

Cardiometabolic Impact of Non-Statins Lipid Lowering Therapies

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Abstract Among the range of lipid modifying medications currently available, statins clearly stand as the primary agent capable of reducing cardiovascular risk. While non-statin lipid-lowering drugs improve lipid parameters, their impact on clinical outcomes is less clear, thus necessitating an even closer look at ancillary effects. Recent studies have reported the potential cardiometabolic effects of statins, yet considerably less information has been published about cardiometabolic changes associated with non-statin lipid-lowering agents. This review describes the cardiometabolic profile of non-statin lipid-lowering agents—fibrates, niacin, omega-3 polyunsaturated fatty acids, ezetimibe, and bile acid sequestrants—and therefore aims to facilitate informed decision-making in the pharmacologic management of lipid abnormalities.

Keywords Lipids · Fibrates · Cardiovascular disease · Diabetes mellitus type 2 · Niacin · Omega-3 polyunsaturated fatty acids · PUFAs · Ezetimibe · Bile acid sequestrants

Cardiovascular disease is the leading cause of mortality in the world. Fortunately, many beneficial therapies exist to both prevent and treat cardiovascular disease, with HMG Co-A reductase inhibitors, or statins, being the pharmacologic pillar of both primary and secondary prevention. Recently, new data has emerged demonstrating the potential dysglycemic effects of statins, prompting the US Food and Drug Administration (FDA) to issue a warning on the labels of this prevalent class of medications, stating that statins increase the risk of raised blood sugar levels and the development of diabetes mellitus

type 2 (DM2). There is renewed interest in examining the impact of statins on glycemic control, obesity, and incidence of DM2. Meanwhile, little has been reported on the cardiometabolic effects of other lipid-lowering agents. The goal of this review is to describe the cardiometabolic profile of non-statin, lipid-lowering agents—fibrates, niacin, omega-3 polyunsaturated fatty acids (PUFAs), ezetimibe, and bile acid sequestrants—and to therefore facilitate informed decision-making in pharmacologic management of lipid abnormalities (Table 1).

Fibrates

Fibrates may be used as monotherapy or in combination therapy with statins, and are currently approved for use in hypertriglyceridemia and hyperlipidemia. Fibrates approved for use within the US include fenofibrate and gemfibrozil. Additional fibrates approved outside of the US include ciprofibrate and bezafibrate.

Fibrates are peroxisome proliferator-activated receptor (PPAR)-alpha agonists, and exert a beneficial effect on low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides. Fibrates reduce LDL levels through accelerated clearance of triglyceride-enriched lipoproteins mediated by cholesteryl ester transfer proteins. They improve HDL by increasing HDL synthesis and decreasing its conversion to lower density lipoproteins. Finally, fibrates reduce triglycerides by reducing hepatic secretion of VLDL and activating lipoprotein lipase [1]. Although fibrates have consistently been shown to improve lipid profiles, their clinical impact on cardiovascular outcomes have been mixed. While some landmark trials, including the Helsinki Heart Study [2] and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) [3], have demonstrated that fibrates reduce coronary heart disease events, other trials, including the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) [4] and Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid [5], have

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Table 1 Impact of lipid-lowering agents on cardiometabolic parameters

Agent	Glucose levels	Insulin resistance	Weight	HgbA1c	DM2 incidence
Fibrates:					
Fenofibrate	N/↓	N/↓	N	N/↓	N
Gemfibrozil	N	N	N	N	N
Ciprofibrate	N	N	N	N	?
Bezafibrate	↓	↓	N	↓	↓
Niacin:					
Short-acting	N/↑	N/↑	N	N/↑	N
Long-acting	N/↑	N	?	N	N/↑
Omega-3 Fatty Acids	N	↓	N/↓	N	N/↓
Ezetimibe	↓	↓	↓	↓	?
Bile Acid Sequestrants	↓	↓	N	↓	↓

Legend: ↑ = Increase, ↓ = Decrease, N = Neutral, ? = Unclear

not demonstrated a benefit. Especially given this conflicting data regarding clinical benefit, it is important to consider the cardiometabolic effects of this drug class.

It is believed that lipid abnormalities may be interrelated with insulin resistance and fibrates, and through the PPAR pathway, may affect important glycemic metabolic parameters. The presence of excess free fatty acids (FFA) may impair insulin secretion by exerting a direct toxic effect on the pancreatic β cells, and by interfering with insulin signaling by inappropriately activating important regulatory proteins like PKC θ , inhibitor κ B kinase (IKK), and c-Jun N-terminal kinase (JNK). The resultant insulin dysregulation leads to further increases in FFA, and propagates this cycle of events. Steiner was one of the first to demonstrate that reducing triglyceride concentrations in humans has the potential to reduce insulin levels [6]. Through this mechanism, and perhaps additional mechanisms that are not yet understood, fibrates have a neutral to beneficial effect on glycemic metabolic parameters.

