Statins After Myocardial Infarction in the Oldest: A Cohort Study in the Clinical Practice Research Datalink Database

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OBJECTIVE: To explore the effect of initiating statins for secondary prevention after a first myocardial infarction (MI) in patients aged 80 years and older.

DESIGN: Retrospective cohort study.

SETTING: Clinical Practice Research Datalink (1999-2016).

PARTICIPANTS: Patients, aged 65 years and older, hospitalized after a first MI without a statin prescription in the year before hospitalization. The age group of 65 to 80 years was included to compare our results to current evidence.

MEASUREMENTS: The primary outcome was a composite of recurrent MI, stroke, and cardiovascular mortality; and the secondary outcome was all-cause mortality. A time-varying Cox model was used to account for statin prescription over time. We compared at least 2 years of statin prescription time with untreated and less than 2 years of prescription time. Analyses were adjusted for potential confounders. The number needed to treat (NNT) was calculated based on the adjusted hazard ratios (HRs) and corrected for deaths during the first 2 years of follow-up.

RESULTS: A total of 9020 patients were included. Among the 3900 patients aged 80 years and older, 2 years of statin prescriptions resulted in a lower risk of the composite outcome (adjusted HR = 0.81; 95% confidence interval [CI] = 0.66-0.99) and of all-cause mortality (adjusted HR = 0.84; 95% CI = 0.73-0.97). During 4.5 years of median follow-up, the NNT for prevention of the primary outcome was 59; and for mortality, the NNT was 36. Correcting for 36.2% deaths during the first 2 years increased the NNT on the primary outcome to 93 and to 61 on all-cause mortality.

CONCLUSION: Our data support statin initiation after a first MI in patients aged 80 years and older if continued for at least 2 years. Especially in patients with a low risk of 2-year mortality, statins should be considered. **J Am Geriatr Soc 68:329-336, 2020.**

Key words: geriatrics; myocardial infarction; secondary prevention; statin; time varying

In patients aged 80 years and older, statin prescription rates for secondary prevention increased from 24% in 1999 to 50% to 80% in 2015.[1,2] Statin treatment is initiated for secondary prevention in 3% of this population annually, so the increase in use is not only caused by the continuation of statins initiated at a younger age.[2] However, there is little evidence to support the initiation of statins for secondary prevention in patients older than 80 years.

Two trials of secondary prevention with statin therapy after myocardial infarction (MI) in older patients (mean age = 75 years) showed 2 to 3 years of statin treatment to prevent MI, stroke, and mortality.[3-5] The trials included relatively healthy participants but few patients aged 80 years and older. In clinical practice compared to trials, patients older than 80 years are typically frail, use numerous concomitant medications, and have one or more comorbid conditions. In addition, in both trials, inclusion was delayed at least 6 months after a cardiovascular event. However, the incidence of cardiovascular event recurrence is higher in the first year after a cardiovascular event than thereafter, which limits the generalizability of the results of these randomized controlled trials (RCTs) to hospitalized patients.[6]

Most observational studies of older populations (mean age = 74-87 years) suggest that statins have a protective effect against MI recurrence and mortality.[7-12] The most recent studies found no effect of statin therapy after an MI.[13,14] Moreover, in these studies, statin use was defined at a fixed moment, mostly at hospital discharge, which does not account for cumulative statin exposure thereafter. Yet, up to

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43% of initially untreated patients are prescribed statins during follow-up, of which 64% within the first year after the primary event, and up to 42% of patients aged 80 years and older discontinue filling statin prescriptions within 2 years of treatment initiation.[14]

The current American Heart Association guidelines on blood cholesterol management recommend statin treatment to patients older than 75 years in the same way as for younger patients, except for a frailty evaluation.[15] Evidence of the benefit of statin therapy in patients aged 80 years and older is needed. We, therefore, performed a large observational cohort study involving older patients. The aim of this study was to evaluate the effect of initiating statin prescription and cumulative prescriptions after a first MI in patients aged 80 years and older on the recurrence of cardiovascular events and mortality.

