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ORIGINAL RESEARCH

# Prevalence of Statin Use and Predictors of Statin Initiation Among Patients with Alcohol-Related Cirrhosis - A Danish Nationwide Cohort Study

Marine Sølling Ramsing, Frederik Kraglund, Peter Jepsen

Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

Correspondence: Marine Sølling Ramsing, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, Aarhus, 8200, Denmark, Tel +45 78 45 00 00, Email anarms@rm.dk



**Purpose:** Statins reportedly increase the survival of patients with cirrhosis due to alcohol-related liver disease (ALD cirrhosis), but this association might be confounded by socioeconomic status. We examined the prevalence of statin use and socioeconomic and demographic predictors of statin initiation and discontinuation among patients with ALD cirrhosis.

**Patients and Methods:** Using Danish nationwide healthcare registries, we examined statin use among patients diagnosed with ALD cirrhosis in 1997–2018. We computed the prevalence of statin use and incidence of statin initiation and discontinuation, and we used multivariable Cox regression to identify predictors of statin initiation and discontinuation.

**Results:** We identified 28,260 patients with ALD cirrhosis in 1997–2018. During this period, the prevalence of statin use rose sharply, reaching 19.0% in late 2018. Among patients diagnosed with ALD cirrhosis after 2010, 16.9% were using statins when they were diagnosed with cirrhosis. Among the patients who did not use statins initially, those with lower educational attainment were more likely to begin taking them than those with higher attainment. Also, cohabiting patients were more likely to begin than patients who lived alone, and employed patients were more likely to begin compared to patients outside the labour force. Among current statin users, unemployment predicted statin discontinuation.

**Conclusion:** The use of statins has become increasingly prevalent among Danish patients with ALD cirrhosis, reaching 19.0% in 2018. Employment, cohabitation, and a short education predicted statin initiation after ALD cirrhosis diagnosis, and unemployment predicted statin discontinuation. Overall, statin use was not a marker of a high socioeconomic status.

**Keywords:** liver cirrhosis, alcoholic, hydroxymethylglutaryl-CoA reductase inhibitors, anticholesteremic agents, socioeconomic factors

## Plain Language Summary

Statin treatment reportedly reduces mortality among patients with alcohol-related cirrhosis of the liver. However, in these patients, statins may be underutilised due to fear of toxic effects on the liver. Furthermore, the reported beneficial effects of statins may be explained by socioeconomic differences between statin users and non-users. Using nationwide registries, we aimed to describe the prevalence and socioeconomic characteristics of statin use among patients with alcohol-related liver cirrhosis. We found that the prevalence of statin use reached 19.0% in 2018. Statin users were more likely than non-users to live with a partner and to be employed, but also more likely to have a lower educational attainment. Our results show that statins are widely used in patients with alcohol-related cirrhosis, and that socioeconomic characteristics cannot fully explain the reduced mortality attributed to statin treatment.

## Introduction

Mounting evidence indicates that statin use reduces mortality in patients with cirrhosis due to alcohol-related liver disease (ALD cirrhosis); a severe liver disease with an expected survival time of less than five years from diagnosis.[1,2] Statins are among the most prescribed classes of medication; used worldwide to lower mortality from cardiovascular diseases.[3–5] In addition to their lipid lowering properties, statins exhibit antioxidative, anti-inflammatory and



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antiproliferative properties, and have recently shown distinct beneficial effects in cirrhosis by reducing portal hypertension, mortality and risk of decompensation.[6–13] However, fear of hepatotoxicity may have kept physicians from prescribing statins, potentially leading to underutilisation among patients with liver disease.[14] As recent research in statins and cirrhosis has left the field in eager optimism, clinicians may have revised their prescribing habits. In that case, socioeconomic and demographic characteristics of statin users may have changed over the last decades, but this possibility has not been addressed by the existing literature. Furthermore, statin adherence has been associated with higher socioeconomic status,[15–18] which is associated with longer survival in patients with cirrhosis.[19] Therefore, it remains unclear if some of the beneficial effects attributed to statin use could in fact be caused by favourable socioeconomic status. To eliminate this concern over confounding, randomized studies are being conducted. However, it will be several years before they are completed, and for now observational studies such as ours are key for clinical decision-making. We hypothesized that more and more patients with alcohol-related cirrhosis are using statins, and that patients who initiate statin treatment are more likely to be employed, be living with a partner and have more years of education.

This study aimed to examine time-trends in prevalence of statin use and predictors of statin initiation and discontinuation among patients with ALD cirrhosis. Such information is important for our understanding of clinical practice, and it provides an important perspective on existing and future studies on the beneficial effects of statins.

