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 [6] 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 [7]. In these cases, direct LDL-C can be performed through specific tests with excellent precision and accuracy [8].

Table 40.1 shows the values for the different lipids according to NCEP/ATP [9]. On finding a patient with a changed lipid profile, one must first determine the cause of this change, which means looking for a secondary cause (Table 40.2) and asking about family history in the search for a genetic cause (primary dyslipidemia).

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 [10, 11]. 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 [12]. In addition, several randomized studies have shown that the control of total cholesterol and LDL-C levels is associated with a decreased risk of cardiovascular events in different groups of patients [13, 14].

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 [15].

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

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Table 40.1 ATP III classification of total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride

Total cholesterol (mg/dL)	
< 200	Desirable
200-239	Boderline high
≥240	High
HDL cholesterol (mg/dL)	
<40	Low
>60	High
LDL cholesterol (mg/dL)	
<100	Optimal
100–129	Near optimal
130–159	Boderline high
160–189	High
≥190	Very high
Triglyceride (mg/dL)	
<150	Normal
150–199	Boderline high
200–499	High
≥500	Very high

Table 40.2 Secondary causes of dyslipidemia

↑ 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
Cholostatic diseases	Thiazide diuretics, β-adrenergic blocking
Protease inhibitors	Orally administered estrogens

HDL-C [16]. 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 [17, 18].

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 [15]. In both sexes HDL-C levels below 40 mg/dL are an independent risk factor for CVD. However, women tend to have higher levels of HDL-C than men, so values >50 mg/dL are considered ideal for females [15].

Triglycerides

Hypertriglyceridemia has also been linked to an increased risk of cardiovascular events, as well as an increased mortality in patients with established CAD [19, 20]. 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 [21]. Some studies, such as SCRIP, which described the presence of small, dense particles in 90 % of individuals with triglyceride levels above 160 mg/dL [22], 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 [23–26].

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 [27, 28], especially in patients with TG between 200 and 500 mg/dL, diabetes, and established cardiovascular disease (CVD) [29, 30]. 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 [9].

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 [31]. 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 [32, 33].

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 [15].

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) [34]. However, the JUPITER study recently suggested a simpler stratification: CRP <2.0 vs. ≥2.0 [35].

Although some studies have suggested that CRP could be a better predictor of cardiovascular risk better than LDL-C [36], larger, more recent studies have shown that the dosage adds little to predictions based on the traditional risk factors [34]. In relation to therapeutic drug monitoring, CRP levels seem to play a more important role since, as demonstrated by a recent study, the reduction in 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) [37].

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 [15].

Homocysteine

Elevated levels of homocysteine (>15 μmol/L) have also been associated with increased cardiovascular risk [38, 39]. However, reduction in its levels with the use of folic acid, vitamin B6, and vitamin B12 showed no risk reduction [40]. Routine screening is therefore not recommended, but in patients stratified as intermediate risk by the Framingham Risk Score (FRS) (see below), its determination can be useful in modifying the rating for high risk [15].

Apolipoproteins

Serum levels of apolipoprotein B (apo B) 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 [41–43]. The optimal level of apoB recommended in patients at risk of CAD is below than 90 mg/dL [15].

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 [44]. 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 [15].

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 [45]. 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 [46]. 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 [47]. However, studies comparing the CCS with the carotid IMT have suggested that the latter, when increased, has proved a better predictor of CAD [48].

These tests, in any case, are not yet recommended in all individuals with dyslipidemia and

Table 40.3 Coronary artery disease risk categories and low-density lipoprotein treatment goals [15]

Risk category	Risk factors/10-year risk[a]	LDL-C treatment goal
Very high risk	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus 1 or more additional risk factor(s)	<70 mg/dL
High risk	≥2 risk factors and 10-year risk >20 % or CHD risk equivalents[b], including diabetes with no other risk factors	<100 mg/dL
Moderately high risk	≥2 risk factors and 10-year risk 10–20 %	<130 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10 %	<130 mg/dL
Low risk	≤1 factor risk	<160 mg/dL

[a]Framingham risk scoring is applied to determine 10-year risk
[b]Diabetes and clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease)

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 [9]. 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 [49, 50]. From 70 years of age, annual screening is recommended [16]. In patients with multiple risk factors for CVD, the lipid profile should be repeated more frequently regardless of age group [15].

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 [9].

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 %) [51].

