

The Lowdown:

Low HDL and Diabetic Dyslipidemia

Patients with diabetes commonly have a low-density lipoprotein cholesterol (LDL-C) no higher than that of the general population. What treatment is warranted to improve their outcome?

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High-density lipoprotein cholesterol (HDL-C) has always been the poor cousin of low-density lipoprotein (LDL) when it comes to outcome data. Currently available medications have a far greater efficacy in decreasing LDL than they do in raising HDL. Hence, it is not surprising that the vast majority of clinical trials which have shaped our practice have focused on LDL lowering. Undeniably, the evidence accrued from these trials has been compelling, but few of them have included individuals with very low HDL levels, and only the most current trials have recruited large numbers of diabetic patients.

How is the diabetic population implicated?

There appears to be some similarity between these patient populations with low HDL-C and those with diabetes, since low HDL confers such a propensity for diabetes that annual screening with a fasting blood glucose is recommended. The 2003 Canadian Practice Guidelines (CPG) for the treatment of dyslipidemia have highlighted recent trials of both statins and fibrates in patients with low HDL-C and/or diabetes, and provide guidance for treating these individuals.

Mr. Cummings' Case

You are giving a post-myocardial infarct discharge to Mr. Cummings, 44, as his two young children play in the corner of the office. He and his wife listen to you intently as you list the respective importance of his new medications. You recall that Mr. Cummings' high-density lipoprotein is 0.68 mmol/L, his low-density lipoprotein is 2.46 mmol/L, and he is now diabetic. He is not yet on lipid-lowering therapy.



What is the best type of lipid therapy to improve the odds of prolonging his life?

For a followup on Mr. Cummings, see page 27.

Diabetes continues to be regarded as an equivalent of coronary artery disease, so adult patients are automatically in the high-risk category. The aim is to achieve an LDL < 2.5 mmol/L, and a total cholesterol (TC)/HDL ratio < 4. Most primary care physicians are relieved that triglycerides (TG) are no longer present as a third treatment goal.

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Table 1

Dosing schedule for niacin therapy

- Week 1: 100 mg three times daily
- Week 2: 250 mg three times daily
- Week 3: 500 mg three times daily
- Week 4: 500 mg in the morning and at noon, then 1,000 mg with evening meal

Should we miss TG?

The United Kingdom Prospective Diabetes Study (UKPDS) trial, which followed over 2,700 diabetic patients for 10 years, observed that TG status had no bearing on cardiac risk. On the other hand, for every 1 mmol/L decrease in LDL, the risk of myocardial infarction (MI) fell by 29%. Moreover, even a tiny (0.1 mmol/L) increase in HDL reduced the risk of MI by 9%.

What is the data on raising HDL therapeutically?

The Veterans Affairs High-density lipid cholesterol Intervention Trial (VA-HIT) randomized 2,531 coronary patients with an LDL < 3.3 mmol/L, and an HDL < 1 mmol/L, to gemfi-

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brozil versus placebo for five years. The most significant results were in the diabetic subgroup, where the rate of coronary heart disease death and MI was reduced by 30%, compared to a 6% reduction in non-diabetics. An unexpected finding was that LDL was completely unchanged by therapy, making this an HDL intervention trial.

A small (but important) trial mentioned in the CPG generated powerful results that attracted attention, even in this era of mega-trials. The HDL-Atherosclerotic Treatment Study (HATS) enrolled only 160 subjects with coronary disease

and a very low HDL of < 0.9 mmol/L. Subjects were randomized to one of the following treatments:

- simvastatin, 20 mg + niacin, 2,000 mg + antioxidants,
- simvastatin, 20 mg + niacin, 2,000 mg, or
- placebo.

The subjects were followed angiographically and clinically over a period of three years. The statin-niacin group demonstrated the most favourable lipid parameters, with an LDL reduction of 42%, and an HDL increase of 26%. It should be noted that the antioxidants seemed to attenuate the increase in HDL, and also impaired angiographic improvements and risk reduction.

In contrast, the results in the simvastatin-niacin group were nothing short of startling, with both angiographic regression of coronary lesions and a 90% reduction in major cardiovascular events. The combination therapy was well tolerated, and was devoid of any deterioration in glycemic control in diabetic subjects.

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What can be said about niacin treatment?

The U.S. now has a slow release form of niacin for once-daily administration, and a combination lovastatin-niacin pill. However, at this time, there is no plan for Canadian release. Actually, Canadian physicians are fairly inexperienced at using niacin, but given the results of the HATS trial, a few pointers might be useful.

