HDL and its Role in Cardiovascular Disease: A Primary Care Perspective

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Abstract

Lipid profiles are a part of the routine blood work ordered by many family physicians. For decades, manipulation of lipid levels has been a central theme in the effort to decrease the impact of cardiovascular disease. In particular, the high density lipoprotein (HDL) fraction has been the subject of much research and controversy. In the 1960's, strong epidemiological evidence demonstrated an inverse relationship between HDL and the risk of cardiovascular disease. This paper sought to examine the risk reduction of such events by therapeutically targeting HDL with niacin, fibrates or the cholesteryl ester transfer protein (CETP) inhibitors. A literature search yielded 5 relevant articles which were then critically analyzed. Results demonstrated no benefit of increasing HDL with niacin, gemfibrozil, bezafibrate or fenofibrate in those patients already treated with statins. However, patients not on statins were found to have a decreased risk of non-fatal MI with niacin and fibrate use. Niacin also reduced the incidence of strokes. Despite disappointing phase three trials with the CETP inhibitors, torcetrapib and dalcetrapib, trials for anacetrapib and evacetrapib are ongoing.

INTRODUCTION

The global impact of cardiovascular mortality and morbidity remains daunting despite an intensive focus on the management of risk factors by health care providers worldwide. From 2000 to 2012, the world has seen an increase in the number of years-of-life lost (YLL) from non-communicable disease. Ischemic heart disease and stroke represent the first and third most common diagnoses driving this change—increasing 16% and 12% respectively over the 12 year time frame. Globally, ischemic heart disease accounts for over 4% of the total YLL in men and almost 8% in women [1]. In 2012, Canadian cardiovascular mortality ranked second in leading causes of death with rates of 112.2 per 100,000 in men and 68.1 per 100,000 in women [2,3].

The role of high density lipoprotein cholesterol (HDL) is frequently cited in theories that have attempted to explain residual cardiovascular risk. The inverse relationship between HDL and risk of ischemic heart disease was first described by Gofman et al. in 1966 [4,5]. Soon after, as part of the Framingham Study, decreased HDL was associated with each major manifestation of coronary heart disease. It was considered to be a more potent vascular risk factor than any other lipid type (including low density lipoprotein cholesterol [LDL]) [6].

After analyzing four large studies—the Framingham Heart Study, the Lipid Research Clinics Prevalence Mortality Follow-up Study, the Coronary Primary Prevention Trial and the Multiple Risk Factor Intervention Trial – Gordon et al. concluded that a 0.03 mmol/L increase in HDL resulted in a 2-3% decrease in the risk of future coronary heart disease [7]. Since that time, HDL as a risk factor in primary cardiovascular disease has been largely accepted [5,8-10]. However, in terms of secondary prevention and the statin treated population, the role of HDL remains contested [10,11]. Re-analysis of data from JUPITER, a primary prevention trial in which 8,900 patients were randomized to rosvastatin versus placebo, demonstrated no relationship between the different quantiles of HDL concentration and coronary risk either at baseline or on treatment [11]. In contrast, post-hoc analysis done on the TNT study population found that the inverse relationship between HDL and cardiovascular events persisted despite taking atorvastatin daily [12]. In 2012, Boekholdt et al. completed a meta-analysis including both the aforementioned study populations and six others for a total of 62,154 patients. This group found the predictive value of cardiovascular events by HDL level persisted despite the use of statins [13]. On the basis of this information, many attempts have been made to decrease cardiovascular risk by targeting HDL specifically.

Recently, Voight et al used the technique of Mendelian randomization to study the relationship between alterations in HDL and cardiovascular risk. The presence of a variant of the LIPC allele (Ans396Ser), which was carried by 2-6% of the study...
population, was found to be associated with an increase in HDL by 0.08 to 0.28 mmol/L per copy. There were no appreciable changes in other cardiovascular risk factors including LDL, triglycerides, body mass index and systolic blood pressure. They analyzed over 116,320 patients but found no association between LIPG Ans396Ser and the risk of myocardial infarctions (OR: 0.99; 95% CI: 0.88 to 1.11; p=0.85) despite epidemiological evidence hypothesizing risk reduction of 13%. Fourteen additional common genetic variants which exclusively affect HDL were evaluated and none were found to be associated with a decrease in risk of myocardial infarction (OR: 0.93; 95% CI: 0.68 to 1.26; p=0.63) [14].

Current Canadian and American Heart Association (AHA) lipid guidelines do not make specific suggestions for targeting an increase in HDL with pharmacotherapy due to a lack of causal evidence for its benefit [15,16]. This review serves to explore both historical and contemporary evidence to help family physicians develop an understanding of the HDL enigma. We review the potential benefits and pitfalls associated with three classes of pharmacotherapeutic agents that have been used to target increases in HDL in the hope of decreasing cardiovascular mortality and morbidity.

