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2026 Taiwan Society of Lipids and Atherosclerosis consensus statement for the identification and management of patients receiving suboptimally tolerable statins

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ABSTRACT

Statins are the cornerstone of lipid-lowering therapy for the prevention of atherosclerotic cardiovascular disease (ASCVD); however, many patients are unable to achieve guideline-recommended low-density lipoprotein cholesterol (LDL-C) targets because of suboptimal tolerance to statins. The 2026 Taiwan Society of Lipid and Atherosclerosis (TSLA) Consensus Statement presents an updated, evidence-based framework for the identification and management of patients receiving suboptimally tolerable statins (STS)—a pragmatic concept that extends beyond the traditional and restrictive definition of statin intolerance (SI). STS encompasses patients who are unable to maintain recommended statin intensity because of real or perceived adverse effects, even when formal SI criteria are not met, thereby addressing a major treatment gap in real-world practice in Taiwan.

This consensus integrates contemporary international evidence and Taiwanese guidelines, including the 2025 Taiwan cholesterol management pathway, and proposes structured, risk-based algorithms for STS management. A tiered therapeutic strategy is recommended: extremely high-risk patients should receive early combination

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therapy with ezetimibe and bempedoic acid, with prompt escalation to PCSK9 inhibition–based agents if LDL-C targets (<55 mg/dL) are not achieved. In high- and very high-risk patients, ezetimibe is the first-line add-on therapy, followed by bempedoic acid and PCSK9-targeted agents as needed, while lifestyle intervention and shared decision-making are emphasized in lower-risk groups. Non-pharmacological options are also reviewed; however, robust cardiovascular outcome data remain limited.

By bridging conceptual and policy gaps between SI and STS, this consensus promotes a patient-centered, precision-based approach to improving LDL-C goal attainment and reducing residual ASCVD risk.

1. Introduction

Statins are the cornerstone of lipid-lowering therapy and have consistently demonstrated robust benefits in reducing low-density lipoprotein cholesterol (LDL-C) and preventing atherosclerotic cardiovascular disease (ASCVD) events across a broad spectrum of patient populations. Landmark trials and meta-analyses have shown that each 1 mmol/L (~39 mg/dL) reduction in LDL-C leads to an approximately 20–25% relative risk reduction in major cardiovascular outcomes, including myocardial infarction, stroke, and cardiovascular mortality [1]. More recently, many international guidelines, including those from the European Society of Cardiology (ESC), National Lipid Association (NLA), Japan Atherosclerosis Society, as well as the consensus from 9 Taiwanese professional societies, uniformly recommend high-intensity statins or maximally tolerated doses as first-line agents to achieve LDL-C targets for patients at high and very high ASCVD risk [2–5].

Despite these recommendations, real-world data consistently show suboptimal attainment of LDL-C targets in clinical practice, partly due to issues of suboptimal tolerability [2,3,5,6]. Statin intolerance (SI), broadly defined as the inability to tolerate statins at doses required to achieve therapeutic goals due to adverse effects—particularly muscle symptoms or hepatic enzyme elevations—has been reported in 5% to 30% of patients depending on the population and study design [3]. In Taiwan, the use of statins has steadily increased over the past two decades, yet the prevalence of statin-related side effects has also risen, necessitating a localized, evidence-based clinical framework to identify and manage statin-intolerant individuals [6]. To date, definitions of SI have varied internationally, but key criteria generally include (1) prior exposure to at least two different statins (including one at the lowest approved daily dose), (2) development of reproducible adverse symptoms or laboratory abnormalities temporally associated with statin use, and (3) symptom resolution or improvement upon discontinuation [3,6,7].

A Taiwanese consensus in 2019 emphasized statin-related muscle and hepatic side effects as primary clinical concerns, and proposed a pragmatic, operational definition tailored for Taiwanese clinicians. However, patients with confirmed SI according to this stringent algorithm may account for only a small proportion of patients receiving suboptimally tolerable statins (STS), who still bear substantially high residual risk of ASCVD. Moreover, evolving pharmacologic options—including ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and more recently, bempedoic acid (BA)—along with emerging clinical trial data such as the CLEAR Outcomes trial, have expanded the armamentarium for managing patients receiving STS [3,8].

Considering these developments, the Taiwan Society of Lipids and Atherosclerosis (TSLA), in collaboration with relevant clinical stakeholders, has developed an updated consensus statement to define, identify, and manage patients receiving STS. This document aims to assist clinicians in Taiwan in optimizing ASCVD risk reduction while addressing the unmet needs of patients with real or perceived SI. Through a practical and patient-centered approach, this statement seeks to close the gap between guideline recommendations and real-world implementation.

2. Global status and definition of SI

2.1. Global guidelines and definitions for patients with SI

Defining SI precisely remains a challenge, as no single, universally accepted definition currently exists across all global medical bodies. However, several major international organizations and national societies have established definitions and criteria to guide clinical practice [3,6,9–12], reflecting an evolving understanding and ongoing efforts toward standardization.

A core concept shared across most definitions is that SI is primarily identified as a clinical syndrome based on a pattern of adverse effects [3]. This pattern typically involves the onset of symptoms or laboratory abnormalities temporally related to statin initiation or dose increase, resolution or improvement upon statin discontinuation or dose reduction, and often, recurrence upon re-exposure (rechallenge). Establishing this causal link through dechallenge and rechallenge, while excluding other potential causes for the symptoms, is fundamental to the diagnosis.

Among the key international bodies, the **National Lipid Association (NLA)** defines SI as "one or more adverse effects associated with statin therapy which resolves or improves with dose reduction or discontinuation" [9]. Crucially, the NLA specifies that to classify a patient as having SI, a minimum of two different statins should have been attempted, with at least one tried at the lowest approved daily dosage. The NLA further distinguishes between complete intolerance (inability to tolerate any dose of any statin) and partial intolerance (inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective) [9]. The 2022 NLA Scientific Statement reiterates this, emphasizing that for classification, "a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage" [3]. The 2014 NLA Expert Panel on Statin Intolerance provided a detailed clinical syndrome definition requiring the inability to tolerate at least two statins (one at the lowest starting dose, another at any dose) due to symptoms or lab abnormalities that are temporally related, reversible, and reproducible, with other causes excluded [9].

The **European Atherosclerosis Society (EAS)**, in its 2015 consensus panel statement, often focuses on statin-associated muscle symptoms (SAMS) or creatine kinase (CK) elevations [10]. Their criteria emphasize the temporal association with statin use, reversibility upon cessation, and reproducibility upon rechallenge. The EAS also highlights the importance of excluding other causes and considering the potential influence of the "nocebo effect". The panel noted that their definition is clinical and may not be appropriate for regulatory purposes. While the 2019 ESC/EAS dyslipidemia guidelines do not provide a formal SI definition, they offer management pathways for patients unable to tolerate statins [11].

The **International Lipid Expert Panel (ILEP)**, in its 2015 unified definition, aligns broadly with the NLA and EAS [12]. It defines SI based on four criteria: 1) The inability to tolerate at least two different statins (one at the lowest starting average daily dose and the other at any dose); 2) Intolerance associated with confirmed intolerable statin-related adverse effect(s) or significant biomarker abnormalities; 3) Resolution or significant improvement of symptoms or biomarker changes upon dose decrease or discontinuation; and 4) Symptoms or biomarker changes not attributable to established predispositions like drug-drug interactions or conditions increasing SI risk.

