

Safety and efficacy of low-density lipoprotein-lowering drugs in the elderly: a network meta-analysis of randomized controlled trials

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<https://doi.org/10.26599/1671-5411.2026.08.004>

ABSTRACT

BACKGROUND Balancing the efficacy of low-density lipoprotein (LDL) reduction with safety presents a significant challenge in the elderly care. While guidelines recommended high-intensity statins as the optimal strategy to lower LDL in high-risk individuals, there are prevailing concerns regarding its side effects and subsequent fatality rate. The effectiveness of different LDL-lowering therapies in this population is also unclear. This study aims to compare the safety and efficacy of various LDL-lowering strategies in elderly population.

METHODS A systematic search was conducted through six databases until March 2025. Randomized controlled trials (RCTs) that evaluate LDL-lowering agents were included. The primary outcome was adverse effects, while secondary outcomes included composite cardiovascular disease (CVD) events, CVD related mortality, all-cause mortality, and LDL level reduction. Risk of bias was assessed using the RoB-2 tool. A network meta-analysis was performed to compare the safety and efficacy with subgroup analysis based on underlying CVD under the cumulative ranking values.

RESULTS Sixteen RCTs ($n = 43,625$) with low to moderate risk of bias were included. Among interventions evaluated for adverse events, moderate-intensity pitavastatin had the highest probability of being the safest. Ezetimibe demonstrated the most favorable safety profile for reducing CVD mortality, while evolocumab was most effective in lowering all-cause mortality. For LDL reduction, the combination of moderate-intensity pitavastatin and ezetimibe was the most effective, followed by moderate-intensity rosuvastatin plus ezetimibe. Subgroup analyses revealed significant differences between CVD and non-CVD populations in CVD mortality ($P = 0.0059$), CVD events ($P = 0.0096$), and LDL reduction ($P = 0.0100$), with more pronounced effects in the non-CVD group, suggesting greater efficacy in primary prevention.

CONCLUSIONS Moderate-intensity pitavastatin showed the highest safety profile, while its combination with ezetimibe was the most effective for LDL reduction.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality globally, with elderly individuals experiencing a significant higher burden of its complications.^[1] Elevated low-density lipoprotein cholesterol (LDL-C) is a modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD).^[2] Over the past decades, lipid-lowering therapies, particularly statins, have proven effective in reducing CVD events in various populations.^[3] However, the management of LDL-C in the elderly presents unique clinical challenges.

High-intensity statin therapy is recommended in interna-

tional guidelines for individual at high or very high cardiovascular risk, regardless of age.^[4] The elderly present distinct clinical challenges, altered pharmacokinetics, heightened vulnerability to adverse effects, polypharmacy, and multimorbidity, that may modify responses to lipid-lowering therapy. Although guidelines endorse high-intensity statins regardless of age, the benefit-risk balance in very old or comorbid patients remains uncertain.^[5]

Recent studies have explored the efficacy of combining statins with non-statin agents like ezetimibe. A clinical trial demonstrated that adding ezetimibe to simvastatin in patients

aged 75 years or older led to a significant reduction in CVD events without increase in adverse effects.^[6] Other trials found that ezetimibe monotherapy reduced the incidence of major CVD events in elderly.^[7]

Although ezetimibe added to statins may provide additional cardiovascular benefit in elderly patients, direct head-to-head comparisons of LDL-lowering strategies remain limited. Evidence is fragmented, and heterogeneity between primary and secondary prevention has not been systematically addressed. Network meta-analysis (NMA) enables comparative evaluation of efficacy and safety across multiple therapies. This study conducts an NMA of randomized controlled trials (RCTs) to assess LDL-lowering strategies in the elderly, with subgroup analyses by CVD status, to inform clinical decision-making and guideline development.

METHODS

Study Design and Objectives

This systematic review and NMA was conducted to evaluate the comparative safety and efficacy of various LDL-lowering therapies specifically in elderly populations. This study followed PRISMA guideline and has been registered in PROSPERO (CRD420251025612). The primary objective of this NMA was to compare the safety levels of LDL-lowering therapies, including combination treatments, in elderly population, measured by adverse events incidents. Secondary objectives included evaluating efficacy based on composite cardiovascular events, cardiovascular mortality, all-cause mortality, and LDL reduction.

Participants were stratified into CVD and non-CVD subgroups: the CVD group included individuals with established ASCVD or prior events, while the non-CVD group comprised those without CVD but with indications such as hypercholesterolemia, mixed dyslipidemia, or elevated cardiovascular risk. RCTs enrolling individuals aged ≥ 60 years and investigating statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, or their combinations were systematically identified across six databases through March 2025. Analyses employed random-effects models, with heterogeneity assessed via I^2 and small-study effects evaluated with funnel plots. Relative rankings of interventions were estimated using surface under the cumulative ranking curve (SUCRA). The review adhered to the Cochrane Handbook and PRISMA guidelines.

Eligibility Criteria

Eligible primary studies were selected based on their PICO-TS (Population, Intervention, Comparator, Outcome, Timing, and Study design) framework. Eligible studies enrolled individuals aged ≥ 60 years receiving LDL-lowering therapy (statins, ezetimibe, PCSK9 inhibitors, or combinations) and included either a control group or a before-after comparison. Outcomes of interest encompassed safety (muscle-related adverse effects, rhabdomyolysis, myopathy, new-onset diabetes mellitus, gastrointestinal symptoms, elevated liver enzymes) and efficacy (composite CVD events, CVD mortality, all-cause mortality, and LDL reduction from baseline). Only RCTs published up to March 2025 were included. Exclusion criteria were inaccessible full texts and non-original research articles. No publication date restrictions were applied.

Search Strategy

This systematic review and NMA was conducted in accordance with the PRISMA guidelines. A comprehensive search of PubMed, ProQuest, ScienceDirect, Cochrane Library, Sage Journals, and Google Scholar was performed without language restrictions for studies published up to March 2025. The strategy combined controlled vocabulary and free-text terms, including MeSH and synonyms, with the following search string: (“elderly” OR “older adults”) AND (“cardiovascular disease” OR “CVD” OR “atherosclerotic cardiovascular disease” OR “ASCVD”) AND (“LDL-lowering therapy” OR “hydroxymethylglutaryl-CoA reductase inhibitors” OR “statins” OR “ezetimibe” OR “PCSK9 inhibitors”). All references were imported into EndNote software (version 7.0, Clarivate Analytics) for management and deduplication.

After deduplication, records were screened by two independent reviewers based on titles and abstracts. Full-text articles of potentially eligible studies were then assessed against the predefined criteria. Disagreements were resolved through discussion or consultation with a third reviewer, with final inclusion determined by consensus in line with the study objectives and outcomes.