METHODS

Data Source

Our study was performed using data from the Clinical Practice Research Datalink (CPRD), which covers more than 11.3 million patients from 674 general practices in the United Kingdom.[16] Data from CPRD were linked to the Hospital Episodes Statistics (HES) and linked to the Office for National Statistics (ONS) database. The protocol for this study was approved by the Independent Scientific Advisory Committee of the CPRD under protocol number 16_177R.

Study Design and Study Population

A cohort study was performed including all patients aged 65 years and older who had been hospitalized for a first MI between January 1999 and February 2016, according to the HES, with a medical history available for at least 365 days before the first MI. Although our research question was primarily focused on patients aged 80 years and older, we included patients aged 65 years up to 80 years to compare our results to current evidence in younger patients. The index date was defined as the date of hospital discharge. Patients with a prior stroke, an indication for secondary cardiovascular risk management, or statin prescriptions in the year before the index date were excluded. All patients with a follow-up of less than 30 days were excluded, to avoid including patients treated in a palliative setting.

Exposure to Statins

Statins were coded according to chapter 2.12 of the British National Formulary,[17] and they included atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin. For the time-varying analysis, the total number of days of statin prescriptions was calculated for each patient. The total follow-up per patient was subsequently divided into 30-day periods, starting on the index date, until the completion of follow-up. A time period ended early if the statin exposure status, according to prescription data, changed before the end of the 30-day period or if any of the outcomes occurred. Each time period, therefore, only contained either prescribed or untreated time. Subsequently, cumulative statin prescription was calculated for each time period.

Clinical Outcome

For the primary outcome, patients were followed up from the index date until they reached the composite end point (MI, stroke, or cardiovascular mortality), they left the CPRD practice, they died, or they reached the study end date. Information on MI or stroke was collected from the HES database, and date of death and cause were retrieved from the ONS database. CPRD data were not used to identify end points given the low specificity of MI recording.[18] For the secondary outcome, patients were followed up until all-cause death, as registered in the ONS database. If patients left the CPRD practice, they were censored at that time, because information on drug prescription thereafter was not available.

Potential Confounders

Known risk factors for cardiovascular diseases were defined as potential confounders and were selected from the CPRD database as Read code diagnoses or measurements before the index date. Selected potential confounders were age, sex, body mass index (BMI), smoking status (ever or never), alcohol abuse (as defined in the CPRD database), social deprivation score (according to the index of multiple deprivation), ethnicity (white or nonwhite), inclusion period (1999-2003, 2004-2008, or 2009-2016; the last period is 2 years longer to account for the time lapse of 2 years before statin treatment effect in the main analysis), frailty status,[19] Charlson comorbidity index (0, 1-2, 3-4, or 5 or greater),[20] hypertension, atrial fibrillation, number of different drugs prescribed in the 90 days before the index date, and cardiovascular drugs and other drugs known to be associated with reduced cardiovascular risk (coded according to the British National Formulary)[17] (Supplementary Table S1). Exposure to cardiovascular risk-modifying drugs after the index date was also a time-varying covariate. Exposure was defined as a prescription for a drug during a specific time period.

Statistical Analysis

Data analysis was performed on cases without missing data for BMI, smoking status, alcohol use, ethnicity, or deprivation score. In subanalyses, missing data were divided at random. Baseline characteristics were compared using χ^2 test for categorical variables and the *t*-test for continuous variables. For the time-varying analyses, Cox proportional hazard analyses were used, with results given as hazard ratios (HRs) with 95% confidence intervals (CIs) and adjusted for all potential confounders. We stratified data by age, 80 years and older and 65 years up to 80 years, after investigating interaction between age and statin prescription.

In the first time-varying analyses, we compared 2 or more years of cumulative statin prescriptions, 1 to 2 years of cumulative statin prescriptions, and less than 1 year of cumulative statin prescriptions with no statin prescription. In subanalysis, patients with less than 6 months of follow-up or reaching the primary outcome within 6 months of the index date were excluded to account for treatment decisions at the index date.

