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Review Article

Expert Opinion on the Use of Inclisiran in Post-Acute Coronary Syndrome Patients in Indonesia

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Abstract

Elevated Low-Density Lipoprotein Cholesterol (LDL-C) levels are an independent risk factor for the progression of Atherosclerotic Cardiovascular Disease (ASCVD). Achieving substantial LDL-C reduction is recognized as a primary therapeutic goal, particularly for those at the highest risk of future cardiovascular events. Statin-based Lipid-lowering Therapy (LLT) remains the cornerstone of secondary prevention in Acute Coronary Syndrome (ACS). However, many high-risk individuals require combination therapy with non-statin agents to achieve guideline-recommended LDL-C targets. A novel, long-acting Small-interfering RNA (siRNA)-based Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitor, inclisiran, has emerged as a therapy that provides rapid and sustained LDL-C reduction. Despite these therapeutic advancements, various hurdles continue to hinder optimal lipid management in Indonesia. To address these challenges, an expert meeting involving cardiologists from multiple cities across Indonesia convened, and the resulting consensus opinion of experts aimed to provide insights into the current hurdles in managing post-ACS and the potential use of inclisiran following high-intensity statin or the highest tolerated dose statins, with or without ezetimibe, in post-ACS patients in Indonesia.

Keywords: acute coronary syndrome, expert opinion, inclisiran, LDL-C, lipid-lowering therapy, lipid management.

Introduction

Cardiovascular Disease (CVD) represents a substantial global health burden, contributing significantly to morbidity and mortality worldwide, particularly in developing countries.[1] In Indonesia, nearly 65% of individuals with CVD are at high risk of recurrent events and death.[2] Atherosclerotic Cardiovascular Disease (ASCVD) constitutes the largest proportion of CVD, with Acute Coronary Syndrome (ACS) representing its most severe clinical manifestation.[3] ACS results from the rupture of an unstable atherosclerotic plaque in the coronary artery. Elevated levels of atherogenic lipoproteins, particularly Low-Density Lipoprotein Cholesterol (LDL-C), play a pivotal role in the initiation and progression of atherosclerosis.[4-5] Therefore, achieving substantial LDL-C reduction is considered a primary therapeutic goal, especially for patients with ACS who are at the highest risk of recurrent ischemic events.[6-7]

The early post-ACS period refers to the phase following hospital discharge and represents the most vulnerable stage after a major coronary event. Findings from the One-ACS registry in Indonesia showed the overall median length of stay was around 5 days.[8] Therefore, the post-ACS period begins on average 5 days after the index hospitalization. Intensive Lipid-lowering Therapy (LLT) is essential for the secondary prevention of ASCVD.[9] Statins have long been the cornerstone of dyslipidemia management; however, many high-risk ASCVD patients require combination therapy with non-statin LLTs to achieve guideline-recommended LDL-C targets. Although most post-ACS patients receive statins alone or in combination with non-statin agents such as ezetimibe during hospitalization, many still fail to reach target LDL-C levels.[5,9]

Recent advances in non-statin therapies have focused on novel agents that achieve rapid and sustained LDL-C reduction. Inclisiran, a first-in-class Small-interfering RNA (siRNA) that inhibits Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), has emerged as an effective adjunct to maximally tolerated statin therapy, with or without ezetimibe, in ASCVD patients requiring intensive LDL-C lowering.[10-11] However, the Cardiovascular Outcome Trial (CVOT) for inclisiran is still ongoing.

Despite therapeutic advancements, post-ACS management in Indonesia remains suboptimal.[8] The barriers to optimal care arise from health system limitations, healthcare provider practices, and patient-related factors.[12] Overcoming these challenges requires a multidisciplinary, collaborative approach that integrates evidence-based guidelines into everyday clinical practice.

This expert opinion article aimed to provide insights into current hurdles in managing post-ACS and the potential use of inclisiran following high-intensity statin therapy or the highest tolerated statin dose, with or without ezetimibe, in post-ACS patients in Indonesia.

Methods

Study Design

This article presents an expert opinion developed during a face-to-face advisory meeting on lipid management strategies for post-ACS patients in Indonesia.

