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2024 Korean Society of Myocardial Infarction/National Evidence-Based Healthcare Collaborating Agency Guideline for the Pharmacotherapy of Acute Coronary Syndromes

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AUTHOR'S SUMMARY

Many countries have published clinical practice guidelines for appropriate clinical decisions, optimal treatment, and improved clinical outcomes in patients with acute coronary syndrome. Developing guidelines specifically tailored to the Korean environment is crucial, considering the treatment system, available medications and medical devices, racial differences, and level of language communication. This is the first Korean acute coronary syndrome guideline stating the 9 key questions for pharmacotherapy in collaboration with the National Evidence-Based Healthcare Collaborating Agency.

ABSTRACT

Many countries have published clinical practice guidelines for appropriate clinical decisions, optimal treatment, and improved clinical outcomes in patients with acute coronary syndrome. Developing guidelines that are specifically tailored to the Korean environment is crucial, considering the treatment system, available medications and medical devices, racial

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Data Sharing Statement
The data generated in this study is available from the corresponding authors upon reasonable request.

differences, and level of language communication. In 2017, the Korean Society of Myocardial Infarction established a guideline development committee. However, at that time, it was not feasible to develop guidelines, owing to the lack of knowledge and experience in guideline development and the absence of methodology experts. In 2022, the National Evidence-Based Healthcare Collaborating Agency collaborated with a relevant academic association to develop internationally reliable guidelines, with strict adherence to the methodology for evidence-based guideline development. The first Korean acute coronary syndrome guideline starts from the 9 key questions for pharmacotherapy.

Keywords: Acute coronary syndrome; Pharmacotherapy; Clinical practice guideline

INTRODUCTION

Despite advances in medicine, the mortality and rehospitalization rates associated with ischemic heart disease, including myocardial infarction (MI), remain significantly high.[1-3] Many countries, including the United States and Europe, have published clinical practice guidelines (CPGs) for acute coronary syndrome (ACS) to promote optimal treatment. Nevertheless, it is necessary to develop a CPG that is specifically tailored to the Korean environment, accounting for the treatment system, available medications and medical devices, racial differences, and level of language communication. Moreover, highly reliable CPGs based on evidence-based guideline development methodologies are required rather than simply summarizing or organizing existing foreign guidelines.

In 2017, the Korean Society of Myocardial Infarction (KSMI) established a guideline development committee. However, owing to a lack of knowledge and experience in guideline development and the absence of methodology experts, guideline development is not feasible. Instead, the KSMI issued expert consensus documents on pharmacotherapy and interventional treatment in 2020 and 2021, which were published in *Korean Circulation Journal* and made available in Korean language on the KSMI website (https://www.ksmi.re.kr/).[4)5)]

Owing to the absence of evidence-based CPGs for ACS in Korea, making comprehensive recommendations for all facets of management, including diagnosis, treatment, and secondary prevention, remains unfeasible. Despite the prevalence of interventional procedures in contemporary care, post-ACS pharmacotherapy remains a cornerstone of management, significantly influencing both short and long-term patient prognoses.[6)7)] Furthermore, whereas coronary interventions for ACS are performed by cardiologists in large hospitals in the early phase following hospitalization, pharmacotherapy involves a wider array of providers, from residents to primary care providers, and spanning patients' lifetimes. Based on the significance of pharmacotherapy, the development committee decided to develop CPGs for pharmacotherapy first.

DEVELOPMENT PROCESS OF PHARMACOTHERAPY GUIDELINES

Guideline development committee
From February 2022, the National Evidence-based healthcare Collaborating Agency (NECA) and the KSMI collaborated to development trustworthy Korean evidence-based practice

S, Lee SH, Hwang D, Choi KH, Park J, Lee HJ, Park DA, Nam CW; Project administration: Kim HK, Yoon CH, Lee JH, Hahn JY, Hong YJ, Hwang JY, Jeong MH, Park DA, Nam CW, Kim W; Resources: Hong YJ, Hwang JY, Park DA; Software: Park DA; Supervision: Yoon CH, Lee JH, Hahn JY, Hong YJ, Hwang JY, Jeong MH, Park DA, Nam CW, Kim W; Validation: Kim HK, Lee SH, Hwang D, Choi KH, Yoon CH, Lee JH, Hahn JY, Park DA, Nam CW, Kim W; Visualization: Kim HK, Lee SH, Hwang D, Choi KH; Writing - original draft: Kim HK; Writing - review & editing: Lee SH, Kim W.

guidelines. We constructed a steering committee (7 members), working group (9 members), and consulting committee (11 members) as the guideline development committee. All the committees included methodological experts and various clinical experts. In particular, the working group paired methodology experts with clinical experts for each key question. The consulting committee consisted of 9 experts recommended by the Korean Society of Cardiology and 2 members of the guideline committee in the Korean Academy of Medical Sciences, and served as external reviewers of the overall methodology and individual guideline recommendations. In addition, the steering committee also served as a conflict of interest committee, and all members who participated in the development of the guidelines disclosed their interests before and during the development of the recommendations, and established conflict of interest management standards. There were 2 cases of conflicts of interest, but in the case of the advisory committee members, it was possible to review the recommendations, and in the case of the steering committee members, it was determined that only information was disclosed considering that the research expenses did not reach the threshold and it was not a clinical trial study. A detailed list of the guideline development committee and declarations conflict of interest were presented in the **Supplementary Data 1**.

Purpose and scope of developing clinical practice guideline

This study aimed to develop a evidence-based CPG for the pharmacological treatment of patients with ACS to address the current medical situation in Korea. The purpose of these guidelines is to help frontline physicians in managing ACS by providing articulated evidence-based recommendations for pharmacotherapy. Therefore, this would have the potential to improve therapeutic efficacy for patients, play a role in promoting their health, and enhance their quality of life. The target population for this guideline was patients diagnosed with ACS, regardless of age, sex, or ST-segment elevation. The users of these clinical guidelines include cardiologists and general physicians who treat patients with ACS at primary, secondary, and tertiary medical institutions. A detailed guideline scope is presented, including the Population, Intervention, Professionals, Outcomes, and Healthcare system (PIPOH) in the **Supplementary Data 2**.

Determination the method of guideline development

Our guideline development group decided to develop this guideline using an adaptive methodology, considering those international guidelines for MI or ACS, such as the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), have all been published within the past 5 years and recent clinical studies in Korea have been published. We systematically searched the guidelines to identify relevant evidence and updated the published literature to incorporate supporting studies to develop recommendations.

Selection of key questions

The members of the committee determined 9 key questions (title of each key questions, numbered with KQ#) pharmacological treatments. Modifications were made based on the opinions of the internal evaluation panel, resulting in a total of 13 recommendation statements. The KQs were established through the Patient, Intervention, Comparison, Outcome (PICO) components and study design (SD), where population (P) represents patients with ACS; intervention (I) represents 9 pharmacological interventions; comparison (C) represents placebo, no treatment, and main alternative therapeutic interventions to compare with the interventions; and outcome (O) represents the clinical effectiveness and safety outcomes. We discuss the importance of the outcome in determining critical and

important outcomes through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for individual KQs. The PICO and SD for each KQs are presented in the **Supplementary Data 3-11**.

Literature searches

A comprehensive search was performed using the international electronic databases PubMed, Ovid-Embase, and Korean databases (KoreaMed and KMbase). Guidelines were also searched in the GIN DB, The National Institute for Health and Care Excellence (NICE) of the United Kingdom, Scottish Intercollegiate Guideline Network (SIGN) of Scotland, and Canadian CPG website. For guideline selection, 1 working member reviewed the titles and abstracts to eliminate articles that were not on the ACS or were not guidelines. 2 working members reviewed the full text to reach a consensus on the final guidelines and selected 13 relevant guidelines. The final guideline inclusion criteria were as follows: (1) guidelines with a standardized score of 65 or above in domain 3 'Rigor of Development' of the Appraisal of Guidelines for Research and Evaluation (AGREE) II assessment tool; (2) guidelines deemed highly necessary for clinical application given the clinical characteristics of the specialty. Of the 13 guidelines, 4 that satisfy the criteria (1) and 4 additional ESC guidelines were selected in consideration of the criteria (2), and a total of 8 guidelines were finally selected.

Literature publications selected in the evidence table from the existing clinical guidelines were reviewed and accepted. To find the latest research that was not reviewed in the 8 guidelines for each key question, a search was performed in international databases such as Ovid-MEDLINE, Ovid-Embase, and Cochrane Database of Systematic Reviews (CDSR; search period: from 1 year before the existing guidelines up to December 12, 2022) and Korean database such as KoreaMed database (search period: from 1 year before the existing guidelines up to December 13, 2022) to update the literature search. Considering the abundance of relevant systemic reviews (SRs) and meta-analyses and to ensure that no major clinical evidence was overlooked, the list of references in existing SRs and meta-analyses was additionally reviewed, and supporting evidence literature for the recommendations included in the existing guidelines was also manually reviewed.

Evidence appraisal and synthesis

In accordance with the committee's decision to review evidence from randomized controlled trials (RCTs) for each key question, quality assessment of the final selected evidence was conducted using the Cochrane Risk of Bias Tool version 1.5. Two researchers independently evaluated the literature, and disagreements were resolved through discussion. Additionally, if consensus could not be reached, another discussion was held with input from a third independent researcher. If Cochrane Risk of Bias assessment results were provided in an existing SR, the results were accepted. In cases where the existing SR had conflicting results or did not present results for "selective reporting bias," 2 researchers independently reassessed the literature.