Fenofibrate

Fenofibrate's effect on cardiometabolic parameters varies with baseline metabolic status. Cardiometabolic impacts of fenofibrate have been best studied in patients with diabetes, with several studies failing to demonstrate significant changes in fasting glucose [7–9], pro-insulin levels [10], hemoglobin A1c [4, 8, 9, 11–14] (HgbA1c), or weight [8–10]. Interestingly, among non-diabetic patients at highest risk for developing diabetes, fenofibrate appears to improve metabolic parameters. Okopien et al. found that fenofibrate reduces glucose levels during oral glucose tolerance testing by 14 % (baseline 164.3 mg/dL, $p < 0.01$), insulin resistance indices ($p < 0.001$), and HgbA1c by 12.7 % (baseline 5.5 %, $p < 0.05$) in patients with at least one risk factor for DM [15]. Among patients with metabolic syndrome, fenofibrate improves insulin resistance [16]; among patients with impaired fasting glucose (IFG), it improves fasting glucose (114 mg/dL to 102 mg/dL, $p < 0.01$), insulin resistance indices ($p < 0.01$), and HgbA1c (5.9 % to

5.3 %, $p < 0.01$) [17]. Among patients with impaired glucose tolerance (IGT), fenofibrate improves glucose levels following sugar-load (baseline 159.6 mg/dL; 7.9 % reduction after 30 days, $p < 0.01$; 6.6 % reduction after 90 days, $p < 0.01$) [18]. Finally, among patients with polymetabolic X syndrome (defined as dyslipoproteinemia with hypertriglyceridemia, low HDL cholesterol, central obesity, hypertension, and increased thrombogenicity), fenofibrate reduces glucose levels during oral glucose tolerance testing, insulin-to-glucose ratios, and insulin levels [12], especially among patients in whom triglycerides levels are also decreased.

For patients with dyslipidemias, including hypertriglyceridemia, in the absence of initial glucose or insulin derangements, most studies have shown no significant fenofibrate-induced changes in fasting glucose, fasting insulin, or HgbA1c [11, 19]. Studies have demonstrated variable results for fenofibrate in insulin-resistance indices—one showing no effect [11] and one showing a reduction [19]. Among overweight men and post-menopausal women without diabetes, fenofibrate reduced serum glucose and insulin levels, but had no impact on insulin sensitivity [20]. The effect of fenofibrate on the incidence of DM2 has only been retrospectively studied within a limited population of 4,000 patients with dyslipidemia, showing no increased risk in the development of DM2 [21], further demonstrating its neutral cardiometabolic effect. Although small studies have shown a benefit for patients who are at higher risk for diabetes, a larger-scale trial examining this effect is highly warranted. Overall, the impact of fenofibrate on cardiometabolic parameters in diabetic patients appears neutral, but may benefit those at highest risk for diabetes, who do not yet have the disease.

Gemfibrozil

In contrast to fenofibrate, several small studies have shown that gemfibrozil has a neutral effect on glycemic metabolic parameters, independent of metabolic status. Among patients with DM2 [22, 23] and patients with isolated hyperlipidemia [24] and hypertriglyceridemia [25, 26], gemfibrozil has no significant

effect on fasting glucose or insulin levels, or glucose levels during oral glucose tolerance testing. Among patients with hypertriglyceridemia with glucose intolerance, gemfibrozil decreased insulin levels only when triglycerides decreased by at least 50 % [27], likely reflecting the relationship between triglycerides and insulin more than anti-glycemic properties of the drug itself. Fasting glucose and HgbA1c levels remained unchanged. Among obese patients without other risk factors, the impact of gemfibrozil is less clear, with one study demonstrating both increased insulin levels and, surprisingly, decreased weight and adiposity [28]. Similar to fenofibrate, gemfibrozil did not alter the incidence of DM2 among a cohort of 4,000 patients with dyslipidemia, further supporting its neutral cardiometabolic profile [21]. Future large-scale studies examining gemfibrozil's cardiometabolic impact would help strengthen its safety profile in those with and those at risk for diabetes.

Ciprofibrate

There are very few studies examining the cardiometabolic profile of ciprofibrate. Among isolated DM2 [29] and metabolic syndrome [30], ciprofibrate exerts a neutral effect on cardiometabolic parameters, as glucose and insulin levels, hemoglobin A1c, weight, and body mass index (BMI) remained unchanged. Future studies should focus on ciprofibrate's impact on DM2 incidence to better delineate its cardiometabolic profile.

