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RESEARCH LETTER

# Efficacy and Safety of Upfront Oral Triple Lipid-Lowering Therapy: A Systematic Review and Single-Arm Meta-Analysis

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## 1 | Introduction

Patients with high cardiometabolic risk remain vulnerable to recurrent atherosclerotic cardiovascular events, particularly those with established cardiovascular disease or a recent acute coronary syndrome (ACS) [1]. In these very-high-risk populations, early and intensive lowering of low-density lipoprotein cholesterol (LDL-C) is a central determinant of secondary prevention [2]. Importantly, the magnitude and timing of LDL-C reduction matter: achieving substantial LDL-C lowering within the first few weeks after an index event is closely linked to improved long-term cardiovascular outcomes [1, 2]. Despite established guidelines, a substantial proportion of patients fail to achieve LDL-C targets in routine clinical practice [3]. Contributing factors include delayed treatment intensification, limited use of early combination therapy and restricted access to advanced lipid-lowering agents [3, 4]. Lipid-lowering therapy (LLT) should be initiated based on the required LDL-C reduction, rather than a stepwise approach [1]. Although PCSK9 inhibitors are highly effective, their early use is constrained by cost, reimbursement limitations and the logistical challenges of initiating injectable therapy [5]. Consequently, most clinicians use oral regimens that can be initiated at hospital discharge and adjusted soon after ACS [6]. The most effective oral strategy involves initiating statins, ezetimibe, and bempedoic acid simultaneously, thereby targeting multiple cholesterol pathways. Simulation studies suggest that this approach may enable most high- and very-high-risk patients to achieve LDL-C targets [2–4]. However, direct clinical evidence remains limited, with randomised trials [7, 8] and even fewer single-arm studies [6] evaluating upfront triple oral therapy. This gap results in uncertainty about the achievable LDL-C reduction and the need for early escalation.

We conducted a systematic review and a single-arm meta-analysis to assess the effectiveness and safety of initiating all three oral lipid-lowering drugs simultaneously. This analysis provides practical evidence to inform real-world clinical decisions.

## 2 | Methods

This systematic review and single-arm meta-analysis was conducted in accordance with preferred reporting Items for systematic reviews and meta-analyses (PRISMA) guidelines [9] and is registered with PROSPERO (CRD420261292704) (Supporting Information). PubMed, Embase and the Cochrane library were searched for studies published up to 21 January 2026, which evaluated simultaneous initiation of statin, ezetimibe and bempedoic acid, with lipid outcomes reported within 4–8 weeks (Figure 1).

Two investigators independently screened and retrieved the eligible studies and extracted data using a standardised form,

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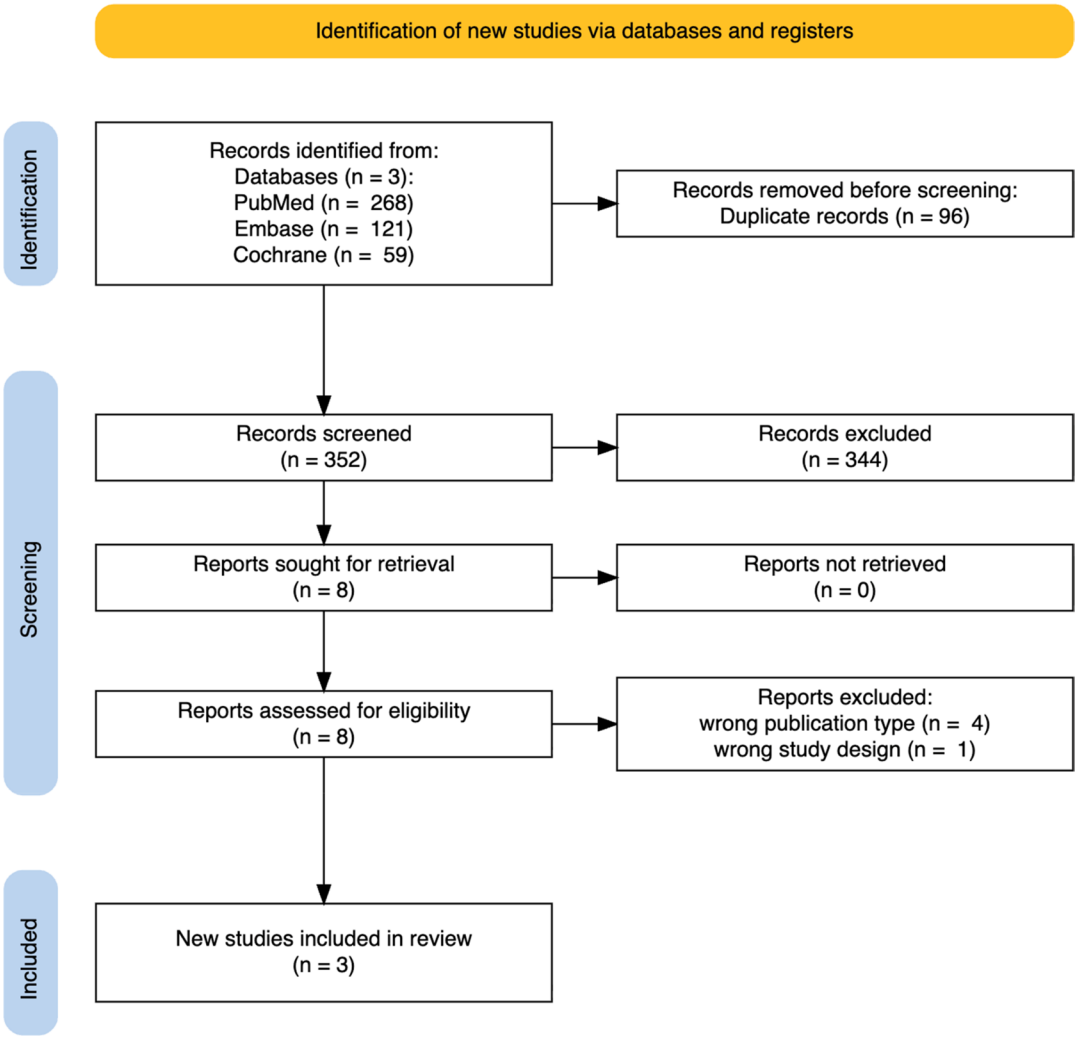


