What's Up With Low HDL?
(VA HIT, HATS, AFCAPS/TexCAPS, ABCA1, SRB1)

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Introduction

While it is clear and accepted that lowering LDL is beneficial in the treatment and prevention of CHD, the treatment of low HDL is controversial and without clear guidelines. Although LDL reduction provides substantial benefits, it in no way prevents or cures all CHD. LDL is an important risk factor, but it's not the only lipid risk factor. Decreased HDL is another important risk factor. There has been considerable interest in novel risk factors or markers for CAD, such as hs-CRP, Lp(a), fibrinogen, EBCT, or Carotid US, etc. However, I would like to suggest that low HDL is an accepted but under treated risk factor that deserves more attention.
I'd like to review the epidemiology, pathophysiology, and therapeutic trials of low HDL and argue for a more aggressive approach to low HDL.

Case

65 yo AAF h/o MI with TC 132, TG 100, LDL 80, HDL 32 on a Simvastatin 40 mg as well as ASA, B Blocker, ACEI, diet, and exercise. She's concerned about her low HDL and asks you for advice. What do you suggest? What should her HDL goal be?

a. Increase Statin, or add one of the following b. Lopid c. Niacin d. Resin e. Zetia f. HRT

a.35 b.40 c.45 d.50 e.55

Prevalence

According to NHANES, HDL < 40 mg/dl occurs in 35% of US men and 15% women[1]. In high risk populations, the incidence is much higher. In the Framingham Heart Study, 57% men with CHD had HDL < 40mg/dl and in the CARE (Cholesterol and Recurrent Events) trial, 40% of women with an MI had HDL < 40 mg/dl. In a study of 8,250 patients with CHD, 42% had a HDL < 35 mg/dl. A study of premature coronary disease showed 40% had low HDL, while only 10% had high LDL. Another study of premature CHD found a HDL < 35 mg/dl occurred three times as frequently compared with controls (57% vs 19%)[2] In a study of 8,500 men with CHD at VA's, 38% had HDL < 35 mg/dl and 63% had HDL < 40 mg/dl. Thus, low HDL is the most common lipoprotein abnormality in patients with CHD.[14,22]

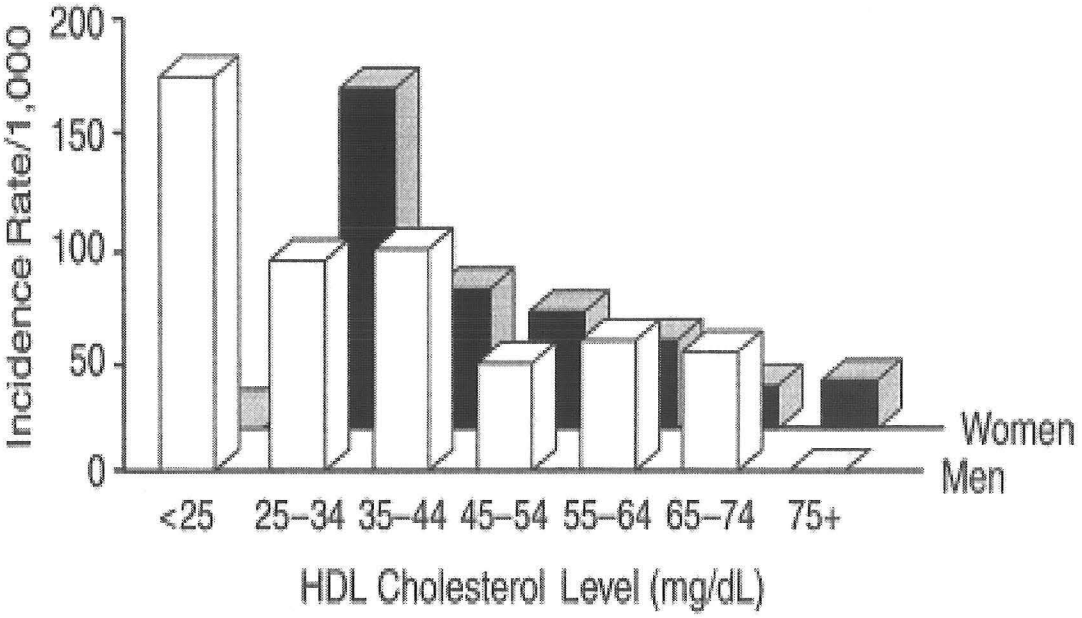

Figure 1 Relation between HDL and CAD

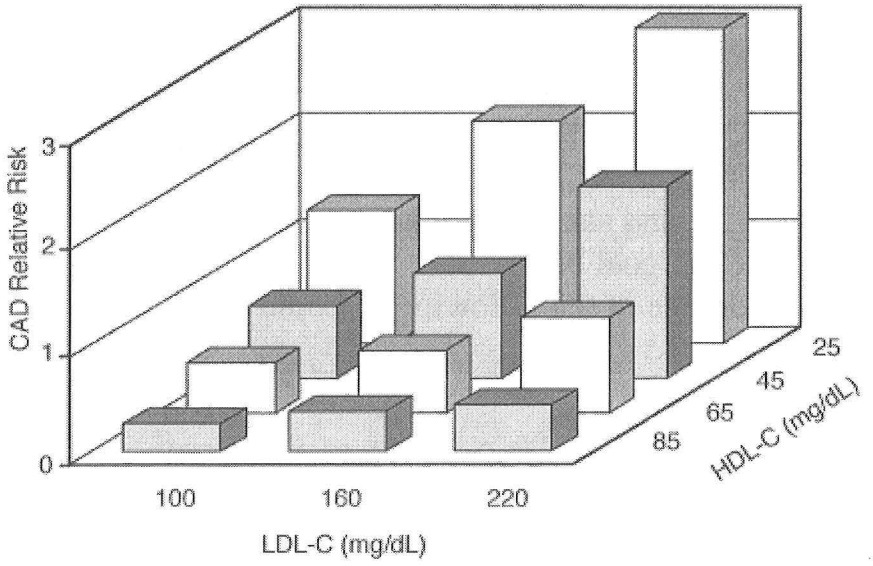

Figure 2 CAD risk predicted by HDL and LDL

Epidemiology

HDL : An independent risk factor

The Framingham Heart Study has shown that HDL is inversely related to CHD in men and women. (fig 1)[2] The risk with low HDL is totally independent of LDL (fig 2) – at any level of LDL, a decrease in HDL increases the risk of CHD[2]. In the Prospective Cardiovascular Munster study (PROCAM), as well as Framingham, the risk associated with HDL was

independent of triglycerides. In the Physicians' Health Study, HDL was predictive regardless if your TC was high or low – but the greatest increase in risk was in those with a low TC.

Besides being a strong, independent predictor of primary coronary events, low HDL is also associated with an unfavorable prognosis in patients with established CHD. In one study, 75 % of patients with HDL < 35mg/dl had a recurrent event vs 45 % of patients with HDL > 35mg/dl.

The protective effect of HDL on atherosclerosis is also suggested by the longevity syndrome in which patients with HDL > 75 mg/dl have reduced CHD and live 5-7 years longer than the average.

The relation between HDL and CV risk was examined in a meta-analysis of 4 large US prospective studies – for every 1 mg/dl increase in HDL, the predicted incidence of coronary events decreases by 2% in men and 3% in women – a very powerful relation[1]. There is also an inverse relationship between HDL and the risk for stroke.[17]

HDL is clearly a well established risk factor for CHD and is independent of LDL and other risk factors.