# Patients and Methods

## Data Sources and Setting

This nationwide registry-based cohort study was conducted using Danish healthcare registries. In Denmark, residents are provided tax-supported free access to general practitioners and hospitals. Therefore, all hospital admissions since 1977 and all outpatient contacts and visits to emergency-rooms since 1995 across the country are recorded in The Danish National Patient Registry (NPR). Data includes relevant dates and discharge diagnoses coded in accordance with the International Classification of Diseases, 10th revision (ICD-10) from 1994.[20]

Dates of death and emigration were drawn from The Danish Civil Registration System, where vital status is continuously monitored.[21] A unique personal identifier is given at birth or immigration, enabling linkage of individual-level data between the NPR and The Danish Civil Registration System. Data on statin prescriptions were drawn from The Danish National Prescription Registry (DNPR), which contains data on all filled drug prescriptions since 1994.[20] A prescription is needed to buy any statin medication in Denmark, and purchases are partly covered by a reimbursement system that counts towards an annual maximum on out-of-pocket costs. Data on socioeconomic status were drawn from nationwide registries hosted by Statistics Denmark.

Statins were introduced to the Danish population on May 19, 1988, as investigators initiated randomisation of 4444 patients for a large randomised placebo study named Scandinavian Simvastatin Survival Study (4S).[22] Simvastatin was later approved as a medical drug for treatment of hypercholesterolemia, dyslipidaemia and for prevention of cardiovascular diseases by the Danish Medicines Agency 18 January 1990.[23] Since then, the prevalence of statin use has increased in the background population, especially among patients older than 60 years (Supplementary Figure S1). Data used to calculate prevalence of statin use among Danish men in the background population are provided by The Danish Healthcare Authorities and are publicly accessible at medstat.dk.

## Study Population

All patients who received their first diagnosis of ALD cirrhosis between 1 January 1997 and 31 December 2018 were identified in the NPR using ICD10 diagnosis codes K70.3 and K70.4 (Figure 1). Patients were followed to death, emigration, or censoring on the 31 December 2018. Patients younger than 30 years at the time of their first diagnosis of ALD cirrhosis were excluded.

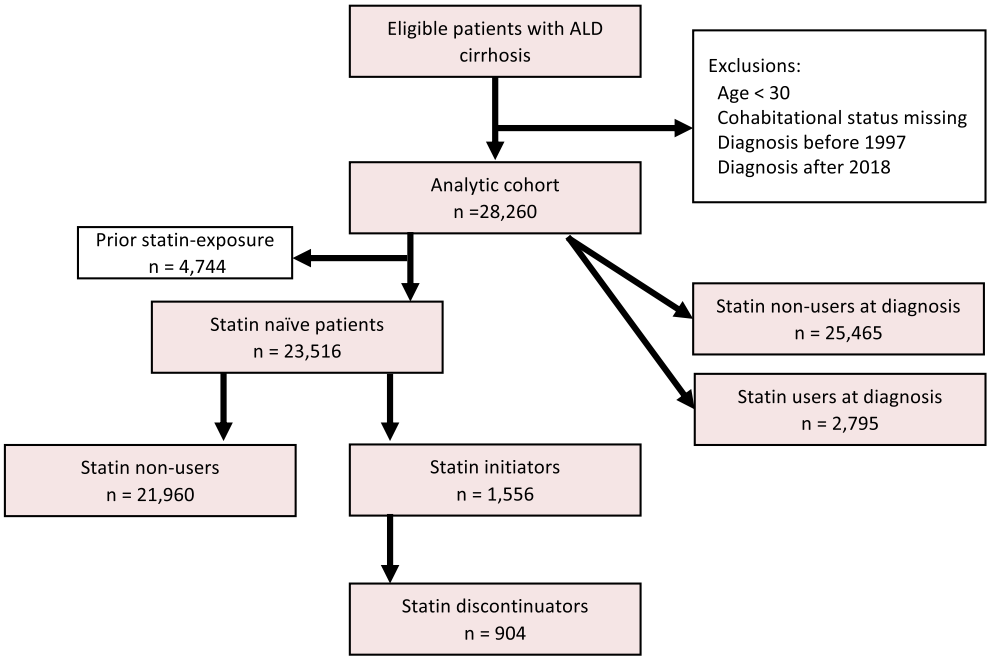


**Figure 1** Distribution of statin non-users, statin continuators and statin initiators in the cohort. The group that initiated statin treatment was compared to statin naïve patients.

## Statin Use and Discontinuation

All statin prescriptions were identified in DNPR from 1 January 1997 to 31 December 2018 and included statins alone and statins in combination with other substances (ATC-codes C10AA and C10Bx). Statin initiation was the date of the first filled prescription after ALD-cirrhosis diagnosis in a patient with no previous statin prescriptions filled. Statin use was defined as beginning on the date of a filled prescription and lasted for two times the prescribed number of tablets, thereby including a "grace period" during which patients counted as statin users. We presumed that patients took one tablet every day. If a patient filled two prescriptions on the same day, the number of tablets were added together. However, if a new prescription was filled while the patient was still considered as "statin user", the patient remained a "statin user", but only the latest prescription was considered. Statin discontinuation was defined as having reached the final day of being a statin user with no new prescriptions filled.

