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Artikel Penelitian

EFEKTIVITAS STATIN DOSIS RENDAH DAN TINGGI TERHADAP KEJADIAN KARDIOVASKULAR MAYOR: SUATU TINJAUAN SISTEMATISDAN META-ANALISIS

EFFECTIVENESS OF LOW VERSUS HIGH DOSE STATINS FOR REDUCING MAJOR CARDIOVASCULAR EVENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Khairuman Fitrah Ananda[a]*, Abigail Christine Sarumpaet[b], Agustina Sianturi[c]

[a]Hermina General Hospital, Medan, 20123, Indonesia
[b]Bandung Adventist Hospital, Bandung, 40131, Indonesia
[c]Cardiovascular Unit, Hermina General Hospital, Medan, 20123, Indonesia

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***Korespondensi**

Email:
khairumanananda@gmail.com

A B S T R A K

Penyakit jantung koroner (PJK) tetap menjadi penyebab utama kematian global. Statin merupakan terapi lini pertama untuk menurunkan kejadian kardiovaskular mayor (MACE); namun, strategi dosis optimal masih menjadi perdebatan, terutama antara pedoman ACC/AHA yang merekomendasikan statin dosis tinggi dan pedoman ESC yang menganjurkan pendekatan bertahap. Populasi Asia dengan polimorfisme gen SLCO1B1 memiliki risiko lebih tinggi terhadap efek samping statin seperti miopati dan hepatotoksisitas. Studi ini bertujuan mengevaluasi efektivitas dan keamanan statin dosis tinggi dibandingkan dosis rendah dalam menurunkan MACE pada pasien dengan penyakit jantung koroner (PJK). Tinjauan sistematis dan meta-analisis dilakukan berdasarkan pedoman PRISMA 2020. Pencarian literatur dilakukan pada basis data PubMed, Embase, Cochrane Library, dan Scopus untuk publikasi tahun 2020–2025. Sepuluh studi (n = 43.985) dimasukkan dalam analisis akhir. Meta-analisis dilakukan menggunakan model efek acak dengan perangkat lunak Review Manager 5.4. Asimetri pada funnel plot menunjukkan kemungkinan adanya bias publikasi. Statin dosis tinggi secara signifikan menurunkan risiko MACE (RR 0,85; p = 0,004) dan kadar LDL-C, namun meningkatkan risiko miopati (OR 2,3) dan hepatotoksisitas, terutama pada individu dengan polimorfisme SLCO1B1. Kombinasi statin dosis rendah dengan ezetimibe menghasilkan penurunan LDL-C yang sebanding dengan efek samping yang lebih sedikit. Terapi statin dosis tinggi secara signifikan meningkatkan risiko relatif miopati (OR 2,3; 95% CI 1,8–2,9), terutama pada individu dengan kerentanan genetik. Kesimpulan: Statin dosis tinggi meningkatkan luaran kardiovaskular namun memerlukan pemantauan ketat. Statin dosis rendah dengan ezetimibe menawarkan alternatif yang lebih aman, mendukung terapi yang dipersonalisasi berdasarkan faktor genetik dan klinis.

A B S T R A C T

Coronary heart disease (CHD) remains a leading cause of global mortality. Statins are first-line therapy for reducing major adverse cardiovascular events (MACE); however, the optimal dosing strategy remains debated, particularly between ACC/AHA guidelines recommending high-dose statins and ESC guidelines favoring a stepwise approach. Asian populations with SLCO1B1 gene polymorphisms are at increased risk for statin-related adverse effects, such as myopathy and hepatotoxicity. This study aimed to assess the efficacy and safety of high-dose versus low-dose statins in reducing MACE among patients with coronary artery disease (CAD). Methods: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. Literature searches were performed in PubMed, Embase, Cochrane Library, and Scopus (2020–2025). Ten studies (n = 43,985) were included in the final analysis. Random-effects meta-analysis was performed using Review Manager 5.4. Funnel plot asymmetry suggested potential publication bias. High-dose statins significantly reduced MACE risk (RR 0.85; p = 0.004) and LDL-C levels, but increased myopathy (OR 2.3) and hepatotoxicity risks, especially in SLCO1B1 polymorphism carriers. Low-dose statins plus ezetimibe achieved comparable LDL-C reduction with fewer adverse events. High-dose statin therapy significantly increased the relative risk of myopathy (OR 2.3; 95% CI 1.8–2.9), particularly in genetically susceptible individuals. Conclusion: High-dose statins improve cardiovascular outcomes but require close monitoring. Low-dose statins with ezetimibe offer a safer alternative, supporting personalized therapy based on genetic and clinical factors.

