

Novel Lipids Targets in the Era of Metabolic Syndrome

Toward a Better Prediction of Cardiovascular Risk

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Abstract

During the last decades, the prevalence of obesity, diabetes mellitus and metabolic syndrome (MetS) has dramatically risen in developed countries. A further increase in MetS and diabetes can be anticipated because of projections of a greater prevalence of obesity in the future. Albeit the cardiovascular (CV) risk in patients with MetS has been considered high, a large proportion of these patients present with normal low-density lipoprotein-cholesterol (LDL-C) levels. Conversely, these patients often display high levels of apolipoprotein B-100 (apoB), triglycerides (TG) and non-high-density lipoprotein-cholesterol (non-HDL-C). Among routine lipoprotein assessment, the use of non-HDL-C has shown several advantages over LDL-C, particularly in the presence of hypertriglyceridaemia. Non-HDL-C is a combined measurement of LDL-C, lipoprotein (a), small dense LDL-C (sd-LDL-C), chylomicron remnants, and intermediate-density lipoproteins. Several studies have shown that non-HDL-C is a strong predictor of subclinical atherosclerosis and CV events as well as a reasonable surrogate of apoB measurement. Moreover, current evidence is supporting that non-HDL-C accurately predicts major CV events even in patients with normal TG values. However, current recommendations suggest non-HDL-C only when TG exceeds 200 mg/dL, recommending the use of LDL-C as the primary target of therapy in all the other conditions. These definitions contrast with the finding of normal LDL-C in obesity, diabetes and MetS, all considered high-risk conditions. Therefore, a redefinition of LDL-C as a predictor of CV events is needed also in the view of an increased prevalence of insulin resistance, abdominal obesity and diabetes.

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Coronary artery disease (CAD), albeit the strong efforts in reducing the burden of morbidity and mortality, remains the first cause of mortality worldwide.^[1] Among the cardiovascular (CV) risk factors, dyslipidaemia is recognized as one of the strongest

factors promoting CAD development.^[2] In the last decades, lipid-lowering therapy (namely 'statins') significantly reduced CV mortality in primary and secondary prevention mainly by lowering low-density lipoprotein-cholesterol (LDL-C) levels.^[2]

Indeed, a linear relationship between LDL-C and CAD risk has been described and during the last years progressively lower target cut-off values for LDL-C have been proposed.^[2] Accordingly, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed LDL-C as the primary target of therapy.^[2] More recently, ATP III recommendations have proposed the use of non-high-density lipoprotein-cholesterol (non-HDL-C) as a secondary therapeutic target in patients with triglycerides (TG) levels ≥ 200 mg/dL. Moreover, a recently published consensus conference focusing on the management of 'cardiometabolic' risk proposed non-HDL-C ≤ 100 mg/dL and apolipoprotein B-100 (apoB) ≤ 80 mg/dL as a target of therapy in high-risk patients, including those with CAD or diabetes mellitus plus one or more CV risk factors.^[3] Indeed, LDL-C has been shown to lose part of its predictive value in hypertriglyceridaemia as a result of the increase in very low-density lipoprotein-cholesterol (VLDL-C), apoB and small dense LDL-C (sd-LDL-C).^[4] Conversely, when TG levels are ≤ 150 mg/dL VLDL-C represents only a small percentage of the lipoproteins pool and their concentration in the blood rarely exceeds 30 mg/dL. In this condition, sd-LDL levels are also strongly reduced.

The calculation of non-HDL-C derives from total cholesterol (TC) minus HDL-C and includes LDL-C, intermediate-density lipoprotein-cholesterol (IDL-C), VLDL-C, TG and lipoprotein

(a) [Lp(a)]. In the presence of elevated TG levels, non-HDL-C has shown to predict the presence and the severity of subclinical atherosclerosis as well as the risk of major CV events better than LDL-C.^[5-8] Importantly, the correlation between LDL-C and non-HDL-C remains linear in patients with normal TG levels, while the association becomes less strong with the increase of TG concentrations over 200 mg/dL. ApoB is found in VLDL-C, IDL-C, large buoyant LDL-C, sd-LDL and Lp(a) in a proportion of one molecule per particle (figure 1). Therefore, apoB represents the total burden of particles considered most atherogenic.^[9,10] In patients with normal LDL-C concentrations, high apoB levels suggest an increase in atherogenic sd-LDL, which are subjected to oxidation and then incorporated into the vessel intima where they trigger and maintain vascular inflammation. In the presence of high TG (≥ 200 mg/dL) and VLDL values ≥ 30 mg/dL, apoB has shown to predict CAD risk and subclinical atherosclerosis better than LDL-C.^[9]