Expert Selection Criteria

The expert panel consisted of ten board-certified cardiologists from six cities in Indonesia (Jakarta, Tangerang, Bandung, Yogyakarta, Medan, and Makassar). Experts were invited based on their clinical experience in managing high-risk ACS and ASCVD patients and their active involvement in national cardiology working groups, including Acute Cardiovascular Care (ACC); Atherosclerosis, Thrombosis, Lipidology, and Regenerative Therapy (ATLR); and Cardiovascular Prevention and Rehabilitation. All participants were practicing clinicians from tertiary referral centers.

Expert Discussion and Voting

The topics covered during the meeting were summarized from current international and national guideline recommendations, available clinical evidence, and the practical challenges encountered by the expert panel in post-ACS lipid management. The discussion was conducted face-to-face with questions guided by the corresponding author, who served as the moderator. Insights were pooled during the discussion. In cases of disagreements or differing views, these were reflected in the narrative to acknowledge uncertainty and variability in real-world clinical practice.

The recommendations presented here reflect the authors' synthesis of the broader expert discussion rather than formally endorsed position statements. Furthermore, this paper was developed based on the agreement of at least 80% of the authors in the expert meeting and a literature review conducted via Google Scholar and Medline searches using the following keywords: ACS, ASCVD, LLT, and inclisiran.

Importance of LDL-C Target Attainment

Patients with ACS are at a higher risk of recurrent ischemic events. Within one year after hospitalization for ACS, the total rates of cardiovascular death, myocardial infarction, and ischemic stroke are estimated to be around 10–15%.[5] Lipid studies over the years have consistently demonstrated the relationship between elevated LDL-C levels and an increased risk of ischemic events. High LDL-C is a major contributor to plaque formation and rupture in atherosclerosis. Limiting arterial exposure to LDL-C as early and as intensively as possible can slow the progression of atherosclerotic plaque.[9,13]

LDL-C serves as a surrogate marker for Major Adverse Cardiovascular Events (MACE); for every 1 mmol/L (39 mg/dL) reduction in LDL-C, there is an associated 20% reduction in cardiovascular risk.[13-14] Current guidelines recommend that patients with established ASCVD should initiate or intensify LLT to achieve strict LDL-C targets. The 2025 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ACS recommend a target LDL-C level below 55 mg/dL for very high-risk individuals (Figure 1).[5] Similarly, the European Society of Cardiology (ESC) guidelines on dyslipidemia recommend lowering LDL-C to <55 mg/dL in very high-risk ASCVD patients. For patients at extreme risk, those who experience recurrent cardiovascular events despite maximally tolerated statin therapy, further LDL-C reduction to <40 mg/dL is advised.[9,15] The Indonesian Heart Association (PERKI) guideline on ACS recommends an LDL-C target below 55 mg/dL, with a more stringent goal of <40 mg/dL for patients who experience recurrent cardiovascular events within 2 years.[16] All guidelines also recommend achieving a reduction of ≥50% in LDL-C from a patient's initial levels.[5,9,15-16] In line with these recommendations, all authors agreed that lowering LDL-C to <55 mg/dL and achieving at least a 50% reduction from baseline are equally important therapeutic goals.

According to the SWEDEHEART registry, LDL-C targets should ideally be achieved within 4–6 weeks post-ACS, as early, intensive LDL-C reduction during this period is strongly associated with a lower risk of recurrent MACE.[17] Therefore, prompt initiation and optimization of LLT are essential to ensure rapid target attainment and improve long-term cardiovascular outcomes.[17] If lifestyle modification alone does not sufficiently lower LDL-C levels, pharmacological therapy should be considered to achieve the recommended targets.[18]

