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SUPPLEMENTARY ARTICLE

Residual cardiovascular risk among people with diabetes

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Type 2 diabetes (T2D) is a growing health concern across both developed and developing countries. Cardiovascular disease (CVD) remains the major cause of increased mortality in this patient population. In recent years, effective low density lipoprotein lowering treatments and other risk reduction strategies have substantially reduced the risk of atherosclerotic CVD, yet patients with T2D continue to remain at increased risk for atherosclerotic CVD. Here, we will briefly review various proposed underlying mechanisms for this residual risk with a more in-depth focus on the potential role of triglyceride-rich lipoproteins in residual risk and potential avenues to target this pharmacologically.

KEYWORDS

cardiovascular disease, clinical trial, dyslipidaemia, lipid-lowering therapy

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1 | INTRODUCTION

Type 2 diabetes (T2D) is a major global public health challenge which impacts an estimated 8.5% of adults[1]. Atherosclerotic cardiovascular disease (CVD) including coronary artery disease and ischaemic stroke is the major cause of increased morbidity and mortality in patients with T2D.[1] Low density lipoprotein (LDL), a known driver of atherosclerosis, is not typically elevated in patients with T2D. However, LDL particles tend to be smaller and denser (sdLDL) and likely more atherogenic.[2] Consequently, LDL lowering therapies have proven very effective in reducing CVD risk in patients with T2D[3]. Treatment with HMG-CoA (hydroxy-3-methylglutaryl-CoA) reductase inhibitors (statins) have been a mainstay of CVD risk management in patients with T2D[3]. More recently, PCSK9 inhibitors have emerged as highly effective LDL-C lowering agents and further reduce CV risk in patients with and without diabetes on statins.[4] Nonetheless, despite these impressive reductions in LDL-C, patients with T2D still have elevated risk of CVD (residual CVD risk): for example, patients with T2D treated with the PCSK9 inhibitor evolocumab still had a major adverse cardiac event rate of ~7%/y.[4] This indicates that non-LDL-targeted therapies are likely needed for CVD protection.[5]

Intriguingly, improving glycaemia and promoting weight loss through lifestyle measures in the LOOK-AHEAD had multiple metabolic benefits but did not translate into reduced CVD over a mean follow-up period of 9.6 years.[6] Similarly, intensive glycaemic control has not been convincingly shown to improve major cardiovascular outcomes except with extended follow-up of about 10 years,[7–9] suggesting improving glycaemia *per se* in T2D may not reduce residual CVD risk. However, T2D treatment with sodium/glucose cotransporter 2 (SGLT2) inhibitors[10,11] and glucagon-like-peptide-1 (GLP-1) analogues[12–14] have generally been shown to lower CVD by mechanisms that have not yet been fully elucidated. Establishing the underlying mechanisms of CVD lowering with these drugs may help further explain the underlying aetiologies of residual CVD.

Ultimately, it is likely that therapeutic strategies targeting multiple underlying CVD risk factors will achieve the ultimate target of minimizing/eliminating residual CVD risk. Concordant with this hypothesis, in the STENO-2 trial patients with T2D and microalbuminuria receiving treatments targeting multiple cardiac risk factors had dramatic lower mortality and CVD.[15] Intensively treated patients lower received low dose aspirin and renin-angiotensin system blockade (irrespective of blood pressure) with targets for glycaemia (HbA1c < 6.5%), total cholesterol (<4.5 mmoL/L), triglyceride (TG) (<1.7 mmoL/L), systolic (<130 mm Hg) and diastolic blood pressure (<80 mm Hg).[15] Nonetheless, such a multi-faceted therapeutic approach, patients with T2D still remain at increased CVD, indicating that further underlying risk factors need to be identified and, as illustrated below, selectively targeted to maximize benefit while preventing unwanted side effects such as bleeding with anti-coagulation or sepsis with anti-inflammatory agents.

2 | ROLE OF INSULIN RESISTANCE IN THE PATHOGENESIS OF T2D

A key underlying feature of T2D is insulin resistance (IR), which is one of the earliest abnormalities in the pathogenesis of T2D.[16] As reviewed in further detail below, IR can potentially impact atherosclerosis via direct effects on the vasculature[17] as well as indirect effects mediated by increased free fatty acid delivery from adipose tissue, dyslipidaemia (increased TG-rich lipoproteins [TRL], decreased high density lipoprotein (HDL) and increased small dense LDL-C),[2] adipose tissue and systemic inflammation[18] and coagulopathy.[19] Ultimately, IR in combination with beta cell failure underpins the development of overt hyperglycaemia and T2D.[16]

2.1 | Underlying mechanisms of insulin resistance and associated pathologies

Prospective studies have indicated that IR is a key early event in the pathogenesis of T2D in the vast majority of patients.[16] It is associated with compensatory hyperinsulinaemia, which can initially maintain euglycaemia, but has been causally linked to complications such as the dyslipidaemia typically seen in IR.[20,21]

