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Consensus Opinion

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Lipid Management for Secondary Prevention in Atherosclerotic Cardiovascular Disease: A Scoping Review and Scientific Report

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Atherosclerotic cardiovascular disease (ASCVD) is associated with a very high risk of secondary cardiovascular events. Elevated low-density lipoprotein cholesterol (LDL-C) is a major determinant in the progression of ASCVD and in the onset of associated adverse events. Consequently, rigorous control of LDL-C is a cornerstone of secondary prevention strategies, typically achieved through statin therapy, either as monotherapy or in combination with ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors. Recent large-scale clinical trials have demonstrated that intensive LDL-C lowering significantly reduces cardiovascular risk, leading to updated guidelines in the United States and Europe that advocate for more aggressive LDL-C treatment targets for secondary prevention in ASCVD. In this context, a working group established in the Japan Atherosclerosis Society performed a scoping review of LDL-C treatment targets for the secondary prevention of ASCVD. The working group systematically reviewed the available evidence for coronary artery disease (including acute and chronic coronary syndrome), atherothrombotic brain infarction, and peripheral artery disease, all of which are defined as ASCVD. The aim was to assess the evidence-based LDL-C treatment targets for the secondary prevention of defined ASCVD in Japanese patients.

Key words: **Atherosclerotic cardiovascular disease, Low-density lipoprotein cholesterol, Secondary prevention, Statin therapy, Japan Atherosclerosis Society**

Introduction

Atherosclerotic cardiovascular disease (ASCVD) encompasses coronary artery disease (CAD) (including acute coronary syndrome [ACS] and chronic coronary syndrome [CCS]), atherothrombotic brain infarction (ATBI), and peripheral artery disease (PAD)[1]. Elevated low-density lipoprotein cholesterol (LDL-C) plays a critical role in the progression of ASCVD and in the onset of secondary cardiovascular events[2, 3]. Therefore, LDL-C management is essential for reducing the risk of secondary cardiovascular events in patients with ASCVD. Lowering of LDL-C is achieved using high-intensity statin therapy, with or without ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. The efficacy of these LDL-C-lowering therapies has been demonstrated in several recent large-scale clinical trials[2].

Based on the results of these trials, strict LDL-C treatment targets have been proposed in recent guidelines for the secondary prevention of ASCVD. The 2022 American College of Cardiology (ACC) Expert Consensus Decision Pathway recommends LDL-C reduction of ≥ 50% from baseline and an LDL-C treatment target of <70 mg/dL for high-risk patients. For very high-risk patients, an LDL-C reduction of ≥ 50% from baseline and an LDL-C treatment target of <55 mg/dL are recommended[2]. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines classify all patients with ASCVD as being at a very high risk and recommend LDL-C reduction of ≥ 50% from baseline with an LDL-C treatment target of <55 mg/dL for secondary prevention[4], whereas the 2022 Japan Atherosclerosis Society (JAS) guidelines proposed an LDL-C treatment target of <100 mg/dL for patients with CAD and <70 mg/dL for high-risk patients with CAD who have ACS, familial hypercholesterolemia (FH), diabetes, or ATBI[5]. The target values for primary prevention population were determined based on the risk score from the Hisayama study[6], while those for secondary prevention population were set based on previous JAS guidelines and a review of the updated evidence.

The prevalence of some risk factors and the incidence of cardiovascular events has been considered to be generally lower in Asian countries, particularly East Asian countries, than in Western countries[7]. At the same time, the risk of cardiovascular events is substantially different even among East Asian countries[8]. Therefore, the existing LDL-C treatment targets for ASCVD in Japan are somewhat less strict than those in Western countries. However, CAD risk factors have increased in Japan, particularly in urban areas, over recent decades[9]. For instance, a recent large-scale trial involving patients with ASCVD showed that the incidence of the primary endpoint (i.e., the composite of cardiovascular death, myocardial infarction [MI], stroke, hospitalization for unstable angina, or coronary revascularization) was comparable between the Asian and non-Asian populations in the placebo arm[10].

In general, setting the LDL-C treatment targets for secondary prevention of ASCVD is challenging when based solely on evidence from Japanese patients. In addition, previous guidelines did not clearly define each category of ASCVD, and the scope of its secondary prevention was still unclear[5]. Herein, a working group organized within the JAS newly defined each category of ASCVD and performed a scoping review to assess the LDL-C treatment targets for the secondary prevention of defined ASCVD, based on the recent clinical evidence.

Methods

The working group consisted of 23 cardiovascular, cerebrovascular, endocrine, and kidney experts who were appointed to evaluate evidence on LDL-C management for secondary ASCVD prevention. The working group conducted a two-stage literature search for evidence on secondary ASCVD prevention **(Supplementary Table 1)**. The primary search was a broad search to identify clinical studies evaluating lipid lowering in ASCVD. Based on the findings of the primary search, the group held its first meeting in September 2023 to select the clinical questions (CQs) to be evaluated. For the secondary search, the group used the "Population, Intervention, Comparison, Outcome" model to structure the CQs for each of CAD, ATBI, and PAD.

This time, to build a consensus opinion, the working group conducted a scoping review with systematic literature searching and evaluated the level of evidence of the identified studies based on the criteria shown in **Table 1** [1, 11, 12]. Then, the working group assessed the LDL-C treatment targets for secondary prevention of ASCVD based on the extracted evidence.

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Table 1. Evidence levels[1, 11, 12]

Evidence Level	Definition
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Data derived from small non-randomized studies, retrospective studies, registries, or expert consensus or opinion

Table 2. ASCVD definitions used in this report

ASCVD	Definition
CAD	
ACS	Within 1 year after ACS event
CCS	≥ 1 year after ACS event or stable CAD (including coronary revascularization) *
ATBI	Cerebral infarction caused by >50% stenosis in the intracranial/carotid arteries (or cerebral infarction with aortic arch atheroma with a maximal thickness of ≥ 4.0 mm)
PAD	Symptomatic lower-extremity artery disease

*Excludes coronary spastic angina and coronary microvascular dysfunction.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; ATBI, atherothrombotic brain infarction; CAD, coronary artery disease; CCS, chronic coronary syndrome; PAD, peripheral artery disease.

Definition of ASCVD

The working group defined each category of ASCVD, including CAD (ACS and CCS), ATBI, and PAD, as shown in **Table 2**. ACS was defined as occurring within 1 year of onset in some large clinical trials such as ODYSSEY OUTCOMES[13] and FOURIER[14]. The working group similarly defined ACS, also in accordance with the 2022 Japanese Circulation Society (JCS) guideline focused update on the diagnosis and treatment of patients with stable CAD[12], and the 2025 ACC/AHA Guideline for the Management of Patients With Acute Coronary Syndromes[15]. Patients with CCS were defined as those who had experienced an ACS event at least 1 year previously or who had stable CAD (or had undergone coronary revascularization). Coronary spastic angina and coronary microvascular dysfunction were excluded from consideration owing to insufficient evidence. Regarding ATBI, although ischemic stroke is mostly classified into five clinical subtypes (large artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology), for our purposes, ATBI was defined as ischemic stroke attributable to >50% stenosis in the intracranial/carotid arteries (or ischemic stroke with aortic arch atheroma with a maximal thickness of ≥ 4.0 mm) in line with the JAS guidelines for prevention of ASCVD 2022[5], based on the TOAST classification of large artery atherosclerosis[16]. Cardioembolism, small-vessel occlusion, stroke of other determined etiology, stroke of undetermined etiology, and transient ischemic attack (TIA) were excluded from consideration owing to insufficient evidence. PAD, also known as lower-extremity artery disease, included chronic limb-threatening ischemia with rest pain/ulceration and symptomatic PAD with intermittent claudication (IC). Asymptomatic PAD was excluded from consideration owing to insufficient evidence.

The statin doses approved in Japan differ from those approved elsewhere. Therefore, high-intensity statin therapy in the context of this report is defined in **Table 3**. The PCSK9 inhibitors approved in Japan as of March 2025 were the monoclonal antibody evolocumab and the siRNA agent inclisiran.

Results

Through discussion at consensus meetings, the working group established eight CQs **(Table 4)**. Two CQs were established for each ASCVD, with one question designed to evaluate if statin therapy is beneficial for the condition and the other designed to assess the LDL-C treatment target for the condition.

Assessment of LDL-C treatment targets for secondary prevention in ASCVD

The working group reviewed the current evidence for each category of ASCVD and assessed LDL-C treatment targets for secondary prevention in each category **(Table 5)**. The following sections describe each category in detail.

Table 3. Definitions of high-intensity statins in Japanese clinical practice

Statin	Intensity
Rosuvastatin	10–20 mg/day
Atorvastatin*	20 mg/day
Pitavastatin	4 mg/day

The AHA/ACC definition of high-intensity statins includes 20–40 mg rosuvastatin and 40–80 mg/day atorvastatin[1]. In contrast, the ESC defined statin doses that reduce LDL-C by ≥ 50% as high-intensity statins[11]. The working group defined statin doses that would lower LDL-C in Japanese patients by the ESC criterion of ≥ 50% as high-intensity statins in Japanese clinical practice.
*Atorvastatin is approved at doses up to 40 mg/day for FH in Japan.
ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; JAS, Japan Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol.

Table 4. CQs addressing LDL-C management for secondary ASCVD prevention

CQ1	Is the early initiation of high-intensity statin therapy beneficial for lipid management in patients with ACS?
CQ2	Is the LDL-C treatment target of <55 mg/dL beneficial in patients with ACS?
CQ3	Is high-intensity statin therapy beneficial for lipid management in patients with CCS?
CQ4	Is the LDL-C treatment target of <70 mg/dL beneficial in patients with CCS?
CQ5	Is statin therapy beneficial for lipid management in patients with ATBI?
CQ6	Is the LDL-C treatment target of <70 mg/dL beneficial in patients with ATBI?
CQ7	Is high-intensity statin therapy beneficial for lipid management in patients with PAD?
CQ8	Is the LDL-C treatment target of <70 mg/dL beneficial in patients with PAD?

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; ATBI, atherothrombotic brain infarction; CCS, chronic coronary syndrome; CQ, clinical question; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease.

