



Ask the Experts: Unresolved Issues and Controversies in the Management of Dyslipidemia for Primary Prevention of Cardiovascular Disease

A continuing education activity entitled *Examining the Benefits of Cardiovascular Risk Reduction in Primary Prevention: Focus on Dyslipidemia* was presented as one of four CE in the Mornings topics at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada. The program was presented by Joseph Saseen, Pharm.D., FCCP, BCPS, Professor, University of Colorado Schools of Pharmacy and Medicine, Aurora, Colorado. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Saseen in a live webinar conducted on February 2, 2010. The highlights of this webinar are described in this and another e-newsletter to be released in April 2010.

Faculty

Joseph Saseen, Pharm.D., FCCP, FNLA, BCPS, CLS
Professor
University of Colorado Denver
Schools of Pharmacy and Medicine
Aurora, Colorado

High-Sensitivity C-Reactive Protein

Risk for cardiovascular disease has long been determined using the Framingham risk score, which provides an estimate of the 10-year risk for "hard" coronary heart disease (i.e., myocardial infarction or coronary death).¹ Multiple versions of this tool have been developed, but the most commonly used version is useful only for patients with at least two major risk factors for coronary heart disease (CHD), which include advanced age (≥ 45 years men or ≥ 55 years women), hypertension, cigarette smoking, family history of premature CHD, and HDL-cholesterol < 40 mg/dL. The Framingham risk score is not useful for patients with atherosclerotic vascular disease or diabetes despite the fact that these patients are at high risk for CHD.

The Reynolds risk score is a newer tool that provides an estimate of the 10-year risk of coronary heart disease (CHD) and stroke and may be a better reflection of cardiovascular risk than the Framingham risk score.^{2,3} In contrast to the Framingham risk score, the Reynolds risk score takes into consideration high-sensitivity C-reactive protein (hsCRP), which is an emerging risk factor for cardiovascular disease (Table 1). High-sensitivity C-reactive protein is thought to play an important role in inflammation and atherosclerosis (Figure 1).⁶ This protein localizes in the intima (i.e., inner lining) of atherosclerotic vessels where it attenuates nitric oxide production, blunts endothelial reactivity, and triggers low-density lipoprotein (LDL) oxidation and other steps in atherogenesis. The protein hsCRP does not accumulate in the intima of normal

Table 1. Established and Emerging Risk Factors for Cardiovascular Disease^{4,5}

Established (Major) Risk Factors

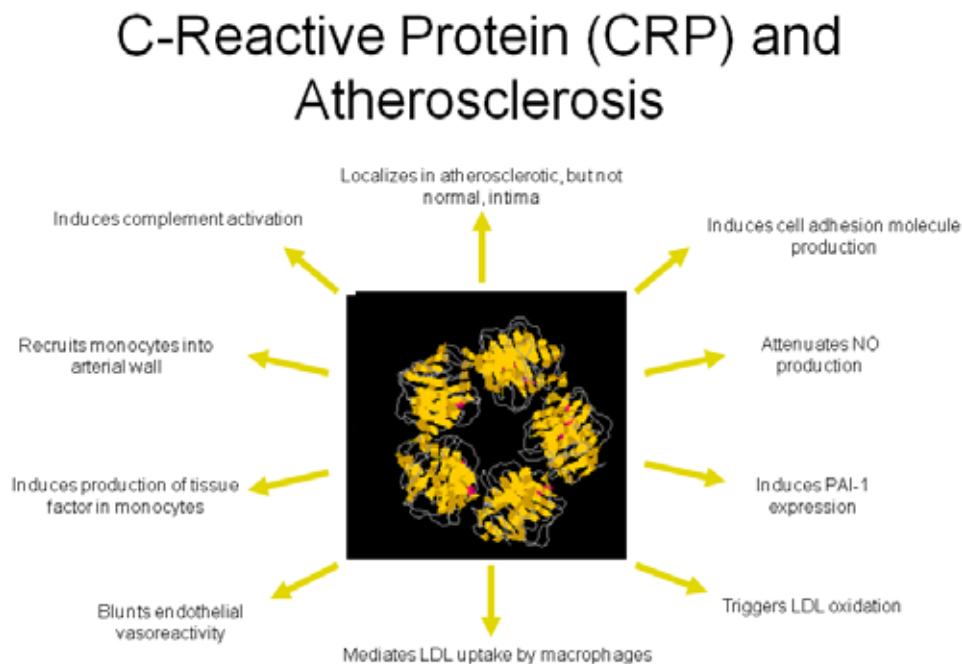
- Age (≥45 yr in men, ≥55 yr in women)
- Hypertension
- Cigarette smoking
- Low HDL cholesterol
- Family history of premature CHD

