Statins in Primary Prevention in People Over 80 Years

Elodie Marcellaud, PharmD, MPH[a,b,*], Jeremy Jost, PharmD, PhD[a,b], Achille Tchalla, MD, PhD[c,d], Julien Magne, PhD[a,e], and Victor Aboyans, MD, PhD[a,e]

In the much older population (≥80 years), the management of cardiovascular diseases requires specific research to avoid a plain transposition of medical practice from younger populations. Whether statins are useful in primary prevention in this population is not clear. The 3 intricate issues requiring attention are (1) the impact of hypercholesterolemia on mortality and major adverse cardiovascular events in subjects >80 years, (2) the efficacy of statins to prevent cardiovascular events at this age, and (3) the safety and tolerance of statins in this population. Three systematic reviews were performed using a search on EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, and Web of Science databases including publication until January 2021. Among the 7,617 references identified, 29 were finally retained. Regarding the first objective (16 studies, 121,250 participants), 7 studies (10,241 participants) did not find total cholesterol and low-density lipoprotein levels associated with an increased rate of major cardiovascular events in octogenarians. A total of 6 studies (14,493 participants) found increased levels associated with events, whereas 3 studies (96,516 participants) found the opposite, with increased risk of major adverse cardiovascular events with lower levels of cholesterol. In 8 studies (436,005 participants) addressing the efficacy of statins, most did not indicate a significant decrease in the rate of major cardiovascular events in these subjects. Finally, regarding tolerance (9 studies, 217,088 participants), the most important side effects in this population were muscular, hepatic, and gastrointestinal disorders. These events were more frequent than in the younger population. In conclusion, in the absence of convincing evidence, the benefit of statins in primary prevention for much older patients is not certain. Their prescription in this setting should only be considered case by case, taking into consideration physiological status, co-morbidities, level of risk, and expected life expectancy. Specific trials are mandatory. **(Am J Cardiol 2023;187:62−73)**

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in older patients. In much older patients, age becomes the predominant risk factor for CVD, and the role of cholesterol is controversial.[1] Despite nonconclusive evidence of the impact of cholesterol on mortality in older subjects and the absence of recommendations in this population, the prescription of statins has significantly increased over the past decade. To address the relevance of prescription of statins in primary prevention in octogenarians (and beyond), we performed simultaneously 3 systematic reviews addressing (1) the impact of hypercholesterolemia on mortality and major adverse cardiovascular events (MACEs) in subjects >80 years, (2) the efficacy of statins to prevent cardiovascular events at this age, and (3) the safety and tolerance of statins in this population.

[a]Inserm U1094, IRD U270, University of Limoges, CHU Limoges, EpiMaCT − Epidemiology of Chronic Diseases in Tropical Zone, U1094 Institute of Epidemiology and Tropical Neurology, Omega Health, Limoges, France; [b]Unit of Clinical Pharmacy, Division of Hospital Pharmacy, Limoges Hospital Center, Limoges, France; [c]Division of Geriatrics, Limoges Hospital Center, Limoges, France; [d]VIESANTE, UR 24134 Ageing Frailty Prevention e-Health, OmegaHealth Institute, University of Limoges, Limoges, France; and [e]Division of Cardiology, Limoges Hospital Center, Limoges, France. Manuscript received June 27, 2022; revised manuscript received and accepted October 6, 2022.

Funding: None.

See page 71 for disclosure information.

*Corresponding author: Tel: (33) 55-05-88-53; fax: (33) 55-05-30-13.

E-mail address: elodie.marcellaud@chu-limoges.fr (E. Marcellaud).

Methods

The 3 systematic reviews are presented according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

The study protocols of the different systematic reviews were previously registered on PROSPERO (CRD42020204386; CRD42020205714; CRD42021205727).

The studies included in review number 1, "Cholesterol and Mortality," met the criteria of (1) patients >80 years (or 75 years), (2) not taking lipid-lowering therapy, and (3) reporting MACE (fatal and nonfatal myocardial infarction [MI] or stroke) and all-cause mortality.

Review number 2, "MACE and Statins," includes studies on (1) patients >80 years (or 75 years) without CVD, (2) taking lipid-lowering therapy, (3) reporting MACE, and (4) comparing statins with placebo or lifestyle changes alone.

The studies included in review number 3, "Tolerance and Statins," met the criteria of (1) patients >80 years (or 75 years), (2) taking lipid-lowering therapy, and (3) reporting statin-related adverse events (AEs), including serious AEs and treatment discontinuation because of AEs.

A search on EMBASE (Science Direct, Scopus), MEDLINE (PubMed), Cochrane Central Register of Controlled Trials, and Web of Science databases was performed to identify studies published before January 2021, without time restriction. Only studies on humans and articles in English and French were included.

0002-9149/
https://doi.org/10.1016/j.amjcard.2022.10.015

For these reviews, the search strategy included the following keywords:

1. impact of cholesterol on mortality: "hypercholesterolemia," "high cholesterol," "cardiovascular mortality," "myocardial infarction," and "stroke."
2. efficacy of statins at age >80 years: "cardiovascular mortality," "myocardial infarction," "stroke," "aged over 80," "octogenarian," "elderly," "statin," "prognosis," "outcome."
3. tolerance of statins in the older patient: "tolerance," "safety," "side effect," "elderly," "octogenarian," "aged over 80," "statin," "adverse effects" (subheading), "Drug Related Side Effects and Adverse Reactions" (Medical Subject Headings [MeSH]), "Drug Tolerance" (MeSH), "Patient Safety" (MeSH), "Aged, 80 and over" (MeSH), "Hydroxymethylglutaryl-CoA Reductase Inhibitors" (MeSH).

Although our interest was focused on subjects >80 years, we retained all studies with participants >65 years because they could report results on subgroups by age. We retained data on patients >75 years because data exclusively on patients >80 years were often limited.

We included both observational and interventional studies. Original articles, clinical trials, and meta-analyses were included in the review. The other types of articles (case report, editorial, letter to the editor, research note, conference abstract, systematic review, review article) were excluded. We also conducted manual searches of relevant journals and reference lists of eligible articles to supplement the electronic search.