METHODS

An electronic literature search of the OVID, PUBMED and Cochrane Library databases was conducted with the following search terms: high density lipoprotein, cardiovascular disease, niacin or nicotinic acid, fibrates or clofibrate or bezafibrate or fenofibrate or gemfibrozil, cholesteryl ester transfer protein (CETP) inhibitors or anacetrapib or dalcetrapib or torcetrapib or evacetrapib. Additionally, the references of meta-analyses were manually reviewed. "The English language", "humans" and "age older than 19" were set as limits in the search. No time criterion was applied to the search. Of the 765 results, 590 were eliminated with title review. Inclusion and exclusion criteria were used to narrow the remaining articles to the most relevant. Trials were included if they were either randomized control trials (RCTs) with strong internal validity or meta-analyses comparing niacin, a fibrate or a CETP inhibitor to placebo. If a study was designed to test the efficacy of a drug in the prevention of cardiovascular disease (as opposed to the increases in HDL resultant from the use of that drug) and had a laboratory marker as the primary outcome, it was excluded. The five final studies were: AIM HIGH [17], HPS 2 THRIVE [18], a meta-analysis by Keene et al. [19], a meta-analysis done by Lee et al. [20] and Dal OUTCOMES [21].

Niacin

Niacin is one of the first medications used to treat low HDL. It is processed by the body into coenzymes used in lipid metabolism. This result in HDL increases between 30-35% as well as other changes to the lipid profile [22].

One of the earliest studies done on niacin in cardiovascular disease was the Coronary Drug Project (CDP). Conducted from 1966 to 1974, the CDP tested secondary prevention of coronary heart disease. 8,341 men were randomly allocated to one of five medication streams or placebo. Of these, three streams (two different estrogen regimes and dextrothyroxine sodium) were stopped prior to the scheduled completion of the study due to safety concerns. However, the remaining two medications, niacin and clofibrate, were continued. The primary endpoint in the CDP was total mortality. The use of niacin was seen to significantly decrease total cholesterol and triglyceride levels and resulted in risk reduction of non-fatal myocardial infarctions (MI) [23]. A 15 year follow-up demonstrated an 11% decrease in total mortality (p=0.0004) [24]. However, significant adverse effects included an increased incidence of a trial fibrillation and other arrhythmias [23].

Following this, many studies assessing the effect of niacin on atherosclerosis were completed. These include CLAS I [25], FATS [26], CLAS II [27], HATS [28] and APREGS [29]. Each of these demonstrated a reduction in progression and increased regression of atherosclerotic lesions with niacin use. Further, testing done in the ARBITER 2 [30] and 6 [31] trials looked at the behavior of atherosclerosis when niacin was used in combination with a statin. Unlike ARBITER 2 which showed no significant difference in atherosclerosis, ARBITER 6 demonstrated superiority of niacin to ezetimibe in reducing mean carotid intima-media thickness [30,31]. However, in ARBITER 6, there were significant changes in LDL and triglycerides in addition to HDL, making these results difficult to interpret [31].

Figure 1 Proposed mechanisms for anti-atherogenic effects of HDL. The pathways involved in decreasing cardiovascular risk are hypothesized as including participation in reverse cholesterol transportation, counter-acting LDL oxidation and restoring endothelial function. Images altered from 54-56.

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein
Perhaps the most relevant niacin trials are the recently published AIM HIGH [17] and HPS2 THRIVE [18] studies. AIM HIGH studied the incidence of cardiovascular events when patients were treated with niacin and a statin. 3,414 patients over the age of 45 participated in this double blinded randomized control trial (RCT). These patients had a history of either coronary heart, cerebrovascular, carotid or peripheral artery disease and dyslipidemia including low levels of HDL, elevated triglycerides and an LDL less than 4.65 mmol/L. They were selected from over 92 clinical centers across North America. The large majority of these patients were Caucasian, male, had hypertension and/or metabolic syndrome. Just over one third had diabetes. All patients were started on 40-80 mg of simvastatin with an additional 10 mg of ezetimibe if necessary. They were then randomized to receive either 1500-2000 mg of extended release niacin or placebo (which contained 50 mg of immediate release niacin to help maintain blinding). The primary outcome was the composite of the first event of death from coronary heart disease, non-fatal MI, ischemic stroke, hospitalization for acute coronary syndrome (ACS) or symptom driven coronary or cerebral revascularization. Baseline analysis demonstrated no significant differences between the patients in the two arms of this study. An intention to treat protocol was used and endpoint data was collected for all patients except for 52. However, there were higher rates of discontinuation of therapy in the treatment cohort (8.4% vs. 9.8% in placebo; p<0.001). Decreased triglycerides (28.6% vs. 8.1%) but did not significantly change LDL (12% decrease vs. 5%). The trial was terminated 19 months early due to lack of efficacy. The primary end point was seen in 16.4% of the niacin group and 16.7% in the placebo (HR: 1.02; 95% CI: 0.87 to 1.21; p=0.80). There was also a non-significant trend for increased ischemic strokes in the treatment group (HR: 1.61; 95% CI: 0.89 to 2.90; p=0.11). This increase in strokes was not seen in prior studies or meta-analyses. Other adverse effects included liver abnormalities, muscle symptoms and rhabdomyolysis [17].

