Dyslipidemia

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Diagnosis

Lipid Profile

The lipid profile is composed of laboratory measurements of TC, TG, HDL-C, and LDL-C. Traditionally, LDL-C is not measured directly in plasma, as calculated by the Friedewald equation [1] LDL-C = TC − HDL − TG/5.

However, this equation is no longer accurate when TG levels are greater than 200 mg/dL and ceases to be valid when they exceed 400 mg/dL or in the presence of chronic diseases such as cholestatic liver disease, poorly controlled diabetes mellitus (DM), and nephrotic syndrome [2]. In these cases, direct LDL-C can be performed through specific tests with excellent precision and accuracy [3].

Table 44.1 shows secondary causes of dyslipidemia with increase of total cholesterol and LDL cholesterol and triglyceride.

LDL-Cholesterol

The increase in cardiovascular risk has been associated not only with elevated levels of TC but also with an increase in LDL-C [4, 5]. More recent studies have shown that this association is not linear and a steep increase in risk occurs when the levels of LDL-C affect more elevated track levels [6]. In addition, several randomized studies have shown that the control of total cholesterol and LDL-C levels is associated

Table 44.1 Secondary causes of dyslipidemia [9]

↑ Total cholesterol and LDL cholesterol	↑ Triglyceride
Hypothyroidism	Diabetes mellitus, hypothyroidism
Nephrosis	Chronic renal failure
Systemic lupus erythematosus	Obesity
Multiple myeloma	Excessive alcohol intake
Anabolic steroid treatment	Corticosteroid, protease inhibitors
Cholestatic diseases	Thiazide diuretics, β-adrenergic blocking
Protease inhibitors	Orally administered estrogens

with a decreased risk of cardiovascular events in different groups of patients [7, 8].

Even in the presence of normal levels of LDL-C, the individual may experience an increase in the small, dense LDL particles. These particles react more easily in the arterial wall and are more susceptible to oxidation. They are therefore associated with an increased risk of cardiovascular events and may be present in 50% of men with CAD. Their presence is often related to low levels of HDL-C and hypertriglyceridemia, as well as metabolic syndrome (MS) and DM [9].

HDL Cholesterol

Low levels of HDL-C are related to increased cardiovascular risk, as evidenced by the Framingham Heart Study, which showed an increased risk of acute myocardial infarction of about 25% for every 5 mg/dL decrease in HDL-C [10]. Studies such as LIPID, CARE, and TNT have reported that low levels of HDL-C are more powerful predictors of cardiovascular events in patients with LDL-C levels less than 125 than in those with levels higher than 125 mg/dL [11, 12].

On the other hand, HDL-C levels >60 mg/dL have been considered a negative risk factor for CAD, so one risk factor can be subtracted from a patient's overall risk profile. In both sexes, HDL-C levels below 40 mg/dL are an independent risk factor for CVD. However, women tend to have higher

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levels of HDL-C than men, so values >50 mg/dL are considered ideal for females [9].

Triglycerides

Hypertriglyceridemia has also been linked to an increased risk of cardiovascular events, as well as an increased mortality in patients with established CAD [13, 14]. This relationship may be due to the direct effect of hypertriglyceridemia as an association of this condition with some other factors that predispose to atherosclerosis, such as low HDL-C, increased coagulation, insulin resistance, and the presence of small, dense LDL-C particles [15]. Some studies, such as SCRIP, which described the presence of small, dense particles in 90% of individuals with triglyceride levels above 160 mg/dL [16], have found an inverse relationship between triglyceride levels and LDL-C diameter.

An additional test that can be performed in an individual with elevated fasting TG is the determination of postprandial triglyceridemia. Some evidence indicates that the TG-rich lipoproteins produced in the postprandial period are atherogenic and that levels of postprandial TG > 150 mg/dL are an independent risk factor for CAD. Better standardization of this cutoff point is, however, still required [17–20].

Non-HDL Cholesterol

In patients with hypertriglyceridemia, in addition to increased LDL, there is an increase in IDL and VLDL, all atherogenic lipoproteins. Thus, the non-HDL cholesterol estimates the total circulating atherogenic lipoproteins better than LDL-C and also appears to better estimate cardiovascular risk [21, 22], especially in patients with TG between 200 and 500 mg/dL, diabetes, and established cardiovascular disease (CVD) [23, 24]. Non-HDL cholesterol should be determined by calculating the difference between the total cholesterol and HDL-C in patients with triglyceride levels greater than 200 mg/dL. The non-HDL cholesterol target is 30 mg/dL higher than established LDL-C risk levels [25].

Additional Tests

Lipoprotein (a)

Lipoprotein (a) corresponds to an LDL-C particle which is found connected to a specific apolipoprotein: apo (a). Serum levels are genetically determined, and the apolipoprotein (a) molecule has an important homology to plasminogen, so there is a competitive effect on the latter. This leads to a prothrombotic effect, thus contributing to atherosclerotic vascular injury [26]. Different studies have shown increased levels of lipoprotein (a) to be an important independent risk factor for coronary artery disease and cerebrovascular disease, especially in Caucasian patients [27, 28].