In an attempt to establish goals for lipid control-based risk, the National Cholesterol Education Program (NCEP) has, since 1988, been developing guidelines, the main objective of which is the reduction in LDL-C. Its latest version was published in 2001 [9], being updated in 2004 [52] through the Adult Treatment Panel III (ATPIII), and classifies coronary risk according to the presence of risk factors and estimates of the FRS: low, moderate, moderately high, and high risk. More recently, patients with recent coronary, carotid, or peripheral vascular disease or with type 2 DM associated with at least one risk factor, in which the LDL-C treatment goal is less than 70 mg/dL [52], are considered to be at very high risk (risk > 40 % in 10 years). Based on this, the most recent guideline published by the American Association of Clinical Endocrinologists stratifies the subject into five different categories of risk [15] (Table 40.3).

Table 40.4 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
Cigarette smoking
Family history of coronary artery disease[a]

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

The first step in estimating risk is to identify the presence of current manifestations of atherosclerotic disease (CAD, cerebrovascula, 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 [51]. Subsequently, the presence of major risk factors for atherosclerotic disease (Table 40.4) and ERF should be evaluated [15]. 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 [2]. 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.

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/apoAI 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 40.4 shows the goals for each risk category and drug treatment associated with lifestyle modification (LSM) in patients at high or very high 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 [9]. However, a single LDL-C target, in general, is not sufficient to reduce all cardiovascular risk [15].

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 hypertriglyceridemia (150–199 mg/dL); moderate hypertriglyceridemia (200–999 mg/dL); severe (1,000–1,999 mg/dL); and very severe (≥2,000 mg/dL) hypertriglyceridemia [53]. 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>1,000 mg/dL, drug therapy should be started immediately, preferably a fibrate, to reduce the risk of pancreatitis [53].

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 [15]. 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.

Lifestyle Change

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 [9].

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, 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 [9].

Considering the positive effect of omega 3 on the lipid profile and cardiovascular risk, its supplementation (at least 1 g of fish oil a day) has been recommended for patients with CVD [15].

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 [54].

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 % [55].

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 [55].

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 of 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 >3-fold 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 >10-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) [56].

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 leads to a 9 % increased relative risk for the development of diabetes [57]. 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 [58]. 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) [59].

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 [13]. CARE, in turn, compared placebo with pravastatin, also showing a reduction in the incidence of coronary events and deaths from CAD [60]. 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 [61].

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 % [62]. 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 [18]. 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 [63].

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) [64, 65]. 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 [66]. 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) [67, 68]. 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 [69].

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 [70].

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 [71]. 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" [14, 72]. 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 [35].

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$ 7,500, whereas WOSCOPS estimated a cost of US$ 27,000 for primary prevention) [13, 71]. 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 apoAI, contributing an increase in HDL-C [15].

Among the main fibrates, the following deserve special mention: gemfibrozil (600–1,200 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 [73].

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 [74, 75], have demonstrated a reduction in coronary events. The FIELD study involving 9,795 subjects with DM2 showed that micronized fenofibrate decreased coronary events, but increased coronary mortality in all cases. However, the results were not significant [76].

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 [77].

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 % [78].

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 [79]. 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 [80].

However, the more recent AIM-HIGHT 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 [81]. 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 [82].

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 [15, 83].

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 [15].

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 [84]. 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 [85]. Additional benefits have also been demonstrated by its association with atorvastatin and rosuvastatin [15].

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 [86]. 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 [87]. 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 [88]. More conclusive results are expected with the completion of IMPROVE-IT in 2013.

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 [15]. One advantage of the use of colesevelam is the reduction of blood glucose levels and it can serve as an adjuvant therapy for DM2 [89].

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 [15].

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 [15].

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 [15].

Future therapies

New phamacological interventions may help, in a near future, to decrease the residual cardiovascular risk which is still significant in patients on statin therapy [90]. Lomitapide, a microssomal triglyceride transfer protein inhibitor which blocks the secretion of APO-B by the liver, and mipomersen, an antisense nucleotide which leads to Apo B *RNA* degradation, are aproved for the treatment of homozygous familial hypercolesterolemia (HoFH). Their effects on LDL-C reduction are from 25–60 %. The frequent finding of fat liver disease with these drugs limits their use at this point. Another class of drugs that are in phase III trials, targets the proprotein convertase subtilisin/kexin type 9 (PCSK9, a protein secreted by the hepatocyte that regulates the surface expression of LDL receptors by targeting them for lysosomal degradation. Two monoclonal antibodies to PCSK9 are in clinical trial development and their LDL-C lowering effects are around 70 % in patients on background of statins. Ongoing studies with two CETP (cholesterol esters transfer protein) inhibitors (anacetrapib and evacetrapib) will provide evidence regarding cardiovascular risk reduction when targeting HDL-C. These compounds can raise HDL-C by 80–100 % in patients on background of statins.

