Lipid-Lowering Agents in Older Individuals: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background: The efficacy of lipid-lowering agents on patient-important outcomes in older individuals is unclear.

Methods: We included randomized trials that enrolled individuals aged 65 years or older and that included at least 1 year of follow-up.
Pairs of reviewers selected and appraised the trials.

Results: We included 23 trials that enrolled 60,194 elderly patients. For primary prevention, statins reduced the risk of coronary artery disease [CAD; relative risk (RR): 0.79, 95% CI: 0.68 to 0.91] and myocardial infarction (MI; RR: 0.45, 95% CI: 0.31 to 0.66) but not all-cause or cardiovascular mortality or stroke. These effects were imprecise in patients with diabetes, but there was no significant interaction between diabetes status and the intervention effect. For secondary prevention, statins reduced all-cause mortality (RR: 0.80, 95% CI: 0.73 to 0.89), cardiovascular mortality (RR: 0.68, 95% CI: 0.58 to 0.79), CAD (RR: 0.68, 95% CI: 0.61 to 0.77), MI (RR: 0.68, 95% CI: 0.59 to 0.79), and revascularization (RR: 0.68, 95% CI: 0.61 to 0.77). Intensive (vs less-intensive) statin therapy reduced the risk of CAD and heart failure. Niacin did not reduce the risk of revascularization, and fibrates did not reduce the risk of stroke, cardiovascular mortality, or CAD.

Conclusion: High-certainty evidence supports statin use for secondary prevention in older individuals. Evidence for primary prevention is less certain. Data in older individuals with diabetes are limited; however, no empirical evidence has shown a significant difference based on diabetes status. **(*J Clin Endocrinol Metab* 104: 1585–1594, 2019)**

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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; I^2, measurement of heterogeneity; LDL, low-density lipoprotein; MI, myocardial infarction; RR, relative risk; RRR, ratio of the relative risk; T2DM, type 2 diabetes mellitis.

It is estimated that in 2050, the proportion of individuals aged 65 years or older will double and reach 16% of the total population (1). The prevalence of atherosclerotic cardiovascular diseases (ASCVDs) is higher in older individuals. Approximately 20% to 30% of myocardial infarction (MI) events that lead to hospitalization or death are in older individuals of whom ~70% suffer from coronary artery disease (CAD) (2, 3). Therefore, primary and secondary prevention of cardiovascular disease in this population is paramount.

Several lipid-lowering therapies have been used for primary and secondary prevention. As a result of safety concerns, niacin and fibrates are not usually recommended in the elderly (4). Statins are often recommended for secondary prevention in individuals aged 65 to 75 years, but the guidelines and recommendations are not consistent as age increases (≥75 years) (5) or for primary prevention in older individuals (≥65 years) (6). These discrepancies in existing recommendations reflect the paucity of evidence showing the benefit in the elderly (65 to 75 years) and very elderly (≥75 years) populations.

The Endocrine Society has formed a task force to develop clinical practice guidelines for the management of diabetes in older adults. This task force has commissioned this systematic review to summarize all available up-to-date evidence in older individuals assessing the effects of lipid-lowering agents in primary and secondary prevention. With the consideration that data in older individuals with diabetes are limited and mainly derived from subgroup analyses of randomized trials, this evidence synthesis was designed to address all individuals aged 65 years and older (with and without diabetes). If sufficient data on individuals with diabetes were found, then they would be summarized separately. If no significant interaction were noted (*i.e.*, the effect of statins did not statistically differ between those with and those without diabetes), then the overall effect may be extrapolated to older individuals with diabetes.

Methods

This systematic review was performed following a prespecified, unpublished protocol that was approved by the Endocrine Society. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (7). Supplemental Material to this manuscript is publicly shared (8).

Eligibility criteria

We included randomized clinical trials measuring the effects of statins, fibrates, niacin, or different low-density lipoprotein (LDL) targets on cardiovascular outcomes in individuals aged 65 years or older. We included trials comparing different forms and doses of statins, fibrates, or niacin and trials comparing statins, fibrates, or niacin with placebo or usual care. The outcomes of interest were all-cause mortality, cardiovascular mortality, MI, CAD, heart failure, stroke, coronary revascularization, and quality of life. The included trials had to have a minimum duration of 12 months of follow-up. We included trials regardless of the language of publication. We excluded trials that included combinations of the included interventions; perioperative management; alternative medicine interventions, such as herbs and supplements; physical activity; or other drugs.

