are deposited in tissues. Lipoproteins, by reducing their concentration in triglycerides, are converted into IDL, which are usually hydrolyzed by the hepatic lipase, and are then converted into LDL, which bind to specific liver or peripheral receptors. Meanwhile, in another cycle - the reverse transport of cholesterol - HDL particles pick up cholesterol deposited in the arterial wall and provide transportation to the liver, where it is subsequently excreted in the bile (Eckardstein, Hersberger & Roher, 2005).

The disorder of lipid metabolism is a key player for the occurrence of cardiovascular disease and particularly heart disease. For many years, cholesterol has been directly related to cardiovascular prognosis. This relationship is very consistent, as an increase of 2 to 3% in the incidence of coronary heart disease is expected for every 1% increase in total cholesterol (Carlson, Bottiger & Ahfeldt, 1979). A review of internationally published studies showed, however, that this association may be even stronger. Thus, a 10% increase in total cholesterol relates to a 38% increase in the risk of coronary-related mortality (Law, Wald & Thompson, 1994). More recently, several clinical studies on the primary and secondary prevention of coronary heart disease emphasized the importance of the LDL fraction (ILIB International Lipid Information Bureau, 2003) allowing the potential for the discrimination of cardiovascular risk. In fact, the risk of each patient may best be defined by the magnitude of the LDL-cholesterol rather than its total cholesterol, which is why international standards for the treatment of dyslipidemia have been oriented to listing the risk thresholds and treatment goals depending on the plasma levels of this lipoprotein. In practical terms, the determination of LDL-cholesterol may be derived by the Friedewald formula, where $LDL\ Cholesterol = Total\ Cholesterol - HDL\ Cholesterol - VLDL\ cholesterol$, VLDL cholesterol are derived from triglycerides/5.

For many years it was difficult to classify unequivocally Triglycerides as an independent risk factor for the occurrence of coronary heart disease, a situation presumably related to the wide fluctuations observed in their concentrations throughout the day, with the

heterogeneity of triglyceride-rich lipoproteins (Quilomicra and VLDL) and its inseparable association with other risk factors. However, several studies have demonstrated a clear correlation between their levels and the occurrence of coronary heart disease, indicating that the presence of high levels of Triglycerides leads to a 13% increase in the risk of cardiovascular disease in men and 37% in women (Castelli, 1986; Criqui, Heiss, Cohn *et al*, 1993; Hokanson & Austin, 1996; Assman, Schulte & von Eckardstein, 1996). With regard to HDL-cholesterol, its inverse relationship with the risk of coronary heart disease is well accepted. In fact, this risk is 2 to 3% lower for each 1mg/dl elevation of HDL-Cholesterol (Gordon, Probstfiel, Garrison *et al*, 1989). The protective properties of this fraction derive not only from its involvement in reverse cholesterol transport, but are also a consequence of its anti-inflammatory capacity and protection against LDL-cholesterol oxidation (Ansell, Navab, Watson *et al*, 2004). On the other hand, it is recognized that individuals with very low levels of HDL-cholesterol have a higher cardiovascular risk. This population is often characterized for having concomitant hypertriglyceridemia, obesity, a sedentary lifestyle, active tobacco intoxication and decreased glucose tolerance (World Health Organization, 1999). In fact, an increased occurrence of cardiovascular events is expected for levels of HDL-cholesterol below 40 mg/dl (1.0 mmol/L) in men and less than 46 mg/dl (1.2 mmol/L) in women (UK HDL-C Consensus Group, 2004).

Recent evidence further stresses the importance of determining the non-HDL-cholesterol, defined by the concentration of LDL-cholesterol + VLDL-cholesterol. This parameter can better translate the risk of cardiovascular mortality than LDL-cholesterol, as it expresses more accurately the lipoprotein atherogenicity (Cui, Blumenthal, Flaws *et al*, 2001).

In recent years, a large number of risk factors for vascular disease have emerged from the international literature (see Table 2), demonstrating the relevance of more complex lipid disorders for the pathophysiology of atherosclerosis. Other emerging risk factors are related to inflammatory markers, as well as by the presence of metabolic changes, subtle changes in coagulation, hormonal disturbances and psychological or behavioral disorders (ILIB International Lipid Information Bureau, 2003).

<p>Lipidic Lipoproteic remnants Lipoprotein (a) Small and dense LDL HDL subspecies apolipoprotein B Apolipoprotein A-1</p> <p>Inflammatory High-sensitivity CRP Homocysteine Interleukin-6 Cell adhesion molecule-1 Selectin-CD40</p> <p>Metabolic Postprandial hyperinsulinemia (insulin resistance)</p>	<p>Coagulation Fibrinogen Von Willebrand Factor Factor VII Plasminogen activator inhibitor (PAI-1)</p> <p>Psychological / Behavioral Alcoholism Depression Social Isolation Loss and social support Low socioeconomic status</p> <p>Hormonal Loss of estrogen production (menopause)</p>
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Table 2. Emerging cardiovascular risk factors.

As we have seen, each stated factor conveys a certain risk to the affected population. However, in everyday clinical practice a large majority of patients have associations of these factors and, as such, have cardiovascular risks that express the magnitude of individual risk factors present in an exponential, rather than additive, trend (Yusuf, Giles, Croft *et al*, 1998; American Heart Association, 2002).

An alternative option, with very promising results in the context of cardiovascular risk stratification and assessment of the effectiveness of lipid-lowering interventions, is the use of lipid ratios, just as the LDL-Cholesterol/HDL-Cholesterol ratio and the Total-Cholesterol/HDL-Cholesterol ratio, which have the added advantage of being easy to use in clinical practice (Gotto, Whitney & Stein, 2000). Changes in these relations have in fact been shown to better indicate the reduction in cardiovascular risk compared with the absolute levels of conventionally used lipid measures (Natarajan, Glick, Criqui *et al*, 2003; Kannel, 2005). On the other hand, the estimated LDL-Cholesterol/HDL-Cholesterol ratio translates, albeit imperfectly, an approach to the relationship of plasma apolipoproteins (apo) A-1 and apo B (Walldius & Jungner, 2005), thus enriching the lipid characterization of each patient, with the possibility of a better discrimination of cardiovascular risk, particularly among groups at intermediate cardiovascular risk (Gotto, Whitney, Stein *et al*, 2000).

Several large studies have demonstrated that the LDL-Cholesterol/HDL-Cholesterol ratio is an excellent predictor of risk of coronary disease and an excellent way to monitor the impact of lipid-lowering therapies (Manninen, Tenkanen, Koskinen *et al*, 1992; Kannel, 2005; Cullen, Schulte, Assmann *et al*, 1997; Stampfer, Sacks, Salvini *et al*, 1991; Gaziano, Hennekens, O'Donnell *et al*, 1997). In the Helsinki Study, a clinical trial with a 5-year follow-up, involving more than 4000 middle-aged men with hyperlipidemia, the LDL-Cholesterol/HDL-Cholesterol ratio had a superior prognostic value compared with isolated values of LDL-Cholesterol and HDL-Cholesterol. The predictive ability of this ratio was particularly strong in patients with concomitant elevation of triglycerides. It was further shown that the LDL-Cholesterol/HDL-Cholesterol ratio together with the fasting triglyceride concentration, allowed the identification of a particular subgroup of patients that had a remarkable 70% reduction in the risk of coronary heart disease with gemfibrozil (lipid-lowering agent) therapy. In the PROSPER trial, a retrospective analysis of 6,000 patients, the LDL-Cholesterol/HDL-Cholesterol ratio was the stronger predictor of cardiovascular events in elderly patients (Packard, Ford, Robertson *et al*, 2005). From this study has emerged the recommendation of pharmacological intervention whenever the LDL-Cholesterol/HDL-Cholesterol ratio values exceed 3.3 units. Another study (PROCAM study) involving about 11,000 men aged between 36 and 65, followed over 4 to 14 years, has documented an extremely important and linear relationship between the LDL-Cholesterol/HDL-Cholesterol ratio and cardiovascular mortality (Cullen, Schulte, Assmann *et al*, 1997). In this study, cardiovascular mortality peaked for LDL-Cholesterol/HDL-Cholesterol values between 3.7 and 4.3 units. In line with these results is the Physician's Health Study, involving 15,000 men (40 to 84 years), where there was a 53% increase in the risk of an acute coronary event for each one-unit increase in the LDL-Cholesterol/HDL-Cholesterol ratio (Stampfer, Sacks, Salvini *et al*, 1991). In another mixed study, involving men and women under the age of 76, the LDL-Cholesterol/HDL-Cholesterol ratio showed a strong relationship with the risk of coronary events (Gaziano, Hennekens, O'Donnell *et al*, 1997), aspect reinforced in an analysis of patients from the Framingham Heart Study, where a clear superiority of LDL-Cholesterol/HDL-Cholesterol ratio in predicting cardiovascular events compared to the levels of isolated LDL-cholesterol and HDL-cholesterol was depicted (Kannel, 2005).

