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The Role of Statins in Reducing Cardiovascular Mortality: A Systematic Review of Long-term Outcomes

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INTRODUCTION

Cardiovascular disease (CVD) remains the foremost cause of mortality globally, despite advancements in therapeutic strategies. Statins, potent HMG-CoA reductase inhibitors, have emerged as cornerstone agents in reducing cardiovascular risk. By lowering LDL cholesterol and exerting anti-inflammatory and plaque-stabilizing effects, statins effectively mitigate the progression of atherosclerosis—a central mechanism in CVD.

This systematic review evaluates the long-term outcomes of statin therapy, focusing on its impact on cardiovascular and all-cause mortality across diverse patient populations, including those with chronic kidney disease and heart failure. The findings underscore the importance of tailored statin use in optimizing cardiovascular outcomes and reducing global disease burden.

Study	Population	Intervention	Comparison	Follow-Up Duration	Primary Outcome(s)	Key Findings (Statistical Data)	Conclusion
Dobre et al., 2013 [9]	6,632 patients with acute MI complicated by acute HF with systolic dysfunction; mean age 64 years; 71% male	Statin therapy at baseline, prescribed to 47% of patients	No statin therapy	Mean follow-up of 16 ± 7 months	All-cause mortality, CV mortality, non-CV hospitalizations	Statin therapy was associated with a 20% lower risk of all-cause mortality (HR 0.80, 95% CI 0.69-0.92, P = 0.001) and a 24% lower risk of CV mortality (HR 0.76, 95% CI 0.65-0.88, P = 0.0002). Higher risk of non-CV hospitalizations (HR 1.16, 95% CI 1.02-1.33, P = 0.02).	Statin therapy may benefit patients with acute HF complicating acute MI by reducing CV and all-cause mortality, though it may increase non-CV hospitalizations. Prospective trials are needed to confirm these findings.
Vallejo-Vaz et al., 2017 [10]	5,529 men aged 45-64 years with primary LDL-C ≥190 mg/dL and no baseline vascular disease; subdivided by LDL-C <190 mg/dL and ≥190 mg/dL	Pravastatin 40 mg daily	Placebo	Initial randomized trial phase: 4.9 years; total follow-up: 20 years	CHD, MACE, CHD death, cardiovascular death, all-cause mortality	Pravastatin reduced the risk of CHD by 27% (P=0.002) and MACE by 25% (P=0.004) during the trial phase. In individuals with LDL-C ≥190 mg/dL, pravastatin reduced CHD death by 28% (P=0.020), cardiovascular death by 25% (P=0.009), and all-cause mortality by 18% (P=0.004) over 20 years.	This study provides strong evidence for the benefits of LDL-C lowering with pravastatin for long-term primary prevention of cardiovascular events and mortality in individuals with elevated LDL-C.
Rossi et al., 2017 [11]	1,060 ambulatory patients with chronic HF and coexisting COPD from the GISSI-HF study	Rosuvastatin 10 mg daily	Placebo	Median follow-up of 3.9 years (IQR: 3.0-4.4)	All-cause mortality, CV death, non-CV death, all-cause hospitalization	No significant difference in all-cause mortality (p = 0.30), CV death (p = 0.88), non-CV death (p = 0.09), or all-cause hospitalization (p = 0.82) between the statin and placebo groups.	Statin use was not associated with a reduction in all-cause, CV, or non-CV mortality or hospitalizations in patients with chronic HF and COPD.
Domanski et al., 2007 [12]	1,024 patients with non-IDC, NYHA class III and IV HF, and left ventricular ejection fraction ≤0.35	Statin therapy at initial screening	No statin therapy	Duration not specified in abstract	All-cause mortality, CV mortality	Statin therapy was associated with a 62% reduction in all-cause mortality (HR 0.38, 95% CI 0.18-0.82, p = 0.0134) and a 58% reduction in CV mortality (HR 0.42, 95% CI 0.18-0.95, p = 0.037) after adjustment for confounding variables.	Statin therapy was independently associated with a significant reduction in all-cause and CV mortality in patients with moderate to severe HF due to non-IDC.
Tonkin et al., 2000 [13]	3,260 patients with unstable angina and 5,754 with previous MI, enrolled 3-36 months post-event	Pravastatin 40 mg daily	Placebo	Mean follow-up of 6.0 years	All-cause mortality, CHD mortality, MI, coronary revascularization, hospital admissions	Pravastatin reduced mortality by 20.6% in the MI group and by 26.3% in the unstable angina group (p = 0.55 for comparison). It significantly reduced rates of CHD mortality, total mortality, MI, revascularization, hospital admissions, and days in hospital among unstable angina patients.	Pravastatin provided significant reductions in mortality and other cardiovascular outcomes in patients with previous unstable angina or MI, with similar benefits across both groups.
Arntz et al., 2000 [14]	126 patients with acute MI and/or PTCA following unstable angina	Pravastatin therapy (combined with cholestyramine and/or niacin as needed)	Usual antilipidemic therapy managed by family physicians	Follow-up at 6 and 24 months	Combined endpoint of total mortality, CV death, nonfatal MI, need for coronary intervention, stroke, and new onset of peripheral vascular disease	At 24 months, 29/56 patients in the control group and 16/70 in the pravastatin group reached a clinical endpoint (p = 0.005; OR 0.28, 95% CI 0.13-0.6). Minimal lumen diameter increased in the pravastatin group (0.13 ± 0.29 mm) and decreased in the control group (-0.18 ± 0.27 mm, p < 0.001).	Immediate pravastatin-based therapy post-acute coronary syndrome significantly improved clinical outcomes and slowed coronary atherosclerosis progression.
Ridker et al., 2010 [15]	3,267 patients with moderate CKD (eGFR <60 ml/min/1.73 m²) and hsCRP ≥2 mg/L, no cardiovascular disease, LDL-C <130 mg/dL	Rosuvastatin 20 mg daily	Placebo	Median follow-up of 1.9 years (up to 5 years)	First cardiovascular event, all-cause mortality	In patients with moderate CKD, rosuvastatin reduced the risk of major cardiovascular events by 45% (HR 0.55, 95% CI 0.38-0.82, p = 0.002) and all-cause mortality by 44% (HR 0.56, 95% CI 0.37-0.85, p = 0.005). Median LDL-C and hsCRP reductions were similar in patients with and without CKD.	Rosuvastatin significantly reduces cardiovascular events and all-cause mortality in CKD patients with elevated hsCRP, supporting its use in primary prevention in this population.