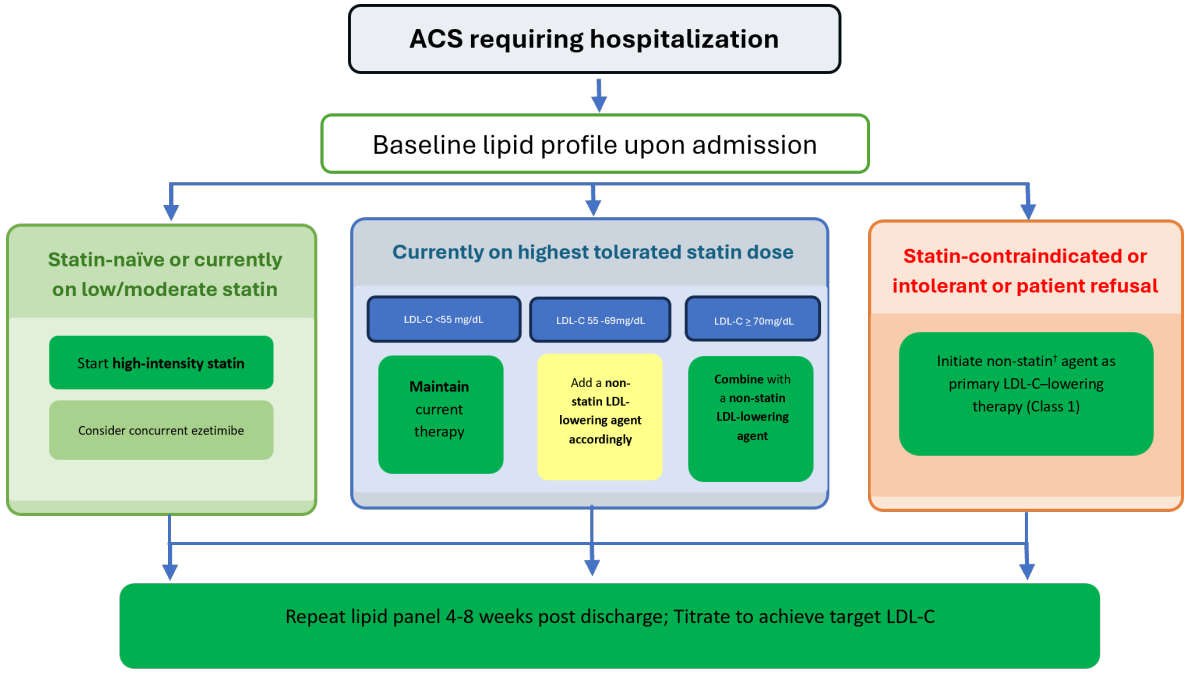

Figure 1. Management of Lipid-Lowering Therapy for Patients with ACS, adapted from the 2025 ACC/AHA guidelines for ACS.[5]

For decades, statins have been the cornerstone of LLT, as they reduce hepatic cholesterol synthesis and are generally well tolerated. High-intensity statin therapy is recommended for all patients with ACS and should be initiated as early as possible during hospitalization. Daily high-intensity statin therapy can lower LDL-C by approximately 50% from baseline.[5,15] For patients already receiving LLT before admission, further intensification during the index ACS hospitalization is advised to achieve additional LDL-C reduction.[5,15] Combination therapy with non-statin LLTs such as ezetimibe or PCSK9 inhibitors (e.g., evolocumab, inclisiran) is recommended for patients who are statin-intolerant or unable to reach LDL-C targets despite maximally tolerated statin therapy. Implementing these evidence-based guidelines, including early and intensive statin therapy combined with additional LLTs when necessary, can significantly improve patient outcomes and reduce the national burden of CVD.[5,10]

Hurdles in Managing Post-Acute Coronary Syndrome

However, post-ACS management in Indonesia remains suboptimal, particularly with respect to attainment of lipid therapeutic targets. The Indonesia-INTERASPIRE study showed that only 8.5% of patients with very high-risk coronary heart disease achieved the recommended LDL-C target of <55 mg/dl.[19] Findings from the One ACS registry also indicated that suboptimal lipid management with high-intensity statin therapy is underutilized among post-ACS patients. Fewer than 60% of ACS patients received high-intensity statins within the first 24 hours, while the remainder were prescribed low- to moderate-intensity statins or no statin at all.[8] Low adherence to treatment guidelines represents another major obstacle, contributing to poor clinical outcomes and higher healthcare costs. Nonadherence to LLT has been reported at 59.2% after 1 year, with a 5% increase in event risk for every 10% decrease in adherence.[20] Several factors contribute to LLT nonadherence, including financial constraints and high drug prices, perceived or actual side effects, limited health literacy, and comorbidities.[21] To enhance LLT adherence, patient education and treatment reminders can be effective.[21] However, the author noted that knowledge alone is insufficient and must be accompanied by changes in attitude and behavior.

