Reducing vascular events risk in patients with dyslipidaemia: an update for clinicians

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***Abstract*:** Reducing the risk of vascular events in patients with dyslipidaemia requires cardiovascular disease risk stratification and lifestyle/pharmacological intervention on modifiable risk factors. Reduction of low-density lipoprotein cholesterol (LDL-C) with statins is highly effective in reducing cardiovascular disease in patients with and without diabetes, but leaves unaddressed a sizeable residual vascular risk (RvR), which is rarely quantified in routine clinical practice. Such RvR may relate to lack of strict target attainment for all atherogenic variables [LDL-C, non-high-density lipoprotein cholesterol (HDL-C) and/or apolipoprotein B_{100}]. Another substantial lipid-related and modifiable RvR component is related to atherogenic dyslipidaemia, especially as global rates of obesity, type 2 diabetes and metabolic syndrome are increasing. Atherogenic dyslipidaemia is associated with insulin-stimulated very-low-density lipoprotein overproduction and reduced reverse cholesterol transport. The hallmark of atherogenic dyslipidaemia is the coexistence of low HDL-C and elevated triglycerides. Therapeutic lifestyle changes and combination lipid-lowering therapy with drugs targeting atherogenic dyslipidaemia (such as fibrates or innovative drugs targeting atherogenic dyslipidaemia and/or apolipoprotein B_{100} metabolism) on top of background statins, have a potential to reduce RvR in high-risk groups, as shown in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which combination therapy with simvastatin plus fenofibrate decreased macrovascular risk in patients with diabetes and atherogenic dyslipidaemia, and retinopathy risk irrespective of baseline lipids.

***Keywords*:** cardiovascular risk, low-density lipoprotein cholesterol, apolipoprotein B, atherogenic dyslipidaemia, metabolic syndrome, diabetes

Introduction

Reducing the risk of vascular events in patients with dyslipidaemia requires the following: cardiovascular disease (CVD) risk stratification (absolute and relative), based on identification of nonmodifiable and modifiable risk factors (RFs), and lifestyle or pharmacological reduction of the level of exposure to the modifiable RFs. Such an approach has had substantial success over the past decades for the common form of hypercholesterolaemia related to raised levels of low-density lipoprotein cholesterol (LDL-C), which is related to increased numbers of circulating LDL. Following implementation of therapeutic lifestyle changes (TLC), many patients with dyslipidaemia will not decrease LDL-C sufficiently, and will require lifelong therapy with a lipid-lowering drug (LLD) in order to reduce this major lipid-related modifiable component of CVD risk. In practice, LDL-C lowering usually means LLD monotherapy, with a statin as the preferred first agent when lifestyle interventions (i.e. diet and exercise) are not sufficiently effective [Genest *et al*. 2009; Katcher *et al*. 2009; Ridker *et al*. 2008; Graham *et al*. 2007; Shepherd *et al*. 2006; LaRosa *et al*. 2005; Colhoun *et al*. 2004; Grundy *et al*. 2004; Bonetti *et al*. 2003; HPS Collaborative Group, 2003; Sacks *et al*. 2000; Brown *et al*. 1990].

Current management of LDL hypercholesterolaemia

Major guidelines recommend 'aggressive' lowering of elevated LDL-C in patients with hypercholesterolaemia [Genest *et al*. 2009; Graham *et al*. 2007; Grundy *et al*. 2004]. Statin therapy is highly effective and usually safe, and is considered the mainstay of dyslipidaemia management.

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Statins act by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A reductase enzyme, with secondary upregulation of hepatic uptake of circulating LDL, thereby substantially decreasing the blood levels of circulating cholesterol [total cholesterol, LDL-C, non-high-density lipoprotein cholesterol (HDL-C)], as a result of lowered LDL particle numbers (LDL-P). Statins also markedly reduce blood levels of apolipoprotein B_{100} (apoB), the major atherogenic apolipoprotein, a single molecule of which is found on each LDL particle, as well as on each one of their triglyceride (TG)-rich precursors, that is, the very-low-density lipoproteins (VLDLs), the intermediate-density lipoproteins and VLDL remnants. Numerous studies have demonstrated the effectiveness of statins in reducing CVD risk in primary and secondary prevention. Data from large randomized controlled trials (RCTs) and meta-analyses of landmark studies have established that CVD risk related to hypercholesterolaemia is proportional to baseline LDL-C level, and that risk reduction following LDL-C lowering with a LLD parallels the achieved magnitude of the decrease in LDL-C, both in primary and secondary prevention, and in nondiabetic and diabetic populations [Ridker *et al.* 2008; Shepherd *et al.* 2006; LaRosa *et al.* 2005; Colhoun *et al.* 2004; Bonetti *et al.* 2003; HPS Collaborative Group, 2003; Sacks *et al.* 2000; Brown *et al.* 1990].

LDL-C targets and 'the lower is better' paradigm

Most guidelines recommend achievement of LDL-C levels based on values obtained from the distribution of calculated or measured LDL-C values in reference, asymptomatic CVD-free populations. A value less than 130 mg/dl was selected for initiating LLD with a statin in patients with CVD or as a target in CVD-free patients with hypercholesterolaemia, with lower values (<100 mg/dl and <70 mg/dl) in higher-risk and highest-risk populations with CVD or considered as CVD equivalent respectively [Genest *et al.* 2009; Graham *et al.* 2007; Grundy *et al.* 2004]. Such linearity in CVD risk reduction, coupled with the availability of a wide range of generic and nongeneric statins, including second- and third-generation statins with marked lipid-lowering effects; the potential to amplify the effects of statins with ezetimibe in order to attain lower LDL-C and/or apoB targets [although the added efficacy of this association (*versus* statins alone) in terms of cardiovascular (CV) events and mortality reduction needs to be confirmed]; the overall safety of the class; and the impressive corpus of evidence-based data from large RCTs, underlies the current paradigm of 'the lower is better' with regard to CVD risk reduction and 'on-statin', achieved LDL-C level [Shepherd *et al.* 2006; LaRosa *et al.* 2005]. LDL-C is unique among modifiable biochemical or clinical variables because its relationship with CVD risk follows a 'J-curve', in contrast with blood pressure, glycaemia, body mass index or glomerular filtration rate. Achieving low LDL-C (<70 mg/dl), however, does not necessarily imply that CVD risk associated with non-LDL dyslipidaemia will be under control, as shown by clinical trials demonstrating higher cardiovascular residual risk when HDL-C was low (<40 mg/dl) [deGoma *et al.* 2008; Barter *et al.* 2007].

