The Lowdown on Dyslipidemias

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What test should I order?

The 2001 Canadian Hypertension Society Recommendations[1] list six tests which should be ordered routinely for a hypertensive patient:

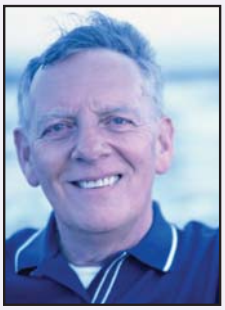
- complete blood count,
- urinalysis,
- biochemistry (including electrolytes and creatinine),
- electrocardiogram,
- a fasting glucose,
- a fasting lipid profile.

Of these tests, the lipid profile is most likely to be "abnormal."

What lipid fraction should I pay most attention to?

Although total cholesterol, triglycerides, the "risk ratio" (total cholesterol/high-density lipoprotein cholesterol [HDL-C]), and low HDL-C are all predictive of future cardiovascular "events," most authorities pay most attention to the low-density lipoprotein cholesterol (LDL-C). Figure 1 shows the relation between the mean LDL concentration and subsequent events. It was published originally by Kastelein,[2] who plotted the mean in-trial LDL concentrations (X axis) versus the rate of cardiovascular events, such as heart attack, stroke, new onset angina. He used the then published trials of primary and secondary prevention, but

John's visit



John, 55, is new to your practice. He consults you for renewal of his antihypertensive prescription.

He is asymptomatic, and his medical history is free of:

- stroke
- heart attack
- angina
- transient ischemic attack
- intermittent claudication

John is uncertain of his blood sugar or lipid profile.

He is a lifetime non-smoker, and has an older brother who recently underwent coronary artery bypass grafting at 59.

John is currently taking Vaseretic® (enalapril) 10/25 tablets once daily. On exam, he looks well, and the following is recorded:

- Blood pressure is 148/88 mmHg
- No clinical left ventricular hypertrophy
- All pulses palpable
- No bruits

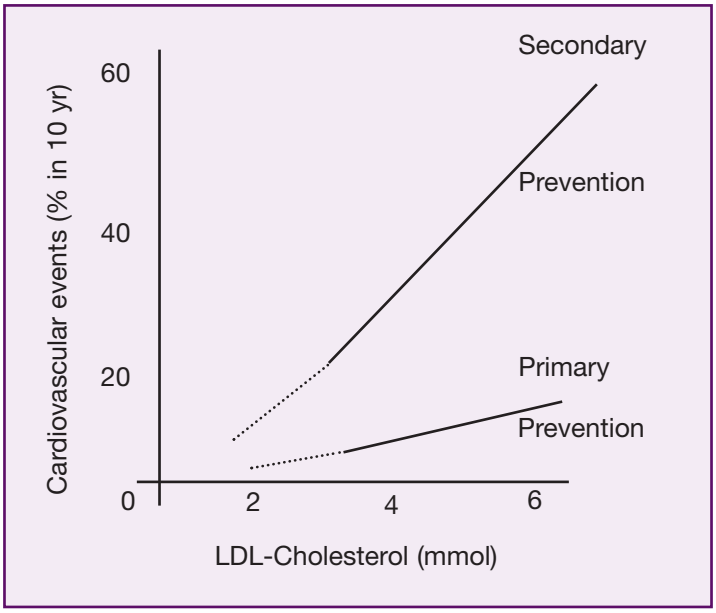


Figure 1. Relation between LDL cholesterol and total cardiovascular events. Adapted from Kastelein JJ: The future of best practice. Atherosclerosis1999; 143(Suppl 1):S17-21.

subsequent trials have supported this concept. There are several conclusions that arise from this figure.

First, both in people with known cardiovascular disease (so called secondary prevention), and without such problems (primary prevention) it is better to have low LDL. We can take this to mean, that for cardiovascular problems, lowering LDL does more good than harm. Next, in patients with known cardiovascular disease, the line is shifted upwards. Such patients are at great risk of further events. We now know that people with diabetes over 30 have a similar increased risk.[3,4] Finally, the slope of the relationship between LDL and events is much steeper in persons with cardiovascular disease. Therefore, the risk/benefit ratio is greater in secondary prevention.

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What LDL is normal?

