The relationship of high-density lipoprotein cholesterol to new-onset diabetes: a review

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Summary Diabetes is an increasingly prevalent disease that has a well-known association with cardiovascular risk, a risk that may even exist in prediabetics. Lower levels of high-density lipoprotein cholesterol (HDL-C) have been associated with increased risk of incident cardiovascular events. Recent prospective studies have shown a potential temporal association between lower levels of HDL-C and development of incident Type 2 diabetes. This article will review the recent studies detailing potential causative association between low levels of HDL-C and incident Type 2 diabetes, examine the potential pathophysiology and mechanisms of such an association, and review associated treatment implications.

Diabetes had an estimated prevalence of 6.4% in 2010, affecting 285 million adults worldwide, and expected to increase to 7.7%, affecting 439 million adults, by 2030 [1]. There is a well-known and strong association of diabetes with increased cardiovascular risk [2,3], an elevated risk that may even exist in prediabetics [4]. Lower levels of high-density lipoprotein (HDL) cholesterol (HDL-C) have been associated with increased risk of incident coronary heart disease [5–8]. By contrast, metabolic syndrome – a syndrome that generally includes a combination of low HDL-C, abdominal adiposity, high triglycerides, hypertension and impaired fasting glucose – is associated with increased risk of cardiovascular disease and Type 2 diabetes (T2DM) beyond that associated with each component risk factor, suggesting a synergistic effect on T2DM risk [9,10]. Indeed, one study demonstrated that HDL-C had an inverse relationship with calcium score and a stronger association in diabetic than nondiabetic patients [11]. The pathophysiology underlying these relationships may not be straightforward and studies suggest a self-perpetuating bidirectional relationship between risk factors such as HDL-C and impaired fasting glucose [12]. Multiple studies have shown that patients with T2DM have lower HDL-C

KEYWORDS
• apolipoprotein A-I • CETP • diabetes • fibrates • HDL • HDL-C • niacin • pancreatic β cell • statin • Type 2 diabetes

Practice points
• Lower levels of high-density lipoprotein (HDL) cholesterol are associated with increased risk of incident cardiovascular events.
• Some population studies suggest an associated risk between low HDL cholesterol and the development of incident Type 2 diabetes.
• Statins slightly increase risk of development of incident Type 2 diabetes.
• Niacin worsens glycemic control.
• CETP inhibitors (torcetrapid and dalcetrapid) are effective agents for increasing HDL but have shown either increased risk or no benefit in regards to risk of death and incident cardiovascular events. They may have some small beneficial effects in regards to glycemic control.
levels with functionally defective HDL particles (HDL-P) [2,13]. Furthermore, recent prospective studies have suggested a temporal association between decreased levels of HDL-C and development of incident diabetes [14]. This review will discuss recent studies detailing potential causative association between low levels of HDL-C and incident T2DM, examine the potential pathophysiology of such an association, and review associated treatment implications.

### Relationship of low HDL-C to incident Type 2 diabetes

HDL exists in complex and dynamic relationships with the major lipoproteins such as VLDL, IDL and LDL. As a marker of heart disease, numerous epidemiologic studies have shown a robust inverse relationship between HDL-C and coronary heart disease (CHD). This is in contrast with triglyceride levels, which have not been shown to be independently predictive of CHD [15]. Similarly, there have been a number of recent studies suggesting a significant association between low HDL-C and the development of incident T2DM. A low level of HDL-C usually does not occur in serologic isolation and is often accompanied by hypertriglyceridemia [16–18]. Clinically, hypertriglyceridemia is often observed in patients with insulin resistance resulting in enhanced lipolysis and free fatty acid synthesis. Therefore, in analyzing the association of low HDL-C and incident diabetes, careful adjustment for coexistent hypertriglyceridemia is essential. This section will review some of the recent and relevant clinical studies that suggest an association between low levels of HDL-C and the development of incident T2DM.

#### LIFE study

The LIFE study was designed to compare the effects of losartan versus atenolol-based antihypertensive therapy on cardiovascular morbidity and mortality [19]. Among the 7485 subjects without a history of diabetes who had baseline HDL-C levels and were followed for approximately 5 years, lower in-treatment HDL-C was strongly associated with increased risk of new-onset diabetes, and when treated as a time-varying covariate had better predictive power than baseline HDL-C for development of incident T2DM [20]. In multivariate Cox models that also adjusted for multiple other T2DM risk factors, the lowest quartile of in-treatment HDL-C (<1.22 mmol/l or 22 mg/dl) remained associated with an almost ninefold increased risk of new diabetes compared with those in the highest quartile of in-treatment HDL-C (>1.78 mmol/l or 32.1 mg/dl) [20].

