Commentary

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Evaluation and management of atherogenic dyslipidemia: beyond low-density lipoprotein cholesterol

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The association between plasma level of low-density lipoprotein cholesterol (LDL-C) and the risk of coronary artery disease (CAD) is beyond dispute. As emphasized in the recently updated Canadian guidelines for the management and treatment of dyslipidemia,[1] a variety of major clinical trials over the past decade have reported that lowering LDL-C levels has a clear benefit in reducing the risk of CAD events. Although significant, the risk reduction afforded by pharmacologic lowering of LDL-C has generally been limited to 30%.[2] In addition, prospective studies such as the Quebec Cardiovascular Study[3] have reported marked overlap in the distribution of LDL-C levels at baseline between men who went on to experience CAD and those who remained asymptomatic over the 5-year follow-up period. Thus, additional factors must modulate the risk of CAD associated with LDL-C. As recognized in the guidelines,[1] established risk factors such as type 2 diabetes, older age, high blood pressure and smoking substantially increase the risk of CAD for any given level of LDL-C. Low level of high-density lipoprotein cholesterol (HDL-C), which is included in the Framingham algorithm for predicting multivariate CAD risk, is also a well-recognized risk factor,[4] and there may be others as well.

The Working Group on Hypercholesterolemia and Other Dyslipidemias[1] now considers diabetic patients over the age of 30 to be at very high risk for CAD and suggests that management of lipid level and blood pressure should be high priorities in their care. For nondiabetic people, the Working Group recommends the Framingham algorithm, which considers age, total cholesterol level, HDL-C level, systolic blood pressure and smoking status, for assessment of CAD risk. The guidelines also propose target values for LDL-C, total cholesterol:HDL-C ratio and triglycerides according to the level of risk estimated by the algorithm.

A new aspect of the guidelines was their emphasis on the "metabolic syndrome," a cluster of risk factors including insulin resistance, elevated plasma triglyceride concentrations, low HDL-C levels and presence of small, dense LDL.[1] The importance of the metabolic syndrome in terms of both prevalence and risk of CAD was also recognized in the recently published recommendations of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (also known as the Adult Treatment Panel).[5] Unfortunately, this highly prevalent atherogenic condition is not currently considered in the Framingham algorithm. To illustrate the potential impact of the metabolic syndrome, we can review the example of a 53-year-old nonsmoking, nondiabetic male who is abdominally obese (waist circumference 101 cm), hypertriglyceridemic (triglyceride level 2.4 mmol/L) and normotensive (blood pressure 124/76 mm Hg). According to the Framingham algorithm, his age counts for 3 risk points. His HDL-C level is low (0.70 mmol/L), which counts for 2 risk points, his total cholesterol level is 5.1 mmol/L, which counts for zero points, and his systolic blood pressure counts for zero points. The total is therefore 5 risk points, which translates to a 10-year risk of only 8%, well below the 14% average risk reported for this age category.[4] On the basis of the risk determined by the Framingham algorithm, the recommended target levels for this patient would be as follows: LDL-C below 5.0 mmol/L, total cholesterol:HDL-C ratio below 7.0 and triglyceride below 3.0 mmol/L. However, the risk of CAD may actually be much higher for this abdominally obese man, who has the features of the metabolic syndrome.

