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REVIEW

Thinking beyond low-density lipoprotein cholesterol: strategies to further reduce cardiovascular risk

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Abstract: Several large statin trials and meta-analyses have demonstrated a reduction in low-density lipoprotein cholesterol (LDL-C) and cardiovascular morbidity and mortality. Some trials have also highlighted the significance of residual cardiovascular risk after treatment of LDL-C to target levels. This reflects the complex nature of residual cardiovascular risk. This residual risk is partially due to low HDL-C and high triglycerides (TG) despite achievement of LDL goals with statin therapy. The NCEP ATP III guidelines reported that low HDL-C is a significant and an independent risk factor for coronary heart disease (CHD) and is inversely related to CHD. Epidemiologic studies have also shown a similar inverse relationship of HDL-C with CHD. High-density lipoprotein cholesterol (HDL-C) may directly participate in the anti-atherogenic process by promoting efflux of cholesterol of the foam cells of atherogenic lesions. Many studies have demonstrated multiple anti-atherogenic actions of HDL-C and its role in promoting efflux of cholesterol from the foam cells. The residual risk by increased TG with or without low HDL-C can be assessed by calculating non–HDL-C and a reduction in TG results in decreased CHD.

Keywords: low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, statins, coronary heart disease

Background

Statin therapy has been shown to lower the cardiovascular morbidity and mortality in virtually every population study. Several large trials and meta-analyses have consistently demonstrated that statins reduce low-density lipoprotein cholesterol (LDL-C) leading to a decrease in the incidence of cardiovascular events.[1–6] Same statin-trials also highlighted the significance of residual cardiovascular risk after treatment of LDL-C to target levels. Obviously all the residual cardiovascular risk is not modifiable because of age and gender issues. This residual cardiovascular risk is complex and is partially due to low high-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG) despite achievement of LDL-C goals with statin therapy. The National Cholesterol Education Program (NCEP) ATP III guidelines reported that low HDL-C is a significant and independent risk factor for coronary heart disease (CHD)[6] and is inversely related to CHD. The nature of the relationship between HDL-C and CHD is not clear. One theory is that HDL directly participates in the atherogenic process. Various studies have demonstrated multiple anti-atherogenic actions of HDL-C (Table 1).[7] Studies in vitro have shown that HDL-C may promote efflux of cholesterol of the foam cells from atherogenic lesions, a process called reverse cholesterol transport. The residual risk by

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Table 1 The multiple anti-atherogenic actions of high-density lipoprotein cholesterol

1. Reverse cholesterol transport
2. Cellular cholesterol efflux
3. Anti-inflammatory action
4. Anti-infectious
5. Anti-oxidative
6. Anti-thrombotic
7. Anti-apoptotic
8. Endothelial repair
9. Vasodilatory activity

increased TG with or without low HDL-C can be assessed by calculating non-HDL-C[6] and modification in TG also result in decreased CHD.[8]

Residual CHD risk in patients treated with statins

A significant cardiovascular risk remains in statin-treated patients as shown in many trials. Although statins are very efficacious they do not eliminate the CHD risk associated with diabetes mellitus (DM).[1,3,9–14] This residual cardiovascular risk issue in such populations was well illustrated by Cholesterol Treatment Trialists (CTT).[15] In a meta-analysis of 90,056 patients, CTT collaborators found that residual CHD risk was particularly high in patients with statin monotherapy in 90,056 patients from 14 statin trials. This meta-analysis demonstrated the safety and efficacy of statin therapy in reducing 5-year incidence of major cardiovascular events (MACE). A reduction of 39 mg/dL of LDL-C was associated with a 20% decrease in the composite end point of non-fatal myocardial infarction (MI), coronary revascularization, and coronary death.[15] This meta-analysis further confirmed a significant reduction in major vascular events with statin therapy in patients with and without DM. However, as revealed in this meta-analysis, CHD events are still higher in diabetic patients treated with statin than those patients without DM on placebo.[15] This was demonstrated in the subgroup analysis of 18,686 patients with DM and 71,370 without DM with mean follow up of 4.3 years.