Another point that reinforces the superiority of the lipid ratios in the stratification of cardiovascular risk arises from the effect of dietary cholesterol on plasma lipid levels. Several studies have demonstrated that these ratios are not affected by dietary cholesterol (Greene, Zerner, Wood *et al*, 2005; Herron, Vega-Lopez, Earl *et al*, 2002). On the contrary, some studies have shown that dietary cholesterol interferes with LDL-cholesterol and HDL-cholesterol, with little variation in the ratio (McNamara, 2000). On average, the predicted change in the LDL-Cholesterol/HDL-Cholesterol ratio per 100 milligrams/day increase in dietary cholesterol is quite small, around 0.01 (McNamara, 2000).

2.3 Cardiovascular risk – Atherogenesis

To understand the sequence of events that occur at the vascular level, resulting in devastating clinical manifestations that are all too familiar, we must look a little closer at the physiology of this system.

One of the most important organs we have without doubt is the vascular endothelium. The endothelium is the inner portion of our vessels, which can be compared to a thin membrane that carpets the blood vessels, and its integrity is fundamental for the maintenance of several potentially unstable equilibria. In this sense, a huge amount of vascular wall or circulating factors are present in close relation to the endothelium, endlessly alternating between defense and aggression, aggression, with Nitric Oxide as the key protector. As the most egregious examples of interaction near the endothelium vicinity, we have the following associations: vasodilation/vasoconstriction; anti-trombotic/pro-trombotic; anti-inflammatory/pro-inflammatory, among others. The relative hegemony of each of these interacting factors will determine the final maintenance of endothelial integrity or, conversely, its dysfunction and destruction (Houston, 2002). Endothelial dysfunction is thus the initial phase of a cascade of events that flow until the onset of clinically overt disease. In a very simplified overview, once the endothelial barrier is compromised, an association of events takes place, mainly with a lipid flooding process of the vascular wall, with the mobilization of inflammatory cells, the expression of chemotactic factors, growth and proliferation of smooth muscle and connective tissue, among others. The histologic consequence of these processes ranges from an initial lipid streak that evolves for an atherosclerotic plaque that may progress to calcification, progressively reducing the vascular lumen (Silva, 2000).

Curiously, most clinical cases are not determined directly by the extreme portion of the atherosclerotic continuum. In other words, cardiovascular events do not usually stem from progressive and insidious arterial occlusion, with consequent ischemia of downstream areas. Of course, cardiovascular events tend to be characterized by their acute nature, that is, by their sudden and unpredictable occurrence. As such, the implicit pathophysiology should express facts that support real-life events. In fact, one of the most important factors in the emergence of cardiovascular events is related to the so-called "atherosclerotic plaque stability". Thus, plaques with a small lipid core, with small inflammation infiltrate, and fitted with a thick, tough outer layer will be less susceptible to disruption by various harmful factors, such as blood pressure, sympathetic activity and other vasoconstrictor stimuli. In contrast, plaques with a rich lipid core, inflammatory activity and a significant weak fibrous cap will present a higher risk of fracture and exposure of their internal contents (Ridolfi & Hutchins, 1977). This in turn will lead to the activation of several factors that promote clotting and platelet aggregation *in-situ* (Falk, 1991), which may also lead to a sudden reduction of the vascular lumen, or even its complete occlusion by thrombosis.

Thus, the atherosclerotic process brings with it a wide array of metabolic, inflammatory and coagulation phenomena, decisively contributing to its clinical expression. Herein lies the justification of the diverse therapeutic targets that aimed for in these patients.

The importance of hypercholesterolemia as a key-player in this cascade of events is unquestioned and widely demonstrated in the published literature. A perfect expression of the interaction between research and practice is surely the publication of recommendations and guidelines that assist clinicians in the rationalization of therapeutic means available. These emerge as regular updates of successive collections of published scientific data, outlined in an admirably succinct way so they can be strategically combined and applied to the most varied health systems worldwide. Regarding the core topic of this paper, we have to address the most relevant recommendations published by the European Society of Cardiology and the National Cholesterol Education Program (NCEP). These recommendations were prepared according to an individual-risk perspective, and the therapeutic goals are defined according to the expected individual risk at long-term. Table 3 summarizes the NCEP guidelines, revealing a clear therapeutic aggressiveness increase based on individual risk, as well as the adoption of progressively reduced target LDL-cholesterol values.

	Target	Therapeutic options	
High risk 10-year risk > 20% Established cardiovascular disease Equivalents of Cardiovascular Disease	LDL < 100 mg/dl	LDL < 100 mg/dl-129 mg/dl Dietary intervention Drug treatment?	LDL ≥ 130 mg/dl Dietary intervention Drug treatment
Intermediate risk ≥ 2 Risk Factors 10-year risk ≤ 20% 10-year risk ≤ 10%	LDL < 130 mg/dl LDL < 130 mg/dl	LDL ≥ 130 mg/dl Dietary intervention Drug treatment LDL 130-160 mg/dl Dietary intervention	LDL ≥ 160 mg/dl Dietary intervention Drug treatment
Low risk 10-year risk ≤ 10% ≤ 1 risk factor	LDL < 160 mg/dl	LDL 160-190 mg/dl Dietary intervention Drug treatment?	LDL ≥ 190 mg/dl Dietary intervention Drug treatment

Table 3. Hypercholesterolemia treatment algorithm of the second Report of the Third National Cholesterol Education Program – NCEP (2001).

These recommendations also included some secondary therapeutic goals, including the attempt to reduce non-HDL cholesterol in patients with triglycerides above 200 mg/dl for values 30 mg/dL higher than the individual target for LDL-cholesterol. Another objective lies in promoting an increase in HDL-cholesterol. Although these objectives are based on a very interventionist philosophy, recent studies may impose additional requirements on these recommendations. In fact, the Heart Protection Study (Heart Protection Study

Collaborative Group, 2002) showed that a reduction of 30% compared to the more restrictive goal (LDL cholesterol <100 mg/dl) was related to an additional 30% reduction in the relative risk of coronary heart disease. The PROVE IT study (Cannon, Braunwald, McCabe *et al*, 2004), enrolled patients who had had acute coronary events and showed that larger reductions of LDL-cholesterol, to levels lower than 100 mg/dl, could significantly provide additional benefit in terms of future cardiovascular mortality and morbidity.

According to these results one has to consider more challenging treatment goals. The aim is to reach values of LDL-cholesterol <70mg/dl in patients with very high cardiovascular risk, such as those combining several primary risk factors (with primary relevance for diabetics), in patients with primary risk factors that are poorly controlled (with special care to the ones that maintain smoking habits), in patients with multiple risk factors of the so-called metabolic syndrome (triglycerides \geq 200 mg/dl, non-HDL-cholesterol > 130 mg/dl, HDL-cholesterol <40 mg/dl) and in patients with history of acute coronary events.

