Stroke

CLINICAL AND POPULATION SCIENCES

Statins After Ischemic Stroke in the Oldest

A Cohort Study Using the Clinical Practice Research Datalink Database

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BACKGROUND AND PURPOSE: Statins are frequently initiated in patients aged 80 years and older after an ischemic stroke, even though evidence on prevention of recurrent cardiovascular disease is scarce. In this study, we seek evidence for statin prescription in the oldest old.

METHODS: We performed a retrospective cohort study in patients aged 65 years and older hospitalized for a first ischemic stroke between 1999 and 2016 without statin prescriptions in the year before hospitalization using the Clinical Practice Research Datalink. The age group 65 to 80 years was included to compare our results to current evidence on statin efficacy. The primary outcome was a composite of recurrent stroke, myocardial infarction, and cardiovascular mortality. 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 <2 years of prescription time. Analyses were adjusted for potential confounders. The number needed to treat was calculated based on the adjusted hazard ratios and corrected for deaths during the first 2 years of follow-up.

RESULTS: Five thousand nine hundred ten patients, aged 65 years and older were included, of whom 3157 were 80 years and older. Two years of statin prescription in patients aged 80 years and older resulted in both a lower risk of the composite end point (adjusted hazard ratio, 0.80 [95% CI, 0.62–1.02]) and all-cause mortality (adjusted hazard ratio, 0.67 [95% CI, 0.57–0.80]). After correction for the mortality of 23.9% of the patients during the first 2 years, the number needed to treat was 64 for the primary outcome during a median follow-up of 3.9 years and 19 for all-cause mortality.

CONCLUSIONS: Statins initiated in patients aged 80 and older, discharged home after hospitalization for an ischemic stroke are associated with a reduction in cardiovascular events.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: cardiovascular disease ■ hospitalization ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ mortality ■ myocardial infarction ■ prescription

Patients aged over 80 years contribute to one-third of all stroke types.[1] Compared with patients below the age of 80 years, they show an increased 30-day and 1-year case-fatality rate after a stroke and an increased risk for cardiovascular recurrence.[1] Statin therapy has been proven effective in preventing cardiovascular disease recurrence after a stroke in patients below the age of 80 years.[2–4] However, clinical practice clearly lacks evidence on the benefits of statin therapy after the age of 80 years.

Therefore, evidence for those younger than 80 years of age is currently used for treatment decision making in patients above the age of 80 years. Despite the lack of evidence, most patients aged 80 years and older with a prior cardiovascular event (including stroke) receive statins.[5,6]

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The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.030755.

For Sources of Funding and Disclosures, see page 1251.

Nonstandard Abbreviations and Acronyms

CPRD	Clinical Practice Research Datalink
HES	Hospital Episodes Statistics
HR	hazard ratio
MI	myocardial infarction
NNT	numbers needed to treat
ONS	Office for National Statistics

The evidence of statin treatment for secondary prevention of stroke recurrence and other cardiovascular events after a stroke in younger patients is based on several trials.[2,4] In these trials, reduction of stroke recurrence and other cardiovascular outcomes occurred after 2 years of statin treatment. A problem with these trials is the moment of trial initiation in a time of upcoming statin use. Patients were recruited up to 6 months after the initial stroke. During follow-up 10% to 21% of patients in the placebo group was found to initiate statin therapy. On the contrary, 15% to 25% of patients in the treated group was found to discontinue statin therapy.[2–4] This cross-contamination may have led to an underestimation in the intention to treat analyses of the effect of statin treatment found in these randomized controlled trial. In patients above the age of 65 in secondary prevention trials, statin therapy showed a relative risk reduction of 22% on all-cause mortality and 25% relative risk reduction on stroke.[7] In a recent meta-analysis of 28 randomized controlled trials in patients with an indication for secondary prevention with statins, most patients were included after coronary events and not after stroke. Statin initiation was associated with a cardiovascular disease risk reduction of 20% in all age groups, even for those aged over 75 years, but in this subgroup not on stroke reduction or all-cause mortality.[8]

Apart from trials, most observational studies have focused on the effect of statins after acute ischemic stroke.[9] These studies claim a protective effect after acute ischemic stroke; however; trial evidence is lacking to support this.[10] To our knowledge, no observational studies have been performed in the oldest old on the effect of statin initiation and cumulative prescriptions after a stroke.