Aside from the patient-related factors, clinical inertia among physicians also poses a significant barrier, often stemming from reluctance or failure to initiate or intensify recommended treatments. Despite clear evidence and guidelines, some clinicians remain hesitant to aggressively lower LDL-C, even in patients with established ACS.[13] Health-system barriers, including limited access to care, unavailable or unaffordable cardiovascular services, and insufficient diagnostic capacity, further hinder optimal secondary prevention, especially in resource-limited settings like Indonesia.[3]

Patients with ACS frequently present with multiple comorbidities, with nearly 50% of ACS patients experiencing at least one co-occurring condition, significantly impacting management and outcomes.[22] Achieving LDL-C targets of <55 mg/dL and controlling other risk factors (e.g., diabetes, hypertension) are recommended to optimize patients' outcomes.[15] The authors also suggested that all comorbidities be addressed simultaneously, without prioritizing one over another, to ensure comprehensive care for post-ACS patients.

Role of siRNA in Early Post-ACS

Recent advancements in non-statin LLTs have expanded treatment options for reducing LDL-C in high-risk ASCVD patients.[5,15-16] Elevated LDL-C is closely linked to increased PCSK9 levels, and genetic studies have shown that individuals with reduced or absent PCSK9 expression exhibit lower LDL-C and a reduced incidence of coronary artery disease. To suppress PCSK9, a novel siRNA-based mechanism has been developed. These siRNA molecules leverage the RNA interference pathway to target and degrade PCSK9 mRNA, thereby preventing its translation and reducing PCSK9 production.[23-24]

Inclisiran, the first-in-class siRNA, acts early in the lipid regulation pathway by silencing PCSK9 mRNA, unlike monoclonal antibodies that target the PCSK9 protein directly. The silencing complex remains active beyond mRNA degradation, resulting in sustained LDL-C reduction and prolonged duration of effect. This mechanism not only enhances efficacy but also prolongs the duration of action. Inclisiran requires a twice-yearly dosing regimen, with an initial subcutaneous injection followed by a second dose at 3 months and subsequent maintenance doses every 6 months thereafter.[20,24-25] Previous studies, including ORION-9, ORION-10, and ORION-11, demonstrated that inclisiran reduced

LDL-C by approximately 50% from baseline in stable populations and was well tolerated.[26]

Although inclisiran represents a promising new therapy, data on its use in post-ACS patients remain limited. The VICTORION-Inception (V-INCEPTION) trial is the first to evaluate inclisiran in participants with recent ACS. The study assessed the administration of inclisiran within the first five weeks post-ACS and its effect on achieving LDL-C targets. Results showed that early initiation of inclisiran with usual care post-ACS led to a mean 46.9% reduction in LDL-C from baseline to day 330 (97.5% CI: −55.4 to −38.5; p<0.001), with significantly more participants achieving LDL-C <55 mg/dL compared with usual care alone (95% CI: 4.97-13.65; p<0.001). These findings suggest that early inclisiran initiation post-ACS may help more high-risk patients achieve LDL-C goals and potentially reduce the risk of recurrent cardiovascular events.[27]

Most treatment-related Adverse Events (AEs) in the inclisiran plus usual care arm were mild-to-moderate injection-site reactions, consistent with findings from the pooled analysis of the ORION-9, ORION-10, and ORION-11 phase 3 trials. In that pooled analysis (n=3,660), clinically relevant injection-site reactions occurred in 5.0% of inclisiran-treated patients versus 0.7% with placebo; all were mild, non-severe, and transient. Overall safety findings, including serious AEs, liver and kidney function, and laboratory parameters, were comparable between groups, confirming the favorable long-term safety and tolerability of inclisiran observed in ORION-10 and ORION-11.[26]

Clinical Outcome Consideration

Inclisiran has demonstrated consistent and durable LDL-C reductions across multiple phase III trials.[26] However, definitive evidence for a reduction in MACE is pending completion of a dedicated CVOT. At present, potential clinical benefit is inferred from the established relationship between LDL-C reduction and cardiovascular risk reduction.

