Effects of Coenzyme Q10 on Statin-Induced Myopathy: A Meta-analysis of Randomized Controlled Trials

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Abstract

Objective: To evaluate the efficacy of coenzyme Q10 (CoQ10) supplementation on statin-induced myopathy.

Participants and Methods: We searched the MEDLINE, Cochrane Library, Scopus, and EMBASE databases (November 1, 1987, to May 1, 2014) to identify randomized controlled trials investigating the impact of CoQ10 on muscle pain and plasma creatine kinase (CK) activity as 2 measures of statin-induced myalgia. Two independent reviewers extracted data on study characteristics, methods, and outcomes.

Results: We included 6 studies with 302 patients receiving statin therapy: 5 studies with 226 participants evaluated the effect of CoQ10 supplementation on plasma CK activity, and 5 studies (4 used in the CK analysis and 1 other study) with 253 participants were included to assess the effect of CoQ10 supplementation on muscle pain. Compared with the control group, plasma CK activity was increased after CoQ10 supplementation, but this change was not significant (mean difference, 11.69 U/L [to convert to μkat/L, multiply by 0.0167]; 95% CI, −14.25 to 37.63 U/L; P = .38). Likewise, CoQ10 supplementation had no significant effect on muscle pain despite a trend toward a decrease (standardized mean difference, 0.53; 95% CI, −1.33 to 0.28; P = .20). No dose-effect association between changes in plasma CK activity (slope, −0.001; 95% CI, −0.004 to 0.001; P = .33) or in the indices of muscle pain (slope, 0.002; 95% CI, −0.005 to 0.010; P = .67) and administered doses of CoQ10 were observed.

Conclusion: The results of this meta-analysis of available randomized controlled trials do not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy. Larger, well-designed trials are necessary to confirm the findings from this meta-analysis.

Statins are the most commonly used drugs in the world, playing an important role in cardiovascular primary and secondary prevention. Recently, more data on the potential adverse effects of statin therapy (statin intolerance) are evident, with statin adverse events occurring in 3% to 15% of patients. The primary adverse effect limiting the use of statins is myopathy, ranging from benign myalgia to very rare cases of potentially fatal rhabdomyolysis. Statin intolerance is a clinical syndrome characterized by the inability to use statins long-term because of significant symptoms or biomarker abnormalities attributable to statins. Intolerance can be classified as either complete, intolerant to any statin at any dose, or partial, intolerant to some statins at some doses (mostly higher ones). Predispositions such as drug-drug interactions, untreated hypothyroidism or parathyroid dysfunction, reduced renal function, electrolyte abnormalities, and febrile illness, as well as many other secondary causes, must be first excluded to diagnose statin intolerance. Hypoparathyroidism has been associated with statin myopathy possibly because hypoparathyroidism with hypocalcemia produces a myopathy with elevated creatine kinase (CK) levels. Management of statin intolerance and myopathies from the Department of Hypertension (M.B.) and Department of Nephrology, Hypertension, and Family Medicine (J.R.), Medical University of Lodz, Lodz, Poland; Department of Functional Sciences (C.S.), Centre for Interdisciplinary Research (C.S., S.D.), Department of Functional Sciences (S.U.), and Department of Cardiology (S.D.), “Victor Babes” University of Medicine and Pharmacy, Affiliations continued at the end of this article.
would represent a substantial caseload in clinical practice owing to the extent of statin use in primary and secondary prevention. Furthermore, primary prevention with statins is likely to be cost-effective and may also improve patient quality of life. Statins interfere with the production of coenzyme Q10 (CoQ10), and this effect has prompted the hypothesis that CoQ10 deficiency plays a role in statin-associated myopathy. Coenzyme Q10 is a fat-soluble, vitamin-like substance found in all cell types throughout the body but especially in the heart, liver, kidney, and brain. Because CoQ10 is fat soluble and is carried in lower-density lipoproteins, reducing low-density lipoprotein particles with statins also decreases the plasma-measured CoQ10 level. Coenzyme Q10 is now widely used as a food supplement. In the United States, for example, CoQ10 is regulated as a food component, meaning that approval of products that contain this compound is not required by the Food and Drug Administration unless specific health claims are made. The total amount of CoQ10 in an adult human body is approximately 2 g, and 0.5 g must be replaced daily by endogenous synthesis and diet. In its reduced form, ubiquinol, CoQ10 acts as a phenolic antioxidant and undergoes hydrogen abstraction by free radicals; therefore, it acts like a chain-breaking antioxidant. In addition to showing potential as an antioxidant and functioning as a cofactor in the mitochondrial respiratory chain, CoQ10 may have gene regulatory properties that might account for its effects on overall tissue metabolism. Administration of CoQ10 increases CoQ10 blood levels in patients treated with statins. However, these studies were based on relatively small sample sizes. Therefore, the precise effect(s) of CoQ10 supplementation has not been established.