1. The Insulin Resistance Epidemic and the Shift towards Atherogenic Dyslipidaemia

In the last decade, the dramatic increase in the prevalence of obesity, metabolic syndrome (MetS) and diabetes has shifted the

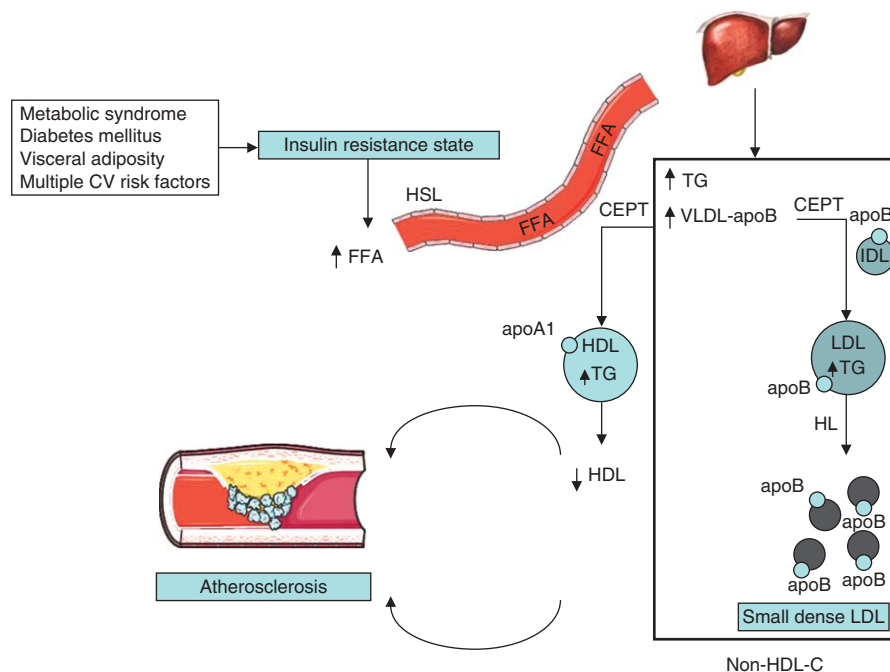


Fig. 1. Schematic representation of lipid changes secondary to insulin resistance and definition of non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B-100 (apoB). **apoA1** = apolipoprotein A1; **CEPT** = cholesteryl ester transfer protein; **CV** = cardiovascular; **FFA** = free fatty acids; **HL** = hepatic lipase; **HSL** = hormone-sensitive lipase; **IDL** = intermediate-density lipoprotein; **LDL** = low-density lipoprotein; **TG** = triglycerides; **VLDL-C** = very low-density lipoprotein-cholesterol; ↓ indicates decrease; ↑ indicates increase.

lipid pattern toward atherogenic dyslipidaemia characterized by an increase in TG and a concomitant decrease in HDL-C, with normal or mildly elevated LDL-C values (≤ 130 mg/dL) in most cases.^[4] Nowadays, prevalence of diabetes ranges from 14% to 20% in the general population with an estimated further dramatic increase for the next decades.^[11,12] Moreover, observational and prospective studies have shown that this condition remains associated with an increased CV morbidity and mortality compared with non-diabetic individuals.^[13-17] Accordingly, data from international registries report that prevalence of diabetes exceeds 20% in patients with acute coronary syndromes.^[18-21] MetS is also dramatically increasing worldwide and its prevalence ranges from 15% to 33%.^[2,22] Importantly, in people aged 60 years or more the prevalence of MetS exceeds 40%.^[23] MetS is a systemic disorder secondary to the variable coexistence of hyperinsulinaemia, hyperglycaemia, obesity, dyslipidaemia and elevated blood pressure, all conditions contributing to systemic inflammation and hypercoagulability.^[23,24] The prevalence of single components of MetS is high and more than 40% of patients have two or more MetS components, suggesting that a large part of the population is at high risk for developing this condition.^[25] Like diabetes, subjects with MetS present a 3-fold increase in the risk of acute coronary events compared with people without the syndrome.^[26-28] Moreover, individual components of MetS are independently associated with an increased CV morbidity and mortality.^[29]

