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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

TABLE 1 Eligibility for Primary Prevention With Statins (Class I or Strong Indication)

Indication for Statin Therapy	ACC/AHA 2013 (5)	NICE-UK 2014/2016 (6)	CCS 2016 (7)	USPSTF 2016 (8)	ESC/EAS 2016 (9)
High estimated 10-yr risk					
Age range, yrs	40–75	30–84	30–75*	40–75	40–65†
Risk model	PCE	QRISK2	Modified FRS-CVD	PCE	SCORE
Predicted endpoints	Nonfatal MI, CHD death, stroke	CHD, stroke, TIA (fatal and nonfatal)	MI, angina, CHD death, heart failure, stroke, TIA, PAD	Similar to ACC/AHA	Fatal ASCVD
Risk threshold for therapy	≥7.5%	≥10%	10%–19% (intermediate), ≥20% (high risk)	≥10%	5% to <10% (high risk), ≥10% (very high risk)
Risk factor requirements	No	No	Yes if 10%–19% risk* No if ≥20% risk	≥1‡	No
LDL-C before treatment, mg/dl	70–189	No	≥135 if 10%–19% risk* No if ≥20% risk	≤190	≥155 if high risk ≥100 if ≥10% risk
LDL-C treatment target, mg/dl	No	High intensity: >40%↓§	<77/>50%↓*	No	<100/≥50%↓ if high risk <70/≥50%↓ if ≥10% risk
High-risk clinical condition					
FH and/or high cholesterol, mg/dl	LDL-C ≥190 ≥21 yrs of age	No§	LDL-C ≥190	No‡	FH or TC >310
Diabetes mellitus	40–75 yrs of age LDL-C ≥70	High-risk type 1§	≥40 yrs of age*	No‡	>40 yrs of age
CKD (eGFR), ml/min/1.73 m^2	No	<60§	<60†	No	30-59 = high risk <30 = very high risk†

*The Framingham Risk Score for general cardiovascular disease (FRS-CVD) is not well validated after 75 years of age. In the modified version, the risk is doubled in case of family history of premature cardiovascular disease (CVD). Equivalent values are provided for low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B. Required risk factors in intermediate risk: men ≥50 years of age and women ≥60 years of age and 1 additional CVD risk factor. Diabetes: ≥40 years of age or ≥15-year duration for ≥30 years of age (type 1) or microvascular disease. Chronic kidney disease (CKD): ≥50 years of age and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 or albumin/creatinine ratio >3 mg/mmol (those on dialysis optional). †Systematic COronary Risk Evaluation (SCORE) is only applicable up to 65 years of age. Statin therapy is not recommended in end-stage renal disease. ‡These recommendations do not pertain to persons with familial hypercholesterolemia (FH) and/or LDL-C >190 mg/dl. Required risk factor includes dyslipidemia, diabetes, hypertension, or smoking. §Patients with FH or receiving renal replacement therapy are not covered under this guideline. Diabetes, high risk: type 1 diabetes >40 years of age or diabetes >10 years or nephropathy or cardiovascular risk factors. In type 2 diabetes, QRISK2-guided statin therapy is recommended. CKD: eGFR <60 ml/min/1.73 m^2 and/or albuminuria. Treatment goal: >40% reduction in non-HDL-C.

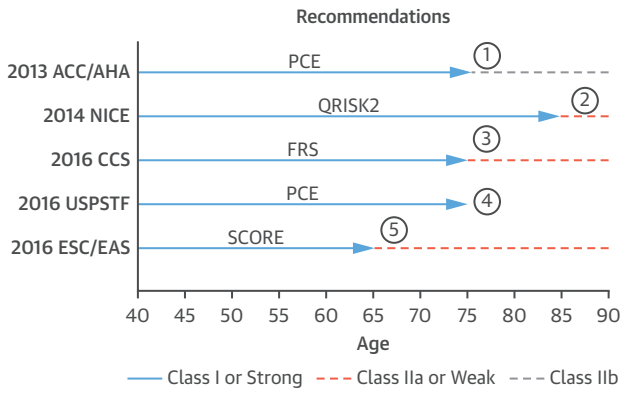
ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CCS = Canadian Cardiovascular Society; CHD = coronary heart disease; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; MI = myocardial infarction; NICE-UK = NICE = UK National Institute for Health and Care Excellence; PAD = peripheral artery disease; PCE = pooled cohort equation; TC = total cholesterol; TIA = transient ischemic attack; USPSTF = U.S. Preventive Services Task Force.