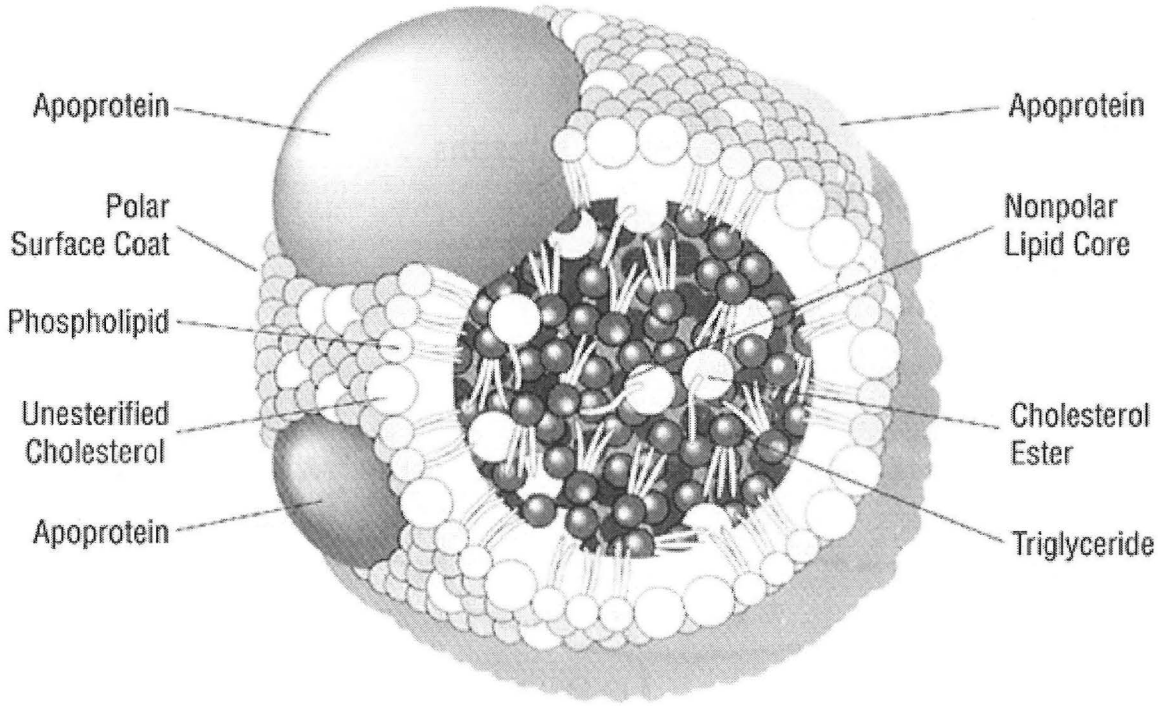

Fig 3 Basic Structure of HDL

HDL Metabolism

HDL's are the smallest and densest of the plasma lipoproteins. HDL is composed of an outer hydrophilic layer of phospholipids and apolipoproteins

covering a hydrophobic core of cholesterol and TG (fig 3). The apoproteins include apo A-I, A-II, C and E. Apo A-I is the main apolipoprotein and is responsible for the antiatherogenic effects of HDL.[3, 21]

Several subtypes of HDL have been identified based on density and apolipoprotein composition, but with unclear ramifications. HDL 2 is larger and less dense, while HDL 3 is smaller and denser. Electrophoresis can separate HDL into 5 subpopulations – HDL 2b, HDL 2a, HDL 3a, HDL 3b, and HDL 3c in decreasing size. In addition, some HDL have only apo A-I, while others have both apo A-I and apo A-II[3].

The antiatherosclerotic effect of HDL is attributed to its role in reverse cholesterol transport. Cholesterol is removed from peripheral tissues by HDL. HDL then transfers the cholesterol to LDL or VLDL, or to the liver for excretion. In addition, HDL is thought to remove cholesterol from macrophages thus preventing foam cell formation.

To form HDL, apo A-I pick up phospholipid and unesterified cholesterol from cell membranes in a reaction mediated by ATP binding cassette transporter (ABCA1) (fig 4). LCAT (lecithin cholesterol acyl transferase) then esterifies the cholesterol to form the cholesterol ester core. LCAT is activated by apo A-I[4,5]

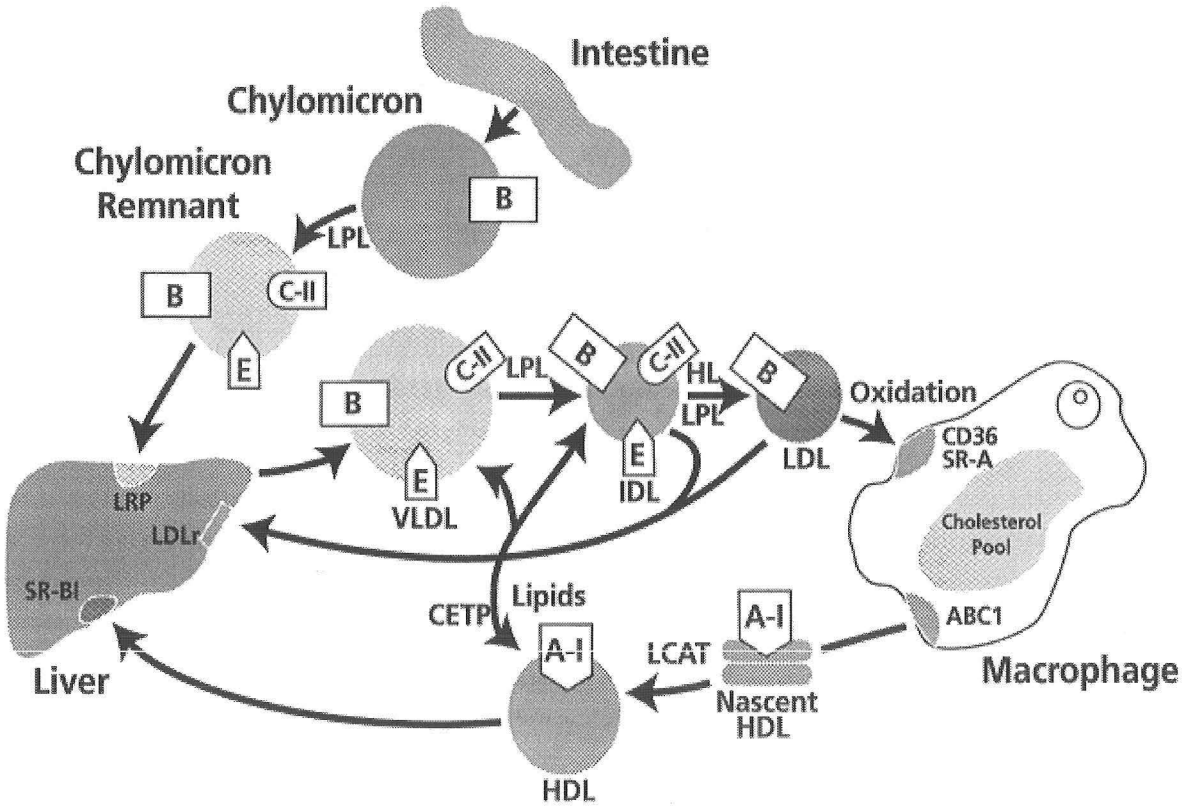

Figure 4 HDL Metabolism

The cholesterol ester can be transferred to LDL or VLDL by cholesterol ester transferase protein (CETP). LDL and VLDL can deliver cholesterol esters to the liver through the LDL receptor or to other tissues. Alternatively, the cholesterol can be delivered directly to the liver from HDL in a process dependent on HDL binding to SRB1 (scavenger receptor type B1) in the liver. Then, the cholesterol can be converted to bile for excretion.[24]

SRB1 is the HDL receptor in the liver- it interacts with HDL to take up cholesterol and releases depleted HDL to pick up more cholesterol.[24] Upregulation of SRB1 enhances reverse cholesterol transport.[15]

HDL also possesses antioxidant, antithrombotic activity in addition to its antiatherogenic reverse cholesterol transport.

By removing cholesterol from the periphery, HDL is thought to prevent or reverse atherosclerosis. In this regard, HDL could be the key to longevity. As opposed to revascularization which treats a focal lesion, improving HDL could protect the entire vasculature and be the long sought after fountain of youth.

New Insights

New insights in the metabolism of HDL have lead to improved understanding of diseases with low HDL and hopefully will translate into new therapies- much like Brown and Goldstein and the LDL receptor. Tangier disease is an autosomal recessive genetic disorder of cholesterol transport characterized by low HDL, cholesterol, and LDL with premature atherosclerosis. Mutations in ABCA1 transporter as the genetic defect in Tangier has prompted considerable interest in the role of these transporters in cholesterol metabolism. Impaired HDL mediated cholesterol efflux from macrophages leads to foam cells throughout the body in Tangier disease (tonsils, cornea, liver, spleen, bone marrow, heart).[4,5]

Four ATP binding cassette (ABC) transporters – ABCA1, ABCG1, ABCG5, and ABCG8 – have been shown to modulate cholesterol metabolism. The ABCA1 transporter facilitates transfer of cholesterol from the periphery to HDL.[4]

Familial hypoalphalipoproteinemia is an autosomal dominant disorder with low HDL and premature CHD. It appears to be due to mutations in the apo A-1 gene.