Because of their heightened CVD risk, patients with the common form of type 2 diabetes mellitus (T2DM) are a choice subgroup to benefit from widespread statin use in primary or secondary CVD prevention, irrespective of baseline LDL-C levels – those patients in primary prevention being considered as secondary prevention equivalent, with lower LDL-C targets than patients without diabetes [American Diabetes Association, 2010; Mazzone *et al.* 2008; Schramm *et al.* 2008; Buyken *et al.* 2007; Hermans, 2007; Juutilainen *et al.* 2005; Haffner *et al.* 1998]. Whether statin therapy affords additional benefits in terms of CVD risk reduction, independently of LDL-C lowering, remains a subject of debate. The potential pleiotropic effects are ascribed to the following: improvement in endothelial function; antioxidant and anti-inflammatory properties; plaque-modifying effects; antithrombotic properties; antiangiogenic effects; vasculogenic actions; and cardioprotective, antihypertrophic effects [Ridker *et al.* 2008; Bonetti *et al.* 2003].

The changing epidemiology of dyslipidaemia

Because of shifting paradigms and stricter targets for LDL-C, an ever-increasing number of patients are being identified with LDL-C hypercholesterolaemia. In addition, rates of dyslipidaemia are increasing worldwide in the wake of the obesity pandemic and the global rising prevalence of the metabolic syndrome (MetS), two comorbid conditions associated with high lipid- and nonlipid-related vascular risk and increased risk for new-onset diabetes [Hermans and Fruchart, 2010; Alberti *et al.* 2009; Grundy *et al.* 2005; Bonora *et al.* 2004; Bruno *et al.*

2004]. This epidemiological drift is characterized by a unique non-LDL-C dyslipidaemia, in which low HDL-C occurs with raised TG, a two-sided metabolic abnormality known as atherogenic dyslipidaemia (AD). The underlying driver of AD is hepatic VLDL overproduction secondary to insulin resistance and compensatory hyperinsulinaemia. Other abnormalities in AD include increased number of circulating LDL-P and reduced rates of reverse, antiatherogenic cholesterol transport [Hermans and Fruchart, 2010; Adiels *et al*. 2008; Assmann *et al*. 2007; Blasiole *et al*. 2007; Kathiresan *et al*. 2006; Brites *et al*. 2000; Davignon and Cohn, 1996; Manninen *et al*. 1992].

Residual vascular risk in patients with dyslipidaemia receiving treatment

Relative CVD risk reduction after statin therapy is usually in the range of 25–35%, depending on baseline level of risk, patient's response to LLD, and dosage or type of statin prescribed. Despite the impressive success story of statins as a class, there are many unmet needs and barriers in CVD risk reduction persisting in patients with dyslipidaemia treated with statins. In real-life conditions, many patients on statins just do not attain their respective LDL-C targets according to current, evidence-based guidelines or recommendations and, as a consequence, remain exposed to an unacceptable level of residual vascular risk (RvR) [Hermans *et al*. 2010c]. Additional lowering of LDL-C, using high doses of powerful statins or the addition of ezetimibe, improves rates of target attainment and, in the case of statins, further decreases CVD events. Achieving very low LDL-C levels still leaves a substantial lipid-related RvR unaddressed because abnormal non-LDL lipids or lipoproteins (e.g. low HDL-C, high TG, or decreased reverse cholesterol transport) are unaffected or only slightly improved by statin therapy [deGoma *et al*. 2008; Friedewald *et al*. 2008; Fruchart *et al*. 2008a, 2008b; Barter *et al*. 2007; Libby, 2005].

The Residual Risk Reduction Initiative (R^3i) reviewed the evidence supporting RvR, and the close link between lipid-related RvR and AD, in two comprehensive call-to-action articles. Among sources of evidence for AD-related RvR were the prespecified or *post hoc* subgroup analyses demonstrating elevated RvR in patients with AD and/or MetS enrolled in landmark trials of statins or fibrates [Fruchart *et al*. 2008a, 2008b]. RvR represents the 'residual risk of incident vascular events or progression of established vascular damage persisting in patients treated with current evidence-based recommended care, including risk from established risk factors, such as dyslipidaemia, high blood pressure, hyperglycaemia, inflammation and unhealthy lifestyles, and risk related to emerging or newer risk factors' [Fruchart et al. 2008a, 2008b]. The grounds for which assessment and intervention in high-risk populations are so relevant for RvR are as follows: a substantial fraction of RvR is modifiable; a major component of RvR is related to dyslipidaemia; and RvR is amenable to reduction through TLC or pharmacological interventions with lipid-lowering or nonlipid drugs [Fruchart *et al*. 2008a, 2008b; Carey et al. 2010].

Nonmodifiable, standard modifiable and emerging risk factors/markers

Reducing RvR in patients with dyslipidaemia should be considered in the continuum of management of individual patients, with risk assessment based on documented risk factors as a first step. Table 1 lists a nonexhaustive series of conventional, emerging or candidate risk factors which may provide clinically relevant information on pathophysiological processes or, relating to modifiable factors, may constitute potentially modifiable targets in contemporary or future vascular RvR management. It is worth noting that despite the identification and provision of current standards of care, major modifiable risk factors are often not at targets in synchrony for a given individual. There may be the potential to further reduce RvR by controlling these unaddressed or emerging risk factors, or even by driving certain RFs below the recommended threshold or physiological range [Hermans and Fruchart, 2010; Genest *et al*. 2009; Hermans *et al*. 2009a, 2009b; Ridker *et al*. 2008; Graham *et al*. 2007; Stratton *et al*. 2006; Assmann *et al*. 2005; Fruchart *et al*. 2004; Grundy *et al*. 2004; Stevens *et al*. 2004; Yusuf *et al*. 2004].

Overweight, obesity, insulin resistance and the metabolic syndrome

Uncovering the presence of a MetS phenotype is an easy and noninvasive means of identifying a substantial component of modifiable RvR. The MetS phenotype is closely associated with obesity, central adiposity, insulin resistance and compensatory hyperinsulinaemia [Alberti *et al*. 2009; Bonora *et al*. 2004; Bruno *et al*. 2004]. The MetS represents a source and an estimate of increased

Table 1. Cardiovascular disease risk factors/markers in patients with dyslipidaemia: standard, emerging and candidate.

