Statins in Older Danes: Factors Associated With Discontinuation Over the First 4 Years of Use

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BACKGROUND AND OBJECTIVE: Use of statins is considerable among older persons. We investigated factors associated with statin discontinuation in new statin users aged 70 years or older within the first 4 years of use.

DESIGN: Register-based descriptive drug utilization study using data from 2008 to 2016.

POPULATION/SETTING: All Danish persons, aged 70 years or older, initiating statin treatment.

MEASUREMENTS: Rates and predictors of statin discontinuation after 1 year (early), 2 years, and 4 years. Predictors of discontinuation were estimated using logistic regression.

RESULTS: We included 83 788 statin initiators. At 1 year, 13% had discontinued their treatment, while another 12% and 13% discontinued after 2 and 4 years, respectively. The overall discontinuation rate over 4 years was 32%. Increasing age was associated with discontinuation at all time points (adjusted odds ratio [OR] = 2.06 [95% confidence interval {CI} = 1.35-3.16] at 1 year, adjusted OR = 3.94 [95% CI, 1.83-8.49] at 4 years, comparing those aged >95 years to those aged 70-74 years). Further, higher comorbidity scores and use of more than 10 medications were modestly associated with discontinuation. Use of statins for secondary prevention was associated with decreased odds of discontinuation compared to primary prevention at 1 year (adjusted OR = 0.74; 95% CI, 0.65-0.83) and at 4 years (adjusted OR = 0.83; 95% CI, 0.72-0.95), along with concomitant use of cardiovascular (CV) therapies. The annual proportion of early discontinuers ranged from 14% to 17% for primary prevention and from 9% to 12% for secondary prevention between 2008 and 2015.

DISCUSSION: Statin discontinuation within the first 4 years after initiation appeared to be influenced most strongly by age, and may also be influenced by comorbidity, polypharmacy, use for secondary prevention, and concomitant CV medication use. Future research should clarify reasons for, and discussions about, statin discontinuation and initiation among older persons, to provide additional insight on this topic. **J Am Geriatr Soc 00:1-8, 2019.**

Key words: medication discontinuation; polypharmacy; statins

Statins reduce risk of cardiovascular disease (CVD), mediated in part by their cholesterol-lowering effect. There is evidence of benefit in persons with a history of CVD (secondary prevention) and those with no CVD but at high overall risk (primary prevention).[1-4] Older persons, and particularly those older than 80 years, are poorly represented in most clinical trials of statins.[5,6] Despite a recent meta-analysis[7] in persons older than 75 years, the efficacy and safety of statins in this age group are still largely unclear, particularly for primary prevention and among those who are frail or have multiple comorbidities.[8] Consequently, there are questions as to whether statins could and should be initiated in this population, and whether discontinuation can or should be considered in existing users.[8-10] Guidelines suggest individualized decisions in this population, incorporating factors such as goals of care, patient preferences, previous cardiovascular (CV) history, comorbidities, and burden of care.[5,11,12] Based on these factors, some patients and prescribers may decide to discontinue statin therapy. Rates of statin discontinuation have previously been investigated, although these studies have mostly focused on the general population,[13-15] either excluding those older than 80 years or grouping them together.[16-18] Existing studies in older persons have further been limited

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by small sample sizes,[17] limited numbers of factors being investigated,[19] or only examining the first year of statin use.[16] Further, some studies have focused on discontinuation primarily from an adherence or persistence standpoint.[13,16]. Given the limited evidence on this topic, we sought to evaluate whether different factors were associated with statin discontinuation within the first 4 years of use in older persons newly initiated on statins.

METHODS

This was a nationwide register-based descriptive drug utilization study conducted in all Danish older persons (aged ≥70 years).

