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VIEWPOINT
Dyslipidaemias

Combination lipid-lowering strategies after acute coronary syndrome: reconsidering cholesterol targets

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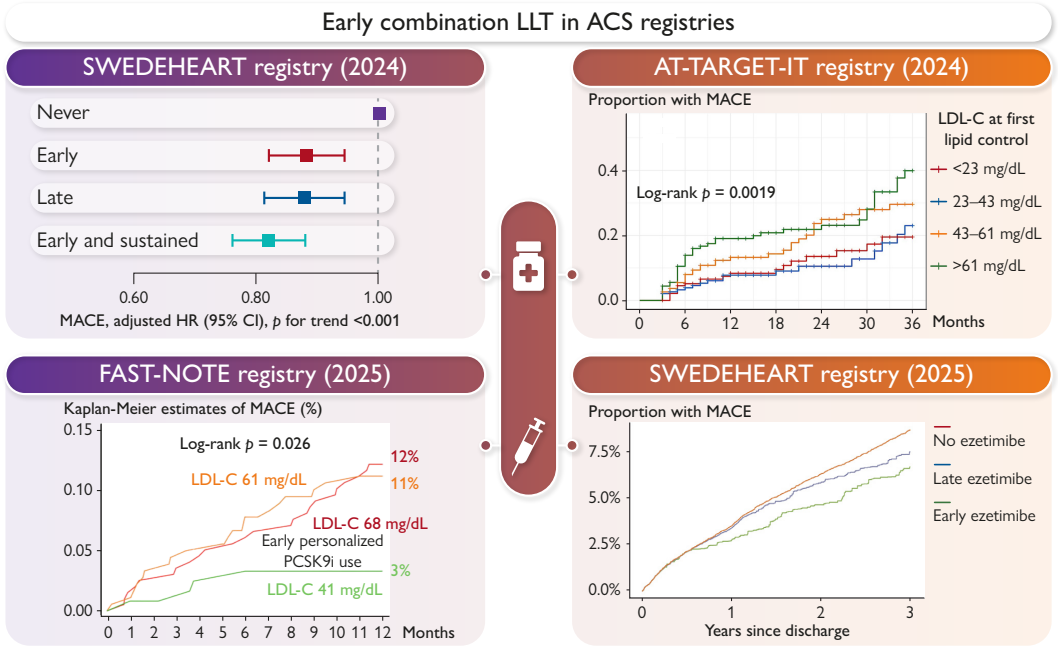
Graphical Abstract



ACS, acute coronary syndromes; **CI**, confidence interval; **HR**, hazard ratio; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy; **MACE**, major adverse cardiovascular events; **PCSK9i**, proprotein convertase subtilisin/kexin type 9 inhibitor

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Impact of early and intensive LDL-C lowering on cardiovascular outcomes in post-ACS patients. Upper left [adapted from SWEDEHEART registry (2024)]: major adverse cardiovascular events (MACE) rate is significantly reduced in patients with early and sustained achievement of LDL-C values <2.2 mmol/L compared with those with late, early, and never achievement of LDL-C values target. Upper right [adapted from AT-TARGET-IT registry (2024)]: event curves through a median follow-up of 11 months across quartiles of LDL-C showed a stepwise lower risk of 4P-MACE in lower quartile of LDL-C values at first lipid control (<23 mg/dL). Lower left [adapted from FAST-NOTE registry (2025)]: the achievement of non-HDL-C goals with strike early and strike strong LLT is associated with a lower occurrence of MACE. Lower right [adapted from SWEDEHEART registry (2025)]: early ezetimibe initiation after myocardial infarction protects against later cardiovascular outcomes during 3 years of follow-up.

