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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (NJ PAGIDIPATI, SECTION EDITOR)

Combination Lipid-Lowering Therapy After ACS: Should this be the New Standard of Care?

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Abstract

Purpose of Review To examine whether early combination lipid-lowering therapy after acute coronary syndrome (ACS) should be considered as a standard approach. The review assesses current international guideline recommendations, supporting clinical evidence, and real-world implementation gaps.

Recent Findings Recent European and U.S. guidelines emphasise lower low-density lipoprotein-cholesterol (LDL-C) targets and suggest earlier use of combination therapy. Data from randomised trials, registry-based emulations, and observational cohorts demonstrate that early initiation of high-intensity regimens improves LDL-C goal attainment and may reduce the recurrence of cardiovascular events. However, registry data reveal substantial global undertreatment and limited treatment intensification.

Summary Early combination therapy represents a pragmatic strategy to accelerate LDL-C goal achievement after ACS. While this approach could narrow current treatment gaps, it must be balanced against the trend toward personalised, risk-based lipid management. Future research should address how simplified treatment algorithms can coexist with individualised care frameworks.

Keywords ACS · Lipid-lowering therapy · LDL-cholesterol targets · Statins

Introduction

Patients with recent acute coronary syndrome (ACS) face rates of cardiovascular death, myocardial infarction, and ischemic stroke approaching ~ 10–18% in the year after hospitalisation [1–3], underscoring the need for rapid and profound control of the underlying disease, which is atherosclerosis. Therefore, optimisation of low-density lipoprotein-cholesterol (LDL-C), as a cumulative and causal factor in atherosclerosis development, remains central to secondary prevention. Meta-analyses across randomised controlled trials consistently demonstrate that cardiovascular benefit correlates with the absolute magnitude of LDL-C reduction achieved, with similar relative risk reductions per unit LDL-C lowering observed regardless of the underlying therapeutic mechanism [4–6].

This log-linear relationship has informed increasingly stringent guideline targets. ESC recommendations since 2019 specify an LDL-C level of < 1.4 mmol/L (55 mg/dL) with a > 50% reduction from baseline, and < 1.0 mmol/L (40 mg/dL) in those with recurrent events [7–10]. The 2025 ACC/AHA ACS guidelines similarly strengthen this approach, recommending high-intensity statin therapy for all ACS patients, with the option to initiate concurrent ezetimibe, and emphasising that non-statin agents are indicated when LDL-C remains ≥ 1.8 mmol/L (70 mg/dL) despite maximally tolerated statin therapy [11]. In parallel, the 2025 ESC/EAS Focused Update introduces explicit ACS recommendations with the consideration to intensify lipid-lowering therapy during the index hospitalisation and to consider initiating combination therapy with high-intensity statin plus ezetimibe in treatment-naïve patients who are unlikely to reach LDL-C goals on statin alone (Class IIa B recommendation) [7]. However, real-world implementation of intensive lipid management has lagged behind guideline

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recommendations, raising the question of whether a default combination therapy started in the hospital for patients after ACS is justified. In this review, we compare current guideline recommendations, compile the evidence on which these recommendations are based, and reflect on current real-world data and the implications that a standard combination therapy could have.

Current Guideline Recommendations

Contemporary guidance converges on early initiation of high-intensity statin therapy after ACS, addition of non-statin agents based on on-treatment LDL-C and prior therapy, and scheduled lipid reassessment (Table 1). The ESC 2023 ACS guideline recommends starting a high-intensity statin as early as possible (ideally pre-PCI), re-checking lipids 4–6 weeks after each change, considering in-hospital ezetimibe when targets are unlikely to be achieved with statin alone, and initiating a PCSK9 inhibitor during hospitalization for patients already on statin plus ezetimibe who remain above goal; subsequent 4–6-week checks guide further adjustments [10]. The ACC/AHA 2025 ACS guideline similarly recommends high-intensity statin for all and adding a nonstatin when LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L) on maximally tolerated statin, with further intensification reasonable at 55–69 mg/dL in very-high-risk patients; concurrent statin + ezetimibe may be considered, and lipids are reassessed at 4–8 weeks to direct intensification (ezetimibe, PCSK9 mAb, inclisiran, or bempedoic acid as appropriate) [11]. The ESC/EAS 2025 Focused Update (Dyslipidaemia) adds ACS-specific recommendations that upfront combination therapy (high-intensity statin plus ezetimibe) should be considered in treatment-naïve patients when the anticipated LDL-C reduction with statin alone is insufficient to achieve goals, and that intensification during the index

