Statin-Associated Myalgias and Muscle Injury—Recognizing and Managing Both While Still Lowering the Low-Density Lipoprotein

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KEYWORDS

• Statin • Myalgia • Weakness • Myotoxicity • Myopathy • Autoantibody

KEY POINTS

- Patients who have muscle discomfort attributable to statins, but do not have muscle enzyme elevations or demonstrable weakness, are defined as having statin-associated muscle symptoms (SAMS).
- Those with CK elevations attributable to statins that resolve with discontinuation of the medication are defined as having statin-associated myotoxicity (SAMT).
- Statin-exposed individuals with elevated CK levels, proximal muscle weakness, and antihydroxy-methyl-glutaryl coenzyme A reductase autoantibodies are defined as having statin-associated autoimmune myopathy (SAAM).
- Patients with SAMS or SAMT can be managed by changing the statin regimen or using alternative lipid lowering medications such as ezetimibe or PCKS9 inhibitors.
- Those diagnosed with SAAM usually require chronic immunosuppressive therapy, should not be reexposed to statins, and may be treated with PCSK9 inhibitors if lipid-lowering therapies are indicated.

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INTRODUCTION

Hyperlipidemia is a major risk factor for developing cardiovascular disease, the most common cause of death for virtually all populations in the United States. Indeed, nearly 30% of adults in the United States have elevated levels of low-density lipoprotein cholesterol (LDL-C), which doubles the risk for heart attack. Statin medications, which lower cholesterol levels by inhibiting hydroxy-methyl-glutaryl coenzyme A reductase (HMGCR), significantly reduce cardiovascular events. Unfortunately, despite their efficacy, only a fraction of those eligible for statin therapy use one of these cholesterol-lowering drugs. For example, one recent study estimated that of those adults at high risk for cardiovascular disease, nearly half are not taking a statin.[1] Thus, underutilization of statins for managing hypercholesterolemia remains a significant public health concern.

Although statins are generally safe and well tolerated, skeletal muscle side effects, which range from mild myalgias to severe rhabdomyolysis, may limit their use in a significant number of patients. In one telling study that included more than 10,000 current and former statin users, muscle side-effects were reported by 25% and 65%, respectively. Furthermore, nearly two-thirds of former users stopped taking statins because of side effects.[2] With the ultimate aim of optimizing compliance with cholesterol-lowering therapy and thereby reducing the risk of cardiovascular disease, this review describes the different types of statin-associated muscle side effects and provide recommendations about how to manage hypercholesterolemia in patients who experience them.

THE SPECTRUM OF STATIN-RELATED MUSCLE SIDE EFFECTS

The term "statin myopathy" has been used to describe a broad range of muscle problems experienced by patients taking statins. However, this term was poorly defined and did not distinguish between patients who had different symptoms, laboratory findings, and histopathological findings on muscle biopsy. In order to capture the heterogeneity of statin-associated muscle complaints, the National Lipid Association Task Force (NLATF) proposed using more precise terminology in 2014.[3] The term "myalgia" was used to describe muscle discomfort in patients without serum creatine kinase (CK) elevations or objective weakness. Those with "myopathy" have muscle weakness (not attributable to muscle pain) with or without CK elevations. Patients with "myositis" have muscle biopsies revealing inflammatory cell infiltrates. The term "myonecrosis" was used to describe a process that includes significant CK elevations that are at least 3-fold higher than untreated baseline levels or the normative upper limit when adjusted for age, sex, and race. And finally, the term "myonecrosis with myoglobinuria" defines the most severe patients, who have CK elevations along with an increased serum creatine greater than or equal to 0.5 mg/dL and, in some cases, acute renal failure due to precipitation of myoglobin in the kidney tubules (ie, rhabdomyolysis).

Although the NLATF-proposed terminology represents a significant improvement over the vague term "statin myopathy," it does not define mutually exclusive disease categories. For example, a patient with muscle weakness, serum CK elevations, and an inflammatory muscle biopsy could be described as having myopathy, myonecrosis, and myositis. Furthermore, since this terminology scheme was proposed, it has become increasingly clear that statins may trigger an autoimmune myopathy associated with autoantibodies recognizing HMGCR.[4] Given the limitations of the NLATF and other existing classification schemes, the author has found it clinically useful to divide statin-related muscle problems into 3 categories: statin-associated muscle

symptoms (SAMS), statin-associated myotoxicity (SAMT), and statin-associated autoimmune myopathy (SAAM) (**Box 1**).