Most recently, HPS 2 THRIVE assessed whether there was a decrease in major vascular events when patients already on effective statin therapy were started on niacin and laropiprant. This double blinded randomized trial involved 245 sites in the United States, Scandinavia and China. 25,673 patients between the ages of 50 and 80, with a history of MI, cerebrovascular disease, peripheral artery disease or diabetes with symptomatic coronary disease participated. Most patients were European men. Approximately one third had diabetes and one third had metabolic syndrome. Prior to randomization, patients had a mean LDL of 1.64 mmol/L and HDL of 1.14 mmol/L. Patients were then assigned either 2 g of niacin with 40 mg of laropiprant daily or
placebo and followed for an average of 3.6 years. Laropiprant is a prostaglandin antagonist shown to decrease flushing from niacin and was used to maintain blinding. Adherence to the treatment medication was poor; falling to 69.9% by the end of the second year. More patients in the treatment group discontinued the medication (25.4% vs. 16.6% in the placebo group; p<0.001). There were significantly more fatal and non-fatal serious adverse events in the niacin group (p<0.001). The most prominent was a 55% increase in disturbances of glucose control (11% vs. 7.5%; p<0.001). An increase in the diagnosis of diabetes (5.7% vs. 4.3%; p<0.001), bleeding, cutaneous and peptic ulcerations, gout, myopathy and rashes were also seen. New side effects which were not previously seen with niacin and laropiprant were also noted. These included infections (8.0% vs. 6.6%; p<0.001) and bleeding (including intracranial and gastrointestinal) (2.5% vs. 1.9%; p<0.001)[18].

On average, treatment with niacin resulted in a decrease of 0.25 mmol/L in LDL, a 0.16 mmol/L increase in HDL and a 0.37 mmol/L decrease in triglycerides. However, no significant difference was seen in the incidence of major vascular events (13.2% in treatment and 13.7% in placebo; RR: 0.96; 95% CI: 0.90 to 1.03; p=0.29). The only individual component of the primary outcome to have a significant result was a decrease in revascularization procedures (RR: 0.90; 95% CI: 0.82 to 0.99; p=0.03). There was no effect on stroke with treatment (RR: 1.00; 95% CI: 0.88 to 1.13; p=0.56). There was also a non-significant increase in the incidence of death from any cause in the treatment group (RR: 1.09; 95% CI: 0.99 to 1.21; p=0.08)[19].

Over the last decade, many attempts have been made to try and understand the somewhat conflicting results of HDL trial data and cardiovascular outcome. However, most of these meta-analyses have examined the role of niacin (as opposed to increased HDL) in cardiovascular disease prevention. One such study, done in 2013 by Lavigne and Karas [32], sought to understand the reduction of cardiovascular events with niacin use through analysis of 11 RCTs and 9,961 patients. They found a decrease in incidence of cardiovascular disease events which included cardiac death, non-fatal MI, hospitalization for ACS, stroke or a revascularization procedure with niacin treatment (OR: 0.66; 95% CI: 0.49 to 0.89; p=0.007). However, interestingly, no significant association was seen between the change in HDL and the risk of cardiovascular events. Thus, it is difficult to attribute these protective findings to the increase in HDL. In fact, Lavigne and Karas suggest that the decreased risk may be due to other properties of niacin [32].

The only meta-analysis found looking specifically at cardiovascular risk reduction by increasing HDL was done by Keene et al [19]. The efficacy in decreasing all-cause mortality by using niacin, fibrates and CETP inhibitors to target low HDL was analyzed. Secondary outcomes included coronary mortality, non-fatal MI, stroke and adverse events. Keene et al. conducted an extensive computerized and manual search for published and unpublished RCTs. Although the authors state the selected studies needed to examine one of the HDL increasing medications and measure one of the aforementioned outcomes, no specific exclusion criteria were listed. In addition, there were significant validity concerns with some of the included RCTs. Many done with niacin had difficulty with blinding due to the predominance of flushing as a side effect. Furthermore, some of the older trials did not explain the methods of randomization and blinding they employed, making validity assessment difficult. High dropout rates were a significant concern in many of the niacin and fibrate studies. Finally, some trials were designed to withhold more than one intervention from the placebo group [25,26,33]. All the included studies were, however, homogenous. The majority of the included participants were men approximately 41 to 73 years old from several continents including Europe, Asia and North America. Of the RCTs that reported ethnicities of participants, a large majority were Caucasian. Turning specifically to the niacin portion of this analysis, 11 RCTs with 35,301 patients were included. Follow up ranged from 6 to 60 months. Niacin was seen to result in increases in HDL of 17-43%. In the 30,310 patients on statins, there was no significant effect of adding niacin on all-cause mortality (OR: 1.03; 95% CI: 0.92 to 1.15; p=0.59), coronary heart disease mortality (OR: 0.93; 95% CI: 0.76 to 1.12; p=0.44), non-fatal MI (OR: 0.85; 95% CI: 0.72 to 1.01; p=0.07) or strokes (OR: 0.96; 95% CI: 0.75 to 1.22; p=0.72). However, in patients not taking statins, niacin lowered the incidence of non-fatal MI (OR: 0.69; 95% CI: 0.56 to 0.85; p=0.0004) and stroke (OR: 0.78; 95% CI: 0.61 to 1.00; p=0.05) [19].