Data Source

We retrieved prescription data from the Danish National Prescription Register, which is considered valid and complete.[20] We retrieved data on comorbidities from the Danish National Patient Register,[21] education level from the Population Education Register,[22] and marital status, region of residence, age, and sex from the Danish Population Register.[23] Each person in Denmark is assigned a unique person number, enabling accurate linkage between registers.

Outcomes of Interest

The primary outcome of interest was factors associated with statin discontinuation at 1, 2, and 4 years after initiating statins. The second outcome of interest was the proportion of patients discontinuing statins in the first year of use (early discontinuation) yearly between 2008 and 2015. Third, we conducted a post-hoc time-to-event analysis investigating factors associated with discontinuation across 4 years.

Definitions

Discontinuation at 1, 2, and 4 Years

We identified all persons, aged 70 years or older, who initiated statins between January 1, 2008, and December 31, 2012, and who had not received a statin prescription within the previous 2 years. Statin initiation and use was based on prescriptions filled at a pharmacy.[24] Early discontinuation was defined as not filling a statin prescription in the 365-day period after the initial prescription. In people not discontinuing at 1 year, we identified those who discontinued between 1 and 2 years after initial use (did not fill statin prescription 366 to 730 days after the first prescription). In those who did not discontinue by year 2, we identified those who discontinued in the period between 2 and 4 years after initial use (did not fill a statin prescription in the periods 731 to 1095 days *and* 1096 to 1460 days after their initial prescription). Baseline characteristics were assessed at the date of the first statin prescription for all analyses. Patients who died or migrated before the 1-, 2-, or 4-year mark were excluded. Those who died in the second year were included in the first-year analysis, while those dying in the third or fourth year were included in the first- and second-year analysis.

To contextualize our findings, we described the overall annual rate of early discontinuation from 2008 to 2015.

Discontinuation in Post-Hoc Time-to-Event Analysis

We identified statin initiators between 2008 and 2012 (as above) and followed them for up to 4 years. The definition of discontinuation was not filling a statin prescription during the duration of the previous prescription plus a 180-day grace period.

Analysis of Factors Associated With Discontinuation

We were interested in the following factors: age, sex, indication for use (primary [no history of a CV event, coronary artery disease, or stroke] vs secondary [previous CV event, coronary artery disease, or stroke] prevention), individual comorbidities, Charlson comorbidity index score, concomitant medications, number of concomitant medications, marital status, education level, and region of residence. Definitions are provided in Supplementary Table S1. Factors of interest (and their categories) are provided in Table 1 and Supplementary Table S2.

For each time point, we first conducted univariable analyses and reported the crude odds of discontinuation (using the odds ratio [OR] and 95% confidence interval [CI] for each factor), as well as multivariable logistic regression incorporating all factors into one model.

In the post-hoc competing risk regression model, the association between factors of interest (described above) and the rate of discontinuation was investigated using a Fine-Gray model and reporting hazard ratios and 95% CIs for each factor. We incorporated all factors into the model and included death as a competing risk. We also plotted a cumulative incidence curve, incorporating the competing risk of death.

Ethics

The Danish Data Protection Authority approved the study (registration number 18/15245). Research Ethics Board approval was not required, according to Danish law, as the study was based solely on register data.

RESULTS

Between 2008 and 2012, we identified 83 788 new users of statins. The overall rate of discontinuation across the first 4 years of use was 32%. During the first year of use, 10 962 (13%) were considered to discontinue their statin, and there were 2099 deaths/migrations. Between 1 and 2 years, another 8431 (12%) were considered to discontinue their statin (and there were 6062 deaths/migrations). Finally, 7492 (13%) were considered to discontinue their statin between 2 and 4 years. Of those discontinuing statins in the first year, 30.4% restarted between year 2 and 4. For those discontinuing statins at 2 years, 23.2% restarted between year 3 and 4. The proportion of early discontinuers ranged from 14% to 17% for primary prevention and from 9% to 12% for secondary prevention (Supplementary Figure S1).