Nonmodifiable
Age
Being a man
Ethnicity
Family history of early-onset CVD
Former tobacco smoking
History of diabetes mellitus
Genes/loci and polymorphisms associated with CAD: *9p21*; *angiotensin-converting enzyme*; *apolipoprotein E4*; *ATP-binding cassette transporter A1*; *CFH*; *connexin 37*; *factor V*; *FLAP*; *galectin 2*; *haptoglobin*; *hepatic cytochrome 2C19*; *kalirin*; *KIF6*; *LRP6*; *LTA4H*; *lymphotoxin α*; *MEF2A*; *MHC2TA*; *PAI-1*; *PCSK9*; *prothrombin (20210A)*; *stromelysin 1*; *TSP 4*; *VAMP8*

Lipid related
Total cholesterol
LDL-C
Apolipoprotein B_{100}
Non-HDL-C
LDL particles number
Hypo-HDL-cholesterolaemia
Decreased apolipoprotein A-I
HDL subtypes distribution
Fasting hypertriglyceridaemia
Postprandial hypertriglyceridaemia
TG-rich lipoprotein remnants
Apolipoprotein CIII(+) apoB lipoproteins
Oxidized LDL
Antibodies to oxidized LDL
Small/dense LDL

Inflammatory
High-sensitivity C-reactive protein
Leucocyte count
Interleukin-6
Matrix metalloproteinase 9
Serum amyloid A
Soluble CD_{40} ligand
Vascular/cellular adhesion molecules
Lipoprotein-associated phospholipase A(2)
Periodontal disease

Behavioural/environmental
Current tobacco smoking
Air pollution (including airborne fine particles)
Sedentary lifestyle (surrogate: television viewing)
Physical inactivity
Quantitative/qualitative sarcopenia
Psychosocial stress
Socioeconomic factors
Decreased fruit and vegetable consumption

Cardiometabolic
Overweight–obesity (surrogate: increased BMI)
Central fat distribution (surrogate: enlarged waist)
Hypertension
Metabolic syndrome (presence *versus* absence)
Metabolic syndrome (score: 3/5–4/5–5/5)
Insulin resistance
Hyperinsulinaemia
Nonalcoholic fatty liver/steatohepatitis
Impaired fasting glucose/impaired glucose tolerance
Postprandial hyperglycaemia
Chronic hyperglycaemia (surrogate: elevated HbA_{1c})
Endothelial dysfunction
(Micro)albuminuria
Erectile dysfunction
Chronic kidney disease
eGFR <60 ml/min/1.73 m^2
Hyperuricaemia
Hyperhomocysteinaemia
Vitamin D deficiency
Sympathetic nervous system hyperactivity
Elevated resting heart rate
Coronary artery calcification
Left ventricular hypertrophy

Coagulation and haemostasis
Platelet activity
Platelet aggregation
Platelet size/volume
Lipoprotein(a)
Fibrinogen
Factor V, VII, and VIII
Fibrinopetide A
Plasminogen-activator inhibitor type 1
Prothrombin fragments 1 + 2
Tissue-plasminogen activator
Von Willebrand factor antigen
D-dimer

Varia
Cystatin-C
Asymmetric dimethylarginine
Iron overload
NT-pro-BNP
Cytomegalovirus
Herpes simplex virus
Helicobacter pylori
Chlamydia pneumoniae
Collagen vascular disease
Nonspecific ST-segment ECG changes
Obstructive sleep apnoea/hypopnoea syndrome
Psoriasis
Rheumatoid arthritis
Systemic lupus erythematosis
HIV infection on highly active antiretroviral therapy

ATP, adenosine trisphosphate; BMI, body mass index; BNP, brain natriuretic peptide; C, cholesterol; CFH, complement factor H; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FLAP, 5-lipoxygenase activating protein; $HbA1_c$, glycated haemoglobin; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; KIF6, kinesin-like protein 6; LDL, low-density lipoprotein; LRP6, low-density lipoprotein receptor-related protein 6; LTA4H, leukotriene A4 hydrolase; MEF2A, myocyte enhancer factor 2a; MHC2TA, major histocompatibility factor class 2 transactivator; PAI-1, plasminogen activator inhibitor 1; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triclycerides (triacylglycerols); TSP 4, thrombospondin 4; VAMP8, vesicle-associated membrane protein 8.

relative CVD risk beyond high LDL-C or other standard risk factors. Identifying a MetS phenotype may be used either as a dichotomic condition (presence *versus* absence), whereas score ranking within MetS syndrome categories represents a simple measure of stepwise rise in CVD risk, from 3/5 to 5/5. Likewise, the full-scale score is a surrogate from normal insulin sensitivity to increasing insulin resistance, from 0/5 to 5/5. Whereas the MetS is not an absolute CVD risk calculator, its presence suggests both increased relative RvR and increased risk to develop T2DM, the former associated with common pathophysiological determinants underlying the five standard CVD risk factors that are the basis of the current MetS definition: enlarged waist; hypertension; hyperglycaemia (as insulin resistance surrogate); low HDL-C; and high TG [Hermans and Fruchart, 2010; Hermans *et al*. 2010a; Sadikot and Hermans, 2010; Alberti *et al*. 2009; Assmann *et al*. 2008; Sadikot and Misra, 2007; Metascreen Writing Committee, 2006; Bonora *et al*. 2004; Bruno *et al*. 2004].

Type 2 diabetes mellitus

Determining RvR in patients with T2DM is of major relevance because a substantial fraction of the risk remains modifiable. Among nongender, nonmodifiable components of RVR in T2DM, ethnicity, certain polymorphisms and family histories should be considered when documenting initial risk. When obtaining family histories, parental history for premature-onset CVD, parental longevity, and family history for overweight and/or diabetes mellitus should be documented. Further, the presence of a MetS, observed in 80–90% of patients with T2DM, is also associated with higher microangiopathy risk in major target organs [Fioretto *et al*. 2010; Hermans and Fruchart, 2010; Hermans *et al*. 2010a, Jones, 2008; Stratton *et al*. 2006; Stevens *et al*. 2004].

