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## Statins for Primary Prevention in Older Adults—Moving Toward Evidence-Based Decision-Making

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### Abstract

**OBJECTIVES**—To determine the efficacy and safety of statins for primary prevention of atherosclerotic cardiovascular disease (ASCVD) events in older adults, especially those aged 80 and older and with multimorbidity.

**METHODS**—The National Institute on Aging and the National Heart, Lung and Blood Institute convened a multidisciplinary expert panel from July 31 to August 1, 2017, to review existing evidence, identify knowledge gaps, and consider whether statin safety and efficacy data in persons aged 75 and older without ASCVD are sufficient; whether existing data can inform the feasibility, design, and implementation of future statin trials in older adults; and clinical trial options and designs to address knowledge gaps. This article summarizes the presentations and discussions at that workshop.

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#### SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**RESULTS**—There is insufficient evidence regarding the benefits and harms of statins in older adults, especially those with concomitant frailty, polypharmacy, comorbidities, and cognitive impairment; a lack of tools to assess ASCVD risk in those aged 80 and older; and a paucity of evidence of the effect of statins on outcomes of importance to older adults, such as statin-associated muscle symptoms, cognitive function, and incident diabetes mellitus. Prospective, traditional, placebo-controlled, randomized clinical trials (RCTs) and pragmatic RCTs seem to be suitable options to address these critical knowledge gaps. Future trials have to consider greater representation of very old adults, women, underrepresented minorities, and individuals of differing health, cognitive, socioeconomic, and educational backgrounds. Feasibility analyses from existing large healthcare networks confirm appropriate power for death and cardiovascular outcomes for future RCTs in this area.

**CONCLUSION**—Existing data cannot address uncertainties about the benefits and harms of statins for primary ASCVD prevention in adults aged 75 and older, especially those with comorbidities, frailty, and cognitive impairment. Evidence from 1 or more RCTs could address these important knowledge gaps to inform person-centered decision-making.

### Keywords

statins; primary prevention; older adults; randomized clinical trial; benefits; risks

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Cardiovascular events are the leading cause of morbidity and mortality in adults aged 75 and older, with coronary heart disease (CHD) and stroke accounting for 60% of deaths in those aged 85 and older.<sup>1</sup> Randomized controlled trial (RCT) evidence supporting the benefit of statin therapy for primary prevention of fatal and nonfatal atherosclerotic cardiovascular disease (ASCVD) events in adults younger than 75 is substantial and consistent. A meta-analysis of 27 RCTs comparing statin therapy with a control or usual care demonstrated a statistically significant reduction in the relative risk of major ASCVD events of 37% for those in the lowest ASCVD risk category (<5.0%) and 49% for those in the moderate ASCVD risk category (5.0–9.9%)<sup>2,3</sup> (Table 1). Although statin therapy reduce low-density lipoprotein cholesterol (LDL-C) levels irrespective of age, evidence supporting reduction of ASCVD events with statin therapy in adults aged 75 and older is limited.<sup>2–6</sup> Assuming efficacy similar to that in RCTs of younger individuals, primary prevention with statins in all adults aged 75 to 94 could prevent 105,000 myocardial infarctions (MIs) and 68,000 CHD-related deaths at an incremental cost of approximately \$25,000 per disability-adjusted life year over 10-years<sup>7</sup>; however, although an estimated 10% to 29% increase in the relative risk of functional limitation or mild cognitive impairment would offset these benefits,<sup>8</sup> highlighting the need to assess the overall health benefit:risk of initiating statins in older adults.

The lack of clear evidence-based guidance for initiating statins in individuals aged 75 and older is emphasized in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Cholesterol Lowering Guideline.<sup>2</sup> Two important aspects of this guideline complicate decision-making in initiating statins for primary ASCVD prevention in older adults: the recommended use of the pooled cohort equations (PCE) to estimate 10-year ASCVD risk in white and black men and women<sup>9</sup> and the stipulation to have a discussion to evaluate the individualized ASCVD benefit and risk of statin therapy, taking into account the

