Coenzyme Q10 supplementation in the management of statin-associated myalgia

Statins are indicated for use as first-line therapy in the prevention of major adverse cardiovascular events (e.g., myocardial infarction, stroke) in patients with or at risk for cardiovascular disease.1 However, muscle-related adverse effects, including myopathy, often limit the use of statins in practice. Myopathy is a general term that encompasses myalgia (muscle pain), muscle weakness, and cramps.2 Statin-associated myalgia (SAM) has occurred in 0.1–5.0% of patients in randomized controlled trials (RCTs) of statins; those figures likely represent an underestimation of SAM frequency due to the studies’ exclusion of patients with a history of SAM or intolerant to statins during the run-in phase.3-5 Symptoms of SAM often include muscle pain, aches, weakness, and cramps, which may or may not correspond to an elevation in serum levels of creatine kinase (CK). In practice, SAM is often managed by lowering the dosage of the suspected offending drug, switching agents, or using alternate dosing strategies (e.g., every-other-day or once-weekly dosing).6 Persistence in prescribing of different statins and statin doses is recommended due to the relative lack of evidence of cardiovascular benefit with other lipid-lowering agents (e.g., ezetimibe, fibrates, niacin).1

The mechanism of SAM is unclear; however, several hypotheses have been proposed. One hypothesis is that inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase results in reduced downstream production of farnesyl pyrophosphate, an intermediary used in the production of coenzyme Q10 (ubiquinone).7-11 Coenzyme Q10 is thought to play an important role in mitochondrial respiration; therefore, a low circulating level of coenzyme Q10 is hypothesized to impair muscle cell mitochondrial function, leading to myopathy. Plasma and muscle cell studies exploring that possibility yielded heterogeneous results and were not designed to measure clinical outcomes, thereby failing to provide support for the aforementioned hypothesis.12-15 Nevertheless, coenzyme Q10 supplementation for the treatment or prevention of SAM is often used in practice, and many patients may choose to self-supplement. The objective of this review is to provide a practical summary of the evidence for coenzyme Q10 supplementation in the treatment or prevention of SAM.

Literature search methods. A systematic literature search was conducted using MEDLINE, the MEDLINE In-Process & Other Non-Indexed Citations database, EMBASE, Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, ClinicalTrials.gov, and Google Scholar; the search period extended from database inception to June 2016. The search terms coenzyme Q10, ubidecarenone, ubiquinone, coQ10, COQ, Q10, statin, hydroxymethylglutaryl-CoA reductase inhibitor, HMG-CoA reductase inhibitor, myopathy, muscular disease, myotoxicity, myalgia, muscle weakness, myositis, and rhabdomyolysis were used. The identified publications included articles on both randomized and nonrandomized studies (cohort studies and case series) and meta-analyses that compared coenzyme Q10 with placebo use or an active comparator for the purpose of preventing or treating SAM in adult patients. The search was limited to articles published in English. A total of 656 articles were identified. One of the authors performed the search, removed duplicate articles, and reviewed the abstracts for relevance. A manual search of the references of included studies was also performed. A total of 10 studies and 1 meta-analysis met the inclusion criteria. Both authors reviewed all included studies in full. Trials were classified as pertaining to prophylaxis if coenzyme Q10 supplementation was initiated prior to or concurrently with statin therapy or if the participants were taking a statin but had not experienced muscle symptoms. Trials were classified as pertaining to treatment if coenzyme Q10 supplementation was initiated while participants were taking a statin and experiencing muscle symptoms.

Trials of coenzyme Q10 for SAM prevention. Three RCTs and 1 nonrandomized study investigated the use of coenzyme Q10 for prophylaxis of SAM.