Table 5. Summary of LDL-C treatment targets (mg/dL) for secondary prevention of ASCVD

ASCVD		Japan			Asia	US	Europe
		This report	JAS[5]	Others			
CAD	ACS[a]	<55	<70			ACC[2] ACC/AHA[15] <70 (<55)	ESC[11] <55
	CCS[b]	<70[c]	<100 (<70)	JCS[12] <70	APSC[60] <70 (<55)	ACC[2] <70 (<55)	ESC/EAS[4] <55
ATBI[d]		<70	<100 (<70)	JSS[e, 93] <100 (<70)		AHA/ASA[e, 87] <100 (<70)	ESO[92] <55
PAD[f]		<70	<120 (<100)			ACC/AHA[117] <70	EAS/ESVM[119] <55

Numbers in parentheses are LDL-C treatment targets under special conditions (see the manuscript body, relevant guidelines, and other documents for details).
[a] Within 1 year after ACS event (definition in this report)
[b] ≥ 1 year after ACS event or stable CAD* (or coronary revascularization) (definition in this report)
*Excludes coronary spastic angina and coronary microvascular dysfunction
[c] <55 mg/dL for patients with FH, history of ≥ 2 ACS events, multivessel CAD with prior ACS event, or co-existing ATBI or PAD
[d] Cerebral infarction attributable to >50% stenosis in the intracranial/carotid arteries (or cerebral infarction with aortic arch atheroma with a maximal thickness of ≥ 4.0 mm) (definition in this report)
[e] Includes TIA
[f] Symptomatic lower-extremity artery disease (definition in this report)
ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; APSC, Asian Pacific Society of Cardiology; ASA, American Stroke Association; ASCVD, atherosclerotic cardiovascular disease; ATBI, atherothrombotic brain infarction; CAD, coronary artery disease; CCS, chronic coronary syndrome; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; ESO, European Stroke Organisation; ESVM, European Society of Vascular Medicine; JAS, Japan Atherosclerosis Society; JCS, Japanese Circulation Society; JSS, Japan Stroke Society; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; TIA, transient ischemic attack.

1. Acute Coronary Syndrome

CQ1 Is the early initiation of high-intensity statin therapy beneficial for lipid management in patients with ACS?

Early initiation of high-intensity statin therapy is beneficial for lipid management in patients with ACS.

(Evidence Level: A)

Summary

• The risk of vascular events is very high in the early phase after ACS. Considerable evidence shows that the early initiation of high-intensity statin therapy is beneficial for reducing the secondary cardiovascular event risk after ACS.

• Early initiation of high-intensity statin therapy is recommended in the 2022 JAS guidelines, because LDL-C may temporarily decrease after ACS onset.

• Patients who respond insufficiently to high-intensity statin therapy have been shown to benefit from the addition of ezetimibe or a PCSK9 inhibitor started in the early stage of ACS, including during hospitalization.

• The working group supports the early initiation of high-intensity statin therapy, with or without ezetimibe or a PCSK9 inhibitor as necessary, in patients with ACS.

■ *Early Recurrence Risk in Patients with ACS and Lipid Management Strategies*

The working group defined patients with ACS as those who had experienced acute MI (AMI) or unstable angina within 1 year. Patients with ACS are at a high risk of recurrence during the period soon after the index event. For instance, a study conducted in the United States evaluating post-discharge early recurrence of MI after the index AMI showed that the 90-day probability of re-admission with recurrent MI was 2.5%, with most of the affected patients developing recurrence within 2 weeks of discharge[17]. Moreover, in patients in the Korea Acute Myocardial Infarction Registry with an index AMI who underwent percutaneous coronary intervention (PCI), the incidence of recurrent AMI was 3.6%, with 19.8% of the affected patients having recurrence within 30 days[18]. The PACIFIC study, a multicenter registry observational study of patients with ACS, showed a high incidence of fatal and non-fatal MI (>35/1,000 person-years), and cardiovascular event risk increased early after the onset of ACS[19]. Although some cases of recurrent AMI are caused by stent thrombosis, early LDL-C management is still considered important for plaque stabilization.

Existing guidelines include recommendations for when to start therapy for ACS. The 2018 ESC/EAS guidelines for the management of dyslipidemias recommend starting therapy for the index ACS during the first 1–4 days of hospitalization[4, 20]. The 2023 ESC guidelines for the management of ACS recommend starting high-intensity statin therapy during hospitalization and propose adding ezetimibe or a PCSK9 inhibitor for patients already receiving a high-intensity statin[11]. Moreover, the 2022 JAS guidelines recommend the early initiation of high-intensity statin therapy regardless of the baseline LDL-C level, on the basis that LDL-C may temporarily decrease after ACS onset[5].

■ *Evidence Supporting Early Intervention with LDL-C-Lowering Therapy*

● Evidence Supporting High-Intensity Statin Therapy

The benefits of high-intensity statin therapy for ACS have been demonstrated in several studies. A meta-analysis of 16 randomized controlled trials (RCTs) involving 26,497 patients with ACS showed that high-intensity statin therapy significantly reduced the risk of major adverse cardiovascular events (MACEs) compared with standard statin regimens (risk ratio [RR] 0.77, 95% confidence interval [CI] 0.68–0.86, $P<0.00001$)[21]. A subgroup analysis within the meta-analysis showed a significant reduction in MACEs in the Asian population (RR 0.77, 95% CI 0.61–0.98).

Japanese data also support the use of high-intensity statin therapy. The CREDO-Kyoto Registry Cohort-2 was a retrospective observational study involving patients who had undergone initial coronary revascularization. The study compared the outcomes of patients treated with high-intensity statins (i.e., atorvastatin, rosuvastatin, or pitavastatin) at discharge with those of patients treated with standard statin therapy (i.e., pravastatin, simvastatin, or fluvastatin). Those treated with high-intensity statin therapy had a significantly lower incidence of MACEs than those treated with standard statin therapy (7.5% vs. 9.6%, $P = 0.0008$)[22].

● Evidence Supporting the Early Initiation of Statin Therapy

Regarding the benefits of early initiation of high-intensity statin therapy for ACS, a meta-analysis of RCTs compared patients treated with high-intensity statin therapy soon before or after PCI with a control group (no statin therapy or low-dose statin therapy). The study showed that the 30-day incidences of MI

and MACEs were significantly lower in the early statin therapy group than in the control group (MI: $P = 0.0007$ and MACEs: $P = 0.0001$)[23]. Moreover, the odds of MACE at 30 days post-PCI were significantly lower in patients treated with early initiation of high-intensity statin therapy. In addition, the incidence of recurrent MI within 30 days was significantly lower in patients who initiated statin therapy before PCI than in those who initiated after PCI ($P = 0.002$).

In the Extended-ESTABLISH trial, Japanese patients with ACS who had undergone PCI were randomized to high-intensity atorvastatin or standard care within 48 hours of event onset. The incidence of initial major adverse cardiac and cerebrovascular events for 6 months after PCI was significantly lower in the high-intensity atorvastatin group than in the standard care group, suggesting that the early initiation of high-intensity statin therapy is a positive prognostic factor[24]. A retrospective study examining the effect of early intervention with high-intensity statins after ACS in Japanese patients showed that an intensive reduction in LDL-C levels at 2 months was significantly associated with a lower risk of subsequent cardiovascular events[25]. Although these studies did not directly compare early treatment initiation with delayed intervention, the reduced risk of cardiovascular events with early intervention shows that the initiation of statin therapy to reduce LDL-C soon after ACS onset is beneficial for reducing the incidence of short- and long-term secondary cardiovascular events.

● Evidence Supporting the Addition of Ezetimibe or a PCSK9 Inhibitor to Statin Therapy

The benefits of adding ezetimibe or a PCSK9 inhibitor to statin therapy after ACS onset have been demonstrated in several studies. For instance, a meta-analysis of 11 studies that added ezetimibe to high-intensity statin therapy within 4–12 weeks of ACS onset ($n = 20,291$) showed a significantly lower MACE risk in the ezetimibe arm than in the statin monotherapy arm (odds ratio [OR] 0.89, 95% CI 0.83–0.96, $P = 0.002$)[26]. In another meta-analysis that evaluated the addition of PCSK9 inhibitor therapy soon after ACS onset, starting a PCSK9 inhibitor within 48 hours of admission significantly reduced the incidence of non-fatal MI (RR 0.59, 95% CI 0.38–0.92) and ACS hospitalization (RR 0.53, 95% CI 0.34–0.83). As the follow-up periods of these studies were relatively short (6–18 months), no significant differences in the incidence of MACEs were observed[27]. In a consensus statement, the ESC emphasizes the importance of lipid-lowering therapy with a "strike early and strike strong" approach to quickly reduce LDL-C in patients with ACS, advocating the initiation of PCSK9 inhibitor therapy in the acute phase in patients with multivessel CAD, polyvascular disease (PVD), FH, or in those who are otherwise at a high risk of event recurrence[28].

Based on this evidence, the working group recognizes the importance of early initiation of statin therapy after ACS onset and considers that strict management of LDL-C levels, with or without ezetimibe or a PCSK9 inhibitor (depending on factors such as patient risk and LDL-C level), is beneficial for reducing secondary events in the short- and long-term.

■ *Efficacy of LDL-C-Lowering Therapy for Plaque Stabilization*

Studies have indicated that coronary artery plaque stabilization contributes to the ability of LDL-C-lowering therapy to reduce secondary cardiovascular events following ACS. Several studies have demonstrated the role of statins in coronary artery plaque regression, showing that statins reduce plaque volume[29]. The effects of statins on plaque composition have also been evaluated in terms of fibrous cap thickness and calcified plaque volume. In the ESCORT study, patients with ACS were randomized to an early statin group (treated with pitavastatin just after enrollment) and a late statin group (started on treatment after 3 weeks)[30]. At the 3-week follow-up, fibrous cap thickness increased significantly by 20 μm in the early statin group ($P = 0.017$), whereas it decreased significantly by 5 μm in the late statin group ($P = 0.020$). These findings suggest that changes in the fibrous cap and other aspects of plaque composition may contribute to the benefits derived from early statin initiation in patients with ACS. Another study investigated the effects of LDL-C-lowering statin therapy following ACS on calcified plaque volume by comparing a group that achieved LDL-C <70 mg/dL with a group that did not. After 1 year, calcified plaque volume increased significantly in the <70 mg/dL group ($P = 0.007$), but it did not change significantly in the ≥ 70 mg/dL group ($P = 0.0552$)[31]. Moreover, low-attenuation plaque volume decreased significantly in the <70 mg/dL group, and the target LDL-C level for low-attenuation plaque volume regression was 64 mg/dL.

Regarding the use of ezetimibe with statin therapy, in the PRECISE-IVUS trial, ezetimibe combined with a statin reduced LDL-C to <70 mg/dL, leading to a greater reduction in plaque volume than statin monotherapy[32]. Although another study found that ezetimibe plus a statin did not result in a significant change in plaque regression or tissue

components compared with statin monotherapy[33], a meta-analysis showed that the combined use of ezetimibe and statin therapy significantly reduced total atheroma volume[34].

PCSK9 inhibitors have also been evaluated in clinical trials. In the GLAGOV trial, patients administered monthly subcutaneous injections of evolocumab in addition to a statin achieved a significantly greater reduction in percentage atheroma volume at week 76 vs placebo[35]. Moreover, in the HUYGENS study, patients with non-ST-segment elevation MI who were started early on evolocumab added to a statin achieved better plaque stabilization and regression than placebo-treated patients at 7 days post-onset[36]. In the PACMAN-AMI trial, patients treated with alirocumab with high-intensity statin therapy at admission achieved significantly more coronary artery plaque regression than placebo-treated patients after 52 weeks[37].

