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Atherogenic dyslipidaemia: the importance of its management in high risk patients

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KEYWORDS
Atherogenic dyslipidaemia;
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Abstract
Low-density lipoproteins (LDL) are the most important atherogenic particles. Statins are first line treatment for LDL lowering. Statins reduce the risk of atherosclerotic cardiovascular disease (CVD), but statin-treated patients may still be at risk of adverse CVD outcomes, even if LDL cholesterol (LDL-c) target levels are attained. A growing number of persons have mildly to moderately elevated triglyceride (TG) levels, often associated with insulin resistance or type 2 diabetes mellitus (T2DM). In this circumstance, the cholesterol present in TG-rich remnant particles contributes to atherogenesis and aggravates CVD risk beyond what would be expected from the LDL-c level. Lowering TG levels by adding fenofibrate to statin therapy has been shown to reduce the incidence of major CVD events in selected T2DM patients. This review explains and explores the role of managing atherogenic dyslipidaemia in individuals with high CVD risk.

PALABRAS CLAVE
Dislipemia aterogénica;
Fenofibrato;
Triglicéridos;
Estatina

Dislipemia aterogénica: la importancia de su tratamiento en pacientes de alto riesgo

Resumen
Las lipoproteínas de baja densidad (LDL) son las partículas aterogénicas más importantes. Las estatinas son el tratamiento de primera línea para descender las LDL. Si bien las estatinas reducen el riego de enfermedad cardiovascular (ECV) aterosclerótica, los pacientes tratados con estatinas pueden permanecer en riesgo de resultados cardiovasculares (CV) adversos, incluso si se han alcanzado los valores objetivo de colesterol unido a LDL (cLDL). Un número creciente de personas presentan valores de triglicéridos (TG) de mediana a moderadamente elevados, a menudo asociados con resistencia a la insulina o diabetes tipo 2 (DMT2). En esta circunstancia, el colesterol presente en las partículas remanentes ricas en TG contribuye a la aterogénesis y agrava el riesgo de ECV más allá de lo que se podría esperar a partir del valor de cLDL. Se ha demostrado que el descenso de los valores de TG mediante la adición de fenofibrato a la terapia con estatina reduce la incidencia de acontecimientos CV mayores en pacientes con DMT2 seleccionados. Esta revisión describe y explora el papel del tratamiento de la dislipemia aterogénica en individuos con alto riesgo de ECV.

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Introduction

Cardiovascular disease (CVD) is responsible for the loss of many years of life.[1] On average, the life expectancy of a sixty-year old man is reduced by 9.2 years if he has a history of myocardial infarction (MI), and 12 years if he has a history of stroke; for a sixty-year old woman, life expectancy is reduced by 11.6 years and 9.8 years, respectively.

Yet, CVD is strongly avoidable. The INTERHEART study showed that nine easily measured and potentially modifiable risk factors (smoking, exercise, fruit and vegetables, alcohol, hypertension, diabetes, abdominal obesity, psychosocial, high apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio) account for an over 90% of the risk of an initial MI.[2] The relative importance of each risk factor depends on the combination of its prevalence and the strength of its association with MI, and can be expressed by the population-attributable risk (PAR), which measures the proportion of MI among those who have the risk factor which would be eliminated if the risk factor was removed. Of the nine risk factors, dyslipidaemia accounted for approximately half the PAR.

Nevertheless, risk factor control is inadequate in a large majority of coronary patients, despite high reported use of medications.[3] Of the 7,998 coronary patients from 24 countries participating in EUROASPIRE IV, 85.7% were on statin therapy, but only 22% men and 17% women had LDL-c below 70 mg/dL.