#### Prevent study

In this prospective study of 6820 non-diabetic Danish patients with a mean age of 49 years followed for 8 years, after multivariate analysis higher HDL-C was found to be associated with lower risk of development of T2DM with an odds ratio (OR) of 0.55 (0.47–0.64) for every 1 standard deviation (SD) increase in HDL-C [21]. Mean baseline HDL-C is this population was 1.34 mmol/l (or 24 mg/dl).

#### ASCOT-BPLA

The ASCOT-BPLA trial was designed to evaluate the cardiovascular effects of different blood pressure regimens and randomized to either atenolol-based or amlodipine-based treatment [22]. In post hoc analysis of 14,120 nondiabetic patients, significant predictors of incident DM included elevated fasting glucose (HR: 5.8; 95% CI: 5.23–6.43), increased BMI (HR: 1.49; 95% CI: 1.38–1.62) as well as high triglyceride levels (HR: 1.12; 95% CI: 1.07–1.17) [22]. Variables that were found to be potentially protective against incident T2DM included amlodipine-based treatment (HR: 0.66; 95% CI: 0.59–0.74), increased HDL-C (HR: 0.72; 95% CI: 0.58–0.89) and aged greater than 55 years and alcohol use. Importantly, although higher fasting glucose levels were found to be the most powerful predictor of new diabetes, increased HDL-C levels remained associated with lower diabetes incidence after adjusting for confounders [22].

#### Framingham Offspring Study

In a population sample that attended the fifth clinic examination of the Framingham Offspring Study in the mid 1990’s, 3140 predominantly Caucasian, nondiabetic subjects with a mean age of 54 years who had an oral glucose tolerance test were followed for an average of 7 years to determine predictors of new-onset T2DM [23]. The mean HDL-C in this population was 36.9 mg/dl at baseline. Predictors of T2DM included impaired fasting glucose, low HDL-C, obesity, triglyceride level, parental history of diabetes and high blood pressure [23]. Similar to ASCOT-BPLA [22], in their simple clinical model that they used to develop...
a T2DM risk algorithm, impaired fasting glucose was the strongest predictor (OR: 7.25; 95% CI: 4.89–10.74), followed by low HDL-C (OR: 2.57; 95% CI: 1.75–3.77).

• San Antonio Heart Study
In a multinational population-based prospective study designed to study T2DM and cardiovascular disease among Mexican Americans and non-Hispanic whites living in San Antonio who were followed for approximately 8 years, 1734 overweight nondiabetic participants were identified [24]. Incident T2DM was associated with lower HDL-C (1.05 mm/l or 18.9 mg/dl in incident T2DM vs 1.24 mm/l or 22.3 mg/dl in nondiabetics; p < 0.001); however, multiple other variables were also associated with T2DM in univariate analyses, including age, ethnicity, family history of diabetes, impaired fasting glucose and metabolic syndrome [24]. Unfortunately, multivariate analysis was not performed to determine if the association of low HDL-C with incident T2DM was independent of other risk factors. Of note, analysis revealed Mexican–Americans to have an excess risk of development of impaired glucose tolerance and development of T2DM compared with non-Hispanic Whites [25].

• GEMS
In a prospective, multinational study of overweight subjects designed to study the genetics of metabolic syndrome, 715 subjects were identified who had low HDL-C (lowest 25th percentile) and elevated plasma triglyceride (upper 25th percentile) [26]. The mean HDL-C of this group was 0.95 mmol/l (or 17 mg/dl) versus 1.63 mmol/l (or 29.3 mg/dl) in the unrelated comparison controls with comparable BMIs recruited from the same centers. The study population with low HDL-C and elevated triglycerides had increased fasting glucose, lower insulin levels as well as higher levels of inflammatory markers such as CRP compared with overweight patients with normal HDL-C and triglyceride levels [26]. Notably, the subjects were not matched for many potential confounders and the study population was younger (mean age: 50 vs 55), more overweight with a higher BMI (28.7 vs 28.2) and waist circumference (98 vs 95 cm), more likely to be a smoker, on a β-blocker (23 vs 5%) and a statin (47 vs 2%), suggesting that this risk of developing diabetes could have been due to alternative factors [27,28].

