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Lipid-Lowering Therapy in Patients 75 Years and Older: Clinical Priority or Superfluous Therapy?

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ABSTRACT

The incidence and prevalence of cardiovascular (CV)-related morbidity and mortality significantly increase with age. In the elderly, hypercholesterolemia with elevated total and low-density-lipoprotein cholesterol is a significant predictor of incident and recurrent CV disease. Multiple lines of evidence have established the benefit of statin therapy to lower cholesterol levels and reduce the risk of CV events as well as prevent progression of subclinical atherosclerotic disease. Elderly patients, particularly those older than 75 years, have not been well represented in randomized clinical trials evaluating lipid lowering therapy. The limited available data from clinical trials do support the benefit of statin therapy in the elderly population. Based upon these data, cholesterol treatment guidelines endorse statin therapy as the primary treatment of hypercholesterolemia in elderly patients, though caution is recommended given the greater number of co-morbid conditions and concern for poly-pharmacy common in the elderly. Additional research is needed to better establish the benefit of statin therapy in the elderly within the context of reducing CV risk, minimizing side effects, and improving overall quality of life.

Despite recent declines in the past three decades, cardiovascular (CV)-related disease remains the most common cause of death for both men and women in the United States.[1] In 2010, approximately 380,000 Americans died of coronary heart disease (CHD). With age being a strong predictor of vascular disease manifestation, 80% of CHD deaths occur among older individuals above age 65 years. Estimates project that the population over 65 years in the US will increase from 12.9% to 20% between 2000 and 2030; with the population over 85 years having the most rapid increase.[2,3] As the elderly population continues to grow and comprise a greater proportion of the US census, the number of individuals living with CV disease (CVD) and CV-related deaths are predicted to increase. Around the world, CVD is also the number one cause of death with estimated numbers projected to reach 23.3 million people by 2030.[4]

Large scale epidemiologic analysis has described a robust and graded association between serum cholesterol levels and incident CV events.[5] Treatment of hypercholesterolemia using 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has demonstrated consistent reductions in CVD events in multiple randomized controlled trials (RCTs) over the past two decades in patients with and without established CHD[6–11] and several trials and aggregate data analyses have shown reductions in CV and total mortality.[8,12,13] Given the extensive and consistent evidence from RCTs, the most recent

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Abbreviations and Acronyms
ACS = acute coronary syndrome
Apo B = apolipoprotein B
CHD = coronary heart disease
CPK = creatinine phosphokinase
CV = cardiovascular
CVD = cardiovascular disease
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
NNT = number needed to treat
TC = total cholesterol
TIA = transient ischemic attack

2013 adult cholesterol treatment guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) recommend a statin as the primary drug therapy for hypercholesterolemia including among the elderly.[14] As the guideline authors acknowledge, data for statin benefit are more limited among older patients and in particular individuals over 75 years. Few RCTs with statins have included elderly patients and treatment recommendations are sometimes extrapolated from data gathered among younger patients. Elderly patients often have multiple co-morbid conditions and a high number of concurrent medications that may increase their risk for side-effects and reduce the potential benefits of statin therapy.

In this review, we aim to detail the CV risks related to hypercholesterolemia among the elderly and to review the benefits and risks of statin therapy in this population. We review the new ACC/AHA cholesterol treatment guidelines, along with international guidelines from the European Society of Cardiology and International Atherosclerosis Society, as they pertain to elderly patients greater than 75 in the context of available data from primary and secondary prevention trials. In addition, we highlight the potential risks associated with statin therapy for older patients and discuss gaps in evidence and needs for future research.

Dyslipidemia and the elderly

Aging is associated with significant changes in cholesterol levels.[15] In the Framingham Heart Study, plasma low density lipoprotein (LDL) cholesterol (LDL-C) values increased progressively with age until 60 in men and 70 in women. Additionally, in the Framingham Offspring Study, apolipoprotein B (apo B) levels were also observed to increase with age in both men and women and more markedly in women after menopause. These noted increases in serum cholesterol are hypothesized to be partly secondary to decreases in LDL catabolism and reductions in hepatic LDL receptor activity observed with increasing age.[16] Co-morbidities such as obesity and diabetes also adversely affect lipid profiles in this population.

While epidemiologic studies across multiple countries have shown a clear positive association between total cholesterol (TC) levels and CHD risk in middle-aged general populations, a similar effect and magnitude of relationship have not been consistently documented in the elderly population.[5] In a meta-analysis done by the Prospective Studies Collaboration of 61 prospective observational studies consisting of close to 900,000 adults from Europe and North America who do not have a history of CHD, a 1 mmol/L (39 mg/dL) lower TC was associated with a lower risk of CHD in men and women between 40 and 49 years (hazard ratio 0.44, 95% CI 0.42–0.48). With increasing age, the association between CHD risk and TC levels remained positive but at a smaller effect size. For a 1 mmol/L (39 mg/dL) lower TC, participants at ages 50–59 and 70–89 had hazard ratios of 0.66 (95% CI 0.65–0.68) and 0.83 (95% CI 0.81–0.85), respectively. However, since absolute risk of events increases in this age group, the absolute number of potentially preventable events is actually higher among older individuals than among younger individuals. Several cohort analyses looking specifically at the elderly found similar positive associations but of varying magnitude. In the Framingham Heart Study, participants aged 60–70 years had roughly a 2% increase in CHD incidence with a 1% increase in TC.[17] The Kaiser Heart Study found in a cohort of 2746 white men 60–79 years that the relative risk for CHD mortality was 1.5 (95% CI 1.2–2.0) for those men who had the highest quartile of serum TC as compared to those men with TC in the three lower quartiles combined.[18] The relative risk for men ages 75–79 years was found not to differ significantly from younger men ages 60–64.

In contrast to these studies, the community-based Established Population for the Epidemiologic Study of the Elderly found no association between TC and CHD risk. In 997 subjects from New Haven, Connecticut, all older than 70 years, those with TC greater than 240 mg/dL had similar rates of all-cause mortality, CHD death, and hospitalization of myocardial infarction (MI) or unstable angina as compared to those who had cholesterol less than 200 mg/dL.[19] In addition, a low high density lipoprotein (HDL-C) level, defined as the lowest tertile, was not found to be associated with CHD risk. The absence of a consistent predictive relationship between TC and CVD in older individuals may be partly explained by the confounding effects on serum TC and mortality from co-morbid conditions and frailty common to the aging population. Corti et al. in a multicenter, longitudinal study of 4066 older men and women from various American cities including New Haven, Connecticut, found that elevated TC was a risk factor for CHD death only after controlling for markers of poor health including chronic conditions, and low serum iron and albumin levels.[20] The Honolulu Heart Program documented a similar finding in a 20 year follow-up cohort study of 3572 Japanese American men aged 71–93 years.[21] They noted that TC levels decreased with increasing age. Age-adjusted mortality rates were significantly higher (risk ratio 1.64, 95% CI 1.13–2.36) only in those participants with the lowest quartile of TC. In contrast to the linear relationship between TC and CHD risk and mortality observed in the younger population, the elderly likely exhibit a U-shaped relationship with very low levels of serum TC being reflective of overall poor health status and predictive of increased overall mortality while elevated TC levels are associated with increased CVD risk.

Statin therapy in the elderly

Multiple randomized clinical trials of statin therapy over the past two decades have shown consistent reductions in CV