Barriers to optimal prevention

Many individuals are unaware of their (very) high risk for cardiovascular disease

The VIVA study —an observational, cross-sectional study conducted between March and May 2011, using a planned representative sample of the adult population resident in Mainland Portugal— showed that 43.3% of the individuals in the high CVD risk category were asymptomatic, non-diabetic and in primary prevention.[4] These are often middle-aged persons unaware of their risk, which is high due to the presence of multiple risk factors, although none markedly elevated; since they feel rather healthy, they do not routinely visit a family physician. A typical individual filling this description is the one presenting abdominal obesity.

Physicians often underestimate cardiovascular disease risk based on perception

A cross-sectional survey of 2,056 physicians from 11 countries showed that only 48% of respondents reported regular use of CVD risk scores to tailor preventive treatment in a case scenario involving a hypothetical patient at intermediate risk.[5] For this case scenario, the disagreement between physician-rated CVD risk and that estimated using Framingham Risk Scores (FRS) was 41%. Cardiologists considered this hypothetical case to be of low risk more frequently (39%) than did endocrinologists (21%) or family physicians (29%).

Most of myocardial infarctions occur in individuals classified as low or moderate cardiovascular disease risk

In a study of 1,267 non-diabetic patients without prior vascular disease, presenting with a first MI, the 10-year FRS was calculated for each patient using their admission demographics and fasting lipid levels.[6] FRS inadequately predicted cardiac risk in the young patients: 63.0% of patients under 40 years of age were classified as low risk (10-year risk for cardiac events < 10%); the proportion of low risk patients was 29.3% for age 40 to 64 years, and 14.2% for age 65 years or higher. A couple of reasons help understand this finding. First, while the majority of people of a relatively younger age are defined as low risk using existing risk scores, a low short-term risk in younger subjects may not reflect their true lifetime risk. Second, the prevalence of type 2 diabetes mellitus (T2DM) is underestimated, and a significant number of individuals presenting to hospital with a MI are newly diagnosed with this condition.

Risk estimation scores are not accurate

Although aetiologically important, risk factors such as serum cholesterol and blood pressure are poor predictors of future CVD events.[7] There is considerable overlap of risk factor levels between patients who die from ischaemic heart disease (IHD) or stroke and those who die from other causes. The serum cholesterol cutoff level that defines the 5% of individuals with the highest levels identifies only 15% of all deaths from IHD. The diastolic blood pressure cutoff level that defines the 5% of individuals with the highest levels identifies only 13% of all deaths from IHD and 24% of all deaths from stroke. The screening performance of CVD risk factors in combination is little better.

The ideal CVD risk estimation tool has yet to be established. Considerable heterogeneity is found among the contemporary risk equations: minimum patient age varies between 30-45 years; some allow treated blood pressure (e.g. FRS); some require a non-fasting lipid profile (e.g. JBS3); some include diabetes (e.g. Framingham CVD, QRISK2); some quantify smoking (e.g. QRISK2); the outcome measured varies from only fatal events to all events, and from only IHD events to any CVD event; some include novel variables (e.g. rheumatoid arthritis, deprivation score).

In selected individuals, evaluation of the atherosclerotic burden using non-invasive imaging methods, such as the coronary artery calcium score, improves the predictive accuracy of the conventional risk estimation scores. This approach may be applied in individuals with calculated CVD risks near decisional thresholds.[8]

Compliance with drug therapy is low in secondary prevention

The TRANSLATE-ACS registry enrolled 7,955 patients with an acute MI, admitted between 2010 and 2012 in 216 USA hospitals, to characterize persistence with secondary prevention medication (aspirin, $P2Y_{12}$ inhibitors, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins) from discharge to six months post-MI.[9] Overall, 31% patients stopped taking at least one

medication by six months. Side effects and physician instruction were the most common reasons for discontinuation (57%). Persistence was higher if provider explained reasons and side effects for each medication, and if a cardiologist was visited within six weeks after hospitalization.

Low compliance with statins and β-blockers after acute MI is associated with shorter long-term survival.[10] These benefits on life expectancy appear to be class-specific, suggesting that they are mediated by drug effects and do not merely reflect an epiphenomenon of "healthy adherer" behavioral attributes.