• IRAS
In a multicenter, multiethnic prospective study initially designed to assess the relationship between insulin resistance and cardiovascular disease [29], 830 nondiabetic patients, mean age of approximately 55 years, were identified and followed for a mean of 5.2 years [30]. This study utilized nuclear magnetic resonance (NMR) spectroscopy to study lipid composition and found that via stepwise logistic regression models low HDL-C (OR: 1.64; 95% CI: 1.28–2.08) and high triglycerides were associated with development of incident T2DM. In addition, they also found that VLDL particle size and small HDL-P were associated with development of incident T2DM independent of metabolic covariables, suggesting that abnormalities in lipoprotein composition occur prior to the development of incident T2DM [30]. The analysis was consistent across the ethnic groups in the study: white, black and Hispanic [30].

• ARIC study
In this prospective study originally designed to study the etiology of atherosclerosis and cardiovascular disease [5], 7915 nondiabetic adults aged 45–64 years were examined to evaluate clinical predictors of incident T2DM [31]. A risk function utilizing logistic regression was developed to predict incident T2DM and found that including HDL-C and elevated triglycerides, in addition to waist, height, hypertension, family history of diabetes, ethnicity and age, improved the area under the receiving operative curve from 0.78 to 0.80 [31]. Unfortunately, the results of further multivariate analysis that demonstrate the association between low HDL-C and incident T2DM were not reported in the article.

Potential mechanisms for the association of T2DM with HDL-C
HDL-C is an integral part of the pathway that delivers cholesterol back to the liver and other steroidogenic organs via the efflux of cholesterol from cholesterol-loaded arterial macrophages [32,33]. However, recent literature has demonstrated that there are additional pleotropic effects of HDL-C that may be protective against the development of incident diabetes. Additionally, HDL-P have been shown to be functionally deficient in patients with T2DM, further suggesting the additional interaction between low HDL-C and HDL-P function [13]. In this section, potential pathways between low HDL-C and development...
of incident T2DM will be reviewed and include: decreased stimulation of pancreatic insulin secretion, effects on peripheral muscle glucose uptake and anti-inflammatory effects.

- **Decreased stimulation of pancreatic β-cell insulin secretion**
  
  In mouse models, excessive accumulation of cholesterol (or lipotoxicity) in pancreatic cells demonstrated decreased pancreatic islet numbers and β-cell mass, decreased insulin content within the pancreatic islets and β cells and impaired glucose-stimulated insulin secretion [14,34-35]. One mouse model demonstrated a direct link between islet cholesterol levels and impaired glucose-stimulated insulin secretion with normal secretion restored by subsequent cholesterol depletion [35]. Additionally, the UK Prospective Diabetes Study found that the β-cell secretory function was approximately 50% decreased at the time of T2DM diagnosis [36,37].

  In human studies, a recent double-blind placebo controlled crossover study in which 13 T2DM patients received both intravenous reconstituted HDL-C (rHDL-C) and placebo on separate days demonstrated that infusion of rHDL-C resulted in approximately a 1.4-fold increase in plasma HDL-C levels, a greater fall in plasma glucose, increased plasma insulin, as well as increased glucose uptake by the peripheral skeletal muscle [38]. Furthermore, a study in which apolipoprotein (apo) A-I or apo A-II proteins, the main apolipoprotein components of HDL-C, were incubated with primary pancreatic islets found increased β-cell insulin secretion [36].

  Another study that was performed in both humans and rats demonstrated that HDL-P partially countered the adverse effects of proatherogenic oxidized LDL-cholesterol particles on β-cell function by preventing activation of the JNK pathway [39]. The JNK pathway, which is induced by oxidized LDL, is part of a larger mechanistic pathway that directly represses the production of insulin and induces β-cell apoptosis [39,40].

  ABCA1 is a key transport protein that mediates the efflux of cholesterol from the pancreas [12,41]. One study demonstrated that mice with specific inactivation of ABCA1 in B cells had markedly impaired glucose tolerance and decreased insulin secretion, yet had normal insulin sensitivity [42]. Mice that lacked the ABCA1 receptor also had significantly higher levels of total cholesterol in the islet cells compared with those that had intact ABCA1 receptor, suggesting a functional role for cholesterol homeostasis in the pathogenesis of impaired glucose-mediated insulin secretion [42]. Another study in mice demonstrated that accumulation of cholesterol in islet cells due to loss of ABCA1 led to impaired insulin secretion via impaired exocytosis of insulin granules [43]. This defect was found to be reversible via acute cholesterol depletion, suggesting a potential therapeutic target [43].