Data Extraction

Upon completion of the final screening process, data were systematically extracted from all eligible studies and organized into a structured dataset. Extracted variables included study characteristics (first author, year of publication, country, study design, sample size, and mean participant age) as well as clinical outcomes. Safety endpoints comprised adverse



events such as muscle symptoms, new-onset diabetes mellitus, gastrointestinal disturbances, and elevated liver enzymes. Efficacy outcomes included composite CVD events, CVD-related mortality, all-cause mortality, and percentage reduction in LDL levels from baseline. Subgroup classification (CVD vs. non-CVD) was defined according to the documented presence or absence of atherosclerotic CVD. Data extraction was independently performed by three authors to ensure consistency and reduce potential bias. Any discrepancies or uncertainties encountered during data extraction were resolved through discussion among the reviewers until consensus was achieved. Only RCT that fulfilled all pre-specified eligibility criteria were included in the final analysis.

Quality Assessment

The methodological quality of included RCTs was independently evaluated by three reviewers using the Cochrane Risk of Bias 2 (RoB-2) tool. This instrument assesses five domains: bias from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Each domain was rated as “low risk,” “some concerns,” or “high risk” in accordance with RoB-2 guidance. Discrepancies were resolved through discussion until consensus was achieved.

The overall certainty of evidence for each outcome was appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. This approach considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty ratings were assigned as high, moderate, low, or very low. The combined application of RoB-2 and GRADE provided a transparent and methodologically rigorous assessment of both individual study quality and the overall strength of evidence in this review.

Statistical Analysis

Statistical analyses synthesized outcomes from RCTs comparing statins, ezetimibe, PCSK9 inhibitors, and combination regimens in elderly populations. For binary outcomes (adverse events, composite CVD events, CVD-related mortality, all-cause mortality), pooled risk ratios (RRs) with 95% CIs were estimated using the Mantel-Haenszel method under a random-effects model. For continuous outcomes (percentage reduction in LDL levels), mean differences with 95% CIs were calculated using the inverse variance method. Where necessary, medians and interquartile ranges or ranges were converted to mean $\pm$ SD using established methods.

Between-study heterogeneity was evaluated using the I^2 statistic, with values $> 25\%$ indicating low to moderate heterogeneity and higher thresholds denoting substantial heterogeneity. Random-effects models were applied throughout to account for variability in study designs, populations, and interventions. Subgroup analyses were conducted by CVD status (CVD vs. non-CVD), with interaction tests used to assess potential effect modification.

A NMA was conducted within a frequentist framework using the netmeta package in R statistical software (R Foundation for Statistical Computing, Vienna, Austria), implemented in RStudio (Posit Software, PBC, Boston, MA, USA), integrating direct and indirect evidence to enable comprehensive comparisons across interventions. Network graphs were generated, with node size proportional to the number of studies per intervention and edge thickness reflecting the number of direct comparisons.

The results of the NMA were summarized through multiple graphical and tabular outputs: (1) forest plots presenting pooled effect estimates with 95% CIs against a common reference; (2) network graphs illustrating the structure and connectivity of treatment comparisons; (3) netleague tables displaying pairwise comparisons with corresponding effect sizes and confidence intervals; and (4) SUCRA values ranking interventions by relative safety and efficacy, with higher values indicating superior performance. SUCRA tables provided an intuitive hierarchy of treatments across outcomes.

For outcomes with at least 10 studies available, publication bias was assessed through visual inspection of funnel plot asymmetry. When asymmetry was observed, potential explanations such as small-study effects, clinical heterogeneity, or selective outcome reporting were considered. Sensitivity analyses were also conducted to test the robustness of findings, including analyses restricted to studies at low risk of bias.

RESULTS

Study Selection

A systematic search across six databases, PubMed ($n = 2161$), ProQuest ($n = 292$), ScienceDirect ($n = 2436$), Cochrane Library ($n = 2234$), Sage Journals ($n = 10$), and Google Scholar ($n = 273$), yielded 7406 records (Figure 1). After removal of duplicates ($n = 46$) in EndNote software (version 7.0, Clarivate Analytics), 7360 unique citations were screened. Title and abstract screening excluded 7312 records, leaving 48 articles for full-text review. Of these, 32 articles were excluded for the fol-



lowing reasons: populations not limited to elderly individuals ($n=9$), ineligible interventions ($n=3$), non-relevant outcomes ($n=8$), incompatible study designs ($n=9$), and unavailable full text ($n=3$). Ultimately, 16 studies met all criteria and were included in the qualitative and quantitative synthesis (Table 1).

Study eligibility and quality were verified through reviewer consensus, with oversight from specialists in internal medicine.

Quality Assessment

Risk of bias was assessed using the Cochrane RoB-2 tool,

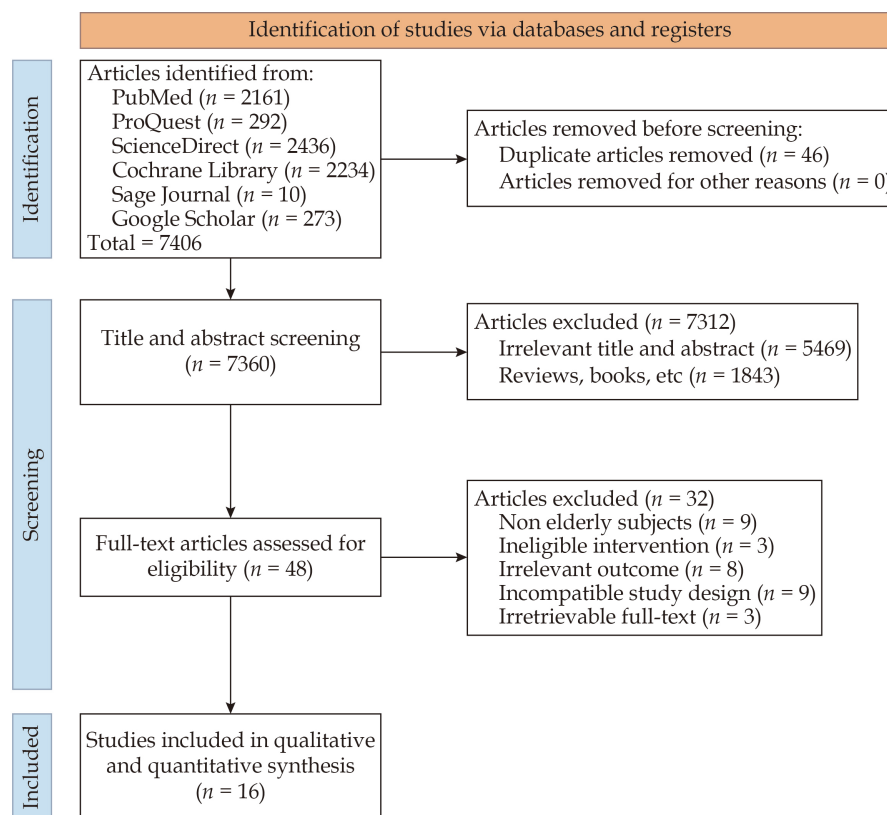


Figure 1 Flow diagram of search strategy and selection process.

Table 1 Characteristics of the included studies.

