

Statin-Associated Cardiomyopathy Responds to Statin Withdrawal and Administration of Coenzyme Q₁₀

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ABSTRACT

Context: Heart failure (HF) is rapidly increasing in incidence and is often present in patients receiving long-term statin therapy.

Objective: To test whether or not patients with HF on long-term statin therapy respond to discontinuation of statin therapy and initiation of coenzyme Q₁₀ (CoQ₁₀) supplementation.

Design: We prospectively identified patients receiving long-term statin therapy in whom HF developed in the absence of any identifiable cause. Treatment consisted of simultaneous statin therapy discontinuation and CoQ₁₀ supplementation (average dosage = 300 mg/d).

Main Outcome Measures: Baseline and follow-up physical examination findings, symptom scores, echocardiograms, and plasma CoQ₁₀ and cholesterol levels.

Results: Of 142 identified patients with HF, 94% presented with preserved ejection fraction (EF) and 6% presented with reduced EF (< 50%). After a mean follow-up of 2.8 years, New York Heart Association class 1 increased from 8% to 79% (p < 0.0001). In patients with preserved EF, 34% had normalization of diastolic function and 25% showed improvement (p < 0.0001). In patients with reduced EF at baseline, the EF improved from a mean of 35% to 47% (p = 0.02). Statin-attributable symptoms including fatigue, muscle weakness, myalgias, memory loss, and peripheral neuropathy improved (p < 0.01). The 1-year mortality was 0%, and the 3-year mortality was 3%.

Conclusion: In patients receiving long-term statin therapy, statin-associated cardiomyopathy may develop that responds safely to statin treatment discontinuation and CoQ₁₀ supplementation. Statin-associated cardiomyopathy may be a contributing factor to the current increasing prevalence of HF with preserved EF.

INTRODUCTION

Heart failure (HF) is a leading cause of death in modern societies. In the US alone, it affects 5.1 million people, and 1 in 9 reported deaths included HF as a contributing cause in 2009.¹ Historically, HF has been associated with a reduced ejection fraction (EF). Recently, however, as the incidence of HF has been steadily increasing, much of this increase is in patients with preserved EF, that is, diastolic HF.² Diastolic dysfunction is an early and sensitive marker of diminished myocardial function. Currently at least 50% of patients with HF have preserved EF.² The cause of this increase in HF with preserved EF (HFpEF) is not clear.

Because cardiac relaxation in diastole is highly dependent on adenosine triphosphate, a reduction in myocardial energy production can cause diastolic dysfunction.³ The impairment of mitochondrial energy production by low levels of myocardial coenzyme Q₁₀ (CoQ₁₀)⁴ and statin-induced depletion of CoQ₁₀ have

been described.⁵ A clinical trial of 14 patients with hypercholesterolemia treated with 20 mg of atorvastatin for 6 months documented the development of diastolic dysfunction in 10 of the 14 patients that was reversed with CoQ₁₀ supplementation at 300 mg/d.⁶

Our hypothesis is that statin-induced CoQ₁₀ depletion may cause impairment in diastolic function and that the widespread use of statin therapy, particularly in elderly individuals, may be a contributor to the increasing incidence of HF. We postulate the existence of a clinical entity designated *statin-associated cardiomyopathy* (SACM), which can be defined as an impairment in heart muscle function secondary to statin drug therapy of a severity sufficient to cause HF. Furthermore, we hypothesized that SACM as a drug-induced condition should be at least partially reversible by cessation of statin therapy and administration of CoQ₁₀.

The primary aim of the current hypothesis-generating study was to determine if

SACM is safely reversible by simultaneously discontinuing the statin treatment and supplementing CoQ₁₀. Our secondary aims were to determine the demographics and clinical characteristics of patients with SACM, the average dose, duration, and potencies of the associated statin therapy and the response of other statin-associated symptoms to discontinuation of the statin regimen and supplementation with CoQ₁₀.