Young et al.16 conducted a double-blind RCT that evaluated coenzyme Q10 200 mg daily versus placebo use in 44 patients (mean age, 59 years; 50% were women) with...
previous self-reported intolerable myalgia while receiving statin therapy. All patients started taking simvastatin (10–40 mg daily based on tolerability) in addition to coenzyme Q10. Patients with a recent myocardial infarction or stroke were excluded from the study. After 12 weeks, the median change in the visual analog scale (VAS) score for myalgia in the coenzyme Q10 group was 4.2 mm on a 100-mm scale, as compared with a median change of 2.1 mm in the placebo group, a difference that was not significant \((p = 0.73)\). Furthermore, between-group differences in the numbers of patients who tolerated simvastatin 40 mg daily (16 of 22 patients in the coenzyme Q10 group versus 13 of 22 patients in the placebo group) or who were on any dose of simvastatin (16 of 22 coenzyme Q10 users versus 18 of 22 placebo users), as well as differences in the median change in plasma CK levels, were not significant. However, the sample size of this study was small; therefore, it was likely not adequately powered to detect significant differences.

Mabuchi et al.\(^1\) performed an RCT involving 49 Japanese patients (mean age, 61 years; 71% were women) with hypercholesterolemia who were taking atorvastatin 10 mg daily and were randomly assigned in a double-blind fashion to receive coenzyme Q10 100 mg daily or a placebo. At 16 weeks, there was no significant difference in mean serum CK levels between the groups. Furthermore, no serious adverse events, withdrawals due to adverse events, or complaints of myalgia or muscle weakness occurred during the study despite a dramatic increase in plasma coenzyme Q10 levels in the treatment group. As with the trial by Young et al., the primary study limitation was a small sample size.

Taylor et al.\(^1\) initially screened 120 patients with prior symptoms of SAM in the lead-in phase of a randomized crossover trial of simvastatin 20 mg daily versus placebo use.\(^1\) Thirty-eight patients (mean age, 58 years; 37% were women) who developed myalgia with simvastatin 20 mg daily (but not with placebo use) were randomly assigned to receive coenzyme Q10 600 mg daily or a placebo in addition to simvastatin 20 mg daily. Participants were initiated on coenzyme Q10 2 weeks prior to starting simvastatin. After 8 weeks, the mean ± S.D. changes from baseline in both the pain severity score and the pain interference score of the Brief Pain Inventory Short Form were not statistically significantly different between the groups \((p = 0.53\) and \(p = 0.56\), respectively). Furthermore, there was no change in muscle strength in either group. Interestingly, the percentage of patients who experienced muscle pain was higher with coenzyme Q10 use (14 of 20 patients [70%], as compared with 7 of 18 placebo users [39%]), although this difference did not reach statistical significance \((p = 0.05)\). Based on their sample size calculation, it appears that the authors failed to recruit enough patients to detect a significant difference in pain scores.

Vidyarthi et al.\(^{19}\) conducted a retrospective, uncontrolled review of data on 43 patients with SAM who were referred to a specialized lipid clinic (baseline demographics were not reported). Clinic patients were instructed to initiate coenzyme Q10 100 mg daily 1 week prior to starting rosuvastatin 5 mg weekly, with the rosuvastatin dose adjusted upward to a maximum tolerated dose. At 16 months, 37 of the 43 patients (86%) were able to tolerate rosuvastatin therapy (dosages ranged from 5 mg weekly to 20 mg daily). All 6 patients who discontinued therapy (5 due to recurrent myalgia and 1 due to elevated liver enzymes) did so within the first 12 weeks. However, conclusions regarding the effect of coenzyme Q10, if any, on statin tolerance in this study cannot be drawn owing to the uncontrolled study design, a lack of coenzyme Q10 product standardization, and the use of an adjunct intervention (slow rosuvastatin dosage adjustment).

**Trials of coenzyme Q10 for SAM treatment.** Five RCTs, 1 nonrandomized study, and 1 meta-analysis were conducted to investigate the use of coenzyme Q10 for the treatment of SAM.

In a nonrandomized study conducted by Langsjoen et al.,\(^{20}\) the researchers recruited 50 patients from cardiology clinics who were experiencing statin-related adverse drug reactions, including SAM. Supplementation with 240 mg of coenzyme Q10 daily reduced the frequency of SAM from 64% to 6%. However, all patients discontinued statin therapy concurrently with the initiation of coenzyme Q10.