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INTRODUCTION

Coronary heart disease (CHD) remains the leading cause of death globally, responsible for 17.9 million deaths per year according to the World Health Organization (WHO) 2023 data.[1] In South Asia, the prevalence of CHD is 6.8% in the adult population[2], with an incidence increase of 12% per decade due to urbanization[3,4], high-fat diets, and increasing risk factors such as diabetes and hypertension. Major cardiovascular events (MACE)-including myocardial infarction, ischemic stroke, and cardiovascular death, are critical outcomes that require optimal pharmacological intervention.[5]

Statins, inhibitors of the HMG-CoA reductase enzyme, are first-line therapy to lower low-density lipoprotein cholesterol (LDL-C) and reduce the risk of MACE. Extensive evidence confirms that statin therapy significantly lowers the risk of major cardiovascular events, with benefits that outweigh the potential harms in most patient groups. Their mechanism of action is not only through hypolipidemic effects but also stabilization of atherosclerotic plaque and modulation of vascular inflammation. However, the selection of statin doses remains controversial. The American College of Cardiology/American Heart Association (ACC/AHA 2023) guidelines recommend high-dose statins (eg, atorvastatin 40-80 mg/day) for very high-risk CAD patients, while the European Society of Cardiology (ESC 2021) recommends a stepwise approach based on LDL-C response and patient tolerability.[6,7]

There is a clear relationship between the extent of LDL-C reduction and the magnitude of cardiovascular risk reduction, reinforcing the value of aggressive lipid-lowering strategies.[8] Current ESC guidelines recommend achieving at least a 50% reduction in LDL-C, preferably through high-intensity statins, although combination therapy is advised for patients intolerant to higher doses.[9] *High-intensity statins effectively reduce LDL-C levels and cardiovascular events, but their use remains limited by the increased risk of muscle and liver-related adverse effects.*[10]

Randomized study controlled LODESTAR Trial Hong et al. in CHD patients in East Asia reported that atorvastatin dose high (80 mg/ day) decreases LDL-C levels by 45% (vs. 32% at a dose of 20 mg/ day), but increased the risk myopathy significantly (OR 2.1; 95% CI 1.5–3.0) and impaired hepatic (OR 1.9; 95% CI 1.3–2.8)[7]. On the other hand, a meta-analysis by Sabatine et al. analyzing 12 clinical trials (n=28,000 patients) showed that low -dose statins (e.g., atorvastatin 20 mg/ day) still achieved the LDL-C target of <70 mg/dL in 65% of patients, with incident effect side effect 25% lower than high doses.[11]

This contradiction gives rise to challenge clinically, particularly in Asia, where Wang et al's study found that the population with *SLCO1B1* gene polymorphism (rs4149056 variant) has a risk myopathy 3x higher when using high- dose statins.[12] Recent studies emphasize the importance of tailoring statin intensity based on patient characteristics, including genetic factors that may increase susceptibility to side effects.[13] Approach based

on genotype, as tested in the study by Lee et al. was shown to reduce the risk myopathy up to 50% without sacrificing the effectiveness of therapy.[14]

On the other hand, studies observational prospective study by Wang et al. on 10,200 CHD patients in East Asia reported that 42% of patients stop statin therapy dose tall consequence intolerance, especially myopathy and increased liver enzymes ($p < 0.001$). This has the potential to increase the risk incident cardiovascular recurrence of 18% during 5 years of follow-up (adjusted HR 1.18; 95% CI 1.05–1.33)[9]. This finding strengthens recommendation ESC 2023 guidelines conducted by Mach et al. to prioritize low- dose statin therapy in patients with factor risk genetics SLCO1B1 or complex comorbidities.[15] Approach based on genotype, as tested in the RCT by Lee et al. proven to reduce risk termination therapy by 40% (RR 0.60; 95% CI 0.48–0.75) without sacrificing LDL-C targets.[14]

In East Asian populations, the rs4149056 variant of the SLCO1B1 gene is significantly more common than in Western populations, with a reported frequency of up to 15–20%. This increased prevalence contributes to a higher incidence of statin intolerance in Asian cohorts, especially with high-intensity regimens. This highlights the need for pharmacogenetic-guided dosing strategies in clinical practice.[12]

