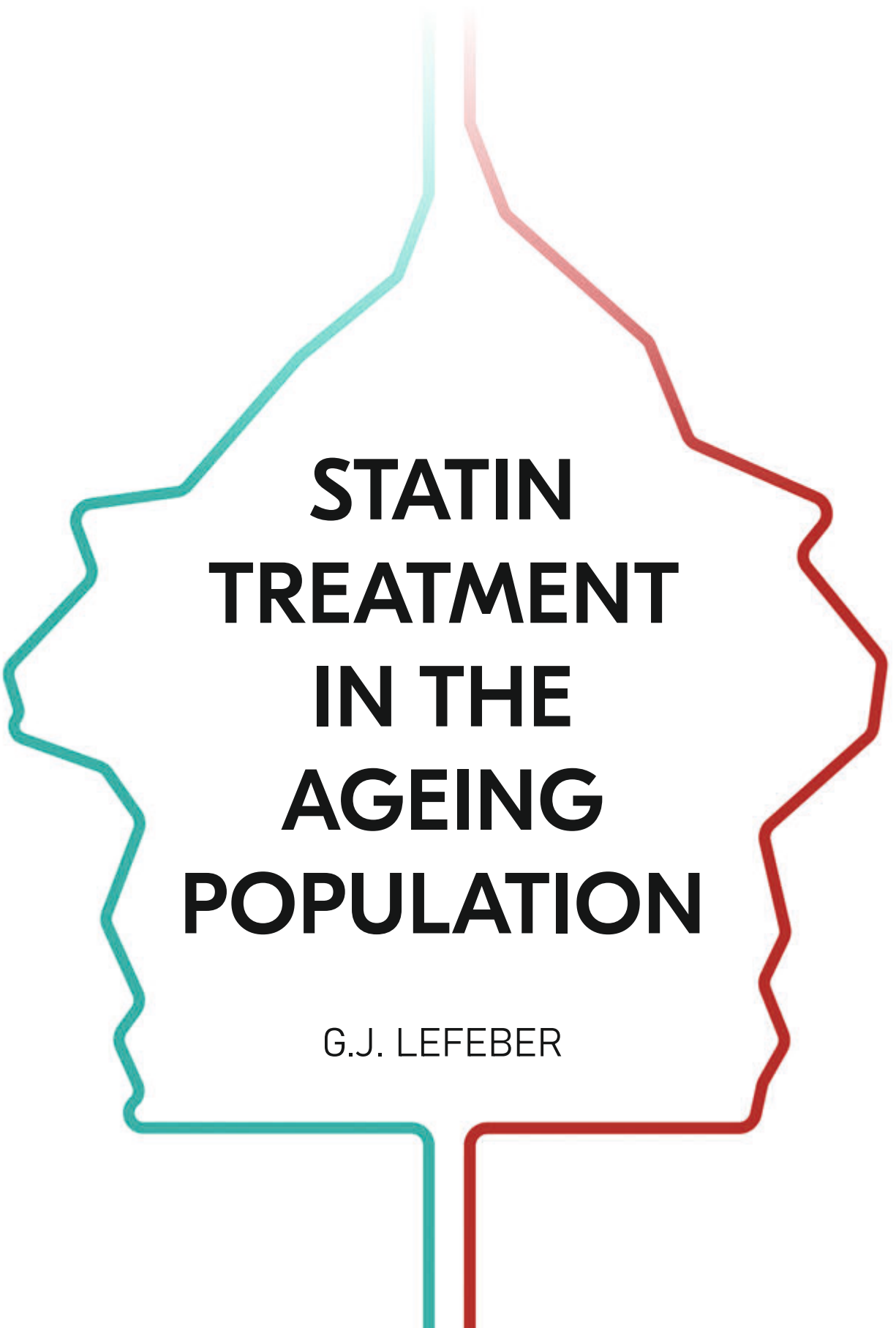

STATIN TREATMENT IN THE AGEING POPULATION

G.J. LEFEBER

Statin treatment in the ageing population

Geert Lefeber

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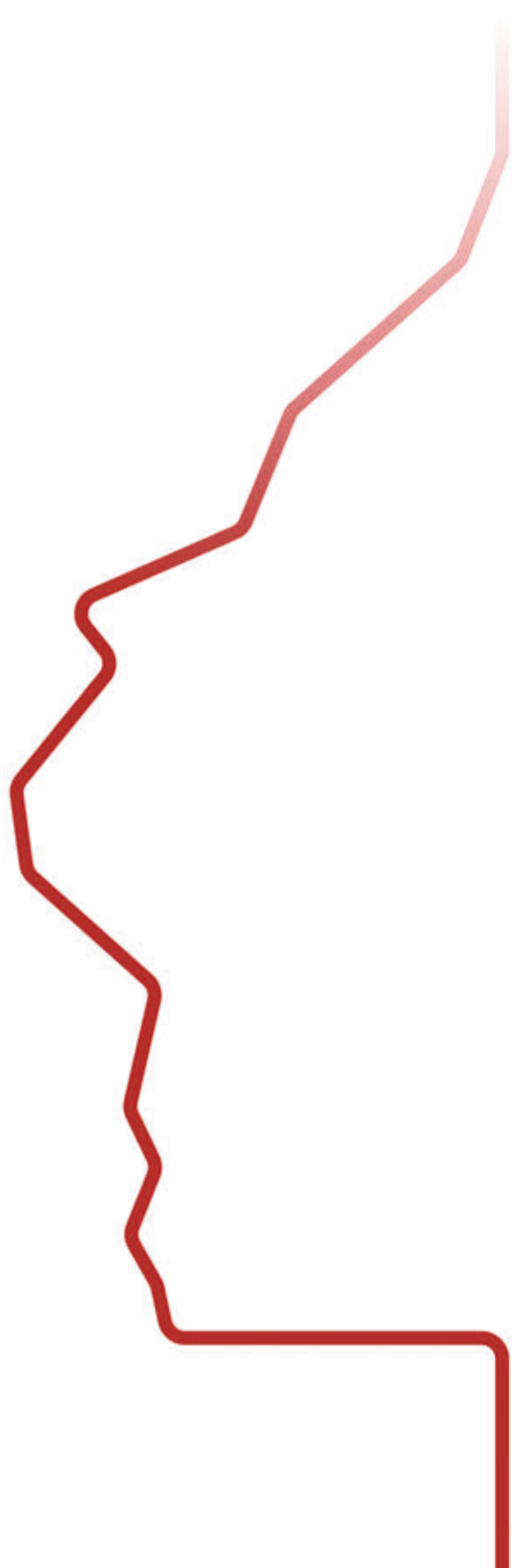
Contents

1

General introduction



Introduction

The 2019 edition of *World Population Prospects*, published by the United Nations, presents a prediction that by 2050, one in six people worldwide will be over 65 years of age, compared to one in 11 in 2019 (1). This demographic shift towards an ageing population is accompanied by an increased demand for healthcare services. Although developing countries are currently in the early stages of this trend, they will eventually face healthcare challenges similar to those in Europe and North America.

In Western countries, the number of patients aged 80 years and older has been increasing and will continue to rise in the coming years. This expansion in the number of older patients is concomitant with patients who have multiple conditions, such as myocardial infarction (MI) and ischemic stroke, which are the most common causes of death after the age of 70 (2). Cardiovascular disease affects up to 89% of men and 92% of women aged 80 years and older (3).

To prevent cardiovascular events in old age, the 2019 Dutch guidelines for cardiovascular risk management in the oldest old, patients after the age of 80, recommend treatment with antihypertensives, antiplatelets, and anticoagulants (4). However, statin treatment is only recommended for non-frail older patients, and until recently, no recommendations existed for statin treatment in the oldest old. Nevertheless, 80% of current patients over the age of 80 who have an indication for secondary prevention are being treated with statins (5).

Additionally, there is growing research interest in using statins in perioperative care to reduce postoperative cardiovascular complications (6). Aortic stenosis affects one in 10 individuals over the age of 80 (7) and was formerly considered a lethal condition since frail older patients were not considered to be sufficiently resilient to recover from significant surgical procedures, such as aortic valve replacement. However, modern minimally invasive techniques, like transcatheter aortic valve implantation (TAVI), allow doctors to successfully treat aortic stenosis even in patients over the age of 80 (8), and recent studies have proven that statin treatment is associated with improved long-term survival after TAVI (9).

Comorbid conditions, frailty, and varying life expectancy warrant tailored treatment decisions in older patients, both regarding the prevention of cardiovascular events and the replacement of aortic valves. Since clinical trial data in the oldest age group is scarce, available guidelines are not necessarily applicable to this cohort. To fill this knowledge gap, well-performed observational studies may support decision-making regarding the older population.

In the following, we present three common patient vignettes to illustrate both the existing knowledge gaps and current understanding concerning the initiation and discontinuation of statin treatment in the oldest old after a cardiovascular event. Additionally, we focus on the care of patients with aortic valve stenosis who are undergoing TAVI.

Statin initiation in the oldest old patients after a first cardiovascular event

Mrs K is an 84-year-old patient who presents at your hospital after her first cardiovascular event. She has well-controlled diabetes and hypertension. She is independent and lives alone, as her husband passed away several years ago. According to the hospital guidelines, initiation of statin treatment is indicated. However, you doubt whether this guideline suits your old patient. You know that current Dutch guidelines for cardiovascular risk management state that older patients have a high risk of recurrence of cardiovascular events and therefore they should be treated with statins like younger patients. Regardless, you sense that, for this patient, the guidelines may not apply. What if she asks you how she could benefit from statin treatment? What would you say? How effective are statins at her age? How long should she take statins to reach the desired effect; what is the time until benefit? Additionally, would it matter if she presented with either a stroke or an MI?

Statins were introduced in the early 1990s, and since then, no other drug class has been more extensively debated over such an extended period (10,11). The Leiden 85+ study, a 1997 observational study in persons over the age of 85, revealed an association between higher cholesterol levels and longevity (12). The effects of cholesterol-lowering therapy were not assessed in this study. Conversely, the PROSPER study, a randomised controlled trial (RCT) from 2002, demonstrates clear benefits of statin therapy in secondary prevention in older patients with a mean age of 75 years (13). However, it was not until 2019 that Dutch guidelines for cardiovascular risk management advised statin treatment for secondary prevention in the oldest old (4). A 2019 meta-analysis that used individual patient data from 28 RCTs confirms the benefits of statins in secondary prevention in older patients (14). This meta-analysis included over 14,000 patients above the age of 75; however, no patients over the age of 82 were included. Because of the limited evidence available regarding the oldest old, current guidelines advise healthcare providers to carefully weigh the risks and benefits of statin initiation in secondary prevention for these patients but do not offer much guidance on doing so. Notably, debates on risks and benefits for older patients specifically concern the use of statins, while there is far less discussion on other cardioprotective drugs (15,16).

Nevertheless, in general practice, prescription rates for secondary prevention in patients aged 80 years and older has increased from 24% between 2001 and 2005 to 80% between 2011 and 2015 (5). In statin-naïve patients at the age of 80, 3% per year receive their initial

statin prescription. Even at the age of 100, one in 200 patients begins statin treatment. Overall, the frailest patients are the most likely to receive statin prescriptions, as these patients more often have cardiovascular comorbidity (5). Yet, 20% of all older patients who have an indication for secondary prevention do not receive a statin prescription. This may be partially due to the guidelines that suggest careful weighing. However, it might also be caused by a lack of belief in the benefits of statins among prescribers and patients (15,16). We know little about the effects of statin treatment after a cardiovascular event in the oldest old. The following questions have already been answered for younger patients, but they also need to be answered for patients over the age of 80: What are the numbers needed to treat to prevent a cardiovascular recurrence or mortality? How long should statins be taken to be effective? What is the survival benefit of statin initiation after a cardiovascular event? Does an old patient live to benefit from statin treatment? Do the benefits of statins outweigh potentially adverse effects?

Statin discontinuation in the oldest old patients

A few years later, Mrs K, now 87 years old, again visits your outpatient clinic. She suffers from multiple comorbidities that make her mildly frail. Part of your geriatric assessment comprises the optimisation of her therapeutic regimen. She is currently using a statin for secondary prevention, and she experiences no side effects. Should the statin be discontinued? You estimate her life expectancy to be longer than two years, and you therefore decide to continue the statin treatment. But if her life expectancy was less than two years, would it be safe to discontinue statin treatment? What if she has mild but bothersome side effects, such as slight muscle aches? What if she becomes moderately or severely frail; would it be wiser to discontinue statin treatment?

Statins are frequently discontinued after the age of 80. Yearly, one in 20 older patients with high risk of cardiovascular events discontinues statin treatment (5). In 50% of overall patients who discontinue statin treatment, the reason for discontinuation is reported in the electronic medical record. In half of these reported reasons, statin treatment was listed as being no longer necessary (17), and discontinuation due to statin-related side effects was documented in 17% of these patients. More than half of the patients who discontinued due to side effects restarted statin treatment within one year, of whom 92% reported no further discontinuation. Of all drugs, statin treatment is within the top five priorities for deprescribing, according to general practitioners (18). Current guidelines offer some direction on discontinuing statin treatment in old, frail patients who are nearing the end of life (19), and most general practitioners are inclined to discontinue statin treatment in patients who have a limited life expectancy (20). However, in older patients who have a high cardiovascular risk and without limited life expectancy, 5% of general practitioners would discontinue statin treatment; this number increases to 35% if the patient is frail. Yet, the harm of statin discontinuation is largely unknown. Three recent observational studies have reported significant associations between statin discontinuation and increased

risk of cardiovascular events and mortality, primarily in patients who are taking statin treatment without a prior cardiovascular event (21–23). Only one trial has been performed on statin discontinuation in patients who have a limited life expectancy (24). In this study, the 60-day mortality increased from 20% to 23%. No statistically significant difference was found, which is likely due to the small sample size. Notably, none of these studies regarding statin discontinuation have accounted for frailty, although frailty itself is an independent risk factor for cardiovascular events (25). The following questions must be answered for all patients: Does discontinuation of statin treatment, when initiated for secondary prevention, lead to an increased risk of cardiovascular recurrence or mortality? Does the frailty status of a patient influence the risks of statin discontinuation?

Statin treatment and short-term outcomes after TAVI

During the geriatric assessment, you suspect that Mrs K, 87 years old, has symptoms related to aortic valve stenosis. After the cardiologist examined her, Mrs K is diagnosed with moderately severe aortic valve stenosis, for which TAVI is considered. The long-term benefits of TAVI are well established, and you expect that the patient will benefit from the procedure. However, what can you tell her about the short-term risks of complications in the TAVI perioperative period? Which parts of the geriatric assessment are predictors for these short-term complications? Would statin treatment improve her short-term complication risk after TAVI and offer long-term benefits, considering that perioperative pleiotropic effects have been suggested of statin treatment?

Prior to the development of the heart-lung machine in the 1960s, no effective treatment was available for aortic valve stenosis (26). Until 1990, patients aged 80 or older with aortic valve stenosis were generally considered unsuitable for cardiac surgery; only the fittest patients in this age group were considered for surgery. On April 16, 2002, the first TAVI was performed on a 57-year-old man who was not eligible for surgery (27). Although this patient died of another cause within four months, this procedure was a major breakthrough in the treatment of otherwise inoperable patients. Since then, the TAVI technique has been significantly improved, resulting in a substantial reduction in procedure-related complications, including acute kidney injury, high degree atrioventricular block, MI, and death (28). Consequently, age alone is no longer a determining factor in the decision to treat aortic valve stenosis (8). As the overall complication rate after TAVI is now much lower than previously, current TAVI guidelines have shifted from patients with symptomatic aortic valve stenosis towards patients with asymptomatic aortic valve stenosis; this shift is due to improved five-year outcomes in patients with presymptomatic aortic valve replacement compared to patients with delayed replacement (29). Generally, TAVI reduces the one-year mortality rate by 20% and the five-year mortality rate by 50% (30).

Because TAVI is a costly procedure, guidelines warrant frailty screening to determine which patients may enjoy long-term benefits from TAVI (30). Predictors of mortality within one year after TAVI include frailty, reduced gait speed, and reduced activities in daily life (31,32). Additionally, predicting one's short-term mortality is important to improve survival shortly after TAVI. Several researchers have investigated the predictors of short-term survival in the first 30 to 90 days after TAVI, reporting conflicting results regarding the predictive value of frailty (33–35). The assessment used to determine frailty in these studies was primarily limited to a single questionnaire or a few measures, while the gold standard of frailty evaluation is a comprehensive geriatric assessment (CGA)(36), which is a multidimensional, multidisciplinary process that identifies medical, psychological, social, and functional needs (37). To our knowledge, no scholars have investigated the predictive value of CGA outcomes on short-term outcomes after TAVI.