In this study, we systematically review all the published trials on CoQ10 supplementation and assess its overall efficacy on muscle pain and elevated plasma CK activity, as measures of statin-induced myalgia. To our knowledge, this is the first systematic review and meta-analysis on this topic.

PARTICIPANTS AND METHODS

Data Sources
This study was designed to conform to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. The search included the MEDLINE, Cochrane Library, Scopus, and EMBASE databases and was limited to randomized controlled trials (RCTs) investigating the efficacy of CoQ10 in reducing statin-induced myopathy in adults published between November 1, 1987, and May 1, 2014. Bibliographies of all retrieved articles were searched for additional relevant publications. Each search strategy included key words related to CoQ10 (coenzyme Q10, ubiquinone) and search terms of interest, including statin intolerance and statin-induced myopathy. Two reviewers (C.S. and S.U.) assessed each article independently to diminish the probability of duplication, analyzing reviews, case studies, and uncontrolled trials. Disagreements were resolved by consensus and discussion with a third party (M.B.).

Study Selection
Inclusion Criteria. The study design had to meet the following criteria: (1) randomized, placebo-controlled, parallel or crossover trial; (2) enrolled population of adults 18 years and older; (3) the intervention group received CoQ10 and the comparison group received placebo; and (4) data regarding the measurement of CK or measures of the severity of myopathic pain were available.

Exclusion Criteria. Studies were excluded if (1) no data were presented regarding myopathy-associated circulating measures of plasma CK activity or severity of myopathic pain (evaluated using subjective measures such as pain severity score, pain interference score, and the short-form McGill Pain Questionnaire, a visual analog scale for pain, weakness, cramps, tiredness, and myalgia score); (2) the study was not conducted in statin-treated individuals; (3) the study was not designed to assess the impact of CoQ10 on myopathy, and, hence, no efficacy measure of myopathy treatment was used; (4) no numerical values were provided; (5) the study did not include a control group; (6) we were unable to obtain adequate details of study methods or results from the article or the investigators; or (7) the study was an ongoing trial.

Quality Assessment. The quality of included studies was assessed using the Jadad scale. This scale encompasses randomization (0-2...
points), blinding (0-2 points), and dropouts and withdrawals (0-1 point). The overall score of a study according to this scale ranges from 0 to 5; higher scores are indicative of better quality.21 Studies with Jadad scores of 2 or less and 3 or more were considered low and high quality, respectively.22

**Statistical Analyses**

The meta-analysis was conducted using Review Manager software version 5.1 (The Cochrane Collaboration). If blood CK levels were collated in milligrams per deciliter, multiplication by 58.8 was used to convert CK activities expressed in microkatal per liter to international units per liter. Standard deviations (SDs) at one time point were calculated using the following formula: $SD = \text{SEM} \times \sqrt{n}$ (SEM indicates standard error of the mean; $n$, number of participants). The SDs of the mean difference were calculated using the following formula: square root $(SD_{pretreatment})^2 + (SD_{posttreatment})^2 - (2R \times SD_{pretreatment} \times SD_{posttreatment})$, assuming a correlation coefficient ($R$) = 0.5. In the case of reporting concentration values provided as the median and interquartile range, the mean and SD were estimated using the recommendations of Hozo et al.23