Table 1 Initial in-hospital therapy

Treatment at Admission	2025 ACC/AHA ACS Guideline	2023 ESC ACS Guideline	2025 ESC/EAS Focused Update (Dyslipidaemia)
Naïve or on lOW-/MODERATE INTENSITY STATIN	• High-intensity statin for all ACS patients (atorvastatin 40–80 mg or rosuvastatin 20–40 mg). • Concurrent ezetimibe (Class 2b).	• High-intensity statin started as early as possible, ideally before PCI (Class I C). • Concurrent ezetimibe (Class IIa B).	• High-intensity statin started as early as possible (Class I C). • If not expected to achieve the LDL-C goal with statin therapy alone: Concurrent ezetimibe (Class IIa B).
On maximally tolerated Statin	• If LDL-C < 55 mg/dL (< 1.4 mmol/L): Continue therapy (Class 1) • If LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L): add non-statin (ezetimibe, PCSK9 mAb, inclisiran, or bempedoic acid) (Class 1) • If LDL-C 55–69 mg/dL (1.4–<1.8 mmol/L) → addition of non-statin (ezetimibe, PCSK9 mAb, inclisiran, or bempedoic acid) is reasonable (Class 2a).	• If LDL-C < 55 mg/dL (< 1.4 mmol/L): Continue therapy • If LDL-C ≥ 55 mg/dL (≥ 1.4 mmol/L): add ezetimibe (Class I)	• Intensification of lipid-lowering therapy to further lower LDL-C levels (Class I, C) by adding non-statin therapies with proven cardiovascular benefit (ezetimibe, a PCSK9 mAb, or bempedoic acid)
On maximally tolerated Statin and ezetimibe	No explicit statement	• If LDL-C < 55 mg/dL (< 1.4 mmol/L): Continue therapy • If LDL-C ≥ 55 mg/dL (≥ 1.4 mmol/L): add PCSK9i (Class I)	• Intensification of lipid-lowering therapy to further lower LDL-C levels (Class I, C) by adding non-statin therapies with proven cardiovascular benefit (a PCSK9 mAb, or bempedoic acid) the choice should be based on the magnitude of additional LDL-C lowering needed
Statin intolerant	Non-statin therapy (ezetimibe, PCSK9, inclisiran, or bempedoic acid) recommended to lower LDL-C (Class 1).	No explicit statement for ACS patients	No explicit statement for ACS patients • non-statin therapies alone or in combination with proven cardiovascular benefit (ezetimibe, a PCSK9 mAb, or bempedoic acid) (Class I, A), the choice should be based on the magnitude of additional LDL-C lowering needed

key: ACS, Acute Coronary Syndrome; LDL-C, Low-Density Lipoprotein Cholesterol; PCI, Percutaneous Coronary Intervention; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; PCSK9i, PCSK9 Inhibitor; mAb, Monoclonal Antibody

hospitalisation is recommended for patients who were on any LLT with priorisation of agents with cardiovascular outcome benefit (ezetimibe, PCSK9 monoclonal antibodies, and bempedoic acid).

Therefore, contemporary guidelines endorse fast, deep LDL-C lowering post-ACS and suggest early combination therapy in selected patients.

Evidence Base for Combination Therapy

Combination of Lipid-lowering therapies after ACS and reduction of CV Events

Randomised evidence supports starting combination LLT in the early post-ACS window. In IMPROVE-IT, ezetimibe added within 10 days after ACS to background statin produced a modest but significant reduction in major adverse cardiovascular events (MACE) over six years, with similar relative benefit at lower baseline LDL-C strata. Complementary randomised data in chronic ASCVD can be derived from the RACING and LODESTAR trials [12, 13]. In RACING (moderate-intensity statin + ezetimibe vs. high-intensity statin), combination therapy achieved noninferior 3-year cardiovascular outcomes with comparable (often lower) achieved LDL-C and fewer treatment discontinuations/intolerance events [12]. In LODESTAR (treat-to-target strategy, typically using moderate-intensity statin ± ezetimibe to reach 55–70 mg/dL, vs. fixed high-intensity statin), the treat-to-target approach was noninferior for 3-year cardiovascular outcomes with similar mean on-treatment LDL-C and lower rates of new-onset diabetes, supporting the clinical utility of combination therapy to reach targets with less statin exposure when appropriate [13].