Sitosterolemia is a rare autosomal recessive disorder with premature CHD. These patients have increased absorption of plant sterols as well as inability to excrete sterols in the bile, leading to elevated levels of sterols and cholesterol. It is caused by mutations in the ABCG5 or ABCG8

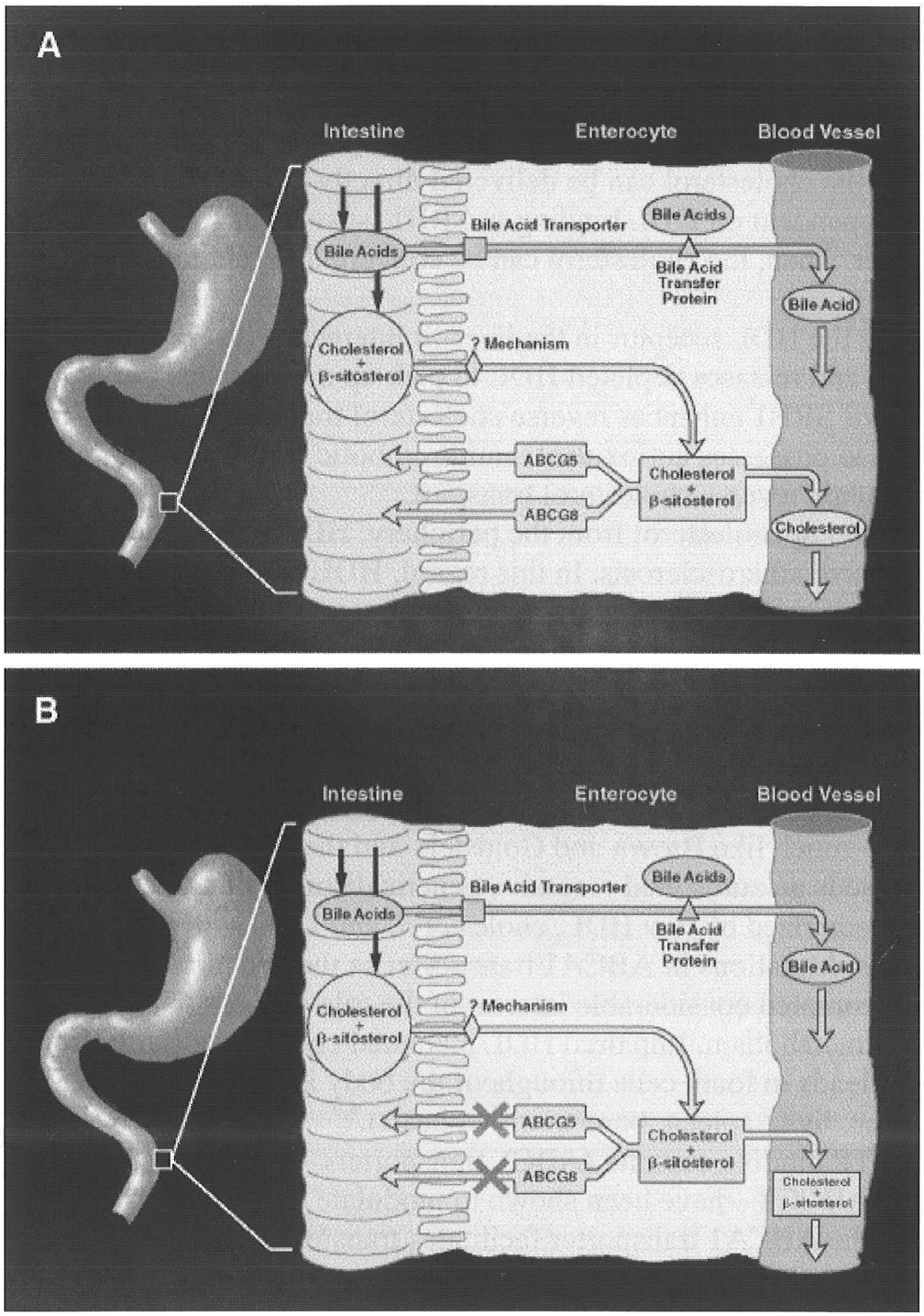

Figure 5 Role of ABC transporters in cholesterol absorption

transporters. The elucidation of the genetic defect in sitosterolemia has provided new insights into cholesterol and sterol absorption.[4]

Cholesterol and sterols are absorbed into the enterocyte by an unknown transporter. After absorption, ABCG5 and ABCG8 mediate the

transport of sterols and cholesterol back into the intestine, thereby decreasing sterol and cholesterol absorption. In sitosterolemia, a mutation in ABCG5 or ABCG8 results in a dysfunctional transporter which fails to eliminate sterols (fig 5).[4]

The new cholesterol absorption inhibitor ezetimibe (Zetia) appears to block the initial transport of sterols and cholesterol into the enterocyte and is useful in lowering sterols and LDL cholesterol.

Cholesterol ester transfer protein (CETP) is involved in the transfer of lipids between lipoproteins. High CETP levels are associated with low HDL. CETP inhibitors have been shown to increase HDL.

Animal Studies

In addition to epidemiologic evidence, animal studies suggest raising HDL may inhibit atherosclerosis. Increased expression of HDL apo A-I gene by gene transfer or oral administration increases HDL and stimulates regression of atherosclerosis in mice and rabbits. Intravenous administration of HDL has been shown to prevent atherosclerosis in rabbits with a 50% reduction in aortic atherosclerosis.[21]

One question regarding HDL is whether it is merely a marker associated with other risk factors or whether it is a true mediator preventing atherosclerotic lesions. The antiatherosclerotic benefit of HDL in the animal models shows the benefit of specifically raising HDL is not related to other risk factors and supports HDL as a direct mediator, not just a marker.

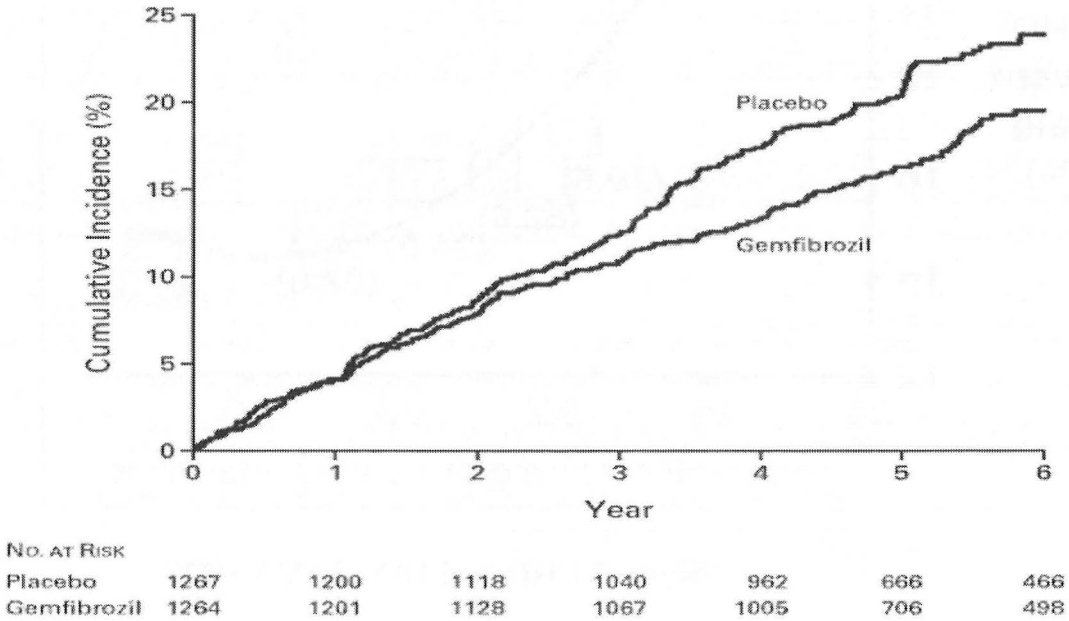

Figure 6 Incidence of CHD Death or MI in VA HIT

Interventional Studies/ Outcome Data

Helsinki Heart Study

In this study, a 1% increase in HDL with Gemfibrozil was associated with a 2-3 % decrease in CHD events.[18, 21] Most of the benefit was confined to the patients with the combination of elevated TG and low HDL. In this subgroup, CHD events were reduced by 70 %.[25]

VA HIT (VA HDL Intervention Trial)

40% patients with CHD have low HDL, but normal LDL. In addition, low HDL is strongly associated with CHD, but the optimal approach was unclear. So, the VA HIT was designed to address the hypothesis that raising HDL would improve events in men with CHD and low HDL and LDL[6].