TABLE 1: Characteristics of the included studies.

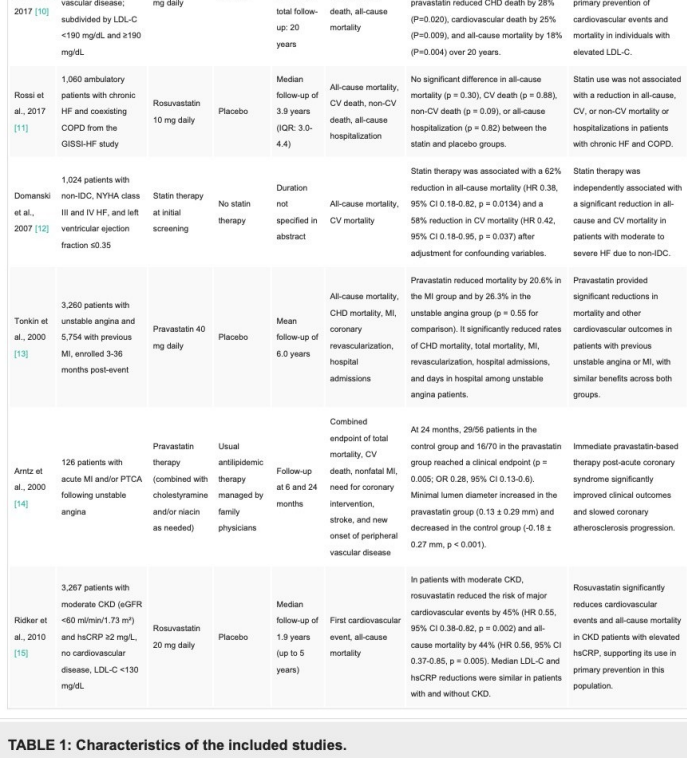

FIGURE 1: The PRISMA flowchart represents the study selection process.

METHODS

Study Design

A systematic review was conducted to evaluate the role of statins in reducing cardiovascular and all-cause mortality. The review adhered to PRISMA guidelines to ensure transparency and methodological rigor.

Search Strategy

A comprehensive search was performed across PubMed, Cochrane Library, Embase, and Scopus databases. Keywords included "statins," "HMG-CoA reductase inhibitors," "cardiovascular mortality," "primary prevention," and "secondary prevention." Boolean operators (AND, OR) were applied to refine the search, and filters restricted results to randomized controlled trials (RCTs) and large cohort studies with follow-up durations exceeding one year.