adverse effects, drug–drug interactions, and patient preferences when deciding to initiate, continue, or intensify statin therapy in individuals aged 75 and older. Although it is stated that the current ACC/AHA calculator can estimate ASCVD risk accurately up to age 79, age drives the calculated risk score such that this instrument always calculates persons aged 75 and older to be at high ASCVD risk (>7.5% 10 year predicted risk), even without other known risk factors,<sup>9</sup> but the guidelines do not indicate that simply achieving 7.5% risk should trigger a statin prescription in those aged 75 and older. This should be decided after discussion of additional factors (ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and personal preference) between the clinician and the individual.<sup>2</sup> The guideline’s recommendation for primary ASCVD prevention in those aged 75 and older is that, “Statin therapy may be considered in selected individuals” (Class IIb; Evidence Level C), but consideration of comorbidities, safety, and focusing on an individual’s priorities of care before initiating therapy are underscored. These cautions underpin the concluding guideline statement that use of statins for primary ASCVD prevention in adults aged 75 and older is a “high priority area of research.” Furthermore, because the PCE 10-year ASCVD risk calculator has not been validated for those aged 80 and older, tools or methods to accurately estimate ASCVD risk in representative populations are needed.

From July 31 to August 1, 2017, the National Institute on Aging (NIA) and the National Heart, Lung, and Blood Institute (NHLBI) convened experts from diverse disciplines (cardiology, geriatrics and gerontology, general internal medicine, endocrinology, clinical pharmacology, biostatistics, clinical investigation, neuropsychology) for a workshop entitled, “Opportunities for Trials on Effects of Statins in Primary Prevention in Older Adults,” to review existing evidence, identify knowledge gaps, and consider whether there is sufficient evidence of statin safety and efficacy in persons aged 75 and older without ASCVD; consider whether existing data can inform the feasibility, design, and implementation of future statin trials in “real-world” older adults without ASCVD; and consider ASCVD clinical trial options and designs to address knowledge gaps. The presentations and discussions at that workshop stimulated and informed this article.

## **Existing Evidence and Remaining Gaps on Statins for Primary ASCVD Prevention in Older Adults**

No RCTs designed and powered a priori to assess whether statins should be initiated for primary prevention in older adults have been completed. Available evidence is derived from observational studies, subgroup and post hoc analyses, and meta-analyses of RCTs (Table 2). In a subgroup analysis from the Heart Protection Study (total n=20, 536 adults), the proportional reduction in the rate of first major vascular events among 28 % of adults 70 years (23.6% vs 28.7% for simvastatin vs placebo) was similar across age categories (< 65 and 65 < 70). However, the majority of participants in the study had history of coronary heart disease (65%), stroke, peripheral arterial disease or diabetes.<sup>10</sup> Similarly, pravastatin was not associated with a significant reduction in a composite endpoint of coronary death, nonfatal MI, and fatal or nonfatal stroke over 3.2 years in the 56% of the 5,804 subjects aged 70 to 82 without existing ASCVD in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).<sup>11</sup>

A post hoc analysis of the Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) compared outcomes associated with pravastatin (40 mg/d) in those aged 75 and older with outcomes in those aged 65 to 74.<sup>12</sup> In 2,867 participants without ASCVD (mean age 71), there was no significant difference in risk of CHD events or all-cause death between pravastatin 40 mg/d and usual care. A trend toward a higher rate of the primary outcome of all-cause mortality was seen in those aged 75 and older receiving pravastatin (hazard ratio (HR)=1.34, 95% confidence interval (CI)=0.98–1.84). Limitations of ALLHAT-LLT study include use of a low-potency statin; use of usual care rather than placebo control; and conduct of the study 15 to 21 years ago, when usual care standards differed from contemporary practice. In addition, 29% of usual care participants were taking a statin (including one of the newer statins entering the market, which were more potent than pravastatin), and 22% of those in the pravastatin arm were not taking a statin by the end of the trial, which may have diluted the LDL-C-lowering difference between the intervention and comparator arms.