Laboratories typically report the "reference" range based on sex and age. In our region this is 1.2-3.8 mmol/L for John. A better way of looking at LDL is through the concept of "goals" (Table 1). This sets a different goal LDL for each level of cardiovascular risk. The cardiovascular risk is, in turn, calculated from other known risk factors:

- age and sex,
- total cholesterol,
- HDL-C,
- systolic blood pressure;
- and smoking.

Patients with known cardiovascular disease (including myocardial infarction, angina, ischemic stroke, transient ischemic attack with abnormal carotid ultrasound, and symptomatic peripheral disease), and patients with diabetes

Table 1
Goal low-density lipoprotein

Level of risk	% with events in 10 years	Goal
very high	> 30	< 2.5
high	20-30	< 3.0
moderate	10-20	< 4.0
low	< 10	< 5.0

Adapted from: Fodor JG, Frohlich JJ, Genest JJ Jr, et al: Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. CMAJ 2000; 162(10):1441-7.

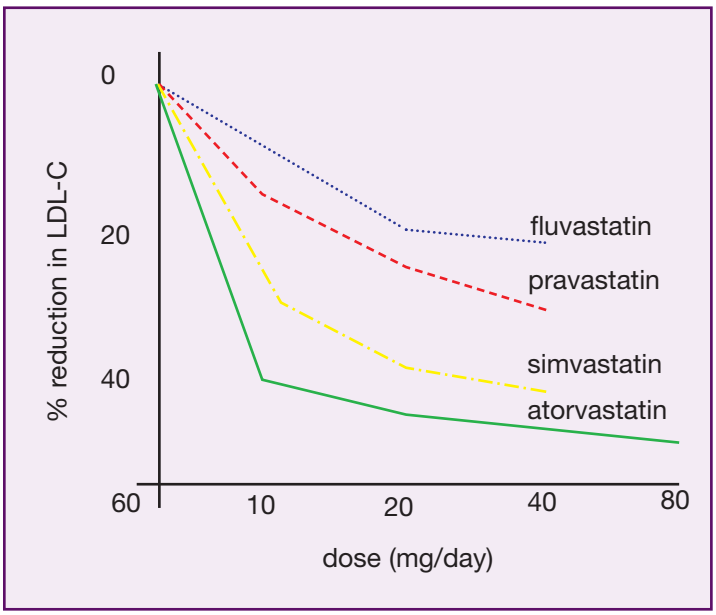

Figure 2. Dose effect curves for LDL lowering for various statins. Adapted from: Jones P, Kafonek S, Laurora I, Hunninghake D. Amer J Cardiol 1998; 81:582-7.

are automatically placed in the very high-risk category. John, our 55-year-old patient with hypertension and a positive family history, should be in the high-risk range. If his LDL cholesterol is greater than goal, he should be treated.

What can I expect from diet and exercise?

Patients whose main lipid abnormality is elevated LDL-C relatively insensitive to dietary changes. In one study of such patients, the American Heart Association Step 2 Diet (for people with known cardiovascular disease) led to only a 5% reduction in LDL.[5] However, diet and exercise changes should not be ignored; in that same iovastatin study, patients randomized to 20 mg plus diet, reduced their LDL by 32% compared to 27% with iovastatin alone. Also, there is considerable interest in the Mediterranean Diet, which, in some hands, leads to much better outcomes compared to a control diet.[6]

Which lipid lowering drug should I prescribe?

The efficacy and adverse effect profile of the HMG CoA reductase inhibitors, commonly called "statins," makes them the drug class of choice (Figure 2).

Low doses of statins lower LDL-C markedly, but increasing the dose pro-

Table 2
Reasons for referral

- Very high cholesterol (> 10.0) or triglycerides (>10)
- Very low HDL cholesterol (< 0.7)
- Hyperlipidemia in the young (< 20 yrs)
- Failure to attain goal LDL despite maximal statin therapy
- Inability to tolerate, or relative contraindication to lipid lowering drugs (*e.g.,* abnormal liver enzymes)
- LDL cholesterol within 10% of goal (for diet and exercise prescription)

HDL: High-density lipoprotein

LDL: Low-density lipoprotein

duces a smaller change. Each time the dose of statin is doubled, LDL-C falls by only 6%. This is the "6% rule." Although uncommon, serious adverse-effects due to statins appear to be dose related. Therefore, start with the lower doses.