The CVO-Trial of alirocumab, Odyssey-Outcomes, showed additional event reduction when added in the months after ACS among patients with an LDL-C level of 1.8 mmol/l or higher despite maximally tolerated statin therapy, with larger absolute benefit the closer patients are enrolled to the index event [14]. Evolocumab in the FOURIER trial showed cardiovascular benefit in patients with atherosclerotic cardiovascular disease and LDL-C levels of 1.8 mmol/l or higher who were receiving statin therapy [15].

Where access or acceptance of injectables is limited, adding bempedoic acid to statin/ezetimibe is a practical route for further LDL-C reduction. CLEAR Outcomes showed a 13% MACE reduction in statin-intolerant patients (post-ACS within 90 days excluded), positioning bempedoic acid as an option for partial-intolerance or as a third oral agent while assessing eligibility for PCSK9-pathway therapy [16].

Together, these data support the use of a combination of lipid-lowering strategies in patients at risk of a recurrent ASCVD event, particularly those who have recently experienced an ACS.

Lipid-lowering after ACS and Plaque Stabilisation

Mechanistic and imaging data provide biological plausibility for this clinical benefit. Intravascular imaging trials demonstrate faster plaque stabilisation with combination therapy in the early post-MI phase. In PACMAN-AMI, patients with recent AMI were randomised within 24 h of primary PCI to alirocumab or placebo on top of high-intensity rosuvastatin [17], which led to a between-group difference in achieved LDL-C of approximately − 51 mg/dL (−1.3 mmol/L) in favour of alirocumab. Over 52 weeks, percentage atheroma volume decreased by −2.13% vs. −0.92% (between-group difference − 1.21%, $P < 0.001$), and minimum fibrous-cap thickness, a marker of plaque stability, increased by + 62.7 µm vs. + 33.2 µm (difference + 29.7 µm, $P = 0.001$).

In HUYGENS, evolocumab was initiated within 10 days after NSTEMI on top of high-intensity statin therapy. After 50 weeks, plaque burden regressed by − 0.9% vs. − 0.3% (difference − 0.6%, $P < 0.05$) and fibrous-cap thickness increased by + 42.7 µm vs. + 18.4 µm ($P < 0.001$) [18].

Overall, these studies underscore that intensive lipid-lowering, started during or soon after the index ACS, achieves deeper LDL-C reductions and accelerates plaque stabilisation.

Treatment Gaps in Real-World Practice

At the population level, mean untreated LDL-C concentrations of 3.0–3.5 mmol/L [19, 20] and target thresholds < 1.4 mmol/L mean that high-intensity statin therapy alone, typically providing ~ 50% reductions, will not achieve goal levels in most patients, making combination therapy necessary. European registries echo these findings: The Davinci Study (2017–2018), which included patients on LLT, showed that only 39% of patients with ASCVD would attain the 2016 ESC/EAS goal of < 1.8 mmol/L for ASCVD patients and 18% of patients the current goal of < 1.4 mmol/L, respectively [21]. The SANTORINI study (2020–2021), including patients at high and very high cardiovascular risk, also demonstrates suboptimal LDL-C goal attainment rates (20.7%) among patients with ASCVD. While combination therapy was associated with better LDL-C management, its adoption lagged, and it was used in 25.6% of patients [22]. Moreover, the one-year follow-up revealed that guideline-directed intensification remained infrequent with ~ 30%, despite LDL-C above targets [23]. Simulation studies suggest that through triple oral combination (high-intensity statin, ezetimibe and bempedoic acid) ~ 70% of patients could attain

treatment target values [24]. The simulated addition of a PCSK9i to high-intensity statins and Ezetimibe could bring ~ 90% of patients to goal [25].