Two reviewers screened independently article titles and abstracts following the selection criteria using RAYYAN QCRI online application for each of the 3 reviews, review number 1, "Cholesterol and Mortality" (EM, JM), review number 2, "MACE and Statins" (EM, VA), and review number 3 "Tolerance and Statins" (EM, JJ). Full-text articles that potentially met the eligibility criteria were retrieved and reviewed by a reviewer (EM) for final eligibility. Discrepancies were resolved by discussion between the reviewers. In lack of consensus, the advice of a third reviewer (VA, JM, or JJ) was sought to conclude.

One reviewer (EM) extracted independently data using an ad hoc extraction form and entered data into Excel (version 16.16.27).

We collected data on the publication (author, year, publication source), the study (sample characteristics, demographics, definition and criterion used for major cardiovascular events, for total cholesterol [TC] and low-density lipoprotein [LDL]-cholesterol levels, for AEs), the participants (age, gender, history of hypertension, diabetes, current treatment), the study design and characteristics (sampling mechanism, treatment allocation mechanism, duration of follow-up), the intervention (statin studied, type, duration, dose), the comparator group, and outcomes (number of events during the study period, type of event).

The retrieved end points were MACE, overall mortality, occurrence of AEs (all AEs, serious AEs, musculoskeletal events, gastrointestinal events, liver disorders, induced diabetes, induced cancer).

The effect size was assessed using hazard ratio (HR) and 95% confidence intervals (CIs). When results derived from several multivariate models were presented, we extracted the associations of the best-fitting model. For AEs, we extracted the frequency of these events in each group.

To assess the quality of the included randomized studies, Cochrane Risk of Bias Tool was used, considering 6 domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. Judgment of risk of bias was made for each domain according to 3 categories: high risk, low risk, and unclear risk of bias.

The Newcastle-Ottawa Scale was used to assess the quality of included nonrandomized studies. The 3 main perspectives used to assess a study were study group selection, group comparability, and outcome of interest verification for cohort studies. For the risk of bias assessment, a "star system" was developed for each of the 3 perspectives: a maximum of 4 stars in the selection categories, a maximum of 3 stars in the outcome categories, and a maximum of 2 stars for comparability.

In review number 1, "Cholesterol and Mortality," studies comparing the effect of high with low cholesterol levels on cardiovascular or overall mortality were used for the synthesis. Comparative studies (statins vs placebo/usual care) were used to synthesize the results of review number 2, "MACE and Statins," whereas studies comparing statins with placebo/usual care or comparing statins in older patients with statins in younger patients were used in review number 3, "Tolerance and Statins."

Quantitative variables were described using position and dispersion indexes (weighted mean, SD, median, interquartile range). Qualitative variables were described using frequencies and percentages.

Results

Among the 7,617 references initially identified by our 3 database searches, 267 articles were assessed in full text. A total of 29 studies meeting our criteria were selected, involving 724,196 participants (25.3% female), with a weighted mean age of 79.8 years. These studies included 5 clinical trials and 24 observational studies. The study selection process is presented in Figure 1. A total of 16 studies were included in review number 1, "Cholesterol and Mortality" (Table 1), 8 for review number 2, "MACE and Statins" (Tables 2 and 3), and 9 for review number 3, "Tolerance and Statins" (Tables 4 and 5).

The overall methodologic quality of the included trials was moderate. Trials were judged at low risk of bias. The results are shown in Supplementary Tables 1 to 3.

Most of the studies were observational in the general population. A sample of patients with diabetes or with other cardiovascular risk factors than hypercholesterolemia (smoker, overweight, hypertensive) was included. The follow-up periods ranged from 2 to 14 years (median follow-up 7.3 years). The main results are summarized in Table 1. Eight studies (104,355 patients) showed higher mortality in case of lower TC.[2–9] Similar results were found with LDL levels in subjects >80 years.[6,7,9] However, Krumholz

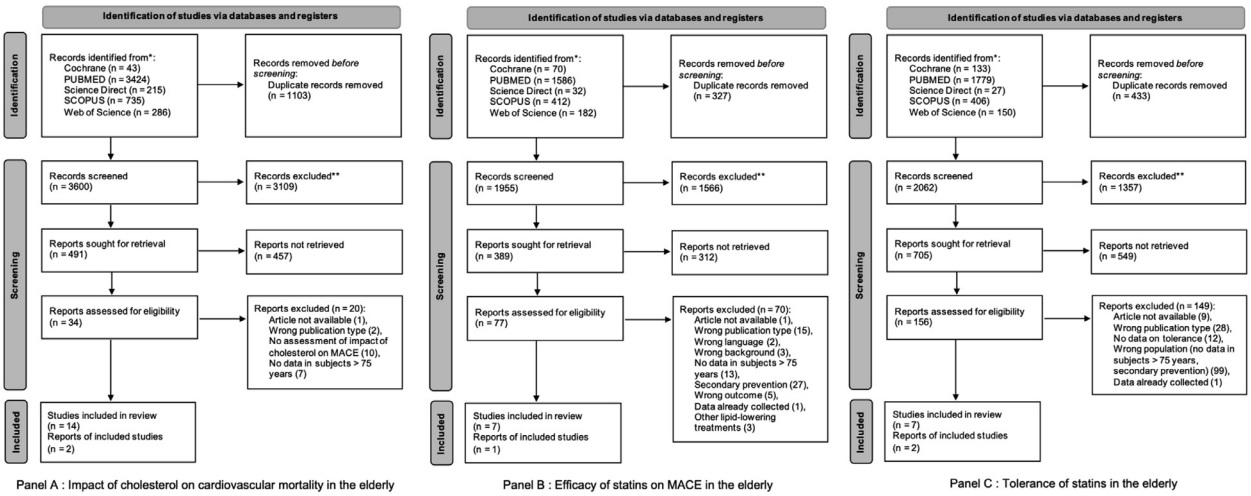

Figure 1. Flow chart of the 3 reviews. (*A*) Impact of cholesterol on cardiovascular mortality in older subjects. (*B*) Efficacy of statins on MACE in older subjects. (*C*) Statins tolerance in older subjects.

et al[10] did not find an association between TC and overall mortality.

In 7 studies (10,241 participants), cardiovascular mortality appeared to be unrelated to TC and LDL levels.[4,6,8–12] Three studies (96,516 participants) reported a decrease in MACE rates with increasing TC levels.[2,5,7] Indeed, Newson et al[5] showed a 21% decrease in cardiovascular mortality for each 1 mmol/L increase in TC (p = 0.01) in subjects >85 years. Wang et al[7] found this association only in women.