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Patients with acute coronary syndromes (ACS) are at increased risk of recurrent atherothrombotic events. Many of these events occur early after the index event, and overall event rates are higher in patients with coronary artery disease (CAD) and prior acute presentations than those with stable manifestations of CAD only.[1] In these patients intensive lowering of LDL cholesterol (LDL-C) reduces cardiovascular (CV) morbidity and mortality, with a benefit proportional to the degree of LDL-C decrease, up to very low LDL-C values.[2] Thus, the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines[3] recommend an LDL-C goal of <55 mg/dL (1.4 mmol/L) and reduction of at least 50% from baseline, and a goal of <40 mg/dL (1.06 mmol/L) for those who experience recurrent CV events within 2 years. To reach these LDL-C targets, ESC/EAS guidelines[3,4] suggest a stepwise approach starting with high-intensity statin, adding ezetimibe, and then proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i), in 4–6 weeks steps if the target is not reached. In the ACS guidelines[4] addition of a PCSK9i during hospitalization is recommended in patients with ACS already on highest tolerated statin plus ezetimibe, if not at target. Yet, registry data indicate that the majority of patients with ACS, remain above LDL-C target and at increased risk of avoidable recurrent ischaemic events. In the multicenter INTERASPIRE study,[5] of 4548 patients with a previous hospitalization for atherosclerotic cardiovascular disease (ASCVD) (from 6 to 24 months before enrolment), 83.7% remained with LDL-C ≥55 mg/dL (1.4 mmol/L). The findings from INTERASPIRE[5] were consistent with less recent data from SURF CHD II[6] and ESC-EORP EUROASPIRE V,[7] reporting low adherence and high percent of lipid-lowering therapy (LLT) reduction and poor LLT dose optimization in patients with ASCVD over time, thus indicating unchanged suboptimal LLT treatment of patients with ASCVD. The DA VINCI study[8] conducted between 2017 and 2018, also reported that only 22% of very high-risk patients achieved 2019 LDL-C target, with combination oral therapy used in only 9% of patients and PCSK9i in 1%. This figure only slightly improved between 2020 and 2021 in the SANTORINI study,[9] reporting that 24.0% of patients were on oral combination LLT. At 1-year follow-up,[10] LLT was escalated in one-third of patients, and combination therapy rose from 25.6% to 37.9%, resulting in LDL-C goal attainment of 30.9%. Notably, PCSK9i was used in only 6.6% of patients. A recent study applying Monte Carlo simulation to DA VINCI data[11] reported the effects of simulated implementation of the 2019 guidelines on LLT target achievement in 1520 very high-risk patients not achieving LDL-C target (corresponding to 61.2% of ACSVD patients included in the registry). Optimization of statin monotherapy alone would obtain LDL-C goal in 12% of patients, whereas stepwise addition of ezetimibe would do so in 42% of patients. Adding PCSK9i to oral therapy, 93.2% of ASCVD patients would reach LDL-C target. Furthermore, optimization of LLT would reduce the 10-year risk of CV events from 36% to 28%, corresponding to relative risk reduction (RRR) of 24% and absolute risk reduction of 8.1%.

These data clearly indicate that (i) triple therapy is needed in the majority of very high-risk patients to achieve LDL-C goals, (ii) therapeutic inertia, limited adherence and lack of dosing optimization play a substantial role in preventing attainment of LDL-C goals, and (iii) social, cultural, economic, and prescription rules are also hampering LDL-C attainment.

The case of very early and very intensive lipid-lowering approach in patients with acute coronary syndromes: pathophysiological evidence

It is well recognized that in ACS patients with recurrent CV events many are attributable to destabilization of non-culprit plaques rather than to failure of revascularization.[12] Recent intracoronary imaging studies[13,14] demonstrated favourable plaque modifications at 50–52 weeks in non-culprit lesions of ACS patients starting in hospital combination therapy with a PCSK9i plus a statin, compared with statin monotherapy.[13,14] Favourable changes resulting from combination therapy and thus more intensive LDL-C lowering include increased minimum fibrous cap thickness, decreased maximum lipid arc on optical coherence tomography (OCT),[13,14] reduced atheroma volume on IVUS and reduced lipid core using NIRS.[14] In PCSK9i treated patients, median LDL-C was substantially lower [28.1 mg/dL (0.73 mmol/L) in HUYGENS[13] and 23.6 mg/dL (0.61 mmol/L) in PACMAN-AMI,[14]] compared with statin plus placebo treated patients [87.2 mg/dL (2.25 mmol/L)[13] and 74.4 mg/dL (1.92 mmol/L)[13], respectively]. Interestingly, sub-analysis of the PACMAN-AMI[15] showed that in patients achieving triple favourable modification of atheroma volume, fibrous cap thickness and lipid core, incidence of major CV events within 54 weeks from ACS was 8% compared with 18% to those who did not ($P < .04$). Consistently, in the CLIMA study,[16] in ASCVD patients undergoing OCT of untreated left descending coronary artery, a minimum lumen area <3.5 mm^2, fibrous cap thickness <75 μm, presence of macrophages and length of lipid arc > 180° were independently predictive of a composite endpoint of CV death and target segment myocardial infarction (MI). More recently, the PREVENT trial,[17] that randomized patients with non-flow-limiting vulnerable plaque identified by intracoronary imaging to medical therapy or revascularization, showed that preventive coronary stenting significantly reduced major CV events compared with medical therapy, mostly driven by reduced revascularization. Finally, a recent meta-regression analysis[18] of LLT studies investigating the association between percent atheroma volume changes and clinical outcomes demonstrated a 14% reduction of adjusted odds ratio of major CV events for any 1% decrease in mean percent atheroma volume ($P = .01$).

