Residual cardiovascular risk in diabetes and obesity: Targeting lipid abnormalities other than LDL cholesterol
Review Article

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ABSTRACT

Background: The majorities of statin-treated patients, in whom low-density lipoprotein cholesterol (LDL-C) targets have been achieved, have had recurrent cardiovascular events (CVE) with an absolute rate remain even higher among patients with disorders of insulin resistance, metabolic syndrome (MetS) and type2 diabetes mellitus (T2DM) as compared to patients devoid of these conditions.

Objectives: Provide updated key messages of lipid and lipoprotein abnormalities as indicator for cardiovascular disease (CVD) risk in patients with T2DM and obesity, as well as the current evidence-based treatment targets and interventions to reduce this risk.

Key messages: The Residual Risk Reduction Initiative (R3I) emphasized atherogenic dyslipidemia (AD) as the chief modifiable contributor to residual cardiovascular risk, especially in conditions associated with insulin-resistant, and call to improve awareness and clinical management. The probable benefit of residual CVD risk reduction suggests a role for treatment of persistently high TG concentration even in statin – treated patients, with TG lowering agents including fibrates, niacin, omega polyunsaturated fatty acids, and other non statin treatment. Therapeutic lifestyle changes including; medically assisted weight loss, physical activity, and dietary changes, as well as improvement of glycemic control should be an adjunct to lipid-lowering pharmacological therapies. Therapy should be concomitantly assessed for treatment tolerance and adequacy with focused laboratory evaluations and patient follow-up. Therapy should be boosted to attain goals according to risk level, and that even more intensive therapy might be warranted in patients with CVD history.

Keywords: Cardiovascular Risk, Type2 diabetes, Obesity, Atherogenic dyslipidemia, Lipid lowering treatment.

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Despite the indubitable evidence ensued over the past half-century, highlighting the featuring role of low-density lipoprotein cholesterol (LDL-C) lowering therapy in reducing the rate of cardiovascular events (CVE) [1]. Analysis of epidemiological data from the last three decades, in the United Kingdom [2], United States [3], and Australia [4], have unveiled a concealed trend toward distinct deceleration in reducing CVE rate and cardiovascular disease (CVD) mortality in younger men and women.

Epidemiological studies, however, have consistently confirmed that young patients with type 2 diabetes mellitus (T2DM) have an increased risk of morbidity and mortality through early years of life, with CVD as the major cause of death [5]. Moreover, Gu and associates reported slighter declines in CVD mortality among diabetics as compared to nondiabetic individuals, specifying that preventive measures may have been less effective for patients with T2DM [6]. In respond to this notion, Poothullil [7], have debated that these observations might possibly be attributed to the weight gain and hyperlipidemia related to insulin and sulfonylurea treatment, preventing individuals with T2DM from fully participating in the declining of CVD mortality. In addition, young patients with T2DM are more susceptible to secondary obesity-related complications, including hypertension, metabolic syndrome (MetS), and nonalcoholic fatty liver disease, all of which are associated with increased CV risk [5]. What is more, the majority of statin-treated patients, in whom LDL-C targets have been achieved, have had recurrent CVE; with an absolute rate remain even higher among patients with disorders of insulin resistance, MetS and T2DM, compared to patients devoid of these conditions [8].

This critical trend has raised concern that the progressive reduction in CVD mortality is being tapered by the counteracting robust increase of obesity in developed countries with a parallel escalation in T2DM and Met S [9]. Over the past two decades, the prevalence of obesity worldwide increased exponentially, with its subsequent triggering effect on the rate of MetS (20-30% of adults population) and T2DM (8.3% of the global population) [10, 11]. Additionally, a remarkable increase in T2DM among children and adolescents has been reported from less than 3% of all new cases in 1990 to around 45% in 2005 [12].

The increasing prevalence of these metabolic diseases and its consequent CVD risk has apprehensively makes the management of its complications of paramount importance. The present article aims to provide updated key messages of lipid and lipoprotein abnormalities as indicator for CVD risk in patients with T2DM and obesity, as well as the current evidence-based treatment targets and interventions to reduce this risk.