## Predictors of Statin Initiation, and Discontinuation

### Socioeconomic Variables

The employment status was obtained from The Labour Force Statistics, hosted by Statistics Denmark. Employment status was updated for each patient every year in late November during follow up and categorised as 1) employed, 2) outside the labour force (including sick-leave and retirement), 3) unemployed or 4) missing. Cohabitation status was drawn from the Danish Civil Registration System, where the status is continually updated on the dates of marriage, registration of partnership, divorce, or widowhood. We categorised cohabitation status as either cohabiting (living with a partner or spouse) or living alone (living without a partner or spouse). Furthermore, patients were cohabiting if they lived on the same address as an individual of the opposite sex with less than 15 years age difference and without a close family relation. This status was updated every year during follow up on 1 January. Information on the highest completed education level for each individual was obtained from The Educational Attainment Register and categorised according to the number of years of education: 1) ≤ 9 years, 2) 10–12 years, 3) 13–16 years 4) ≥ 17 years, or 5) missing (Supplementary Figure S2).

### Comorbidities

Comorbidities were identified through discharge diagnoses from the NPR. The discharge diagnoses were obtained from 1977 to 31 December 2018, but the data was not exhaustive before 1994. Comorbidities were included in the regression models as binary

and time-dependent variables, changing from 0 to 1 on the first day of hospitalisation with one of the defining diagnoses. The ICD-10 diagnosis codes used are listed in Supplementary Table S1. From these codes, metabolic syndrome-related disease was defined as having any of the following diagnoses: hypertension, hyperlipidaemia, obesity, or diabetes. Diabetes also included having filled a prescription of an antidiabetic drug. Cardiovascular disease included atherosclerosis, thromboembolism, and ischaemic heart disease. Decompensation was defined as any of the following: ascites, spontaneous bacterial peritonitis, bleeding from oesophageal or gastric varices, or hepatorenal syndrome. In addition to the diagnosis codes for decompensated cirrhosis, we included the procedure codes for drainage of ascites fluid, treatment of variceal bleeding, and transjugular intrahepatic portosystemic shunt, coded according to the Nomesco Classification of Surgical Procedures. We also included the ATC codes of a filled prescription for spironolactone, furosemide, non-selective beta-blockers, or lactulose to our definition of decompensation. We could not identify hepatic encephalopathy because it does not have an ICD-10 diagnosis code.

## Statistical Analysis

### Prevalence of Statin Use

The prevalence of statin use was computed for each day during the study period as the number of statin users in the ALD cirrhosis cohort on a given day divided by the total number of patients in the ALD cirrhosis cohort on the same day. The prevalence of statin use was calculated with respect to calendar date and with respect to time since the first diagnosis of ALD cirrhosis among patients diagnosed after 2010.

### Statin Initiation

The analyses of statin initiation excluded all patients who had filled a prescription for statins before cirrhosis diagnosis (Figure 1). First, the cumulative incidence function, with death before statin initiation as a competing event, was used to compute the probability of becoming a statin initiator with respect to time since ALD cirrhosis diagnosis. Cox proportional hazards regression was used to estimate the association between the time to statin initiation and the following predictors: age group; sex; highest educational attainment; cohabitation status at diagnosis; employment status at diagnosis; and the following diagnoses, all of which were included in the regression model as time-dependent binary variables: metabolic syndrome-related disease, cardiovascular disease, and decompensation of cirrhosis. We included all the variables in univariable analyses and in a multivariable analysis. In separate analyses, we calculated incidence rates and conducted the multivariable analysis for three calendar time periods: 1 January 1997 through 31 December 2009, 1 January 2010 through 31 December 2014, and 1 January 2015 through 31 December 2018. Patients diagnosed in the earlier periods, who were still at risk of statin initiation in a later period, contributed risk-time to all involved periods.

### Statin Discontinuation

The cumulative incidence of statin discontinuation among patients who initiated statin treatment after their first ALD cirrhosis diagnosis was computed with respect to years since statin initiation, again with death as a competing event. We used Cox proportional hazards regression to identify factors associated with a short time to discontinuation. The factors included in this multivariable regression model were age group, sex, and socioeconomic variables.