observed in younger individuals. In addition, 2 meta-analyses have provided important insights. Based on 8 RCTs (n = 24,674; ≥65 years of age), Savarese et al. (30) found that primary prevention with statins was highly effective in reducing the risk of myocardial infarction (MI) (RR: 0.60; 95% confidence interval [CI]: 0.43 to 0.85) and stroke (RR: 0.76; 95% CI: 0.63 to 0.93), but not all-cause mortality or cardiovascular death. More recently, Ridker et al. (20) provided age-stratified outcome data from the JUPITER and HOPE-3 trials. In elderly individuals 65 to 70 years of age, rosuvastatin reduced the risk of a composite endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death) substantially by 49% (RR: 0.51; 95% CI: 0.38 to 0.69), and the risk was reduced by 26% (RR: 0.74; 95% CI: 0.61 to 0.91) in those ≥70 years of age. The efficacy was similar in individuals ≥70 and <65 years of age, indicating little heterogeneity in treatment effect by age. Today, nearly all apparently healthy elderly individuals have RCT evidence supporting statin efficacy (31).

PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE). For apparently healthy very elderly individuals, only 1 (2014 NICE) of the 5 guidelines continues to provide a strong risk-based recommendation for initiating primary prevention with statins (**Figure 1, Central Illustration**). Thus, although the SCORE-dependent ESC/EAS guidelines provide risk-based indication for statins only up to 65 years of age, the QRISK2-dependent NICE guidelines do so up to 84 years of age. Because everyone >75 years of age exceeds the 10% 10-year QRISK2 threshold for treatment, the NICE guidelines indirectly provide a strong, universal statin indication over the range of 76 to 84 years of age. This guideline also provides a specific treatment recommendation for atorvastatin 20 mg in individuals ≥85 years of age, as "statins may be of benefit in reducing the risk of nonfatal myocardial infarctions" (**Figure 1**).

Very elderly people pose a troubling dilemma for the cardiovascular community, guideline writers, and clinical practitioners. Although they are at high risk of near-term ASCVD by virtue of their age alone, evidence of efficacy for primary prevention with statins is sparse in this age group, as only few have been included in RCTs (**Table 2**). Thus, the decision to initiate primary prevention with statins in people older than 75 years of age cannot be based directly

FIGURE 1 Recommendations for Primary Prevention With Statins in Apparently Healthy People



Guideline Recommendations in Elderly

1. "Statin therapy may be considered in selected individuals" (age >75, Class IIb)
2. "For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction"
3. FRS is not well validated beyond age 75, and indications for statins are less well defined in this age group
4. There is no recommendation for statins in people >75 years old
5. SCORE is not applicable beyond age 65, but "statin therapy should be considered in older adults, particularly in the presence of hypertension, smoking, diabetes and dyslipidemia" (Class IIa)

Handling of individuals >65 years of age differs substantially among contemporary European and North American guidelines, partly because of the performance (applicability) of the risk model used. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FRS = Framingham Risk Score for general cardiovascular disease; NICE = National Institute for Health and Care Excellence; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

on RCT evidence (32). Further, extrapolation of efficacy and safety data from those ≤75 years of age to those >75 years of age should be done cautiously, considering comorbidity, polypharmacy, potential side effects, and limited life expectancy (33). Efficacy of statin therapy in the very elderly, however, is well documented in secondary prevention trials (34). The PROSPER (Pravastatin in elderly individuals at risk of vascular disease) trial, for example, specifically assessed the benefit of statins in elderly individuals and demonstrated improved outcomes among elderly with known vascular diseases (13).