Centripetal adiposity and adipose tissue dysfunction are key underlying features of IR. Compromised adipose storage capacity, as seen in patients with centripetal obesity, is posited to result in increased free fatty acid delivery from adipose tissue to insulin sensitive organs such as liver and skeletal muscle.[22] Ectopic lipid deposition has been causally implicated in impaired insulin signalling and IR in animal models. Acute increase in free fatty acid in both mice and insulin sensitive humans results in reduced insulin signalling acutely.[22] Human genetic studies have also demonstrated that compromised adipose storage capacity characterised by increased centripetal adiposity and/or lack of femoro-gluteal adiposity is tightly linked to IR.[23,24] Compromised adipose storage capacity also has additional deleterious effects including induction of adipose apoptosis and inflammation[25] with recruitment of macrophages and lymphocytes and systemic secretion of inflammatory cytokines by macrophages and lymphocytes which can further impair insulin signalling.[18] Compromised adipose storage is also associated with increased Free Fatty Acid (FFA) delivery to the liver and gut which contributes to the characteristic dyslipidemia seen in IR/T2D.[2,26]

Does IR/hyperinsulinaemia directly contribute to CVD? Recent Mendelian randomization studies have indicated that common genetic variants which increase fasting insulin are also associated with an increased the risk of CVD,[27] suggesting a causal link. Epidemiological studies have demonstrated that IR is a risk factor for CVD independent of glycaemia.[28,29]

Can targeting IR attenuate CVD risk? In the UKPDS study, the insulin sensitizer metformin, which predominantly affects hepatic insulin sensitivity, has been shown to modestly reduce CVD in patients with T2D.[30] However, the results of treatments with the other major class of insulin sensitizing medication namely Peroxisome proliferator-activated receptors (PPAR) gamma agonists, which increase adipogenesis and thus adipose storage capacity, have been mixed. Treatment with rosiglitazone, but not pioglitazone has been associated with an increased risk of CVD in some,[31–33]but all studies[34] suggesting that this may be a rosiglitazone specific effect. Notably pioglitazone, in contrast to rosiglitazone, has greater beneficial effects on lowering TG and increasing HDL.[35] There is no convincing evidence from large well-powered Randomized Controlled Trial (RCT) of a beneficial effect of pioglitazone in reducing Major Adverse Cardiac Events (MACE). However, in meta-analyses of secondary prevention studies in patients with IR with and without overt T2D, pioglitazone reduced the risk of MACE but had no effect on mortality, and increased the risk of heart failure.[33,36] Pioglitazone has also been shown in an RCT to reduce the risk of myocardial infarction (MI) or stroke in patients with IR and ischaemic stroke.[37] Side effects including weight gain, oedema and increased fracture risk limit its use.[37] As these potentially beneficial effects of pioglitazone were seen in patients with IR without overt T2D, it is likely that these effects are independent of improvement in glycaemia and related to improvement in IR.[33,36] Nonetheless, given the pleiotropic effects of the drug, the precise underlying mechanism(s) are unclear.

In summary, IR is a key component of T2D and increases the risk of CVD. The insulin sensitizers metformin and pioglitazone, lower the risk of atherosclerosis, however, adverse side effects of pioglitazone limit its therapeutic utility.

3 | MECHANISTIC LINKS BETWEEN IR AND CVD

We will now review potential mechanisms by which IR which may predispose to CVD and contribute to residual CVD, with a particular focus on diabetic dyslipidaemia.

3.1 | Direct effects of IR on the vasculature

Insulin can bind to its receptor to activate the insulin receptor substrate (IRS)—Phosphoinositide 3-kinase (PI3K) pathway. In addition it can also activate the mitogen-activated protein kinase (MAPK) pathway.[17] Under conditions of IR, insulin signalling via PI3K is impaired and the resultant hyperinsulinaemia has been shown to increase MAPK signalling in vascular cells such as endothelial cells and vascular smooth muscle cells in experimental settings.[17] This has pro-atherogenic effects including vasoconstriction due to endothelin-1 secretion, proliferation of vascular smooth muscle cells, secretion of pro-coagulant factors such as Plasminogen activator inhibitor-1 (PAI-1) and secretion of chemo-attractant proteins and cell adhesion molecules which promote recruitment of macrophages.[17] Therefore, IR can have multiple effects on the vasculature in experimental settings which can impact atherosclerosis. However, although epidemiological studies have established IR as a risk factor for atherosclerosis, these effects appear to be dependent on associated metabolic abnormalities such as dyslipidaemia.[28,29]

3.2 | Indirect effects of IR on atherogenicity

3.2.1 | Inflammation

Inflammation is now established as an important process in atherosclerotic plaque development and progression in animal models.[38]

Macrophages and T lymphocytes are present in atherosclerotic plaques and are thought to secrete cytokines such as Tumour Necrosis Factor-alpha (TNF-α) and interleukin 1β (IL-1β) which contribute to atherosclerotic disease.[38] As noted above, obesity and IR, which are major drivers of T2D, are associated with chronic low grade adipose inflammation and elevated circulating concentration of inflammatory cytokines[18] including TNF-α and IL-1β, both of which are linked to atherosclerosis. This suggests that IR/T2D and CVD may share underlying inflammatory aetiologies. If that is the case, therapies targeting inflammation may potentially improve IR and prevent CVD.