Table 1
Comparison of key society definitions of SI.

Feature	NLA (USA) [3,9]	EAS (Europe) [10,11]	TSLA (Taiwan) [6]
Core Definition	Adverse effects related to statin, improved after discontinuation or dose reduction	Muscle symptoms/CK elevation related to statin, improved after discontinuation, recurrent on rechallenge	Unacceptable symptoms/lab abnormalities related to statin, improved after discontinuation, recurrent on rechallenge (switching to another statin)
Minimum Statins Tried	≥2	Not explicitly specified, but rechallenge emphasized	≥2
Lowest Dose Requirement	At least one at the lowest approved daily dose	Not specified	At least one at the lowest starting daily dose (per Taiwan FDA)
Symptoms/ Abnormalities	Any related adverse effects	Mainly SAMS or CK elevation	Unacceptable symptoms (mainly muscle/liver) or lab abnormalities
Reversibility/ Recurrence	Improved after discontinuation or dose reduction	Improved after discontinuation, recurrent on rechallenge	Improved after discontinuation, recurrent on switching to another statin
Exclusion of Other Causes	Implied	Explicitly required	Explicitly required
Intolerance Classification	Complete vs. partial intolerance	Not classified	Not explicitly classified, but rhabdomyolysis qualifies as SI

A common thread in the NLA [3,9], EAS [10,11], ILEP [12], and TSLA [6] approaches is the requirement or strong recommendation to try different statins before confirming intolerance. This implicitly acknowledges that intolerance may not always be a class effect but could be related to the specific properties of an individual statin, suggesting that switching agents is a viable strategy for many patients experiencing adverse effects [13].

In Taiwan, the **Taiwan Society of Lipids and Atherosclerosis (TSLA)** published an expert consensus statement in 2019 [6], providing specific criteria adapted for the local context. The TSLA definition requires fulfilling four criteria:

1. Assessment of at least two different statins, including one administered at the lowest starting daily dose according to Taiwan Food and Drug Administration (FDA)-approved package inserts, and another statin at any daily dose. Examples of the lowest starting doses include atorvastatin 10 mg, rosuvastatin 5 mg, simvastatin 5 mg, and pravastatin 10 mg.
2. Development of unacceptable symptoms (often muscular or hepatic) or abnormal laboratory results after starting statins.
3. Reversibility of adverse effects upon discontinuation and reproducibility upon rechallenge (specifically termed "switch" to another statin in their myalgia scoring system to emphasize trying different agents).
4. Exclusion of other possible etiologies for the symptoms or laboratory abnormalities.The TSLA consensus also notes that any documented episode of statin-related rhabdomyolysis automatically qualifies as SI.

Table 1 provides a comparison of these key society definitions.

2.2. *Statin-associated muscle symptoms*

Statin-associated muscle symptoms (SAMS) are the most frequently reported adverse effects of statin therapy and a leading cause of treatment modification or discontinuation [13]. While SAMS do not necessarily result in complete SI, they contribute to the emergence of a clinical subgroup described as receiving STS [10,13]. These individuals, though not meeting criteria for SI, still fail to achieve guideline-recommended lipid-lowering intensity due to muscle-related side effects.

Patients with SAMS typically present with the following features [6]:

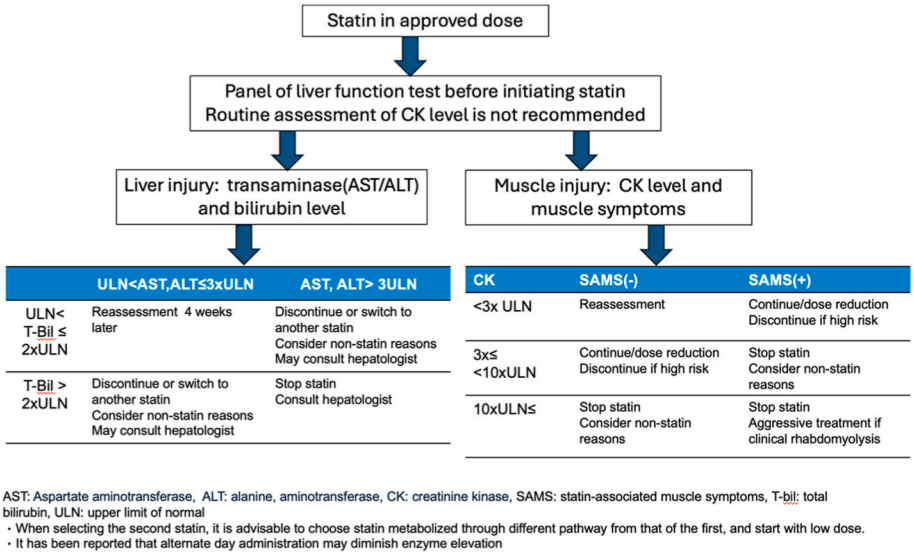

Fig. 1. Recommended approaches to adverse events (liver injury and muscle injury) during statin administration. For liver injury, AST, ALT and T-bilirubin are checked to determine the severity of liver injury. Management is guided by the magnitude of transaminase elevation relative to the upper limit of normal and the presence of hyperbilirubinemia. Alternative causes of liver dysfunction, including acute viral hepatitis, hepatobiliary disease, systemic illness, and concomitant hepatotoxic medications, should be evaluated concurrently. For muscle injury, statin-associated muscle symptoms (SAMS) and CK are checked to determine the severity of muscle injury. The severity of muscle involvement is determined by the extent of CK elevation in conjunction with symptom status, which guides subsequent dose adjustment, temporary interruption, or discontinuation of statin therapy.

- Myalgia: muscle aches, or soreness without creatine kinase (CK) elevation
- Myopathy: muscle symptoms with mild to moderate CK elevation (<10x ULN)
- Myositis: rare and typically autoimmune-related
- Rhabdomyolysis: very rare, severe muscle damage with marked CK elevation and potential renal complications

The onset of symptoms often occurs within 4 weeks of initiating statin therapy [6,14,15]. Many are nonspecific and overlap with age-related or activity-induced discomfort. Diagnosis is primarily clinical, based on the timing of symptom onset, resolution after dose reduction or statin withdrawal, and recurrence upon rechallenge. Most patients receiving STS due to SAMS fall within the spectrum of myalgia or mild myopathy and a normal CK does not exclude SAMS.

A thorough assessment is essential to rule out other causes of muscle symptoms, such as hypothyroidism, Vitamin D deficiency, physical overexertion, rheumatologic conditions or drug interactions, especially with CYP3A4 inhibitors [12,14,15]. Some clinical assessments such as the SAMS-CI (Clinical Index) tool may help confirm or refute statin causality but are not mandatory in routine practice.

For patients with SAMS who fall into the STS category, management should be pragmatic, emphasizing tolerability over rigid target LDL-C goals [6]. Fig. 1 shows the following flowchart for assessment and management of SAMS, including dose adjustment and switching of statins, adjunctive therapy, patient communication, and follow-up.