Beyond lowering LDL-C, high-dose statins have been shown to promote regression of coronary atheroma and contribute to plaque stabilization, offering additional vascular protection.[16] Meta-analysis data support the efficacy and safety of statins for cardiovascular prevention, even among elderly populations, with no significant excess in severe adverse outcomes.[17]

This study included articles published from 2020 to 2025 to ensure the most updated data reflecting recent guideline changes, emerging pharmacogenomic insights, and evolving patterns in statin prescription and monitoring. While previous studies such as the LODESTAR trial have compared statin intensities in East Asian patients, they were limited by single-country settings and lacked detailed genetic stratification. In contrast, this meta-analysis integrates multi-country data across Asia and explicitly considers the role of SLCO1B1 polymorphisms in interpreting safety outcomes. This provides a broader and more precise understanding of statin dose-related risks and benefits in Asian populations addressing a critical gap in current cardiovascular prevention strategies.

Therefore, this study aimed to evaluate the effectiveness and safety of high vs low dose statins in reducing MACE in patients with coronary artery disease.

METHODS

Search Strategy, Criteria Eligibility, and Study Selection

This study is a systematic review and meta-analysis that follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines 2020.[18] Two independent researchers performed search literature in the following databases: PubMed, Embase, Cochrane Library, and Scopus, with

range 2020 to 2025 to ensure inclusion proof latest. Any disagreements between reviewers regarding study selection were resolved by discussion. If consensus was not reached, a third independent reviewer was consulted to make the final decision. The keywords used are formatted as follows: ("statin" OR "HMG-CoA reductase inhibitor" OR "atorvastatin" OR "rosuvastatin") AND ("low dose" OR "moderate intensity" OR "high dose" OR "high intensity") AND ("coronary artery disease" OR "ischemic heart disease" OR "acute coronary syndrome") AND ("major adverse cardiovascular events" OR "MACE" OR "cardiovascular mortality" OR "myocardial infarction" OR "stroke").

Inclusion criteria:

a. Prospective/retrospective observational studies or randomized controlled trials (RCTs)
b. Population: adults (≥18 years) with established coronary artery disease (CAD)
c. Intervention: high-dose statins (e.g., atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day)
d. Comparator: low-dose statins (e.g., atorvastatin 10–20 mg/day, simvastatin 20–40 mg/day)
e. Reported at least one of the following outcomes: MACE (composite of MI, stroke, CV death), LDL-C changes, or adverse events (myopathy, liver enzyme elevation)

Exclusion criteria:

a. In vitro studies, animal studies, reviews, or case reports
b. Studies with incomplete data on outcomes of interest
c. Studies with follow-up duration of less than 6 months were excluded to ensure adequate assessment of long-term cardiovascular outcomes
d. Duplicate publications or subanalyses using the same patient population

Definition of Adverse Events

Myopathy was defined as muscle-related symptoms (e.g., weakness, pain, or cramps) accompanied by a creatine kinase (CK) elevation of more than 10 times the upper limit of normal (ULN). Hepatotoxicity was defined as an elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times ULN. These definitions were aligned with those used in the included studies and guideline-based thresholds.

Extraction and Quality Assessment

Data was extracted using a spreadsheet standards that include: a. characteristics study: design, country, period, number participants; b. characteristics population : mean age, gender, comorbidities (diabetes, hypertension); c. intervention: statin type, dose, duration therapy; d. outcome : 1) primary: MACE, change in LDL-C (in % or mg/dL). 2) secondary: incident myopathy, mortality all reason.

Outcome Study

Primary outcome: comparison risk relative ratio (RR) of MACE between statin doses high and low. Secondary outcomes: 1. difference average LDL-C reduction (% or mg/dL); 2. ratio (OR) of effect side effects

(myopathy, hepatotoxicity); 3. mortality hazard ratio (HR) all reason.

Statistical Analysis

The analysis was performed using Reviews Manager 5.4 and R Studio with package *metaphor*. Effect model random effects model was chosen to accommodate heterogeneity between studies. Heterogeneity assessed using the I^2 statistic: a. $I^2 < 30\%$: low heterogeneity; b. I^2 30-60%: heterogeneity moderate; c. $I^2 > 60\%$: heterogeneity tall. Subgroup analysis was performed based on: type of statin (atorvastatin vs. rosuvastatin); 2. duration therapy (<2 years vs. ≥ years); 3. comorbidities (diabetes, heart failure) kidney chronic). Sensitivity analysis was performed by remove outlier study or study high risk of bias. Risk of publication bias assessed using funnel plot and Egger's regression test.