Currently it appears that targeting low HDL with niacin in patients who are already on statin therapy has no added cardiovascular benefit. There is evidence of harm and this strategy not be pursued. However, there is data that supports the use of niacin in patients who are not taking currently statins to reduce both non-fatal MI and stroke. This trial data is summarized in (Table 1).

Prior to the initiation of niacin, the American Heart Association (AHA) lipid guidelines suggest baseline measures of hepatic transaminases, hemoglobin A1C and uric acid be obtained and then repeated every six months during therapy. Additionally, given the side effect profile, certain patients should not receive niacin. This includes patients with elevated transaminases, poorly controlled hyperglycemia, and acute gout, abdominal pain with no apparent cause, gastrointestinal or cutaneous symptoms, weight loss or new onset atrial fibrillation [15].

**Fibrates**

Fibrates are α peroxisome proliferator receptor (PPAR-α) agonists and therefore, regulate the synthesis, elimination and oxidation of many different particles of the lipid profile, including HDL [20,34].

As above, one arm of the Coronary Drug Project was designed to investigate clofibrate in the secondary prevention of coronary heart disease. Although it decreased cholesterol and triglyceride levels, it did not lower total or all-cause specific mortality. In fact, it was seen to increase the incidence of various non-fatal cardiovascular events including pulmonary emboli, thrombophlebitis, a trial fibrillation, intermittent claudication and angina pectoris (81.3% vs. 75.8%) [23]. This increased harm signal was also seen by Geizerova et al. When clofibrate was studied in ischimic heart disease, there were significantly more deaths from all causes and causes other than ischemic heart disease with treatment (3% vs. 2.4% in the high cholesterol
Table 1: Summary of all included Niacin studies.

<table>
<thead>
<tr>
<th>Study Publication Year</th>
<th>Population</th>
<th>Follow Up (months)</th>
<th>Therapy</th>
<th>Primary outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>Coronary Drug Project[25] 1975</td>
<td>8,341 men aged from 30-64 years old with evidence of ≥ 1 MIs more than 3 months ago</td>
<td>60</td>
<td>Conjugated estrogens 2.5 mg daily (ended early)</td>
<td>Total mortality, cause specific mortality and nonfatal cardiovascular outcomes</td>
<td>Clofibrate: (significance z&gt;2.58 or z&lt;-2.58) TC: 6.5% decrease TG: 22.3% decrease Primary outcome: 0.9% decrease in all-cause mortality compared to placebo (z=-0.60) 1.6% decrease in cardiovascular mortality compared to placebo (z=-1.17) 5.5% increase in number of patients with nonfatal cardiovascular outcomes (z=3.61) Niacin: TC: 9.9% decrease TG: 26.1% decrease Primary outcome: 1.2% decrease in all-cause mortality compared to placebo (z=-0.19) 0.1% decrease in cardiovascular mortality compared to placebo (z=-0.12) 1.2% decrease in number of patients with nonfatal cardiovascular outcomes (z=-0.83)</td>
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<tr>
<td>CLAS I[25] 1987</td>
<td>162 men between 40 and 59 years old with previous coronary bypass surgery and angiographic evidence of atherosclerosis</td>
<td>24</td>
<td>Niacin 3-12 g daily and colestipol 30 g daily</td>
<td>Angiographic coronary global change score</td>
<td>Niacin and colestipol: HDL: 3.7% increase (p&lt;0.001) Primary outcome: 3.8% less patients had progression in native arteries (p=0.001) 5.3% less patients had new lesions in native arteries (p=0.23)</td>
</tr>
<tr>
<td>FATS[26] 1990</td>
<td>146 men ≤ 62 years old with elevated apolipoprotein B and family history of CAD All had evidence of coronary atherosclerosis on angiogram</td>
<td>30</td>
<td>Niacin 125mg BID -1.5g QID and colestipol 5-10g TID Lovastatin 20-40 mg BID and colestipol Placebo +/- colestipol</td>
<td>Average percentage change between two angiographic studies for the worst lesion in nine proximal segments</td>
<td>Niacin and colestipol: HDL: increased 15% (p&lt;0.05) Primary outcome: decreased 0.9% compared to placebo (p&lt;0.005) Lovastatin and colestipol: HDL: increased 43% (p&lt;0.05) Primary outcome: decreased 0.7% compared to placebo (p=0.02)</td>
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<tr>
<td>CLAS II[27] 1990</td>
<td>103 men (subgroup from CLAS I who did not require further bypass surgery)</td>
<td>24</td>
<td>Niacin 3-12 g daily and colestipol 30 g daily</td>
<td>Angiographic coronary global change score</td>
<td>Niacin and colestipol: HDL: 37% increase (p&lt;0.001) Primary outcome: 29.9% less patients had progression in native arteries (p=0.001) 26.1% less patients had new lesions in native arteries (p=0.001)</td>
</tr>
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</table>
Almost a decade later, fibrates were brought back into favor with the publication of the Helsinki Heart Study (HHS) in 1987 [37,38]. Here 5,081 men with no history of cardiovascular disease were randomized to either gemfibrozil or placebo. A 34% reduction in cardiac death, fatal and non-fatal MI was seen (p<0.02). This was driven largely by a 37% reduction in non-fatal MI (p<0.05) [38]. Results consistent with these findings were also seen in the VA HIT study [39]. Here, in patients with a documented history of coronary heart disease, treatment with gemfibrozil resulted in a 22% reduction of coronary heart disease deaths (95% CI: -2 to 41%; p=0.07) and 23% decrease of non-fatal MI (95% CI: 4 to 30%; p=0.02) [39]. Bezaflibrate, on the other hand, in the Bezaflibrate Infarction Prevention study did not reduce mortality, non-fatal MI or sudden death [40].