Patients often decide to discontinue medications because of negative news stories

Our society is increasingly exposed to numerous and disparate sources of health information. The way health stories are covered by the lay media has an impact on healthcare related behavior.

Media exposure during the early period following initiation of statin therapy may play a role in the patients' attitude towards statin therapy and thus the decision to discontinue or continue treatment.[11,12] Between 1995 and 2010, 674,900 individuals with age ≥ 40 years were initiated on statin therapy in Denmark. During this period, there were a total of 1,931 statin-related news stories published in Danish newspaper and magazine articles, Danish radio and television stations, and Danish websites and news bureau feeds. One hundred and ten were graded as negative, 1,090 as neutral, and 731 as positive statin-related news stories. Negative statin-related news stories increased early discontinuation (defined as no second dispense of the drug during the six months following the first dispense) of both the statin and the antihypertensive medication. On the contrary, positive statin-related news stories reduced early statin discontinuation. Furthermore, negative statin-related news stories were associated with increased risk of MI and death from CVD.

Cardiovascular disease prevention requires a multifactorial approach

The medications used to treat one CVD risk factor may have an adverse effect on another risk factor, thus compromising the ultimate goal of treatment, which is to prevent CVD rather than to simply correct each risk factor individually.

In the ASCOT study, a total of 19,257 primary prevention hypertensive patients at high CVD risk were randomized to an amlodipine-based regimen or an atenolol-based regimen. Of these, 10,305 subjects with total cholesterol ≤ 253 mg/dL and not on lipid-lowering therapy were further randomized to atorvastatin or placebo. Notably, the relative risk reduction in the primary endpoint of non-fatal MI or fatal IHD with atorvastatin allocation was significantly greater among those allocated the amlodipine-based regimen (53% reduction, $P < 0.0001$) than among those allocated atenolol-based treatment (16% reduction, P = not significant).[13] There were no apparent differences between the amlodipine-based and atenolol-based regimens in the extent to which total cholesterol and Low-density lipoprotein cholesterol (LDL-c) were lowered by atorvastatin. However, high-density lipoprotein cholesterol (HDL-c) increased in the amlodipine-based group of patients, and decreased in the atenolol-based group. Furthermore, serum triglyceride (TG) levels fell throughout the trial among those patients assigned amlodipine-based therapy, but not among those in the atenolol-based group. These differential changes on HDL-c and TG, in addition to the possible anti-atherosclerotic properties of dihydropyridines (and the pleiotropic effects of angiotensin-converting enzyme inhibition, which was allowed as add-on therapy for blood pressure control in the amlodipine-based group), may explain the observation described above. Ultimately, the ASCOT study suggests that two patients taking the same dose of a specific statin, and having identical LDL-c levels, may not derive the same CVD risk reduction.

Atherogenic dyslipidaemia

What is it and how common is it?

Atherogenic dyslipidaemia (AD) is characterized by increased levels of total TG and very-low-density lipoprotein (VLDL) TG, decreased levels of HDL-c, as well as levels of LDL-c that are normal or moderately increased.[14] The LDL particles in AD are smaller and more dense, and have an increased atherogenic potential; small, dense HDL particles also occur.

AD is a highly prevalent condition, even in statin-treated patients, yet AD is generally under treated and under controlled.[15,16] The prevalence of AD was reported in the DYSlipidemia International Study, which was conducted on 22,063 statin-treated outpatients in Europe and Canada, and showed that elevated TGs and low HDL-c levels were persistent in 38.8% and 26.4% of these patients, respectively. These lipid abnormalities are particularly common in diabetic patients: 44.5% had elevated TG and 29.9% had low HDL-c levels.

Is it a clinically relevant issue?