Residual CV risk and Atherogenic Dyslipidemia: Residual CV risk, according to the Residual Risk Reduction

Initiative (R3I); a worldwide academic initiative established to address this issue, is defined as the risk of CVE that persists despite achievement of current evidence-based treatment goals for LDL-C, blood pressure, and glycemic control [13]. The R3I stressfully emphasized atherogenic dyslipidemia (AD) as the chief modifiable contributor to residual cardiovascular risk, especially in conditions associated with insulin-resistant, and call to improve awareness and clinical management of AD by identified three key priorities for action: recognition of AD in patients at high risk with or without diabetes; implementation and adherence to guideline-based therapies; and to improve therapeutic strategies for managing AD [14].

Atherogenic dyslipidemia often associated with obesity, glucose intolerance, diabetes, and metabolic syndrome is demarcated as an imbalance between apoprotein B-containing proatherogenic triglyceride-rich lipoproteins (TRLs) and apoprotein AI-containing antiatherogenic high-density lipoproteins (HDL) [13]. As illustrated in Table 1, TRLs comprise two clusters: chylomicrons (CM) and their remnants (CMR), each are carrying one Apo B 48: and very-low density lipoproteins (VLDL) and their remnants (VLDLR), each are carrying one ApoB100.

Table 1: Distribution of fasting and non-fasting TRLs particles and their major corresponding apoproteins.

Fasting		Non-Fasting	
Triglyceride-Rich Lipoproteins	Apoproteins	Triglyceride-Rich Lipoproteins	Apoproteins
Chylomicrons Remnants	ApoB48	Chylomicrons	ApoB48
VLDL	ApoB100	Chylomicrons Remnants	ApoB48
VLDL Remnants	ApoB100	VLDL	ApoB100
		VLDL Remnants	ApoB100

Among TRLs, non-fasting particles are considered as a major contributor to residual CV risk, even in patients on statins whose LDL-C reaches target. These lipoproteins are a mixture of CMR and VLDLR. Their atherogenicity is related to their ability to deliver cholesterol into vessels walls [15]. Accordingly, atherogenic dyslipidemia is characterized by low levels of HDL cholesterol (HDL-C), high levels of triglycerides (TG), and a high LDL particle number (LDL-P), and it is best recognized from results of a non-fasting lipid panel by the presence of high levels of non-HDL cholesterol and/or low total cholesterol/HDL-C ratio [16].

Indicators of Residual CV Risk: The use of non-fasting as opposed to fasting TG levels, prompted by their proposed superiority as predictors of CVE [17, 18], was highly substantiated in the scientific statement of the American Heart Association (AHA) on TG and CVD [19]. The statement suggests the use of non-fasting TG level> 200 mg/dL in screening for hypertriglyceridemia, and recommend for further follow-up with fasting TG level to designate borderline high (150–199 mg/dL), high (200–499 mg/dL), and very high (> 500 mg/dL) TG levels, with optimal fasting TG level defined as<100 mg/dL as indicator of metabolic health. Moreover, whenever TG level surpasses 200 mg/dL, the latest NCEP ATP III guidelines support the use of non-HDL-C in preference to LDL-C as a secondary target for lipid therapy [20]. More so, non-HDL-C which measures the cholesterol content in all atherogenic Apo B-containing lipoproteins, including LDL, intermediate density lipoprotein (IDL), lipoprotein(a), VLDL,VLDLR, CM, and CMR, has been reported to predict CV risk better than LDL-C [21].

