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Residual Vascular Risk in T2DM: The Next Frontier

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1. Introduction

In T2DM, macro- and microvascular complications represent the major cause for morbi-/mortality, decreased quality of life and healthcare costs. Current guidelines for standards of care in T2DM emphasize the significance of multifactorial intervention on standard modifiable variables, in order to achieve recommended levels of blood glucose, LDL-C and blood pressure. T2DM patients achieving such targets represent a minority. Many of those not meeting those targets are exposed to high residual vascular risk (RVR) to develop incident micro- and macrovascular events and/or to suffer from progression of existing complications. Determining RVR in T2DM patients is of major relevance, as a substantial fraction of it is modifiable, including a lipid-related fraction, associated with both LDL and non-LDL lipids and lipoproteins. Atherogenic dyslipidemia (AD) is characterized by raised fasting triglycerides and low HDL-C. AD contributes to RVR of micro- and macrovascular disease in T2DM, even when LDL-C and/or hyperglycemia are controlled. The presence of a metabolic syndrome, or its score, is an additional means to capture modifiable components of RVR for micro- and macroangiopathy. AD is best prevented and addressed by therapeutic lifestyle changes, fibrates, or nicotinic acid. In the ACCORD Lipid trial, RVR of macrovascular events was high despite background simvastatin, and was substantially decreased in patients with AD following bitherapy with fenofibrate plus simvastatin. In FIELD and/or ACCORD trials, fenofibrate also decreased RVR of retinopathy progression, irrespective of baseline lipids, reduced albuminuria incidence and risk of diabetes-related lower-limb amputations. These data suggest a wider role for fenofibrate in the management of multisite microvessel RVR in T2DM. As regards other anti-dyslipidaemic drugs, ongoing trials will establish whether targeting low HDL-C with niacin reduces RVR in high-risk T2DM patients.

2. Standards of care in T2DM and target attainments

In type 2 diabetes mellitus (T2DM), vascular complications represent the major cause for morbi-/mortality, decreased quality of life and healthcare costs. These chronic, long-term complications arise in the setting of elevated residual vascular risk (RVR) factors. These factors may not only damage *macrovessels*, leading to premature-onset coronary artery disease (CAD), cerebrovascular disease (transient ischemic attack (TIA) and/or stroke), or

peripheral arterial disease (PAD), but also affect *microvessels* leading to "diabetic complications", i.e. diabetes-specific long-term complications of chronic hyperglycemia: retinopathy, nephropathy or neuropathy. Certain vascular diabetic complications such as PAD, TIA/stroke, nephropathy or erectile dysfunction may arise from a combination of macro- and microangiopathies [1-6].

Low-density lipoprotein cholesterol (LDL-C)

Due to the overall efficacy of statins, and the relatively low baseline level of LDL-C in T2DM, LDL-C may be considered as the easiest-modifiable single parameter in diabetic patients [4,5,7-15]. However, in the recent *Centralized Pan-European survey on the under-treatment of hypercholesterolaemia* (CEPHEUS), a primary care survey from 8 European countries, under-treatment of hypercholesterolaemia was highly prevalent, with low total and LDL-C target attainment observed across countries [16,17]. In CEPHEUS, patients with the highest CV risk were T2DM patients with established cardiovascular disease (CVD) (i.e. patients in true secondary CV prevention). Yet, these highest-risk patients achieved the lowest level of LDL-C target attainment, with only 27% attaining the <70 mg/dL target. Moreover, only 58% of T2DM patients without CVD achieved LDL-C target <100 mg/dL. Eight modifiable variables were associated with LDL-C target attainment in CEPHEUS [17]:

1. normal body mass index;
2. being a non-smoker;
3. not having a metabolic syndrome (MetS) phenotype;
4. current treatment with a statin;
5. belonging to a medium-high CVD risk category;
6. good treatment adherence;
7. high patient's awareness of his/her current LDL-C level; and/or
8. frequency of cholesterol reviews.

Six non-modifiable factors were also associated with LDL-C target attainment:

1. age >70 years;
2. male gender;
3. history of diabetes;
4. history of hypertension;
5. absence of PAD; and/or
6. receiving LLD for secondary prevention.

Blood pressure (BP)

Controlling BP values in T2DM is of paramount importance, as it improves both macro- and microvascular outcomes. Such control is nevertheless challenging, as in the common form of T2DM, associated with the MetS and insulin resistance (IR), hypertension is not only highly prevalent, but also responds poorly to BP-lowering monotherapy intervention, and often requires multiple BP-lowering therapies on top of therapeutic lifestyle changes (TLC). In a recent study, only 16% of hypertensive T2DM treated with BP-lowering drug(s) in a tertiary-care setting achieved target BP <130<80 mmHg (<125<75 mmHg in case of proteinuria) [18].