Recently, a more contemporary trial, the FIELD study, investigated the prevention of cardiovascular disease in type 2 diabetes and dyslipidemia or peripheral artery disease or diabetes with dyslipidemia. Almost a decade later, fibrates were brought back into favor with the publication of the Helsinki Heart Study (HHS) in 1987 [37,38]. Here 5,081 men with no history of cardiovascular disease were randomized to either gemfibrozil or placebo. A 34% reduction in cardiac death, fatal and non-fatal MI was seen (p<0.02). This was driven largely by a 37% reduction in non-fatal MI (p<0.05) [38]. Results consistent with these findings were also seen in the VA HIT study [39]. Here, in patients with a documented history of coronary heart disease, treatment with gemfibrozil resulted in a 22% reduction of coronary heart disease deaths (95% CI: -2 to 41%; p=0.07) and 23% decrease of non-fatal MI (95% CI: 4 to 30%; p=0.02) [39]. Bezaflibrate, on the other hand, in the Bezaflibrate Infarction Prevention study did not reduce mortality, non-fatal MI or sudden death [40].

### Table: Trials Investigating Fibrates

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>Participants</th>
<th>Intervention</th>
<th>Primary Outcomes</th>
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<tbody>
<tr>
<td>HATS [36] 2001</td>
<td>160 patients with coronary disease, low HDL and normal LDL</td>
<td>24</td>
<td>Simvastatin 10-20 mg OD and niacin 0.25g -1g BID Antioxidants (800 IU vitamin E, 1000 mg of vitamin C, 25 mg of beta carotene and 100 µg of selenium) Simvastatin, niacin and antioxidants Placebo</td>
<td>Mean change per patient from initial to final arteriogram in percent stenosis of most severe lesion in 9 proximal coronary segments Simvastatin and niacin HDL: increase 18% (p&lt;0.001) Primary outcome: decreased 0.4% compared to placebo (p&lt;0.001) Simvastatin, niacin and antioxidants HDL: increased 6% (p&lt;0.001) Primary outcome: increased 0.7% compared to placebo (p&lt;0.005) Antioxidants HDL: decreased 3% (p&gt;0.05) Primary outcome: increased 1.9% compared to placebo (p&gt;0.05)</td>
</tr>
<tr>
<td>ARBITER 2 [31] 2004</td>
<td>167 patients with known coronary heart disease and low HDL</td>
<td>12</td>
<td>Niacin 0.5-1g OD to background statin Placebo</td>
<td>Change in common carotid intima thickness after 1 year Niacin: HDL: increased 21% (p=0.002) Primary outcome: 68% decrease compared to placebo (p=0.08)</td>
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<tr>
<td>AFREGS [29] 2005</td>
<td>143 military retirees younger than 76 years old with low HDL and angiographic coronary disease</td>
<td>30</td>
<td>Gemfibrozil 600mg BID, niacin 0.240g - 3g daily and cholestyramine 2g-16g daily Placebo</td>
<td>Percentage change in global angiographic stenosis Gemfibrozil, niacin and cholestyramine: HDL: 36% increase (p&lt;0.001) Primary outcome: 1.91% decrease in global stenosis compared to placebo (p=0.04)</td>
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<tr>
<td>ARBITER 6 [31] 2009</td>
<td>363 patients with coronary heart disease or at risk for such receiving long term statin with low HDL and low to normal LDL</td>
<td>14</td>
<td>Niacin 0.5-2g daily Ezetimibe 10 mg daily</td>
<td>Change in mean common carotid intima-media thickness Niacin: HDL: 18.4% increase (p&lt; 0.001) Primary outcome: 19.29% decrease compared to ezetimibe (p= 0.01)</td>
</tr>
<tr>
<td>AIM HIGH [17] 2011</td>
<td>3,414 patients older than 45 yo with a history of either coronary heart, cerebrovascular, carotid or peripheral artery disease and dyslipidemia</td>
<td>36</td>
<td>niacin 1.5-2 g daily and Simvastatin 40-80 mg OD ± ezetimibe 10 mg daily placebo (50 mg of immediate release niacin) and Simvastatin 40-80 mg OD ± ezetimibe 10 mg daily</td>
<td>First event of the composite of death from coronary heart disease, nfMI, ischemic stroke, hospitalization for acute coronary syndrome, symptomatic driven coronary or cerebral revascularization Niacin: HDL: 25% increase (p&lt;0.001) Primary outcome: 0.3% decrease compared to placebo (p=0.80)</td>
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<tr>
<td>HPS 2 THRIVE [40] 2014</td>
<td>25,673 patients between 50-80 yo with a history of MI, cerebrovascular disease, peripheral artery disease or diabetes with symptomatic coronary disease</td>
<td>48</td>
<td>Niacin 1-2 g daily and laropiprant 20-40 mg daily added to simvastatin 40mg daily ± ezetimibe 10 mg daily placebo added to simvastatin 40mg daily ± ezetimibe 10 mg daily</td>
<td>First major vascular event: nfMI, death from coronary causes, stroke or arterial revascularization Niacin: HDL: 14% increase Primary outcome: 0.5% decrease compared to placebo (p= 0.29)</td>
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</table>