2531 men from 20 VA's with CHD with HDL < 40mg/dl, LDL <140mg/dl, and TG < 300mg/dl were treated in a randomized, double blind trial with Gemfibrozil (Lopid) 1200mg/day vs placebo for 5 years. Baseline HDL was 32mg/dl, LDL was 111mg/dl, and TG was 160 mg/dl.

HDL increased 6% and TG decreased 31% with no change in LDL.

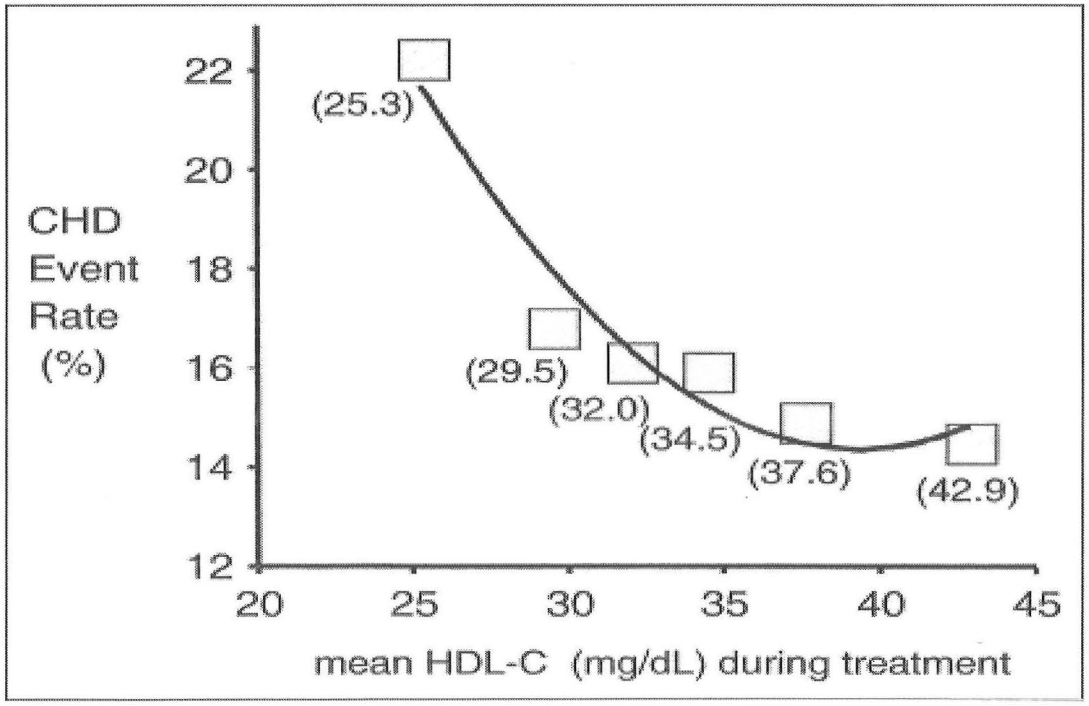

Figure 7 CHD and HDL in VA HIT

The 4.4% Absolute Risk Reduction (ARR) in CHD death or MI gives a Number Needed to Treat (NNT) of 23 over 5 years. This NNT is more favorable than two statin studies of secondary prevention, CARE and LIPID, which had NNT of 33 and 28 over 5 years, respectively.

Multivariate analysis shows that the reduction in CHD death or MI was strongly correlated with the achieved HDL (fig 7), but was independent of LDL or TG.[20]

In addition, Gemfibrozil was shown to be cost effective - $6,300 to $17,100 for each QALY saved.[19]

Thus, Gemfibrozil reduced CHD death or MI by 22% in men with CHD and low HDL but with normal LDL and TG. The magnitude of the benefit was greater than CARE and LIPID statin studies with moderate LDL levels. The reduction in CV events was dependent on raising HDL, but independent of TG or LDL.

AFCAPS/TexCAPS (Air Force/ Texas Coronary Atherosclerosis Prevention Study)

Statins have clearly shown that lowering LDL reduces CV events in patients with high TC or at high risk. However, most patients with CHD have average TC. AFCAPS/TexCAPS evaluated the effect of a statin in primary prevention in healthy patients with average TC and LDL, but below average HDL[7]. 6,605 healthy men and women were treated with 20- 40 mg Lovastatin or placebo for 5 years. Average TC 221 mg/dl, LDL 150 mg/dl, TG 158 mg/dl, and HDL 36 mg/dl for men and 40 mg/dl for women.

There was a 25% reduction in LDL, 15% reduction in TG, and 6% increase in HDL with Lovastatin.

Lovastatin reduced the first acute major coronary event (fatal or nonfatal MI, unstable angina, sudden cardiac death) by 37%. It also reduced MI by 40%, unstable angina by 32%, and revascularization by 33%. (fig 8)

The 2.8% ARR translates into a NNT of 50 for the primary end point.

AFCAPS/TexCAPS showed that a statin is effective in preventing the first coronary event in healthy patients with average TC, but low HDL. The CV event rate in the low HDL subgroup was reduced by Lovastatin to a rate similar in the desirable HDL subgroup.[21] Thus, the increased risk of low HDL was "taken away" by the statin and most of the benefit was in the low HDL group.

However, the relationship between changes in HDL and CHD events with statins is unclear. The HDL increase in the 4S was a significant predictor of benefit, but it did not correlate in WOSCOPS, CARE, and LIPID.

