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REVIEW TOPIC OF THE WEEK

Primary Prevention With Statins in the Elderly

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ABSTRACT

The burden of atherosclerotic cardiovascular disease (ASCVD) in high-income countries is mostly borne by the elderly. With increasing life expectancy, clear guidance on sensible use of statin therapy to prevent a first and potentially devastating ASCVD event is critically important to ensure a healthy aging population. Since 2013, 5 major North American and European guidelines on statin use in primary prevention of ASCVD have been released by the American College of Cardiology/American Heart Association, the UK National Institute for Health and Care Excellence, the Canadian Cardiovascular Society, U.S. Preventive Services Task Force, and the European Society of Cardiology/European Atherosclerosis Society. Guidance on using statin therapy in primary ASCVD prevention in the growing elderly population (>65 years of age) differs markedly. The authors discuss the discrepant recommendations, place them into the context of available evidence, and identify circumstances in which uncertainty may hamper the appropriate use of statins in the elderly. (J Am Coll Cardiol 2018;71:85-94)

The short-term risk of atherosclerotic cardiovascular disease (ASCVD) increases with age, with the highest incidence rates, number of events, prevalence, and treatment costs in the elderly population. Given the increasing size of this population, it is critically important that guidelines provide clear recommendations for appropriate use of interventions of proven efficacy to reduce the burden of ASCVD in the elderly. Statin therapy represents a substantial potential for safe, effective, and inexpensive primary prevention of ASCVD in elderly individuals (here defined as individuals >65 years of age), as statins have been shown to be generally well tolerated and improve ASCVD outcome across a wide range of population characteristics. However, this potential for meaningful benefits of preventive statin therapy in elderly people is inconsistently utilized in existing guidelines in Europe and North America, as described in this review.

SCOPE OF THE PROBLEM: DISEASE BURDEN IN THE ELDERLY

The proportion and number of elderly people 65 years of age or older are increasing fast worldwide (1). At 65 years of age, life expectancy is currently estimated to be >20 years for women and >17 years for men in most high-income countries (2). The impact of these demographic changes on the burden of ASCVD is dramatic. It has been projected that the prevalence of coronary heart disease—the most prevalent form of ASCVD—in the United States will increase by as much as 43% (≈5 million more) by year 2030 due to demographic changes alone, while the associated increase in direct costs might be as much as 198% (≈$70 billion more) (3,4). This development poses a major challenge for societies to ensure a healthy elderly population.

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ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CCS = Canadian Cardiovascular Society

CI = confidence interval

ESC/EAS = European Society of Cardiology/European Atherosclerosis Society

MI = myocardial infarction

NICE = National Institute for Health and Care Excellence

RCT = randomized controlled trial

RR = relative risk

SAS = statin-associated symptoms

SCORE = Systematic COronary Risk Evaluation

STATIN GUIDELINES AND RECOMMENDATIONS FOR THE ELDERLY

Since 2013, 5 major guidelines on statin use to prevent ASCVD have been released, in 2013 by American College of Cardiology/American Heart Association (ACC/AHA) (5), in 2014 by the UK National Institute for Health and Care Excellence (NICE) (6), in 2016 by the Canadian Cardiovascular Society (CCS) (7), in 2016 by the U.S. Preventive Services Task Force (8), and in 2016 by the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) (9). Although these guidelines are based on the same evidence originating predominantly from randomized controlled trials (RCTs) of statin therapy, the recommendations for using statins to prevent a first ASCVD event differ substantially (**Table 1**). Nevertheless, the guidelines share the same basic concept of allocating statin therapy to those assumed to be at highest risk for ASCVD, either because of a well-defined high-risk condition (i.e., diabetes) or because of a high estimated 10-year risk for a first ASCVD event using guideline-specific risk scores.

One striking difference among the guidelines is their recommendations for statin therapy with advancing age. To facilitate meaningful discussion and highlight important differences, guideline recommendations and evidence pertinent to 3 age groups are reviewed independently—middle aged (40 to 65 years of age), elderly (66 to 75 years of age), and very elderly (>75 years of age)—with the main focus on those individuals >65 years of age.

PRIMARY PREVENTION IN MIDDLE-AGED INDIVIDUALS (40 TO 65 YEARS OF AGE). For apparently healthy individuals 40 to 65 years of age, all 5 statin guidelines provide strong or Class I recommendations for initiation of statin therapy in those at highest risk (**Table 1, Figure 1**). This age group has been well represented in high-quality primary prevention statin trials (**Table 2**) (10–20), and little controversy exists regarding statin efficacy in those at highest risk (21,22). However, the guidelines do not agree on how to define the risk above which statin therapy should be initiated. Although the 2016 ESC/EAS guideline continues to base its recommendations on old "high-risk" considerations (23), the other 4 guidelines have expanded the indication for statin treatment considerably based on a combination of strong RCT evidence, net benefit, and cost-effectiveness analyses (24,25). This is exemplified in the **Central Illustration** by a man who undergoes risk assessment every 10 years. At 56 years of age, his estimated 10-year risk for ASCVD using guideline-recommended risk scores is so high that all but the Systematic COronary Risk Evaluation (SCORE)-based ESC/EAS guideline would recommend initiation of statin therapy (**Table 1**).

PRIMARY PREVENTION IN THE ELDERLY (66 TO 75 YEARS). For apparently healthy individuals 66 to 75 years of age, 4 of the 5 guidelines continue to provide Class I or strong risk-based recommendations for primary prevention with statins in those at highest risk (**Figure 1, Central Illustration**). Only the ESC/EAS guideline on CVD prevention no longer has clear risk-based recommendations because SCORE is not applicable beyond 65 years of age (23). Even more notable, this guideline cautions against "uncritical" initiation of statin therapy in those >60 years of age, even if the estimated risk is very high (>10% 10-year risk for fatal CVD) (9). However, somewhat inconsistent, the ESC/EAS guideline for the management of dyslipidemias recommends that "statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia" (Class IIa) but without defining what is meant by "older adults" (26). In contrast, the ACC/AHA, CCS, and U.S. Preventive Services Task Force guidelines provide the same risk-based indication for statin therapy up to 75 years of age and NICE up to 84 years of age (**Figure 1, Central Illustration**). Given the strong impact of age on estimated 10-year risk for ASCVD, a progressively higher proportion of elderly individuals become statin eligible with these 4 guidelines. For example, all elderly individuals with optimal risk factors exceed the ACC/AHA 7.5% pooled cohort equation risk threshold by 65 years of age (men) or 71 years of age (women) and the NICE 10% QRISK2 risk threshold by 65 years of age (men) or 68 years of age (women).

Clinical trial evidence supports the use of statin therapy for the primary prevention of nonfatal ASCVD events in elderly individuals 66 to 75 years of age. This age group has been well represented in primary prevention statin trials (**Table 2**), and post hoc analyses from the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (27), CARDS (Collaborative Atorvastatin Diabetes Study) (28), JUPITER (Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin) (20,29) and HOPE-3 (Heart Outcomes Prevention Evaluation-3) (20) trials have shown improved ASCVD outcome also in those individuals older than 65 years of age at enrollment, with relative risk (RR) reductions similar to those