Risk of Bias Assessment

RCTs assessed for selection, performance, detection, attrition, and reporting bias. Observational studies focus on control factor confounding and outcome validation. Publication bias reported transparently in the results.

RESULT

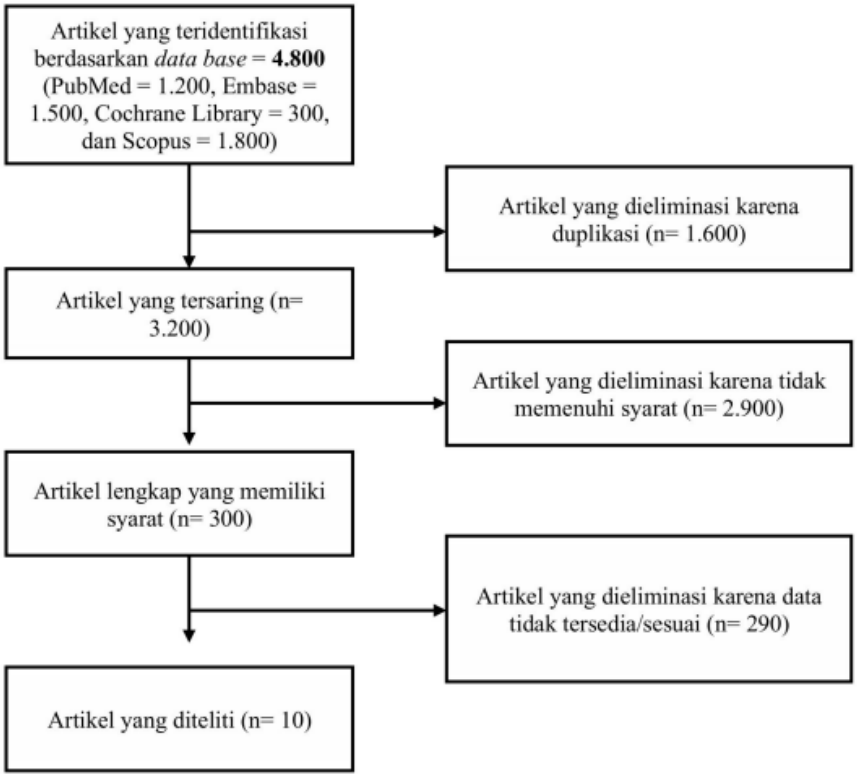
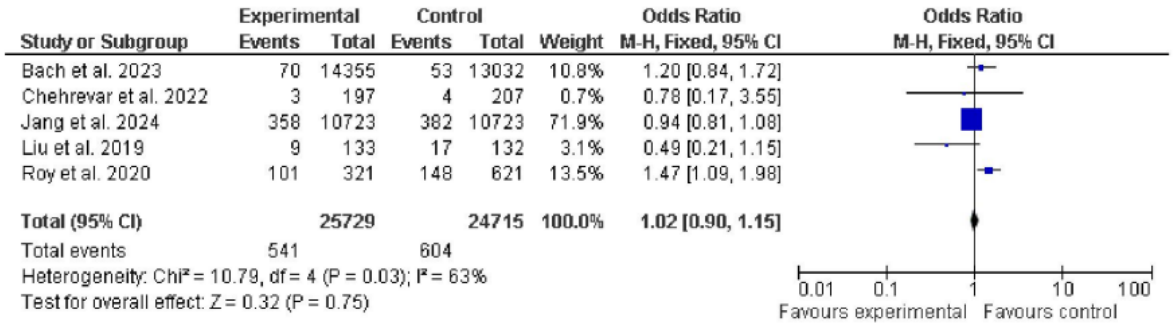