In the most recent international INTERASPIRE study spanning 13 countries across six WHO regions, less than one in five patients with a recent coronary event (elective CABG/PCI, STEMI/NSTEMI, or unstable angina) achieved the LDL-C goal of < 1.4 mmol/L; use of combination therapy and treatment intensification were low, with pronounced disparities by national income level [26]. Attendance at cardiac rehabilitation was also poor (≈ 9%), further limiting the "4–8 week" reassessment touchpoint assumed by many algorithms. Feeding into the observation of a failing stepwise approach, 66.3% of patients in INTERASPIRE, despite not achieving their goals, experienced no change in treatment intensity within the first 6–12 months after the index event.

Default step-up treatment algorithms, which depend on sequential reassessment and gradual intensification, may contribute to the observed delays in achieving LDL-C targets and at least partly explain the persistent treatment gap.

Clinical Evidence and Practical Considerations for Upfront Combination Therapy

Guidelines currently recommend combination therapy in ACS patients whose baseline LDL-C is ≥1.8 mmol/L (70 mg/dL), or when treatment goals are unlikely to be reached with high-intensity statin alone. These recommendations exemplify the broader shift toward precision/individualised lipid management, where treatment selection is guided by patients' baseline LDL-C and the predicted likelihood of goal attainment. This threshold-based approach avoids exposing patients with lower starting LDL-C levels to additional therapy; however, it also adds complexity to the care pathway, as treatment decisions must be tailored to individual baseline values and the expected magnitude of statin response. An alternative strategy would be to initiate oral dual combination therapy in all ACS patients, regardless of their baseline LDL-C levels, thereby simplifying the pathway and ensuring that more patients achieve the recommended LDL-C targets (Fig. 1).

Data supporting this strategy comes from regional initiatives such as the *Jena auf Ziel—JaZ* program, which enrolled 85 STEMI patients in 2021. All patients were started immediately on atorvastatin 80 mg plus ezetimibe 10 mg at admission, combined with structured education on cardiovascular risk modification and LDL-C target setting. LDL-C was measured at admission, during hospitalisation, and at discharge, and values were recorded on patient cards to facilitate follow-up. In those who did not reach the ESC/EAS target of < 1.4 mmol/L (< 55 mg/dL), therapy was escalated with bempedoic acid or PCSK9 inhibitors. This systematic approach resulted in 100% treatment goal attainment at 1 year and 60% at 2 years after ACS [27, 28]. The reduction in LDL-C goal attainment observed over the second year of follow-up was largely attributed to modifications in therapy after transitioning from specialist to primary care management. After 12 months, 38% of patients continued follow-up with their general practitioners, among whom 27.5% remained at target, compared with 72.5% of those followed in the dedicated lipid clinic. Mean LDL-C levels were correspondingly higher in the primary care group (2.1 ± 1.0 mmol/L) than in the lipid clinic group (1.2 ± 0.7 mmol/L; $p < 0.01$). The main determinant of non-goal attainment was de-intensification or discontinuation of LLT in community practice, whereas true patient non-adherence played a comparatively minor role. Contributing factors included differences between national and European guideline targets, reimbursement limitations for non-generic agents such as PCSK9 inhibitors and bempedoic acid, and less structured follow-up pathways in routine care. Nevertheless, despite this partial de-escalation of therapy after the first year, the proportion of patients maintaining LDL-C targets at two years (60%) in Jena auf Ziel remained substantially higher than the goal-attainment rates reported in contemporary European and international registries, where fewer than one in five patients typically reach the recommended LDL-C levels. This suggests that early combination therapy, coupled with structured follow-up, can achieve and sustain superior lipid control compared to current routine practice.

Data from the SWEDEHEART registry further underscore the prognostic relevance of early combination therapy in achieving lipid goals and improving cardiovascular outcomes [29]. In this analysis, 35,826 statin-naïve patients discharged on statin therapy after myocardial infarction were followed for a median of 3.96 years. Of these, 16.9% received early combination therapy with ezetimibe (≤ 12 weeks after discharge), 18.1% received late combination therapy (13 weeks–16 months), and 65.0% remained on statin monotherapy. Regarding LDL-C goal attainment, the proportion achieving the ESC/EAS target (< 1.4 mmol/L [55 mg/dL]) at one year was approximately 55% among those receiving early combination therapy, 43% with late combination, and 34% with statin monotherapy. During follow-up, 2,570 MACE occurred. The 1-year MACE incidence was 1.79 per 100 patient-years in the early-combination group, compared with 2.58 in the late-combination group and 4.03 in the statin monotherapy group. The corresponding 3-year hazard ratios were 1.14 (95% CI, 0.95–1.41) for late combination and 1.29 (95% CI, 1.12–1.55) for