In turn, 3 studies (8,355 participants) showed an increased risk of MACE with higher TC levels.[1,3,13] Upmeier et al[1] reported significantly higher cardiovascular mortality with increased TC levels in noninstitutionalized patients aged 70 years (n = 1,032) with 12 years follow-up in Finland. In the Established Populations for Epidemiological Studies of the Elderly project, Corti et al[13] demonstrated that high TC levels predicted an increased risk of death from coronary heart disease in patients >65 years (n = 4,066) after adjustment for cardiovascular risk factors and frailty indicators. Curb et al[14] showed "U-shape" association between TC and LDL and MACE in older Asian-American men (n = 2,424), with greater risk of CHD-mortality in those with low- and high levels of TC and LDL cholesterol than in those in the intermediate ranges. One study (3,188 patients) identified an increased risk of MACE with higher LDL levels.[15] Mortensen et al[15] demonstrated that elevated LDL-cholesterol levels were significantly associated with higher cardiovascular mortality in patients aged 80 to 100 years without cardiovascular history.

Regarding the risk of MI, we found 3 studies (6,834 patients) with a significant association between higher LDL and increased risk of MI.[12,15,16]

Regarding the risk of stroke, Lind et al[8] found that increased LDL levels were significantly associated with a higher risk of stroke at ages 77 and 82 years. This was not found in the other 4 studies investigating the relation between stroke risk and LDL levels.[3,9,12]

Taking all the reports into consideration, the evidence weighs in favor of the lack of significant association between TC and LDL levels and major cardiovascular events in subjects >75 years and free of CVD. The risk associated with TC loses its strength and becomes no longer significant in the older patient, for whom age becomes the predominant risk factor.

Most studies were conducted in general populations; only 2 studies were selectively conducted in older male physicians and ambulatory adults with stage 1 or 2 hypertension with CHD risk factors.[17,18] Follow-up periods ranged from 2 to 7.7 years (median follow-up 5 years). Women were most represented, and >75% of participants had hypertension (Table 2). The main events reported in those studies are reported in Table 3.

The 3 clinical trials included in our review (n = 9,660 participants) reported no association between statin use and overall mortality.[17,19,20] In the 5 observational studies included (n = 452,657 participants), 2 found an association between statin use and overall mortality.[18,21] Orkaby et al[18] reported a significant 18.0% risk reduction under statins in older subjects (p = 0.03).

Regarding the MACE, the Justification for the Use of Statins in Prevention Trial Evaluating Rosuvastatin (JUPITER) (n = 3,239 participants) showed a reduction in the incidence of major cardiovascular events in healthy older subjects without hyperlipidemia but with C-reactive protein levels.[20] The other 3 trials (n = 6,421 participants) did not reveal any significant decrease in the MACE in participants ≥75 years under statins.[17,18]

In 5 observational studies, 2 small studies (with 49 and 124 participants, respectively) did not find any significant decrease in the MACE in participants ≥75 years under statins.[18,22] Ramos et al[22] reported a significant decrease in cardiovascular events in subjects with diabetes aged 75 to 84 years treated with statins, but this association was not found in counterparts without diabetes.

Three observational studies (n = 403,533 participants) have shown a decrease in MACE in older subjects under statins.[21,23,24] Orkaby et al[21] found a decrease in MACE under statins in a cohort of veterans. Kim et al[23] reported an association between statins and reduced MACE in subjects

Table 1
Characteristics and main results of the observational studies included in review number 1, "Cholesterol and Mortality"

First author, country	N participants (% women)	Mean age, years (sd)	Mean follow-up (years)	Compared groups	MACE	All-cause mortality	Limits	High cholesterol risk factor for MACE
Bathum [2], Denmark	26367 (55.7)	> 70*	7.3	TC ≥ 251mg/dL vs TC < 193mg/dL	High TC: reduced risk	High TC: reduced risk		o
Casiglia [3], Italy *CASTEL cohort*	3257 (60.8)	73.8 (5)	12	M : TC ≥ 180mg/dL vs TC < 180mg/dL W : TC ≥ 196mg/dL vs TC < 196mg/dL	High TC: no association in women and increased risk in men	High TC: reduced risk		+
Corti [13], USA *The EPESE study (1997)*	4066 (NA)	79.2	5	TC ≥ 240mg/dL vs TC = 160-200mg/dL TC < 4,15mg/dL vs TC = 160-200mg/dL TC = 160-200mg/dL vs TC = 201-240mg/dL	High TC : increased risk	No association	Information bias (cause of death), missing data	+
Curb [14], USA *Honolulu Heart Program*	2424 (0)	77.6	6	LDL < 120 mg/dL vs LDL = 120-129 mg/dL LDL > 129 mg/dL vs LDL = 120-129 mg/dL TC < 200 mg/dL vs TC = 200-219 mg/dL TC > 219 mg/dL vs TC = 200-219 mg/dL	Increased risk with LDL < 120 mg/dL and > 129 mg/dL Increased risk with TC < 200 mg/dL and > 219 mg/dL	NA	Limited to Japanese-Americans Only men included	+
Krumholz [10], USA *The EPESE Study (1994)*	997 (61)	78.8 (5.9)	5	TC ≥ 240mg/dLvs TC < 200mg/dL	No association	No association	Information bias (cause of death)	o
Liang [4], Swedish *Swedish National study on Aging and Care in Kungsholen (SNAC-K)*	3090 (NA)	73.3 (10.4)	7.5	TC ≥ 240mg/dL vs TC < 200mg/dL	No association	High TC: reduced risk	Lack of mortality data Changes in confounding factors not studied	o
Lind [16,] Sweden	526 (0)	82	5	NA	High LDL: increased risk with MI and stoke	NA	Included only men No study of lifestyle changes	+
Mortensen [15], Denmark *Age specific group 80 − 100 years old*	3188 (56)	83	7,7	NA	High LDL: increased risk	NA		+
Newson [5], Netherlands *Age specific group > 85 years old*	325 (80)	88.7 (3.1)	13.9	NA	High TC: 21% decrease in MACE by increasing 1mM	High TC: reduced risk	Small sample of subjects > 85 years old Survival bias	o

(*continued on next page*)

Table 1 (***Continued***)