Comparative Efficacy and Clinical Consideration of PCSK9-Targeting Therapies

PCSK9 monoclonal antibodies (evolocumab and alirocumab) have been extensively studied in large outcome trials, demonstrating robust reductions in LDL-C and consistent reductions in MACE. Specifically, network meta-analyses and pooled data suggest that evolocumab and alirocumab may achieve slightly greater LDL-C lowering than inclisiran, with evolocumab achieving approximately 60% relative reduction in LDL-C and alirocumab both demonstrating strong efficacy in head-to-head analyses of lipid-lowering agents.[28-30] In contrast, inclisiran has shown consistent ~50% reductions in LDL-C in Phase III trials with a twice-yearly dosing schedule, and its impact on cardiovascular outcomes is being evaluated in ongoing dedicated outcome studies.[31-32]

From a practical standpoint, PCSK9 mAbs typically require more frequent injections (biweekly to monthly), which can pose challenges in terms of patient adherence and injection logistics, whereas inclisiran's administration after an initial dose and a 3-month interval, followed by six-monthly maintenance, may offer greater convenience.[31,33] However, wide uptake of both therapies in clinical practice, particularly in low- and middle-income settings such as Indonesia, remains constrained by cost, reimbursement pathways, and health system logistics.[34]

Complementing these findings, real-world data from the KOMODO registry demonstrated that patients initiating inclisiran had significantly higher treatment adherence and persistence compared with those receiving PCSK9 monoclonal antibodies. At 12 months, the mean adherence of days covered (PDC) was 0.90 for inclisiran, 0.71 for alirocumab, and 0.70 for evolocumab, with approximately 80% of patients remaining on inclisiran therapy compared with about 56% for monoclonal antibodies. This improved adherence may be partly attributable to inclisiran's twice-yearly dosing regimen, which reduces treatment frequency and may lessen the burden of therapy for patients.[35]

In Indonesia, inclisiran is indicated to reduce LDL-C in adults with clinical ASCVD or Heterozygous Familial Hypercholesterolemia (HeFH), who require additional lowering of LDL-C as an adjunct to diet and maximally tolerated statin therapy with or without other LLTs.[36] The authors agreed that inclisiran is primarily intended to reduce LDL-C rather than directly prevent MACE. Although the V-INCEPTION study did not achieve a full 50% LDL-C reduction, some authors considered the results clinically meaningful, as the LDL-C levels achieved approached <55 mg/dL. Not all authors agreed that inclisiran can be included in the guidelines based on the results of V-INCEPTION. However, in clinical practice, all

authors would recommend it to their patients if patients failed to reach the guideline-recommended LDL-C targets after using high-intensity statins or the highest tolerated statin dose, with or without ezetimibe, for the first 4 weeks following hospital discharge.

The Way Forward for Lipid Management in Indonesia

Indonesia has adopted lipid therapy guidelines from both the ACC/AHA and the ESC for the management of ACS. PERKI has published recommendations on a stepwise approach for adding non-statin LLTs, such as ezetimibe and PCSK9 inhibitors, for individuals who are statin-intolerant or unable to achieve LDL-C targets with maximally tolerated statin therapy after 4–6 weeks (Figure 2).[16]

However, the authors agreed that inclisiran may be initiated in hospitalized patients following ACS whose LDL-C levels remain above target with high-intensity statins or the maximally tolerated statin dose, with or without ezetimibe.

In Indonesia and similar lower- and middle-income settings, the implementation of advanced LLTs is influenced not only by clinical efficacy but also by accessibility, affordability, reimbursement structures, drug availability, and healthcare delivery infrastructure. Although PCSK9 monoclonal antibodies have demonstrated cardiovascular outcome benefits in large, randomized trials, their uptake in many Asian contexts has been limited by high costs and restricted insurance coverage, leading to suboptimal utilization among eligible patients.[37] Economic evaluations in developing healthcare