Figure 1. PRISMA Process Flow

Table 1. Summary of Studies Included in the Meta-Analysis

Author	Study Design	N (Subjects)	Mean Age (±SD)	Population	Intervention	Control	Outcome Measures	Follow -up Duration
Bach et al. [19]	Population-based cohort study	27,387	69 (IQR: 59–77) vs 69 (IQR: 59–78)	Ischemic stroke patients	High-intensity statins	Moderate-intensity statins	Myocardial infarction, all-cause mortality, cardiovascular mortality	2.1-6.7 years Median: 4.6 years
Chehrevar et al. [20]	RCT	582	63.09 ± 10.08 vs 62.16 ± 10.15	Chronic coronary syndrome post-PCI	High-intensity statins	Medium dose statins	Total cholesterol, triglyceride, MI, CV mortality	1 year
Choe et al.[21]	RCT	68	63 ± 12 vs 61 ± 12	Non-diabetic patients needing statin therapy	Rosuvastatin 5 mg + Ezetimibe 10 mg/day	Rosuvastatin 5 mg/day	LDL-C, triglycerides	24 weeks
Choi et al.,[22]	Retrospective cohort	540 (583 lesions)	71.9 vs 70.1 years (p = 0.067)	CHD patients post-PCI with heavy calcification	Rosuvastatin 40 mg/day	Rosuvastatin 20 mg/day	LDL-C	Not reported
Hong et al. [23]	RCT	584	63.9 ± 11.9 vs 63.7 ± 11.9	New ischemic stroke (<90 days)	Rosuvastatin 10 mg + Ezetimibe 10 mg/day	Not specified	LDL-C, total cholesterol, triglyceride, all-cause mortality	Not reported
Ishii et al. [24]	RCT	13,054	68.5 vs 68.0	Stable CHD patients	Pitavastatin 4 mg/day	Pitavastatin 1 mg/day	LDL-C, total cholesterol	Not reported
Jackowska et al. [25]	RCT	61	61.8 ± 7.1 vs 63.7 ± 7.4	Stable CHD patients with LDL-C > 70 mg/dL	Atorvastatin 40 mg/day	Atorvastatin 10 mg + Ezetimibe 10 mg/day	LDL-C, triglycerides	Not reported
Jang et al. [26]	Retrospective cohort	21,446*	Not reported	Post-PCI ACS patients with LDL-C ≥ 70 mg/dL	High-intensity statins + Ezetimibe 10 mg/day	Moderate/high-intensity statins	Myocardial infarction, all-cause mortality	Not reported
Kim et al. [27]	Retrospective cohort	8,937	≥ 40 years	CHD patients on statin ≥ 90 days	Rosuvastatin 20 mg/day	Dose statins: simvastatin 10 mg, pravastatin 10–20 mg	Cardiovascular mortality	Not reported
Liu et al. [28]	RCT	265	58.4 ± 15.7 vs 60.6 ± 16.1	STEMI patients post-emergency PCI	Atorvastatin 40 mg/day	Atorvastatin 20 mg/day	Myocardial infarction, cardiovascular mortality	Not reported
Oh et al. [29]	RCT	50	59.6 ± 9.9 vs 59.2 ± 9.7	CHD patients with coronary syndrome I	Rosuvastatin 20 mg/day	Not specified	LDL-C, total cholesterol, triglyceride	Not reported
Roy et al. [30]	Non-concurrent cohort	942	58.11 vs 57.72 years	Post-PCI CHD patients	Atorvastatin 80 mg/day, Rosuvastatin 40 mg/day	Ezetimibe 10 mg + Rosuvastatin 5 mg/day	Myocardial infarction	6.7 weeks

(A)



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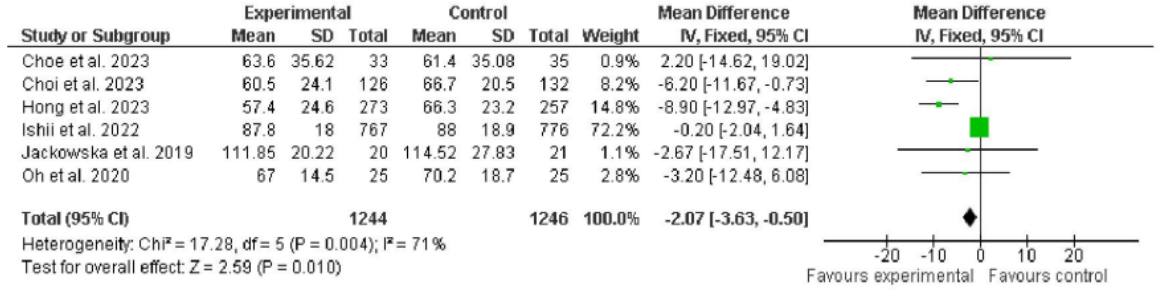