The characteristics of the study population are outlined in Table 1, according to each time point (information on

Table 1. Baseline characteristics at each time point

Characteristics	Early (<1 y)			1-2 y			2-4 y		
	Overall (n = 83 788)	Continuers (n = 72 826)	Discontinuers (n = 10 962)	Overall (n = 70 727)	Continuers (n = 62 296)	Discontinuers (n = 8431)	Overall (n = 56 234)	Continuers (n = 48 742)	Discontinuers (n = 7492)
Median Age, y (IQR)	75 (72-80)	75 (72-80)	76 (72-80)	75 (72-80)	75 (72-80)	76 (72-80)	75 (72-79)	75 (72-79)	76 (72-80)
70-74	36 629 (43.7)	32 097 (44.1)	4532 (41.3)	31 657 (44.8)	28 129 (45.2)	3528 (41.8)	26 622 (47.3)	23 410 (48.0)	3212 (42.9)
75-79	24 666 (29.4)	21 463 (29.5)	3203 (29.2)	20 902 (29.6)	18 450 (29.6)	2452 (29.1)	16 824 (29.9)	14 603 (30.0)	2221 (29.6)
80-84	14 516 (17.3)	12 488 (17.1)	2028 (18.5)	11 960 (16.9)	10 404 (16.7)	1556 (18.5)	8885 (15.8)	7559 (15.5)	1326 (17.7)
85-89	6431 (7.7)	5480 (7.5)	951 (8.7)	5107 (7.2)	4405 (7.1)	702 (8.3)	3329 (5.9)	2733 (5.6)	596 (8.0)
90-94	1391 (1.7)	1170 (1.6)	221 (2.0)	1004 (1.4)	833 (1.3)	171 (2.0)	544 (1.0)	417 (0.9)	127 (1.7)
≥95	155 (0.2)	128 (0.2)	27 (0.2)	97 (0.1)	75 (0.1)	22 (0.3)	30 (0.1)	20 (0.0)	10 (0.1)
Female	47 033 (56.1)	40 429 (55.5)	6604 (60.2)	39 381 (55.7)	34 292 (55.0)	5089 (60.4)	31 261 (55.6)	26 688 (54.8)	4573 (61.0)
Indication									
Primary	51 192 (61.1)	43 628 (59.9)	7564 (69.0)	42 831 (60.6)	37 514 (60.2)	5317 (63.1)	34 846 (62.0)	30 075 (61.7)	4771 (63.7)
Secondary	32 596 (38.9)	29 198 (40.1)	3398 (31.0)	27 896 (39.4)	24 782 (39.8)	3114 (36.9)	21 388 (38.0)	18 667 (38.3)	2721 (36.3)
Charlson comorbidity score									
Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
0	34 959 (41.7)	29 823 (41.0)	5136 (46.9)	29 518 (41.7)	25 858 (41.5)	3660 (43.4)	24 667 (43.9)	21 370 (43.8)	3297 (44.0)
1-2	35 800 (42.7)	31 552 (43.3)	4248 (38.8)	30 542 (43.2)	27 018 (43.4)	3524 (41.8)	24 040 (42.7)	20 851 (42.8)	3189 (42.6)
3-4	10 629 (12.7)	9339 (12.8)	1290 (11.8)	8768 (12.4)	7745 (12.4)	1023 (12.1)	6335 (11.3)	5474 (11.2)	861 (11.5)