Bezafibrate

Amongst the fibrates, bezafibrate has the most beneficial effect on cardiometabolic parameters, likely related to its unique mechanism of action. In addition to the usual PPAR alpha agonist action of the fibrate class, bezafibrate appears to be a pan-PPAR agonist, with additional action at the gamma and delta PPAR receptors. By activating the gamma receptor, bezafibrate exerts action similar to the thiazolidinediones, a well-validated oral hypoglycemic agent used in diabetes. Delta PPAR antagonism has been associated with the development of several chronic diseases, including diabetes and obesity, and atherosclerosis-modulation of this receptor appears to preferentially change the body's fuel preference from glucose to lipid metabolism, reversing the typical profile seen in insulin-resistant muscle tissue [31]. Although the results of early, small studies were mixed [32–41], recent larger-scale studies including the Japan Bezafibrate Clinical Effectiveness and Tolerability (J-BENEFIT) and Bezafibrate Infarction Prevention trial (BIP) have demonstrated a clear benefit on glycemic parameters. J-BENEFIT, a prospective cohort study of 3,316 patients with DM2, demonstrated a 13 % reduction in fasting glucose levels, and improvements in hemoglobin A1c (7.7 % to 7.2 %, $p < 0.001$) with greatest improvements amongst those with higher HgbA1c levels and those with the shortest duration of DM2 [36]. Among 2,504 patients in

the BIP study with coronary artery disease, bezafibrate prevented increases in fasting blood glucose and insulin resistance indices seen in the placebo group [42]. Subgroup analysis showed reductions in glucose levels in patients with glucose intolerance [43], and those with obesity [44].

Independent of baseline metabolic status, patients did not experience a significant change in their weight or BMI with bezafibrate [35]. This supports the hypothesis that pan-PPAR agonists that include a component of PPAR gamma/delta activation might offset some of the weight gain issues otherwise seen with selective PPAR gamma agonists [45]. Most convincingly, subgroup analyses of the BIP study also showed a 12 % absolute reduction in the incidence of DM (54.4 % vs. 42.3 %; $p = 0.04$) and a mean delay of 10 months in onset of DM (4.6 +/- 2.3 vs. 3.8 +/- 2.6, $p = 0.004$) among patients with glucose intolerance [43], as well as a 10 % absolute reduction (37 % vs. 27.1 %, $p = 0.01$) in incidence and a mean delay of 24 months in those with just obesity [44]. Flory et al. further illustrated bezafibrate's superiority to other fibrates in this regard in a retrospective study demonstrating a reduced incidence of DM (8.5/1,000 person-year) in the bezafibrate group as compared to users of other fibrates (14.4/1,000 person-years) [46].

In summary, fibrates do not worsen glycemic metabolic parameters, and may potentially provide some benefit in cardiometabolic parameters. Through its pan-PPAR mechanism of action, bezafibrate demonstrates the greatest promise to improve metabolic parameters but requires further validation. A large meta-analysis of primary data within various at-risk populations would shed light on possible cardiometabolic benefits of fibrates. However, as with any drug, the ultimate determinant of benefit is in clinical outcomes rather than simply biochemical or other surrogate measures.

Niacin (Nicotinic acid)

Niacin formulations that are FDA-approved for use in hypercholesterolemia include short-acting niacin and long-acting niacin (Niaspan). While the mechanisms are not completely understood, niacin increases HDL-cholesterol by reducing cholesterol transfer from HDL to LDL and very-low-density lipoprotein (VLDL), and by reducing hepatic excretion uptake [47]. Increases in HDL lead to reverse cholesterol transport, reducing levels of cholesterol in arterial wall macrophages. Niacin also lowers LDL and TG levels through inhibition of VLDL production in the liver. Despite its ability to increase HDL, studies examining niacin's impact on cardiovascular outcomes, including the landmark trials Atherothrombosis Intervention and Metabolic Syndrome with Low HDL High triglyceride (AIM-HIGH) and Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), have been disappointing. Niacin has not only failed to demonstrate an

improvement in cardiovascular outcomes, but also may worsen glycemic metabolic parameters through poorly understood mechanisms, albeit transiently.

Short-acting

Short-acting niacin has a negative effect on fasting glucose and HgbA1c that is transient, lasting several weeks. During a span of just 2–3 weeks at doses <1.5 g/day, niacin increases levels of blood glucose by 4–17 % (3.6–16.2 mg/dL); it also increases insulin levels in the fasting state [48, 49] and following a glucose load [48], as well as worsens insulin sensitivity [50–52]. Amongst a higher-risk population with cardiovascular disease, niacin increased blood glucose levels by an additional 3 % while fasting (8.1 vs. 5 mg/dl) and 7 % following glucose load (16.9 vs. 4.8 mg/dl) compared to placebo at 5 years, but did not impact either HgbA1c levels or incidence of DM2 [52].