However, the lack of standardization in the measurement of this lipoprotein limits its use, so its evaluation is not routinely recommended. Nonetheless, its determination could be useful in White patients with CAD and in subjects with a family history of CAD of unknown origin [10].

C-Reactive Protein

C-reactive protein (CRP) is a highly sensitive marker of chronic inflammatory conditions such as atherosclerosis, and its elevation has been associated with increased cardiovascular risk. Its levels can be divided into <1 mg/L (low risk), 1–3 mg/L (intermediate risk), and > 3 mg/L (high risk) [29]. However, the JUPITER study suggested a simpler stratification: CRP <2.0 vs. ≥2.0 [30].

Although some studies have suggested that CRP could be a better predictor of cardiovascular risk than LDL-C [31], larger, more recent studies have shown that the dosage adds little to predictions based on the traditional risk factors [29]. In relation to therapeutic drug monitoring, CRP levels seem to play a more important role since, as demonstrated by a more recent study, the reduction in the risk of coronary events appears to be greater not only when the LDL-C drops below 70 mg/dL but also when CRP has decreased levels in response to treatment (less than 2 mg/L) [32].

The dosage of CRP, however, should not be performed routinely but may be useful in estimates of intermediate risk or in evaluating residual risk in patients with LDL-C < 130 mg/dL [10].

Homocysteine

Elevated levels of homocysteine (>15 μmol/L) have also been associated with increased cardiovascular risk [33, 34]. However, reduction in its levels with the use of folic acid, vitamin B6, and vitamin B12 showed no risk reduction [35]. Homocysteine measurement is not recommended because its benefit is not well established [10].

Apolipoproteins

Serum levels of apolipoprotein B (apoB) reflect the levels of small, dense LDL particles, recognized as atherogenic. Some studies have suggested that the elevation of apoB is equivalent or even superior to LDL-C and non-HDL cholesterol in predicting cardiovascular risk, even in patients

with insulin resistance and DM2 [36–38]. The optimal level of apoB recommended in patients at risk of CAD is below 90 mg/dL, while for individuals with CAD or established diabetes plus other risk factors, the ideal target is <80 mg/dL, and for individuals at extreme risk, the target for apoB is <70 mg/dL [10].

Perhaps even more useful is the assessment of apoB/apolipoprotein AI (apoA-I), as this ratio has been a stronger risk predictor than the LDL-C/HDL-C ratio [39]. The dosage of apoB and apoA-I is indicated in patients with TG >150 mg/dL and HDL-C below 40 mg/dL to assess residual risk, even in those with LDL-C within the target range, including patients with CAD and DM2 [10].

Carotid Intima-Media Thickness and Coronary Calcium Score

The measurement of carotid intima-media thickness (IMT) and the coronary calcium score (CCS) are noninvasive imaging tests and have emerged, in recent years, as markers for CAD.

The CCS is an estimate of the amount of coronary plaques in an individual [40]. A CCS of zero reflects a low likelihood of coronary disease, and the patient is classified as low risk, with an annual event rate of only 0.11% in the asymptomatic individual [41]. This appears to be true even in diabetic patients, as it has already been shown that in these cases, a CCS of zero indicates survival similar to nondiabetic patients also with a CCS of zero, so in these cases, lipid-lowering therapy would not need to be as aggressive or even necessary [42]. However, studies comparing the CCS with the carotid IMT have suggested that the latter, when increased, has proved a better predictor of CAD [43].

These tests, in any case, are not yet recommended in all individuals with dyslipidemia, and their usefulness would probably be greater in those patients initially classified as intermediate risk, in whom they could provide a better explanation of the need for therapy and lipid goals.

In Whom Should Serum Lipids Be Measured?

The lipid profile should be carried out in every adult from the age of 20. In patients without risk factors and an appropriate lipid profile, the test can be repeated every 5 years [4]. From the age of 45 years in men and 55 years in women, this frequency should be increased to one to two times a year, considering the high prevalence (21–49%) of dyslipidemia in this age group as evidenced by some studies [44, 45]. From 70 years of age, annual screening is recommended [11]. In patients with multiple risk factors for CVD, the lipid profile should be repeated more frequently regardless of age group [10].

Screening for dyslipidemia should also be performed in all patients with established coronary artery disease (CAD), diabetes, hypertension, obesity, and family history of primary dyslipidemia [4].

Cardiovascular Risk Assessment

The diagnostic approach to dyslipidemia involves not only the diagnosis but also the assessment of cardiovascular risk to which the individual is exposed. This risk stratification is essential to initiate the most appropriate treatment for the patient. After all, not all patients with abnormal lipid levels are candidates for drug therapy, and both the indication for and the aggressiveness of therapy to be instituted should be based on the individual risk of developing CVD. The risk that an individual has of a coronary event in 10 years (death or MI) can be classified as high (greater than 20%), intermediate (between 10% and 20%), and low (less than 10%) [46].