Abdominal obesity appears to be the key clinical feature of MetS and promotes the cluster of CV risk factors, which define the syndrome (insulin resistance, dyslipidaemia, hypertension). Indeed, visceral obesity and increased intra-abdominal fat have been shown to precede the development of insulin resistance in humans.^[30,31]

During the last decade, abdominal obesity has largely exceeded the prevalence of general obesity and a community-based sample from the Framingham population showed that nearly one-third of patients have abdominal subcutaneous obesity, and over 40% present with visceral obesity. Accordingly, the prevalence of MetS is significantly higher among these patients.^[32,33]

2. Pathophysiology of Atherogenic Dyslipidaemia

Insulin resistant states and particularly the MetS are conditions associated with metabolic alterations leading to vascular inflammation and atherosclerosis. As previously described, the individual components of the MetS such as hypertension, atherogenic dyslipidaemia (low HDL-C, high TG and apoB levels) and insulin resistance are predictive of CV events inde-

pendently from the syndrome.^[29] Particularly, atherogenic dyslipidaemia has been associated with a 3- to 6-fold increase in the risk of CV events.^[34] A pivotal role in triggering the cardio-metabolic cascade is played by the increase of visceral adiposity with a consequent development of insulin resistance and hyperinsulinaemia.^[35] Insulin resistance causes metabolic changes by several mechanisms leading to increased levels of sd-LDL, low HDL-C and mild or severe hypertriglyceridaemia defining the phenotype of atherogenic dyslipidaemia.^[36]

Atherogenic dyslipidaemia is a common finding in patients with MetS and diabetes and its prevalence grows with that of visceral obesity. The latter, together with insulin resistance, causes overproduction of VLDL-apoB, decreased catabolism of apoB lipoprotein-containing particles and accelerated degradation of HDL-apoA1 particles. Insulin resistance in the adipose tissue significantly reduces or eliminates hormone-sensitive lipase (HSL) inhibition, thus facilitating an increased free fatty acid release (FFA) in the circulation (figure 1). Moreover, hypertrophic adipocytes are defective in the incorporation of FFA into TG. Such excess of FFA is subjected to liver reuptake, promoting the synthesis of TG rich VLDL-C and apoB.^[37,38] The latter are substrates for the cholesterol ester transfer protein (CETP), which transfers TG to LDL-C and HDL-C in exchange for cholesteryl esters. After CETP-mediated TG transfer from VLDL-C to LDL-C, the latter becomes a substrate for the hepatic lipase (HL) whose activity is strongly increased in the presence of insulin resistance (figure 1). HL-mediated hydrolysis makes LDL-C poor of TG and phospholipids, which become smaller and more prone to oxidation in the vascular wall. These processes also cause an altered conformation of apoB, which induce a weaker than normal binding to the LDL-C receptor, a reduced internalization into the liver and thus a prolonged residence time into the circulation. As a result, the binding of sd-LDL to their receptor weakens, thus prolonging persistence in the circulation. This, in turn, increases the chance of sd-LDL to penetrate into the vessel intima where their oxidation promotes vascular inflammation and atherosclerosis.^[39-42]

3. Non-High-Density Lipoprotein-Cholesterol (non-HDL-C) and Apolipoprotein B-100 (apoB): Towards a Better Prediction of Subclinical Atherosclerosis