2.3. Statin-associated liver abnormalities

Up to approximately 3% statin-treated patients have elevations of serum liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) in the first year of statin therapy [16]. The statin-related transaminases elevation is thought to be a class effect, with more reports in some statins [17]. However, the elevation is usually mild (<3X the upper limit of normal [ULN]) and does not represent liver injury clinically or histologically in the absence of increasing bilirubin or hepatic synthetic dysfunction [18–20]. Dose-related asymptomatic increases in liver transaminases greater than 3 times the ULN occur in approximately 1% of patients [21]. The increase of transaminases often returns to baseline without discontinuation or dose adjustment of statin therapy. There are several explanations about statin and transaminases release; however, the exact mechanism is still not clear [17]. The incidence of clinically significant drug-induced liver injury (DILI) attributable to statins is rare. A systematic review reported that the incidence of statin-related liver failure is about 1 per one million person-years [22]. In a post-market review between years 2000 to 2009 conducted by the United States (US) FDA, a low incidence of statin-associated serious hepatotoxicity (2 per one million patient-years) was reported (US FDA. FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. Available at: http://www.fda.gov/drugs/drugsafety/ucm293101.htm.) DILI in patients with statin therapy is more likely idiosyncratic in nature [19]. Additionally, there was no evidence demonstrating the effectiveness of regular monitoring liver function in detection of DILI after starting statin therapy [17,20,23]. Therefore, it is not necessary to regularly monitor liver function in patients receiving statins [10]. Flowchart for assessment and management of liver injury under statin is shown in Fig. 1.

2.4. Other statin-associated intolerances

In addition to SAMS and hepatotoxicity, statin therapy can be associated with a range of other adverse effects that may impair adherence. Gastrointestinal complaints—including nausea, dyspepsia, abdominal pain, constipation, or diarrhea—occur in approximately 5–10% of patients [10,24]. Central nervous system (CNS) effects such as headache, insomnia, dizziness, and cognitive complaints are reported in up to 3–5%, though causality remains debated [25,26]. Memory issues or confusion may occur in <2% of users but typically resolve after discontinuation [27]. Dermatologic reactions, including rash, pruritus, and alopecia, have also been reported with statin therapy, although they are uncommon. Evidence suggests that these adverse effects may share underlying mechanisms with other non-muscle toxicities, potentially linked to statin-induced mitochondrial dysfunction [28]. Sexual dysfunction, including erectile dysfunction, has been reported in 1–2% of male patients [29,30]. Statins have also been associated with a modest increase in the risk of new-onset diabetes mellitus, with an estimated 9–12% relative risk increase, particularly in patients with pre-existing risk factors [31]. Although these non-muscle, non-hepatic side effects are less common, they are clinically important and can lead to discontinuation if not proactively addressed. Clinicians should regularly assess for these symptoms and provide reassurance or consider alternative strategies when necessary.

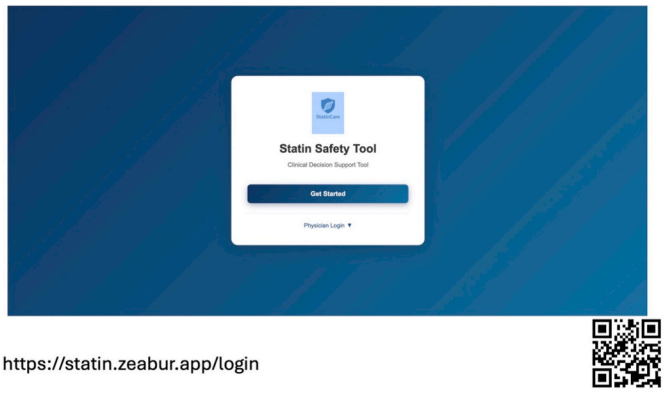

Fig. 2. The web platform to provide quick assessment of whether patients have SI. Patients or health professionals can easily access the platform for free by scanning the QR code or by searching the web address: https://statin.zeabur.app/login. This digital platform is designed according to SI diagnostic algorithm [6] to stepwise identify whether patients have SI. After providing the initial data requested, the platform will provide feedback with the next recommended step. After the adjustment according to the suggestion, users can use the platform again to check for the next suggestion. If at least two attempts according to the suggestions have been done without amelioration, users can confirm the presence of SI.

To fast assess whether SI is present, we provide an app for a quick screening (https://statin.zeabur.app/login). Physicians or patients can just scan the QR code for a direct access to the entry portal (Fig. 2). This platform is designed according to Taiwanese SI guidelines [6] to stepwise identify whether patients have SI. After providing the initial data requested, the platform will feedback with the next step suggested. After the adjustment suggested by the feedback, users can use the platform again to check for the next suggestion. After at least two attempts according to the suggestions, users can conclude whether SI is the likely diagnosis.

3. ASCVD risk in patients with SI

When assessing ASCVD risk in patients with SI, several important considerations should be taken into account:

1. **Patient population susceptible to SI:** Individuals who are prone to developing SI often share clinical characteristics and comorbidity profiles (such as elderly, obesity, diabetes, CKD) [13] that are also associated with higher baseline ASCVD risk.
2. **Impact of SI on treatment adherence:** By definition, SI prevents patients from receiving guideline-recommended statins, thereby increasing ASCVD risk.

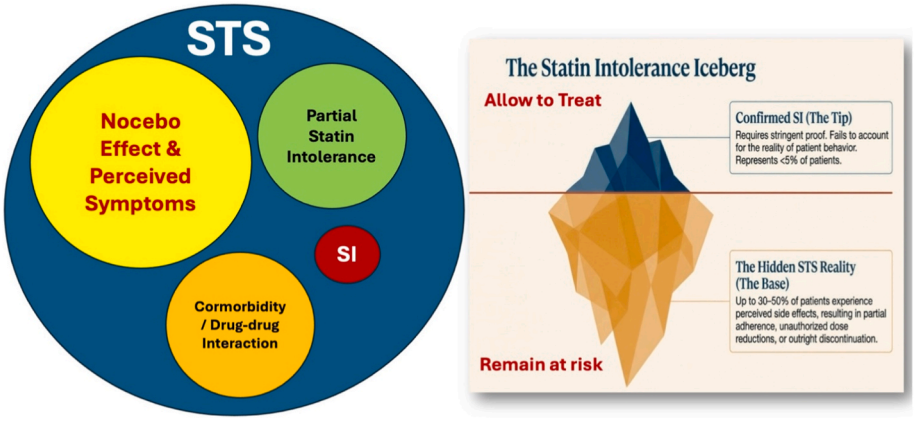

Fig. 3. The concept illustration of STS. STS is defined by patients who have been receiving maximally tolerable statins or are completely intolerant to statins for any reason (including discontinuing statin therapy due to real or perceived side effects [nocebo effect]) but still cannot achieve the individual therapeutic goals according to the "2025 Consensus on the Clinical Pathway of Blood Cholesterol Management in Taiwan" [4]. This STS population is estimated to encompass over half of all ASCVD patients. Genuine SI patients, who may allow treatment with non-statin lipid-lowering agents in health insurance system, are estimated to account for only less than 5% of patients with STS [41], leaving the majority of STS patients still at risk. Except for nocebo effects and SI, patients may receive STS because of co-morbidities, drug-drug interaction, or partial SI. Any other reasons which are not shown in this figure, such as statin availability- or physician inertia-related underuse of statins, are also included in the concept of STS. (see Sections 4 and 5 for details).

3. **Risk classification:** It is essential to determine whether the patient falls into the primary or secondary prevention category, as this significantly influences risk assessment and treatment strategy.