**Legend:**
- **TC** = Total Cholesterol
- **TG** = Triglycerides
- **HDL** = High-Density Lipoprotein
- **LDL** = Low-Density Lipoprotein
- **RCT** = Randomized Controlled Trial
- **nfMI** = non-fatal Myocardial Infarction
- **PE** = Pulmonary Embolus
- **TIA** = Transient Ischemic Attack
- **CAD** = Coronary Artery Disease
- **IHD** = Ischemic Heart Disease
Table 2: Summary of all included fibrate studies.

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>1975</td>
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<td>Conjugated estrogens 5 mg daily (ended early)</td>
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<td></td>
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<td>Dextrothyroxine sodium 6 mg daily (ended early)</td>
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<td></td>
<td>Clofibrate 1.8 g daily</td>
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<td></td>
<td>Niacin 3 g daily</td>
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<td></td>
<td></td>
<td></td>
<td>Placebo</td>
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<tr>
<td>Geizerova et al</td>
<td>15 745 men between 30-59 years old</td>
<td>60</td>
<td>Group I: men in the upper third of serum cholesterol distribution on clofibrate 1.6 g daily</td>
<td>Fatal IHD, nMI and acute coronary insufficiency and all-cause mortality</td>
<td>Clofibrate: TC: 8.2-9.7% decrease Fatal IHD: 0.1% increase compared to Group II (p=0.05) and 0.7% increase compared to Group III (p&lt;0.01) nMI and acute coronary insufficiency: 1.6% decrease compared to Group II (p&lt;0.05) and 2.9% increase compared to Group III All-cause mortality: 1.1% increase compared to Group II (p&lt;0.05) and 2% increase compared to Group III</td>
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<td>1978</td>
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<td>Group II: men in upper third of serum cholesterol on placebo</td>
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<td>Group III: men in lowest third of serum cholesterol on placebo</td>
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<tr>
<td>HHS</td>
<td>4 081 asymptomatic men aged between 40-55 years old</td>
<td>60</td>
<td>Gemfibrozil 600mg BID</td>
<td>Cardiac endpoints (Fatal MI, nMI and cardiac death)</td>
<td>Gemfibrozil: HDL: 9% increase (p&lt;0.05) Cardiac endpoint: 34% decrease compared to placebo (p&lt;0.02)</td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA HIT</td>
<td>2 531 patients with coronary heart disease less than 74 years of age</td>
<td>61</td>
<td>Gemfibrozil 1 200 mg daily</td>
<td>Combined nfMI and coronary heart disease death</td>
<td>Gemfibrozil: HDL: 6% increase (p&lt;0.001) Primary outcome: 4.4% decrease compared to placebo (p=0.006)</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
diabetes. 9,795 patients were randomized to either fenofibrate or placebo and followed for non-fatal MI or coronary death. There was a reduction in non-fatal MI (RR: 0.76; 95% CI 0.62-0.94; p<0.01). However, a non-significant increase in both coronary heart disease mortality (RR: 1.19; 95% CI 1.00-1.45; p=0.22) and total mortality (7.3% vs. 6.6% in the placebo group) was seen with allocation to fenofibrate. These non-significant increases may reflect a more widespread usage of statins amongst the placebo group than in the fibrate group (17% vs. 8%; p<0.0001) [41].

Next, the ACCORD trial investigated whether simvastatin and fenofibrate therapy decreased cardiovascular risk in 5,518 type 2 diabetic patients. Unlike the FIELD study, no difference was found in the time to the first cardiovascular event: non-fatal MI, stroke or cardiovascular death (HR: 0.92; 95% CI: 0.79 to 1.08; p=0.32) [42]. This difference suggests that concurrent statin use decreases the benefit of fenofibrate therapy. Fibrate trial data is summarized in (Table 2).