≥5	2400 (2.9)	2112 (2.9)	288 (2.6)	1899 (2.7)	1675 (2.7)	224 (2.7)	1192 (2.1)	1047 (2.1)	145 (1.9)
Concomitant medication use									
Antiplatelets	46 463 (55.5)	41 293 (56.7)	5170 (47.2)	39 712 (56.1)	35 283 (56.6)	4429 (52.5)	30 932 (55.0)	26 981 (55.4)	3951 (52.7)
ACEIs or ARBs	40 637 (48.5)	35 826 (49.2)	4811 (43.9)	34 730 (49.1)	30 829 (49.5)	3901 (46.3)	27 768 (49.4)	24 286 (49.8)	3482 (46.5)
β-Blockers	26 161 (31.2)	23 251 (31.9)	2910 (26.5)	22 419 (31.7)	19 995 (32.1)	2424 (28.8)	17 704 (31.5)	15 471 (31.7)	2233 (29.8)
CCBs	25 206 (30.1)	22 158 (30.4)	3048 (27.8)	21 465 (30.3)	19 056 (30.6)	2409 (28.6)	17 052 (30.3)	14 850 (30.5)	2202 (29.4)
Anticoagulants	8022 (9.6)	7096 (9.7)	926 (8.4)	6792 (9.6)	6074 (9.8)	718 (8.5)	5276 (9.4)	4636 (9.5)	640 (8.5)
Oral AHGs	9201 (11.0)	8152 (11.2)	1049 (9.6)	7862 (11.1)	7116 (11.4)	746 (8.8)	6269 (11.1)	5573 (11.4)	696 (9.3)
Insulin	1758 (2.1)	1539 (2.1)	219 (2.0)	1463 (2.1)	1307 (2.1)	156 (1.9)	1052 (1.9)	950 (1.9)	102 (1.4)
Dementia drugs	722 (0.9)	651 (0.9)	71 (0.6)	570 (0.8)	514 (0.8)	56 (0.7)	368 (0.7)	317 (0.7)	51 (0.7)
Antidepressants	11 839 (14.1)	10 468 (14.4)	1371 (12.5)	9946 (14.1)	8875 (14.2)	1071 (12.7)	7535 (13.4)	6521 (13.4)	1014 (13.5)
Concomitant medications									
Median (IQR)	6 (4-9)	6 (4-9)	6 (4-9)	6 (4-9)	6 (4-9)	6 (4-9)	6 (4-9)	6 (4-9)	6 (4-9)
0-4	26 317 (31.4)	22 394 (30.8)	3923 (35.8)	22 087 (31.2)	19 374 (31.1)	2713 (32.2)	18 341 (32.6)	15 881 (32.6)	2460 (32.8)
5-9	39 761 (47.5)	34 783 (47.8)	4978 (45.4)	33 887 (47.9)	29 905 (48.0)	3982 (47.2)	27 073 (48.1)	23 576 (48.4)	3497 (46.7)
≥10	17 710 (21.1)	15 649 (21.5)	2061 (18.8)	14 753 (20.9)	13 017 (20.9)	1736 (20.6)	10 820 (19.2)	9285 (19.0)	1535 (20.5)
Marital status									
Single/widowed	25 077 (29.9)	21 782 (29.9)	3295 (30.1)	20 964 (29.6)	18 390 (29.5)	2574 (30.5)	16 098 (28.6)	13 795 (28.3)	2303 (30.7)
Married	50 295 (60.0)	43 954 (60.4)	6341 (57.8)	42 913 (60.7)	38 002 (61.0)	4911 (58.2)	34 871 (62.0)	30 458 (62.5)	4413 (58.9)
Divorced	8407 (10.0)	7081 (9.7)	1326 (12.1)	6841 (9.7)	5897 (9.5)	944 (11.2)	5258 (9.4)	4483 (9.2)	775 (10.3)