Evidence is also available from studies conducted in Japan. In a Japanese trial, patients administered evolocumab plus a statin 1 week after ACS onset had greater fibrous cap thickness and more lipid-rich plaque regression than those administered statin monotherapy[38]. Furthermore, in a trial conducted to evaluate the effects of short-term (3-month) evolocumab treatment on coronary artery plaques, treated patients had significantly greater minimum fibrous cap thickness than standard-of-care patients, even after evolocumab discontinuation[39]. Multiple meta-analyses have also shown that combination PCSK9 inhibitor therapy leads to plaque regression and increases fibrous cap thickness[40, 41], and plaque regression is associated with reductions in clinical events. For instance, a meta-analysis of RCTs evaluating MACE risk during lipid-lowering therapy showed that a 1% across-study decrease in atheroma volume was associated with a significant 25% reduction in MACEs (OR 0.75, 95% CI 0.56–1.00, $P = 0.046$)[42].

■ *Early Statin Initiation and LDL-C Monitoring in ACS*

According to the 2022 JAS guidelines, the early initiation of high-intensity statin therapy after ACS is critical for reducing subsequent cardiovascular events[5]. However, the rate of statin use is low in Japan. An analysis of data from a claims database in Japan showed that patients with ACS had a mean LDL-C level of 85.0 mg/dL, and statins were used in only 54.0% of patients[43]. Although statins were prescribed to 93.6% of patients following ACS in the EXPLORE-J study, high-intensity statins (20 mg atorvastatin, ≥ 10 mg rosuvastatin, or 4 mg pitavastatin) were prescribed to only 8.2% of patients[44]. In a Japanese retrospective study of patients with ACS who had undergone PCI, the rate of statin use was significantly lower in patients with an LDL-C level of <100 mg/dL at admission (57.7%) than in those with an LDL-C level of ≥ 100 mg/dL at admission (77.3%)[45].

The low rate of statin use in patients with low LDL-C after ACS may be explained by low prescription rates. The working group therefore urges healthcare professionals to understand the importance of early initiation of high-intensity statin therapy during hospitalization. Healthcare professionals should also monitor LDL-C after statin administration, and if the patient fails to achieve the LDL-C treatment target, stricter management of LDL-C levels should be considered by adding ezetimibe or a PCSK9 inhibitor.

CQ2 Is the LDL-C treatment target of <55 mg/dL beneficial in patients with ACS?

The LDL-C treatment target of <55 mg/dL may be reasonable in patients with ACS.

(Evidence Level: A)

Summary

- The benefits of an LDL-C treatment target of <55 mg/dL in reducing cardiovascular events have been demonstrated in patients with ACS in the IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials.
- Patients in the AT-TARGET-IT registry who achieved an LDL-C level of <55 mg/dL had a significantly lower incidence of MACEs than those who did not achieve the target.
- Considering the evidence, an LDL-C treatment target of <55 mg/dL may be reasonable for secondary prevention in patients with ACS.

■ *Guideline Recommendations on the LDL-C Treatment Target for ACS*

Guideline-recommended LDL-C treatment targets for patients with high-risk CAD, including those with ACS, have become stricter in recent years. The 2022 ACC Expert Consensus Decision Pathway[2] defined patients at a very high risk as those with major ASCVDs other than an ACS event (e.g., history of MI, ischemic stroke, history of symptomatic PAD) within the past 1 year or with multiple high-risk conditions (e.g., age ≥ 65 years, FH, PCI, coronary artery bypass surgery, or diabetes mellitus). The ACC

Expert Consensus Decision Pathway proposes a reduction of ≥ 50% in LDL-C from baseline and an LDL-C treatment target of <55 mg/dL **(Table 5)**. The 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline[15] states that adding a non-statin lipid-lowering agent in patients with ACS, who are already on maximally tolerated statin therapy, is recommended as Class I for LDL-C ≥ 70 mg/dL and as Class IIa for LDL-C 55 to 69 mg/dL. The 2019 ESC/EAS guidelines for the management of dyslipidemias classify patients with ASCVD, including ACS, as being at very high risk. For secondary prevention, the guidelines recommend an LDL-C reduction of ≥ 50% from baseline and an LDL-C treatment target of <55 mg/dL[4]. These guidelines are based on evidence from the IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials.

■ *Evidence Supporting LDL-C Treatment Targets in ACS*

The IMPROVE-IT trial, which evaluated ezetimibe as a treatment for patients with ACS, provided the first evidence supporting an LDL-C treatment target of <55 mg/dL for ACS management[46]. The trial compared simvastatin (40 mg) plus ezetimibe (10 mg) with simvastatin monotherapy in 18,144 patients with ACS. The group treated with combination therapy achieved a mean LDL-C level of 53.7 mg/dL compared with 69.5 mg/dL in the statin monotherapy group. The combination therapy group had a significantly lower incidence of MACEs (primary endpoint) (hazard ratio [HR] 0.936, 95% CI 0.89–0.99, $P = 0.016$). These risk reductions have also been consistently observed in patients with a baseline LDL-C level of <70 mg/dL[47].

In the AT-TARGET-IT registry, of the 771 patients with ACS who received a PCSK9 inhibitor during hospitalization or at discharge, those who achieved an LDL-C level of <55 mg/dL at the first measurement had a significantly lower incidence of MACEs during follow-up (median: 11 months) than those who did not ($P<0.0001$)[48].

The FOURIER trial evaluated the efficacy of evolocumab added to a statin in high-risk patients with ASCVD (MI, stroke, or symptomatic PAD) (n = 27,564). The mean LDL-C in the evolocumab group decreased from 92 mg/dL to 30 mg/dL (compared with 86 mg/dL in the placebo group), and the evolocumab group had a significantly lower incidence of the primary endpoint (composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) (HR 0.85, 95% CI 0.79–0.92, $P<0.001$) and the key secondary endpoint (composite of cardiovascular death, MI, or stroke) (HR 0.80, 95% CI 0.73–0.88, $P<0.001$) compared with the placebo group[49]. An analysis stratified by LDL-C level at 4 weeks after the FOURIER trial showed that the risk of the primary endpoint and the key secondary composite endpoint decreased monotonically to an LDL-C level of <20 mg/dL[50]. These risk reductions were consistently observed, both in patients with a baseline LDL-C level of <70 mg/dL and in those with an LDL-C level of ≥ 70 mg/dL[51].

A subgroup analysis of the FOURIER trial, which included patients with previous MI (n = 22,351), also showed that evolocumab significantly reduced the incidence of the primary endpoint (HR 0.89, 95% CI 0.82–0.96, $P = 0.002$) and the key secondary endpoint (HR 0.82, 95% CI 0.74–0.91, $P<0.001$)[52]. Another analysis of the FOURIER trial in which patients were stratified by the duration since the index MI (≤ 1 year, n = 5,711 ACS patients) or remote MI (>1 year, n = 16,609 CCS patients) showed that in patients with recent MI, evolocumab significantly reduced the incidence of the primary endpoint by 19% ($P = 0.004$) and the key secondary composite endpoint by 25% ($P = 0.003$)[14].

Other subgroup analyses have investigated the impact of race. A subgroup analysis of Asian patients in the FOURIER trial (n = 2,723) showed a decrease of 21% in the incidence of the primary endpoint (HR 0.79, 95% CI 0.61–1.03) consistent with non-Asian patients (HR 0.86, 95% CI 0.79–0.93; $P_{interaction} = 0.55$)[10].

In the ODYSSEY OUTCOMES trial, the PCSK9 inhibitor alirocumab or placebo was added to statin therapy in patients with ACS who were admitted within 72 hours of the index event. After 4 months, patients in the alirocumab group achieved an average LDL-C reduction to 40 mg/dL and had a 15% lower risk of cardiovascular events than patients administered statin monotherapy (HR 0.85, 95% CI 0.78–0.93, $P<0.001$)[13]. The efficacy and safety of long-term PCSK9 inhibitor therapy were evaluated in an open-label extension of the FOURIER trial (FOURIER-OLE), which showed that the risk of the primary and secondary endpoints decreased to a very low mean LDL-C level of <20 mg/dL over 5 years[53]. In the OSLER studies, where long-term (up to 5 years) evolocumab treatment was evaluated in hypercholesterolemic, high-cardiovascular-risk Japanese patients on statin therapy, the treatment allowed the maintenance of strict LDL-C management (OSLER-1; 42.7 mg/dL, OSLER-2; 35.4 mg/dL), and the addition of evolocumab showed no new adverse event signals[54, 55].

Inclisiran is a siRNA that inhibits the hepatic

synthesis of PCSK9. As inclisiran leads to a sustained reduction in LDL-C with twice-yearly administration, it is expected to have good treatment adherence. In a pooled analysis of two phase 3 trials of inclisiran in patients with ASCVD (ORION-10) and patients with ASCVD or an ASCVD risk equivalent (ORION-11), sustained reductions in LDL-C and a good long-term safety profile were observed[56]. Inclisiran resulted in sustained reductions in LDL-C of ≥ 50% over 1 year in Asian patients[57]. Although no studies have evaluated the effects of inclisiran on cardiovascular events in patients with ASCVD, a pooled analysis of three phase 3 trials (ORION-9, -10, and -11) (n = 3,655) showed that inclisiran was associated with a 26% reduction in the risk of MACEs compared with placebo (OR 0.74, 95% CI 0.58–0.94)[58]. However, there are currently no data demonstrating cardiovascular outcomes with inclisiran in the Japanese population. Although inclisiran is positioned as an emerging agent with potential cardiovascular benefits, domestic data on its long-term safety and efficacy are needed.

Based on the results of the FOURIER and ODYSSEY OUTCOMES trials, the ACC Expert Consensus Decision Pathway proposes evolocumab or alirocumab as the first PCSK9 inhibitor and then considers inclisiran if warranted by poor adherence or adverse events[2]. There is no clear guidance on whether to use evolocumab or inclisiran in Japan, so the appropriate agent should be selected according to the patient's background and adherence.

Based on these findings, the LDL-C treatment target of <55 mg/dL may be beneficial for secondary prevention in patients with ACS **(Table 5)**. Following the initiation of high-intensity statin therapy after ACS onset, LDL-C should be re-evaluated 4 to 8 weeks after treatment initiation[11, 15], and the addition of ezetimibe or a PCSK9 inhibitor should be considered if the patient has not achieved the LDL-C treatment target. Furthermore, from a cost-effectiveness perspective, US and European guidelines recommend using ezetimibe prior to using a PCSK9 inhibitor[4, 59], and this approach is also considered reasonable in Japan. The LDL-C treatment target ≥ 1 year after ACS onset is reviewed in the section on CCS management.

2. Chronic Coronary Syndrome

CQ3 Is high-intensity statin therapy beneficial for lipid management in patients with CCS?

High-intensity statin therapy is beneficial for lipid management in patients with CCS.

(Evidence Level: A)

Summary

• The ACC Expert Consensus Decision Pathway, the AHA/ACC guidelines for the management of patients with CCS, and the Asian Pacific Society of Cardiology (APSC) consensus recommend high-intensity statin therapy for essentially all patients with CCS.

• A meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaboration showed that high-intensity statin therapy significantly reduced the risk of MACEs in patients with dyslipidemia at low risk of cardiovascular events compared with low-to-moderate-intensity statin therapy.

• The working group supports the administration of high-intensity statin therapy to patients with CCS.