In the Arterial Disease Multiple Intervention Trial (ADMIT) study, Elam et al. examined the pattern of increases in fasting glucose over time [53]. Among patients without diabetes, niacin yielded a 6 % increase (6.3 mg/dL, $p < 0.001$) in fasting glucose at 18 weeks, which subsequently normalized through 48 weeks without changes in HgbA1c or increased incidence of DM2 compared to placebo. Among patients with DM2, niacin demonstrated a more significant impact on fasting glucose compared to placebo at 18 weeks, increasing fasting glucose by 8.1 mg/dL (5 %, $p < 0.04$), while placebo decreased fasting glucose by 8.7 mg/dl (-5 %, $p < 0.04$). This effect within pre-existing diabetes is consistent with a prior study by Garg and Grundy, who demonstrated a trend toward higher mean plasma glucose levels with niacin as compared to placebo, as well as worse HgbA1c levels by 0.9 % with niacin compared to an improved HgbA1c by 0.9 % ($p < 0.002$) with placebo at 8 weeks [54]. However, similar to non-DM, fasting glucose again normalized through 48 weeks with no difference in HgbA1c, although the placebo group did demonstrate a statistically significant decrease of HgbA1c by 0.3 % ($p < 0.05$) [53]. These data suggest that the metabolic changes of short-acting niacin occur with initiation and uptitration, and are short-lived, perhaps owing to receptor-mediated tolerance or desensitization. At no point does niacin impact weight, either in short- [50] or long-term studies [54], amongst healthy patients [50] or those with comorbidities like diabetes [54].

Long-acting

Like its short-acting counterpart, long-acting niacin has a transient, negative glycemic effect, manifest by a worse fasting glucose and an increase in DM2 incidence, which appear to remit after several weeks. Among a non-diabetic population, increases in fasting glucose occur as soon as 4 weeks [55]. However, there is no associated increase in the incidence of impaired fasting glucose at 12 weeks [56] or DM2 at 6 months

[57]. On the other hand, among patients with IGT at baseline, long-acting niacin increases the incidence of DM2 as soon as 12 weeks [56], and lasts as long as 24 weeks [58••]. Again, these negative metabolic effects appear to be transient, as increased fasting glucose levels amongst euglycemic patients normalize as soon as 18 weeks [55], and increased levels above the DM2 threshold among patients with IGT remit by 64 weeks [58••].

Consistent with these findings, the AIM-HIGH [59] and HPS-THRIVE [60] trials provide further long-term data on long-acting niacin at 3 years and 4 years, respectively, in large cohorts of patients at high cardiovascular risk, including patients with diabetes. AIM-HIGH compared long-acting niacin in combination with a statin, showing minimal differences in glucose, insulin levels, and HgbA1c as compared to statin alone. HPS-THRIVE compared long-acting niacin in combination with both statin and laropiprant, and showed no significant increases in the incidence of DM2 or major diabetes-related complications. Of note, both studies showed higher rates of drug discontinuation due to diabetic complications including hyperglycemia compared to placebo, which occurred in 0.9 % of AIM-HIGH subjects and in 0.5 % of HPS-THRIVE subjects. While not reported in these studies, adjustments in anti-diabetic medication regimens have previously been reported [55, 57], though their significance in the setting of unchanged biomarkers is unclear.

In summary, both short-acting and long-acting niacin worsen glycemic metabolic parameters transiently. The clinical impact of this temporary increase is unclear. Given the absence of clinical outcomes studies demonstrating cardiovascular benefit, niacin may be best avoided, especially in patients with or at risk for diabetes.

Omega-3 Fatty Acids

The PUFAs, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are used for the treatment of severe hypertriglyceridemia (>500 mg/dL). PUFAs lower fasting and post-prandial triglyceride levels in a dose-dependent manner, requiring 4 grams daily to reduce triglyceride levels by approximately 30 % [61, 62]. FDA-approved formulations include Lovaza (omega-3-acid ethyl esters), containing both EPA and DHA [63], and Vascepa (icosapent ethyl), which is an EPA-only formulation [64]. With the use of a combined EPA/DHA PUFA (Lovaza), there is also a mild increase in HDL (~3 %), a small increase in LDL [65] (~5 %) secondary to increased conversion of VLDL cholesterol to HDL and LDL [61], as well as an increase in LDL particle size [66]. This effect is likely driven by the DHA component, as DHA monotherapy also increases both LDL and HDL levels [67]. Meanwhile, the EPA-only formulation (Vascepa) significantly reduces triglyceride levels without increasing LDL cholesterol levels [68].

While some older clinical trials have shown significant reductions in cardiovascular events with PUFAs [69–71], more recent studies with contemporary medical management of cardiovascular risk have failed to demonstrate such benefit [72, 73]. These findings include a recent meta-analysis of 48 randomized, controlled trials with 36,913 participants and 41 cohort analyses [73].