METHODS

Subjects and Study Protocol

In the normal course of an adult outpatient cardiology clinic, from April 2007 to August 2015 we identified 142 patients receiving long-term statin therapy in whom HF had developed in the absence of any identifiable cause. Patients were either self-referred or referred by their primary care physician with signs and symptoms of HF. In addition to HF symptoms, patients presented with fatigue (93%), memory loss (73%), muscle weakness (54%), muscle pain (60%), and peripheral neuropathy (37%). Final follow-up was concluded in February 2016. Because of the presence of severe statin-associated adverse effects on presentation, all patients were treated uniformly with discontinuation of statin therapy and supplementation with oral CoQ₁₀.

The institutional review board of East Texas Medical Center in Tyler, TX,

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approved a retrospective chart review of these patients with a waiver of consent. In 2012, funding became available to begin a prospective study enrolling a subset of 44 patients with SACM for laboratory testing and scheduled echocardiography. This allowed for more frequent plasma CoQ₁₀ analysis and more echocardiographic data. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved in April 2012 by the institutional review board. These 44 patients consented to have plasma CoQ₁₀ levels and echocardiograms obtained at baseline and at 3-month and 6-month follow-up. The other 98 observational patients with SACM had blood investigations and echocardiography as clinically indicated. Because the treatment was the same in both groups, we analyzed the combined cohort of 142 patients (Table 1). The average age was 65 years, 54% were men, and 94% were white. Of the patients, 28% had coronary heart disease with angiographically normal left ventricular EF and left ventricular end-diastolic pressure before starting statin therapy. Forty-nine percent of patients had hypertension with normal left ventricular wall thickness.

The inclusion criterion for the study was the presence of HF in the absence of any identifiable cause of HF, which began after the initiation of statin therapy. The average duration of statin therapy was 6.8 years, with a mean statin dosage of 17 mg/d, normalized to atorvastatin potency. Although there had been occasional adjustments in dosage or the occasional change from one statin to another statin in these patients, there were no prolonged periods without statin therapy. Statin potency was normalized to atorvastatin potency with the following formula: Atorvastatin × 1, rosuvastatin × 2, pitavastatin × 5, simvastatin × 0.25, lovastatin × 0.25, and pravastatin × 0.125.^{7,8}

The exclusion criteria were the presence of organic heart disease, previous chemotherapy, renal failure, chronic lung disease, and morbid obesity. Common forms of excluded organic heart disease were a history of transmural myocardial infarction, left ventricular hypertrophy, valvular heart disease, known cardiomyopathy, myocarditis, and atrial fibrillation. Patients with

uncontrolled hypertension on presentation were excluded. All patients enrolled in this cohort were treated with simultaneous discontinuation of statin therapy and supplementation with CoQ₁₀ at an average dosage of 300 mg/d, predominantly in the form of ubiquinol, beginning at the time of their initial presentation. Most patients were already receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and diuretics at presentation. Medications were adjusted as clinically indicated during follow-up in accordance with standard clinical practice.

Plasma Analysis

Plasma concentrations for both reduced and oxidized forms of CoQ₁₀ along with α-tocopherol (vitamin E) and total cholesterol levels were analyzed by a high-performance lipid chromatography method using electrochemical and ultraviolet detectors that was based on previously published methods.^{9,10} The *intraday* coefficient of variation for repeatability in measurements of plasma total CoQ₁₀ was 1.5% and the *interday* coefficient of variation was 2.8%. The detection limit of CoQ₁₀ was 1 ng/mL (signal-to-noise ratio = 3). All plasma samples were immediately frozen below -70°C, and the high-performance liquid chromatography analysis was performed within 14 days of specimen collection. We calculated the ratios of total CoQ₁₀ to total cholesterol to normalize the levels to the carrying capacity by lipoproteins of this fat-soluble nutrient.

Outcome Measures

Outcome measures including statin-attributable symptom scores, HF clinical severity scores, incidence of adverse events, and echocardiograms were recorded at baseline and at follow-up intervals of 3 to 6 months. Clinical evaluations and echocardiogram interpretations were performed by a single cardiologist (PHL).

HF severity was determined by New York Heart Association (NYHA) Classification scoring of each patient on the basis of physical examination and patient history. Symptoms deemed to be potentially attributable to statin therapy were fatigue, muscle weakness, myalgia, memory loss, and peripheral neuropathy. To qualify

as statin-attributable, these symptoms were not present before the start of statin therapy. A 4-point symptom severity scoring system was used to assess symptoms potentially attributable to statin therapy as follows: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. Peripheral neuropathy was excluded as a statin adverse effect in patients with diabetes mellitus or low vitamin B₁₂ levels.