In November 2018, the American College of Cardiology (ACC) and the American Heart Association (AHA) [4] issued new guidelines on controlling blood cholesterol as shown in Figs. 44.1 and 44.2. There are also new ACVD risk enhancer lists in order to refine risk categorization (Tables 44.2 and 44.3).

The 10-year ASCVD risk was estimated using the Cohort Equations developed by the Risk Assessment Working Group. The necessary parameters included gender, age, race, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic BP, use of antihypertensive medication, diabetes, and smoking [4]. The parameters have not been applied to individuals under the age of 40 or older than 75 years.

The first step in estimating risk is to identify the presence of current manifestations of atherosclerotic disease (CAD, cerebrovascular, and peripheral vascular disease). Likewise, attention must be paid to the occurrence of the atherosclerotic disease equivalents such as diabetes type 1 or 2 and abdominal aortic aneurysm, which would put the individual in the category of high risk at least [46]. Subsequently, the presence of major risk factors for atherosclerotic disease (Table 44.4) and ERF should be evaluated [10]. The ERF is most useful in cases initially classified as intermediate risk.

The Framingham Study, conducted in the USA, provided sufficient epidemiological evidence to permit risk evaluation of CAD in 10 years in an individual, using scores and cardiovascular risk tables. The FRS considers blood pressure, sex, age, smoking status, and TC and HDL-C levels [47]. If the risk is classified as intermediate, there is a need to consider other factors associated with cardiovascular risk to minimize the possibility of under- or overestimating the risk.
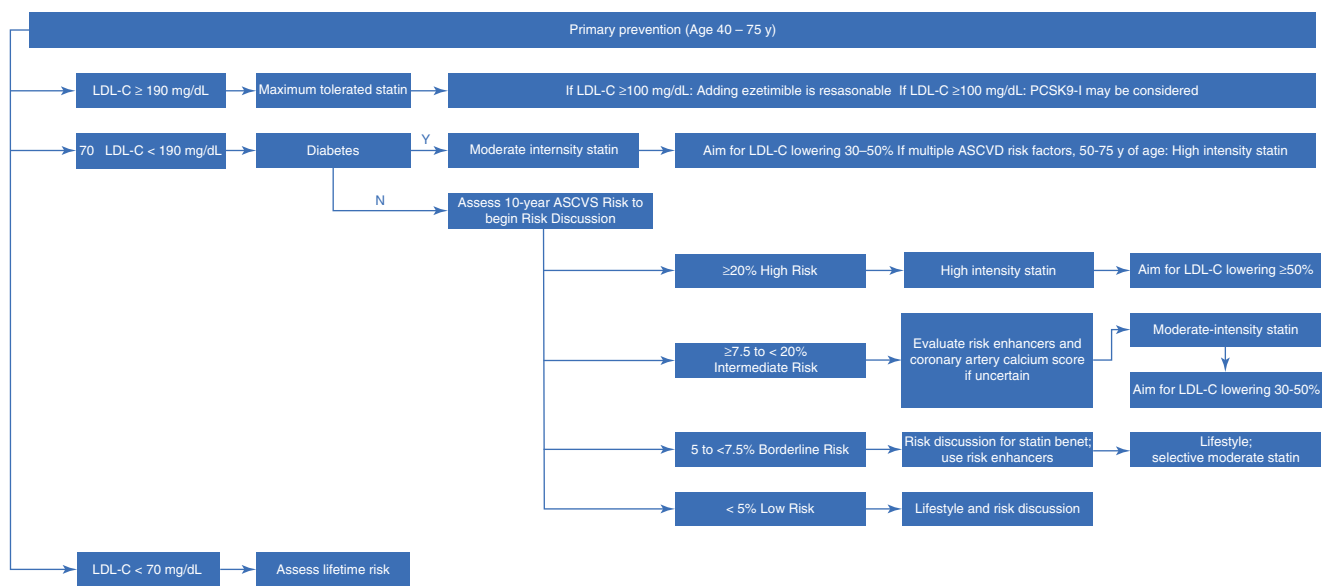
Fig. 44.1 Overview of primary ASCVD prevention [9] – according to the ACC Guidelines, 2018
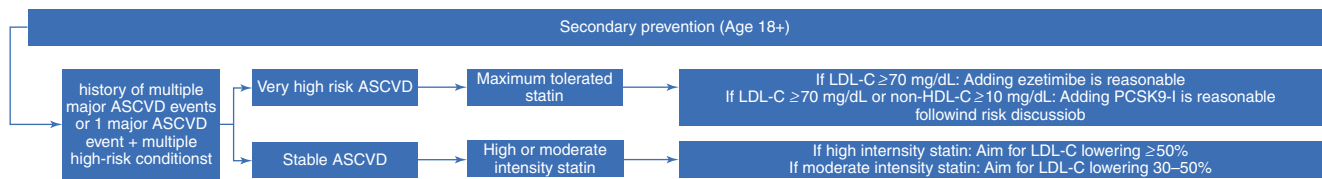