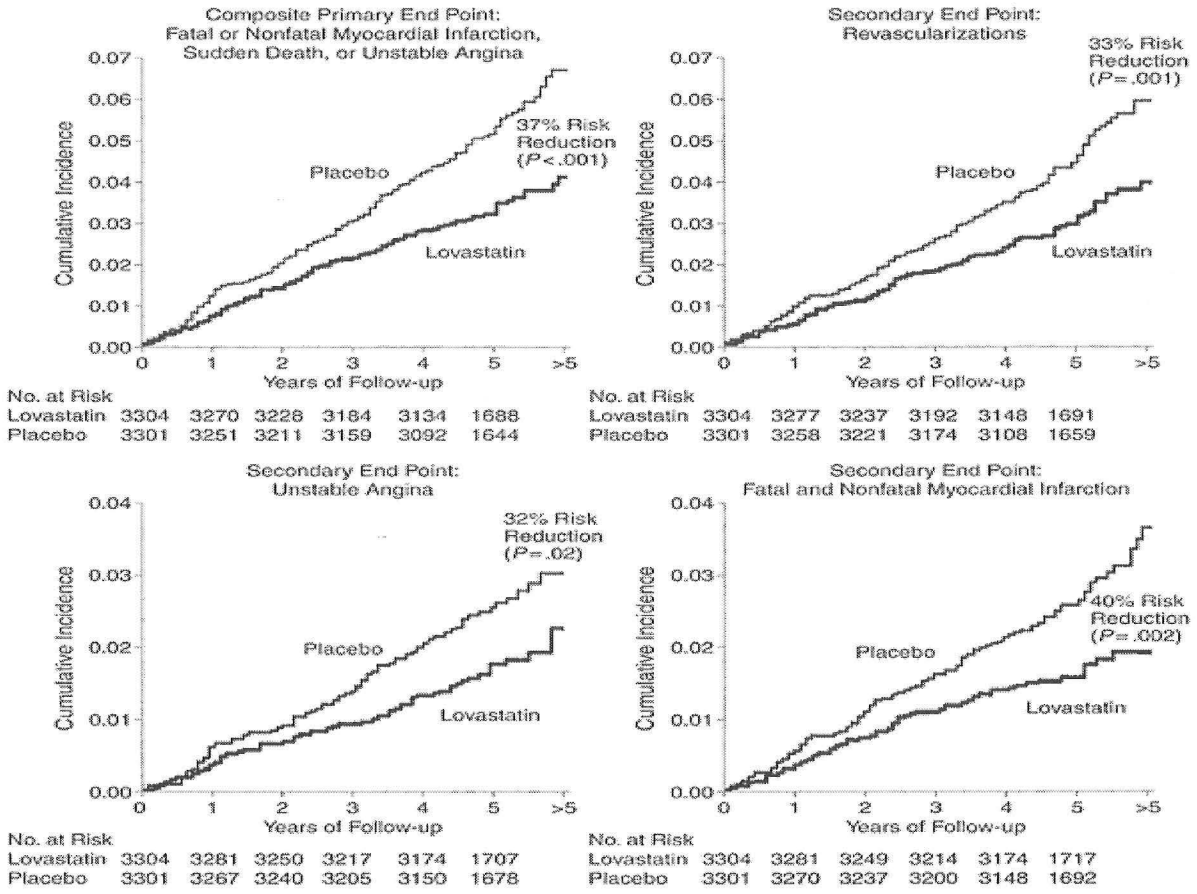

Figure 8 Primary and Secondary Endpoints in AFCAPS/TexCAPS

HATS (HDL Atherosclerosis Treatment Study)

It is predicted that each 1% reduction in LDL reduces CV events by 1 to 1.5%. Similarly, a 1 mg/dl increase in HDL should reduce CV events 2 to 3%. If the benefits of raising HDL and lowering LDL are independent and of similar magnitude, then simultaneous alterations of 30 to 40% in both LDL and HDL might reduce events by 60 to 80%. HATS is a study of the combination of Simvastatin and Niacin in patients with CHD and a low HDL[8].

In a 3 year, double blind trial, 160 patients with CAD, low HDL, and normal LDL were randomized to one of 4 groups – 1. Simvastatin plus Niacin, 2. Antioxidants, 3. Simvastatin- Niacin and Antioxidants, or 4. placebos. Patients had HDL < 35 mg/dl for men or < 40 mg/dl for women, as well as LDL < 145 mg/dl. Simvastatin was started at 10-20 mg and targeted to a LDL < 90 mg/dl. Simvastatin was also given to the placebo group if their LDL>140mg/dl. Slow release Niacin was titrated from 250mg BID to 1000mg BID. Patients who's HDL had not increased by 5mg/dl at 3 months,

8mg/dl at 8 months, and 10 mg/dl at 12 months were switched to immediate release Niacin (to allow higher doses) at 3 or 4 grams/day to meet HDL targets. Niacin "placebo" was 50mg to provoke flushing without affecting lipids.

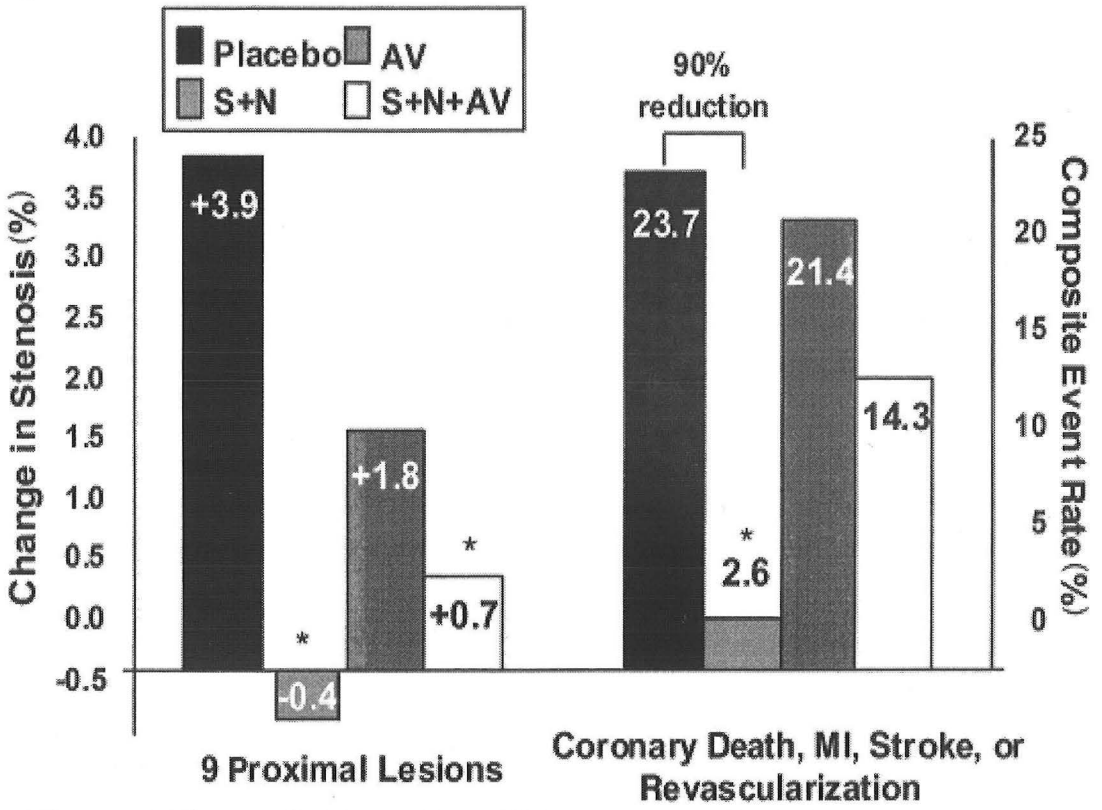

Figure 9 Change in Stenosis and Event rates with Simvastatin + Niacin in HATS

The Simvastatin-Niacin lowered LDL by 42% and raised HDL by 26%.

The Simvastatin –Niacin alone group caused a .4% **regression** of the average stenosis on cardiac catheterization vs significant **progression** with placebo or antioxidants. (fig 9)

The primary endpoint of coronary death, MI, CVA, or revascularization was only 3% with Simvastatin- Niacin, but was 24 % and 21 % with placebo and antioxidants. (fig 9)

Simvastatin plus Niacin provided marked clinical and angiographic benefit in patients with CHD, normal LDL, and low HDL. Coronary stenosis regressed and clinical events were reduced by 60 to 90 %. Clearly, the study was small and requires a larger confirmatory trial. But, these findings could apply to the 40 % of CHD patients with low HDL who might benefit from therapy targeted at both LDL and HDL. If confirmed, the 60 to 90 %

reduction in events with combination therapy could represent a substantial advance over current practice and furthers the role of increasing HDL as an important treatment.

Antioxidants were of no benefit which concurs with 4 large negative trials of vitamins (and may even be harmful).

A combined extended release Niacin and lovastatin pill is now available.

AFREGS (Armed Forces Regression Study)

As reported at the American College of Cardiology meeting,143 patients with stable CAD with low HDL but normal TC were treated with 3 drug therapy. At baseline patients had a TC 196 mg/dl and HDL 34 mg/dl. They were treated with Niacin, Gemfibrozil, and Cholestyramine. Treated patients had a 38% rise in HDL, 46% decrease in TG, and 22% decrease in LDL.

The combined event rate was reduced by 52% in patients on triple therapy. Coronary angiography demonstrated a net regression of CAD in the treatment group, while placebo patients showed atherosclerotic progression.

Raising HDL with combination therapy in high risk patients with low HDL again shows angiographic regression and improved CV outcomes.

BIP (Bezafibrate Infarction Prevention)

As reported at the American College of Cardiology meeting, 3026 patients with CAD and HDL < 45 mg/dl were treated with Bezafibrate for 8.2 years. The treated group had a 17% increase in HDL with a reduction in coronary and total mortality.