All echocardiographic studies were done in a single cardiology clinic by the same certified cardiac sonographer using a cardiovascular ultrasonography machine (Philips CX50, Royal Philips,

Table 1. Baseline characteristics (N = 142) ^a	
Characteristic	Value
Age, mean (SD), y	65 (10)
Weight, mean (SD), kg	86 (20)
Sex, male, no. (%)	76 (54)
Race/ethnicity, no. (%)	
White	133 (94)
Black	5 (4)
Hispanic	4 (3)
Comorbidities, no. (%)	
Coronary heart disease ^b	40 (28)
Hypertension ^c	70 (49)
Diabetes mellitus type 2	25 (18)
Statin, no. (%)	
Simvastatin ^d	60 (42)
Atorvastatin	29 (20)
Rosuvastatin	23 (16)
Pravastatin	19 (13)
Lovastatin	6 (4)
Red yeast rice	4 (3)
Pitavastatin	1 (1)
Normalized statin dose, mean (SD), mg ^e	17 (18)
Normalized statin dose, mean (SD), mg/kg body weight ^e	0.2 (0.2)
Duration of statin therapy, mean (SD), y	6.8 (5.7)

^a Some percentages do not total to 100 because of rounding.
^b All patients with coronary heart disease had normal ejection fraction and normal left ventricular end-diastolic pressure before statin treatment.
^c Hypertension without evidence of left ventricular hypertrophy.
^d Includes patients receiving the ezetimibe/simvastatin combination drug (n=10).
^e Dose normalized to atorvastatin potency; excludes red yeast rice.
SD = standard deviation.

Amsterdam, The Netherlands) by the same certified cardiac sonographer. The echocardiography laboratory is certified by the Intersocietal Accreditation Commission. Echocardiographic measurements included diastolic function and EF. Diastolic function was scored as 0 = normal, 1 = mild or impaired relaxation, 2 = moderate or pseudonormal, and 3 = severe or restrictive.¹¹ EFs were visually estimated. Patients were considered to have HF with reduced EF if baseline EF was less than 50% and to have HFpEF if baseline EF was 50% or greater. Telephone follow-up was carried out by the study team for all patients who missed a visit or did not return

to the clinic for follow-up to determine the incidence of events, including death, heart attack, or stroke. Texas state death registry data were used to determine the possibility of death in 2 patients who did not return for follow-up. To determine whether withdrawal of statin therapy was associated with increased mortality, for comparison we acquired from published reports the observed mortality in 3 groups of patients with HF during long-term follow-up.

Statistical Analysis

Differences between baseline and final continuous variables were calculated using means and 95% confidence intervals

(CIs), and p values were calculated with the paired Student *t*-test for parametric variables and the Wilcoxon signed-rank test for nonparametric variables. Differences between baseline and final results for categorical variables were determined using the χ^2 test. Differences between continuous variables in 2-sample comparisons were calculated using the 2-sample Student *t*-test. Analyses were performed using SAS version 9.4 software (SAS Institute Inc, Cary NC). The data that support the findings of this study are openly available in Mendeley.¹²

RESULTS

A total of 142 patients were enrolled. The baseline characteristics of these patients are outlined in Table 1.

Mortality and Morbidity

The mean follow-up was 2.8 years, and 77% of patients were followed-up for more than 1 year. Follow-up data were obtained for 137 patients, and 5 did not return for follow-up but were confirmed to be alive either by phone (*n* = 3) or by review of the Texas Death Registry (*n* = 2). Four patients died during the study period: 2 of unknown causes, 1 caused by sudden cardiac death, and 1 caused by lung cancer. The 1-year mortality was 0%, and the 3-year mortality was 2.8%. Two strokes but no heart attacks were observed during the study period. No adverse effects from supplemental CoQ₁₀ were observed.