Caso et al.\(^{21}\) compared the effects of coenzyme Q10 100 mg daily and vitamin E 400 IU daily in a double-blind RCT involving 32 patients with hyperlipidemia who were taking statins and presented to cardiology clinics with myopathic symptoms. The most commonly used statin was simvastatin (22 of 32 patients [69%]). There were important between-group differences at baseline: Patients in the coenzyme Q10 group were younger on average than those in the vitamin E group (58 years versus 64 years), and the former group had fewer women (6 of 18 patients versus 9 of 14 patients). After 30 days, the mean ± S.E.M. changes from baseline in the pain severity score of the Brief Pain Inventory (BPI) in the coenzyme Q10 and vitamin E groups were −2.0 ± 0.4 and 0.3 ± 0.3 points, respectively \((p < 0.001)\). (The BPI pain severity score is derived from patient ratings of pain on a numeric scale ranging from 0 [no pain] to 10 [worst imaginable pain].) Furthermore, 16 of 18 patients (89%) in the coenzyme Q10 group reported a reduction in pain, compared with 3 of 14 patients (21%) treated with vitamin E. However, interpretation of these results is limited by the low enrollment and differences in baseline characteristics that increased the risk of myalgia in the vitamin E group.

A randomized placebo-controlled study by Bookstaver et al.\(^{22}\) enrolled 76 patients (mean age, 62 years; 58% were

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women) who were actively experiencing myalgia (in 2 or more extremities for at least 2 weeks) that had begun within 60 days of initiation or an increase in the dosage of statin therapy. Most of the patients (44 of 76 [58%]) were taking simvastatin. Patients were randomly assigned in a double-blind fashion to receive coenzyme Q10 50 mg twice daily or a placebo. At 1 month, patients in both groups had a significant improvement from baseline in the mean pain score. However, between-group differences in the mean change from baseline in theVAS score and the median change in scores on the Sensory Pain Rating Index subscale of the McGill Pain Questionnaire were not significant (p = 0.94 and p = 0.24, respectively) at 3 months. Five and 3 patients in the coenzyme Q10 and placebo groups, respectively, withdrew from the study due to ongoing myalgia.

A trial by Bogsrud et al.23 enrolled 41 patients (median age, 58 years; 56% were women), who experienced SAM while taking atorvastatin and then had recurrent SAM after a washout and rechallenge with atorvastatin 10 mg daily. Patients were randomly assigned to double-blind treatment with coenzyme Q10 400 mg daily in combination with selenium 200 µg daily or a matching placebo for 12 weeks. Three pain scoring instruments were used: a VAS, the Giessener Symptoms Complaints Checklist, and the Buss–Perry Aggression Questionnaire. Minimal details were given regarding the changes from baseline in pain scores for either group; however, the investigators acknowledged that there were no significant differences in symptom scores or results of muscle function tests between the groups. The frequency of patients reporting improved pain, defined as a change of at least 18 mm on a 100-mm VAS, was 50% (10 of 20 patients) in the treatment group and 38% (8 of 21 patients) in the placebo group, a difference that did not reach statistical significance. It is important to note that coenzyme Q10 and selenium were not investigated individually in this study; thus, the results may have been influenced by the presence of selenium.

Fedacko et al.24 assessed the effect of coenzyme Q10 and selenium in patients with SAM using a 2 x 2 factorial design. Sixty statin-treated patients with tolerable myalgia were randomly assigned in a double-blind fashion to use of coenzyme Q10 200 mg daily or selenium 200 µg daily (or both) or placebo use. In the coenzyme Q10 group, the mean age of patients was 60 years, and 22 of 34 patients (65%) were women. In the placebo group, the mean age was 55 years, and 19 of 26 patients (73%) were women. Patients randomly assigned to coenzyme Q10 use had a significantly higher mean pain score at baseline than placebo users (6.7 points versus 5.3 points, p < 0.05). After 3 months, the reduction in the VAS score for muscle pain (0 = no pain, 10 = worst pain ever) was greater in the coenzyme Q10 group than in the placebo group (–3.5 versus –0.1, p < 0.01). Coenzyme Q10 supplementation also significantly improved muscle weakness and cramps. Selenium did not significantly improve SAM. As in the trial conducted by Caso et al.,25 low enrollment—and the resulting differences in study group baseline characteristics—may have confounded the results.