Through its anti-inflammatory properties [74], PUFAs may have positive pleiotropic effects on cardiometabolic parameters. Chronic, low-grade inflammation occurring in the adipose tissue of obese individuals is frequently linked to the pathogenesis of insulin resistance and the metabolic syndrome [75]. Mechanistically, there is evidence to suggest that the anti-inflammatory effects of PUFAs, through the inhibition of various cytokines such as interleukin-1 beta and tumor necrosis factor-alpha [76], help to improve this insulin resistance, while increased hepatic fatty acid oxidation inhibits lipogenesis (with a subsequent decrease in triglycerides) and increases secretion of various weight-regulating gut hormones, including adiponectin [77–81], leptin, and visfatin [75]. In addition to enhanced oxidative metabolism, there is also evidence of increased glycolytic and total metabolism with ingestion of PUFAs, which may contribute to weight loss [82]. Through these mechanisms, PUFAs appear to have a beneficial effect on cardiometabolic profile.

Epidemiological studies have reported a lower prevalence of impaired glucose tolerance and DM2 in populations consuming large amounts of dietary omega-3 fatty acids [83]. There is some, albeit limited, data to suggest that PUFAs may reduce insulin resistance [84–86] and potentially delay progression to DM2 [83], as well as reduce body fat mass [87, 88], exert anti-obesity effects [89–93] and enhance satiety [94].

With respect to insulin resistance, in a study of 324 young (age 20–40), overweight or obese participants randomized to 1 of 4 possible levels of dietary PUFA content (lean fish, fatty fish, combo EPA/DHA fish oil supplement, or control), omega-3 fatty acid consumption was directly associated with positive effects on insulin resistance, and this finding remained significant even after adjusting for weight loss, TG reduction, increased omega-3 PUFA levels in erythrocyte membranes or adiponectin changes [85].

Regarding glycemic impact, there have been several meta-analyses addressing the use of PUFA in subjects with diabetes. One performed by Friedberg et al. reviewed 26 trials of patients with both type 1 and type 2 diabetes and concluded that the use of fish oil (2 to 22 g /day) slightly raised fasting glucose levels among non-insulin-dependent diabetics and significantly lowered fasting glucose levels among insulin-dependent diabetics, without significantly affecting HgbA1c [65]. Montori et al. conducted a meta-analysis of 18 trials and concluded that fish oil had no statistically significant effect on glycemic control [95]. Another large meta-analysis of 23 trials

examining patients with non-insulin-dependent diabetes found no overall effect of fish oil on fasting glucose or HgbA1c levels [96].

PUFAs may modestly assist weight-loss efforts. In a study of 69 overweight patients randomly assigned to either a daily fish meal (3.65 g omega-3 fatty acids), a weight-loss regimen, the two regimens combined, or a control group for 16 weeks, weight decreased by a mean of 5.6 ± 0.8 kg with energy restriction, with the greatest weight decrease occurring in the fish plus weight-loss group [89]. Substituting dietary saturated fat with PUFA also decreases abdominal fat distribution [97]. In a study of 84 obese men and women who underwent abdominal surgery, central obesity was inversely associated with omega-3 fatty acid levels present in subcutaneous and omental adipose tissue. This observation suggests that PUFA may be protective against abdominal obesity [98]. Additionally, in 120 subjects with metabolic syndrome randomly assigned to receive 1 gram of fish oil daily for 6 months versus placebo, treatment with omega 3 supplements was associated with a statistically significant, placebo-corrected 1.6-kg weight loss [99].

Thus, for individuals with severe hypertriglyceridemia, there are data to suggest that PUFAs, through their pleiotropic effects, may improve cardiometabolic parameters including insulin resistance, glucose control, and weight. Future studies should focus on utilizing the full 4-g daily dose of PUFAs to examine these parameters in large-scale studies within at-risk cohorts.

Ezetimibe

Ezetimibe affects lipid metabolism by selectively inhibiting the intestinal absorption of dietary and biliary cholesterol. It is the first agent in the class of selective cholesterol absorption inhibitors. Ezetimibe acts on the brush border of intestinal mucosal cells, inhibiting the Neimann-Pick C1-Like 1 Protein (NPC1-L1) activity, thereby suppressing the transport of cholesterol in the diet and bile across the small intestinal border into the liver [100]. It does this without affecting the absorption of triglycerides or fat-soluble vitamins [101]. Reduced hepatic stores of cholesterol lead to upregulation of LDL receptors, promotion of LDL metabolism, and lower serum levels of LDL cholesterol.

Patients with diabetes or established coronary heart disease need to achieve lower LDL targets. Multiple studies have shown that the use of ezetimibe can help reach these difficult-to-achieve levels. Adding ezetimibe to statin therapy leads to a 26–28 % reduction in LDL cholesterol compared to statin therapy alone in patients with diabetes or CHD [102, 103]. Gaudiani et al. studied the effect of adding ezetimibe to 20 mg of simvastatin versus doubling the dose of simvastatin to 40 mg in type 2 diabetics treated with thiazolidinediones in a

parallel-group, double-blind, randomized, controlled trial [104]. She found a statistically significant reduction in LDL-C (-20.8 % vs. -0.3 %), as well as significant incremental declines in non-HDL-C, VLDL, and apoprotein B. Ezetimibe had no apparent effect on glucose, HgbA1c, insulin, or FFAs in this study. In addition to lowered LDL-C, ezetimibe monotherapy often, though not always, leads to increased HDL-C and decreased triglycerides [105].