Mortality was examined based on tertiles of change in HDL. Mortality dropped with increasing HDL and change in HDL was a reflection of compliance. Total mortality was 15 % in the placebo group compared to 16% in the HDL group with the smallest effect, 13% in the HDL group which increased 3 – 8 mg/dl , and 11.7% in the HDL group that increased 8 – 34 mg/dl.

Similarly to VA HIT, a fibrate was shown to improve outcomes by raising HDL in high risk patients with low HDL.

Metabolic Syndrome

NCEP defines the metabolic syndrome as meeting 3 of 5 criteria: central obesity with waist circumference > 40 inches in men or > 35 inches in women, fasting glucose> 110 mg/dl, TG > 150 mg/dl, BP > 130/85 mm Hg, or HDL < 40 in men or < 50 in women. Insulin resistance is a key component to the syndrome. Unfortunately, it is very common and signifies

patients who are high risk and should be targeted for aggressive therapy. Low HDL often accompanies the metabolic syndrome.

Nonpharmacologic Therapy

With nonpharmacologic therapy, one can consider if changes in HDL are simply associated changes or if the change in HDL plays a direct role in mediating the effect of these important risk factors.

Diet, Weight Loss

There is a clear correlation between elevated BMI and low HDL.[26] Optimal BMI should be the goal to minimize CAD risk. Although weight loss improves the lipid profile, dieting can actually lower HDL transiently. For each kg of wt loss with active dieting, HDL can fall by 8%.[22] However, once weight is stabilized, there is an increase in HDL of 1 mg/dl for every 3 kg lost.[26]

Other studies have shown weight loss in obese patients can increase HDL. HDL increased .8 mg/dl for every unit decrease in BMI.[21]

General low fat diets can lower HDL, whereas monounsaturated fat have a more neutral effect on HDL. In recommending a diet to patients with low HDL, not only should the total calories be restricted to achieve appropriate weight, but saturated fats and trans fatty acids should be substituted with monounsaturated fats, such as olive or canola oil.[21]

There are no magic diets to raise HDL.

Although diet and weight loss are important components to treating patients with vascular disease or at risk, they are often insufficient in optimizing HDL.

Exercise

Aerobic exercise is the probably the most important nonpharmacologic treatment for raising low HDL. The average increase ranges from 10 – 20 % and a "dose response" relationship has been reported, with a 1 mg/dl increase in HDL for every 4-5 miles/week of running. [22]

The duration of exercise rather than the intensity appears to have the biggest influence on HDL. [22]

The exact mechanism of HDL modulation with exercise is unknown, but may be due to stimulation of LPL (lipoprotein lipase).

Alcohol

Moderate alcohol consumption is associated with reduced CHD and raises HDL by 5 –10 %.[22] This occurs with beer, wine, or liquor. The

mechanism of alcohol's raising HDL is unknown and whether HDL is responsible for alcohol's cardioprotection is unknown. This HDL effect appears to account for half of the CAD benefit attributed to moderate alcohol consumption. However, the definition of "moderate" is no more than 2 drinks/day for men and no more than 1 drink/day for women. In addition, there are multiple adverse effects of increased intake of alcohol and there is no long term prospective study on the effect of alcohol on HDL and outcomes vs drug therapy.

Smoking Cessation

Cigarette smoking has a dose dependent effect on HDL. Smoking caused a 5 – 9 mg/dl reduction in HDL vs controls. This is yet another reason to help your patients quit smoking.

Pharmacologic Therapy

Fibrates

Fibrates raise HDL by 5 – 20%. The effect appears related to the TG level. In one study, patients with a low TG (<95 mg/dl) only had a 4% rise in HDL, while patients with TG 95 – 150 mg/dl had a 15% increase in HDL. In addition, the magnitude of the HDL increase is greatest with the lowest baseline HDL.[16]

The fibrates gemfibrozil (Lopid) and fenofibrate (Tricor) raise HDL by activating the Peroxisome Proliferator-Activated Receptor alpha (PPAR alpha) – a nuclear receptor that regulates lipid metabolism. Through activation of PPAR alpha, fibrates also increase HDL by induction of apo A-I and A-II. Fibrates, through PPAR alpha, upregulate ATP binding cassette A1 (ABCA1) transporter and receptor SRB-1 and promote cholesterol efflux.[13,15]

The fibrates are well tolerated, with rare gallstones, dyspepsia, and LFT abnormalities.[21] The increased risk of myopathy with fibrates and statins makes combination therapy complicated. This drug interaction is not related to cytochrome P450, but instead gemfibrozil's impairment of statin glucuronidation which impairs statin clearance. This interaction may affect different statins to different degrees, i.e. Cervastatin (Baycol).

One can consider using fibrates in low HDL patients', particularly with elevated triglycerides and low LDL, or if fit into VA HIT.

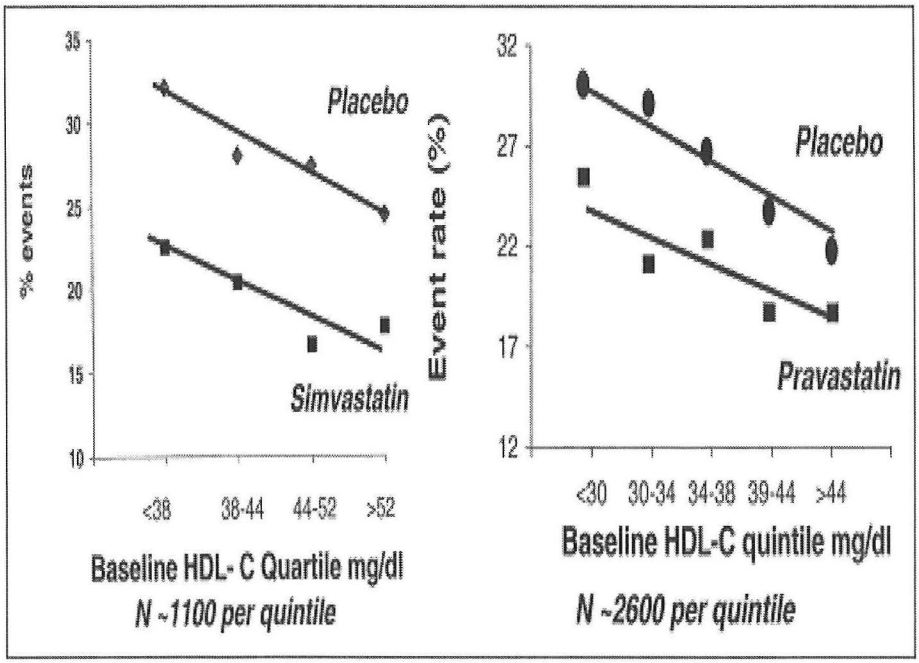

Figure 10 HDL and Coronary Events with Statins

Statins

The HMG-CoA reductase inhibitors (statins) are the most potent drugs for lowering LDL and have the most outcome data, but only raise HDL by 5 – 10 %. It is difficult to determine how much an increase in HDL contributes to the clinical benefits of statins. Although trials have consistently shown that statins reduce coronary events in patients with low HDL, those patients with low HDL taking statins continue to have a greater risk than those with higher HDL's. (fig 10)

Statins increase HDL by decreasing CETP, which transfers cholesterol from HDL to VLDL, and by increasing apo A-1.

The statins may have variable effects on HDL – but with unclear implications. Atorvastatin doesn't increase HDL as much as Simvastatin. A new, potent, just-released statin, Rosuvastatin, is the most potent for LDL lowering and produced a 12 % increase in HDL vs 3% with Atorvastatin[10]. Rosuvastatin may have more favorable effect on LDL, with comparable or better effect on HDL.

The effect of Fibrates and Statins on HDL may be additive, but one must exercise caution due to the increased risk of myopathy with the combination.

One can consider using a statin for low HDL, particularly if there is an indication for a statin to lower LDL or in a high risk patient (Heart Protection Study) or if fit into AFCAPS/TexCAPS or HATS.