STATIN-ASSOCIATED MUSCLE SYMPTOMS

Patients who experience muscle discomfort, such as myalgias or cramps, without CK elevations or demonstrable muscle weakness can be classified as having SAMS. Although this seems to be the most common type of statin-related muscle problem, estimates of its prevalence have varied widely between studies. For example, in the retrospective and unblinded PRediction of Muscular Risk in Observational Conditions (PRIMO) study, 832 (10.5%) of 7924 hyperlipidemic patients reported muscle pain while on statin therapy.[5] In contrast, a meta-analysis including 26 randomized controlled clinical trials in which muscle symptoms were reported found that these symptoms occurred in 12.7% of statin-treated and 12.4% of placebo-treated subjects ($P = .06$).[6] This study raises 2 points. First, it suggests the possibility that the high rate of muscle symptoms in observational studies may be at least partially due to the fact that patients know and anticipate that muscle pain may be a side effect of statins, an example of the "nocebo effect." Second, it underscores the high prevalence of background nonspecific muscle pain even in patients not on statin therapy. Indeed, this study has been taken by some to suggest that muscle pain alone is rarely, if ever, a consequence of the toxic effect of statins on muscle. However, none of the clinical trials included in the meta-analysis were specifically designed to capture the true prevalence of muscle symptoms in those exposed to statins.

The Effect of Statins on Muscle Performance (STOMP) study was designed, in part, to determine how often muscle pain that occurs in statin-treated patients is directly

Box 1
Typical clinical features of the statin-associated muscle conditions

Statin-associated muscle symptoms (SAMS)
- Muscle discomfort present
- Normal manual muscle strength testing
- Normal CK levels
- Resolution with discontinuation of statins
- Recurrence with statin rechallenge
- Lipids managed by changing the statin regimen or using alternative agents

Statin-associated myotoxicity (SAMT)
- Muscle discomfort common
- Muscle weakness possible
- Elevated CK levels present
  - Minimal SAMT: CK ≤3-fold greater than normal limit
  - Mild SAMT: CK >3-fold greater than normal limit
  - Moderate SAMT: CK >10-fold greater than normal limit
  - Severe SAMT: CK >50-fold greater than normal limit
- Resolution with discontinuation of statins
- Recurrence with statin rechallenge (advisable only in selected patients)
- Lipids managed by changing the statin regimen or using alternative agents

Statin-associated autoimmune myopathy (SAAM)
- Muscle discomfort common
- Muscle weakness common
- Elevated CK levels present (>5-fold greater than normal limit)
- Does not resolve with discontinuation of statins; requires immunosuppression
- Disease flares likely with statin rechallenge (not advised)
- Lipids managed by using a PCSK9 inhibitor

related to the medication. In this study, 420 statin-naïve subjects were treated with either 80 mg of atorvastatin or placebo for 6 months. Among these, 19 statin-treated and 10 placebo-treated subjects reported new muscle pain or cramping that lasted more than 2 weeks, resolved within 2 weeks of treatment cessation, and returned within 4 weeks of treatment reinitiation ($P = .05$).[7] Taken together with data from 2 other double-blind, placebo-controlled studies in which subjects with a history of statin intolerance were treated with statin or placebo, washed out, and then treated with the alternative therapy,[8,9] the STOMP trial suggests that in as many as half of statin-treated patients with muscle discomfort, this symptom is not due to the statin.

Given that there is no definitive diagnostic test to establish whether muscle discomfort can be directly attributed to statin use, physicians must rely on clinical features to determine how likely it is that a patient has SAMS. The location and pattern of muscle symptoms may be informative in that symmetric and proximal symptoms are more likely due to statins than asymmetric and/or distal muscle symptoms. In the authors' experience, SAMS is more often characterized by persistent myalgias than intermittent cramping.[10] In addition, most relevant studies (eg, STOMP) have shown that muscle symptoms tend to occur earlier in patients with verified SAMS than in those with nonspecific muscle symptoms.[7,8] Furthermore, once statins are discontinued, patients with SAMS usually experience a marked improvement in their symptoms within weeks; when symptoms persist longer than 8 weeks, alternative diagnoses should definitely be sought. Finally, once statins have been discontinued and muscle symptoms have resolved, statin rechallenge is likely to provoke muscle symptoms in a relatively short time, most often within 4 weeks. These statin rechallenges, although usually unblinded, are critical for establishing the likelihood that a patient has SAMS.