Glycemic control and glycated haemoglobin (HbA_{1c})

Maintaining HbA_{1c} at target is an additional and constant challenge in T2DM, due to relentless loss of β-cell function over time and perpetual requirement for progressive stepping-up of glucose-lowering therapies [3,19,20]. Despite a large choice of oral and

parenteral therapies to lower blood glucose, target attainment as regards glucose control, or that of its surrogate HbA_{1c}, remains suboptimal. Among U.S. adults with diabetes in 1999–2002, only 49.8% had an HbA_{1c} <7.0% [19], a proportion similar to that found 10 years later in the *OPtimal Type 2 dIabetes Management Including Benchmarking and Standard trEatment* (OPTIMISE) trial [21].

Multifactorial intervention

Current guidelines for standards of care in T2DM emphasize the significance of multifactorial intervention on major modifiable RFs to achieve recommended levels of glucose, LDL-C and BP [12-15]. In the Steno study, a multifactorial intervention aimed at achieving recommended levels of critical indicators, including HbA_{1c} as surrogate for contemporary glucose exposure, LDL-C and systolic BP (SBP), was highly effective in reducing (micro)vascular complications [22-24].

As each of these three major modifiable targets have distinct determinants, natural histories and responses to TLC or pharmacotherapy, it comes to no surprise that only a fraction of T2DM patients will reach all three targets in synchrony in real-life conditions, leaving a majority of T2DM patients exposed to incident micro-/macrovascular events over time, or to progression of existing complications [18,21].

Many factors associated with failure to meet critical targets (HbA_{1c}, LDL-C. SBP) in T2DM represent previously identified barriers to chronic diseases management:

- age;
- disease duration;
- ethnicity;
- hyperglycaemia, hypertension and dyslipidaemia are mostly asymptomatic conditions, both in primary or secondary prevention;
- chronic disease misrepresentation;
- faulty perception of risk related to metabolic diseases is frequently observed among many T2DM patients, especially from ethnic minorities;
- patients are often poorly compliant to TLC;
- impractical, conflicting, or competing guidelines;
- many patients are poorly adherent to prescribed treatment regimens and/or to self-monitoring of blood glucose;
- fear of hypoglycaemia;
- concerns about weight gain;
- fear, misperception of the natural history of T2DM and of the risk/benefit ratio of adding exogenous insulin;
- delaying tactics at the time when lifelong insulin supplementation is deemed necessary (insulinophobia);
- reluctance to resort to subcutaneous injections or to perform capillary blood glucose self-testing;
- variations among patients in pharmacological response to antidiabetic, lipid-lowering and/or BP-lowering drugs;
- reluctance of physicians and patients to increasing drug dosage or to switching drugs within classes, or to resorting to combined therapies;
- complex treatment schemes and side-effects;
- wrong perception of potential side-effects;

- insufficient counseling;
- physicians and healthcare providers inertia delaying diagnosis or stepping-up of successive interventions;
- insufficient or unfrequent laboratory follow-up;
- competing T2DM-related co-morbidities and complications: obstructive sleep apnoea syndrome, chronic kidney disease or left ventricular dysfunction;
- lack of patient empowerment and responsibility for self-care;
- social pressures and discrimination related to aspects of diabetes management;
- low socioeconomic or educational status;
- unsupportive/overstretched healthcare systems.

3. Residual vascular risk in T2DM

RVR in T2DM is best defined as "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 dyslipidemia, high blood pressure, hyperglycemia, inflammation and unhealthy lifestyles, and risk related to emerging or newer risk factors" [4,5].

Determining macro- and micro- RVR in T2DM patients after implementation of standards of care is especially relevant when dealing with a chronic condition in which a substantial fraction of risk remains addressable, eg. by further lowering of exposure levels to standards RFs for micro- and macroangiopathy. Besides those modifiable components to RVR, one should also consider in risk assessment non-gender, non-modifiable components of RVR in T2DM, such as ethnicity, certain polymorphisms, and familial histories for (*i*) premature-onset CVD; (*ii*) obesity; and/or (*iii*) impaired glucose homeostasis or diabetes.

For macrovascular RVR, the usual approach involves single-variable assessment (HbA_{1c}, SBP and LDL-C) and targeting with TLC and/or pharmacotherapy. Due to an overwhelmingly glucocentric approach to T2DM management, the hierarchy of priorities follows a sequence in which hyperglycemia control ranks first, followed on a par with BP control and LDL-C lowering with statin as preferred agent, and then with a needs assessment for aspirin therapy as antiplatelet agent in high-risk patients [12-15].

Combined assessment of the harmful effects of multiple coexisting modifiable variables on RVR is rarely done for an individual T2DM patient, even though multifactorial intervention was demonstrated to be highly-effective in reducing micro- and macrovascular RVR [22-24].