The establishment of a therapeutic basis grounded in the control of cardiovascular risk factors has demonstrated its strong validity, and is further reinforced for its effectiveness in terms of cost-benefit. Improved control of risk factors almost certainly contributed to the 50% reduction in cardiovascular mortality observed in the United States of America between 1980 and 1990, with 43% attributable to the verified pharmacological advances (Hunink, Glodman, Tosteson *et al*, 1997). In the Netherlands, similar results were observed, and primary prevention was responsible for a 40% decline in mortality from coronary heart disease between 1978 and 1985 (Grobee & Bots, 1996). The adoption of dietary measures in Finland, relying on an increase in the consumption of fruits and vegetables and a reduction of saturated fats intake, has resulted in a 65% reduction in mortality from coronary heart disease in a time horizon of 20 years (Pekka, Pirjo & Ulla, 2002).

Despite the promising results indicated by these data, only 35% of Americans with a formal indication for dietary or pharmacological therapy, according to the recommendations of the NCEP (2001), are complying with it (Hoerger, Bala, Bray *et al*, 1988). In Canada, a study carried out between 1988 and 1993, including patients at high cardiovascular risk admitted to hospitals, showed very low percentages in relation to lipid dosing prescription (28%) and early dietary (22%) or pharmacological (8%) therapy (The Clinical Quality Improvement Network (CQIN) Investigators, 1995).

In Europe, results have fallen below expectations. An important follow-up study - EUROASPIRE - between 1995 and 1996, involving nine European countries, showed that 86% of the enrolled patients had hypercholesterolaemia. Nevertheless, only 32% were on medication, and among those treated only 21% had achieved the target lipid levels (EUROASPIRE Study Group, 1997; EUROASPIRE I and II Group, 2001).

In Asia and the Pacific, the outlook is not encouraging either. In patients hospitalized for acute coronary events, quite small rates of lipid profile dosing (1 to 58%) were observed, as well as for the prescription of diet (1 to 32%) or pharmacological (6 to 60%) therapy to patients with high Cholesterol levels (Asian-Pacific CHD Risk Factor Collaborative Group, 1998).

The control of risk factors in clinical practice is thus a vaguely realized desideratum. The EUROASPIRE study has clarified some trends from 1995 to 2000. If the positive results have raised expectations, with an improvement seen in the control of hypercholesterolemia and hypertension, they are still accompanied by other rather disappointing indicators, such as those of smoking habits, obesity and diabetes, whose prevalence has been steadily increasing (EUROASPIRE Study Group, 1997; EUROASPIRE I and Group II, 2001). In the

United States of America the results are also somewhat disappointing. In survivors of acute myocardial infarction or stroke, the control percentages for some primary risk factors are below expectations, particularly for smoking habits (18%), control of hypercholesterolemia (46%), diabetes (48%) and hypertension (53%) (Qureshi et al, 2001).

As in almost all chronic conditions, the real picture lags far behind the expectations and available resources. Regarding hypercholesterolemia, the current situation is even less understandable, given its clear and strong association with the prevailing causes of death and incapacity, and the public awareness of the problem and in consideration of the demonstrated effectiveness of the available lipid-lowering drugs, that may have a quite favorable impact upon the prognosis of patients.

3. Original research data

3.1 Aim

Given the demonstrated role-playing of blood cholesterol in the atherosclerotic continuum, we designed two studies to ascertain the usefulness of the LDL-cholesterol/HDL-cholesterol, Triglycerides/HDL-cholesterol and Total-cholesterol/HDL-cholesterol ratios in predicting cardiovascular risk, through its relation to cardiovascular events and peripheral arterial disease (PAD) in two different clinical and experimental settings.

3.2 Study 1 – Usefulness of the lipidic ratios predicting peripheral artery disease in hypertensive patients: A retrospective analysis

The importance of the lipidic profile is well established in atherosclerotic processes related to coronary artery disease. Its relation with atherosclerosis in other vascular territories, particularly the inferior limbs has also received strong support from several experimental settings and in different clinical contexts. In order to address whether the lipid ratios can predict the occurrence of obstructive peripheral artery disease (PAD) we conducted a cross-sectional study in a sample of hypertensive patients. The study population consisted of 920 Portuguese nationals, aged between 20 and 91 years (mean 64.23 ± 12.30 years).

3.2.1 Methods

A total of 920 hypertensive patients (51.3% female, age 64.22 ± 12.01 years) were consecutively included in the study. None of the patients were taking drugs or were in situations known to affect lipoprotein metabolism. Total cholesterol, triglycerides and HDL cholesterol were measured. LDL cholesterol was obtained by Friedewald's formula (if triglycerides <3.39 mmol/l) or by ultracentrifugation. The LDL-Cholesterol/HDL-Cholesterol, Total Cholesterol/HDL-Cholesterol and Triglycerides/HDL-Cholesterol ratios were calculated in all patients. Blood pressure and heart rate were measured in standard conditions. Ankle-Brachial index (ABI) was estimated bilaterally as the ratio of ankle (left and right) systolic blood pressure and brachial (highest upper limb) systolic blood pressure. The normal range for ABI was 0.9-1.3 mmHg, and individuals with ABI<0.9 were classified as having peripheral arterial disease.

All data was processed using STATA for Windows, version 11.1. The distribution of the variables was tested for normality using the Kolmogorov-Smirnov test, and for homogeneity of variance by Levene's test. Simple descriptive statistics were used to characterize the sample and the distribution of variables. Logistic regression analysis was used to determine the influence of the lipidic parameters on the occurrence of PAD.

Groups were compared using the χ^2 test for categorical variables and the Student's t test (2 groups) or ANOVA with the post-hoc Tukey test (3 groups) for quantitative variables. A value of $P \leq 0.05$ was taken as the criterion of statistical significance for a 95% confidence interval.

3.2.2 Results

The general characteristics of the studied population are summarized in Table 4. Mean age was 64.23 ± 12.30 , with a similar proportion of men versus women (49% and 51%, respectively).

	Total (n=920)	No PAD Patients (n=803)	PAD Patients (n=117)	<i>p</i> -value (PAD versus No PAD)
Age, years	64.23±12.30	63.23±12.30	69.88±8.15	<0.01
Sex, men:women	49:51	48:52	52:48	0.462
Body Mass Index, Kg/m ²	28.79±11.85	28.92±12.53	27.94±5.31	0.416
CV events history, no:yes	88:12	90:10	75:25	<0.01
Tobacco Consumption, no:yes	89:11	89:11	88:12	0.856
Dyslipidemia, no:yes	40:60	42:58	26:74	<0.01
Diabetes, no:yes	66:34	68:32	54:46	<0.01
SBP, mmHg	150.14±20.69	148.97±19.60	157.81±25.59	<0.01
DBP, mmHg	86.28±10.91	86.59±10.63	84.20±12.43	0.025
Heart Rate, bpm	70.52±10.48	69.12±9.42	71.22±9.21	0.791
Plasma Glucose, mg/dl	112.42±39.65	111.35±39.10	119.61±42.60	0.035
Plasma Creatinine, mg/dl	0.88±0.22	0.87±0.21	0.96±0.26	<0.01
eGFR, ml/min/1.73m ²	84.73±23.28	85.86±23.40	76.94±20.88	<0.01
ABI	1.09±0.14	1.12±0.12	0.8±0.10	<0.01

PAD - peripheral artery disease; CV - cardiovascular events; SBP - systolic blood pressure; DBP - diastolic blood pressure; eGFR - estimated Glomerular Filtration Rate; ABI - Ankle-Brachial Index

Table 4. Characteristics of the study population, in general and stratified for the presence or absence of peripheral artery disease.

Mean body mass index was 28.79 ± 11.85 , indicating an overweighted population. With regard to cardiovascular risk factors, all patients were hypertensive, 60% had dyslipidemia and 34% were diabetic; 11% were smokers and 12% had a personal history of cardiovascular events (mainly Stroke). About 37% were medicated for cardiovascular pathologies, with 13.6% of the patients undertaking statins. This factor was controlled in all the multivariable analysis. Peripheral artery disease (PAD) was encountered in 117 patients (12.7%). Patients with PAD were older, and had a worst metabolic and hemodynamic profile. The proportion of patients with a personal history of cardiovascular events was also greater in patients with PAD (25% versus 10%, $p < 0.01$). The Ankle-Brachial Index (ABI) was also significantly lower

in patients with PAD, as expected. Interestingly, patients with PAD also had a significantly lower estimated glomerular filtration rate (76.94 ± 20.88 ml/min/ 1.73m^2 versus 85.86 ± 23.40 ml/min/ 1.73m^2 in patients without PAD).