WHY THE AGE CAP ON RISK-BASED STATIN RECOMMENDATIONS? The risk for ASCVD increases dramatically with age. Why then do all strong risk-based statin recommendations expire at a certain but quite different guideline-dependent age?

TABLE 2 Enrollment of Elderly and Very Elderly in Primary Prevention Statin Trials

Study Name, Year (Ref. #)	No.	Mean Age (yrs)	Age Range (yrs)	Elderly	Very Elderly (≥75 yrs of Age)
WOSCOPS, 1995 (10)	6,595	55	Men 45–64	0	0
AFCAPS/TexCAPS, 1998 (11)	6,605	Men 58 Women 62	Men 45–73 Women 55–73	Men 20% ≥65 yrs of age Women 33% ≥65 yrs of age	0
ALLHAT-LLT, 2002 (12)	10,355	66	≥55	28% ≥65 yrs of age*	7%*
PROSPER, 2002 (13)	3,239 (no ASCVD)	75 (whole cohort)	70–82 (whole cohort)	100% ≥70 yrs of age	NR
ASCOT-LLA, 2003 (14)	10,305	63	40–79	64% >60 yrs of age 23% >70 yrs of age	NR
CARDS, 2004 (15)	2,838	62	40–75	40% ≥65 yrs of age 12% >70 yrs of age	0
MEGA, 2006 (16)	7,832	58	40–70	23% ≥65 yrs of age	0
JUPITER, 2008 (17)	17,802	66	Men ≥50 Women ≥60	58% ≥65 yrs of age† 32% ≥70 yrs of age†	NR
HOPE-3, 2016 (18)	12,705	66	Men ≥55 Women ≥65/60	52% ≥65 yrs of age† 24% ≥70 yrs of age†	NR

*Primary prevention data reported by Han et al. (19). †Reported by Ridker et al (20).

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HOPE-3 = Heart Outcomes Prevention Evaluation-3; JUPITER = Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR = not reported; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS = West of Scotland Coronary Prevention Study.

CENTRAL ILLUSTRATION **Age-Dependent Implementation of Guidelines in Clinical Practice**

Sex: Male	SBP: 135 mm Hg	HDL cholesterol: 37 mg/dL	Race: White
Smoker	Total cholesterol: 232 mg/dL	Diabetes: No	No antihypertensives

	Age 56	Age 66	Age 76	Age 86
PCE:	18%	26%	34%	NA
QRISK2:	17%	28%	43%	NA
Framingham:	31%	49%	NA	NA
SCORE:	4%	NA	NA	NA

Guideline Recommendation				
ACC/AHA	✓ Class I	✓ Class I	— Class IIb	— Class IIb
NICE	✓ Strong	✓ Strong	✓ Strong	— Specific recommendation for individuals ≥85 years
CCS	✓ Strong	✓ Strong	—	—
USPSTF	✓ Level B	✓ Level B	✗	✗
ESC/EAS	✗	— Class IIa	— Class IIa	— Class IIa

✓ : Strong Statin Recommendation — : Weak Statin Recommendation ✗ : Not Recommended for Statin

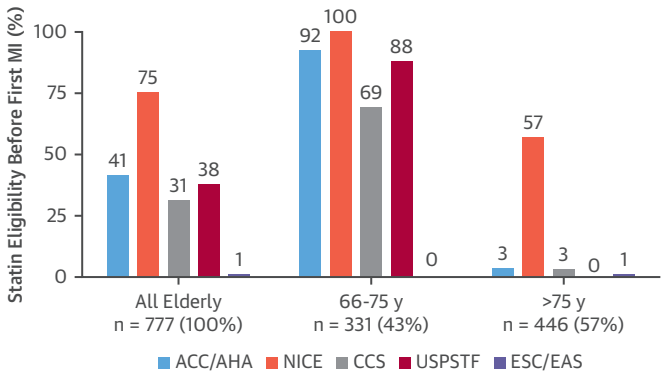
Mortensen, M.B. et al. J Am Coll Cardiol. 2018;71(1):85–94.