We performed a second time-varying analysis comparing data for patient-time of statin prescriptions lasting more

than 2 years with data for patient-time of statin prescriptions lasting less than 2 years, including untreated time. We chose 2 years of statin prescriptions as the cutoff point, since in most trials, the time to benefit of statin treatment is 2 years,.[3,21,22] Sensitivity analysis was performed after excluding patients with less than 2 years of follow-up. We calculated the number needed to treat (NNT) from the HRs.[23] To account for immortal time bias during the first 2 years of follow-up in the more than 2-year statin prescription group, NNTs were adjusted for mortality during the first 2 years by dividing the NNT by the survival probability 2 years after the index date.[24] The median duration of follow-up was calculated from patients with more than 2 years of follow-up. To further investigate the dose-response and patient follow-up patterns, a Kaplan-Meier curve was added for the first 5 years of follow-up comparing patient-time with statin prescriptions lasting more than 2 years with data for patient-time of statin prescriptions lasting less than 2 years, including untreated time.[25] At each year plus 30 days, to account for prescription lag, the number of patients contributing to each prescription group was calculated. Furthermore, the cumulative loss of patients was categorized as reaching the primary outcome, mortality, or being lost to follow-up, including reaching the study end date.

We generated the data analysis for this article using SAS software, version 9.4, of the SAS System for Windows (Copyright © 2015; SAS Institute Inc).

RESULTS

Study Population

The data of 33 151 patients older than 65 years with a first MI were available. Of these patients, 9020 fulfilled the inclusion criteria (Supplementary Figure S1), 3900 of whom were aged 80 years and older; 2594 (67%) of these patients had been prescribed a statin within 90 days of the index date (Table 1). We included 5020 patients aged 65 to

Table 1. Baseline Table

Variable	Those Aged ≥80 y		Those Between the Ages of 65-80 y	
	First 90 d Statin Prescription (n = 2594)	First 90 d Untreated (n = 1306)	First 90 d Statin Prescription (n = 4305)	First 90 d Untreated (n = 815)
Enrollment time period				
1999-2003	376 (14.5)	477 (36.5)	1314 (30.5)	497 (61.0)
2004-2008	1006 (38.8)	354 (27.1)	1596 (37.1)	144 (17.7)
2009-2016	1212 (46.7)	475 (36.4)	1395 (32.4)	174 (21.4)
Age, mean (SD), y	85 (4.1)	86.9 (4.6)	72.5 (4.3)	73.9 (3.8)
Men	1217 (46.9)	515 (39.4)	2714 (63.0)	468 (57.4)
White	2555 (98.5)	1297 (99.3)	4223 (98.1)	793 (97.3)
Index of multiple deprivation:				
First quintile (least deprived)	578 (22.3)	249 (19.1)	956 (22.2)	133 (16.3)
Second quintile	657 (25.3)	305 (23.4)	1085 (25.2)	193 (23.7)
Third quintile	571 (22.0)	328 (25.1)	903 (21.0)	161 (19.8)
Fourth quintile	441 (17.0)	239 (18.3)	737 (17.1)	174 (21.4)
Fifth quintile (most deprived)	347 (13.4)	185 (14.2)	624 (14.5)	154 (18.9)
Ever smoker	1424 (54.9)	637 (48.8)	2636 (61.2)	493 (60.5)
Body mass index, mean (SD), kg/m^2	25.8 (4.3)	25.1 (4.6)	26.7 (4.4)	26.6 (5.2)
Alcohol abuse	42 (1.6)	24 (1.8)	124 (2.9)	27 (3.31)
Frailty index				
Fit	587 (22.6)	196 (15.0)	2487 (57.8)	345 (42.3)
Mild frailty	1068 (41.2)	456 (34.9)	1409 (32.7)	330 (40.5)
Moderate frailty	703 (27.1)	427 (32.7)	371 (8.6)	109 (13.4)
Severe frailty	236 (9.1)	227 (17.4)	38 (0.9)	31 (3.8)
Charlson comorbidity index				
0	945 (36.4)	396 (30.3)	2308 (53.6)	316 (38.8)
1-2	1149 (44.3)	588 (45.0)	1635 (38.0)	385 (47.2)
3-4	421 (16.2)	253 (19.4)	310 (7.2)	90 (11.0)
≥5	79 (3.1)	69 (5.3)	52 (1.2)	24 (2.9)
Hypertension	1480 (57.1)	760 (58.2)	1842 (42.8)	371 (45.5)
Atrial fibrillation	329 (12.7)	250 (19.1)	236 (5.5)	86 (10.6)
No. of drugs at baseline				
0-1	426 (16.4)	169 (12.9)	1381 (32.1)	176 (21.6)
2-4	787 (30.3)	324 (24.8)	1554 (36.1)	235 (28.8)
5-9	1031 (39.8)	518 (39.7)	1107 (25.7)	278 (34.1)
≥10	350 (13.5)	295 (22.6)	263 (6.1)	126 (15.5)