Fig. 44.2 Overview of secondary ASCVD prevention [9] – according to the ACC Guidelines, 2018

Table 44.2 ASCVD risk enhancers [9]

Family history of premature ASCVD
Persistently elevated LDL-C ≥ 160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity factors (e.g., south Asian ancestry)
Lipid/biomarkers:
Persistently elevated triglycerides (≥175 mg/mL)
In selected individuals if measured:
Hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or > 125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9

According to the ACC Guidelines, 2018

Table 44.3 Diabetes-specific risk enhancers that are independent of other risk factors in diabetes [9]

Long duration (≥10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
Albuminuria ≥30 μg albumin/mg creatinine
eGFR <0.9
Retinopathy
Neuropathy
ABI <0.9

According to the ACC Guidelines, 2018

Table 44.4 Major coronary artery disease risk factors

Advancing age
High total serum cholesterol level
High non-HDL-C
High LDL-C
Low HDL-C
Diabetes mellitus
Hypertension
Chronic kidney disease
Cigarette smoking
Family history of coronary artery disease[a]

[a]Definite myocardial infarction or sudden death before the age of 55 years in father or other male first-degree relative or before the age of 65 years in mother or other female first-degree relative

Thus, the classical risk factors do not appear sufficient to predict all risk, and in this context, the role of the emerging risk factors (C-reactive protein, lipoprotein (a), apoB/apoA-I ratio, microalbuminuria, homocysteine, left ventricular hypertrophy, the thickness of the carotid artery intima-media complex (IMT), CCS) has been gaining strength.

Treatment

Treatment Goals

The reduction in LDL-C levels, especially in individuals at risk of CVD, remains the main therapeutic target in dyslipidemia. Table 44.5 shows the goals for each risk category, and drug treatment associated with lifestyle modification (LSM) in patients at high, very high, or extreme risk should be initiated immediately, having statins as first-choice drugs. Even if the initial target is not reached, the reduction of at least 30–40% in the initial LDL-C levels has shown a decrease in cardiovascular risk [4]. However, a single LDL-C target, in general, is not sufficient to reduce all cardiovascular risk [10].

The goal for TG is <150 mg/dL. However, the exact level at which TG starts to confer risk is unknown. Endocrine Society Guidelines suggested a new TG classification: mild (150–199 mg/dL), moderate (200–999 mg/

dL), severe (1000–1999 mg/dL), and very severe (≥2000 mg/dL) hypertriglyceridemia. Lifestyle changes (LSC) should be started in the presence of hypertriglyceridemia and drug therapy in cases in which LSC failed. Only in those individuals with TG >1000 mg/dL, drug therapy should be started immediately, preferably a fibrate, to reduce the risk of pancreatitis [48, 49].

For HDL-C, in the presence of associated hypertriglyceridemia or other risk factors, a target at least >40 mg/dL should be pursued. The major question occurs in individuals with isolated lowering of HDL-C in the absence of CVD and/or risk factors due to the absence of clinical trials supporting the benefit of increasing this lipid in this group of patients [10]. However, once it has been decided to raise their HDL-C levels, regular physical activity should be instituted, and smoking cessation should also be encouraged, as these measures are known to be effective in increasing HDL-C. If a drug is required, nicotinic acid remains the most effective option.

Table 44.6 shows lipid target of the patient with coronary artery disease (CAD) with the goal of total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, and apoB.

Lifestyle Change (LSC)

All patients with dyslipidemia should initiate LSC, based on diet reorientation (low in saturated fat and high in fiber), regular physical activity, and smoking cessation. This therapeutic approach corresponds to the first option in patients at low risk, in which pharmacological treatment should only be initiated 6 months after an attempt to normalize lipemia with LSC, and in those at intermediate risk, in whom the start of lipid-lowering medication should be considered only 3 months later [4].

The type of fat intake is fundamental to the management of dyslipidemia. The saturated fat intake should be limited (<7% of total calories), and trans fats should also be avoided, since they are associated with elevated LDL-C, decreased HDL-C,

Table 44.5 Coronary artery disease risk categories and low-density lipoprotein treatment goals [15]

Risk category	Risk factors/10-year risk[a]	LDL-C treatment goal
Extreme risk	Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dl Established clinical cardiovascular disease in patients with DM, CKD ¾, or HeFH History of premature ASCVD (<55 male, <65 female)	<55 mg/dl
Very high risk	Established or recent hospitalization for ACS, coronary, carotid, or peripheral vascular disease, 10-year risk >20% Diabetes or CKD ¾ with one or more risk factor(s) HeFH	<70 mg/dL
High risk	≥2 risk factors and 10-year risk 10–20% Diabetes or CKD ¾ with no other risk factors	<100 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10%	<100 mg/dL
Low risk	0 factor risk	<130 mg/dL