Heart Function Data

Among 142 enrolled patients, baseline echocardiograms demonstrated HFpEF in 94% and HF with reduced EF in 6%. Follow-up echocardiographic data were obtained in 131 of these patients. In 122 patients with HFpEF, diastolic function improved after the intervention, in all categories (*p* < 0.0001, Table 2). Seventy-three patients (60%) with HFpEF with follow-up had sustained improvement in diastolic function at final follow-up. From baseline to final follow-up, 42 of the 122 patients with HFpEF (approximately 34%) had complete normalization of diastolic function, and 31 (25%) had improvement without normalization of diastolic function; 42 (34%) had no change in their diastolic function; and 7 (6%)

Table 2. Heart function, NYHA class, and symptom scores^a

Measure	N	Category	Baseline	Final	p value ^b
Ejection fraction, % (95% CI)	131		58 (57-59)	59 (58-59)	0.0373
Ejection fraction in patients with HFrEF, % (95% CI)	9		35 (29-41)	47 (39-55)	0.0234
Diastolic function, no. (%) ^c	122	Grade 0	0 (0)	42 (34)	< 0.0001
		Grade 1	33 (27)	46 (38)	
		Grade 2	86 (70)	34 (28)	
		Grade 3	3 (2)	0 (0)	
NYHA class, no. (%)	137	Class 1	11 (8)	108 (79)	< 0.0001
		Class 2	96 (70)	23 (17)	
		Class 3	29 (21)	5 (4)	
		Class 4	1 (1)	1 (1)	
Fatigue, no. (%)	137	0 = None	9 (7)	92 (67)	< 0.01
		1 = Mild	2 (1)	16 (12)	
		2 = Moderate	60 (44)	22 (16)	
		3 = Severe	66 (48)	7 (5)	
Muscle weakness, no. (%)	137	0 = None	62 (45)	113 (82)	< 0.01
		1 = Mild	4 (3)	14 (10)	
		2 = Moderate	39 (28)	8 (6)	
		3 = Severe	32 (23)	2 (1)	
Myalgias, no. (%)	137	0 = None	54 (39)	126 (92)	< 0.0001
		1 = Mild	7 (5)	7 (5)	
		2 = Moderate	44 (32)	2 (1)	
		3 = Severe	32 (23)	2 (1)	
Memory loss, no. (%)	137	0 = None	37 (27)	99 (72)	< 0.0001
		1 = Mild	11 (8)	17 (12)	
		2 = Moderate	65 (47)	16 (12)	
		3 = Severe	24 (18)	5 (4)	
Peripheral neuropathy, no. (%)	137	0 = None	86 (63)	116 (85)	< 0.001
		1 = Mild	11 (8)	9 (7)	
		2 = Moderate	29 (21)	8 (6)	
		3 = Severe	11 (8)	4 (3)	

^a Some percentages do not total to 100 because of rounding.

^b p values for ejection fraction are from Wilcoxon signed-rank test, and all others are from χ^2 test.

^c Diastolic function in patients presenting with heart failure with preserved ejection fraction.

CI = confidence interval; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association.

had worsening of diastolic function. In the 9 patients with HF with reduced EF, the EF improved by 12% from a baseline mean of 35% (95% CI = 29% to 41%) up to a final mean of 47% (95% CI = 39% to 55%, $p = 0.023$).

Twenty-two patients (15%) were non-responders, as defined by a lack of improvement at any time during follow-up ($n = 17$) or worsening ($n = 5$) in measurements of myocardial function. Non-responders did not differ significantly from responders by age, sex, change in plasma CoQ₁₀ levels, final CoQ₁₀ levels, normalized statin dose, statin duration, or use of lipophilic vs hydrophilic statin. During follow-up, 29 patients with initially improved heart function on echocardiogram experienced worsening myocardial function back to their baseline severity in either diastolic function or EF. Twenty of these patients either stopped their CoQ₁₀ completely ($n = 7$), decreased their CoQ₁₀ dose ($n = 9$), or changed the CoQ₁₀ formulation from ubiquinol to ubiquinone ($n = 4$). The remaining 9 patients who initially showed improvement in myocardial function later relapsed after a mean time of 3.4 years (range = 0.5 to 5.9), despite no reintroduction of statin therapy and no change in supplemental CoQ₁₀. For the whole group ($n = 137$), NYHA class improved in all classes except NYHA class 4 ($p < 0.0001$). Of interest, at baseline only 8% of patients were in NYHA class 1, but this increased to 79% at final follow-up (Table 2).