Note. Characteristics of patients, according to statin prescription status in the first 90 days of the index date. Values are number (percentage), unless stated otherwise. All differences were significant, with $P < .05$, except for mean age and ethnicity.

Table 2. Comparison of More Than 2 Years of Statin Prescription, 1 to 2 Years of Statin Prescriptions, and Less Than 1 Year of Statin Prescriptions With No Statin Prescription

							Patients With >6 mo FU[a]	
Variable	Prescription Group	PY	Events	IR/1000	HR	HR Adj.	HR	HR Adj.
Aged ≥80 y								
Primary outcome	Untreated	2540	362	142	Ref.		Ref.	
	<1 y	3032	311	103	0.58 (0.50-0.68)	0.80 (0.67-0.95)	0.80 (0.64-1.00)	1.12 (0.88-1.42)
	1-2 y	1863	130	70	0.74 (0.57-0.96)	0.98 (0.75-1.29)	0.74 (0.57-0.96)	1.01 (0.77-1.34)
	≥2 y	4076	254	62	0.61 (0.48-0.77)	0.79 (0.62-1.02)	0.61 (0.48-0.77)	0.82 (0.63-1.06)
All-cause mortality	Untreated	2673	626	234	Ref.		Ref.	
	<1 y	3175	437	138	0.50 (0.44-0.57)	0.71 (0.62-0.82)	0.62 (0.52-0.73)	0.88 (0.73-1.05)
	1-2 y	1978	239	121	0.71 (0.59-0.85)	0.99 (0.81-1.20)	0.71 (0.59-0.85)	1.02 (0.84-1.24)
	≥2 y	4439	516	116	0.53 (0.46-0.63)	0.79 (0.67-0.94)	0.53 (0.46-0.63)	0.82 (0.69-0.98)
Between the Ages of 65-80 y								
Primary outcome	Untreated	1903	159	84	Ref.		Ref.	
	<1 y	5197	220	42	0.39 (0.31-0.49)	0.51 (0.41-0.65)	0.78 (0.54-1.14)	1.02 (0.68-1.52)
	1-2 y	4061	90	22	0.52 (0.35-0.75)	0.72 (0.49-1.05)	0.50 (0.34-0.73)	0.80 (0.54-1.18)
	≥2 y	16 701	414	25	0.41 (0.29-0.56)	0.62 (0.44-0.88)	0.41 (0.29-0.56)	0.65 (0.46-0.92)
All-cause mortality	Untreated	1975	252	128	Ref.		Ref.	
	<1 y	5352	265	50	0.33 (0.27-0.39)	0.53 (0.44-0.65)	0.51 (0 40-0.65)	0.74 (0.58-0.95)
	1-2 y	4223	195	46	0.59 (0.46-0.77)	0.97 (0.75-1.25)	0.59 (0.46-0.77)	0.96 (0.74-1.25)
	≥2 y	17 893	800	45	0.36 (0.29-0.45)	0.62 (0.49-0.78)	0.35 (0.28-0.43)	0.60 (0.47-0.76)

Abbreviations: Adj., adjusted; FU, follow-up; HR, hazard ratio; IR, incidence ratio; PY, patient-years; Ref., reference group.
[a]Excluding all patients with a primary event within the first 6 months of follow-up or less than 6 months of follow-up in the Clinical Practice Research Datalink practice database.

80 years, of whom 4305 (86%) had been prescribed a statin within 90 days of the index date. All variables, except age distribution and ethnicity, were significantly different between patients prescribed or not prescribed a statin within 90 days of the index date (Table 1).