The pathophysiology of acute coronary syndromes (ACS) is changing.[17] Statin use is on the rise, and together with other preventive measures statins have modified the atherosclerotic disease. Indeed, plaques obtained from more recent patients with symptomatic carotid artery disease reveal significantly more fibrous, non-inflammatory characteristics ("stable" plaques). Plaque rupture has declined as a cause of ACS, while superficial erosion appears on the rise. The clinical presentation of ACS is shifting from ST-elevation MI to non-ST elevation ACS, at the same time as stroke incidence and case fatality are declining. Finally, the risk profile and demographics of ACS patients are shifting worldwide: the burden of ACS is now global; younger age, female gender, obesity, insulin resistance, T2DM, high TG, low HDL-c, and less LDL excess are now more common features of ACS patients. Interventions that target TG-rich lipoproteins, HDL function, and inflammation have the potential to address the contemporary individual who remains vulnerable to ACS despite LDL-c reduction based on statin therapy.

The pathophysiology of AD is intricately linked to insulin resistance and elevated TG levels.[18] In adipose tissue, insulin resistance impairs the inhibition of TG hydrolysis and causes the release of an increased amount of free fatty acids (FFA); in the liver, together with increased flux of FFA, insulin resistance causes an increased production of TG and secretion of

VLDL particles. In the presence of hypertriglyceridaemia, cholesteryl ester transfer protein (CETP) promotes the transfer of TG from TG-rich VLDL to LDL and HDL particles and, reciprocally, cholesteryl esters are transferred from the two latter particles to the VLDL. Hepatic lipase, whose activity is increased in insulin resistance states, hydrolyses the TG-enriched LDL particles, leading to small, dense, cholesterol-depleted LDL particles. Likewise, hydrolysis of the TG-enriched HDL particles leads to small, dense HDL3 particles, and an increased release of free ApoA1.

Mild to moderately elevated TG levels become hazardous by three mechanisms.[19] First, the VLDL particles that have lost TG in exchange for cholesteryl esters, are sufficiently small to enter the intima, they are more easily trapped in the intima than LDL, and because these remnant particles contain cholesterol, they are an additional source of cholesterol (beyond LDL) for atherogenesis (Fig. 1). The cholesterol content of TG-rich lipoproteins is referred to as remnant cholesterol. Second, the small dense LDL particles are more susceptible to oxidation and hence to generate atheroma, since LDL modification is critical for the atherogenicity of LDL. Third, oxidation of the fatty acids belonging to the TG present in small dense LDL and in the TG-rich lipoprotein remnants, generates products that modify ApoB, which becomes recognizable by macrophage scavenger receptors.