(Continues)

Table 1 (Contd.)

Characteristics	Early (<1 y)			1-2 y			2-4 y		
	Overall (n = 83 788)	Continuers (n = 72 826)	Discontinuers (n = 10 962)	Overall (n = 70 727)	Continuers (n = 62 296)	Discontinuers (n = 8431)	Overall (n = 56 234)	Continuers (n = 48 742)	Discontinuers (n = 7492)
Education, y									
7-10	41 768 (49.8)	36 623 (50.3)	5145 (46.9)	35 554 (50.3)	31 558 (50.7)	3996 (47.4)	28 386 (50.5)	24 777 (50.8)	3609 (48.2)
11-12	6256 (7.5)	5386 (7.4)	870 (7.9)	5253 (7.4)	4583 (7.4)	670 (7.9)	4184 (7.4)	3615 (7.4)	569 (7.6)
≥13	10 566 (12.6)	9073 (12.5)	1493 (13.6)	8866 (12.5)	7707 (12.4)	1159 (13.7)	7159 (12.7)	6106 (12.5)	1053 (14.1)
Unknown	25 198 (30.1)	21 744 (29.9)	3454 (31.5)	21 054 (29.8)	18 448 (29.6)	2606 (30.9)	16 505 (29.4)	14 244 (29.2)	2261 (30.2)

Note. Data are given as number (percentage), unless otherwise indicated.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AHG, antihyperglycemic; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQR, interquartile range.

Figure 1. Cumulative incidence of discontinuation over 4 years (curve begins at 180 days due to grace period).

individual diseases and region of residence not included; Supplementary Table S2 provides the full table). The characteristics listed are those at baseline (ie, initiation of statin). Figure 1 displays the cumulative incidence of discontinuation across 4 years. Figure 2 displays the proportion of people who discontinued statins in each age group.

The adjusted ORs and 95% CIs are displayed in Figure 3 (early) and Figure 4 (at 2 and 4 years). Individual diseases and region are not included in these Figures (Supplementary Table S3 provides full results). The odds of discontinuation consistently increased with each increasing age group at all time points. Men were less likely to discontinue statins at all time points. Using a statin for secondary prevention was associated with reduced odds of discontinuation for early use and after 4 years compared to primary prevention. At 2 years, secondary prevention was associated with reduced odds of discontinuation, but the difference was not statistically significant. Looking at specific diseases, having a history of myocardial infarction was associated with reduced odds of discontinuation at each time point, whereas stroke was associated with reduced odds of discontinuation at 1 and 2 years, but not at 4 years. Having dementia was associated with reduced odds of discontinuation at all time points.

Figure 2. Proportion of patients in each age group who discontinued statins over 4 years.