First author, country	N participants (% women)	Mean age, years (sd)	Mean follow-up (years)	Compared groups	MACE	All-cause mortality	Limits	High cholesterol risk factor for MACE
Odden [11], USA Age specific group > 85 years *Cardiovascular Health Study*	1542 (63)	88 (3.1)	5	NA	No association	NA		o
Takata [6], Japan	207 (56)	85	10	TC ≥ 290mg/dL vs TC < 175mg/dL	No association	High TC: reduced risk High LDL: reduced risk	Small samples Information bias	o
Tikhonoff [12], Italy	3120 (60.8)	73.8 (5.3)	11.1	NA	High LDL: increased risk with MI & no association with stroke TC: no association	High TC: reduced risk		+
Upmeier [1], Finland	1032 (64)	70*	12	TC > 259mg/dL vs TC < 205mg/dL	High TC: increased risk LDL: no association	No association	Small samples	+
Wang [7], Taipei *Taipei City Geriatric Health Examination Database*	69 824 (51.9)	73.5	3.6	TC > 222mg/dL vs TC between 175-197mg/dL	High TC, High LDL: reduced risk in women	High TC: reduced risk High LDL: reduced risk		o
Weverling-rijnsburger [8] Netherlands *Leiden 85-plus study*	724 (72.4)	89	10	TC > 251mg/dL vs TC < 193mg/dL	TC: no association	TC: 15% decrease by increasing 1mM	Survival bias	o
Weverling-rijnsburger [9] Netherlands *Second cohort of the Leiden 85-Plus Study*	561 (67)	85	2.6	TC > 293mg/dL vs TC < 179mg/dL	LDL / TC: no association	High TC: 1.6 times lower risk High LDL: 1.4 times lower risk		o

CASTEL = CArdiovascular STudy in the ELderly; EPESE = Established Populations for Epidemiologic Studies of the Elderly; LDL = low-density lipoproteins; M = male; MI = myocardial infarction; mM = millimole; TC = total cholesterol; W = women.

* Age at entry.

Table 2
Characteristics of the studies included in review number 2, "MACE and Statins"

Study	Country	Inclusion date	Age at entry (years)	Mean follow-up (years)	n participants (statins/comparator)	Statins vs comparator	Women n (%)	HTA n (%)	Diabetes n (%)
Clinical trials									
ALLHAT-LLT [17]	USA, Puerto Rico, US Virgin Islands, Canada	1994	≥ 75	4.3	726 (375/351)	Pravastatin 40mg vs usual care	412 (56.8)	726 (100)	367 (50.6)
PROSPER [19] *Subgroup primary prevention*	Scotland, Ireland, Netherlands	1997-1999	70 - 82	3.2	3239 (1585/1654)	Pravastatin 40mg vs placebo	1895 (58.5)	2316 (71.5)	395 (12.2)
JUPITER [20] *Subgroup 70 − 97 years*	USA, Canada, Europe, Central and South America, South, Israel, South Africa	2003 - 2006	M ≥ 50 W ≥ 60	2	5695 (2878/2817)	Rosuvastatin 20mg vs placebo	2933 (51.5)	3730 (65.5)	NA
Observational study									
PHS cohort [18]	USA	1999	≥ 70	7.1	2260 (1130/1130)*	Statins vs no statins	0 (0)	1684 (74.5)	294 (13)
VHA cohort [21]	USA	2002 - 2016	≥ 75	6.8	384159 (57178/326981)	Statins (simvastatin, lovastatin, pravastatin, atorvastatin, rosuvastatin, fluvastatin) vs no satins	10372 (2.7)	298876 (77.8)	89893 (23.4)
Cohort SCOPE-75 study [23]	South Korea	2005 - 2016	> 75	5.2	1278 (639/639)*	Statin (Atorvastatin, rosuvastatin, pravastatin) vs no statins	805 (63)	1224 (95.8)	405 (31.7)
SIDIAP cohort [22]	Spanish	2006 - 2007	≥ 75	7.7	46864 (7502/39362)	Statins (simvastatin, pravastatin, lovastatin, Fluvastatin, rosuvastatin, atorvastatin) or no statins	29852 (63.7)	28915 (61.7)	7873 (16.8)
Cohort ASPREE [24]	Australia, USA	2010	≥ 70	5	18096 (5629/12467)	Satins vs no statins	10134 (56)	13463 (74.4)	1864 (10.3)

ALLHAT-LLT = The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASPREE = The Aspirin in Reducing Events in the Elderly; JUPITER = Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; M = male; PHS = Physicians' Health Study; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; SCOPE-75 = Statin and clinical outcomes of primary prevention in subjects aged >75 years; SIDIAP = Spanish Information System for the Development of Research in Primary Care; VHA = Veterans Health Administration; W = women.

* Propensity score match.

Table 3
Main results of the studies included in review number 2, "MACE and Statins"

Study	Mean age (years)	Statins	Comparator	MACE			All-cause mortality		
				n (%) Events (statins)	n (%) Events (comparator)	HR (IC95%)	n (%) Events (statins)	n (%) Events (comparator)	HR (IC95%)
Clinical trials									
ALLHAT-LLT [17]	78.5	Pravastatin 40mg	Usual care	31 (8.3)	39 (11.1)	0.70 (0.43-1.13)	92 (24.5)	65 (18.5)	1.34 (0.98-1.84)
PROSPER [19] *Sub-group primary prevention*	75.4	Pravastatin 40mg	Placebo	181 (11.4)	200 (12.1)	0,94 (0.77-1.15)	298 (10.3)†	306 (10.5)†	0.97 (0.83-1.14)†
JUPITER [20] *Sub-group 70 − 97 years*	74	Rosuvastatin 20mg	Placebo	75 (2.6)	119 (4.2)	0.61 (0.46-0.82)	131 (3.8)	183 (4.7)	0.80 (0.62-1.04)
Observational study									
PHS cohort [18]	76	Statins	No statins	169 (15)	193 (17)	0.86 (0.70-1.06)	227 (20.1)	276 (24.4)	0.82 (0.69-0.98)
VHA cohort [21]	81.1	All statins	No statins	66.3‡	70.4‡	0.92 (0.91-0.94)	78.7‡	98.2‡	0.75 (0.74-0.76)
Cohort SCOPE-75 study [23]	78	Statins (atorvastatin 10-20mg or similar)	No statins	44 (6.9)	77 (12.1)	0.59 (0.41-0.85)	23 (3.6)	43 (6.7)	0.56 (0.34-0.93)
SIDIAP cohort [22] *Non-diabetic cohort*	80.8								
75 − 84 years old		Statins	No statins	600 (12.5)	3229 (11.9)	0.94 (0.86-1.04)	1109 (23.1)	7075 (26.1)	0.98 (0.91-1.05)
≥ 85 years		Statins	No statins	115 (15.5)	801 (12.7)	1.00 (0.80-1.24)	471 (63.4)	4077 (64.5)	1.00 (0.90-1.11)
Diabetic cohort									
75 − 84 years old		Statins	No statins	271 (15.4)	865 (17.7)	0.76 (0.65-0.89)	503 (28.7)	1752 (35.9)	0.84 (0.75-0.94)
≥ 85 years		Statins	No statins	30 (14.9)	159 (15.3)	0.82 (0.53-1.26)	140 (69.7)	696 (67.1)	1.05 (0.86-1.28)
Cohort ASPREE [24]	74.2	All statins	No statins	188 (7.5)	570 (10.3)	0.68 (0.57-0.82)	289 (11.1)	718 (12.4)	0.87 (0.75-1.01)