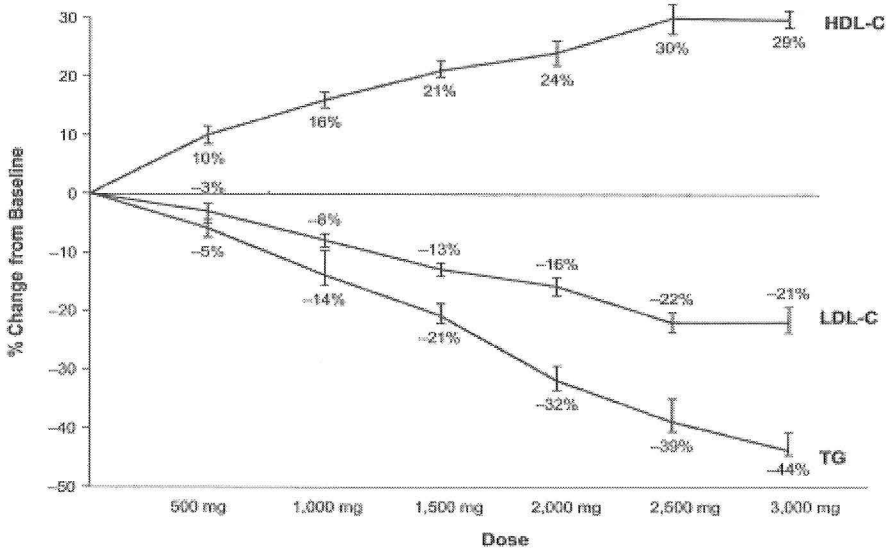

Figure 11 Efficacy of ER Niacin

Niacin

Niacin is the most potent agent for raising HDL, both as monotherapy and in combination, with increases of 15 to 30%. Fortunately, it raises HDL at relatively low doses. The HDL response to Niacin is also dose dependent. (fig 11) The effects of statins and Niacin on HDL are additive.[16]

Importantly, Niacin is effective in raising HDL in patients with isolated low HDL. In a direct comparison, Niacin was more effective than Lopid at raising HDL in patients with low HDL. Niaspan 2000 mg increased HDL 26 % vs 13 % with Lopid 600 mg BID[9]. (fig 12)

The mechanism of Niacin raising HDL is unclear, but is thought to decrease hepatic production of VLDL and increase apo A–I.[16]

Niacin has the advantage of lowering LDL, VLDL, and TG, in addition to raising HDL.[21] Immediate release Niacin is inexpensive, but can be limited by the side effects. Aspirin can be given to block the prostaglandin mediated flushing. The newer sustained release and extended release (Niaspan) Niacins have less side effects and are once daily compared to the older immediate release Niacin, but should be limited to 2 gm/day due to concerns for hepatotoxicity. Immediate release and sustained release Niacin are available over the counter, which makes them more affordable, but less well studied.

Patients with Diabetes and the metabolic syndrome often have a low HDL, as well as elevated TG and small dense LDL, and have high CV risk. Given their high risk and associated low HDL, Diabetics might dramatically benefit from Niacin to help raise their HDL, but concern existed over the potential hyperglycemia with Niacin. However, Grundy et al showed that Niaspan can be used in DM without significant effect on glycemic control. There was no change in HgbA1C using Niaspan 1000 mg in DM, but a small increase from 7.2 to 7.5 % at 16 weeks using Niaspan 1500 mg (p=.048)[27]. Thus, in patients with DM and low HDL with or without elevated LDL or TG, Niacin may be effective as monotherapy or as combination. Glucoses should be monitored for possible worsening glucose control and therapy adjusted accordingly.

Niacin can be considered for low HDL patients with isolated low HDL or combined hyperlipidemia or in combination therapy or if fit into HATS.

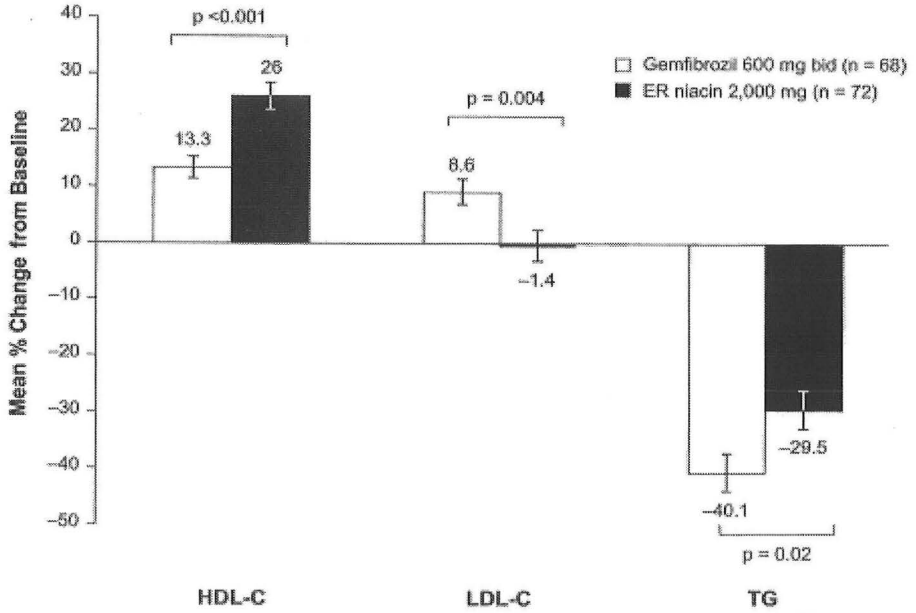

Figure 12 Efficacy of ER Niacin vs Gemfibrozil

Ezetimibe (Zetia)

Zetia is a new agent that blocks cholesterol absorption in the small intestine and is used as a second line therapy for LDL, with 15 to 20% LDL reductions. It can raise HDL 2-3% alone or in combination with statins.

Resin

Resins are second line agents for LDL, but are minimally effective for HDL, raising it 3-5%

Fish Oil

Fish Oil lowers TG, but doesn't raise HDL substantially.

Thiazolidinediones (TZD or Glitazones)

Thiazolidinediones are insulin sensitizers for type 2 DM that also raise HDL from 7 – 13 % in patients with DM.[16] The mechanism is uncertain as well as the contribution of glucose control on the HDL effect. Other insulin sensitizers, like the biguinide Metformin, however, do not raise HDL. Glitazones are agonists of PPAR gamma, a nuclear receptor that regulates adipocyte and carbohydrate metabolism. Consider TZD in DM with poor control and low HDL.

Hormones

Although estrogen raises HDL, it does not improve CV events or survival. So, it can not be recommended for the treatment of low HDL or CVD, and should be used for the treatment of menopausal symptoms.

In addition, anabolic steroids and progestins lower HDL.

More research is needed to define the mechanism by which current drugs raise HDL and newer drugs are needed that are more effective in raising HDL.

Future Targets/Therapies

CETP

The ATP binding cassette transporter-A1 (ABCA1) allows for uptake of cholesterol by HDL, where it undergoes esterification through lecithin cholesterol acyltransferase (LCAT). Cholesterol ester transferase protein (CETP) helps transfer cholesterol from HDL to VLDL and LDL. The LDL cholesterol can then be cleared by the liver or deposited in atherosclerotic plaque. If CETP is inhibited, the transport of cholesterol to VLDL and LDL is inhibited and may possibly reduce VLDL and LDL, while increasing HDL. It is unknown if inhibition of CETP would be anti-atherogenic or pro-atherogenic. For example, patients with mutations in CETP have increased HDL but increased CAD.

CETP inhibition increases HDL and CETP inhibitors are in development to determine their effect on HDL, other lipoproteins, and atherosclerosis[10]. A phase 2 study of a CETP inhibitor decreased CETP activity 37 %, LDL 7% and increased HDL 34 %, without change in TG or TC.

Animal studies have suggested a vaccine to CETP peptide may result in reduced CETP activity, reduced LDL, increased HDL, and reduced atherosclerosis.

PPAR agonists

Peroxisome proliferator activator receptors (PPAR) are involved in glucose metabolism (PPAR gamma) and lipid metabolism (PPAR alpha). PPAR alpha activation is thought to mediate the action of fibrates on HDL by increasing synthesis of HDL apolipoproteins (apo A-1 and A-2) and increasing LPL (lipoprotein lipase).[15] New PPAR agonists may have favorable effects on TG and HDL. Some investigational drugs have both PPAR alpha and gamma agonist action and may therefore improve both glucose and lipid metabolism[10].