Although current evidence suggests that LDL-C has still not passed its prime in stratifying CV risk, novel targets have emerged in the last few years paralleling the dramatic increase in diabetes and MetS.^[43] Differently from LDL-C, which in-

cludes the pool of atherogenic and non-atherogenic lipoprotein particles, non-HDL-C contains VLDL-C, IDL-C, LDL-C and TG (figure 1). Patients with MetS and diabetes display an increased concentration of apoB and TC despite normal LDL-C values. Prospective studies showed that apoB added a predictive value to LDL-C and the concordance of LDL-C with apoB was poor.^[44] Conversely, the correlation between non-HDL-C and apoB has been shown to be strong. This is not surprising since non-HDL-C reflects the presence of VLDL-C and sd-LDL in all particles where apoB is present in a proportion of one molecule per lipoprotein (figure 1). Importantly, the correlation between non-HDL and apoB was maintained even in patients with normal levels of TG and VLDL-C. On the other hand, the correlation between LDL-C and apoB further weakened when TG exceed 200 mg/dL.

Non-HDL-C has been confirmed to be as good as or better than other widely recommended lipoprotein measurements in detecting subclinical atherosclerosis and coronary calcifications in young and middle-aged adults without overt CV disease.^[5-8] In asymptomatic patients with electron beam computed tomography (EBCT)-defined subclinical atherosclerosis, none of the traditional lipid parameters (TC, LDL-C, HDL-C, TC/HDL-C and TG levels) significantly correlated with the extent of calcified plaque burden.^[7] In some of these studies, non-HDL-C showed better prediction of atherosclerosis than other lipoproteins even in patients with normal or mildly elevated TG levels.^[6] Although there is a strong correlation of non-HDL-C with apoB, the latter has been shown in several studies to better predict the presence and the severity of CAD.^[4] However, this issue still remains under discussion.^[45-47]

4. Comparison Between Low-Density Lipoprotein-Cholesterol and non-HDL-C in Predicting Cardiovascular Events

A large number of prospective studies compared non-HDL-C with other lipoprotein parameters in the prediction of CAD.^[48-58] In the BARI (Bypass Angioplasty Revascularization Investigation) trial, which enrolled patients with mild or severe hypertriglyceridaemia, non-HDL-C was the best predictor of long-term major CV events after a median 5-year follow-up.^[48] A prospective study conducted on diabetic patients without overt CV disease showed that non-HDL-C was better than LDL-C and non-inferior to apoB in predicting 6-year fatal and non-fatal CV events and coronary revascularization.^[49] A further study conducted on 19 381 subjects of the Framingham population showed that non-HDL-C was superior to LDL-C

only in diabetic patients.^[50] Conversely, Ridker and colleagues^[51] found that non-HDL-C predicted CAD better than LDL-C in a population of women free of CV disease and with a low prevalence of diabetes (HR 2.51 vs 1.62) [table I]. In this study, apoB was superior to LDL-C but not to non-HDL-C in predicting CAD. Similarly, a prospective Framingham cohort study enrolling mostly patients without diabetes and with normal TG levels confirmed the superiority of non-HDL-C over LDL-C in predicting fatal and non-fatal myocardial infarction after a 22-year follow-up.^[52] In the Lipid Research Clinics Prevalence Program, patients enrolled showed normal TG values (mean value 136 mg/dL), normal VLDL-C (mean value 27 mg/dL) and a low prevalence of diabetes (4%). After a 19-year follow-up, a 30 mg/dL increment of non-HDL-C was associated with a 19% increase in CV death compared with a 15% increase calculated for LDL-C.^[53] A Chinese study, conducted on 3568 men and women free of CV disease at baseline and with a very low prevalence of atherogenic dyslipidaemia (mean BMI 23.5, mean TG 127 mg/dL, 13% diabetic patients), confirmed that non-HDL-C was associated with a higher risk of fatal and non-fatal myocardial infarction, stroke or coronary revascularization after a 13-year follow-up (odds ratio [OR] 1.98 vs 1.86)^[54] [table I]. In this study, apoB was superior to non-HDL-C in predicting CV events; however, the confidence interval for apoB was wide (HR 2.74 vs 1.98) [table I]. Among diabetic patients with normal or mildly elevated TG (≤ 150 mg/dL) enrolled in the Strong Heart Study, non-HDL-C confirmed the prediction of CV death and non-fatal CAD better than LDL-C after a 9-year follow-up (OR 1.8 vs 1.66).^[55] Similar results were found in the health professional's follow-up study.^[56] However, although a strong correlation was observed, apoB was superior to non-HDL-C in predicting fatal or non-fatal CAD (table I). A more recent population-based cohort prospective study confirmed the strong predictive value of non-HDL-C over LDL-C in predicting CAD risk. Importantly, the overall performance of apoB and apoB/apoA1 ratio for prediction of CV events did not offer incremental utility over TC/HDL-C and non-HDL-C.^[57] Finally, a recent meta-analysis involving more than 100 000 patients has confirmed the direct relationship between the magnitude of lowering non-HDL and CV risk reduction.^[58]