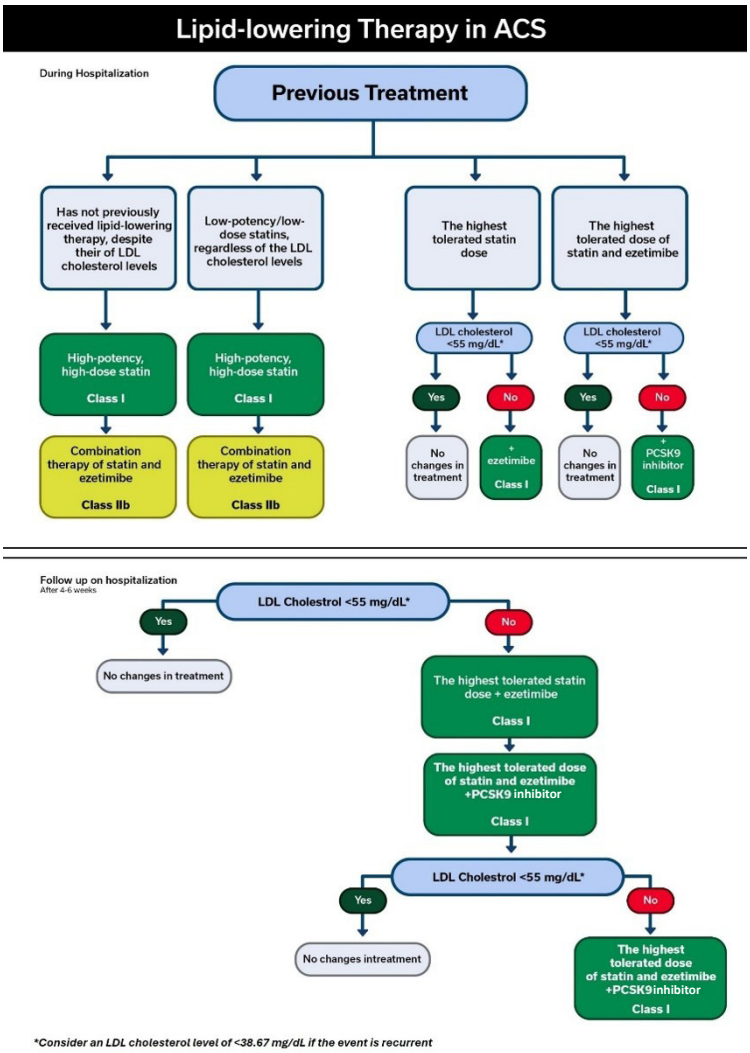

Figure 2. Lipid-Lowering Therapy for Patients with ACS, adapted from PERKI Guidelines for ACS.[16]

systems further suggest that, at current pricing levels, both PCSK9 monoclonal antibodies and inclisiran may face cost-effectiveness challenges.[38] Broader access to these therapies in Indonesia will likely depend on pricing strategies, reimbursement policies, and integration within national cardiovascular care pathways.[39] Thus, cost considerations and long-term treatment sustainability should be discussed with patients prior to therapy initiation.

The ACC/AHA guidelines recommend inclisiran for patients with CVD,[5] although the CVOTs for inclisiran are still ongoing. The two large-scale outcome studies, ORION-4 (NCT03705234) and VICTORION-2P (NCT05030428), are designed to evaluate the long-term cardiovascular benefits of inclisiran and are expected to be completed in 2026 and 2027, respectively.[40-41] All authors agreed to lean toward the ACC/AHA guideline stepwise approach, acknowledging inclisiran as a potential PCSK9-targeting therapy that can be included in clinical practice while recognizing that CVOT data are still pending. Inclusion of inclisiran in the national guideline should be based on its LDL-C–lowering efficacy, safety profile, and sustainability. Additionally, a cost-effectiveness analysis is essential before considering its inclusion in the national formulary.

Given the current situation in Indonesia, the authors recognized the importance of addressing low LDL-C target attainment, limited awareness of high-intensity statin use, and clinical inertia. If high-intensity statins are not optimized, escalation to PCSK9-targeted therapies may be delayed or underutilized. To assess the magnitude of the problem, the authors proposed a national research initiative that uses Jaminan Kesehatan Nasional (JKN, National Health Insurance Program) data to evaluate LDL-C target achievement among post-ACS patients. Furthermore, a nationwide physician survey should be conducted to assess adherence to clinical guidelines and the affordability of high-intensity statins.

Enhancing multidisciplinary collaboration is also crucial to improving lipid management in Indonesia. Cooperation between PERKI and the Indonesian Society of Internal Medicine (PAPDI) could help advocate policy changes within the Ministry of Health and JKN to ensure routine laboratory monitoring for patients on high-intensity statins and continuity of therapy even after LDL-C targets are reached.