Several meta-analyses of RCTs of statins for primary prevention in adults aged 65 and older have been reported, but persons aged 80 and older, especially those with geriatric syndromes (e.g., frailty, sarcopenia, functional, cognitive decline) and multiple chronic conditions, are underrepresented in the contributing studies.<sup>3–6,13–15</sup> (Tables 1 and 2) A meta-analysis of data from two placebo-controlled RCTs,<sup>15</sup> Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (mean age 66),<sup>16</sup> in which rosuvastatin (20 mg) was used, and Heart Outcomes Prevention Evaluation (HOPE-3) (mean age 66),<sup>17</sup> in which low-dose rosuvastatin (10 mg) was used, reported a 26% reduction with rosuvastatin in risk of the composite endpoint of nonfatal MI, nonfatal ischemic stroke, and cardiovascular death in participants aged 70 and older (mean age 74), but the magnitude of the effect was statistically significant only in JUPITER (Figure 1).<sup>15</sup>

## Noncardiovascular Outcomes and Potential Harms of Statins in Older

### Adults

Most primary prevention RCTs have evaluated the effect of statins on ASCVD outcomes. These studies have rarely evaluated non-ASCVD outcomes and were underpowered to detect harms. Measures of overall universal health outcomes meaningful to older adults, such as dementia- and disability-free survival, physical and cognitive function, independence, and health-related quality of life (QOL), are crucial to convey individualized risks and benefits of statins needed to provide care concordant with people's priorities.<sup>18,19</sup> Age-associated changes may increase vulnerability to harmful outcomes, such as cognitive decline, muscle symptoms, and fatigue. (Table 3, Supplementary Table S1). Thus, more robust and consistent measurement of global health outcomes that older adults value is needed in future trials of statins for primary prevention in older adults.<sup>18,19</sup>

Reports on a possible relationship between statins and cognitive decline are conflicting. A Cochrane review of 2 large placebo-controlled RCTs of statins to prevent dementia in 26,340 participants (aged 40 to 82, n=11,610 aged 70) reported no statin-related reduction in incident dementia.<sup>20</sup> There were limitations of the included RCTs involving the cognitive

assessments used, and the studies included participants at moderate to high vascular risk only. In contrast, several observational studies reported a protective effect of statin therapy against incident dementia (HR=0.80, 95% CI=0.68–0.95).<sup>21</sup> A longitudinal study of older adults with baseline normal cognition noted a slower rate of annual worsening of cognitive performance in statin users than in nonusers (n=2,363),<sup>22</sup> and statin users (n=1224, mean age 72.8 ± 8.17) out-performed nonusers in measures of attention. Older adults at highest risk of cognitive decline, including very old individuals and persons with low education levels, are underrepresented in most trials. Assessment of the potential protective effect of statins against incident and worsening dementia in RCTs is limited because measures of cognition and dementia are rarely a prespecified outcome and are assessed using various methods at various time points, including passive collection of adverse events in some studies. Thus, existing data highlight the need for validated measures of cognition to assess populations with differing baseline cognitive function and dementia risk in adequately powered RCTs of statins.

In contrast to the purported protective effect of statins against dementia, several postmarketing reports of cognitive impairment associated with statins (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) weeks to years after statin use have prompted a labeling change by the U.S. Food and Drug Administration,<sup>23</sup> although a meta-analysis of placebo-controlled trials failed to show significant adverse effects of statins on cognition in cognitively normal subjects (n=45,564 participants from 18 RCTs, 9 of which included participants aged ≥ 65) or those with Alzheimer's disease (n=1,153 participants from four RCTs; mean age > 68).<sup>24</sup> Future studies should evaluate whether statins have a deleterious effect on cognition in oldest adults.

Data are also needed on statin-associated muscle symptoms (SAMS) in older adults to clarify their incidence, pathophysiology, and possible effect on muscle strength, fatigue, frailty, physical function, and risk of falls.<sup>25</sup> A Dutch observational study of adults aged 75 and older compared 1,261 statin users with 3,094 nonusers and found no difference in prevalence of muscle complaints (3.3% vs 2.5%, P = .18).<sup>26</sup> Recent genome-wide association studies have shown that common variants in *SLCO1B1*\*5 are strongly associated with greater risk of simvastatin-induced myopathy<sup>27</sup> and other mild statin-induced side effects.<sup>28</sup> The clinical significance and underlying mechanism of SAMS could be elucidated by including prospective definitions of SAMS<sup>29</sup> and objective measurement of strength and activity and by using well-established diagnostic biomarkers such as creatinine kinase levels in future studies. Methods to integrate statin withdrawal and rechallenge and to assess muscle structure and function would clarify the clinical importance of SAMS and help distinguish it from common musculoskeletal conditions in older adults, including arthritis, sarcopenia, frailty, and deconditioning. It is important to determine whether age-related alterations in skeletal muscle structure and function increase vulnerability to SAMS, as well as the potential influence of comorbidities, polypharmacy, pharmacokinetics, pharmacodynamics, and frailty on the risk of SAMS.

