

Brief Research Report

Statin-induced myopathy is rare

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Dan Med J 2026;73(9):A02260103. doi: 10.61409/A02260103

ABSTRACT

INTRODUCTION. Statin-induced myopathy (SIM) is a rare but serious complication of statin therapy. Immune-mediated necrotising myopathy linked to anti-3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (anti-HMGCR) antibodies requires timely recognition. This study examined the occurrence and documentation of SIM and the use of antibody testing in a regional cohort.

METHODS. This was a register-based study using data from regional registries and medical records (2020-2024). Patients with creatine kinase (CK) > 10 × the upper limit of normal while receiving statin therapy were identified, characterised and compared, with a special focus on anti-HMGCR antibody testing and documentation of statin intolerance.

RESULTS. Among 1,003 patients, 32 (3.2%) were considered to have SIM. These patients had a higher median CK than other patients (7,800 versus 3,783 U/l; $p < 0.001$). High-intensity therapy was more frequent in SIM (72% versus 52%; $p = 0.02$), with a prevalence ratio of 2.34 (95% CI: 1.09-5.00). Anti-HMGCR testing was performed in 56% of SIM cases; antibody-positive patients had lower CK and higher eGFR. Documentation of statin intolerance in the electronic record CAVE field (adverse drug reaction) was present in only 59%.

CONCLUSIONS. Severe SIM is uncommon (4.3 cases/100,000 patient-years), but documentation and diagnostic testing are inconsistent. Systematic recording and broader antibody testing may improve patient safety.

FUNDING. None.

TRIAL REGISTRATION. Not relevant.

Statins are central to atherosclerotic cardiovascular disease prevention [1]; yet, some patients develop muscle-related adverse effects ranging from myalgia to rhabdomyolysis [2].

Within this spectrum of statin-associated muscle symptoms, statin-induced myopathy (SIM) represents a serious and treatable condition that requires accurate diagnosis and appropriate management [3]. At the severe end of the spectrum, rhabdomyolysis is exceedingly rare but clinically consequential [2]. Diagnosing SIM remains challenging due to a strong nocebo effect (> 25% in placebo arms of statin trials [4], poor creatine kinase (CK) symptom correlation [5], heterogeneous diagnostic criteria [3] and infrequent dechallenge-rechallenge testing [5, 6].

Not all clinically significant and treatable statin-associated muscle effects reflect direct drug toxicity. A distinct immune-mediated necrotising myopathy (IMNM) is driven by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase (anti-HMGCR) antibodies, characterised by persistent weakness and elevated CK levels despite statin

withdrawal, and typically requires immunosuppressive therapy [7]. Anti-HMGCR IMNM is rare, with an estimated incidence of 2-3 cases per 100,000 person-years in statin users [8, 9]. Because anti-HMGCR testing is not routinely considered in the diagnostic work-up of suspected SIM, affected patients may be under-recognised or experience substantial diagnostic delay in clinical practice [10, 11].

We aimed to identify patients with SIM, characterise their background and diagnostic workup, and evaluate the clinical consequences, with a particular focus on documentation of statin intolerance in electronic medical records and the use of anti-HMGCR antibody testing.

Methods

Design and setting

Retrospective, register-based, cross-sectional quality assessment of all adults admitted to hospitals in the Central Denmark Region from 1 August 2020 to 31 August 2024.

Population and case ascertainment

Cases were identified via the regional business intelligence portal by linking CK > 10 × upper limit of normal (ULN) with recorded statin prescriptions and, when available, relevant ICD-10 codes (DG729, DG720, DG728, DG722, DG737, DG724, DM609, DM608, DM332). Current/recent statin use was defined as a prescription ≥ 14 days before the CK peak.