Data sources and searches

A medical reference librarian developed and executed the search strategy. We searched Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, and Scopus from the inception of each database to 29 June 2016. We first followed an umbrella review approach (9–12), in which we identified published systematic reviews and selected trials from these reviews. A second search was performed to update the search strategies of existing systematic reviews. This was not necessary for niacin (13) but was deemed necessary for statins (14) and fibrates (15) (updated through 23 August 2016).

Study selection

Search results were uploaded into an online platform (DistillerSR, Evidence Partners, Ottawa, ON, Canada). Abstract and full-text screening was performed by 10 reviewers (O.J.P., L.L.-M., V.S., R.R.-G., G.S.-B., N.A.-V., K.B., A.H., M.R.G., J.P.B.) who worked independently and in duplicate. References included by at least one reviewer were retrieved. Following the abstract screening, the eligibility of the reports was assessed through full-text screening. Any disagreements were resolved by a consensus between two reviewers (O.J.P. and L.L.-M.). Additional references were sought from clinical experts from the Endocrine Society.

Data collection and management

The reviewers performed data extraction independently and in duplicate using a standardized form. Reviewers used a web-based data collection form (DistillerSR) to extract (i) inclusion and exclusion criteria, (ii) baseline characteristics [mean age, sex, mean LDL, type 2 diabetes mellitus (T2DM), hypertension, and history of cardiovascular disease], (iii) intervention characteristics (type of lipid-lowering agent or LDL target goal, dose, frequency, and duration), (iv) events and risk measures for outcomes of interest at the longest follow-up time (all-cause mortality, cardiovascular mortality, MI, acute coronary syndrome, heart failure, stroke, coronary revascularization, and quality of life), (v) whether the trial was performed in an elderly population or if the trial planned a subgroup analysis according to age, (iv) whether the trial was stopped early and if so, the justification, and (vii) risk of bias indicators.

Through the inclusion and exclusion criteria, we classified trials as either a primary or a secondary prevention trial following the definition reported in the 2013 American College of Cardiology/American Heart Association "Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults" (4). Trials were classified as primary prevention when they included people without ASCVDs, such as coronary heart disease, stroke, and atherosclerotic peripheral artery disease. Secondary prevention trials included people with any of these conditions.

For trials reporting fatal and nonfatal events, we extracted information on the combined outcome (*e.g.*, fatal and nonfatal stroke). If this information was not available, we extracted data on

nonfatal events. If cardiovascular mortality was not reported, it was imputed from death events as a result of MI, acute coronary syndrome, heart failure, stroke, or coronary revascularization.

Risk of bias

The risk of bias was assessed using the Cochrane Collaboration tool for randomized clinical trials (16). This tool takes into consideration seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. We summarized the risk of bias in all domains to produce an overall risk of bias for every trial, which primarily depended on random sequence generation and incomplete outcome data. This overall judgment was "high" if there was concern for high risk of bias in either of these two domains, "unclear" if the risk of bias was judged to be unclear in at least one of the domains, or "low" if risk of bias was judged to be low for both domains. As a result of the nature of the interventions and outcomes, we chose random sequence generation and incomplete outcome data as key quality domains owing to their relevance and the potential influence on effect estimates, respectively (17). Disagreements were resolved by two reviewers (O.J.P. and L.L.-M.).

Summary measures and synthesis of results

We calculated relative risks (RRs) and 95% CIs for each outcome of interest with the application of the random-effects model. Heterogeneity was assessed visually by inspection of forest plots and use of measurement of heterogeneity (I^2; >50% suggests a high level of inconsistency across trials). Possible causes of heterogeneity were explored using various *a priori* established subgroup analyses. For the subgroup analyses, we tested for interactions among subgroups following the method suggested by Altman and Bland (18): we calculated the ratio of the RRs (RRR) of the subgroups. One subgroup analysis was based on primary vs secondary prevention. We also explored the effect of T2DM, age strata (≥65 to 75 years, ≥75 years), and hypertension. When possible, we performed sensitivity analyses using age, trials stopped early, funding by industry, or risk of bias criteria. All statistical analyses were performed using Stata v15.0 (StataCorp LLC, College Station, TX).