**FIGURE 1** | Study selection. PRISMA flow diagram depicting identification, screening, eligibility assessment, and inclusion of studies for the systematic review and single-arm meta-analysis.

including study design, patient characteristics, statin intensity, lipid parameters, follow-up duration and adverse events.

Primary outcomes were percentage LDL-C reduction and achievement of LDL-C < 55 mg/dL and < 70 mg/dL at 6–8 weeks. Secondary outcomes included non–HDL cholesterol, triglycerides, ApoB (apolipoprotein B), high-sensitivity C-reactive protein (hsCRP) and safety. Random-effects meta-analyses were performed, with heterogeneity assessed using $I^2$ and $\tau^2$. Statistical analyses were conducted using RStudio, with results reported as pooled estimates and 95% confidence intervals. When variance data were unavailable, the largest reported standard deviation from comparable outcomes at the same time point was conservatively imputed [10]. Risk of bias was assessed based on study design, completeness of follow-up and outcome reporting (Supporting Information and Figures S1A and S1B).

## 3 | Results

### 3.1 | Study Characteristics and Baseline Profile

Three studies met the inclusion criteria: two randomised controlled trials [7, 8] and one prospective real-world cohort [6] (Table S1). Because comparator arms differed substantially across the randomised trials (placebo in one and dual therapy in the other), the analysis focused on the triple-therapy arms, comprising a total of 266 patients. Lipid outcomes were measured between 6 and 8 weeks after starting triple therapy. The average age was 59.5 years (95% CI: 55.4–63.5; $I^2 = 44.3\%$) (Figure S2A). The pooled baseline LDL-C was 134.1 mg/dL (95% CI: 85.8–182.3; $I^2 = 97.7\%$) (Figure S2B). Baseline triglyceride levels showed a pooled mean of 145.8 mg/dL (95% CI: 127.9–163.7; $I^2 = 0\%$) (Figure S2C). Overall, these findings indicate that included populations were at elevated cardiometabolic risk.



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### 3.2 | LDL-C Reduction and Target Attainment

In all three studies, starting triple oral therapy led to an average LDL-C reduction of 59.5% at 6–8 weeks (95% CI: 52.6%–66.3%; $I^2 = 22.5\%$) (Figure 2A). Overall, 64.9% (95% CI: 45.4%–80.5%; $I^2 = 63.1\%$) of patients reached LDL-C below 55 mg/dL (Figure 2B), and about 85% (95% CI: 72.0%–93.0%; $I^2 = 36.9\%$) reached below 70 mg/dL at 6–8 weeks (Figure 2C). In a focused analysis restricted to statin-naïve ACS patients (three studies; $n = 231$), the pooled proportion achieving LDL-C < 55 mg/dL was 67.0% (95% CI: 49.0%–81.1%; $I^2 = 45.7\%$) (Figure 2D).

### 3.3 | Secondary Lipid Parameters and Inflammation

Mean percent reduction in non-HDL-cholesterol was 53.5% (95% CI: 40.6%–66.4%; $I^2 = 55.1\%$), mirroring LDL-C reductions and indicating effective lowering of total atherogenic lipoprotein burden (Figure S3A). Triglyceride levels also decreased by 15.4% (95% CI: 4.9%–25.8%; $I^2 = 0\%$) (Figure S3B). Quantitative pooling for ApoB and hsCRP was not feasible due to incomplete variance reporting. Descriptive analyses demonstrated consistent and clinically meaningful reductions with triple lipid-lowering therapy, with ApoB reductions ranging from 38.6% to 53.5% and hsCRP reductions ranging from 47.7% to 83.6% across studies.