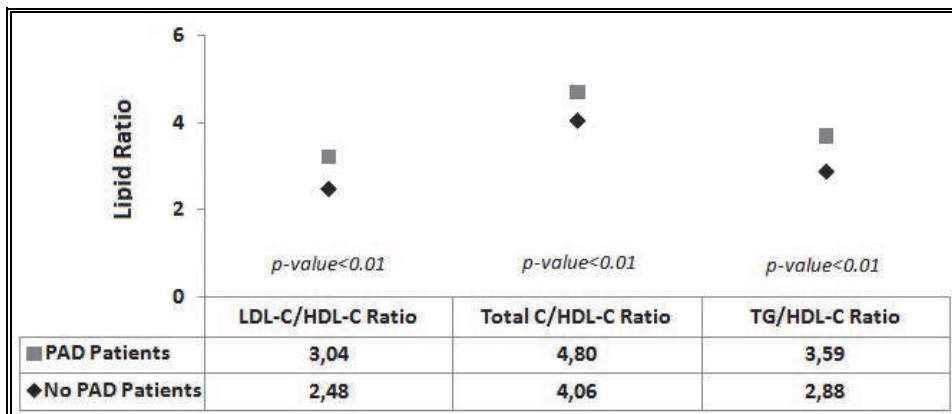
Regarding the overall and the comparative lipidic profile (depicted in table 5), significant differences amongst patients with and without PAD were only observed for the three considered lipidic ratios, expressing higher values when PAD was present, and for the HDL-cholesterol, with the PAD patients reaching lower HDL levels (although tendentially, $p\text{-value}=0.073$).

	Total (n=920)	No PAD Patients (n=803)	PAD Patients (n=117)	<i>p-value</i> (PAD versus No PAD)
Plasma Total Cholesterol, mg/dl	196.61 \pm 41.15	197.06 \pm 41.18	193.68 \pm 40.98	0.400
Plasma LDL-Cholesterol, mg/dl	116.31 \pm 37.62	116.17 \pm 41.18	193.68 \pm 40.98	0.763
Plasma HDL-Cholesterol, mg/dl	54.46 \pm 21.47	54.96 \pm 21.56	51.14 \pm 20.65	0.073
Plasma Triglycerides, mg/dl	134.84 \pm 67.88	134.20 \pm 41.18	139.09 \pm 66.02	0.460
LDL-Colesterol/HDL- Colesterol Racio	2.55 \pm 2.45	2.48 \pm 2.11	3.04 \pm 2.03	<0.01
Total Cholesterol/HDL- Colesterol Racio	4.15 \pm 2.95	4.06 \pm 2.48	4.80 \pm 2.05	<0.01
Triglicerídeos/HDL- Colesterol Racio	2.97 \pm 2.98	2.88 \pm 2.44	3.59 \pm 2.33	<0.01

Table 5. Lipid profile of the study population.

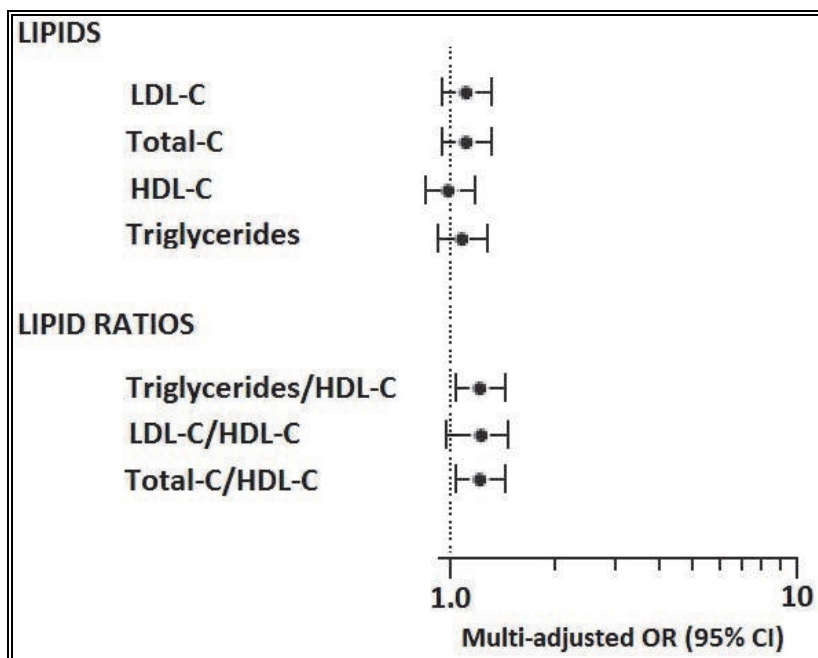
Figure 1 further illustrates the differences in the lipidic ratios among patients with and without PAD, with all three considered ratios presenting significant differences between the considered groups.

A multivariable logistic regression analysis was also performed considering PAD as the dependent variable (dichotomized in normal/abnormal), and forcing each lipidic parameter (either individual lipis or lipid ratios) in a model adjusted for the conventional Framingham cardiovascular risk factors (age, sex, diabetes, blood pressure, smoking status and body mass index). The observed Odds Ratios (OR) with 95% confidence intervals is depicted in figure 2. Although there's an appreciable tendency of association with PAD in all lipid variables, it reaches statistical significancy only for the lipidic ratios. In fact, the OR for LDL-cholesterol, Total-cholesterol, HDL-cholesterol and Triglycerides were respectively 1.004 (IC: 0.999-1.010, $p=0.1$), 1.001 (IC: 0.996-1.007, $p=0.4$), 0.993 (IC: 0.980-1.004, $p=0.2$) and 1.001 (IC: 0.998-1.004, $p=0.2$). For the LDL-cholesterol/HDL-cholesterol ratio, the multiaadjusted OR was 1.06 (IC: 0.999-1.120, $p=0.052$), with a marginally significant association with PAD. For the Total-cholesterol/HDL-cholesterol and the Triglycerides/HDL-cholesterol ratios, the adjusted OR were respectively 1.051 (IC: 1.011-1.200, $p=0.01$) and 1.050 (IC: 1.002-1.110, $p=0.04$). A further analysis showed that the association of the lipid ratios with PAD was tendentially linear, particularly for the Total-cholesterol/HDL-cholesterol ratio.



PAD - peripheral artery disease

Fig. 1. Representation of the comparative lipid ratios in patients with and without peripheral arterial disease.



OR - Odds Ratio

Fig. 2. Adjusted Odds Ratios for Peripheral Artery Disease for the individual lipidic variables and for the lipidic ratios. The Odds Ratios are multi-adjusted to conventional Framingham cardiovascular risk factors.

3.3 Study 2 – Usefulness of the lipidic ratios in a low-to-moderate cardiovascular risk population: A sub-analysis of the EDIVA (Estudo de Distensibilidade Vascular) project

The EDIVA project was an epidemiological study assessing cardiovascular risk through sequential Pulse Wave Velocity measurement (Maldonado, Pereira, Polónia *et al*, 2011), but since serum lipids were available for all the included patients, we re-analyzed the EDIVA database aiming to address the delineated objective: to ascertain the usefulness of The LDL-Cholesterol/HDL-Cholesterol, Total Cholesterol/HDL-Cholesterol and Triglycerides/HDL-Cholesterol ratios in the general population. The study population consisted of 2200 Portuguese nationals (1290 men and 910 women), aged between 18 and 91 years (mean 46.33 ± 13.76 years). Of these, 668 had low cardiovascular risk, and 1532 were patients with hypertension, diabetes and/or dyslipidemia. Individuals defined as having low cardiovascular risk were those who had had no chronic disease, had never been prescribed chronic pharmacological therapy, and had a normal physical exam, electrocardiogram, blood and urine tests, these characteristics having remained unchanged for at least two annual assessments. The patient group was under pharmacological therapy for at least one of the above pathologies.