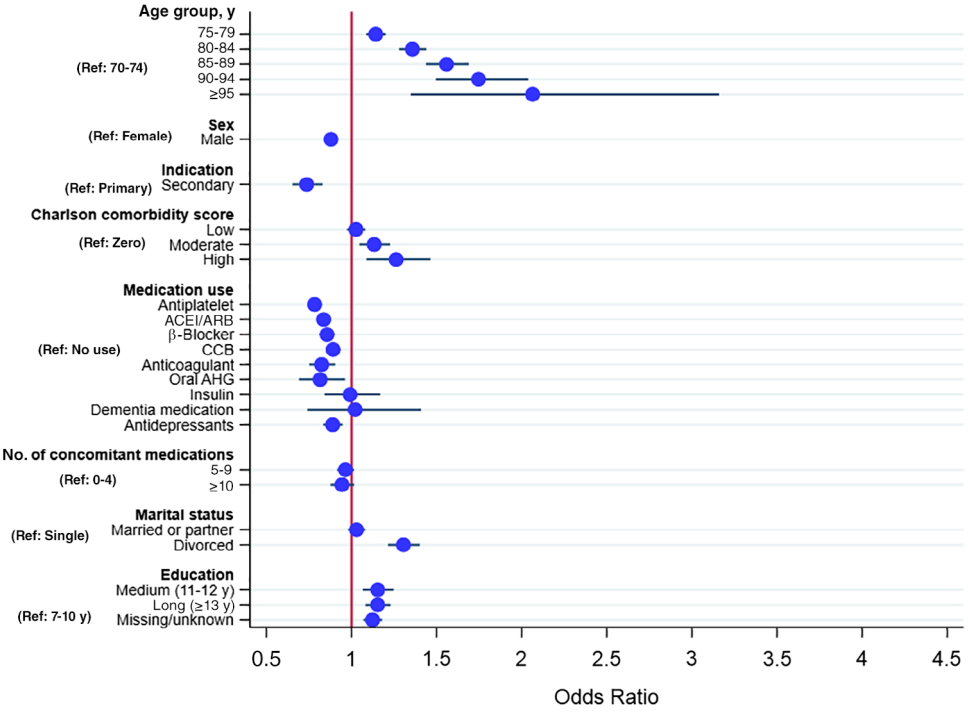

Figure 3. Factors associated with early statin discontinuation (adjusted odds ratios and 95% confidence intervals). ACEI indicates angiotensin-converting enzyme inhibitor; AHG, antihyperglycemic; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Ref, reference category. [Color figure can be viewed at wileyonlinelibrary.com]

Having a moderate or high comorbidity score was associated with increased odds of early discontinuation. At 2 years, only a high score was associated with increased odds of discontinuation, while at 4 years, low and moderate scores were associated with increased odds of discontinuation. In terms of concomitant medications, use of CV therapies was associated with reduced likelihood of statin discontinuation at all time points. Antidepressant use was associated with reduced odds of discontinuation at 1 and 2 years, but not at 4 years. The total number of concomitant medications was not associated with odds of discontinuation in the first year. However, at both 2 and 4 years, use of 10 or more medications was associated with increased odds of discontinuation compared to use of 0 to 4 medications. We also investigated sociodemographic factors and found that being divorced and increasing levels of education were generally associated with increased odds of discontinuation at all time points. Regional differences in discontinuation were observed at all time points. Results from the competing risk regression model (post-hoc analysis) were similar to the main analysis (Supplementary Table S4); however, the associations of discontinuation with increasing age and medication use were attenuated.

DISCUSSION

In this nationwide register study, discontinuation of statins was common in new users older than 70 years, with approximately 32% having discontinued therapy after 4 years. These results are consistent with existing research on rates of statin discontinuation[18] in older incident users, although our rate of early statin discontinuation was lower than what was reported in a 2018 systematic review.[18] This may reflect differences in the definition of discontinuation, with our definition being conservative relative to others.

Several limitations with our study need to be acknowledged. Given the many factors investigated at each time point, there is a possibility of type I errors. Further, we could not capture the specific reason for discontinuation and do not know whether a physician was consulted or the patient discontinued on his/her own. We investigated factors prespecified by our team and available in the registries. However, there may be other factors associated with discontinuation that we did not evaluate. We may have captured some people who were previously on statins and restarted. However, we used a 2-year grace period at the beginning of the follow-up period to protect against this. We used a conservative definition of discontinuation to avoid categorizing people with irregular filling patterns as discontinuing. However, it is possible that we classified those with irregular filling patterns as discontinuing. Approximately 30% of those discontinuing in the first year restarted statins. Restarters may represent those stopping on their own and restarting after discussion with a prescriber or those with extremely irregular filling patterns. We excluded people who died during the study period, as we did not want to capture individuals where death was the reason for discontinuation. However, in doing this, we also likely excluded some people whose statin was discontinued purposefully in the period leading up to their death. It is possible that these people tended to be in poorer health (ie, more comorbidities, more medications) than those who did not die. Thus, by excluding these persons instead of classifying them as discontinuers, some of our results on (eg, comorbidity status) may have been biased toward the null.