According to the AACE Guidelines, 2017

Abbreviations: *ACS* acute coronary syndrome, *ASCVD* atherosclerotic cardiovascular disease, *CKD* chronic kidney disease, *DM* diabetes mellitus, *HDL-C* high-density lipoprotein cholesterol, *HeFH* heterozygous familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol

[a]Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥ 140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dl), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage ¾, evidence of coronary artery calcification, and age (men ≥45; women ≥55 years). Subtract one risk factor if the person has high HDL-C

Table 44.6 Lipid target of the patient with coronary artery disease (CAD) [15]

Total cholesterol (mg/dL)	<200
HDL cholesterol (mg/dL)	As high as possible, at least >40 in both sexes
LDL cholesterol (mg/dL)	<100, <70 (all high-risk patients)
Triglyceride (mg/dL)	<150
apoB, mg/dL	<90 (patients at risk of CAD, including those with diabetes)
Established diabetes	<80 (patients with CAD or plus ≥1 additional risk factor

According to the AACE Guidelines, 2017

and increased cardiovascular risk. Unsaturated fatty acids should make up 10–20% of caloric intake. Polyunsaturated fatty acids are represented by omega 3 (found in vegetable oils and cold-water fish), the benefits associated with CVD; omega 6 (found in soybean, corn, and sunflower oil), associated with reduction in LDL-C; and TG, although they can also decrease HDL-C. Monounsaturated fatty acids reduce LDL-C, but with no effect on the HDL-C [4].

Considering the positive effect of omega 3 on the lipid profile and cardiovascular risk, its supplementation (at least 2–4° g of fish oil a day) has been recommended for patients with CVD [10].

Statins

Statins represent the drugs of choice in hypercholesterolemia treatment. They act by inhibiting HMG-CoA reductase, an enzyme involved in the synthesis of endogenous cholesterol. Since the intracellular levels of cholesterol decrease with the use of the drug, there is an increase in LDL-C receptors in cell membranes, enhancing LDL-C clearance [50].

The decrease in LDL-C serum levels can range from 25% to 55%, depending on the drug used. There may also be a fall in triglyceride levels of 15–25% and an increase in HDL-C of around 2–10% [51].

Simvastatin (dose of 20–80 mg per day) and pravastatin (dose of 20–40 mg a day) must be taken at night. However, atorvastatin (dose of 10–80 mg per day) and rosuvastatin (dose of 10–40 mg per day), more potent in reducing LDL-C, have a longer half-life and can therefore be administered at any time of the day. Rosuvastatin is the most effective drug for raising HDL-C levels [51].

On the whole, it is not recommended to exceed the dose of 40 mg of simvastatin and of 20 mg of atorvastatin and rosuvastatin, because larger doses will contribute little to the decrease in LDL-C, and there is an increased risk of side effects. Thus, in the absence of response, the most sensible thing to do is to introduce another class of drug.

In general, statins are well tolerated, although the following may occur: hepatotoxicity in 1.4% of cases (a > threefold increase in transaminases indicates a dosage reduction or discontinuation of the drug) and myalgia and CPK elevation to 15.4% and 0.9% of cases, respectively (in cases of a > ten-fold rise in CPK or persistence of muscle symptoms, the drug should be discontinued). Rhabdomyolysis is rare, occurring in 0.2% of individuals, and its risk increases in cases of association of drugs with fibrates (except fenofibrate). Among the contraindications to statin therapy, the following may be mentioned: pregnancy, breastfeeding, and acute liver diseases (in cases of renal failure and chronic liver disease, the drug can be used) [52].

Recent clinical trials suggested that the statins may increase the incidence of diabetes. A meta-analysis of 13 randomized statin trials of over 91,000 patients suggested that these drugs compared with placebo lead to a 9% increased relative risk for the development of diabetes [53]. However, the benefit of cardiovascular risk reduction by statin therapy seems to exceed the risk of diabetes. A risk–benefit analysis showed that the risk of diabetes was increased, but the statins were favorable in high-risk and secondary prevention populations [54]. A recent analysis from the JUPITER (a primary prevention trial) evaluated 17,603 subjects without previous CVD or diabetes and showed that, in subjects with one or more diabetes risk factors, the statin therapy was associated with a 39% reduction in the primary endpoint (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularization, or cardiovascular death) and a 28% increase in diabetes (a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed) [55].

The major advantage of statins is their positive effect on cardiovascular disease, constituting a class of drug with strong evidence of reducing overall mortality when used in both primary and secondary prevention.

Benefits in Secondary Prevention

Several studies have reported the benefits of statin therapy in patients with proven CAD, regardless of the presence of dyslipidemia.

The 4S study compared simvastatin (up to a maximum dose of 40 mg) with placebo, and, in addition to reporting a decrease in coronary events and CAD mortality, it was the first study to show a decrease in overall mortality [8]. CARE, in turn, compared placebo with pravastatin, also showing a reduction in the incidence of coronary events and deaths from CAD [56]. HPS (UK Heart Protection Study), comparing simvastatin 40 mg with placebo, showed a reduction of about one-third in the risk of myocardial infarction (MI), stroke, and myocardial revascularization, in addition to its beneficial effect on overall mortality and CAD, irrespective of baseline cholesterol (33% had LDL-C lower than 116 mg/dL). The benefit in patients with low LDL-C levels reflects a possible additional effect of statins in addition to that related to the reduction in cholesterol levels [57].