Data collection

Data were managed in REDCap v13.5. All suspected SIM cases and cases with uncertain classification were reviewed by two reviewers, and the final SIM classification was made by consensus. The following variables were recorded: demographics; statin type/dose/intensity; timing versus CK peak; CK peak (top-coded at 7,800 U/l; non-systematic dilutional re-analyses excluded for cross-site comparability); estimated glomerular filtration rate (eGFR)/chronic kidney disease (CKD); interacting drugs (macrolides, azoles, protease inhibitors, ciclosporin, amiodarone, imatinib); predispositions (diabetes, hypothyroidism, prior rhabdomyolysis, inherited myopathy, alcohol misuse, fibrates); anti-HMGCR testing. CK measurements were performed on clinical indication rather than as routine monitoring.

Statistics

Continuous variables are presented as medians (IQR) and categorical variables as n (%). Group comparisons were performed using the Wilcoxon rank-sum test or the Kruskal–Wallis test, while CK analyses used Tobit regression with right-censoring at 7,800 U/l. Categorical comparisons were made using χ^2 or Fisher's exact test. Prevalence ratios with 95% CIs were estimated using Poisson regression with robust SEs. Two-sided $p < 0.05$ was considered significant. Analyses were conducted in R v4.4.2.

Denominator and incidence

Statin user denominators were achieved from Danish national drug statistics [12]; to align with the accrual window, we included one-third of 2020 users, full counts for 2021–2023 and two-thirds of 2024 users. Incidence was defined as cases per accumulated statin user-years with exact Poisson 95% CIs.

Approval

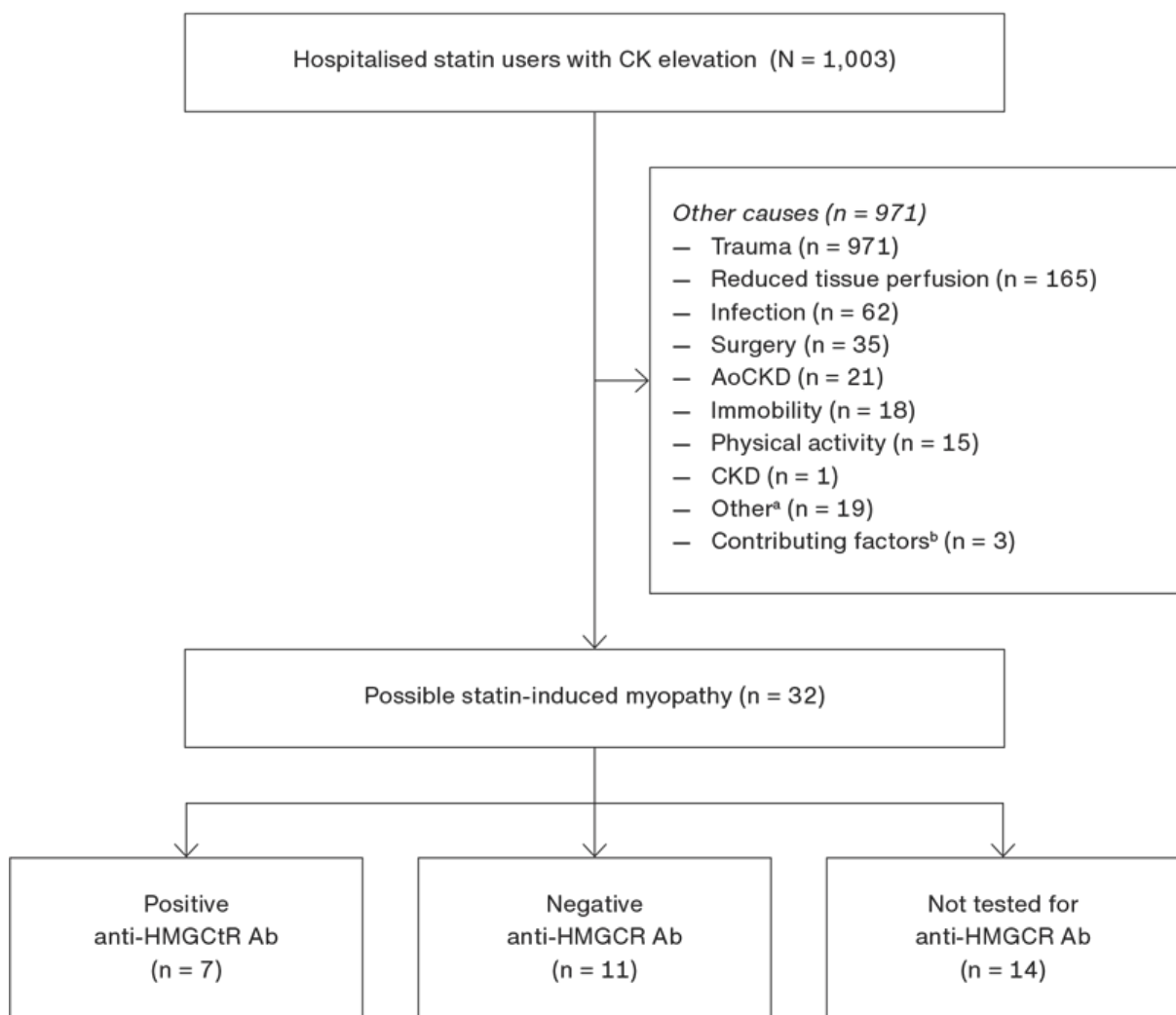
The project was approved by the institutional review boards of all participating hospitals in accordance with the Danish legislation on quality control studies.

