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Letters

Application of the Statin-Associated Muscle Symptoms-Clinical Index to a Randomized Trial on Statin Myopathy

Evidence suggests 10% to 25% of patients experience statin-associated muscle symptoms (SAMS) (1), which may result in poor adherence and a greater incidence of cardiovascular events and costs (2,3). Although there are no uniformly accepted diagnostic criteria for SAMS, the SAMS Clinical Index (SAMS-CI) may distinguish between SAMS and nonspecific muscle symptoms. The SAMS-CI has been described elsewhere (4) and assesses SAMS as "probable" (score 9 to 11), "possible" (score 7 to 8), and "unlikely" (score 2 to 6) based on 4 scales: location; pattern; timing of onset; and timing of improvement after statin withdrawal.

TABLE 1 Patient Classifications and Test Evaluation Statistics for the SAMS-CI by SAMS Category With 2 Different Scoring Systems

	Number of Patients Receiving SAMS-CI Classification		
Original Scoring*	**Probable (9-11 Points)**	**Possible (7-8 Points)**	**Unlikely (2-6 Points)**
SAMS category			
Confirmed SAMS	11	11	20
Symptoms on placebo	0	1	34
Symptoms on both	2	8	11
Symptoms on neither	0	0	20
Revised Scoring†	**Probable (9-11 Points)**	**Possible (5-8 Points)**	**Unlikely (2-4 Points)**
SAMS category			
Confirmed SAMS	11	25	6
Symptoms on placebo	0	3	32
Symptoms on both	2	12	7
Symptoms on neither	0	1	19

Number of patients identified as probable, possible, and unlikely on the SAMS-CI by category of patients identified with confirmed SAMS (symptoms on statin only), symptoms on placebo, symptoms on both statin and placebo, and symptoms on neither statin or placebo from the CoEnzyme Q10 In Statin Myopathy trial (5) as well as relevant test evaluation statistics (followed by 95% confidence intervals), are shown for the original SAMS-CI scoring system and the revised scoring system based on ROC analysis). *Sensitivity: 52.4% (36.4% to 68.0%); specificity: 85.5% (75.6% to 92.6%); PPV: 66.7% (51.9% to 78.8%); NPV: 76.5% (70.0% to 81.9%). †Sensitivity: 85.7% (71.5% to 94.6%); specificity: 76.3% (65.2% to 85.3%); PPV: 66.7% (56.7% to 75.3%); NPV: 90.6% (82.0% to 95.4%).

NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristics; SAMS = statin-associated muscle symptoms; SAMS-CI = Statin-Associated Muscle Symptoms Clinical Index.

We retrospectively applied data from the CoQ10 (Coenzyme Q10 in Statin Myopathy) study (5) to the SAMS-CI. The CoQ10 trial enrolled 120 patients with history of SAMS. Patients entered a randomized, double-blind, crossover trial of simvastatin (20 mg/day) or placebo for 8 weeks. After the first phase, patients underwent a 4-week washout period and were crossed over to the opposite treatment. Muscle symptoms during each phase were stratified into 4 groups: patients who experienced muscle symptoms on simvastatin alone; on placebo alone; on both treatments; or on neither treatment. Patients experiencing muscle symptoms on simvastatin alone (43 of 120 patients [36%]) were classified as having confirmed SAMS.

Historical patient data from case report forms were extracted and entered into the SAMS-CI by the lead investigator (blinded to SAMS status). These data were used to complete parts A, B, and C of the SAMS-CI, whereas data from the 20 mg daily simvastatin rechallenge was used to complete part D. Two patients (1 with confirmed SAMS, 1 without) had incomplete data and were not included. Analysis of variance with Tukey post hoc adjustments ($p < 0.05$) were used to analyze continuous SAMS-CI scores among the 4 categories of patients. Test evaluation statistics (sensitivity, specificity, positive predictive value, negative predictive value [NPV]) were calculated by combining probable/possible categories to define true positives (confirmed SAMS, probable/possible categorization), false positives (no SAMS, probable/possible categorization), true negatives (no SAMS, unlikely categorization) and false negatives (SAMS, unlikely categorization), and a receiver operating characteristic curve analysis was used to examine best fit of the scoring system to optimize test statistics.

SAMS-CI scores were significantly higher in patients with confirmed SAMS (6.7 ± 2.0 points) than any other group, although patients with muscle symptoms on both treatments (5.7 ± 2.5 points) also had higher scores than patients with muscle symptoms on placebo (2.4 ± 1.2 points) or neither treatment (2.2 ± 0.9 points). Test evaluation characteristics are presented in Table 1 both with the original scoring system as well as a revised scoring system in which the cutoff for classification of "unlikely" was lowered to 4 points based on results from receiver operating characteristic analysis.

In this analysis, we applied the SAMS-CI to a study in which SAMS was confirmed with a crossover trial assessing patient-reported muscle symptoms. Patients with confirmed SAMS exhibited higher scores than patients with muscle symptoms on placebo alone, muscle symptoms on both treatments, or no muscle symptoms on either treatment. However, patients with muscle symptoms on both treatments also exhibited higher scores than the other 2 groups, and only one-half of the patients with confirmed SAMS were appropriately classified by the SAMS-CI as having "possible" or "probable" SAMS. Sixty-five of 76 (86%) patients who did not test positive for SAMS were classified as "unlikely" with the index such that NPV was 76.5%; lowering the cutoff for classification as "unlikely" from 6 to 4 points increased NPV to 90.6%. These results suggest the SAMS-CI may be an effective tool to identify patients with self-reported SAMS who are unlikely to have true SAMS. The findings require confirmation in prospective studies, with potential revision of the scoring system, but provide evidence that the SAMS-CI may help clinicians to encourage statin adherence in those patients who believe they are intolerant because of muscle symptoms.

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Patients With an ICD Remain at Risk for Painful Shocks in Last Moments of Life

Patients with an implantable cardioverter-defibrillator (ICD) are at risk of unnecessary painful shocks at the end of life when tachytherapy is still active. In 2010, the European Heart Rhythm Associations and the American Heart Rhythm Society published statements on ICD-therapy in patients nearing end of life (1,2). Subsequently, the Netherlands Association for Cardiology released the national guideline "ICD/pacemakers in the last phase of life" in 2013. The current study was performed to evaluate the practice of ICD tachytherapy deactivation before death over the past 10 years to reveal areas for improvement.

All patients who received an ICD or cardiac resynchronization therapy-defibrillator at our institution and who died between 2006 and 2015 were evaluated. Follow-up was recorded in electronic patient files and the survival status of patients was retrieved from municipal civil registries. Patient records were reviewed to identify cause of death, ICD therapy status, and type of device at time of death. Causes of death were categorized according to a modified Hinkle-Thaler Classification (3).

Between 2006 and 2015, 949 patients with an ICD died (mean age 72 ± 10 years; 734 [77%] males; 577 [61%] primary prevention; median time from first ICD 4.5 years [interquartile range: 2 to 7 years]). Baseline characteristics of patients withdrawn from tachytherapy before death did not differ from those who were not (data not shown). Overall, 321 (34%) devices were deactivated before death. A Kruskal-Wallis H