Several drugs, including beta blockers, RAAS inhibitors, and statins, have been investigated to find potential targets that may improve patients' long-term survival after TAVI (6,38,39). Beta blockers have not been found to be associated with short- and long-term survival after TAVI; however, both RAAS inhibitors and statins were associated with increased long-term survival after TAVI, although most research has focussed on statin treatment after TAVI. In a meta-analysis of observational studies, statin treatment was associated with improved one- and two-year survival rates after TAVI (6). Although this may be an expected effect of statin treatment overall, two recent studies have suggested short-term benefits of statin treatment at the time of TAVI in patients both with and without coronary artery disease. These suggested short-term benefits involve the pleiotropic effects of statins that prevent perioperative complications (40,41).

It can be concluded that two important questions remain unanswered: What are the predictors of short-term adverse events after TAVI? Is statin treatment associated with a lower risk of perioperative complications during and after TAVI?

The aims of this thesis are:

- To explore the benefits of initiating statin treatment for secondary prevention in patients aged 80 years and older.
- To explore the importance of continuous treatment after initiating statin treatment for secondary prevention in patients aged 80 years and older.
- To evaluate the effect of discontinuing statin treatment that began after a first MI or stroke on the risk of recurrence of cardiovascular events and mortality in both fit and frail patients.
- To identify predictors of postoperative adverse events following TAVI.
- To assess whether statin treatment is associated with a lower risk of short-term adverse events following TAVI.

Outline of this thesis

Chapter 2 focusses on the initiation and discontinuation of statin treatment after a cardiovascular event in the oldest old. We used data from the Clinical Practice Research Datalink, an ongoing database that contains general practitioner data for 60 million patients from the past 30 years, including dispensing records, and offers data linkages to hospital episode statistics as well as mortality data. In **Chapter 2.1,** we present our findings on statin initiation after a first MI in patients who are over the age of 80 as well as the risk reduction of cardiovascular recurrence and mortality. In **Chapter 2.2,** we present our findings on statin initiation after a first stroke in statin-naïve patients who are over the age of 80 and the risk reduction of cardiovascular recurrence and mortality. **Chapter 2.3** is dedicated to the discontinuation of statin treatment in older patients who are at high risk for cardiovascular recurrence. We present the results of statin discontinuation in older patients on the recurrence of cardiovascular events and non-cardiovascular mortality.

Chapter 3 focusses on predictors from the geriatric assessment of short-term outcomes following TAVI and the possible association of statin treatment with these outcomes. We used continuous prospectively collected data from over 600 patients who were potentially eligible for TAVI and were assessed with a standardised comprehensive assessment at University Medical Center Utrecht from 2014 until 2021. In **Chapter 3.1,** we assess predictors of short-term outcomes after TAVI, including 90-day mortality, 90-day readmissions, and periprocedural complications. In **Chapter 3.2,** we report whether statin treatment is associated with these short-term outcomes after TAVI.

Chapter 4 focusses on discussing the results of the studies as well as their implications for daily practice and future perspectives for research.

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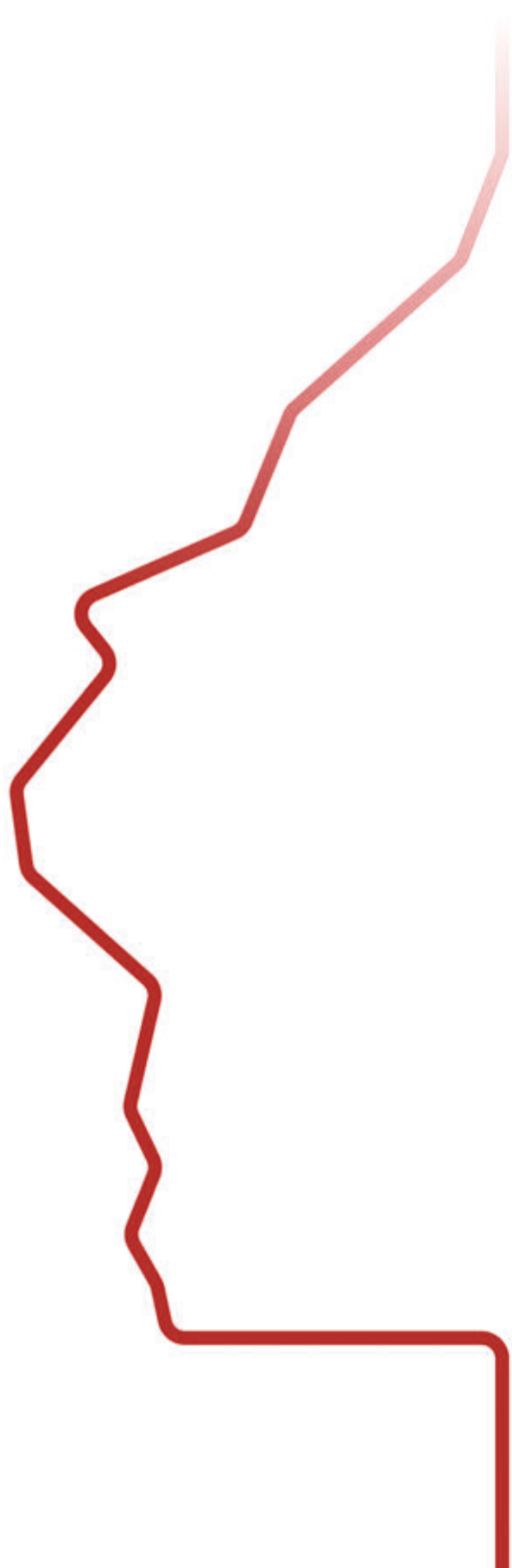
2

Initiation and discontinuation of statins in the oldest old in secondary prevention



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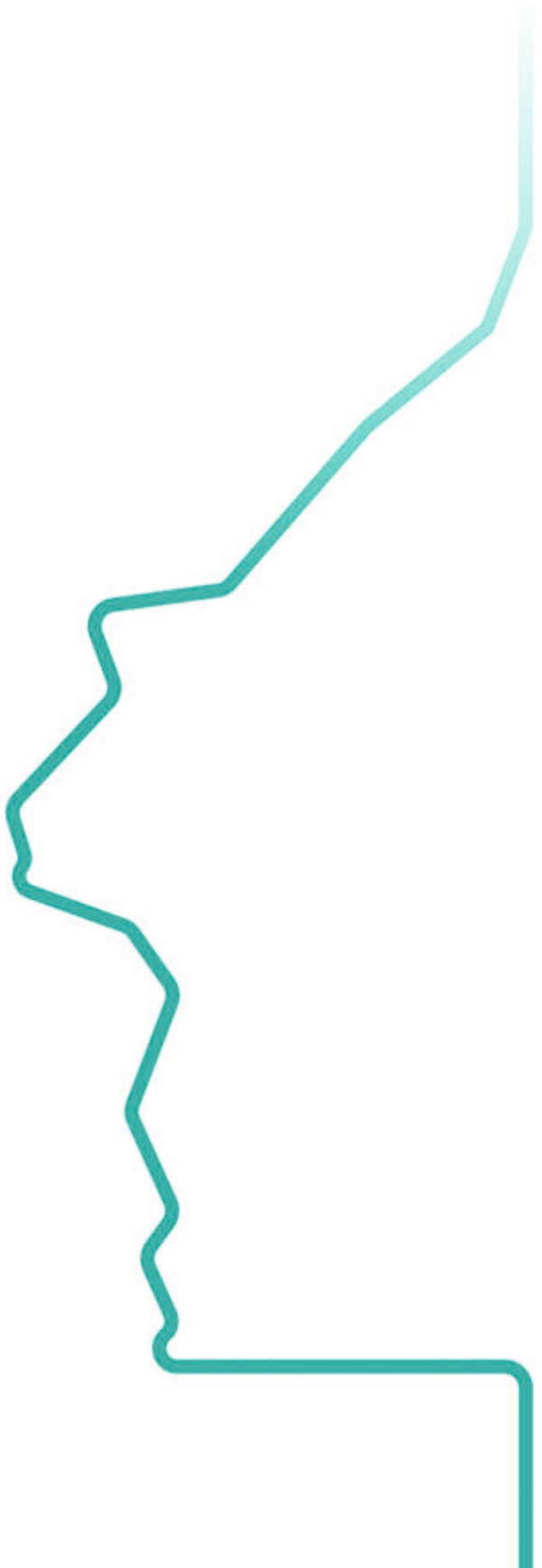

Statins after Myocardial Infarction in the Oldest: A Cohort Study in the Clinical Practice Research Datalink Database.

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JAGS 2020;68:329-336

Abstract

Objective: To explore the effect of initiating statins for secondary prevention after a first myocardial infarction in patients aged 80 and above.

Design: Retrospective cohort study.

Setting : Clinical Practice Research Datalink (1999 to 2016).

Participants: Patients aged 65 years and above hospitalized after a first myocardial infarction without a statin prescription in the year before hospitalization. The age group 65-80 years was included to compare our results to current evidence.

Measurements: The primary outcome was a composite of recurrent myocardial infarction, 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 two years of statin prescription time with untreated and less than two 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 two years of follow-up.

Results: 9020 patients were included. Among the 3900 age 80 and older two years of statin prescriptions resulted in a lower risk of the composite outcome (adjusted HR 0.81 (95% confidence interval 0.66 to 0.99), and on all-cause mortality (adjusted HR 0.84 (0.73 to 0.97). During 4.5 years median follow-up, the NNT for prevention of the primary outcome was 59 and for mortality 36. Correcting for 36.2% deaths during the first two 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 and above if continued for at least two years. Especially in patients with a low risk of two-year mortality statins should be considered.

Introduction

In patients aged 80 and older, statin prescription rates for secondary prevention increased from 24% in 1999 to 50-80% 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 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 two to three years of statin treatment to prevent MI, stroke and mortality(3–5). The trials included relatively healthy participants but few patients aged 80 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 RCTs to hospitalized patients(6).

Although most observational studies of older populations (mean age 74–87) 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 a 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 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 and older discontinue filling statin prescriptions within 2 years of treatment initiation(14).

The current American Heart Association guidelines on blood cholesterol management recommends statin treatment to patients above the age of 75 in the same way as for younger patients accept for a frailty evaluation(15). Evidence of the benefit of statin therapy in patients aged 80 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 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 UK(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 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 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 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 endpoint (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 endpoints 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 non-white), inclusion period (1999-2003, 2004-2008, 2009-2016; the last period is two years longer to account for the time lapse of two years before statin treatment effect in the main analysis), frailty status(19), Charlson comorbidity index (0, 1-2, 3-4, 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 sub-analyses, missing data were divided at random. Baseline characteristics were compared using chi-square 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 up to 80 years after investigating interaction between age and statin prescription.

In the first time-varying analyses, we compared two or more years of cumulative statin prescriptions, one to two years of cumulative statin prescriptions, and less than one year of cumulative statin prescriptions with no statin prescription. In sub analysis, patients with less than six months of follow-up or reaching the primary outcome within six 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 two years with data for patient-time of statin prescriptions lasting less than two years, including untreated time. We chose two years of statin prescriptions as cut-off point, since in most trials, the time to benefit (TTB) of statin treatment is two 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 two years of follow-up in the more than 2 year statin prescription group, NNTs were adjusted for mortality during the first two years by dividing the NNT by the survival probability 2 year after the index date (24). The median duration of follow up was calculated from patients with more than 2 years follow up. To further investigate the dose response and patient follow-up patterns, a Kaplan-Meier curve was added for the first five years of follow-up comparing patient-time with statin prescriptions lasting more than two years with data for patient-time of statin prescriptions lasting less than two 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 paper using SAS software, Version 9.4 of the SAS System for windows (Copyright © 2015 SAS Institute Inc., Cary, NC, USA.).

Results

Study population

The data of 33,151 patients older than 65 years with a first MI were available. Of these, 9020 patients fulfilled the inclusion criteria (supplementary figure S1), 3900 of whom were aged 80 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 65–80 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).

Table 1 baseline table

	80 years and older		Between the age of 65 and 80	
	1st 90 days statin prescription (n=2,594)	**1st 90 days untreated (n=1,306)**	**1st 90 days statin prescription (n=4,305)**	**1st 90 days untreated (n=815)**
Enrolment time period:				
1999 to 2003	376 (14.5)	477 (36.5)	1314 (30.5)	497 (61.0)
2004 to 2008	1006 (38.8)	354 (27.1)	1596 (37.1)	144 (17.7)
2009 to 2016	1212 (46.7)	475 (36.4)	1395 (32.4)	174 (21.4)
Age in years mean (SD)	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)
Caucasian	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	657 (25.3)	305 (23.4)	1085 (25.2)	193 (23.7)
Third	571 (22.0)	328 (25.1)	903 (21.0)	161 (19.8)
Fourth	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)	25.8 (4.3)	25.1 (4.6)	26.7 (4.4)	26.6 (5.2)

Table 1 Continued

	80 years and older		Between the age of 65 and 80	
	1st 90 days statin prescription (n=2,594)	**1st 90 days untreated (n=1,306)**	**1st 90 days statin prescription (n=4,305)**	**1st 90 days untreated (n=815)**
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 to 2	1149 (44.3)	588 (45.0)	1635 (38.0)	385 (47.2)
3 to 4	421 (16.2)	253 (19.4)	310 (7.2)	90 (11.0)
5 or more	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)
Number 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 of more	350 (13.5)	295 (22.6)	263 (6.1)	126 (15.5)

Legend: Characteristics of patients, according to statin prescription 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.

Primary outcome

As shown in table 2, more than two years of statin prescriptions compared to no statin prescription was nearly significant associated with a reduction of the primary endpoint in patients aged 80 years and older (adjusted HR 0.79, 95% CI 0.62–1.02) and a significant association in patients aged 65–80 years (adjusted HR 0.62, 95% CI 0.44–0.88) (Table 3). While statin prescription for one to two 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 six months or with less than six 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 2 Comparison of more than two years of statin prescription, one to two years of statin prescriptions, and less than one year of statin prescriptions with no statin prescription.

Age 80 and older	**Prescription group**	**PY**	**Events**	**IR/ 1000**
Primary outcome	Untreated	2,540	362	142
	< 1 year	3,032	311	103
	1-2 years	1,863	130	70
	≥ 2 years	4,076	254	62
All-cause mortality	Untreated	2,673	626	234
	< 1 year	3,175	437	138
	1-2 years	1,978	239	121
	≥ 2 years	4,439	516	116
Between the age of 65 - 80	**Prescription group**	**PY**	**Events**	**IR/ 1000**
Primary outcome	Untreated	1,903	159	84
	< 1 year	5,197	220	42
	1-2 years	4,061	90	22
	≥ 2 years	16,701	414	25
All-cause mortality	Untreated	1,975	252	128
	< 1 year	5,352	265	50
	1-2 years	4,223	195	46
	≥ 2 years	17,893	800	45

* Excluding all patients with a primary event within the first six months follow-up or less than six months of follow-up in the CPRD practice database. Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted;

Table 3 shows the effect of more than two years of statin prescription duration compared to less than two years of statin prescription on the primary outcome (i.e. the composite endpoint of MI, stroke, and cardiovascular mortality). Two years of statin prescriptions was significantly associated with a risk reduction of the primary endpoint in both age groups (≥80 years and 65–80 years), but the association was less pronounced in the older age group (adjusted HR 0.81, 95% confidence interval 0.66–0.99, and adjusted HR 0.67, 95% CI 0.53–0.84, respectively). Excluding patients with less than two years follow-up did not significantly change these results (adjusted HR 0.80, 95% confidence interval 0.65–0.98 in patients aged 80 and above, and adjusted HR 0.64, 95% CI 0.51–0.80, in patients between the age of 65 and 80 respectively). 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 two years, the NNT in the patients aged 80 and older increased more than that for patients aged 65–80 years (NNT 92.5 and 72.5, respectively).