Various calculators were proposed to estimate absolute risk in nondiabetic and diabetic patients [25-31]. At present, the best means to predict macrovascular residual risk of CAD (nonlethal or lethal) and stroke (nonlethal or lethal) in patients in primary macrovascular prevention is the T2DM-specific calculator *United Kingdom Prospective Diabetes Study* (UKPDS) *Risk Engine* [25,27,28]. It computes risk from the following variables: (*i*) known T2DM duration, (*ii*) age, (*iii*) gender, (*iv*) ethnicity, (*v*) smoking status, (*vi*) atrial fibrillation, (*vii*) current HbA_{1c} level, (*viii*) SBP, (*ix*) total cholesterol and (*x*) high-density lipoprotein cholesterol (HDL-C).

In a diabetic RVR perspective, such calculations of absolute predicted risk should ideally be performed prior to, and following implementations of standards of care to control hyperglycemia, high BP and hypercholesterolemia, with updated levels as input for estimating the magnitude of risk reduction. Such an approach will yield relevant figures

regarding (*i*) absolute vascular risk for CAD (nonlethal or lethal) and stroke (nonlethal or lethal), (*ii*) RVR for CAD (nonlethal or lethal) and stroke (nonlethal or lethal), together with (*iii*) absolute and (*iv*) relative decreases in CAD (nonlethal or lethal) and stroke (nonlethal or lethal) risks [25,27,28].

In order to illustrate RVR in T2DM from real-life conditions, we systematically assessed *UKPDS Risk* in 429 consecutive T2DM outpatients in primary macrovascular prevention. Eighty percent were White Caucasians, with a male-to-female ratio of 59:41. Mean age (1 standard deviation [SD]) was 62 (12) years, and known diabetes duration 12 (8) years. Sixteen percent were current smokers. Major modifiable variables in this cohort receiving standards of care in an academic setting were: total cholesterol: 173 (39) mg/dL; HDL-C: 48 (14) mg/dL; SBP: 137 (18) mmHg; and HbA_{1c}: 7.6 (1.47)%. The 10-year *UKPDS Risk Engine* estimated RVR values are illustrated in **Figure 1**. For the entire cohort, 10-year risk of CAD was high (almost 20%), a level in accordance with the status of *secondary-prevention equivalent* proposed for T2DM in primary macrovascular prevention [1,2]. According to gender, male T2DM patients had a 62% higher absolute risk for CAD than female patients, although the difference between genders was less marked for fatal CAD or stroke, and abolished for fatal stroke, illustrating the loss of protective effects afforded by the female gender in T2DM. Despite their primary CVD prevention status, those 429 patients had a high prevalence of microangiopathies: 46% (any microangiopathy); 21% (retinopathy); 23% (peripheral neuropathy); and 36% (albuminuria). These figures highlight the complexity of defining RVR in diabetic patients, who may at any time belong to different risk categories according to (*i*) the micro- *vs*. macrovascular level of dichotomy, and (*ii*) which target organs are under scrutiny.

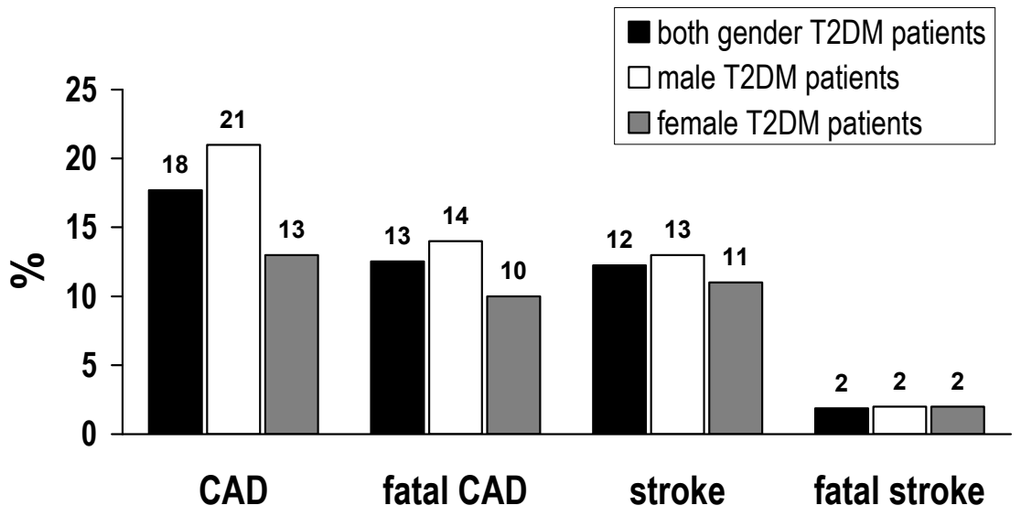

Fig. 1. *UKPDS Risk Engine's* 10-year prediction estimates for developing non-fatal and fatal coronary artery disease (CAD), fatal CAD, non-fatal and fatal stroke in T2DM patients of both gender (n=429; solid bars), both groups in primary cardiovascular prevention.The UKPDS Risk Engine computes the following variables, i.e. (1) known T2DM duration, (2) age, (3) gender, (4) ethnicity, (5) smoking status, (6) atrial fibrillation, (7) HbA1c level, (8) systolic BP, (9) total cholesterol (C) and (10) HDL-C.

