Statins in older Danes: factors associated with discontinuation over the first four years of use

Running title: Statin discontinuation in older Danes

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Impact statement: This work is novel. Previous studies on this topic have focused primarily on the first year after initiation and/or have included limited numbers of factors of interest. We investigated statin discontinuation over the first four years of use, and examined factors of particular importance in older persons, such as polypharmacy and multi-morbidity. We identified several factors associated with increased likelihood of discontinuation in initiators of statins across four years. These findings shed light on how and why statins may be discontinued in this population. Our findings also suggest that statin discontinuation is a situation commonly encountered when caring for older persons, which underscores the need for more clinical evidence and guidance on this topic.
Abstract

Background and objective: Despite limited evidence on benefits, use of statins in the oldest old is considerable. We investigated factors associated with statin discontinuation in new statin users ≥70 years of age within the first four years of use.


Population/setting: All Danish persons ≥70 years of age, initiating statin treatment.

Measurements: Rates and predictors of statin discontinuation after one year (early), two years, and four years. Predictors of discontinuation were estimated using logistic regression.

Results: We included 83,788 statin initiators. At one year, 13% had discontinued their treatment, while another 12% and 13% discontinued after two and four years. The overall discontinuation rate over four years was 32%. Increasing age was associated with discontinuation at all timepoints (aOR 2.06 [95% CI 1.35 to 3.16] at one year, aOR 3.94 [95% CI 1.83 to 8.49] at four years, comparing age 95+ to age 70 to 74). Further, higher co-morbidity scores and use of 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 one year (aOR 0.74 [95% CI 0.65 to 0.83]) and at four years (aOR 0.83 [95% CI 0.72 to 0.95]), along with concomitant use of cardiovascular therapies. The annual proportion of early discontinuers ranged from 14 to 17% for primary prevention and 9 to 12% for secondary prevention between 2008 and 2015.

Discussion: Statin discontinuation within the first four years after initiation appeared to be influenced most strongly by age, and may also be influenced by co-morbidity, polypharmacy, use for secondary
prevention, and concomitant cardiovascular medication use. Future research should clarify reasons and discussions around statin discontinuation and initiation among older persons, to provide additional insight on this topic.

**Keywords:** Statins, medication discontinuation, polypharmacy
**Introduction**

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 the oldest old (aged 80+), are poorly represented in most clinical trials of statins.\(^5\)\(^,\)\(^6\) Despite a recent meta-analysis\(^7\) in persons age 75+, the efficacy and safety of statins in this age group is still largely unclear, particularly for primary prevention and among those who are frail or have multiple co-morbidities.\(^8\) 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 history, co-morbidities, 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, though these studies have mostly focused on the general population\(^13\)\(^-\)\(^15\), either excluding those 80+ or grouping them together.\(^16\)\(^-\)\(^18\) Existing studies in older persons have further been limited 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 from an adherence or persistence standpoint\(^13\)\(^,\)\(^16\), failing to acknowledge that there may be valid reasons for statin discontinuation in older persons (e.g. based on the burden of medication use, or in the context of frailty) and subsequently not exploring this further. Given the limited evidence on this topic, we sought to evaluate whether different factors were associated with statin discontinuation within the first four 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 (≥70 years).

**Data source**

We retrieved prescription data from the Danish National Prescription Register\(^{20}\), 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 one, two, and four 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.

**Definitions**

*Discontinuation at one, two, four years*

We identified all persons aged 70 or older who initiated statins between January 1, 2008 and December 31, 2012, and who had not received a statin prescription within the previous two years. Early discontinuation was defined as not filling a statin prescription in the 365-day period after the initial prescription. In people not discontinuing at one year, we identified those who discontinued between one and two 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 two, we identified those who discontinued in the period between two and four years after initial use (did not fill a statin prescription in the periods 731 to 1,095 days and 1,096 to 1,460 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 one, two, or four year mark were excluded.

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

**Analysis of factors associated with discontinuation**

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

For each timepoint, 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.

**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 four years of use was 32%. During the first year of use, 10,962 (13%) were considered to discontinue their statin, and there were 2,099 deaths/migrations. Between one and two years, another 8,431 (12%) were considered to discontinue their statin (and there were 6,062 deaths/migrations). Finally, 7,492 (13%) were considered to discontinue their statin between two and four years. Figure 1 shows the proportion of persons considered early discontinuers each year from 2008 to 2015, broken down by primary and secondary prevention. The proportion of early discontinuers ranged from 14 to 17% for primary prevention and 9 to 12% for secondary prevention.