Despite these impressive findings on lipid-lowering with ezetimibe, the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, examining simvastatin with or without ezetimibe in patients with heterozygous familial hypercholesterolemia, called into question whether beneficial clinical outcomes can be expected with this medication [106]. In this study, using carotid IMT as a surrogate end point, no clinically significant regression of carotid plaque was seen at 24 months with ezetimibe, despite significant reductions in atherogenic lipoproteins.

Most subsequent trials have compared combination therapy with statin-and-ezetimibe versus placebo. In the Stop Atherosclerosis in Native Diabetics (SANDS) trial, aggressive lipid-lowering, with ezetimibe as one of the medications used, and blood pressure control in diabetic patients led to a reduction in carotid IMT [107]. The randomized, placebo-controlled Study of Heart and Renal Protection (SHARP) trial demonstrated that patients with renal disease, already at high risk of acquiring CAD, had one-sixth fewer atherosclerotic events if they were in the group taking simvastatin and ezetimibe versus placebo [108]. Additionally, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial investigated ezetimibe and simvastatin versus placebo on aortic stenosis progression and found no significant effect on this primary outcome, but a significant decrease in the secondary end point of coronary events and need for surgical revascularization [109]. With the current uncertainty regarding ezetimibe's clinical benefit, the medical community awaits the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, which is an ongoing investigation comparing simvastatin and ezetimibe with simvastatin alone in subjects with high-risk acute coronary syndrome [110]. The primary endpoints are cardiovascular death, major coronary events, and stroke.

Mechanisms for ezetimibe's glycemic actions are not fully understood, but may relate to persistent improvements in free fatty acids leading to improved glucose tolerance. Ezetimibe also appears to improve peripheral insulin sensitivity through the insulin-signaling pathway in the pancreatic islets. In diabetic murine models, Zhong et al. were able to demonstrate improvements in fasting glucose, oral glucose tolerance testing, and HgbA1c after 6 weeks of ezetimibe compared to placebo [100]. Through immunohistochemical staining of pancreatic tissue and in vitro perfusion of pancreatic islet cells

for the detection of insulin secretion in the first phase, they also discovered improved first-phase insulin secretion and increased insulin expression in the pancreatic tissue of ezetimibe-treated mice compared to placebo-treated mice. HgbA1c levels in treated mice were significantly reduced. This group concluded that while ezetimibe lowers serum lipids, it also improves glucose tolerance, recovers the first phase of insulin secretion, and protects the function of the β cells in mice.

In another animal study, ezetimibe blunted the effect of a high-saturated fat, high-sucrose diet on the weight of LDL receptor-deficient mice, though it did not improve adipose tissue inflammatory markers or glucose homeostasis in these animals. Despite this, there were extraordinary (>85 %) reductions in the atherosclerotic lesion area thought to be solely from the reduction of atherogenic lipoproteins. The implication here is that ezetimibe's CAD outcomes may be affected through decreased LDL alone without correlation to other cardiometabolic effects [111].

A small number of clinical studies have examined ezetimibe's effects on other cardiometabolic parameters. A small 2012 study showed that ezetimibe reduced atherogenic lipoproteins in Japanese patients with diabetes and glucose intolerance, while also improving waist circumference and glucose metabolism in the subset with insulin resistance [112]. The LDL-C was reduced significantly after just 12 weeks of treatment (-20 %, $p < 0.01$); interestingly, only a minority of these patients were on other lipid-lowering agents. Another small study of 38 Japanese subjects showed that ezetimibe reduced metabolic syndrome-related factors over 8 weeks [113]. Clear improvements were seen in body weight, waist circumference, blood pressure, microalbuminuria, and biomarkers of inflammation and oxidative stress. Nakamura et al. studied the effects of ezetimibe treatment on early-phase diabetic nephropathy in 32 DM2 patients with hypercholesterolemia and microalbuminuria. After 6 months of ezetimibe treatment there were significant improvements in HgbA1c, LDL cholesterol, TGs, and urinary albumin excretion [114]. In addition to the more widely published effects on lipid-lowering and atherosclerosis, ezetimibe appears to improve weight, insulin sensitivity [115], and HgbA1c [114]. Furthermore, ezetimibe has the potential to reduce the incidence and severity of diabetes [116] both in experimental animals and man. Nonetheless, pending the results of IMPROVE-IT, these potential cardiometabolic effects must be considered in light of the absence of demonstrable clinical outcomes benefits with ezetimibe.