■ *Guideline-Recommended Management of Dyslipidemia in Patients with CCS*

High-intensity statin therapy for patients with CCS is recommended in lipid management guidelines, including Japanese guidelines. The 2023 AHA/ACC guidelines for the management of patients with CCS recommend high-intensity statin therapy with the goal of reducing LDL-C by at least 50% to reduce the risk of MACEs[59]. The APSC consensus for CCS also recommends high-intensity statin therapy at the highest tolerated dose for all patients with clinically manifesting CCS, regardless of their level of risk[60]. The JCS 2022 Guideline Focused Update on the diagnosis and treatment of patients with stable CAD also recommends high-intensity statin therapy for stable CAD (i.e., CCS)[12].

In each of these guidelines, the meta-analysis performed by the CTT Collaboration[61] is referenced as evidence to support the recommendation for statin therapy in patients with CCS. A meta-analysis of five trials that compared more intensive with less intensive statin regimens demonstrated that more intensive regimens significantly reduced the onset of MACEs by 15% compared with less intensive regimens (P< 0.0001). Moreover, a reduction in cardiovascular event risk with statins was observed regardless of the baseline LDL-C level. The 27-trial meta-analysis by the CTT Collaboration showed that every 1 mmol/L decrease in LDL-C with statin therapy reduced the risk of cardiovascular events in patients with a history of vascular disease by 21% (RR 0.79, 95% CI 0.77–0.81)[62].

Based on the existing evidence and guideline recommendations, the working group proposes that

high-intensity statin therapy is beneficial in patients with CCS.

CQ4 Is the LDL-C treatment target of <70 mg/dL beneficial in patients with CCS?

The LDL-C treatment target of <70 mg/dL may be reasonable in patients with CCS.

(Evidence Level: A)

The LDL-C treatment target of <55 mg/dL may be considered for patients with CCS with FH, a history of ≥ 2 ACS events, multivessel CAD with a prior ACS event, or a history of ATBI or PAD.

(Evidence Level: B)

Summary

- Current guidelines recommend an LDL-C treatment target of <70 mg/dL for patients with CCS.
- Considering the evidence, an LDL-C treatment target of <70 mg/dL may be reasonable for secondary prevention in patients with CCS.
- For patients with CCS and particular risk factors, such as FH, a history of ≥ 2 ACS events, multivessel CAD with a prior ACS event, or a history of ATBI or PAD, the LDL-C treatment target of <55 mg/dL may be considered given the very high risk of recurrence of cardiovascular events in these populations.

■ *LDL-C Treatment Target for CCS*

LDL-C treatment targets for CCS are proposed in current guidelines. The 2022 ACC Expert Consensus Decision Pathway recommends a reduction of ≥ 50% in LDL-C and an LDL-C treatment target of <70 mg/dL for patients who are not at a very high risk (i.e., CCS and other ASCVD patients with ≤ 1 risk conditions, such as diabetes mellitus or age ≥ 65 years)[2]. A reduction in LDL-C of ≥ 50% and an LDL-C treatment target of <55 mg/dL are recommended for patients who are at a very high risk (i.e., with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions, or PVD) **(Table 5)**. The 2023 AHA/ACC guidelines for the management of patients with CCS also recommend a reduction in LDL-C of ≥ 50% and an LDL-C treatment target of <70 mg/dL[59].

The 2019 ESC/EAS guidelines for the management of dyslipidemias classify all patients with ASCVD, including those with clinically or imaging-confirmed CCS, as being at a very high risk, and these guidelines recommend a reduction of ≥ 50% in LDL-C and an LDL-C treatment target of <55 mg/dL[4].

The APSC consensus for CCS defined the risk factors for CCS as coronary artery lesions, other vascular diseases (PAD, cerebrovascular disease), and complications (e.g., diabetes mellitus, poor kidney function, or cardiac failure due to CAD). The APSC consensus recommends a reduction of ≥ 50% in LDL-C and an LDL-C treatment target of <70 mg/dL for patients with one of these risk factors, and a reduction of ≥ 50% in LDL-C and an LDL-C treatment target of <55 mg/dL for patients with ≥ 2 risk factors[60]. The JCS 2022 Guideline Focused Update on the diagnosis and treatment of patients with stable CAD recommends a reduction of ≥ 50% in LDL-C and an LDL-C treatment target of <70 mg/dL in patients with stable CAD[12].

The REAL-CAD trial evaluated LDL-C treatment targets for CCS in detail[63]. In the trial, Japanese patients with CCS who had ACS at least 3 months earlier were treated with either high-dose (4 mg/day) or low-dose (1 mg/day) pitavastatin, and the incidence of ASCVD was significantly lower in the high-dose group. An investigation of the relationship between LDL-C at 6 months and 5-year cardiovascular outcomes showed that the risk of cardiovascular events decreased monotonically to an LDL-C level of 70 mg/dL[64].

In the prespecified secondary analysis of the FOURIER trial, patients were stratified by ACS (MI within 12 months of randomization) and CCS (MI >12 months prior to randomization). In the CCS cohort, 90.4% achieved LDL-C <70 mg/dL by week 4, and evolocumab reduced the incidence of the primary endpoint by 8% (95% CI 0.84–1.01, P = 0.075) and the incidence of the combined key secondary endpoints (cardiovascular death, MI, or stroke) by 15% (HR 0.85, 95% CI 0.76–0.96, P = 0.009)[14].

Based on these findings and guideline recommendations, an LDL-C treatment target of <70 mg/dL may be reasonable for patients with CCS **(Table 5)**.

■ *Patients with CCS Requiring More Aggressive LDL-C Lowering Therapy*

For secondary prevention in CCS, a more aggressive LDL-C treatment target (<55 mg/dL) may be considered for patients with CCS with FH, a history of ≥ 2 ACS events, multivessel CAD with a prior ACS event, or co-existing ATBI or PAD because these populations are at a very high risk of cardiovascular event recurrence **(Table 6)**.

A history of ≥ 2 ACS events and multivessel

Table 6. CCS patients with an LDL-C treatment target of < 55 mg/dL

Familial hypercholesterolemia
History of ≥ 2 ACS events
Multivessel CAD with prior ACS event
Co-existing ATBI or PAD

ACS, acute coronary syndrome; ATBI, atherothrombotic brain infarction; CAD, coronary artery disease; CCS, chronic coronary syndrome; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease.

CAD with a history of an ACS event are considered coronary artery risk factors based on a subgroup analysis of patients with a history of MI in the FOURIER trial (n = 22,351)[52]. In the placebo arm of the analysis, the incidence of the primary endpoint was significantly higher in patients with ≥ 2 prior MIs than in those with one prior MI (22.4% vs 12.8%, adjusted HR 1.78, 95% CI 1.59–1.99, P < 0.001) and significantly higher in those with residual multivessel CAD than in those without (19.4% vs 13.6%, adjusted HR 1.39, 95% CI 1.24–1.56, P < 0.001). Evolocumab reduced the risk of the primary endpoint in these at-risk patients by 18% and 21%, respectively. In the IMPROVE-IT trial, the incidence of MACEs was also significantly higher in patients with ACS with prior coronary artery bypass grafting than in those without (56% vs. 32%; HR 1.45, 95% CI 1.33–1.58, P < 0.001)[65].

Several cohort studies have shown that patients with FH are at a high risk of ASCVD onset[66-68]. In the FAME study, which involved Japanese patients with FH, 22.8% of the patients with heterozygous FH (HeFH) (n = 762) had prior CAD[69]. In a Japanese study, 13.6% of patients with HeFH (n = 147) had asymptomatic intracranial artery stenosis/occlusion[70]. Regarding the risk of cardiovascular events in patients with FH during secondary prevention of ASCVD, a meta-analysis involving patients with ACS (n = 31,287) showed that those with FH (n = 2,338) were at a significantly higher cardiovascular event risk (RR 1.91, 95% CI 1.55–2.35)[71]. Determining the FH status is therefore important when diagnosing patients with CCS. FH should be suspected, and a differential diagnosis should be made if high-intensity statin therapy fails to sufficiently reduce LDL-C levels.

Several recent studies have also evaluated the efficacy of PCSK9 inhibitors for reducing LDL-C in patients with FH. A meta-analysis of 10 studies showed that PCSK9 inhibitors significantly reduced LDL-C by 49.59% (95% CI 43.67%–55.52%) compared with placebo[72]. In a Japanese post-marketing study, evolocumab reduced LDL-C from 145.3 mg/dL at baseline to 56.0 mg/dL at week 4 in patients with HeFH (n = 2,009), and from 170.5 mg/dL at baseline to 98.4 mg/dL at week 4 in patients with homozygous FH (HoFH). These LDL-C reductions were maintained through week 104 in both HeFH and HoFH[73].

Diabetes mellitus and chronic kidney disease (CKD) are risk factors for cardiovascular events in patients with CAD. Multiple guidelines state that coexisting diabetes mellitus is a risk factor that substantially increases the risk of cardiovascular event recurrence in patients with CAD[2]. The data from the placebo arms of the IMPROVE-IT and ODYSSEY OUTCOMES trials show that coexisting diabetes mellitus substantially increases the risk of MACEs, and that LDL-C-lowering therapy reduces MACEs in patients with coexisting diabetes mellitus[74]. CKD is also widely recognized as an independent risk factor in the context of secondary prevention of ASCVD[75]. An analysis of risk factors showed that kidney dysfunction was a greater risk factor for MACEs than poor glucose control and high systolic blood pressure[76, 77]. An analysis of the FOURIER trial, in which patients were stratified by kidney function, showed that evolocumab treatment resulted in a sustained reduction in the absolute risk of cardiovascular events regardless of baseline kidney function based on the estimated glomerular filtration rate[78]. Patients with both diabetes mellitus and CKD are at an even greater risk of cardiovascular events. A database study of 162,730 patients hospitalized for MI compared the impact of concomitant diabetes mellitus and CKD with that of prior CVD on the risk of recurrent CVD. The risk of event recurrence in patients with both diabetes mellitus and CKD was significantly higher than in patients with prior CVD (HR 1.18, 95% CI 1.14–1.22)[79]. As no large-scale trials have evaluated the benefits of an LDL-C treatment target of < 55 mg/dL for patients with CCS with concomitant diabetes mellitus and CKD, the working group does not present an LDL-C treatment target specifically for this population. This needs to be re-evaluated after the results of a study of high-risk patients with diabetes mellitus and other conditions become available[80].

Risk of Cardiovascular Events in Patients with PVD

The results of registry studies and large-scale clinical studies have shown that PVD (i.e., the presence of ≥ 2 of CAD, ATBI, and PAD) places patients at a high risk of ASCVD. The REACH Registry is an international prospective cohort consisting of patients with either established ASCVD (CAD, PAD, or cerebrovascular disease) or ≥ 3 risk factors for atherosclerotic arterial disease (n = 68,236)[81]. The incidence of composite cardiovascular events was markedly higher in patients with CAD with cerebrovascular disease than in those with CAD alone. It was also much higher in patients with CAD and PAD than in those with CAD alone. A subgroup analysis of the Japanese population from the REACH Registry found a substantially higher incidence of composite cardiovascular events in patients with cerebrovascular disease and CAD or cerebrovascular disease and PAD than in those with cerebrovascular disease alone[82].