For parallel and crossover trials, net changes in measurements (change scores) were calculated as follows: (measure at end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at end of follow-up in the control group – measure at baseline in the control group). A random effects model and the generic inverse variance method were used to accommodate for the heterogeneity of studies in terms of design, duration, nature of included populations (underlying disease, age, sex, body mass index, and specimen type [plasma or serum]), and statin type and dosage used. To evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the 1-study-removed approach. Heterogeneity analysis was performed using the Cochran Q test and the $I^2$ index. Mean difference was used as the summary statistic for the meta-analysis of CK data. To address the intersudy variability in assessing the severity of pain, standardized mean difference was used as the summary statistic. The association between changes in the evaluated outcome measures (plasma CK activity and severity of muscle pain) and administered doses of CoQ10 (100-400 mg/d) was tested in a random effects meta-regression analysis using the unrestricted maximum likelihood method.

Publication bias was assessed visually using funnel plots of standard error vs mean difference (in the case of CK activity) or standardized mean difference (in the case of severity of muscle pain). In cases of asymmetry, missing studies were imputed using the Duval and Tweedie trim-and-fill method. In addition, the presence of publication bias was further evaluated using Begg rank correlation and Egger weighted regression tests. Meta-regression and publication bias analyses were performed using Comprehensive Meta-Analysis software version 2 (Biostat).

**RESULTS**

**Search Results and Trial Flow**

Initial screening for potential relevance excluded articles whose titles or abstracts were clearly irrelevant. After assessment, 6 articles met the inclusion criteria and were selected for the final meta-analysis.24-29 A summary of the study selection process is shown in Figure 1.

**Study Characteristics**

Of 226 participants randomized, 118 were allocated to receive CoQ10 therapy and 108 to the control group in the 5 studies presenting data regarding plasma CK activity.24-29 The number of participants in these trials ranged from 32 to 60. In total, 253 participants were randomized, of whom 134 were allocated to receive CoQ10 therapy and 119 to the control group in 5 studies that addressed myalgia (4 studies used in the CK analysis24-26,28,29 and 1 other study26 presenting data regarding muscle pain). The number of participants in these trials ranged from 32 to 76. Included studies were published between 2007 and 2013 and were conducted in the United States, Japan, Slovakia, New Zealand, and Norway. A wide range of CoQ10 dosing (100-400 mg/d) was used in the included trials. Duration of supplementation with CoQ10 ranged from 30 days and 3 months. All the trials were designed as parallel-group studies and had high quality according to the Jadad scale. Demographic characteristics and baseline biochemical parameters of the included studies are shown in Table 1.
Sensitivity Analysis
We performed a leave-one-out sensitivity analysis to evaluate the robustness of the association results. We iteratively removed one study at a time and recalculated the summary of effect size. For CK, $I^2$ ranges from 0% to 35%, where 0% represents no heterogeneity and larger values represent increasing heterogeneity (Table 2). For muscle pain, $I^2$ ranges from 70% to 92%, showing increased heterogeneity (Table 3).

Effect of CoQ10 Therapy on Plasma CK Activity
Compared with the control group, CoQ10 therapy did not significantly modify plasma CK activity (mean difference, 11.69 U/L [to convert to pmol/L, multiply by 0.0167]; 95% CI, $-14.25$ to $37.63$ U/L; $P=0.38$) (Figure 2). No significant interstudy heterogeneity for this outcome was found ($I^2=16$%; $P=0.32$). Likewise, random effects meta-regression did not suggest any dose-effect association between changes in plasma CK activity and administered doses of CoQ10 (slope, $0.002$; 95% CI, $-0.005$ to $0.010$; $Z=0.43$; $tau^2=0.61$; $P=0.67$) (Figure 3).

Effect of CoQ10 Therapy on Muscle Pain
In 24 of 26 of the included studies, CoQ10 had a statistically significant effect on muscle pain. In the remaining 3 studies, CoQ10 did not have a significant effect on muscle pain compared with the control group. The standardized mean difference was $-0.53$ (95% CI, $-1.33$ to $0.28$; $P=0.20$) (Figure 4). Significant interstudy heterogeneity for this outcome was found ($I^2=89$%; $P<0.001$). Random effects meta-regression did not suggest any dose-effect association between changes in the indices of muscle pain and administered doses of CoQ10 (slope, $0.002$; 95% CI, $-0.005$ to $0.010$; $Z=0.43$; $tau^2=0.61$; $P=0.67$) (Figure 5).