We, therefore, performed a large observational cohort study involving older patients with stroke in daily practice. The aim of this study was to evaluate the effect of initiating statin treatment and cumulative prescriptions after a first stroke in patients aged 80 years and older on the recurrence of cardiovascular events and mortality.

METHODS

Data Source

The data that support the findings of this study are available from the corresponding author upon reasonable requests after permission by the Clinical Practice Research Datalink (CPRD). Our study was performed using data from the CPRD, covering >11.3 million patients from 674 general practices in the United Kingdom.[11] 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. CPRD has obtained ethical approval from a multicenter research ethics committee for all purely observational research using CPRD data without attaining consent from individual patients.

Study Design and Study Population

A cohort study was performed including all patients aged 65 and older who had been hospitalized for a first ischemic stroke between January 1999 and February 2016, according to the HES, with a medical history available for at least 365 days before the ischemic stroke. Our population of interest were those aged 80 years and above. To allow ascertaining that our observational study design was able to detect beneficial effects of statins in this age group, we included patients aged 65 to 80 years to compare our data to existing evidence. The index date was defined as the date of hospital discharge. Patients with a prior stroke or myocardial infarction (MI), or statin prescriptions in the year before the index date were excluded. To avoid including patients treated in a palliative setting all patients with a follow-up duration of <30 days were excluded. The sample size was determined by the maximum number of patients with a first ischemic stroke in the selected age groups within CPRD/HES.

Exposure to Statins

Statins were coded according to Chapter 2.12 of the British National Formulary[12] and 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 prescription status changed before the end of the 30-day period or if any of the outcomes occurred. Each time period, therefore, only contained either statin prescribed or untreated time. Subsequently, cumulative statin prescription for each patient was calculated after each time period.

Clinical Outcome

For the primary outcome, patients were followed-up from the index date until they reached one of the components of 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, 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.[13] For the secondary outcome, patients were followed-up until death of any cause, as registered in the ONS database. If in the ONS database a noncardiovascular cause of death was recorded and according to the HES database a cardiovascular event occurred within the 30 days before death, the cause of death

was recorded as cardiovascular. 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, 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 non-White), inclusion period (1999–2003, 2004–2008, 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 (fit, mild frailty, moderate frailty, severe frailty),[14] Charlson comorbidity index (0, 1–2, 3–4, 5 or greater),[15] 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 increased cardiovascular risk coded according to the British National Formulary[12]; (Table I in the Data Supplement). Exposure to cardiovascular risk modifying drugs after the index date was also a time-varying covariate. Such 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 body mass index, smoking status, alcohol use, ethnicity, or deprivation score. In sub-analyses, missing data were divided at random. Baseline characteristics were compared using χ^2 for categorical variables and the unpaired *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% CIs and adjusted for all potential confounders. We stratified data by age—80 years and older and 65 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, one to 2 years of cumulative statin prescriptions, and <1 year of cumulative statin prescriptions with no statin prescription.

We performed a second time-varying analysis comparing data for patient-time of statin prescriptions lasting >2 years with data for patient-time of statin prescriptions lasting <2 years, including untreated time. We chose 2 years of statin prescriptions as cutoff point, since in most trials, the time to benefit of statin treatment is 2 years.[16–18] Sensitivity analysis was performed after excluding patients with <2 years of follow-up. We calculated the numbers needed to treat (NNT) from the HRs and the incidence ratio after 2 years of follow-up.[19] To account for immortal time bias during the first 2 years of follow-up in the >2 year statin prescription group, NNTs were adjusted for mortality during the first 2 years by dividing the NNT by the survival probability 2 year after the index date.[20] The median duration of follow-up was calculated from patients with >2 years 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 >2 years with data for patient-time of statin prescriptions lasting <2 years, including untreated time.[21] 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 over the years was categorized as reaching the primary outcome, mortality, being lost to follow-up, or reaching the study end date.