Certainty in the body of evidence

The certainty of the evidence (also referred to as the quality of evidence) for each outcome was evaluated with the Grading of Recommendations Assessment, Development and Evaluation approach (19). Randomized trials start as having a high certainty of evidence but can be downgraded for the following reasons: (i) risk of bias, (ii) inconsistency, (iii) indirectness, (iv) imprecision, and (v) publication bias. Each domain was assessed as to what extent it could modify the results (effect size). Each outcome was judged as unlikely (no concern), likely (serious concern), or very likely (very serious concern) to have an impact on the certainty of the results. Estimates were judged imprecise if their 95% CI did not exclude an important benefit or harm, regardless of sample size.

Results

Characteristics of the included trials

We included 23 trials that enrolled a total of 60,194 individuals aged 65 years or older. The process of study selection is depicted in the online repository (8). One trial compared niacin with placebo (145 participants) (20), two trials compared fibrates with placebo (1266 participants) (21, 22), 17 trials compared statins with placebo (50,322 participants) (23–39), and three trials compared intensive statin therapy with less-intensive statin therapy (8,461 participants) (40–42). Only four (17%) trials, which included a total of 8071 participants, included solely people aged 65 years or older (20, 23, 31, 40). One-third of the trials reported data that were relevant to this review as a subgroup analysis in older trial participants (22, 24–30, 32–39, 41, 42). Both trials assessing the effects of fibrates included people with ASCVD (secondary prevention) (21, 22). Of the trials assessing the effects of statins compared with placebo, nine trials included people without known ASCVD (primary prevention) (23–29, 31, 43), and eight trials included people with known ASCVD (secondary prevention) (31–38). Moreover, three trials assessing the effect of intensive statin compared with less-intensive statin intervention were secondary prevention trials (40–42). Overall, eight (35%) trials were judged as having a low risk of bias (22, 26, 27, 31, 33–35, 39), and 15 (65%) had an unclear status (20, 21, 23–25, 28–30, 32, 36–38, 40–42). Details are provided in the online repository (8).

Primary prevention in trials comparing statins with placebo trials

Nine primary prevention trials with a follow-up time ranging from 1 to 8 years included a total of 24,246 elderly patients without ASCVD (23–29, 31, 43). Three trials used pravastatin in doses of 10 to 40 mg (29, 31, 43), two trials used atorvastatin in doses of 10 mg (25, 26), one trial used lovastatin in doses of 20 to 40 mg (24), and one trial used fluvastatin XL in a dose of 80 mg (23). Statins, compared with placebo, significantly reduced the risk of CAD (RR: 0.79, 95% CI: 0.68 to 0.91; moderate certainty) and MI (RR: 0.45, 95% CI: 0.31 to 0.66; high certainty). In contrast, the risk of all-cause mortality, cardiovascular mortality, heart failure (all patients were hypertensive), revascularization, and stroke was not significantly reduced by the intervention (Fig. 1; Table 1).

Subgroup analysis

A subgroup analysis, according to age (≥65 to 75 years and ≥75 years), did not show any significant influence of age on all-cause mortality, cardiovascular mortality, heart failure, or stroke. For CAD, the risk remained consistent in the subgroup of patients aged ≥65 to 75 years (RR: 0.77, 95% CI: 0.61 to 0.97; moderate certainty), but the risk was not significant in the subgroup of patients aged ≥75 years (RR: 0.70, 95% CI: 0.43 to 1.13; low certainty); nonetheless, the difference between the subgroups was nonsignificant (RRR: 1.10, 95% CI: 0.64 to 1.88). The reduction of all-cause mortality, cardiovascular mortality, and stroke risk as a