For each key question, the finally selected articles were classified by SD, and relevant information was extracted following a pre-determined data extraction format. Working members responsible for specific KQs extracted the data, and the NECA research team in charge of the methodology reviewed it. For data suitable for meta-analysis, evidence synthesis was performed. Considering the diversity of clinical target populations and intervention mechanisms in the subject area, a fixed-effects model was used. In most cases, the outcome variables were binary; thus, the effect measures were presented as risk ratios

(RRs) with 95% confidence intervals (CIs). In cases of heterogeneity, subgroup analyses were conducted to explore the causes of heterogeneity. Furthermore, a subgroup analysis was performed by country of study to estimate the health outcomes in Asian populations. Publication bias was assessed using funnel plots and Egger test if at least 10 studies were included in the synthesis. Review Manager (RevMan) 5.4 was used for the meta-analysis and statistical significance was determined at a significance level of 5%.

Development of clinical recommendations

The level of evidence (LOE) was determined using GRADE methodology. For each key question, the LOE for critical and important outcomes was rated as 'High/Moderate/Low/Very Low' (**Table 1**).[8] The strength of the recommendations (direction and strength) was determined by considering 4 factors as outlined in the GRADE methodology: LOE, effect size (balancing benefits and harms), patient values and preferences, and resources (costs) and feasibility. The strength of the recommendations was categorized as either 'Strong' or 'Weak,' with 'No Recommendation' to be given in cases with high uncertainty or difficulty determining the direction of recommendation (**Table 2**).[9] However, most directions and strength of recommendations were determined through informal consensus among the development committee.

The draft recommendations, prepared by the working members after reviewing evidence, were presented at a full committee meeting (attended by more than 70% of the development committee members) to arrive at an informal consensus. In cases in which consensus could not be reached through discussion, 2 options were presented, and the option with more than 70% agreement was chosen as the consensus. If a consensus could not be reached effectively, a modified recommendation was discussed at a subsequent meeting to arrive at an agreement.

Table 1. Definition of level of evidence using GRADE methodology

Level of evidence	Definition
High	Very confident that the estimate of the effect is close to that of the true effect.
Moderate	Moderately confident in the effect estimate: The estimate of the effect is likely to be close to the true effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Table 2. Definition and implication of recommendations

Grading	Definition and implication
Strong	Desirable effects clearly outweigh undesirable effects, or vice versa.
	1. Strong recommendations are not necessarily recommendations with high priority. This means that it can be applied as best to most or everyone who is subject to the intervention.
	2. Recommendation may change when higher quality evidence becomes available (with low- or very low-quality evidence).
Weak	Desirable effects slightly outweigh with undesirable effects, or vice versa.
	1. The best action may differ depending on circumstances or patients or social values (with high-quality evidence).
	2. Alternative approaches are likely to be better for some patients under some circumstances (with moderate-quality evidence).
	3. Other alternatives may be equally reasonable. Future research is very likely to have an important impact (with low- or very low-quality evidence).
No recommendation	If any of the following conditions are met.
	1. The reliability of the estimate of effect is too low, and speculation of the recommendation is too high.
	2. Regardless of the reliability of the estimate of the effect, there is little difference in the scale of effect size. Value, preference, and resource use are unknown, or diversity is too huge to determine the direction of the recommendation.
	3. Two alternatives lead to unwanted outcomes that are too different, and the individual patient's response to those outcomes is too different to be concluded from a general value and preference perspective.

External review

The opinions of cardiologists from various specialties were publicly collected through a public hearing of the draft recommendations, and the opinions of external experts on the advisory committee were investigated for revision. The collected expert opinions were reviewed to revise the draft recommendations, and the final level of agreement was confirmed through a survey of external experts on the advisory committee.

Developing tool for facilitating implementation

Our Guideline Development Group developed a treatment decision flowchart to facilitate the real-world application of the pharmacotherapy recommendations for patients with ACS. This was reviewed by an external expert, revised, and made into an infographic with the recommendations and distributed on the society's website.

Update and funding

Approximately every 3 years, and more frequently if needed, the KSMI will determine the need for revisions to the guidelines by examination the current study and the likelihood that any new data will affect the recommendations.

LIPID-LOWERING THERAPY

KQ 1. Statin

Backgrounds

Dyslipidemia is an important risk factor for the development and progression of atherosclerosis, making proper management crucial for preventing the occurrence of diseases related to atherosclerosis. Statins are well-known drugs that lower low-density lipoprotein cholesterol (LDL-C) levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. Previous clinical studies have indicated that statins in patients specifically act by lowering LDL-C levels and can reduce the incidence of cardiovascular events in both primary and secondary prevention aspects.[10-12] Therefore, most studies presuppose that the use of statins is mandatory in patients with ACS and have mainly focused on the intensity of statin or more aggressive LDL-C-lowering treatment strategies.[12-14] In this treatment guideline, a systematic review of previous literature was conducted to evaluate the efficacy and safety of statins in patients with ACS compared with placebo or no treatment.

Rating the quality of evidence

A systematic review to answer the key question identified 5 recommendation-supporting documents from existing guidelines, 44 documents from the latest systematic review articles, and 3,212 documents from electronic database searches. Through a selection process conducted independently by 2 reviewers, 12 RCTs were finally selected based on the prespecified inclusion and exclusion criteria (**Supplementary Data 3**). Among the 12 RCTs (n=18,095), 6 were from Asian countries, 3 were from Europe, 1 was from South America, and 2 were from other regions. The articles were published between 2000 and 2018.

A meta-analysis of 12 RCTs comparing the use of statins with no treatment or placebo in patients with ACS revealed no significant differences in all-cause death, cardiovascular death, or revascularization. However, statin use was associated with a 24% reduction in the risk of MI (RR, 0.76, 95% CI, 0.65–0.88) and a 17% reduction in the risk of major adverse cardiac and cerebrovascular events (MACCE) (RR, 0.83, 95% CI, 0.76–0.91). Evidence certainty for critical outcomes such as all-cause death, cardiovascular death, MI, and MACCE was assessed using the GRADE tool, resulting in a low overall evidence level owing to downgrading by the risk of bias, imprecision, and publication bias concerns. The detailed process is provided in the **Supplementary Data 3**.

Recommendations development process
Both the ESC and ACC/AHA guidelines recommend high-intensity statins regardless of the initial LDL-C levels in patients with ACS as Class I, with reports suggesting their benefits and efficacy.[15-17] Consistent findings from systematic reviews and previous studies affirm the benefits of high-intensity statins for secondary prevention in patients with ACS. The discrepancy between the grade of recommendation and the LOE is mainly due to the limited number of RCTs directly comparing the use of statins with placebo or no treatment in patients with ACS.

Asymptomatic elevation of liver enzyme, serum aminotransferase levels exceeding 3 times the upper limit of normal (ULN), often resolves with dose reduction. When combined with an increased level of serum bilirubin, statins should be discontinued, and monitoring of liver function is needed.[18] Statin-induced myopathy is an unexplained muscle weakness or pain commonly involving in the bilateral proximal parts such as the hip flexor region, upper chest, and shoulders. If creatine kinase level is elevated more than 10 times the ULN (or 5 times the ULN in a vulnerable patient), statins should be discontinued.[19] Even considering the potential risks, such as hepatotoxicity, muscle toxicity, and the onset of diabetes mellitus, the benefits outweigh the risks, making statin prescriptions appropriate for patients with ACS in the early stage of hospitalization (**Table 3**).

Table 3. Recommendations for lipid-lowering therapy

Key question	Recommendation	Strength of recommendation	Level of evidence
Statin	High-intensity statins are recommended for patients with ACS. [Clinical considerations] 1. Timely use of high-intensity statins early upon admission lowers the risk for MACCE and MI. 2. The occurrence of hepatotoxicity, muscular toxicity, and diabetes mellitus potentially linked to high-intensity statin use should be periodically monitored. 3. When using high-intensity statins, it is important to ensure that LDL-C levels are reduced to below 55 mg/dL and by at least 50% from the baseline, and the use of additional LDL-C-lowering agent should be considered. 4. Caution is needed in patients with acute liver failure or decompensated liver cirrhosis. Physicians should be cautious when co-administering cyclosporine, cytochrome P-450 inhibitors, antibiotics, and antifungals.	Strong	Low
Non-statin LDL-C lowering agent combination therapy	If the target LDL-C is not met in patients with ACS, non-statin LDL-C-lowering agent combination therapy is recommended. [Clinical considerations] 1. The goal is to lower LDL-C to below 55 mg/dL and by 50% from the baseline. 2. In patients with ACS, adding non-statin LDL-C-lowering agents to statin therapy reduces the risk of MACCE and MI compared to statin monotherapy. 3. Non-statin LDL-C-lowering agents currently available in Korea include ezetimibe and PCSK9 inhibitors. 4. If statin use is contraindicated due to hepatotoxicity or muscle toxicity, the use of non-statin LDL-C-lowering agents can be considered. 5. Hepatotoxicity and muscle toxicity are known to be rare with non-statin LDL-C-lowering agents, and the incidence of these adverse effects is not elevated when combined with statin.	Strong	Low

ACS = acute coronary syndrome; LDL-C = low-density lipoprotein-cholesterol; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; PCSK9 = proprotein convertase subtilisin-kexin type 9.