RESULTS

Study Population

Data of 33 151 patients older than 65 years with a first ischemic stroke were available. Of these, 5910 patients fulfilled the inclusion criteria (Figure I in the Data Supplement), of whom 3157 were aged 80 and older. In 1638 (52%) of the patients aged 80 years and older, a statin had been prescribed within 90 days of the index date, while 38% having moderate to severe frailty (Table 1, extended medical history and medication see Tables I and II in the Data Supplement). We included 2753 patients aged 65 to 80 years, of whom 1723 (63%) had been prescribed a statin within 90 days of the index date. All variables, except age and ethnicity, were distributed significantly different between patients being prescribed and not being prescribed a statin within 90 days of the index date.

Primary Outcome

As shown in Table 2, >2 years of statin prescriptions compared with no statin prescriptions was significantly associated with a lower risk of the primary end point (ie, the composite end point of nonfatal MI or stroke, and cardiovascular mortality) in both patients aged 80 years and older and in the 65 to 80 years group (adjusted HR, 0.70 [95% CI, 0.52–0.92] and 0.67 [95% CI, 0.49–0.91], respectively). Statin prescription for one to 2 years compared with no prescription in patients aged 80 years and older was nearly statistically significant associated with prevention of the primary end point (adjusted HR, 0.79 [95% CI, 0.59–1.07]), while in patients between the age of 65 and 80 no association was found (adjusted HR, 1.00 [95% CI, 0.69–1.46]). Statin prescription for <1 year had a significant beneficial effect on the primary outcome in both age groups (adjusted HR, 0.43 [95% CI, 0.29–0.41], and adjusted HR, 0.43 [95% CI, 0.34–0.54], respectively).

Table 3 shows the effect of >2 years of statin prescription compared with <2 years of statin prescription (including no statin prescription) on the primary outcome. In patients aged 80 years and older there was a trend towards a lower risk, although not significant (adjusted HR, 0.80 [95% CI, 0.62–1.02]). In those aging 65 to 80 years the risk of the primary end point was significantly reduced (adjusted HR, 0.74 [95% CI,