The recent meta-analyses [13,32] identified several predisposing factors for SI that overlap with established ASCVD risk factors. Accordingly, patients prone to SI often represent a population with a less favorable baseline cardiovascular risk profile, even before the impact of suboptimal statin exposure is taken into account. These results highlight that addressing modifiable risk factors is especially critical—not only to reduce the likelihood of developing SI and enable patients to tolerate standard dose of statin, but also to directly mitigate ASCVD risk.

Risk stratification of patients with SI should also consider whether the patient is undergoing primary or secondary prevention. The recently published CLEAR Outcomes study [8], a randomized controlled trial (RCT) specifically designed for patients with SI, demonstrated that treatment with an ATP citrate lyase inhibitor (BA) significantly reduced ASCVD risk. Among patients with SI and a mean baseline LDL-C of 139 mg/dL, BA reduced the risk of composite 3-point adverse events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) by 15% and 4-point adverse events (3-point adverse events plus coronary revascularization) by 13% compared to placebo. Additionally, the benefits exhibited by BA were more significant in patients with primary prevention compared to those patients with secondary prevention. The findings from the CLEAR Outcomes study emphasized the enhanced risk in SI patients who are unable to further lower LDL-C levels through effective pharmacologic therapies. Furthermore, the subgroup analysis of the CLEAR Outcomes study also revealed that among participants in the placebo arm, ASCVD events were more frequent in those classified as secondary prevention compared to those classified as primary prevention group. This finding underscores the need for more aggressive ASCVD risk assessment and management in SI patients within the secondary prevention cohort. Beyond LDL-C, contemporary precision lipid management also requires attention to residual risk markers such as apoB, non-HDL-C, and lipoprotein(a) [Lp(a)]. ApoB reflects the total concentration of circulating atherogenic lipoprotein particles and, together with non-HDL-C, may stratify ASCVD risk more accurately than LDL-C alone, particularly in patients with elevated triglycerides, diabetes mellitus, obesity, or metabolic syndrome, in whom LDL-C may underestimate atherogenic burden [4,33]. In addition, Lp(a) is an independent causal risk factor for ASCVD and may further refine risk assessment beyond conventional lipid parameters [34]. Therefore, in patients with SI or STS, attainment of LDL-C targets alone should not preclude further evaluation of residual risk; persistent elevation of apoB, non-HDL-C, or Lp(a) may support earlier intensification of non-statin therapy and more comprehensive cardiovascular risk management.

Apart from CLEAR Outcomes trial, a landmark study supporting this concept is the Treating to New Targets (TNT) trial [35], a RCT involving patients aged 35–75 years with coronary artery disease (CAD), 58% of whom had a history of myocardial infarction and 19–20% were female. The TNT trial compared high-intensity statin (atorvastatin 80 mg/day) with moderate-intensity statin (atorvastatin 10 mg/day) and showed that these high-risk patients receiving only 10 mg/day of atorvastatin had a 22% higher risk of experiencing adverse cardiovascular events compared to those receiving high-intensity 80 mg/day dosage, implying that even patients with only partial SI still have a higher risk than patients without SI.

In conclusion, among patients with SI, those in the secondary prevention category carry a higher ASCVD risk than those in the primary prevention group. Moreover, failure to initiate or maintain statin therapy, as recommended by clinical guidelines, further increases ASCVD risk in patients with SI. Residual risk assessment should also extend beyond LDL-C alone, with consideration of apoB, non-HDL-C, and Lp(a) when clinically appropriate.

4. Patients receiving STS

4.1. Patients receiving STS vs. patients with SI

Currently, there is no universally definite definition of SI. According to the International Lipid Expert Panel (ILEP) [12], SI refers to the inability to tolerate a statin dose sufficient to achieve recommended cardiovascular risk reduction, thereby limiting optimal treatment in patients at risk for or with established ASCVD. The NLA offers a broader definition, encompassing any adverse effects that impact quality of life and result in dose reduction or discontinuation of an otherwise beneficial statin [9]. Similarly, the Luso-Latin American Consortium (LLAC) and the Canadian Consensus Working Group (CCWG) define SI as the inability to tolerate any statin dose or to escalate to higher doses, provided symptoms cannot be attributed to drug-drug interactions or underlying conditions known to increase susceptibility to SI [36,37]. Despite these varying definitions, common themes emerge: SI leads to suboptimal statin therapy, either through failure to titrate to guideline-recommended doses or inability to initiate statins.

Table 2
The major conceptual differences between SI and STS.

	SI	STS
Identification	Dechallenge/ Rechallenge protocols to prove symptoms	Clinical reality of failure to achieve recommended intensity and LDL-C targets
Minimun statins tried	≥2	Any suboptimal use or complete non-adherence
Inclusion of nocebo effects	Excluded	Fully acknowledged as a valid barrier to care
Primary clinical goal	Prove causality of adverse effect	Lower ASCVD risk without delay

ASCVD, atherosclerostic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; SI, statin intolerance; STS, suboptimally tolerable statins.

In clinical practice, SI is often based on perceived symptoms that are difficult to verify as statin-induced [38]. Several findings support this complexity: (1) No consistent biochemical or pathological markers are reliably detected in SI patients; (2) In placebo-controlled, cross-over trials involving patients with self-reported SI, statin-associated symptoms are often not reproducible with blinded statin administration compared to placebo; (3) Other statin-associated symptoms, such as cognitive impairment, remain yet unconfirmed in large-scale cohort studies; (4) Some clinical scoring systems have been developed to estimate the probability of true SI, though these tools are imprecise and not commonly implemented in routine care [10,12,39,40]. Actually, patients with genuine SI have been reported to account for only less than 5% of patients who discontinue their statins [41]. Given these limitations, we propose a more pragmatic term: "Suboptimally Tolerable Statins" (STS). STS emphasizes the clinical relevance of identifying patients who, for any reason—whether physiological, psychological, preference-based, statin/dose availability- or physician inertia-related—are unable or unwilling to take sufficient statins to achieve guideline-recommended LDL-C targets rather than verifying whether symptoms are causally related to statin use (see concept illustration in Fig. 3). Table 2 also summarizes the major conceptual differences between SI and STS. This concept highlights that clinicians should prioritize early initiation of non-statin lipid-lowering therapies to reduce ASCVD risk in this vulnerable population. We recommend adopting the practical and comprehensive framework of STS alongside the conventional SI definitions. In agreement with this notion, the recent study enrolling patients with untargeted LDL-C and inadequate statin use for any reasons also demonstrates significant cardiovascular benefit of using non-statin lipid-lowering therapy [8]. This more flexible approach better reflects real-world clinical challenges and encourages timely and effective ASCVD risk management.