It is worth noting that statin exposure can cause mild CK elevations, usually within the normal range, even in patients who do not experience muscle symptoms. For example, in the STOMP study, statin-treated patients experienced a 20 IU/L increase in CK over baseline compared with those treated with placebo.[7] And although studies have shown that modest statin-related CK increases may occur more often in those who develop SAMS,[11,12] observing a mild CK increase while on statins may not be specific enough to have diagnostic utility in individual patients.

Based on these clinical observations, a tool known as the Statin-Associated Muscle Symptoms Clinical Index (SAMS-CI; **Fig. 1**) was developed[13] to help clinicians determine the probability of SAMS in statin-treated patients who develop muscle symptoms. Although the SAMS-CI still needs to be validated in large-scale clinical trials, preliminary studies suggest that less than 10% of patients with a score of 4 or less (out of 11 possible points) have SAMS. However, because only half of those with confirmed SAMS had scores of 6 or more, the SAMS-CI seems most useful for identifying those patients least likely to have true SAMS.[10]

Although circumstances may vary, diagnosis of suspected SAMS should usually begin by documenting the location, pattern, and timing of muscle symptoms as detailed on the SAMS-CI. Next, statins should be stopped and the timing of muscle symptom improvement should be documented; failure to improve after 4 to 8 weeks strongly suggests the patient does not have SAMS and alternative causes for the patient's symptoms should be sought. During the statin wash out period, factors that may contribute to the risk of statin intolerance should be eliminated if possible. This includes testing for and treating hypothyroidism and vitamin D deficiency. Assuming that the muscle symptoms do resolve and that the patient meets the American College of Cardiology and the American Heart Association guidelines for initiating treatment with a statin, rechallenging the patient with a statin regimen is an essential component