Lipid-related residual vascular risk

Non-HDLs and cholesterol

RvR is inferred from current levels and target achievement of variables assessing atherogenic lipoproteins and their cholesterol load: LDL-C, LDL-P, non-HDL-C and apoB. apoB represents the most accurate estimate of CVD risk related to circulating cholesterol. In retrospect, it is somewhat regrettable that the high correlation between apoB and non-HDL-C became a major argument for delaying the introduction of apoB into routine clinical practice. This high correlation however does not mean that both parameters will always provide the same information regarding baseline and post-LLD RvR. Lack of clinical equivalence in certain situations may affect clinical decision, to the point that patients with high RvR should ideally be assessed using all three major atherogenic variables (LDL-C, non-HDL-C and apoB). In patients with diabetes, however, non-HDL-C appears to be a valid surrogate to apoB, and is an excellent biometrical measurement equivalent to the determination of this apolipoprotein, as recently reported using discriminant ratio and unbiased equivalence methodology [Hermans *et al*. 2011; Sniderman *et al*. 2009; Ballantyne *et al*. 2008; Jones, 2008; Sulkes *et al*. 2008; Ahmad *et al*. 2007; Ballantyne *et al*. 2006; Denke, 2005; Pischon *et al*. 2005; Sniderman, 2005; Lu *et al*. 2003].

Non-LDLs and non-LDL dyslipidaemia

A major component of post-statin lipid abnormalities associated with RvR appears to result from abnormal levels of TG-rich lipoproteins and their remnants, and from a decreased number and/or functionality of HDLs. This component of RvR is inferred from current levels, and target achievement, of the following variables: HDL-C, fasting TG, postprandial TG, TG-rich lipoprotein cholesterol (non-HDL-C minus LDL-C), and lipoprotein(a) [Hermans and Fruchart, 2010; Adiels *et al*. 2008; Mazzone *et al*. 2008; Assmann *et al*. 2007; Blasiole *et al*. 2007; Kathiresan *et al*. 2006; Brites *et al*. 2000; Davignon and Cohn, 1996; Manninen *et al*. 1992].

Atherogenic dyslipidaemia

AD represents a vivid example of a frequently overlooked, yet modifiable, lipid-related RvR condition. The hallmark of AD is raised fasting TG and low HDL-C levels, the underlying lipogenic processes driven by TG-rich VLDL hepatic overproduction as a result of selective liver insulin sensitivity to portal and systemic compensatory hyperinsulinaemia to whole-body insulin resistance. AD contributes to two out of five criteria defining the MetS, and is clearly a major contributor driving RvR in patients with MetS and T2DM [Hermans and Fruchart, 2010; Alberti *et al*. 2009; Adiels *et al*. 2008; Blasiole *et al*. 2007; Brites *et al*. 2000; Manninen *et al*. 1992].

The lipid and lipoprotein abnormalities in AD include the following:

1. a decrease in LDL size, often obscuring the absolute increase in LDL-P, such a diminution being a frequently overlooked marker for the presence of atherogenic TG-rich lipoproteins;
2. an increase in fasting and/or postprandial TG-rich $apoB_{48}$ and/or $apoB_{100}$-carrying lipoproteins and their remnants;
3. an absolute increase in hepatic VLDL production;
4. a relative shift toward overproduction of a highly atherogenic subset of apoCIII-carrying VLDL [Mendivil *et al*. 2010; Zheng *et al*. 2010];
5. detrimental changes in HDL composition and size, negatively affecting their antiatherogenic quality and shortening their natural history: lesser atheroprotective HDL subclasses, TG enrichment of HDL, secondary HDL remodelling and reduced half life, together with reduced nascent HDL production.

Most importantly, the abnormalities associated with AD are little affected by statin therapy, and frequently persist in patients with LDL-C at or near the target [Carey et al. 2010]. In T2DM, epidemiological and landmark intervention studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial, have clearly documented that AD also contributes to RvR of macrovascular disease, even when LDL-C and/or hyperglycaemia are controlled at baseline with background statin [ACCORD Study Group *et al*. 2010a; Fruchart *et al*. 2010].

Screening for AD and ranking its severity represents another unsolved issue in RvR management. One approach is to define AD as the combined occurrence of high TG levels and low HDL-C. This is not performed routinely for the following reasons: a lack of consensual cutoff values across gender, ethnicities and underlying conditions; a requirement for baseline lipid values prior to any LLD, and/or prior to insulin administration in T2DM; a *sine qua non* association criterion does not capture imbalances in respective contributions between these non-LDL lipid abnormalities; and a coincident criterion may underestimate the magnitude of AD in groups with spontaneously low TG, or with elevated TG levels prior to TG-lowering or insulin therapies [ACCORD Study Group *et al*. 2010a; Fruchart *et al*. 2010; Hermans and Fruchart, 2010; Dehout *et al*. 2008; Sumner *et al*. 2005].

In ACCORD Lipid, the presence of AD in patients with T2DM was defined as having concurrent HDL-C less than the first tertile plus TG greater than the third tertile of the study population baseline distribution of these two non-LDL parameters [ACCORD Study Group *et al*. 2010a]. Another approach to define AD, this time as a continuous variable, is to consider that both HDL-C and TG are continuous CVD risk variables themselves, which exert mutually reinforcing effects on RvR. As such, computing a ratio from log fasting TG (numerator) and fasting HDL-C (denominator) appears intuitively logical [Hermans *et al*. 2010a; Kim-Dorner *et al*. 2010; Bittner *et al*. 2009; Cordero *et al*. 2009; da Luz *et al*. 2008; Kannel *et al*. 2008; Dobiásová and Frohlich, 2001]. The TG to HDL-C ratio was also identified as an accurate marker for the presence of other features of the MetS, and also correlates with LDL-P size [Cordero *et al*. 2008; Hanak *et al*. 2004]. Interestingly, raised log(TG)/HDL-C values in patients with T2DM are related to both residual cardiometabolic risk and β-cell function loss. Normal values of log(TG)/HDL-C in nondiabetic, LLD-free, normal weight controls are 0.036 (mean); 0.034 *(*median); 0.012 (standard deviation*)*; 0.014–0.067 (range); and 0.029–0.042 (interquartile range) [Hermans *et al*. 2010b].