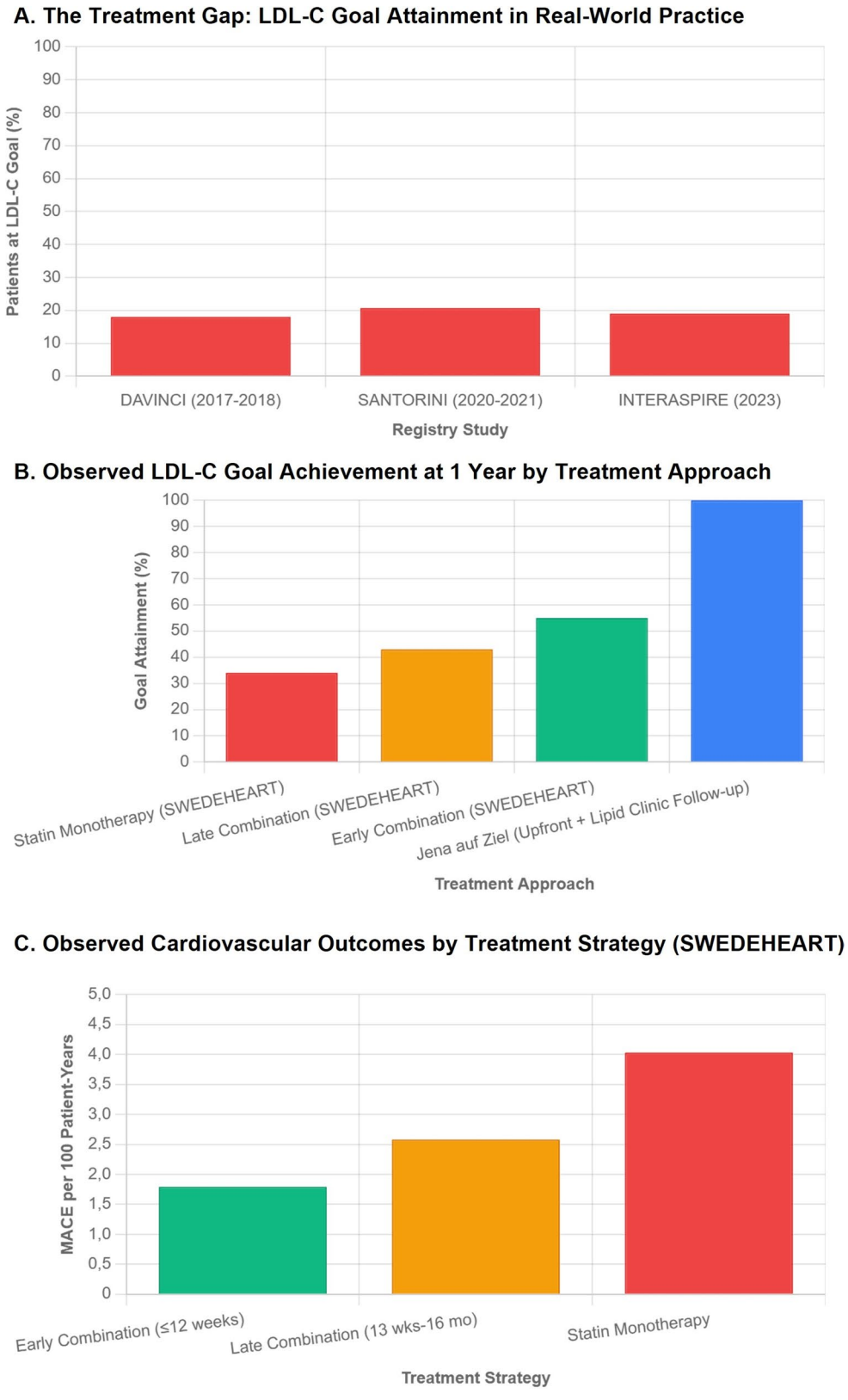


Fig. 1 Early Combination Lipid-Lowering Therapy After Acute Coronary Syndrome: From Evidence to Implementation. Definitions used for early and late combination refer to the SWEDEHEART analysis by Leosdottir [29]: early combination = statin + ezetimibe initiated ≤ 12 weeks post-discharge) and late combination = statin + ezetimibe initiated 13 weeks up to 16 months post-discharge). LDL-C: low-density lipoprotein cholesterol