Atherogenic dyslipidemia

Both DM and metabolic syndrome are associated with atherogenic dyslipidemia, which is characterized by high TG, elevated small dense LDL-C and low HDL-C. Such dyslipidemia confers a high risk of CHD on patients.[16] According to NCEP ATPIII, elevated TG is a marker for atherogenic remnant lipoproteins[6] and the most readily available measure of this atherogenic remnant lipoprotein is very LDL (VLDL). A combination of both of these atherogenic lipoproteins (TG and VLDL) represents non-HDL-C. Furthermore, NCEP III guidelines state that non-HDL-C is calculated by subtracting HDL-C from total cholesterol and should be the secondary target if TG is >200 mg/dL. All three components of atherogenic dyslipidemia (LDL-C, HDL-C, and TG) are interrelated and each component predicts CHD risk.

Low-density lipoprotein cholesterol

It is not uncommon that LDL and LDL-C are used synonymously. LDL-C is a combination of lipoprotein (LDL) and lipid-like cholesterol. Cholesterol is packaged into lipoproteins in the form of cholesterol esters to make LDL-C. Lipoproteins differ in size and its cholesterol ester content. Therefore, small dense LDL particles can be more in number for the same level of blood cholesterol. The number of LDL-particles is an important predictor for risk from these lipoproteins when small LDL is present. The LDL-C value measured in a standard lipid profile does not provide information about the size of LDL particles. For example, a patient with normal LDL-C may have the majority of their cholesterol in small dense particles thus having more particles and placing the patient at higher risk for CHD.[17]

High-density lipoprotein cholesterol

HDL-C and HDL are not synonymous and a clear distinction should me made. HDL is a high-density lipoprotein which enables lipids like cholesterol to be transported back to liver. HDL-C represents HDL particle with cholesterol ester inside. Low HDL-C is another independent risk factor for CHD. It is a strong risk factor and is inversely associated with CHD risk.[6] In an observational study, it was found to have a 2% to 3 % decrease in the risk of CHD for every 1 mg/dL increase in HDL.[18] Another trial, Treating to New Targets (TNT), demonstrated a lower risk of CHD in groups with higher HDL.[19] Although the mechanism is not clear, it is believed that the anti-atherogenic effect of HDL-C may be a result of reverse cholesterol transport (RCT), and anti-oxidant and anti-inflammatory properties.[20] Furthermore, the size of HDL-C particles may also be important. The action of CETP (cholesterol ester transfer protein) plays an important role in determining the size of HDL-C particles. CETP is a plasma lipid transfer protein secreted by the liver. It facilitates the

exchange of TG from VLDL particle for cholesterol esters from HDL-C, resulting in smaller HDL-C particles. These resultant smaller HDL-C particles are readily cleared by the kidneys resulting in lower HDL-C particles.

Triglycerides

The independent prognostic value of TG was demonstrated in the Pravastatin or Atorvastatin Evaluation and Infectious Therapy-Thrombolysis in Myocardial infarction (PROVE IT-TIMI)-22[8] trial. This trial evaluated the role of intensive statin therapy in patients with acute coronary syndrome (ACS) admitted to hospital. After 2 years of follow up, significantly lower events occurred in patients with LDL-C $<$ 70 mg/dL. The relationship of LDL and TG to composite endpoints of CHD was assessed in this trial. After a multivariate adjustment, there were significantly fewer events in a treatment group with TG $<$ 150 mg/dL compared to the group with TG $>$ 150 mg/dL.[8] Therefore, TG $<$ 150 mg/dL was associated with lower CHD risk independent of LDL-C level, and achieving both optimal LDL and TG may be an important strategy in ACS patients.

Treating beyond low-density lipoprotein cholesterol

According to NCEP and American Diabetes Association (ADA), LDL-C is the primary therapeutic target in lipid management. As described above, there are several other atherogenic particles which contribute to the CHD risk after LDL-goals are met. Therefore, non-HDL-C is a secondary therapeutic target.[6,21] The American College of Cardiology (ACC) and ADA statement defines highest risk groups with known cardiovascular disease or patients without cardiovascular disease with DM associated with one or more risk factors such as smoking, hypertension, and family history of premature coronary artery disease (CAD). The 2008 ACC/ADA consensus statement sets specific lipid/lipoprotein goals based on cardiovascular risk based on lipoprotein abnormalities and cardiometabolic risk. The goals for these highest risk patients are LDL-C $<$ 70 mg/dL, non-HDL-C $<$ 100 mg/dL, and apolipoprotein B (Apo B) $<$80 mg/dL.[22] Although statins are the initial drugs of choice, combination therapy may be needed as a strategy to meet lipid goals beyond just LDL-C target.