4.2. *Identification algorithm for patients receiving STS*

The central concept of identifying patients receiving STS is to reduce ASCVD risk "as soon as possible" particularly for higher-risk patients. Confirming SI or adjusting statins should not be a reason to delay the use of non-statin lipid-lowering therapies to help early reach the LDL-targets. We encourage adopting shared decision-making tools, health education tools, or other media to mitigate nocebo effects and enhance maximally tolerable statin adherence; however, the endeavor does not exclude the use non-statin lipid-lowering drugs in parallel, if patients

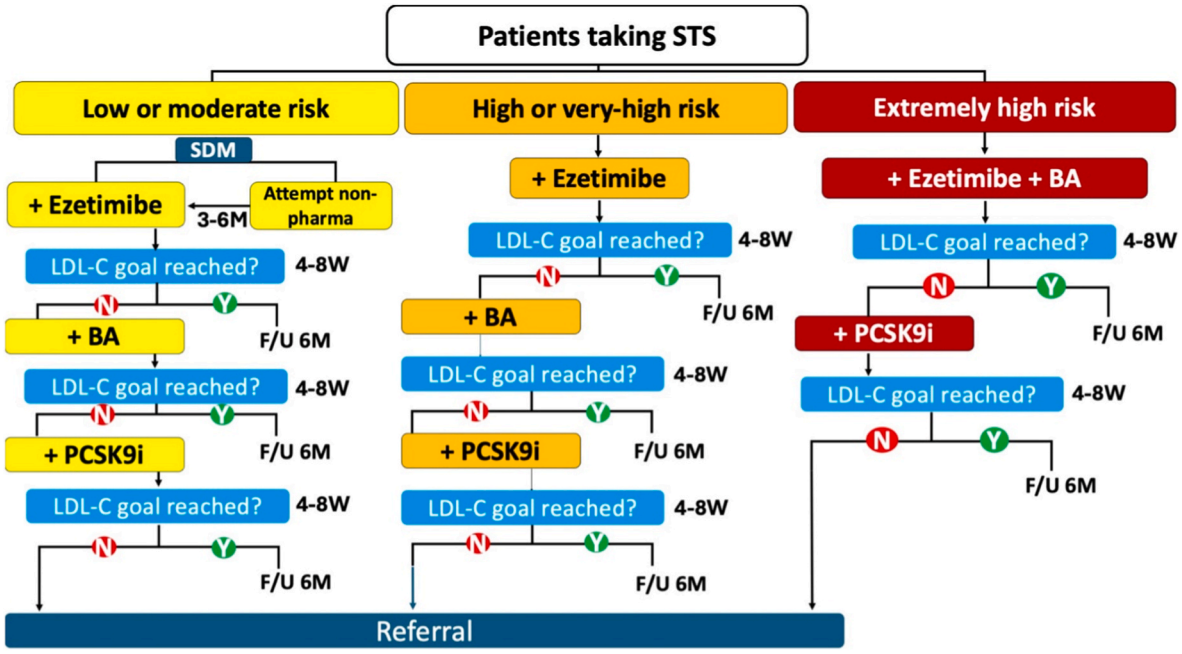

Fig. 4. The algorithm for managing patients receiving STS. Patients with STS may be divided into two categories: those belong to secondary prevention (including extremely high-risk and very high-risk groups) and those belong to primary prevention (including low-, moderate-, and high-risk groups), according to the "2025 Consensus on the Clinical Pathway of Blood Cholesterol Management in Taiwan" [4]. The central spirit of this algorithm is to achieve timely reduction of ASCVD risk and should not exclude further adjustment of statins or lifestyle modification at the same time. Of note, patients with "extremely high-risk", initial combination of BA and ezetimibe is recommended for early goal attainment to prevent potentially imminent ASCVD events. For patients with "very-high risk" or "high risk", a stepwise addition of non-statin lipid lowering agents is recommended. The recommended period to recheck LDL-C after initiation of a therapy is 4-8 weeks.
Rapid LDL goal achievement is not as strictly required for low- or moderate-risk patients as in extremely high-risk or very high-risk patients. And thus, it may allow shared decision-making (SDM) to start with non-pharmacological intervention (non-pharma) or ezetimibe therapy. The recommended period to recheck LDL-C level is 3-6 months after initial non-pharmacological intervention and 4-8 weeks after initiation of a drug therapy. If the initial non-pharmacological intervention fails to reach the LDL target, ezetimibe therapy can be started. If the LDL-C target is reached, the level should be followed 6 months later to ensure that the target is maintained. For details, please refer to Section 6.3.
BA, bempedoic acid; PCSK9i, PCSK9 inhibition-based agents, including inhibitors or siRNAs; Y, yes, LDL-C goal achieved; N, no, LDL-C goal not achieved; F/U, follow-up; W, weeks; M, months.

Table 3
Risk stratification and LDL-C targets.

Risk levels	Low	Moderate	High	Very High	Extremely High
LDL-C targets	<130 mg/dl	<115 mg/dl	<100 mg/dl	<70 mg/dl	<55 mg/dl
Criteria	Cardiovascular risk factors: **Low:** 1 risk factor; **Moderate:** ≥2 risk factors 1) Hypertension 2) Age (male ≥45y, female ≥55y) 3) Family history of early onset CAD (male <55y, female <65y) 4) HDL-C (male <40 mg/dL, female <50 mg/dL) 5) Smoking 6) Metabolic syndrome (≥3 items): - Waist circumference (male ≥90 cm, female ≥80 cm) - Elevated BP (≥130/85 mmHg or using anti-hypertension therapy) - Elevated fasting glucose (≥100 mg/dL or using DM therapy) - Elevated fasting TG (≥150 mg/dL or using TG-lowering therapy) - Low HDL-C (male <40 mg/dL, female <50 mg/dL)		1) Diabetes mellitus 2) Chronic kidney disease (pre-dialysis CKD, including UACR ≥30 mg/g or eGFR <60 mL/min/1.73 m2 for ≥3 months) 3) LDL-C ≥190 mg/dL 4) CAC score ≥400	Diagnosis of clinical ASCVD including: 1) History of ACS 2) Received coronary revascularization (PCI or CABG) 3) History of ischemic stroke/transient ischemic attack with atherosclerosis-related disease 4) Peripheral artery disease (has received revascularization, has symptoms related to limb ischemia, or has undergone amputation) 5) Imaging examination confirms significant plaque burden, defined as ≥50% diameter stenosis, including: - Coronary artery angiography - Coronary or peripheral computed tomography angiography - Carotid or peripheral ultrasound	1) CAD with any one of the following clinical conditions: - Recent MI within 1 year - History of ≥2 Mis - Multivessel CAD - ACS and diabetes mellitus - Peripheral artery disease or carotid stenosis 2) Peripheral artery disease with CAD OR carotid stenosis

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; TG, triglyceride; UACR, urine albumin-creatinine ratio. (Modified from: Li YH and Shih CL. *Acta Cardiol* Sin 2025; 41:161-165 [4]. with permission).

receiving STS identified.

The identification algorithm for patients receiving STS is designed to distinguish this broad clinical group from those with strictly defined SI [6] (cf. Section 2). Whereas SI requires reproducible adverse effects confirmed through dechallenge and rechallenge with at least two statins, STS encompasses patients who remain unable to achieve LDL-C targets at any doses of tolerable statins or who discontinue statins due to real or perceived side effects, including nocebo-related symptoms, or any other reasons (see Fig. 3).