  In humans, a study in a Mexican population with a unique genetic polymorphism of the ABCA1 gene that was associated with low HDL-C, obesity and T2DM demonstrated a significant decrease in cholesterol efflux compared with those with normal ABCA1 receptor – however, these were unpublished data and not subject to peer review [43]. In a study of 24 patients with T2DM with reduced expression of ABCA1 there was reduced cholesterol efflux in macrophages leading to increased cholesterol accumulation compared with controls without T2DM [43]. The increased cholesterol accumulation appeared to primarily be due to ABCA1 downregulation since upregulating the receptor via exogenous means reduced the intracellular cholesterol accumulation [44]. Additionally, heterozygous carriers of disruptive mutations in ABCA1 were also found to have impaired insulin secretion without insulin resistance, further demonstrating the importance of the ABCA1 receptor for normal β-cell function in humans [45].

  Another HDL-mediated cholesterol transporter, ABCG1, was found to have complimentary roles with the ABCA1 transporter: mice with combined deficiency of both ABCG1 and ABCA1 had greater defects in β-cell function compared with deficiency of either transporter individually [46]. Loss of these transporters in macrophages also leads to increased inflammation via the increased expression of proinflammatory cytokines when challenged with free cholesterol or oxidized LDL [47].

- **Peripheral skeletal muscle uptake**
  
  HDL-C enhances cellular uptake of cholesterol in the peripheral tissue by increasing plasma insulin via its effects on pancreatic β cells, and also by binding to surface receptors on skeletal muscle (ABCA1), activating the AMPK pathway, which directly promotes glucose intake into the
skeletal muscle [12]. This is an important finding considering that skeletal muscle accounts for the majority of glucose utilization in the body [12]. Furthermore, cellular studies have demonstrated skeletal muscle to be an important regulator of reverse cholesterol transport and HDL-C levels [48]. Skeletal muscle was also demonstrated to have similar reverse cholesterol transport receptors previously found in the liver, called liver X receptors (LXR) [48]. These receptors, when activated, increase reverse cholesterol transport. Inflammatory markers have been shown to inhibit LXR activity in macrophages thus inhibiting cholesterol uptake [49].

ApoA-I is the main protein component of HDL-C and has been shown to directly activate the AMPK pathway leading to improved glucose uptake in muscle and decreased liver production [8,50]. As mentioned previously, a study in which rHDL-C was infused in 13 T2DM patients not only showed beneficial effects on the plasma insulin, HDL-C and glucose levels, but also demonstrated increased activation of the AMP-activated protein kinase pathway verified by peripheral muscle biopsy and increased peripheral glucose uptake by approximately 178% [38].

In a recent study of mice with overexpression of ApoA-I, not only did the mice with increased ApoA-I have elevated fasting glucose and higher Hgb A1C levels, but they also expressed decreased muscle glucose uptake and reduced muscle mitochondrial capacity [51,52]. Thus, in these mice there was evidence of impaired skeletal muscle mitochondrial function and cellular respiration with decreased HDL-C levels. This study, as nicely elucidated by the accompanying editorial, should spur interest in examining whether treatment to raise HDL-C levels may reduce the incidence of T2DM [51].

- **Anti-inflammatory actions**

Multiple studies in T2DM patients have shown increased features of inflammation (cytokines, immune cells and β-cell apoptosis) in pancreatic islets and increased number of macrophages [41,53,54]. Moreover, the ABCA1 receptor has also been shown to function as an anti-inflammatory receptor independent of cholesterol influx [55].

Fatty acids also seem to play a role in the relationship between inflammation and insulin resistance [56]. One study demonstrated that fatty acids induced inflammation via release of cytokines that can directly inhibit insulin signaling and contribute to insulin resistance [14,57].

As for a potential role of HDL-C, a study in mouse cells demonstrated adipocytes transfer cholesterol to HDL-C using the ABCA1 pathway [58] and that this pathway is downregulated with adipocyte inflammation, leading to lower levels of HDL-C [58].