In apparently healthy individuals with risk factors shown in the box, all but the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines provide a strong indication for statin therapy in the range of 56 to 66 years of age. Above 75 years of age, only the National Institute for Health and Care Excellence (NICE) guideline provides a well-defined indication for statin therapy. See Table 1 for risks above which statin therapy is recommended. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; Framingham = Framingham Risk Score for general cardiovascular disease; NA = not applicable; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

Although the pooled cohort equations are applicable up to 79 years of age, the ACC/AHA and U.S. Preventive Services Task Force guidelines clearly state that after 75 years of age there are too few data and inadequate evidence for a strong risk-based statin recommendation. A similar view is found in the CCS guideline, which also emphasizes that the recommended Framingham risk model is not well validated after 75 years of age. Although the NICE guideline recognizes the lack of adequate evidence after 75 years of age, a strong risk-based statin recommendation is provided up to 84 years of age without any explanation—but possibly because QRISK2 is applicable up to this age. The ESC/EAS guideline recommends SCORE for risk assessment, though SCORE is applicable only up to 65 years of age. The appropriateness of this age limitation and not providing an alternative class I statin recommendation after 65 years of age is not discussed.

These discrepant statin recommendations do matter. Evaluated in real-life consecutive nondiabetic patients with a first MI, statin eligibility before the event (detection rate) varied from 1% with the ESC/EAS guideline to 75% with the NICE guideline (Figure 2). The SCORE-dependent ESC/EAS guideline is a striking outlier, with an extraordinary low potential to prevent a first MI in people older than 65 years of age. In contrast, only the NICE guideline offers a real potential to prevent such events after 75 years of age. This guideline also provides a weaker statin recommendation specifically for primary prevention of nonfatal MI in people ≥85 years of age.

FIGURE 2 Detection Rate in Elderly Individuals >65 Years of Age With a First MI

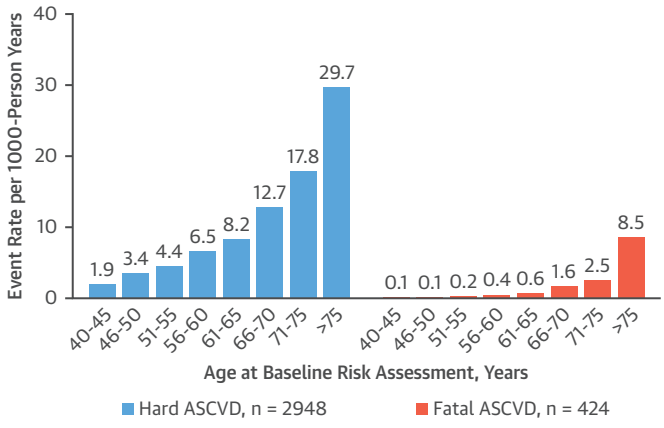


Proportion of apparently healthy elderly patients with first myocardial infarction (MI) who would have qualified for statin therapy (Class I recommendation) before the event. The data are based on 1,399 consecutive patients, of whom 777 (56%) were >65 years of age, hospitalized with a first MI in Denmark in 2010 to 2012 (54). Abbreviations as in Figure 1.

SPECIAL CONSIDERATIONS ON STATIN TREATMENT IN THE ELDERLY

For primary prevention with statins, net benefit of treatment is what counts for the individual person and cost effectiveness for the society. Treating acute and chronic ASCVD is costly, and broader use of inexpensive statins to prevent a first ASCVD event in the elderly is most likely cost effective and could very well be cost saving (35).

FIGURE 3 Relationship Between Hard and Fatal ASCVD Events



In apparently healthy individuals from a contemporary general population (the Copenhagen General Population Study, n = 48,814, ≥40 years of age), fatal atherosclerotic cardiovascular disease (ASCVD) events constitute only a minor proportion of hard ASCVD (fatal coronary heart disease and stroke plus nonfatal myocardial infarction and stroke) events. Among elderly people 65 to 75 years of age, the ratio was ≈7 to 8 and among very elderly people >75 years of age was ≈3.5. Adapted with permission from Mortensen et al. (25).