With respect to microangiopathy, individual RVR assessment is limited to an "educated guess" relating *hyperglycemia exposure time* (with known diabetes duration as surrogate) to *hyperglycemia severity* (with current HbA_{1c} as surrogate). Unfortunately, there exists no assigned microvascular calculator available for estimating 10-year absolute risk in major target organs, such as retina, kidney or peripheral nerves destined to diabetic patients or to prediabetic patients with rapid loss of β-cell function and as such at very high risk for new-onset T2DM. Such a limitation in microangiopathic RVR represents a truly unmet need for T2DM management. Such is also the case when it comes to estimating absolute RVR in end-organs at risk for combined micro- and macroangiopathies, such as PAD in lower limbs, cerebrovascular disease, certain subtypes of nephropathy, or erectile dysfunction. Other limitations of current risk calculators for T2DM patients include: (*i*) the complexity of the underlying pathophysiological processes; (*ii*) the poor predictive value of (micro)albuminuria as surrogate to diabetes-related nephropathy; (*iii*) the lack of effective clinical surrogate for early-neuropahy; and (*iv*) the exclusion of familial histories for diabetes, early-onset CVD, obesity and/or IR and of their mutual metabolic/vascular impacts [25-32].

4. Atherogenic dyslipidemia

A major component of modifiable RVR is lipid-related, both associated with LDL and non-LDL, including atherogenic dyslipidemia (AD). Epidemiological studies and landmark intervention trials clearly established that AD contributes to RVR for macrovascular disease in T2DM, even when LDL-C and/or hyperglycemia are controlled at baseline. The hallmark of AD is raised fasting TG and low HDL-C levels, two routinely available markers of a series of complex and deleterious metabolic abnormalities which affect, in a proatherogenic way, LDL and non-LDL lipoproteins composition and numbers. These abnormalities also diminish, in an antiatherogenic way, the dynamics and magnitude of reverse cholesterol transport [33-45].

The underlying process driving AD in T2DM or nondiabetic patients consists of (*i*) overproduction by the liver of TG-rich, apolipoprotein B_{100}(apoB)-carrying lipoproteins of the very-low density lipoprotein (VLDL) class, as a direct result of (*ii*) whole body IR and compensatory hyperinsulinemia, leading to (*iii*) raised portal insulin levels, which affect (*iv*) VLDL assembly and export by the hepatocyte, as a consequence of preserved insulin sensitivity of select pathways for lipogenesis and TG-rich lipoproteins synthesis [33,34,36,37,41,45].

Screening for AD provides a clinically-relevant and easy means to capture RVR associated with low HDL-C, high TG and their determinants. Such screening is not routinely performed due eg. to lack of general agreement on criteria or cut-offs based on current *vs.* baseline HDL-C and TG values. One way to diagnose AD consists of establishing the combined occurrence of high TG levels and low HDL-C. This seemingly easy estimation is rarely performed as such, due to (*i*) lack of consensual cut-off values across gender, race/ethnicities or underlying conditions; (*ii*) the requirement for baseline lipid values (prior to lipid-lowering drugs (LLD)); and (*iii*) the limiting fact that a *sine qua non* co-occurrence definition does not take into account the linearity of these non-LDL abnormalities, since both HDL-C and TG are continuous CVD risk variables [35,38,39,40,42,44,45]. Such an approach based on co-occurrence may also underestimate AD prevalence and severity in T2DM subpopulations with spontaneously low (Afro-

Americans, sub-Saharan Africans) or elevated TG levels [46-48]. A more rationale approach would be to use ratios between TG and HDL-C in order to incorporate each component's information as continuous variable while increasing the epidemiological potency by having the atherogenic TG variable as *numerator* together with the anti-atherogenic HDL-C as *denominator* [35,38,39,40,45]. We showed that *log*(TG)/HDL-C is a simple means to estimate AD and the residual CV risk it confers to T2DM patients. Thus, this AD surrogate ratio was associated with major cardiometabolic and glucose homeostasis determinants, as well as with poorer metabolic control, and related to macroangiopathy prevalence and estimated *UKPDS* CAD risk [44].

5. Metabolic syndrome

Low HDL-C and high TG are part of the MetS definition, either as individual AD component or in combination. The presence of a MetS phenotype or its score (from 0/5 to 5/5) is another simple means to capture RVR. Identifying a MetS phenotype may be used as a dichotomic state (presence *vs.* absence). In addition, score ranking within MetS syndrome categories, besides providing a stepwise surrogate for IR/hyperinsulinemia, also provides a simple means to determine increasing CV risk categories (from 1/5 to 5/5 for T2DM patients). While the MetS is not an absolute risk calculator, its presence hints to heightened relative RVR, as a result of exposure to standard CV RFs (underlying the current definition, such as hypertension and hyperglycemia) or due to the presence of AD. MetS ranking is also associated with lesser target achievement for key variables, such as HbA_{1c}, SBP or LDL-C. In addition, the MetS also associates with microangiopathy prevalence in major target organs [18,49-55].