Publication Bias Analysis
Funnel plots of standard error vs effect size suggested potential publication bias for the effects of CoQ10 on plasma CK activity (Figure 6). Trim-and-fill correction imputed 2 theoretically missing studies, leading to an effect size of 1.79 U/L (95% CI, $-31.92$ to $35.51$ U/L). The Begg rank correlation test (Kendall tau with continuity correction, 0.30; $Z=0.73$; 2-tailed $P=0.46$) and the Egger linear regression test (intercept, 0.76; 95% CI, $-0.92$ to 2.43;
TABLE 1. Demographic Characteristics and Baseline Biochemical Parameters of the Studies Selected for Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Caso et al., 2007</th>
<th>Bookstaver et al., 2012</th>
<th>Fedacko et al., 2013</th>
<th>Mabuchi et al., 2007</th>
<th>Young et al., 2007</th>
<th>Bogsrud et al., 2013</th>
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<td>Randomized, double-blind, placebo-controlled, parallel trial</td>
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<td>Randomized, double-blind, placebo-controlled, parallel trial</td>
<td>Randomized, double-blind, placebo-controlled, parallel trial</td>
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<tr>
<td>Duration of trial</td>
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<td>3 mo</td>
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<td>12 wk</td>
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<td>Inclusion criteria</td>
<td>Patients treated for hyperlipidemia with statin and reporting myopathic symptoms</td>
<td>Patients currently receiving a statin who developed new-onset myalgias in &gt;2 extremities within 60 d of initiation or a dosage increase</td>
<td>Statin-treated patients with muscle pain or muscle weakness or tiredness or muscle cramps, with or without elevated CK levels</td>
<td>Hypercholesterolemic patients treated with atorvastatin with no serious adverse events and no concerns about myalgia or muscle weakness</td>
<td>Patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy</td>
<td>Patients who had experienced previous or ongoing statin-induced myopathy with atorvastatin therapy</td>
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<td>CoQ10 intervention (mg/d)</td>
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<td>59.6±8.9</td>
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<td>Patients</td>
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<tr>
<td>Patients</td>
<td>28.1±1.0</td>
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<td>29.0±6.1</td>
<td>23.3±2.7</td>
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<td>27.0 (22.2-35.0)</td>
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<td>27.2±4.1</td>
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<td>Patients</td>
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<td>Pain interference score</td>
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<td>VAS muscle pain</td>
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<td>VAS muscle weakness</td>
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<td>VAS muscle cramps</td>
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<td>VAS Gießener Symptom Complaints</td>
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*a BMI = body mass index; CK = creatine kinase; CoQ10 = coenzyme Q10; NS = not stated; VAS = visual analog scale.

* SI conversion factor: To convert CK values to µkat/L, multiply by 0.0167.

* Values are expressed as mean ± SD or median (minimum-maximum) unless otherwise stated.
t = 1.44, df = 3.00; 2-tailed P = .24) suggested no evidence of publication bias. With respect to the impact of CoQ10 on muscular pain severity score (Figure 6), trim-and-fill—imputed effect size was the same as observed effect size. Likewise, there was no evidence of publication bias according to the results of the Begg rank correlation test (Kendall tau with continuity correction, e0.50; Z = 1.22; 2-tailed P = .22) and the Egger linear regression test (intercept, e7.66; 95% CI, e34.35 to 19.02; t = 0.91; df = 3.00; 2-tailed P = .43).

**DISCUSSION**

To our knowledge, the present systematic review is the first to assess the effects of CoQ10 supplementation on statin-induced myopathy and to provide a thorough synthesis of results from RCTs. We observed a lack of a significant effect of CoQ10 supplementation on statin-induced myopathy.