The characteristics of the study population are outlined in Table 1, according to each timepoint (information on individual diseases and region of residence not included; see Supplementary Table S2 for full table). The characteristics listed are those at baseline (i.e. initiation of statin). 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 two and four years). Individual diseases and region are not included in these Figures—see Supplementary Table S3 for full results. The odds of discontinuation consistently increased with each increasing age group at all time points. Men were more likely to discontinue statins at all timepoints. Using a statin for secondary prevention was associated with reduced odds of discontinuation for early use and after four years compared to primary prevention. At two 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 (MI) was associated with reduced odds of discontinuation at each timepoint, whereas stroke was associated with reduced odds of discontinuation at one and two years, but not at four years. Having dementia was associated with reduced odds of discontinuation at all timepoints.
Having a moderate or high co-morbidity score was associated with increased odds of early discontinuation. At two years, only a high score was associated with increased odds of discontinuation, while at four years, low and moderate scores were associated with increased odds of discontinuation. In terms of concomitant medications, use of cardiovascular therapies was associated with reduced likelihood of statin discontinuation at all timepoints. Antidepressant use was associated with reduced odds of discontinuation at one and two years, but not at four years. The total number of concomitant medications was not associated with odds of discontinuation in the first year. However, at both two and four years, use of 10 or more medications was associated with increased odds of discontinuation compared to use of 0-4. 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 timepoints. Regional differences in discontinuation were observed at all timepoints.

**Discussion**

In this nationwide register study, discontinuation of statins was common in new users aged 70+, with approximately 32% of users having discontinued therapy after four years. The rate of early discontinuation remained relatively stable between 2008 and 2015. These results are consistent with previously published reports on rates of statin discontinuation in incident older persons though our rate of early statin discontinuation was lower than what was reported in a 2018 systematic review. This may reflect differences in the definition of discontinuation (our definition of discontinuation was conservative relative to other methods).

Increasing age appeared to be the strongest predictor of statin discontinuation, particularly beyond age 90. Factors consistent with a higher burden of care (e.g. use of 10+ medications, moderate or high co-
morbidity score) may also influence statin discontinuation, though an association with high medication burden was only present in the period two to four years after initiation. While the associations were modest, these findings suggest that increasing complexity and burden of care may increase likelihood of statin discontinuation in older persons, and that they may become increasingly important beyond one year after initiation. Using a statin for secondary prevention was associated with reduced odds of discontinuation. We also found that people taking concomitant CV therapies may be less likely to discontinue statin therapy across the first four years of use. This is reflective of our findings surrounding secondary prevention, since people taking statins for secondary prevention would generally be taking other CV therapies. Finally, we observed that men, and those with a diagnosis of dementia, had a reduced likelihood of discontinuation at all timepoints.

Several limitations need to be acknowledged. We could not capture the reason for discontinuation and do not know whether a physician was consulted about discontinuation or the patient discontinued on their own. Further, we may have captured some people who were previously on statins and restarted. However, we used a two-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 very irregular filling patterns as discontinuing. 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 in the period before their death. It is possible that these people tended to be in poorer health (i.e. more co-morbidities, more medications) than those who did not die. This could have biased some of our results on (e.g. co-morbidity status, number of concomitant medications) towards the null.
Previous studies have reported increasing age as a predictor of statin discontinuation but typically grouped the oldest old together (e.g. all persons aged 80+). We found that the likelihood of discontinuation continues to increase with each increasing age group beyond age 70. These findings are in line with those of Gulliford et al.\(^5\) Though age may not be appropriate as a trigger of statin discontinuation\(^5,24\) it is possible that with advanced age and increasing uncertainty surrounding the benefit of statins, the indication becomes less compelling, prompting discontinuation. The effect of burden of medication use and co-morbidity status has not been widely explored in relation to statin discontinuation. Gulliford et al. found that discontinuation rates were modestly increased with increasing frailty in prevalent users (\(>1\) year of use)\(^19\) while Noaman et al. found no effect of co-morbidity status.\(^17\) In our study, a moderate or high co-morbidity score was 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 two and four years after initiation. This suggests that increasing complexity and burden of care may increase likelihood of statin discontinuation in older persons. Our findings on discontinuation in secondary versus primary prevention are consistent with previous research.\(^18\) 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.\(^15,18\) Our results on age, indication, co-morbidity, and concomitant medication are at least partly in line with a purposeful discontinuation process. Survey and interview data show that GPs consider offering statin discontinuation in the context of limited life expectancy, frailty, polypharmacy, and primary prevention\(^25,26\) which is consistent with factors we found to be associated with statin discontinuation. 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.\textsuperscript{15,27} This may reflect patients with a stronger commitment to medical treatment\textsuperscript{15} or patients with few other co-morbidities outside of CV problems. Yang et al. surmised that taking medication unrelated to CV problems may make statin discontinuation more likely, since there may be greater motivation to manage other problems.\textsuperscript{15} Lower rates of early statin discontinuation have previously been reported for people with dementia, though higher rates of discontinuation have been found with prevalent use.\textsuperscript{13,28} Our findings on the influence of dementia at two and four years following initiation are discordant with previous reports. The reasons for this are unclear, though 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,\textsuperscript{26,29} the influence of severity has not been explored to our knowledge.