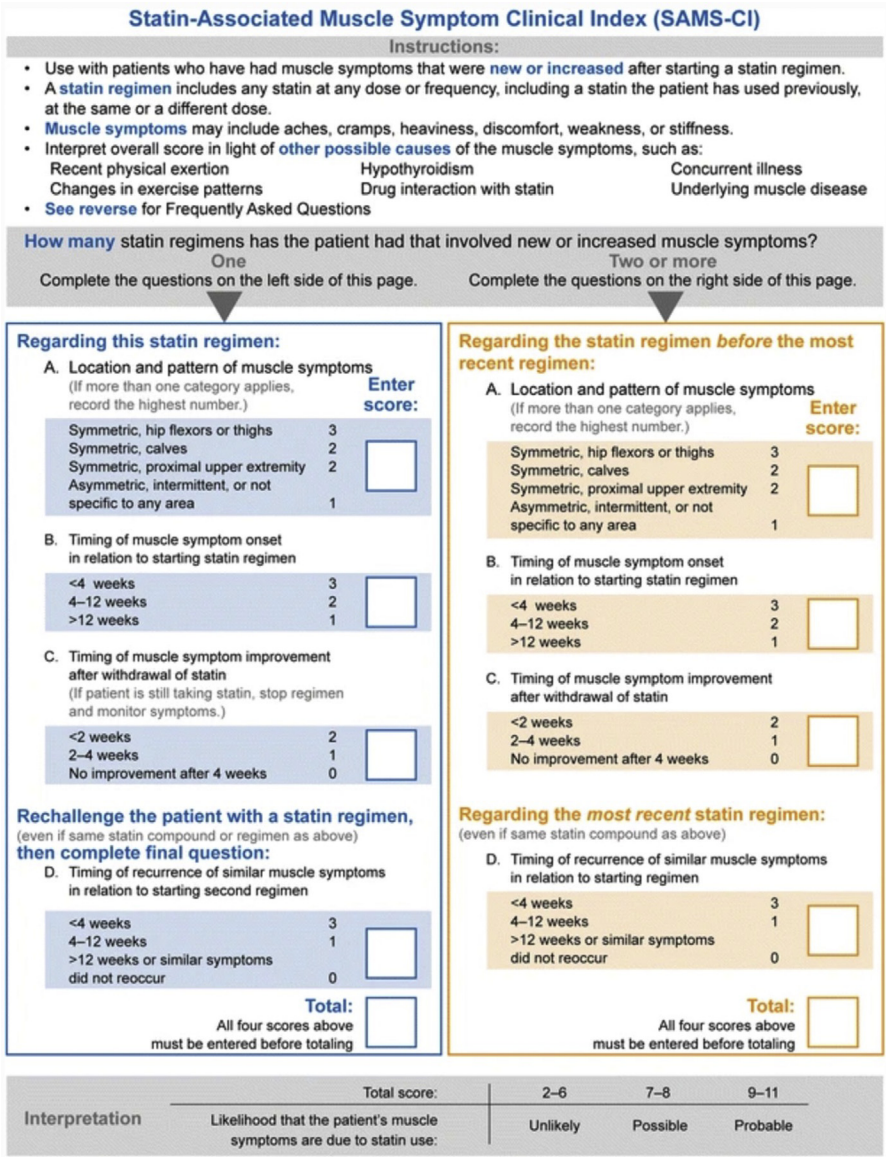

Fig. 1. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI). (*From* Rosenson RS, Miller K, Bayliss M, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): Revision for Clinical Use, Content Validation, and Inter-rater Reliability. Cardiovasc Drugs Ther 2017;31(2):182; with permission.)

of the diagnostic process. No further workup is required for those who do not experience a return of muscle symptoms with the statin rechallenge. However, in those whose symptoms return, especially if they have SAMS-CI scores of 5 or greater, the statin should be stopped until symptoms resolve and then an alternative statin regimen may be initiated. For example, rosuvastatin, atorvastatin, and pitavastatin

have long half-lives and can be given every other day (or even once per week) resulting in a lower weekly dose of statin. Although some patients with SAMS tolerate these lower dose regimens, which may not be inferior to daily dosing to reduce LDL-C and triglyceride levels,[14] it remains to be shown how effectively it reduces the risk of cardiovascular events.

Nonstatin medications should be considered for patients who do not reach their target cholesterol levels after demonstrated intolerance to 2 or 3 different statin regimens. The 2017 Focused Update of the 2016 American College of Cardiology Expert Consensus Decision Pathway provides detailed recommendations for choosing an alternative to statins in different statin-intolerant patient populations.[15] Specific recommendations vary depending on the age of the patient, whether the statin is prescribed for primary or secondary prevention, and the presence of certain comorbidities. In most cases, either ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is recommended for statin-intolerant patients who would benefit from a reduction in cholesterol levels. Several studies have shown that these agents are less likely to cause muscle symptoms than statin medications and that patients treated with PCSK9 inhibitors may have even fewer muscle symptoms than those on ezetimibe.[9,16,17]

STATIN-ASSOCIATED MYOTOXICITY

The author defines SAMT as statin-induced CK elevations with or without muscle discomfort and/or weakness. By this definition, SAMT encompasses a broad range of patients, from those with modest asymptomatic CK elevations to those with very high CK elevations, myoglobinuria, weakness, and acute renal failure (ie, rhabdomyolysis). “Minimal” SAMT will be defined when CK elevations are at less than 3-fold higher than untreated baseline levels or the normative upper limit (see[18] for normative values based on sex and race). And in keeping with the NLATF terminology, “mild,” “moderate,” and “severe” SAMT will be defined by CK levels that are elevated by 3-fold to 10-fold, 10-fold to 50-fold, and greater than 50-fold, respectively.