HR	HR adj.	patients with > 6 months FU *	
		HR	HR adj.
ref.		ref.	
0.58 (0.50-0.68)	0.80 (0.67-0.95)	0.80 (0.64-1.00)	1.12 (0.88-1.42)
0.74 (0.57-0.96)	0.98 (0.75-1.29)	0.74 (0.57-0.96)	1.01 (0.77-1.34)
0.61 (0.48-0.77)	0.79 (0.62-1.02)	0.61 (0.48-0.77)	0.82 (0.63-1.06)
ref.		ref.	
0.50 (0.44-0.57)	0.71 (0.62-0.82)	0.62 (0.52-0.73)	0.88 (0.73-1.05)
0.71 (0.59-0.85)	0.99 (0.81-1.20)	0.71 (0.59-0.85)	1.02 (0.84-1.24)
0.53 (0.46-0.63)	0.79 (0.67-0.94)	0.53 (0.46-0.63)	0.82 (0.69-0.98)
HR	**HR adj.**	**patients with > 6 months FU ***	
		HR	**HR adj.**
ref.		ref.	
0.39 (0.31-0.49)	0.51 (0.41-0.65)	0.78 (0.54-1.14)	1.02 (0.68-1.52)
0.52 (0.35-0.75)	0.72 (0.49-1.05)	0.50 (0.34-0.73)	0.80 (0.54-1.18)
0.41 (0.29-0.56)	0.62 (0.44-0.88)	0.41 (0.29-0.56)	0.65 (0.46-0.92)
ref.		ref.	
0.33 (0.27-0.39)	0.53 (0.44-0.65)	0.51 (0 40-0.65)	0.74 (0.58-0.95)
0.59 (0.46-0.77)	0.97 (0.75-1.25)	0.59 (0.46-0.77)	0.96 (0.74-1.25)
0.36 (0.29-0.45)	0.62 (0.49-0.78)	0.35 (0.28-0.43)	0.60 (0.47-0.76)

Table 3 Effect of more than two years of statin prescriptions compared with no or less than two years of statin prescriptions.

Age 80 and older	**Prescription group**	**PY**	**Events**	**IR/ 1000 PY**	**HR**
Primary outcome	< 2 years	7,436	803	108	ref.
	≥ 2 years	4,076	254	62	0.64 (0.63-0.78)
All-cause mortality	< 2 years	7,826	1,302	166	ref.
	≥ 2 years	4,439	516	116	0.61 (0.54-0.70)
Between the age of 65 and 80	**Prescription group**	**PY**	**Events**	**IR/ 1000 PY**	**HR**
Primary outcome	< 2 years	11,162	469	42	ref.
	≥ 2 years	16,701	414	25	0.48 (0.39-0.60)
All-cause mortality	< 2 years	11,550	712	62	ref.
	≥ 2 years	17,893	800	45	0.40 (0.38-0.52)

[†] the % of patients who died with two years of the index date according to the ONS database and patients leaving a CPRD practice were included. Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted; NNT, number needed to treat

Figure 1. 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 supplementary data (Supplementary figure S2).

Secondary outcomes

As described in table 2, more than two 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, one to two 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 one 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 six months of follow-up or patients with primary event during the first six months in patients aged 65-80 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 two years of statin prescriptions compared with less than two 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. HR's for individual components of the primary outcome are available in supplementary table S2 and S3.

HR adj.	NNT	NNT adj	2 yr † (%)	NNT † adj	Median FU in 2 event free year survivors (years)
					4.5
0.81 (0.66-0.99)	30.9	59.0	36.2	92.5	
					4.8
0.84 (0.73-0.97)	15.7	39.1	36.2	61.3	
HR adj.	**NNT**	**NNT adj**	**2 yr † (%)**	**NNT † adj**	**Median FU in 2 year event free survivors (years)**
					6.7
0.67 (0.53-0.84)	38.7	61.3	15.5	72.5	
					7.2
0.73 (0.62-0.85)	16.1	36.5	15.5	43.2	

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 endpoint (MI, stroke, and cardiovascular mortality) and the secondary outcome (all-cause mortality) after two years of prescriptions, which was also seen in patients aged 65–80 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 and older, the NNT was comparable in the two age groups. After correction for deaths during the first two 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 65–80 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 PROSPER study (treatment for 3 years)(3). This effect can be partly explained by the increase in competing risks in very 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 rate of cardiovascular events and all-cause mortality were higher in the first two 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 one year of statin prescriptions to be beneficial, but this benefit disappeared after we excluded patients who experienced a cardiovascular event in the first six months after the index date. This was probably caused by survivor treatment selection(27), competing medical issues(28) or 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 six 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 and older(14). This might be explained by the large proportion of patients in the user group (43%) that discontinued therapy within two years of statin initiation and by the exclusion of patients who started statin therapy more than two months after the event.

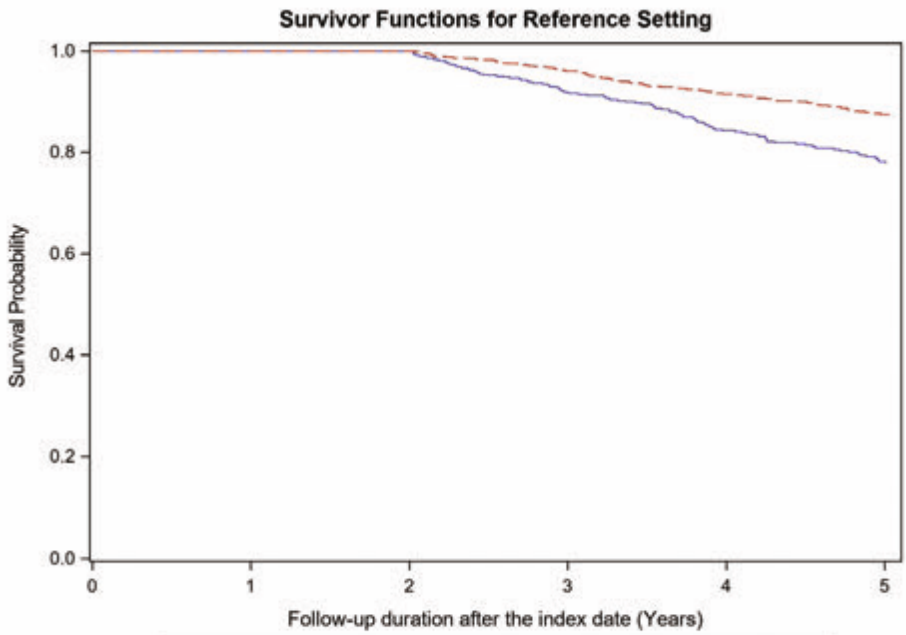
Strengths and limitations

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 and older. Our finding of a beneficial association of statins in patients aged 65-80 years group is comparable to that of randomized controlled trials 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 six months of treatment. In our analysis, less than two 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 two 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 risk exist as well, patient are censored due to all cause mortality or loss to follow-up, mostly in the less than two 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 whether or not 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.

Figure 1 Time varying Kaplan-Meier curve for the primary outcome in patients aged 80 and above: comparison of more than two years of statin prescriptions with no or less than 2 years of statin prescriptions.



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

	0 + 90 days	1	2	3	4	5
< 2 years	3900	2594	1043	489	326	215
≥ 2 years	.	.	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

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.

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 two 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.

Lastly, 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 policymakers

Our results confirm that patients need to take statins for minimally two years after a first MI to achieve benefit, regardless of a patient's age. If patients aged 80 and older are at high risk of dying within two 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 doctors to decide whether or not to initiate preventive treatment with statins in their oldest old patients.

Conclusion

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

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All authors have completed the ICMJE uniform disclosure form at 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 three years; no other relationships or activities that could appear to have influenced the submitted work.

Author contributions:

Contributions of the authors of this manuscript were as follows. Geert Lefeber was involved in the conception and design of the study, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. Patrick C. Souverein was involved in conception and design of the study, acquisition of data, critical revision of the manuscript, and supervision. Anthonius de Boer and Marcel Bouvy were involved in conception and design of the study and critical revision of the manuscript. Huiberdina Koek and Wilma Knol were involved in conception and design of the study, analysis and interpretation of data, critical revision of the manuscript and supervision.

Transparency declaration:

The lead author (Geert Lefeber) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; 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) is 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 advice on the interpretation or writing up of results.

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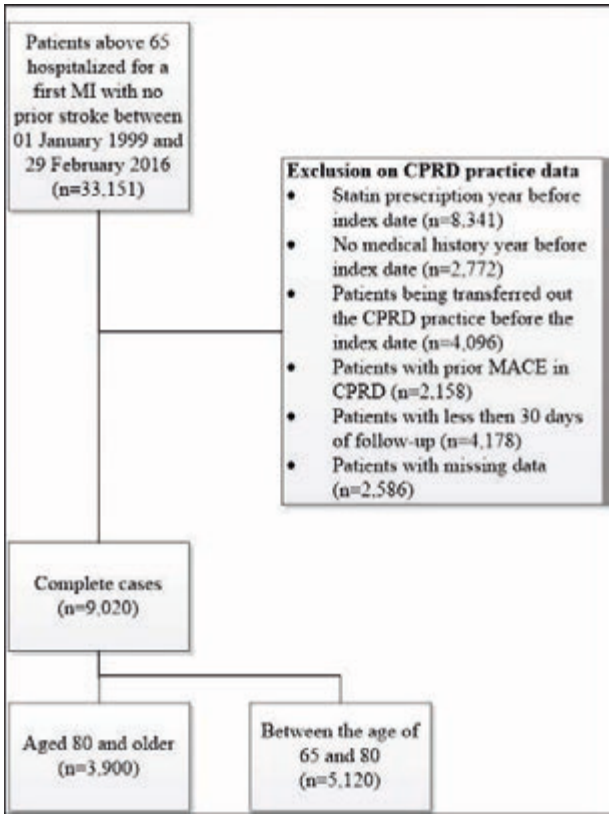
Supplementary data chapter 2.1

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 and above and between the age of 65 and 80.

	Between the age of 65 and 80				
	Untreated (1,903 PY)	**<1 year (5,197 PY)**	**≥1-2 years (4,061 PY)**	**<2 year (11,162 PY)**	**≥2 year (16,701 PY)**
Antiplatelet at baseline	22.0	14.5	13.1	15.4	13.4
Antiplatelet during follow-up	56.6	82.9	87.1	79.6	83.6
Oral anticoagulants at baseline	3.7	1.8	1.5	2.0	1.2
Oral anticoagulants during follow-up	12.1	7.2	6.8	8.0	9.7
Beta blokker at baseline	15.6	14.7	14.5	14.8	14.4
Beta blokker during follow-up	35.2	66.5	68.8	61.6	66.8
RAAS inhibitors at baseline	23.3	19.2	18.9	19.8	16.4
RAAS inhibitors during follow-up	47.3	73.5	79.6	70.9	79.1
Calcium channel blocker at baseline	19.5	18.0	18.6	18.5	17.8
Calcium channel blocker during follow-up	20.8	19.1	19.8	19.7	23.3
Diuretics at baseline	26.6	21.5	20.3	22.0	20.4
Diuretics during follow-up	40.7	29.9	30.5	32.1	33.8
Nitrates at baseline	12.7	9.4	8.9	27.0	26.5
Nitrates during follow-up	23.4	30.3	24.6	9.8	9.3
NSAID at baseline	15.6	14.5	15.7	15.1	16.0
NSAID during follow-up	8.5	6.5	6.2	6.8	5.8
Glucosteroids at baseline	9.1	6.5	5.9	6.7	4.5
Glucosteroids follow-up	8.6	5.5	4.9	5.8	5.5
Oral antidiabetics at baseline	8.4	4.7	5.1	5.5	4.3
Oral antidiabetics during follow-up	8.5	5.5	7.0	6.6	9.4
Insulin therapy at baseline	1.5	1.2	0.9	1.1	0.9
Insulin therapy during follow-up	5.0	3.7	3.4	3.8	3.5
Antipsychotic at baseline	2.0	2.2	2.0	2.1	2.0
Antipsychotic during follow-up	2.5	2.0	2.1	2.1	2.1

Supplementary Table S1 Continued

	80 years and older				
	Untreated (3,540 PY)	**<1 year (3,032 PY)**	**≥1-2 years (1,863 PY)**	**<2 year (7,436 PY)**	**≥2 year (4,076 PY)**
Antiplatelet at baseline	25.8	23.1	21.7	23.7	20.3
Antiplatelet during follow-up	60.7	80.7	83.3	74.4	79.8
Oral anticoagulants at baseline	4.1	3.1	2.6	3.3	2.7
Oral anticoagulants during follow-up	7.7	6.9	7.5	7.3	10.2
Beta blokker at baseline	19.8	18.7	19.5	19.3	17.9
Beta blokker during follow-up	37.4	60.9	63.2	53.3	61.3
RAAS inhibitors at baseline	27.5	28.4	29.3	28.3	24.0
RAAS inhibitors during follow-up	44.5	68.0	72.5	61.0	70.4
Calcium channel blocker at baseline	21.8	23.9	24.5	23.3	24.0
Calcium channel blocker during follow-up	18.8	18.3	18.6	18.5	20.1
Diuretics at baseline	38.4	35.0	36.4	36.5	35.6
Diuretics during follow-up	52.8	46.0	46.2	48.4	47.2
Nitrates at baseline	15.1	12.0	11.7	28.7	31.7
Nitrates during follow-up	26.6	30.6	28.5	13.0	10.7
NSAID at baseline	13.8	14.3	13.3	13.9	15.8
NSAID during follow-up	6.4	4.9	4.1	5.2	3.7
Glucosteroids at baseline	8.4	7.7	7.5	7.9	6.2
Glucosteroids follow-up	8.1	6.7	6.2	7.1	5.1
Oral antidiabetics at baseline	8.6	5.3	5.0	6.4	3.2
Oral antidiabetics during follow-up	8.4	6.0	6.4	7.0	5.6
Insulin therapy at baseline	2.3	1.2	1.6	1.7	0.6
Insulin therapy during follow-up	3.7	1.9	2.1	2.6	2.0
Antipsychotic at baseline	3.5	3.0	2.3	3.0	2.1
Antipsychotic during follow-up	4.3	2.6	2.7	3.2	2.9

Given values are percentages of time in the analysis under baseline medication treatment and medication treatment during follow up. PY, patient–years.

Supplementary Table S2 Comparison of effect of more than two years of statin treatment, one to two years of statin treatment, and less than one year of statin with no treatment on the individual components of the primary outcome.