Cardiovascular disease risk estimation, calculation, risk equivalent and residual vascular risk assessment

Besides individual or combined assessment of standard modifiable variables, the absolute RvR of incident macrovascular events in patients with dyslipidaemia and without diabetes is based on the presence or levels of major standard risk factors. Integrative risk calculation is made easier for the clinician thanks to various charts, algorithms and calculators, such as Framingham, SCORE, PROCAM, QRISK, or Reynolds Risk Score [Wilson, 2009; Coleman *et al*. 2007; Eichler *et al*. 2007; Assmann *et al*. 2002; Kothari *et al*. 2002; Stevens *et al*. 2001]. As for patients without diabetes, RvR in patients with dyslipidaemia and T2DM can be also inferred from major risk factors using the T2DM-specific UK Prospective Diabetes Study risk engine [Stevens *et al*. 2001]. Of special concern is the complexity of staging patients with T2DM according to levels of

vascular prevention. For instance, a given patient may qualify as being both in primary prevention for coronary artery disease and in secondary prevention for retinopathy. In addition, patients with T2DM who respond to LLD therapy may differ according to end organ (macro- *versus* microvascular) and response to therapy may also differ according to baseline non-LDL lipids. Thus, in the ACCORD Lipid trial, macrovascular RvR was high in patients with T2DM despite statin monotherapy and LDL-C at or near the target. This risk was substantially decreased following combination therapy with LLD and fenofibrate only in patients with AD. However, the results from the ACCORD Eye substudy showed that this same combination decreased RvR of retinopathy progression irrespective of baseline non-LDL lipids [ACCORD Study Group *et al.* 2010a, 2010b; Fruchart *et al.* 2010].

Unmet needs and barriers for residual risk factor reduction in patients with dyslipidaemia

Proof of concept

Additional data are needed from RCTs in order to confirm the potential beneficial effect of combination therapy with LLD and a background statin to decrease a non-LDL-C-related modifiable component of RvR in patients with AD and/or the MetS and without diabetes, and also in various ethnic populations across the globe.

Risk calculators

Risk factors underlying RvR in patients with dyslipidaemia do not act in isolation, and their detrimental effect may be additive or potentiating. Confirmatory validation is needed for current risk calculators in computing post-LLD lipid values for RvR assessment or estimation of achieved risk reduction. In the future, an ideal RvR risk calculator should provide absolute and relative global CVD risk based on pathophysiology of atherosclerosis, with a lesser input from age, in order to start treating people with atherogenous lipid profiles from an earlier age onwards. Calculators should incorporate the presence of a positive family history for early-onset CVD, and take into account baseline *versus* post-statin levels of non-HDL-C, apoB, other non-LDL abnormalities, and encompass some measure of AD or its severity, together with diabetes duration and degree of glucose control, renal function, ethnicity, high-sensitivity C-reactive protein ($_{hs}$CRP) level, and the presence of subclinical signs of early atherosclerosis. An ideal risk calculator should provide both global and relative CVD risk estimates, as well as end-organ (coronary artery disease, cerebrovascular) risk and, in patients with diabetes, also provide RvR for microvascular disease according to the end organ (retina, kidney, nerves).

Laboratory assessment

Measuring pre- or post-statin LDL-C obviously will not capture all baseline CVD risk or its reduction in patients with dyslipidaemia, especially when LDL-C is calculated from routine lipid panels and not measured in patients with elevated TG or features of the MetS, and/or T2DM. A recent review was carried out of the underappreciation of opportunities for LDL-C management, and the implications of LLD, in patients with cardiometabolic states related to the frequent discordance between LDL-C and LDL-P in states of insulin resistance and compensatory hyperinsulinaemia [Rosenson *et al.* 2010]. Such patients often have 'normal' or near-normal LDL-C levels, sometimes even below target, while still being at elevated RvR because of raised LDL-P and non-LDL dyslipidaemia. Whereas the presence of AD and non-HDL-C can be inferred or calculated from the baseline lipid panel, additional determinations of apoB, apoA-I and lipoprotein(a) will help refine RvR [Hermans *et al.* 2011; Ballantyne *et al.* 2008, 2006; Jones, 2008; Sulkes *et al.* 2008; Ahmad *et al.* 2007; Denke, 2005; Pischon *et al.* 2005; Sniderman, 2005]. At present, there is no agreement on standardization or generalization of apoB measurement, nor on how to address issues such as fasting/postprandial hypertriglyceridaemia or LDL-P/LDL-C discordance [Sniderman *et al.* 2009; Ballantyne *et al.* 2008, 2006; Sulkes *et al.* 2008; Ahmad *et al.* 2007; Denke, 2005; Pischon *et al.* 2005; Sniderman, 2005]. The ongoing debate on standard *versus* expanded lipid panels is due to reactivate at the time the next National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) recommendations are issued. The pros and cons of expanded *versus* standard panels were reviewed by Sulkes and colleagues [Sulkes *et al.* 2008].

Current guidelines do not recommend widespread use of expanded lipid panels in RvR assessment, even in patients treated with statins [Genest *et al.* 2009; Graham *et al.* 2007; Grundy *et al.* 2004]. In the case of patients with high

cardiometabolic risk, however, there is a strong rationale for concurrent routine determination of LDL-C, non-HDL-C and apoB in order to ascertain whether a patient reaches all three targets. Regarding LDL-C and non-LDL-C therapeutic targets, a recent joint consensus statement from the American Diabetes Association and the American College of Cardiology Foundation recommends two sets of targets for LDL-C, non-HDL-C and apoB for patients with cardiometabolic risk, such as those with AD. LDL-C, non-HDL-C and apoB levels less than 100 mg/dl, less than 130 mg/dl and less than 90 mg/dl respectively are recommended for patients without diabetes or known CVD but with at least two additional major CVD risk factors, or with diabetes and without major CVD risk factors. LDL-C, non-HDL-C and apoB levels less than 70 mg/dl, less than 100 mg/dl and less than 80 mg/dl respectively are recommended for patients with the highest CVD risk, that is, known CVD or diabetes plus at least one additional major CVD risk factor [Brunzell *et al.* 2008].

A simple and almost costless means to increase doctors' and patients' awareness of non-LDL-dyslipidaemia would consist of systematically calculating non-HDL-C on routine laboratory lipid reports. Other potential improvements to routine laboratory lipid assessment or reporting may include the following:

1. a decrease in the level of TG above which LDL-C calculation is deemed imprecise or clinically discordant with estimated LDL-C;
2. for atherogenic ratios, providing doctors with the non-HDL-C/HDL-C ratio instead of or in addition to the total cholesterol/HDL-C ratio, because the former provides a costless surrogate, albeit as effective as the apoB/apoA-I ratio, as recently reported in patients with diabetes [Hermans *et al.* 2007];
3. the establishment of ethnic-specific cutoffs for defining the presence of AD, including values for patients of Afro-American descent or from sub-Saharan Africa [Dehout *et al.* 2008; Sumner *et al.* 2005];
4. the provision of the log(TG)/HDL-C ratio to better characterize non-LDL dyslipidaemia and AD, AD as a continuous rather than a dichotomic variable [Bittner *et al.* 2009; da Luz *et al.* 2008; Kannel *et al.* 2008; Dobiásová and Frohlich, 2001].