The risk that an individual will develop SAMT after statin exposure depends on several factors including their age and gender, the type and dose of statin prescribed, the coadministration of other medications, and the presence of genetic susceptibility factors. A 2008 paper published by the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group illustrates how multiple factors contribute to the risk of SAMT.[19] In this randomized trial of 12,064 patients with prior myocardial infarction, simvastatin was administered to 6031 patients at a dose of 80 mg each day and to 6033 patients at a dose of 20 mg per day. Although just 8 (0.1%) patients on the lower dose of simvastatin developed SAMT (as defined by CK levels at least 3 times greater than the normal limit or 5 times greater than the baseline), 98 (1.6%) patients on the higher statin dose developed this side effect. Among patients on 80 mg of simvastatin each day, this adverse event was 2.3 times more likely in those older than 65 years and 1.6-times more likely in women than in men. Those with impaired renal function had a 2.4-fold increased risk of SAMT. Furthermore, the concurrent use of amiodarone or calcium channel antagonists resulted in an 8.8-fold and 2.7-fold increased risk of developing SAMT, respectively. Finally, this study demonstrated that the rs3471512C allele of the *SLCO1B1* gene (encoding the solute carrier organic anion transporter family member 1B1 protein) confers significant risk for developing SAMT. Specifically, the risk of developing SAMT during the first year among those taking 80 mg of simvastatin each day was 0.6%, 3%, and 18% for those with 0, 1, and 2 copies of the C allele, respectively. Based on the results

of the SEARCH collaborative study, it is now recognized that most patients should be started on a low dose of simvastatin and that amiodarone should be avoided in patients taking simvastatin, especially at higher doses. However, genetic testing is not yet routinely performed to identify those patients at highest risk for SAMT.

In patients with suspected SAMT, the first intervention should be to discontinue the statin and document that the CK level returns to normal or baseline. Of note, although checking a baseline CK level before statin initiation is not currently recommended by most published guidelines, knowing the baseline value for the individual patient can be very helpful in those who develop muscle symptoms. Consequently, some clinicians do favor checking the baseline CK before starting statin therapy. That being said, there is no practical role for subsequent monitoring of CK levels in asymptomatic patients who are on statins.

At the same time that statins are discontinued, alternative diagnoses should also be considered. These include exposure to other potential myotoxins (eg, colchicine), endocrinopathies (eg, hypothyroidism), and idiopathic inflammatory myopathies (eg, inclusion body myositis). In SAMT patients, initial CK level reductions should be expected in the first few weeks after stopping the statin and a return to normal levels should rarely take longer than a month. In the event that the CK continues to increase or does not substantially decrease within this time frame, additional alternative diagnoses should be considered. As these include SAAM (discussed later) and previously unrecognized adult-onset inherited myopathies (eg, acid maltase deficiency), evaluation by a neuromuscular specialist would be recommended.

In those with suspected minimal or mild SAMT, a statin rechallenge could be considered to confirm the diagnosis. Depending on individual circumstances, a statin rechallenge might also be performed in some patients with suspected moderate SAMT. For example, some clinicians would consider a statin rechallenge in a white female patient with a CK of 3000 IU/L who experienced muscle discomfort but no weakness while on a statin. However, the author would not recommend a diagnostic statin rechallenge for those with suspected severe SAMT, especially if the patient suffered from renal dysfunction as part of their initial presentation. Furthermore, any statin rechallenge in a suspected SAMT patient should be done cautiously, using a low-dose statin once per week and slowly increasing the frequency or weekly dose while measuring CK levels at regular intervals. In those with documented SAMT based on CK level increases on rechallenge, or in those for whom statin rechallenge seems too risky, hypercholesterolemia should be managed with alternative agents such as ezetimibe or PCSK9 inhibitors.

STATIN-ASSOCIATED AUTOIMMUNE MYOPATHY

Anti-HMGCR myopathy is a subtype of immune-mediated necrotizing myopathy characterized by the presence of muscle weakness, elevated CK levels, and autoantibodies recognizing HMGCR.[4,20] Although some patients develop anti-HMGCR myopathy without having ever been prescribed a statin, exposure to statins is a significant risk factor for developing anti-HMGCR myopathy, and patients who develop the disease in this context are defined as having SAAM. Of note, SAAM is exceptionally rare and has been estimated to occur in just 2 or 3 of every 100,000 patients treated with these agents.[4] One study suggested that those with preexisting diabetes and/or atorvastatin exposure may be at the greatest risk for this adverse event.[21] Although patients with SAAM typically present with myalgias, symmetric proximal muscle weakness, and CK levels greater than 1000 IU/L,[4] occasional SAAM patients may present with muscle pain and elevated CK levels before muscle weakness becomes

apparent. Importantly, SAAM is an autoimmune disease that can be confirmed based on the presence of autoantibodies recognizing HMGCR. Statin-exposed patients with muscle pain, weakness, and/or CK elevations who test negative for anti-HMGCR autoantibodies may have SAMS or SAMT but do not have SAAM.[22,23]