Serum concentration of high sensitivity C reactive protein (hsCRP), a marker of inflammation, are associated with CVD and treatment of patients with elevated hsCRP with statins lowers CVD, even in the absence of elevated LDL,[39,40] suggesting that consistent with animal data, inflammation increases CVD risk in humans. Does targeting inflammation directly affect CVD? As discussed above, IL-1β is a pro-atherogenic cytokine. IL-1β inhibition with canakinumab, has been shown to reduce CVD by ~15% in patients with elevated hsCRP, an effect seen with and without T2D.[41,42] These finding are scientifically very important as they represent the first convincing evidence that a strategy that targets inflammation reduces CV risk. The long-term feasibility of this therapy remains to be determined given potential side effects, including sepsis and cost.[41] Intriguingly, although canakinumab reduced CVD in patients with T2D, it did not affect glycaemia in the long term.[42] It did not prevent incident T2D in normoglycaemic patients and those with pre-T2D. Furthermore, the magnitude of reduction in CVD risk in patients with T2D compared to those without.[42] These results suggest that IL-1 β contributes to CVD risk in patients with inflammation but likely does not play a major role in the aetiology of T2D and residual CVD risk in patients with T2D.

Can other established anti-inflammatory therapies attenuate CVD risk? The Cardiovascular Inflammation Reduction Trial (CIRT) trial recently reported the effects of methotrexate compared to placebo in patients with established CVD and either T2D or metabolic syndrome.[43] While there was no significant difference in CV events between treatments, there were also no differences in IL-1β, C Reactive Protein (CRP) or IL-6 between the two groups.[43]

TNF-α has also been implicated in both atherosclerosis and IR based on animal studies.[18,38] However, TNF-α blockade has not been shown to convincingly improve IR in humans,[44] but observational studies hint at potential CVD risk reduction in patients with rheumatoid arthritis.[45] No prospective RCTs have been undertaken with these agents in patients with T2D.

In summary, targeting inflammation with IL-1β blockade can reduce CVD risk in patients with and without T2D. Although there is convincing evidence from animal studies that atherosclerosis and IR may share inflammatory mechanisms, it remains to be determined whether targeting these pathways to reduce IR and residual CVD risk is viable in humans.

3.2.2 | Coagulopathy

IR is associated with plasminogen activator 1 which increases the risk of thrombosis.[46] These effects are likely due to both direct effects of IR as well as indirect effects mediated by TRL and oxidized LDL.[19] IR is also associated with an increase in fibrinogen and von Willibrand factor.[19] In addition hyperglycaemia has been causally linked to increased thrombin-antithromibin complex.[47]

Can targeting the coagulation pathway reduce CVD risk in patients with T2D? Acetyl Salicylic Acid, Aspirin (ASA) has been shown to modestly prevent CVD in patients with T2DM without CVD, but the increased risk of major bleeds suggest that this is not an overall effective strategy for primary prevention.[48] In a secondary prevention trial (COMPASS), addition of the Factor Xa inhibitor rivaroxaban to aspirin reduced major cardiovascular events in patients with established CVD by 24% but increased rates of major bleeding by 70%. Rivaroxaban was not superior to aspirin alone.[49] Approximately 38% of patients in the trial had diabetes, with a similar magnitude of effect in the diabetes subgroup,[49] which suggests that this pathway likely does not contribute to the increased residual CVD risk in patients with T2D. In the ongoing THEMIS trial (ClinicalTrials.gov Identifier: NCT01991795), patients with diabetes and Coronary Artery Disease (CAD) without prior MI or stroke are being randomized to ticagrelor or placebo in addition to aspirin to determine if the combination is better than aspirin alone.

In summary, targeting the coagulation pathway reduces CVD risk in patients with T2D, but the benefit must be balanced in a given patient against the risk of major bleeds. Whether the combination of ticagrelor with aspirin is superior to aspirin alone, the current standard anti-platelet treatment in secondary CVD prevention in diabetes, remains to be seen.

3.3 | Diabetic dyslipidaemia

Patients with IR, metabolic syndrome and T2D characteristically have both elevated TG and TRL with low HDL (Figure 1).[2] HDL and TG levels are closely intertwined as high TG concentration directly impacts HDL clearance.[50] Epidemiological studies have consistently demonstrated that low HDL and high TG predict risk of CVD.[2]

4 | TRL KINETICS IN HEALTH, IR AND T2D

TRL, which contain apolipoprotein B (apoB), come from two sources: the liver secretes very low density lipoprotein (VLDL) particles in the fasted and post-prandial state, while the gut secretes chylomicron.[26] Each TRL particle has one apoB particle: VLDL contains apoB-100, while chylomicron contain a shorter version of apoB which is 48% of the size of apoB-100 namely apoB-48. VLDL undergoes lipolysis to yield intermediate density lipoprotein (IDL) and eventually LDL, while chylomicron lipolysis yields chylomicron remnant particles.[2] TRL remnants from VLDL and chylomicron undergo hepatic clearance by common pathways.[26]

IR is associated with increased TRL from both the liver and gut and invariably associated with hepatic steatosis.[21,51] This is due to both increased production and reduced clearance with a net effect of increased TRL particle number.[51] Notably, humans and mice with insulin receptor mutations paradoxically do not manifest increased TG/TRL suggesting that lack of insulin action/IR per se does not cause increased TRL.[21] Mechanistic studies in both animals and humans have revealed that increased free fatty acid flux, in combination with

