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Review Article

2019 Taiwan Society of Lipids and Atherosclerosis expert consensus statement on statin intolerance

Shih-Chieh Chien ^{a,1}, Po-Sheng Chen ^{b,c,1}, Yi-Hsiang Huang ^{d,e},
Sung-Chun Tang ^f, Yi-Heng Li ^{b,*}, Hung-I Yeh ^{g,h,**}

^a Department of Critical Care Medicine, MacKay Memorial Hospital, Taipei, Taiwan

^b Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

^c Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

^d Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

^e Institute of Clinical Medicine, National Yang Ming University School of Medicine, Taipei, Taiwan

^f Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan

^g Departments of Internal Medicine and Medical Research, MacKay Memorial Hospital, Taipei, Taiwan

^h Department of Medicine, Mackay Medical College, New Taipei City, Taiwan

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Statin reduces low-density lipoprotein cholesterol and improves clinical outcomes in high risk patients. In general, statin is a safe and well-tolerated medication. However, varieties of adverse effects are reported in some patients and may interfere long-term drug compliance. Statin-associated muscle events and liver function change account for most of these adverse effects. Patients are regarded as statin intolerance if they need to discontinue statin therapy due to these adverse effects. To date, there is no universal standard definition of statin intolerance. But a pragmatic definition of statin intolerance is essential and helpful for clinicians in daily practice. In this article, after expert consensus meetings and literature review, criteria were recommended to identify patients with statin intolerance in Taiwan. The purpose of this statement is to help health care professionals in Taiwan to diagnose and manage individuals who develop muscular and hepatic side effects after statin therapy.

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* Corresponding author. Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng Li Road, Tainan 70403, Taiwan.

** Corresponding author. Division of Cardiology, Department of Internal Medicine, MacKay Memorial Hospital, 92, Section 2, Chung Shan North Road, Taipei 10449, Taiwan.

E-mail address: heng@mail.ncku.edu.tw (Y.-H. Li).

¹ Drs. Chien and Chen contributed equally to this work.

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Introduction

Statins substantially lower the plasma low-density lipoprotein cholesterol (LDL-C) level and improve clinical outcomes in patients with atherosclerotic cardiovascular disease (ASCVD).¹ Guidelines have been developed to advocate the prescription of statins and emphasize the importance of statin intensity or achieving optimal LDL-C target in eligible populations.^{2–4} The number of statin users steadily grows worldwide, including in Taiwan.^{5,6} A study from Taiwan National Health Insurance Database showed a continuous growing trend of statin users from 1.4% in 2002 to 6.3% in 2011. The use of moderate- to high-intensity statins also increased over time in Taiwan.⁶ With the growing number of statin users, the potential adverse effects caused by statins are likely increasing concurrently and statin intolerance may become a disturbing concern.

In general, statins are considered to be safe and well-tolerated. However, side effects occur in 10–25% of statin users in real-world clinical practice and, thereby, some of the statin users are unable or unwilling to continue statins. These patients are recognized as statin intolerance.^{7–9} Discontinuation of statin therapy among eligible individuals leads to unfavorable outcome.^{10–12} In fact, many previously reported side effects of statins are difficult to prove the causal relationship and remain controversial. Current evidences showed that statin therapy exerted neutral or even beneficial effects on cognition, renal function and sleep quality.^{13–16} There were no proved associations of statin use with occurrence of intracranial hemorrhage, cancer and tendon rupture.^{1,17,18} There were also conflicting results from different studies regarding the issues of statin-associated interstitial lung disease and depression.^{19–22} Statins lower testosterone production with a trivial magnitude and do not carry clinical significance.²³ The risk of new onset diabetes appears to be increased among individuals treated with statin, however, the cardiovascular benefits of statin therapy outweigh the hazards of incident diabetes.^{24–26} Therefore, this statement focused on statin-related muscular and hepatic side effects which are the most common reasons of statin discontinuation. The recommendations were established based on review of current evidences and consensus of experts after several rounds of meetings convened throughout the country. The purpose of this statement is to define statin intolerance caused by muscular and hepatic side effects in Taiwan and to assist clinicians in assessing and managing individuals who develop these side effects after statin therapy.