The greater risk of incident diabetes mellitus (DM) associated with statin use is of special concern for older adults, especially older women, because it is likely that age-related changes in body composition and metabolism increase vulnerability to DM.<sup>30</sup> A meta-

analysis of 17 trials reported greater risk of incident DM (odds ratio=1.09, 95% CI=1.02–1.17),<sup>31</sup> with a higher risk reported with higher-intensity than moderate-intensity statins.<sup>32</sup> A RCT showed that only participants with 1 or more risk factors for DM (e.g., high body mass index, glycosylated hemoglobin, high fasting blood sugar, metabolic syndrome) progressed to DM after statin initiation.<sup>33</sup>

## Can Current Data Be Extrapolated to Older Adults?

Given the limited numbers of older adults included in RCTs of statins for primary prevention, is it reasonable to extrapolate trial data from persons younger than 75 to this population? Age-related concerns that limit the generalizability of existing data from younger to older adults are shown in Supplementary Table S1.

The strength of the association between high serum LDL cholesterol and an increase in the risk of ASCVD events becomes weaker with advancing age, in part because of survival bias, despite the increasing absolute risk of ASCVD in older adults.<sup>34,35</sup>(Figure 1A) Thus, the efficacy of statins in mitigating the risk of incident ASCVD events by lowering LDL-C is less clear in those aged 75 and older, particularly as they age further. Age-associated changes in pharmacodynamics and pharmacokinetics, declining kidney function, other comorbid conditions, and polypharmacy may influence the benefit-to-harm ratio of statins in older adults. Moreover, better understanding of how age-related alterations in body composition (adipose, free water), drug metabolism, drug-protein binding, and reduced renal clearance affect the potency and effect of specific statins on clinical outcomes may identify ways to lessen their harms.

It is likely that the differences in time to benefit (the time for a population to realize the intended benefits of a medication) of statins to reduce risk of CHD, ischemic stroke, or non-ASCVD outcomes, versus time to harm, especially in the setting of advancing age with limited life-span, influence decision-making on if and when statins are recommended for preventive therapy. Older adults with limited life expectancy may be exposed to the immediate risks of statins adversely affecting QOL, with little likelihood of surviving long enough to reap their benefits. The timing of initiation and duration of statin therapy were identified as crucial evidence gaps that necessitate careful planning of enrollment criteria for future trials. Whether future RCTs enroll statin-naïve participants, those who are already taking statins, or both may depend on the feasibility of enrollment. Feasibility challenges may also determine whether future RCTs could be placebo controlled. Evidence to support guidance on when to stop statin therapy in older adults with a limited lifespan is also needed.

## The Statin Therapy for Reducing Events in the Elderly Trial

Launched in 2015, the Statin Therapy for Reducing Events in the Elderly (STAREE) trial is comparing the effect of atorvastatin 40 mg/d (starting at 20 mg/d and titrated to 40 mg/d) with that of placebo on the composite co-primary outcomes of time from randomization to death or development of dementia or significant disability and to a major fatal or nonfatal cardiovascular event in 18,000 adults aged 70 and older ([www.staree.org/au](http://www.staree.org/au)). Secondary outcomes include the individual composite endpoint components, new-onset DM, incident

cancer, cognitive decline or incident dementia, frailty or disability, need for permanent residential care, and QOL. Eligible participants must be independent living (without assistance), and exclusion criteria include known ASCVD, DM, dementia or a Modified Mini-Mental State Examination score less than 78 at entry, total cholesterol greater than 290 mg/dL, an estimated glomerular filtration rate less than 45 mL/min per 1.73 m<sup>2</sup>, chronic liver disease, serious intercurrent illness likely to cause death within the next 5 years, unwillingness to stop current statin or other lipid-lowering therapy, absolute contraindication to statin therapy, or long-term use of selected cytochrome P450 3A4 inhibitors.