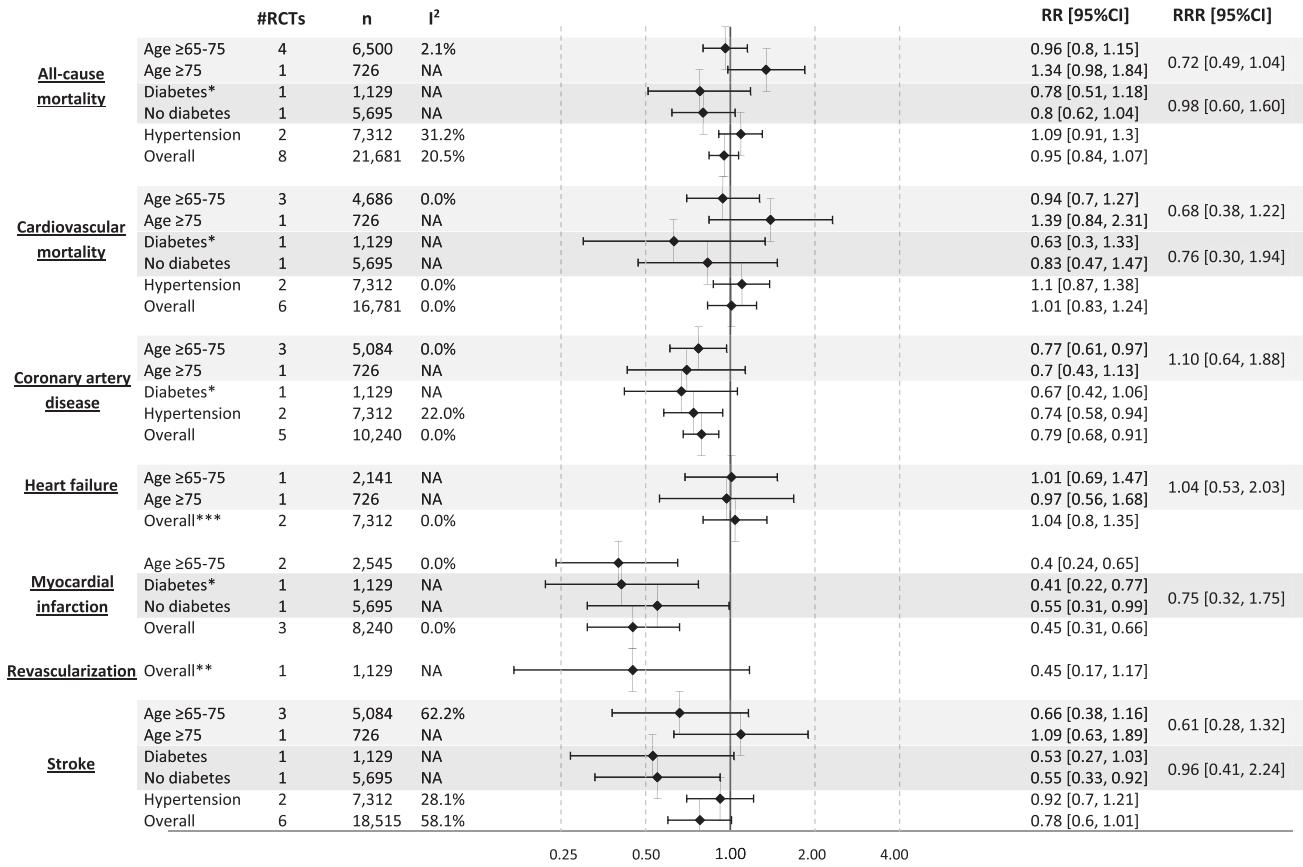

Figure 1. Primary prevention forest plot comparing statins with placebo. *All participants were ≥65 to 75 years. **All participants were ≥65 to 75 years and had diabetes. ***All participants were hypertensive. #, number; n, number of participants.

result of treatment with statins compared with placebo was not different in the elderly population with and without T2DM. One study reported that statins, compared with placebo, did not significantly reduce the risk of CAD in elderly patients with T2DM (RR: 0.67, 95% CI: 0.42 to 1.06; moderate certainty; Fig. 1; Table 1) (26).

Sensitivity analysis

Sensitivity analysis modified only the effect estimates on stroke. The nonsignificant effect of statins on stroke risk (RR: 0.78, 95% CI: 0.60 to 1.01) reached statistical significance when the analysis was restricted to trials that exclusively enrolled older individuals or had a subgroup analysis by age planned *a priori* (RR: 0.51, 95% CI: 0.33 to 0.78) (28, 29). Heterogeneity was low for most analyses but was substantial for the outcome of stroke (I^2: 58.1%).

Secondary prevention in trials comparing statins with placebo

Eight secondary prevention trials included a total of 12,539 elderly patients with ASCVD and had a follow-up that ranged from 2.3 to 11.3 years (31–38). Five trials used pravastatin in 40 mg doses (31, 34–37), two trials used atorvastatin in doses of 10 to 80 mg (33, 38), and one trial used simvastatin in doses of 20 to 40 mg (32). Statins significantly reduced all-cause mortality (RR: 0.80, 95% CI: 0.73 to 0.89; high certainty), cardiovascular mortality (RR: 0.68, 95% CI: 0.58 to 0.79; high certainty), CAD (RR: 0.68, 95% CI: 0.61 to 0.77; high certainty), MI (RR: 0.68, 95% CI: 0.59 to 0.79; high certainty), and revascularization (RR: 0.68, 95% CI: 0.61 to 0.77; high certainty). However, statins did not reduce the risk of heart failure or stroke compared with placebo (Fig. 2; Table 2).