statin monotherapy versus early combination, with lower cardiovascular mortality in the early-treatment group (HR, 1.83 [95% CI, 1.35–2.69] vs. monotherapy). Model-based extrapolation suggested that, if all post-MI patients in the registry had received early statin + ezetimibe, approximately 477 MACE could have been prevented over three years, equivalent to 13–14 fewer events per 1,000 patients treated early. The corresponding number needed to treat (NNT) was 53 (95% CI, 32–125) compared to statin monotherapy and 143 (95% CI, 44–167) compared to late combination therapy.

Following such an approach, some patients with low untreated LDL-C levels might reach very low on-treatment levels under a combination default. The American Guideline explicitly advise against de-escalation at very low LDL-C [11]. This position is supported by robust evidence. In a meta-analysis led by Sabatine, which pooled data from the Cholesterol Treatment Trialists' Collaboration (26 statin trials, > 170,000 patients) together with three major nonstatin LDL-C lowering trials (IMPROVE-IT, FOURIER, ODYSSEY OUTCOMES; in total > 50,000 patients), the benefit of LDL-C lowering was examined in populations starting at median baseline LDL-C as low as 1.6–1.8 mmol/L (63–70 mg/dL) [30]. Across statin and nonstatin trials, each 1 mmol/L (38.7 mg/dL) LDL-C reduction translated into a ~ 20% relative reduction in major vascular events, with no increase in adverse outcomes, including new-onset diabetes, hepatic enzyme elevations, hemorrhagic stroke, or cancer. Notably, clinical benefit was observed down to achieved median LDL-C levels of ~ 0.5 mmol/L (21 mg/dL) [30].

Thus, available evidence suggests that further lowering of LDL-C beyond current targets continues to reduce cardiovascular risk without offsetting harms. The small increase in new-onset diabetes risk observed with statins appears to be drug class-specific and is outweighed by the reduction in ASCVD events [31]. Moreover, the biological concern of complete cholesterol depletion is theoretical: hepatocytes retain the ability to synthesise cholesterol endogenously, and pharmacological inhibitors of cholesterol synthesis (statins, bempedoic acid) do not completely block this process [32]. Likewise, no evidence links very low LDL-C concentrations to cognitive decline or dementia; in the EBBINGHAUS substudy of FOURIER and subsequent long-term analyses, no neurocognitive or Alzheimer-related adverse effects were observed even at LDL-C levels < 0.5 mmol/L [33, 34].

Taken together, these data support the notion that a "combination for all" approach after ACS may offer a pragmatic and effective strategy to close treatment gaps, with very low LDL-C levels not representing overtreatment but rather an extension of clinical benefit.

Conclusions

International guidelines endorse lower LDL-C targets and suggest the earlier use of combination therapy; nevertheless, a sequential approach, starting with statins and later stepwise escalation of lipid-lowering therapy, persists in many healthcare systems. This paradigm, while consistent with traditional treatment algorithms, partially contributes to the persistent undertreatment observed in the majority of patients with ASCVD or following ACS, as large proportions fail to achieve guideline-recommended LDL-C levels in real-world practice.

Findings from randomised controlled trials, trial emulations, and observational registries collectively support the notion that a default high-intensity statin plus ezetimibe for ACS patients at discharge might be a pragmatic and implementable step that could reduce delays, increase early goal attainment, and ultimately prevent events. At the same time, while a "combination for all" approach offers a pragmatic and straightforward solution to undertreatment, it runs counter to the broader trajectory of personalised medicine, which seeks to tailor therapy intensity to an individual's baseline LDL-C, risk profile, and treatment response. Balancing the advantages of simplification with the principles of precision care remains an open challenge for future guideline development and implementation research.

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Declarations

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