Apo A-1

Apo A-1 is the major apolipoprotein of HDL and is involved in reverse cholesterol transport. Upregulation of apo A-1 or administration of apo A-1 may increase reverse cholesterol transport. These potential treatments are in the early phase of development[10].

HDL dynamics

Therapies might be aimed at augmenting reverse cholesterol transport. Potential targets include ABCA-A1, LCAT, and SRB1[10].

If therapies prove successful in enhancing reverse cholesterol transport, this would represent an attractive adjunct to lowering LDL with statins. Reducing cholesterol synthesis with statins, coupled with enhanced return of cholesterol through upregulation of reverse cholesterol transport, would represent complimentary benefits in reducing CAD.

Arguments against using low HDL as a target for therapy

Low HDL is associated with other known risk factors (DM, obesity, inactivity, HTN). So, maybe it's the company HDL keeps, not the low HDL itself. However, the risk has been shown to be independent.

The current drugs to raise HDL aren't specific – their benefit may be multifactorial and not due to their HDL effect. However, the benefit has been shown to be related to the HDL effect.

There are instances where low HDL is not associated with increased risk and high HDL is not protective. However, the antiatherogenic effects of reverse cholesterol transport are better assessed by the flow of cholesterol than the level of HDL.

Lack of trials with low HDL. However, there are trials now available with more data hopefully to come.

Reasons to use low HDL as a risk factor and target for therapy

Inexpensive, Easy to measure, Readily available
Common , Independent risk factor
Reverse cholesterol transport
Treating patients with low HDL improves outcomes

Guidelines

Although the National Cholesterol Education Panel Adult Treatment Panel guidelines (NCEP ATP III) do not set target levels for HDL, they recognize the importance of HDL in risk assessment.[12] ATP III changed the definition of low HDL from < 35 mg/dl to < 40 mg/dl and HDL is used to modify goals of LDL therapy as a risk factor. HDL is also incorporated into the Framingham 10 year risk assessment. After LDL and non HDL goals are reached, drug therapy targeting low HDL "can be considered in high risk patients." However, no targets or goals are set for HDL to help guide therapeutic decisions.

ADA

On the other hand other groups have set specific goals for HDL which makes the strategy confusing. The American Diabetes Association takes an aggressive stance and recommends a goal HDL > 45 for all male diabetics and > 55 for all female diabetics, as well as LDL < 100, TG <150, BP <130/80, and HgbA1C < 7. [11] However, raising HDL to these levels is very difficult in all of your DM patients.

The Expert Group on HDL Cholesterol

The Expert Group on HDL Cholesterol published recommendations in the American Journal of Cardiology in April, 2003[1].

" Ample evidence supports the importance of HDL for CHD risk. Raising HDL should be considered important, as is lowering LDL, to prevent CHD, and increased prominence should be given to HDL as an intervention target."

"1. HDL > 40mg/dl be recommended as a goal for patients with CV disease and those without CV disease but at high risk, and especially those with type 2 DM or features of the metabolic syndrome.

2. Lifestyle changes that include smoking cessation, weight loss, a diet moderate in unsaturated fat rather than low fat, and regular exercise should be encouraged to reach this HDL goal.

3. Consideration be given to fibrate therapy for the previously mentioned patients with low HDL and low risk LDL, defined as below the threshold for LDL lowering drugs. Niacin may also be considered in appropriate patients.
4. These recommendations would apply to patients who do not require statin therapy to reduce LDL, and to those who are being treated with statins in accordance with current guidelines."

Suggestions

Without clear consensus, one must weigh the available evidence and decide for oneself what he/she will recommend for their patients until more standardized guidelines or definitive studies come out. Until then specific goals for HDL are unclear. I would follow NCEP III first and then consider aggressive therapy based on the current literature. The following is my own personal suggestion for your consideration.

Before initiating treatment for low HDL, a search should be made for secondary conditions that depress HDL. Acute illness such as an MI, infection, surgery, etc that results in acute inflammatory response can alter lipid levels. Chronic diseases such as diabetes, hypothyroidism, renal, and obstructive liver disease alter lipid levels. These diseases should be screened for and appropriately treated as well. In addition, drugs like anabolic steroids and progestins can lower HDL. Elevated TG and the metabolic syndrome is a common association with low HDL. Patient's secondary causes should be evaluated and treated and lifestyle maximized. They should be risk stratified and then treated according to their individual risks and benefits as well as their desires.

Secondary Prevention

High risk patients with vascular disease, DM, or Framingham 10 year risk over 20% should be considered for aggressive therapy. If the LDL > 100 mg/dl, a statin should be initiated. Once LDL goal of < 100 mg/dl is reached, if the HDL remains < 30 or 35 or 40 mg/dl, one can consider adding Niacin or a fibrate to the statin. Warnings for myopathy should be given.

If the TG > 400 mg/dl, a fibrate or Niacin should be initiated. Once the TG are reduced, if the HDL remains < 30 or 35 or 40 mg/dl , a second agent should be considered.

If the LDL is initially < 100 mg/dl and HDL < 40 mg/dl, one should consider staring Niacin, with a fibrate and statin as alternatives.

Primary Prevention

The Framingham 10 year risk assessment can help with treatment decisions. Those with risks of 10 – 20 % over 10 years can be treated somewhat similarly to the highest risk patients, using statins if the LDL > goal, fibrates for elevated TG, and otherwise using Niacin.

For those with Framingham risk < 10% in 10 years, other nontraditional risk markers may be helpful. One may consider more aggressive therapy for low HDL if the patient also had an abnormal EBCT, carotid US, hs-CRP, lp(a), homocysteine, small dense LDL etc. The exact utility of these novel risk markers hasn't been clearly established, but has potential use. In addition, the presence of severely low HDL or a single but severe traditional risk factor such as a severe early family history may persuade one towards more aggressive therapy.

Case

65 yo AAF h/o MI with TC 132, TG 100, LDL 80, HDL 32 on a Simvastatin 40 mg as well as diet and exercise. She's concerned about her low HDL and asks you for advice. What do you suggest? What should her HDL goal be?

a. Increase Statin b. Lopid c. Niacin d. Resin e. Zetia f. HRT
a. 35 b. 40 c. 45 d. 50 e. 55

ANSWER: I would answer c. Add Niacin as per HATS. (could consider b. Lopid as per VA HIT) As for her goal, one could answer b. 40 as per Expert Group on HDL, but is clearly controversial. Realize if she were a diabetic, the ADA suggests 55 as her goal.

Conclusions

Low HDL is the most common lipid abnormality in patients with CAD and is predictive of CV events, even with normal TC.

Exercise is the most important lifestyle intervention

Niacin, fibrates, and statins have all been shown to raise HDL and improve outcomes in patients with low HDL. Niacin is the most potent, but is less well tolerated.

No clear consensus exists for HDL goals but I would follow NCEP III and then consider more aggressive treatment of low HDL for individual patients after reach LDL and non HDL goals.

Treatment decisions need to be individualized to the patient's risk for CVD and patient's desires.

Clinical trials show that modest increases in HDL significantly reduce CV events.

Clinical trials show that targeting patients with low HDL improves outcomes.

New insights into HDL metabolism (ABCA1, SRB1) have explained pathologic states, reinforced the role of HDL, and provided new targets for therapy.

Future investigations of HDL will hopefully result in new agents and new indications of existing agents to enhance the vascular protective effects of HDL.

More outcome data focusing on low HDL is needed, but until then the existing epidemiologic and therapeutic data support for more aggressive therapy for low HDL.

Although clinical trials of cholesterol lowering drugs have demonstrated substantial success in reducing CAD morbidity and mortality, current therapy falls far short of curing or preventing atherosclerosis. Niacin and statin combination has proven very effective in improving LDL and HDL and, although in need of confirmation, HATS has suggested a combination may reduce CAD to a point where true prevention is possible. Other drugs in development may increase HDL and enhance cholesterol return from the periphery and be complementary to statins. Future trials will need to determine whether combined use of lipid altering drugs with complimentary action that improve HDL will result in atherosclerotic outcome benefits to a degree that "cure" might be reasonably used.

Even if one was skeptical of the direct effect of low HDL, the studies argue that these patients are at high risk and benefit from medical therapy.

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