The most important rule is to start low and go slow. This minimizes the harmless, but annoying symptoms most individuals notice with a too-rapid dose titration. These symptoms include facial tingling or flushing, and less-common epigastric distress. Acetylsalicylic acid (ASA) will ameliorate the flushing when taken before the niacin.

A simple algorithm for patients is presented in Table 1. If patients tolerate the initial dose, but become symptomatic at the next dose level, they may return to the lower dose and work up more slowly. The goal is long-term risk reduction. Therefore, it is acceptable to take a few months to work up the dose when the trade-off could be a 90% reduction in cardiovascular events.

The Heart Protection Study

The largest lipid lowering trial to date, The Heart Protection Study (HPS) trial, investigated the effect of treating normal LDL levels in a high-risk population (*i.e.*, individuals over 40, with established vascular disease or diabetes, or both). There were 20,000 subjects in the HPS, with a

A followup on Mr. Cummings

Mr. Cummings should be given down-to-earth lifestyle advice. He should also be referred to a cardiac rehabilitative program in order to facilitate his progress. There is a clear need for statin therapy. However, given his very low HDL level, the physician should explain how to incorporate an escalating dose of niacin into his therapy.

LDL and TC/HDL ratio can be achieved simply by increasing the dose of the statin rather than resorting to combination therapy with a fibrate.

high proportion of females and elderly patients.

The trial also included nearly 6,000 diabetic patients randomized to simvastatin, 40 mg, or placebo, with or without antioxidants.

Once again, the antioxidants were found to be ineffective.

However, statin therapy benefited all subgroups, even those with baseline LDL levels < 3.0 mmol/L. Major coronary events and stroke were reduced by 24% at any level of initial LDL. It is enormously reassuring to inform patients who are wary of initiating statin therapy that, in this massive trial, the incidence of alanine aminotransferase (ALT) > 3 times the normal level was 0.04% in the placebo group and 0.09% in the simvastatin group.

As well, the incidence of withdrawal from study medication due to myalgias was 0.05% in both groups.

Do guidelines support statin use?

Because of the HPS, the revised guidelines state that those at high risk should immediately start

Frequently Asked Questions

1. Which is more important: achieving the LDL goal or the target TC/HDL ratio?

Both values need to be achieved. The ratio is particularly useful if the LDL goal is hovering at 2.5 mmol/L, and there is question about intensification of therapy; if the ratio is still not at goal, then the dose should be increased.

2. Do new guidelines mean all my high-risk patients with an LDL at goal on 20 mg of simvastatin need to increase to 40 mg?

Yes. This is presumably because of the pleiotropic effects of simvastatin are better expressed at this dose.


3. What factors should be considered in the younger age group?

Affordability, compliance, and, in females, contraception are all important factors influencing therapy in this age group.

therapy with the equivalent of simvastatin, 40 mg (*i.e.*, atorvastatin, 20 mg, lovastatin, 80 mg, or rosuvastatin, 10 mg daily), regardless of LDL level.

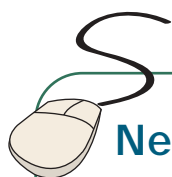
The new guidelines emphasize that the wealth of data supports statin use in diabetic patients and in those with low HDL-C. In most incidences, the LDL and TC/HDL ratio can be achieved simply by increasing the dose of the statin rather than resorting to combination therapy with a fibrate. If dual therapy is necessary, then a safe and effective approach would be a statin-niacin combination. Once the condition is stabilized, appropriate monitoring of the levels of ALT, aspartate aminotransferase, and creatine kinase is required every six months.

Gemfibrozil and statins are a dangerous combination, and their pairing should be avoided completely. It is prudent to remember that all fibrates should be avoided in renal insufficiency.

Surely, lifestyle issues play a part. Patients need to know that smoking cessation will increase HDL by roughly 0.2 mmol/L. Abdominal weight loss, exercise, and improved glycemic control are also very beneficial. 

Suggested Readings

1. Genest J, Frohlich J, Fodor G, et al: Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. *CMAJ* 2003; 169(9):921-4.
2. Rubins HB, Robins SJ, Collins D, et al: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999; 341(6):410-8.
3. Brown BG, Zhao XQ, Chait A, et al: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001; 345(22):1583-92.
4. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomized placebo-controlled trial. *Lancet* 2002; 360(9326):7-22.



Net Readings

1. Canadian Diabetes Association: 2003 Clinical Practice Guidelines
www.diabetes.ca/cpg2003
2. Recommendations for the Management of Dyslipidemia and the Prevention of CVD
www.cmaj.ca/cgi/data/169/9/921/DC1/1