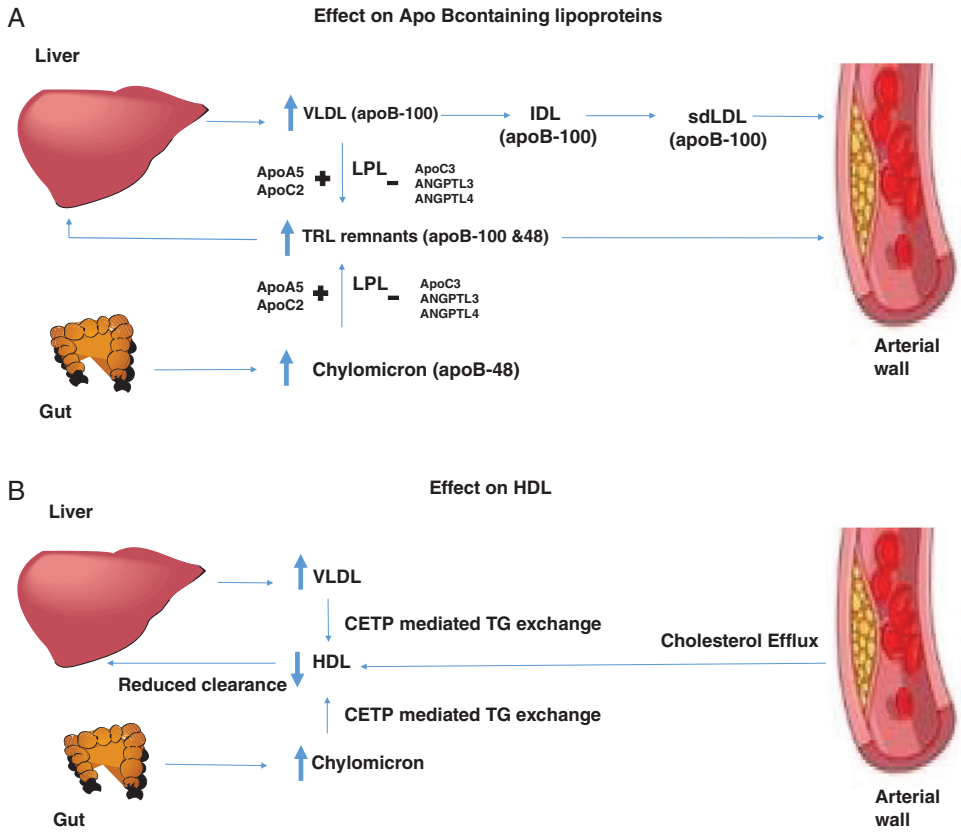

FIGURE 1 A, Insulin resistance and type 2 diabetes is associated with an increased production of triglyceride-rich lipoproteins (TRL). The liver produces VLDL (very low density lipoprotein) which undergoes lipolysis to yield IDL (intermediate density lipoprotein) and ultimately LDL (low density lipoprotein) cholesterol. In states of IR and T2D, LDL_C particles tends to be small and dense (sdLDL) and potentially more atherogenic. ApoB-100 is the major lipoprotein component of VLDL, IDL and LDL. The gut produces apoB-48 containing chylomicrons. Lipolysis of VLDL and chylomicrons by LPL on the endothelial surface produces TRL remnants which have atherogenic properties. Preclinical and human genetics have demonstrated that various proteins including ApoC2 and ApoA5 promote LPL-mediated TRL lipolysis, while ApoC3, ANGPTL3 and ANGPTL4 inhibit LPL-mediated TRL lipolysis. ApoC3, ANGPTL3 and ANGPTL4 are being evaluated as potential TG and TRL lowering therapies. TRL remnants are removed from the circulation by the liver via LDL receptor and LDL receptor related protein. B, In IR and T2D, HDL-C is low which impacts cholesterol efflux from atherosclerotic plaques. This is due to increased clearance in part due to the increased triglyceride content of HDL-C particles mediated by via CETP-dependent transfer of TG from TRL

hyperinsulinaemia, drives increased production of TRL particles.[21,52] In addition, IR is associated with reduced hepatic clearance of TRL particles potentially due to free fatty acid mediated increase in apoCIII (which regulates TRL clearance) and competition between liver and gut TRL particles for clearance through common saturable pathways.[2,26,53] In addition to IR, increased dietary and circulating glucose likely directly contribute to increased TRL production and reduced clearance, which is pertinent for patients with T2D.[54–56]

5 | ATHEROGENIC PROPERTIES OF TRL REMNANT PARTICLES

Increased TRL particles can affect the composition of LDL-C and HDL and modulate reverse cholesterol transport and thus contribute to CVD risk as discussed below. In addition, there is evidence from in vitro, animal and human studies, that TRL particles undergo lipolysis to yield cholesterol rich remnant particles with pro-atherogenic properties.[2] Histological analysis of atherosclerotic plaques reveals the presence of both apoB-100 and apoB-48. In in vitro studies, TRL remnant particles up-regulate the expression of monocyte chemoattractant particle 1 (MCP-1), a key step in the recruitment of monocytes to vascular endothelial cells.[57] It also up-regulates a number of cellular adhesion molecules such as VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intracellular adhesion molecule-1). These processes facilitate retention of monocytes and formation of foam cells.[57] TRL particles promote vascular smooth muscle cell proliferation in vitro, a key step in plaque progression. TRL particles can also impact coagulation pathways (discussed above) by increasing PAI-1 expression in endothelial cells.[57]

In summary, TRL remnant particles likely have multiple pro-atherogenic properties in experimental studies.