### 3.4 | Safety Outcomes

Overall, adverse events were infrequent and predominantly mild. Safety data were available for 261 patients across three studies. The pooled proportion of drug discontinuation was 3.0% (95% CI: 1.0%–13.0%; $I^2 = 29.1\%$) (Figure S4A). Myalgia occurred in 5.0% of patients (95% CI: 0.0–38.0; $I^2 = 16.5\%$), whereas gout was reported in 2.0% (95% CI: 0.0–25.0; $I^2 = 0\%$) (Figures S4B and S4C). Transaminase elevations greater than three times the upper limit of normal were uncommon, with a pooled prevalence of 2.0% (95% CI: 0.0–12.0; $I^2 = 0\%$) (Figure S4D).

## 4 | Discussion

This single-arm meta-analysis provides focused evidence on the early efficacy and short-term safety of upfront oral triple lipid-lowering therapy, addressing an important gap in cardiometabolic care. Unlike prior studies centred on stepwise intensification [11], this analysis quantifies the LDL-C reduction achievable with simultaneous initiation of a statin, ezetimibe and bempedoic acid.

Across studies, an approximately 60% reduction in LDL-C was consistently achieved within 6–8 weeks. This effect persisted despite differences in statin intensity, with high-intensity statins

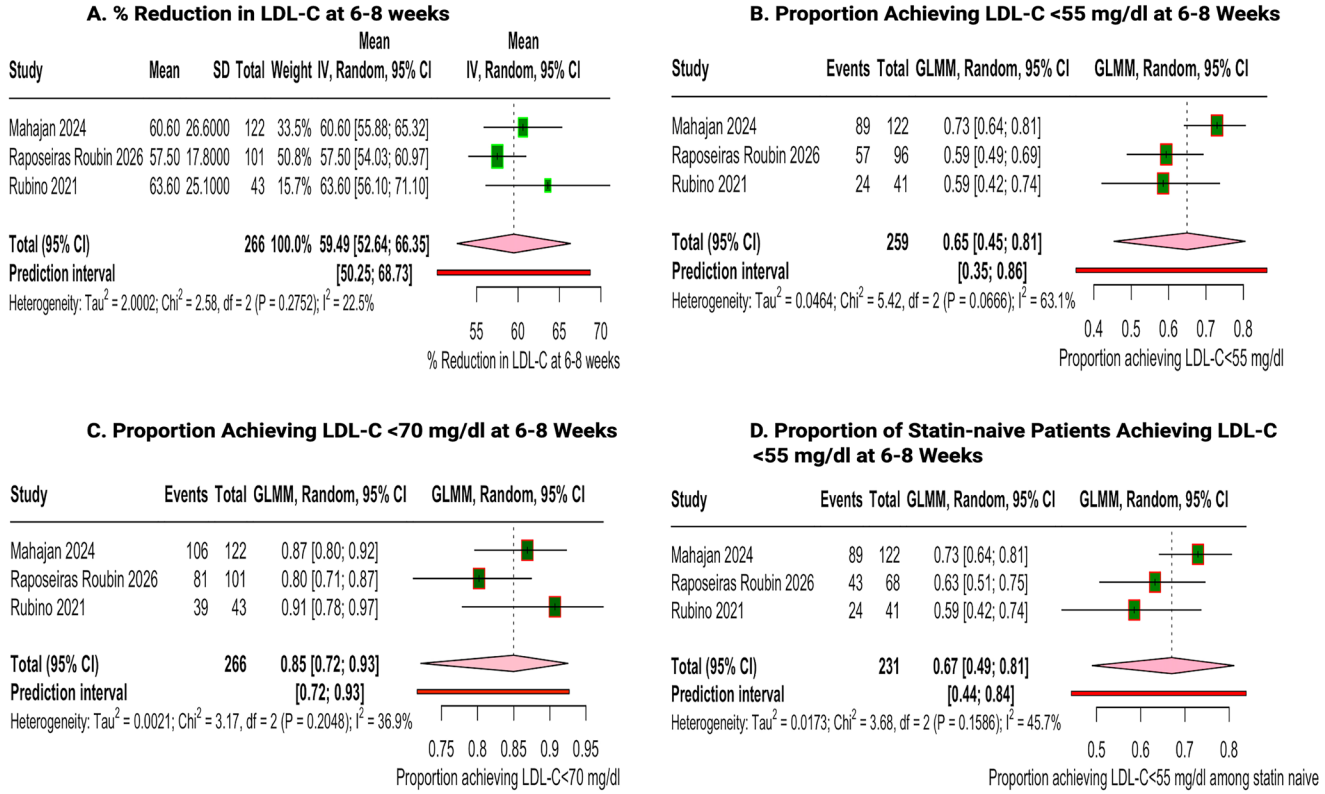


**FIGURE 2** | Early lipid-lowering efficacy of upfront oral triple therapy. Forest plots showing (A) pooled percent reduction in LDL-cholesterol at 6–8 weeks following simultaneous initiation of statin, ezetimibe, and bempedoic acid, (B) pooled proportion of patients achieving LDL-C < 55 mg/dL and (C) LDL-C < 70 mg/dL at 6–8 weeks. (D) Shows pooled proportion of statin-naïve acute coronary syndrome patients achieving LDL-C < 55 mg/dL at 6–8 weeks. Diamonds represent pooled estimates from random-effects models; horizontal bars indicate 95% confidence intervals. Prediction intervals are displayed where applicable. For the statin-naïve subgroup analysis (D), all patients in Mahajan et al. were statin-naïve at baseline, and patients in Rubino et al. were statin-naïve following a 6-week washout. In Raposeiras-Roubín et al., statin-naïve data were extracted from the predefined subgroup analysis.



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in Mahajan et al. [6] and Raposeiras et al. [8], and moderate-intensity atorvastatin (20 mg) in Rubino et al. [7]. The consistency of effect highlights the additive benefit of combination therapy and supports its use in patients with partial statin intolerance. Study populations differed, with Mahajan et al. and Raposeiras et al. enrolling ACS patients requiring urgent lipid lowering, whereas Rubino et al. studied hypercholesterolaemia without atherosclerotic cardiovascular disease. Although heterogeneity was low for percentage LDL-C reduction ($I^2 = 22.5\%$), substantial heterogeneity was observed for LDL-C < 55 mg/dL attainment ($I^2 = 63.1\%$), likely reflecting differences in baseline LDL-C, statin exposure and clinical context. Despite these differences, the consistency of early percentage LDL-C reduction across studies suggests a robust pharmacologic effect of combination therapy. These findings may support consideration of upfront triple oral therapy as an effective first-line strategy in very-high-risk