6. New and emerging risk markers and factors

Many candidates RFs were proposed in the last decades to improve CVD risk assessment or RVR appraisal, although few, if any, are globally acknowledged in guidelines as part of standards of care and follow-up. These candidate RFs include eg. biological markers of low-grade subclinical systemic inflammation, markers of plaque instability, of endothelial dysfunction, or of proatherothrombotic conditions. None of these emerging markers/RFs are at present used as input variables in CVD risk calculators. Other emerging RFs for risk assessment in T2DM include potentially modifiable variables contributing to, or associated with RVR, such as the MetS phenotype, IR /hyperinsulinemia, adverse lifestyle habits (excessive caloric intake, Westernized diets, smoking, high ethanol intake, sedentarity), high-cardiometabolic risk anthropometrics (abnormal distribution/expansion of fat tissue, sarcopenia), or other comorbidites increasingly described as associated with the common form of T2DM (sleep-related breathing disorders, chronic kidney disease, left ventricular systolic/diastolic dysfunction, or non-alcoholic fatty liver disease) [56-74].

Table 1 enumerates a non-exhaustive series of non-modifiable and modifiable markers/RFs for micro-/macroangiopathy which may be at play in accruing RVR in T2DM patients, including inflammatory, behavioural/environnemental, and proatherothrombotic, whereas **Table 2** lists markers/RFs related to lipids and lipoproteins or to cardiometabolic factors involved in T2DM-related RVR [45,56-74].

Non-modifiable
- age
- male gender
- ethnicity
- family history:
  - *early-onset CVD*
  - *overweight / obesity*
  - *IFG / IGT / T2DM*
- former tobacco smoking
- small size at birth for gestational age
- right handedness
- genes / loci and polymorphisms associated with:
  - *CVD*
  - *β-cell function loss*
  - *overweight / obesity*

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 / environnemental
- current tobacco smoking
- air pollution (including airborne fine particles)
- sedentary lifestyle (*surrogate* : TV viewing)
- physical inactivity
- quantitative / qualitative sarcopenia
- psychosocial stress
- low socioeducative status
- low income
- decreased fruit and vegetable consumption

Coagulation - haemostasis - platelets
- platelet activity
- platelet agregation
- platelet size / volume
- aspirin resistance
- lipoprotein(a)
- fibrinogen
- factor V, VII, and VIII
- fibrinopetide A
- PAI-1
- prothrombin fragments 1 + 2
- tissue-plasminogen activator
- von Willebrand factor antigen
- D-dimer

Varia
- cystatin-C
- asymmetric dimethylarginine
- nongenetic causes of iron overload
- hemochromatosis
- elevated ferritinaemia
- Nt-proANP and Nt-proBNP
- endothelin-1
- urotensin II
- *Cytomegalovirus, Herpes simplex* virus
- *Helicobacter pylori*
- *Chlamydia pneumoniae*
- collagen vascular disease
- non-specific ST-segment ECG changes
- coronary artery calcifications
- left ventricular dysfunction
- obstructive sleep apnoea / hypopnoea syndrome
- psoriasis
- rheumatoid arthritis
- systemic lupus erythematosis
- HIV infection on highly-active antiretroviral therapy
- hypoglycemia unawareness

**: see Table 2 for lipid and cardiometabolic risk factors. ANP: Atrial natriuretic peptide; BNP: brain natriuretic peptide; CVD: cardiovascular disease; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; NAFLD: nonalcoholic fatty liver disease; PAI-1: plasminogen activator inhibitor type 1; T2DM type 2 diabetes mellitus; TV: television.*

Table 1. Micro or macrovascular disease risk factors/markers in T2DM patients: standard, emerging and candidate

7. Reducing residual vascular risk in T2DM

a. Targets attainment.

Reducing RVR must be part of a *continuum* in managing individual patients. RVR assessment is the next logical step after implementation of good clinical practices. Despite RFs identification and standards of care provision, all major modifiable RFs rarely attain all recommended targets for a given individual in real-life conditions [12-17,21-24]. This supports a more global approach to further reduce RVR [4-6,75-84]:

Lipids and lipoproteins	**Cardiometabolic**
total cholesterol	overweight - obesity (*surrogate* : increased BMI)
LDL-C	central fat distribution (*surrogate* : enlarged waist)
apolipoprotein B_{100}	hypertension
non-HDL-C	metabolic syndrome (presence *vs* . absence)
LDL particles number	metabolic syndrome (*score* : 3/5 - 4/5 - 5/5)
hypo-HDL-cholesterolaemia	insulin resistance / hyperinsulinaemia
decreased apolipoprotein A-I	dysadipokinemia (adiponectin, resistin, *etc* …)
HDL subtypes distribution	non-alcoholic fatty liver / steatohepatitis / NAFLD
fasting hypertriglyceridemia	chronic hyperglycaemia (*surrogate* : elevated HbA_{1c})
postprandial hypertriglyceridemia	endothelial dysfunction
TG-rich lipoprotein remnants	erectile dysfunction
apolipoprotein CIII(+)-carrying apoB lipoproteins	(micro)albuminuria
oxidized LDL	glomerular hyperfiltration
antibodies to oxidized LDL	CKD - eGFR <60 ml/min/1.73 m^2
small-dense LDL	end-stage renal failure / dialysis
lipoprotein(a)	hyperuricemia
lipoproteins glycation	hyperhomocysteinemia
lipoprotein receptors glycation	vitamin D deficiency
lipid metabolism enzymes glycation	sympathetic nervous system hyperactivity