Statin intolerance

Statin intolerance should fulfill the following four criteria: (1) At least 2 statins are assessed for tolerability - one statin at the lowest starting daily dose and another statin at any daily dose; (2) Development of either objectionable symptoms or abnormal results of laboratory testing after statins; (3) The adverse effects are reversible upon statin discontinuation but reproducible by rechallenge; (4) Exclude other possible etiology. The definitions of the lowest starting daily dose are based on Taiwan Food and Drug Administration (FDA) approved package inserts of various

statins. If statins are not administered daily (alternative day or twice weekly), a cumulative lowest weekly dose can be utilized to define the lowest dose (Table 1). The similar criteria of statin intolerance were also adopted by other society, expert statement or international clinical trial.^{27–29} Additionally, any documented episode of statin-related rhabdomyolysis should be regarded as statin intolerance regardless of prior intolerant experiences. Patients who can only tolerate some types or doses of statins are referred as “partial” statin intolerance in the International Lipid Expert Panel statement.²⁸ To simplify the approach of statin intolerance in Taiwan, this group of patients was not discussed in this statement since our purpose is to identify those with complete statin intolerance due to muscular and hepatic adverse effects and reinforce nonstatin strategy.

Statin-associated muscle events

Statin-associated muscle events (SAMEs) are reported as the most frequent side effects in statin users. Clinical presentations vary from mild symptoms to apparent muscle injury, presenting with marked creatine kinase (CK) elevation and/or rhabdomyolysis. SAMEs are reversible by prompt discontinuation of statins or down-titration of the dose.^{5,9,30,31}

Definition

There are four major clinical presentations of SAMEs: myalgia, myopathy, myositis and rhabdomyolysis. Myalgia refers to any statin-associated muscle symptom with normal CK value and it accounts for the main part of all SAMEs.³¹ However, there are controversies about how to define “statin-associated” muscle symptoms. This is because various muscle complaints (pain, aching, tenderness, stiffness, cramping, or weakness) could be caused by chronic physical activity or preexisting muscle disease.^{32,33} Moreover, muscle complaints are subjective and difficult to be validated. Statin-associated myalgia is more likely if (1) the involved regions are symmetrical and proximal (hip, thigh, or calf), (2) symptoms onset is close to the initial exposure to statins (less than 4 weeks), (3) symptoms quickly relieved (within 2 weeks) after statins withdraw, and (4) the same symptoms recur after statins rechallenge. A modified scoring system to define statin-associated myalgia in Taiwan is suggested in this statement to prevent overdiagnosis (Table 2). This scoring system was

Table 1 Lowest daily dose of statins defined in the Taiwan Food and Drug Administration approved package inserts.

Statin	Daily lowest dose	Cumulative weekly lowest dose
Atorvastatin	10 mg	70 mg
Fluvastatin	20 mg	140 mg
Lovastatin	20 mg	140 mg
Pitavastatin	1 mg	7 mg
Pravastatin	10 mg	70 mg
Rosuvastatin	5 mg	35 mg
Simvastatin	5 mg	35 mg

Table 2 Myalgia score for statin intolerance.

Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Non-specific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks after statins	3
Symptoms onset 4–12 weeks after statins	2
Symptoms onset >12 weeks after statins	1
Withdrawal	
Improves upon statins withdrawal (<2 weeks)	2
Improves upon statins withdrawal (2–4 weeks)	1
Does not improve upon statins withdrawal (>4 weeks)	0
Switch to another statin	
Same symptoms reoccur upon <4 weeks	3
Same symptoms reoccur upon 4–12 weeks	1
Statin-associated myalgia clinical index score	
Likely	≥7
Unlikely	<7

