

Northern Light: A Commentary on the 2009 Canadian Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in Adults

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Coronary heart disease (CHD)² remains a leading cause of death and disability in both Canada and the US. Major established independent risk factors for CHD include increased age, male sex, hypertension, smoking, diabetes, increased total cholesterol [>240 mg/dL (6.2 mmol/L)] associated with increased LDL cholesterol [>160 mg/dL (4.2 mmol/L)], and decreased HDL cholesterol [<40 mg/dL (1.0 mmol/L)] (1). Based on the long-term follow-up of participants in the Framingham Heart Study, point systems have been developed allowing for the calculation of the 10-year risk of CHD (2). Studies by Ridker et al. (3), as well as other investigators, have documented that family history of premature CHD and increased high-sensitivity C-reactive protein (hsCRP) are also independent CHD risk factors, and a modified point system known as the Reynolds Risk Score has been developed that includes these factors for calculating 10-year risk of CHD (3). The recently released third iteration of the Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease includes both of these CHD risk prediction systems in their guidelines, and in part incorporates family history of premature heart disease (age <60 years in a first-degree relative) and increased hsCRP (>2 mg/L) (4).

Alterations in plasma lipid and lipoproteins have long been known to affect CHD risk based on experience in various animal models fed atherogenic diets and clinical observations in patients with familial hy-

percholesterolemia. Epidemiologic studies such as the Seven Countries Study and the Framingham Heart Study have supported these observations. Human dietary intervention studies in the 1960s and 1970s, in which animal fat was replaced with vegetable oils, showed that CHD risk could be reduced with dietary change. The beneficial effects of niacin in the Coronary Drug Project reported in 1975 further supported the concept that lipid modification could be beneficial for CHD risk reduction. It was not until 1985, after the completion of the 1984 Lipid Research Clinics Coronary Primary Prevention Trial with cholestyramine, however, that a consensus panel at the NIH concluded that an increased LDL cholesterol was a strong independent risk factor for CHD, and that lowering LDL cholesterol would reduce CHD risk. This conference led to the convening of the first Adult Treatment Panel of the National Cholesterol Education Program of the NIH and the release of the first guidelines for LDL cholesterol lowering in 1988, the same year that lovastatin came on the market in the US. Since that time, there have been 3 formal iterations of the Adult Treatment Panel guidelines for the treatment of hypercholesterolemia in the US, the most recent being in 2001 (1). In 2004, some members of the panel recommended an optional, even more aggressive, LDL cholesterol treatment target of <70 mg/dL (1.8 mmol/L) for those with CHD or at very high risk for CHD.

Beginning in 1994, with the release of the findings of the Scandinavian Simvastatin Survival Study, it became evident that statins could significantly lower the risk of CHD morbidity and mortality in hypercholesterolemic men and women with heart disease. The following year, the West of Scotland Study documented that statin treatment was also beneficial in lowering CHD risk in hypercholesterolemic men without CHD. This was followed by the CARE (Cholesterol and Recurrent Events) and LIPID (Long Term Intervention with Pravastatin in Ischaemic Disease) trials showing benefits from statin therapy in CHD patients with normal LDL cholesterol levels at baseline, as well as AFCAPS/TEXCAPS (Air Force Coronary Artery Prevention Study/Texas Coronary Artery Prevention Study)

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Received December 22, 2009; accepted February 2, 2010.

Previously published online at DOI: 10.1373/clinchem.2009.139196

² Nonstandard abbreviations: CHD, coronary heart disease; hsCRP, high-sensitivity C-reactive protein; CARE, Cholesterol and Recurrent Events; LIPID, Long Term Intervention with Pravastatin in Ischaemic Disease; AFCAPS/TEXCAPS, Air Force Coronary Artery Prevention Study/Texas Coronary Artery Prevention Study; TNT, Treating to New Targets; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Trial; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin.

documenting benefit from statin therapy in men and women without CHD, relatively normal LDL cholesterol levels, and low HDL cholesterol values. In both CARE and AFCAPS/TEXCAPS, it was documented that hsCRP concentrations affected on-trial CHD risk. The large Heart Protection Study released in 2002 further supported the concept that statin therapy was beneficial in all patients regardless of baseline LDL cholesterol. In these and many other statin intervention studies, however, it was documented that residual risk remained despite statin therapy, especially in those with low HDL cholesterol levels as observed in the TNT (Treating to New Targets) trial and those with increased hsCRP concentrations as observed in CARE, AFCAPS/TEXCAPS, and patients with acute coronary syndrome in PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Trial).