Subgroup analysis

Secondary prevention trials did not report data separately for elderly people aged 75 years or older. Only data on all-cause mortality, CAD, MI, revascularization, and stroke were found for people aged ≥65 to 75 years. No subgroup analyses could be performed according to age stratification or T2DM.

Sensitivity analysis

The reduction in all-cause mortality (RR: 0.80, 95% CI: 0.73 to 0.89) became nonsignificant when the analysis was limited to not-for-profit-funded trials (38) (RR: 0.95, 95% CI: 0.75 to 1.18).

Secondary prevention in trials comparing intensive statin treatment with less-intensive statin treatment

Three trials that included a total of 8461 elderly people compared intensive with less-intensive statin interventions

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Table 1. Summary of Findings and Confidence in the Body of Evidence Comparing Statins With Placebo for Primary Prevention

Outcomes	Population Group	RR [95% CI]	Baseline Risk per 1000 Patients	Risk Difference per 1000 Patients	n of Participants (n of Studies)	Quality of Evidence (Domain of Concern)
All-cause mortality	Overall	0.95 [0.84, 1.07]	63	3	21,681 (8)	Moderate (imprecision)
	≥65–75 years	0.96 [0.80, 1.15]	81	3	6500 (4)	Moderate (imprecision)
	≥75 years	1.34 [0.98, 1.84]	185	−63	726 (1)	Low (imprecision, risk of bias)
	DM	0.78 [0.51, 1.18]	NA	NA	1129 (1)	Moderate (imprecision)
	No DM	0.80 [0.62, 1.04]	47	9	5695 (1)	Low (imprecision, risk of bias)
	Hypertension	1.09 [0.91, 1.30]	92	−8	7312 (2)	Moderate (imprecision)
Cardiovascular mortality	Overall	1.01 [0.83, 1.24]	24	0	16,781 (6)	Moderate (imprecision)
	≥65–75 years	0.94 [0.70, 1.27]	49	3	4686 (3)	Low (imprecision, risk of bias)
	≥75 years	1.39 [0.84, 2.31]	71	−28	726 (1)	Low (imprecision, risk of bias)
	DM	0.63 [0.30, 1.33]	31	11	1129 (1)	Moderate (imprecision)
	No DM	0.83 [0.47, 1.47]	9	2	5695 (1)	Low (imprecision, risk of bias)
	Hypertension	1.10 [0.87, 1.38]	38	−4	7312 (2)	Moderate (imprecision)
CAD	Overall	0.79 [0.68, 0.91]	63	13	10,240 (5)	Moderate (risk of bias)
	≥65–75 years	0.77 [0.61, 0.97]	63	15	5084 (3)	Moderate (risk of bias)
	≥75 years	0.70 [0.43, 1.13]	111	33	726 (1)	Low (imprecision, risk of bias)
	DM	0.67 [0.42, 1.06]	74	24	1129 (1)	Moderate (imprecision)
	Hypertension	0.74 [0.58, 0.94]	58	15	7312 (2)	High
Heart failure	Overall	1.04 [0.80, 1.35]	29	−1	7312 (2)	Low (imprecision, risk of bias)
	≥65–75 years	1.01 [0.69, 1.47]	51	−1	2141 (1)	Low (imprecision, risk of bias)
	≥75 years	0.97 [0.56, 1.68]	71	2	726 (1)	Low (imprecision, risk of bias)
MI	Overall	0.45 [0.31, 0.66]	18	10	8240 (3)	High
	≥65–75 years	0.40 [0.24, 0.65]	56	33	2545 (2)	High
	DM	0.41 [0.22, 0.77]	56	33	1129 (1)	High
	No DM	0.55 [0.31, 0.99]	11	5	5695 (1)	Moderate (risk of bias)
Revascularization	Overall	0.45 [0.17, 1.17]	23	13	1129 (1)	Moderate (imprecision)
Stroke	Overall	0.78 [0.60, 1.01]	31	7	18,515 (6)	Moderate (imprecision)
	≥65–75 years	0.66 [0.38, 1.16]	36	12	5084 (3)	Moderate (imprecision)
	≥75 years	1.09 [0.63, 1.89]	66	−6	726 (1)	Low (imprecision, risk of bias)
	DM	0.53 [0.27, 1.03]	43	20	1129 (1)	Moderate (imprecision)
	No DM	0.55 [0.33, 0.92]	14	6	5695 (1)	Moderate (risk of bias)
	Hypertension	0.92 [0.70, 1.21]	40	3	7312 (2)	Moderate (imprecision)