originally developed based on the STOMP (Effect of STatins On Skeletal Muscle Performance) study and PRIMO (PRediction of Muscular Risk in Observational Conditions) studies and was also adopted by other societies.^{8,9,31,33} Myopathy is used as a collective term that encompasses all forms of muscle disorder. Subjective reports of muscle weakness are frequent, ranging from 27% to 55%, but does not severely influence basic performance.^{8,33,34} Therefore, the term of muscle weakness or myopathy should be regarded as one of statin-associated muscle symptom instead of a specific clinical entity. Myositis is defined as elevation of serum CK level above upper limit of normal (ULN) indicating muscle damage or inflammation. Once the CK level is $> 10 \times \text{ULN}$, a diagnosis of rhabdomyolysis can be made. The threshold of $\text{CK} > 10 \times \text{ULN}$ to define rhabdomyolysis or severity of myositis is generally adopted by clinical studies.^{35–38} Clinicians should carefully investigate the patient's clinical manifestations of rhabdomyolysis, such as acute renal failure, electrolyte imbalance, and myoglobinuria. The above-mentioned definitions of SAMEs are suggested in this statement. There are different definitions by other societies. Table 3 shows the definitions of SAMEs from the American College of Cardiology (ACC) and the American Heart Association (AHA), the Canadian Working Group (CWG), the National Lipid Association (NLA), the European Atherosclerosis Society (EAS) and the International Lipid Expert Panel (ILEP).

Risk factors

Clinicians should assess the potential predisposing factors or risk factors when there are SAMEs. Recent viral infection, common myopathies such as polymyalgia rheumatica, hypothyroidism, renal or liver dysfunction, alcohol consumption, and trauma or excessive physical activity all could be the predisposing factors of SAMEs.^{9,30,33} Advanced age, female sex, physical disability, and lower body mass index are

risk factors of SAMEs.^{5,9} Moreover, Asian populations are more likely to have the 421C > A polymorphism in the drug efflux transporter ATP-binding cassette G2 gene (ABCG2). Subjects with the variant allele are expected to have almost double plasma concentration of administered statins, including rosuvastatin, simvastatin, and atorvastatin.⁵ As a consequence, Asian populations are considered at higher risk of developing SAMEs. The concomitant medications which share the same hepatic cytochrome P450 system (CYP) isoenzymes with statins for metabolism could increase plasma concentrations of statins. CYP3A4 is the predominant pathway for metabolism of most medications. The majority of metabolisms of fluvastatin, pitavastatin, and rosuvastatin are not dependent on CYP3A4 and, therefore, these statins have less risk of statin-drug interaction.⁹

Mechanisms

There are some proposed mechanisms for the myotoxic effects of statins. First, statins inhibit HMG-CoA reductase and thereby, decrease the downstream intermediaries, such as mevalonate, isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate. This results in reduced prenylation of small guanosine triphosphate-binding proteins involved in cell growth and maintenance.³⁹ Additionally, production of ubiquinone (coenzyme Q10), which may influence antioxidant capacities and mitochondrial function, decreases as well.⁴⁰ Third, statins are suggested to possess pro-apoptotic effect and to induce skeletal muscle atrophy by up-regulation of atrogen-1 gene.⁴¹ Fourth, in a biopsy-based study, aberrant expression of ryanodine receptors (RyR) was found in patients with statin-associated muscle damage indicating the possible role of altered calcium homeostasis by statin therapy.⁴² Finally, immune response is responsible for some forms of statin-associated myopathy with the formation of autoantibody against HMG-CoA reductase and myonecrosis in muscle biopsy.⁴³ Clinical symptoms or increased CK level would persist despite cessation of the statins in this rare form statin-induced myopathy.

Management

Careful assessment to confirm the causality between the adverse events and statins is the first and most important step. Potential predisposing factors should be identified and eliminated. Further decision of continuing statin should be made after reassessing individuals' risks and benefits. Reduced or alternative statin strategy is generally thought to be safe and practical. Once the SAMEs are suspected, clinicians need to evaluate the patients' symptoms with the proposed scoring system and measure the CK levels. The term "switch" is used instead of "rechallenge" in our myalgia scoring system. This is to emphasize that exposures of two different statins are warranted to diagnose statin intolerance (Table 2). For calculating the score, it is necessary to recognize the characteristics of myalgia, time intervals of symptoms onset and offset in the relation to the statin initiation and withdrawal. Switch to another statin could be tried 2–4 weeks after resolution of the events. CK

Table 3 Comparison of definition of statin-associated muscle events in different societies.