Analysis of the placebo group from the FOURIER trial showed that the incidence of major cardiovascular events was significantly higher in patients with PAD and MI/stroke than in those with PAD, MI, or stroke alone (PAD alone vs. PVD: 10.3% vs. 14.9%, P = 0.0028; MI/stroke alone vs. PVD: 7.6% vs. 14.9%, P = 0.0001)[83]. In the placebo group of the FOURIER trial, the incidence of first acute arterial events (composite of acute coronary, cerebrovascular, or peripheral vascular events) was significantly higher in patients with PVD than in those with MI alone (MI alone vs. PVD, P < 0.001)[84]. In the ODYSSEY OUTCOMES trial, the incidence of MACEs was 10.0% in patients with ACS alone, but it was higher in patients with PVD (24.0%)[85].

LDL-C Treatment Target in Patients with PVD

Existing guidelines recommend a strict LDL-C treatment target of < 55 mg/dL for patients with PVD based on the results of large-scale studies. The 2022 ACC Expert Consensus Decision Pathway, which classifies patients with multiple major ASCVD events as being at very high risk, recommends lowering LDL-C by ≥ 50% from baseline and achieving an LDL-C treatment target of < 55 mg/dL[2]. Moreover, the 2019 ESC/EAS guidelines for the management of dyslipidemias set an LDL-C treatment target of < 55 mg/dL for all patients with ASCVD.

The efficacy of aggressive LDL-C reduction on cardiovascular event risk in patients with PVD has been analyzed in large-scale clinical trials. In the IMPROVE-IT trial, the relative risk reduction with ezetimibe for major cardiovascular events showed no interaction in patients with or without PVD ($P_{interaction}$ = 0.75)[86]. The P values for the interaction of PVD status with the effect of evolocumab on the primary endpoint and key secondary endpoint in the FOURIER trial were $P_{interaction}$ = 0.19 and 0.38, respectively[49]. PVD status was not found to interact with the effect of alirocumab on the risk of major cardiovascular events in the ODYSSEY OUTCOMES trial ($P_{interaction}$ = 0.92)[85]. Alirocumab reduced the absolute risk in patients with monovascular disease and disease in two or three vascular beds by 1.4%, 1.9%, and 13.0%, respectively ($P_{interaction}$ = 0.0006), providing greater risk reduction as the number of affected vascular beds increased.

As explained above, it has been shown that aggressive LDL-C-lowering by combining ezetimibe or PCSK9 inhibitors may be effective for preventing cardiovascular events in patients with PVD. Therefore, an LDL-C treatment target of < 55 mg/dL may be reasonable for patients with CAD + ATBI or CAD + PAD. However, the number of patients with ATBI + PAD in the PVD group was small, even in the FOURIER trial (2.5%)[83], so the working group does not present the LDL-C treatment target of < 55 mg/dL in this population, owing to insufficient evidence.

3. Atherothrombotic Brain Infarction

CQ5 Is statin therapy beneficial for lipid management in patients with ATBI?

Statin therapy is beneficial for lipid management in patients with ATBI.

(Evidence Level: A)

Summary

- ATBI is a condition of systemically advanced arteriosclerosis, and it is often complicated by CAD or other ASCVDs.
- Many RCTs and meta-analyses have demonstrated that statin therapy for ATBI significantly reduces the risk of stroke and ischemic stroke recurrence.
- The working group supports statin therapy for preventing stroke recurrence in patients with ATBI.

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Definition and Pathology of ATBI

The working group defined ATBI as ischemic stroke attributable to > 50% stenosis in the intracranial/carotid arteries (or ischemic stroke with aortic arch atheroma with a maximal thickness of ≥ 4.0 mm) in accordance with the 2022 JAS guidelines for the prevention of ASCVD[5]. TIA and lacunar

infarction were excluded from the assessment because these conditions have diverse pathologies and no relevant studies have evaluated TIA and lacunar infarction independently. Aortic arch atheroma with a maximal thickness of ≥ 4.0 mm has been identified as a high-risk condition in the context of ASCVD, including ischemic stroke[87], so this condition was included in the definition of ATBI.

The proportion of cases of ATBI among patients with ischemic stroke has recently increased in Japan in association with lifestyle changes[88]. ATBI is a condition of systemically advanced arteriosclerosis, so it is often comorbid with other ASCVDs. A meta-analysis of 17 trials involving 4,869 patients with acute ischemic stroke showed that the prevalence of asymptomatic CAD in this population was 52% and the prevalence of asymptomatic ≥ 50% coronary stenosis was 32% (95% CI 19%–47%)[89]. A Japanese study found CAD to be present in 39 of 104 patients with ischemic stroke (37.5%)[90]. Another Japanese study in patients with extracranial carotid artery stenosis who had undergone carotid artery stenting (n = 112) demonstrated that the incidence of CAD when ≥ 1 coronary arteries had stenosis of ≥ 75% was 49.1%[91], showing a strong correlation between carotid artery and coronary artery stenosis. These findings suggest that ATBI includes advanced arteriosclerosis and places patients at a high risk of ischemic stroke recurrence and ASCVDs, including CAD.

Guideline-Recommended Lipid Management Strategies for ATBI

Several guidelines have discussed statin-based lipid-lowering therapy for ATBI. The 2021 AHA/American Stroke Association (ASA) guidelines for stroke prevention in patients with stroke and TIA recommend 80 mg/day atorvastatin to reduce the risk of stroke recurrence in patients with ischemic stroke with no known coronary heart disease, no major cardiac sources of embolism, and an LDL-C level of >100 mg/dL[87]. The 2022 European Stroke Organisation guidelines for the treatment of patients with intracranial atherosclerotic disease classify patients with symptomatic intracranial atherostenosis to be at a very high risk and recommend aggressive vascular risk factor management in this population[92]. The 2021 Japan Stroke Society (JSS) guidelines for the treatment of stroke[93] recommend proactive administration of statins for the prevention of recurrent non-cardiogenic stroke or TIA in patients with non-cardiogenic stroke or TIA.

Evidence Supporting Statin Therapy for Patients with ATBI

Evidence suggests that LDL-C-lowering statin therapy as part of lipid management for patients with ATBI is beneficial for preventing ischemic stroke recurrence. A meta-analysis of 11 RCTs and 12 cohort studies in patients with ischemic stroke[94] showed that statin therapy significantly reduced the incidence of stroke of any type (11 RCTs: OR 0.87, 95% CI 0.77–0.97, P = 0.02; 12 cohort studies: OR 0.80, 95% CI 0.66–0.96, P = 0.02). In addition, statin therapy significantly reduced the recurrence of ischemic stroke in three cohort studies evaluating stroke recurrence (OR 0.67, 95% CI 0.61–0.75). Another meta-analysis of 43 studies that followed patients with prior ischemic stroke or hemorrhagic stroke[95] showed that in patients with prior ischemic stroke, statin therapy significantly reduced ischemic stroke risk (RR 0.74, 95% CI 0.66–0.83, P<0.001) and did not significantly increase hemorrhagic stroke risk (RR 1.36, 95% CI 0.96–1.91, P = 0.08). In patients with prior hemorrhagic stroke, statin therapy did not significantly affect the risk of hemorrhagic stroke recurrence (RR 1.04, 95% CI 0.86–1.25, P = 0.70), but it was related to significant decreases in mortality (RR 0.49, 95% CI 0.36–0.67, P<0.001) and poor functional outcomes (RR 0.71, 95% CI 0.67–0.75, P<0.001).

In the J-STARS study, Japanese patients who had experienced non-cardioembolic ischemic stroke (n = 1,578) were randomized to a pravastatin group or a non-statin group and followed for 4.9 years. Although the incidences of total stroke and TIA did not differ significantly between the groups, atherothrombotic infarction occurred significantly less frequently in the pravastatin group (adjusted HR 0.33, 95% CI 0.15–0.74, P = 0.0047), whereas the incidence of intracranial hemorrhage did not differ significantly between the groups (adjusted HR 1.00, 95% CI 0.45–2.22, P = 1.00)[96]. An analysis stratified by the mean LDL-C level through the final observation after randomization in the J-STARS study showed significantly lower incidences of stroke and TIA in patients with a mean LDL-C level of 80–100 mg/dL after treatment initiation[97].

Based on this evidence and the fact that ATBI is a condition of systemically advanced atherosclerosis, the working group proposes statin therapy for preventing ischemic stroke recurrence and ASCVD in patients with ATBI.

CQ6 Is the LDL-C treatment target of <70 mg/dL beneficial in patients with ATBI?

The LDL-C treatment target of <70 mg/dL

may be considered in patients with ATBI.
(Evidence Level: B)

Summary

• In the Treat Stroke to Target (TST) trial, an aggressive LDL-C treatment target of <70 mg/dL significantly reduced the risk of MACEs in patients with ATBI.

• In the FOURIER trial, evolocumab significantly reduced MACEs in patients with ischemic stroke without increasing hemorrhagic stroke risk.

• A meta-analysis of LDL-C-lowering therapies for stroke showed that reducing the LDL-C level to < 70 mg/dL reduced the risk of ischemic stroke recurrence and cardiovascular events without increasing hemorrhagic stroke risk.

• Considering the evidence, an LDL-C treatment target of <70 mg/dL may be considered for secondary prevention in patients with ATBI.

Guideline Recommendations on the LDL-C Treatment Target for ATBI

For patients with ischemic stroke or TIA who have atherosclerosis (intracranial, carotid artery, aorta, aortic arch, or coronary artery), the 2021 AHA/ASA guidelines for stroke prevention in patients with stroke and TIA recommend an LDL-C treatment target of <70 mg/dL with, for example, a statin combined with ezetimibe or a PCSK9 inhibitor[87] **(Table 5)**. In line with the ESC/EAS guidelines, the 2022 European Stroke Organisation guidelines for the treatment of patients with intracranial atherosclerotic disease[92] state that patients with asymptomatic atherostenosis should be considered to be at very high risk and managed with an LDL-C treatment target of <55 mg/dL.

The 2021 JSS guidelines for the treatment of stroke[93] state that in patients with non-cardiogenic stroke or TIA, an LDL-C treatment target of <100 mg/dL for lipid control to prevent the recurrence of non-cardiogenic stroke or TIA is reasonable. The guidelines also state that in patients with non-cardiogenic stroke or TIA and CAD, an LDL-C treatment target of <70 mg/dL may be reasonable for stroke prevention.

Evidence Supporting LDL-C Treatment Targets in ATBI

The relationship between LDL-C-lowering therapy and ischemic stroke risk reduction as secondary prevention in patients with ASCVD has been evaluated in recent large-scale studies, such as the TST trial[98-100], which enrolled patients with ischemic stroke, and the FOURIER, IMPROVE-IT, and ODYSSEY OUTCOMES trials, which included patients with ASCVD.