References

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837–47.
2. Wilson PW. Established risk factors and coronary artery disease: the Framingham Study. Am J Hypertens. 1994;7(7 Pt 2):7S–12.
3. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation. 1998; 97(10):946–52.
4. Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med. 2005;353(1):46–57.
5. Holvoet P, Collen D, Van de Werf F. Malondialdehyde-modified LDL as a marker of acute coronary syndromes. JAMA. 1999;281(18):1718–21.
6. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499.
7. Faas FH, Earleywine A, Smith G, Simmons DL. How should low-density lipoprotein cholesterol concentration be determined? J Fam Pract. 2002;51(11):972–5.
8. Nauck M, Warnick GR, Rifai N. Methods for measurement of LDL-cholesterol: a critical assessment of

direct measurement by homogeneus assys versus calculation. Clin Chem. 2002;48:236–54.
9. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.
10. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA. 1986;256(20):2823–8.
11. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Tisk Factor Intervention Trial. Multiple Risk Factor Intervation Trial Research Group. Arch Intern Med. 1992;152:1490–500.
12. Pfeffer MA, Sacks FM, Moye LA, et al. Influence of baseline lipids on effectiveness of pravastatin in the CARE Trial. Cholesterol And Recurrent Events. J Am Coll Cadiol. 1999;33:125–30.
13. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344:1383–9.
14. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled tria. Lancet. 2003;361(9364):1149–58.
15. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, Shepherd MD, Seibel JA, Kreisberg R, Goldberg R, AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012;18(1):1–78.
16. Rosenson RS. Low HDL-C: a secondary target of dyslipidemia therapy. Am J Med. 2005;118(10): 1067–77.
17. Sacks FM, Tonkin AM, Craven T, Pfeffer MA, Shepherd J, Keech A, et al. Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors. Circulation. 2002;105(12):1424–8.
18. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425–35.
19. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450–8.
20. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298(3):299–308.
21. Miller BD, Alderman EL, Haskell WL, Fair JM, Krauss RM. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. Circulation. 1996;94(9):2146–53.
22. Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, Hennekens CH. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. JAMA. 1996;276(11):882–8.
23. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298:309–16.
24. Cohn JS. Postprandial lipemia and remnant lipoproteins. Clin Lab Med. 2006;26:773–86.
25. Lekhal S, Børvik T, Nordøy A, Hansen JB. Increased postprandial triglyceride-rich lipoprotein levels in elderly survivors of myocardial infarction. Lipids. 2008;43(6):507–15.
26. Tentolouris N, Stylianou A, Lourida E, Perrea D, Kyriaki D, Papavasiliou EC, et al. High postprandial triglyceridemia in patients with type 2 diabetes and microalbuminuria. J Lipid Res. 2007;48(1):218–25.
27. Ballantyne CM, Grundy SM, Oberman A, Kreisberg RA, Havel RJ, Frost PH, Haffner SM. Hyperlipidemia: diagnostic and therapeutic perspectives. J Clin Endocrinol Metab. 2000;85(6):2089–112.
28. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 2005;294(3):326–33.
29. Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G. Bypass Angioplasty Revascularization Investigation. Non-high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 2002;106:2537–42.
30. Jialal I, Miguelino E, Griffen SC, Devaraj S. Concomitant reduction of low-density lipoprotein-cholesterol and biomarkers of inflammation with low-dose simvastatin therapy in patients with type 1 diabtes. J Clin Endocrinol Metab. 2007;92:3136–40.
31. Steyrer E, Durovic S, Frank S, Giessauf W, Burger A, Dieplinger H, et al. The role of lecithin: cholesterol acyltransferase for lipoprotein (a) assembly. Structural integrity of low density lipoproteins is a prerequisite for Lp(a) formation in human plasma. J Clin Invest. 1994;94(6):2330–40.
32. Ariyo AA, Thach C, Tracy R. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. N Engl J Med. 2003;349(22):2108–15.

33. Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, et al. Lipoprotein(a) levels and risk of future coronary heart disease: Large-scale prospective data. Arch Intern Med. 2008;168(6):598–608.
34. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350:1387–97.
35. RidKer PM, Danielson E, Fonseca FA, JUPITER Study Group, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
36. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347: 1557–65.
37. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-Reactive Protein Levels and Outcomes after Statin Therapy. N Engl J Med. 2005;352:20–8.
38. Lonn E, Yusuf S, Arnold MJ, Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Eng J Med. 2006;355:746.
39. Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E, Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators. Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial. Ann Intern Med. 2007;146:761–7.
40. Stranger O, Herrmann W, Pietrzik K, et al. Clinical use and rational management of homocysteine, folic acid, and B vitamins in cardiovascular and thrombotic diseases. Z Kardiol. 2004;93:439–53.
41. Jiang R, Schulze MB, Li T, Rifai N, Stampfer MJ, Rimm EB, Hu FB. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. Diabetes Care. 2004; 27(8):1991–7.
42. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet. 2001;358:2026–33.
43. Sniderman A, Williams K, Cobbaert C. ApoB versus non-HDL-C: what to do when they disagree. Curr Atheroscler Rep. 2009;11:358–63.
44. Kastelein JJ, van der Steeg WA, Holme I, TNT Study Group; IDEAL Study Group, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation. 2008; 117:3002–9.
45. Elkeles RS, Godsland IF, Feher MD, Rubens MB, Roughton M, Nugara F, PREDICT Study Group, et al. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. Eur Heart J. 2008;29(18):2244–51.
46. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol. 2005;46:158–65.
47. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol. 2004;43:1663–9.
48. Stein JH, Johnson HM. Carotid intima-media thickness, plaques, and cardiovascular disease risk: implications for preventive cardiology guidelines. J Am Coll Cardiol. 2010;55:1608–10.
49. Goff Jr DC, Bertoni AG, Kramer H, et al. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. Circulation. 2006; 113:647–56.
50. Wynder EL, Harris RE, Haley NJ. Population screening for plasma cholesterol: community-based results from Connecticut. Am Heart J. 1989;117:649–56.
51. Third report of the National Cholesterol Education Program (NCEP). Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Circulation. 2002;106:3143.
52. Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll Cardiol. 2004;44(3):720–32.
53. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and treatment of hypertriglyceridemia: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012; 97(9):2969–89.
54. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science. 2001;292(5519):1160–4.
55. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152–60.
56. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Krumholz HM. Circulation. 2006; 114(25):2788–97.
57. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–42.
58. Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ, et al. Statins, Risk of Diabetes, and Implications on Outcomes in the General Population. J Am Coll Cardiol. 2012;60(14):1231–8.
59. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012;380(9841):565–71.
60. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol

and Recurrent Events Trial investigators. N Engl J Med. 1996;335(14):1001–9.
61. MRC/BHF. Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7–22.
62. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685–96.
63. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011; 305(24):2556–64.
64. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495–504.
65. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711–8.
66. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292(11):1307–16.
67. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295(13):1556–65. Epub 2006 Mar 13.
68. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291(9):1071–80.
69. Crouse 3rd JR, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007;297(12): 1344–53.
70. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2001;365:2078–87.
71. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20):1301–7.
72. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615–22.
73. Gotto Jr AM, Moon JE. Recent clinical studies of the effects of lipid-modifying therapies. Am J Cardiol. 2012;110(1):15A–26.
74. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317(20):1237–45.
75. Haim M, Benderly M, Brunner D, Behar S, Graff E, Reicher-Reiss H, et al. Elevated serum triglyceride levels and long-term mortality in patients with coronary heart disease: the Bezafibrate Infarction Prevention (BIP) Registry. Circulation. 1999;100(5):475–82.
76. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61.
77. Brown BG, Zhao XQ. Nicotinic acid, alone and in combinations, for reduction of cardiovascular risk. Am J Cardiol. 2008;101(8A):58B–62.
78. Guyton JR, Goldberg AC, Kreisberg RA, Sprecher DL, Superko HR, O'Connor CM. Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. Am J Cardiol. 1998;82(6):737–43.
79. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001;345(22):1583–92.
80. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004;110(23):3512–7.
81. Investigators AIM-HIGH. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. Am Heart J. 2011;161(3):538–43.
82. Yadav R, France M, Younis N, Hama S, Ammori BJ, Kwok S, Soran H. Extended-release niacin with laropiprant : a review on efficacy, clinical effectiveness and safety. Expert Opin Pharmacother. 2012 Jun; 13(9):1345–62.
83. Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). Am J Cardiol. 2005;95(2):254–7.
84. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with

primary hypercholesterolemia. Eur Heart J. 2003; 24(8):729–41.
85. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002;40(12):2125–34.
86. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431–43.
87. Investigators SHARP. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.
88. Bang CN, Greve AM, Boman K, et al. Effect of lipid lowering on new-onset atrial fibrillation in patients with asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Am Heart J. 2012;163(4):690–6.
89. Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL. Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. Clin Ther. 2007;29:74–83.
90. Kones R. Reducing residual risk: modern pharmacochemistry meets old-fashioned lifestyle and adherence improvement. *Ther Adv Cardiovasc Dis* 2013 [Epub ahead of print] DOI: 10.1177/1753944712467828.