Previous studies have also reported that increasing age is a predictor of statin discontinuation.[19] Although age alone may

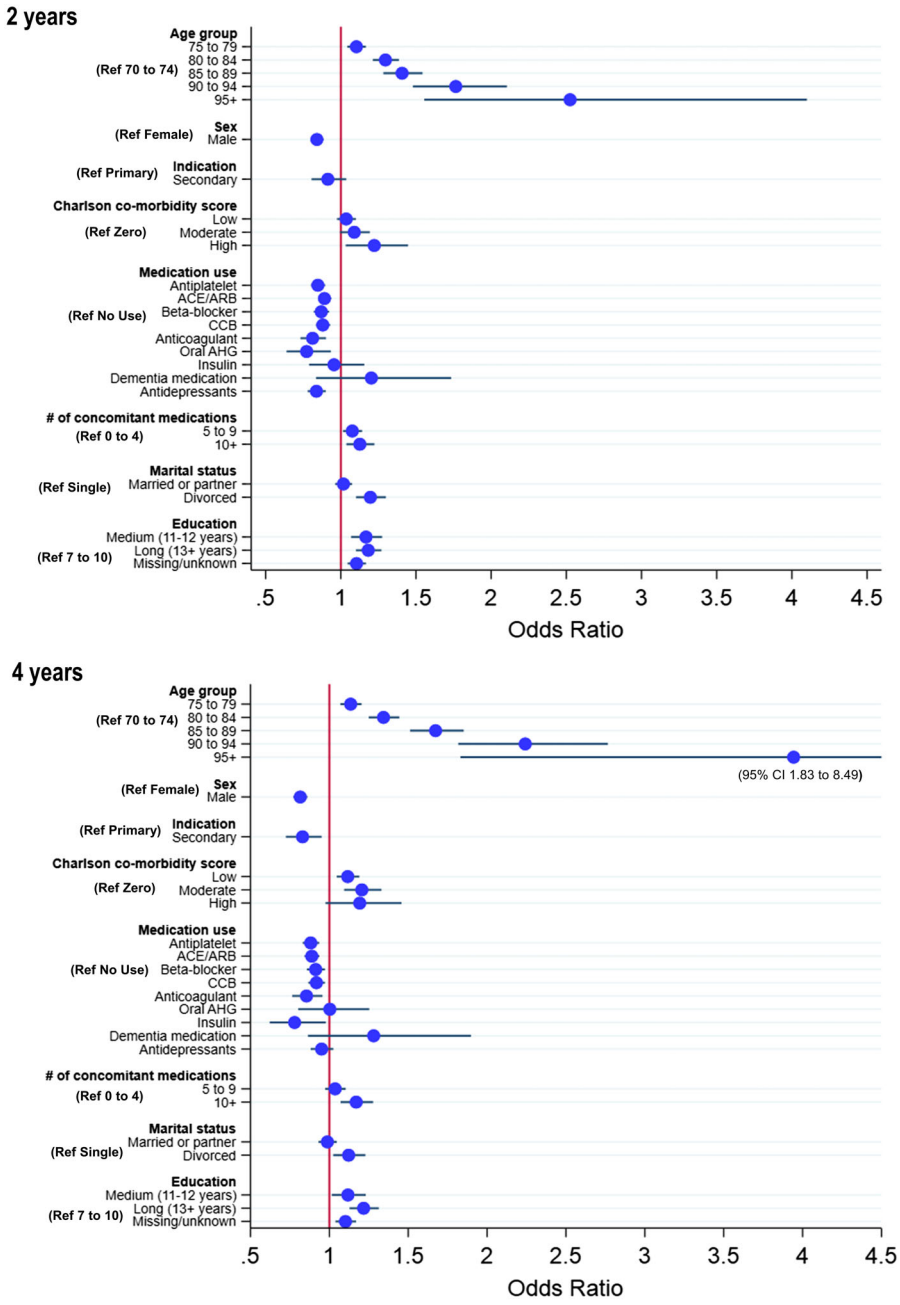

Figure 4. Factors associated with statin discontinuation at 2 and 4 years (adjusted odds ratios and 95% confidence intervals). ACE-I indicates angiotensin-converting enzyme inhibitor; AHG, antihyperglycemic; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; Ref, reference category. [Color figure can be viewed at wileyonlinelibrary.com]