We have shown that asymptomatic men with elevated waist circumference and moderate hypertriglyceridemia[6] are characterized by an atherogenic triad of metabolic abnormalities (hyperinsulinemia, elevation of apolipoprotein B and small, dense LDL particles) that substantially increases their risk for CAD, even in the absence of elevated cholesterol, elevated LDL-C and other traditional risk factors.[7] Because of low HDL-C levels, the total cholesterol:HDL-C ratio of these abdominally obese, insulin-resistant men is often elevated to 7 or more. Data from the Quebec Cardiovascular Study[8] indicate that elevation of the ratio to this level may be associated with an increased risk of CAD, even in the absence of elevated LDL-C levels. When the men in the Quebec Cardiovascular Study were stratified into tertiles according to baseline total cholesterol:HDL-C ratio and were further classified on the basis of median LDL-C level, there was a clear relation between total cholesterol:HDL-C ratio and risk of CAD, irrespective of LDL-C level (Table 1). Indeed, despite a highly significant difference in LDL-C (more than 1.0 mmol/L) between men below and those at or above the median LDL-C level, there was no significant difference in risk of CAD between these 2 groups, for any category of total cholesterol:HDL-C ratio (Table 1). Thus, because our 53-year-old man with abdominal obesity had the fea-

tures of the metabolic syndrome (hyperinsulinemia, elevated apolipoprotein B concentrations and small, dense LDL), we could predict from this cluster a substantially increased risk of CAD despite an apparently low risk estimated from the Framingham algorithm. Futhermore, had the total cholesterol:HDL-C ratio (7.3) alone been considered, we would have predicted at least a 2.4-fold increase in the patient's risk of CAD (Table 1).

These results further emphasize the importance of calculating the total cholesterol:HDL-C ratio and making it a therapeutic target.[1] However, they also remind us that, irrespective of whether LDL-C level is elevated, a high total cholesterol:HDL-C ratio indicates higher risk of CAD. Elevation of the total cholesterol:HDL-C ratio in the absence of marked elevation of LDL-C level is a salient feature of insulin-resistant, abdominally obese patients, as well as of type 2 diabetic patients, most of whom are abdominally obese.[6] Among men in the top tertile for total cholesterol:HDL-C ratio (ratio at least 6.4), there was a high prevalence of the metabolic syndrome (almost 40%), but there was no difference in the prevalence of this syndrome between subjects with low and high LDL-C levels (Table 2). Furthermore, the group with elevated total cholesterol:HDL-C ratio but low LDL-C level had a higher prevalence of obesity (defined as body mass index of at least 30) than those with elevation of both total cholesterol:HDL-C ratio and LDL-C levels (26.2% v. 13.5%). Thus, elevation of the total cholesterol:HDL-C ratio is often accompanied by an underlying metabolic syndrome resulting from obesity, a condition that may not be associated with elevated LDL-C level. We acknowledge that pharmacotherapy aimed at lowering LDL-C is legitimate; however, given that the risk of CAD associated with elevation of the total cholesterol:HDL-C ratio does not vary substantially with LDL-C level, we propose that more attention should be paid to the management of the causal factor responsible for atherogenic dyslipidemia in these patients: abdominal obesity. Therefore, we recommend that waist circumference, the best and simplest correlate of abdominal obesity,[6] be measured and recorded for these patients. Furthermore, given that the Veterans Affairs High Density Lipoprotein Intervention Trial[9] has reported the benefits of therapy to increase HDL-C among diabetic and abdominally obese hyperinsulinemic patients, strong efforts should be made to reduce waist girth and increase HDL-C levels in these high-risk "normocholesterolemic" patients. Reducing body weight by reducing the caloric density of foods consumed (i.e., less fat and refined sugar) and increasing energy expenditure through a more active lifestyle thus appear to be legitimate objectives for better management of propensity for CAD in high-risk patients with the metabolic syndrome.

Table 2: Prevalence of metabolic syndrome* and obesity†

Tertiles for total cholesterol:HDL-C ratio‡	n	Condition; prevalence, %	
		Metabolic syndrome	Obesity
First tertile (ratio < 5.0)			
LDL-C < 3.9	549	0.7	9.7
LDL-C ≥ 3.9	149	3.0	3.7
Second tertile (ratio 5.0–6.4)			
LDL-C < 3.9	327	12.0	17.4
LDL-C ≥ 3.9	378	18.9	9.9
Third tertile (ratio ≥ 6.4)			
LDL-C < 3.9	176	38.0	26.2
LDL-C ≥ 3.9	524	38.2	13.5

*Metabolic syndrome defined by atherogenic metabolic triad of hyperinsulinemia, elevated level of apolipoprotein B and high level of small, dense LDL particles.
†Obesity defined as body mass index of at least 30.
‡Each tertile is subdivided according to LDL-C level (less than 50th percentile and greater than or equal to the 50th percentile). The LDL-C level for the 50th percentile was 3.9 mmol/L.