Study	Country	Year	Follow-up duration	Population			Intervention	Outcome
				Inclusion criteria	Mean age	Sample size		
Shepherd, <i>et al.</i> ^[8]	Scotland, Ireland, Netherlands	2002	3 years	70-82 years with a history of, or risk factors for, vascular disease	75.4	5804	Placebo vs. Moderate pravastatin	CVD mortality, all-cause mortality, CVD events, adverse events
Neil, <i>et al.</i> ^[9]	United Kingdom, Ireland	2006	3.9 years	LDL cholesterol levels < 4.14 mmol/L (< 160 mg/dL), triglyceride levels < 6.78 mmol/L (< 600 mg/dL), and presence of at least one other CVD risk factor	69	1129	Placebo vs. Atorvastatin	All-cause mortality, CVD events
Kjekshus, <i>et al.</i> ^[10]	19 European countries, Russia, South Africa	2007	32.8 months	Patients who were at least 60 years of age, had chronic NYHA class II, III, or IV heart failure of ischemic cause, and ejection fraction of no more than 40%	73	5459	Placebo vs. Rosuvastatin	All-cause mortality, CVD mortality
Wenger, <i>et al.</i> ^[11]	256 sites in 14 countries	2007	4.9 years	Patients with coronary heart disease, LDL cholesterol levels between 130 and 250 mg/dL, and triglyceride levels less than 600 mg/dL	69.9	3809	Atorvastatin 10 mg vs. Atorvastatin 80 mg	CVD mortality, CVD events



Continued

Study	Country	Year	Follow-up duration	Population			Intervention	Outcome
				Inclusion criteria	Mean age	Sample size		
Footy, <i>et al.</i> ^[12]	N/A	2010	12 weeks	With moderate or high ASCVD risk	N/A	1289	Moderate simvastatin plus ezetimibe vs. Moderate atorvastatin vs. High atorvastatin	All-cause mortality, LDL levels, adverse event
Drewes, <i>et al.</i> ^[13]	Netherlands, Scotland	2014	3.2 years	Age of 70-82 years, history of or risk factors for CVD	75.3	1172	Placebo vs. Low pravastatin	All-cause mortality, CVD events, CVD mortality
Rogers, <i>et al.</i> ^[14]	N/A	2014	Median 33 months	Age > 60 years, NYHA class II, III, IV	N/A	5011	Placebo vs. Rosuvastatin	All-cause mortality, CVD mortality
Liu, <i>et al.</i> ^[15]	China	2017	1 years	ACS patients confirmed by angiography, age between 80 and 90 years	84	264	Atorvastatin and ezetimibe combined therapy vs. Double dose atorvastatin	CVD mortality
Bach, <i>et al.</i> ^[6]	N/A	2019	Median 6 years	ACS patients who were hospitalized within the preceding 10 days, and who had LDL levels between 50-125 mg/dL	N/A	18,144	Moderate simvastatin plus placebo vs. Moderate simvastatin plus ezetimibe	All-cause mortality, CVD mortality
Ouchi, <i>et al.</i> ^[17]	Japan	2019	Median 4.1 years	Age > 75 years with elevated LDL without history of coronary artery disease	80.6	3796	Placebo vs. Ezetimibe	All-cause mortality, CVD mortality
Dong, <i>et al.</i> ^[16]	China	2021	6 years	Hypertensive patients aged > 60 years	70.11	1244	Placebo vs. Rosuvastatin	CVD mortality, all-cause mortality, CVD events, LDL levels
Chou, <i>et al.</i> ^[17]	China Taiwan, Australia, New Zealand	2022	12 weeks	Adults hypercholesterolemia/mixed dyslipidemia	N/A	388	Low pitavastatin plus ezetimibe vs. Low pitavastatin vs. Ezetimibe	LDL levels, adverse event
Lee, <i>et al.</i> ^[16]	South Korea	2023	3 years	Previous myocardial infarction, ACS, history of coronary revascularization, ischemic stroke, peripheral arterial disease	77	3780	Moderate rosuvastatin plus ezetimibe vs. High rosuvastatin	All-cause mortality, CVD events, CVD mortality
Cha, <i>et al.</i> ^[19]	South Korea	2024	6 months	Patients aged > 70 years with established ASCVD	76.9	561	Rosuvastatin and ezetimibe combined therapy vs. Moderate intensity statin	LDL levels, adverse event
Kuwabara, <i>et al.</i> ^[20]	Japan	2024	24 weeks	Age > 75 years who had LDL cholesterol > 140 mg/dL, no history of coronary heart disease, and no recent use of lipid lowering drugs	80.5	1061	Ezetimibe vs. Diet therapy	LDL levels
Al Said, <i>et al.</i> ^[21]	United States or European	2025	N/A	LDL > 70 mg/dL or non-high-density lipoprotein > 100 mg/dL while on optimized lipid lowering therapy (statin, ezetimibe)	N/A	2526	Placebo vs. Evolocumab	All-cause mortality, CVD events, CVD mortality

ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; LDL: low-density lipoprotein; N/A: not available; NYHA: New York Heart Association.

which evaluates five domains: randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of outcomes (D4), and selection of reported results (D5). Overall, most included studies demonstrated a low risk of bias across all domains. Five studies (Shepherd, *et al.*^[8] Drewes, *et al.*^[13] Rogers, *et al.*^[14] Chou, *et al.*^[17] and Cha, *et al.*^[19]) were judged to have “some concerns”, primarily related to deviations from intended interventions (D2). Importantly, all studies were rated as low risk for missing outcome

data (D3), measurement of outcomes (D4), and selection of reported results (D5). A detailed summary of domain-level risk of bias assessments is presented in Figure 2.

Network Evidence for Safety of LDL-lowering Therapies

The network graph demonstrated a well-connected structure, with placebo as the central comparator (Figure 3). The forest plot depicted in Figure 4, indicated a borderline, non-