Emerging Risk Factors

- C-reactive protein
- Coronary artery calcium
- Lipoprotein(a) level
- Homocysteine level
- Leukocyte count
- Fasting blood glucose level
- Periodontal disease
- Ankle-brachial index
- Carotid intima-media thickness

CHD = coronary heart disease; HDL = high-density lipoprotein

Figure 1. C-Reactive Protein and Atherosclerosis



NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1.
 Verma S et al. *Circulation*. 2002; 106:913-9.

vessels.

In a 2003 statement, the Centers for Disease Control and Prevention and the American Heart Association described the considerations in selecting an analyte (constituent of blood or other body fluid that can be measured) for use as a marker of inflammation that predicts cardiovascular risk.⁷ In this statement, hsCRP is identified as the analyte of choice to associate inflammation with cardiovascular risk. The level of cardiovascular risk correlates with measured hsCRP levels (Table 2). In a recently published (2010) meta-analysis of 160,309 people without vascular disease from 54 long-term prospective studies, elevated CRP was continuously associated with the risk of CHD, ischemic stroke, vascular death, and non-vascular death.⁸ Various diseases, medications, and other factors can affect hsCRP levels (Table 3) and should be taken into consideration in interpreting measurements to predict cardiovascular risk. Many of these factors are unrelated to atherogenesis.

The usefulness of statin therapy (rosuvastatin 20 mg/day) for primary prevention of cardiovas-

**Table 2.
Cardiovascular Risk
Based on High-Sensitivity
C-Reactive Protein
Measurement⁷**

- Low risk: < 1 mg/L
- Average risk: 1 to 3 mg/L
- High risk: > 3 mg/L

**Table 3. Considerations in Interpreting
hsCRP Measurements^{7,9}**

Factors that can increase hsCRP levels

- Chronic infection
- Chronic inflammation
- Cigarette smoking
- Hypertension
- Obesity
- Metabolic syndrome
- Diabetes mellitus
- Low HDL or high TG levels
- Estrogen therapy

Factors that can decrease hsCRP levels

- Weight loss
- Smoking cessation
- Consistent exercise
- Moderate alcohol intake
- Aspirin
- Statins
- Fibrates
- Niacin
- Selective estrogen-receptor modulators
- Thiazolidinediones

HDL = high-density lipoprotein;
hsCRP = high-sensitivity C-reactive protein;
TG = triglycerides

cular events was evaluated in the JUPITER study of 17,802 patients who were at risk for CHD because of advanced age (≥ 50 years for men and ≥ 60 years for women) and elevated hsCRP levels (≥ 2 mg/L) but not substantial hypercholesterolemia (LDL cholesterol < 130 mg/dL).^{10,11} The primary endpoint was a composite of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The study was planned for 3.5 years, but it was stopped prematurely after a median follow-up time of 1.9 years because statin therapy was associated with a significant 44% reduction in the incidence of the primary endpoint compared with placebo. The median LDL cholesterol concentration after 12 months was significantly lower in the statin group than in the placebo group (55 mg/dL versus 110 mg/dL, respectively). One in four patients receiving statin therapy achieved an LDL cholesterol less than 44 mg/dL. These findings demonstrate the potential cardiovascular benefit from lipid-lowering therapy in patients with elevated hsCRP levels, even if hypercholesterolemia is not present.

Although hsCRP is now accepted as a cardiovascular risk marker in patients without cardiovascular disease, the best way to use the information provided by measurements to reduce cardiovascular risk is unclear. Reducing elevated hsCRP levels might eventually be a dual or secondary treatment goal in patients with atherosclerotic vascular disease, after or along with achieving LDL cholesterol goal values. However, this practice currently is not advocated as a standard of care, and the best use of hsCRP appears to be as an additional risk marker in primary prevention patients. The precise hsCRP level beyond which cardiovascular risk increases is unknown. The use of the hsCRP level as a basis for treatment decisions has not yet been incorporated into dyslipidemia treatment guidelines. Additional research is needed to clarify these unresolved issues.

Diabetes Mellitus

Dyslipidemia is one of several cardiometabolic risk factors that often occur in clusters.¹² Other cardiometabolic risk factors include insulin resistance, hyperglycemia, obesity (particularly central adiposity), and hypertension.