patients who are substantially above LDL-C targets. However, patients requiring more profound LDL-C reduction or those with elevated lipoprotein(a) > 50 mg/dL (~20%–25% prevalence) may be less likely to achieve adequate control with the ~60% reduction observed with oral therapy alone, as Lp(a)-associated cholesterol contributes to measured LDL-C. Such patients may require earlier escalation to PCSK9 inhibitors [12, 13]. This analysis provides an estimate of the magnitude of early LDL-C reduction achievable with simultaneous initiation of oral triple therapy, which may help guide early treatment expectations and inform timely escalation strategies when LDL-C targets are not achieved. Safety assessment was limited to 6–8 weeks and reflects only early tolerability. Longer-term adverse effects of bempedoic acid may emerge with prolonged use. In CLEAR Outcomes (median follow-up 40.6 months), hyperuricemia (10.9% vs. 5.6%), gout (3.1% vs. 2.1%), and cholelithiasis (2.2% vs. 1.2%) were more frequent with bempedoic acid than placebo, along with modest increases in creatinine and hepatic enzymes [14]. Longer-term surveillance remains necessary. Limitations include the small number of studies, short follow-up, substantial heterogeneity in LDL-C target attainment due to differences in study populations and urgency of intervention, inability to perform comparative meta-analysis because of heterogeneous comparator arms, lack of clinical outcome data and absence of lipoprotein(a)-specific analyses.

## 5 | Conclusion

Upfront oral triple therapy with a maximally tolerated statin, ezetimibe and bempedoic acid achieves substantial early LDL-C reduction of approximately 60%, with acceptable short-term tolerability. These findings provide clinically relevant benchmarking data on the early lipid-lowering efficacy achievable with intensive oral therapy. However, given the small number of studies, short follow-up duration, and heterogeneity in study populations, these results should be interpreted as exploratory. Larger studies with longer follow-up are needed to define the durability of LDL-C reduction and long-term safety.

### Author Contributions

K.M. conceptualised the study. K.M., S.J., D.D., and A.B.M.K.-H. conducted the literature search, entered data, and analysed it. J.S., S.H., P.G.M., and N.M. critically reviewed the manuscript for important intellectual content. All authors contributed equally to manuscript preparation. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.


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The authors have nothing to report.


### Disclosure

Artificial intelligence was not used in any form in the planning, execution, and manuscript preparation of the study.

### Conflicts of Interest

N.M. is a freelance Data Science and translation research consultant. This work was conducted independently and is unrelated to the author Kunal Mahajan's full-time employment. The other authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70663.


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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** dom70663-sup-0001-Supinfo.docx.



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