Table 1. Baseline Table

	Eighty years and older (n=3157)		Between the age of 65 and 80 (n=2753)	
	First 90 d statin treatment (n=1638)	First 90 d untreated (n=1519)	First 90 d statin treatment (n=1,723)	First 90 d untreated (n=1030)
Enrolment time period				
1999–2003	86 (19.1)	365 (80.9)	224 (31.6)	484 (68.4)
2004–2008	531 (53.0)	472 (47.0)	667 (72.3)	255 (27.7)
2009–2016	1021 (60.0)	682 (40.0)	832 (74.1)	291 (25.9)
Age in years mean (SD)	85.3 (4.1)	86.8 (4.7)	73.5 (4.0)	73.7 (4.1)
Men	627 (38.28)	497 (32.72)	913 (52.99)	541 (52.52)
white	1613 (98.47)	1502 (98.88)	1665 (96.63)	1005 (97.57)
Index of multiple deprivation				
First quintile (least deprived)	386 (23.57)	289 (19.03)	383 (22.23)	209 (20.29)
Second	392 (23.93)	382 (25.15)	444 (25.77)	232 (22.52)
Third	360 (21.98)	354 (23.30)	357 (20.72)	215 (20.87)
Fourth	284 (17.34)	266 (17.51)	293 (17.01)	199 (19.32)
Fifth quintile (most deprived)	216 (13.19)	228 (15.01)	246 (14.28)	175 (16.99)
Ever smoker	869 (53.05)	709 (46.68)	1033 (59.95)	550 (53.40)
Body mass index, mean (SD)	25.6 (4.5)	25.3 (4.7)	26.8 (4.8)	26.5 (4.9)
Alcohol abuse	33 (2.01)	47 (3.09)	75 (4.35)	57 (5.53)
Frailty index				
Fit	341 (20.82)	287 (18.89)	857 (49.74)	470 (45.63)
Mild frailty	675 (41.21)	537 (35.35)	650 (37.72)	395 (38.35)
Moderate frailty	461 (28.14)	478 (31.47)	185 (10.74)	143 (13.88)
Severe frailty	161 (9.83)	217 (14.29)	31 (1.80)	22 (2.14)
Charlson comorbidity index				
0	652 (39.80)	555 (36.54)	946 (54.90)	491 (47.67)
1–2	681 (41.58)	652 (42.92)	638 (37.03)	417 (40.49)
3–4	255 (15.57)	259 (17.05)	126 (7.31)	106 (10.29)
5 or more	50 (3.05)	53 (3.49)	13 (0.75)	16 (1.55)
Hypertension	1001 (61.11)	915 (60.24)	847 (49.16)	532 (51.65)
Atrial fibrillation	372 (22.71)	397 (26.14)	229 (13.29)	140 (13.59)
Number of drugs before the index date				
0–1	344 (21.00)	285 (18.76)	576 (33.43)	317 (30.78)
2–4	522 (31.87)	423 (27.85)	598 (34.71)	320 (31.07)
5–9	605 (36.94)	590 (38.84)	449 (26.06)	303 (29.42)
10 of more	167 (10.20)	221 (14.55)	100 (5.80)	90 (8.74)

Characteristics of patients, according to statin treatment status in the first 90 days of the index date. Values are number (percentages) unless stated otherwise. All differences were significant with $P<0.05$ except for mean age and ethnicity.

0.57–0.96]). As the event rate was much higher in the older age group, the NNT was lower in patients aged 80 years and older (24.1 compared with 39.9 in those aging 65–80 years). After adjusting for mortality in the first 2 years, the NNT increased in both age groups (NNT 48.8 and 68.0, respectively).

The Figure shows the Kaplan-Meier curve for primary event free survival in patients aged 80 and older. Curves and data for loss to follow-up for patients between the age of 65 and 80 are available in the Data Supplement (Figures II and III in the Data Supplement).

Secondary Outcomes

More than 2 years of statin prescription compared with no statin prescription improved all-cause mortality in patients aged 80 years and older and nearly in the 65 to 80 years group (HR, 0.59 [95% CI, 0.49–0.72]; 65–80 years adjusted HR, 0.85 [95% CI, 0.67–1.08], respectively). One to 2 years of statin prescription significantly lowered the risk on all-cause mortality in both patient groups (≥80 years adjusted HR, 0.71 [95% CI, 0.57–0.88]; 65–80 years adjusted HR, 0.71 [95% CI, 0.52–0.96]). Less than one year of statin prescription

Table 2. Comparison of Effect of >2 Years of Statin Treatment, 1 to 2 Years of Statin Treatment, and <1 Year of Statin With No Treatment