5.1 | Evidence in support of atherogenicity of TRL particles from human studies

5.1.1 | Epidemiological studies

Plasma TG concentration is invariably increased in most patients with metabolic syndrome and T2D.[26] In prospective epidemiological studies, plasma TG and in particular non-fasted TG is a predictor of CVD. In the Copenhagen City Heart study and Copenhagen General Population study of >90 000 individuals, non-fasted TG concentration

greater than ~1.5 mmol/L were associated with an almost linear increase in myocardial infarction, coronary artery disease, ischaemic stroke and mortality.[58] In prospective studies in women, plasma TG and ApoB concentration were an excellent predictor of CVD,[59] particularly in those with LDL-C concentration less than the median population concentration. Similarly, plasma TG and TRL were a predictor of peripheral arterial disease risk.[60] The predictive power of plasma TG for future CVD was reversed after adjustment of plasma TG for non-HDL cholesterol (a surrogate measure of TRL and TRL remnant particles) and HDL.[61] This suggests that TRL and their remnants may be atherogenic.

5.1.2 | Genetic studies

Common genetic variants which increase plasma TG and consequently TRL are associated with increased risk of CVD.[62] This effect remains significant even with TG raising alleles that do not impact HDL-C or LDL-C, suggesting a direct causal effect.[62] Similarly, rare loss of function mutations in *LPL* encoding lipoprotein lipase and *APOA5* which result in reduced TG clearance and hypertriglyceridemia are also associated with increased CVD risk. Gain of function mutations in LPL and loss of function mutations in *ANGPTL4* and *APOC3* which all increase TG and TRL clearance are associated with reduced CVD risk.[63–66] Thus, the available genetic evidence also suggests that TRL particles are likely atherogenic.

5.2 | Indirect effects of TRL particles

In addition to the effects described above, TRL can affect the composition of LDL-C and HDL-C and indirectly increase atherogenicity. VLDL particles yield sdLDL particles in states of IR and T2D which are postulated to be more atherogenic by mechanisms including reduced clearance due to reduced binding to the LDL receptor, increased retention in vessel walls due to increased binding to proteoglycans, greater susceptibility to oxidation (which can activate coagulation pathways and endothelial dysfunction).[67–71] Consistent with this, epidemiological studies have demonstrated that sdLDL particles are predictive of incident coronary artery disease.[72]

HDL facilitates reverse cholesterol transport, whereby cholesterol particles are removed from atheromas and cleared by the liver.[73] In addition, HDL has pleiotropic effects including putative anti-inflammatory and anti-oxidative properties. In epidemiological studies, low HDL is consistently associated with increased risk of ischaemic heart disease, stroke, peripheral vascular disease and major cardiovascular events.[74] HDL-C facilitates reverse cholesterol transport, a process by which atherogenic cholesterol rich particles are transported from atheromas to the liver for clearance, potentially preventing progression of atherosclerotic disease. Increased TG/TRL in T2D alter HDL-C particle composition, which can potentially inhibit reverse cholesterol transport and HDL clearance by the liver[50] and increase atherosclerotic risk.

6 | TARGETING COMPONENTS OF DIABETIC DYSLIPIDAEMIA TO REDUCE CVD RISK IN PATIENTS WITH IR AND T2D

In this section, we will summarise the available evidence from RCT targeting components of diabetic dyslipidaemia. Notably, many of these trials were carried out in patients with and without IR and/or T2D. We have therefore reported overall outcomes as well as those in patients with likely IR (using hypertriglyceridaemia and low HDL as a surrogate marker) and/or T2D.

6.1 | CVD outcomes with HDL-C increasing drugs

Niacin is a drug that decreases ApoA1 (the major lipoprotein component of HDL) clearance and increases HDL-C (Table 1). In addition, it reduces VLDL secretion from the liver and adipose tissue lipolysis which ultimately reduces plasma TG.[75] Flushing, an adverse effect of niacin is due to stimulation of prostaglandin D2 and E2 synthesis.[75]

In the AIM-HIGH trial, patients with established CVD and low HDL-C were randomized to niacin or placebo treatment.[76] Thirty-four percentage of patients had diabetes and 81% had metabolic syndrome (and were thus likely IR). They were all also treated with simvastatin with or without ezetimibe, to achieve LDL <2.0 mmol/L. Despite an increase in HDL-C from 0.91 to 1.08, no difference was seen in major cardiovascular end points. Notably, niacin reduced TG from 1.85 to 1.38 mmol/L and LDL from 1.91 to 1.6 mmol/L.[76] Whether the lack

TABLE 1 Summary of CVD trials with HDL increasing drugs

Trial	Drug	Patient population	Statin use	HDL	TG	LDL	CVD outcomes
AIM HIGH	Niacin	Established CVD	Yes	19% increase	25% decrease	16% decrease	Neutral
HPS 2-Thrive	Niacin-laropiprant	Established vascular disease	Yes	14% increase	Not reported	15% decrease	Neutral
ILLUMINATE	Torcetrapib	High CVD risk	Yes	72% increase	8% decrease	25% decrease	CV events increased by 25%
dal-OUTCOMES	Dalcetrapib	Recent acute coronary syndrome	Yes	31-40% increase	Not reported	No change	Neutral
ACCELERATE	Evacetrapib	High risk for vascular disease	Yes	130% increase	5% decrease	31% decrease	Neutral
HPS3/ TIMI55-REVEAL	Anacetrapib	Atherosclerotic vascular disease	Yes	104% increase	Not reported	Non-HDL-C reduced by 18%	9% decrease in first major coronary event

Abbreviations: CVD, cardiovascular disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

of efficacy of niacin in a patient population with established CVD and likely IR was due to the relatively modest effects on HDL and TG is unknown.