Age 80 and older	Prescription group	PY	Events	IR/ 1000 PY	HR	HR adj.
Non fatal MI	Untreated	2,580	110	43	ref.	
	< 1 years	3,055	86	28	0.49 (0.37-0.66)	0.60 (0.44-0.83)
	1-2 years	1,887	28	15	0.92 (0.50-1.71)	1.06 (0.56-2.00)
	≥ 2 years	4,151	51	12	1.06 (0.56-2.00)	1.18 (0.61-2.29)
Non fatal stroke	Untreated	2,632	31	12	ref.	
	< 1 years	3,149	29	9	0.71 (0.41-1.22)	0.83 (0.46-1.50)
	1-2 years	1,952	19	10	1.04 (0.49-2.24)	1.20 (0.52-2.74)
	≥ 2 years	4,358	30	7	0.63 (0.31-1.25)	0.67 (0.31-1.45)
Fatal MI	Untreated	2,673	7	3	ref.	
	< 1 years	3,174	77	24	0.65 (0.47-0.91)	0.92 (0.64-1.32)
	1-2 years	1,978	31	16	0.90 (0.52-1.56)	1.40 (0.79-2.48)
	≥ 2 years	4,439	51	11	0.52 (0.32-0.87)	0.74 (0.43-1.28)
Fatal Stroke	Untreated	2,673	17	6	ref.	
	< 1 years	3,174	13	4	0.49 (0.23-1.06)	1.04 (0.46-2.36)
	1-2 years	1,978	9	5	1.26 (0.42-3.82)	1.71 (0.55-5.33)
	≥ 2 years	4,439	15	3	0.50 (0.20-1.23)	0.86 (0.31-2.43)
CV mortality	Untreated	2,673	232	87	ref.	
	< 1 years	3,174	202	64	0.62 (0.51-0.76)	0.92 (0.74-1.14)
	1-2 years	1,978	90	46	0.66 (0.49-0.89)	0.91 (0.66-1.24)
	≥ 2 years	4,439	197	44	0.56 (0.43-0.72)	0.76 (0.58-1.01)

Supplementary Table S2 Continued

Between the age of 65 and 80	Prescription group	PY	Events	IR/ 1000 PY	HR	HR adj.
Non fatal MI	Untreated	1,909	64	34	ref.	
	< 1 years	5,228	101	19	0.41 (0.29-0.57)	0.45 (0.31-0.64)
	1-2 years	4,097	21	5	0.24 (0.12-0.50)	0.26 (0.12-0.55)
	≥ 2 years	17,028	115	7	0.51 (0.26-1.02)	0.56 (0.27-1.14)
Non fatal stroke	Untreated	1,961	17	9	ref.	
	< 1 years	5,317	26	5	0.60 (0.30-1.16)	0.58 (0.29-1.17)
	1-2 years	4,182	16	4	0.92 (0.36-2.35)	1.07 (0.40-2.92)
	≥ 2 years	17,533	92	5	0.44 (0.21-0.94)	0.71 (0.32-1.57)
Fatal MI	Untreated	1,975	32	16	ref.	
	< 1 years	5,352	34	6	0.27 (0.16-0.46)	0.39 (0.23-0.68)
	1-2 years	4,223	25	6	0.61 (0.29-1.28)	0.92 (0.44-1.93)
	≥ 2 years	17,893	82	5	0.41 (0.19-0.84)	0.63 (0.29-1.36)
Fatal Stroke	Untreated	1,975	8	4	ref.	
	< 1 years	5,352	4	1	0.24 (0.07-0.87)	0.34 (0.09-1.32)
	1-2 years	4,223	4	1	0.63 (0.14-2.76)	0.70 (0.12-4.01)
	≥ 2 years	17,893	21	1	0.18 (0.06-0.55)	0.37 (0.11-1.22)
CV mortality	Untreated	1,975	78	39	ref.	
	< 1 years	5,352	99	18	0.37 (0.27-0.51)	0.62 (0.44-0.87)
	1-2 years	4,223	59	14	0.59 (0.37-0.93)	0.96 (0.61-1.53)
	≥ 2 years	17,893	259	14	0.36 (0.24-0.54)	0.64 (0.42-0.97)

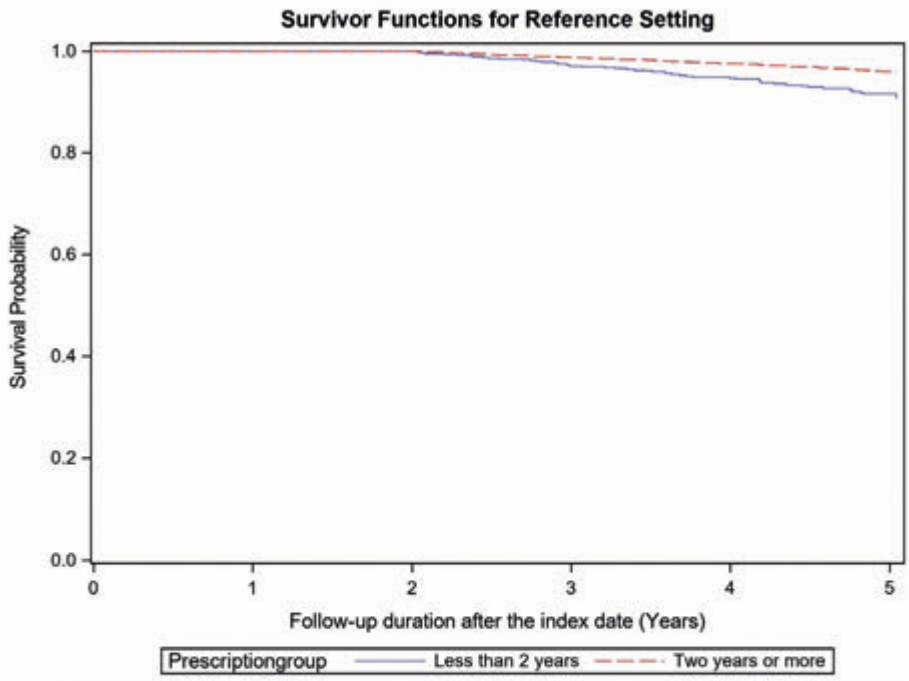
Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted.

Supplementary Table S3 Effect of more than two years of statin treatment compared with no or less than two years of statin prescriptions on the individual components of the primary outcome.

Age 80 and older	Prescription group	PY	Events	IR/ 1000 PY	HR	HR adj.
Non fatal MI	no and < 2 years	7,524	224	30	ref.	
	≥ 2 years	4,151	51	12	0.68 (0.44-1.06)	0.84 (0.54-1.32)
Non fatal stroke	no and < 2 years	7,735	79	10	ref.	
	≥ 2 years	4,358	30	7	0.62 (0.36-1.08)	0.67 (0.37-1.19)
Fatal MI	no and < 2 years	7,826	186	24	ref.	
	≥ 2 years	4,439	51	11	0.58 (0.38-0.88)	0.71 (0.46-1.10)
Fatal Stroke	no and < 2 years	7,826	39	9	ref.	
	≥ 2 years	4,439	15	3	0.66 (0.30-1.45)	1.12 (0.49-2.56)
CV mortality	no and < 2 years	7,826	524	67	ref.	
	≥ 2 years	4,439	197	44	0.64 (0.52-0.80)	0.82 (0.66-1.04)
Non fatal MI	no and < 2 years	11,235	186	17	ref.	
	≥ 2 years	17,028	115	7	0.64 (0.40-1.02)	0.77 (0.48-1.25)
Non fatal stroke	no and < 2 years	11,460	59	5	ref.	
	≥ 2 years	17,533	92	5	0.51 (0.31-0.83)	0.68 (0.41-1.13)
Fatal MI	no and < 2 years	11,550	91	8	ref.	
	≥ 2 years	17,893	82	5	0.47 (0.29-0.77)	0.64 (0.39-1.06)
Fatal Stroke	no and < 2 years	11,550	16	1	ref.	
	≥ 2 years	17,893	21	1	0.23 (0.11-0.51)	0.36 (0.16-0.85)
CV mortality	no and < 2 years	11,550	236	20	ref.	
	≥ 2 years	17,893	259	14	0.45 (0.35-0.60)	0.69 (0.52-0.92)

Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted.

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

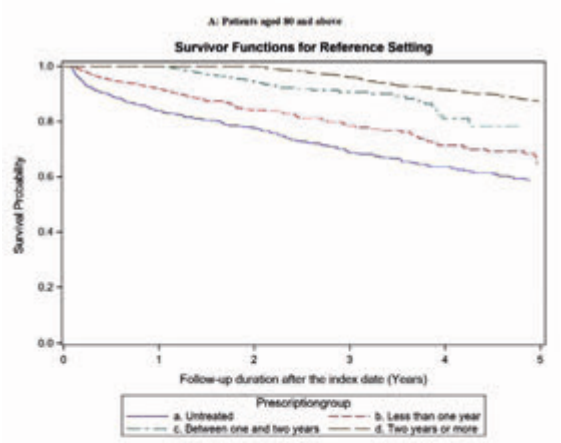


Patients contributing time at year-point + 30 days (crossectional)

	0 + 90 days	1	2	3	4	5
< 2 years	5120	4278	1536	577	375	264
≥ 2 years	.	.	2194	2694	2446	2136
Total in analysis	5120	4278	3730	3271	2821	2400
Cumulative primary outcome	.	292	401	486	558	650
Cumulative loss to mortality	.	185	324	433	553	654
Cumulative loss to follow-up	.	22	85	173	283	410
Cumulative study end	.	343	580	757	905	1006

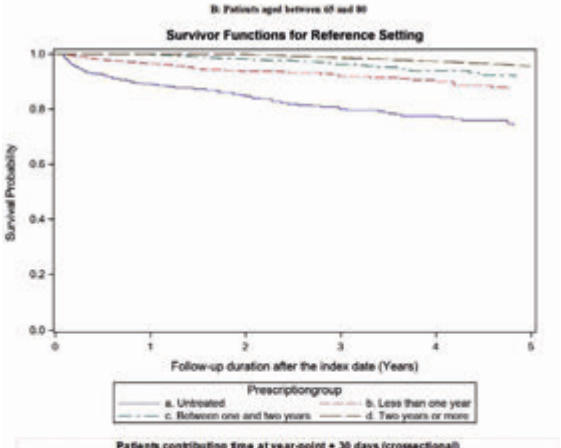
Numbers at each year refer to the remaining patients at risk, reached the primary outcome or have been censored by all-cause mortality, loss-to-follow-up or reaching the study end date respectively.

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



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

	0 + 90 days	1	2	3	4	5
UNTREATED	1306	616	396	260	182	119
< 1 year	2594	687	189	125	91	68
1 to 2 years	.	1291	458	104	53	28
> 2 years	.	.	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



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

	0 + 90 days	1	2	3	4	5
UNTREATED	815	401	271	183	131	93
< 1 year	4305	1051	280	183	123	90
1 to 2 years	.	2826	985	211	121	81
> 2 years	.	.	2194	2694	2446	2136
Total in analysis	5120	4278	3730	3271	2821	2400
Cumulative primary outcome	.	292	401	486	558	650
Cumulative loss to mortality	.	185	324	433	553	654
Cumulative loss to follow-up	.	22	85	173	283	410
Cumulative study end	.	343	580	757	905	1006

Numbers at each year refer to the remaining patients at risk, reached the primary outcome or have been censored by all-cause mortality, loss-to-follow-up or reaching the study end date respectively.

2.2

Statins after Ischemic Stroke in the Oldest: a Cohort Study using the Clinical Practice Research Datalink database.

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Abstract

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 65-80 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 two years of statin prescription time with untreated and less than two 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 two years of follow-up.

Results: 5,910 patients, aged 65 years and older were included, of whom 3,157 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 endpoint (adjusted HR 0.80; 95% confidence interval, 0.62-1.02) and all-cause mortality (adjusted HR 0.67; 95% confidence interval, 0.57-0.80). After correction for the mortality of 23.9% of the patients during the first two years, the NNT was 64 for the primary outcome during a median follow-up of 3.9 years and 19 for all-cause mortality.

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

Introduction

Patients aged over 80 years contribute to one-third of all stroke types[1]. Compared to 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].

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 two 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 six months after the initial stroke. During follow-up 10-21% of patients in the placebo group was found to initiate statin therapy. On the other hand, 15-25% 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 stroke patients 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 CPRD. Our study was performed using data from the Clinical Practice Research Datalink (CPRD), covering more than 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 65–80 years in order 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 less than 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 endpoint (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 endpoints 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 non-cardiovascular 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 recoded 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 two years longer to account for the time lapse of two 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] (supplementary data Table I). 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 chi-square 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% confidence intervals (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 two or more years of cumulative statin prescriptions, one to two years of cumulative statin prescriptions, and less than one 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 more than two years with data for patient-time of statin prescriptions

lasting less than two years, including untreated time. We chose two years of statin prescriptions as cut-off point, since in most trials, the time to benefit of statin treatment is two years, [16–18]. Sensitivity analysis was performed after excluding patients with less than 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 two years of follow-up in the more than 2 year statin prescription group, NNTs were adjusted for mortality during the first two 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 more than 2 years follow-up. To further investigate the dose response and patient follow-up patterns, a Kaplan-Meier curve was added for the first five years of follow-up comparing patient-time with statin prescriptions lasting more than two years with data for patient-time of statin prescriptions lasting less than two 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, 5,910 patients fulfilled the inclusion criteria (supplementary figure I), of whom 3,157 were aged 80 and older. In 1,638 (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 supplementary tables I - II). We included 2,753 patients aged 65–80 years, of whom 1,723 (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, more than two years of statin prescriptions compared to no statin prescriptions was significantly associated with a lower risk of the primary endpoint (i.e. the composite endpoint of non-fatal MI or stroke, and cardiovascular mortality) in both patients aged 80 years and older and in the 65-80 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 two years compared with no prescription in patients aged 80 years and older was nearly statistically significant associated with prevention of the primary endpoint (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 less than one 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 1 baseline table

	80 years and older (n=3,157)		Between the age of 65 and 80 (n=2753)	
	1st 90 days statin treatment (n=1,638)	**1st 90 days untreated (n=1,519)**	**1st 90 days statin treatment (n=1,723)**	**1st 90 days untreated (n=1,030)**
Enrolment time period:				
1999 to 2003	86 (19.1)	365 (80.9)	224 (31.6)	484 (68.4)
2004 to 2008	531 (53.0)	472 (47.0)	667 (72.3)	255 (27.7)
2009 to 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)
Caucasian	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 to 2	681 (41.58)	652 (42.92)	638 (37.03)	417 (40.49)
3 to 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)

Table 1 Continued

	80 years and older (n=3,157)		Between the age of 65 and 80 (n=2753)	
	1st 90 days statin treatment (n=1,638)	**1st 90 days untreated (n=1,519)**	**1st 90 days statin treatment (n=1,723)**	**1st 90 days untreated (n=1,030)**
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)

Legend: 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.

Table 3 shows the effect of more than two years of statin prescription compared to less than two 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% confidence interval 0.62–1.02). In those ageing 65–80 years the risk of the primary endpoint was significantly reduced (adjusted HR 0.74, 95% CI 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 to 39.9 in those aging 65-80 years). After adjusting for mortality in the first two years, the NNT increased in both age groups (NNT 48.8 and 68.0, respectively).

Figure 1. 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 supplementary data (Supplementary figures II - III).

Secondary outcomes

More than two years of statin prescription compared to no statin prescription improved all-cause mortality in patients aged 80 years and older and nearly in the 65-80 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 two 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 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 more than two years of statin prescription compared with less than two 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 65-80 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 to patients ageing between 65 and 80 years (14.8 and 177.0 respectively, after adjusting for mortality in the first two years this changed to 19.4 and 202, respectively). Except for the positive effect on cardiovascular mortality, more than two years of statin prescription was not significantly associated with all other secondary outcomes (supplementary table III - IV).

Table 2 Comparison of effect of more than two years of statin treatment, one to two years of statin treatment, and less than one year of statin with no treatment.

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

Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted;

Table 3 Effect of more than two years of statin treatment compared with less than two years of statin treatment or no statin treatment

Age 80 and older	Prescription group	PY	Events	IR/ 1000 PY after 2 years	HR
Primary outcome	< 2 years	5,176	847	113	ref.
	≥ 2 years	1,953	133	68	0.60 (0.47-0.77)
All-cause mortality	< 2 years	5,640	1,091	254	ref.
	≥ 2 years	2,175	287	132	0,52 (0,44-0,61)
Between the age of 65 and 80	**Prescription group**	**PY**	**Events**	**IR/ 1000 PY after 2 years**	**HR**
Primary outcome	< 2 years	6,194	488	60	ref.
	≥ 2 years	4,793	160	33	0.56 (0.44-0.72)
All-cause mortality	< 2 years	6,659	522	88	ref.
	≥ 2 years	5,404	318	59	0.67 (0.55-0.81)

[†] the % of patients who died with two years of the index date according to the ONS database and patients leaving a CPRD practice were included. Ref., reference group; PY, patient–years; HR, hazard ratio; adj, adjusted; NNT, number needed to treat; FU, follow-up.