Clinical entity	ACC/AHA	NLA	CWG	EAS/ILEP
Myopathy	Any disease of muscle	weakness	Any disease of muscle	—
Myalgia	SAMS, CK $\leq$ ULN	Aching, stiffness, cramps	SAMS, CK $\leq$ ULN	Normal CK
Myositis	SAMS, CK $>$ ULN	Inflammation Myo-necrosis Mild 3X $<$ CK $\leq$ 10X ULN Moderate 10X $<$ CK $\leq$ 50X ULN Severe CK $>$ 50X ULN	SAMS, CK $>$ ULN HyperCKemia Mild grade1 ULN $<$ CK $\leq$ 5X Mild grade2 5X $<$ CK $\leq$ 10X ULN Moderate 10X $<$ CK $\leq$ 50X ULN Severe CK $>$ 50X ULN	= myopathy CK $>$ 10X ULN
^a Rhabdomyolysis	CK $>$ 10X ULN	CK $>$ 3X ULN	CK $>$ 10X ULN	CK $>$ 40X ULN (EAS) CK $>$ 50X ULN (ILEP)

ACC/AHA: American College of Cardiology/American Heart Association; CK: creatine kinase; CWG: The Canadian Working Group; EAS: The European Atherosclerosis Society; ILEP: International Lipid Expert Panel; NLA: National Lipid Association; SAMS: statin-associated muscle symptoms; ULN: upper limit of normal.

^a Careful assessments of muscle symptoms, evidence of renal damage and the presence of myoglobinuria are important to make a clinical diagnosis of rhabdomyolysis.

measurements could assist diagnosis and define the severity of muscle damage. Routine measurement of CK level before statin therapy is not usually mandatory but reasonable for those at risk to develop SAMEs, such as in patients with polypharmacy, established muscle disease, or high intensity of physical activity.

Fig. 1 summarizes the management of SAMEs and diagnosis of statin intolerance. Subjects who are asymptomatic with slight elevation of CK level ($<3 \times$ ULN) usually could tolerate the statins therapy in the subsequent treatment course and are not likely to develop more severe side effects.^{27,44} Withdrawing the drugs is not necessary but CK value should be reassessed after 2–4 weeks. Once subjects are symptomatic or CK levels increase to within $3–10 \times$ ULN, prompt withdrawal of statins is recommended. After CK levels return within ULN and symptoms resolve, restarting statin with reduced dose is encouraged. A different statin with a lower intensity can be considered. Recurrent symptoms and CK level should be monitored carefully after reexposure to statin and the dose should be gradually titrated to the maximal tolerated dose to achieve optimal lipid goal. Nonstatin therapies, including ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors could be used as a combination therapy to statin if lipid goal cannot be achieved under maximal tolerated statin dose or as a monotherapy if statins are intolerant. Rhabdomyolysis is suspected if there is impaired renal function and CK level $>10 \times$ ULN. Supportive treatment with adequate hydration is necessary and statins should be stopped. The patients experiencing rhabdomyolysis are categorized as statin intolerance. Direct switch to non-statin therapies without re-exposure an alternative statin is reasonable. To diagnose unusual types of autoimmune myopathy, muscle biopsy might be helpful for those who have persistently elevated CK levels despite discontinuation of statins. There are some supplementary therapies under investigation for relief of muscle symptoms. Because circulating coenzyme Q10 level is influenced by statins, supplementation of coenzyme Q10 is putative to be an

effective treatment of statin associated myopathy. However, double-blind clinical trial and meta-analysis showed that coenzyme Q10 did not improve statin-related muscle symptoms.^{45–47} The effects of vitamin D for statin associated myopathy are also inconclusive.⁴⁸