# Results

During the 1997–2018 period, we identified 28,260 patients diagnosed with ALD cirrhosis (Figure 1). In this cohort, statin use did not occur until the summer of 1998, and the total prevalence of statin users among patients diagnosed with ALD cirrhosis was below 1% until mid-November 2001 and then rose to 19.0% by the end of 2018 (Figure 2). Approximately half of the patients who used statins were ‘continuators’, as they were already using them before they were diagnosed with ALD cirrhosis, and the other half were “initiators”, as they began using them after they were diagnosed with ALD cirrhosis. The proportion of initiators was 7.9% by the end of 2018, and was relatively stable, indicating that around 8% of today’s patients with ALD cirrhosis are using statins which they did not use before they were diagnosed with cirrhosis.

Among the 28,260 patients with ALD cirrhosis, the 2795 patients who used statins at the time of diagnosis were older than the 25,465 patients who did not (median age of 65 years ([IQR: 58–70] vs 58 years [IQR: 51−65]) (Table 1). They were also more likely to be men (73.5% among users vs 68.3% among non-users), outside the labour force (73.5% vs

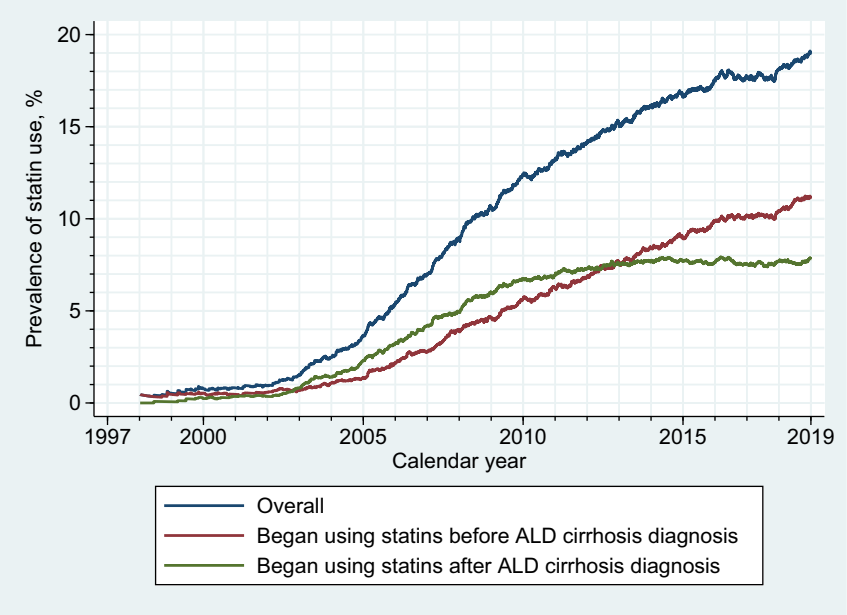


**Figure 2** Prevalence of statin use among patients with ALD cirrhosis with respect to calendar year. (Blue) Overall statin users after diagnosis. (Red) Statin user after first ALD cirrhosis diagnosis, initiated treatment before diagnosis. (Green) Statin user after first ALD cirrhosis diagnosis, initiated treatment after first ALD cirrhosis diagnosis.

61.8.%), cohabiting (52.7.0% vs 40.4%), and more likely to suffer from cardiovascular disease (49.4% vs 12.9%), metabolic syndrome-related diseases (77.3% vs 29.8%) and decompensation (73.8% vs 65.1%). The prevalence of diabetes in the cohort was 23.9% among men, and 18.2% among women at the time of diagnosis.

**Table 1** Characteristics of Users and Non-Users at Time of Diagnosis of ALD Cirrhosis

| **Individuals, No. (%)** | **Non-Users** | **Users** |
|---|---|---|
| Number of patients | 25,465 | 2795 |
| Age at diagnosis in years, median (interquartile range [IQR]) | 58 (51–65) | 65 (58–70) |
| Female sex, N (%) | 8083 (31.7) | 742 (26.5) |
| Education, N (%) | | |
| • ≥ 17 years | 761 (3.0) | 106 (3.8) |
| • 3–16 years | 2649 (10.4) | 342 (12.2) |
| • 10–12 years | 10,895 (42.8) | 1229 (44.0) |
| • ≤ 9 years | 10,224 (40.1) | 1028 (36.8) |
| • Missing | 936 (3.7) | 90 (3.2) |
| Employment status, N (%) | | |
| • Outside labour force | 15,735 (61.8) | 2053 (73.5) |
| • Employed | 6275 (24.6) | 516 (18.5) |
| • Unemployed | 3104 (12.2) | 189 (6.8) |
| • Missing | 351 (1.4) | 37 (1.3) |
| Cohabitation status, N (%) | | |
| • Alone | 15,165 (59.6) | 1322 (47.3) |
| • Cohabiting | 10,300 (40.4) | 1473 (52.7) |
| Cardiovascular disease, N (%) | 3273 (12.9) | 1380 (49.4) |
| Metabolic syndrome-related disease, N (%) | 7582 (29.8) | 2159 (77.2) |
| Decompensation, N (%) | 16,569 (65.1) | 2062 (73.8) |