Bile acid sequestrants

The bile acid sequestrants (BAS) exert their action by removing bile acids from enterohepatic circulation, with the main

clinical formulations in the US being cholestyramine, colestipol, and colesevelam. Colestimide/colestilan is a newer, non-absorbed, non-calcium-based phosphate that also seems to have fewer side effects than the first generation BAS and is being used outside the US [117].

BAS are large molecules that act through an ion exchange system, effectively trapping bile acids in the gut. When bile acids are bound in the intestine by these resins and lost in the feces instead of being recycled to the liver, cholesterol production is diverted to bile acid synthesis in the hepatocyte, via cholesterol 7- α -hydroxylase, thereby depleting the liver lipid pool. This results in an upregulation of the LDL receptor and increased serum clearance of LDL cholesterol leading to a 15–25 % reduction of this lipid particle. A clear benefit to these medications is that they are true non-systemic agents with virtually no drug-drug interactions [118].

Bile acid sequestrants are among the oldest agents studied for lipid-lowering. The 1984 study, Lipid Research Clinics Coronary Primary Prevention Trial, showed that over 7.4 years, cholestyramine, the first BAS, significantly reduced coronary heart disease, death, and nonfatal myocardial infarction by 19 % compared to placebo in 3,806 asymptomatic, middle-aged men with hypercholesterolemia. This trial is considered a seminal work for its strong evidence illustrating that lipids have a causal role in the pathogenesis of coronary heart disease [119]. In fact, BAS (and niacin) were the drugs of choice for hypercholesterolemia when the National Cholesterol Education Project made its first recommendations in 1988. Multiple trials have demonstrated significant decreased regression of coronary plaque along with decreased coronary events with the use of bile acid sequestrants [120].

There are several proposed mechanisms describing BAS impact on glycemic parameters. BAS appear to deactivate the intestinal and hepatic farnesoid X receptors (FXR). Bile acids provide negative feedback regulation by binding to the FXRa receptor, which, when activated, inhibits liver X receptor (LXR) activity. The LXR seems to be a glucose sensor involved in gluconeogenesis, glucagon synthesis, and adipose tissue functionality. In "deactivating" this inhibition, BAS lead to positive downstream metabolic effects. BAS may also act on the G-protein-coupled receptor TGR5, which induces the hormone glucagon-like peptide-1 (GLP-1). This incretin helps with insulin production and insulin sensitivity in diabetics with obesity. Bile acids may also affect direct gene expression of key cell-signaling pathways in glucose homeostasis. In addition, BAS may change the composition of the luminal bile acid, which seems to be dysregulated in diabetics, potentially leading to decreased intestinal glucose uptake, though data are conflicting about this specific effect [121].

BAS consistently improve glucose and HgbA1c levels in patients with DM2. Garg and Grundy showed in a small trial that cholestyramine 16 g/day lowered fasting plasma glucose

from a mean of 131 mg/dL to 116 mg/dL, with a trend toward lower HgbA1cs by 0.5 % over 6 weeks [122]. Other studies with the newer BAS have subsequently demonstrated significantly reduced HgbA1c levels in patients with diabetes, along with effective control on lipids [123–125].

The Glucose-Lowering Effect of WelChol (GLOWS) trial examined colesevelam in 65 type-2 diabetics with inadequate glucose control on oral agents alone in a 12-week, double-blind, placebo-controlled study, showing a 1.0 % decrease in HgbA1c, with reductions in fructosamine levels and postprandial glucose [126]. Change in body weight did not differ between the colesevelam and placebo arms. These findings were corroborated by Goldberg et al. who showed improvements in glucose control and HgbA1c (-0.5 %) without hypoglycemia or weight gain compared to placebo within a population of DM2 taking insulin [127]. Similar effects on HgbA1c without weight gain have also been shown when colesevelam is used in combination with metformin [124] or sulfonylureas [125].

Colestimide/colestilan is associated with weight loss, improved blood glucose, and insulin levels, while inducing carbohydrate catabolism [128]. One study showed that colestilan treatment for 8 weeks in high-fat-fed hyperlipidemic (APOE*3 Leiden (E3L) transgenic) mice led to decreased body weight, visceral and subcutaneous fat, and plasma cholesterol and TG levels despite increased food intake. Another investigation in 40 postmenopausal women, which was not double-blind or placebo-controlled, showed that 12-week administration of colestimide/colestilan along with diet instruction significantly reduced body weight and body mass index from 62.9 +/- 5.7 kg to 58.0 +/- 5.4 kg (mean +/- SD) and from 26.1 +/- 2.0 kg/m² to 23.9 +/- 2.0 kg/m², respectively. The control group showed no differences. It is thought that the sensation of abdominal fullness along with decreased fat absorption is what accounts for this weight loss [129]. Despite these newer studies, the overwhelming evidence is that BAS are weight-neutral, though there is promise that newer formulations may lead to weight loss.