Abbreviations: DM, diabetes mellitus; n, number; NA, not applicable.

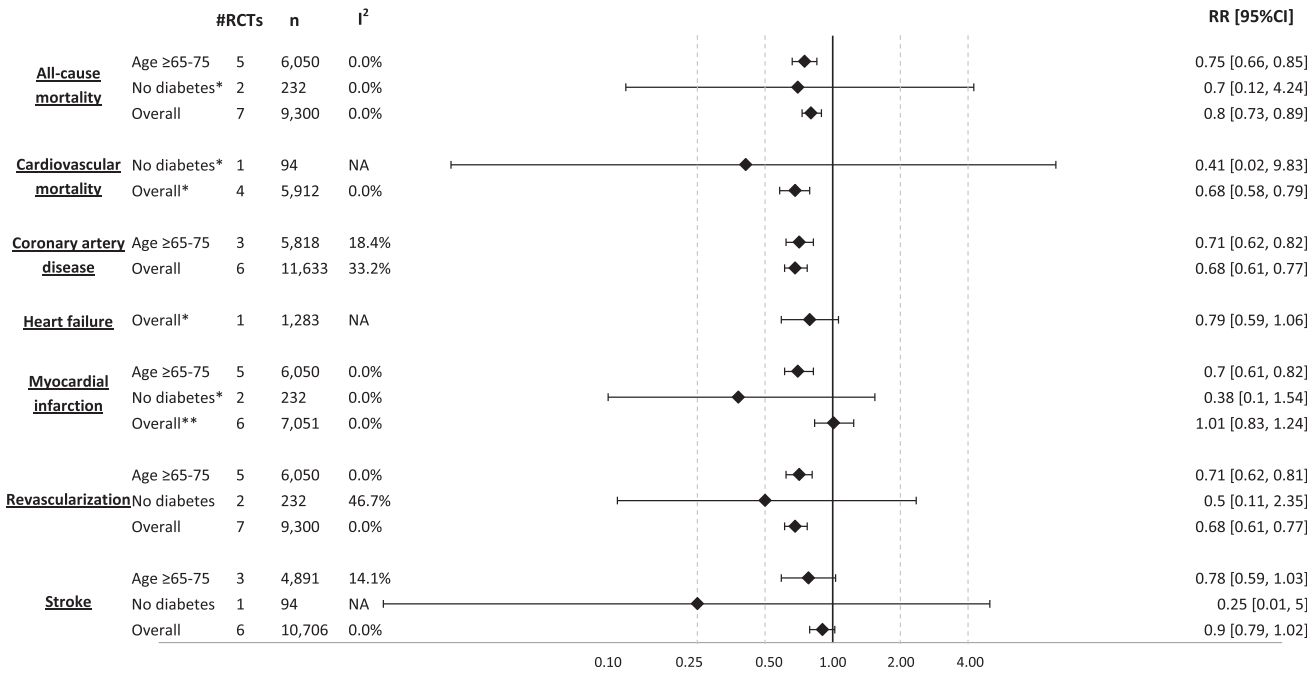

Figure 2. Secondary prevention forest plot comparing statins with placebo. *All patients were ≥65 to 75 years. **All patients were ≥65 to 78 years. #, number; n, number of participants.

(40–42). The follow-up ranged from 1 to 6 years. One study comparing intensive statin treatment with less-intensive statin treatment demonstrated a significant reduction in the risk of CAD (RR: 0.79, 95% CI: 0.71 to 0.88; moderate certainty) and heart failure (RR: 0.67, 95% CI: 0.50 to 0.90; moderate certainty) (42). In contrast, no significant risk reduction was found for all-cause mortality, cardiovascular mortality, MI, revascularization, or stroke (8).