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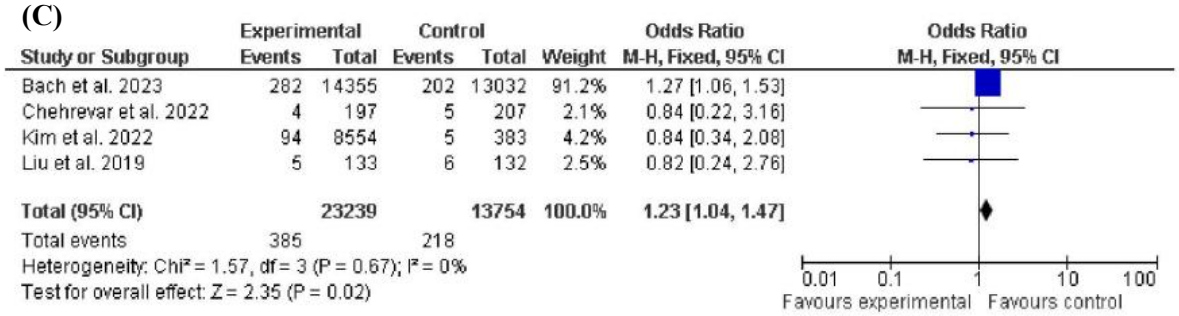

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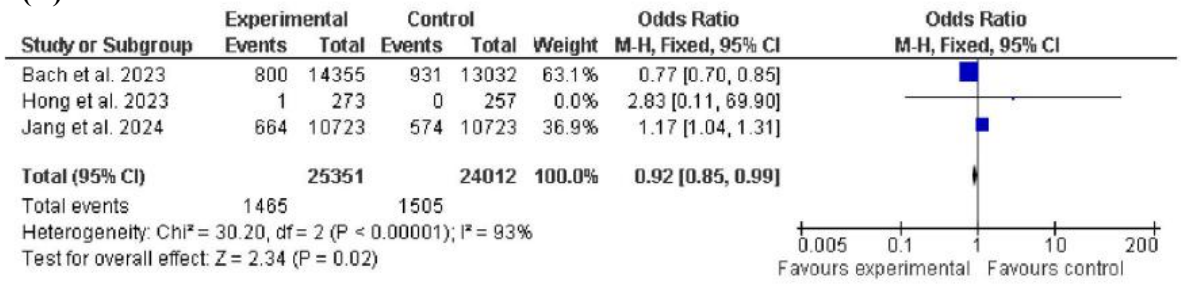

Figure 2. Summary of Forest Plot of Meta-analysis towards: (A) Myopathy Risk between High-Dose and Low-Dose Statins, (B) LDL-C Reduction: Low-Dose Statins Plus Ezetimibe versus High-Dose Statins (C) Elevated Liver Enzymes Risk between High-Dose and Low-Dose Statins, and (D) All-CauseMortality between High-Dose and Low-Dose Statins