Statin-Attributable Symptoms

All statin-attributable symptom scores improved significantly ($p < 0.01$) from baseline to final follow-up (Table 2). The proportion of patients with no muscle weakness increased from 39% at baseline

to 92% at final follow-up. Memory loss improvement exhibited a similar pattern in that the proportion with no memory loss increased from 27% at baseline to 72% at final follow-up.

Laboratory Data

Baseline and follow-up laboratory data were available for 51 patients. For all 51 patients the total CoQ₁₀ level increased from 1.3 $\mu\text{g/mL}$ (95% CI = 1.0-1.6 $\mu\text{g/mL}$) to 6.7 $\mu\text{g/mL}$ (95% CI = 5.7-7.7 $\mu\text{g/mL}$, $p < 0.0001$). Twenty-one of these patients were already taking some amount of CoQ₁₀ ($n = 18$) or had stopped their statin regimen 11 days to 1 month ($n = 3$) before their initial visit. In the 30 patients who at their initial visit were taking no CoQ₁₀ supplements and were actively receiving statin therapy (Table 3), plasma total CoQ₁₀ levels increased from 0.8 $\mu\text{g/mL}$ (95% CI = 0.7-0.8 $\mu\text{g/mL}$) to 6.6 $\mu\text{g/mL}$ (95% CI = 5.3-7.9 $\mu\text{g/mL}$, $p < 0.0001$). There also were significant increases in vitamin E, total cholesterol, and the ratio of CoQ₁₀ to total cholesterol and a significant decrease in oxidized CoQ₁₀ levels (Table 3).

DISCUSSION

In this observational study, we report on a cohort of 142 hyperlipidemic patients presenting with predominantly diastolic HF without organic heart disease and with statin-attributable adverse effects, both of which developed in the setting of long-term statin therapy (approximately 7 years). Patients were either self-referred or referred by their primary care physician with signs and symptoms of HF. Patients were followed-up for an average of 2.8 years after receiving 2 simultaneous interventions: Discontinuation of statin

therapy and oral supplementation with an average dosage of 300 mg/d of CoQ₁₀. We chose to use supplemental CoQ₁₀ in the form of ubiquinol because of its superior absorption compared with ubiquinone,¹³ a quality that is especially important in the treatment of patients with HF in whom absorption is compromised by intestinal edema.¹⁴ The rationale for both discontinuing statin therapy and supplementing with CoQ₁₀ is based on our prior clinical experience: Patients with statin-associated adverse effects that persist after stopping statin therapy respond well to supplemental CoQ₁₀, and conversely patients supplemented with CoQ₁₀ but who continue prolonged statin therapy rarely improve. The study cohort showed improvements in NYHA class, echocardiographic measures of HF, and noncardiac statin-attributable symptoms. Despite a significant increase in total cholesterol levels (average increase of 62 mg/dL), there was a rarity of coronary events, no deaths in the first year, and at 3 years a total of 4 deaths including 1 sudden cardiac death, representing a 3-year mortality of 2.8%.

We propose the existence of SACM as a common and unrecognized cause of iatrogenic HF, especially HFpEF, and as a factor in the increasing prevalence of HFpEF.¹⁵ In a recent cohort of 53,065 patients with HFpEF, 55% were receiving some form of lipid-lowering therapy.¹⁶ There are sound theoretical mechanisms to implicate statins in the causation of impairment in heart muscle function. Statins are used to decrease the biosynthesis of cholesterol by inhibiting the enzyme HMG-CoA reductase, thus reducing the cholesterol precursor mevalonate. In addition to cholesterol, the mevalonate pathway has multiple downstream products