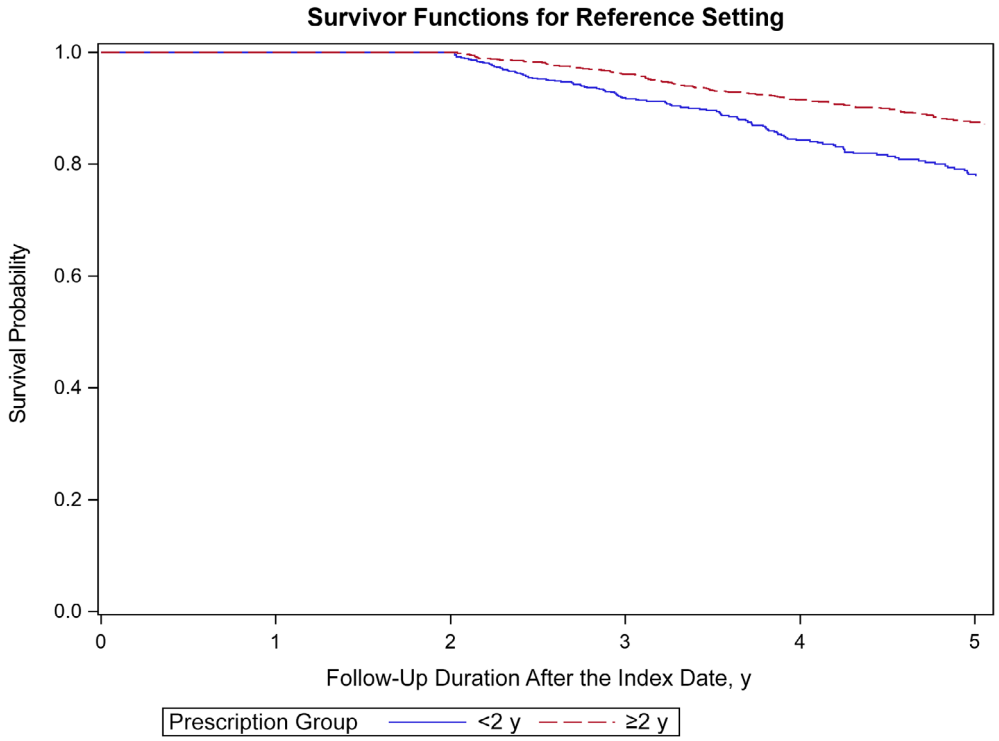
Primary Outcome

As shown in Table 2, more than 2 years of statin prescriptions compared to no statin prescription was nearly significantly associated with a reduction of the primary end point in patients aged 80 years and older (adjusted HR = 0.79; 95% CI = 0.62-1.02); and there was a significant association in patients aged 65 to 80 years (adjusted HR = 0.62; 95% CI = 0.44-0.88) (Table 3). While statin prescription for 1 to 2 years had no effect on the primary outcome compared with no treatment in both age groups (adjusted HR = 0.98 [95% CI = 0.75-1.29] and adjusted HR = 0.72 [95% CI = 0.49-1.05], respectively), statin prescription for less than 1 year was significantly associated with a reduction of the primary outcome in both age groups (adjusted HR = 0.80 [95% CI = 0.67-0.95] and adjusted HR = 0.51 [95% CI = 0.41-0.65], respectively). This association disappeared after the exclusion of patients with a primary outcome within the first 6 months or with less

Table 3. Effect of More Than 2 Years of Statin Prescriptions Compared With No or Less Than 2 Years of Statin Prescriptions

Variable	Prescription Group	PY	Events	IR/1000 PY	HR	HR Adj.	NNT	NNT Adj	2 y, %[a]	NNT Adj.[a]	Median FU, y[b]
Aged ≥80 y											
Primary outcome	<2 y	7436	803	108	Ref.						4.5
	≥2 y	4076	254	62	0.64 (0.63-0.78)	0.81 (0.66-0.99)	30.9	59.0	36.2	92.5	
All-cause mortality	<2 y	7826	1302	166	Ref.						4.8
	≥2 y	4439	516	116	0.61 (0.54-0.70)	0.84 (0.73-0.97)	15.7	39.1	36.2	61.3	
Between Ages 65-80 y											
Primary outcome	<2 y	11 162	469	42	Ref.						6.7
	≥2 y	16 701	414	25	0.48 (0.3-0.60)	0.67 (0.53-0.84)	38.7	61.3	15.5	72.5	
All-cause mortality	<2 y	11 550	712	62	Ref.						7.2
	≥2 y	17 893	800	45	0.40 (0.38-0.52)	0.73 (0.62-0.85)	16.1	36.5	15.5	43.2	