KQ 2. Non-statin low-density lipoprotein cholesterol-lowering agents added to statin

Backgrounds

Concerns regarding residual cardiovascular risk even after using high-intensity statins or statin intolerance have prompted the consideration of additional lipid-lowering agents.[20][21] In addition to statins, ezetimibe and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have been developed and are used as LCL-C-lowering agents in clinical practice. Ezetimibe reduced LDL-C levels by inhibiting cholesterol absorption in the small intestine. PCSK9 binds to LDL receptors in the blood and induces receptor degradation. In addition to statins, a PCSK9 inhibitor, a monoclonal antibody against PCSK9, reduces LDL-C levels. Therefore, this reduces the risk of cardiovascular events in addition to statin.[22-24] To determine the efficacy and safety of combining non-statin LDL-C-lowering agents with statins in patients with ACS, a systematic literature review was conducted.

Rating the quality of evidence

A systematic review to answer this key question identified 8 recommendation-supporting documents from existing guidelines, and 1,443 documents from electronic database searches. Through a selection process conducted independently by 2 reviewers, 3 RCTs were ultimately selected based on the prespecified inclusion and exclusion criteria. Among the 3 RCTs (n=38,802), 2 RCTs were multi-national studies, and the other was from Japan. All the RCTs were published between 2015 and 2018. The risk of bias was evaluated using the Cochrane risk of bias version 1.5, which showed a low risk of bias in multi-national studies but a high-risk of bias in a study from Japan due to issues in random sequence generation, allocation concealment, and blinding.

A meta-analysis of the 3 RCTs found no significant differences in all-cause death, and cardiovascular death. However, the non-statin LDL-C-lowering agent in combination with statins was associated with a 13% reduction in the risk of MI (RR, 0.87, 95% CI, 0.82–0.93), a 7% reduction in the risk of revascularization (RR, 0.93, 95% CI, 0.89–0.97), and an 8% reduction in the risk of MACCE (RR, 0.92, 95% CI, 0.88–0.95). Evidence certainty for critical outcomes such as all-cause death, cardiovascular death, MI, and MACCE was assessed using the GRADE tool, resulting in a 'Low' overall LOE due to downgrading for imprecision, and publication bias concerns. The detailed process is provided in the **Supplementary Data 4**.

Recommendations development process

The 2023 ESC guidelines recommend the stepwise use of ezetimibe and PCSK9 inhibitors if LDL-C targets are not achieved with the maximally tolerated dose of statins.[17] The target goal of LDL-C level is less than 55 mg/dL and a 50% reduction from baseline levels in recent guidelines and expert consensus documents.[17][25] In this systematic review, it was found that there are few studies on the efficacy and safety of combining non-statin LDL-C-lowering agents with statins, and even fewer studies have focused specifically on patients with ACS. The overall LOE was rated as 'Low,' but individual study results and meta-analyses suggested that combining non-statin LDL-C-lowering agents with statins may be beneficial. Ezetimibe can cause muscle-related side effects, rhabdomyolysis, and gallbladder-related adverse effects, but these are rare.[26] In addition, the combination of statins with ezetimibe does not significantly increase the frequency of these adverse effects.[22][27] PCSK9 inhibitors primarily cause injection site reactions, with no significant increase in adverse effects when combined with statins compared with statin monotherapy.[24][28] Thus, the benefits of currently available non-statin LDL-C-lowering agents outweigh the risks, making their use recommendable (**Table 3**, **Figure 1**).
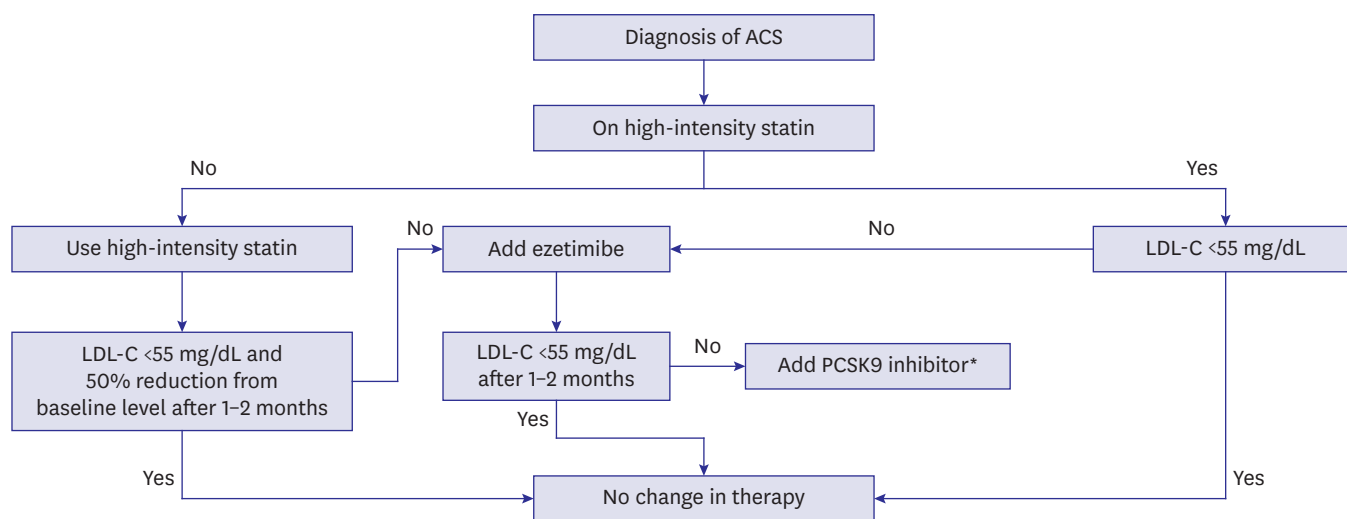
Figure 1. Lipid lowering therapy in patients with ACS.
ACS = acute coronary syndrome; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin-kexin type 9.
*The insurance coverage for PCSK9 inhibitor in Korea is applied for patients when LDL-C is higher than 70 mg/dL after using maximally tolerated statin plus ezetimibe.

Evidence gaps and future research suggestions
There is limited direct evidence for the initial use of high-intensity statins with stepwise addition of ezetimibe and PCSK-9 inhibitors, and for the validation of target LDL-C level goals in patients with ACS. Although the statin hypothesis refers to the idea that statins have a pleiotropic effect in the amelioration of endothelial dysfunction, antioxidant properties, and inflammation reduction which is not shared with other LDL-C-lowering agents, the LDL hypothesis assumes that LDL-C reduction is a crucial factor in the reduction of MACCE regardless of the lipid-lowering agents used.[29] Current guideline recommendations are deemed to be a compromise between the 2 hypotheses.

The optimal target goal of LDL-C and upfront combination treatment with high-intensity statins and ezetimibe are also controversial.[30] Although most participants in the KSMI survey were aware of the changes in the LDL-C target goal in the ESC guidelines, 52% of the Korean cardiologists did not agree with lowering LDL-C to below 55 mg/dL. The major reason was that the safety and efficacy of intensive LDL-C-lowering therapy have not yet been proven in Korean patients.[31]

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS

KQ 3. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers
Backgrounds
Although the reperfusion strategy has shifted from thrombolysis to primary percutaneous coronary intervention (PCI) for patients with acute myocardial infarction (AMI), pharmacological treatments that can significantly improve patient survival remain limited. Among these treatments, inhibitors of the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), have gained attention. These inhibitors can suppress ventricular remodeling, improve hemodynamics, and are expected to reduce the incidence of decompensated heart failure.

Rating the quality of evidence

To identify the primary studies relevant to the key question, 10 supporting references from existing guidelines, 29 selected references from recent systematic literature reviews, and 5,036 references from electronic databases were reviewed. Based on predefined literature selection criteria, 2 independent reviewers prioritized related references included in the existing guidelines (n=7), followed by references from previous systematic reviews (n=5), and newly published literature (n=1). This process led to the final selection of 13 RCTs.

Among the 13 selected studies, 10 compared the use of ACEi with placebo, and 3 compared ACEi with ARB. The 10 studies comparing ACEi with placebo (n=99,351) were predominantly from European countries (8 studies), with the remaining 2 studies published in the United States and China. Most of these studies were published in the 1990s, with 1 study published in 2021. Among these, 2 studies focused on patients with left ventricular ejection fraction (LVEF) ≤40%, and 1 study focused on patients with LVEF >40%. The 3 studies comparing ACEi with ARB (n=20,526) included 2 studies published in Europe in the early 2000s and 1 study published in Japan in 2009.

KQ 3-1. Angiotensin-converting enzyme inhibitors versus placebo

A meta-analysis of 10 RCTs comparing ACEi with placebo in patients with ACS showed that ACEi significantly reduced the risk of all-cause mortality by 9% (RR, 0.91, 95% CI, 0.87–0.94), cardiovascular mortality by 21% (RR, 0.79, 95% CI, 0.71–0.89), and readmission due to heart failure by 4% (RR, 0.96, 95% CI, 0.93–0.99). No significant differences were observed in the incidence of MI.