Modifying residual cardiovascular risk beyond LDL with statins

As discussed before, it is crucial to modify all the atherogenic risk factors for better outcomes in patients with atherosclerotic vascular disease. To modify the risk beyond statin therapy, the following drugs are available.

1. Omega-3 fatty acids
2. Niacin
3. Fibrates
4. Combination of statins with niacin
5. Combination of statins with fibrates.

Omega-3 fatty acids

The 2007 National Lipid Associations (NLA) safety task force concluded that omega therapy is a safe therapeutic option for lowering TG.[23] Observational studies have shown several cardiovascular benefits such as a decrease in cardiac dysrrythmias, sudden cardiac death, and a decrease in blood pressure.[24] The mechanism of action of omega-3 fatty acids in the reduction of TG is unclear. There is evidence that omega-3 fatty acids increase TG clearance from circulating VLDL particles by increasing lipoprotein lipase (LPL) activity. Some studies have shown an increase of HDL-C with high doses of omega-3 fatty acids. In the JELIS study (Japan Epa Lipid Intervention Study), a combination of omega-3 fatty acids and statin was compared with statin monotherapy. There was a 19% reduction in major coronary events by the combination therapy as compared to statin alone.[25] Another trial, COMBOS (COMBination of prescription Omega-3 plus Simvastatin) which also showed that a combination of omega-3 fatty acids and simvastatin reduced non-HDL-C, TG and raised HDL as compared to statin monotherapy.[26] The AFFORD trial (Atorvastatin Factorial with Omega-3 fatty acids Risk Reduction in Diabetes)[27] did not show any benefit of residual cardiovascular risk reduction in the diabetic population. It is important to note that dietary supplement of omega-3 fatty acids is not subject to FDA regulation and thus higher doses of fish oil supplement may be required to be equivalent to the prescription form of omega-3 fatty acids (Lovaga, previously called Omacor).[23]

Niacin

Niacin has long been recognized for its lipid-modifying effect. It has a well established safety profile based on clinical evidence over 20 years. This is the most effective agent in raising HDL-C and had been used for past 5 decades.[28] No major trials showed any potential interaction of niacin with statins. The Coronary Drug Project (CDP) was an outcome, randomized trial conducted between 1966 and 1975 with a mean follow up of 6.2 years in men with history of previous MI.[29] The primary end point of mortality did not decrease in the niacin group. However, a significant

reduction in composite outcome of CHD death, non-fatal MI, and cerebrovascular events occurred in this group. There was also a significant reduction of cardiovascular surgery (47%) in the niacin group.[29,30] It should be added that 9 years after the termination of the trial, there was an 11% (P = 0.0004) mortality reduction in the niacin group compared to the placebo group.[31]

Niacin decreases hepatic synthesis of TG, leading to reduced synthesis of VLDL particles, and increased degradation of APO-B and decreased catabolism of APO A.[32,33] Recent studies also indicate that it increase APO A-1, thereby increasing HDL-C.[34] It may also enhance ABC A-1 (ATP binding cassette) transporter transcription leading to HDL-mediated cholesterol efflux from peripheral cells.[35]