Although anti-HMGCR testing is highly sensitive and specific for SAAM, the test may have a false-positive rate of about 0.5%.[22] To avoid misdiagnosis based on this test, only patients with a relatively high pretest probability of having SAAM should be screened for these autoantibodies. For example, patients without CK elevations should not be tested for anti-HMGCR autoantibodies. Furthermore, patients with minimal or mild CK elevations (<10-fold greater than normal limits) should only be tested for anti-HMGCR autoantibodies if their CK levels do not begin to decline within a few weeks (and eventually normalize) after stopping the statin. In contrast, it may be reasonable to screen for anti-HMGCR autoantibodies on initial presentation in patients who have at least moderate CK elevations (>10-fold greater than normal limits), especially if they are also weak. Of note, patients with elevated CK levels, symmetric proximal muscle weakness, and anti-HMGCR autoantibodies can be diagnosed with SAAM without performing electromyography, muscle imaging, or muscle biopsy.[20]

SAAM is usually a chronic autoimmune disease requiring long-term treatment by an experienced rheumatologist or neurologist. Guidelines recently published by a working group of the European Neuromuscular Center suggest that treatment should begin with corticosteroids along with a second agent such as methotrexate or IVIG.[20] Because IVIG may be effective as monotherapy,[24] this approach may also be considered, especially in patients with diabetes or another contraindication to steroids. Importantly, patients with SAAM should never be rechallenged with statins, which may cause disease flare. Although controlled trials remain to be performed, one case series including 8 subjects with SAAM suggests that PCSK9 inhibitors seem to be safe and effective in this population.[25]

SUMMARY

Although statins are generally safe and well tolerated, some patients experience muscle complaints that can limit their use, leading to an increased risk of cardiovascular events. In this review, diagnostic and management approaches were proposed for 3 major types of statin side effects: SAMS, SAMT, and SAAM. Patients with SAMS, who have muscle discomfort and elevated CK levels, must be diagnosed based on their clinical features and recurrence of symptoms following a statin rechallenge. Making a definite diagnosis of SAMS can be challenging given that many individuals have background nonspecific muscle discomfort; future work to define a biomarker for SAMS would be of great potential clinical utility. Hypercholesterolemia can usually be managed effectively in these patients by using an alternative statin regimen or nonstatin cholesterol-lowering agent. The diagnosis of SAMT is often more straightforward because these patients have high CK levels that recur on statin rechallenge (if deemed safe). These patients also usually tolerate an alternative statin regimen or another type of cholesterol-lowering agent. Finally, patients with SAAM can be diagnosed based on the presence of anti-HMGCR autoantibodies. These patients require immunosuppressive therapy and should not be reexposed to statins. Rather, if indicated, their hypercholesterolemia may be managed with a PCSK9 inhibitor. Fortunately, as shown here, after arriving at the correct diagnosis, it should be possible to effectively manage hypercholesterolemia and reduce the chance of cardiovascular events in patients with each type of statin intolerance.

CLINICS CARE POINTS

- In patients with suspected statin-associated muscle symptoms, a statin rechallenge is required to confirm the diagnosis.
- Statins may cause mild CK elevations, usually within the normal range, even in patients who do not experience muscle symptoms.

In patients with suspected statin-associated myotoxicity, other causes, such as hypothyroidism and inflammatory myopathies, should be excluded.

- Ezetimibe or PCSK9 inhibitors can be used to manage lipid levels in those who cannot tolerate statins.
- Testing for anti-HMGCR autoantibodies should be done in patients who are on statins and have CK levels greater than 1000 IU/L.
- Patients with statin-associated autoimmune myopathy and anti-HMGCR autoantibodies usually require chronic immunosuppression.

DISCLOSURE

None.

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