Although STAREE is expected to bolster the evidence base of the efficacy and safety of statin therapy for primary prevention in older adults, several aspects of the design are worth highlighting. First, it is likely that enrolling participants aged 70 and older will lead to having approximately half of enrollees being aged 70 to 75, which directly overlaps with data available from JUPITER and HOPE-3 and limits much-needed data on those aged 80 and older.<sup>15</sup> Second, exclusion of individuals with common comorbidities (e.g., DM, kidney disease) will lower cardiovascular event rates and reduce generalizability to the growing population of older adults with these comorbidities. Third, inclusion of development of dementia (even if mild) as part of the co-primary endpoint may preclude the ability of the trial to address disability, functional status, and QOL outcomes in individuals with established dementia. Finally, because the trial's main sites are in Australia, limited racial and ethnic diversity and differences in background medical care may affect generalizability of the findings to the increasingly diverse U.S. population of older adults.

## Potential Trial Options to Guide Decision-Making on Statins for Primary Prevention in Octogenarians and Beyond

One or more prospective, placebo-controlled RCTs could address the important knowledge gaps identified regarding the efficacy and safety of statins in persons aged 75 and older without ASCVD, especially those aged 80 and older and with multiple chronic conditions. Future clinical trial design considerations include a traditional efficacy RCT versus a large simple pragmatic RCT embedded in healthcare networks and implemented in “real-world” settings; inclusion and exclusion of participants with specific comorbidities, cardiovascular risk factors, frailty, and functional or cognitive impairment; the optimal lower age cut-off of participants for inclusion in the study ( 70, 75, or 80) to address existing knowledge gaps; choice and daily dosage of statin therapy; and trial duration. Examples of 2 potential trial designs are summarized in Table 4.

Several outcomes were discussed including one representing global health, such as freedom from dementia and disability and an ASCVD efficacy outcome, such as fatal and nonfatal ASCVD events. These outcomes could be considered as primary and secondary endpoints or as co-primary endpoints. A pragmatic RCT could ideally leverage existing networks of healthcare systems (e.g., Health Care Systems Research Network,<sup>36</sup> Cardiovascular Research Network,<sup>37</sup> NIH Collaboratory,<sup>38</sup> Patient-Centered Outcomes Research Network<sup>39</sup>). Randomization could occur at the level of the individual, the site, or the healthcare system.

Many design elements, including variables and outcomes of importance to older adults, could be incorporated into either type of trial design. A recruitment strategy that ensures adequate enrollment of individuals in their 80s and 90s; women; underrepresented minorities; and clinical, functional, and social characteristics consistent with the general U.S. population of older adults without clinical ASCVD would best help to fill knowledge gaps. Additionally, incorporation of validated measures of cognition, physical function, disability, frailty, SAMS, health-related QOL, and burden of multimorbidity are needed in future clinical trials. The lack of evidence supports the need for future placebo-controlled trials in “real-world” older adults who are truly representative of this population. Other considerations for future trials in older adults include specific statin selection and dosage, potential drug–drug interactions, specific statin properties affecting potency (protein-binding, metabolism and clearance), and drug safety considerations. Existing data support the need for future RCTs that exceed 4 years of follow-up to evaluate efficacy for the main endpoints, which could be challenging if recruiting a high proportion of the oldest adults (e.g., aged 85).

## **Feasibility Analyses of the Eligible Population Within Kaiser Permanente Northern California and Kaiser Permanente Northwest**

Retrospective cohort analyses in 2 large integrated healthcare delivery systems providing comprehensive care for approximately 4.8 million people in Northern California, Oregon, and Washington (~0.6 million) presented at the workshop evaluated the feasibility of a primary prevention statin trial in older adults. Adults aged 75 and older with at least 12 months of continuous enrollment before entry and no known ASCVD were identified between October 1, 2010, and September 30, 2015. Of the 269,155 eligible persons aged 75 and older, 41% were receiving a statin at entry. Those with DM (65%) and chronic kidney disease (51%) had the highest rates of statin use. Of those not taking statins at entry, 30% initiated a statin, mainly atorvastatin or simvastatin. For statin users, the annual incidence of death was 6.5% and of the composite of MI or ischemic stroke was 0.3%.