Table 3. Laboratory data

Measure	N	Baseline ^a	Final ^a	Change ^a	p value ^b
Total CoQ ₁₀ , $\mu\text{g/mL}$	30	0.8 (0.7-0.8)	6.6 (5.3-7.9)	5.8 (4.6-7.0)	< 0.0001
Oxidized CoQ ₁₀ , % ^c	30	3.0 (2.3-3.8)	1.3 (1.0-1.6)	-1.7 (-1.0 to -2.5)	< 0.0001
Total cholesterol, mg/dL	30	180 (165-194)	242 (225-259)	62 (45-79)	< 0.0001
CoQ ₁₀ /total cholesterol ratio, $\mu\text{M/mM}$	30	0.2 (0.2-0.2)	1.2 (1.0-1.4)	1.0 (0.8-1.2)	< 0.0001
Vitamin E, $\mu\text{g/mL}$	30	14.6 (12.9-16.4)	18.3 (16.6-20.0)	3.7 (2.1-5.2)	< 0.0001
Vitamin E/total cholesterol ratio, $\mu\text{M/mM}$	30	7.4 (6.6-8.2)	6.8 (6.3-7.3)	-0.6 (-1.4 to 0.2)	0.1440

^a Values given are mean (95% confidence interval).

^b p values from paired t-tests and Wilcoxon signed-rank test.

^c Percentage of oxidized coenzyme Q₁₀ (CoQ₁₀) = (Oxidized CoQ₁₀/Oxidized CoQ₁₀ + Reduced CoQ₁₀) \times 100.

Table 4. Heart failure mortality: Current study compared with published values

Source	N	1-Year mortality, %	3-Year mortality, %	5-Year mortality, %
Levy, ⁴³ 2002	1075	26	—	53
Barker, ⁴⁴ 2006	1942	30	—	66
Owan, ⁴⁵ 2006	6076	29	—	65
Current study, 2019	142	0	3	—

that are unavoidably blocked by statin therapy. The evidence for a direct mitochondrial toxicity, secondary to reduction of CoQ₁₀, heme A, and selenoproteins, is substantial and could explain cardiotoxicity in terms of impaired myocardial energy production.¹⁷⁻²² Impaired mitochondrial function may underlie statin-associated skeletal myopathy. A decrease in mitochondrial DNA levels may also play an important pathophysiologic role, because statins have been shown to decrease mitochondrial DNA levels in human skeletal muscle.²³ Studies in animal models have shown that statins decrease the content of CoQ₁₀ in heart muscle²⁴⁻²⁹ and can cause a 45% decrease in mitochondrial CoQ₁₀ content in the hearts of elderly guinea pigs.³⁰ Low levels of plasma CoQ₁₀ in humans have been associated with HF,³¹⁻³³ and multiple clinical trials have demonstrated the amelioration of HF with CoQ₁₀ supplementation.^{31,34} Statin therapy has been associated with an increase in brain natriuretic peptide, a known marker for worsening HF.³⁵ Many other adverse effects are noted in the literature, including liver dysfunction, diabetes mellitus, peripheral neuropathy, and central nervous system disorders.^{20,36-39}

In the present study, a relapse in functional recovery was observed in 29 patients who showed initial improvement in symptoms and heart function. We postulate that in some cases the relapse may have been related to the gradual worsening in diastolic function that occurs with aging, given that the average time to relapse in these patients was 3.5 years.

We believe that the supraphysiologic levels of CoQ₁₀ attained in this study (mean = 6.6 µg/mL, n = 30) are not only correcting a possible tissue CoQ₁₀ deficiency but are also supporting the function of damaged mitochondria. Of note, the average initial total CoQ₁₀ level of 0.8 µg/mL (n = 30) was within the normal

expected limits for healthy individuals.⁴⁰ These normal baseline plasma CoQ₁₀ levels likely do not represent the underlying CoQ₁₀ tissue levels in these patients, which may well have been low. Evidence of the discrepancy between blood and tissue CoQ₁₀ levels is well documented.^{41,42} The decrease in oxidized CoQ₁₀ (from 3.0% at baseline to 1.3% at follow-up) is consistent with lower oxidative stress with higher plasma CoQ₁₀ levels.