In the future, laboratory assessment of atherogenic/atheroprotective particle kinetics (production, clearance) will hopefully become routine measurements, together with baseline and post-LLD markers of the intensity of reverse cholesterol transport.

LDL-C lowering

Cholesterol is the cause of atherosclerosis and enters arterial walls as part of an atherogenic lipoprotein particle, generally an apoB-carrying LDL. Most of the increase in cholesterol content within an atherosclerotic plaque takes place between the asymptomatic state and the symptomatic state as a result of increased atherogenic particle burden. Implementing 'aggressive' LDL-C lowering with a statin after a CVD event in a patient with high LDL-C, while effective in reducing new-onset events, is physiopathologically untimely, and LDL-C lowering therapies should be implemented much earlier in life in all patients with dyslipidaemia [Friedewald *et al.* 2008; Libby, 2005].

The issue of further LDL-C lowering in patients at LDL-C target to enhance RvR reduction is at present not settled, neither is the issue of high-dose statin therapy *versus* statin amplification with ezetimibe to further decrease LDL-C. Whenever feasible, lipid-related RvR should be addressed by 'aggressive' reduction of supranormal baseline LDL-C levels using existing LLD and, in the future, with new LDL-C lowering agents [Costet, 2010; Watts *et al.* 2009]. Whereas statins are considered a safe and effective LLD for the vast majority of patients with dyslipidaemia, the observed rates of side effects and toxicity in real life appear higher than those reported from landmark RCTs, especially myalgia with or without muscle enzymes elevation. This may be partly explained by RCT design, with prerandomization exclusion of statin-intolerant volunteers during the run-in period on LLD.

It is ironic that despite the wide availability of statins and ezetimibe, and at times when one debates the force reduction of LDL-C into the below-normal range, undertreatment of diagnosed patients with elevated LDL-C remains worryingly prevalent. In the Centralized Pan-European survey on the Under-treatment of Hypercholesterolaemia (CEPHEUS) study, a European primary care setting survey on the undertreatment of hypercholesterolaemia, poor target attainment was observed across countries for patients with and without diabetes

with respect to LDL-C target attainment [Hermans *et al.* 2010c]. In CEPHEUS, patients with the highest CVD risk (T2DM in secondary CVD prevention) had the worst level of LDL-C target attainment. Thus only 58% of patients with T2DM and without coronary heart disease (CHD), and a mere 27% of patients with T2DM and CHD attained LDL-C targets of less than 100 mg/dl and less than 70 mg/dl respectively. In this survey, eight modifiable variables were associated with LDL-C target attainment: normal body mass index; not smoking; not having a MetS; current treatment with a statin; belonging to a medium–high CVD risk category; good treatment adherence; high patient awareness of current LDL-C level; and/or frequency of cholesterol reviews. Six nonmodifiable factors were also associated with LDL-C target attainment: age over 70 years; being a man; history of diabetes; history of hypertension; absence of peripheral arterial disease; and/or receiving LLD for secondary prevention [Hermans *et al.* 2010c].

Many factors associated with failure to meet LDL-C targets are shared with known barriers to the management of chronic diseases: the asymptomatic nature of dyslipidaemia during the primary prevention stage; lack of adherence to TLC; resistance to drug treatment; reluctance to increase LLD dosage or to switch LLD within classes, or to resort to combination LLD; misconception of potential side effects; poor adherence to prescribed treatment regimens; insufficient counselling; inertia on the part of doctors and healthcare providers in addressing all aspects of dyslipidaemia; faulty risk perception; insufficient laboratory follow-up checks; chronic disease misrepresentation; competing comorbidities or other chronic conditions; lack of patient empowerment and responsibility for self care; low socioeconomic or educational status; and increasingly unsupportive or overstretched healthcare systems.

Achievement of non-LDL-C targets

Lack of target attainment for non-LDL-C dyslipidaemia is not surprising in view of the current, overtly LDL-C-centric approach to dyslipidaemia management, especially in cardiology and primary care settings. Whereas some additional benefit would be expected from a policy aiming to further lower LDL-C in patients receiving more potent statin therapy (i.e. higher dosage, more powerful molecules, ezetimibe amplification), RvR is poised to remain elevated unless non-LDL dyslipidaemia is directly targeted, especially in patients with T2DM or the MetS, as shown in *post hoc* subgroup analyses of landmark trials or, recently, in ACCORD Lipid [ACCORD Study Group *et al.* 2010a]. In obesity, the MetS, insulin resistance and T2DM, a preponderance of small/dense LDLs prior to LLD may lead, in the absence of concurrent apoB or LDL-P measurements, to faulty perception of CVD risk because LDL-C is not markedly elevated. Relatively low baseline LDL-C levels may not only delay statin initiation but also affect LLD selection policy, with lower doses and/or less powerful statins preferred because the magnitude of the desired decrease in LDL-C appears small, and the LDL-C targets are potentially easier to attain.

While such interventions may be effective in attaining LDL-C targets in isolation, they frequently leave non-HDL-C and/or apoB above targets, and have little effect on AD components. In patients with obesity, the MetS or T2DM, statin monotherapy guided by isolated LDL-C assessment is associated with lesser likelihood of achieving non-HDL-C, apoB, HDL-C and TG targets, despite often attaining LDL-C targets, because of a preponderance of small/dense LDLs at baseline [Hermans and Fruchart, 2010]. Besides resorting to currently available combination LLD, newer pharmacological agents directed at high TG and/or low HDL-C are under development, including drugs directly targeting AD, and specific therapies that increase HDL quantity and quality or enhance reverse cholesterol transport [Costet, 2010; Watts *et al.* 2009]. Among novel HDL-directed pharmacotherapeutic strategies, promising results were recently reported on the safety and usefulness of directly augmenting apolipoprotein A-I (apoA-I) levels using intravenous apoA-I therapy (with recombinant apoA-I Milano/phospholipids, purified native apoA-I/phospholipids or autologous delipidated HDL), or following administration of oral upregulators of endogenous apoA-I production (RVX-208) [deGoma and Rader, 2011; Nicholls *et al.* 2011; Waksman *et al.* 2010].

Lifestyle interventions

Adoption of and long-term compliance to TLC should be improved because hypo-HDL-cholesterolaemia and high TG, the hallmark of AD states, as well as the three other defining

components of the MetS and insulin resistance are all particularly sensitive to TLC [Volek *et al.* 2008].