5. Non-HDL-C and apoB as Primary Therapeutic Targets in High-Risk Patients

Evidence throughout the last decade has suggested that non-HDL-C and apoB are novel predictive markers reflecting CAD risk better than LDL-C in a large part of the population.

Table I. Principal studies comparing low-density lipoprotein-cholesterol (LDL-C), non-high-density lipoprotein-cholesterol (non-HDL-C) and apolipoprotein B-100 (apoB) in predicting subclinical atherosclerosis and major cardiovascular (CV) events

Study	n	Follow-up (y)	Population	Outcomes	Key findings	HR
Simon et al. ^[6]	723	CS	Asymptomatic men, mean age 48 y, 6% diabetic patients, average TG 130 mg/dL	CV risk and subclinical atherosclerosis	ApoB and non-HDL-C were the best predictors of subclinical atherosclerosis detected by EBCT	Coronary calcium score: LDL-C: 1.26 (1.01–1.55)* Non-HDL-C: 1.33 (1.07–1.64)* apoB: 1.35 (1.09–1.68)*
Frontini et al. ^[6]	1 203	CS	Asymptomatic young adults; mean age 36 y, average TG 140 mg/dL, average BMI 28	Subclinical atherosclerosis (carotid IMT)	Non-HDL-C, TC/HDL and apoB were the best predictors of IMT	LDL-C: 1.1 (1.01–1.21) Non-HDL-C: 1.75 (1.1–2.8)* apoB: 2.1 (1.4–3.3)*
Orakzai et al. ^[7]	1 611	CS	Asymptomatic individuals, mean age 53 y, TG 142 mg/dL, BMI 28	Coronary artery calcification detected by EBCT	Non-HDL-C was more strongly associated with coronary calcifications than other lipoprotein parameters	Coronary calcium score >0 LDL-C: 0.68 (0.45–1.02) Non-HDL-C: 1.9 (1.23–2.93)*
Bittner et al. ^[48]	1 514	5	Patients enrolled in the BARI trial, multivessel CAD, mean age 61 y, 18% diabetic patients, average TG 184 mg/dL	Non-fatal MI	Non-HDL-C was superior to LDL-C in predicting CV events	LDL-C: 1.033 (0.981–1.088) Non-HDL-C: 1.049 (1.006–1.093)*
Jiang et al. ^[49]	746	6	Diabetic men free of CV disease, average BMI 27.1, average TG 182 mg/dL	Fatal CAD, non-fatal MI, fatal stroke, non-fatal stroke, coronary revascularization	ApoB and non-HDL-C were the best predictors of CV events	LDL-C: 1.63 (0.94–2.81)* Non-HDL-C: 2.25 (1.24–4.08)* ApoB: 2.31 (1.25–4.27)*
Ridker et al. ^[51]	15 632	10	Women free of CV disease, 3% diabetic patients, average BMI 26.3	CV death or non-fatal MI, stroke or coronary revascularization	Non-HDL-C was superior to LDL and as equal as apoB in predicting CV events	LDL-C: 1.62 (1.17–2.25)* Non-HDL-C: 2.51 (1.69–3.72)* apoB: 2.50 (1.68–3.72)*
Liu et al. ^[52]	5 794	22	Men and women free of CAD, 6.8% diabetic patients, average BMI 24, average TG 111 mg/dL, average VLDL-C 25 mg/dL	Fatal and non-fatal MI or sudden CV death	Non-HDL-C was superior to LDL-C in predicting CV outcomes	LDL-C: 2.04 (1.44–2.90)* Non-HDL-C: 2.21 (1.57–3.31)*
Pischon et al. ^[56]	739	6	243 men with a previous CAD event and 496 healthy controls, 6% diabetic patients, average BMI 26, average TG 130 mg/dL	Fatal or non-fatal MI	ApoB and non-HDL-C were the best predictors of CV events	LDL-C: 2.07 (1.24–3.45)* Non-HDL-C: 2.75 (1.62–4.67)* ApoB: 2.98 (1.76–5.06)*
Ingelsson et al. ^[57]	3 322	15	Men and women free of CAD, mean age 51 y, 4% diabetic patients	MI, angina pectoris or CV death	ApoB and non-HDL-C were superior to LDL-C in predicting CV events	Male gender: LDL-C: 1.11 (0.97–1.27)* Non-HDL-C: 1.22 (1.06–1.4)* ApoB: 1.37 (1.20–1.57)* (a similar trend reported for female gender)