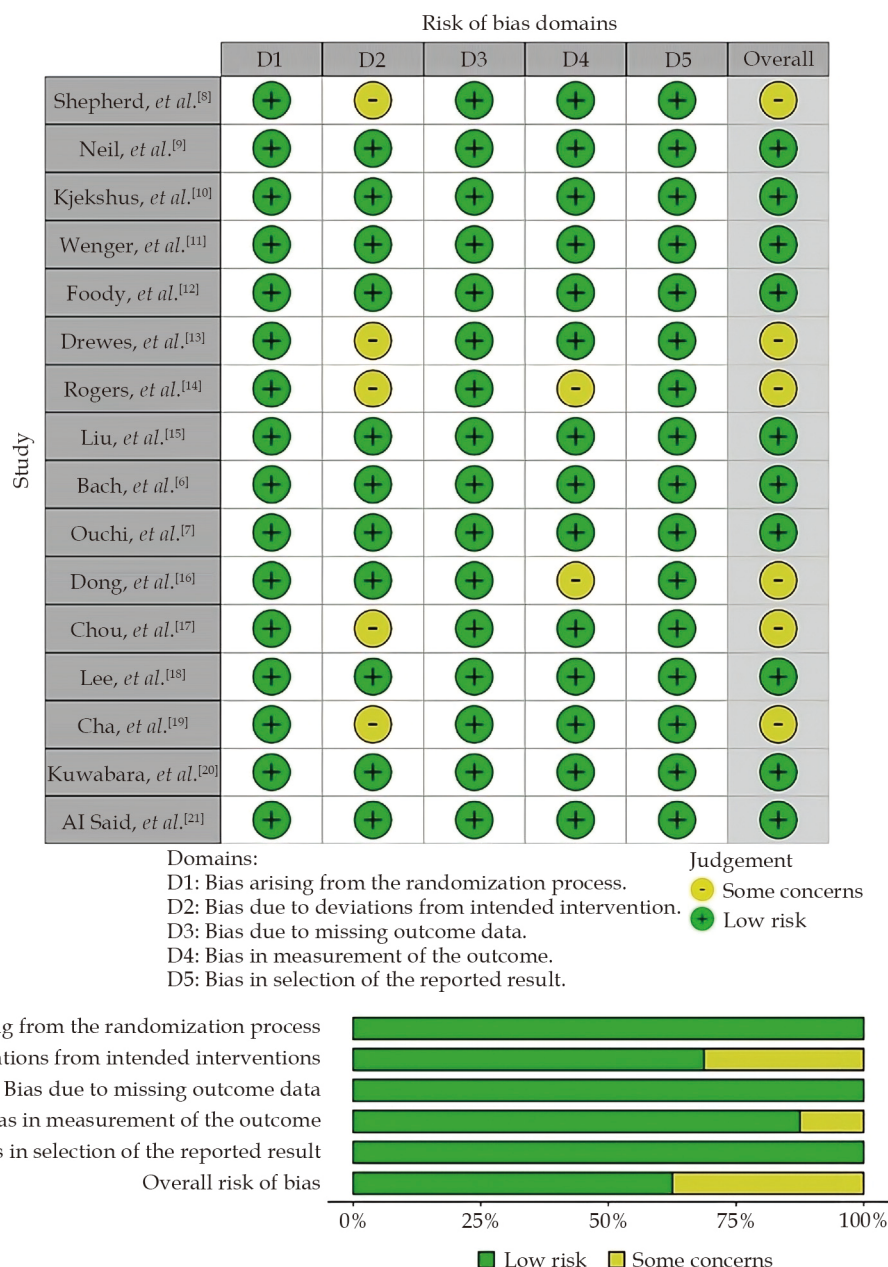


Figure 2 Risk of bias assessment.

significant reduction in adverse events with lipid-lowering interventions (RR = 0.80, 95% CI: 0.63-1.01, $P=0.057$). Subgroup analysis showed a significant benefit in CVD patients ($P=0.037$), but not in non-CVD patients ($P=0.084$). However, no significant interaction between subgroups was observed (common effects $P=0.066$, random effects $P=0.082$). Moderate heterogeneity ($I^2=61.5\%$) supported the use of a random-effects model.

The netleague analysis shown in the supplemental material, Table 1S indicated that moderate pitavastatin, evolocumab, and high rosuvastatin combined with ezetimibe were con-

sistently associated with more favorable RRs compared with other treatments. These findings were consistent with SUCRA rankings (Figure 5), where moderate pitavastatin showed the highest probability of being the safest intervention (SUCRA = 0.588), followed by evolocumab and high rosuvastatin plus ezetimibe. Conversely, ezetimibe monotherapy and high-intensity statins ranked lowest, suggesting greater risk of adverse outcomes. Bridging analysis positioned ezetimibe centrally in the network, frequently serving as a comparator to agents such as high atorvastatin, moderate simvastatin, and



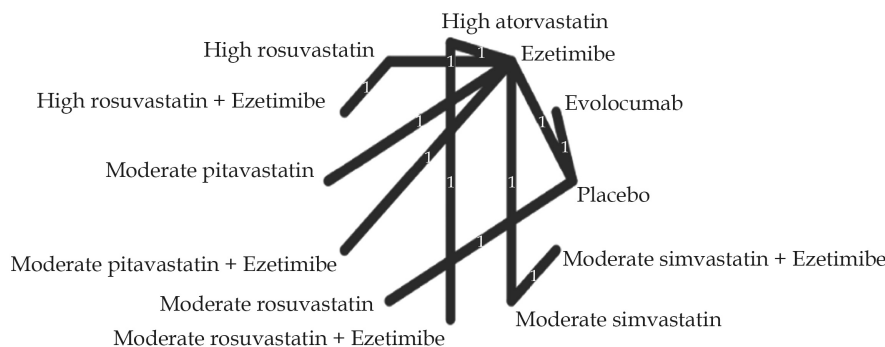


Figure 3 Network connection of trials reporting adverse events.

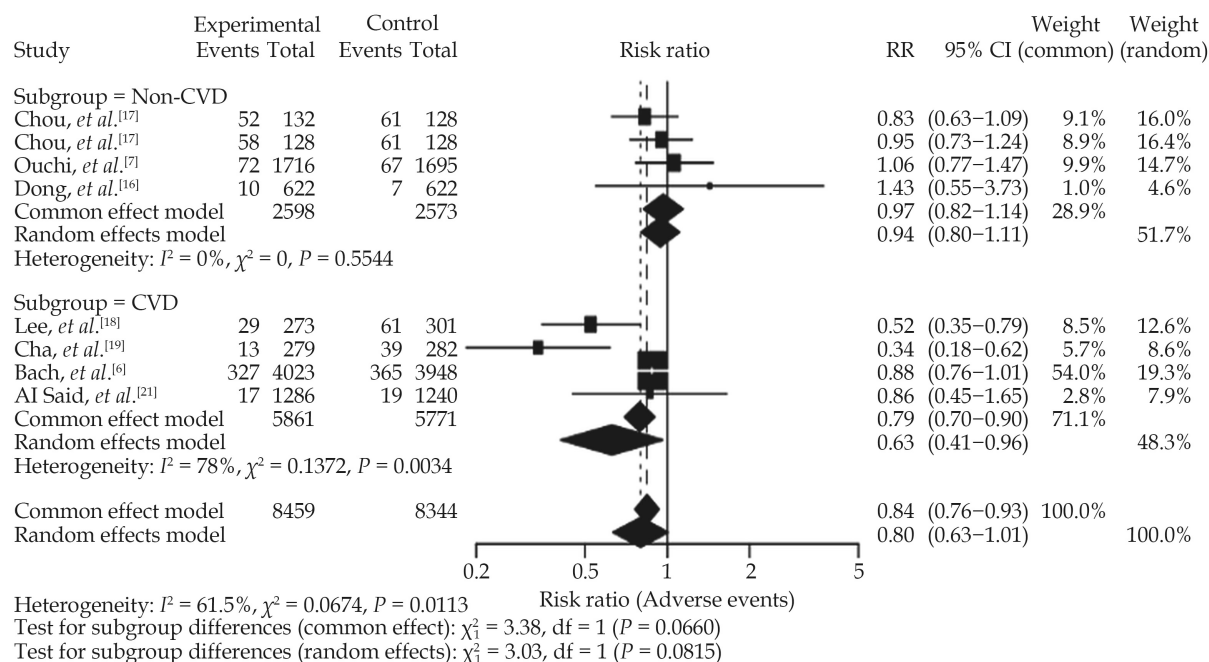


Figure 4 Forest plot of safety outcome. CVD: cardiovascular disease.

high rosuvastatin, reflecting its widespread use and potential mechanistic overlap. Funnel plot asymmetry suggested possible publication bias or small-study effects, with several studies falling outside the 95% confidence limits.