Combination therapy with lipid-lowering drugs

The complementary mechanisms of action of available LLD classes make them effective in combination therapy for T2DM or the MetS. However, combination therapy may raise other issues, such as compliance, cost, education and potential side effects from drug–drug interactions, although most of these can be addressed by rigorous pre- and postclinical testing, monitoring and, in certain patients, use of fixed-dose combinations. Combination therapy may allow LDL-C and non-LDL-C targets to be reached with a lower dose of statins and/or less potent/generic statins, thereby reducing not only the cost but also the potential for statin-related side effects developing over time [Chapman *et al.* 2010; Fruchart, 2010; Rosenson *et al.* 2010; Sacks *et al.* 2010; Rosenson, 2009; Ducobu *et al.* 2008; Friedewald *et al.* 2008; Polonsky and Davidson, 2008; Davidson, 2005].

A lipid-lowering therapy solely guided by the LDL-C target may not systematically deliver synchronous attainment of all atherogenic cholesterol targets because LLDs do not produce strictly proportional decreases in LDL-C, LDL-P, non-HDL-C and apoB [Sniderman *et al.* 2009; Ballantyne *et al.* 2008]. The lower the achieved LDL-C, however, the more likely it is that all critical variables (LDL-C, LDL-P, non-HDL-C and apoB) will attain their respective targets because over 90% of circulating apoB are found in LDL, which account for the bulk of non-HDL-C as well. This adds another logical rationale for titrating statins, or using more potent statins, and/or adding NPC1L1 inhibitors, such as ezetimibe, when further reduction in LDL-P is contemplated; or for considering combination therapies, in addition to a background statin and TLC, in order to attain all LDL-related targets (ezetimibe, bile acid sequestrants, niacin, fibrates), or to impact further on non-LDL features of dyslipidaemia, such as low HDL-C and/or elevated TG (fibrates, niacin, omega-3 fatty acids) [Sniderman *et al.* 2009; Ballantyne *et al.* 2008; Friedewald *et al.* 2008; Jones, 2008; Sulkes *et al.* 2008; Denke, 2005; Libby, 2005].

Numerous new LLDs are currently under study. They include VLDL production inhibitors (antisense oligonucleotides; small interfering RNA targeting apoB; apoB lipidation inhibitors; VLDL assembly inhibitors; microsomal triglyceride transfer protein inhibitors; farnesoid X receptor ligands), drugs affecting LDL receptor (squalene synthase inhibitors; thyromimetics; LDL receptor mRNA assembly or LDL receptor degradation modulators; PCSK9 modulators) or reverse cholesterol transport (cholesteryl transfer protein inhibitors; apoA-I Milano) [Costet, 2010; Watts *et al.* 2009]. Watts and colleagues reviewed a series of pharmacological and non-pharmacological interventions which may potentially have an impact, alone or in combination, on various aspects of apoB metabolism in the MetS by decreasing TG levels, LDL-C levels, VLDL-apoB (fractional clearance rate, production or concentration) or LDL-apoB (fractional clearance rate, production or concentration). These interventions include weight loss, exercise, phytosterols, peroxisome proliferator-activated receptor (PPAR-α, PPAR-γ or PPAR-δ) agonists, statins, niacin, fish oil, cholesterol absorption inhibitors, cholesterylester transfer protein inhibitors, endocannabinoid receptor blockers, $apoB_{100}$ antisense inhibitors, microsomal triglyceride transfer protein inhibitors, plus the possible combinations of statin plus fibrate, statin plus niacin, statin plus ezetimibe, and statin plus fish oil [Watts *et al.* 2009].

Additional trials and epidemiological data

There is an unmet need for supplementary, long-term outcomes data from statistically powered RCTs with combination LLD therapy using a background statin in patients with and without diabetes, taking into account the expected lower rates of incident CVD events in a post-statin era. Specifically, there is a surprising lack of RCTs on combination therapy in populations with AD at baseline. Such data would confirm and update current evidence derived from *pre hoc* or *post hoc* specified subgroups with AD. Globally, the proof of concept for RvR in various statin-treated patient groups is no longer needed, although additional data are needed to confirm that raising circulating levels of low HDL-C with standard or newer LLDs, alone or in combination, may favourably impact on RvR.

An 'ideal' type of RCT addressing AD-related RvR should enrol a large multiethnic population with high baseline CVD risk as a result of AD and/or other risk factors. It should include a mix of patients in primary or secondary vascular prevention, mostly without diabetes but with a

substantial subgroup with prediabetes or T2DM, all with confirmed AD at study entry, and treated with a background statin in order to achieve a baseline target LDL-C. Patients would then be randomized to either receive LLD treatment with a statin alone or combination therapy (fibrate, niacin, omega-3 fatty acids, other dietary interventions or new therapies acting on AD or its components) plus a statin. Prespecified subgroup analyses would be conducted for gender, primary *versus* secondary prevention, presence of the MetS, T2DM and ethnicity, and in patients with T2DM, microvascular endpoints as well [Hermans and Fruchart, 2010]. Such a design, implemented to some degree in ongoing niacin trials, should also be a prerequisite for candidate drugs targeting AD-related RvR. Thereafter, the next step would consist of translating new evidence on AD-related RvR and its management into guidelines and recommendations [Millán Núñez-Cortés *et al.* 2011; AIM HIGH; HPS2-THRIVE].

Education

There is a frequent lack of awareness of RvR in patients with dyslipidaemia receiving treatment and in healthcare providers. RvR assessment requires estimating both the absolute level of CVD risk before, and remaining after LDL-C lowering therapy, which is currently only inferred from post-statin LDL-C. Doctors, especially in primary care, and paramedical staff often have little, if any, knowledge on AD determinants and non-LDL dyslipidaemia, including common conditions such as elevated non-HDL-C and apoB, low HDL-C, or fasting/postprandial hypertriglyceridaemia. Patients and doctors should also have a better understanding of the concepts of RvR caused by LDL-P. Doctors should systematically screen their patients for AD or the presence/score of a MetS. Doctors also need to better understand the concept of variance of laboratory results, for example for TG, when making decisions about standard or expanded lipid panels in baseline/post-LLD conditions.