Statin discontinuation is thus common in new users over 70 years of age. Given rates of statin use in this population,\textsuperscript{30} it is therefore 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 in this area. Statin use should be individualized and based on values and preferences in all age groups, but particularly among the oldest old. While statin treatment should likely not be discontinued based on age alone, the uncertainty surrounding the benefit of statins grows with advancing age (i.e. beyond 85 or 90 years of age), which may prompt consideration of discontinuation. Prescribers appear to consider statin discontinuation in the context of low life expectancy, frailty, polypharmacy, multiple co-morbidities, and with low perceived benefit (i.e. primary prevention).\textsuperscript{25,26} The discontinuation observed in register-based studies could therefore at least partly reflect a purposeful and considered decision based on these factors rather than simply lack of “persistence” or adherence. It is also possible that increasing medication burden and increasing co-morbidity may lead a person to prefer discontinuation (either in collaboration with a healthcare
provider or on their own). Thus, the decision to discontinue would be consistent with their goals and preferences. Given the high rate of discontinuation in older statin initiators, it is possible that statins may be initiated in some persons in a manner not consistent with their goals and preferences, leading to subsequent and possibly avoidable discontinuation. Further research will likely help us better understand how initiation and discontinuation decisions can best be made in the oldest old.

In conclusion, statin discontinuation is common in older persons within the first four years of after initiation. Statin discontinuation may be influenced by multiple factors in older persons. Increasing age appears to have the biggest influence on increasing likelihood of statin discontinuation, while increasing co-morbidity and use of 10 or more medications may also be associated with an increased likelihood of discontinuation. Use for secondary prevention and use of concomitant CV therapies were associated with reduced odds of statin discontinuation. This points, at least in part, to the possibility of purposeful statin discontinuation decisions based on person-specific factors and an acknowledgement of limitations in evidence of benefit following statin use among the oldest old. Future research should help clarify reasons for statin initiation and discontinuation among the oldest old specifically, and investigate clinical outcomes following statin discontinuation. This will help inform and facilitate decision-making surrounding statins in clinical practice.

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Conflict of interest

The authors have no conflicts of interest to declare.

Authorship contributions
All authors conceived and designed the study. WT conducted analysis and drafted the manuscript. All authors provided critical revisions and feedback on the manuscript. All authors approved the final manuscript for submission. Morten Olesen helped with data management and STATA advice. The authors would like to acknowledge and thank him for his assistance.

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<thead>
<tr>
<th>Age category</th>
<th>Less than 1 year</th>
<th>1 to 2 years</th>
<th>2 to 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;70)</td>
<td>(n=83,788)</td>
<td>(n=72,286)</td>
<td>(n=10,962)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>75 (72-80)</td>
<td>75 (72-80)</td>
<td>75 (72-80)</td>
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<tr>
<td>70 to 74</td>
<td>36,629 (43.7%)</td>
<td>32,097 (44.1%)</td>
<td>4,532 (41.3%)</td>
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<tr>
<td>75 to 79</td>
<td>24,666 (29.4%)</td>
<td>21,463 (29.5%)</td>
<td>3,203 (29.2%)</td>
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<td>80 to 84</td>
<td>14,516 (17.3%)</td>
<td>12,488 (17.1%)</td>
<td>2,028 (18.5%)</td>
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<td>85 to 89</td>
<td>6,431 (7.7%)</td>
<td>5,480 (7.8%)</td>
<td>951 (8.7%)</td>
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<td>90 to 94</td>
<td>1,391 (1.7%)</td>
<td>1,170 (1.6%)</td>
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<tr>
<td>95+</td>
<td>155 (0.2%)</td>
<td>128 (0.2%)</td>
<td>27 (0.2%)</td>
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**Concomitant medication use**