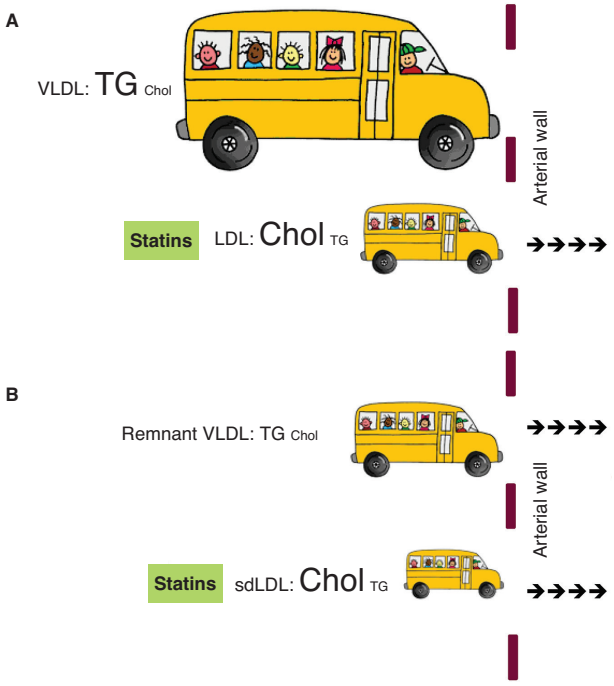

Figure 1 A simplistic explanation on the role of triglycerides (TG) in cardiovascular disease (CVD). TG can be degraded by most cells, but cholesterol cannot. Indeed, cholesterol not TG accumulates in intimal foam cells and in atherosclerotic plaques, and remnant lipoproteins just like low-density lipoproteins (LDL) are sufficiently small to enter the intima. Lipids circulate in lipoprotein particles, and particle size is a major determinant of the particle's capacity to promote the atherosclerotic lesion, which is the substrate for CVD. A) When TG levels are normal, very-low-density lipoproteins (VLDL) particles are too big to enter the intima. Although some cholesterol is present in the VLDL particles, only the cholesterol present in the LDL particles can contribute to atherogenesis. In such conditions, it seems intuitive that LDL-cholesterol lowering through statin therapy is sufficient to control the part of the CVD risk that is attributable to lipids. B) When TG are mildly or moderately increased, other ApoB-containing lipoproteins, beyond LDL, acquire atherogenic activity. Remnant VLDL particles enriched in cholesterol are sufficiently small to enter the intima. In such conditions, statins will have less cholesterol-lowering effects because they have a smaller effect on VLDL than on LDL. Chol, cholesterol; sdLDL, small dense LDL.

Non-HDL-c, which is easily calculated by subtracting the HDL-c level from the total cholesterol level, is a more comprehensive measure of the cholesterol in all the lipoprotein particles that can enter the intima, and not just the LDL particles.[14] Non-HDL-c may be a better marker of CVD risk than LDL-c in patients with high TG and T2DM, metabolic syndrome or chronic kidney disease. Non-HDL-c should be used as a target for treatment of residual CVD risk in patients with AD. In a given person, the goal for non-HDL-c is to not exceed 30 mg/dL above the LDL-c goal recommended for the person's CVD risk category.

The importance of reaching the non-HDL-c target was demonstrated by a meta-analysis on individual patient data from 62,154 statin-treated patients in eight large randomized statin trials.[20] Compared with patients reaching both the LDL-c and non-HDL-c target (set at 100 mg/dL and 130 mg/dL, respectively), patients reaching the LDL-c target but not the non-HDL-c target had a 32% increased risk of major CVD events. On the other hand, patients reaching only the non-HDL-c target (but not the LDL-c target) had similar risk of major CVD events as for those who achieved target levels for both LDL-c and non-HDL-c.

Non-HDL-c is emerging as a major target for the management of CVD risk. Several scientific societies and guidelines acknowledge the advantages of non-HDL-c as a target for clinical intervention.[21-24] Non-HDL-c is viewed as a secondary treatment target by some, while others recommend it for the primary treatment target (replacing LDL-c) or as a co-primary target.

How should we treat the atherogenic dyslipidaemia -related residual cardiovascular disease risk?

LDL-c lowering with statins remains the backbone treatment for reducing the dyslipidaemia-related CVD risk.[25] A meta-analysis conducted on individual patient data from randomized trials showed that statin treatment reduces the risk of a major vascular event by 21% per 1 mmol/L (39 mg/dL) of LDL-c reduction; for the same LDL-c reduction, vascular mortality is decreased by 12% and coronary deaths by 20%.

Fenofibrate is a peroxisomal proliferator-activated receptor alpha (PPARα) agonist that exerts a range of lipid-modifying effects, due to changes in the expression of genes that modify lipid metabolism.[26] Fenofibrate upregulates ApoA5 synthesis and down-regulates ApoC3, thereby increasing lipolysis and plasma clearance of TG-rich lipoproteins; fenofibrate also decreases the availability of FFA, which inhibits the formation of TGs and VLDL. Furthermore, fenofibrate increases the synthesis of ApoA1 and ApoA2, the major proteins in HDL; it decreases CETP activity, thereby increasing HDL-c levels; and increases scavenger receptors class B1 expression, which helps mediate cholesterol efflux from macrophages. Finally, fenofibrate causes a shift in the phenotype

of LDL particles from the small and dense to the larger, more buoyant LDL particles, which are easily cleared and less likely to become oxidized.