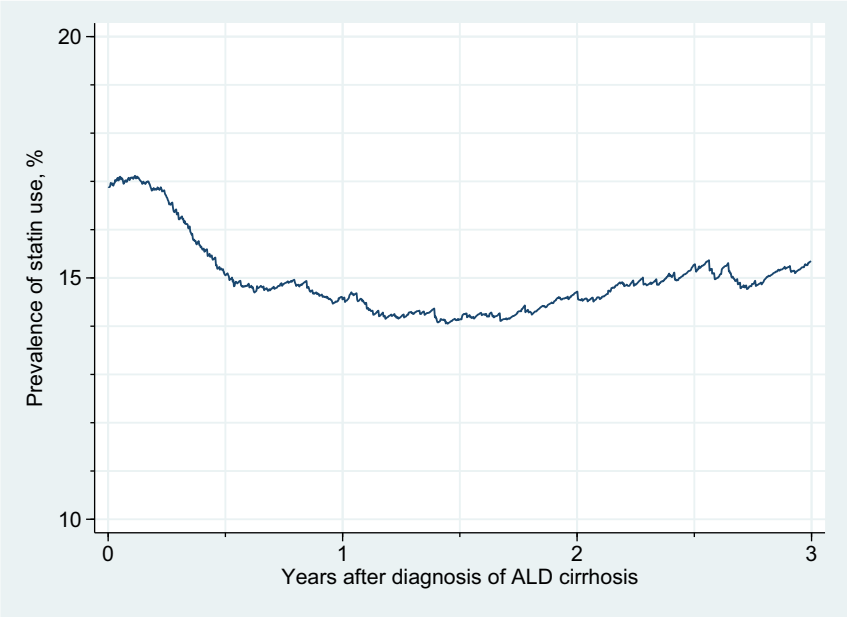


**Figure 3** Prevalence of statin use among patients with ALD cirrhosis with respect to time since cirrhosis diagnosis. This analysis is restricted to patients diagnosed with ALD cirrhosis after 1 January 2010.

Among the 11,878 patients who were diagnosed with ALD cirrhosis after 1 January 2010, 16.9% were already using statins when they were first diagnosed with cirrhosis (Figure 3). The prevalence decreased to 15.1% during the first six months with the cirrhosis diagnosis and stayed around 15% for the remainder of the follow-up period.

## Statin Initiation

Among patients diagnosed with ALD cirrhosis after 2010, the cumulative incidence function revealed that 2.5% initiated statin treatment within the first 3 years after diagnosis, and the pace of statin initiation after diagnosis of ALD cirrhosis was constant at around 0.8% per year (Supplementary Figure S3). The incidence rate of statin initiation was 16.6 (95% confidence interval (CI): 15.4–17.9) per 1000 person-years in the years before 2010, rose to 22.1 (95% CI: 20.2–24.1) per 1000 person years between 2010 to 2015, and then decreased in the years after 2015 to 18.1 (95% CI: 16.2–20.1) per 1000 person years. Predictors of statin initiation included having ≤ 9 or 10–12 years of education compared to ≥ 17 years of education, with hazard ratios (HR) of 1.42 (95% CI: 1.02–1.98) and 1.50 (95% CI: 1.08–2.07), respectively. In the multivariable analysis, being employed compared to being outside the labour force predicted a higher rate of statin initiation with a HR of 1.15 (95% CI: 1.00–1.32). Regarding cohabitation status, living with a partner predicted statin initiation with a HR of 1.11 (95% CI: 1.00–1.23). Compared to ages under 50 years, all older age groups predicted an increased rate of statin initiation after diagnosis. Other predictors included metabolic syndrome-related disease (HR: 2.9, 95% CI: 2.68–3.31) and cardiovascular disease (HR: 4.19, 95% CI: 3.78–4.66). Decompensation predicted a reduced rate of statin initiation (HR: 0.64, 95% CI: 0.56–0.73) (Table 2). These associations were largely stable in the three periods, including employment status and cohabitation status (Table 3).

## Statin Discontinuation

Of the patients who initiated statin treatment after ALD cirrhosis diagnosis, 27% (95% CI: 25–29%) stopped again within 1 year, and 49% (95% CI: 47–52%) stopped within 3 years (Supplementary Figure S4). Statin users who were unemployed were more likely to stop using statins (HR vs patients who were outside the labour force: 1.61, 95% CI: 1.22–2.13) than those who were employed (HR vs patients who were outside the labour force: 1.05, 95% CI: 0.87–1.28). The other socioeconomic variables education, sex, and cohabitation status did not predict statin discontinuation (Table 4).