The algorithm (Fig. 4) begins with risk stratification according to the 2025 Taiwan cholesterol management consensus, classifying patients into low, moderate, high, very-high, and extremely high ASCVD risk categories (Table 3) [4] according to the criteria mentioned in table. A stepwise lower level of LDL-C targets (<130, <115, <100, <70, <55 mg/dl) are given for the escalating risk levels (low, moderate, high, very-high, and extremely high risks, respectively). For each risk group, the algorithm evaluates current statin exposure, tolerability, and LDL-C goal attainment. Patients who are unable to reach therapeutic targets with any tolerated statin doses are labeled as "STS." Importantly, the algorithm integrates shared decision-making and stepwise addition of non-statin lipid-lowering therapies, such as ezetimibe, BA, or PCSK9 inhibition-based agents, depending on the patient's ASCVD risk and treatment response (For details, please refer to Section 6.3. and Fig. 4). Several of the most updated international guidelines or consensus statements also support this concept [5,42,43].

This pragmatic framework acknowledges the gap between rigid SI definitions and real-world practice, thereby providing clinicians with a structured pathway to identify STS patients and initiate appropriate adjunctive therapies.

5. The potential gap between health policies derived from SI and STS

A critical gap exists between health policies traditionally derived from the concept of SI and the broader clinical reality of STS use. Most guideline definitions of SI, such as those from the NLA, EAS, and TSLA (see Table 1), require rigorous criteria including failed trials of at least two different statins, symptom resolution upon discontinuation, and

reproducibility upon rechallenge [2,3,6]. This stringent framework identifies only a small subset of patients not receiving optimal statins either in strength or in dosage, often underestimating the large population who cannot achieve LDL-C targets because they can tolerate only low or intermittent statin doses, or discontinue therapy due to real or perceived side effects (including nocebo effects) [1,7] (see Fig. 3). Consequently, health policies that link reimbursement or treatment access solely to SI definitions risk excluding a large subset of high-risk patients from timely non-statin therapies such as ezetimibe, PCSK9 inhibition agents, or BA.

The Imperial College group has recently published an interesting report showing that "taking tablets" *per se*, either statin or placebo, is the major cause of symptoms, leading to ~20% of patients discontinuing the tablets after one month of treatment [44,45]. In other words, only this nocebo effect may potentially account for as high as one-fifth of patients with STS in the real-world practice. The recently published real-world data from the T-SPARCLE Registry or the National Health Insurance Research Database (NHIRD) in Taiwan also perfectly reflect this gap, showing that only 39-71% of ASCVD patients use statins and less than 10% use non-statin lipid-lowering agents at one year after indexed hospitalization [46]. Moreover, the overall LDL-C goal-achieving rate is only 33% [47], leaving the majority of ASCVD patients still at substantial risk. Although physicians may make every effort to communicate with their patients to fill the gap between SI and STS, the gap-related increase in ASCVD risk cannot be ignored and should be properly managed according to the spirit of patient-centeredness.

Further clinical evidence showing that action taken to further lower the LDL-C levels by non-statin therapy in patients receiving STS comes from CLEAR Outcomes trial. It demonstrates that therapies like BA significantly reduce major cardiovascular events in loosely defined "statin-intolerant" cohorts, further highlighting the need to broaden policy frameworks to STS populations [8]. Failure to address this policy-practice gap may perpetuate undertreatment of dyslipidemia, hinder LDL-C goal attainment, and leave a substantial portion of patients with elevated residual cardiovascular risk [4].

6. Management of patients receiving STS

6.1. Expert opinions on non-pharmacological therapies and other management

For patients receiving STS, some may choose to use dietary supplements and functional foods as adjunctive therapy in addition to medications. Evidence suggests that certain dietary supplements may be beneficial for dyslipidemia; however, data on their long-term safety and efficacy in preventing cardiovascular events remain limited [11,48,49]. The following is a review of common suggestions and an evaluation of the clinical evidence supporting their use.

6.1.1. Lifestyle modification and diet suggestions

Lifestyle modification remains the cornerstone of lipid management, particularly for patients with STS. For these patients, rigorous adherence to a healthy lifestyle is paramount, as it may optimize lipid profiles. As detailed in the 2022 Taiwan lipid guidelines for primary prevention and 2024 guidelines of TSOC on primary prevention of ASCVD [33,50,51], all patients are advised to consume a heart-healthy diet that emphasizes plant-based foods, lean protein, and restricts trans fats, processed red meat, and refined carbohydrates. Maintenance of ideal body weight, smoking cessation and minimizing in alcohol consumption are strongly advocated. Regular exercise, emphasizing total accumulated physical activity, should be encouraged. While recognizing potential barriers to these modifications, clinicians should engage in shared decision-making to enhance adherence before or alongside the use of non-statin therapies or functional foods.

6.1.2. Red Yeast Rice (RYR)

Red yeast rice (RYR) is a fermented rice product that naturally contains varying amounts of monacolin K, a compound with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor activity [52]. Multiple randomized controlled trials and systematic reviews have demonstrated that RYR can reduce total cholesterol and LDL-C by approximately 15–25%, lower triglycerides by about 5–10%, and increase HDL-C by around 5–10% [53–55]. Although RYR shares a similar mechanism of action with statins, studies have shown that RYR supplementation is generally safe and not associated with an increased incidence of muscular adverse effects, even in patients with SI [52,56].

Nevertheless, while the majority of patients tolerate RYR well, rare but serious adverse reactions have been reported in isolated case reports [57,58]. Additional concerns include the variability of active ingredient content among commercial RYR products and the potential contamination with citrinin, a mycotoxin that may be produced during rice fermentation. Long-term exposure to citrinin has been associated with nephrotoxicity. Notably, in 2023–2024, Japan reported cases of acute kidney injury and even fatalities linked to RYR products, which were found to be contaminated with blue mold (*Penicillium adametzioides*) during production [59,60]. Therefore, it is recommended that patients choose RYR products that comply with national manufacturing regulations to ensure product safety and quality.

6.1.3. Fish oil

Fish oil, also known as marine omega-3 polyunsaturated fatty acids (PUFAs) supplementation, primarily contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). High-dose EPA and DHA supplementation (4 g/day) typically reduces triglyceride (TG) levels by approximately 20–40%. However, the effects on total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) may vary, with levels either increasing or decreasing depending on the specific product formulation [61]. Some studies have also demonstrated that certain fish oil preparations—particularly EPA-only formulations—can reduce the risk of ASCVD in high-risk patients [62,63]. A recent double blind, randomized, placebo-controlled study from Canadian and Australian groups has shown that fish oil supplement (4 g/day), with 1.6 g of EPA and 0.8 g of DHA, is particularly useful for patients receiving hemodialysis in ASCVD prevention. In this study, serious cardiovascular events were dramatically reduced by 43% and cardiac death by 45% in the fish oil supplement group [64]. Most research indicates that fish oil supplementation is generally well tolerated; however, it may increase the risk of atrial fibrillation. Additionally, caution should be exercised in patients using antithrombotic agents due to a potential increased risk of bleeding [62,65]. However, the recent study in patients receiving hemodialysis did not demonstrate that fish oil supplement led to an increase of bleeding risk [64].

6.1.4. Vitamin D

Vitamin D deficiency has been found to increase the risk of myalgia in patients receiving statin therapy [66]. Studies have shown that vitamin D supplementation can reduce serum total cholesterol, LDL-C, and TGs levels, but does not increase HDL-C levels [67]. Although vitamin D supplementation is considered to have the potential to improve adherence to statin therapy, current evidence is still insufficient to support its routine use. Given the lack of robust evidence, vitamin D supplementation is only partially recommended for patients who develop statin-associated myopathy during statin treatment and are confirmed to have low vitamin D levels [68–70].