Discussion

Main findings

Initiating statin prescription followed by continuation for at least two years after a first stroke in patients aged 80 years and older compared to no prescription is associated with a risk reduction of the primary composite endpoint (non-fatal MI or non-fatal stroke and cardiovascular mortality) in line with results in patients aged 65–80 years. Comparing more than two years of statin prescription to less than two 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 endpoint as well, The calculated NNT is lower in patients aged 80 years and older compared to those aged 65-80 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 65-80 years are in line with the results of the trial evidence when comparing two years of statin prescription to less than two years of statin prescription including being untreated [8]. In

HR adj.	NNT	NNT adj	2 yr † (%)	NNT † adj	Median FU in 2 year event free survivors (years)
					3.9
0.80 (0.62-1.02)	24.1	48.8	23.9	64.1	
					4.2
0,67 (0,57-0,80)	10.0	14.8	23.9	19.4	
HR adj.	**NNT**	**NNT adj**	**2 yr † (%)**	**NNT † adj**	**Median FU in 2 year event free survivors (years)**
					5.4
0.74 (0.57-0.96)	39.9	68	12.5	77.7	
					5.9
0.93 (0.76-1.13)	37.1	177.1	12.5	202.3	

patients over 80 years, we found a near significant effect for statin prescription for over two years compared to less than two 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 endpoint was found in patients aged 65 to 80 years when comparing between one and two 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 two years of statin prescription compared to 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 two years of prescription. The risk reduction found for less than 1 year of statin prescription in patients aged 65-80 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 two year after randomization, showing no effect of less than one year of statin therapy[2,4]. On the other hand, 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

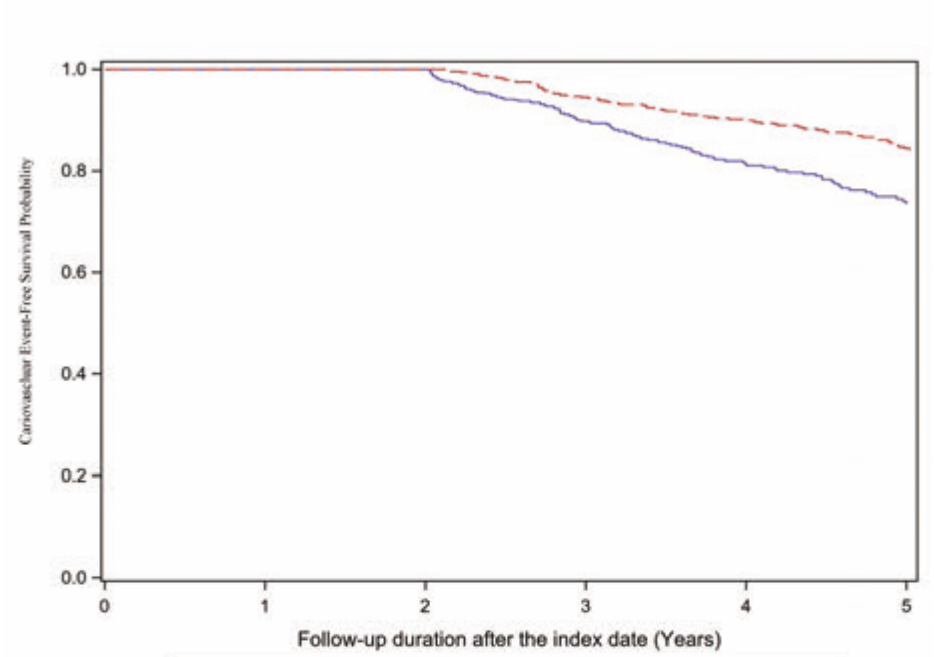
This is the first observational study investigating the initiation and cumulative duration of statin prescription for secondary prevention of cardiovascular disease after a first stroke

in patients aged 80 years and older. Our finding of a beneficial effect of statins on the primary outcome in patients aged 65-80 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 can not be completely ruled out.

This study showed that the most robust endpoints had a more robust effect compared to less robust endpoints (stroke, MI of the primary endpoint). 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 endpoints might be influenced by factors like stoke 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 less than one 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 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

Figure 1 Time varying Kaplan-Meier curve for the primary outcome in patients aged 80 and above: comparison of more than two years of statin prescriptions with no or less than 2 years of statin prescriptions.



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

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.

after two years of statin prescription in the older patients compared to 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 two 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 post discharge.

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 post stroke protocols. In case of a positive decision regarding initiation of statins, efforts should be made to keep patients adherent to statins for at least two years regardless of a patient's age, except when the prognosis of the patient clearly deteriorates during these two years.

Future research

In this study, we investigated the duration of statin treatment, but not the cholesterol level targets and harm. In order 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 two 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 (e.g. preferences of patients and physicians, pill burden, expected benefit harm ratio) on how these decisions are made.

Conclusion

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.

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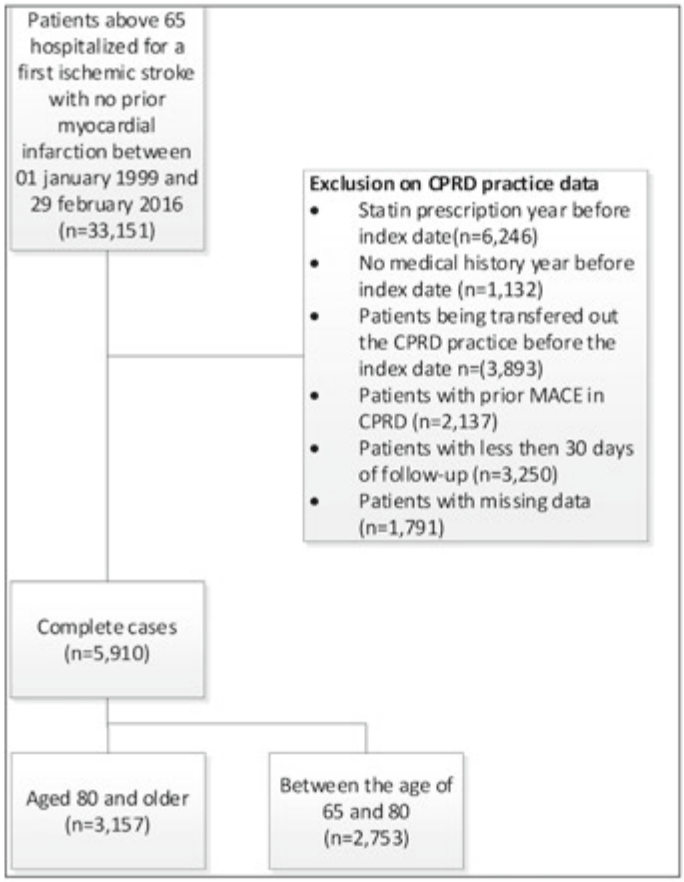
Supplementary data chapter 2.2

Supplementary Figure I Inclusion flowchart



Supplementary Table I Individual components of the Charlson comorbidity index at baseline.

	80 years and older (n=3,157)		Between the age of 65 and 80 (n=2753)	
	1st 90 days statin treatment (n=1,638)	1st 90 days untreated (n=1,519)	1st 90 days statin treatment (n=1,723)	1st 90 days untreated (n=1,030)
CCI in strata:				
0	652(39.8)	555(36.5)	946(54.9)	491(47.7)
1 to 2	681(41.6)	652(42.9)	638(37.0)	417(40.5)
3 to 4	255(15.6)	259(17.1)	126(7.3)	106(10.3)
> 4	50(3.1)	53(3.5)	13(0.75)	16(1.6)
Individual components of the CCI:				
Myocardial infarction	0(100)	0(100)	0(100)	0(100)
Transient ischemic attack	47(2.87)	67(4.4)	25(1.5)	29(2.8)
Congestive heart failure	104(6.4)	157(10.3)	29(1.7)	49(4.8)
Connective tissue disorder	153(9.3)	110(7.2)	73(4.2)	56(5.4)
Dementia	48(2.9)	83(5.5)	15(0.87)	17(1.7)
Diabetes	140(8.6)	178(11.7)	151(8.8)	128(12.4)
Diabetes with complications	33(2.0)	29(1.9)	25(1.5)	25(2.4)
Liver disease	3(0.18)	6(0.39)	4(0.23)	8(0.78)
Peptic ulcer	110(6.7)	90(5.9)	80(4.6)	42(4.1)
Peripheral vascular disease	78(4.8)	106(7.0)	72(4.2)	48(4.7)
Pulmonary disease	299(18.3)	263(17.3)	288(16.7)	178(17.3)
Cancer	216(13.2)	196(12.9)	134(7.8)	123(11.9)
Paraplegia	7(0.43)	18(1.2)	14(0.81)	13(1.3)
Renal disease	330(20.2)	280(18.4)	139(8.1)	79(7.7)
Metastatic cancer	5(0.31)	5(0.33)	3(0.17)	7(0.68)
Severe liver disease	1(0.06)	1(0.07)	0(100)	1(0.10)
HIV	0(100)	0(100)	0(100)	0(100)

Legend: Individual components of the Charlson comorbidity index of patients at baseline, according to statin treatment status in the first 90 days of the index date. Values are number (percentages).

Supplementary Table II Time under percentual prescription of medication at baseline and during follow-up for each prescription group in patients aged 80 and above and between the age of 65 and 80.

	80 years and older				
	Untreated (2,316 PY)	**<1 year (1,820 PY)**	**≥1-2 years (1,040 PY)**	**<2 year (5,176 PY)**	**≥2 year (1,954 PY)**
Antiplatelet at baseline	27.2	25.9	26.1	26.5	27.1
Antiplatelet during follow-up	55.0	70.6	69.4	63.3	66.4
Oral anticoagulants at baseline	4.3	3.7	4.6	4.2	3.6
Oral anticoagulants during follow-up	14.5	19.1	22.7	17.7	23.6
Beta blokker at baseline	20.5	24.2	25.8	22.9	25.9
Beta blokker during follow-up	17.4	22.8	23.5	20.5	25.1
RAAS inhibitors at baseline	28.4	33.9	33.1	31.3	27.6
RAAS inhibitors during follow-up	30.9	45.3	46.6	39.1	51.2
Calcium channel blocker at baseline	20.5	23.3	22.3	21.8	21.8
Calcium channel blocker during follow-up	21.6	27.9	28.4	25.2	27.9
Diuretics at baseline	38.3	36.7	35.1	37.1	38.7
Diuretics during follow-up	43.3	36.9	39.4	40.3	42.8
Nitrates at baseline	3.2	3.3	3.8	3.3	4.0
Nitrates during follow-up	3.8	3.6	4.1	3.8	4.8
NSAID at baseline	9.8	11.0	11.3	10.5	14.8
NSAID during follow-up	4.3	3.7	2.4	3.7	2.3
Glucosteroids at baseline	4.8	5.3	4.4	4.9	4.3
Glucosteroids follow-up	5.5	5.5	4.7	5.3	4.7
Oral antidiabetics at baseline	6.2	4.1	4.0	5.0	3.0
Oral antidiabetics during follow-up	6.9	5.9	6.2	6.4	4.8
Insulin therapy at baseline	1.2	0.9	0.3	0.9	0.0
Insulin therapy during follow-up	1.6	1.1	0.9	1.3	1.1
Antipsychotic at baseline	5.0	4.0	4.0	4.4	4.4
Antipsychotic during follow-up	5.0	3.7	3.7	4.3	3.5

	Between the age of 65 and 80				
	Untreated (2,246 PY)	<1 year (2,387 PY)	≥1-2 years (1,562 PY)	<2 year (6,195 PY)	≥2 year (4,793 PY)
Antiplatelet at baseline	17.0	14.2	14.9	15.4	15.0
Antiplatelet during follow-up	50.8	67.2	70.8	62.2	67.5
Oral anticoagulants at baseline	4.1	3.5	3.2	3.6	2.4
Oral anticoagulants during follow-up	17.5	20.7	20.9	19.6	23.4
Beta blokker at baseline	18.1	19.7	22.0	19.7	24.6
Beta blokker during follow-up	18.7	21.6	23.6	21.1	25.9
RAAS inhibitors at baseline	23.1	23.6	23.8	23.5	22.1
RAAS inhibitors during follow-up	31.3	48.3	53.4	43.5	58.8
Calcium channel blocker at baseline	17.1	16.4	19.3	17.4	18.0
Calcium channel blocker during follow-up	21.9	25.5	28.6	25.0	29.9
Diuretics at baseline	26.6	22.1	21.8	23.7	23.9
Diuretics during follow-up	31.1	31.4	35.0	32.2	40.1
Nitrates at baseline	3.4	2.0	2.2	2.5	2.3
Nitrates during follow-up	3.5	2.8	3.2	3.2	4.1
NSAID at baseline	12.5	11.5	13.0	12.3	12.2
NSAID during follow-up	6.8	5.7	5.2	6.0	4.2
Glucosteroids at baseline	3.4	2.9	2.8	3.1	2.5
Glucosteroids follow-up	4.3	3.6	4.2	4.0	4.0
Oral antidiabetics at baseline	6.8	5.1	5.0	5.7	4.6
Oral antidiabetics during follow-up	9.0	8.3	9.9	9.0	13.2
Insulin therapy at baseline	1.9	1.3	1.3	1.5	1.2
Insulin therapy during follow-up	2.8	1.9	1.9	2.2	2.3
Antipsychotic at baseline	5.2	2.8	2.7	3.6	2.8
Antipsychotic during follow-up	5.1	3.0	2.6	3.6	2.9

Given values are percentages of time in the analysis under baseline medication treatment and medication treatment during follow up. PY, patient–years.

Supplementary Table III Comparison of effect of more than two years of statin treatment, one to two years of statin treatment, and less than one year of statin with no treatment on the individual components of the primary outcome.

Age 80 and older	Prescription group	PY	Events	IR/ 1000 PY	HR	HR adj.
Non fatal MI	Untreated	2492	23	9	ref.	
	< 1 years	1957	8	4	0.38 (0.17-0.88)	0.35 (0.14-0.88)
	1-2 years	1131	10	9	0.82 (0.33-2.02)	0.90 (0.34-2.40)
	> 2 years	2121	12	6	0.99 (0.34-2.83)	0.97 (0.30-3.10)
Non fatal stroke	Untreated	2335	287	123	ref.	
	< 1 years	1838	63	34	0.21 (0.16-0.28)	0.27 (0.20-0.36)
	1-2 years	1050	21	20	0.68 (0.38-1.22)	0.81 (0.44-1.46)
	> 2 years	2001	30	15	0.81 (0.44-.149)	0.96 (0.52-1.80)
Fatal MI	Untreated	2516	35	14	ref.	
	< 1 years	1980	14	7	0.46 (0.24-0.89)	0.57 (0.29-1.15)
	1-2 years	1144	12	10	0.85 (0.37-1.95)	1.09 (0.45-2.64)
	> 2 years	2175	15	7	0.79 (0.32-1.98)	0.90 (0.33-2.47)
Fatal Stroke	Untreated	2516	94	37	ref.	
	< 1 years	1980	34	17	0.39 (0.26-0.58)	0.48 (0.31-0.73)
	1-2 years	1144	15	13	1.09 (0.51-2.36)	1.29 (0.60-2.81)
	> 2 years	2175	24	11	0.98 (0.46-2.06)	1.29 (0.60-2.81)
CV mortality	Untreated	2516	299	119	ref.	
	< 1 years	1980	114	58	0.42 (0.33-0.52)	0.50 (0.39-0.63)
	1-2 years	1144	62	54	0.69 (0.50-0.96)	0.82 (0.58-1.15)
	> 2 years	2175	108	50	0.52 (0.38-0.69)	0.65 (0.48-0.90)
Non CV mortality	Untreated	2516	367	146	ref.	
	< 1 years	1980	156	79	0.39 (0.06-2.78)	0.41 (0.06-2.95)
	1-2 years	1144	93	81	0.68 (0.45-1.02)	0.72 (0.47-1.10)
	> 2 years	2175	179	82	0.50 (0.39-0.64)	0.55 (0.42-0.72)

Supplementary Table III Continued

Between the age of 65 and 80	Prescription group	PY	Events	IR/1000 PY	HR	HR adj.
Non fatal MI	Untreated	2379	13	5	ref.	
	< 1 years	2549	18	7	1.17 (0.55-2.48)	1.42 (0.64-3.14)
	1-2 years	1677	16	10	2.60 (1.04-6.53)	2.18 (0.78-6.13)
	> 2 years	5242	32	6	0.76 (0.35-1.66)	0.61 (0.26-1.43)
Non fatal stroke	Untreated	2250	176	78	ref.	
	< 1 years	2407	61	25	0.23 (0.17-0.31)	0.31 (0.23-0.43)
	1-2 years	1585	26	16	0.95 (0.51-1.77)	1.18 (0.63-2.23)
	> 2 years	4939	49	10	0.65 (0.36-1.17)	0.86 (0.47-1.57)
Fatal MI	Untreated	2383	16	7	ref.	
	< 1 years	2571	7	3	0.33 (0.13-0.85)	0.45 (0.17-1.20)
	1-2 years	1705	7	4	0.86 (0.28-2.62)	0.93 (0.29-2.97)
	> 2 years	5404	22	4	0.72 (0.29-1.80)	0.93 (0.33-2.56)
Fatal Stroke	Untreated	2383	41	17	ref.	
	< 1 years	2571	15	6	0.29 (0.16-0.54)	0.42 (0.22-0.80)
	1-2 years	1705	4	2	0.24 (0.07-0.77)	0.30 (0.09-1.03)
	> 2 years	5404	18	3	0.31 (0.15-0.68)	0.51 (0.22-1.17)
CV mortality	Untreated	2383	104	44	ref.	
	< 1 years	2571	55	21	0.46 (0.32-0.64)	0.63 (0.44-0.90)
	1-2 years	1705	30	18	0.61 (0.37-0.99)	0.81 (0.49-1.34)
	> 2 years	5404	113	21	0.49 (0.32-0.64)	0.65 (0.45-0.96)
Non CV mortality	Untreated	2383	187	78	ref.	
	< 1 years	2571	97	38	0.29 (0.04-2.07)	0.57 (0.08-4.2)
	1-2 years	1705	49	29	0.54 (0.31-0.925)	0.82 (0.46-1.45)
	> 2 years	5404	205	38	0.67 (0.48-0.92)	1.10 (0.78-1.56)

Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted.