For successful implementation of a primary prevention RCT, the question of equipoise between providers and participants must be assessed. Given that 41% of older adults without ASCVD take statins, further feasibility studies may be necessary to assess whether providers and patients in healthcare systems are willing to be randomly assigned to statin or placebo or to stop a statin that is being taken. Although these preliminary data support the feasibility of an adequately powered RCT, they also highlight a likely limited window of opportunity to conduct such a trial before the use of statin therapy increases further in older adults.

## **Conclusion**

There is a critical evidence gap relating to the benefits and risks of initiating statins for primary prevention in older adults, especially those aged 80 and older with multiple chronic conditions, which existing data or extrapolating evidence from trials in adults younger than 75 cannot address. Elucidation of how age-associated changes in physiology, body composition, and pharmacokinetics may increase vulnerability to statin-related harms and incorporation of validated methods to identify the risk of primary ASCVD events in adults



aged 75 and older are warranted to fill these gaps. One or more prospective, placebo-controlled RCTs that include specific design elements pertinent to age-related changes could provide evidence to support person-centered decision-making regarding whether to initiate statins for primary prevention in adults aged 75 and older without ASCVD. Inclusion of global health outcomes important to older adults, including survival free of dementia and disability, independence, QOL, cognitive function, SAMS, and DM, in future trials would further contribute to informed decision-making. Possible trial designs include traditional RCTs and pragmatic RCTs, which are relevant to the majority of older adults currently seen in clinical practice. Feasibility data from 2 large healthcare delivery systems suggest that there is sufficient power for ASCVD events, but given that more than 40% of adults aged 75 and older without ASCVD are taking statins for primary prevention without supporting evidence of benefit, the timeliness of future trials in this setting is important, as is the willingness of providers and participants to be randomized.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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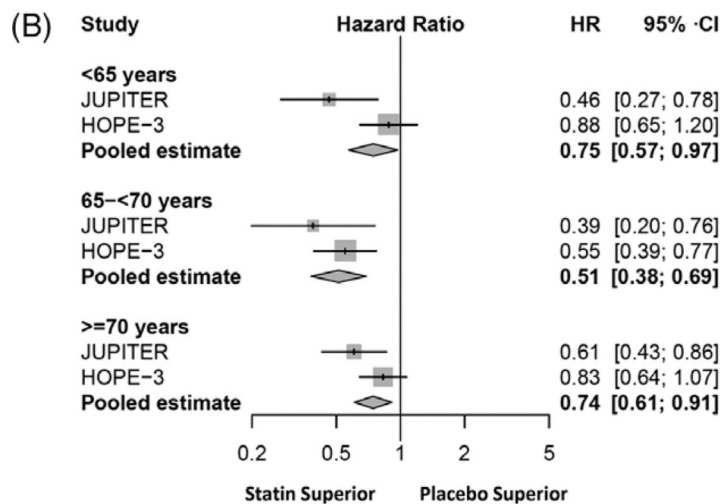
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(A) Effects of rosuvastatin on the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the JUPITER and HOPE-3 primary prevention trials, stratified by age.

Age Group	Trial	N	Rosuvastatin N (IR*)	Placebo N (IR*)
< 65 years	JUPITER	7,458	20 (0.27)	45 (0.59)
	HOPE-3	6,059	78 (0.46)	88 (0.53)
65-< 70 years	JUPITER	4,649	12 (0.24)	30 (0.61)
	HOPE-3	3,559	50 (0.50)	91 (0.91)
≥ 70 years	JUPITER	5,695	51 (0.82)	82 (1.36)
	HOPE-3	3,086	107 (1.25)	125 (1.50)

\*rates are per 100 person-years. The test for heterogeneity by age for the effects of statin therapy on clinical outcomes was non-significant (P=0.10).