Compared to statins alone, combination therapy with niacin and statins has shown greater efficacy with uncompromised safety in patients with dyslipidemia. Safety and efficacy have been evaluated in SEACOAST (Safety and Efficacy of a combination of Extended Release Niacin and Simvastatin trial) and OCEAN (Open label Evaluation of the safety and Efficacy of a combination of Niacin ER and Simvastatin) trials.[36,37] SEACOAST compared the safety and efficacy of simvastatin monotherapy with fixed dose combination of niacin ER and simvastatin in patients with mixed dyslipidemia. In SEACOAST-I trial, fixed dose combination of niacin ER and simvastatin (1000/20 and 2000/20) showed significant dose-related improvements in non-HDL-C, HDL, TG, and lipoprotein(a) compared to simvastatin monotherapy. The most notable results were the 24% increase in HDL-C, 38% reduction in TG, and 25% reduction of lipoprotein(a) in a group treated with niacin/simvastatin combination.[36] This has been further demonstrated in SEACOAST-II trial, which showed a 17.1% reduction in primary end point of non-HDL-C with niacin/simvastatin 2000/40 compared to a 10.1% reduction in simvastatin 80 mg monotherapy. The OCEAN trial was a randomized, open label, multicenter study which evaluated the safety and efficacy of a fixed dose combination of niacin and simvastatin in patients with elevated non-HDL.[37] The primary end point was long-term safety and secondary endpoints were the serum levels of non-HDL-C, IDL-C, and TG. In the subgroup of patients who failed to reach their goals with simvastatin as baseline therapy, 82% achieved non-HDL goals, 85% reached HDL goals, 67% reached HDL goals, and 64% reached TG target (65% reached all combined goals).[37]

Another excellent clinical outcome trial (HATS) demonstrated efficacy of the combination treatment with niacin and simvastatin. This trial, the HDL-Atherosclerosis Treatment Study (HATS) was a double-blind, placebo-controlled trial in which 160 patients with low HDL and low LDL < 145 mg/dL were enrolled. Coronary angiography was done at baseline and 2-year follow up and the endpoints were the angiographic change in CAD and occurrence of first cardiovascular event such as MI, death, coronary revascularization, and stroke. There was a slight progression of angiographic CAD in the placebo group (3.9% changes) and regression of angiographic CAD (0.4% change) in the treatment group with niacin and simvastatin. The authors concluded that treatment with niacin/simvastatin in CAD patients with low HDL resulted in slight regression of atherosclerosis but translated into 90% reduction in clinical events over a 3-year period.[38]

Furthermore, the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) evaluated effects of niacin ER added to background of statin therapy.[39] This was a double-blind, placebo-controlled study of once-daily niacin ER 1000 mg added to background statin therapy in 167 patients with known CAD with low HDL-C levels. The primary end point was change in carotid intima-media thickness (CIMT) after 12 months. The change in CIMT was 0.044 mm in the placebo group compared to 0.023 mm in the niacin group. The subgroup analysis of this study also showed that statin-treated patient had a similar CIMT progression regardless of insulin resistance status. One hundred thiry patients of ARBITER-2 who completed the blinded 12 months study end point were followed for an additional 12 months on open label as a prespecified extension study of ARBITER-2, called ARBITER-3.[40] The patients in ARBITER-3 included patients from ARBITER-2 who were on combination of niacin/statin and continued on the same regimen and for total of 2-year period. This also included patients from ARBITER-2 who were initially on statin and were switched to niacin/statin and followed for an additional 12 months. There was a significant regression of atherosclerosis as measured by CIMT at both 12 months and 24 months compared to statin therapy alone.[40] Discussion on niacin would be incomplete without mentioning its common side effect, flushing. Such flushing is initially seen in 80% patients and disappears over period of time. Recent data have suggested that flushing may be a marker of high lipid response to niacin therapy.[41] This was assessed in subgroup analysis of 77 patients in ARBITER-2. Interestingly, patients who reported flushing had a significantly greater response to increase in HDL-C than those patients without flushing. If these results are confirmed in larger trials, patients may be convinced that flushing is less of a nuisance and will therefore adhere to niacin treatment.

Fibrates and fenofibrates

Several studies have shown the cardiovascular benefits of fibrate therapy. The Helsinki Heart Study (HHS)[42] showed a 71% reduction in CHD in patients taking gemfibrozil compared to patients receiving placebo, and similar results were seen in VA-HIT (Veterans Affairs-High density lipoprotein Intervention Trial)[37] which showed a 41% reduction in CHD and stroke with gemfibrozil compared to placebo in a subgroup of patients with DM. The BIP trial[43] (Bezafibrate Infarction Prevention) evaluated the long-term cardiovascular benefit of bezafibrate therapy. This study demonstrated significant long-term cardiovascular protection which was attenuated by unbalanced use of non-study lipid-lowering drugs.