Akin to niacin, multiple meta-analyses assessing the cardiovascular protection offered by fibrates have been conducted. One such analysis by Lee and colleagues, examined 6 RCTs with cardiovascular protection offered by fibrates have been conducted. The aim was to analyze the treatment effect summarized in (Table 2).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Age Range</th>
<th>Treatment</th>
<th>Control</th>
<th>Outcome</th>
<th>Hazards Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIELD</td>
<td>6,409</td>
<td>40-75</td>
<td>Fenofibrate</td>
<td>Placebo</td>
<td>First event</td>
<td>0.92</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5,518</td>
<td>40-75</td>
<td>Fenofibrate</td>
<td>Placebo</td>
<td>First event</td>
<td>0.92</td>
</tr>
</tbody>
</table>

TC = Total Cholesterol; TG = Triglycerides; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein
RCT = Randomized Controlled Trial
nMI = non-fatal Myocardial Infarction; PE = Pulmonary Embolus; TIA = Transient Ischemic Attack; CAD = Coronary Artery Disease; IHD = Ischemic Heart Disease

In summary, gemfibrozil, bezafibrate and fenofibrate should not be combined with statins to target low LDL as they provide no added benefit. However, without concurrent statin therapy, these three fibrates can decrease the risk of non-fatal MI. Clofibrate should never be used to target low LDL as it is associated with increased risk of mortality. If starting therapy, the AHA guidelines suggest monitoring renal function prior to the
initiation of fenofibrate therapy, at the 3 month mark and then every 6 months thereafter [15].

**CETP inhibitors**

The CETP inhibitors prevent the transfer of cholesteryl ester from HDL to other lipoproteins, resulting in increased HDL and decreased LDL levels [45-47]. These are developing medications in phase three testing and are not currently available for widespread clinical use.

In 2007 several publications regarding the first of the inhibitors, torcetrapib, were published. Initially, ILLUSTRATE [45], RADIANCE 1 [46] and RADIANCE 2 [47] all demonstrated significant increases in HDL (53% to 63.4%) and decreases in LDL (17% to 20%). When combined with a statin however, no additional reduction in the progression of coronary or carotid atherosclerosis was seen [45-47].

A larger trial, ILLUMINATE, randomized 15,067 patients with known cardiovascular disease on a statin to either torcetrapib or placebo. After 12 months, there was a 72.1% increase in HDL (p<0.001) and a 24.9% decrease in LDL (p<0.001). However, increased risk of all cause death (HR: 1.58; 95% CI: 1.14 to 2.19; p=0.006) and major cardiac events including hospitalization for unstable angina, stroke and death (HR: 1.25; 95% CI: 1.09 to 1.1; p=0.001) resulted in the early termination of this study. The major contributors to increased non-cardiovascular deaths were cancer and infection [44].

The Dal OUTCOMES trial [21] studied cardiovascular risk reduction in patients with recent ACS through the use of another CETP inhibitor, dalcetrapib. 15,871 patients from over 935 sites and 27 countries were randomized to either 600 mg of dalcetrapib or placebo. All patients were at least 45 years old and had an LDL of less than or equal to 2.6 mmol/L with statin use. The patients were largely Caucasian men from Europe, Israel or North America. Approximately 25% had diabetes, 67% had hypertension and 63% had metabolic syndrome. Randomization was stratified based on country and presence of elevated cardiac biomarkers at the index event. The primary outcome was a composite of coronary heart disease death, major non-fatal coronary event or ischemic stroke. Discontinuation rates were comparable in both groups (21% in the treatment group vs. 19% in placebo). All patients except 1.6% in the dalcetrapib group and 1.3% in placebo were accounted for at the end of the study. An intention to treat protocol was used. Dal OUTCOMES was terminated after 31 months of follow up due to futility. Despite a 31-40% increase in HDL, there was no significant effect on the primary end point (HR: 1.04; 95% CI: 0.93 to 1.16; p=0.52) or any of its individual components. Effect on LDL with treatment was not observed.