Secondary prevention in trials comparing niacin with placebo

One trial enrolled 145 patients with a follow-up of 1.5 years (20). Only revascularization data were reported and did not show a significant difference between niacin and placebo (8).

Secondary prevention in trials comparing fibrate with placebo

Two trials compared fibrate with placebo (21, 22). One trial compared 400 mg gemfibrozil with placebo and included 1266 elderly men (≥65 to 75 years) (21). The risk of stroke was not significantly decreased after a follow-up of 5.1 years. The second trial compared 1200 mg gemfibrozil with placebo (22). This trial did not show a significant reduction in cardiovascular mortality or CAD. Additionally, their subgroup analysis by age group, ≥65 to 75 and ≥75 years old, did not reveal a statistically significant interaction (8).

Pooling primary and secondary prevention trials comparing statins with placebo

We combined 17 trials, including elderly people receiving statins as primary prevention, secondary prevention, or both (23–39). Statins significantly decreased the risk of mortality (RR: 0.91, 95% CI: 0.86 to 0.97), cardiovascular mortality (RR: 0.88, 95% CI: 0.79 to 0.97), CAD (RR: 0.91, 95% CI: 0.86 to 0.97), MI (RR: 0.72, 95% CI: 0.65 to 0.79), revascularization (RR: 0.69, 95% CI: 0.62 to 0.77), and stroke (RR: 0.82, 95% CI: 0.72 to 0.94). However, no effect on the risk of heart failure was found (8). A significant difference between primary and secondary prevention appears to be present only for the outcomes of all-cause mortality (RRR: 1.18, 95% CI: 1.02 to 1.38) and MI (RRR: 0.66, 95% CI: 0.44 to 0.99).

Discussion

Main findings

We conducted a systematic review and meta-analysis evaluating the effect of lipid-lowering agents in older individuals. In the primary prevention trials, statins reduced the risk of CAD and MI compared with placebo. No difference was found between two predefined age strata (≥65 to 75 and ≥75 years) or by diabetes status. In the secondary prevention trials, statins reduced the risk of all-cause mortality, cardiovascular mortality, CAD, MI, and revascularization compared with placebo. Intensive statin treatment reduced the risk of CAD and heart failure compared with less-intensive statin treatment. No important effect was noted for fibrates or niacin in older individuals. The certainty of the evidence is greater for secondary prevention. The reduction in the risk of stroke was only substantial when primary and secondary trials were combined, an approach that might be questioned considering the plausible differences between primary and

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Table 2. Summary of Findings and Confidence in the Body of Evidence Comparing Statins With Placebo for Secondary Prevention

Outcomes	Population Group	RR [95% CI]	Baseline Risk per 1000 Patients	Risk Difference per 1000 Patients	n of Participants (n of Studies)	Quality of Evidence (Domain of Concern)
All-cause mortality	Overall	0.80 [0.73, 0.89]	174	35	9300 (7)	High
	≥65–75 years	0.75 [0.66, 0.85]	189	47	6050 (5)	High
	No diabetes	0.70 [0.12, 4.24]	26	8	232 (2)	Low (serious imprecision)
Cardiovascular mortality	Overall	0.68 [0.58, 0.79]	130	42	5912 (4)	High
	No diabetes	0.41 [0.22, 9.83]	9	5	94 (1)	Low (serious imprecision)
CAD	Overall	0.68 [0.61, 0.77]	177	57	11,633 (6)	High
	≥65–75 years	0.71 [0.62, 0.82]	215	62	5818 (3)	High
Heart failure	Overall[a]	0.79 [0.59, 1.06]	138	29	1283 (1)	Moderate (imprecision)
MI	Overall	0.68 [0.59, 0.79]	124	40	7051 (6)	High
	≥65–75 years	0.70 [0.61, 0.82]	133	40	6050 (5)	High
	No diabetes	0.38 [0.10, 1.54]	61	38	232 (2)	Low (serious imprecision)
Revascularization	Overall	0.68 [0.61, 0.77]	142	45	9300 (7)	High
	≥65–75 years	0.71 [0.62, 0.81]	158	46	6050 (5)	High
	No diabetes	0.50 [0.11, 2.35]	104	52	232 (2)	Low (serious imprecision)
Stroke	Overall	0.90 [0.79, 1.02]	82	8	10,706 (6)	Moderate (imprecision)
	≥65–75 years	0.78 [0.59, 1.03]	68	15	4891 (3)	Moderate (imprecision)
	No diabetes	0.25 [0.01, 5.00]	38	29	94 (1)	Low (serious imprecision)

Abbreviation: n, number.