Obesity, with its associated chronic inflammation and as part of the greater metabolic syndrome, may also play a role in conjunction with low HDL-C levels [49]. With the reduced anti-inflammatory function of the lower levels of HDL-C, the enhanced inflammatory state via inflammatory cytokines will inhibit insulin receptor substrates and lead to insulin resistance [49].

Furthermore, HDL-C isolated from healthy subjects was found to stimulate nitric oxide production, reduce endothelial oxidant stress and improve endothelium-dependent vasodilation compared with HDL-C from diabetic subjects [59]. The findings in diabetic subjects were improved when they were given niacin to boost HDL-C, suggesting a potential therapeutic option [59]. However, further studies have shown that higher niacin doses were associated with deleterious effects on glucose control and insulin resistance [60–62].

**Treatment implications**

Given the associations of low HDL-C with increased T2DM and mechanisms as described above, there could be therapeutic potential in raising HDL-C levels to reduce T2DM incidence among those at high risk. This section will review some of the current literature regarding the major HDL-C-raising medicine classes and the evidence on prevention of incident T2DM.

- **Statins**

Statins are HMG-CoA reductase inhibitors that lower LDL cholesterol levels, raise HDL-C levels and have other pleiotrophic effects such as improvement of endothelial dysfunction, anti-oxidant effects and anti-inflammatory effects [63]. Given the mechanisms described previously, statins could be conceived to be beneficial in the prevention of incident of T2DM; however, studies examining the relationship of incident T2DM to statin therapy have mostly proved to have the opposite effect. An often cited, landmark meta-analysis of 13 studies involving 91,140 participants demonstrated a 9% increased risk of incident diabetes (OR: 1.09; 95% CI: 1.02–1.17) among patients randomized
to statin therapy, estimating one case of incident diabetes for every 255 nondiabetic patients treated for 4 years with an effect primarily seen in patients greater than 60 years of age with little statistical heterogeneity between trials and statins [64,65]. However, this was in contrast with the four to five cardiovascular events prevented for every 255 patients treated with statins for 4 years [66], thus estimating a benefit–risk ratio of 9:1 [65]. The vast majority of individual studies of this issue confirm the findings of this meta-analysis. However, some individual statin trials have been shown to be protective against the development of incident diabetes. For example, in WOSCOPS, a randomized double blind placebo controlled trial designed to test the clinical efficacy of 40 mg of pravastatin as primary prevention for coronary events with follow-up of 4.9 years, 5974 self-reported nondiabetics with nonelevated fasting glucose levels with mean age of 55 years were identified and used to prospectively study the effects of pravastatin therapy on the risk of developing diabetes [67]. Multivariate analysis demonstrated a 30% lower risk of incident diabetes for those on pravastatin (HR: 0.70; 95% CI: 0.50–0.99) [67]. Although mean HDL-C levels of the nondiabetics were 1.14 mmol/l (or 44 mg/dl) and 1.05 mmol/l (or 40.6 mg/dl) for those that developed incident diabetes, this difference was not statistically significant and HDL-C was not a significant predictor of incident T2DM (HR: 0.86; 95% CI: 0.67–1.11; p = 0.24) [67]. In a smaller study of 35 consecutive nondyslipidemic, nondiabetic patients with mean age of 55 years who were given 40 mg/day of fluvastatin and followed for 8 weeks, insulin sensitivity improved by measure of insulin resistance scores that utilized fasting glucose levels and immunoreactive insulin assays [68]. The HDL-C levels also improved from 45.9 to 50.4 mg/dl after treatment with fluvastatin (p < 0.0001) but there was no significant correlation between HDL-C and insulin resistance score (p = 0.736) [68]. However, this was a small study with no comparison group or placebo control.