Colesevelam was FDA-approved for the treatment of DM2. While other BAS may have cardiometabolic benefit, colesevelam is the only BAS, and only lipid-lowering drug, that has an FDA indication for both glycemic and lipid control [130].

Investigational Agents: Glitizars

Emerging interest in the cardiometabolic profiles of various lipid-lowering agents has prompted development of newer agents capable of simultaneously improving both lipid and glucose control. The dual PPAR- α / γ agonists, also known as the "glitizars," have been extensively investigated

for the combined treatment of hyperlipidemia and type 2 diabetes. Similar to bezafibrate, which is actually a pan-PPAR and binds to the delta-PPAR receptor as well, these agents combine the beneficial lipid-modulating properties of PPAR-alpha agonism with the insulin-sensitizing effects of PPAR-gamma agonism [131] and hold the potential to prevent both the macrovascular and microvascular complications of chronic hyperglycemia [132]. Despite the promise of glitazars as a combination strategy for the co-treatment of hyperlipidemia and DM2 [133], agents such as muraglitazar (Bristol-Myers Squibb), tesaglitazar (AstraZeneca), and aleglitazar (Hoffman-La Roche) have not yet obtained FDA approval due to associated adverse events.

The investigational agents muraglitazar (Bristol-Myers Squibb) and tesaglitazar (AstraZeneca) initially advanced to phase III trials, but further development was ultimately discontinued due to adverse side effects. In trials comparing muraglitazar versus pioglitazone (an FDA-approved PPAR-gamma agonist indicated for the treatment of diabetes) and placebo, muraglitazar demonstrated greater improvements in total cholesterol, HDL cholesterol, and TG levels, as well as HgbA1c reduction, but had an increased rate of all-cause mortality and adverse cardiovascular events (including myocardial infarction, stroke, and transient ischemic attacks), as well as a greater incidence of weight gain, edema, and heart failure [134, 135]. In four phase III trials [136–139], tesaglitazar demonstrated significant reductions in insulin, fasting plasma glucose, triglyceride levels, and non-HDL cholesterol, as well as increased levels of HDL-cholesterol, adiponectin, and leptin, but was associated with significant increases in serum creatinine, and decreases in glomerular filtration rate.

Meanwhile, aleglitazar (Hoffman-La Roche), after demonstrating promising results in phase II trials with beneficial effects on glucose and lipid variables [140] without significant adverse effects, was recently under investigation in phase III trials before the studies were terminated in July 2013 following a scheduled meeting of the data safety and monitoring board [141]. Evidently, the ALECARDIO trial, which included 7,228 patients with recent acute coronary syndrome and DM2 randomized to aleglitazar 150 µg or placebo daily and hoped to demonstrate a delayed time to cardiovascular end points (cardiovascular death, myocardial infarction, or stroke), was terminated due to the increased incidence of bone fractures, heart failure, and gastrointestinal bleeding without improvement in primary outcomes [142]. These findings also halted the ALEPrevent trial, which included another 17,000 subjects.

Although these agents have failed to obtain FDA approval, the dual PPARs remain an attractive target. It is hoped that future agents will continue to demonstrate both lipid-lowering and glucose-lowering abilities without associated adverse events.

Conclusions

It is well-established that reducing risk factors results in fewer CHD events and deaths. Despite this, risk factors are not often well-controlled. In fact, it has been shown that only 7.3 % of patients with diabetes attain appropriate targets for hyperglycemia, dyslipidemia, and hypertension with usual care [143]. In addition to developing ways to better manage dyslipidemia, there is emerging emphasis on the cardiometabolic profile of various lipid-lowering agents, especially given the prevalence of comorbid hyperglycemia with diseases of lipid metabolism. Although statins have been examined in a systematic manner, other agents including fibrates, niacin, omega-3 polyunsaturated fatty acids, ezetimibe, and bile acid sequestrants have not. Future studies should focus on these agents' effects on glycemic control, weight, and incidence of diabetes. Agents that target disorders of both glycemic and lipid metabolism, such as the dual and pan PPARs, carry great promise, but still warrant further investigation. Finally, while newer lipid-lowering agents—PCSK9 inhibitors, cholesteryl ester transfer protein (CETP) inhibitors, apolipoprotein B-100 synthesis inhibitors such as mipomersen, and microsomal triglyceride transfer protein (MTP) inhibitors such as lomitapide—demonstrate potential for effective treatment of lipid disorders, their cardiometabolic profiles must be examined before we embrace them in the medical landscape. Understanding mechanisms of action for lipid-lowering therapies and their effects on other important cardiometabolic parameters should allow practitioners to select the most appropriate medications for their patients in the future.

Compliance with Ethics Guidelines

Conflict of Interest Parag Goyal, Leon I. Igel, Keith LaScalea, and William B. Borden declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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