Otherwise, Apo B has been suggested as a superior predictor of CVD not only to LDL-C, but even to non-HDL-C [22]. The rationale behind this superiority is of three fold; first, in hypertriglyceridemia, cholesterol content in LDL is less than normal: secondly, Apo B computes each LDL particle similarly no matter how much cholesterol it contains: and thirdly, LDL particle number (LDL-P) may be more relevant to atherosclerosis than how much cholesterol they carry. However, ATP III guidelines disfavor the use of Apo B because of limited assay accessibility in clinical laboratories and the lack of a national standardization program [20]. Nevertheless, in view of the accumulated data reported since ATP III was released in 2001, and in the presence of standardization, a report of the thirty-person/ten-country panel including international experts has recommended a revision of this assessment [23].

In the consensus statement endorsed by the American Diabetes Association (ADA) and the American College of Cardiology (ACC), the panel concluded that patients with T2DM with relatively normal levels of LDL-C may suffer increased levels of small dense LDL particles. Hence, assessment of CV risk might be better served by NMR-measured LDL-P or it's more widely available alternate measure, namely the Apo B [24]. Thereafter, the American Association for Clinical Chemistry (AACC) published their position statement on the role of lipoproteins in CVD risk, suggesting that a reduction in LDL-P or Apo B is a better indicator than reduction in LDL-C for the assessment of residual CV risk and therapeutic effectiveness [25]. The AACC consensus paper also states that non-HDL-C, like LDL-C, may not reflect the residual risk associated with increased LDL-P, leaving patients treated to LDL-C or non-HDL-C goals with potential residual risk, unless they have achieved consistently low LDL-P.

On the other side, the antiatherogenic HDL represents a complex mixture of various particles in terms of origin, size, composition and structure with different biological functions. This functional heterogeneity has so far hindered a liable interpretation for the results obtained from studies rely on the simple measurements of HDL-C; because this measure may include an amount of functionally impaired HDL that in fact accelerate atherogenesis. Subsequently, high HDL-C may not always indicate the protective antiatherogenicity of these particles, nor are low HDL-C always reflect HDL dysfunction [26]. Nevertheless, currently there is no sufficient clinical evidence to support the use of HDL subclasses analysis, or any applied method of assessing HDL functionality.

However, the number of HDL particles (HDL-P), rather than its own cholesterol content, seems to be more inversely related to CVE and may eventually reflect residual

CV risk [27]. But unlike the atherogenic Apo B-containing lipoproteins, each HDL particle carries between two and five Molecules of Apo AI and, therefore, the level of Apo AI do not accurately reflect HDL-P.

Non-Statin Lipid Lowering Interventions to Reduce CVD Residual Risk: To date, statins are still considered the most effective lipid-lowering drugs used in clinical practice for both primary and secondary CVD prevention. In addition to their non-HDL-C lowering capacity, mainly via their LDL-C lowering action, a parallel TG lowering effect of statins was reported with the highest effect at higher baseline TG level [28]. Moreover, trials of statin revealed that increased baseline TG levels is a strong predictor of increased CVD risk [29], and that statins reduced CVD in patients who had high baseline TG levels [30]. This has provided a rationale for statin and non-statin therapy in the modification of CVD risk among patients with mild to moderate hypertriglyceridemia.

Contrary to the discernible association between LDL-C lowering therapy and CVD risk reduction, pharmacological intervention trials targeting TG reduction have failed to reach dependable conclusions, mainly due to the simultaneous impact of these interventions on other lipid and lipoprotein fractions, as well as on their proatherogenic and antiatherogenic properties[31]. However, the probable benefit of residual CVD risk reduction suggests a role for treatment of persistently high TG concentrations, even in statin-treated patients, with TG lowering agents including fibrates, niacin, omega-3 polyunsaturated fatty acids, and other non-statin treatments.

Fibrates, with its prominent lowering effect on plasma TG have been tested in numerous studies and randomized clinical trials covering various populations [32, 33]. The post hoc analysis of these trials exposed a statistically significant reduction in relative risk for CVD events, which was greater in patients with AD as to those without this condition [34, 35]. This notion was additional confirmed by a recent systematic review and meta-analysis, encompassing 18 trials, and reporting a 10% relative risk reduction for major CVE and a 13% relative risk reduction for coronary events, with subgroup analysis revealing that fibrates significantly reduced cardiovascular events in individuals with hypertriglyceridemia (defined as TG level > 200 mg/dL) and alone or in combination with low HDL-C (levels < 40 mg/dL) [36]. Therefore, in appropriate patients with AD, fibrates either as monotherapy or combined with statins, are consistently associated with reduced risk of cardiovascular events. Accordingly, fibrates currently constitute an indispensable part of the modern anti-dyslipidemic arsenal for patients with atherogenic dyslipidemia [37].