Multifactorial intervention and benchmarking

Upstream of RvR assessment and reduction, efforts should be made to markedly reduce the huge proportion of people with hypertension, dyslipidaemia and diabetes (or prediabetic conditions such as the MetS) who are still undiagnosed, and thus do not receive proper treatment. Current standard of care recommendations for patients with T2DM emphasize the significant impact of multifactorial interventions on major modifiable risk factors, such as implemented in the STENO trial, to achieve recommended levels of the following critical indicators: HbA_{1c} (glycated haemoglobin, surrogate for recent glucose exposure), LDL-C and systolic blood pressure (SBP). Yet, for patients with T2DM to achieve all targets is exceedingly rare; the vast majority remain at high RVR to develop incident micro- and macrovascular events and/or to suffer from progression of existing complications [Gaede *et al.* 2008, 2003; Jones, 2008].

The non-interventional, Optimal Type 2 Diabetes Management including Benchmarking and Standard Treatment (OPTIMISE) trial, performed across various European countries, investigated the effect of doctor's benchmarking on quality of care, assessed according to the percentage of patients with T2DM achieving preset targets provided by international guidelines for HbA_{1c}, LDL-C and SBP. Doctors were randomly assigned to receive either benchmarked feedback or nonbenchmarked feedback on their patients' modifiable outcome indicators (HbA_{1c}, fasting glycaemia, total cholesterol, HDL-C, LDL-C and TG). At baseline, the percentage of patients achieving preset targets was highly unsatisfactory: 51% (HbA_{1c}); 27% (SBP); and 35% (LDL-C), with a mere 5% (!) achieving all three targets [Hermans *et al.* 2010d].

Guidelines and recommendations

Guidelines and recommendations are constantly evolving. In general, current guidelines are based on absolute risk instead of lifetime risk, and not surprisingly, central to LDL-C given the wealth of evidence on the linearity of the decrease in CVD risk that parallels post-statin LDL-C reduction. The current LDL-C-based approach does not sufficiently target LDL-P and apoB, and replacing cholesterol-based guidelines with apoB-based recommendations to fully appreciate the effects of LLD on hypercholesterolaemia is long overdue. Another intrinsic advantage of apoB determination over the conventional LDL calculation using Friedewald's formula that guidelines should put emphasis on, including screening on a population basis, is the simple fact that apoB measurement does not require fasting conditions. The rationale for using apoB, apoA-I and their ratio as indicators of cardiac risk and as targets for LLD is strongly based

on scientific evidence [Hermans *et al*. 2007; Walldius and Jungner, 2006; Yusuf *et al*. 2004; Walldius *et al*. 2001].

From a RvR reduction perspective, guideline revisions should at least consider the following: redefining 'normal' LDL-C; establishing desirable levels for all atherogenic markers, including nonfasting TG; raising family history for premature-onset CVD to the level of a CHD equivalent in CVD risk stratification; reorienting LLD initiation criteria toward atherosclerosis pathogenesis; promoting a lipoprotein-based *versus* a LDL-C-based approach; upgrading non-HDL-C from a selective secondary target to a generalized primary target alongside LDL-C and apoB; providing AD cutoffs and post-LLD targets in patients with and without diabetes; defining subgroups of patients who might benefit from assessment of LDL-P or atherogenic particle size (baseline, poststatin or post-combination LLD); and providing specific target values for pre- and post-LLD expanded lipid panels, because some lipid measurements do not always exhibit parallel and proportionate shifts after TLC or LLD monotherapy or combination therapy. In addition, guidelines should provide additional guidance on issues such as below-target LDL-C lowering in the infranormal range for very-high-risk patients at current LDL-C target; defining patient subgroups in whom pharmacogenetic testing is worth considering [Damani and Topol, 2007]; defining subgroups who might benefit from serial assessment of $_{hs}$CRP (baseline, poststatin or post-combination LLD) or other inflammatory markers; and, in general, encourage earlier, longer and stronger interventions against LDL-C and AD in younger patients with dyslipidaemia.

The pros and cons of changing the approach to current management of LDL-C were reviewed by Forrester, who compared an approach based on small, incremental changes in recommendations *versus* more substantial changes [Forrester, 2010]. At present, LLD initiation is based on a history of CV events or an absolute 10-year risk estimation; statin use is advocated for those who meet risk criteria; choice of statin within the class is *ad libitum*; and treatment targets are stratified by risk [Genest *et al*. 2009; Graham *et al*. 2007; Grundy *et al*. 2004]. The following changes or reappraisals to LDL-C management all have some potential to improve CVD risk management in patients with dyslipidaemia: LLD initiation should be based on pathogenesis, with relative risk being assessed with respect to an individual's age group; statin use should be further stratified according to pharmacogenetics; a generic statin should be used first in asymptomatic patients; the treatment target on statins should aim towards the 'putative normal range' in all patients in the absence of drug toxicity [Forrester, 2010].

Patient subgroups, specific populations and type 2 diabetes mellitus

Increasing numbers of patients with dyslipidaemia also belong to specific subgroups, dealing with additional targets or priorities: T2DM, MetS, high-risk ethnogeographical populations, chronic kidney disease, and congestive heart failure. In T2DM, non-LDL dyslipidaemia and AD should be targeted by TLC, and combination therapy with a background statin. Among current LLDs targeting AD, PPAR-α agonists appear ideally suited to address AD-related lipid and lipoprotein abnormalities associated with RvR in patients with diabetes, and possibly those without, at LDL target, from VLDL overproduction to decreased reverse cholesterol transport [Hermans, 2010; Jun *et al*. 2010; Fruchart, 2009; Fruchart and Duriez, 2002; Staels *et al*. 1998]. In ACCORD Lipid, RvR of macrovascular events in diabetes was decreased with a lipid-lowering bitherapy combining fenofibrate on top of background simvastatin in patients with AD [ACCORD Study Group *et al*. 2010a; Fruchart *et al*. 2010a]. Fenofibrate also markedly decreased RvR of retinopathy progression, irrespective of baseline lipids and independently of glucose control [ACCORD Study Group *et al*. 2010b]. Nevertheless, as in patients without diabetes, innovative treatments are also needed for patients with T2DM to improve glycaemic control and clinical micro- and macrovascular outcomes.

Conclusion

Lipid-related RvR is frequently overlooked in patients with dyslipidaemia treated with statins, and on the rise globally because of rising rates of AD. Standard lipid panels, risk calculators and guidelines, as a result of their overwhelming LDL-C-based approach, are not designed to specifically address RvR. This is in spite of the fact that a substantial part of the risk is lipid related and modifiable by lifestyle changes, reinforcement of lipid-lowering therapy, or combination therapy with current or newer drugs targeting

AD and its underlying quantitative and qualitative lipoprotein abnormalities.

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