Abbreviations: Adj., adjusted; FU, follow-up; HR, hazard ratio; IR, incidence ratio; NNT, number needed to treat; PY, patient-years; Ref., reference group.
[a]The percentage of patients who died within 2 years of the index date, according to the Office for National Statistics database, and patients leaving a Clinical Practice Research Datalink practice were included.
[b]In 2-year event-free survivors.



Patients Contributing Time at Year Point + 30 Days (Cross-Sectional)

	0 + 90 d	1	2	3	4	5
<2 y	3900	2594	1043	489	326	215
≥2 y	.	.	886	970	749	573
Total in analysis	3900	2594	1929	1459	1075	788
Cumulative primary outcome	.	510	730	881	1004	1092
Cumulative loss to mortality	.	411	629	818	954	1073
Cumulative loss to follow-up	.	26	95	179	255	315
Cumulative study end	.	359	517	563	612	632

Figure 1. Time-varying Kaplan-Meier curve for the primary outcome in patients aged 80 years and older: comparison of more than 2 years of statin prescriptions with no or less than 2 years of statin prescriptions. Kaplan-Meier curve on primary event-free survival probability in patients aged 80 years and older. Numbers at each year refer to the remaining patients at risk, reaching the primary outcome, or being censored by all-cause mortality, loss-to-follow-up, or reaching the study end date.

than 6 months of follow-up (adjusted HR = 1.12 [95% CI = 0.88-1.42] and adjusted HR = 1.02 [95% CI = 0.6-1.52], respectively).

Table 3 shows the effect of more than 2 years of statin prescription duration compared to less than 2 years of statin prescription on the primary outcome (ie, the composite end point of MI, stroke, and cardiovascular mortality). Two years of statin prescriptions was significantly associated with a risk reduction of the primary end point in both age groups (≥80 and 65-80 years), but the association was less pronounced in the older age group (adjusted HR = 0.81 [95% CI = 0.66-0.99] and adjusted HR = 0.67 [95% CI = 0.53-0.84], respectively). Excluding patients with less than 2 years of follow-up did not significantly change these results (adjusted HR = 0.80 [95% CI = 0.65-0.98] in patients aged ≥80 years, and adjusted HR = 0.64 [95% CI = 0.51-0.80] in patients between the age of 65 and 80 years). As the event rate was much higher in the older age group, the NNT was similar in both age categories (59.0 and 61.3, respectively). After correction for mortality in the first 2 years, the NNT in the patients aged 80 years and older increased more than that for patients aged 65 to 80 years (NNT = 92.5 and 72.5, respectively).

Figure 1 shows the Kaplan-Meier curve for primary event-free survival in patients aged 80 years and older. Curves for the primary analysis and secondary analysis and data for loss to follow-up for patients between the ages of 65 and 80 years are available in the supplementary data (Supplementary Figures S2 and S3).

Secondary Outcomes

As described in Table 2, more than 2 years of statin prescriptions compared with no statin treatment was associated with an improved all-cause mortality in both age groups of patients (≥80 years adjusted HR = 0.79 [95% CI = 0.67-0.94]; 65-80 years adjusted HR = 0.62 [95% CI = 0.49-0.78), comparable to the effect on the primary outcome. In contrast, 1 to 2 years of statin prescriptions was not associated with an effect on all-cause mortality in either patient group (≥80 years adjusted HR = 0.99 [95% CI = 0.81-1.20]; 65-80 years adjusted HR = 0.97 [95% CI = 0.7-1.25]). Less than 1 year of statin prescriptions had a comparable beneficial association on all-cause mortality as on the primary outcome, which remained after