	Prescription group	PY	Events	IR/1000 PY	HR	HR adjusted
Age 80 and older						
Primary outcome	Untreated	2316	595	257	Ref	
	<1 y	1820	169	93	0.29 (0.24–0.35)	0.43 (0.29–0.41)
	1–2 y	1040	83	59	0.70 (0.52–0.94)	0.79 (0.59–1.07)
	≥2 y	1954	133	68	0.59 (0.45–0.77)	0.70 (0.52–0.92)
All-cause mortality	Untreated	2516	666	265	Ref	
	<1 y	1980	270	136	0.48 (0.41–0.56)	0.54 (0.46–0.63)
	1–2 y	1144	155	135	0.66 (0.54–0.82)	0.71 (0.57–0.88)
	≥2 y	2175	287	132	0.49 (0.41–0.59)	0.59 (0.49–0.72)
Between the age of 65 and 80						
Primary outcome	Untreated	2246	293	130	ref.	
	<1 y	2387	130	54	0.21 (0.26–0.40)	0.43 (0.34–0.54)
	1–2 y	1562	65	42	0.84 (0.59–1.22)	1.00 (0.69–1.46)
	≥2 y	4793	160	33	0.50 (0.37–0.68)	0.67 (0.49–0.91)
All-cause mortality	Untreated	2383	291	122	Ref	
	<1 y	2571	152	59	0.42 (0.34–0.52)	0.63 (0.51–0.79)
	1–2 y	1705	79	46	0.51 (0.38–0.68)	0.71 (0.52–0.96)
	≥2 y	5404	318	59	0.56 (0.45–0.70)	0.85 (0.67–1.08)

HR indicates hazard ratio; IR, incidence ratio; PY, patient-years; and Ref, reference group.

had a comparable beneficial effect on all-cause mortality in both age groups (≥80 years adjusted HR, 0.54 [95% CI, 0.46–0.63]; 65–80 years adjusted HR, 0.63 [95% CI, 0.51–0.79]). The beneficial effect of >2 years of statin prescription compared with <2 years of statin prescription (including no statin prescription) on all-cause mortality was significant in patients aged 80 years and older (adjusted HR, 0.67 [95% CI, 0.57–0.80) and not significant in the 65 to 80 years group (adjusted HR, 0.93 [95% CI, 0.76–1.13]), as shown in Table 3. In patients aged 80 years and older the adjusted NNT was lower compared with patients aging between 65 and 80 years (14.8 and 177.0, respectively, after adjusting for mortality in the first 2 years this changed to 19.4 and 202, respectively). Except for the positive effect on cardiovascular mortality, >2 years of statin prescription was not significantly associated with all other secondary outcomes (Tables III and IV in the Data Supplement).

DISCUSSION

Main Findings

Initiating statin prescription followed by continuation for at least 2 years after a first stroke in patients aged 80 years and older compared with no prescription is associated with a risk reduction of the primary composite end point (nonfatal MI or nonfatal stroke and cardiovascular mortality) in line with results in patients aged 65 to 80 years. Comparing >2 years of statin prescription to <2 years of statin prescription, including untreated time, resulted in a near significant association, most likely as a result of a loss of power due to competing risks given the strong association with the secondary outcome all-cause mortality. Less than one year of statin treatment was associated with a risk reduction in the primary end point as well. The calculated NNT is lower in patients aged 80 years and older compared with those aged 65 to 80 years, resulting from the higher absolute risk of cardiovascular event recurrence and all-cause mortality in the older patients.

Comparison of Results With Other Studies

The results of our study that showed a positive effect of statin prescription on our primary outcome as well as on all-cause mortality for the patient group aged between 65 to 80 years are in line with the results of the trial evidence when comparing 2 years of statin prescription to <2 years of statin prescription including being untreated.[8] In patients over 80 years, we found a near significant effect for statin prescription for over 2 years compared with <2 years of statin prescription including no prescription. This is in line with a recent meta-analysis including subgroup analysis after the age of 75 years showing a risk reduction of up to 20%.[8]

No difference for our primary end point was found in patients aged 65 to 80 years when comparing between one and 2 years of statin prescription to being untreated, which also seems in line with the trial on statin treatment after stroke when looking at their Kaplan-Meier curves.[2,4] Between one and 2 years of statin prescription

Table 3. Effect of >2 Years of Statin Treatment Compared With <2 Years of Statin Treatment or no Statin Treatment