NET BENEFIT CONSIDERATIONS IN THE ELDERLY. The main goal of primary prevention with statins is to achieve net benefit from treatment. Considering potential harms is therefore a crucial part of appropriate decision making (36). As frailty, comorbidity, and polypharmacy may increase the risk for adverse statin-associated symptoms (SAS), the "risk-benefit" balance in the elderly could theoretically tip in favor of withholding statin therapy if such conditions are present. Limited life expectancy for whatever reason may also limit the potential benefit of statin therapy. Thus, initiation of statin therapy should always be preceded by a careful weighing of potential harms and benefits.

Well-documented SAS across all age groups are musculoskeletal issues and diabetes (37). RCT data on adverse effects have the strength of being unbiased, but may not be able to reliable detect rare events. Nevertheless, RCT data indicate that statins are safe and well tolerated in elderly individuals >65 years of age (38), with the caveats that limited data exist on the very old and that the elderly people enrolled in RCTs may be more robust than are those individuals routinely seen in clinical practice. Based on data from primary prevention statin trials (13,28,29) and a meta-analysis (39), muscle discomfort and pain reported in RCTs appear to be unrelated to age and statin therapy. However, because patients treated with statins in clinical practice are told about possible side effect, muscle symptoms will often mistakenly be perceived as statin induced—the so-called nocebo effect (40). Although rare, a higher risk for myopathy, including rhabdomyolysis, has been reported in elderly compared with younger patients treated with high-dose statin therapy, particularly simvastatin 80 mg/day (41).

The modestly increased risk for statin-induced diabetes is possibly age related and occurs almost exclusively among individuals with components of the metabolic syndrome who are already predisposed to develop diabetes (37,42). As new onset diabetes often requires additional drug therapy, this may be problematic especially in elderly patients.

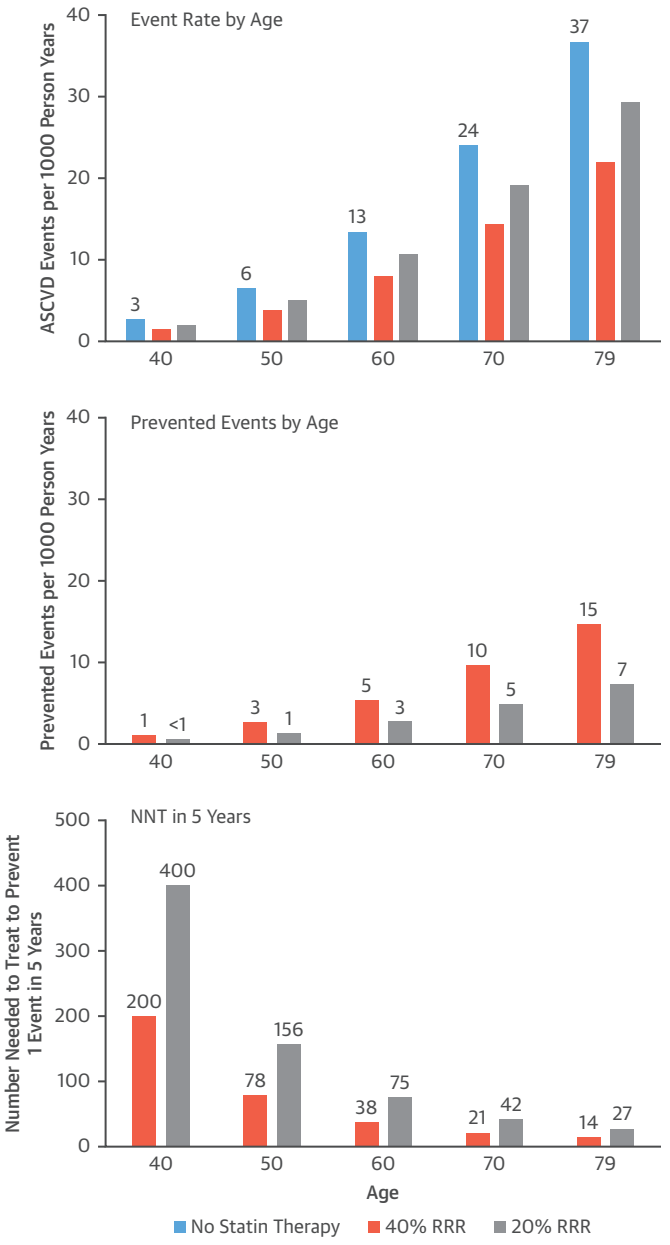
As recently reviewed, current evidence does not support a previous suspicion that statin therapy might cause memory loss, cognitive impairment, or dementia (38,43,44). Important to consider before initiating statin therapy in the elderly is polypharmacy and the associated risk for drug-drug interactions (32,33). This is especially relevant for