**Table 2** Predictors of Statin Initiation (N=1556) Among the Patients (N=23,516) Who Were Diagnosed with ALD Cirrhosis and Had Not Previously Used Statins

| Hazard Ratio (95% CI) | Univariable Analysis | Multivariable Analysis (Adjusted) |
|---|---|---|
| Age | | |
| • < 50 | Ref | Ref. |
| • 50–59 | 1.68 (0.40–2.03) | 1.41 (1.17–1.70) |
| • 60–69 | 2.33 (1.94–2.79) | 1.66 (1.37–2.01) |
| • ≥ 70 | 2.15 (1.75–2.65) | 1.35 (1.08–1.68) |
| Women | 0.93 (0.83–1.03) | 1.08 (0.97–1.20) |
| Education | | |
| • ≥ 17 years | Ref | Ref. |
| • 13–16 years | 1.17 (0.82–1.66) | 1.27 (0.89–1.81) |
| • 10–12 years | 1.35 (0.98–1.88) | 1.50 (1.08–2.07) |
| • ≤ 9 years | 1.25 (0.90–1.73) | 1.42 (1.02–1.98) |
| • Missing | 1.20 (0.78–1.84) | 1.42 (0.92–2.19) |
| Employment status | | |
| • Outside labour force | Ref | Ref. |
| • Employed | 0.87 (0.77–0.99) | 1.15 (1.00–1.32) |
| • Unemployed | 0.69 (0.56–0.86) | 1.01 (0.81–1.26) |
| • Missing | 0.57 (0.21–1.52) | 0.55 (0.20–1.46) |
| Cohabitation status | | |
| • Alone | Ref | Ref. |
| • Cohabiting | 1.21 (1.09–1.34) | 1.11 (1.00–1.23) |
| Metabolic syndrome-related disease | 3.61 (3.26–4.00) | 2.98 (2.68–3.31) |
| Cardiovascular disease | 5.02 (4.54–5.55) | 4.19 (3.78–4.66) |
| Decompensated cirrhosis | 0.80 (0.70–0.90) | 0.64 (0.56–0.73) |

## Discussion

In this nationwide cohort study, we found that the proportion of statin users among patients with ALD cirrhosis has risen from none at the beginning of 1998 to 19.0% in late 2018, including 7.9% who began using statins after they were diagnosed with cirrhosis. This finding demonstrates that clinicians are willing to prescribe statins to patients with ALD cirrhosis. However, patients with decompensated ALD cirrhosis are less likely to initiate statin treatment. Consequently, statin initiators are a relatively healthy subset of patients with ALD cirrhosis. They are generally older, they have generally completed fewer years of education, and they are more likely to be cohabiting and employed.

There are important limitations to acknowledge in this study. The validity of our results depends on the validity of the registries used. The DNPR was used to account for statin prescriptions, and it generally has very good quality and coverage.[25] However, since we only had the date of purchase and the number of tablets purchased, we had to make certain presumptions including a grace period that might have led us to slightly overestimate the true prevalence of statin use. Another limitation is the lack of data on the indication for starting and stopping statin use. This information is not recorded in our data sources, and we emphasize that our goal was to identify predictors of statin use, not to understand why patients were using them. In other words, this descriptive study investigated prediction rather than causality and did therefore not require adjustments for confounders.[24]

The dates of death and birth and cohabitation status were drawn from The Danish Civil Registration System, which is essentially complete in terms of validity and coverage.[21] The validity and coverage of the registries hosted by Statistics Denmark from which we obtained data on employment status and education level are also high.[26,27] In our cohort, 3.6% of patients had missing data on education, most likely because they immigrated to Denmark or completed their education