Many small studies have reported that CoQ10 might improve statin tolerance by preventing statin-associated myopathy.1,3,24,26 This effect was attributed to the decline in CoQ10 levels during statin therapy.1-3 This effect has also been proposed as a hypothetical mechanism for another important statin adverse event: new-onset diabetes.30,31 In most instances, however, the studies of CoQ10 supplementation and statin intolerance had methodological limitations (mainly owing to small numbers of patients included), leaving this hypothesis unproven. In the present analysis, we provide the most reliable evidence to date, including information on 302 individuals with or without CoQ10 supplementation from randomized trials assessing the species effect of CoQ10 therapy on poststatin myalgia and plasma CK activity. Contrary to findings from several smaller studies, we observed no significant effect of CoQ10 supplementation on statin-related myopathy.

According to the available studies, the commonly used doses of CoQ10 are 50 to 300 mg/d in cardiovascular diseases, being safe and well tolerated at doses up to 1200 mg/d.32 Several studies have reported that CoQ10 supplementation reduces the symptoms of statin-induced

<table>
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<tr>
<th>Reference, year</th>
<th>CoQ10 group (No.)</th>
<th>Control group (No.)</th>
<th>Effect size</th>
<th>95% CI</th>
<th>Z value</th>
<th>P value</th>
<th>Tau²</th>
<th>Q</th>
<th>df (Q)</th>
<th>I² (%)</th>
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<td>−14.25 to 37.63</td>
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<td>Leave-one-out sensitivity analysis</td>
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<td>.29</td>
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<td>Bogsrud et al, 2013</td>
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<td>87</td>
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<td>0.90</td>
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<td>549.06</td>
<td>4.63</td>
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CoQ10 = coenzyme Q10.

<table>
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<tr>
<th>Reference, year</th>
<th>CoQ10 group (No.)</th>
<th>Control group (No.)</th>
<th>Effect size</th>
<th>95% CI</th>
<th>Z value</th>
<th>P value</th>
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<td>134</td>
<td>119</td>
<td>−0.53</td>
<td>−1.33 to 0.28</td>
<td>1.28</td>
<td>.20</td>
<td>0.74</td>
<td>36.63</td>
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<td>Leave-one-out sensitivity analysis</td>
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<tr>
<td>Caso et al, 2007</td>
<td>116</td>
<td>105</td>
<td>−0.39</td>
<td>−1.33 to 0.54</td>
<td>0.82</td>
<td>.41</td>
<td>0.82</td>
<td>32.94</td>
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<td>Young et al, 2007</td>
<td>112</td>
<td>97</td>
<td>−0.77</td>
<td>−1.67 to 0.13</td>
<td>1.68</td>
<td>.09</td>
<td>0.74</td>
<td>27.12</td>
<td>3</td>
<td>89</td>
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<td>Fedacko et al, 2013</td>
<td>100</td>
<td>93</td>
<td>−0.16</td>
<td>−0.71 to 0.38</td>
<td>0.59</td>
<td>.56</td>
<td>0.21</td>
<td>10.11</td>
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<td>83</td>
<td>−0.67</td>
<td>−1.72 to 0.38</td>
<td>1.25</td>
<td>.21</td>
<td>1.03</td>
<td>31.85</td>
<td>3</td>
<td>91</td>
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<tr>
<td>Bogsrud et al, 2013</td>
<td>114</td>
<td>98</td>
<td>−0.62</td>
<td>−1.65 to 0.40</td>
<td>1.20</td>
<td>.23</td>
<td>0.99</td>
<td>35.80</td>
<td>3</td>
<td>92</td>
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CoQ10 = coenzyme Q10.
myopathy, especially when treated with CoQ10 at high doses (≥600 mg/d). Recently, it has also been reported that polymorphisms in the \textit{SLCO1B1} gene, which encodes the protein responsible for hepatic uptake of statins, and the \textit{COQ2} (coenzyme Q2 4-hydroxybenzoate polyprenylntransferase) gene, important in the synthesis of CoQ10, are strongly associated with statin-induced myopathy. Therefore, deficiency of CoQ10 may be involved in the pathogenesis of statin-induced myopathy, interfering with the endogenous synthesis of CoQ10 in the body. However, this has not been confirmed in the presented meta-analysis. Notably, the effect sizes that were calculated in the present study were independent of the administered doses of CoQ10.