not be an appropriate trigger of statin discontinuation,[5,25] it is possible that with advanced age and increasing uncertainty surrounding the benefit of statins, the indication becomes less compelling. It has also been suggested that total cholesterol may decline in the last years of life, which could prompt discontinuation.[26] The effect of burden of medication use and comorbidity status has not been widely explored in relation to statin discontinuation. One previous study found that discontinuation rates were modestly increased with increasing frailty in prevalent users (>1 year of use)[19] while another found no effect of comorbidity status.[17] In our study, a moderate or high comorbidity score was generally associated with a modest increased likelihood of discontinuation, while a high burden of medication use was associated with a modest increase in odds of discontinuation at 2 and 4 years after initiation. Our findings on discontinuation in secondary vs primary prevention are also consistent with previous research.[18] Recent reviews have highlighted limitations in evidence surrounding statin use in older people for primary prevention, raising questions surrounding benefits and harms in this population.[27,28] Discontinuation may be less likely in secondary prevention because the indication for statins is more compelling or because those with a history of manifest CVD are more motivated to continue therapy.[15,18]

Survey and interview data show that prescribers appear to consider statin discontinuation in the context of low perceived benefit (ie, primary prevention), low life expectancy, frailty, polypharmacy, and multiple comorbidities.[29,30] Consistent with this research, our findings suggest an influence of age, indication, medication use, and burden of comorbidities on discontinuation. Thus, it is possible that the discontinuation observed could at least partly reflect a purposeful and considered discontinuation process.

We observed lower associated odds of discontinuation in persons with concomitant CV medication use and persons with dementia. Previous studies have reported that concomitant CV medication use reduces likelihood of discontinuation.[15,31] This may reflect patients with a stronger commitment to medical treatment[15] or patients with few other comorbidities outside of CV problems. Lower rates of early statin discontinuation have previously been reported for people with dementia, although higher rates of discontinuation have been found with prevalent use.[13,32] Our findings on the influence of dementia at 2 and 4 years are discordant with previous reports. The reasons for this are unclear, although it is possible that the difference is a result of our excluding those who died—these persons may have had more advanced dementia and may have been more likely to discontinue therapy. While statin discontinuation has been examined in persons with dementia,[32,33] the influence of severity has not been explored, to our knowledge.

Given rates of statin use in older people,[34] potential discontinuation is likely an issue frequently encountered by healthcare practitioners. This underscores the need for clinical evidence surrounding statin initiation as well as discontinuation in this age group, and guidance on shared decision-making. Given the high rate of discontinuation in older statin initiators, it is possible that statins may be started in some persons in a manner not consistent with their goals, preferences, and health context, leading to subsequent and possibly avoidable discontinuation. Further research on discussions surrounding statin initiation and discontinuation will likely help us better understand how initiation and discontinuation decisions can best be made in older people.

In conclusion, statin discontinuation is common in older persons in the first 4 years after initiation. Such discontinuation is positively associated with multiple factors, in particular increasing age, but also increasing comorbidity and high medication use, while using statins for secondary prevention and use of concomitant CV therapies are associated with reduced odds of statin discontinuation. Future research should help clarify reasons for, and discussions about, statin initiation and discontinuation among older people specifically, as well as investigate clinical outcomes following statin discontinuation. This will help inform and facilitate shared decision-making approaches surrounding statin use in this population.

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Authorship Contributions

All authors conceived and designed the study. W.T. conducted analysis and drafted the manuscript. All authors provided critical revisions and feedback on the manuscript. All authors approved the final manuscript for submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Description of factors of interest included for the study.

Supplementary Figure S1. Proportion of early discontinuers by year and indication.

Supplementary Table S2. Baseline characteristics at each time point.

Supplementary Table S3. Association between discontinuation and factors of interest at each time point (crude and full model).

Supplementary Table S4. Association between discontinuation and factors of interest over 4 years using the Fine and Gray model.