Data extraction

Studies were included based on the following criteria:

Population: Adults (≥18 years) at risk of cardiovascular mortality, including high-risk groups with chronic kidney disease, diabetes, or heart failure.

Intervention: Statin therapy (e.g., atorvastatin, rosuvastatin) compared to placebo, non-statin therapies, or standard care.

Outcomes: Primary outcome—cardiovascular mortality; secondary outcomes—all-cause mortality and major adverse cardiovascular events (MACE).

Study Design: RCTs and large observational cohort studies published in English.

Studies focusing solely on pediatric populations, pregnancy, or with insufficient outcome data were excluded.

Eligibility Criteria

Key data were extracted, including study characteristics (sample size, demographics, duration), intervention details (statin type, dosage), comparator groups, and outcomes (mortality rates, MACE). Two independent reviewers cross-verified data to ensure accuracy and resolve discrepancies.

Data analysis

A narrative synthesis of findings was performed, highlighting effect sizes and statistical significance of mortality outcomes across studies. Subgroup analyses explored variations in efficacy based on comorbidities, statin type, and dosage. Risk of bias was assessed using standardized tools to evaluate methodological quality.

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Risk of Bias
Dobre et al., 2013 [9]	Low Risk	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Vallejo-Vaz et al., 2017 [10]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Rossi et al., 2017 [11]	Low Risk	Low Risk	High Risk	Unclear	Low Risk	Low Risk	Unclear	Moderate Risk
Domanski et al., 2007 [12]	Low Risk	Unclear	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Moderate Risk
Tonkin et al., 2000 [13]	Low Risk	Low Risk	Unclear	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Arntz et al., 2000 [14]	Unclear	Unclear	High Risk	Unclear	Low Risk	Low Risk	Low Risk	Moderate Risk
Ridker et al., 2010 [15]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

TABLE 2: A summary of the quality assessment process.

RESULTS

The study selection process followed PRISMA guidelines and identified 511 records across four databases. After removing duplicates and screening titles and abstracts, 354 records remained, with 117 not retrievable. Following full-text assessment, 230 studies were excluded, leaving 7 studies for inclusion. These studies involved diverse populations with varying cardiovascular risks and examined statin therapies (pravastatin, rosuvastatin, atorvastatin) versus placebo or usual care. Outcomes included cardiovascular and all-cause mortality, with many also assessing major adverse cardiovascular events (MACE). Results showed significant mortality reductions, particularly in high-risk groups. Quality assessment revealed mostly low risk of bias, with some moderate risks in areas like allocation concealment and blinding. Overall, the evidence supports statins' long-term benefits in improving cardiovascular outcomes.

Discussion:

This systematic review highlights the positive effects of statins on reducing cardiovascular and all-cause mortality across high-risk populations. Statin therapy consistently demonstrated significant mortality reductions, particularly in patients with acute myocardial infarction, elevated LDL-C, chronic heart failure, chronic kidney disease, and other comorbidities. However, specific subgroups, such as those with coexisting chronic heart failure and COPD, showed less benefit, emphasizing the importance of patient-specific factors in treatment outcomes. Statins primarily reduce cardiovascular mortality by lowering LDL-C and exerting anti-inflammatory effects, stabilizing atherosclerotic plaques, and reducing oxidative stress. Variations in statin efficacy depend on factors like potency and lipid solubility.

The review's strengths include rigorous inclusion criteria, a broad spectrum of studies, and long-term follow-up. Limitations involve heterogeneity in study designs, statin dosages, and patient populations, which may affect generalizability. The review suggests that statin therapy should be tailored to individual patient profiles, especially in high-risk groups like those with chronic kidney disease or elevated inflammatory markers. Future research should focus on long-term data, exploring combinations of statins with newer lipid-lowering agents, and evaluating personalized statin dosing strategies.

CONCLUSIONS

This systematic review emphasizes the crucial role of statins in reducing cardiovascular and all-cause mortality, particularly in high-risk populations, reinforcing their importance in both primary and secondary prevention. Statins effectively lower LDL-C levels and provide additional benefits through anti-inflammatory and plaque-stabilizing effects, improving long-term outcomes. Tailoring statin therapy to individual patient profiles—accounting for comorbidities, cholesterol levels, and disease severity—can optimize benefits and minimize risks. While statins show substantial potential for improving survival and reducing cardiovascular events, further research is needed to refine treatment strategies and enhance patient outcomes.

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