Table 1: Relative risk of coronary artery disease (CAD) in 2103 middle-aged men initially asymptomatic for this condition in the Quebec Cardiovascular Study

Tertile for ratio of total cholesterol:HDL-C*	n	Mean LDL-C (and SD), mmol/L	RR† (and 95% CI)		p‡
First tertile (ratio < 5.0)					
LDL-C < 3.9 mmol/L (reference)	549	3.01 (0.53)	1.0		
LDL-C ≥ 3.9 mmol/L	149	4.34 (0.39)	1.5	0.53–4.34	0.44
Second tertile (ratio 5.0–6.4)					
LDL-C < 3.9 mmol/L	327	3.30 (0.44)	1.9	0.93–4.00	0.08
LDL-C ≥ 3.9 mmol/L	378	4.47 (0.48)	2.2	1.06–4.37	< 0.05
Third tertile (ratio ≥ 6.4)					
LDL-C < 3.9 mmol/L	176	3.30 (0.43)	2.4	1.09–5.33	< 0.05
LDL-C ≥ 3.9 mmol/L	524	4.80 (0.66)	3.6	1.93–6.76	< 0.001

Note: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SD = standard deviation, RR = relative risk, CI = confidence interval.
*Each tertile is subdivided according to LDL-C level (less than the 50th percentile and greater than or equal to the 50th percentile; the LDL-C level for the 50th percentile was 3.9 mmol/L). Within each tertile, there was no significant difference between the 2 LDL-C groups, as indicated by the substantial overlap in 95% CIs.
†Adjusted for diabetes, systolic blood pressure, medication use at baseline, family history of CAD and smoking habits.
‡For comparison with reference group.

Finally, the pharmacologic agents that are available to induce significant weight loss[10,11] have been tested primarily in women at low risk of CAD.[12] Despite the increasing recognition of abdominal obesity as the most prevalent cause of the atherogenic metabolic syndrome, randomized trials are urgently needed to verify whether pharmacotherapy targeted to abdominal obesity is effective in preventing CAD events and related deaths.

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References

1. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 2000; 162:1441-7. Available: www.cma.ca/cmaj/vol-162/issue-10/1441.htm
2. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary heart disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282:2340-6.
3. Després JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B. HDL-cholesterol as a marker of coronary heart disease risk: the Québec cardiovascular study. *Atherosclerosis* 2000;153:263-72.
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
5. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
6. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Alméras N, et al. Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia, hyperapolipoprotein B, small, dense LDL) in men? *Circulation* 2000;102:179-84.
7. Lamarche B, Tchernof A, Mauriège P, Cantin B, Dagenais GR, Lupien PJ, et al. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease. *JAMA* 1998;279:1955-61.
8. Lemieux I, Lamarche B, Couillard C, Pascot A, Cantin B, Dagenais GR, et al. Cholesterol/HDL cholesterol ratio vs. LDL cholesterol/HDL cholesterol ratios as indices of IHD risk in men: the Quebec Cardiovascular Study. *Arch Intern Med*. In press.
9. Robins S, Collins D, Rubins HB. Diabetes, hyperinsulinemia and recurrent coronary events in the VA-High Density Lipoprotein Intervention Trial (VA-HIT) [abstract]. *Circulation* 2000;102:II-847.
10. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. *Lancet* 1998;352:167-72.
11. James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet* 2000;356:2119-25.
12. Després JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 2001;322:716-22

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