Collectively, these data indicate that (i) plaque volume and morphology assessed by intravascular imaging predict ischaemic events in ASCVD patients, including those with ACS (ii) very early and very intensive lipid lowering is associated with favourable plaque changes, and (iii) favourable changes of plaque characteristics identified by intravascular coronary imaging studies predict prognosis.

Early and intensive LDL cholesterol reduction in acute coronary syndromes patients: the clinical evidence

Cholesterol treatment trialists (CCT) metanalysis[2] and data from randomized clinical studies with PCSK9i[19,20] showed that the plaque

stabilization process that sustains clinical benefit is time dependant, with risk reduction effects that accrue over time. In fact, CCT metanalysis[2] reported a 12%–14% risk reduction of major CV events for 1 mmol/L of LDL-C reduction in the first year of treatment consistent with data from SPIRE trial,[21] reporting a 14% RRR in the first year. Benefits rise to 17% RRR in the second year, identical to 17% RRR in the FOURIER trial,[19] and to 20%–22% from the third year and beyond.[2] Thus, a much larger LDL-C absolute reduction would be needed in the first year of treatment to obtain the same clinical benefit obtained with same reduction of LDL-C in the following years. This suggests the need for a very aggressive LDL-C reduction strategy, which would provide both larger relative and absolute risk reduction in patients early after ACS. In fact, three randomized trials assessed the benefit of intensive vs less intensive reduction of LDL-C in ACS patients.[20,22,23] All three demonstrated that a more intensive LLT, using high-intensity statins,[22] or statin plus ezetimibe,[23] or PCSK9i,[20] significantly reduced major CV events, compared with less intensive treatment. Notably, the lowest LDL-C value reached in these trials in intensively treated patients was 53.7 mg/dL (1.39 mmol/L) in IMPROVE-IT[23] and 48 mg/dL (1.24 mmol/L) at 12 months [that raised to 66.4 mg/dL (1.71 mmol/L) at 48 months] in ODYSSEY OUTCOMES trial.[20] Consistent with trials are data from SWEDEHEART registry,[9] showing that statin treated patients in the lowest quartile of LDL-C or non-HDL-C at 2 months post-MI were at lowest risk of 1-year recurrent ischaemic events, with greatest benefit observed in patients reaching and maintaining lowest values early (2 months) after MI. Notably, benefit was already statistically significant at 1 year in those achieving the lowest LDL-C levels at month 2. Yet, median LDL-C was 70 mg/dL (1.81 mmol/L), a value above the recommended target and far from those of imaging studies. In addition, a recent analysis from SWEDEHEART[24] reported that early (≤12 weeks) implementation of combination therapy with statin and ezetimibe in patients with MI resulted in 40% of patients reaching target at 1 year, that was associated with 1-year MACE rate of 1.79 compared with 2.58 for those with late combination therapy and 4.03 for those not on ezetimibe. However, neither randomized clinical trials nor the SWEDEHEART registry[12] explored benefit of LDL-C reduction at levels <50 mg/dL (1.29 mmol/L) in ACS, a relevant consideration since favourable plaque changes, that predict clinical outcome, are observed at LDL-C levels substantially lower than 55 mg/dL (1.5 mmol/L) in imaging studies. In a *post hoc* analysis from ODYSSEY OUTCOMES trial[25] patients reaching very low levels of LDL-C in the first months after ACS (15 mg/dL (0.39 mmol/L), subsequently rising to higher values, showed more favourable prognosis compared with those remaining at higher LDL-C values early after ACS. Data from FOURIER trial,[19] including a subgroup with recent MI,[26] in which a median value of LDL-C of 30 mg/dL (0.78 mmol/L) in evolocumab treated patients was achieved, also showed clinical benefits that were more evident in recent post-MI patients. More recently the Italian AT-TARGET-IT registry[27] reported data in 771 ACS patients in whom a PCSK9i (on top of statin/ezetimibe combination) was introduced during ACS hospitalization, followed up for 11 months. Median LDL-C value of 43 mg/dL (1.11 mmol/L) [from a median entry value of 137 mg/dL (3.54 mmol/L)] was reached at first measurement 34 days post-ACS and remained stable throughout follow-up. A significant reduction of major CV events and all-cause mortality was observed across quartiles of on treatment LDL-C, with a lower quartile of LDL-C < 23 mg/dL (0.59 mmol/L), as well in patients below vs above the median values. Finally, a recent real-world Italian study[28] also reported a significantly reduced incidence of MACE in ACS patients treated with statins plus PCSK9i as clinically needed started during hospitalization compared with a previous group of patients treated with a stepwise LLT approach. Notably, patients treated with PCSK9i reached a value of LDL-C of 41 mg/dL (1.06 mmol/L) compared with 61 mg/dL (1.58 mmol/L) reached in those treated using a stepwise approach.