Trial registration: not relevant.

Results

Among 1,003 patients with elevated CK, 32 (3.2%) were classified as SIM (**Figure 1**). SIM occurred in 1.9% (9/479) of low-intensity and 4.4% (23/524) of high-intensity users, yielding a prevalence ratio of 2.34 (95% CI: 1.09-5.00; $p = 0.02$). As expected, CK was higher in SIM than in non-SIM cases (7,800 U/l (IQR: 5,959-7,800) versus 3,784 (2,515-6,392)), with 20 reaching the assay limit. Age, sex, eGFR, CKD and statin type did not differ significantly between SIM and non-SIM cases (**Table 1**).

FIGURE 1 Flow diagram of patient inclusion and exclusion.



Anti-HMGCR Ab = anti-3-hydroxy-3-methylglutaryl-CoA reductase antibody; AoCKD = acute-onset chronic kidney disease; CK = creatine kinase; CKD = chronic kidney disease.

a) Include checkpoint inhibitor-induced myositis, hepatorenal syndrome, idiopathic myositis, malignant neuroleptic syndrome and severe hypokalaemia.

b) 3 patients were classified as having contributing factors and were excluded due to an uncertain diagnosis.

TABLE 1 Patient characteristics: total cohort and statin-induced myopathy subgroups.

	Panel A: SIM versus other			Panel B: SIM by anti-HMGCR antibody status			
	SIM (N _s = 32)	other (N _s = 971)	p value	anti-HMGCR+ (N _s = 7)	anti-HMGCR- (N _s = 11)	not tested (N _s = 14)	p value
Gender, n (%)			0.8 ^d				0.12 ^f
Female	15 (47)	437 (45)		2 (29)	8 (73)	5 (36)	
Male	17 (53)	534 (55)		5 (71)	3 (27)	9 (64)	
Age, median (Q1-Q3), yrs	75 (68-79)	77 (70-83)	0.10 ^a	73 (70-81)	75 (65-79)	75 (66-79)	> 0.9 ^a
CK, median (Q1-Q3), U/l ^a	7,800 (5,959-7,800)	3,784 (2,515-6,392)	< 0.001 ^a	5,040 (3,824-7,397)	7,800 (7,800-7,800)	7,800 (6,654-7,800)	0.016 ^a
eGFR, median (Q1-Q3), ml/min./1.73 m ²	55 (15-77)	46 (27-70)	> 0.9 ^a	83 (70-89)	36 (10-74)	24 (12-62)	0.006 ^a
CKD, n (%)	5 (16)	149 (15)	> 0.9 ^f	0	3 (27)	2 (14)	0.3 ^f
Statin therapy intensity, n (%)			0.024 ^d				0.2 ^f
Low	9 (28)	470 (48)		4 (57)	2 (18)	3 (21)	
High ^b	23 (72)	501 (52)		3 (43)	9 (82)	11 (79)	
CAVE entry, n (%) ^c	-	-	-	4 (57)	6 (55)	9 (64)	> 0.9 ^f