	Prescription group	PY	Events	IR/ 1000 PY after 2 y	HR	HR adj.	NNT	NNT adjusted	2 y, %*	NNT adjusted*	Median FU in 2 y event free survivors, y
Age 80 and older											
Primary outcome	<2 y	5176	847	113	Ref						3.9
	≥2 y	1953	133	68	0.60 (0.47–0.77)	0.80 (0.62–1.02)	24.1	48.8	23.9	64.1	
All-cause mortality	<2 y	5640	1091	254	Ref						4.2
	≥2 y	2175	287	132	0.52 (0.44–0.61)	0.67 (0.57–0.80)	10.0	14.8	23.9	19.4	
Between the age of 65 and 80											
Primary outcome	<2 y	6194	488	60	Ref						5.4
	≥2 y	4793	160	33	0.56 (0.44–0.72)	0.74 (0.57–0.96)	39.9	68	12.5	77.7	
All-cause mortality	<2 y	6659	522	88	Ref						5.9
	≥2 y	5404	318	59	0.67 (0.55–0.81)	0.93 (0.76–1.13)	37.1	177.1	12.5	202.3	

CPRD indicates Clinical Practice Research Datalink; FU, follow-up; HR, hazard ratio; NNT, number needed to treat; ONS, Office for National Statistics; and PY, patient-years.

*The % of patients who died with 2 years of the index date according to the ONS database and patients leaving a CPRD practice were included.

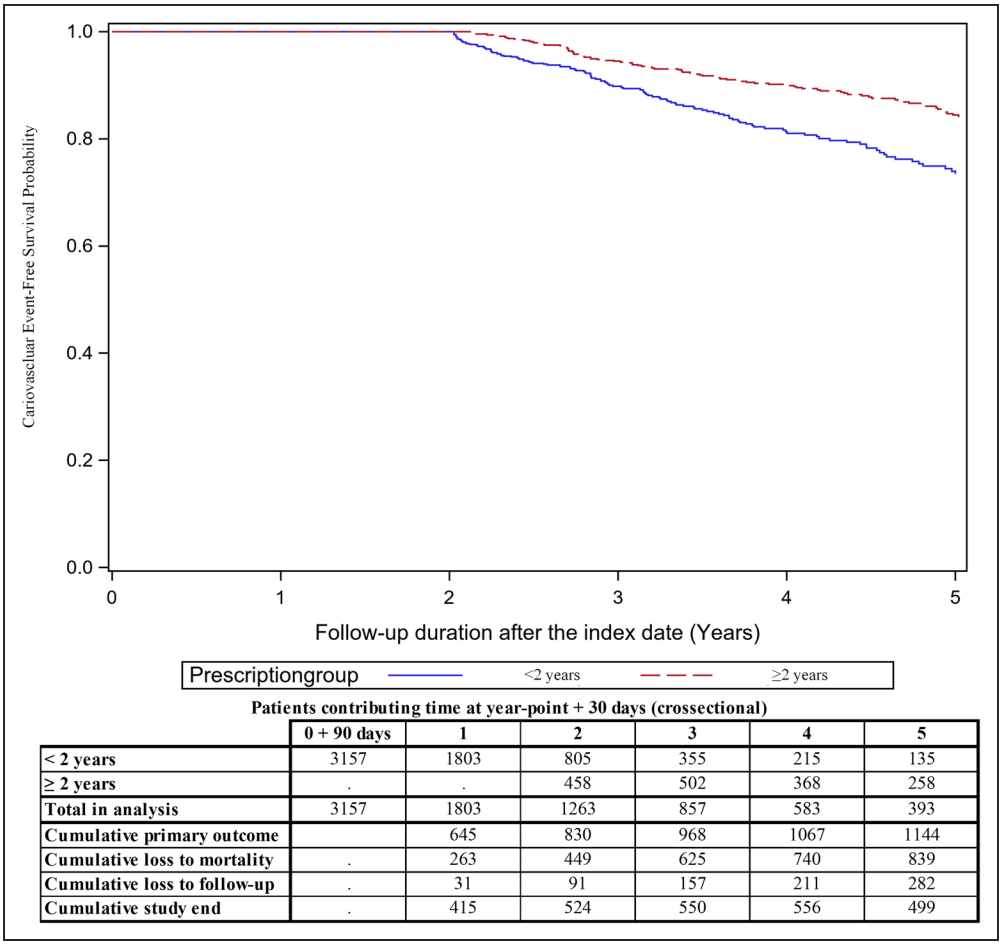
compared with being untreated in patients over 80 years showed a near significant effect, which may indicate that statin prescription may benefit patients above the age of 80 also before 2 years of prescription. The risk reduction found for <1 year of statin prescription in patients aged 65 to 80 years is in line with results found in other observational studies on early statin initiation.[9] However, this might be caused by selective prescription to more healthy patients resulting in healthy user bias. In contrast, the survival curves of the statin trials after stroke on major cardiovascular events (as well as any cardiovascular events) overlap during the first 2 year after randomization, showing no effect of <1 year of statin therapy.[2,4] On the contrary, all randomized controlled trials had an inclusion delay of several months, resulting in missing a potential pleiotropic effect during the early period after stroke.