Statin-associated liver function change

Up to about 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.⁴⁹ The statin-related transaminases elevation is thought to be a class effect.⁵⁰ However, the elevation is usually mild ($<3 \times$ ULN) and does not represent liver injury clinically or histologically in the absence of increasing bilirubin or hepatic synthetic dysfunction.^{51–53} 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.⁵⁰ The incidence of clinically significant drug-induced liver injury (DILI) attributable to statins is rare. A systemic review reported that the incidence of statin-related liver failure is about 1 per one million person-years.⁵⁴ In a post-market review between years 2000–2009 conducted by the United States FDA, a low incidence of statin-associated serious hepatotoxicity (≤ 2 per one million patient-years) was reported.⁵⁵ DILI in patients with statin therapy is more likely idiosyncratic in nature.⁵² Additionally, there was no evidence demonstrating the effectiveness of regular monitoring liver function in detection of DILI after starting statin therapy.^{50,53,56} Therefore, it is not necessary to regularly monitor liver function in patients taking statins.^{50,55}

Statins in chronic liver disease

Another challenging issue is whether statin therapy can be used in patients with chronic liver disease (CLD), such as

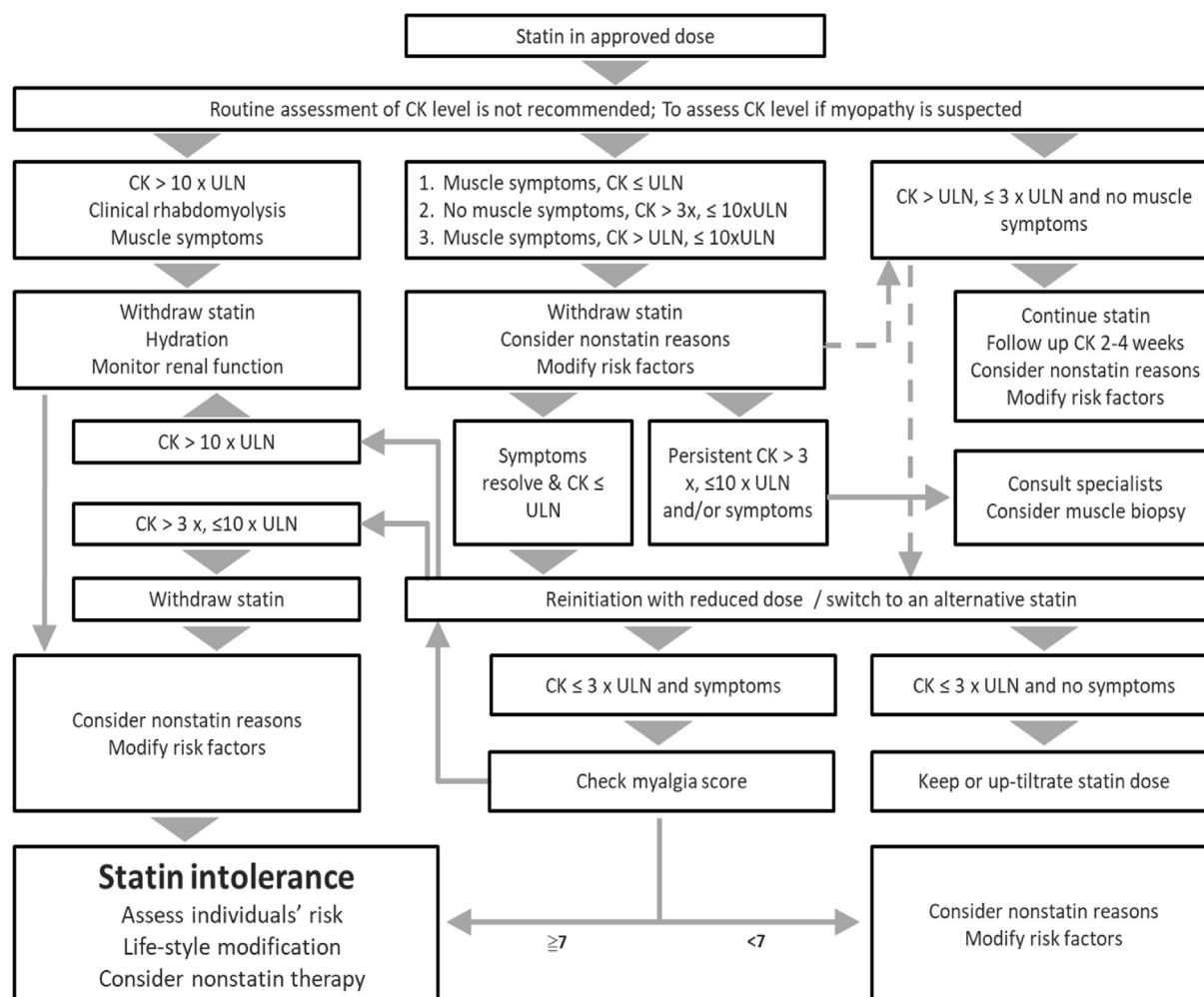


Fig. 1 Management of statin-associated muscle events and diagnosis of statin intolerance. CK, creatine kinase; ULN, upper limit of normal. *Dotted arrow indicates early reinitiation of statin can be considered while patients are asymptomatic and CK level decrease less than $3 \times \text{ULN}$ but not within normal range.

chronic hepatitis B or C, nonalcoholic fatty liver disease (NAFLD) and liver cirrhosis. Basically, it is not contraindicated to use statins in CLD patients without decompensation or acute exacerbation.