Starting Primary Prevention Earlier With Statins

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The 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was based on a systematic review of randomized trials with atherosclerotic cardiovascular disease (ASCVD) outcomes and meta-analyses of these trials published through 2011. With evidence of an ASCVD risk reduction benefit greatly outweighing the potential for adverse effects, the guideline recommends statin therapy for primary prevention in those with ≥7.5% 10-year ASCVD risk and consideration of statin therapy in those with 5% to <7.5% 10-year ASCVD risk. Subsequent meta-analyses of the statin trials support these recommendations and have additionally found a reduction in total mortality in lower-risk subjects. Additional evidence from imaging trials and epidemiologic studies suggests that initiation of statin therapy earlier in the course of ASCVD could have the potential to more effectively prevent age-related progression of atherosclerosis. Given the high levels of suboptimal risk factors in adults and the safety and availability of low-cost generic statins, a consideration of all the available evidence strongly supports earlier intervention for the primary prevention of ASCVD. In conclusion, earlier initiation of statin therapy has the potential to have a large long-term impact on the heavy burden of cardiovascular disease in the aging populations. **(Am J Cardiol 2014;114:1437−1442)**

Despite tremendous advances in prevention and treatment, atherosclerotic cardiovascular diseases (ASCVDs) remain leading causes of death, morbidity, and health care costs in the United States.[1] Concerns regarding the benefit, cost, and safety have limited primary prevention recommendations for statins in lower-risk subjects. Recently, however, after a rigorous systematic review of evidence from randomized, controlled ASCVD outcomes trials, the new American College of Cardiology/American Heart Association (ACC/AHA) 2013 Guideline for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease in Adults recommended initiation of statin therapy for primary prevention in lower-risk healthy adults.[2] Based on the same evidence reviewed for the 2013 ACC/AHA cholesterol guidelines, the recent National Institute for Healthcare Excellence (NICE) primary prevention guideline made similar recommendations.[3]

This paper reviews evidence from recent meta-analyses, clinical trials, and epidemiologic studies' data supporting the recent recommendations for statin use in primary prevention.

Overview of Recent Primary Prevention Guidelines

The 2013 ACC/AHA cholesterol guideline recommendations for primary prevention in those without diabetes were made after reviewing evidence from the 3 exclusively primary prevention statin trials and data from meta-analyses of statin trials published through 2011.[4−8] Based on this high level of evidence, moderate- or high-intensity statin therapy is now recommended for healthy subjects aged 40 to 75 years with a 10-year ASCVD risk ≥7.5% with low-density lipoprotein cholesterol (LDL-C) levels of 70 to 189 mg/dl. Moderate-intensity statin therapy is considered reasonable for those with a 10-year ASCVD risk of 5% to <7.5%. The 10-year ASCVD risk estimates are based the risk of nonfatal myocardial infarction (MI), coronary heart disease (CHD) death, and fatal and nonfatal stroke. The 2013 ACC/AHA recommendations for statin use were based on an extrapolation of the potential for an ASCVD risk reduction exceeding the potential for adverse events over a 10-year treatment period.

The NICE primary prevention guideline recommends initiation of atorvastatin 20 mg for primary prevention for those with >10% 10-year cardiovascular (CVD) risk estimated by the QRISK equation.[3] This risk cut point is similar to the 7.5% 10-year risk of "hard" ASCVD cut point used in the 2013 ACC/AHA cholesterol guideline. The QRISK equations also include "softer" end points of angina, arterial revascularizations, and transient ischemic attack, along with the hard ASCVD outcomes used in the 2013 ACC/AHA cholesterol guideline. The risk cut point identified by the NICE guideline therefore appears to identify individuals with similar or lower risk than the 2013 ACC/AHA cholesterol guideline.

Meta-Analysis of Statins in Low-Risk Subjects

Two meta-analyses of subjects and trial-level clinical trial data have shown that statin therapy reduces ASCVD events in healthy subjects at lower risk than has been previously appreciated.[9,10] These meta-analyses additionally found that statins also reduce total mortality in lower-risk subjects.

The most interesting data come from the 2012 Cholesterol Treatment Trialists (CTT) meta-analysis of individual-level data from 27 statin trials, 12 of which included subjects without clinical ASCVD. This analysis found that

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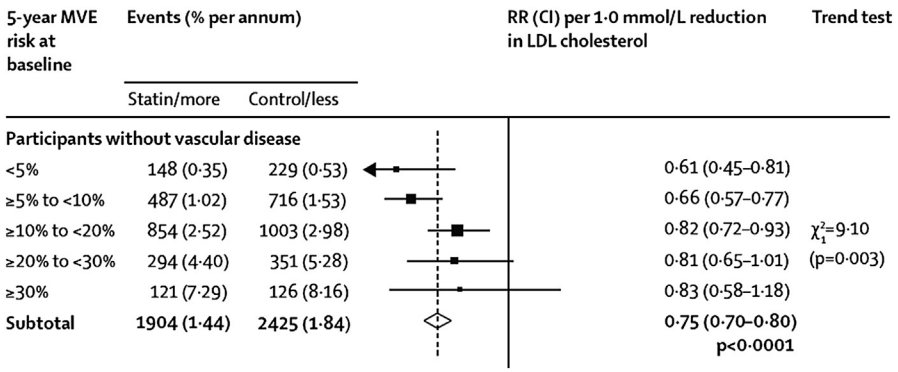

Figure 1. Effects on major ASCVD (nonfatal myocardial infarction, CHD death, stroke, or coronary revascularization) events per 1.0 mmol/L (39 mg/dl) reduction in LDL-C in participants without vascular disease at study entry (adapted from Figure 2 CTT 2012 meta-analysis[10]). MVE = major vascular events; RR = relative risk.