### Table 3: Summary of all included CETP inhibitor studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Follow Up (months)</th>
<th>Therapy</th>
<th>Primary outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILLUSTRATE [45]</td>
<td>1,188 patients between 18 to 75 years of age with cardiac stenosis on angiography</td>
<td>24</td>
<td>Torcetrapib 60 mg daily and atorvastatin 10-80 mg daily</td>
<td>Change in percent atheroma volume</td>
<td>Torcetrapib and atorvastatin: HDL: 61% increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo and atorvastatin 10-80 mg daily</td>
<td>Change in atheroma volume: 0.07% decrease compared to placebo (p=0.72)</td>
<td>Torcetrapib and atorvastatin: HDL: 61% increase</td>
</tr>
<tr>
<td>RADIANCE 1 [46]</td>
<td>850 patients with heterozygous familial hypercholesterolemia</td>
<td>24</td>
<td>Torcetrapib 60 mg daily and atorvastatin 20-80 mg daily</td>
<td>Annualized change in maximum carotid intima-media thickness for 12 carotid artery segments</td>
<td>Torcetrapib and atorvastatin: HDL: 54% increase in HDL (p&lt;0.001) Primary outcome: 11% decrease compared to placebo (p=0.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo and atorvastatin 20-80 mg daily</td>
<td>Yearly change in maximum intima-media thickness for 12 carotid artery segments</td>
<td>Torcetrapib and atorvastatin: HDL: 63.4% increase (p&lt;0.0001) Primary outcome: 17% decrease compared to the placebo group (p=0.46)</td>
</tr>
<tr>
<td>RADIANCE 2 [47]</td>
<td>752 aged 18-70 years old</td>
<td>20</td>
<td>Torcetrapib 60 mg daily and atorvastatin 10-80 mg daily</td>
<td>Time to first occurrence of a major cardiovascular event</td>
<td>Torcetrapib and atorvastatin: HDL: 72.1% increase (p&lt;0.001) Primary outcome: 25% increase with treatment (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo and atorvastatin 10-80 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILLUMINATE [44]</td>
<td>15,067 between 40 and 75 years old with a history of CVD</td>
<td>18</td>
<td>Torcetrapib 60 mg daily and atorvastatin (variable dose)</td>
<td>Time to first occurrence of a major cardiovascular event</td>
<td>Torcetrapib and atorvastatin: HDL: 31-40% increase (p=0.001) Primary outcome: 0.3% increase in number of events compared to placebo (p=0.52)</td>
</tr>
<tr>
<td>Dal OUTCOMES [21]</td>
<td>15,871 patients 45 years or older with acute ACS</td>
<td>31</td>
<td>Dalcetrapib 600 mg daily</td>
<td>Composite of death from coronary heart disease, major non-fatal coronary event or ischemic stroke</td>
<td>Dalcetrapib: HDL: 31-40% increase (p=0.001) Primary outcome: 0.3% increase in number of events compared to placebo (p=0.52)</td>
</tr>
</tbody>
</table>

TC = Total Cholesterol; TG = Triglycerides; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; RCT = Randomized Controlled Trial; nMI = non-fatal Myocardial Infarction; PE = Pulmonary Embolus; TIA = Transient Ischemic Attack; CAD = Coronary Artery Disease; IHD = Ischemic Heart Disease
was minimal but a 4-10% increase in triglycerides was seen. The side effect profile included increased systolic blood pressure (significant increase of 0.6 mmHg), diarrhea and insomnia [21].

Other CETP inhibitors include anacetrapib and evacetrapib both of which have been found to decrease LDL (11.2% to 39.8%) and increase HDL (78.5% to 138.1%) [48,49]. Phase 3 testing is currently underway in the REVEAL and ACCELERATE trials [51]. Data from these trials is summarized in Table 3.

Keene et al. have examined the CETP inhibitors studies (specifically torcetrapib, dalcetrapib and anacetrapib) as part of their meta-analysis including 8 trials and 36,011 patients. They found no significant decrease in all-cause mortality, coronary heart disease mortality (OR: 1.00; 95% CI: 0.80 to 1.24; p=0.31), non-fatal MI (OR: 1.05; 95% CI: 0.93 to 1.18; p=0.41) or stroke (OR: 1.14; 95% CI: 0.90 to 1.45; p=0.29) with the use of any CETP inhibitor. Torcetrapib was found to significantly increase mortality in this analysis (OR: 1.53; 95% CI: 1.12 to 2.09; p=0.007) [19].

Recommendations on the use of the CETP inhibitors will await the results of further trials involving anacetrapib and evacetrapib (REVEAL and ACCELERATE). Further investigations of torcetrapib and dalcetrapib have been abandoned.

CONCLUSIONS

There are three groups of medications that therapeutically target HDL. After a careful literature review, current evidence suggests that the addition of niacin, gemfibrozil, bezafibrate or fenofibrate to statin therapy, with the goal of increasing HDL, offers no additional protective cardiovascular benefit. However, each of these agents can reduce the risk of risk of non-fatal MI when used in isolation.

In addition, niacin may decrease the incidence of stroke. Phase three trials of dalcetrapib and torcetrapib has been disappointing; we await trial results of the two remaining CETP inhibitors (anacetrapib and evacetrapib).

There are several possibilities that may explain the lack of cardiovascular protection seen when targeting HDL. First, it is possible that HDL is no longer a risk determinant in secondary prevention when patients are already receiving other evidence-based treatments. Also, perhaps HDL changes in composition and/or function following an acute coronary event which may act to change its overall contribution to a second episode [21].

Another enticing theory is the HDL function hypothesis. The model suggests that the capacity of HDL to promote efflux of cholesterol from cells, rather than HDL levels per se, regulate its inherent ability to modulate and affect cardiovascular risk. Indeed, recent studies have demonstrated associations between HDL efflux capacity and atherosclerotic cardiovascular disease risk even after adjusting for HDL level and particle concentration [10,21,52,53]. The development of agents that can enhance this process may resurrect the importance of HDL if they can be shown to effect cardiovascular risk, and in doing so, bring this lipid particle back to the prominence that was once anticipated by Gofman et al. almost 50 years ago [4].

To conclude, the principal lipid target, as outlined in both the Canadian and AHA cholesterol treatment guidelines [15,16], remains LDL. Currently available agents that alter HDL offer no cumulative benefit in addition to statin therapy. We await new therapies designed to alter HDL form and function and reassess its role in cardiovascular disease prevention.

REFERENCES


34. Fenofibrate: Drug Information. 2014.