KQ 3-1-1. Angiotensin-converting enzyme inhibitors versus placebo in patients with left ventricular ejection fraction ≤40%

A meta-analysis of 2 studies focusing on patients with LVEF ≤40% found that the use of ACEi significantly reduced the risk of all-cause mortality rate by 18% (RR, 0.82, 95% CI, 0.75–0.91), readmission due to heart failure by 27% (RR, 0.73, 95% CI, 0.59–0.90), and the incidence of MI by 18% (RR, 0.82, 95% CI, 0.70–0.96) compared to placebo. Confidence in evidence of critical outcomes, including all-cause mortality, cardiovascular mortality, and readmission due to heart failure, was assessed using the GRADE evaluation tool. The overall LOE for this key question is 'Moderate,' reflecting the lowest evidence level among the critical outcomes. The detailed process is provided in the **Supplementary Data 5**.

KQ 3-1-2. Angiotensin-converting enzyme inhibitors versus placebo in patients with left ventricular ejection fraction >40%

Only 1 study was included in the analysis of patients with LVEF >40%. The results showed no significant differences between the ACEi group and placebo groups in terms of all-cause mortality and readmission for heart failure. Owing to the wide CIs for the effect estimates, small sample size, and number of events in each group, the precision domain was downgraded by 2 levels. No downgrading factors were found in the other domains, resulting in a final evidence level of 'Low.' Therefore, the overall LOE regarding this key question is 'Low.'

KQ 3-2. Angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers

Based on the results of a meta-analysis of 3 RCTs comparing ARB use with ACEi use in patients with ACS, ARB use showed no significant difference compared to ACEi use in the following outcomes: all-cause mortality (RR, 1.01, 95% CI, 0.94–1.08), cardiovascular

mortality (RR, 1.00, 95% CI, 0.93–1.08), readmission due to heart failure (RR, 1.14, 95% CI, 0.98–1.34), incidence of MI (RR, 1.01, 95% CI, 0.88–1.15), MACCE (RR, 0.82, 95% CI, 0.45–1.47). Confidence in the evidence for critical outcomes, including all-cause mortality, cardiovascular mortality, readmission due to heart failure, and the important outcomes of MI and MACCE, were assessed using the GRADE evaluation tool. The overall LOE for this key question is 'Low.' The detailed process is provided in the **Supplementary Data 5**.

Recommendations development process
ACEi demonstrated a clear reduction in all-cause mortality, readmission due to heart failure, and MI, especially in patients with LVEF ≤40%. However, for patients with LVEF >40%, the effect on major outcomes has not been demonstrated, and the available literature is insufficient, resulting in a low overall LOE. ACEi have a blood pressure-lowering effect, which may limit their use in patients with a slightly low or normal blood pressure. Some patients experience acute kidney injury, hyperkalemia, dry cough, or angioedema. Nevertheless, considering the benefits of ACEi, it is expected that the treatment benefits outweigh the risks even in patients with LVEF >40%. In the 2023 ESC guideline, the use of ACEi is recommended (Class I, LOE: A) for patients with heart failure symptoms, LVEF ≤40%, diabetes mellitus, hypertension, or chronic kidney disease, and for all patients with ACS regardless of LVEF (Class IIa, LOE: A). The NICE guidelines recommend the indefinite use of ACEi and ARB after hemodynamic stabilization in patients with ACS.

During the overall research team meeting, the following modifications and supplements were made: the inclusion of 'heart failure' along with 'LVEF' as a major clinical factor to consider when using ACEi in patients with ACS. Clinical evidence for the long-term use of ACEi was insufficient, and recommendations related to this are excluded. ARB is not recommended equally with ACEi but as a substitute when ACEi is intolerable. The opinion from external experts included conditions for using recommendations if the recommendation grade was weak. This was integrated by presenting recommendations based on whether LVEF is ≤40% or >40%. There was also a suggestion to detail the types of drugs; however, because the drug names were clearly described in the study characteristics table, the recommendations were finalized without additional revisions (**Table 4**, **Figure 2**).

Table 4. Recommendations for renin-angiotensin-aldosterone system inhibitors

Key question	Recommendation	Strength of recommendation	Level of evidence
ACEi/ARB	The use of ACEi is recommended for patients with ACS with LVEF ≤40% or heart failure.	Strong	Moderate
	The use of ACEi may be considered for patients with ACS with LVEF >40%.	Weak	Low
	ARB may be considered as an alternative to ACEi for patients with ACS with LVEF ≤40% or heart failure	Weak	Low
	[Clinical considerations]		
	1. LVEF measurement before using ACEi is recommended.		
	2. The specific drugs used in major clinical studies may be considered first when choosing ACEi or ARB (ACEi: captopril, ramipril, zofenopril, lisinopril, trandolapril; ARB: losartan, valsartan).		
MRA	Additional use of MRA is recommended for patients with ACS with heart failure.	Strong	High
	[Clinical considerations]		
	1. Additional use of MRA is especially recommended for patients with ACS with LVEF ≤40%.		
	2. Additional use of MRA may induce electrolyte imbalances, such as hyperkalemia, so its use in patients with elevated baseline potassium levels or impaired kidney functions should be carefully weighed.		

ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; ACS = acute coronary syndrome; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.
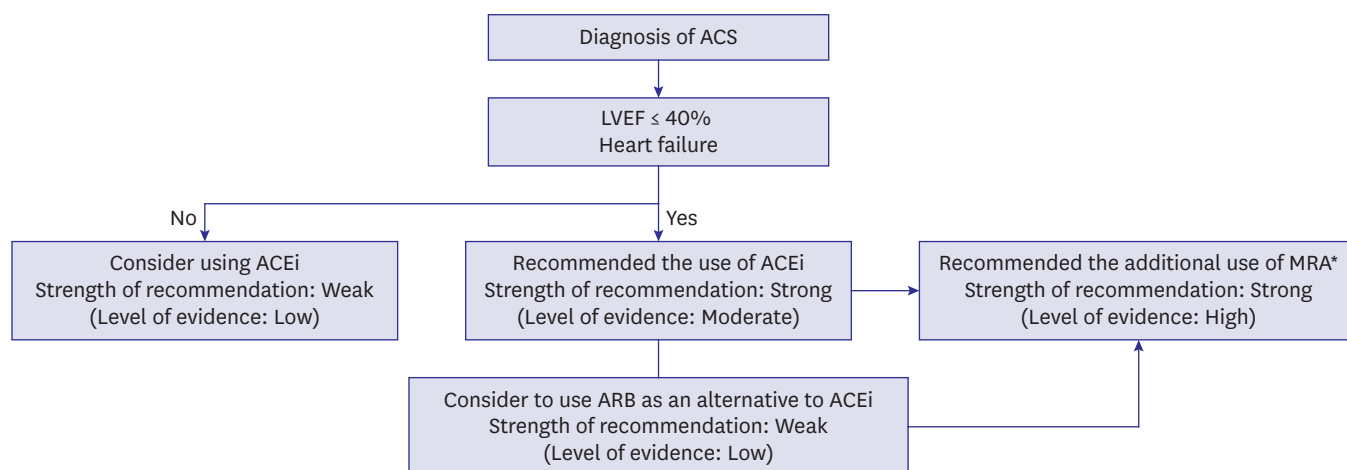
Figure 2. Renin-angiotensin-aldosterone system inhibitors use in patients with ACS.
ACEi = angiotensin-converting enzyme inhibitors; ACS = acute coronary syndrome; ARB = angiotensin receptor blockers; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.
*The criteria related to LVEF were inconsistent in the use of MRA.

Evidence gaps and future research suggestions
Further research is needed to supplement the lack of clear data on the efficacy of ACEi and ARB in patients with AMI and LVEF >40%.

In the Valsartan in Acute Myocardial Infarction (VALIANT) study, a major clinical trial comparing ARB and ACEi, 4.6–5.0% of patients reduced the dose of ACEi due to a dry cough, and 2.1–2.5% discontinued the ACEi. In contrast, 1.7% of patients reduced the dose of ARB, and 0.6% discontinued the ARB (p<0.05).[32] The relative risk of a dry cough due to ACEi in East Asians, including Korea, was 2.7 times higher than that in Western populations in a meta-analysis. Additionally, a retrospective cohort study reported lower medication adherence to ACEi among Asians compared to non-Asians, which warrants attention.[33-35] Therefore, ARB may be considered as a substitute for ACEi when prescribed to Korean patients. However, studies demonstrating the effect of ARB in patients with ACS have limited evidence, as they compared ARB with ACEi rather than placebo.

The addition of angiotensin receptor neprilysin inhibitor was raised as a key question; however, owing to the lack of clear results from large-scale clinical studies, this was considered for future guideline revisions.

KQ 4. Mineralocorticoid receptor antagonist
Rating the quality of evidence
Two supporting references from existing guidelines, 11 selected references from recent systematic literature reviews, and 615 references from electronic databases were reviewed. Based on the predefined literature selection criteria, 2 independent reviewers prioritized the related references included in the existing guidelines, followed by references from previous systematic reviews (n=4), and newly published literature. A total of 4 RCTs were finally selected. Among the 4 selected studies (n=8,246), 3 were from European countries, and 1 was a joint study from Europe and the United States, published between 2005 and 2014.