Because the etiologic role of CoQ10 deficiency in statin-associated myopathy was not proved, deficiency of CoQ10 can still be considered as a predisposing factor, especially in patients with other CoQ10-depleting conditions. There are several possible benefits of CoQ10 administration that are connected with its potential to enhance adenosine-5'-triphosphate production, antioxidant activity, expression of multiple genes, membrane stabilizing properties, protective effect against low-density lipoprotein oxidation, and inhibitory effects on proinflammatory cytokines and other

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
Study or subgroup & \multicolumn{3}{c|}{CoQ10} & \multicolumn{3}{c|}{Control} & \multicolumn{2}{c|}{Mean difference} \\
& Mean & SD & Total & Mean & SD & Total & inverse variance random. & 95% CI \\
\hline
Mabuchi et al.\textsuperscript{27} 2007 & 80 & 275.31 & 24 & -11 & 79.37 & 25 & 4.8% & 91.00 (-23.45 to 205.45) \\
Caso et al.\textsuperscript{24} 2007 & 28 & 85.75 & 18 & -30 & 121.02 & 14 & 10.4% & 58.00 (-16.75 to 232.75) \\
Young et al.\textsuperscript{28} 2007 & 18.75 & 11.88 & 22 & 15.75 & 7.46 & 22 & 74.2% & 3.00 (-2.86 to 8.86) \\
Bogsrud et al.\textsuperscript{29} 2013 & 52 & 309.67 & 20 & 21 & 214.4 & 21 & 2.4% & 31.00 (-132.79 to 194.79) \\
Fedacko et al.\textsuperscript{26} 2013 & -24.12 & 245.34 & 34 & -2.94 & 65.47 & 26 & 8.1% & -21.18 (-107.40 to 65.04) \\
\hline
Total (95% CI) & 118 & 10.00 & 91.00 (–23.45 to 205.45) & 108 & 1.48 & 58.00 (-16.75 to 232.75) & 100.0% & 11.69 (-14.25 to 37.63) \\
\hline
\end{tabular}
\caption{Study or subgroup & \multicolumn{3}{c|}{CoQ10} & \multicolumn{3}{c|}{Control} & \multicolumn{2}{c|}{Mean difference} \\
& Mean & SD & Total & Mean & SD & Total & inverse variance random. & 95% CI \\
\hline
Mabuchi et al.\textsuperscript{27} 2007 & 80 & 275.31 & 24 & -11 & 79.37 & 25 & 4.8% & 91.00 (-23.45 to 205.45) \\
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\hline
Total (95% CI) & 118 & 10.00 & 91.00 (–23.45 to 205.45) & 108 & 1.48 & 58.00 (-16.75 to 232.75) & 100.0% & 11.69 (-14.25 to 37.63) \\
\hline
\end{table}

\section*{FIGURE 2.} Meta-analysis of the effect of coenzyme Q10 (CoQ10) supplementation on plasma creatine kinase activity compared with the control group.

\section*{FIGURE 3.} Meta-regression plot of the mean change in plasma creatine kinase (CK) activity according to the administered doses of coenzyme Q10 (CoQ10). The size of each circle is inversely proportional to the variance of change.
More recent studies have found that adding CoQ10 to statin treatment may protect hepatocytes from statin-induced injuries and reduce their adverse effects. In patients with coronary artery disease undergoing statin therapy, 300 mg/d of CoQ10 supplementation may essentially enhance antioxidant enzyme activities and decrease inflammation. In aged athletes taking statins, 200 mg/d of CoQ10 improved muscle performance (as measured by time to anaerobic threshold), muscle strength (as measured by leg extension repetitions), and leg strength (as measured by quadriceps muscle repetitions).