• Fibrates
Fibrates are PPAR ligands that have HDL-C raising and triglyceride lowering effects [69]. By activating PPAR, they decrease fatty acid levels, increase adipogenesis, and improve insulin sensitivity via decreased peripheral muscle fatty acid uptake [70]. There have been some recent landmark trials, such as the ACCORD trial, that did not show any reduction of cardiovascular events with the addition of fibrates to a statin in patients with established diabetes, but unfortunately effects on insulin sensitivity or A1c levels were not reported in post hoc analyses [71]. In the BIP study, designed to investigate the safety and efficacy of administering bezafibrates to patients with coronary artery disease for secondary prevention, a post hoc subgroup analysis was performed on 303 nondiabetic patients with a mean age of 61 years with impaired fasting glucose (110–125 mg/dl) in which roughly half received 400 mg of bezafibrate once a day with a follow-up period of approximately 6 years [69]. At baseline, the mean HDL-C was approximately 34 mg/dl with no significant difference between the two groups, but the placebo group had a slightly higher BMI and lower prevalence of ACE-I utilization [62]. Over the follow-up period, bezafibrate therapy was associated with reduced fasting blood glucose levels, a lower incidence of new onset diabetes (42% in the bezafibrate group vs 54.4% in the placebo group; p = 0.04) and an increase in the mean time until onset of new T2DM (4.6 vs 3.8 years, p = 0.004). After multivariate analysis, bezafibrate treatment was an independent predictor of reduced risk of new diabetes (HR: 0.70; 95% CI: 0.49–0.99) [69].

• Niacin
Niacin (nicotinic acid), an effective HDL-C increasing medication via its effect on the liver and increased HDL-C biogenesis, has demonstrated some inhibition of atherosclerosis and has anti-inflammatory effects [60,72–74]. Thus, in theory, niacin would also seem promising as a potential therapy for those with low HDL-C and increased risk of incident T2DM. Quite the contrary, deleterious effects on glucose control and insulin resistance at higher levels of niacin have been noted in studies and previous guidelines from the National Lipid Association, American Heart Association and American Diabetic Association warn of such risk when initiating niacin [60]. In the NAUTILUS study, a multicenter open-label trial that enrolled 566 patients with dyslipidemia with mean HDL-C 0.85 mmol/l (32.9 mg/dl) in men and 0.95 mmol/l (36.7 mg/dl) in women, a mean age of 56 years, and 58% with T2DM at baseline, patients were given extended-release niacin with a target dose of 2000 mg daily and followed for 15 weeks [61]. After the 15-week period,
HBA1c increased by >0.2% in almost half the population and >1% in 9% of the population, and 6.4% also received intensified antidiabetic therapy. There were no comparison group in this study unfortunately and therefore risk assessments could not be performed. Similar findings were demonstrated in a randomized double blind placebo-controlled trial of 131 patients with hyperlipidemia with mean age of 54 years and HDL-C levels of approximately 45 mg/dl that were followed for 25 weeks and given extended-release niacin with goal dose of 3000 mg a day [61,62]. Finally, a meta-analysis of 30 trials with a total of 4749 subjects demonstrated 2.3% of patients receiving niacin developed hyperglycemia versus 0.4% in the control group, for a relative risk of 3.04 (95% CI: 1.28–7.21; p = 0.01) [60]. In sum, the literature points to increased glucose intolerance when patients are treated with niacin.

- **Thiazolidinediones**

As previously mentioned, Brunham et al. inactivated the ABCA-1 receptor in β cells which caused impaired glucose-sensitive insulin secretion and elevated pancreatic islets cholesterol levels. The addition of rosiglitazone restored normal glucose tolerance and lowered the free cholesterol level in pancreatic islet cells [42]. This class of medication is frequently used clinically to treat diabetes due to its insulin-sensitizing effects [75]. However, compounds within this class have differing effects on lipoproteins, independent of glycemic control. In a randomized, double blind multicenter trial of 735 patients with T2DM and dyslipidemia not treated with lipid-lowering agents, patients that were randomized to pioglitazone had greater increases in HDL-C (5.2 vs 2.4; p < 0.001), smaller increases in LDL and reduced triglyceride levels (versus an increase) compared with those that were randomized to rosiglitazone [76]. The patients in the pioglitazone group demonstrated a reduction in triglycerides versus an increase in the rosiglitazone group [76].