6.1.5. Coenzyme Q10 (CoQ10, ubiquinone)

Coenzyme Q10 (CoQ10, ubiquinone) is a product of the mevalonate pathway. Statins inhibit the upstream steps of this pathway, resulting in decreased ubiquinone levels [71]. Supplementation with CoQ10 may modestly reduce total cholesterol, LDL-C, and triglycerides, and may

slightly increase HDL-C [72]. However, previous randomized controlled trials have yielded inconsistent results regarding whether CoQ10 supplementation can improve adherence to statin therapy. Furthermore, meta-analyses do not support the use of CoQ10 supplementation for the treatment of statin-associated myalgia or for improving patient adherence to statin therapy [73,74]. Therefore, current evidence does not support the routine use of CoQ10 supplementation in patients receiving statin therapy.

In summary, although dietary supplements and functional foods may offer some benefits for lipid management in patients with STS, their overall efficacy and evidence for cardiovascular event prevention are limited. Individualized assessment and combining these products with lifestyle changes with appropriate medications are recommended, and further long-term studies are needed to confirm their safety and effectiveness.

6.2. Pharmacological therapies

6.2.1. Ezetimibe

In patients who are unable to tolerate statins at doses sufficient to achieve LDL-C targets—or in whom statins are contraindicated—ezetimibe is recommended as an effective and well-tolerated second-line therapy. Ezetimibe selectively inhibits intestinal cholesterol absorption via the NPC1L1 transporter, reducing LDL-C levels by approximately 15–20% as monotherapy and by an additional 15–20% when combined with statins [75]. Major guidelines, including the 2021 ESC/EAS and 2018 AHA/ACC, endorse ezetimibe as the first-line non-statin agent in patients not achieving therapeutic LDL-C goals despite maximally tolerated statins, or in those with SI. In post–acute coronary syndrome patients, the IMPROVE-IT trial demonstrated that ezetimibe added to simvastatin significantly reduced cardiovascular events compared to simvastatin alone, with no increase in adverse effects [76]. Furthermore, genetic studies have supported its benefit, showing that inactivating mutations in the NPC1L1 gene are associated with lower LDL-C and reduced coronary artery disease risk [77]. In an open-labeled, randomized, controlled trial, EWTOPIA 75 study, ezetimibe therapy alone successfully reduces 44% of cardiovascular events in a primary prevention cohort enrolling patients aged ≥75 years [78]. Ezetimibe is also an appropriate agent in triple combination therapy, alongside statins and PCSK9 inhibitors, particularly in very high-risk patients who require aggressive LDL-C lowering. Its favorable safety profile, oral administration, low systemic exposure, and relatively low cost make it suitable for patients with suboptimal statin tolerance, offering a practical and evidence-based approach to lipid management.

6.2.2. PCSK9 inhibition-based agents

Current guidelines based on multiple RCTs and meta-analysis suggest LDL-C lowering to certain targets to reduce ASCVD risk is based on disease severity and risk of ASCVD. PCSK9 inhibitors (PCSK9i), which inhibit the binding of PCSK9 to LDL receptors on the surface of hepatocytes and inducing their degradation, significantly reduce plasma LDL-C levels [79–81]. Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) studies demonstrated PCSK9i using monoclonal antibodies reduced LDL-C levels up to 60%, leading to reduction of ASCVD events in very high-risk, statin-treated populations [79,80]. Inclisiran, a small interference RNA (siRNA) targeting PCSK9 mRNA, has shown promising long-lasting reductions in LDL-C levels of approximately 50% for up to 6 months [81]. Even though the randomized controlled trials for CV outcomes are still ongoing (ORION-4, NCT03705234; VICTORION-2 PREVENT, NCT05030428), patient-level, pooled analysis of LDL-C lowering efficacy trials, which included patients with heterozygous familial hypercholesterolemia, ASCVD, or ASCVD risk equivalent on maximally tolerated statin-therapy, showed inclisiran significantly reduced composite major cardiovascular events [82]. All these data supported that PCSK9-targeted therapy using monoclonal antibodies, or potentially siRNA, may represent a preferred therapeutic option for patients receiving STS or with SI. Using a precise protocol to identify patients who were truly SI, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks (52.8% vs. 16.7%) [39]. A meta-analysis including 14 trials showed PCSK9i may reduce non-fatal MI and stroke in adults at very high or high cardiovascular risk who are receiving maximally tolerated statin therapy or are patients with SI [83]. Recently, VESALIUS-CV trial has further demonstrated that evolocumab significantly reduce 3-point major cardiovascular events (MACE) by 25% and 4-point MACE by 19% in the primary prevention cohort, further providing the evidence to underpin the role of PCSK9i in ASCVD primary prevention [84].

6.2.3. ATP citrate lyase inhibitor

ATP citrate lyase inhibitor, BA, targets cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Similar to statins, it reduces hepatic cholesterol synthesis, raises LDL receptor expression, and increases clearance of LDL-C from the circulation [85–88]. Different from statins, BA is a prodrug that is activated only in the liver but not in skeletal muscle. Therefore, it may reduce the potential for adverse effects on muscles [87,88].

In the CLEAR (Cholesterol Lowering via BA, an ACL-Inhibiting Regimen) Serenity study, 345 patients with hypercholesterolemia and a history of intolerance to at least 2 statins were randomized to BA 180 mg or placebo once daily for 24 weeks. BA was safe and well tolerated, and significantly reduced LDL-C levels (BA versus placebo: −21.4%) [89]. In the CLEAR Tranquility study, patients with a history of SI and an LDL-C ≥100 mg/dL while on stable lipid-modifying therapy, including 100% ezetimibe coverage, were enrolled. BA significantly reduced LDL-C levels by 28.5% more than placebo ($p < 0.001$; −23.5% BA, +5.0% placebo) [90].

CLEAR outcomes trial is a double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins and had, or were at high risk for, cardiovascular disease. The use of BA was associated with a lower risk of major adverse cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, in those patients who could not tolerate to statins [8]. In the subgroup analysis of CLEAR outcomes trial, BA treatment was associated with reduced MACE in high-risk primary prevention patients [91]. Prespecified analysis of the CLEAR outcomes trial also demonstrated that patients without diabetes had no increase in new-onset diabetes or worsening HbA1c with BA [92].

Recently, there was a multicenter, randomized-controlled trial which included patients with hypercholesterolemia at risk for cardiovascular events and an inadequate response to statins (79%) or SI (21%) in Japanese patients. After 12 weeks, treatment with BA significantly reduced LDL-C levels when compared to placebo (60 mg: −10.6%, $P = 0.002$; 120 mg: −21.9%, $P < 0.001$; 180 mg: −21.3%, $P < 0.001$; placebo: −1.9%). In patients with SI, the treatment effects of BA were more prominent (60 mg: −20.4%, $P < 0.001$; 120 mg: −27.4%, $P < 0.001$; 180 mg: −31.3%, $P < 0.001$; placebo: 1.0%). There were infrequent adverse events related to muscular and hepatic disorders, and no new or worsening cases of diabetes [93].