Supplementary Table IV Effect of more than two years of statin treatment compared with no or less than two years of statin prescriptions on the individual components of the primary outcome.

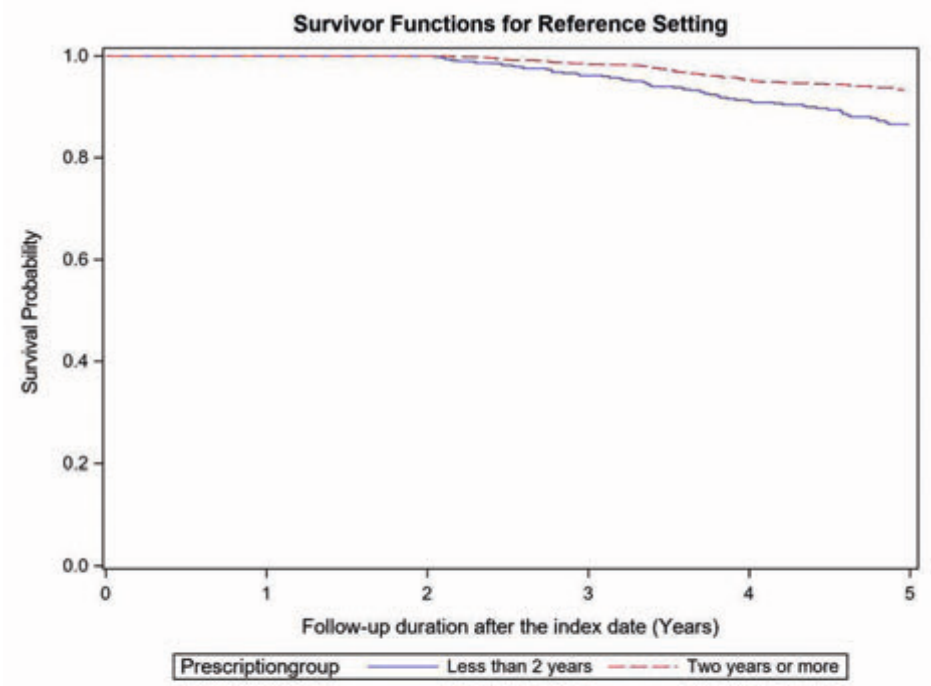
Age 80 and older	Prescription group	PY	Events	IR/ 1000 PY	HR	HR adj.
Non fatal MI	no and < 2 years	5581	41	7	ref.	
	≥ 2 years	2121	12	6	1.00 (0.40-2.48)	1.27 (0.50-3.26)
Non fatal stroke	no and < 2 years	5223	371	71	ref.	
	≥ 2 years	2001	30	15	0.76 (0.45-1.30)	1.03 (0.60-1.75)
Fatal MI	no and < 2 years	5640	61	11	ref.	
	≥ 2 years	2175	15	7	0.61 (0.29-1.26)	0.77 (0.35-1.68)
Fatal Stroke	no and < 2 years	5640	143	25	ref.	
	≥ 2 years	2175	24	11	0.70 (0.39-1.26)	0.91 (0.50-1.66)
CV mortality	no and < 2 years	5640	475	84	ref.	
	≥ 2 years	2175	108	50	0.56 (0.43-0.73)	0.75 (0.57-0.99)
Non CV mortality	no and < 2 years	5640	616	109	ref.	
	≥ 2 years	2175	179	82	0.50 (0.41-0.61)	0.63 (0.51-0.78)

Supplementary Table IV Continued

Between the age of 65 and 80	Prescription group	PY	Events	IR/ 1000 PY	HR	HR adj.
Non fatal MI	no and < 2 years	6605	47	7	ref.	
	≥ 2 years	5242	32	6	0.73 (0.40-1.32)	0.63 (0.34-1.18)
Non fatal stroke	no and < 2 years	6242	263	42	ref.	
	≥ 2 years	4939	49	10	0.60 (0.38-0.94)	0.84 (0.53-1.35)
Fatal MI	no and < 2 years	6659	30	5	ref.	
	≥ 2 years	5404	22	4	0.79 (0.38-1.66)	1.00 (0.45-2.20)
Fatal Stroke	no and < 2 years	6659	60	9	ref.	
	≥ 2 years	5404	18	3	0.39 (0.20-0.77)	0.61 (0.30-1.23)
CV mortality	no and < 2 years	6659	189	28	ref.	
	≥ 2 years	5404	113	21	0.58 (0.43-0.78)	0.77 (0.56-1.06)
Non CV mortality	no and < 2 years	6659	333	50	ref.	
	≥ 2 years	5404	205	38	0.73 (0.57-0.93)	1.07 (0.83-1.40)

Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted.

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

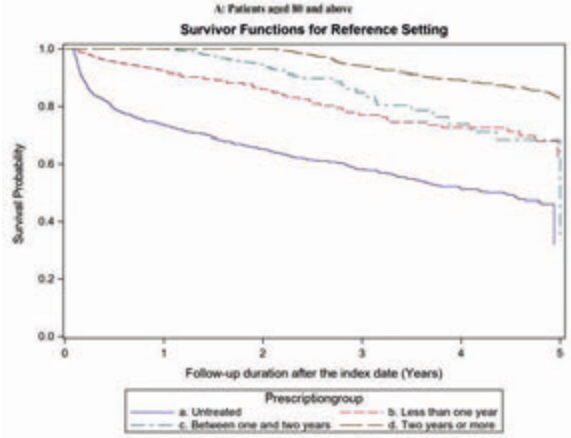


Patients contributing time at year-point + 30 days (crossectional)

	0 + 90 days	1	2	3	4	5
< 2 years	2753	2016	979	491	324	224
≥ 2 years			706	911	790	663
Total in analysis	2753	2016	1685	1402	1114	887
Cumulative primary outcome	.	317	401	462	544	593
Cumulative loss to mortality	.	139	221	292	348	415
Cumulative loss to follow-up	.	16	64	117	181	255
Cumulative study end	.	265	382	480	566	603

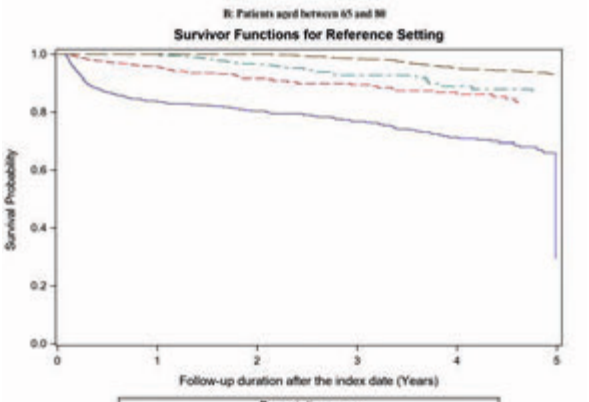
Numbers at each year refer to the remaining patients at risk, reached the primary outcome or have been censored by all-cause mortality, loss-to-follow-up or reaching the study end date respectively.

Supplementary Figure III Time varying Kaplan-Meier curve for the primary outcome in patients aged 80 and above and between the age of 65 and 80: comparison of more than two years of statin prescriptions, one to two years of statin prescriptions, and less than one year of statin prescriptions with no statin prescriptions.



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

	0 – 90 days	1	2	3	4	5
UNTREATED	1658	599	583	243	136	79
< 1 year	1519	490	122	71	59	31
1 to 2 years	.	724	300	41	20	22
≥ 2 years	.	.	458	502	368	258
Total in analysis	3177	1813	1263	857	583	393
Cumulative primary outcome	.	645	830	968	1047	1144
Cumulative loss to mortality	.	285	449	623	740	859
Cumulative loss to follow-up	.	31	91	167	211	282
Cumulative study end	.	415	524	660	556	499



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

	0 – 90 days	1	2	3	4	5
UNTREATED	1723	507	336	252	168	113
< 1 year	1090	597	179	139	95	73
1 to 2 years	.	902	444	100	63	38
≥ 2 years	.	.	706	911	790	663
2793	2793	2016	1885	1402	1114	887
Cumulative primary outcome	.	317	402	462	544	593
Cumulative loss to mortality	.	159	226	292	348	415
Cumulative loss to follow-up	.	16	64	117	181	265
Cumulative study end	.	265	382	480	566	603

Numbers at each year refer to the remaining patients at risk, reached the primary outcome or have been censored by all-cause mortality, loss-to-follow-up or reaching the study end date respectively.

2.3

Discontinuation of statins initiated for secondary prevention in older patients: a cohort study using the Clinical Practice Research Datalink database.

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In preparation

Abstract

Objective: Previous literature showed that five percent of older patients, both fit and frail, discontinue statin treatment that was initiated for secondary prevention every year. Therefore, we aimed to study the effect of discontinuing statins in both fit and frail older patients, initially initiated for secondary prevention, on the recurrence of cardiovascular events.

Design: General population-based cohort study.

Setting: The United Kingdom Clinical Practice Research Datalink linked with the Hospital Episode Statistics Admitted Patient Care and Office for National Statistics databases.

Participants: 9,630 patients of 65 years and older, hospitalised between 1999 and 2016 for a first ischemic stroke or myocardial infarction, who did not receive statin prescriptions in the year before hospital admission and started statin prescription within 90 days after hospital discharge. Of all patients 3,454 (35.9%) were 80 years or older and 4,468 (46.4%) were women.

Main outcomes and measurements: A time varying Cox proportional hazard model was used to account for statin exposure status over time, comparing time on statin treatment with time after statin discontinuation on the composite outcome recurrence of stroke, myocardial infarction, and cardiovascular mortality. Statin discontinuation was defined as at least 90 days without statin prescriptions. Participants were followed until the primary outcome occurred, statin therapy was reinitiated, lost to follow up occurred, they died or reached the study end. Analyses were adjusted for potential confounders. The model was also stratified for frailty.

Results: During follow-up 2604 (27.0%) patients discontinued statin treatment after using statin treatment for a median of 637 days. Discontinuation of statin treatment compared to continued statin treatment was associated with a higher risk of the primary outcome (7.0 versus 3.7 events per 100 person years; adjusted hazard ratio 1.47, 95% confidence interval 1.26 to 1.72). Of all primary outcomes after discontinuation, 23.6% occurred within 90 days after statin discontinuation. After stratifying for frailty, the association persisted in both fit patients (5.3 v 2.4 events per 100 person years; 1.99, 1.12.3 to 3.55) and in severely frail patients (14.3 v 10.6 events per 100 person years; 1.43, 1.02 to 1.99).

Conclusion: In older patients on statin treatment for secondary prevention after a stroke or myocardial infarction, discontinuation of statin treatment is associated with a higher risk of cardiovascular events in both fit and severely frail patients.

Trial registration: This study was approved by the CPRD Research Data Governance process, (protocol no. 23_002570).

Introduction

Statin treatment initiated after cardiovascular events is effective in reducing recurrent cardiovascular events, also in old age[1]. In daily practice, especially after the age of 80, statin discontinuation is common[2]. Most cardiovascular risk reduction guidelines recommend continuation of statin treatment with some considerations for discontinuation of statin treatment in frail older patients, nearing the end of life[3,4]. General practitioners see a shortened life expectancy as the most common reason to discontinue statin treatment, followed by primary prevention as indication, frailty and side effects[5]the risks of statins might outweigh the potential benefits. It is unclear which factors influence general practitioners' (GPs. Yearly, 5.2% of patients over 80 years and using statins for secondary prevention discontinue statin treatment, for primary prevention the prevalence of discontinuation is 6.5%. In all statin using severely frail patients 7.1% discontinue statin treatment yearly, compared to 5.0% in 'fit' patients [2]. Currently, the potential cardiovascular harm of statin discontinuation recommendations is mostly unknown.

The few studies on the association of statin discontinuation, mostly in chronic statin users, show that discontinuation of statin treatment increases the risk of major cardiovascular events (MACE)[6–9]studying all subjects who turned 75 in 2012-14, with no history of cardiovascular disease and with a statin medication possession ratio ≥80% in each of the previous 2 years. Statin discontinuation was defined as three consecutive months without exposure. The outcome was hospital admission for cardiovascular event. The hazard ratio comparing statin discontinuation with continuation was estimated using a marginal structural model adjusting for both baseline and time-varying covariates (cardiovascular drug use, comorbidities, and frailty indicators. In patients, hospitalised for a cardiovascular event and discharged on statin treatment, both the first 90 days of statin discontinuation and persistent statin discontinuation thereafter was associated with a higher risk of rehospitalisation for cardiovascular events or cardiovascular mortality[8]treatment adherence and persistence are still a concern. Methods We constructed a retrospective population-based cohort of patients, who initiated statin treatment within 90 days after discharge from hospital for ASCVD using the claims database of Taiwan National Health Insurance. Proportion of days covered (PDC. In another study, patients aged 65 and older using long-term a combination of cardio-protective drugs, including statins, were followed until statin discontinuation while maintaining the other cardio-protective drugs[9]. Patients discontinuing statin treatment had a higher risk of cardiovascular outcomes and a higher incidence rate for hospital admission for cerebrovascular and ischemic heart disease. A third study included all patients aged 75 and older, with a minimum of five years of statin treatment[7]. In the secondary prevention sub-analysis, the occurrence of (MACE) was higher in the statin discontinuation group, corresponding to one excess MACE per 77 person years. Although frailty is an individual predictor of cardiovascular events, frailty was not included as covariate in previous studies [10].

The aim of our study, therefore, was to investigate the effect of discontinuing statin treatment in older patients that were initially initiated on statin treatment after a stroke or MI primarily on the recurrence of cardiovascular events and secondarily on non-cardiovascular mortality. We will investigate whether the effect of discontinuing statin treatment is modified by frailty level. In addition, we aim to explore the time between statin discontinuation and recurrence of cardiovascular events.

Methods

Data source

Our study was performed using data from the Clinical Practice Research Datalink (CPRD), covering more than 11.3 million patients from 674 general practices in the UK[11]. Data from CPRD were linked to the Hospital Episodes Statistics (HES) and linked to the Office for National Statistics (ONS) database. This study was approved by the CPRD Research Data Governance process, (protocol no. 23_002570).

Study design and study population

A cohort study was performed including all patients aged 65 and older who had been hospitalised for a first ischemic stroke or myocardial infarction (MI) between January 1999 and February 2016, according to the HES database, with a medical history available in the CPRD database for at least 365 days prior to the event. The index date was defined as 90 days after the date of hospital discharge to allow patients time to receive their first statin prescription. We excluded patients if according to the CPRD database they already had a prior stroke or MI, or if patients received statin prescriptions in the year prior to the index date since we set out to explore the effect of discontinuation of first-time statin use or if patients did not receive a statin prescription within 90 days after hospital discharge, as our special interest was the discontinuation of statins. Furthermore, patients who declined permission for re-use healthcare data for research were excluded. The sample size was determined by the maximum number of patients with a first ischemic stroke or MI 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 time per patient was subsequently divided into 30-day periods, starting on the index date, until the completion of follow-up or reaching the primary or secondary outcome. A time period ended earlier if the statin prescription status changed before the end of the 30-day time-period. After 90 days without statin prescription the time counted as discontinued time. Each time period therefore only added to either statin continuation or discontinuation time.