^{50,52} The pharmacokinetic of statins was not affected in patients with Child's A liver cirrhosis⁵⁰ and two previous studies reported that the incidence of severe liver transaminases elevation was similar in patients with elevated baseline liver enzyme compared to those with normal baseline liver enzyme.^{57,58} There was also no evidence supporting that statin adversely influenced clinical outcome or course of CLD.⁵⁹ However, there is emerging concern regarding the drug-drug interaction between statins and medications used for viral hepatitis because they share the same cytochrome P450 enzyme for metabolism. Change of statin or adjustment of statin dosage should be considered in such situation.⁵² Statin therapy should be avoided in patients with decompensated CLD and considered starting therapy only after remission of underlying diseases and recovery of abnormal liver function. Baseline liver function should be obtained before initiating statin therapy.^{30,52} In patients with normal liver panel, statin therapy may be started and recheck transaminase within 12 weeks. If it is normal, no regular

liver function monitor is necessary thereafter unless clinical symptoms/signs indicating hepatic disease. Fig. 2 shows the management of hepatic enzyme change in statin users and the diagnosis of statin intolerance. In those having statin therapy with clinical suspicion of hepatic dysfunction, statin should be hold and patients should receive comprehensive survey for possible etiology. In patients without persistent elevated hepatic transaminases or evidence of hepatic failure, the same statin may be resumed with the same or reduced dosage or switched to other statins. In patients with persistent elevated hepatic transaminases ($\geq 3 \times \text{ULN}$) after statin therapy, expert consultation should be considered (Fig. 2).

Summary

Although a variety of side effects resulting from statin therapy have been reported, most of them are devoid of solid evidence supporting causal relationship with statin. Identifying patients with statin intolerance by the recommended criteria helps to avoid unnecessary discontinuation of statin which are associated with unfavorable outcomes.