In the TST trial, 2,860 patients (2,148 French patients and 712 South Korean patients) with prior ischemic stroke or TIA who also had atherosclerotic disease, including stenosis of an extracranial or intracranial cerebral artery, were randomly assigned to a statin and ezetimibe regimen with an LDL-C treatment target of 90–110 mg/dL (higher-target group) or <70 mg/dL (lower-target group)[98]. The mean LDL-C level decreased from 135 mg/dL at baseline to 65 mg/dL in the lower-target group and 96 mg/dL in the higher-target group, and the incidence of MACEs was significantly lower in the lower-target group than in the higher-target group (8.5% vs. 10.9%, HR 0.78, 95% CI 0.61–0.98, $P = 0.04$). Although the incidence of MACEs in patients with prior ischemic stroke ($n = 2,449$) was significantly lower in the lower-target group (HR 0.67, 95% CI 0.52–0.87), in patients with prior TIA ($n = 405$), the incidence of MACEs was significantly higher in the lower-target group (HR 2.06, 95% CI 1.03–4.12). The risk of intracranial hemorrhage did not differ significantly between the lower-target and higher-target groups (HR 1.38, 95% CI 0.68–2.82). A comparison of statin/ezetimibe dual therapy with statin monotherapy showed that the incidence of MACEs was significantly lower in the lower-target group than in the higher-target group (HR 0.60, 95% CI 0.39–0.91, $P = 0.016$) among patients on dual therapy, whereas there was no significant difference (HR 0.92, 95% CI 0.70–1.20, $P = 0.52$) among patients on statin monotherapy[99]. Risk factors for intracranial hemorrhage included anticoagulant therapy and stage 2 hypertension, but an LDL-C treatment target of <70 mg/dL was not associated with an increased risk of intracranial hemorrhage[100]. The results of the TST trial indicated that an LDL-C treatment target of <70 mg/dL is reasonable for lipid management in patients with ATBI, and that adding ezetimibe may be preferable to statin dose escalation for LDL-C management.

In the FOURIER trial, the population with ASCVD included patients with ischemic stroke. An overall analysis of the FOURIER trial showed that the evolocumab group experienced a decrease in LDL-C to 30 mg/dL and a significant reduction in the risk of MACEs and ischemic stroke compared with the placebo group (HR 0.75, 95% CI 0.62–0.92, $P = 0.0005$)[49, 101] but the incidence of hemorrhagic stroke did not differ significantly between the groups (HR 1.16, 95% CI 0.68–1.98, $P = 0.59$). A subgroup

analysis of patients with prior ischemic stroke in the FOURIER trial (n = 5,337, 3,366 of whom had stroke alone [63.1%]) showed a consistent trend in the evolocumab group of MACEs risk reduction (HR 0.85, 95% CI 0.72–1.00, P = 0.047), ischemic stroke (HR 0.92, 95% CI 0.68–1.25, $P_{interaction}$ = 0.087), with no significant increase in the risk of hemorrhagic stroke (HR 0.99, 95% CI 0.47–2.07)[101].

In the IMPROVE-IT trial, which included patients with ACS (n = 18,144), those treated with simvastatin plus ezetimibe achieved a reduction in LDL-C to 53.2 mg/dL and a significant decrease in the incidence of ischemic stroke (HR 0.79, 95% CI 0.67–0.94, P = 0.008) without a significant increase in the incidence of hemorrhagic stroke (HR 1.38, 95% CI 0.93–2.04, P = 0.11)[46]. In the subgroup of patients with prior stroke (n = 682), those treated with ezetimibe plus statin therapy experienced a significant reduction in the incidence of ischemic stroke (HR 0.60, 95% CI 0.38–0.95, P = 0.030)[102]. Likewise, in the ODYSSEY OUTCOMES trial, which also included patients with ACS (n = 18,924), those administered add-on alirocumab achieved a reduction in LDL-C to 40 mg/dL and a significant decrease in the risk of ischemic stroke (HR 0.73, 95% CI 0.57–0.93, P = 0.01), without a significant increase in the risk of hemorrhagic stroke (HR 0.83, 95% CI 0.42–1.65, P = 0.59)[13, 103].

LDL-C-Lowering Therapy and Hemorrhagic Stroke

Although the incidence of hemorrhagic stroke in Japan has recently decreased[88], it still tends to be higher in Japan than in Western countries[104]. A relationship between low LDL-C and hemorrhagic stroke risk has long been discussed[105]. Therefore, the working group carefully evaluated the evidence on the association between the LDL-C target and hemorrhagic stroke risk in patients with ATBI. The 2023 AHA Scientific Statement suggested that the risk of a hemorrhagic stroke associated with statin therapy in patients without a history of cerebrovascular disease is non-significant, and achieving a very low LDL-C level does not increase that risk[106]. Hence, the benefits of statin therapy in terms of reducing the overall risk of stroke and other major cardiovascular events may outweigh the potential risk of hemorrhagic stroke.

The results of several meta-analyses evaluating the relationship of statin use with hemorrhagic stroke are inconsistent. One meta-analysis[94] reported no significant increase in the risk of hemorrhagic stroke associated with statin use in patients with a history of stroke (seven RCTs: OR 1.15, 95% CI 0.62–2.13, P = 0.66, eight cohort studies: OR 0.93, 95% CI 0.71–1.21, P = 0.59). Another meta-analysis[95] reported no significant increase in the risk of hemorrhagic stroke in either patients with a history of ischemic stroke (RR 1.36, 95% CI 0.96–1.91, P = 0.08) or a history of hemorrhagic stroke (RR 1.04, 95% CI 0.86–1.25, P = 0.70). A meta-analysis of RCTs evaluating statin use in patients with prior ischemic stroke or TIA[107] showed a significant increase in hemorrhagic stroke (RR 1.43, 95% CI 1.02–2.02, P = 0.04), but this was mainly driven by the findings of the SPARCL trial.

The SPARCL trial was an RCT that compared the incidence of recurrent stroke in 4,713 patients without CAD who had experienced a stroke or TIA within the previous 6 months and who were assigned to either 80 mg atorvastatin or placebo[105]. The atorvastatin group experienced a decrease in LDL-C to a mean of 72.9 mg/dL (placebo: 128.5 mg/dL), together with a significant decrease in ischemic stroke risk (HR 0.78, 95% CI 0.66–0.94), but the risk of hemorrhagic stroke significantly increased (HR 1.66, 95% CI 1.08–2.55). A post hoc analysis was conducted of patients classified by disease type to determine the cause. The analysis showed that in patients with lacunar infarction, hemorrhagic stroke occurred significantly more in the atorvastatin group than in the placebo group (n = 20 vs. n = 4; HR 4.99, 95% CI 1.71–14.61), but among patients with large-vessel atheroembolic or cardioembolic involvement, there was no difference in the occurrence of hemorrhagic stroke (n = 8 vs. n = 7; HR 1.16, 95% CI 0.42–3.19)[108]. The post hoc analysis also showed no association between the achieved LDL-C level and hemorrhagic stroke, and there was no significant increase in hemorrhagic stroke risk, even among those with an LDL-C level of $<$52 mg/dL. Multivariable analysis of hemorrhagic stroke risk factors showed that the risk was significantly higher in patients with prior hemorrhagic stroke (HR 5.81, 95% CI 2.91–11.60, P $<$0.001) and in patients with stage 2 hypertension at the last visit (HR 6.19, 95% CI 1.47–26.11, P = 0.01). Both the SPARCL and TST trials showed that hypertension is a significant risk factor for hemorrhagic stroke, highlighting the importance of blood pressure management for patients with a history of stroke.

Multiple recent cohort studies have also reported no association between statin therapy and hemorrhagic stroke risk, as mentioned in the AHA Scientific Statement[106]. A study based on data from the National Health Insurance Database of Taiwan compared patients with statin exposure after intracranial hemorrhage (n = 1,702) using propensity score matching with patients without statin exposure (n = 1,702). Ten-year all-cause mortality was

significantly lower in the statin group (32.7% vs. 42.8%, $P<0.0001$), whereas no significant difference was observed in hemorrhagic stroke recurrence ($P = 0.29$)[109]. A similar analysis, also using data from the National Health Insurance Database of Taiwan, compared acute ischemic stroke patients from the statin cohort ($n = 39,366$) with those from the non-statin cohort matched by propensity scores ($n = 39,366$). All-cause mortality was significantly lower in the statin group ($P<0.0001$), and this group had a lower intracerebral hemorrhage risk ($P<0.0001$)[110].

A propensity score-matched cohort study conducted in Denmark found that statin users and statin non-users with prior intracerebral hemorrhage had a comparable incidence of intracerebral hemorrhage recurrence ($n = 2,728$) (HR 0.90, 95% CI 0.72–1.12). However, in those with prior ischemic stroke ($n = 52,964$), statin users had a significantly lower incidence of ischemic stroke recurrence (HR 0.53, 95% CI 0.45–0.62)[111].

A recent nationwide cohort study conducted in Finland retrospectively analyzed consecutive patients treated with high-intensity, moderate-intensity, or low-intensity statins early after ischemic stroke ($n = 45,512$, median 5.9-year follow-up). High-intensity statin use resulted in a significant decrease in the risks of all-cause death (high- vs. low-intensity: HR 0.83, 95% CI 0.78–0.89, $P<0.0001$) and ischemic stroke (HR 0.77, 95% CI 0.70–0.84, $P<0.0001$), but there was no significant difference in intracerebral hemorrhage risk (HR 0.93, 95% CI 0.70–1.23, $P = 0.619$)[112].

In the TST trial, treatment with ezetimibe plus a statin reduced the LDL-C level to <70 mg/dL without increasing intracranial hemorrhage risk[100]. Moreover, in a subgroup analysis of the FOURIER trial, the addition of a PCSK9 inhibitor reduced the LDL-C level to approximately 30 mg/dL, without significantly increasing hemorrhagic stroke risk[101]. A meta-analysis investigated the association between LDL-C-lowering therapies, including ezetimibe and PCSK9 inhibitors, and stroke risk[113]. A significant decrease in stroke risk was maintained to an achieved LDL-C level of 30 mg/dL ($P = 0.044$), with no significant increase in hemorrhagic stroke risk to an LDL-C level of 30 mg/dL. In another meta-analysis[114], treatment with ezetimibe or a PCSK9 inhibitor did not affect hemorrhagic stroke risk (RR 1.14, 95% CI 0.64–2.03, and RR 0.86, 95% CI 0.43–1.74, respectively). Overall, the achieved LDL-C level was not associated with hemorrhagic stroke risk.

In a post-marketing study of evolocumab conducted in Japan, a safety set consisting of 3,724 patients (1,607 with high-risk hypercholesterolemia and 2,117 with FH) was followed for 104 weeks[73]. The LDL-C level in patients with high-risk hypercholesterolemia decreased from 106.4 mg/dL at baseline to 36.1 mg/dL at week 4 and was maintained at <40 mg/dL thereafter. The incidence of cardiac disorders was 7.3%, and the incidence of nervous system disorders was 1.7%. The incidence of serious hemorrhagic stroke-related events was 0.44% in patients who achieved an LDL-C level of <40 mg/dL and 0.32% in those with an LDL-C level of ≥ 40 mg/dL. However, it remains necessary to continuously assess the relationship between low LDL-C and hemorrhagic stroke risk in Japanese patients with ATBI.