Niacin is another agent approved for the treatment of AD. It favorably lowers all atherogenic lipoprotein classes, explicitly Apo B-containing lipoproteins, including lipoprotein (a). Conversely, niacin increases hepatic Apo A1 synthesis and reducing HDL clearance from the circulation which results in a potent effect on raising HDL-C levels. In addition, niacin also has been reported to lower TG levels [38]. However, two large trials, namely, the AIM-HIGH and the HPS2-THRIVE, conducted to assess the clinical benefits of adding extended release niacin to an intensive statin therapy, have failed to detect the expected clinical reduction in CVE beyond statin therapy alone, despite an observed increases in HDL-C levels as well as a reduction in TG levels during both studies [39,40]. Even with these negative results, niacin remains a treatment option and may play a role in the treatment of certain conditions and among specific patient groups like statin intolerant patients.

Omega-3 polyunsaturated fatty acids (PUFAs), another non-statin lipid lowering agent, have a dose-dependent TG-lowering effect, with the greatest action observed in patients with hypertriglyceridemia [41]. Doses as high as 4 g/day, have been reported to be associated with 5-10% adverse increases in LDL-C levels [42]. Although large clinical trials have reported a reduction in major CVE with omega-3 fatty acid supplementation [43], these cardiovascular benefits are thought to be predominantly a result of effects on cardiac rhythm rather than on lipoprotein metabolism. Likewise, the JELIS [44] confirmed that combination of polyunsaturated fatty acids with low-dose statin decreased the rate of major CVE as compared to statin alone; with minimal reduction in TG level suggesting that the observed risk reduction was not mediated by its TG lowering effect.

The AACE/ACE CVD Risk Factor Modifications Algorithm: Through the Comprehensive Diabetes Management Algorithm [45], representing the current official position of the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), a separate algorithm embracing hypertension and dyslipidemia routes was devoted for the management of CVD risk among diabetic patients. Six lipid parameters were proposed for the assessment of CVD risk in dyslipidemia route, with the desirable levels for these measures described for two general risk categories (Table2).

Table 2: The AACE / ACE desirable lipid levels according to risk categories [45].

Lipid Parameters	Risk Categories	
	Moderate*	High**
LDL-C (mg/dL)	< 100	< 70
Non-HDL-C (mg/dL)	< 130	< 100
TG (mg/dL)	< 150	< 150
TC/HDL-C	< 3.5	< 3.0
Apo B (mg/dL)	< 90	< 80
LDL-P (nmol/L)	< 1200	< 1000

* DM but no other major risk and/or age <40.
** DM + major CVD risk(s) (HTN, Family history, low HDL-C, smoking) or CVD.

Attempting to modify CVD risk factor, the document stressed that intensifying therapeutic lifestyle changes including; medically assisted weight loss, physical activity, and dietary changes, as well as improvement of glycemic control should be an adjunct to lipid-lowering pharmacological therapies, with statin as the first line treatment, in addition to non-statin agents (fibrate, omega 3

ethyl esters, and niacin) if TG levels are >500 mg/dL. However, for statin-intolerance, alternate statin and lower statin dose or frequency should be tried before prescribing any non-statin LDL-C lowering agent (e.g., ezetimibe, colesevelam and/or niacin).

The AACE/ACE current official position, as a final point, recommended concomitant assessment of treatment tolerance and adequacy with focused laboratory evaluations and patient follow-up, and affirmed that therapy should be boosted to attain goals according to risk level, and that even more intensive therapy might be warranted in patients with CVD history.

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