In relation to the statin dose, there is no justification for the use of aggressive therapy in stable patients. CARDS, for instance, demonstrated that the use of atorvastatin at a dose of 10 mg, in type 2 diabetics, was able to reduce the risk of cardiovascular events by 35% [58]. Also, even though TNT has shown that 80 mg of atorvastatin has led to an additional reduction in events when compared to a 10-mg dose, there

was a higher incidence of adverse effects with the higher dose [13]. Furthermore, a recent meta-analysis of data from more than 30,000 patients without DM showed that intensive therapy was associated with an increased occurrence of new cases of DM [59].

Aggressive treatment, however, has proven its benefits in patients with acute coronary syndrome (ACS). In this case, the drug should be started even prior to discharge from the hospital stay and in high doses, as shown by studies PROVE-IT and MIRACL, demonstrating the advantage of an 80-mg dose of atorvastatin compared to a less aggressive therapy (pravastatin at a dose of 40 mg) [60, 61]. The absence of similar results using an 80-mg dose of simvastatin in ACS, shown by the A to Z study, suggested that in patients with high levels of inflammation, statins are important because of their pleiotropic effects [62]. Thus, an aggressive treatment is justified only for ACS cases, and atorvastatin at a dose of 80 mg should be the drug of choice in this situation.

Beneficial Effects on Atheromatous Plaque

Both REVERSAL and ASTEROID have studied stable coronary patients accompanied with intracoronary ultrasound and showed that the use of 80 mg of atorvastatin led to plaque stabilization (REVERSAL) and that rosuvastatin induced the regression of atheroma (ASTEROID) [63, 64]. METEOR, in turn, studied patients at low risk (primary prevention), showing that there was progression of carotid IMT in individuals who used the placebo compared with those on rosuvastatin 40 mg for 2 years [65].

A recent study compared rosuvastatin and atorvastatin at maximum doses and demonstrated a similar effect on atheroma volume reduction, despite the greater effects of rosuvastatin on LDL-C and HDL-C [66].

Benefits of Primary Prevention

WOSCOPS was a primary prevention study in middle-aged men which showed a reduction in coronary events and mortality in this group of patients with the use of pravastatin 40 mg/day [67]. The same was observed for the AFCAPS/TexCAPS (with lovastatin) and ASCOT-LLA (with atorvastatin 10 mg), both with the added advantage of having also evaluated women and having included patients with cholesterol levels closer to "normal" [9, 68]. More recently, JUPITER compared the use of rosuvastatin with placebo in patients with LDL-C < 130 mg/dL, but with CRP ≥2.0 mg/L, being discontinued owing to the evident reduction in cardiovascular morbidity and mortality in the statin group [30].

Although there is evidence of benefits of primary prevention treatment, not all patients should be treated, so the cost–benefit should be considered (4S estimated the cost per life saved per year for secondary prevention of about US$ 7500, whereas WOSCOPS estimated a cost of US$ 27,000 for primary prevention) [8, 67]. Treatment should therefore be reserved for those patients with a higher CAD risk, considering the LDL-C levels and associated risk factors.

Fibrates

Fibrates are the drugs of choice in hypertriglyceridemia treatment and reduce TG by 20–35%, but they also have an effect on HDL-C (elevation of 6–18%) and on LDL-C (variable effect, reducing or even increasing its levels). They act via activation of peroxisome proliferator-activated receptor alpha (PPAR-alpha), leading to the activation of lipoprotein lipase (LPL) (responsible for the hydrolysis and removal of plasma triglycerides), reduced VLDL synthesis in the liver, and increased synthesis of apoA-I, contributing an increase in HDL-C [10].

Among the main fibrates, the following deserve special mention: gemfibrozil (600–1200 mg/day), fenofibrate (200 mg/day in its micronized form), and ciprofibrate (100 mg/day). They can cause fatigue, gallstones, gastrointestinal disturbances, rash, headache, and, more rarely, elevated transaminases and CPK. Rhabdomyolysis has been described when statins are associated with gemfibrozil, which therefore should not be used in this type of combination therapy. Fibrates should be avoided in cases of renal failure [69].

Although there is a decrease in lipid levels with the use of fibrates, they have not been shown, in the long term, to produce the same clinical results as statins. Some studies, however, such as the Helsinki Heart Study and BIP [70, 71], have demonstrated a reduction in coronary events. The FIELD study involving 9795 subjects with DM2 showed that micronized fenofibrate decreased coronary events but increased coronary mortality in all cases. However, the results were not significant [72].