Strengths and Limitations

This is the first observational study investigating the initiation and cumulative duration of statin prescription for secondary prevention of cardiovascular disease after a first stroke in patients aged 80 years and older. Our finding of a beneficial effect of statins on the primary outcome in patients aged 65 to 80 years group is comparable to that of published randomized controlled trials thereby supporting 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 stroke. Data sources for our outcomes, the combination of ONS, HES, and CPRD databases, have shown a good validity for cardiovascular diagnoses.[22]

The decision whether or not to initiate statin treatment at discharge is not random—it is associated with relevant known and unknown prognostic factors. We, therefore, investigated several durations of statin prescriptions, to account for prescription bias over time. Prescription bias or confounding by indication, however, could not be completely ruled out in patients above the age of 80. To account for prescription bias, we collected many potential baseline confounders, however, residual confounding cannot be completely ruled out.

This study showed that the most robust end points had a more robust effect compared with less robust end points (stroke, MI of the primary end point). The NNT to reduce all-cause mortality is lower than the NNT required to reduce the primary outcome in patients aged 80 years and older. Although we corrected for immortal time bias, residual bias might result from survivor bias. This survivor bias probably is most pronounced in the older age group, given the highest incidence rate for all-cause mortality in these patients. This leads to an overestimation of the NNT for all-cause mortality, particularly in the oldest age group. The less robust end points might be influenced by factors like stroke subtype and severity of stroke or MI. As this information was not available, residual confounding might explain the less pronounced effects of the primary outcomes. We did not have information on stroke severity. In an observational study, with reported National Institutes of Health Stroke Scales, higher scores were associated with less chance of receiving statin prescriptions.[23] Both differences in patient population and stroke severity could have led to an overestimation of our results and might explain the discrepancy between our findings from <1 year of statin prescription compared clinical trial outcomes. In our study, we defined statin treatment as having an active prescription for a statin; however, we do not know whether the patients actually took the prescribed statin, which may have led to underestimation of the actual effect of statin therapy. Furthermore, we did not take into account the dose of statin prescriptions, because our data, unfortunately, do not allow this examination this could have



Patients contributing time at year-point + 30 days (crossectional)

	0 + 90 days	1	2	3	4	5
< 2 years	3157	1803	805	355	215	135
≥ 2 years	.	.	458	502	368	258
Total in analysis	3157	1803	1263	857	583	393
Cumulative primary outcome		645	830	968	1067	1144
Cumulative loss to mortality	.	263	449	625	740	839
Cumulative loss to follow-up	.	31	91	157	211	282
Cumulative study end	.	415	524	550	556	499

Figure. Time-varying Kaplan-Meier curve for the primary outcome in patients aged 80 and above: comparison of >2 y of statin prescriptions with no or <2 y of statin prescriptions.