Network Evidence for Efficacy of LDL-lowering Therapies

This NMA provides a comprehensive evaluation of the comparative efficacy of LDL-lowering therapies in individuals aged 60 years and older, across four key outcomes: CVD-related mortality, all-cause mortality, CVD events, and LDL-C reduction displayed in Figures 6–9 with generation of net-league table shown in the supplemental material, Tables 2S–5S. The network structures were well-connected across all outcomes, with placebo consistently serving as the most common comparator. Frequent direct comparisons, particularly

those involving moderate-intensity statins and their combinations with ezetimibe, contributed to the strength and coherence of the network.

For CVD-related mortality, lipid-lowering interventions were associated with a borderline significant reduction (RR = 0.89, 95% CI: 0.79–1.00, $P = 0.047$). Subgroup analyses revealed significantly different treatment effects between patients with and without established CVD ($P = 0.021$ and $P = 0.044$), and the overall test for subgroup differences was significant, suggesting that baseline CVD status influences treatment efficacy. SUCRA analysis identified ezetimibe, moderate pravastatin, and evolocumab as the most effective interventions, while combination therapies such as moderate rosuvastatin plus ezetimibe ranked lower in their likelihood of reducing cardiovascular mortality.

All-cause mortality results showed a similar pattern, with a

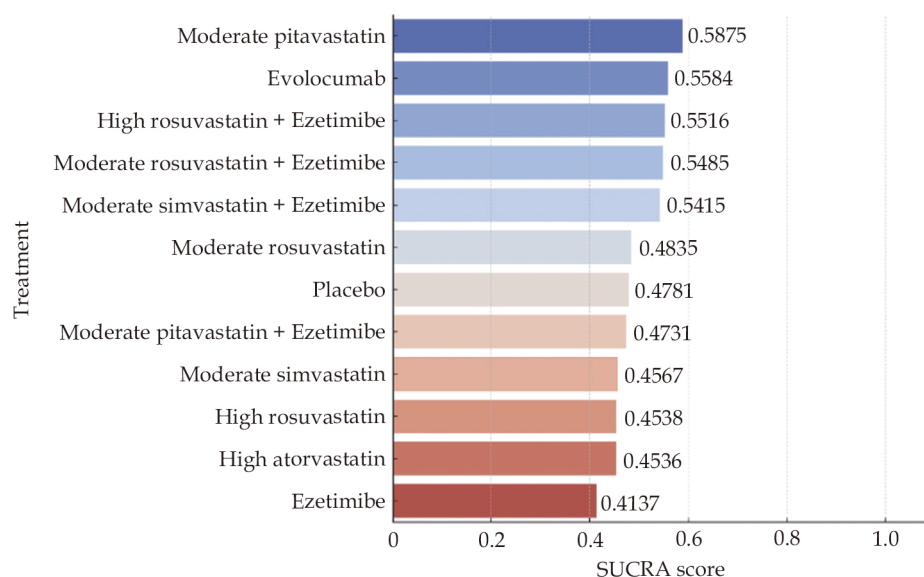


Figure 5 SUCRA ranking for safety outcome. SUCRA: surface under the cumulative ranking curve.

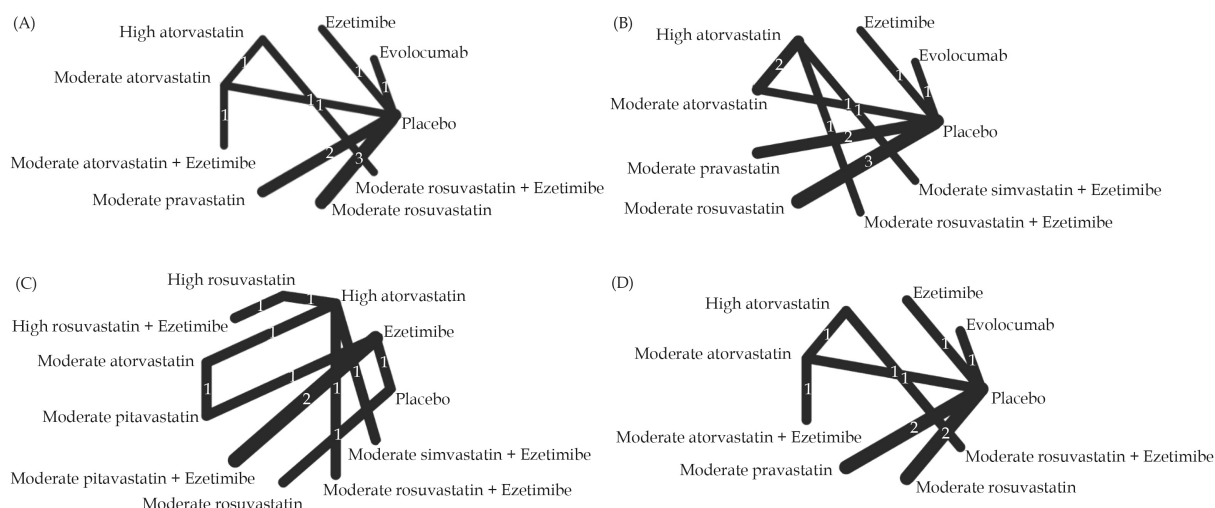


Figure 6 Forest plot for efficacy outcome. (A) CVD mortality; (B) all-cause mortality; (C) LDL reduction; and (D) CVD events. CVD: cardiovascular disease; LDL: low-density lipoprotein.

borderline statistically significant overall effect ($RR = 0.95$, 95% CI: 0.91–1.00, $P = 0.046$), primarily driven by effects in patients with CVD ($P = 0.045$). SUCRA rankings placed evolocumab, moderate rosuvastatin, and moderate pravastatin as the top interventions, suggesting consistent benefit in reducing mortality risk. In contrast, combination therapies such as moderate simvastatin plus ezetimibe were among the least effective in this domain.

In terms of cardiovascular event reduction, lipid-lowering therapies demonstrated a clear benefit ($RR = 0.89$, 95% CI: 0.83–0.96, $P = 0.0044$), with stronger effects observed in CVD populations. A significant interaction by baseline CVD status ($P = 0.0096$) was noted. The most effective treatments, according to

SUCRA rankings, were moderate atorvastatin, ezetimibe, and moderate rosuvastatin plus ezetimibe. Placebo and moderate rosuvastatin alone ranked lowest, highlighting the superiority of combination strategies in this outcome.