Probably the last large placebo-controlled statin intervention trial to ever be done was the recently completed JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) (5). Those who completed the study comprised 17 802 individuals selected for no CHD, LDL cholesterol <130 mg/dL (3.4 mmol/L), and hsCRP >2.0 mg/L. Participants were randomized to placebo or rosuvastatin at a dose of 20 mg/day. The rosuvastatin treatment group had a 44% reduction in the primary endpoint (myocardial infarction, stroke, revascularization, hospitalization for unstable angina, or death from CHD). The primary endpoint risk for CHD was lowered by 55% if an LDL cholesterol of <70 mg/dL was achieved, by 62% if a hsCRP of <2.0 mg/L was achieved, by 65% if both these goals were achieved, and by 79% if an LDL cholesterol of <70 mg/dL and a hsCRP of <1.0 mg/L were both achieved (5).

The recently released Canadian guidelines have incorporated some of these findings (4). This panel recommended that plasma lipids (total cholesterol, triglycerides, HDL cholesterol, calculated LDL cholesterol) be measured in men 40 years or older, and in postmenopausal women or those 50 years or older. They also recommended that a lipid profile be done in patients of any age if they had diabetes, hypertension, cigarette smoking, obesity, family history of premature CHD (<60 years in a first degree relative), an inflammatory disease, chronic renal failure, any evidence of atherosclerosis, infection with human immunodeficiency virus, xanthomas, xanthelasmas, premature arcus, or erectile dysfunction. They recommended lipid screening in children with a family history of lipid abnormalities.

For patients with CHD, peripheral vascular disease, any evidence of atherosclerosis, most diabetic patients, and those with Framingham 10-year CHD risk of >20% or a Reynolds CHD risk of >20%, an LDL cholesterol target of <2 mmol/L (80 mg/dL) or greater than a 50% reduction in LDL cholesterol from baseline

is recommended. An alternate target of an apolipoprotein B concentration of <80 mg/dL was also listed. In the moderate CHD risk category of 10%–20% based on the Framingham score, the panel recommended the same LDL cholesterol and apolipoprotein B targets as for the high-risk category; however, therapy should be initiated only if 1 of the following are present: LDL cholesterol >3.5 mmol/L (130 mg/dL), total cholesterol/HDL cholesterol ratio >5.0, hsCRP concentration >2.0 mg/L in a man >50 years of age or a woman >60 years, or the use of the Reynolds Risk Score resulted in risk reclassification into the high-risk category. The panel recommended no clear goal in the <10% CHD risk category based on the Framingham score, but they did recommend initiating therapy if baseline LDL cholesterol was ≥ 5.0 mmol/L (190 mg/dL), with a goal of 50% or more LDL cholesterol lowering (4).

The authors contend that their guidelines are simple and easy to follow. However, I found these guidelines to be somewhat inconsistent. Why jump back and forth between the Framingham risk assessment and the Reynolds score? Why not just use the Reynolds Risk score if family history and hsCRP values are available, and use the Framingham score if they are not available? Also, if one accepts the premise that hsCRP is an important risk factor, why not accept the intervention trial data from JUPITER and other studies and try to optimize not only LDL cholesterol, but also hsCRP values? The other issue is simplicity and whether doctors will use risk scoring systems to calculate 10-year risk of CHD. Studies indicate that compliance with this part of the US guidelines is very poor. Guidelines are undergoing revisions all the time. The next iteration of the United Guidelines will be released in 2010, will probably use the risk assessment program from Framingham (4), and will probably focus on LDL cholesterol targets of <70 mg/dL (1.8 mmol/L) in CHD patients and high-risk individuals. Hopefully, they will make some effort to incorporate family history of premature CHD and hsCRP as the Canadians have done. It will not be until the completion of combination trials using statin plus niacin analogs and statin plus cholesteryl ester transfer protein inhibitors vs statin alone by 2012–2014 that we will have a better idea as to how to treat 2 other independent CHD risk factors: low HDL cholesterol and increased lipoprotein or Lp(a). Ultimately, physicians and patients together have to make their own decisions as to management. At this point, it does appear that doctors would be well advised to optimize all the risk factors for CHD in their high-risk or CHD patients, focusing not just on LDL cholesterol, but also on hsCRP, HDL cholesterol, and Lp(a).

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 re-

quirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: E. Schaefer, AstraZeneca.

Stock Ownership: None declared.

Honoraria: E. Schaefer, AstraZeneca.

Research Funding: None declared.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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