Based on the evidence, lipid management using statin therapy is reasonable, and an LDL-C treatment target of <70 mg/dL may be considered for secondary prevention in patients with ATBI **(Table 5)**. The addition of ezetimibe or evolocumab to statin therapy is reasonable for patients with ATBI who do not achieve the LDL-C treatment target with statins alone. For patients with PVD who have both ATBI and CAD (CCS), a stricter LDL-C treatment target of <55 mg/dL may be reasonable owing to the high risk of cardiovascular events[81] (see CQ4).

4. Peripheral Artery Disease

CQ7 Is high-intensity statin therapy beneficial for lipid management in patients with PAD?

High-intensity statin therapy is beneficial for lipid management in patients with PAD.

(Evidence Level: A)

Summary

- Cardiovascular event risk in patients with PAD is very high, comparable to that of patients with a history of MI or stroke.
- High-intensity statin therapy has proven to be beneficial in reducing cardiovascular events in patients with PAD.
- However, studies in Japan and other countries have shown that statin therapy is underprescribed to patients with PAD, which may indicate an insufficient appreciation of the benefits of statins for secondary prevention in patients with PAD.
- The working group supports high-intensity statin therapy for PAD.

Risk of Cardiovascular Events in Patients with PAD

PAD is a high-risk condition for cardiovascular

events in Japanese patients, as shown in the Hisayama Study[115] and in the subgroup analysis of the Japanese population in the REACH Registry[82]. Based on these results, PAD is classified as a high-risk factor for cardiovascular events in the 2022 JAS guidelines[5]. In the REACH Registry, which included 68,236 patients with atherothrombosis (CAD, cerebrovascular disease, and PAD), the 1-year risks of a cardiovascular event in patients with only CAD, cerebrovascular disease, or PAD were 13.04%, 9.87%, and 17.44%, respectively. This indicates that the risk of cardiovascular events in patients with PAD may be equivalent to or higher than that in patients with CAD or cerebrovascular disease[81]. In the placebo group of the FOURIER trial, patients with PAD without prior MI or stroke had a significantly higher risk of cardiovascular events than patients with prior MI or stroke without PAD (10.3% vs. 7.6%; adjusted HR 2.07, 95% CI 1.42–3.01, $P = 0.0001$)[83]. These findings indicate that the risk of cardiovascular events in patients with PAD may be similar to or greater than the risk in patients with MI or stroke, suggesting that patients with PAD require strict intervention, similar to patients with CAD or ATBI.

Although statin therapy has proven to be beneficial for secondary prevention in PAD, it is underprescribed in patients with PAD compared with patients with other ASCVDs, especially CAD[4, 116-118]. Lipid management guidance for PAD has not been established in Japan. However, the working group defined PAD as a high-risk condition, similar to the other ASCVDs mentioned in this report, warranting consideration of the optimal LDL-C treatment target. Based on the reviewed studies, the working group defined PAD as symptomatic lower-extremity PAD in this report.

Guideline-Recommended Lipid Management Strategies for PAD

For lipid-lowering therapy in patients with PAD, high-intensity statins are recommended in current guidelines from Europe, the United States, and Asia. The 2024 ACC/AHA guidelines for the management of lower-extremity PAD indicate lipid-lowering therapy with high-intensity statins for the prevention of MACEs and major adverse limb events (MALEs) in all patients with PAD[117]. The 2019 ESC/EAS guidelines for the management of dyslipidemias state that PAD is associated with a very high risk of coronary artery events, and that the maximum tolerated statin dose is indicated for this condition[4]. The EAS/European Society of Vascular Medicine (ESVM) Joint Statement on PAD[119] and the 2024 ESC guidelines for the management of peripheral arterial and aortic diseases[118] also recommend the maximum tolerated statin dose, with the addition of ezetimibe or a PCSK9 inhibitor if the treatment target is not reached. The APSC Consensus Statement recommends statins for all patients with PAD[120]. In the 2022 JAS guidelines for prevention of ASCVD, statin therapy is recommended for PAD based on evidence related to lesions in lower-extremity arteries[5].

Evidence Supporting Statin Therapy for PAD

Several studies and recent meta-analyses have shown that statin therapy for PAD contributes to the secondary prevention of ASCVD. A 4-year follow-up of the 5,861 patients with PAD in the REACH Registry showed that statin users had a significantly lower (18%) risk of composite adverse limb outcomes than non-users (HR 0.82, 95% CI 0.72–0.92, $P = 0.0013$)[121].

A meta-analysis of 39 trials comparing statin use and non-use or high- and low-intensity statins in patients with PAD ($n = 275,670$)[122] showed that statin therapy significantly decreased all-cause mortality by 42% (HR 0.58, 95% CI 0.49–0.67, $P < 0.01$) and the risk of MACEs by 35% (HR 0.65, 95% CI 0.51–0.80, $P < 0.01$), as well as significantly increasing amputation-free survival by 56% (HR 0.44, 95% CI 0.30–0.58, $P < 0.01$). A meta-analysis of 22 observational studies and two RCTs in patients with PAD ($n = 268,611$)[123] showed that statin therapy significantly reduced all-cause mortality by 32% (OR 0.68, 95% CI 0.60–0.76) and MACEs by 16% (OR 0.84, 95% CI 0.78–0.92). Another meta-analysis of 51 studies ($n = 138,060$ patients with PAD)[124] found that statin therapy significantly reduced the incidence of MALEs by 30% (HR 0.702, 95% CI 0.605–0.815), amputations by 35% (HR 0.654, 95% CI 0.522–0.819), and all-cause mortality by 39% (HR 0.608, 95% CI 0.543–0.680).

Studies have also evaluated the relationship between statin intensity and the effects of secondary prevention in PAD. A study of 155,647 patients with PAD registered in the United States Veterans Health Administration database showed that high-intensity statins significantly reduced amputation risk by 22% (adjusted HR 0.78, 95% CI 0.68–0.89) and mortality risk by 15% (adjusted HR 0.85, 95% CI 0.80–0.90) compared with low- and moderate-intensity statins[125]. A meta-analysis also showed that high-intensity statin therapy significantly reduced all-cause mortality by 36% compared with low-intensity statin therapy (HR 0.64, 95% CI 0.54–0.74, $P < 0.01$)[122].

Evidence Supporting Statin Therapy for PAD in Japan

Evidence supporting the use of statin therapy for patients with PAD has also been reported in Japan. In a prospective cohort study of 1,107 patients with de novo IC, the baseline rate of statin use was 52.8%. Statin use was associated with reductions in all-cause mortality ($P = 0.048$), MACEs ($P = 0.001$), and major adverse cardiovascular and limb events (MACLEs; $P = 0.010$)[126]. In another prospective cohort study involving 1,219 patients with PAD, the baseline mean LDL-C level was 113 mg/dL, the rate of statin use was 52.1%, and the mortality rate over approximately 6 years of follow-up was 51.4%[127]. The multivariate analysis showed that statin use was associated with significant differences in overall survival (HR 0.351, 95% CI 0.267–0.462, $P<0.001$), MACEs (HR 0.384, 95% CI 0.306–0.482, $P<0.001$), and MACLEs (HR 0.381, 95% CI 0.305–0.475, $P<0.001$).

The findings of these studies indicate that statin use significantly decreases the risk of cardiovascular and lower-limb events in Japanese patients with PAD. Moreover, statins reduce cardiovascular events in patients with PAD, even in patients with a baseline LDL-C level of approximately 100 mg/dL. These findings led the working group to conclude that high-intensity statin therapy is beneficial in patients with PAD, irrespective of the baseline LDL-C level. However, in terms of Japanese clinical practice for PAD, the rate of statin use is only about 50%, with many patients having a baseline LDL-C level of approximately 100 mg/dL[127, 128]. Increasing the use of statins for lipid management in patients with PAD is therefore an issue that must be addressed.

CQ8 Is the LDL-C treatment target of <70 mg/dL beneficial in patients with PAD?

The LDL-C treatment target of <70 mg/dL may be considered in patients with PAD.

(Evidence Level: B)

Summary

- Based on clinical trial results, the 2024 ACC/AHA guidelines for the management of lower-extremity PAD recommend an LDL-C treatment target of <70 mg/dL, and the 2024 ESC guidelines for the management of peripheral arterial and aortic diseases recommend a treatment target of <55 mg/dL.
- Considering the evidence and guideline recommendations, the LDL-C treatment target of <70 mg/dL may be considered for secondary prevention in patients with PAD.

Guideline Recommendations on the LDL-C Treatment Target for PAD

Regarding the LDL-C treatment target for PAD, the 2024 ACC/AHA guidelines for the management of lower-extremity PAD recommend an LDL-C treatment target of <70 mg/dL based on large-scale clinical studies[117] **(Table 5)**. The 2022 ACC Expert Consensus Decision Pathway recommends an LDL-C treatment target of <70 mg/dL and a reduction in LDL-C of ≥ 50% for patients with PAD and other ASCVDs who are not at very high risk (i.e., with ≤ 1 risk condition, such as diabetes mellitus or age ≥ 65 years)[2]. The 2024 ESC guidelines for the management of peripheral arterial and aortic diseases classify patients with PAD as being at very high risk, and thus recommend an LDL-C treatment target of <55 mg/dL and a reduction in LDL-C of ≥ 50%[4, 118]. The EAS/ESVM Joint Statement on PAD similarly recommends an LDL-C treatment target of <55 mg/dL[119]. All these guidelines recommend high-intensity statin therapy to achieve the LDL-C treatment target, with the addition of ezetimibe or a PCSK9 inhibitor as necessary[119].

Evidence Supporting LDL-C Treatment Targets in PAD

In an observational study, patients who achieved the LDL-C treatment target of <70 mg/dL over a short period of time (average 4.8 months) had a lower incidence of MACEs at 2 years (4% vs. 10%, $P = 0.002$) and lower all-cause mortality (2% vs. 7%, $P = 0.007$) than those who did not achieve the treatment target ($n = 342$), indicating that achieving an LDL-C treatment target of <70 mg/dL is an independent predictor of reduced mortality and cardiovascular events[129].

In the IMPROVE-IT trial, ezetimibe significantly reduced MACEs in patients with PVD (i.e., ACS and PAD or stroke)[86]. Although no direct evidence suggests that ezetimibe reduces cardiovascular event risk in patients with PAD, the 2024 ACC/AHA guidelines for the management of lower-extremity PAD[117] recommend its use in patients with PAD whose LDL-C levels remain ≥ 70 mg/dL, in line with the ASCVD guideline recommendation[1].

A subgroup analysis of patients with PAD in the FOURIER trial ($n = 3,642/27,564$) showed that the LDL-C level decreased from 94 mg/dL to 31 mg/dL with evolocumab, supporting its use. Moreover, the primary endpoint (composite of cardiovascular death, MI, stroke, hospital admission for unstable angina, or

coronary revascularization) was significantly reduced by 21% (HR 0.79, 95% CI 0.66–0.94, $P = 0.0098$) and the incidence of MALEs was reduced by 57% (HR 0.43, 95% CI 0.19–0.99, $P = 0.042$). Furthermore, the risk of MACLEs consistently decreased along with LDL-C, to a level as low as 10 mg/dL. In patients with PAD without prior MI or stroke ($n = 1,505$), those treated with evolocumab experienced a significant reduction in the primary endpoint (HR 0.67, 95% CI 0.47–0.96, $P = 0.0283$)[83].