[a]Age ≥65 to 75 years.

secondary prevention populations. Data on older individuals with diabetes remained limited; however, we did not observe a statistically significant difference between the effect estimates in individuals with and without diabetes, potentially revealing that the evidence from the overall older population can be extrapolated to individuals with diabetes.

Practical implications

Although current guidelines support the use of statins for primary prevention in older individuals (44), the efficacy of statins across different cardiovascular outcomes and different elderly age groups (≥65 to 75 years and ≥75 years) remains unclear. Our findings showed that statins reduce the risk of CAD and MI by 21% and 55%, respectively, compared with placebo. Two previous systematic reviews suggested similarly important effects on MI, all-cause mortality, and cardiovascular mortality (45, 46). These reviews, however, were in disagreement about the effect of statins on stroke. We found a nonsignificant reduction in the risk of stroke. Surprisingly, distinctions between people aged ≥65 to 75 years and ≥75 years were not made in previous reviews. Efforts have been made by pooling results from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin and Heart Outcomes Prevention Evaluation-3 Trial (27). However, the effect estimates were reported for composite outcomes, and age groups differed from the current guidelines (6). Guideline recommendations are stronger for people aged ≥65 to 75 years than for those aged ≥75 years (6). We did not identify any statistically significant subgroup differences supporting this guideline. Our review highlights the scarcity of evidence for individuals ≥75 years of age. Only one trial (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; n = 726) provided data for this age group (43).

Very little discussion about the use of statins for secondary prevention in the elderly population is available in the literature, probably because of the well-known efficacy of statins across all age groups (47). Findings from a meta-analysis published in 2008, which included only trials with elderly people (≥65 years), supported the use of statins (48). Nonetheless, our meta-analysis did not find any statistically significant difference in the risk of stroke between treatment with statins and treatment with placebo. A possible explanation may relate to stroke definition in various meta-analyses (48).

Prescriptions of higher doses or more potent statins in older people may increase the risk of adverse effects, drug–drug interactions (49), and nonadherence rates (50). Therefore, evidence for intensive statin therapy in the elderly population should be scrutinized. Similar to a prior analysis (51), we found no reduction in mortality resulting from intensive statin therapy. Unlike the aforementioned meta-analysis (51), we did not include the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (33) or Myocardial Ischemia Reduction with Acute Cholesterol Lowering (52) Trials in our analysis. The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events Trial was excluded, because patients in the comparison group received cointerventions that might have affected the outcomes of interest; the Myocardial Ischemia Reduction with Acute Cholesterol Lowering Trial was excluded, as a result of a follow-up of <12 months. The Cholesterol Treatment Trialists' Collaboration revealed that higher doses of statins significantly reduced the risk of any major vascular events compared with lower doses in adults (14). Our analysis of older people aged ≥65 to 75 years showed a reduction in the risk of CAD and heart failure. When MI, a component of the CAD outcome, was analyzed, the findings became nonsignificant.

Unlike a recent Cochrane review assessing the effects of fibrates on secondary prevention of cardiovascular outcomes in adults (15), our analysis showed that fibrates did not decrease the risk of cardiovascular mortality, CAD, or stroke in elderly people. In addition, fibrates are known to cause muscle toxicity. This adverse effect is especially higher in people receiving statins (53). The adverse effects of fibrates therefore seem to outweigh their possible benefits. Likewise, niacin is associated with adverse effects and poor tolerability. In addition, it does not decrease the risk of revascularization (54). In the elderly, fibrates and niacin are, therefore, not usually acknowledged in clinical guidelines or recommended in clinical practice.

Strengths and limitations

Evidence regarding lipid-lowering agents remains limited in the very elderly population. Data focusing on older individuals with diabetes remain primarily derived from subgroup analyses, which might be misleading. The strengths of this review relate to the comprehensive literature search and the *a priori* protocol that was developed in collaboration with clinical experts from the Endocrine Society.

Conclusion

High-certainty evidence supports statin use for secondary prevention in older individuals. Evidence for statins prescribed as primary prevention is less certain. Data on older individuals with diabetes are limited; however, no empirical evidence shows a significant difference based on diabetes status.

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