- **CETP inhibitors**

CETP is a glycoprotein that promotes transfer of cholesteryl esters from HDL to VLDL and LDL and other proatherogenic apoB proteins [77]. Deficiency of this protein is associated with increased levels of HDL-C and reduced coronary heart disease [77]. To determine if medications that reduce CETP would be beneficial in humans, the ILLUMINATE trial tested whether torcetrapib, a CETP inhibitor, could reduce major cardiovascular events. This trial was a randomized, double-blind study of 15,067 patients with a history of cardiovascular disease or diabetes, mean age of 81 years and a mean HDL-C level of approximately 49 mg/dl; patients were randomized to atorvastatin with placebo or atorvastatin plus torcetrapib [78]. Notably, torcetrapib effectively raised HDL-C: at 12 months HDL-C increased by 34.2 mg/dl in the torcetrapib group versus 0.5 mg/dl in the atorvastatin monotherapy arm (p < 0.001). The trial was terminated early due to increased risk of death and cardiac events in the torcetrapib arm. [78]. The etiology of the increased mortality with torcetrapib remains unclear, but was postulated by the authors to be either an off-target pharmacologic effect or possibly due to generation of dysfunctional or proatherogenic HDL-C [78]. Furthermore, in a subsequent *post hoc* analysis of the ILLUMINATE trial on the 6661 diabetic patients, the patients in the torcetrapib plus atorvastatin arm had lower plasma glucose (0.33 mmol/l lower; p < 0.0001) and insulin levels at 3 months and lower levels of mean A1c at 12 months compared with the atorvastatin plus placebo arm (7.16 vs 7.36%; p < 0.001) [79]. Another randomized, multicenter, placebo-controlled trial of a different CETP inhibitor, dalcetrapib, was performed in 15,871 patients with a recent acute coronary syndrome [80]. The primary end point was a composite of death from coronary heart disease, a major nonfatal coronary event or ischemic stroke. The study stopped early due to futility after 71% of the projected prespecified primary end points had been reached, with no significant difference in the primary end point between treatment arms after a mean follow-up of 31 months. Dalcetrapib had a powerful effect on HDL-C, with 31–40% increases in HDL-C in the treatment arm versus 4–11% in the placebo arm, with minimal effects on LDL cholesterol levels and no effect on fasting plasma glucose or glycated hemoglobin. The authors postulated that the lack of cardiovascular benefit may have been due to high rates of optimal medical therapy (i.e., statins, β-blockers and antiplatelet therapy) for a secondary prevention cohort. They also postulated that HDL-C may be more effective in those without coronary artery disease and that the composition of HDL-C may be altered in the presence of coronary artery disease, potentially...
mitigating any protective effects that might have been derived from directly raising HDL-C. In another small randomized, controlled placebo-controlled trial of 25 healthy subjects of whom ten received a daily dose of a CETP inhibitor and the others received placebo for a total of 14 days, beneficial changes on HDL-C levels (+0.55 mmol/l vs -0.10 mmol/l, placebo group; p < 0.0001), triglycerides (-0.06 mmol/l vs +0.9 mmol/l in placebo group; p < 0.05), and LDL-C (-0.86 mmol/l vs +0.03 mmol/l in placebo group; p < 0.0001) were demonstrated at 14 days. Furthermore, in murine pancreatic cells, the CETP group also showed a greater than twofold increase in postprandial insulin and C-peptide compared with the placebo group [81]. There are ongoing studies evaluating other CETP inhibitors (anacetrapib and evacetrapib) [82]. It remains to be seen whether the discordance between positive increases in HDL-C and the negative clinical outcomes are a class effect or specific only to torcetrapib and dalcetrapib.

### Conclusion

Population-based studies suggest a significant association between low HDL-C and an increased risk of developing diabetes. Although there have been no specific studies designed to test the hypothesis that raising HDL-C levels in patients with low HDL-C can reduce the risk of incident diabetes, the impact of various treatments on diabetes risk and glucose metabolism in these patients has been varied. Although results with statin therapy have been mixed, most studies and meta-analyses have demonstrated an increased risk of incident diabetes in patients treated with statins. Fibrates may have a protective effect, but this has only been demonstrated in a few small studies. Niacin can raise HDL-C modestly, but like statins it can slightly increase the risk of incident T2DM. CETP inhibitors have the largest effects on HDL-C, however, the increased mortality seen in the ILLUINATE trial raises significant safety concerns with regards to the use of these drugs.

### Future perspective

Ultimately, there is an intriguing set of epidemiologic, experimental and animal data supporting a metabolic interplay between low HDL-C, hyperglycemia and incident T2DM. However, it remains an unproven proposition that increasing HDL-C can prevent the future development of incident T2DM. Until further clinical evidence can substantially support this hypothesis, low HDL-C continues to be a marker of T2DM risk rather than a target for therapy.

### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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**Demonstrates that treatment with torcetrapib improves glycemic control in atorvastatin-treated patients with Type 2 diabetes mellitus.**


**Demonstrates that in patients with recent acute coronary syndrome, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent cardiovascular events.**