BMI=body mass index; **CAD**=coronary artery disease; **CS**=cross-sectional study; **EBCT**=electron beam computed tomography; **HDL-C**=high-density lipoprotein-cholesterol; **HR**=hazard ratio; **IMT**=intimal-media thickness; **MI**=myocardial infarction; **TC**=total cholesterol; **TG**=triglycerides; **VLDL-C**=very low-density lipoprotein-cholesterol. * p<0.05 with 95% CIs.

Indeed, prevalence of hypertriglyceridaemia is high in the general population, particularly in diabetic patients.^[59,60] Given the coming of age of obesity, MetS and diabetes, the use of more adequate predictive tools might help to better stratify CV risk. Albeit ATP III recommendations proposed non-HDL-C and apoB as a secondary target of therapy,^[61] prospective studies conducted on populations with normal or mildly elevated TG showed that non-HDL-C and apoB may reflect CAD risk also in patients without atherogenic dyslipidaemia.^[54-56] These observations may suggest a potential role for non-HDL-C and apoB as a primary target of therapy. However, studies evaluating the advantage of using non-HDL and apoB over LDL-C on statin therapy are still scarce. After a 16-week treatment with rosuvastatin 20 mg in the MERCURY II trial, only 38% of high-risk hypertriglyceridaemic patients reached the combined target values of LDL-C (≤ 100 mg), non-HDL-C (< 130 mg/dL) and apoB (< 90 mg/gL).^[62] Despite most of the patients reaching the LDL-C target value, a small proportion of patients reached the target non-HDL-C and apoB. Importantly, the proportion of patients reaching all lipid targets (LDL-C, non-HDL-C and apoB) was equal to that of patients reaching LDL-C < 70 mg/dL, thus suggesting that only when LDL-C is < 70 mg/dL are sd-LDL and VLDL-apoB concentrations strongly reduced. Indeed, the same statin treatment determined a greater reduction from baseline for LDL-C compared with non-HDL-C and apoB (51.6% vs 46.7% vs 40.2%, respectively). Other studies conducted in high-risk patients on statin therapy with simvastatin and atorvastatin showed that lowering non-HDL-C paralleled the relative risk reduction of major CV events.^[63-65] However, these studies did not consider the proportion of patients reaching the target of non-HDL-C and its impact on the development of future CV outcomes.

6. Conclusions

Non-HDL-C and apoB have been shown to provide additional information on CV risk assessment, particularly in the presence of visceral adiposity, insulin resistance and hypertriglyceridaemia, all conditions whose prevalence is dramatically increasing worldwide. These parameters have also been shown to correlate better than LDL-C with the presence and the severity of atherosclerotic disease at any levels as well as with the long-term risk of CAD. Importantly, non-HDL-C and apoB confirmed a predictive power of CV events superior to LDL-C also in patients with normal or mildly elevated TG values. In view of the MetS and diabetes epidemic, as well as a large increase in the prevalence of CV risk factors, non-HDL-C

and apoB are destined to be considered as primary therapeutic targets and to replace LDL-C calculation because of their better prediction of CV risk. However, large prospective studies on statin therapy are needed to evaluate the prognostic impact of reaching the suggested target of non-HDL-C and apoB instead of LDL-C in high-risk patients.

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