Based on a meta-analysis of the results from 4 RCTs comparing the addition of mineralocorticoid receptor antagonist (MRA) to existing treatment in patients with ACS, the

addition of MRA significantly reduced the risk of all-cause mortality by 14% (RR, 0.86, 95% CI, 0.77–0.95), cardiovascular mortality by 16% (RR, 0.84, 95% CI, 0.75–0.95), and readmission due to heart failure by 13% (RR, 0.87, 95% CI, 0.76–0.99). There was no significant difference in the risk of MI, and no studies have reported MACCE. Confidence in the evidence for key outcomes, including all-cause mortality, cardiovascular mortality, and readmission due to heart failure, was assessed using the GRADE evaluation tool. The overall LOE for this key question is 'High,' reflecting the lowest evidence level among the key outcomes (**Supplementary Data 6**).

Recommendations development process
The additional use of MRA in patients with ACS significantly reduced the risk of all-cause mortality, cardiovascular mortality, and readmission due to heart failure, demonstrating its clinical benefits. However, MRA can cause electrolyte imbalances such as hyperkalemia, Therefore, it should be used with caution in patients with elevated baseline potassium levels or impaired renal function. Additionally, MRA can cause gynecomastia and erectile dysfunction in male patients, which may lead to a lower preference in this population.

During the decision-making process, the development committee modified and supplemented the following: although the patients included in the major studies on the additional use of MRA were patients with ACS and heart failure, the criteria related to LVEF were inconsistent. Similarly, because the criteria for LVEF for additional MRA use differed in CPGs from other countries, we decided to delete the content related to LVEF from our guideline recommendations and included it in the clinical considerations section (**Table 4**, **Figure 2**).

Evidence gaps and future research suggestions
Further research is needed to supplement the lack of evidence regarding the benefits and risks of additional MRA use in patients with LVEF >40% and heart failure symptoms.

BETA BLOCKER

KQ 5. Beta blocker
Backgrounds
The use of beta blockers in patients with ACS was known to improve prognosis before the era of reperfusion. However, with advancements in PCI and coronary artery bypass graft (CABG), most patients with ACS now receive reperfusion therapy, necessitating the re-establishment of evidence for the use of oral beta blockers. Thus, we conducted a systematic literature review to confirm the safety and efficacy of oral beta blockers following ACS depending on whether cardiac function was impaired.

Rating the quality of evidence
A total of 81 supporting references from existing guidelines, 81 selected references from recent systematic literature reviews, and 5,348 references from electronic databases were reviewed. Based on predefined literature selection criteria, 2 independent reviewers prioritized the related references included in the existing guidelines (n=6), followed by references from previous systematic reviews and newly published literature (n=1). Finally, 7 RCTs were selected. Among the 7 selected studies (n=14,902), 4 were from European countries, 1 was a joint study from the US and Europe, and 1 each from the US and Japan. The publications ranged from 1996 to 2018. Two studies focused on ACS patients, while the remaining 5 studies focused on heart failure patients.

KQ 5-1. All patients with acute coronary syndrome

Based on a meta-analysis of 7 RCTs comparing beta blockers use with placebo in patients with ACS, beta blocker use significantly reduced the risk of all-cause mortality by 28% (RR, 0.72, 95% CI, 0.66–0.79), cardiovascular mortality by 26% (RR, 0.74, 95% CI, 0.66–0.82), readmission due to heart failure by 26% (RR, 0.74, 95% CI, 0.64–0.86), and MI by 35% (RR, 0.65, 95% CI, 0.45–0.92). The overall LOE for this key question is 'Moderate.'

KQ 5-1-1. Acute coronary syndrome patients with left ventricular ejection fraction ≤40%

Based on a meta-analysis of 6 RCTs comparing beta blockers use with placebo in ACS patients with LVEF ≤40%, beta blockers use significantly reduced the risk of all-cause mortality by 28% (RR, 0.72, 95% CI, 0.66–0.79), cardiovascular mortality by 27% (RR, 0.73, 95% CI, 0.65–0.82), readmission due to heart failure by 25% (RR, 0.75, 95% CI, 0.65–0.87), and MI by 36% (RR, 0.64, 95% CI, 0.43–0.93). The overall LOE for this key question is 'Moderate.' The detailed process is provided in the **Supplementary Data 7**.

KQ 5-1-2. Acute coronary syndrome patients with left ventricular ejection fraction >40%

Based on 1 RCT, beta blockers use in ACS patients with LVEF >40% showed no significant difference in the risks of all-cause mortality, cardiovascular mortality, readmission due to heart failure, or MI compared with placebo. The overall LOE for this key question is 'Very Low.' The detailed process is provided in the **Supplementary Data 7**.

Recommendations development process
In patients without contraindications to beta blockers use (such as those in shock with low blood pressure, acute heart failure, brady-arrhythmias, or active airway diseases), administration of oral beta blockers following ACS can reduce mortality. This evidence confirms the significant health benefits of beta blocker use in patients with ACS with LVEF ≤40%, including reductions in all-cause mortality, cardiovascular mortality, readmission due to heart failure, and MI. In patients with LVEF >40%, although the evidence is unclear, the pharmacological benefits of beta blockers suggest that their administration is more beneficial.

There is limited evidence from randomized studies on patients with preserved LVEF or no signs of heart failure. Therefore, non-randomized studies have been reviewed to address this gap. Early use of beta blockers reduced mortality in patients with MI with preserved cardiac function and no heart failure in a French prospective cohort study, but discontinuation of the drug after one year did not increase mortality.[36] Discontinuing beta blockers after 1 year increased the risk of death or readmission for ACS in French patients with MI.[37] Continued use of beta blockers beyond 1 year reduced mortality in Korean patients with MI without heart failure.[38] However, in Danish patients, no mortality reduction was observed with the use of beta blockers from 3 months to 3 years post-MI.[39] Thus, evidence on the use of beta blockers and their duration in patients with preserved LVEF is still inconclusive (**Table 5**, **Figure 3**).

Evidence gaps and future research suggestions
Further research is needed to confirm the continued efficacy of beta blockers in the current era of aggressive reperfusion therapy, and to determine the safety and effectiveness of beta blockers in patients with ACS with preserved cardiac function and no heart failure. Ongoing studies such as 'BEtablocker Treatment After Acute Myocardial Infarction in Revascularized Patients Without Reduced Left Ventricular Ejection Fraction' (BETAMI; NCT03646357),

Table 5. Recommendations for beta blocker

Key question	Recommendation	Strength of recommendation	Level of evidence
Beta blocker	The use of oral beta blocker is recommended for ACS patients with reduced ejection fraction (LVEF ≤40%).	Strong	Moderate
	The use of oral beta blocker may be considered for ACS patients with preserved ejection fraction and no evidence of heart failure.	Weak	Very Low
	[Clinical considerations]		
	1. Contraindications should be checked before using beta blockers. The following are the contraindications:		
	- Signs of acute heart failure (e.g., pulmonary edema)		
	- Hypotension due to shock		
	- Bradycardia		
	- Reactive airway disease		
	2. LVEF measurement before using beta blocker is recommended.		

ACS = acute coronary syndrome; LVEF = left ventricular ejection fraction.
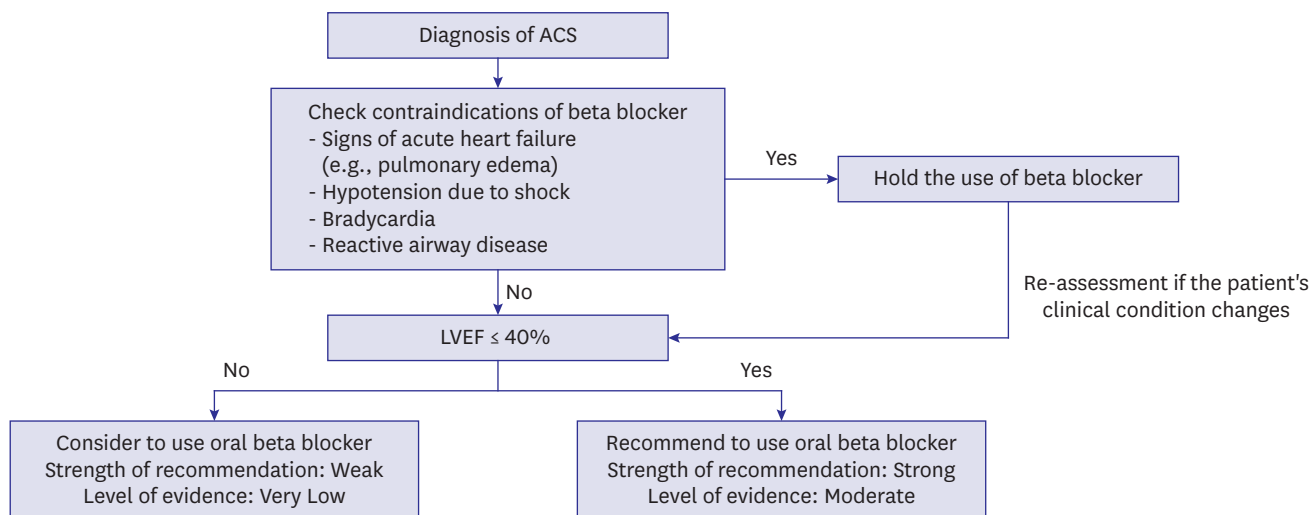

Figure 3. Beta blocker use in patients with ACS.
ACS = acute coronary syndrome; LVEF = left ventricular ejection fraction.

'Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction' (DANBLOCK; NCT03778554),[40] rationale and design of the pragmatic clinical trial 'TREatment With Beta-blockers After myOcardial Infarction withOut Reduced Ejection fracTion' (REBOOT; NCT03596385), 'Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction' (REDUCE-AMI),[41] 'Assessment of β-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization' (ABYSS),[42] and 'SMart Angioplasty Research Team: DEcision on Medical Therapy in Patients with Coronary Artery Disease or Structural Heart Disease Undergoing Intervention' (SMART-DECISION; NCT04769362) will provide more precise recommendations for beta blockers use and duration in these patients.

ANTIPLATELET THERAPY

KQ 6. Dual antiplatelet therapy
Backgrounds
The cornerstone of treating patients with ACS involves revascularization therapies, such as PCI using drug-eluting stents implantation or CABG. Dual antiplatelet therapy (DAPT), which consists of aspirin and a P2Y$_{12}$ receptor inhibitor, is essential for preventing recurrent

ischemic events. However, long-term use of DAPT could increase the risk of bleeding, necessitating the appropriate use of antiplatelet agents based on ischemic and bleeding risks. Therefore, a systematic literature review was conducted to determine the optimal duration of DAPT in patients with ACS and whether extending DAPT beyond 12 months in high-risk ischemic patients could reduce ischemic risks.

Rating the quality of evidence
A total of 21 supporting references from existing guidelines, 48 selected references from recent systematic literature reviews, and 4,753 references from electronic databases were reviewed. Based on the predefined literature selection criteria, 2 independent reviewers prioritized related references included in the existing guidelines (n=2), followed by references from previous systematic reviews (n=3) and newly published literature. Finally, 5 RCTs were selected. Among the 5 selected studies (n=38,802), 2 were from the United States, 2 from Europe, and 1 from Korea. The publications ranged from 2001 to 2019. Of the selected studies, 4 addressed KQ 6-1, and 1 addressed KQ 6-2. For KQ 6-1, the studies were divided into 2 groups based on different comparison groups. Confidence in the evidence for key outcomes, including all-cause mortality, cardiovascular mortality, MI, MACCE, major bleeding, and important outcomes such as net adverse cardiac events (NACE), stent thrombosis, stroke, and total bleeding, was assessed using the GRADE evaluation tool.

KQ 6-1-1. Patients with acute coronary syndrome: dual antiplatelet therapy versus aspirin monotherapy

In 1 RCT comparing clopidogrel plus aspirin with placebo plus aspirin in patients with ACS, clopidogrel use did not show a significant difference in cardiovascular death or stroke risk compared with placebo. However, clopidogrel use significantly reduced the risk of MI (RR, 0.78, 95% CI, 0.68–0.90) but increased the risk of major bleeding (RR, 1.38, 95% CI, 1.13–1.67) and total bleeding (RR, 1.69, 95% CI, 1.48–1.94). The study did not report all-cause mortality, MACCE, NACE, or stent thrombosis. The overall LOE for this key question is 'Moderate.' The detailed process is provided in the **Supplementary Data 8**.

KQ 6-1-2. Patients with acute coronary syndrome: 12-month dual antiplatelet therapy versus short-term (3–6 months) dual antiplatelet therapy followed by aspirin monotherapy

Based on 3 RCTs comparing 12-month DAPT with 3–6 months of DAPT followed by aspirin monotherapy in patients with ACS, the meta-analysis showed no significant difference in all-cause mortality, cardiovascular mortality, MI, MACCE, major bleeding, stroke, NACE, or stent thrombosis between the 2 groups. However, 12-month DAPT was associated with a 38% increase in all-cause of bleeding risk (RR, 1.38, 95% CI, 1.00–1.90). The overall LOE for this key question is confirmed as 'Very Low' due to the lowest LOE among the critical outcomes. The detailed process is provided in the **Supplementary Data 8**.

KQ 6-2. High-risk ischemic patients with Acute coronary syndrome: aspirin plus ticagrelor versus aspirin monotherapy

In 1 RCT conducted over a period of 12–36 months in high-risk ischemic patients with ACS, the combination of ticagrelor and aspirin was found to significantly decrease the risks of MI (RR, 0.83, 95% CI, 0.73–0.95), MACCE (RR, 0.85, 95% CI, 0.77–0.94), and stroke (RR, 0.78, 95% CI, 0.63–0.98), but significantly increased the risk of major bleeding (RR, 2.25, 95% CI, 1.68–3.01) as compared with the placebo and aspirin. This study did not report any all-cause bleeding, NACE, or stent thrombosis. The overall LOE for this key question was confirmed to

be 'Moderate' because it had the lowest LOE among the key outcomes. The detailed process is provided in the **Supplementary Data 8**.

Recommendations development process
Compared with aspirin monotherapy, DAPT increases the risk of bleeding regardless of treatment duration. The clinical benefits of 12-month DAPT in patients with ACS, including a reduction in MI, outweigh the increased risks of bleeding. In high-risk ischemic patients with low bleeding risk, 1 study showed that extended DAPT administration beyond 12 months increased major bleeding but reduced the risks of MI, MACCE, and stroke. This finding supports a weak recommendation for extended use, although further research is required (**Table 6**, **Figure 4**). Both the 2023 ESC and 2021 ACC/AHA guidelines, similarly with our recommendation, recommended 12-month DAPT in patients with ACS (Class I). The ESC guidelines rated the evidence level as A,[17] whereas the ACC/AHA guidelines rated it as B–R

Table 6. Recommendations for anti-platelet therapy

Key question	Recommendation	Strength of recommendation	Level of evidence
DAPT	DAPT consisting of aspirin and P2Y$_{12}$ receptor inhibitor recommended for patients with ACS to prevent ischemic events during 12 months.	Strong	Moderate
	Extended use of DAPT (>12 months) may be considered for patients with ACS with high ischemic risk and low bleeding risk.	Weak	Moderate
	[Clinical considerations]		
	1. Since the use of DAPT increases the risk for bleeding, the assessment of bleeding risk is required. High bleeding risk is defined as PRECISE DAPT score ≥25 or meeting the ARC-HBR criteria.		
	2. High ischemic risk is defined as follows. More than 12 months of DAPT may be considered for patients with these risk factors with a low bleeding risk.		
	- Age ≥65 years		
	- Diabetes mellitus		
	- Recurrence of MI		
	- Multi-vessel disease		
	- Chronic kidney disease		
De-escalation of DAPT	De-escalation of DAPT may be considered for event-free patients with ACS after 1–3 months of onset.	Weak	Moderate
	[Clinical considerations]		
	1. The DAPT de-escalation strategy is as follows.		
	1) Switching from potent P2Y$_{12}$ receptor inhibitors to clopidogrel.		
	2) Reducing the dose of prasugrel from 10 mg to 5 mg.		
	3) P2Y$_{12}$ receptor inhibitor monotherapy with early discontinuation of aspirin.		
	2. Aspirin monotherapy with early discontinuation P2Y$_{12}$ receptor inhibitor is not included.		
DAPT + PPI	Addition of proton pump inhibitor to DAPT may be considered for patients with ACS at risk of gastrointestinal bleeding.	Weak	Very Low
	[Clinical considerations]		
	Conditions with anticipated risk for gastrointestinal bleeding:		
	1. History of gastrointestinal bleeding or ulcer		
	2. Concurrent use of anticoagulants		
	3. Current use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroids		
	4. Having 2 out of following:		
	- Age ≥65 years		
	- Indigestion		
	- GERD		
	- *Helicobacter pylori* infection		
	- Chronic alcohol drinker		
Anti-thrombotic therapy	Dual antithrombotic therapy (NOAC + P2Y$_{12}$ receptor inhibitor) may be preferentially considered for patients with ACS with high bleeding risk with indication for chronic oral anticoagulants.	Weak	Very Low
	[Clinical considerations]		
	Compared to triple therapy (warfarin + P2Y$_{12}$ receptor inhibitor + aspirin), dual antithrombotic therapy (NOAC + P2Y$_{12}$ receptor inhibitor) may be considered first in terms of lowering bleeding risk.		