3.3.1 Methods

The study's aims were explained to all participants and their informed consent was obtained. The methodology used to collect the data was approved by the Portuguese Data Protection Commission and the study was approved by the Ethics Committees of the hospitals involved. Mean follow-up was 2 years.

This was a prospective, multicenter, observational study monitoring the occurrence of major adverse cardiovascular events (MACE) – death, stroke, transient ischemic attack, myocardial infarction, unstable angina, peripheral arterial disease, revascularization or renal failure. Follow-up of the patients consisted of annual assessments including, blood pressure (BP) measurement, laboratory tests, including serum lipids, and clinical observation. Total cholesterol, triglycerides and HDL cholesterol were measured. LDL cholesterol was obtained by Friedewald's formula (if triglycerides < 3.39 mmol/l) or by ultracentrifugation. The LDL-Cholesterol/HDL-Cholesterol, Total Cholesterol/HDL-Cholesterol and Triglycerides/HDL-Cholesterol ratios were calculated in all patients. At each consultation, the subjects' weight and height were measured and body mass index (BMI) was calculated in kg/m². Blood pressure and heart rate were measured in standard conditions, in a supine position and after a 10-minute resting period, by an experienced operator and using a clinically validated (class A) sphygmomanometer (Colson MAM BP 3AA1-2®; Colson, Paris) (Pereira & Maldonado, 2005). Three measurements were taken and the arithmetic mean was used in the analysis. All participants underwent routine fasting laboratory tests. At the first consultation they filled out a questionnaire concerning relevant personal and family history, smoking habits, alcohol consumption and medication.

Data from the sample subjects were processed using STATA for Windows, version 11.1. The distribution of the variables was tested for normality using the Kolmogorov-Smirnov test, and for homogeneity of variance by Levene's test. Simple descriptive statistics were used to characterize the sample and the distribution of variables. Cox proportional hazards analysis was used to determine the influence of the lipidic parameters on the occurrence of the specified cardiovascular events. C-Statistics was calculated to address the reliability of the lipidic parameters as prognostic variables.

Groups were compared using the χ^2 test for categorical variables and the Student's *t* test (2 groups) or ANOVA with the post-hoc Tukey test (3 groups) for quantitative variables. A value of $P \leq 0.05$ was taken as the criterion of statistical significance for a 95% confidence interval.

3.3.2 Results

The general characteristics of the study population are summarized in Table 6. Mean age was 46.33 ± 13.77 , indicating a relatively young sample, with similar proportions of men and women (59% and 41%, respectively). With regard to cardiovascular risk factors, 52% of the patients were hypertensive, 33% had dyslipidemia and 11% were diabetic; 17% were smokers and 15% had a family history of cardiovascular events. About 37% were medicated for cardiovascular pathologies, with 13.6% of the patients undertaking statins. This factor was controlled in all the multivariable analysis. Mean follow-up is currently 21.42 ± 10.76 months. A total of 50 non-fatal MACE (2.2% of the sample) were recorded, including 27 cases of stroke, 19 of coronary events, 2 of renal failure and 2 of occlusive peripheral arterial disease.

	Total	No MACE		MACE	<i>p</i> -value (MACE vs No MACE)
		Low Risk Patients	Patients	Patients	
N,%	2200	32%	66%	2%	
Age, years	46.33±13.77	40.00±13.42	49.03±13,14	50.00±10,21	0.360
Sex, men:women*	59:41	60:40	58:42	46:54	0.104
Body Mass Index, Kg/m ²	27.18±5.50	25.90±4.21	27.71±4.45	28.59±5.75	0.348
Waist, cm	89.82±11,05	86.83±10,30	90.63±11,00	90.00±13,06	0.917
Family History, no:yes*	85:15	92:8	83:17	60:40	0.020
Tobacco Consumption, no:yes*	83:17	78:22	85:15	78:22	0.243
Hypertension, no:yes*	48:52	100:0	26:74	14:86	0.109
Dyslipidemia, no:yes*	67:33	100:0	53:47	60:40	0.311
Diabetes, no:yes*	89:11	100:0	85:15	86:14	0.941
SBP, mmHg	142.51±21.05	129.17±14.33	147.83±14.33	161.08±17.34	<0.001
DBP, mmHg	84.52±12.29	77.43±10.11	87.32±11.87	92.08±10.07	<0.001
PP, mmHg	57.99±15.29	51.74±11.90	60.05±15.86	66.20±12.93	<0.001
MAP, mmHg	103.85±14.02	94.68±1.26	107.48±13.52	117.14±11.43	<0.001
Heart Rate, bpm	70.56±12.24	68.21±12.58	71.49±11.87	78.20±13.01	0.001
Plasma Glucose, mg/dl	100.44±31.54	90.86±9.16	103.70±3.75	110.32±39.64	0.406
Plasma Creatinine, mg/dl	1.31±5.08	0.90±1.77	1.43±5.99	1.53±2.92	0.996

MACE - major acute cardiovascular events; SBP - systolic blood pressure; DBP - diastolic blood pressure; PP - pulse pressure; MAP - mean blood pressure

Table 6. General characteristics of the study cohort, depending on the presence of MACE and conventional cardiovascular risk factors.

Regarding the lipidic profile, patients with MACE presented higher levels of the different lipidic parameters, as illustrated in table 7, in particular the lipidic ratios were significantly higher in patients with MACE (5.76±1.74 versus 6.75±1.98 for Total Cholesterol/HDL-Cholesterol ratio, 3.24±1.32 versus 4.51±1.49 for LDL-Cholesterol/HDL-Cholesterol ratio, 3.17±1.34 versus 4.35±1.67 for Triglycerides/HDL-Cholesterol ratio, *p-value*<0.01). So, overall, the patients with MACE were characterized by an unfavorable metabolic profile compared to the asymptomatic patients.

	No MACE (n=2150)	MACE (n=50)	<i>p-value</i>
Plasma Total Cholesterol, mg/dl	221.37±34.01	238.43±36.12	<0,01
Plasma LDL-Cholesterol, mg/dl	141.37±31.22	163.26±41.12	<0,01
Plasma HDL-Cholesterol, mg/dl	41.22±11.07	36.19±7.28	<0,01
Plasma Triglycerides, mg/dl	156.37±34.01	181.43±36.12	<0,01
LDL-Cholesterol/HDL-Cholesterol Ratio	2.98±2.32	4.51±1.49	<0,01
Total Cholesterol/HDL-Cholesterol Ratio	4.76±2.11	6.75±1.98	<0,01
Triglycerídeos/HDL-Cholesterol Ratio	3.17±2.32	4.35±1.67	<0,01