Apo: apolipoprotein; BMI: body mass index; C: cholesterol; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NAFLD: nonalcoholic fatty liver disease; T2DM type 2 diabetes mellitus; TG: triclycerides (triacylglycerols).

Table 2. Lipid, lipoproteins and cardiomatabolic micro- and macrovascular disease risk factors/markers in TD2M patients: standard, emerging and candidate

1. continuous strive towards conventional target attainment, including reinforcement of TLC, higher drug dosages, drug switches or combination therapies;
2. addressing identified barriers to chronic diseases management using an individualized patient-based approach;
3. force-driving major modifiable RFs below recommended thresholds or physiological ranges ("*the lower is better*" paradigm);
4. impacting upon emerging risk factors, but this often means venturing beyond guidelines, or using off-label medications, or resorting to newer therapies not always supported by evidence from randomized clinical trials.

b. Non-LDL dyslipidemia and macroangiopathic RVR

As regards non-LDL dyslipidemia, AD can be improved by TLC, fibrates, or nicotinic acid [45,85-93]. In T2DM, data from the recent *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) Lipid trial reinforce the residual risk hypothesis for macroangiopathy, since despite achieving a mean LDL-C of 80 mg/dl, patients in the pre-specified subgroup with AD (defined as having both baseline TG ≥204 mg/dl and baseline HDL-C ≤34 mg/dl; numbering 17% of the ACCORD cohort) experienced a 70% higher relative rate (7% higher absolute rate) of incident major CV events (composite of CVD death, nonfatal myocardial infarction and nonfatal stroke) over a mean 4.7 year follow-up when compared to patients without AD [94,95].

In ACCORD Lipid, although in the whole T2DM cohort the main macrovascular outcome was negative, a prespecified subgroup of T2DM patients with AD treated with combination LLD therapy [simvastatin *plus* fenofibrate] had a 31% reduction in major CV events, compared to those treated with simvastatin alone (12.4% incidence [simvastatin *plus*

fenofibrate] *vs.* 17.3% [simvastatin monotherapy]), amounting to a 5% absolute RVR reduction. The number-needed-to-treat was low, calculated at 20 T2DM patients with AD receiving LLD biotherapy over 5 years to prevent one major CV event. This number compares very favourably with those from landmark intervention trials with LLD in diabetic or nondiabetic populations. When primary outcome in the whole cohort was analyzed according to gender, another prespecified analysis, data for men showed a strong indication that they benefited from combination therapy (11.2% [fenofibrate] *vs.* 13.3% events [placebo]), while data for women were not as conclusive. Thus, whereas the *P* value for interaction related to gender was significant (0.0106), the confidence interval of the effect in females (9.1% [fenofibrate] *vs.* 6.6% events [placebo]) was not only wide, but also encroached the line of unity.

In ACCORD, AD was present in only one-sixth of the population under study, a subgroup which however markedly benefited in terms of macrovascular RVR reduction from combined therapy [94,95]. Whether in real-life conditions a higher proportion of T2DM patients might benefit from combination therapy [simvastatin *plus* fenofibrate] as a result of having AD as a comorbidity, is a tentative hypothesis. In ACCORD Lipid, the low recorded AD prevalence was a result not only of inclusion criteria, sequential exclusion of tertiles, intrinsic characteristics of the study population, and a relatively high proportion of volunteers of Afro-American ethnicity, who often have naturally low-to-normal triglycerides levels and less prone to suffer from AD [46-48].

We sought to investigate whether AD prevalence was akin to that observed in the ACCORD Lipid trial in an unselected, mostly Caucasian T2DM patients sample (*n*=974), consecutively attending our academic diabetes clinic. As ACCORD Lipid cutoffs, based on study-specific tertiles are unapplicable to other T2DM populations, we selected another approach to define AD, based on the co-occurrence of low HDL-C and high TG, with cutoffs derived from the harmonized definition of the MetS [51,53,55]. We also checked patient's file in order to retrieve pre-LLD HDL-C and TG values in patients on lipid-lowering drug(s), in order to establish the true, unbiased presence of AD (**Table 3**).