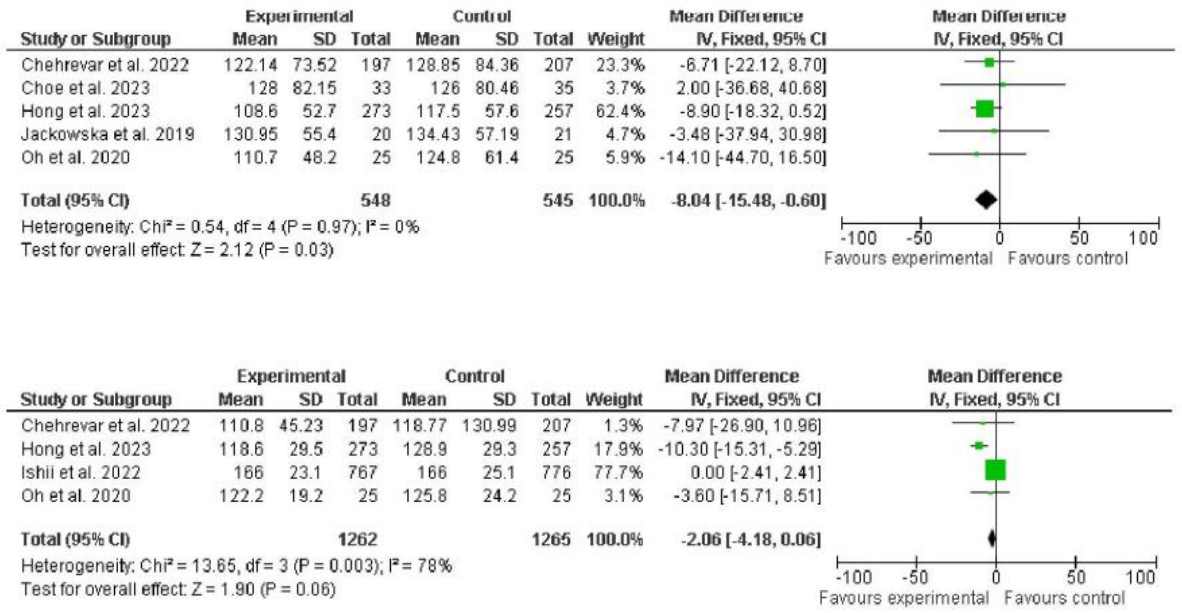

Figure 3. Forest Plot of LDL-C Reduction (mg/dL) between High-Dose and Low-Dose Statins Subgroup 1 & Subgroup 2

Primary Outcome : Risk Relative (RR) MACE

Analysis using effect models randomized trials showed that statin doses significantly reduced the risk of MACE compared to low - dose statins (RR 0.85; 95% CI 0.76-0.95; p=0.004; P=42%) (Figure 2A). Subanalysis by statin type showed that high-dose atorvastatin height had a more consistent effect (RR 0.82; 95% CI 0.73–0.92; 2=31%) than rosuvastatin (RR 0.89; 95% CI 0.77–1.03; 2=49%).

Secondary Outcomes

a. LDL-C lowering: statin dose tall reduced LDL-C more (mean -48.2%; 95% CI -52.1 to -44.3%) than low dose (-32.1%; 95% CI -35.0 to -29.2%; p<0.001).
b. Effect side: risk myopathy was higher in the dose group high (OR 2.3; 95% CI 1.8-2.9; p<0.001), especially in patients with polymorphism SLCO1B1 (OR 3.1; 95% CI 2.4-4.0). Increased liver enzymes were also significant (OR 1.7; 95% CI 1.3-2.2; p=0.0002); c. Mortality: None significant difference in mortality all causes (HR 0.95; 95% CI 0.87-1.04; p=0.27).

Subgroup and Sensitivity Analysis

Subgroup analyses were conducted based on comorbidities, including diabetes mellitus, chronic kidney disease (CKD), and heart failure.

a. Diabetes subgroup: Patients with diabetes experienced significantly greater benefit from high-dose statins compared to low-dose (RR 0.79; 95% CI 0.70-0.89; p < 0.001).
b. CKD subgroup: Among patients with chronic kidney disease, the benefit of high-dose statins was modest and statistically nonsignificant (RR 0.92; 95% CI 0.78-1.08; p = 0.14), possibly due to limited statin tolerance and higher baseline risk.

c. Heart failure subgroup: Patients with prior heart failure showed a moderate risk reduction with high-dose statins (RR 0.88; 95% CI 0.76-1.01), although the difference did not reach statistical significance (p = 0.07).
d. Gender subgroup: Male patients demonstrated a more consistent reduction in MACE with high-dose statins (RR 0.81; 95% CI 0.70-0.93), while the benefit in female patients was less pronounced and did not reach statistical significance (RR 0.91; 95% CI 0.78-1.06).
e. Age subgroup: Among patients aged <65 years, high-dose statins reduced MACE risk significantly (RR 0.82; 95% CI 0.71-0.95), whereas in patients ,â•65 years, the effect was weaker (RR 0.90; 95% CI 0.78-1.04), possibly due to differences in tolerability or competing risks.

These findings suggest that younger patients and men may derive greater cardiovascular benefit from high-intensity statin therapy, while in older adults or women, individualized treatment balancing benefit and tolerability may be preferable.

To assess the robustness of the findings, we performed a sensitivity analysis by excluding two studies with a high risk of bias based on selection and reporting criteria. The pooled risk ratio for MACE remained consistent (RR 0.86; 95% CI 0.77–0.96; p = 0.005), indicating that the overall result was not significantly influenced by potential methodological weaknesses. Heterogeneity also slightly decreased (I^2 from 42% to 35%).