ACS = acute coronary syndrome; ARC-HBR = Academic Research Consortium for High Bleeding Risk; DAPT = dual antiplatelet therapy; GERD = gastroesophageal reflux disease; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulants; PPI = proton pump inhibitor; PRECISE DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy.
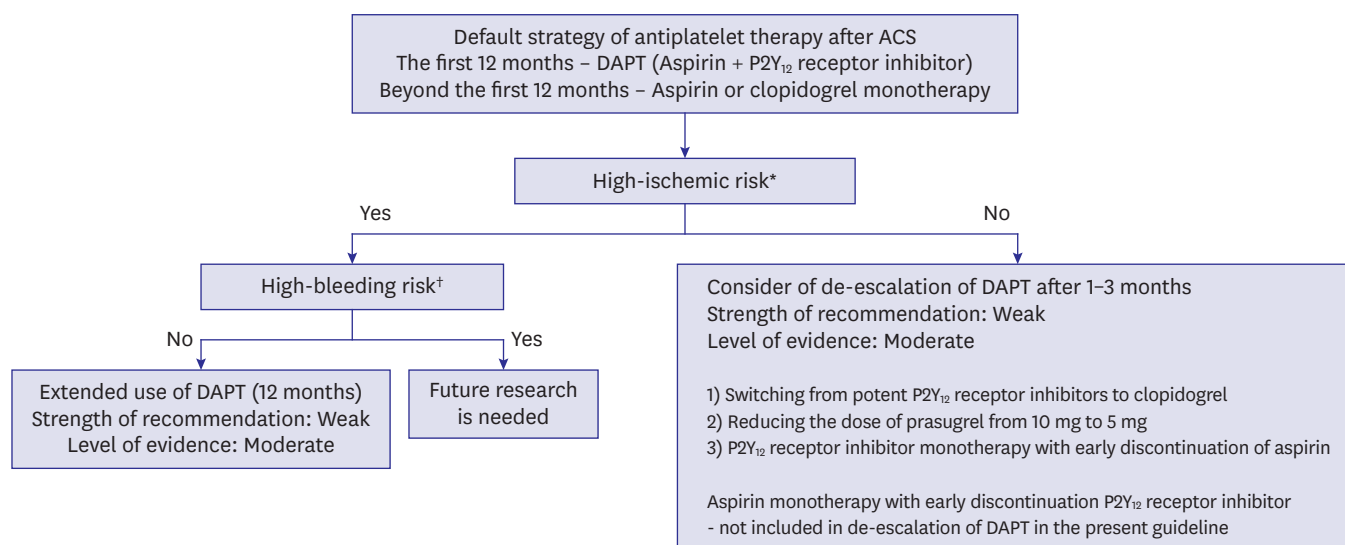
Figure 4. Dual antiplatelet therapy strategies in patients with ACS.
ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; PRECISE DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; ARC-HBR = Academic Research Consortium for High Bleeding Risk.
*High ischemic risk patients refer to patients with age ≥65 years, diabetes mellitus, recurrence of myocardial infarction, multi-vessel disease, and chronic kidney disease, but there may be changed regarding to the clinical situation.
†High bleeding risk is defined as PRECISE DAPT score ≥25 or meeting the ARC-HBR criteria.

(moderate-quality evidence from RCTs).[43] For extended administration of DAPT in high-risk ischemic patients with ACS, the ESC guidelines recommended Class IIa, and the ACC/AHA guidelines recommended Class IIb, both with an evidence level of A.

Evidence gaps and future research suggestions
Recent advancements in stents and techniques used in interventional procedures, along with an increasing emphasis on bleeding risks, have led to numerous studies exploring $P2Y_{12}$ receptor inhibitor monotherapy after discontinuing aspirin (refer to KQ 7). Considering that most studies included in this guideline were conducted in Western populations, and that Asians, including Koreans, have a relatively higher bleeding risk than ischemic risk, it would be beneficial to conduct well-designed studies on Korean patients.[44] Additionally, with the growing use of more potent $P2Y_{12}$ receptor inhibitors such as prasugrel and ticagrelor in patients with ACS, there is an increased risk of bleeding. Therefore, future studies should focus on evaluating the utility of personalized antiplatelet therapy based on individual bleeding, ischemic risks, and genetic clopidogrel resistance.

KQ 7. De-escalation of dual antiplatelet therapy
Backgrounds
In patients with ACS, major bleeding events are known to impact mortality over 1 year as significantly as recurrent MI.[45] Non-access site bleeding accounts for 60–70% of all bleeding events and increases the mortality rate by approximately 4 times compared to cases without bleeding.[46] Notably, East Asians, including Koreans, have been reported to have a lower risk of ischemia but a higher risk of bleeding than other ethnicities.[47] Therefore, efforts to reduce bleeding events in Korean patients with ACS are crucial.

The risks of ischemic and bleeding events tend to change dynamically over time following revascularization. The risk of bleeding gradually decreases over time, whereas the risk of

ischemic events drops sharply within the first 1–3 months post-procedure.[48] This dynamic risk profile forms the basis for considering a stepwise de-escalation strategy in DAPT.

Rating the quality of evidence
To identify the primary studies relevant to this key question, 11 supporting references from existing guidelines, 61 selected references from recent systematic literature reviews, and 4,753 references from electronic databases were reviewed. Based on predefined literature selection criteria, 2 independent reviewers prioritized the related references included in the existing guidelines (n=4), followed by references from previous systematic reviews (n=4) and newly published literature (n=1). A total of 9 RCTs were selected. Among the 9 selected studies (n=15,021), 5 were from European countries, and 4 were from Korea, with publications ranging from 2016 to 2021. Six studies focused on patients with AMI who underwent PCI, and the remaining 3 studies focused on patients with ACS.

A meta-analysis of 9 RCTs comparing conventional DAPT with a stepwise de-escalation strategy in patients with ACS showed no significant differences in the risks of all-cause mortality, cardiovascular mortality, MI, stroke, or stent thrombosis between the 2 strategies. However, the stepwise de-escalation strategy significantly reduced the risk of all-cause bleeding by 32% (RR, 0.68, 95% CI, 0.60–0.76, I^2=74%), major bleeding by 28% (RR, 0.72, 95% CI, 0.56–0.94), MACCE by 20% (RR, 0.80, 95% CI, 0.68–0.96), and NACE by 26% (RR, 0.74, 95% CI, 0.66–0.82, I^2=65%). The confidence LOE for the critical outcomes, including all-cause mortality, cardiovascular mortality, MI, major bleeding, MACCE, important outcomes such as all-cause bleeding, NACE, stroke, and stent thrombosis, was assessed using the GRADE evaluation tool. The overall LOE for this key question, based on the lowest LOE among the key outcomes, was evaluated as 'Moderate.' The detailed process is provided in the **Supplementary Data 9**.

Recommendations development process
The 2021 ACC/AHA and 2023 ESC guidelines recommended a stepwise de-escalation strategy, that involves discontinuing aspirin early and continuing $P2Y_{12}$ receptor inhibitor monotherapy after 1–3 months of DAPT, as Class IIa (moderate recommendation, ACC/AHA; weight of evidence favors usefulness/efficacy).[17][43] Both guidelines rated the LOE as A, based on 3–4 RCTs. The 2023 ESC guidelines evaluate the strategy of switching from stronger $P2Y_{12}$ receptor inhibitors such as prasugrel or ticagrelor to clopidogrel based on RCTs with an evidence level of A, but considered a Class IIb recommendation, which is a weaker recommendation.[17]

In this guideline, we discussed whether to issue a stronger recommendation than the European and American guidelines, based on the Korean RCTs published after the 2020 European guidelines, such as the 'TicAgrelor Versus CLOpidogrel in Stabilized Patients With Acute Myocardial Infarction' (TALOS-AMI) trial which involved unguided switching from ticagrelor to clopidogrel after 1 month[49] and the 'Harmonizing Optimal Strategy for Treatment of coronary artery diseases – comparison of REDUCtion of prasugrEl dose or POLYmer TECHnology in ACS patients' (HOST-REDUCE-POLYTECH ACS) trial which involved unguided reducing prasugrel dosage from 10 mg to 5 mg after 1 month.[50] In the present analysis of this guideline, 50% of studies were conducted in Korea, revealing that the benefits in terms of bleeding events, MACCE, and NACE were more pronounced in Korean patients than European studies. However, the development committee decided that the evidence was insufficient to recommend the strategy uniformly for all patients, because of

the lack of studies on high-risk patients with ischemia. Thus the recommendation grade was weak (**Table 6**, **Figure 4**).

Evidence gaps and future research suggestions
The HOST-REDUCE-POLYTECH ACS, 'Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome' (TICO), and TALOS-AMI trials presented subgroup analysis results for patients with high-risk ischemic factors or complex lesion procedures.[51-54] The TICO study defined high-risk ischemic factors as the insertion of 3 or more stents, total stent length of 60 mm or more, left main coronary artery lesions, chronic total occlusion lesions, bifurcation lesions, diabetes mellitus, and chronic kidney disease. There was no significant difference in MACCE occurrence between ticagrelor monotherapy after 3 months and conventional DAPT.[52] The HOST-REDUCE-POLYTECH ACS study analyzed patients with high-risk procedural factors (3 or more stents, 3 or more lesions, left main coronary artery, bifurcation lesions, severe calcification, stent length of 60 mm or more) and found no difference in MACCE occurrence between the group with reduced-dose prasugrel after 1 month and the group that continued the standard dose during 1 year.[53] The TALOS-AMI study compared de-escalation to clopidogrel with ticagrelor-based DAPT among patients with high ischemic risk (history of diabetes or chronic kidney disease, multivessel PCI, at least 3 lesions treated, total stent length greater than 60 mm, at least 3 stents implanted, left main PCI, or bifurcation PCI with at least 2 stents). There was no difference in a composite of cardiovascular death, MI, ischemic stroke, ischemia-driven revascularization, or stent thrombosis during 1 year.[54]

Meta-analysis studies and RCTs conducted in Korea have consistently shown that a stepwise de-escalation strategy for DAPT reduced bleeding events without increasing MACCE. However, there may have been high-risk ischemic patient groups that were not included in these RCTs. Further studies are required to address this high-risk patient group.