Current guidelines recommend re-evaluating lipid levels 4–6 weeks after treatment initiation or dose adjustment to assess goal attainment and monitor safety. Collaboration with the Indonesian Association of Clinical Pathology (PDS Patklin) could also explore incorporating LDL-C target values (<55 mg/dL) in laboratory reports for ASCVD patients. The authors' recommendations from the expert meeting are summarized in Table 1.

Table 1. Summary of expert opinion recommendations.

No.	Recommendations
1.	The primary goal of treatment is to lower LDL-C to <55 mg/dL and achieve a 50% reduction from baseline. For patients with recurrent cardiovascular events within 2 years, lowering LDL-C to <40 mg/dL should be considered.
2.	Clinical inertia among doctors is a barrier to LLT in ACS patients, alongside statin intolerance, the cost of drugs such as PCSK9 inhibitors, and patient compliance.
3.	Patient education, lifestyle modification, and treatment reminders proved to be effective in improving ASCVD/ACS patient compliance with LLT. Knowledge alone does not guarantee compliance; it must be followed by changes in attitudes and practices.
4.	An aggressive LDL-C reduction with a stepwise approach was supported by the expert discussion for post-ACS patients in Indonesia to prevent future ischemic events.
5.	Inclisiran was not considered appropriate as a first-line treatment for post-ACS patients, and it is not recommended for statin-naive post-ACS patients, as a stepwise approach is preferred. However, it may be used in hospitalized ACS patients already on high-intensity statins or the highest-tolerated statin dose, with or without ezetimibe, who have uncontrolled LDL-C.
6.	There is a need for cooperation between PERKI and PAPDI to encourage changes in the Ministry of Health and JKN policies regarding the requirement for regular LDL-C laboratory tests in patients already taking high-intensity statins and to ensure the sustainability of therapy even if LDL-C target has been achieved.
7.	There is a need to design a national study in Indonesia to assess the achievement of LDL-C targets in post-ACS patients and to conduct a survey of physicians to evaluate guideline adherence and the affordability of high-intensity statins.

These recommendations represent the author's synthesis of expert panel discussion and clinical perspectives. Structured voting was used to inform discussion, but was not intended to establish a formal consensus recommendation.

Conclusion

Patients with ACS are at a higher risk of recurrent ischemic events. Therefore, the current treatment goal is to lower LDL-C to <55 mg/dL and achieve a ≥50% reduction from baseline. Based on current evidence from the V-INCEPTION study and the 2025 ACC/AHA guidelines on ACS management, non-statin therapies, including inclisiran, may be considered for patients already on maximally tolerated statin therapy who have not achieved their LDL-C target within 4 weeks after hospital discharge.

List of Abbreviations

ACC	Acute Cardiovascular Care
ACC/AHA	American College of Cardiology/ American Heart Association
ACS	Acute Coronary Syndrome
AEs	Adverse Events
ASCVD	Atherosclerotic Cardiovascular Disease
ATLR	Atherosclerosis, Thrombosis, Lipidology, and Regenerative Therapy
CVD	Cardiovascular Disease
CVOT	Cardiovascular Outcome Trial
ESC	European Society of Cardiology
HeFH	Heterozygous Familial Hypercholesterolemia
JKN	Jaminan Kesehatan Nasional
LDL-C	Low-Density Lipoprotein Cholesterol
LLT	Lipid-lowering Therapy
MACE	Major Adverse Cardiovascular Events
PAPDI	Indonesian Society of Internal Medicine
PDC	Proportion of Days Covered
PCSK9	Proprotein Convertase Subtilisin/ Kexin Type 9
PDS Patklin	Indonesian Association of Clinical Pathology
PERKI	Indonesian Heart Association
siRNA	Small-interfering RNA
V-INCEPTION	VICTORION-Inception.

Ethical Clearance

This article is based on the opinions of leading experts and does not contain any studies with human participants or animals performed by any of the authors.

Publication Approval

All authors consent to the publication of this manuscript.

Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, giving insight/feedback and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Conflict of Interest

None.

Availability of Data and Materials

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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