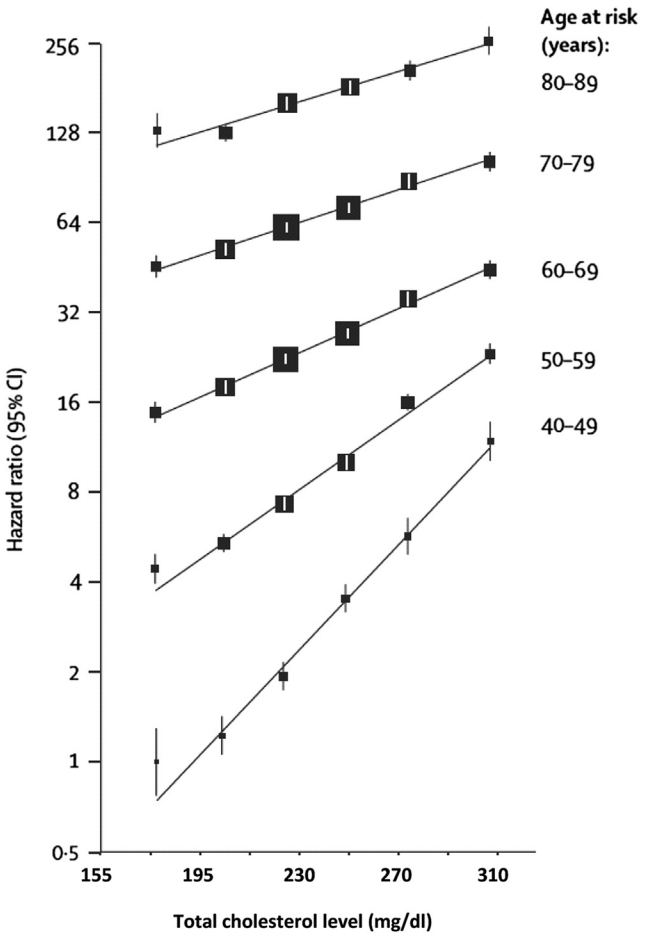

Figure 2. Age-specific associations of atherosclerotic coronary heart disease mortality and total cholesterol level from the Prospective Studies meta-analysis of 892,337 apparently healthy adults in 61 cohorts.[41]

among primary prevention subjects with a range of baseline LDL-C levels, those with a <10% 5-year risk of a major ASCVD event experienced a greater relative reduction in ASCVD risk per 39 mg/dl (1 mmol/L) reduction in LDL-C as those with ≥10% 5-year major ASCVD risk (Figure 1).[10]

Because coronary revascularization constituted about 1/2 of the major ASCVD end points in the CTT analysis, a 5% to <10% 5-year major ASCVD risk extrapolates to approximately the same 5% to <10% 10-year risk of a "hard" ASCVD event (nonfatal and fatal MI and stroke), as was used in the 2013 ACC/AHA cholesterol guidelines.[11] Thus, the CTT data support the use of statin therapy for the primary prevention of ASCVD in lower-risk subjects.

Cholesterol Epidemiology Over the Life Span

A meta-analysis of data from almost 90,000 women and men from 61 prospective observational studies definitively illustrates the relation between cholesterol levels at a given age and risk of atherosclerotic CHD mortality over an average 13-year period of follow-up (Figure 2).[41] Subjects aged 40 to 49 and 50 to 59 years have a greater relative risk associated with each 39 mg/dl (1 mmol/L) increase in cholesterol than those in older decades of age. The relative reduction in ASCVD risk is even more striking when there is lifetime exposure to lower LDL-C levels. Loss-of-function mutations to the proprotein convertase subtilisin/kexin type 9 (*PCSK-9*) serine protease gene in middle-aged black subjects were associated with 28% lower LDL-C levels but an 88% reduction in CHD over a 15-year observation.[12] Notably, this striking reduction in CHD events occurred in the setting of a high prevalence of risk factors: body mass index 29.5 kg/m^2, hypertension in 37%, diabetes 13%, and smoking 27%. These epidemiologic findings appear to be consistent with the greater relative risk reduction observed in lower-risk adults in the statin trials, in which advancing age is the major contributor to increasing ASCVD risk.[13]

Pathophysiology of Earlier Cholesterol Lowering

Imaging trials performed in subjects with clinical CHD have shown that statins stabilize atherosclerotic plaque and induce regression in a dose-related fashion.[14–16] It is reasonable to think that when statins are initiated earlier in the course of atherosclerosis, reduction in LDL-C levels could even more effectively induce plaque stabilization and regression when the disease process is less advanced. Imaging trials do suggest that statins may have greater effects on atherosclerotic progression when given earlier in the course of the disease because of greater reductions in lipid core volume, inflammation, and early fibrotic changes.[17–20] Statin therapy also appears to have beneficial effects on vascular remodeling as evidenced by reductions in vascular stiffness