In the HSP-2 THRIVE study, the effects of a combination of laropripant, a prostaglandin D2 inhibitor, with niacin were evaluated.[77] Patients with established vascular disease on statins were randomized to receive niacin/laropripant or placebo—32% of patients had diabetes. Despite a 14% increase in HDL-C and 0.25 mmol/L reduction in LDL-C (mean baseline LDL-C 1.6 mmol/L), there was no significant difference in major cardiovascular event rate. There was, however, an increased risk of adverse events including new onset diabetes and worsening glycaemic control,[77] precluding this as a viable treatment for patients with T2D. In summary, increasing HDL and lowering TG with niacin does not appear to have beneficial effects on CVD risk reduction in patients with IR and T2D.

Subsequently, a number of trials have evaluated the effects of CETP inhibitors which inhibit the exchange of cholesteryl esters on HDL-C with TG and thus increase HDL-C. These trials were performed in patients with and without T2D and some may have included patients with type 1 diabetes. In patients with high risk of coronary artery disease, including 45% with T2D, torcetrapib increased risk of CVD and death despite a 72% increase in HDL-C and 25% reduction in LDL-C.[78] The mechanisms underlying the increased CVD and death are not established but may be mediated in part due to adverse effects on blood pressure and hypokalemia.[78] In a subsequent trial, patients with recent acute coronary syndrome, 25% of whom had diabetes, were treated with the CETP inhibitor dalcetrapib or placebo.[79] Despite a 30% to 40% increase in HDL-C (and no significant changes in LDL-C), there was no difference in major cardiovascular outcomes.[79] More recently, the CETP inhibitor evacetrapib[80] increased HDL-C by 130% and lowered LDL-C by 31% compared to placebo in patients at high risk of CVD, including 68% with diabetes, but did not affect major cardiovascular events. Finally, in patients with established atherosclerotic disease, 37% of whom had diabetes, addition of the CETP inhibitor anacetrapib, increased HDL-C by 104% and reduced non-HDL cholesterol by 18%. It reduced major cardiovascular events by 9% over 4 years. These effects are likely mediated by the latter non-HDL effects.[81] Given the modest CV event reduction observed in the trial and the very long half-life of the molecule, the development of this drug has been stopped.

Although CETP inhibition does not appear to have beneficial CVD benefits, it may have beneficial glycaemic effects. Consistent with prior genetic and experimental data, CETP inhibition with torcetrapib improved fasting glucose and HbA1c in patients with T2D.[82] A recent meta-analysis of trials with CETP inhibitors, reported a reduced incidence of T2D.[83] The modest effects suggest that this is unlikely to translate into an efficacious therapy for T2D.

Was the general lack of efficacy of HDL-C increasing therapies entirely unpredictable? Human genetic studies have suggested that rare loss of function variants in genes such as *SRB1* which have major HDL increasing effects are not necessarily athero-protective.[84] Similarly common genetic variants, including some in *CETP* that increase HDL do not protect from CVD.[85,86] It is worth noting that although these genetic variants are associated with increased HDL-C they do not necessarily improve reverse cholesterol transport.

In summary, increasing HDL-C by CETP inhibition in patients at high risk of CVD does not appear to reduce this risk in a meaningful way. As alluded to above, the percentage of patients with T2D in these trials ranged between 37% and 68% and therefore a lack of efficacy in reducing residual CVD risk likely extends to patients with T2D. Notably, these therapies do not appear to facilitate reverse cholesterol transport. Whether targeting reverse cholesterol transport is a viable pharmacological strategy for attenuating residual CVD risk in patients with T2D remains to be seen.

6.2 | CVD outcome trials with TG lowering drugs

Unlike HDL lowering, there is strong evidence, both genetic and experimental, suggesting that lowering TRL and TRL remnants will likely lower CVD in patients with IR and T2D (Table 2). Nonetheless, this remains an active area of clinical research which has not been conclusively resolved to date. An ideal RCT would include patients