statins metabolized by CYP3A4 (i.e., atorvastatin). Close monitoring is important to avoid or treat possible SAS. Importantly, adverse effects of statins usually resolve rapidly after discontinuation of treatment.

MORBIDITY VERSUS MORTALITY BENEFIT IN THE ELDERLY. In primary prevention it is no longer tenable to focus only on longevity and all-cause mortality (45), as ASCVD morbidity and treatment costs are increasing. The majority of ASCVD events in the elderly are nonfatal events (**Figure 3**), and the proportion of elderly individuals >65 years of age living with chronic disease is increasing (46). Thus, patient preferences are critical important for well-informed shared decision making. If a patient only values longevity, there are little data to support primary prevention with statins in people >65 years of age. On the other hand, if preventing nonfatal and potentially disabling MI or stroke is of value to the patient, it might be reasonable to initiate statin therapy. From this perspective, it is noteworthy that the relative importance that people assign to avoiding death compared with avoiding nonfatal events appears to be highly age dependent. Although younger individuals <65 years of age weigh avoiding death highest, elderly individuals ≥65 years put a much higher weight on avoiding MI or stroke than death (47). These differences are compatible with elderly individuals having a greater focus on quality of life and avoiding disability than on extending life (48).

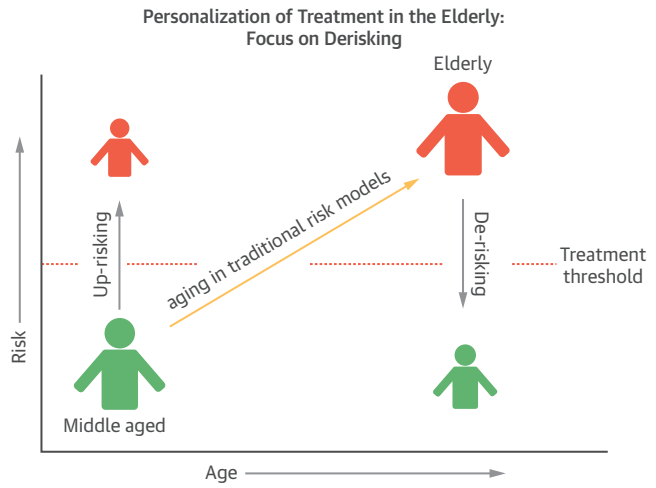
RR, ABSOLUTE RISK, AND NUMBER NEEDED TO TREAT IN THE ELDERLY. There are good reasons to believe that the magnitude of benefit with statins may be substantial in elderly people. As the RR reduction with statin therapy is similar for those at low and high risk of ASCVD, the absolute benefit of treatment with statins is highly dependent on absolute ASCVD risk (49). Thus, even in case of a smaller relative benefit with statin therapy in elderly people, the absolute benefit is likely higher because of the higher risk for ASCVD (**Figure 4**). Assuming different efficacy of statin therapy in various age groups ranging from a RR reduction of 20% to 40% (arbitrarily chosen), it can be estimated that the absolute risk reduction with statin therapy in a 79-year-old person may be considerably higher than in a similar 60-year-old person even if efficacy of treatment should be only one-half of that in the younger person. This translates into much lower number needed to treat in 5 years to prevent 1 event in elderly compared with younger individuals.