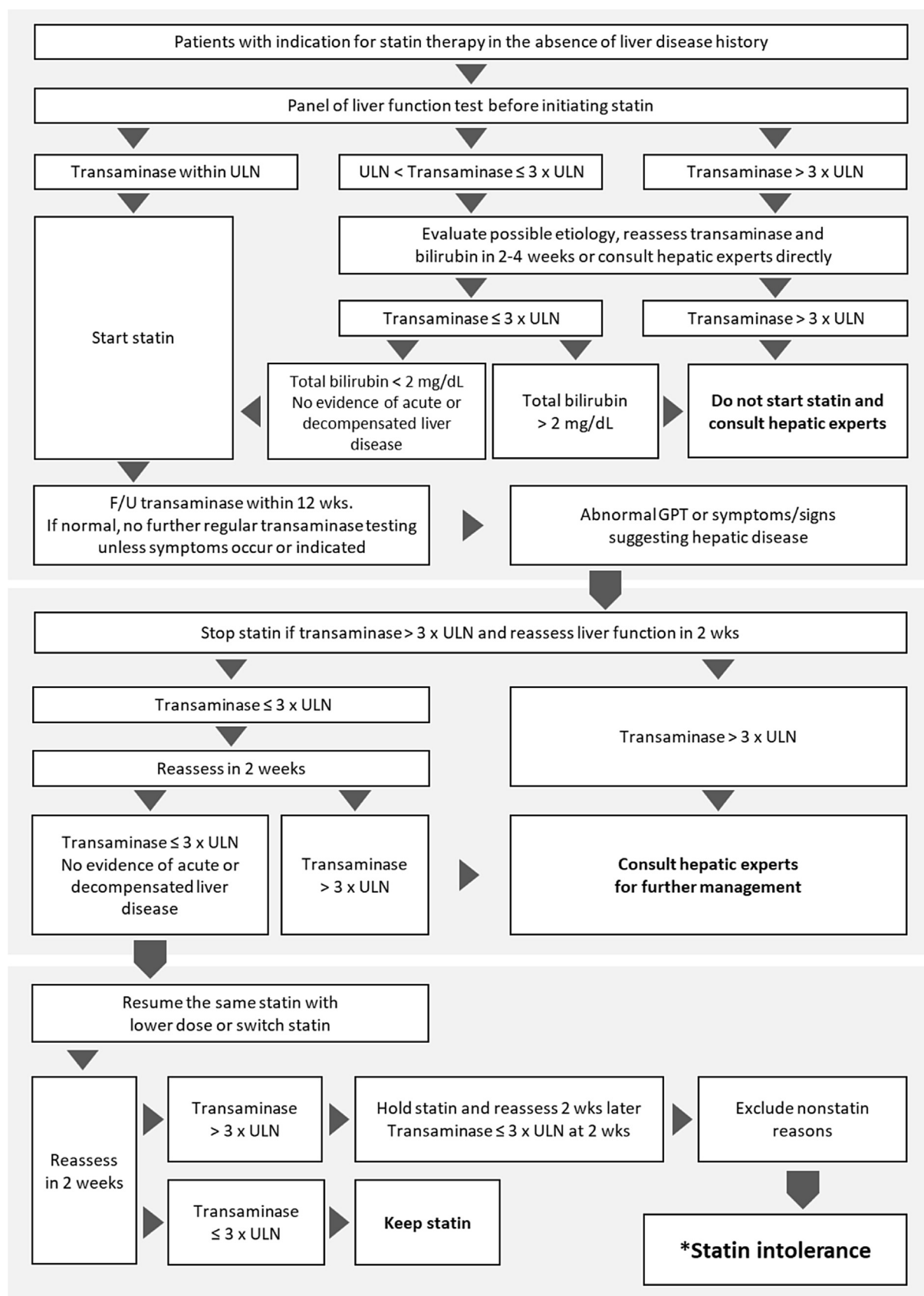


Fig. 2 Management of statin-associated liver function change and diagnosis of statin intolerance. GPT, glutamic-pyruvic transaminase, also known as alanine aminotransferase (ALT); ULN, upper limit of normal. *Statin intolerance is diagnosed if there are at least 2 statins are assessed.

Myalgia without elevated CK accounts for the majority of SAMEs which are the most frequent side effects related to statin use. We recommend a modified myalgia scoring system to recognize statin-related myalgia. In patients with more severe SAMEs characterized by myalgia and elevated CK, the decision to resume statin or switch to nonstatin therapy after recovery is based on the consideration of patients' risks and benefits. Statin-induced rhabdomyolysis is defined as statin intolerance and direct switch to non-statin therapy is suggested. Transient elevation of liver transaminases is not uncommon, however, the incidence of DILI resulting from statin is rare. Regularly monitoring liver function after initiating statin therapy is not recommended unless there are suspected symptoms/signs. Comprehensive assessment and hepatic experts consultation to exclude other possible etiologies is fundamental in patients with persistent or more severe liver function impairment.

Document reviewers

Juey-Jen Hwang, Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan and Wayne H.-H. Sheu, Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan.

Conflicts of interest

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