Yet, it must be acknowledged that no evidence from randomized studies with PCSK9i on top of statins plus ezetimibe is available. In fact, in the FOURIER trial[19] (patients with stable CAD) no interaction in the benefit of evolocumab was observed between 1440 patients assuming statins plus ezetimibe compared with those on statins only, whereas no data are available from the ODYSSEY OUTCOMES trial.[20] The results of ongoing multicenter RCTs, EVOLVE-MI (NCT05284747) and AMUNDSEN (NCT04951865), will assess the effects of evolocumab on top of routine lipid management in patients with ACS, in comparison to standard-of-care alone and provide definitive evidence on early use of PCSK9i in ACS patients.

Closing the implementation gap and looking ahead

Pathophysiological and clinical data collectively suggest that (i) a target lower than 55 mg/dL (1.4 mmol/L) of LDL-C may be more appropriate post-ACS, (ii) early triple therapy combination is effective in reducing residual risk in ACS patients, and (iii) addition of injectable LLT to dual oral therapy (either statin or bempedoic acid plus ezetimibe)[29,30] is needed in the majority of patients to achieve recommended LDL-C target. In fact, imaging and clinical studies in patients with ACS indicate that lowering LDL-C below 40 mg/dL (1.03 mmol/L) continues to accrue reduction of major CV events and all-cause mortality in ACS patients. Thus, it would be reasonable to reconsider LDL-C target and foster pragmatic therapeutic algorithms for reaching early and even lower than currently recommended LDL-C target in ACS patients. Yet, due to the inter-individual variability of response among patients, while fostering widespread intensive reduction of LDL-C, this approach will likely get some patients to 'overshoot' the minimum goal.

The economic impact of this strategy is a matter of concern when considering lowering of LDL-C targets and wider use of injectable drugs. A limitation worth recognizing is that economic constraints may limit the generalizability among different countries and health systems. Notably, a recent cost-effectiveness analysis, using the consolidated Health Economic Evaluation Reporting Standards, included studies of evolocumab in ASCVD, concluded for a cost-effectiveness of this approach, especially in the high-risk population.[31] Although these analyses are barely generalizable due to different cost of drugs and reimbursement policy at single-country level, it is conceivable that cost-effectiveness would be even more favourable if purposely addressing the highest risk category of early post-ACS patients.

Conclusions

This article reports personal considerations of the authors that, although founded on available scientific evidence, are not intended to represent guidelines. Although an even more stringent LDL-C target for ACS patients appears reasonable for the future, ongoing randomized clinical trials will fill the remaining gaps on evidence. Finally, the authors emphasize from the evidence reported the current stringent need for a more efficacious implementation of current guidelines targets that are still broadly unmet in clinical practice, resulting in substantial avoidable residual risk for ACS patients.

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Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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