Clinical outcome

For the primary outcome, patients were followed up from the index date until they reached one of the components of the composite endpoint (non-fatal MI, non-fatal stroke, or cardiovascular mortality) or until they reinitiated statin therapy, left the CPRD practice, died of non-cardiovascular reason or reached the study end date. Information on MI or stroke was collected from the HES database, date and cause of death were retrieved from the ONS database. For the secondary outcome, patients were followed up until a non-cardiovascular death, as registered in the ONS database. If in the ONS database a non-cardiovascular 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 counted as cardiovascular. If patients left the CPRD practice, they were censored, because information on drug prescription thereafter was not available.

Potential confounders

All 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 non-white), inclusion period (1999-2003, 2004-2008, 2009-2016), frailty status according to the electronic frailty index readily available in every general practitioner practice in England (fit, mild frailty, moderate frailty, severe frailty)[13]but currently available tools require additional resource. OBJECTIVES: to develop and validate an electronic frailty index (eFI, the individual components of the Charlson comorbidity index (CCI)[14], hypertension, atrial fibrillation, cardiovascular drugs and other drugs known to be associated with higher cardiovascular risk (coded according to the British National Formulary)[12].

Statistical analysis

Data analysis was performed on cases with available data for BMI, smoking status, alcohol use, ethnicity, and deprivation score. Chi-square analysis revealed that missing data were randomly divided. For the time-varying analyses, Cox proportional hazard analyses were used to compare incidence rates of outcomes in statin discontinuation compared to continuation of statin treatment, with results presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and adjusted for all potential confounders. Frailty status, CCI and exposure to cardiovascular risk modifying drugs after the index date were included as time-varying covariates, accounting for changes in frailty status, comorbidity, and drug exposure during a specific time period. We stratified data by inclusion diagnosis, either ischemic stroke or MI, age, either 80 years and older or 65 up to 80 years and time varying frailty status. Interaction terms were included in the time varying analysis to investigate presence of interaction between all covariates and statin discontinuation and the primary outcome.

To investigate longitudinal patterns of the occurrence of the primary outcome, we constructed unadjusted and adjusted Kaplan-Meier curves comparing time on statin treatment with time after discontinuation of statin treatment[15]. For each year after the index date, we calculated the number of participants contributing to the statin continuation or discontinuation group and the cumulative loss of participants due to restarting statin treatment, reaching the primary outcome or non-cardiovascular mortality, being lost to follow-up, or reaching the study end date.

To investigate the primary outcome in the statin discontinuation group, a life table was added starting follow-up at the time of statin discontinuation. A life table was added, categorized for participants discontinuing statin treatment within one year of statin initiation, between one and two years, between two and three years and over 3 years after statin initiation.

To account for a possible end of life decisions in the discontinuation of statin therapy, the initial time varying cox regression analysis was repeated after excluding events during the first 30, 60 and 90 days in the discontinuation group. During this period, patients reaching the primary outcome were termed lost to follow up.

We performed our data analysis for this paper using SAS, version 9.4 software (SAS Institute Inc., Cary, NC, USA.).

Results

Study population

Data of 57,510 patients older than 65 years with a first ischemic stroke or MI were available in the HES database. Of these, 9,630 patients fulfilled the in- and exclusion criteria (supplementary data Figure 1), of whom 6,583 (68.4%) were included after a MI and 3,248 (33.7%) after an ischemic stroke. A total of 201 patients were included after both an MI and stroke. The mean at baseline was 77.7 years (standard deviation 7.28) and most patients were either fit (31.9%) or mildly frail (43.1%). Patients had few comorbidities with a CCI between one and two (68.1%), including the initial stroke or MI. Most patients received cardiovascular drugs, including antiplatelet (90.1%), anticoagulants (10.8%), beta blockers (59.4%) and RAAS inhibitors (70.7%) (Table 2). During follow-up 2,604 patients discontinued statin treatment after using statin treatment for a median of 637 days. Supplement table 1 shows the changes in baseline parameters at one and two years, comparing patients continuing statin treatment to those who discontinued.

Table 1 baseline table: Characteristics of patients initially initiated on statin treatment 90 days after hospitalisation for a first myocardial infarction or stroke.

Baseline statin users	9,630 (100)
Enrolment time period:	
1999 to 2003	1,931 (20.1)
2004 to 2008	3,607 (37.5)
2009 to 2016	4,092 (42.5)
Age in years mean (SD)	77.7 (7.28)
Men n (%)	5,162 (53.6)
Caucasian	9,439 (98)
Index of multiple deprivation:	
First quintile (least deprived)	2,166 (22.5)
Second	2,419 (25.1)
Third	2,049 (21.3)
Fourth	16,483 (17.1)
Fifth quintile (most deprived)	1,348 (14.0)
Ever smoker	5,592 (58.1)
Body mass index mean (SD)	26.3 (4.5)
Alcohol abuse	252 (2.6)
Frailty index - time varying	
Fit	3,070 (31.9)
Mild frailty	4,150 (43.1)
Moderate frailty	1,918 (19.9)
Severe frailty	492 (5.1)
Charlson comorbidity index - time varying	
0	0 (0)
1 to 2	6,554 (68.1)
3 to 4	2,495 (25.9)
5 or more	581 (6.0)
Hypertension	4,826 (50.1)
Atrial fibrillation	1,055 (11.0)

CCI diagnosis - time varying	
Myocardial infarction	6,583 (68.4)
Cerebrovascular disease	3,248 (33.7)
Congestive heartfailure	903 (9.4)
Rheumatological disease	672 (7.0)
Dementia	163 (1.7)
Diabetes (Mild)	1,063 (11.1)
Liver disease mild	33 (0.34)
Peptic ulcer	531 (5.5)
Peripheral vascular disease	529 (5.5)
Pulmonary disease	1,843 (19.1)
Cancer	1,031 (10.7)
Diabetes complicated	164 (1.7)
Paraplegia	37 (0.38)
Renal disease	1,247 (13.0)
Metastatic cancer	30 (0.31)
Moderate/severe liver disease	5 (0.05)
HIV	1 (0.01)
Comedication	
Antiplatelet	8,679 (90.1)
Oral anticoagulants	1,042 (10.8)
Beta blokker	5,723 (59.4)
RAAS inhibitors	6,804 (70.7)
Calcium channel blocker	2,117 (22.0)
Diuretics	3,439 (35.7)
Nitrates	3,091 (32.1)
NSAID	598 (6.2)
Glucosteroids	514 (5.3)
Oral antidiabetics	518 (5.4)
Insulin therapy	243 (2.5)
Antipsychotic	259 (2.7)

Values are number (percentages) unless stated otherwise; CCI, Charlson comorbidity index.

Table 2 Comparison of effect of statin discontinuation and statin continuation.

All patients	Prescription group	PY	Events	IR/100 PY	HR	HR adj.
Primary outcome	Statin continuation	34.002	1.266	3.7	ref.	
	Discontinuation	2.928	205	7.0	2.09 (1.80-2.43)	1.47 (1.26-1.72)
Non-cardiovascular mortality	Statin continuation	35.926	1.276	3.6	ref.	
	Discontinuation	3,110	350	11.3	3.28 (2.90-3.70)	1.77 (1.56-2.02)
After Myocardial infarction	**Prescription group**	**PY**	**Events**	**IR/100 PY**	**HR**	**HR adj.**
Primary outcome	Statin continuation	25.251	849	3.4	ref.	
	Discontinuation	2.026	130	6.4	2.13 (1.77-2.57)	1.42 (1.17-1.74)
Non-cardiovascular mortality	Statin continuation	26.466	859	3.2	ref.	
	Discontinuation	2.113	241	11.4	3.65 (3.16-4.16)	1.85 (1.58-2.17)
After stroke	**Prescription group**	**PY**	**Events**	**IR/100 PY**	**HR**	**HR adj.**
Primary outcome	Statin continuation	8.752	417	4.8	ref.	
	Discontinuation	902	75	8.3	1.88 (1.47-2.42)	1.58 (1.21-2.06)
Non-cardiovascular mortality	Statin continuation	9,460	417	4.4	ref.	
	Discontinuation	997	109	10.9	2.56 (2.07-3.17)	1.63 (1.29-2.05)
Between the age of 65 and 80	**Prescription group**	**PY**	**Events**	**IR/100 PY**	**HR**	**HR adj.**
Primary outcome	Statin continuation	24.54	621	2.5	ref.	
	Discontinuation	1.725	77	4.5	1.92 (1.51-2.44)	1.62 (1.26-2.08)
Non-cardiovascular mortality	Statin continuation	25.855	630	2.4	ref.	
	Discontinuation	1,820	175	9.6	4.02 (3.39-4.76)	2.20 (1.83-2.64)
Age 80 and older	**Prescription group**	**PY**	**Events**	**IR/100 PY**	**HR**	**HR adj.**
Primary outcome	Statin continuation	9.461	645	6.8	ref.	
	Discontinuation	1.203	128	10.6	1.70 (1.40-2.06)	1.38 (1.12-1.69)
Non-cardiovascular mortality	Statin continuation	10.071	646	6.4	ref.	
	Discontinuation	1,290	175	13.6	2.11 (1.78-2.50)	1.43 (1.19-1.72)

Frailty status Primary outcome	Prescription group	PY	Events	IR/100 PY	HR	HR adj.
Fit	Statin continuation	17,630	428	2.4		
	Discontinuation	1.185	63	5.3	2.29 (1.33-3.95)	1.99 (1.12-3.55)
Mild frailty	Statin continuation	11.902	509	4.3		
	Discontinuation	1.118	88	7.9	2.13 (1.64-2.75)	1.68 (1.28-2.21)
Moderate frailty	Statin continuation	3.754	253	6.7		
	Discontinuation	513	38	7.4	1.74 (1.35-2.25)	1.39 (1.06-1.82)
Severe frailty	Statin continuation	716	76	10.6		
	Discontinuation	112	16	14.3	1.57 (1.16-2.13)	1.43 (1.02-1.99)
Frailty status Non-cardiovascular mortality	**Prescription group**	**PY**	**Events**	**IR/100 PY**	**HR**	**HR adj.**
Fit	Statin continuation	18.511	425	2.3		
	Discontinuation	1.229	108	8.8	2.74 (1.55-4.84)	1.53 (0.80-2.91)
Mild frailty	Statin continuation	12,660	512	4.0		
	Discontinuation	1.214	142	11.7	3.68 (2.98-4.54)	1.99 (1.58-2.51)
Moderate frailty	Statin continuation	3.976	254	6.4		
	Discontinuation	542	71	13.1	2.52 (2.05-3.09)	1.67 (1.35-2.08)
Severe frailty	Statin continuation	779	85	10.9		
	Discontinuation	126	29	23.0	2.57 (2.06-3.22)	1.83 (1.42-2.35)

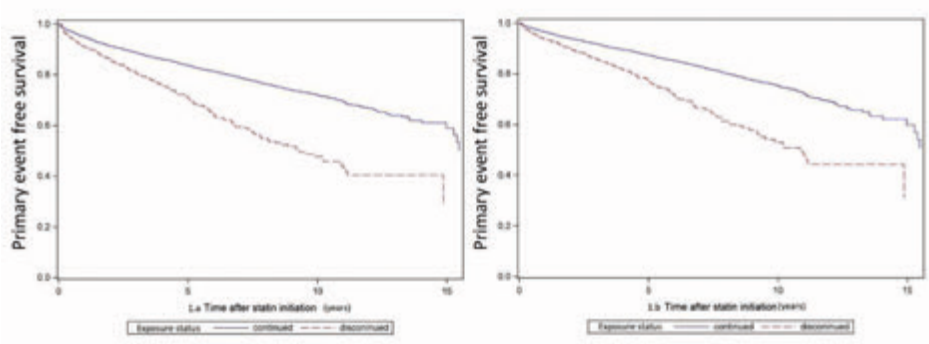
Primary outcome, composite recurrent stroke, myocardial infarction and cardiovascular mortality; Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted.

Primary outcome

Discontinuation of statin treatment was overall significantly associated with a higher risk of the primary outcome (i.e., the composite endpoint of non-fatal MI or stroke, and cardiovascular mortality) compared to continuation of statin treatment (7.0 versus 3.7 events per 100 PY; adjusted HR 1.47, 95% confidence interval 1.26 to 1.72) (Table 2). We found this association both in patients after MI (6.4 v 3.4 events per 100 PY; 1.42, 1.17 to 1.74) and after stroke (8.3 v 4.8 events per 100 PY; 1.58, 1.21 to 2.06). Both in the age group between 65 and 80 (4.5 v 2.5 events per 100 PY; 1.62, 1.26 to 2.08) and in the age group 80 years and older (10.6 v 6.8 events per 100 PY; 1.38, 1.12 to 1.69) we found a higher risk when comparing statin discontinuation with continuing statin use. After stratifying for frailty level, statin discontinuation was associated with a higher risk for the primary outcome across all frailty groups, with the highest HR in de most fit group (5.3 v 2.4 events per 100 PY; 1.99, 1.12 to 3.55) and the lowest HR in the most severe frailty group (14.3 v 10.6 events per 100 PY; 1.43, 1.02 to 1.99).

After the first month of statin discontinuation the risk difference for the primary outcome between statin discontinuation and continuation increases linear during follow up time (Figure 1). When investigating only statin discontinued time, we found 48 (23.4%) of all 205 primary outcomes after statin discontinuation occurred during the first 90 days after statin discontinuation (Figure 2). After 90 days, the primary outcome in the discontinuation group is less frequent and shows a stable pattern over time. The higher incidence of the primary outcome during the first months after statin discontinuation seems more pronounced after a longer period of statin treatment.

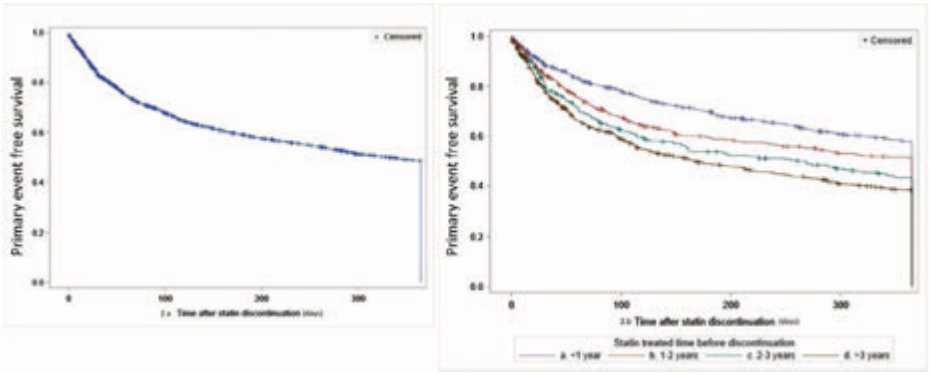
Figure 1. Time varying Kaplan-Meier curve for the primary outcome: comparison of continued statin prescriptions with statin discontinuation figure 1.a unadjusted 1.b adjusted.



All patients (at follow-up year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Statin	6,953	5,385	4,233	3,317	2,581	2,027	1,575	1,168	828	582	382	235	130	72	25
Statin discontinuation	559	533	451	357	277	202	136	101	72	52	33	16	12	4	2
Statin restart	297	579	787	928	1,033	1,103	1,150	1,190	1,234	1,254	1,265	1,270	1,276	1,280	1,281
Non CV mortality	348	596	783	942	1,071	1,165	1,234	1,308	1,356	1,390	1,407	1,424	1,432	1,436	1,438
Primary outcome	466	740	913	1,054	1,158	1,247	1,315	1,371	1,408	1,430	1,450	1,466	1,474	1,477	1,480
Loss to follow-up	776	1,361	1,842	2,232	2,573	2,829	3,052	3,236	3,389	3,513	3,620	3,693	3,735	3,766	3,789
Withdrawn alive	231	436	621	800	937	1,057	1,168	1,256	1,343	1,409	1,473	1,526	1,571	1,595	1,615

Kaplan-Meier curve on primary event free survival probability. 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, reaching the study end date or restarted statin treatment respectively.

Figure 2 Survival curve on the primary outcome (2.a) after statin discontinuation and (2.b) stratified for statin treatment time after the index date before discontinuation.



After excluding events during the first 30 days after statin discontinuation, a higher risk for cardiovascular events persisted after statin discontinuation (supplementary table S2). There was insufficient power to show a higher risk for cardiovascular events after excluding events during the first 60 and 90 days after statin discontinuation.