<table>
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<tr>
<th>Medication category</th>
<th>Overall</th>
<th>Continuers</th>
<th>Discontinuers</th>
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</thead>
<tbody>
<tr>
<td>ACEIs or ARBs</td>
<td>46,465 (53.5%)</td>
<td>41,293 (56.7%)</td>
<td>5,170 (47.2%)</td>
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<tr>
<td>Beta-blockers</td>
<td>40,637 (48.5%)</td>
<td>35,826 (49.2%)</td>
<td>4,811 (43.9%)</td>
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<tr>
<td>CCBs</td>
<td>26,161 (31.2%)</td>
<td>23,251 (31.9%)</td>
<td>2,910 (26.5%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>25,206 (30.1%)</td>
<td>22,158 (30.4%)</td>
<td>3,048 (27.8%)</td>
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<tr>
<td>Oral AHGs</td>
<td>8,022 (9.0%)</td>
<td>7,096 (9.7%)</td>
<td>926 (8.4%)</td>
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<tr>
<td>Insulin</td>
<td>9,201 (11.0%)</td>
<td>8,152 (11.2%)</td>
<td>1,049 (9.6%)</td>
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<td>Dementia drugs</td>
<td>1,758 (2.1%)</td>
<td>1,539 (2.1%)</td>
<td>219 (2.0%)</td>
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<tr>
<td>Antidepressants</td>
<td>722 (0.9%)</td>
<td>651 (0.9%)</td>
<td>71 (0.6%)</td>
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<tr>
<td>Overall</td>
<td>11,839 (14.1%)</td>
<td>10,468 (14.4%)</td>
<td>1,371 (12.5%)</td>
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**Concomitant medications**

<table>
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<th>Medication category</th>
<th>Overall</th>
<th>Continuers</th>
<th>Discontinuers</th>
</tr>
</thead>
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<tr>
<td>Median (IQR)</td>
<td>6 (4-9)</td>
<td>6 (4-9)</td>
<td>6 (4-9)</td>
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<tr>
<td>0 to 4</td>
<td>26,317 (31.4%)</td>
<td>22,394 (30.8%)</td>
<td>3,923 (35.8%)</td>
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<tr>
<td>5 to 9</td>
<td>39,761 (47.5%)</td>
<td>34,783 (47.8%)</td>
<td>4,978 (45.4%)</td>
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<tr>
<td>10+</td>
<td>17,710 (21.1%)</td>
<td>15,649 (21.5%)</td>
<td>2,061 (18.8%)</td>
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**Marital status**

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<th>Marital status</th>
<th>Overall</th>
<th>Continuers</th>
<th>Discontinuers</th>
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</thead>
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<tr>
<td>Single/widowed</td>
<td>25,077 (29.0%)</td>
<td>21,782 (29.9%)</td>
<td>3,295 (30.1%)</td>
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<tr>
<td>Married</td>
<td>50,259 (60.4%)</td>
<td>43,954 (57.8%)</td>
<td>6,341 (57.9%)</td>
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<tr>
<td>Divorced</td>
<td>8,407 (10.0%)</td>
<td>7,081 (9.7%)</td>
<td>1,326 (12.1%)</td>
</tr>
</tbody>
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**Education**

<table>
<thead>
<tr>
<th>Education level</th>
<th>Overall</th>
<th>Continuers</th>
<th>Discontinuers</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 to 10 years</td>
<td>41,768 (49.8%)</td>
<td>36,623 (50.3%)</td>
<td>5,145 (46.9%)</td>
</tr>
<tr>
<td>11 to 12 years</td>
<td>6,256 (7.5%)</td>
<td>5,386 (7.4%)</td>
<td>870 (7.9%)</td>
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<tr>
<td>13+ years</td>
<td>10,566 (12.6%)</td>
<td>9,073 (12.5%)</td>
<td>1,493 (13.6%)</td>
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<tr>
<td>Unknown</td>
<td>25,198 (30.1%)</td>
<td>21,744 (29.9%)</td>
<td>3,494 (31.5%)</td>
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</tbody>
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**Abbreviations:** ACEI = angiotension converting enzyme inhibitor; AHG = antihyperglycemic; ARB = angiotension receptor blocker; CCB = calcium channel blocker; IQR = interquartile range
**Figures**

Figure 1. Proportion of early statin discontinuation by year and indication.

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).

Abbreviations: ACEI = angiotension converting enzyme inhibitor; AHG = antihyperglycemic; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Ref = reference category

Figure 4. Factors associated with statin discontinuation at two and four years (adjusted odds ratios and 95% confidence intervals).

Abbreviations: ACEI = angiotension converting enzyme inhibitor; AHG = antihyperglycemic; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CI = confidence interval; Ref = reference category

**Supplementary material**

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

Supplementary Table S2. Baseline characteristics at each timepoint.

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