For LDL-C reduction, the pooled mean difference across treatments was -13.06 mg/dL (95% CI: -22.08 to -4.05 , $P = 0.0045$). Significant effects were observed in both CVD and non-CVD populations, with mixed populations showing borderline effects. High heterogeneity ($I^2 = 98.8\%$) supported the use of a random-effects model. SUCRA analysis ranked moderate pitavastatin plus ezetimibe, moderate rosuvastatin plus ezetimibe, and moderate pitavastatin highest for LDL-lowering efficacy. Treatments such as placebo, moderate atorvastatin,

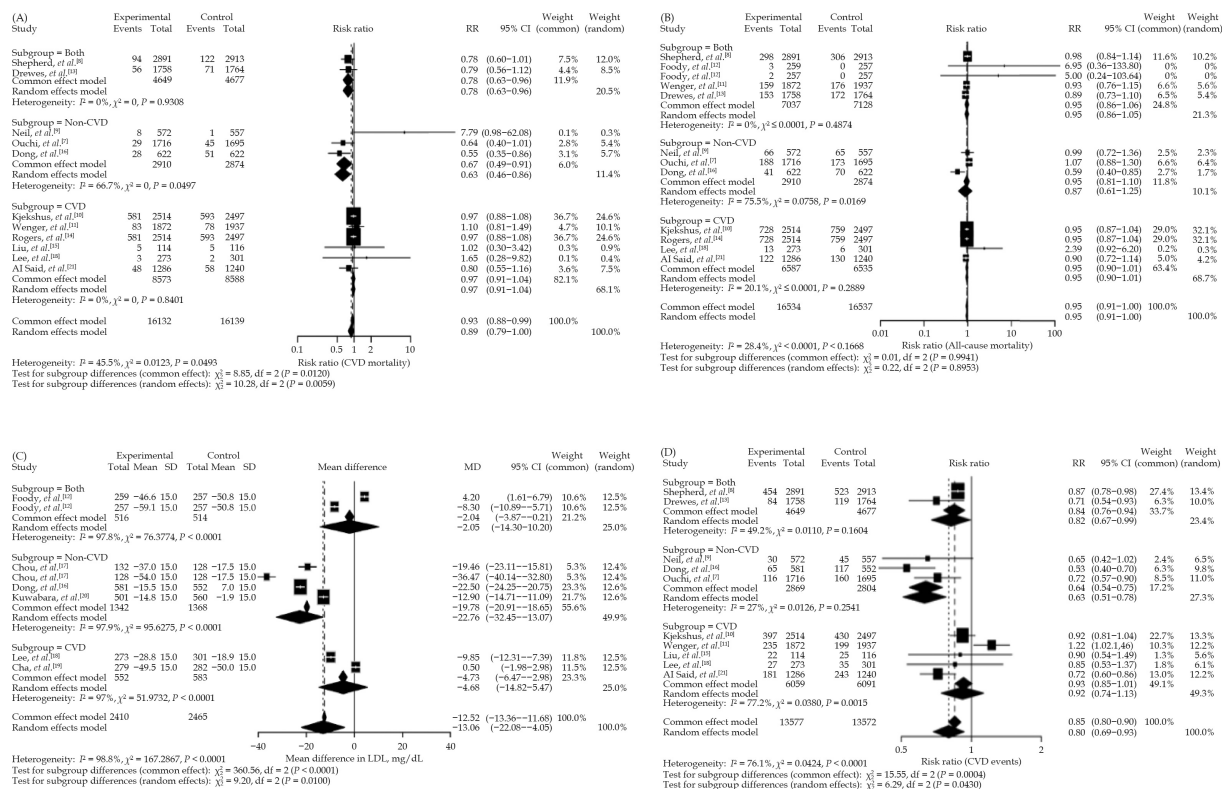


Figure 7 Forest plot for efficacy outcome. (A) CVD mortality; (B) all-cause mortality; (C) LDL reduction; and (D) CVD events. CVD: cardiovascular disease; LDL: low-density lipoprotein.

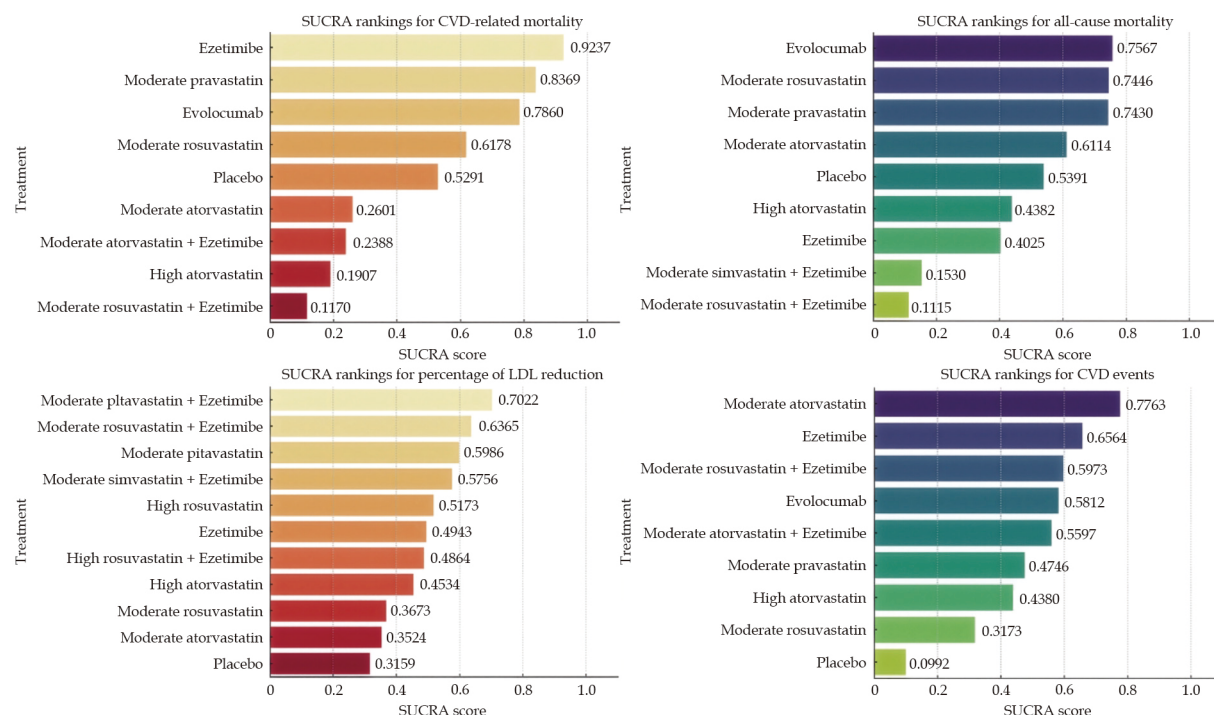


Figure 8 SUCRA ranking for efficacy outcome. CVD: cardiovascular disease; LDL: low-density lipoprotein; SUCRA: surface under the cumulative ranking curve.