With such criteria and stringent use of baseline lipids values, we observed a higher prevalence of AD (35%), similar in both genders. In our survey, mean pre-LLD triglycerides were 203 mg/dl *vs.* 167 mg/dl for current values, representing an average difference of 36 mg/dl (18%), a difference sufficient to otherwise underestimate AD prevalence unless pre-LLD TG values are available. Such a confounding effect of LLD was not observed as regards HDL-C. In this analysis, the expected differences in the general population between genders were observed for HDL-C and apolipoprotein A-I level. Female patients also had significantly higher total cholesterol and significantly lower AD ratio [*log*(TG)/HDL-C] levels (**Table 3**).

Whatever AD prevalence data, notwithstanding the beneficial effects of fenofibrate on microvascular residual risk, a substantial proportion of unselected T2DM patients may potentially benefit from combination therapy to substantially decrease a modifiable component of AD-related RVR [94,95]. Such a likely assumption needs however to be confirmed from both epidemiological sources documenting the real-life prevalence of AD, and also from prospective randomised controlled trials, in which only fenofibrate-naïve patients with untreated AD would be included, with AD defined by consensual criteria, such as MetS thresholds for non-LDL dyslipidemia or trial-dependent AD cutoffs derived *a posteriori* on tertiles of non-LDL lipids at study entry such as in ACCORD Lipid [45]. Future trial should also investigate whether triple therapy (simvastatin *plus* fenofibrate *plus*

nicotinic acid), aimed at further correction of most aspects of hypercholesterolemia and AD, will provide proportionate benefit for RVR in T2DM.

		both genders	males	females	*p*
n		***974***	***637***	***337***	
atherogenic dyslipidemia *	%	**35**	**35**	**35**	*NS*
pre-LLD total cholesterol	$mg.dl^{-1}$	**230** (43)	**225** (42)	**240** (43)	*<0.0001*
pre-LLD LDL-C	$mg.dl^{-1}$	**145** (35)	**143** (35)	**150** (35)	*0.0170*
pre-LLD HDL-C	$mg.dl^{-1}$	**47** (13)	**45** (12)	**52** (15)	*<0.0001*
pre-LLD TG	$mg.dl^{-1}$	**203** (167)	**201** (155)	**208** (193)	*NS*
anti-dyslipidemic drug(s)	%	**65**	**66**	**63**	*NS*
statin - fenofibrate - ezetimibe	%	**53 - 21 - 3**	**55 - 22 - 3**	**51 - 18 - 3**	*NS*
total cholesterol	$mg.dl^{-1}$	**179** (43)	**175** (42)	**186** (44)	*0.0001*
non-HDL-C	$mg.dl^{-1}$	**132** (42)	**130** (41)	**135** (42)	*NS*
apolipoprotein B_{100}	$mg.dl^{-1}$	**90** (27)	**89** (27)	**92** (27)	*NS*
LDL-C	$mg.dl^{-1}$	**99** (35)	**98** (35)	**102** (36)	*NS*
HDL-C	$mg.dl^{-1}$	**47** (14)	**44** (13)	**52** (15)	*<0.0001*
apolipoprotein A-I	$mg.dl^{-1}$	**149** (30)	**143** (28)	**163** (31)	*<0.0001*
triglycerides	$mg.dl^{-1}$	**167** (120)	**171** (128)	**161** (105)	*NS*
***log* (TG).HDL-C^{-1}**		**0.051** (0.025)	**0.054** (0.026)	**0.046** (0.021)	*<0.0001*

*Mean (1 SD) values; * : atherogenic dyslipidemia was defined as the concurrence of low HDL-C (<40 mg/dl in males; <50 mg/dl in females) and elevated fasting triglycerides (>150 mg/dl in both genders) as defined by the NCEP-ATP III cutoffs used to define the discrete lipid components of the metabolic syndrome score. Lipid values used to define AD were baseline (pre-LLD) lipids levels in patients treated with LLD(s). HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LLD: lipid-lowering drug(s); T2DM: type 2 diabetes mellitus; TG: triglycerides. p: statistical value from Student's t test; NS: not significant (p value = or > 0.05).*

Table 3. Atherogenic dyslipidemia prevalence, lipid-lowering drug(s) therapy, and baseline vs. current lipids and lipoproteins values in unselected T2DM patients

c. Microangiopathic residual vascular risk

Diabetic eye disease includes diabetic retinopathy (DRP) and non-vessel comorbidities, such as cataract or glaucoma [96]. DRP is a microangiopathy affecting the retinal blood vessels resulting predominantly from poor metabolic control, which produces microvascular occlusion and leakage, leading to progressive retinal damage which may end in complete visual loss as a result of maculopathy or ischemic/proliferative retinopathy [96-100]. Few modifiable risk factors are identified with respect to DRP: poor metabolic (i.e. glycemic) control; hypertension, especially if poorly-controlled; LDL and non-LDL dyslipidemia; anemia and possibly, tobacco smoking. The recently published ACCORD Eye substudy highlighted the limits of conventional approaches based on near-normalization of two key modifiable variables (HbA_{1c} and high blood pressure). In ACCORD, DRP outcomes were defined as a ≥3-steps DRP progression on the EDTRS scale, or development of DRP requiring laser therapy or vitrectomy [101-103].