**Figure 1.**

Meta-analyses of Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) and Heart Outcomes Prevention Evaluation-3 (HOPE-3) for efficacy of rosuvastatin for primary atherosclerotic cardiovascular disease (ASCVD) prevention in older adults. (A) Effects of rosuvastatin on the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the JUPITER and HOPE-3 primary prevention trials. \*Numbers of individuals at risk, incidence rates, and hazard ratios for nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the JUPITER and HOPE-3 primary prevention trials, stratified according to age. (B) Meta-analysis within age subgroups of the JUPITER and HOPE-3 primary prevention trials evaluating the effects of rosuvastatin on the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Reused with permission from Ridker PM et al. Primary Prevention With Statin Therapy in the Elderly. New Meta-Analyses From the Contemporary JUPITER and HOPE-3 Randomized Trials. *Circulation* 2017;135:1979–1981. Available at <https://www.ahajournals.org/journal/circ>

**Table 1.** Meta-Analyses of Randomized Trials of Statins for Primary Prevention Not Limited to Older Adults

Study	Studies, n	Participants, n	Follow-Up, Years	Age Criteria	Age	CVD Outcome	Non-CVD outcome
Cholesterol Treatment Trialists collaborators <sup>3</sup>	22 statin v placebo 5 high-dose vs low-dose statin	134,537	4.8-5.1	No restriction	59 ± 8 61 ± 9	-For low ASCVD risk (<5.0%), fatal and nonfatal ASCVD event, RR=0.57, 95% CI=0.36-0.89 -For medium ASCVD risk (5.0-9.9%), fatal and nonfatal ASCVD event, RR=0.61, 95% CI=0.5 to -0.74	Annual excess risk of hemorrhagic stroke per 1.0 mmol/L low-density lipoprotein cholesterol reduction was 0.5/1,000 people over 5 years; Absolute excess risk of DM was 0.1% per year
U.S. Preventive Services Task Force <sup>4-6</sup>	19 RCTs; statin vs placebo	71,344	0.5-6	No restriction	51-66	All-cause death, RR=0.86, 95% CI=0.80-0.93; cardiovascular mortality, RR=0.69, 95% CI=0.54-0.88; stroke, RR=0.71, 95% CI=0.62-0.82; myocardial infarction, RR=0.64, 95% CI=0.57-0.71; composite cardiovascular outcomes, RR=0.70, 95% CI=0.63-0.78	Statins vs placebo: No significantly greater risk of myalgia (RR=0.96, 95% CI=0.79-1.16), liver-related harm (RR=1.10, 95% CI=0.90-1.35), or DM (RR=1.05, 95% CI=0.91-1.20). One RCT found that high-intensity statins were associated with greater risk of DM (RR=1.25, 95% CI=1.05-1.49).

CVD=cardiovascular disease; ASCVD=atherosclerotic CVD; RR=relative risk; CI=confidence interval; DM=diabetes mellitus; RCT=randomized controlled trial.

**Table 2.**  
 Meta-Analyses of Randomized Trials of Statins for Primary Prevention in Older Adults

Study	Studies, n	Participants	Follow-Up, Years	Age Criterion, Years	Mean Age, Years	CVD Outcome	Non-CVD outcome
Savarese et al. <sup>13</sup>	7 RCTs, placebo vs statin, 1 open label	N=24,674 without atherosclerotic CVD; 43% female	3.5	65	73	- 1.2% ARR in MI (NNT=84) - 0.7% ARR in stroke (NNT=143) - No significantly lower CVD mortality	No significant difference in all-cause mortality
Teng et al. <sup>14</sup>	8 RCTs, statin vs placebo or usual care <sup>1</sup>	N=25,952 (n=12,974 statin, 12,978 placebo)	3.5	>65	72.7	- Major adverse cardiovascular events (RR=0.82) -MI (RR=0.74) -Non-fatal MI (RR=0.75) -No significant difference in fatal MI or stroke	No significant difference in all-cause mortality or significant adverse events, including myalgia, transaminitis, and new-onset DM
Ridker et al. <sup>15</sup>	2 RCTs, rosuvastatin vs placebo	N=8,781	Median: JUPITER, 1.8 HOPE-3, 5.6	70	JUPITER, median 66 HOPE-3, mean 65.7	-Nonfatal MI, nonfatal ischemic stroke and CV death, HR=0.74, 95% CI=0.61-0.91	JUPITER: DM: rosuvastatin, n=270, 3%; placebo, n=216, 2.4%; HR=1.25, 95% CI=1.05-1.49, P=.01. In those with DM risk factors who were taking rosuvastatin, 134 vascular events or deaths were prevented at the cost of 54 new cases of DM. Progression to DM in those taking rosuvastatin occurred $\approx$ 5.4 weeks earlier than with placebo. HOPE-3: muscle pain or weakness: rosuvastatin, n=367, 5.8%; placebo, n=296, 4.7%, P=.005; no significant difference in withdrawals because of muscle symptoms (rosuvastatin, n=83, 1.3%; placebo, n=76, 1.2%, P=.63); rhabdomyolysis or myopathy (rosuvastatin, n=2; placebo, n=1), cancer (rosuvastatin, n=267; placebo, n=286); cataract surgery (rosuvastatin, n=241, 3.8%; placebo, n=194, 3.1%, P=.02) <sup>17</sup>