Fibrates work by activating peroxisome proliferator-activated (PPRA) alpha receptors which modulate several aspects of lipid metabolism by increasing expression of APO A-1, APO-11, and ABCA1, and lowering expression of APO C-111. They also increase HDL-C particles. Fibrates increase LPL synthesis which clears VLDL clearance and lowers TG. They also increase B-oxidation of fatty acids leading to a decrease in TG and VLDL production.[44,45]

Fenofibrate therapy was tested in FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial.[46] This study was planned to extend the findings of the HHS and VA-HIT studies by investigating the long-term effect of fenofibrates in the largest trial of patients (total 9795) with type 2 DM with a 5-year follow up. The fenofibrates showed a 11% reduction (insignificant) in primary end point of CHD but the study did show a 24% reduction in non-fatal MI and a 21% reduction in coronary revascularization (significant). The interesting aspects of this study were certain prespecified tertiary endpoints like effects on microvascular complication of DM such as microalbuminuria, diabetic retinopathy, and amputation due to non-traumatic causes. In the overall analysis for prespecified endpoints, there was a regression of microalbuminuria in the fenofibrate group.[46] There was also a beneficial effect in the subgroup with diabetic retinopathy. The fenofibrate group showed a 31% reduction in the need for first laser treatment compared to placebo, and benefits progressively increased thereafter.[47] Fenofibrates also reduced the number needing non-traumatic amputation in these diabetes patients. This demonstrates the beneficial effects of fenofibrate in preventing macro- and microvascular complications of DM.

Combination of fibrates and statins

As fibrates modify all aspects of dyslipidemia, their use in combination with statins is very attractive.[48] Both agents have the potential for myopathy and the risk of adverse events depends on the pharmacokinetic interaction between their affects on statin metabolism and clearance.[49–53] Several studies have shown that gemfibrozil interferes with the metabolism of statins by inhibiting glucoronidation. This possibly can raise statin levels, predisposing the patients to myopathy.[48,49] In contrast, fenofibrate does not interfere with statin metabolism and therefore may be safer to use in combination with statin therapy.[49] Because of this pharmacokinetic interaction, the National Lipid association (NLA) safety task force has recommended avoidance of usage of gemfibrozil in combination with statins, and fenofibrates may be the preferred fibrate to use in combination with statins.[54] It has been also stated in NCEP ATP-III update in 2004 that, unlike gemfibrozil, fenofibrates does not increase rate of myositis when used in conjunction with moderate doses of statins.[55] There are several ongoing trials to address this issue of combination therapy of omega-3 fatty acids, niacin, fibrates, and statins.[56,57]

Other drugs on the horizon

CETP inhibitors

The action of CETP plays an important role in determining the size and blood levels of HDL particles. Low HDL-C level constitutes a major risk factor for CHD. In view of lack of effective therapeutic intervention for low HDL-C, CETP inhibition offered a very attractive strategy to raise HDL-C. A CETP inhibitor was investigated in a trial in which torcetrapib markedly increased HDL-C levels as monotherapy as well as in combination with a statin.[58] Unfortunately its development was halted in phase III trial in 2006 due an increase in all-cause mortality in the treatment group with monotherapy or in combination with atorvastatin.

Apo A-1 Milano

Apo A-1 Milano is a naturally occurring mutated variant of the Apo A-1 found in human HDL. Apo A-1 Milano mutation was discovered by accident, present in 3.5% of the population of small village in Italy, Limone sul Garda. These carriers were found to have significantly reduced cardiovascular disease despite low HDL and high TG. Clinical trials with recombinant Apo A-1 Milano published in JAMA[59] showed a significant regression of coronary atherosclerosis as measured by intravascular ultrasound. Although promising, these results require confirmation in larger trials.

Conclusion

Large trials have consistently shown a significant benefit of LDL-C intervention but there is a significant residual risk

for cardiovascular events especially in high-risk patients with DM. This residual risk is predominantly due to low HDL-C and increased TG. NCEP has suggested the use of niacin or a fibrate as an addional agent for mixed dyslipidemia. Ongoing trials will be needed to demonstrate the incremental cardiovascular disease benefits and safety of combination regimens.

Disclosures

The authors report no conflicts of interest.

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