FIGURE 4 Conceptual Relationship Between Age and Absolute Benefit of Statin Therapy



Calculations based on the pooled cohort equations assuming a population of nonsmoking men with systolic blood pressure 135 mm Hg, total cholesterol 232 mg/dl, and high-density lipoprotein (HDL) cholesterol 37 mg/dl without diabetes or hypertension. **(Top)** Estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) before and after statin therapy assuming 40% and 20% relative risk reduction (RRR). **(Middle)** The absolute risk reduction with statins increases substantially with age. **(Bottom)** The number needed to treat (NNT) in 5 years to prevent 1 ASCVD event becomes lower with aging, even in case of lower efficacy of treatment.

FIGURE 5 The Concept of Derisking in Elderly People



Age is the most important determinant of predicted risk of ASCVD using traditional risk models. Thus, because of increasing age alone, most elderly individuals >65 years of age will eventually exceed the risk-based treatment thresholds for statin therapy by most guidelines. Given the increasing elderly population and the associated concern about overtreatment with statins, the challenge in elderly individuals is therefore to identify those who are at truly low risk for ASCVD despite a high predicted risk with traditional risk models.

DEPRESCRIBING STATIN THERAPY IN THE VERY OLD. In patients at high risk for ASCVD adherence to prescribed statin therapy is critically important. However, discontinuing primary prevention with statin therapy is reasonable to consider in elderly, frail people at increased risk for SAS and low chance of benefit because of limited life expectancy. Quality of life may improve, but RCTs and guidelines provide no or only limited guidance on how to approach and discuss this difficult question (33). The benefit of statin therapy persists after discontinuation of therapy (long-term legacy benefit), without evidence of any rebound adverse effects in primary prevention (50).

FUTURE PERSPECTIVES

As discussed in this review, limited evidence are available on statin therapy for primary prevention of ASCVD in very elderly individuals >75 years of age. The STAREE (STAtins for Reducing Events in the Elderly) trial, a primary prevention trial currently underway, recruits individuals ≥70 years of age to determine efficacy and safety of statin treatment in elderly people (51). This trial will likely provide important insights for the older population.

With the broadened indication for statin therapy in all but the ESC/EAS guideline, most elderly individuals will eventually qualify for treatment. However, the appropriateness of treating all elderly needs reconsideration. Thus, accurate identification of elderly individuals at truly low risk is gaining increasing interest. This situation is the opposite in younger individuals, where the challenge is to identify novel biomarkers that can help "up-risking" those who do not qualify for statins but are at truly high risk for a future ASCVD event. A promising approach to personalize treatment in elderly people is "derisking" by use of negative risk markers (i.e., absence of coronary artery calcification) to identify those at so low risk that statin therapy may safely be withheld (**Figure 5**) (52,53). In the BioImage study of elderly individuals, for example, absence of coronary artery calcification was prevalent (≈1 of 3) and associated with exceptionally low ASCVD event rates (53). Derisking is not considered in current guidelines but deserves to be discussed when the guidelines are updated.

For the ESC/EAS guidelines it is time to address the inherent limitations of SCORE (not applicable beyond 65 years of age, and morbidity does not count) (23).

CONCLUSIONS

The recommendations for statin therapy in elderly >65 years of age differ substantially among the 5 major guidelines currently used in North America and Europe. At one end of the spectrum, the 2016 ESC/EAS guidelines miss great opportunities for safe, cheap, and evidence-based prevention in elderly individuals 66 to 75 years of age. At the other end of the spectrum, the 2014 NICE guideline provides near-universal treatment recommendations well into the very elderly >75 years of age where RCT evidence is sparse and more uncertain. If these guidelines are followed stringently in clinical practice, the large heterogeneity in treatment recommendations will have tremendous variable impact on ASCVD prevention in elderly individuals >65 years of age. Until more evidence is available for those individuals >75 years of age, initiation of primary prevention with statins in this age group must be based on well-informed shared decision making. To curb the increasing burden of ASCVD, guidelines need to address the rapidly changing landscape of population demographics with clear and strong guidance on how to best allocate preventive statin treatment into old age. Indeed, there are reasons to believe that the benefit of statin treatment in elderly people may be

substantial for both the individual patient and for the society.

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