KQ 8. Proton pump inhibitor with dual antiplatelet therapy
Backgrounds
DAPT using aspirin and $P2Y_{12}$ receptor inhibitors significantly increases the risk of gastrointestinal (GI) bleeding in patients with ACS.[55] Proton pump inhibitor (PPI) is known to reduce the risk of GI bleeding by inhibiting gastric acid secretion when used long-term with antiplatelet agents such as aspirin in patients at risk for GI bleeding.[56] However, clopidogrel requires 2 oxidation steps via cytochrome P450 system in the liver to become active, and PPI also metabolize through the cytochrome system, particularly by inhibiting the CYP2C19 enzyme that primarily activates clopidogrel. This interaction may reduce the effectiveness of clopidogrel and increase MACCE.[57] Therefore, a systematic review was conducted to determine whether the addition of PPI to DAPT in patients with ACS can reduce the risk of GI bleeding without increasing MACCE.

Rating the quality of evidence
We reviewed 5 supporting documents from existing guidelines and identified 799 articles through an updated literature search. Based on the predefined selection criteria, 2 reviewers independently performed the screening and selection processes. Priority was given to the relevant literature included in the existing guidelines (n=1); however, no additional relevant systematic review articles were found during the latest search and no newly published articles were identified. Therefore, only 1 RCT was finally selected.[58] The final selected RCT (n=3,761) is the 'Clopidogrel and the Optimization of Gastrointestinal Events Trial' (COGENT) study,

which reported the clinical effects of adding omeprazole to conventional DAPT in patients with coronary artery disease. Hence, this study also included patients with chronic coronary syndrome (CCS) rather than exclusively focusing on patients with ACS.

The addition of omeprazole to conventional DAPT significantly reduced the risk of overall GI bleeding and upper GI bleeding compared with conventional DAPT alone (hazard ratio [HR], 0.34, 95% CI, 0.18–0.63; HR, 0.13, 95% CI, 0.03–0.56, respectively). However, there were no significant differences in the risks of MACCE, all-cause mortality, MI, stroke, or severe complications. Confidence in the effect estimates for critical outcomes, such as bleeding, all-cause mortality, cardiovascular mortality, and MACCE, and important outcomes, such as MI, stroke, NACE, and stent thrombosis, were evaluated using the GRADE tool. The overall LOE for this key question, based on the lowest LOE among the key outcomes, was determined to be 'Very Low.' The detailed process is provided in the **Supplementary Data 10**.

Recommendations development process
The COGENT study demonstrated that the addition of a PPI significantly reduced the risk of overall and upper GI bleeding when used alongside DAPT. Despite concerns that omeprazole might increase ischemic risk owing to its strong interactions with CYP2C19, the COGENT study did not find a significant increase in MACCE. However, it is important to note that this study was terminated early, with only 3,761 participants and a 6-month observation period, which aimed for 5,000 participants over a 1–2-year period. Therefore, the possibility of a significant difference in MACCE during the intended observation period cannot be completely excluded. Long-term PPI use is associated with hypomagnesemia and an increased risk of osteoporosis-related fractures, especially with high doses over a year.[59] Considering these findings, it is reasonable to add a PPI for patients with ACS on DAPT who are at risk of GI bleeding, balancing the benefits and potential risks.

The 2023 ESC guidelines strongly recommended the addition of a PPI with DAPT for patients with ACS at high risk of GI bleeding based on the COGENT trial and the 'PROlonging Dual-antiplatelet treatment after Grading stent-induced Intimal hYperplasia study' (PRODIGY) sub-analysis.[17][60] These studies primarily focused on the absence of increased ischemic events rather than bleeding reduction. The development committee agreed not to issue a strong recommendation as the ESC did, because of the lack of robust evidence.

Evidence gaps and future research suggestions
A recent study of 8,163 Korean patients reported that 61% exhibited a loss-of-function allele in the CYP2C19 gene, significantly increasing the risk of cardiovascular death, MI, and stent thrombosis, particularly in patients with ACS.[61] This suggests that a decrease in CYP2C19 activity due to PPI administration could potentially increase MACCE. More RCTs focusing on patients with ACS are needed to provide stronger evidence for our recommendations, especially considering the higher frequency of MACCE in these patients than those with CCS. Further research on the effects of PPIs on antiplatelet efficacy in patients with CYP2C19 loss-of-function alleles and subsequent clinical outcomes is necessary.

KQ 9. Anti-thrombotic therapy in patients requiring oral anticoagulation
Backgrounds
Chronic oral anticoagulation is indicated in approximately 7–10% of patients with ACS, predominantly owing to coexisting atrial fibrillation.[17] The risk profiles for ischemic and bleeding events evolve dynamically over time following interventional procedures. The risk

of bleeding gradually increased over time, whereas that of ischemic events sharply decreased after 1–3 months. Hence, dual antithrombotic therapy (DAT) might be considered instead of triple antithrombotic therapy (TAT) or DAPT without oral anticoagulation. The 'What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing' (WOEST) study was the first to compare the safety and efficacy of DAT with TAT in patients undergoing PCI who required chronic oral anticoagulation. The study revealed that DAT significantly reduced bleeding events by 64% compared to TAT without increasing the risk of death, MI, revascularization, stroke, or stent thrombosis.[62]

Unlike previously used vitamin K antagonists such as warfarin, non-vitamin K antagonist oral anticoagulants (NOACs) offer the advantages of rapid onset and shorter half-life. They also exhibit fewer drug interactions, thus potentially offering a safer alternative to warfarin. Therefore, this systematic review was conducted to evaluate the safety of NOAC-based DAT in patients with ACS who required chronic oral anticoagulation.

Rating the quality of evidence
We reviewed 8 supportive documents from existing guidelines, 15 selected from recent systematic reviews, and 3,530 additional records identified through electronic databases. Based on predefined criteria and independent screening by 2 reviewers, we selected 2 supportive documents from existing guidelines and 2 from systematic reviews, culminating in a total of 4 RCTs for final inclusion.[63-66] The 4 included RCTs (n=8,676) were conducted between 2016 and 2019. One study was conducted in Europe, 2 were conducted jointly in Europe and the United States, and 1 included patients worldwide.

A meta-analysis of the 4 RCTs comparing DAT with TAT in the included patient population showed that DAT significantly reduced the risk of major bleeding events by 30% (RR, 0.70, 95% CI, 0.59–0.83). No significant differences were observed in other key outcomes including all-cause mortality, cardiovascular mortality, stroke, MI, and MACCE. DAT also significantly reduced the risk of overall bleeding events by 37% (RR, 0.63, 95% CI, 0.58–0.69) compared with TAT, with no difference in stent thrombosis risk. Confidence in the effect estimates for critical outcomes, such as all-cause death, cardiovascular death, stroke, major bleeding, MI, and MACCE, and important outcomes, such as NACE, bleeding, and stent thrombosis, was evaluated using the GRADE tool. The overall level of LOE for this key question, based on the lowest confidence level for the key outcomes, was determined to be 'Very Low.' The detailed process is provided in the **Supplementary Data 11**.

Recommendations development process
The meta-analysis included 4 RCTs, which also included patients with CCS, owing to the lack of RCTs that solely targeted patients with ACS. DAT offers significant reductions in bleeding events compared with TAT owing to the absence of aspirin and the safety profile of NOACs compared with warfarin. Although evidence for reducing the recurrence of major ischemic events is still limited, the overall assessment suggests that DAT presents more benefits than risks when compared with TAT. Considering the need for more robust evidence, the recommendation strength is considered weak.

Evidence gaps and future research suggestions
The NICE guidelines emphasize that long-term TAT increases bleeding risk but do not clearly define when aspirin is stopped. The 2023 ESC guidelines recommended switching to DAT after 1 week of TAT (Class I, LOE: A) based on the results of previous RCTs.[62-66] However, these

studies did not specifically target patients with ACS. Clinical studies specifically targeting patients requiring chronic oral anticoagulant therapy are needed. Although DAT reduces bleeding risk compared to TAT, there are concerns about increased ischemic risk, such as MI and stent thrombosis. The WOEST-3 trial (NCT04436978) enrolled patients with atrial fibrillation who underwent PCI and randomized within 72 hours after PCI to guideline-directed therapy (edoxaban plus P2Y$_{12}$ receptor inhibitor plus limited duration of aspirin) or a 30-days DAPT strategy (P2Y$_{12}$ receptor inhibitor plus aspirin, immediately discontinued edoxaban) followed by DAT (edoxaban plus P2Y$_{12}$ receptor inhibitor) with a sample size of 2,000 patients.[67]

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
List of guideline development committee and declarations conflict of interest

Supplementary Data 2
Detailed guideline scope

Supplementary Data 3
KQ 1. Statin

Supplementary Data 4
KQ 2. Non-statin low-density lipoprotein cholesterol-lowering agents added to statin

Supplementary Data 5
KQ 3. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Supplementary Data 6
KQ 4. Mineralocorticoid receptor antagonist

Supplementary Data 7
KQ 5. Beta blocker

Supplementary Data 8
KQ 6. Dual antiplatelet therapy

Supplementary Data 9
KQ 7. De-escalation of dual antiplatelet therapy

Supplementary Data 10
KQ 8. Proton pump inhibitor with dual antiplatelet therapy

Supplementary Data 11
KQ 9. Anti-thrombotic therapy in patients requiring oral anticoagulation

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