A placebo-controlled study by Skarlovnik et al.25 enrolled 50 statin-treated patients (mean age, 65 years; 54% were women) with mild-to-moderate muscle pain for at least 6 months despite multiple failed management strategies, such as gradual dose decreases or a switch to a different statin. Patients were randomly assigned to use of coenzyme Q10 50 mg twice daily or a placebo for 30 days. The mean ± S.E.M. changes from baseline in the Brief Pain Inventory pain severity score and pain inference score were 1.0 and 1.4 points, respectively, in the coenzyme Q10 group; neither score changed in the placebo group (p < 0.05 for both between-group comparisons). Although the improvements in pain scores with coenzyme Q10 were statistically significant, they likely did not translate into a clinically meaningful benefit due to the small absolute differences documented.

A meta-analysis of 5 of the previously discussed RCTs was published in 2015.26 All trials were considered to be of high quality, as per the Jadad score, which is a tool used to assess the general quality of RCTs.27 However, all studies were limited by small sample size (which may introduce differences in known or unknown baseline characteristics) and short follow-up. Pain assessment with a variety of scoring tools indicated that the mean net change in pain score associated with use of coenzyme Q10, as compared with placebo use, was –0.53 (95% confidence interval, –1.33 to 0.28; p = 0.20); however, there was high heterogeneity among the evaluated studies (I² = 89%), and the between-group difference in mean changes from baseline in plasma CK levels (assessed in 4 studies) was not significant.

**Discussion.** The proposed pharmacologic mechanism of SAM is a relative deficiency of coenzyme Q10.6 To date, studies have not shown a consistent statin effect on muscle coenzyme Q10 levels despite several studies showing a reduction in serum coenzyme Q10 levels with different statins, including atorvastatin and simvastatin, which questions the physiological plausibility of this theory. Furthermore, the best available evidence does not uniformly suggest that coenzyme Q10 supplementation has any benefit on clinically meaningful outcomes, such as reduction of myalgia, frequency of myalgia resolution, and statin tolerability. None of the 3 RCTs evaluating coenzyme Q10 use for prevention of SAM yielded positive results.16–18 For the treatment of SAM, the data are heterogeneous: 3 of the reviewed trials had positive results,21,22,25 while 2 of the trials were neutral.22,23 However, a meta-analysis of these trials did not demonstrate a benefit of coenzyme Q10 use overall.26 Serious adverse events with coenzyme Q10 use were
not reported in any of the reviewed studies, and coenzyme Q10 is generally considered to be well tolerated.

When evaluating these results, several important limitations must be considered. SAM is a clinical diagnosis comprising generalized, subjective symptoms that is entirely based on patient self-report. Some of the studies included in our literature review had complicated lead-in phases or inclusion criteria that required a temporal relationship between myalgia and statin therapy, but such requirements were not consistent among the reviewed studies. Therefore, it is possible that patients included in the studies may not have had actual statin-induced myalgia, as other etiologies are difficult to rule out. Furthermore, there was significant statistical heterogeneity among the studies, as well as clinical heterogeneity with regard to issues including sample size and characteristics, pain scales used, coenzyme Q10 and statin doses and regimens, and length of follow-up. All of the trials enrolled a small number of patients, and several trials did not include power calculations. Moreover, the results of the trials that showed significant benefits of coenzyme Q10 supplementation were driven by the absence of a placebo effect, while trials that did not show significant benefits tended to show a much more pronounced placebo effect. There may be several explanations for this effect, including loss of blinding and unreported differences between groups. For example, the majority of trials did not report on the concomitant use of analgesics for SAM, which is an important potential confounder. Finally, although intrastudy product standardization was consistent, there was considerable interstudy variability regarding the specific manufacturing company and dose of coenzyme Q10 used. Unfortunately, this limits the ability to make a recommendation for a specific coenzyme Q10 product and dose.

**Conclusion.** Evaluation of the literature suggests that coenzyme Q10 supplementation for the prevention or treatment of SAM does not have a beneficial effect on clinically meaningful outcomes such as reduction of myalgia, frequency of myalgia resolution, and statin tolerability. In the absence of further well-designed clinical trials, routine coenzyme Q10 supplementation for prophylaxis or treatment of SAM is not recommended.

2. Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. *Am J Cardiol.* 2006; 97(suppl):69C-76C.

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