6.3. Management algorithm for patients receiving STS

Patients receiving STS represent a heterogeneous group distinct from those with confirmed SI (cf. Fig. 3). Rather than a complete inability to tolerate statins, these patients often maintain partial adherence or use submaximal doses due to perceived or mild adverse effects. A core principle of management is to preserve statin exposure whenever possible while integrating adjunctive non-statin agents to achieve LDL-C goals, as underscored by the ESC/EAS 2025 updated guideline [43] and

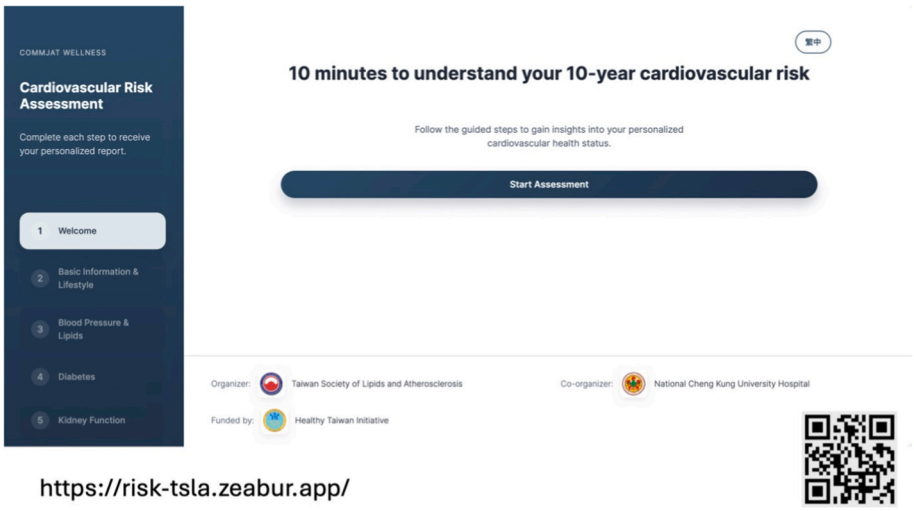

Fig. 5. The web platform to provide fast assessment of risk categories and the recommended LDL-C levels. People or health professionals can easily access the platform for free by scan the QR code or by searching the web address: https://risk-tsla.zeabur.app/. And the risk category together with the recommended LDL-C level will appear after step-by-step providing the related information.

2025 Taiwan consensus [4] frameworks. Although endeavoring to preserve statin therapy, this population often fails to achieve LDL-C targets. Hence, early identification and tiered management of these patients are crucial to closing the gap between real-world care and ideal ASCVD risk reduction. The algorithm prioritizes patient-centered assessment, sequential therapeutic escalation, and reinforcement of adherence and education to mitigate the nocebo effect [45,94]. The management of patients with STS requires a structured, evidence-based, and patient-centered approach integrating both pharmacological and non-pharmacological strategies. Although real-world reimbursement policy and pharmacoeconomic uncertainty may substantially limit the implementation of this consensus, there has been many researches showing that using BA [95] and PCSK9 inhibition-based agents [96,97] in ASCVD prevention is cost-effective. Recently, Taiwanese government has initiated a "pay-for-performance" project to reinforce the LDL-C control quality in secondary prevention population. The related data derived from this project is expected to provide more solid evidence regarding the cost-effectiveness of these non-statin lipid-lowering drugs in Taiwan. The primary goal of this consensus is timely attainment of LDL-C targets recommended by the 2025 Taiwan cholesterol management consensus [4], filling the gap between real-world practice and clinical evidence, thereby minimizing residual ASCVD risk.

The central spirit of this management algorithm is to achieve ASCVD risk reduction as soon as possible once STS is identified. Therefore, adopting this algorithm does not mean that further adjustment of statins or lifestyle modification to enhance the goal attainment is excluded. Whether BA is more effective than ezetimibe in ASCVD reduction is still an issue of controversy [98,99], ezetimibe is still chosen as the first-line add-on after statins in most of published guidelines [4,5,42,43], probably because of its low cost and low percentage of adverse effect.

For patients receiving STS who are at extremely high risk, an upfront ezetimibe and BA combination should be initiated to expedite LDL-C goal attainment and reduce imminent event risk. If LDL-C target (<55 mg/dL) is not achieved within 4-8 weeks, PCKS9 inhibition-based agents can be added (Fig. 4). If the LDL-C target is still not achieved within 4-8 weeks after the triple non-statin combination, patients are recommended to be referred to lipid experts for further genetic study and management. If patients reach the LDL-C goal after each step of escalation therapy, a regular 6-month follow-up is still necessary to ensure that the LDL-C target is maintained.

For patients receiving STS who are at high or very high risk, ezetimibe can be added first in addition to originally maximally tolerable doses of statins. If LDL-C treatment target (<100 mg/dL or <70 mg/dL, respectively) is not reached within 4-8 weeks, BA can be added. If the target remains unmet, PCSK9 inhibition-based agents can be considered (Fig. 4). If the LDL-C target remains unmet after 4–8 weeks despite triple non-statin combination therapy, referral to a lipid specialist is advised for advanced genetic evaluation and individualized management. Conversely, if the LDL goal is achieved at any stage of therapy escalation, continued monitoring every 6 months is recommended to ensure sustained goal attainment.

For patients receiving STS at low or moderate risk (Fig. 4), rapid goal attainment is not imminent. And thus, it may allow non-pharmacological attempts, including a more stringent diet control and/or other interventions mentioned in section 6.1.1. Alternatively, ezetimibe may be added directly after shared decision-making (SDM). If the LDL-C treatment target (<130 mg/dL or <115 mg/dL, respectively) is not achieved after 3-6 months of nonpharmacological intervention, ezetimibe can be given. If the goal is still not attained with 4-8 weeks of ezetimibe treatment, BA may be added. If the target remains unmet, PCSK9 inhibition-based therapy may be considered. For those whose LDL-C targets are met at any step, continuous monitoring and a regular follow-up every 6 months are still needed to ensure continuous goal attainment. Referral to a lipid clinic for a survey of background genetic variants and specific management should be considered if LDL-C targets are still not achieved after the triple non-statin therapy.

The suggested management algorithms for patients receiving STS were presented in Fig. 4. By aligning clinical practice with Taiwan's updated LDL-C-management pathway, this algorithm aims to close the therapeutic gap for patients unable to tolerate full-dose statins and thereby reduce their long-term ASCVD burden. In agreement with our consensus, the recent published expert opinion from European group also recommends similar algorithm [5]. To enhance the risk stratification and STS identification, we also provide a web platform: https://risk-tsla.zeabur.app/(See Fig. 5 for the web page and QR code) to quickly and easily calculate risk levels to enhance the stepwise escalation of therapies in the algorithms.

7. Conclusion

The 2026 TSLA Consensus provides a comprehensive, evidence-based framework for the identification and management of patients receiving STS, bridging the gap between traditional definitions of SI and real-world clinical practice. By integrating individualized risk stratification and a stepwise therapeutic algorithm combining statins with non-statin agents such as ezetimibe, BA, and PCSK9 inhibition-based

therapies, this consensus aims to optimize LDL-C goal attainment and reduce residual ASCVD risk across all prevention levels. Beyond pharmacologic therapy, it also emphasizes the importance of lifestyle modification, adherence support, and shared decision-making. These recommendations reflect TSLA's commitment to advancing lipid management in Taiwan through pragmatic, precision-based, and patient-oriented care.

Declaration of competing interest

None.

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