While glycemic control intensification significantly reduced the rate of progression of DRP (by a relative 33% and an absolute 3.1%, respectively), it was associated with serious safety

concerns, as higher all-cause mortality was observed in the intensive glycemic control group [104]. This led to premature termination of the glycemic arm of the ACCORD trial. Another source of disappointment from the ACCORD trial for microvascular RVR reduction was the lack of efficacy of BP normalization to improve primary DRP outcomes [105]. These findings highlights the current pitfalls of current approaches to DRP management based on a "*the lower the better*" paradigm for the two major standard modifiable risk factors, i.e. HbA_{1c} and BP [104].

As regards lipids, landmark statin trials in T2DM or in subgroups with T2DM failed to identify a beneficial effect of LDL- lowering on any type on diabetic microangiopathies. On the other hand, epidemiological evidence links AD with RVR for diabetic retinopathy and/or nephropathy in T2DM [4-6,100,104]. The *REsiduAl risk, Lipids and Standard Therapies* (REALIST) studies are two *Residual Risk Reduction Initiative*-initiated worldwide epidemiological retrospective case-control surveys designed to assess AD-related macro- and microvascular residual risk. These are performed in non-diabetic and T2DM patients (REALIST MICRO) receiving current standards of care, with LDL-C levels at or near goal, treated or not with a statin. Pilot results from REALIST MICRO show a highly-significant and strong association between AD and microangiopathy incidence, even when LDL-C is controlled [107,108].

In the ACCORD Eye substudy, fenofibrate decreased RVR of DRP progression, assessed using the validated EDTRS scale, and irrespective of baseline lipids. The efficacy of fenofibrate was most obvious in patients with DRP at baseline, i.e. those in secondary DRP prevention [101-104]. Such a beneficial effect confirms the previously documented benefits of fenofibrate on DRP. This, in the *Fenofibrate Intervention and Event Lowering in Diabetes* (FIELD) study, a previous other large randomised controlled trial, a decreased requirement for DRP-related laser therapy was observed in T2DM treated with fenofibrate (*vs.* placebo). Such decreased requirement was however neither a primary outcome endpoint nor a "hard endpoint" for DRP progression assessment [88,104,106].

Results from ACCORD Eye therefore markedly raise the level of clinical evidence for a beneficial effect of this PPAR-α agonist on DRP. The FIELD study also showed that fenofibrate decreased new-onset albuminuria and diabetes-related non-traumatic amputations in T2DM patients [109]. In a recent assessment of fenofibrate's renal effects (FIELD washout sub-study), decreased albuminuria and reduced estimated glomerular filtration rate (eGFR) loss over 5 years were observed in patients allocated to the fenofibrate arm [110]. These observations confirm that fenofibrate not only reduces albuminuria or delay its onset, but also diminishes the natural history of progressive eGFR impairment in T2DM, despite an early and reversible increase in plasma creatinine [104,110-114]. As regards other LLD, future trials will establish whether targeting low HDL-C with nicotinic acid, alone or on top of background statin, reduces RVR of macroangiopathy in high-risk T2DM patients [90-93,115]. Safe and effective combination of LLDs (bi- or tritherapies) targeting most aspects of dyslipidemia are likely to become standards of care in high-risk populations such as patients with T2DM [45,75,91,104,115-118].

8. Benchmarking

Innovative approaches are needed to improve individual and overall target achievement with the aim of reducing RVR. Benchmarking targeting physicians is one of those newer approaches. The goal of the non-interventional randomised OPTIMISE trial was to

investigate in 6 European countries the effect of physician's benchmarking on quality of care, assessed according to the percentage of T2DM patients achieving pre-set targets for three key modifiable variables (HbA_{1c}, LDL-C and SBP), as recommended by international guidelines. At baseline, the percentage of patients achieving targets was highly unsatisfactory: 51% (HbA_{1c}); 27% (SBP); and 35% (LDL-C), with a mere 5% reaching all three targets at study entry. Physicians were randomly assigned to receive either benchmarked feedback or non-benchmarked feedback on their patients' modifiable outcome indicators (HbA_{1c}, fasting glycaemia, total cholesterol, HDL-C, LDL-C and TG). At study end, the percentage of patients achieving all targets almost doubled, suggesting that benchmarking may be an innovative approach to improve target attainment of modifiable variables affecting RVR in T2DM patients [21,119,120].

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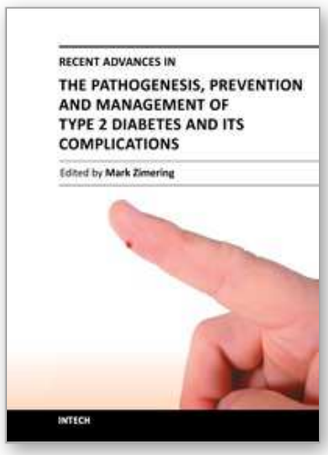

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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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