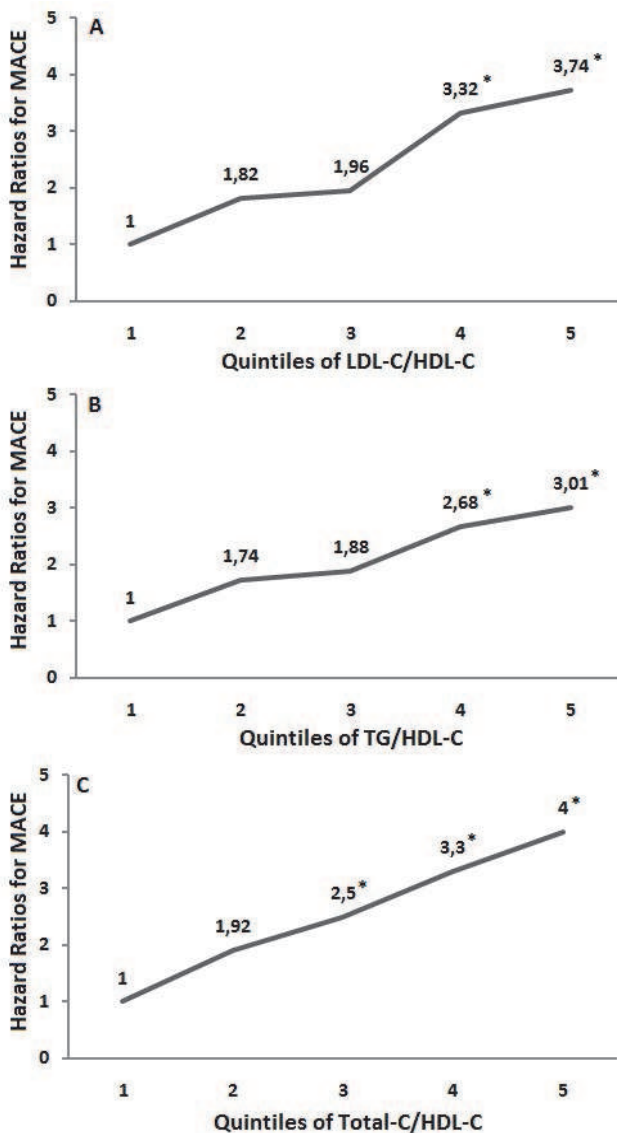
MACE - major acute cardiovascular events; SBP - systolic blood pressure; DBP - diastolic blood pressure; PP - pulse pressure; MAP - mean blood pressure

Table 7. Lipid profile of the study cohort, stratified for the presence or absence of of MACE.

In the multivariable model analysis, adjusting for all conventional Framingham cardiovascular risk factors (age, sex, diabetes, blood pressure, smoking status and body mass index), the lipids ratios were associated with MACE, with stronger associations than the ones observed for the individual lipidic variables. Overall, the Total-Cholesterol/HDL-Cholesterol was found to be the best single predictor of MACE. In figure 3 we plot the hazard ratios for quintiles of the lipid ratios. A linear increase of the hazard ratios across quintiles of the Total-Cholesterol/HDL-Cholesterol is clearly depicted, while for the other ratios only the upper-extreme quintiles showed an important association with cardiovascular events.

Comparative data of risk association for those in the extreme quintiles of each lipidic variable is presented in figure 4. Of note, one can see that the combination of two individual lipidic components into a single variable provides stronger association with cardiovascular risk, as expressed by the depicted hazard ratios for the lipid ratios. On the other hand, the lipid ratio with the strongest association was the Total-Cholesterol/HDL-Cholesterol ratio, in line with the data depicted in figure 3.

The ROC curve analysis provided the Areas-Under-the-Curve (AUC, equivalent to the C-statistics) for the different lipid parameter considered in the analysis. The parameters with the biggest AUC were the Total-cholesterol/HDL-cholesterol ratio (AUC=0.703, IC:0.65-0.77) and the LDL-cholesterol/HDL-cholesterol (AUC=0.701, IC:0.64-0.79).



* p -value < 0.01.

Fig. 3. Adjusted Hazard Ratios for major acute cardiovascular events distributed according to quintiles of the lipid ratios. A) Hazard ratios for quintiles of the LDL-Cholesterol/HDL-Cholesterol ratio; B) Hazard ratios for quintiles of the Triglycerides/HDL-Cholesterol ratio; C) Hazard ratios for quintiles of the Total-Cholesterol/HDL-Cholesterol ratio. The hazard ratios are multi-adjusted to conventional Framingham cardiovascular risk factors.

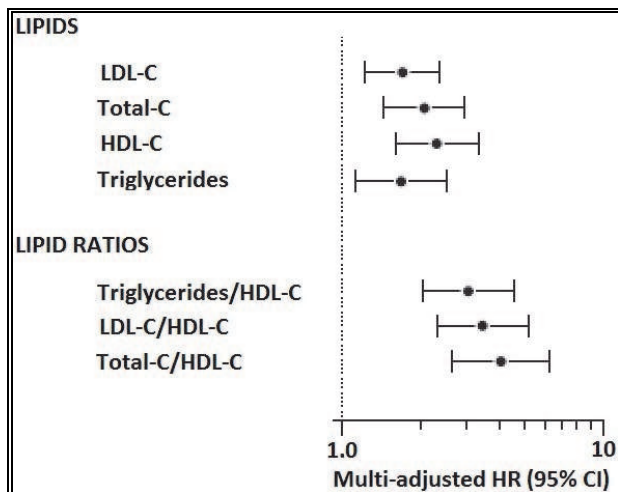


Fig. 4. Adjusted Hazard Ratios for major acute cardiovascular events amongst those in the extreme quintiles of each considered lipidic parameter. The hazard ratios are multi-adjusted to conventional Framingham cardiovascular risk factors.

4. Discussion and conclusions

As previously mentioned, cardiovascular disease, as an expression of atherosclerotic processes, is the leading cause of death in industrialized countries. The key role played by cholesterol in essential pathophysiologic processes that lead to the occurrence of clinically significant cardiovascular events is well recognized. In contemporary clinical practice, this notion is well entrenched, and the individual cardiovascular risk definition incorporates, among other factors, the lipid profile, including the Total Cholesterol, LDL Cholesterol, HDL Cholesterol and triglycerides. A practical evidence of the aforementioned is the fact that the major cardiovascular risk tables currently available (e.g. the Framingham score or the EuroSCORE), incorporate lipid parameters in the definition of thresholds of risk. On the other hand, therapeutic decisions and monitoring have been largely centered on the conventional lipid profile. Even the international recommendations (such as those issued by the National Cholesterol Education Program - NCEP, 2001) recommend target levels of LDL and HDL -cholesterol to determine cardiovascular risk and evaluate the effectiveness of lipid-lowering therapies. However, some studies have indicated important limitations of these parameters in the prediction of cardiovascular risk, particularly in patients with intermediate cardiovascular risk (Gotto, Whitney, Stein *et al*, 2000).

However, more recent evidence has suggested other lipidic components to optimize the definition of cardiovascular risk in clinical practice. In fact, several studies have expressed the superiority of the levels of apolipoprotein (apo) B, apo A-1 and its ratio, both in predicting cardiovascular events and in the evaluation of treatment efficacy (Packard & Marcovina, 2006; Yusuf, Hawken, Ounpuu, *et al*, 2004; Meisinger, Loewel, Mraz *et al*, 2005; Barter, Ballantyne, Carmena *et al*, 2006; Kim, Chang, Choi *et al*, 2005). In fact, considering that each lipidic particle contains one molecule of the atherogenic apo B, then its levels are a direct measure of the number of potentially atherogenic particles in the different

conventional lipid components (Walldius & Junger, 2006). In contrast, the concentration of apo A-1 translates the number of anti-atherogenic particles contained in the HDL-cholesterol, thus enclosing the conceptual framework of apoB/apoA-1 ratio as a measure of the ratio of atherogenic particles versus anti-atherogenic particles transported in the blood. Despite the growing enthusiasm about the potential of these emerging parameters for their best performance in the definition of cardiovascular risk, there still remain some questions that limit their dissemination in clinical practice. The central question is very practical, and focuses on the cost-benefit relation associated with a change in the traditional clinical approach. In fact, it is not yet clear whether the superiority of these new lipid parameters over the more conventional ones for risk stratification is enough to justify the additional cost inherent to their laboratory determination (Pischon, Girman, Sacks *et al*, 2005). Furthermore, despite the current literature supporting apolipoproteins as better predictors of cardiovascular events, its use may not be the most practical operational perspective. Moreover, it is not yet clear whether the replacement of conventional parameters for emerging ones will translate into clear clinical benefit, or if, conversely, it will confuse the various protagonists over the clinical decision frame.