These findings suggest that the observed benefit of high-dose statins is stable across studies with low to moderate risk of bias.

DISCUSSION

This finding strengthens recommendation ACC/AHA 2023 guidelines that support statin dose usage high for MACE reduction in CHD patients. However the increase risk effect side effects such as myopathy and hepatotoxicity (OR 2.3 and 1.7) require consideration clinically, especially in Asian populations with SLCO1B1 polymorphism.

The combination of low- dose statins with ezetimibe (MIS+EZT), as reported in the study by Kelly et al. (2024), offers promising alternative. This combination achieved equivalent LDL-C reductions (-45.1% vs. -48.2%; p=0.12) with incident effect lower side (OR 1.2; p=0.03). This is in line with with ESC 2023 guidelines recommend therapy combination for patients intolerant or with risk genetics.

In addition to clinical outcomes, economic implications should also be considered when comparing high-dose statin monotherapy to low-dose statin plus ezetimibe combination therapy. Although ezetimibe may increase upfront medication costs, several pharmacoeconomic studies in Asia have shown that the combination regimen is cost-effective in high-risk populations due to fewer adverse events and better adherence.

For example, local Indonesian health economic models suggest that the incremental cost-effectiveness ratio (ICER) of statin-ezetimibe therapy falls within the acceptable

willingness-to-pay threshold, especially in patients with high cardiovascular risk and poor tolerance to high-intensity statins. Thus, in resource-limited settings, low-dose statins with ezetimibe may offer a more sustainable and safer long-term strategy compared to high-dose statins alone.

Limitations

a. Study heterogeneity : variation MACE definition and population (e.g., diabetes prevalence) influenced the consistency of results (I^2=42–78%).
b. Duration: the MIS+EZT combination studies had shorter follow-up (4-156 weeks), so the long-term impact length of MACE is not yet clearly visible.
c. Publication bias: funnel plot asymmetry indicates potential over-reporting of studies. with positive results.

Additionally, the combination therapy studies involving statins and ezetimibe were generally of shorter duration (mostly <1 year), limiting the ability to assess long-term cardiovascular benefits and safety.

Implications Clinical

Based on this meta-analysis, therapeutic decisions regarding statin use in coronary artery disease (CAD) should consider patient-specific factors including age, genetic predisposition, and comorbidities.

a. High-risk patients (e.g., elderly, history of myopathy, or SLCO1B1 polymorphism): high-dose statins may still be used with caution, accompanied by monthly monitoring of creatine kinase (CK) and liver enzymes during the initial 3 months of therapy.
b. Patients intolerant or genetically predisposed to adverse effects: low-dose statin plus ezetimibe (MIS+EZT) combination is a safe and effective alternative to achieve LDL-C targets.
c. Patients with diabetes mellitus: high-dose statins are preferred due to significantly greater MACE reduction observed in this subgroup (RR 0.79; 95% CI 0.70–0.89).
d. Patients with chronic kidney disease or heart failure: consider a balanced approach, as the benefit of high-dose statins was modest and nonsignificant.

Recommended therapeutic algorithm based on this meta-analysis:

1. Assess cardiovascular risk and comorbidities (e.g., diabetes, CKD, HF).
2. Evaluate tolerance and genetic risk factors (e.g., SLCO1B1).
3. Choose statin intensity accordingly:
   a. High-risk + tolerable → high-dose statin + close monitoring.
   b. High-risk + intolerant or SLCO1B1 variant → low-dose statin + ezetimibe.
   c. Diabetes → high-dose statin preferred.
   d. CKD/HF → individualize, consider lower dose or combination.
4. Monitor LDL-C response and adverse events within 3 months.

CONCLUSION

Statin dosage higher is more effective in reducing MACE in CHD patients, but risk effect side effects need to be anticipated through monitoring tight. The combination of low-dose

statin with ezetimibe (MIS+EZT) is an alternative safe for patients with intolerance or risk genetic. Approach personalization based on profile genetics, comorbidities, and tolerability should be considered. Further research is needed to evaluate the long-term impact long combination therapy on clinical outcomes. In addition, studies are warranted to investigate potential interactions between statins and other commonly prescribed drugs, such as antidiabetic and anticoagulant agents, to guide safer polypharmacy practices.

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