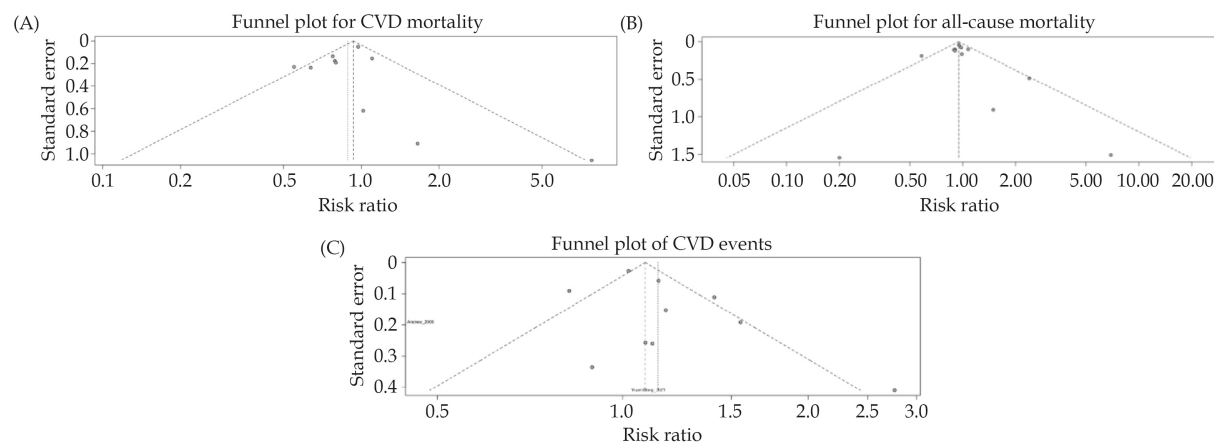


Figure 9 Funnel plot for efficacy outcome. (A) CVD mortality; (B) all-cause mortality; and (C) CVD events. CVD: cardiovascular disease.

Table 2 GRADE analysis.

Outcome	Final certainty rating	Key justification
Adverse effects, safety	Moderate	Moderate certainty due to borderline significance, moderate heterogeneity ($I^2 = 61.5\%$), and some small-study effects suggested by funnel plot asymmetry.
CVD-related mortality	Moderate	Moderate certainty supported by near-significant pooled estimates, moderate heterogeneity ($I^2 = 45.5\%$), and presence of publication bias indicated by funnel asymmetry.
All-cause mortality	Moderate	Moderate certainty due to borderline significance, low-to-moderate heterogeneity ($I^2 = 28.4\%$), but some small-study effects visible in funnel plot asymmetry.
Composite CVD events	High	High certainty supported by significant pooled effect, consistent findings across studies, and moderate heterogeneity ($I^2 = 71.6\%$) without significant concerns for publication bias.
LDL reduction, %	Moderate	Moderate certainty due to strong effect sizes, but very high heterogeneity ($I^2 = 98.8\%$) and potential publication bias indicated by funnel plot asymmetry.

CVD: cardiovascular disease; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; LDL: low-density lipoprotein.

and moderate rosuvastatin had the lowest SUCRA scores.

Network bridges further illustrated relationships between treatment groups in the supplemental material, [Tables 2S–5S](#). High atorvastatin and high rosuvastatin were linked due to similar intensity levels, while moderate atorvastatin and moderate pitavastatin appeared to serve comparable roles within moderate-intensity statin therapy. Ezetimibe and its combination with pitavastatin also formed a distinct cluster, reflecting potential mechanistic synergy. These connections provide additional interpretive value in understanding how therapies align in the absence of direct head-to-head comparisons.

GRADE Analysis for Each Outcome

The overall certainty of evidence for each outcome was evaluated using the GRADE framework, as detailed in [Table 2](#). The outcomes were rated as high or moderate certainty based on five key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

The certainty of evidence for composite CVD events was rated as high, supported by significant pooled estimates, con-

sistent results across trials, and acceptable heterogeneity, indicating strong confidence in the effectiveness of LDL-lowering therapies for reducing cardiovascular events in elderly populations. Evidence for adverse events was rated as moderate, reflecting borderline significance, moderate heterogeneity, and indications of publication bias, leaving some uncertainty regarding comparative safety. Both CVD-related mortality and all-cause mortality were rated as moderate certainty, due to nearly significant estimates, moderate heterogeneity, and funnel plot asymmetry suggesting publication bias and small-study effects. LDL reduction was also rated as moderate certainty, with large, consistent effects across regimens but substantial heterogeneity and possible small-study effects limiting confidence in the findings.

In summary, the GRADE analysis supports that most clinical outcomes in this NMA, particularly composite cardiovascular events, are backed by moderate to high certainty evidence, reinforcing the clinical relevance of LDL-lowering strategies in elderly populations at varying levels of cardiovascular risk.



DISCUSSION

This NMA included 16 RCTs with 43,625 participants aged ≥ 60 years, evaluating the efficacy and safety of commonly used LDL-lowering therapies. To our knowledge, it is the first comprehensive NMA focused on elderly populations, providing up-to-date evidence on the comparative benefits and risks of these interventions.

Safety of LDL-lowering Therapies for Elderly

Among the treatments evaluated, moderate pitavastatin and evolocumab ranked highest in terms of safety. This observation aligns with findings from recent systematic reviews that highlight the well-established tolerability of pitavastatin. Compared to other statins, particularly simvastatin and atorvastatin, pitavastatin is associated with a lower incidence of statin-associated muscle symptoms, including myalgia and elevated creatine kinase levels. It also appears to have a more favorable metabolic profile, with a reduced likelihood of impairing glycemic control or contributing to new-onset diabetes mellitus, especially when compared to atorvastatin and rosuvastatin. In addition, pitavastatin has demonstrated good renal safety, requiring no dose adjustment in patients with mild-to-moderate renal impairment and showing a low risk of nephrotoxicity. These characteristics support its suitability, particularly in populations at higher risk of adverse effects.^[2] Evolocumab, a PCSK9 inhibitor, also demonstrated consistent safety, in line with a study of long-term evaluations in high-risk populations.^[23]

The SUCRA ranking of adverse effects in this study indicated that high-intensity statins and ezetimibe monotherapy were associated with the highest number of reported side effects. This finding contrasts with some prior studies, which have suggested that ezetimibe generally has a more favorable safety profile. The discrepancy may be due to the data extraction used in our study, where adverse effects were quantified based on the number of reported events. Evidence found that ezetimibe is associated with fewer and milder side effects, which most likely to be documented compared to more severe side effects.^[24,25] Our findings suggest a different observation where ezetimibe may be associated with a greater number of reported side effects in the elderly compared to younger adults. The observed differences may be attributable to variations in dosage requirements or drug tolerability among the elderly population.

The apparently higher safety ranking of several interventions relative to placebo may be attributed to the methodological properties of SUCRA, which reflects relative ranking pro-

portunities rather than absolute differences in adverse event risk. Adverse event estimates may also be influenced by between-study heterogeneity, indirect comparisons within the network, and the placebo effect, an important consideration in LDL-lowering therapies where muscle-related symptoms are frequently reported even among placebo recipients.