In contrast to this line of argument, several studies have also emerged affirming quite clearly the advantages of using lipid ratios, based on conventional parameters, such as those studied in this work. This is based on the fact that, on the one hand, they add cardiovascular risk discriminative capacity to the individual lipid parameters, and on the other, they are more favorable than the apolipoproteins considering cost and immediate operationalization (Gotto, Whitney & Stein, 2000). As mentioned earlier, several studies have shown fairly consistently that changes in these ratios are favorable indicators of cardiovascular disease risk, above the absolute levels of individual lipids (Natarajan, Glick, Criqui *et al*, 2003; Kannel, 2005). Accumulating evidence in this regard is quite broad, spreading over several clinical frameworks (Manninen, Tenkanen, Koskinen *et al*, 1992; Kannel, 2005; Cullen, Schulte, Assmann *et al*, 1997; Stampfer, Sacks, Salvini *et al*, 1991; Gaziano, Hennekens, O'Donnell *et al*, 1997; Packard, Ford, Robertson *et al*, 2005). The results presented here clearly fall into this line, reinforcing the belief in the superiority of the lipid ratios, particularly the Total-Cholesterol/HDL-Cholesterol and the LDL-Cholesterol/HDL-Cholesterol ratios, over the classic lipid parameters, predicting peripheral arterial disease in hypertensive patients (in a high cardiovascular risk) and predicting future major cardiovascular events (including stroke and myocardial infarction) in a low-to-intermediate cardiovascular risk population. One of the curious aspects extracted from the second presented study was the existence of a linear relationship for the Total-Cholesterol/HDL-Cholesterol ratio with the risk of MACE, something not apparent in the LDL-Cholesterol/HDL-Cholesterol ratio. This same result was reproduced in the Quebec Cardiovascular Study, in which more than 2.000 middle-aged men were followed for 5 years, monitoring the occurrence of major cardiovascular events (Lemieux, Lamarche, Couillard *et al*, 2001). The lipid parameters with better performance in predicting risk in this study were the Total-Cholesterol/HDL-Cholesterol ratio and the LDL-Cholesterol/HDL-Cholesterol ratio, although only the first stated ratio expressed a linear relationship with risk. One possible explanation for this result is metabolic in nature. In fact, it is well documented that patients with dyslipidemia showing high triglycerides and low HDL-cholesterol (generally patients with abdominal obesity and insulin resistance), often have marginal or even normal levels of LDL-Cholesterol (Lamarche, Després, Moorjani *et al*, 1996). Moreover, LDL-Cholesterol concentrations are often estimated indirectly from 3 measurements (Total-Cholesterol, Triglycerides and HDL-

Cholesterol), which may include a variation that can reach 25% (Schechtman & Sasse, 1993), with a potential and quite significant impact in the LDL-Cholesterol/HDL-Cholesterol ratio, eventually under-estimated. By contrast, the two components included in the Total-Cholesterol/HDL-Cholesterol ratio are measured directly. Supporting the superiority of these ratios over the isolated lipid parameters, is their unique ability to reflect the bidirectional cholesterol traffic (in and outward) through the arterial intima in a way that the individual LDL and HDL-Cholesterol levels cannot reach (Kannel, 2005). Consistent with this assumption, another recent cohort prospective study, involving over 15.000 women followed over a period of 10 years, demonstrated that the Total-Cholesterol/HDL-Cholesterol ratio alongside the non-HDL Cholesterol were predictors of future cardiovascular events, as good or better than apolipoprotein fractions (Ridker, Rifai, Cook *et al*, 2005).

Of course, there are still unresolved issues, such as the definition of a cut-off in these ratios from which lipid-lowering therapy should be considered. The current guidelines of the NCEP (2001) recommend a cut-off of 2.5 for the ratio LDL-cholesterol/HDL-cholesterol. However, recent studies suggest that the risk of cardiovascular events begins to have significant expression for values between 3.3-3.7 (Cullen, Assmann & Schulte, 1997), in line with the results we reported here.

Given all the data currently available, as long as the fundamental reservations to the routine use of apolipoproteins are not exceeded, the use of lipid ratios in clinical practice is strongly advised, both in risk stratification and therapeutic decision and in monitoring its effectiveness.

5. Acknowledgments

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6. References

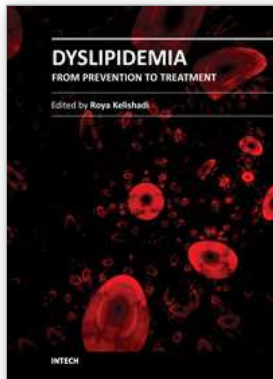
- Allender, S.; Scarborough, P.; Preto, V., et al. (2008). *European cardiovascular disease statistics*. European Heart Network, Belgium.
- American Heart Association. (2002). *Heart disease and stroke statistics – 2003 update*. Dallas, Tex: American Heart Association.
- American Heart Association. (2003). Statistical facts sheet-populations. *International Disease Statistics*. Dallas, Tex: American Heart Association.
- Ansell, B.J.; Navab, M.; Watson, K.E.; et al. (2004). Anti-inflammatory properties of HDL. *Rev Endocr Metab Disord*, 5:351-358.
- Asian-Pacific CHD Risk Factor Collaborative Group. (1998). Risk factor management in CHD patients in Asia: current status. *Atherosclerosis*, 136:S31.
- Assman, G.; Schulte, H.; von Eckardstein, A. (1996). Hypertriglyceridemia and elevated lipoprotein (a) are risk factors for major coronary events in middle-aged men. *Am J Cardiol*, 77: 1179-1184.
- Barter, P.J.; Ballantyne, C.M.; Carmena, R.; et al. (2006). Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*, 259:247-258.

- Bots, M.L.; Grobee, D.E. (1996). Decline of coronary heart disease mortality in The Netherlands from 1987 to 1985: contributions of medical care and changes over time in presence of major cardiovascular risk factors. *J Cardiovasc Risk*, 3:271-276.
- Cannon, C.P.; Braunwald, E.; McCabe, C.H.; *et al.* (2004). Pravastatin or Atorvastatin evaluation and infection therapy: thrombolysis in myocardial infarction 22 investigators. Intensive versus moderate lipi lowering with statins after acute coronary syndromes. *N Eng J Med*, 350:1495-1504.
- Carlson, L.A.; Bottiger, L.E.; Ahfeldt, P.E. (1979). Risk factors for myocardial infarction in the Stockholm Prospective Study . A 14-year follow-up focusing on the role of plasma triglycerides and cholesterol. *Acta Med Scand*, 206:351-360.
- Castelli, W.P. (1986). The triglyceride issue: a view from the Framingham. *Am Heart J*, 112:432-437.
- Criqui, M.H.; Heiss, G.; Cohn, R. *et al.* (1993). Plasma triglyceride level and mortality from coronary heart disease. *N Eng J Med*, 328:1120-1125.
- Cui, Y.; Blumenthal, R.S.; Flaws, J.A.; *et al.* (2001). Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*, 161:1413-1419.
- Cullen, P.; Schulte, H.; Assmann, G. (1997). The Munster Heart Study (PROCAM) Total Mortality in Middle-Aged Men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers. *Circulation*, 96:2128 - 2136.
- Eckardstein, A.; Hersberger, M.; Roher, L. (2005). Current understanding of the metabolism and biological actions of HDL. *Curr Opin Clin Nutr Metab Care*, 8:147-152.
- EUROASPIRE I and II Group. (2001). Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. *Lancet*, 357:995-1001.
- EUROASPIRE Study Group. (1997). EUROASPIRE: A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. *Eur Heart J*, 18:1569-1582.
- European guidelins on cardiovascular disease prevention in clinical practice. (2003). Third joint task force of european and other societies on cardiovascular disease prevention in clinical practice. *European J Card Prev and Rehab*, 10:S1-S10.
- Falk, E. (1991). Coronary thrombosis: pathogenesis and clinical manifestations. *Am J Cardiol*, 68:28B-35B.
- Gaziano, J.M.; Hennekens, C.H.; O'Donnell, C.J.; *et al.* (1997). Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation*, 96:2520 - 2525.
- Gordon, D.J.; Probstfield, J.L.; Garrison, R.J.; *et al.* (1989). High-density lipoprotein cholesterol and cardiovascular disease: four prospective american studies. *Circulation*, 79:8-15.
- Gotto, A.M.; Whitney, E.; Stein, E.A.; *et al.* (2000). Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex CAPS). *Circulation*, 101:477 - 484.
- Gotto, A.M.; Whitney, E.; Stein, E.A.; *et al.* (2000). Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/Tex CAPS). *Circulation*, 101:477-484.