**Table 3** Multivariable Analysis of Predictors of Statin Initiation Stratified by Calendar Year

| | Before 1 Jan 2010 | 1 Jan 2010–1 Jan 2015 | After 1 Jan 2015 |
|---|---|---|---|
| Statin initiators (N) | 687 | 529 | 340 |
| Incidence rate per 1000 person-years | 16.6 | 22.1 | 18.1 |
| **Hazard ratio (95% CI)** | | | |
| Age | | | |
| • < 50 | Ref. | Ref. | Ref. |
| • 50–59 | 1.31 (1.00–1.70) | 1.28 (0.93–1.75) | 1.80 (1.07–3.01) |
| • 60–69 | 2.03 (1.56–2.65) | 1.11 (0.80–1.54) | 1.85 (1.09–3.12) |
| • ≥ 70 | 1.23 (0.88–1.72) | 1.14 (0.79–1.65) | 1.84 (1.05–3.21) |
| Women | 1.26 (1.07–1.47) | 0.94 (0.78–1.13) | 1.04 (0.82–1.30) |
| Education | | | |
| • ≥ 17 years | Ref | Ref | Ref |
| • 13–16 years | 1.09 (0.64–1.87) | 1.34 (0.73–2.46) | 1.52 (0.71–3.27) |
| • 10–12 years | 1.26 (0.77–2.05) | 1.67 (0.95–2.92) | 1.67 (0.82–3.41) |
| • ≤ 9 years | 1.17 (0.71–1.91) | 1.46 (0.83–2.58) | 1.80 (0.87–3.69) |
| • Not classified | 1.72 (0.93–3.18) | 0.84 (0.36–1.92) | 1.58 (0.62–4.03) |
| Employment status | | | |
| • Outside labour force | Ref. | Ref. | Ref |
| • Employed | 1.03 (0.84–1.27) | 1.20 (0.94–1.53) | 1.58 (1.17–2.14) |
| • Unemployed | 0.97 (0.65–1.45) | 0.87 (0.62–1.24) | 1.15 (0.73–1.79) |
| • Missing | 0.54 (0.20–1.45) | - | - |
| Cohabitation status | | | |
| • Alone | Ref. | Ref. | Ref |
| • Cohabiting | 1.27 (1.09–1.48) | 0.98 (0.82–1.17) | 1.01 (0.80–1.26) |
| Metabolic syndrome-related disease | 3.18 (2.72–3.73) | 3.29 (2.75–3.95) | 2.30 (1.85–2.88) |
| Cardiovascular disease | 4.40 (3.75–5.15) | 3.69 (3.08–4.42) | 4.82 (3.86–6.02) |
| Decompensated cirrhosis | 0.70 (0.58–0.85) | 0.55 (0.44–0.68) | 0.67 (0.51–0.90) |

several decades ago. In a preliminary analysis, we found that these patients had an increased mortality rate, so we grouped them separately.

The validity of diagnosis codes in the NPR is another concern, and generally the validity depends on the type of diagnosis. In the case of alcohol-related cirrhosis, one study reported a positive predictive value of the diagnosis code to be 92.4% (95% CI: 86.0–98.8).[28] The possible misclassification is therefore limited, and unlikely to bias our estimation of the prevalence of statin use or predictors of statin initiation, as it is unlikely to have changed during the study period, or to be systematically different between statin users and non-users. It should be noted that our results may not generalise to patients with ALD cirrhosis who have not been hospitalised. However, all patients treated for cirrhosis are worked-up and treated in public hospitals, and healthcare is fully tax-financed in Denmark. Also it should be noted that the population in Denmark is relatively homogeneous, which may limit the external validity.

A final potential limitation to acknowledge is alcohol intake. Unfortunately, we did not have data on alcohol intake, so we do not know whether patients who consumed alcohol were more or less likely to use statins.

Among patients with cirrhosis, the prevalence of statin-users at the time of diagnosis was 26.9% in a large cohort study from 2008 to 2018 with data from American veterans (the VOCAL cohort).[29] A Danish cohort study reported the prevalence of statin prescriptions to be 15% in 1995 through 2014.[11] Differences in healthcare systems and prescription

**Table 4** Multivariable Analysis of Predictors of Statin Discontinuation (n=904) Among Patients Who Began Using Statins After They Were Diagnosed with ALD Cirrhosis (n=1556)

| Hazard Ratio (95% CI) | Univariable Analysis | Multivariable Analysis (Adjusted) |
|---|---|---|
| Age | | |
| • < 50 | Ref. | Ref. |
| • 50–59 | 0.79 (0.61–1.02) | 0.83 (0.64–1.08) |
| • 60–69 | 0.66 (0.51–0.84) | 0.72 (0.55–0.94) |
| • ≥ 70 | 0.78 (0.60–1.02) | 0.87 (0.65–1.16) |
| Women | 0.98 (0.85–1.12) | 0.99 (0.86–1.13) |
| Education | | |
| • ≥ 17 years | Ref | Ref |
| • 13–16 years | 1.19 (0.74–1.91) | 1.19 (0.74–1.91) |
| • 10–12 years | 1.13 (0.73–1.76) | 1.12 (0.72–1.74) |
| • ≤ 9 years | 1.10 (0.71–1.71) | 1.07 (0.69–1.66) |
| • Missing | 1.15 (0.65–2.01) | 1.13 (0.64–1.99) |
| Employment status | | |
| • Outside labour force | Ref | Ref |
| • Employed | 1.10 (0.92–1.32) | 1.05 (0.87–1.28) |
| • Unemployed | 1.75 (1.34–2.27) | 1.61 (1.22–2.13) |
| • Missing | 1.45 (0.60–3.50) | 1.49 (0.61–3.59) |
| Cohabitation status | | |
| • Alone | Ref | Ref |
| • Cohabiting | 0.95 (0.83–1.08) | 0.98 (0.85–1.12) |

practices across countries and time-periods result in differences in the prevalence of statin prescriptions. As we show in the present study, the prevalence of statin users among patients with alcohol-related liver cirrhosis has increased from 1997 to 2018, and it may continue to do so. Still, statin users and non-users in the VOCAL cohort were comparable to those in our cohort in terms of comorbidities. However, more patients in our cohort were decompensated at the time of diagnosis, which could explain why we found fewer statin users at the time of diagnosis; 16.9% of patients were statin users at diagnosis after 2010. The Danish cohort study calculated the prevalence in an earlier time-period and included patients only after their second statin prescription and only if the total time of statin treatment lasted at least one month.