TABLE 2 Summary of CVD trials with TG lowering drugs

Trial	Drug	Patient population	Statin use	HDL	TG	LDL	CVD outcomes
HHS	Gemfibrozil	Non-HDL-C >5.2 mmol/L. Asymptomatic with no prior CVD	No	19.4% increase	52% decrease	8.4% decrease	34% reduction in CVD, no mortality benefit
VA-HIT	Gemfibrozil	Established CVD, HDL <1 mmol/L, LDL <3.6 mmol/L	No	6% increase	31% lower	No significant difference	24% reduction MACE
BIP	Bezafibrate	Coronary artery disease	No	18% increase	21% decrease	6.5% decline	Neutral
FIELD	Fenofibrate	Type 2 diabetes with and without CVD	Not at baseline	1.2% increase	22% decrease	5.8% decrease	24% reduction non-fatal MI, 11% decrease on CVD events
ACCORD	Fenofibrate	Type 2 diabetes with and without CVD	Yes	No significant change vs placebo	25% decrease	No significant difference vs placebo	Neutral
JELIS	Eicosapentaenoic acid (EPA)	Hypercholesterolaemic patients on low dose statin	Yes	No significant change	5% decrease vs placebo	25% decrease	19% decrease
REDUCE-IT	Icosapent ethyl	High risk CVD	Yes	No significant change	18.3% reduction	3.1% increase vs 10.2% increase in placebo	25% reduction

Abbreviations: CVD, cardiovascular disease; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

with T2D and IR with characteristic dyslipidaemia with elevated TG and low HDL-C assigned to TG lowering therapy vs placebo. As illustrated below, in many instances these studies included participants without the characteristic dyslipidaemia of IR and T2D with subsequent post-hoc subgroup analysis suggesting a beneficial effect in patients with raised TG and low HDL. This post-hoc analysis may be a useful guide in determining the TG and HDL thresholds for inclusion in future TG lowering trials.

6.2.1 | Fibrates

This class of medication activates the Peroxisome proliferator-activated receptor alpha (PPAR-alpha)[87] to increase TRL clearance and likely reduce VLDL production.

In the Helsinki Heart study, patients with elevated non-HDL cholesterol which is a surrogate measure of LDL-C, TRL and TRL-remnants, were evaluated with fibrate treatment vs placebo. Treatment of patients with elevated non-HDL cholesterol (>5.2 mmol/L) with gemfibrozil resulted in a 34% reduction in CVD but no effect on mortality.[88] In a secondary prevention study (VA-HIT), treatment with gemfibrozil in patients with low HDL (<1 mmol/L) and mild hypertriglyceridemia (mean plasma TG 1.8 mmol/L), resulted in a 24% reduction in major cardiovascular events associated with a 6% increase in HDL-C and 31% reduction in TG.[89] Notably patients in this trial had a mean LDL-C of 2.9 mmol/L which did not change significantly during the course of the study, suggesting these effects were independent of changes in LDL-C. Only 25% of patients had T2D and therefore whether this medication would be effective in statin-treated patients treated to current LDL targets is not known.[89] In contrast, in the BIP study,[90] treatment of patients with prior coronary artery disease (LDL 4.6-6.4 mmol/L, plasma TG <3.3 mmol/L and HDL <1.16 mmol/L) with bezafibrate did not reduce the composite primary outcome of fatal and non-fatal myocardial infarction and sudden death despite an 18% increase in HDL-C and 21% decrease in TG.[90] Post-hoc analysis revealed that in those with TG >2.25 mmol/L, there was a 39% reduction in the primary outcome.[90] Only 10% of patients had T2D precluding definitive evidence in this subgroup.

In contrast to the above studies in which patients with T2D were under-represented, the FIELD study was conducted exclusively in patients with T2D. They had modestly elevated TG with relatively normal HDL-C (mean TG 1.9 mmol/L, mean HDL-C 1.1 mmol/L) and elevated LDL-C (mean LDL-C 3.07 mmol/L). They were not taking statins at baseline and assigned to fenofibrate or placebo treatment.[91] There was no significant effect of treatment on the primary outcome of coronary events although there was a reduction in non-fatal MI and total CVD.[91] Whether the relatively modest dyslipidaemia contributed to the neutral primary outcome is not known.

The results of fibrate CVD outcome trials conducted in patients with elevated LDL by current standards were mixed, with a suggestion that a subgroup of patients with elevated TG and low HDL may benefit. As statins can potently lower LDL and reduce CVD risk, an unanswered question was whether a combination of treatment with statins and fibrates would lower CVD risk in patients with T2D. In the ACCORD study,[92] patients with T2D treated with a statin were randomized to treatment with fenofibrate or placebo. Despite a 25% reduction in TG (mean TG reduced from 1.85 to 1.38 mmol/L), no differences in major CV events were seen over a mean follow-up of 4.7 years.[92] Subsequent post-hoc subgroup analysis suggested that patients with TG >2.3 mmol/L and HDL <0.88 mmol/L did have a reduction in the primary outcome[92]—these results need confirmation in a prospective RCT.

In summary, CVD outcome trials with fibrates have generally been disappointing, particularly on a background of statin treatment. Subsequent post-hoc analysis in patients with elevated TG/low HDL-C, which is frequently seen in T2D, revealed favourable effects of fibrate therapy in a meta-analysis of these studies.[93] These data necessitate the need for well-designed randomized placebo controlled CVD outcome studies in patients with T2D and clearly defined thresholds for TG and HDL-C. A further concern with current fibrate therapies are that they are not selective PPAR alpha agonists. More recently, a selective PPAR alpha agonist pemafibrate[94] has been developed and is being evaluated in patients with T2D at high risk of CVD (~66% with established CVD) with TG >2.25 mmol/L and HDL <0.88 mmol/L treated with moderate-high intensity statin treatment (PROMINENT trial, Clinical trials.gov NCT03071692). This well-designed trial utilizing TG and HDL thresholds based on post-hoc subgroup analysis of previous fibrate trials, will likely yield important insights pertaining to the TRL hypothesis of residual CVD risk in T2D.