The combination of fenofibrate with a statin generally leads to a significant improvement in all lipid parameters. In the SAFARI study, fenofibrate-simvastatin treatment increased HDL-c and ApoA1 levels, reduced levels of total cholesterol, LDL-c, TG, non-HDL-c and ApoB, and improved the LDL subclass pattern *versus* baseline and simvastatin monotherapy.[27]

The clinical benefits of fenofibrate-statin combination therapy in patients with AD are supported by data from the ACCORD Lipid trial (Fig. 2).[28,29] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was designed to test the effect of intensive treatment of blood glucose and either blood pressure or plasma lipids on CVD outcomes in 10,251 patients with T2DM at high risk for CVD. A subgroup of 5,518 patients were enrolled in the ACCORD Lipid trial, and randomized to receive either fenofibrate or placebo, which were masked and begun one month after starting open-label simvastatin. Patients who had a TG level in the highest third (≥ 204 mg/dL) and an HDL-c level in the lowest third (≤ 34 mg/dL) at baseline were considered as the AD subgroup for a prespecified analysis. In patients treated with simvastatin alone, the rate of cardiovascular (CV) death, MI or stroke (primary endpoint) was 70% higher in the presence of AD. Compared with simvastatin monotherapy, a 31% risk-rate reduction in CV death, MI or stroke was obtained with fenofibrate-simvastatin therapy in patients with AD (NNT [number needed to treat] for 5 years to prevent 1 event = 20), and the reductions in both major coronary events (coronary death, non-fatal MI or unstable angina) and CV mortality were also significant in these patients. In a post-hoc analysis of patients on statin at baseline who had reached target LDL-c levels (< 100 mg/dL) but failed to reach target non-HDL-c levels (≥ 130 mg/dL), fenofibrate-simvastatin combination therapy led to a very significant reduction in CVD events compared with simvastatin monotherapy (8.8% *versus* 16.3%, respectively).

Of the ACCORD Lipid trial participants, 4,644 survivors at the end of the study consented to an additional five years nontreatment, observation-only ACCORDION study (mean total follow-up 9.0 years).[30] Only 144 ACCORDION participants (4.3%) were continued or started on fibrate therapy following completion of ACCORD. In spite of this, the primary outcome in study participants with AD who were randomized to fenofibrate was 27% lower during the combined trial plus posttrial period, suggesting a legacy effect. This finding is supported by fenofibrate's slowing effect on the progression of coronary atherosclerosis in patients with T2DM.[31]

The safety and tolerability of fenofibrate in combination with statins has been addressed in a consensus paper.[14]

Future perspectives

Three ongoing studies address the role of TG-lowering therapy in patients with AD.

REDUCE-IT

REDUCE-IT (NCT01492361) is evaluating whether AMR101, a highly purified ethyl ester of eicosapentaenoic acid, combined with statin therapy, will be superior to the statin therapy alone, when used as a prevention in reducing long-term CVD events in high-risk patients with mixed dyslipidemia.[32] Approximately 8,000 patients age ≥ 45 years with established CVD or age ≥ 50 years with diabetes mellitus and one additional risk factor have been randomized. Randomization required fasting TG ≥ 150 mg/dL and < 500 mg/dL and LDL-c > 40 mg/dL and ≤ 100 mg/dL with stable statin (± ezetimibe) for at least four weeks. Follow-up will continue in this event-driven trial until approximately 1,612 adjudicated primary-efficacy endpoint events (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) have occurred.