How safe are statins?

In general, statins are safe. Serious adverse events reported to the U.S. Food and Drug Administration (FDA), occur at about two per million prescriptions.[7] In the Heart Protection Study, only 0.09% of over 10,000 subjects taking simvastatin 40 mg daily, had persistent elevation of liver enzymes, not statistically different than the 0.04% incidence in placebo treated patients. Moreover, although 33% of subjects randomized to simvastatin complained of myalgia at some time during the five-year trial, so did 33% of placebo treated patients.[8]

What if the patient doesn't reach the LDL goal?

Adding a second drug, either a low-dose resin (*e.g.,* cholestyramine 4 g twice daily) or ezetimibe 10 mg daily, can lead to greater LDL lowering.[9,10] Whether this will translate into improved outcomes is unknown, but it seems likely in view of the concept shown in Figure 1.

Back to John's case

In John's case, complete blood count, electrolytes, creatinine, electrocardiogram and fasting glucose were normal. However:

- total cholesterol was 6.5,
- triglycerides was 2.2,
- HDL-C was 1.0 mmol/L
- LDL-C was 4.5 mmol/L

As he has a positive family history, his goal LDL-C is 3.0. A recently published trial, the ASCOT-LLA, studied such patients.[14] Atorvastatin 10 mg daily reduced LDL-C to 2.32 mmol/L (compared with 3.27 mmol/L in placebo treated patients), and total cardiovascular events and procedures by 21%. The absolute risk reduction was 2% for this endpoint.

John should be offered diet and exercise, and if he does not reach his target LDL-C within 6 months, a statin should be prescribed. His blood pressure is borderline; he may need a third drug. The current enalapril/hydrochlorothiazide combination is acceptable.

What if I can't measure LDL-C?

LDL-C is rarely measured directly, rather it is calculated from the Freidewald formula:
LDL-cholesterol = Total cholesterol–(HDL-C+triglycerides/2.2).

This gives a reasonably reliable estimate of LDL-C unless the triglyceride concentration is greater than 4.5 mmol/L. In such cases, I prefer to start with a fibrate. Although outcome data with fibrates is sparse, the studies which have been done tend to be positive. Fibrates, like statins, do more good than harm, especially in people with diabetes.[11]

What about using more than one lipid lowering agent?

There are virtually no outcome trials comparing combinations of lipid lowering agents with single agents. One study looked at the effect of simvastatin and niacin on cardiovascular events, and found very few events, as well as a low incidence of adverse effects.[12] Unfortunately, that study did not have a simvastatin-only arm. There is concern, particularly with statins and fibrates, of an increase of myositis. Indeed, of the 31 deaths from rhabdomyolysis in patients taking cerivastatin, reported to the FDA, 12 were taking gemfibrozil.[7] Patients taking both a statin and a fibrate should be told to report any severe, unexplained muscle pain or weakness. In this event, a serum creatine-kinase (CK) should be measured, and both drugs stopped if CK is greater than five times the norm.

Should I worry about which antihypertensive drug I prescribe?

In the '80s data were published suggesting that "old" antihypertensive drugs lead to a less-than-expected reduction in coronary artery disease events. An hypothesis to explain this result stated that diuretics and beta adrenergic blockers have an adverse effect on the lipid profile, which in turn abrogated the beneficial effects of blood pressure lowering. The recently published ALLHAT trial does not support this hypothesis.[13] Beta blockers, however, can elevate serum triglycerides by up to 45%, so they are relatively contraindicated in patients whose triglycerides are elevated.

When should I refer?

Follow the referral guidelines (Table 2).

Many centres have dedicated lipid clinics or cardiac risk factor reduction clinics, which offer diet and exercise prescriptions in addition to drug therapy. CME

Take-home message

Points to remember, when dealing with dyslipidemias:

- Treating elevated lipid levels does more good than harm.
- The concept of reserving expensive drugs for those patients at highest risk is driven more by economic than scientific considerations.
- Clinical trails are of short duration compared to the human life span.

Dyslipidemias

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Net Readings

1. Preventative Health Care: www.md-phc.com/education/second.html
2. American Family Physician: www.aafp.org/afp/980501ap/ahmed.html
3. American Heart Association: www.americanheart.org