The optimal management of dyslipidemia for primary prevention of cardiovascular events in patients with diabetes mellitus is the subject of debate. In a 2008 consensus statement, the American Diabetes Association and the American College of Cardiology Foundation recommended lipoprotein treatment goals for patients with dyslipidemia, including patients with diabetes, based on cardiometabolic risk (Table 4). These goals are particularly aggressive for patients at the highest cardiometabolic risk, which include primary prevention patients with diabetes and at least one major cardiovascular risk factor. The treatment of dyslipidemia in primary prevention patients with diabetes has been addressed in evidence-based guidelines in the past, but the 2008 recommendations are more aggressive than ever before.

Dyslipidemia in patients with diabetes is characterized by small, dense LDL particles that are atherogenic. Concentrations of LDL cholesterol are not necessarily elevated. Many patients with diabetes have mixed dyslipidemia, with low high-density lipoprotein (HDL) cholesterol, high triglycerides, or both.

The Heart Protection Study demonstrated that statin therapy is beneficial in reducing vascular events in patients with or without diabetes.¹³ In the Collaborative Atorvastatin Diabetes Study (a landmark study known as CARDS), 2838 men and women 40-75 years of age with diabetes, a baseline LDL cholesterol < 160 mg/dL (i.e., a level that is not elevated), and at least one cardiovascular risk factor (e.g., hypertension, cigarette smoking) but no history of cardiovascular disease (i.e., primary prevention patients) were randomly assigned to receive atorvastatin 10 mg or placebo once daily.¹⁴ The primary endpoint was the

time to first occurrence of acute CHD events, coronary revascularization, or stroke. The study was planned to last for approximately 6 years, but it was stopped early after a median of 3.9 years because the incidence of the primary endpoint was 37% lower in patients receiving atorvastatin than in patients receiving placebo, a difference that is significant. The mean LDL cholesterol at the time of study termination was significantly lower in the atorvastatin treatment group (82 mg/dL) than in the placebo group (121 mg/dL). The CARDS findings demonstrate the cardiovascular benefit from statin therapy to reduce LDL cholesterol in patients with diabetes, even if their LDL cholesterol is not particularly high. Future research will help clarify the uncertainty that remains about the optimal approach to managing dyslipidemia in patients with diabetes and other patients at high cardiometabolic risk, including how low the goal concentration of LDL cholesterol and other lipoproteins should be.

Table 4. Lipoprotein Treatment Goals in Patients with Dyslipidemia Based on Cardiometabolic Risk¹²			
Level of Risk and Examples of Types of Patients	Goal Value (mg/dL)		
	LDL-C	Non-HDL-C	ApoB
<i>Highest Risk</i>			
1. Known CVD 2. DM with ≥ 1 major CVD risk factor ^a	< 70	< 100	< 80
<i>High Risk</i>			
1. No known CVD or DM but at least 2 major CVD risk factors ^a 2. DM with no major CVD risk factors ^a	< 100	< 130	< 90
ApoB = apolipoprotein B; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol			
^a Other major CVD risk factors (beyond dyslipidemia) include cigarette smoking, hypertension, and family history of premature coronary artery disease.			

Planned and coordinated by ASHP Advantage.
Supported by an educational grant from Merck



References

1. National Cholesterol Education Program. Estimate of 10-year risk for coronary heart disease: Framingham point scores. http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm (2010 Jan 16).
2. Reynolds risk score: calculating heart and stroke risk for women and men. <http://www.reynoldsriskscore.org/> (2010 Jan 15).
3. Ridker PM, Buring JE, Rifai N et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007; 297:611-9.
4. Grundy SM, Cleeman JI, Merz CN et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004; 110:227-39.
5. Helfand M, Buckley DI, Freeman M et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009; 151:496-507.
6. Verma S, Wang CH, Li SH et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation*. 2002; 106:913-9.
7. Pearson TA, Mensah GA, Alexander RW et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003; 107:499-511.
8. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010; 375:132-40.
9. Backes JM, Howard PA, Moriarty PM. Role of C-reactive protein in cardiovascular disease. *Ann Pharmacother*. 2004; 38:110-8.
10. O'Riordan M. JUPITER halted: rosuvastatin significantly reduces cardiovascular morbidity and mortality. March 31, 2008. <http://www.theheart.org/article/852735.do>.
11. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359:2195-207.

12. Brunzell JD, Davidson M, Furberg CD et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008; 31:811-22.
13. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002; 360:7-22.
14. Colhoun HM, Betteridge DJ, Durrington PN et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004; 364:685-96.