STRENGTH

STRENGTH (NCT02104817) is evaluating whether a mixture of omega-3-carboxylic acids will reduce residual CVD risk in statin-treated patients. Approximately 13,000 patients with established CVD or other high CVD risk conditions (including diabetes mellitus) have been randomized. Randomization required fasting TG ≥ 180 mg/dL and < 500 mg/dL, LDL-c

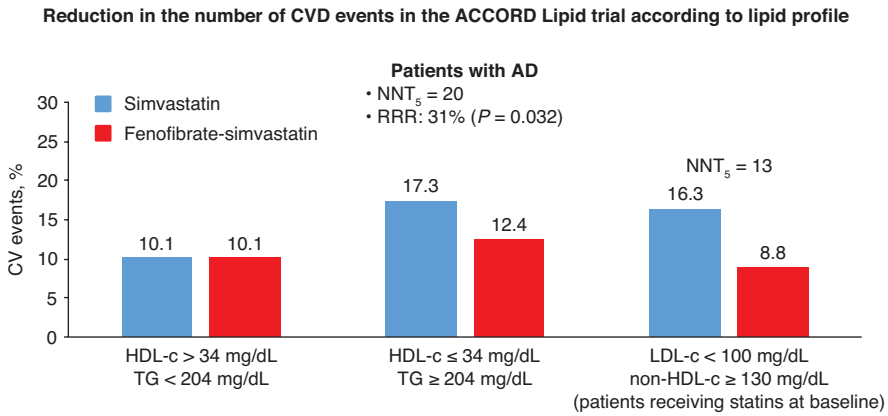

Figure 2 Effect of fenofibrate-simvastatin combination therapy in patients with atherogenic dyslipidaemia (AD). CV: cardiovascular; CVD: cardiovascular disease; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; NNT: number needed to treat; RRR, relative risk reduction; TG: triglycerides.

< 100 mg/dL, and HDL-C < 42 mg/dL for men or HDL-C < 47 mg/dL for women, with stable statin therapy for at least four weeks. Follow-up will continue in this event-driven trial until a sufficient number of primary-efficacy endpoint events (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) have occurred.

PROMINENT

PROMINENT (NCT03071692) is evaluating whether pemafibrate, a potent selective PPARa modulator, will reduce CVD events in statin-treated patients with T2DM. The study will randomize approximately 10,000 patients with established CVD or in primary prevention with age ≥ 50 years if male or ≥ 55 years if female. Randomization requires fasting TG ≥ 200 mg/dL and < 500 mg/dL, and HDL-C < 40 mg/dL. Follow-up will continue in this event-driven trial until a sufficient number of primary-efficacy endpoint events (CV death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina requiring unplanned coronary revascularization) have occurred.

Conclusions

There is still a very large potential for interventions aimed at reducing the global burden of atherosclerotic CVD. LDL-c is far from being adequately controlled in persons with (very) high risk of CVD. Everyone has a relevant role in CVD prevention. People should know their CVD risk and adhere to treatment recommendations. The media may help in patient education, and should deliver accurate information to the public. Healthcare professionals should apply the best evidence to practice, and monitor the results of treatment. Policy makers ought to identify opportunities for increasing health (reducing disease) and prioritize interventions based on these and on their value.

Statins reduce CVD risk, but statin-treated patients may still be at risk of CVD events, even if LDL-c target levels are attained. Indeed, in a growing number of patients, cholesterol present in TG-rich remnant particles contributes to atherogenesis and significant residual CVD risk. Lowering TG levels by adding fenofibrate to statin therapy has been shown to reduce major CVD events in T2DM patients with AD.

Non-HDL-c, which accounts for the cholesterol present in all atherogenic lipoproteins, may be a better CVD risk marker than LDL-c, especially in patients with mildly to moderately elevated TG levels and T2DM or metabolic syndrome. The goal for non-HDL-c is to not exceed 30 mg/dL above the LDL-c goal recommended for the person's CVD risk category. Several scientific societies and guidelines acknowledge the advantages of non-HDL-c as a target for clinical intervention.

Conflicts of interest

The author declares having received honoraria for consultancies and lectures from the following entities: Abbott, AstraZeneca, Bial Portela, JABA Recordati, Merck Sharp & Dohme, Mylan, Tecnimede.

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