ALLHAT-LLT = The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASPREE = The Aspirin in Reducing Events in the Elderly; JUPITER = Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; MACE = Major Adverse Cardiovascular Events; PHS = Physicians' Health Study; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; SCOPE-75 = Statin and clinical outcomes of primary prevention in subjects aged >75 years; SIDIAP = Spanish Information System for the Development of Research in Primary Care; VHA = Veterans Health Administration.

† Global cohort.

‡ Events / 1000PA.

Table 4
Characteristics of the clinical trials included in review number 3, "Tolerance and Statins"

Study	N participants (statins/ comparator)	Mean age (years)	Mean follow-up (years)	Statins	Comparator	Reported adverse events (statins vs. comparator)
Bruckert et al.[25]	1229 (607/622)	75.5	4-5	Fluvastatin 80mg	Placebo	Gastrointestinal disorder (1.3% vs 1.6%), muscular adverse effects (0% vs 0.6%), hepatic disorders (1.7% vs 0.3%)
Chan et al.[26]	60 (30/30)	75	0,5	Pravastatin 10mg	Placebo	Gastrointestinal disorders (6.7% vs 10%), muscular adverse effects (3.3% vs 6.7%)
Glynn et al.[20] *JUPITER*	5695 (2878/2817)	≥ 70	2	Rosuvastatin 20mg	Placebo	Gastrointestinal disorders (23.1% vs 22.1%), cancer (5% vs 5.5%), hepatic disorders (2.1% vs 2.1%), incident diabetes (2.9% vs 2.3%), muscular adverse effects (17.3% vs 16.7%)
Shepherd et al.[19] *PROSPER*	5804 (2891/2913)	75.3	3.2	Pravastatin 40mg	Placebo	Myalgia (1.3% vs 1.1%), hepatic disorder (0.04% vs 0.04%), cancer (8.4% vs 6.9%), cognition

>75 years. However, when subgroup analysis was performed in participants aged >80 years, this association was no longer significant (HR 0.69, 95% CI 0.35 to 1.35).[23] Zhou et al[24] used the Aspirin in Reducing Events in the Elderly (ASPREE) trial cohort in the subgroup aged ≥75 years and found that statin use was associated with significantly reduced risks for MACE (adjusted HR 0.71, 95% CI 0.56 to 0.91).

Considering each cardiovascular event, most of the studies (n = 6; n = 432,743 participants) did not indicate any significant decrease in the rates of stroke or MI in participants >75 years under statins.[17−22]

Data on the safety of statins in octogenarians are poorly reported in the literature. The 9 studies included in this review enrolled mainly subjects aged between 75 and 80 years. Seven studies investigated the safety of statins versus placebo,[19,20,22,24−27] and 2 studies investigated older versus younger subjects.[28,29] The main side effects are summarized in Tables 4 and 5.

AEs most frequently reported were musculoskeletal (5%) and gastrointestinal disorders (19%). The occurrence of these events was not significantly different between the statin group and the placebo or usual care group. The reported side effects were more frequent in the older than in the younger subjects, but this difference was not significant.[20,22,28]

In the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, a greater number of cancer cases were reported in participants under pravastatin than in placebo. However, a meta-analysis on pravastatin trials, including the PROSPER trial, found no significant association between this drug and cancer.[19]

In the JUPITER trial, a small but significant increase was found in the risk of developing diabetes in the rosuvastatin group (3% of newly diagnosed diabetes in rosuvastatin group vs 2.4% in placebo).[30] Despite being not significant, a similar proportion was identified in a subgroup analysis of participants >70 years (2.9% of newly diagnosed diabetes in rosuvastatin group vs 2.3% in placebo).[20] Macedo et al[27] reported an increased risk of type 2 diabetes in statin users, apparent as soon as the first year in subjects without hypertension or cardiovascular history.

The cognitive risk associated with statins has been studied in 2 trials. In the ASPREE trial, no association was reported between statin use and dementia (adjusted HR 1.13, 95% CI 0.90 to 1.43).[24] In the PROSPER trial, cognition and statin use were prospectively studied, and pravastatin had no effect on cognitive function.[19]

Discussion

Despite few discordances, most studies were in favor of (1) a lack of association between TC and LDL and global mortality or MACE in subjects >75 years free of CVDs; (2) a lack of significant efficacy of statins to reduce mortality or MACE in the same setting; and (3) a nonsignificant increase of side effects under statins in this population versus younger subjects, without higher incidence than that in placebo in trials. Among these side effects, no increased risk of cognitive issues has been flagged in the trials. Most frequently reported AEs included hepatic, gastrointestinal, and musculoskeletal disorders. However, all these conclusions need to be considered cautiously because specific studies and trials on octogenarians (and beyond) were scarce, and most data were collected from subgroup analysis, broadening the age band to 75+ years to collect some information. Indeed, older subjects were often excluded from randomized clinical trials.