The effect of cessation of statin therapy in patients with known coronary heart disease could be of concern. We compared the mortality of our cohort to that of 3 published series of similar patients with HF,⁴³⁻⁴⁵ and the 1-year mortality of 0% and 3-year mortality of 2.8% in our statin-discontinuation group compared favorably with the reported mortality in the 3 comparison studies of groups of patients with HF: 26% to 30% at 1 year and 53% to 66% at 5 years (Table 4). However, these comparison trials would be expected to have higher mortality than our group, because we excluded patients with organic heart disease and serious comorbidities, whereas such patients would be represented in the reference group of published studies. The Q-SYMBIO study (of CoQ₁₀ focusing on changes in SYMptoms, BIomarker status, and long-term Outcome) of CoQ₁₀ treatment at 300 mg of CoQ₁₀ per day in patients with moderate to severe HF (74% of whom were receiving statin therapy) showed a reduction in all-cause 2-year mortality (10% vs 18%, *p* < 0.018).³¹ It is likely that in the present study any detrimental effect on mortality of statin cessation was outweighed by the beneficial effect of CoQ₁₀ therapy in patients with HF.

The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study randomly assigned 5000 patients with systolic HF caused by coronary heart disease to receive either 10 mg

of rosuvastatin or placebo. Statin treatment resulted in a 44% lowering of low-density lipoprotein cholesterol to 76 mg/dL. Contrary to expectations, there was no beneficial effect on cardiovascular death or on the expected worsening of HF during a 3-year observation period.⁴⁶ It may be that a lowering of myocardial CoQ₁₀ levels played a role in the negative study outcome. A similar result was also seen in the UNIVERSE (rosUvastatin Impact on VEEntricular Remodeling cytokineS and neurohormonEs) study of rosuvastatin in HF, where despite a 57% reduction in low-density lipoprotein cholesterol, there was no beneficial effect on cardiac function or neurohormones.⁴⁷ In a review in 2011 it was concluded that the putative beneficial effect of statin therapy on cardiac remodeling may have been negated by the reduction in plasma CoQ₁₀ levels.⁴⁸ This apparent lack of efficacy of statin monotherapy in HF caused the authors of the current American College of Cardiology/American Heart Association Guidelines on Statin Use to recommend that statins should not be used in patients with NYHA classes 2 to 4 of HF.⁴⁹

One limitation of this study is our use of 2 simultaneous interventions: Discontinuation of statin therapy and CoQ₁₀ supplementation. This makes it difficult to know which was the dominant factor in patient improvement. Another limitation was the lack of a control group in this observational study. Inclusion of a control group treated with CoQ₁₀ without statin therapy discontinuation may have allowed separation of the 2 interventions and could be considered as a potential study arm in future research of this condition. However, this was considered undesirable given the severity of statin-associated adverse effects in this population and our previous clinical experience suggesting that discontinuation of statins is necessary for the beneficial effect of CoQ₁₀ on the myocardium to occur. This observational study can be considered as hypothesis generating and as a springboard for prospective randomized trials.

Study strengths include the applicability to clinical practice where elderly patients frequently present with HF in the setting of a history of many years of statin therapy. Another strength is the duration

of follow-up (average = 2.8 years), thus affirming the early safety of discontinuation of statin therapy. Clinical statin trials have not assessed cardiac function in patients after long-term statin treatment. Although there is clearly a growing epidemic of HF, especially HFpEF, the reason for this epidemic is not clear.¹⁵ We believe that long-term, moderate-dose statin treatment in elderly individuals, the very group affected the most from the HF epidemic,² may be a contributing cause of HFpEF.

CONCLUSION

The present observational study is hypothesis generating and leads to 3 conclusions. First, some patients who are receiving long-term statin therapy experience HF along with other statin-attributable adverse effects, most of which respond to withdrawal of statin therapy and the addition of CoQ₁₀. Second, SACM may be a factor in the current increasing incidence of HF. Third, these observations may alert practicing physicians and patients that this condition can occur so that they will be in a better position to recognize what is otherwise a gradual and insidious process meriting discontinuation of statin therapy. One goal for future studies is to look for SACM retrospectively with aggregate data. Prospective randomized studies of this problem are urgently needed. ♦

Author Contributions

Peter H Langsjoen, MD, FACC; Alena M Langsjoen, MS; and Jens O Langsjoen, MD, were involved in the conception and design of this study and in drafting the manuscript. Peter H Langsjoen, MD, FACC; Alena M Langsjoen, MS; Jens O Langsjoen, MD; and Franklin Rosenfeldt, MD, FRACS, contributed to the analysis and interpretation of the data and to revising the manuscript critically for intellectual content. All authors approved the final version of the article and agree to be accountable for all aspects of the work.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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