CK = creatine kinase; CKD = chronic kidney disease; HMGCR = 3-hydroxy-3-methylglutaryl-CoA reductase; ULN = upper limit of normal; SIM = statin-induced myopathy.

a) CK-ULN: men 280 U/l; women 210 U/l.

b) Atorvastatin 40-80 mg, rosuvastatin 20-40 mg or simvastatin > 40 mg.

c) Adverse drug reaction registration: statin intolerance.

d) Pearson's χ^2 -test.

e) Wilcoxon rank sum test.

f) Fisher's exact test.

g) Kruskal-Wallis rank sum test.

Anti-HMGCR antibodies were tested in 18/32 (56%) SIM patients (seven positive, 11 negative, 14 untested). CK was lower in antibody-positive than in antibody-negative or untested cases (5,040 U/l (IQR: 3,824-7,397) versus 7,800 (7,800-7,800) and 7,800; $p = 0.02$). High-intensity therapy was used in 9/11 (82%) antibody-negative versus 3/7 (43%) antibody-positive patients (OR: 0.19; 95% CI: 0.01-2.08; $p = 0.14$). In the total cohort, antibody-negative SIM accounted for 1.7% (9/524) of high-intensity and 0.4% (2/479) of low-intensity users, whereas antibody-positive SIM was similarly distributed (0.6% (3/524) versus 0.8% (4/479)). eGFR differed across antibody-positive, antibody-negative and untested patients (83, 36, and 24 ml/min./1.73 m²; $p = 0.006$); intensity distribution did not ($p = 0.09$).

Despite confirmed or probable SIM, only 59% had statin intolerance ("CAVE") recorded in the electronic medical records CAVE field, with no difference by antibody status (Table 1).

Severe SIM was rare, with an incidence of 4.3 cases per 100,000 patient-years (95% CI: 3.0-6.1). This estimate was based on 740,442 patient-years from the fully exposed population during the study period.

Discussion

The incidence of SIM aligns with previous estimates of 3-10 per 100,000 patient-years [3, 13], reaffirming that serious muscle toxicity is an uncommon complication of statin therapy.

Clinical documentation and diagnostic follow-up were inconsistent. Documentation of statin intolerance was missing in 41% of SIM cases, and anti-HMGCR antibody testing was performed in only 56% despite its diagnostic utility in confirming IMNM [10]. The clinical implications of these gaps were illustrated by a patient with documented statin intolerance who was subsequently prescribed high-dose atorvastatin during a cardiology admission but avoided re-exposure by not redeeming the prescription. These gaps highlight risks of compromised prescribing safety and underscore the need for systematic documentation and broader antibody testing.

This study has several limitations. Exposure time in the background population was estimated from annual prescription data [12] and may have been underestimated. Inclusion was restricted to hospitalised patients with statins recorded in their medical files, potentially omitting cases of statin discontinuation prior to hospital admission. CK measurements were obtained on clinical indication with heterogeneous timing relative to symptom onset, limiting interpretation of peak values. The absence of statistically significant differences in age,

kidney function, CKD status or statin type should be interpreted with caution, as the comparator group included many older patients with non-SIM CK elevation and the number of SIM cases was small. No drug-drug interactions (e.g., macrolides) were identified. This is surprising given their known SIM association, but may reflect limited clinical awareness. Technical constraints also prevented identification of any anti-HMGCR-tested patients not included in the cohort, but the CK > 10 × ULN criterion likely captured most relevant cases.

Conclusions

Severe SIM was infrequent, and clinical documentation and antibody testing were inconsistent. Strengthening these aspects of care could improve recognition and management of statin-related muscle injury.

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Accepted 29 June 2026

Published 18 August 2026

Conflicts of interest CT reports financial support from or interest in Novo Nordisk. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2026;73(9):A02260103

doi 10.61409/A02260103

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