This meta-analysis encompassed all published RCTs of CoQ10 supplementation for the treatment of statin intolerance, and we did not find any statin-induced myopathy effect. These findings are consistent with the few recent studies that did not find an improvement in statin tolerance or myalgia after supplementation with CoQ10 compared with placebo; however, other small studies found that CoQ10 supplementation is safe and may reduce the symptoms of statin-induced myopathy. However, the sensitivity analyses of the present systematic review confirmed that the effect size is robust and is representative of all included
studies rather than a single study. Therefore, this meta-analysis suggests that CoQ10 supplementation for statin-induced myopathy is not an effective option. Because adverse effects of statins may be reversed by supplementation of mevalonate, a precursor of cholesterol, we can speculate that the lack of effectiveness of CoQ10 administration in statin-induced myopathy may be related to another deficiency in the mevalonate pathway, such as the depletion of farnesyl and geranylgeranyl pyrophosphate, with consecutive reductions in guanine nucleotide binding proteins.

Furthermore, no significant dose-effect association was observed in the meta-regression analysis, although the impact of higher doses of CoQ10 (600-1200 mg/d) still merits further investigation. The Coenzyme Q10 in Statin Myopathy study (clinicaltrials.gov Identifier: NCT01140308), an ongoing randomized trial of CoQ10 supplementation, will determine its utility for decreasing pain intensity in 135 patients with statin-associated myopathy. After the pain symptoms are documented using the Brief Pain Inventory (Short Form), the patients will be randomized to receive simvastatin, 20 mg/d, plus either CoQ10, 600 mg/d, or placebo. This study may explain various gaps in the statin-induced myalgia field. This will include the percentage of individuals with a history of self-reported muscle pain who report symptoms during placebo treatment along with the percentage of self-reported muscle pain with verified myalgia on simvastatin therapy.

This review also facilitates identification of future research priorities. Because statin intolerance is a growing problem, considering the current guidelines, a consensus for terminology, criteria for diagnosis, and appropriate treatments are urgently needed. One such attempt has been recently presented by the experts of the National Lipid Association. They defined myalgia as an unexplained muscle discomfort often described as “flu-like” symptoms with a normal CK level. They also recommended a valuable index, the Myalgia Clinical Index Score, for patients with statin-associated myopathy. The National Lipid Association also suggested the definition of statin intolerance as adverse symptoms, signs, or laboratory abnormalities attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living (such as sleep, work/housework, or leisure time activity), leading to a decision to stop or reduce statin therapy. Both definitions of myalgia and statin intolerance offer useful tools for better diagnosis of these phenomena and a basis for further discussions and next recommendations.

The present meta-analysis has several limitations. Most important, there were few eligible RCTs, and most had small numbers of patients (N<60). Furthermore, the included studies were heterogeneous regarding factors such as population characteristics, study design, CoQ10 dose, and duration of supplementation. However, the impact of heterogeneity on estimated effect sizes was minimized by choosing a random effects mode of analysis and the generic inverse variance method to accommodate the heterogeneity of
studies in terms of design, duration, nature of included populations (underlying disease, age, sex, and body mass index), specimen type (plasma or serum), and statin type and dosages that were used. The included studies also did not analyze the other parameters, such as muscle strength, exercise performance, and measures of mitochondrial and respiratory function, for which CoQ10 supplementation might be of some benefit. Finally, sensitivity analysis was conducted using the 1-study-removed approach to evaluate the influence of each study on the overall effect size.

CONCLUSION
This meta-analysis of available RCTs does not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy. Furthermore, large-scale, well-designed trials with higher CoQ10 doses are warranted, particularly those in which changes in myopathy-associated circulating and objective measures are among the primary outcomes.

ACKNOWLEDGMENTS
Drs Banach and Serban contributed equally to this meta-analysis.

Abbreviations and Acronyms: BMI = body mass index; CK = creatine kinase; CoQ10 = coenzyme Q10; RCT = randomized controlled trial; VAS = visual analog scale

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Potential Competing Interests: Dr Mumtaz has received research grants and served as a consultant for AgenInc. Dr Toth serves on the Speakers Bureau for Amaarin, AstraZeneca, GS, Kowa, and Merck. He also serves as a consultant for Aegerion, Agen, AstraZeneca, Atherotech, Kowa, Liposcience, Merck, Novartis, and Regeneron.

Dr Jones serves on the Scientific Advisory Board and receives grant support from Atherotech Diagnostics Lab, and he serves as a consultant for Sanofi-Regeneron Pharmaceuticals.

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REFERENCES