- Greene, C.M.; Zern, T.L.; Wood, R.J.; *et al.* (2005). Maintenance of the LDL cholesterol: HDL cholesterol ratio in an elderly population given a dietary cholesterol challenge. *J Nutr*, 135:2793 - 2798.
- Haffner, S.M.; Letho, S.; Ronnema, T.; *et al.* (1988). Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. *N Eng J Med*, 339:229-234.
- Heart Protection Study collaborative group.(2002). MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360(9326):7-22.
- Herron, K.J.; Vega-Lopez, S.; Conde, K.; *et al.* (2002). Pre-menopausal women classified as hypo- or hyper-responders, do not alter their LDL/HDL ratio following a high dietary cholesterol challenge. *J Am Coll Nutr*, 21:250 - 258.
- Higgins, M.; Kannel, W.; Garrison, R.; *et al.* (1988). Hazards of obesity: the Framingham experience. *Acta Med Scand*, Suppl 723:23-36.
- Hoerger, T.J.; Bala, M.V.; Bray, J.W.; *et al.* (1988). Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *Am J Cardiol*, 82:61-65.
- Hokanson, J.E.; Austin, M.A. (1996). Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*, 3:213-219.
- Houston, M. (2002). *Vascular Biology and Clinical Practice*. Hanley & Belfus Inc. Philadelphia.
- Hunink, M.L.; Glodman, L.; Tosteson, A.N.A.; *et al.* (1997). The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. *JAMA*, 277:535-542.
- ILIB International Lipid Information Bureau. (2003). *Dyslipidemia and coronary heart disease*. 3rd Edition. 2003 International Lipid Information Bureau. New York.
- Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. (2004). *Circulation*, 110:227-239.
- Kannel, W.B. (2005). Risk stratification of dyslipidemia: Insights from the Framingham Study. *Curr Med Chem Cardiovasc Hematol Agents*, 3:187 - 193.
- Kaplan's Clinical Hypertension. (2002). Lippincot Williams & Wilkins.
- Kim, H.K.; Chang, S.A.; Choi, E.K.; *et al.* (2005). Association between plasma lipids, and apolipoproteins and coronary artery disease: a cross-sectional study in a low-risk Korean population. *Int J Cardiol*, 101:435-440.
- Lamarche, B.; Després, J.P.; Moorjani, S.; *et al.* (1996). Triglycerides and HDL cholesterol as risk factors for ischemic heart disease: results from the Québec Cardiovascular Study. *Atherosclerosis*, 119:235-245.
- Law, M.R.; Wald, N.J.; Thompson, S.G. (1994). By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischemic heart disease? *BMJ*, 308:367-372.
- Lemieux, I.; Lamarche, B.; Couillard, C.; *et al.* (2001). Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men. *Arch Intern Med*, 161:2685-2692.
- Maldonado, J.; Pereira, T.; Polónia, J.; *et al.* (2011). Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de Distensibilidade Vascular) project. *J Hypertens*, 29(4):669-75.

- Manninen, V.; Tenkanen, L.; Koskinen, P.; *et al.* (1992). Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*, 85:37 - 45.
- Marcovina, S.; Packard, C.J. (2006). Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. *J Intern Med*, 259:437-446.
- McNamara, D.J. (2000). The impact of egg limitations on coronary heart disease risk: Do the numbers add up? *J Am Coll Nutr*, 19:540S - 548S.
- Meisinger, C.; Loewel, H.; Mraz, W.; *et al.* (2005). Prognostic value of apolipoprotein B and A-I in the prediction of myocardial infarction in middle-aged men and women: results from the MONICA/KORA Augsburg cohort study. *Eur Heart J*, 26:271-278.
- Mosca, J.; Grundy, S.M.; Judelson, D.; *et al.* (1999). Guide to preventive cardiology in women. AHA/ACC scientific statement: consensus panel statement. *Circulation*, 99:2480-2484.
- Natarajan, S.; Glick, H.; Criqui, M.; *et al.* (2003). Cholesterol measures to identify and treat individuals at risk for coronary heart disease. *Am J Prev Med*, 25:50 - 57.
- Packard, C.J.; Ford, I.; Robertson, M.; *et al.* (2005). The PROSPER Study Group: Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation*, 112:3058 - 3065.
- Pekka, P.; Pirjo, P.; Ulla, U. (2002). Influencing public nutrition for non-communicable disease prevention: from community intervention to national programme - experiences from Finland. *Public Health Nutr*, 5:245-251.
- Pereira, T.; Maldonado, J. (2005). Performance of the Colson MAM BP 3AA1-2 automatic blood pressure monitor according to the European Society of Hypertension validation protocol. *Rev Port Cardiol*, 24:1341-1351.
- Pischon, T.; Girman, C.J.; Sacks, F.M.; *et al.* (2005). Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*, 112:3375-3383.
- Qureshi, A.I.; Suri, M.F.K.; Guterman, L.R.; *et al.* (2001). Ineffective Secondary Prevention in Survivors of Cardiovascular Events in the US Population: Report From the Third National Health and Nutrition Examination Survey. *Arch Intern Med*, 161:1621-1628.
- Ridker, P.M.; Rifai, N.; Cook, N.R.; *et al.* (2005). Non-HDL cholesterol, apolipoproteins A-1 and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*, 294 (3):326-333.
- Ridolfi, R.L.; Hutchins, G.M. (1977). Relationship between coronary artery lesions and myocardial infarcts: ulceration of atherosclerotic plaques precipitating coronary thrombosis. *Am Heart J*, 93:468.
- Schectman, G.; Sasse, E. (1993). Variability of lipid measurements: relevance for the clinician. *Clin Chem*, 39:1495-1503.
- Silva, J. (2000). *Colesterol, lípidos e doença vascular*. Lidel, Edições Técnicas Lda.
- Stampfer, M.J.; Colditz, G.A.; Willet, W.C.; *et al.* (1991). Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses Health Study. *N Engl J Med*, 325:756-762.
- Stampfer, M.J.; Sacks, F.M.; Salvini, S.; *et al.* (1991). A prospective study of cholesterol apolipoproteins and the risk of myocardial infarction. *N Engl J Med*, 325:373 - 381.

- The Clinical Quality Improvement Network (CQIN) Investigators. (1995). Low incidence of assessment and modification of risk factors in acute care patients at high risk for cardiovascular events, particularly among females and the elderly. *Am J Cardiol*, 76:570-573.
- UK HDL-Consensus Group. (2004). Role of fibrates in reducing coronary risk: a UK consensus. *Curr Med Res Opin*, 20:241-247.
- Walldius, G.; Junger, N. (2006). The apo B/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy - a review of evidence. *J Int Med*, 259:493-519.
- Walldius, G.; Junger, I. (2005). Rationale for using apolipoprotein B and apolipoprotein A-1 as indicators of cardiac risk and as targets for lipid-lowering therapy. *Eur Heart J*, 26:210 - 212.
- Wilson, P.; D'Agostino, R.B.; Levy, D.; et al. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation*, 97:1837-1847.
- World Health Organization. (1999). *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation*. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization.
- World Health Organization. (2002). *The world health report 2002: reducing risks, promoting life*. Geneva: World Health Organization.
- Yusuf, H.R.; Giles, W.H.; Croft, J.B.; et al. (1998). Impact of multiple risk factor profiles on determining cardiovascular disease risk. *Prev Med*, 27:1-9.
- Yusuf, S.; Hawken, S.; Ounpuu, S.; et al. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*, 364:937-952.
- Yusuf, S.; Reddy, S.; Ounpuu, S.; et al. (2001). Global burden of cardiovascular diseases part I: general considerations. *Circulation*, 104:2746-2753.



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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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