6.2.2 | Omega-3-fatty acids

These fatty acids can lower plasma TG/TRL potentially by increasing clearance of TRL particles[95] although this is not a consistent finding[96] and may be dependent on dose and preparation. In the Japanese JELIS clinical trial, supplementation with eicosapentaenoic acid (EPA) at a daily dose of 1.8 mg in hypercholesterolaemic patients treated with low dose statin reduced plasma TG by 9% vs 4% in placebo and LDL-C by 25%. This was associated with a reduction in major CVD outcomes by 19%.[97] The precise mechanisms underlying these data are unclear but are unlikely to be due to the very modest TG lowering. Sixteen percentage of patients in this RCT of >18 000 participants had diabetes. Post-hoc subgroup analysis revealed no between group differences in primary outcome among those with diabetes.[97]

More recently, the REDUCE-IT trial[98] assessed the effect of treatment with high dose Icosapent Ethyl (4 mg daily), a purified EPA only preparation, in patients at high risk of CVD with 70% with a history of CVD. Notably, 57.9% of patients had T2D and 60.7% had TG >2.25 mmol/L and 20% had both TG >2.25 mmol/L and HDL <0.88 mmol/L. There was a highly significant 25% reduction in major CV events over 5 years and 26% reduction in CV death and non-fatal MI and stroke. This was associated with an 18.3% reduction in TG. However, EPA was beneficial irrespective of baseline and post-treatment TG suggesting that these effects may be TG independent. There was a small increased risk of atrial fibrillation and bleeding in the EPA group, although the mechanisms are not clear.[98] Further secondary prevention trials assessing the effects of high dose purified EPA are waited including RESPECT-EPA (UMIN clinical trials registry UMIN000012069) and EVAPORATE (Clinical Trials.gov NCT0 2926027). The STRENGTH trial (ClinicalTrials.gov Identifier: NCT02104817), a randomized placebo controlled double blind trial,

will assess the effects of 4 g epanova, a mixture of omega-3-fatty acids in statin-treated patients at high risk of CVD (50% with established CVD) and TG >2 mmol/L and HDL-C <1.08 mmol/L (men) or 1.2 mmol/L (women).[99]

In summary, purified high dose EPA may reduce CVD risk in patients with and without T2D on statins but these effects may be independent of TG lowering.

6.2.3 | Emerging TG lowering therapies

A number of therapies that lower plasma TG by increasing TRL clearance have been developed. A particularly compelling feature of these drugs is that they target pathways that are known to lower TG and reduce CVD in human genetic models. These include *APOC3* antisense oligonucleotide treatment[100,101] which lowers TG by up to 70% in humans. Other potential targets include inhibition of *ANGPTL3* and *ANGPTL4* which have proved efficacious in rodents and monkeys.[102,103] Whether these highly efficacious TG lowering agents will ultimately reduce CVD risk in patients with T2D remains to be seen.

7 | BARIATRIC SURGERY AS A POTENTIAL THERAPY FOR RESIDUAL CVD

Obesity is a major driver of IR and T2D. As discussed above weight loss through changes in lifestyle can improve glycaemic and metabolic parameters, although there is no evidence to date that it improves CV outcomes.[6] In addition, it is seldom sustained. Bariatric surgery is the only treatment that has been shown to sustain weight loss and improve mortality.[104] Roux-on-Y gastric bypass and sleeve gastrectomy are currently the commonest procedures.[104] In addition, it improves glycaemia and can cause partial/complete remission of T2D in RCT.[104,105] It also improves dyslipidaemia, insulin sensitivity and hypertension.[104,105] Observational data suggests that compared to usual care, bariatric surgery reduces macrovascular disease in patients with T2D and obesity.[105] This data needs to be confirmed with RCT and if so the underlying mechanisms elucidated as this may provide important insights into the aetiology of residual CVD risk. The data further suggests that therapies targeting multiple facets of metabolic dysfunction in T2D are likely to have major CVD benefits.

8 | CONCLUSIONS

In spite of the emergence of potent LDL-C lowering therapies, patients with T2D remain at increased risk for CVD. This is likely multifactorial. Despite strong epidemiological evidence for the association of low HDL-C with residual CVD, therapies that increase HDL-C without impacting reverse cholesterol transport have generally not proven beneficial. Similarly, treatment with insulin sensitizers, anti-coagulants and anti-inflammatory agents have been mixed, despite convincing pre-clinical and epidemiological data suggesting that these factors contribute to CVD risk in T2D. There is very suggestive experimental, epidemiological and genetic evidence for a causal role of TRL in atherosclerosis. Post-hoc subgroup analysis of TG lowering therapies suggests that patients with T2D and high TG and low HDL, may benefit from TG lowering therapies. However, we currently have no convincing prospective randomized double blind control trial data to support that. A number of studies that are currently underway will help establish or refute the TRL hypothesis of residual CVD risk in T2D. A better understanding of the mechanism of action of proven treatments that have cardio-protective effects may also help design better treatments. Ultimately, we envision that a combination of therapies targeting the atherogenic milieu of IR and T2D will likely eliminate the residual CVD risk among people with diabetes.

CONFLICT OF INTERESTS

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