In a small RCT involving patients with PAD or IC ($n = 70$)[130], evolocumab reduced LDL-C to approximately 40 mg/dL, significantly increased maximal walking time and brachial flow-mediated dilatation (vs. placebo: $P = 0.01$ and $P < 0.001$, respectively), and significantly reduced carotid intima–media thickness (vs. placebo; $P < 0.001$). In a Japanese observational study, 30 patients with chronic limb-threatening ischemia were assigned to evolocumab ($n = 14$) or no evolocumab ($n = 16$). The patients in the evolocumab-treated group experienced an LDL-C reduction from 83–89 mg/dL to <40 mg/dL, and 12-month amputation-free survival was significantly higher in the evolocumab-treated group ($P = 0.02$). These findings also support the use of PCSK9 inhibitors in patients with PAD[131].

Based on the evidence, high-intensity statin therapy with an LDL-C treatment target of <70 mg/dL may be considered in patients with PAD **(Table 5)**, and if the target LDL-C is not achieved, the addition of ezetimibe or a PCSK9 inhibitor is reasonable. For patients with PVD who have PAD and CAD (CCS), a stricter LDL-C treatment target of <55 mg/dL may be considered because of their high risk of cardiovascular events (see CQ4).

6. Future Perspectives

In this report, the working group defined each category of ASCVD and assessed LDL-C treatment targets for the secondary prevention of ASCVD based on the latest clinical evidence. In this section, we acknowledge the limitations and issues that need to be further addressed. First, the domestic evidence supporting LDL-C treatment targets remains limited. In particular, evidence supporting the LDL-C treatment target of <55 mg/dL for patients with ACS and CCS with specific risk factors **(Table 6)** needs to be further accumulated in the Japanese population. Second, whether these LDL-C treatment targets could be applicable to very elderly patients remains uncertain, because large-scale clinical evidence on the efficacy of LDL-C-lowering therapy in the very elderly population is still lacking. Further research is required to establish stricter LDL-C targets in the very elderly population while considering the remaining healthy life expectancy. Third, other lipid parameters, such as triglycerides and high-density lipoprotein cholesterol (HDL-C), are excluded from this report, as relevant evidence on the appropriate treatment targets for these lipid parameters is scarce. Fourth, we did not perform a cost-effectiveness analysis of LDL-C-lowering therapy for the secondary prevention of ASCVD. Although PCSK9 inhibitors have been shown to meet cost-effectiveness thresholds in the US[132] and other countries[133], their high cost remains a potential barrier to their clinical use. The cost-effectiveness of LDL-C-lowering therapy, including PCSK9 inhibitors, should be further evaluated in Japan. Moreover, when considering the cost–benefit profile, it is necessary to consider each patient's remaining healthy life expectancy. Finally, we evaluated the level of evidence for each CQ through a scoping review with systematic literature searching, but not with standard systematic review methods. These issues should be addressed in future studies and guideline revisions.

Currently, clinical trials using newer classes of lipid-lowering agents other than statins, ezetimibe, or PCSK9 inhibitors are underway. Bempedoic acid is a lipid-lowering agent that inhibits the cholesterol synthesis pathway by downregulating ATP citrate lyase. The CLEAR Outcomes trial reported the results of bempedoic acid in statin-intolerant patients (those who were unable or unwilling to receive statins owing to an adverse effect that had started or increased during statin therapy and that resolved or improved after discontinuation of statin therapy) with a history of, or at high risk for ASCVD ($n = 13,970$). Bempedoic acid achieved a reduction in mean LDL-C to 29.2 mg/dL, which was significant compared with placebo, and it significantly reduced the risk of MACEs (HR 0.87, 95% CI 0.79–0.96, $P = 0.004$)[134]. However, the study included only statin-intolerant patients, so we await further evidence to evaluate this regimen for secondary prevention in ASCVD. In a phase 3 trial in Japan, bempedoic acid elicited a significant LDL-C reduction in patients with high LDL-C who had inadequate response to statins or statin intolerance, including 31.3% of whom were secondary prevention patients[135]. Bempedoic acid will soon become available on the Japanese market.

The cholesteryl ester transfer protein inhibitor obicetrapib, which was developed in Japan, has undergone non-Japanese and Japanese phase 2 trials[136, 137]. The drug improved lipid indices, including LDL-C, apolipoprotein B, and non-

HDL-C, and was well-tolerated. A phase 3 trial of obicetrapib is now underway in Japan.

Conclusion

In this scientific report, the working group clarified the definition of ASCVD and conducted a scoping review of the latest evidence on LDL-C-lowering therapy for the secondary prevention of ASCVD. The LDL-C treatment targets were assessed for individual ASCVD, including CAD (ACS and CCS), ATBI, and PAD. These LDL-C treatment targets for the secondary prevention of ASCVD are lower than those in previous domestic guidelines. However, because evidence from Japanese patients remains limited, those were primarily based on evidence from global clinical trials and international guidelines. Therefore, further verification in Japanese patients is warranted, particularly considering the ethnic differences in cardiovascular risk, and cost–effectiveness should be also evaluated.

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Supplementary Table 1. Literature search and extraction methods

Primary search: Overall search query (PubMed)	
((cholesterol lowering[Title] OR lipid lowering[Title] OR lipid-lowering[Title] OR lipid management[Title] OR dyslipidaemia[Title] OR dyslipidemia[Title] OR hypercholesterolemia[Title] OR (LDL cholesterol[Title]) OR (low-density lipoprotein[Title]) OR statin[Title] OR atorvastatin[Title] OR pitavastatin[Title] OR rosuvastatin[Title] OR pravastatin[Title] OR simvastatin[Title]) AND (cardiovascular[Title/Abstract] OR (atherosclerotic cardiovascular[Title/Abstract]) OR ASCVD[Title/Abstract] OR CVD[Title/Abstract] OR cardiac[Title/Abstract] OR coronary[Title/Abstract] OR myocardial infarction[Title/Abstract] OR cerebrovascular[Title/Abstract] OR stroke[Title/Abstract] OR PAD[Title/Abstract] OR (peripheral arterial disease[Title/Abstract]))) OR (PCSK9[Title] OR evolocumab[Title] OR alirocumab[Title] OR ezetimibe[Title] OR inclisiran[Title]) AND (("2013/1/1"[Date - Create] : "3000"[Date - Create]))	
Secondary search: Search queries for the individual clinical questions (CQs) (PubMed)	
CQ1	Is the early initiation of high-intensity statin therapy beneficial for lipid management in patients with ACS?
CQ2	Is the LDL-C treatment target of <55 mg/dL beneficial in patients with ACS?
	(acute coronary syndrome[Title/Abstract] OR myocardial infarction[Title/Abstract] OR percutaneous coronary intervention[Title/Abstract] OR PCI[Title/Abstract] OR coronary artery bypass graft[Title/Abstract] OR CABG[Title/Abstract]) AND (cholesterol lowering[Title] OR lipid lowering[Title] OR lipid-lowering[Title] OR lipid management[Title] OR dyslipidaemia[Title] OR dyslipidemia[Title] OR hypercholesterolemia[Title] OR (LDL cholesterol[Title]) OR (low-density lipoprotein[Title]) OR LDL-C[Title] OR statin*[Title] OR atorvastatin[Title] OR pitavastatin[Title] OR rosuvastatin[Title] OR pravastatin[Title] OR simvastatin[Title] OR PCSK9[Title] OR evolocumab[Title] OR alirocumab[Title] OR ezetimibe[Title] OR inclisiran[Title]) AND (("2013/1/1"[Date - Create] : "3000"[Date - Create]))
CQ3	Is high-intensity statin therapy beneficial for lipid management in patients with CCS?
CQ4	Is the LDL-C treatment target of <70 mg/dL beneficial in patients with CCS?
	(chronic coronary syndrome[Title/Abstract] OR stable coronary[Title/Abstract] OR stable angina[Title/Abstract] OR unstable angina[Title/Abstract] OR angina of effort[Title/Abstract]) AND (cholesterol lowering[Title] OR lipid lowering[Title] OR lipid-lowering[Title] OR lipid management[Title] OR dyslipidaemia[Title] OR dyslipidemia[Title] OR hypercholesterolemia[Title] OR (LDL cholesterol[Title]) OR (low-density lipoprotein[Title]) OR LDL-C[Title] OR statin*[Title] OR atorvastatin[Title] OR pitavastatin[Title] OR rosuvastatin[Title] OR pravastatin[Title] OR simvastatin[Title] OR PCSK9[Title] OR evolocumab[Title] OR alirocumab[Title] OR ezetimibe[Title] OR inclisiran[Title]) AND (("2013/1/1"[Date - Create] : "3000"[Date - Create]))
CQ5	Is statin therapy beneficial for lipid management in patients with ATBI?
CQ6	Is the LDL-C treatment target of <70 mg/dL beneficial in patients with ATBI?
	(cerebrovascular[Title/Abstract] OR stroke[Title/Abstract] OR aortic arch[Title/Abstract] OR carotid[Title/Abstract]) AND (cholesterol lowering[Title] OR lipid lowering[Title] OR lipid-lowering[Title] OR lipid management[Title] OR dyslipidaemia[Title] OR dyslipidemia[Title] OR hypercholesterolemia[Title] OR (LDL cholesterol[Title]) OR (low-density lipoprotein[Title]) OR LDL-C[Title] OR statin*[Title] OR atorvastatin[Title] OR pitavastatin[Title] OR rosuvastatin[Title] OR pravastatin[Title] OR simvastatin[Title] OR PCSK9[Title] OR evolocumab[Title] OR alirocumab[Title] OR ezetimibe[Title] OR inclisiran[Title]) AND (("2013/1/1"[Date - Create] : "3000"[Date - Create]))
CQ7	Is high-intensity statin therapy beneficial for lipid management in patients with PAD?
CQ8	Is the LDL-C treatment target of <70 mg/dL beneficial in patients with PAD?
	(PAD[Title/Abstract] OR peripheral artery disease[Title/Abstract] OR peripheral arterial disease[Title/Abstract] OR limb ischemia[Title/Abstract] OR claudication[Title/Abstract] OR lower extremity bypass[Title/Abstract] OR lower extremity arterial disease[Title/Abstract] OR lower extremity arteriosclerosis[Title/Abstract]) AND (cholesterol lowering[Title] OR lipid lowering[Title] OR lipid-lowering[Title] OR lipid management[Title] OR dyslipidaemia[Title] OR dyslipidemia[Title] OR hypercholesterolemia[Title] OR (LDL cholesterol[Title]) OR (low-density lipoprotein[Title]) OR LDL-C[Title] OR statin*[Title] OR atorvastatin[Title] OR pitavastatin[Title] OR rosuvastatin[Title] OR pravastatin[Title] OR simvastatin[Title] OR PCSK9[Title] OR evolocumab[Title] OR alirocumab[Title] OR ezetimibe[Title] OR inclisiran[Title]) AND (("2013/1/1"[Date - Create] : "3000"[Date - Create]))