Niacin

Niacin can be used instead of fibrates and statins (or in association with them) in the treatment of hypercholesterolemia, hypertriglyceridemia, or mixed hyperlipidemia, since it reduces the hepatic synthesis of VLDL and, consequently, its LDL-C metabolite. But the action that makes it unique among oral lipid-lowering drugs is its inhibitory effect on the transport of cholesterol from HDL-C to VLDL and on the clearance of HDL-c, thereby increasing the plasma levels of this lipoprotein [73].

Niacin is, therefore, the most effective drug for treating patients with low levels of HDL-C without other lipid

abnormalities and can increase HDL-C by 30%. To exert its effect on HDL-C, in general, doses of 1–1.5 g/day are necessary. Higher doses (3 g/day) are more effective on LDL-C and triglycerides as well as on lipoprotein (a), which can be reduced by 35% [74].

There are three types of drug preparation, according to the speed of its release: fast (often causes flushing), intermediate (causes less flushing), and slow (the main limitation of which is hepatotoxicity). Of these three, the second is the option of choice and should be initiated at a dose of 500 mg, with a gradual increase (every month) to 1–2 g/day as a single dose taken immediately after dinner.

The biggest question now about this drug is whether there would be some benefit from its combination with statins in the prevention of cardiovascular events. Studies evaluating the use of statins plus niacin in CAD patients showed that this association decreased mortality and cardiovascular events, suggesting an additional protection when therapy for an increase in HDL-C is instituted [75]. The ARBITER2 study, in turn, showed a tendency of reduction in carotid IMT progression with the use of niacin in coronary patients already on statins, suggesting a beneficial effect of the drug on the anatomical progression of atherosclerosis [76].

However, the AIM-HIGH study failed to show any additional benefits of adding niacin to statin therapy in patients with a mean LDL-C of 71 mg/dL and suggested a higher occurrence of stroke in individuals treated with niacin [77]. This study, therefore, increased doubts about the advantage of the combination of statin and niacin, so one must await the results of HPS2-THRIVE, currently in progress, for clarification of this issue.

Among the side effects of drugs, the main one is flushing, mediated by the action of prostaglandin D and often responsible for the discontinuation of therapy. This effect can be prevented with the use of aspirin 325 mg 30 min before drug intake. More recently, laropiprant, a prostaglandin receptor antagonist, has been used in combination with niacin, significantly reducing the incidence of flushing, as well as its intensity, without changing the lipid effect [78].

A negative effect of the drug on glucose metabolism with increased insulin resistance and elevated blood glucose has also been demonstrated. However, these changes have been shown to be transient and can be effectively controlled with adjustments to the treatment regime with oral antidiabetic agents or insulin in individuals with DM2 [10, 79].

Ezetimibe

Ezetimibe is used at a dose of 10 mg/day in the treatment of hypercholesterolemia, reducing intestinal cholesterol absorption by inhibiting the cholesterol transport protein present in the brush border of the enterocyte without interfering with the absorption of fat-soluble vitamins and triglycerides [10].

Although its use alone can reduce LDL-C by about 17%, its main therapeutic use is in combination with statins in an attempt to avoid the need to increase the dose of the latter in unresponsive cases [80]. Ezetimibe can produce a further 14% reduction in LDL-C levels when added to the isolated use of statins and has the advantage of being well tolerated [81]. Additional benefits have also been demonstrated by its association with atorvastatin and rosuvastatin [10].

However, there is still no conclusive data showing the benefits of this drug in reducing cardiovascular events. ENHANCE, involving 720 patients with familial heterozygous hypercholesterolemia, showed no significant difference in the progression of carotid IMT between the group treated with statin alone and those associated with ezetimibe, despite the more significant reduction in LDL-C in the second group [82]. On the other hand, the SHARP study showed a reduced incidence of cardiovascular events in subjects with chronic renal failure using simvastatin 20 mg/day plus ezetimibe 10 mg/day [83]. In addition, preliminary data from SEAS have shown a 20% reduction in ischemic events by 20% in the group using simvastatin 40 mg/day plus ezetimibe 10 mg/day when compared to the placebo group [84].

The IMPROVE-IT study showed a significant reduction of the primary endpoint (composed of cardiovascular death, MI, unstable angina requiring rehospitalization, coronary revascularization, or stroke) in patients with acute coronary syndrome (ACS) prior to the use of ezetimibe/simvastatin compared with only simvastatin [85].

Bile Acid Sequestrants

Colestipol, colesevelam, and cholestyramine act by inhibiting the absorption of bile salts, which, as a result, reduces cholesterol absorption. They are therefore options in the treatment of hypercholesterolemia, particularly in combination with statins, and can decrease LDL-C by 15–25%. They can also raise HDL-C slightly (4–8%) but should be avoided in hypertriglyceridemia, since they may increase TG levels [10]. One advantage of the use of colesevelam is the reduction of blood glucose levels, and it can serve as an adjuvant therapy for DM2 [85].

Its main drawback is the impaired tolerance resulting from its gastrointestinal effects (nausea, meteorism, constipation), leading eventually to high rates of noncompliance. Colesevelam, however, seems to be better tolerated [10].