RCT=randomized controlled trial; CVD = cardiovascular disease; ARR=absolute risk reduction; NNT=number needed to treat; MI=myocardial infarction; RR=relative risk; HR=hazard ratio; CI=confidence interval; DM=diabetes mellitus.

Evidence Gaps Regarding Statins for Primary Prevention in Adults Aged 75 and Older Without Atherosclerotic Cardiovascular Disease

Table 3.

Characteristics	Area Requiring New Clinical Trial Evidence
Patient groups	<ul style="list-style-type: none"> <li>• Larger numbers of older adults, especially aged 80, with characteristics representative of the target U.S. population (e.g., multimorbidity, at risk for functional or cognitive decline, polypharmacy)</li> <li>• Data in older women</li> <li>• Data in underrepresented subpopulations such as minorities</li> </ul>
Inclusion of measures important to older adults	<ul style="list-style-type: none"> <li>• Universal health outcomes</li> <li>• Measures of cognition, function, health-related quality of life, frailty, multiple chronic condition burden, disability, incident dementia, and atherosclerotic cardiovascular disease</li> </ul>
Time to benefit	<ul style="list-style-type: none"> <li>• Data on optimal time to start or stop statin therapy</li> </ul>
Specific statin	<ul style="list-style-type: none"> <li>• Dose and type of statin based on individualized risk assessment</li> </ul>



**Table 4.** Summary of Possible Randomized Trial Options of Statins for Primary Prevention in Older Adults without Atherosclerotic Cardiovascular Disease (ASCVD)

Design Features	Pragmatic Clinical Trial	Traditional Clinical Trial
Randomization	Individual-level randomization, at level of healthcare system, or according to site or provider within a healthcare system	Individual-level randomization
Age criteria	75, with significant number	80
Target population	No known clinical ASCVD and not currently taking statins. Cohort will include significant number of women, minorities, participants with frailty, mobility limitations, cognitive impairment, targeted comorbidities.	No known clinical ASCVD and not currently taking statins. Cohort will include significant number of women, minorities, participants with frailty, mobility limitations, cognitive impairment, targeted comorbidities.
Intervention	Statin vs placebo. High-dose atorvastatin (80 mg/d) should be avoided. If lower dose initiated, plan for up-titration could be considered, but goal serum LDL-C is unclear in older adults.	Statin vs placebo. High-dose atorvastatin (80 mg/d) should be avoided. If lower dose initiated, plan for up-titration could be considered, but goal serum LDL-C is unclear in older adults.
Variables to be considered for inclusion	Measures of cognitive function, physical function, SAMS, health-related quality of life, disability, comorbidities, medications, symptom burden	Measures of cognitive function, physical function, SAMS, health-related quality of life, disability, comorbidities, medications, symptom burden
Treatment duration	Average 4–5 years	Average 4 years
Outcomes	Two outcomes considered as primary and secondary endpoints vs co-primary endpoints: - Survival free of dementia or persistent physical disability - Fatal and nonfatal CVD events	Two outcomes considered as primary and secondary endpoints vs co-primary endpoints: - Survival free of dementia or persistent physical disability - Fatal and nonfatal CVD events
Sample size	15,000–17,000	13,000
Power	90% at 2-sided alpha of 0.05 to detect 13% reduction in incidence of death, dementia, and persistent physical disability and 18% reduction in incidence of composite CVD outcome	90% at 2-sided alpha of 0.025 to detect 15% reduction in incidence of death, dementia, and persistent physical disability and 18% reduction in incidence of composite CVD outcome

LDL-C=low-density lipoprotein cholesterol, SAMS=statin induced muscle symptoms, CVD=cardiovascular disease.