the exclusion of patients with less than 6 months of follow-up or patients with a primary event during the first 6 months in those aged 65 to 80 years (≥80 years adjusted HR = 0.88 [95% CI = 0.73-1.05]; 65-80 years adjusted HR = 0.74 [95% CI = 0.58-0.95]). The association of more than 2 years of statin prescriptions compared with less than 2 years of statin prescriptions (including no statin prescriptions) on all-cause mortality was comparable to the effect on the primary outcome in both age groups (≥80 years adjusted HR = 0.84 [95% CI = 0.73-0.97]; 65-80 years adjusted HR = 0.73 [95% CI = 0.60-0.85]), as shown in Table 3. HRs for individual components of the primary outcome are available in Supplementary Tables S2 and S3.

DISCUSSION

Main Findings

Statin prescription initiated after a first MI in patients aged 80 years and older is associated with a reduced risk of the primary composite end point (MI, stroke, and cardiovascular mortality) and the secondary outcome (all-cause mortality) after 2 years of prescriptions, which was also seen in patients aged 65 to 80 years, although the relative association was smaller in the older patient group. Given the higher absolute risk of cardiovascular event recurrence and all-cause mortality in patients aged 80 years and older, the NNT was comparable in the two age groups. After correction for deaths during the first 2 years of follow-up, the NNT increased more in the older patient group than in the younger patient group.

Comparison of Results With Other Studies

Our results are comparable to those of a meta-analysis of the data for patients aged 65 to 80 years from secondary prevention trials, with estimated relative risk reductions of 26% to 30% on similar composite outcomes and of 26% on all-cause mortality.[5] However, the NNT was higher in both age groups in our study than the NNT of 48 in the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study (treatment for 3 years).[3] This effect can be partly explained by the increase in competing risks in old individuals. Given the inclusion and exclusion criteria of most trials, the included patients in trials have less competing risk.[24] Furthermore, most trials did not include patients during the high-risk period directly after the event. In our study, the rates of cardiovascular events and all-cause mortality were higher in the first 2 years of follow-up than later, suggesting that fewer patients survived long enough to achieve benefit, leading to a higher NNT. A Cochrane review of 18 controlled trials of early initiation of statins after MI did not detect a beneficial effect on most cardiovascular outcomes, except for unstable angina, which was not included in our outcomes.[26] Surprisingly, in our analysis, we also found up to 1 year of statin prescriptions to be beneficial, but this benefit disappeared after we excluded patients who experienced a cardiovascular event in the first 6 months after the index date. This was probably caused by survivor treatment selection,[27] competing medical issues,[28] pleiotropic early statin initiation effects, or other unknown differences between comparison groups.

We found a positive association of statin prescriptions, consistent with the findings of most previous observational studies.[7-11] However, none of these studies accounted for unmeasured confounding variables during the first 6 months of follow-up or cumulative statin exposure, as these become visible only after the index date. These studies tended to report a greater effect of statin therapy than we found, which probably is an overestimation. One study using the data from the CPRD database reported no beneficial effect of statins on MI recurrence in patients aged 80 years and older.[14] This might be explained by the large proportion of patients in the user group (43%) who discontinued therapy within 2 years of statin initiation and by the exclusion of patients who started statin therapy more than 2 months after the event.

Strengths and Limitations

This is the first study with a large sample to investigate the initiation and cumulative statin prescriptions for secondary prevention after a first MI in patients aged 80 years and older. Our finding of a beneficial association of statins in patients aged 65 to 80 years is comparable to that of RCTs and supports the validity of our findings in the older (≥80 years) age group. The external validity is high, as all eligible patients, even the most frail, were included in our analysis, reflecting the real-life population of older patients with a first MI. Data sources for our outcomes, the combination of ONS, HES, and CPRD databases, have shown a good validity for cardiovascular diagnoses.[29] Furthermore, by comparing different durations of statin prescriptions, we could account for unmeasured confounding during the first 6 months of treatment. In our analysis, less than 2 years of statin prescriptions appeared not to be effective in patients older than 80 years.