Combination Therapy

In many situations, the isolated use of only a single lipid-lowering agent is not sufficient to achieve lipid targets, and it is preferable to combine two different classes of drug rather than increase the dose of the medication in use. After all, in

the treatment of hypercholesterolemia, for example, an increase in dose can only further reduce by 6% in the amount of LDL-C, in addition to which it considerably increased the risk of side effects such as increased liver transaminases and muscle injury.

Combination therapy is therefore usually recommended when (1) monotherapy fails to reduce cholesterol levels to the desired target; (2) increasing the dose of medication in use is accompanied by adverse events; or (3) the patient has a mixed dyslipidemia (elevated LDL-C and TG with HDL-C reduction).

In the first case, three types of combination can be considered: statin + ezetimibe, especially after the positive results presented by SHARP, although this combination needs to be better evaluated in future studies [84], statin + bile acid sequestrants, and statin + niacin, a combination whose cardiovascular benefit remains inconclusive [10].

In the presence of side effects with the increase of statin doses, the best matches would be combinations with ezetimibe or bile acid sequestrant. In cases of mixed hyperlipidemia, the combination with fibrates, avoiding gemfibrozil, or with niacin is the best option [10].

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 inhibitors have been approved by regulatory agencies for the treatment of individuals with inadequate low-density lipoprotein (LDL-C) levels. They are able to reduce LDL-C by up to 60% in patients with statin therapy. In addition, they produce clinical benefits, such as reductions in stroke rates or myocardial infarction. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme (serine protease) encoded by the PCSK9 gene, which is produced predominantly in the liver [47, 86, 87]. PCSK9 binds to the low-density lipoprotein (LDL-R) receptor on the surface of hepatocytes, leading to LDL-R degradation and higher plasma LDL-C (LDL-C) levels [88, 89]. Alirocumab and evolocumab are human monoclonal antibodies that bind to free PCSK9 plasma, promoting the degradation of this enzyme [4–7]. As a result, less free PCSK9 is available in plasma to bind to LDL-R. This results in a greater fraction of the recycling of LDL-R to the surface of hepatocytes. As a direct consequence, the liver has the ability to remove more LDL-C from the circulation, resulting in lower plasma LDL-C levels.

Another potential method of interference with PCSK9 is to block its synthesis, which is dependent on messenger RNA. Other mechanisms, in addition to the reduction of LDL-C, by which PCSK9 antibodies may improve cardiovascular outcomes were postulated [9]. These include a reduction in inflammation and oxidative stress in the atherosclerotic plaques and inhibition of the prothrombotic path-ways. They are indicated for patients with acute coronary syndrome.

Circulating levels of PCSK9 are upregulated in the presence of statins, suggesting that inhibition of the PCSK9 pathway may complement the LDL-C lowering effect of statins.

The recommended dose of evolocumab in primary or mixed dyslipidemia is 140 mg subcutaneously every 2 weeks or 420 mg once monthly; both doses are clinically equivalent [28, 40, 68].

The initial dose of alirocumab is 75 mg subcutaneously once every 2 weeks. The maintenance dose is 75–150 mg subcutaneously once every 2 weeks [12]. Plasma levels of low-density lipoprotein (LDL-C) cholesterol should be measured within 4–8 weeks of starting or changing the dose, and an increase in dosage to 150 mg may be initiated if LDL-C reduction is inadequate.

An alternative dose of alirocumab for patients who prefer a less frequent dosage is 300 mg once every 4 weeks. For patients receiving this scheduled dose, LDL-C should be measured immediately prior to the next scheduled dose. If LDL-C reduction is inadequate, 150 mg every 2 weeks can be given by starting the new dose on the next scheduled dosing date. LDL-C should be measured within 4–8 weeks.

The ODYSSEY OUTCOMES studies with alirocumab and FOURIER with evolocumab showed similar results with low rates of cardiovascular events among patients who were treated with PCSK9 inhibitors [90].

Future Therapies

New pharmacological interventions may help, in a near future, to decrease the residual cardiovascular risk, which is still significant in patients on statin therapy [89]. Lomitapide, a microsomal triglyceride transfer protein inhibitor which blocks the secretion of apoB by the liver, and mipomersen, an antisense nucleotide which leads to apoB RNA degradation, are approved for the treatment of homozygous familial hypercholesterolemia (HoFH). Their effects on LDL-C reduction are from 25% to 60%. The frequent finding of fat liver disease with these drugs limits their use at this point.

In the REVEAL study, the use of anacetrapib (a cholesterol ester transfer protein) resulted in a lower incidence of coronary events (comprised of coronary death, myocardial infarction, or coronary revascularization) in patients with atherosclerotic vascular disease who remained at high risk, despite effective statin-based treatment [91, 92]. Inclisiran is a synthetic small interfering RNA with a prolonged action that selectively suppresses hepatic production of PCSK9. According to the findings of the ORION-1 phase II trial led to a sustained reduction in plasma cholesterol of low-density lipoproteins [93, 94].

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