Our data suggest that statins might be underutilised among patients with alcohol-related cirrhosis. First, the increase in utilisation during 2000–2010 in the background population happened 3–4 years ahead of a similar increase in our cohort. Second, the prevalence of diabetes is higher in our cohort at the time of diagnosis (23.9% of men, 18.2% of women), compared to the prevalence in the background population (peaks around age 80 in 19% of men, 15% of women).[30] Additionally, among the non-users, 12.9% had cardiovascular diseases and 29.8% had metabolic syndrome-related disease, so indications for statin initiation may be present. Unfortunately, we did not have data on blood lipids to further explore underutilisation within this cohort.

In general, patients with decompensated cirrhosis show low serum cholesterol level due to impaired metabolic homeostasis;[31] therefore, the lower prevalence of statin use could be from lack of indication, rather than from lack of willingness to prescribe.

This is the first study to describe socioeconomic predictors of statin initiation among patients with ALD cirrhosis. We showed that patients with less than 12 years of education were more likely to initiate statin treatment after diagnosis. Patients with ALD cirrhosis generally have a lower socioeconomic status compared to the background population,[32] so it may be problematic to compare socioeconomic characteristics within this group to other patient cohorts. Besides, predictors of adherence may be very different from predictors of initiation and of discontinuation. Statin adherence

has been reported to be associated with higher socioeconomic status and higher educational attainment.[17,18] A Swedish study found that patients with ≤ 9 years of education were less likely to use statin medications compared to patients with more than 12 years of educational attainment (odds ratio: 0.89 (95% CI: 0.84–0.94).[33] However, the finding is not consistent. An American study found that patients with a high school diploma or less had higher odds of statin use compared to college graduates (odds ratio: 1.45 (95% CI: 1.11−1.90)).[34] A Danish study of statin discontinuation among Danes aged 70 and older found no strong association between statin discontinuation and years of education.[35] This varying effect of education on the likelihood of statin use could be explained by incomparable study designs, varying time periods, variations in demographics and comorbidities, besides differences in the healthcare systems and the prescribing guidelines.

This study expands on our current understanding of the clinical management of patients with ALD cirrhosis. Future studies must expect around 20% of patients with ALD cirrhosis to be statin users, as prescribers do not consider cirrhosis as an absolute contraindication. Patients with ALD cirrhosis are prescribed statins for either primary or secondary prevention of cardiovascular events, and throughout the study period, cardiovascular disease and metabolic-syndrome related diseases were significant predictors of statin initiation. Patients were less likely to initiate statin treatment if they were decompensated, indicating that statin users may generally be healthier in terms of their liver disease. Future studies of the effect of statins on ALD cirrhosis should therefore adjust their findings for the severity of the liver disease, and the comorbidities for which statin treatment was prescribed. Moreover, statin initiation was associated with lower educational attainment, so statin users did not have more favourable socioeconomic status. However, statin initiation was also associated with cohabitation and employment, which correlates well with a relatively well-preserved liver function.

In conclusion, the use of statins has become common practice among patients with ALD cirrhosis in Denmark. Statin initiation after diagnosis is associated with cardiovascular comorbidities, older age, and low, not high, educational attainment, being employed and cohabiting with a partner. Among those who have begun using statins, however, unemployment is associated with discontinuation. Thus, the association between statin use and socioeconomic characteristics is complex, and statin use should not be interpreted as a marker of high socioeconomic status. It is, however, a marker of relatively well-preserved liver function. These findings should be helpful to those who design or analyse studies of statin use among patients with cirrhosis.

## Abbreviations

ALD cirrhosis, Cirrhosis caused by alcohol-related liver disease; NPR, The Danish National Patient Registry; ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; DNPR, The Danish National Prescription Registry; ATC Classification System, Anatomical Therapeutic Chemical Classification System; IQR, Interquartile range; HR, Hazard ratio; CI, Confidence interval.

## Data Sharing Statement

This study was conducted using Danish healthcare registries. Access to the data sources for this study is restricted and maintained by Danish health data authorities and only available through an application.

## Ethics Approval and Informed Consent

This nationwide registry-based cohort study was conducted in accordance with Danish law. No individual consent was needed because we used pseudonymized data from Danish healthcare registries. We did not have contact with patients or their medical charts, so we did not need permission from an ethics committee to conduct the study.

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## Disclosure

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