Our study also had some limitations. We accounted for competing risk during the first 2 years of follow-up, but not during hospitalization or up to 30 days after discharge. If these competing risks are taken into account, the NNT may increase further.[30] During follow-up, competing risks exist as well and patients are censored due to all-cause mortality or loss to follow-up, mostly in the less than 2 year prescription group, which may result in underestimating the effect of statin treatment. Another limitation is unmeasured confounding. In our study, we defined statin treatment on the basis of a prescription for a statin; however, we do not know whether the patients actually took the prescribed statin, which may lead to underestimation of the actual effect of statin therapy. The decision of whether to initiate statin treatment at discharge or thereafter is not random—it is associated with relevant known and unknown prognostic factors, including healthy user bias. This may overestimate the actual effect of statin therapy.

The decision to discontinue statin treatment by either the patient or the physician is also not random and may be directed by changes in the life expectancy of the patient. This may explain the larger association found for all-cause mortality of over 2 years of statin treatment, which could result in overestimation of the effect of statin treatment. Furthermore, the HES database is for hospitalized patients,

whereas not all frail patients will be referred to a hospital in acute situations, which could lead to overestimation.

Last, we performed our analysis on complete cases only; however, missing data were not associated with the initiation of statin therapy during the first 90 days after an event or with the primary outcome.

Implications for Clinicians and Policy Makers

Our results confirm that patients need to take statins for minimally 2 years after a first MI to achieve benefit, regardless of a patient's age. If patients aged 80 years and older are at high risk of dying within 2 years of a first MI, it is not beneficial to initiate statin therapy. If initiation of statin treatment is considered beneficial in contributing to patient-centered goals, it is important to ensure that the patient remains adherent because short-term treatment was not found to be beneficial.

Given our results, future research should focus on developing clinical decision support tools to determine life expectancy and, thus, aid physicians to decide whether to initiate preventive treatment with statins in their oldest patients.

CONCLUSION

Our data support starting statins in patients aged 80 years and older after a first MI if it is likely that the patient will take the drug for at least 2 years. As the association is seen after minimally 2 years of statin prescriptions, the oldest patients (aged >80 years) with a low 2-year mortality risk should be considered for statin treatment.

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Conflict of Interest: All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Transparency Declaration: The lead author (Geert Lefeber) affirms that the article is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned and registered have been explained.

Ethical Approval: The study was approved by the Independent Scientific Advisory Committee for Clinical Practice Research Datalink (CPRD) research (protocol No. 16_177R). No further ethical approval was required for the analysis of the data. CPRD has obtained ethical approval from a multicenter research ethics committee for all purely observational research using CPRD data.

Data Sharing Statement: Data from the Clinical Practice Research Datalink (CPRD) are available directly from CPRD. Full code lists are available from the corresponding author at g.j.lefeber@umcutrecht.nl.

Patient and Public Involvement Statement: No patients were involved in the design or execution of the study or were asked to advise on the interpretation or writing up of results.

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SUPPORTING INFORMATION

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

Supplementary Figure S1: Inclusion flowchart.

Supplementary Table S1: Time Under Percentual Prescription of Medication at Baseline and During Follow-Up for Each Prescription Group in Patients Aged 80 Years and Older and Between the Ages of 65 and 80 Years

Supplementary Table S2: Comparison of Effect of More Than 2 Years of Statin Treatment, 1 to 2 Years of Statin Treatment, and Less Than 1 Year of Statin With No Treatment on the Individual Components of the Primary Outcome

Supplementary Table S3: Effect of More Than 2 Years of Statin Treatment Compared With No or Less Than 2 Years of Statin Prescriptions on the Individual Components of the Primary Outcome

Supplementary Figure S2: Time-varying Kaplan-Meier curve for the primary outcome in patients between the ages of 65 and 80 years: comparison of more than 2 years of statin prescriptions with no or less than 2 years of statin prescriptions.

Supplementary Figure S3: Time-varying Kaplan-Meier curve for the primary outcome in patients aged 80 years and older and between the ages of 65 and 80 years: comparison of more than 2 years of statin prescriptions, 1 to 2 years of statin prescriptions, and less than 1 year of statin prescriptions with no statin prescriptions.