In most studies, we noticed the absence of increased cardiovascular risk with higher LDL-cholesterol and TC levels in 80+ subjects. A U-shape relation between MACE and cholesterol levels has been revealed.[14] Although there is a nonsignificant increase in cardiovascular mortality for very high compared with intermediate levels of TC and LDL cholesterol in patients >80 years, this trend is also observed for low TC and LDL levels. It is likely to be associated with physiological and metabolic changes, such as activation of inflammation and coagulation systems that may occur with aging. Inflammation has also been associated with changes in lipids.[14,31] It has been suggested that low cholesterol in the older patient may be considered a marker of frailty and/or a marker of co-morbidities.[13,32,33] Frailty in older patients is a condition known to increase the risk of

Table 5
Characteristics of observational studies included in review number 3, "Tolerance and Statins"

Study	N participants (statins/ comparator)	Mean age (years)	Mean follow-up (years)	Statins	Comparator	Reported adverse events (statins vs. comparator)
Macedo et al.[27] *CPRD cohort* *Sub-group 80-85 years*	135868 (29516/ 106352)	80-85	5.43*	Atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin	No statins	Incident diabetes (20.3 events per 1000PA vs 13.8 events per 1000PA)
Nanna et al.[29] *PALM registry*	3292 (666/2626)	> 75	NA	Rosuvastatin < 20mg or atorvastatin < 40mg in elderly > 75 years	Rosuvastatin < 20mg or atorvastatin < 40mg in subject < 75 years	Muscle effects (27.3% vs 33.3%)
Ramos et al.[22] *SIDIAP cohort* *Full cohort*	46864 (7502/ 39362)	> 75	7.7	Statins	No statins	Myopathy (0% vs 0.1%), incident cancer (14.6% vs 14.5%), hepatic disorders (0.07% vs 0.04%)
Skilving et al.[28]	180 (33/147)	64.7	1	Simvastatin ≥ 75 years	Simvastatin < 75 years	Myopathy (26% vs 14%)
Zhou et al.,[24] *Cohort SIDIAP*	18096 (5629/ 12467)	≥ 70	5	Statins	No statins	Dementia (6.9% vs 6.3%)

disability and need for care.[34] Low total cholesterol has also a strong association with malnutrition.[35,36]

Despite the absence of any convincing evidence of cardiovascular mortality risk associated with cholesterol levels in octogenarians, statins are widely used in primary prevention in this population. It appears that statin use is not associated with a reduction in cardiovascular events. A meta-analysis including 28 randomized clinical trials showed that the reduction in major cardiovascular events was proportionally lower in subjects >75 years than in younger subjects. In a subgroup analysis of patients treated for primary prevention, the reduction in major cardiovascular events was not significant.[37] This makes age the most important risk factor for cardiovascular events.

To date, there are no data to prove that much older subjects would benefit most from statin therapy.[38] Trials addressing the "elderly," such as the PROSPER trial, enrolled patients aged 70 to 82 years with an average age of 75.4 years.[19] There is no evidence to suggest that treating older subjects with statins for several years would prolong life expectancy.[39] Currently, the Statin Therapy for Reducing Events in the Elderly (STAREE) trial (NCT02099123) is investigating whether treatment with atorvastatin 40 mg compared with placebo prolongs overall survival or disability-free survival in healthy older adults (≥70 years). Beyond the highly expected general results, a closer look at participants >80 years of age will be important.

Table 6
Scores proposed in the literature for a geriatric assessment

Geriatric assessment	Score
Nutritional status	Mini Nutritional Assessment (MNA)
Functional evaluation	Activities of Daily Living (ADL), Instrumental Activities of Daily Living (iADL)
Mobility assessment	Short Physical Performant Battery (SPPB)
Mental health functions	
Cognitive disorders	Mental-State Examination (MMSE)
Mood disorders	Mini Geriatric Depression Scale (Mini-GDS)
Co-morbidities	Charlson Comorbidity Index (CCI)
Frailty	Clinical Frailty Scale (CFS)

The 2013 guideline from the American College of Cardiology and the American Heart Association showed no direct evidence of benefit from the use of statins in primary prevention in subjects >75 years.[40] The 2019 European Society of Cardiology guidelines on Dyslipidemias allowed the possibility for prescribing statins in primary prevention in patients >75 years at high or very high risk.[41] This is based on the data from the analysis of 2,200 subjects in this age group in the Cholesterol Treatment Trialists' Collaboration, with a 13% risk reduction of MACE per 1-mmol-cholesterol reduction.[37] However, the results were no longer significant when focused on participants without vascular disease, and the impact on mortality was not reported.

Safety data in this population are also limited because of the small number of older subjects included in randomized clinical trials. Statins appear to have overall a good safety profile in older subjects. Nevertheless, the polypharmacy and co-morbidities in this population may favor the appearance of adverse effects. It is plausible that older subjects attribute statin-related AEs to their chronic disease and/or age and would be less likely to complain. Older adults are at greater risk for adverse muscle effects because of age-related alterations in drug metabolism, low muscle mass, polypharmacy, and co-morbidities. In addition, the clinical effect of statin-associated muscle effects on functional impairment, fall risk, and disability is likely to be greater in older adults.[42] Regarding the risk of cognitive impairment associated with statins issued by the Food and Drug Administration in 2012, recent data are reassuring.

The older population is very heterogeneous, ranging from fully physically and intellectually active subjects to frail subjects and even subjects with disabilities and dementia. A thorough assessment is therefore necessary before discussing case by case the interest in statins in this setting.[43] The recent publication of SCORE-OP (Systematic COronary Risk Evaluation Older Persons), a specific scale to assess the cardiovascular risk in older patients recommended in the latest European guidelines, could be of major

interest for taking the decision.[44] However, this scale identifies all subjects >80 years as being at very high cardiovascular risk. To guide the reader in a quick assessment of physical and cognitive health and life expectancy in older subjects, Table 6 enlists some scores proposed in the literature. In some cases, referral to a geriatric specialist may be necessary for a comprehensive geriatric assessment.

For those reaching these ages who were under statins initiated at a younger age, it is conceivable to continue the treatment if well tolerated, in the absence of occurrence of other conditions which may challenge its continuation (e.g., the occurrence of end-stage renal disease or severe heart failure, in which the effect of statins has been shown as neutral).[45,46] In the latter cases, deprescription would be wise. It appears that survival is not affected when statins prescribed for primary or secondary prevention of CVD are discontinued in subjects with limited life expectancy.[47] Recently, various observational studies evaluating the association between statin discontinuation and the rate of MACE in subjects ≥75 years on long-term statin therapy have been published. During 5.5 years of follow-up, Thompson et al[48] showed that statin discontinuation was associated with a higher rate of MACE than was continued statin therapy in older patients receiving long-term statin therapy for primary prevention (HR 1.32, 95% CI 1.18 to 1.48). Rea et al[49] reported that statin discontinuation was associated with an increased risk of cardiovascular events (HR 1.14, 95% CI 1.03 to 1.26). Giral et al[50] have also shown that statin discontinuation was associated with an increased risk of hospitalization for cardiovascular events in 75-year-old subjects without history of CVD during 2.5 years of follow-up (HR 1.33, 95% CI 1.18 to 1.50). In these different observational studies, the reasons for statin discontinuation were not known, constituting potentially a bias for the interpretation of the results.