CVD Events and Associated Mortality

Multiple studies support the cardiovascular benefits of ezetimibe. The PRECISE-IVUS trial showed that combining ezetimibe with atorvastatin resulted in greater coronary plaque regression than atorvastatin alone. In the EWTOPIA 75 trial, ezetimibe reduced composite cardiac events by 60% and coronary revascularization by 62%. Additionally, a secondary analysis of the IMPROVE-IT trial found that ezetimibe was particularly effective in reducing cardiovascular events among patients over 75 years of age.^[26,27]

LDL Level Reduction

Aligned with our results, combination therapy with ezetimibe and moderate-intensity statins has consistently shown superior LDL reduction in previous studies, including in elderly populations. Additionally, in the IMPROVE-IT trial, this regimen led to a modest but significant 6.4% reduction in major cardiovascular events (HR = 0.936, 95% CI: 0.887–0.988, $P = 0.016$).^[28,29]

The notable effect of ezetimibe in lowering LDL levels and reducing CVD risk in the elderly may be attributed to age-related changes in cholesterol metabolism. With advancing age, cholesterol absorption increases, primarily due to upregulation of NPC1L1, a key intestinal transporter, while cholesterol synthesis declines. Additionally, there is downregulation of ABCG5 and ABCG8, efflux transporters responsible for pumping cholesterol back into the intestinal lumen, which further enhances net cholesterol absorption. Consequently, absorption becomes a dominant pathway, making older adults particularly responsive to therapies targeting this mechanism. This supports the use of a combined lipid-lowering strategy involving statins and cholesterol absorption inhibitors in this population.^[30]

All-cause Mortality

In our study, evolocumab ranked highest for reducing all-cause mortality and third for lowering cardiovascular mortality. Although few trials have evaluated PCSK9 inhibitors with these specific endpoints, one trial (ODYSSEY OUTCOMES) showed a 22% reduction in the primary outcome among individuals aged ≥ 65 years (HR = 0.78, 95% CI: 0.68–0.91),



compared to an 11% reduction in those under 65 years (HR = 0.89, 95% CI: 0.80–1.00). The secondary outcome, including all-cause death, myocardial infarction, or ischemic stroke, was also significantly reduced in the older age group. A similar trend was observed in the FOURIER trial, where evolocumab consistently reduced major cardiovascular events across all age groups with older individuals experienced comparable relative risk reductions and greater absolute benefit. Taken together, these findings reinforce the efficacy of PCSK9 inhibitors in the elderly, particularly in those with elevated cardiovascular risk profiles.^[31]

LDL Lowering Therapies for Primary Prevention

Comparisons of subgroups based on CVD status showed that LDL-lowering therapies are more effective in non-CVD populations. Significant differences were observed in CVD-related events, mortality, and percentage of LDL reduction, highlighting the potential value of LDL-lowering medications for primary prevention of future cardiovascular events and improvement of overall prognosis. Aligned with our study, several observational studies have demonstrated the effectiveness of statin therapy for the primary prevention of ASCVD in older adults.^[32] For example, in U.S. veterans aged ≥ 75 years, statins were linked to lower ASCVD incidence (HR = 0.92) and cardiovascular mortality (HR = 0.80).^[33] A Danish cohort study similarly found a 23% lower risk of major vascular events in patients over 70 years old initiating statin therapy.^[34] Thus, while statin therapy clearly reduces cardiovascular events in older patients with established CVD, emerging evidence suggests that it is also beneficial for primary prevention in those without CVD. Furthermore, statin use for primary prevention has been associated with cardiovascular benefit in individuals aged ≥ 70 years without significant risk of developing diabetes mellitus. These findings suggest that primary prevention may yield greater benefit compared to secondary prevention, particularly in terms of reducing initial disease burden and long-term outcomes.^[35]

Balancing Safety and Efficacy

Based on our findings, we recommend initiating lipid-lowering therapy in elderly patients with moderate-intensity statins, preferably pitavastatin, given their favorable balance of efficacy and safety and lower incidence of adverse effects. In individuals with insufficient LDL-C reduction or elevated cardiovascular risk, adding ezetimibe to moderate-intensity statins can improve lipid control while preserving tolerability, consistent with current evidence and clinical recommendations. For frail, multimorbid, or polypharmacy patients, therapy should empha-

size safety through the use of well-tolerated agents such as pitavastatin or low-dose combinations.

Our findings highlight important distinctions in the balance of safety and efficacy among LDL-lowering therapies in older adults. In terms of safety, moderate-intensity pitavastatin and evolocumab demonstrated the most favorable profiles. Pitavastatin was associated with a lower incidence of statin-associated muscle symptoms, better metabolic tolerance, and minimal renal impact, aligning with previous evidence supporting its use in patients at higher risk of adverse effects. On the efficacy side, ezetimibe-based therapies emerged as particularly effective in reducing LDL levels and cardiovascular risk. Furthermore, subgroup analyses and observational data suggest that LDL-lowering therapies offer substantial benefit for primary prevention in elderly individuals without established CVD.

LIMITATIONS

This study has several limitations. Firstly, prior medication use among participants in CVD-focused trials was often undocumented, which may have contributed to the moderate heterogeneity observed, particularly where baseline LDL-lowering therapy differed before study initiation. Secondly, the analysis was restricted to statins, ezetimibe, and PCSK9 inhibitors in line with guideline recommendations, thereby excluding other lipid-lowering agents that may be relevant. Thirdly, variability in age ranges across study inclusion criteria represents another potential source of heterogeneity, limiting comparability between populations. Last but not least, lifestyle factors (e.g., smoking, diet, physical activity) and genetic conditions such as familial hypercholesterolemia were inconsistently reported, reducing the ability to account for these confounders. Future research should address these limitations to strengthen the robustness and generalizability of findings.

Future research should prioritize direct comparisons of LDL-lowering therapies in elderly populations, with specific consideration of frailty, comorbidities, and polypharmacy. In this study, ezetimibe was associated with the highest incidence of adverse effects, suggesting possible age-related differences in dosing requirements or tolerability. Further investigation into optimized ezetimibe dosing strategies for elderly patients is warranted. In addition, cost-effectiveness analyses of combination regimens are needed to inform personalized, value-based care in this population.

CONCLUSIONS

Moderate-intensity pitavastatin and PCSK9 inhibitor offered the best safety profiles in older adults. Ezetimibe-based



combinations showed higher efficacy in lowering LDL and reducing cardiovascular events, particularly in primary prevention. These findings support starting with moderate-intensity pitavastatin in the elderly, with ezetimibe or PCSK9 inhibitors added as needed to optimize outcomes safely. Primary prevention, compared to secondary prevention, may yield better benefit for short-term and long-term outcomes.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies. All authors had no conflicts of interest to disclose.

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Please cite this article as: Niaga KJK, Supinto PA, Tjandra KC, Martin A, Drew C, Seno KHNH, Felix, Nugraha LAK, Tantowi F. Safety and efficacy of low-density lipoprotein-lowering drugs in the elderly: a network meta-analysis of randomized controlled trials. *J Geriatr Cardiol* 2026; 23(8): 515–528. DOI: 10.26599/1671-5411.2026.08.004