Kaplan-Meier curve on primary event-free survival probability in patients aged 80 and above. 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, respectively.

resulted in both under- and overestimation of the results. The decision to discontinue statin treatment by either the patient or the physician probably is also not random and may be directed by changes in patients' life expectancy. This may in part explain the stronger association found for all-cause mortality after 2 years of statin prescription in the older patients compared with the younger patients. Thus, healthy survivor bias might have resulted in overestimation of these effects of statin prescription on the primary outcome as well. Once a patient reached over 2 years of statin prescription, discontinuation of the statin prescription did not change the exposure group status of the patient, which in turn may lead to an underestimation. In addition, leaving a CPRD practice might also not have been a random decision. More frail patients are probably censored by being transferred out to a nursing home, which probably occurred in 282 patients of the patients aged 80 years and older group that were lost to follow-up. Furthermore, we collected data on the primary outcome from the HES database, a database with hospital discharge diagnoses. Not all patients, particularly those who are more frail, will be referred to a hospital in acute situations. As frail patients were less likely to receive statin prescriptions and have a higher risk of mortality, this might have led to an overestimation of the effect of statin prescription.

Lastly, patients who were lost to follow-up during the first 30 days after hospital discharge or who died during hospital stay were not included in our analysis, as statin exposure status was unknown during this period. If these patients would have been taken into account, the NNT of statin initiation during hospital admission would be higher. Thus, the results of our study apply to patients who are alive and not lost to follow-up 30 days postdischarge.

Implications for Clinicians and Policymakers

Our results provide evidence for initiating statins after a first stroke in patients above the age of 80 years to prevent cardiovascular disease recurrence Although prescription rates increase over time, in our study up to 40% of the patients aged 80 years and older, did not receive

a statin prescription within 90 days after discharge even in 2016. Guidelines give limited recommendations on the initiation and discontinuation of statin treatment in older patients.[24] Current evidence should be better implemented in guidelines and local poststroke protocols. In case of a positive decision regarding initiation of statins, efforts should be made to keep patients adherent to statins for at least 2 years regardless of a patient's age, except when the prognosis of the patient clearly deteriorates during these 2 years.

Future Research

In this study, we investigated the duration of statin treatment, but not the cholesterol level targets and harm. To be able to decide whether benefits outweighs harm and which is the most appropriate dose and type of statin, more research is deemed necessary in the oldest old.

Considering our results, it is hardly ethical to warrant a placebo randomized controlled trial, especially when considering the fact that statin therapy generally is adopted in most guidelines. However, comparing 2 different low-density lipoprotein cholesterol targets after acute stroke, might seem feasible in the oldest old, this has recently been done in younger patients.[25] Given the much higher competing risks in old age and the difficulties in earlier trials with discontinuation and spontaneous initiation of statin therapy next to placebo, large observational studies are an appealing alternative to a randomized controlled trial in the oldest old, while they generally are more feasible. Observational studies can yield sufficient evidence to further support decision making concerning initiating statin therapy with the optimal type, dose and benefit harm ratio in the oldest old. Clearly, in our study, several considerations were made whether or not to initiate statin therapy by the patients and physicians. Much is to be learned about the impact and interplay of these considerations (eg, preferences of patients and physicians, pill burden, expected benefit harm ratio) on how these decisions are made.

Conclusions

Statins initiated in patients aged 80 and older, discharged home after having been hospitalized for an ischemic stroke are associated with a reduction in cardiovascular events.

ARTICLE INFORMATION

Received May 11, 2020; final revision received October 16, 2020; accepted November 23, 2020.
The podcast and transcript are available at https://www.ahajournals.org/str/podcast.

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Sources of Funding

None.

Disclosures

None.

Supplemental Materials

Figures I–III
Tables I–IV

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