Discontinuing statin therapy in some patients may improve quality of life while reducing overall health care costs. Finally, the choice to continue or not statin therapy requires patient-centered decision making with an unbiased discussion between the physician and the patient.

Our review presents some limitations, mainly related to the lack of ad hoc trials and cohorts in much older subjects, and we cannot exclude that the available data present some selection bias with the exclusion of most patients with diseases and frailty. All studies collected in this systematic review are not concordant. The methods used allow us to collect qualitative and not quantitative data.

In our systematic review, we addressed 3 different issues in the same report. We believed that this is a strength of our systematic review to address the 3 intricate questions regarding the pros and cons for the prescription or deprescription of statins in much older patients.

In conclusion, in the light of our systematic review, the association between hypercholesterolemia and the occurrence of cardiovascular events and mortality is weak in older patients. In primary prevention, the usefulness of statins in octogenarians remains uncertain. Statins should only be considered with caution, taking into consideration the general physiological state and frailty, the presence of comorbidities, the estimation of cardiovascular risk, life expectancy, and individual preference. Despite more than 30 years of use in clinical practice, there is still room for trials in this setting. Although the results of the STAREE trial (NCT02099123) in primary prevention in adults >70 years are highly awaited, we hope that the subgroup >80 years will be large enough to address our question.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.10.015.

1. Upmeier E, Lavonius S, Lehtonen A, Viitanen M, Isoaho H, Arve S. Serum lipids and their association with mortality in the elderly: a prospective cohort study. *Aging Clin Exp Res* 2009;21:424–430.
2. Bathum L, Depont Christensen R, Engers Pedersen L, Lyngsie Pedersen P, Larsen J, Nexøe J. Association of lipoprotein levels with mortality in subjects aged 50 + without previous diabetes or cardiovascular disease: a population-based register study. *Scand J Prim Health Care* 2013;31:172–180.
3. Casiglia E, Mazza A, Tikhonoff V, Scarpa R, Schiavon L, Pessina AC. Total cholesterol and mortality in the elderly. *J Intern Med* 2003;254:353–362.
4. Liang Y, Vetrano DL, Qiu C. Serum total cholesterol and risk of cardiovascular and non-cardiovascular mortality in old age: a population-based study. *BMC Geriatr* 2017;17:294.
5. Newson RS, Felix JF, Heeringa J, Hofman A, Witteman JCM, Tiemeier H. Association between serum cholesterol and noncardiovascular mortality in older age. *J Am Geriatr Soc* 2011;59:1779–1785.
6. Takata Y, Ansai T, Soh I, Awano S, Nakamichi I, Akifusa S, Goto K, Yoshida A, Fujii H, Fujisawa R, Sonoki K. Serum total cholesterol concentration and 10-year mortality in an 85-year-old population. *Clin Interv Aging* 2014;9:293–300.
7. Wang MC, Hu HY, Lin IF, Chuang JT. Plasma lipid concentrations and survival in geriatric population: a retrospective cohort study. *Medicine (Baltimore)* 2019;98:e18154.
8. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet* 1997;350:1119–1123.
9. Weverling-Rijnsburger AWE, Jonkers IJAM, van Exel E, Gussekloo J, Westendorp RGJ. High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Arch Intern Med* 2003;163:1549–1554.
10. Krumholz HM, Seeman TE, Merrill SS, Mendes de Leon CF, Vaccarino V, Silverman DI, Tsukahara R, Ostfeld AM, Berkman LF. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994;272:1335–1340.
11. Odden MC, Shlipak MG, Whitson HE, Katz R, Kearney PM, Defilippi C, Shastri S, Sarnak MJ, Siscovick DS, Cushman M, Psaty BM, Newman AB. Risk factors for cardiovascular disease across the spectrum of older age: the cardiovascular health study. *Atherosclerosis* 2014;237:336–342.
12. Tikhonoff V, Casiglia E, Mazza A, Scarpa R, Thijs L, Pessina AC, Staessen JA. Low-density lipoprotein cholesterol and mortality in older people. *J Am Geriatr Soc* 2005;53:2159–2164.
13. Corti MC, Guralnik JM, Salive ME, Harris T, Ferrucci L, Glynn RJ, Havlik RJ. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med* 1997;126:753–760.
14. Curb JD, Abbott RD, Rodriguez BL, Masaki K, Popper J, Chen R, Petrovitch H, Blanchette P, Schatz I, Yano K. Prospective association between low and high total and low-density lipoprotein cholesterol and coronary heart disease in elderly men. *J Am Geriatr Soc* 2004;52:1975–1980.

15. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70−100 years: a contemporary primary prevention cohort. *Lancet* 2020;396:1644–1652.
16. Lind L, Sundström J, Ärnlöv J, Lampa E. Impact of aging on the strength of cardiovascular risk factors: a longitudinal study over 40 years. *J Am Heart Assoc* 2018;7:e007061.
17. Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, Pressel SL, Blaum CS, ALLHAT Collaborative Research Group. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. *JAMA Intern Med* 2017;177:955–965.
18. Orkaby AR, Gaziano JM, Djousse L, Driver JA. Statins for primary prevention of cardiovascular events and mortality in older men. *J Am Geriatr Soc* 2017;65:2362–2368.
19. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG. PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;360:1623–1630.
20. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons With elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med* 2010;152:488.
21. Orkaby AR, Driver JA, Ho YL, Lu B, Costa L, Honerlaw J, Galloway A, Vassy JL, Forman DE, Gaziano JM, Gagnon DR, Wilson PWF, Cho K, Djousse L. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. *JAMA* 2020;324:68–78.
22. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L, Blanch J, Marrugat J, Elosua R, Grau M, Elosua-Bayes M, García-Ortiz L, Garcia-Gil M. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ* 2018;362:k3359.
23. Kim K, Lee CJ, Shim CY, Kim JS, Kim BK, Park S, Chang HJ, Hong GR, Ko YG, Kang SM, Choi D, Ha JW, Hong MK, Jang Y, Lee SH. Statin and clinical outcomes of primary prevention in individuals aged >75 years: the SCOPE-75 study. *Atherosclerosis* 2019;284:31–36.
24. Zhou Z, Ofori-Asenso R, Curtis AJ, Breslin M, Wolfe R, McNeil JJ, Murray AM, Ernst ME, Reid CM, Lockery JE, Woods RL, Tonkin AM, Nelson MR. Association of statin use With disability-free survival and cardiovascular disease among healthy older adults. *J Am Coll Cardiol* 2020;76:17–27.
25. Bruckert E, Lièvre M, Giral P, Crepaldi G, Masana L, Vrolix M, Leitersdorf E, Dejager S. Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients. *Am J Geriatr Cardiol* 2003;12:225–231.
26. Chan P, Tomlinson B, Lee CB, Pan WH, Lee YS. Beneficial effects of pravastatin on fasting hyperinsulinemia in elderly hypertensive hypercholesterolemic subjects. *Hypertension* 1996;28:647–651.
27. Macedo AF, Douglas I, Smeeth L, Forbes H, Ebrahim S. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice pesearch datalink. *BMC Cardiovasc Disord* 2014;14:85.
28. Skilving I, Eriksson M, Rane A, Ovesjö ML. Statin-induced myopathy in a usual care setting-a prospective observational study of gender differences. *Eur J Clin Pharmacol* 2016;72:1171–1176.
29. Nanna MG, Navar AM, Wang TY, Mi X, Virani SS, Louie MJ, Lee LV, Goldberg AC, Roger VL, Robinson J, Peterson ED. Statin use and adverse effects among adults >75 years of age: insights from the patient and provider assessment of lipid management (PALM) registry. *J Am Heart Assoc* 2018;7:e008546.
30. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, Study Group JUPITER. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–2207.
31. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J. Fried LP, Cardiovascular Health Study. Frailty and activation of the inflammation and coagulation systems with and without clinical Comorbidities: Results from the cardiovascular health study. *Arch Intern Med* 2002;162:2333–2341.
32. Schupf N, Costa R, Luchsinger J, Tang MX, Lee JH, Mayeux R. Relationship between plasma lipids and all-cause mortality in nondemented elderly. *J Am Geriatr Soc* 2005;53:219–226.
33. Reuben DB, Ix JH, Greendale GA, Seeman TE. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: MacArthur studies of successful aging. *J Am Geriatr Soc* 1999;47:402–406.
34. Morley JE, Perry HM, Miller DK. Editorial: something about frailty. *J Gerontol A Biol Sci Med Sci* 2002;57:M698–M704.
35. Schalk BWM, Visser M, Deeg DJH, Bouter LM. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. *Age Ageing* 2004;33:266–272.
36. Hazzard WR. Depressed albumin and high-density lipoprotein cholesterol: signposts along the final common pathway of frailty. *J Am Geriatr Soc* 2001;49:1253–1254.
37. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;393:407–415.
38. Boccara F. Never too old for lipid-lowering therapy. *Arch Cardiovasc Dis* 2021;114:524–526.
39. Lloyd SM, Stott DJ, de Craen AJM, Kearney PM, Sattar N, Perry I, Packard CJ, Briggs A, Marchbank L, Comber H, Jukema JW, Westendorp RGJ, Trompet S, Buckley BM, Ford I. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *PLoS One* 2013;8:e72642.
40. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):3024-3025] [published correction appears in J Am Coll Cardiol. 2015 Dec 22;66(24):2812]. *J Am Coll Cardiol* 2014;63:2889–2934.
41. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188.
42. Rich MW. Aggressive lipid management in very elderly adults: less is more. *J Am Geriatr Soc* 2014;62:945–947.
43. Richter D, Guasti L, Walker D, Lambrinou E, Lionis C, Abreu A, Savelieva I, Fumagalli S, Bo M, Rocca B, Jensen MT, Pierard L, Sudano I, Aboyans V, Asteggiano R. Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A Consensus Document of the Council for Cardiology Practice (CCP), Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPCCS). *Eur J Prev Cardiol* 2022;29:216–227.
44. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B, ESC National Cardiac Societies, ESC Scientific Document Group Visseren. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227–3337.
45. Chan KE, Thadhani R, Lazarus JM, Hakim RM. Modeling the 4-D study: statins and cardiovascular outcomes in long-term hemodialysis patients with diabetes. *Clin J Am Soc Nephrol* 2010;5:856–866.

46. Kjekshus J, Dunselman P, Blideskog M, Eskilson C, Hjalmarson A, McMurray JV, Waagstein F, Wedel H, Wessman P, Wikstrand J, CORONA Study Group. A statin in the treatment of heart failure? Controlled rosuvastatin multinational study in heart failure (CORONA): study design and baseline characteristics. *Eur J Heart Fail* 2005;7:1059–1069.
47. Kutner JS, Blatchford PJ, Taylor DH, Ritchie CS, Bull JH, Fairclough DL, Hanson LC, LeBlanc TW, Samsa GP, Wolf S, Aziz NM, Currow DC, Ferrell B, Wagner-Johnston N, Zafar SY, Cleary JF, Dev S, Goode PS, Kamal AH, Kassner C, Kvale EA, McCallum JG, Ogunseitan AB, Pantilat SZ, Portenoy RK, Prince-Paul M, Sloan JA, Swetz KM, Von Gunten CF, Abernethy AP. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med* 2015;175:691–700.
48. Thompson W, Morin L, Jarbøl DE, Andersen JH, Ernst MT, Nielsen JB, Haastrup P, Schmidt M, Pottegård A. Statin discontinuation and cardiovascular events among older people in Denmark. *JAMA Netw Open* 2021;4:e2136802.
49. Rea F, Biffi A, Ronco R, Franchi M, Cammarota S, Citarella A, Conti V, Filippelli A, Sellitto C, Corrao G. Cardiovascular outcomes and mortality associated with discontinuing statins in older patients receiving polypharmacy. *JAMA Netw Open* 2021;4:e2113186.
50. Giral P, Neumann A, Weill A, Coste J. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J* 2019;40:3516–3525.