The interaction analyses tested positive for RAAS inhibitor treatment. In RAAS untreated time, statin discontinuation was associated with a higher risk on the primary outcome (9.5 v 4.9 events per 100 PY; 1.59, 1.28 to 1.98), in RAAS treated time, statin discontinuation was not significant associated with a higher risk on the primary outcome (4.7 v 3.3 events per 100 PY; 1.23, 0.96 to 1.58).

Secondary outcomes

Discontinuation of statin treatment was associated with a higher risk for the secondary outcome non-cardiovascular mortality (11.3 versus 3.6 events per 100 PY; adjusted HR 1.77, 95% confidence interval 1.56 to 2.02). When stratifying for inclusion diagnosis, this higher risk was also shown for both the MI group (11.4 v 3.2 events per 100 PY; 1.85, 1.58 to 2.17) and the stroke group (10.9 v 4.4 events per 100 PY; 1.63, 1.29 to 2.05). In both age groups of 65 to 80 years (9.6 v 2.4 events per 100 PY; 2.20, 1.83 to 2.64) and 80 years and older (13.6 v 6.4 events per 100 PY; 1.43, 1.19 to 1.72) discontinuation of statin treatment was associated with a higher risk of the secondary outcome. Stratification for frailty showed that statin discontinuation increased the risk of non-cardiovascular mortality in all categories.

After excluding events during the first 30, 60 and 90 days after statin discontinuation, a higher risk of statin discontinuation on non-cardiovascular mortality persisted (supplementary table S2).

Discussion

Discontinuation of statin treatment, initially initiated after a cardiovascular event, is associated with a higher risk of both recurrent cardiovascular events and non-cardiovascular mortality in older patients. This higher risk was found in patients receiving statin treatment after an MI as well as after a stroke, and in patients between the age of 65 and 80 as well as in those of 80 years and older. Throughout all frailty categories, statin discontinuation was associated with a higher risk for both cardiovascular recurrence and non-cardiovascular mortality. This higher risk of both cardiovascular events and non-cardiovascular mortality seems to mainly occur shortly after statin discontinuation.

Strengths and weaknesses of the study

To our knowledge, this is the first study taking into account frailty status while investigating the effect of statin discontinuation on cardiovascular recurrence in older patients using statins, initially initiated after a primary cardiovascular event. The external validity is high, as all eligible patients, even the most frail, were included in our analysis, thereby reflecting a real-life population of patients initiating statin treatment after a first cardiovascular event. Data sources with a good validity for both our primary and secondary outcomes were used in this study[16].

The most important limitation is that we don't know the reason why patients discontinued statin treatment. This could have led to residual confounding especially considering the higher risk of non-cardiovascular mortality. We defined statin discontinuation as a period of 90 days without statin prescription, to limit the influence of discontinuation due to expected limited life expectancy. Although several trials showed an effect of statin treatment on overall mortality, however such an effect was not found for non-cardiovascular mortality, thereby, not completely ruling out residual confounding [17].We found the highest risk on cardiovascular recurrence during the first 90 days after statin discontinuation. The risk seems more pronounced when statin treatment was discontinued following a longer period of statin treatment. This effect can be explained by an actual higher risk during the first period after statin discontinuation or by residual confounding.

We performed interaction analysis, showing interaction for RAAS inhibition and not for any of the other variables including cardiovascular drugs. The incidence of the primary outcome in patients treated with RAAS inhibitors was low, resulting in a lack of power to show a statistically significant association between statin discontinuation and cardiovascular recurrence. We did not find a loss of statistical significance in patients not treated with RAAS inhibitors, for whom the incidence of cardiovascular events was higher.

Comparison with previous studies

We showed a clear association between frailty and higher risk of cardiovascular recurrence after statin discontinuation in a population with a much higher overall risk for

cardiovascular recurrence. None of the previous studies included frailty, an individual high-risk predictor of cardiovascular events, in their analysis. In general, our findings are in line with previous studies on discontinuation of statin treatment after secondary prevention. Statin discontinuation was defined in most studies as 90 days of non-prescription of statin treatment[6–9]treatment adherence and persistence are still a concern. Methods We constructed a retrospective population-based cohort of patients, who initiated statin treatment within 90 days after discharge from hospital for ASCVD using the claims database of Taiwan National Health Insurance. Proportion of days covered (PDC. We found a higher risk during the first 90 days after statin discontinuation. None of the earlier observational studies investigated the primary outcome separately in the statin discontinuation group. Thompson at al found in their secondary prevention subgroup in patients stable on statin treatment for at least 5 years a higher risk of cardiovascular recurrence, HR 1.28, after statin discontinuation compared to a HR of 1.47 in our study. However, we defined statin discontinuation as 90 days after the last prescription period whereas they defined statin discontinuation as 180 days without statin treatment. The difference in observed risk can be explained by the high incidence of events during the period between 90 and 180 days after statin discontinuation.

To our knowledge, only one randomized controlled study investigated the effect of statin discontinuation in 381 patients with a life expectancy of less than one year[18]. In patients who discontinued statin treatment the 60-days mortality was 23.8%, compared to 20.3% in patients who continued statin treatment. The study was underpowered to demonstrate a statistically significant risk difference. Although not statistically significant, the increased incidence (3.5%) is in line with our findings showing a higher risk within the first 90 days after statin discontinuation.

Implications for clinicians and policymakers

Given our results, one can question the validity of giving considerations in guidelines for discontinuation of statin treatment in patients, including older frail patients. Especially in patients not suffering from side effects of statin treatment, one should be cautious to discontinue statin treatment even in limited life expectancy if continuing statin treatment is in line with patient centred goals. Statin discontinuation in the frailest, might be more harmful than previously assumed. Clinicians can embed the found risk of discontinuation from this study in their discussion with older patients about weighting risks and benefits of statin discontinuation especially in patients with the highest cardiovascular risk, the frail older patient.

Future research

Future observational studies on statin discontinuation need to find ways to account for reasons for discontinuation associated with end-of-life decisions . In designing studies concerning discontinuation of statin treatment it is important to account for both frailty

as well as timing of events after discontinuation. Furthermore, studies on the effect of statin discontinuation should be adequately powered.

Conclusion

In older patients on statin treatment for secondary prevention after a stroke or myocardial infarction, discontinuation of statin treatment is associated with a higher risk of cardiovascular events in both fit and severely frail patients.

Sources of funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosures: None

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request after permission by the CPRD.

Patient and public involvement statement

No patients were involved in the design or execution of the study or were asked to advice on the interpretation or writing up of results.

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Supplementary data

Supplementary table S1. Baseline table and Statin users and Discontinuation of study participants at year 1 and 2

	1 year follow-up		2 year follow-up	
	Statin	Discontinuation	Statin	Discontinuation
	(n= 6,953)	(n= 559)	(n= 5,385)	(n= 533)
Baseline information	92.6	7.4	91.0	9.0
Enrolment time period:				
1999 to 2003	1,583 (22.8)	86 (15.4)	1,368 (25.4)	94 (17.6)
2004 to 2008	2,823 (40.6)	204 (36.5)	2,327 (43.2)	227 (42.6)
2009 to 2016	2,547 (36.6)	269 (48.1)	1,690 (31.4)	212 (39.8)
Age in years mean (SD)	76.9 (7.1)	79.3 (7.3)	76.2 (6.8)	78.8(7.3)
Men n (%)	3,823 (55.0)	246 (44.0)	3,026 (56.2)	239 (44.8)
Caucasian	6,818 (98.1)	541 (96.8)	5,287 (98.2)	517 (97.0)
Index of multiple deprivation:				
First quintile (least deprived)	1,573 (22.6)	135 (24.2)	1,225 (22.8)	130 (24.4)
Second	1,756 (25.3)	131 (23.4)	1,370 (25.4)	121 (22.7)
Third	1,473 (21.2)	125 (22.4)	1,135 (21.1)	123 (23.1)
Fourth	1,173 (16.9)	103 (18.4)	916 (17.0)	94 (17.6)
Fifth quintile (most deprived)	978 (14.1)	65 (11.6)	739 (13.7)	65 (12.2)
Ever smoker	3,994 (57.4)	326 (58.1)	3,072 (57.1)	305 (57.2)
Body mass index mean (SD)	26.4 (4.4)	26.0 (5.0)	26.5 (4.3)	26.4 (5.1)
Alcohol abuse	167 (2.4)	18 (3.2)	117 (2.2)	17 (3.2)
Frailty index - time varying				
Fit	1,985 (28.6)	127 (22.7)	1,399 (26.0)	103 (19.3)
Mild frailty	3,060 (44.0)	229 (41.0)	2,412 (44.8)	218 (40.9)
Moderate frailty	1,470 (21.1)	152 (27.2)	1,196 (22.2)	148 (27.8)
Severe frailty	438 (6.3)	51 (9.1)	378 (7.0)	64 (12.0)
Charlson comorbidity index - time varying				
0	0 (0)	0 (0)	0 (0)	0 (0)
1 to 2	4,585 (65.9)	321 (57.4)	3,465 (64.4)	308 (57.8)
3 to 4	1,985 (28.6)	176 (31.5)	1,641 (30.5)	173 (32.5)
5 or more	383 (5.5)	62 (11.1)	279 (5.2)	52 (9.8)
Hypertension	3,410 (49.0)	285 (51.0)	2,588 (48.1)	287 (53.9)
Atrial fibrillation	713 (10.3)	68 (12.2)	499 (9.3)	65 (12.2)

Supplementary table S1. Continued

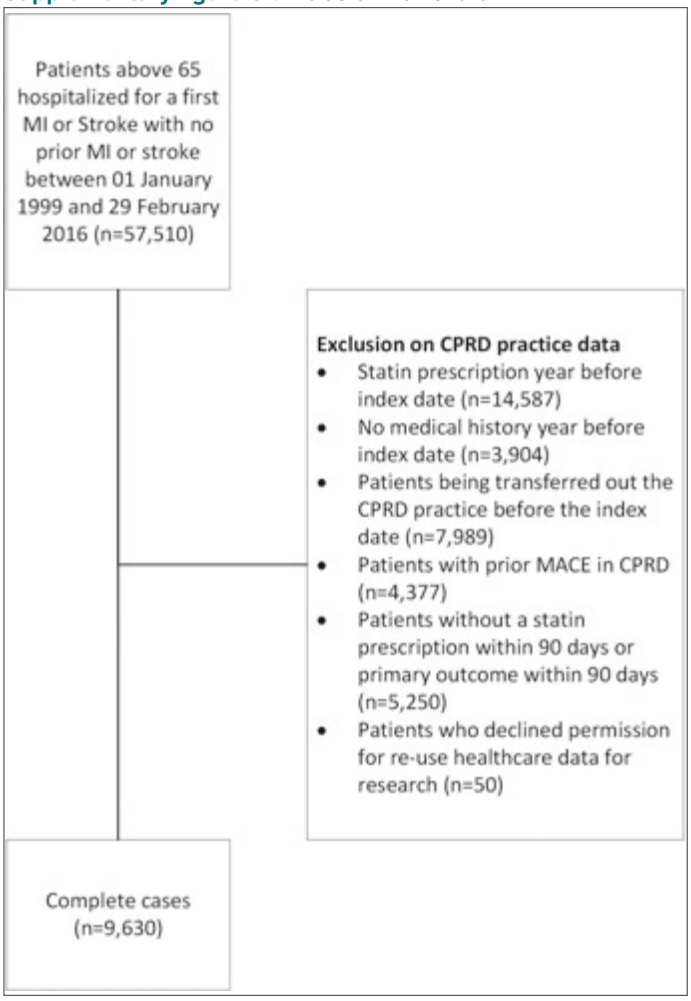
	1 year follow-up		2 year follow-up	
	Statin (n= 6,953)	Discontinuation (n= 559)	Statin (n= 5,385)	Discontinuation (n= 533)
CCI diagnosis - time varying				
Myocardial infarction	4,896 (70.4)	358 (64.0)	3,874 (71.9)	348 (65.3)
Cerebrovascular disease	2,229 (32.1)	217 (38.8)	1,647 (30.6)	210 (39.4)
Congestive heartfailure	692 (10.0)	75 (13.4)	536 (10.0)	70 (13.1)
Rheumatological disease	460 (6.6)	48 (8.6)	358 (6.7)	46 (8.6)
Dementia	155 (2.2)	12 (2.2)	126 (2.3)	18 (3.4)
Diabetes (Mild)	781 (11.2)	60 (10.7)	636 (11.8)	61 (11.4)
Liver disease mild	25 (0.4)	2 (0.4)	21 (0.4)	2 (0.4)
Peptic ulcer	387 (5.6)	26 (4.7)	303 (5.6)	31 (5.8)
Peripheral vascular disease	397 (5.7)	36 (6.4)	319 (5.9)	38 (7.1)
Pulmonary disease	1,331 (19.1)	117 (20.9)	1,029 (19.1)	115 (21.6)
Cancer	722 (10.4)	72 (12.8)	556 (10.3)	60 (11.3)
Diabetes complicated	101 (1.5)	20 (3.6)	75 (1.4)	16 (3.0)
Paraplegia	24 (0.4)	4 (0.7)	18 (0.3)	4 (0.8)
Renal disease	1,043 (15.0)	125 (22.4)	873 (16.2)	116 (21.8)
Metastatic cancer	14 (0.2)	3 (0.5)	12 (0.2)	1 (0.2)
Moderate/severe liver disease	4 (0.1)	0 (0)	5 (0.1)	0 (0)
HIV	1 (0.01)	0 (0)	1 (0.02)	0 (0)
Comedication				
Antiplatelet	5,963 (85.8)	363 (64.9)	4,494 (83.5)	350 (65.7)
Oral anticoagulants	767 (11.0)	70 (12.5)	612 (11.4)	60 (11.3)
Beta blokker	3,995 (57.5)	222 (39.7)	3,118 (57.9)	220 (41.3)
RAAS inhibitors	5,069 (72.9)	301 (53.9)	3,977 (73.9)	286 (53.7)
Calcium channel blocker	1,510 (21.7)	100 (17.9)	1,194 (22.2)	108 (20.3)
Diuretics	2,399 (34.5)	176 (31.5)	1,864 (34.6)	186 (34.9)
Nitrates	1,321 (19.0)	73 (13.1)	1,020 (18.9)	73 (13.7)
NSAID	353 (5.1)	27 (4.8)	293 (5.4)	24 (4.5)
Glucosteroids	322 (4.6)	41 (7.3)	263 (4.9)	39 (7.3)
Oral antidiabetics	424 (6.1)	32 (5.7)	345 (6.4)	34 (6.4)
Insulin therapy	145 (2.1)	11 (2.0)	115 (2.1)	8 (1.5)
Antipsychotic	165 (2.4)	17 (3.0)	115 (2.1)	14 (2.6)

Supplementary table S2. Comparison of effect of statin discontinuation and statin continuation excluding events during the first 30, 60 and 90 days after statin discontinuation.

Primary outcome	Prescriptiongroup	PY	Events	IR/100 PY	HR	HR adj.
	Statin continuation	34,002	1,502	4.4	ref.	ref.
main analysis	Discontinuation	2,928	205	7.0	2.09 (1.80-2.43)	1.47 (1.26-1.72)
Lag 30 days	Discontinuation	2,928	174	5.9	1.76 (1.50-2.07)	1.25 (1.06-1.48)
Lag 60 days	Discontinuation	2,928	163	5.6	1.65 (1.40-1.95)	1.17 (0.99-1.39)
Lag 90 days	Discontinuation	2,928	157	5.4	1.59 (1.34-1.88)	1.13 (0.95-1.35)
Non-cardiovascular mortality	**Prescriptiongroup**	**PY**	**Events**	**IR/100 PY**	**HR**	**HR adj.**
	Statin continuation	35,926	1,284	3.6	ref.	ref.
main analysis	Discontinuation	3,110	350	11.3	3.28 (2.90-3.70)	1.77 (1.56-2.02)
Lag 30 days	Discontinuation	3,110	300	9.6	2.80 (2.47-3.18)	1.52 (1.33-1.74)
Lag 60 days	Discontinuation	3,110	272	8.7	2.54 (2.22-2.89)	1.38 (1.20-1.58)
Lag 90 days	Discontinuation	3,110	248	8.0	2.31 (2.01-2.65)	1.25 (1.08-1.45)

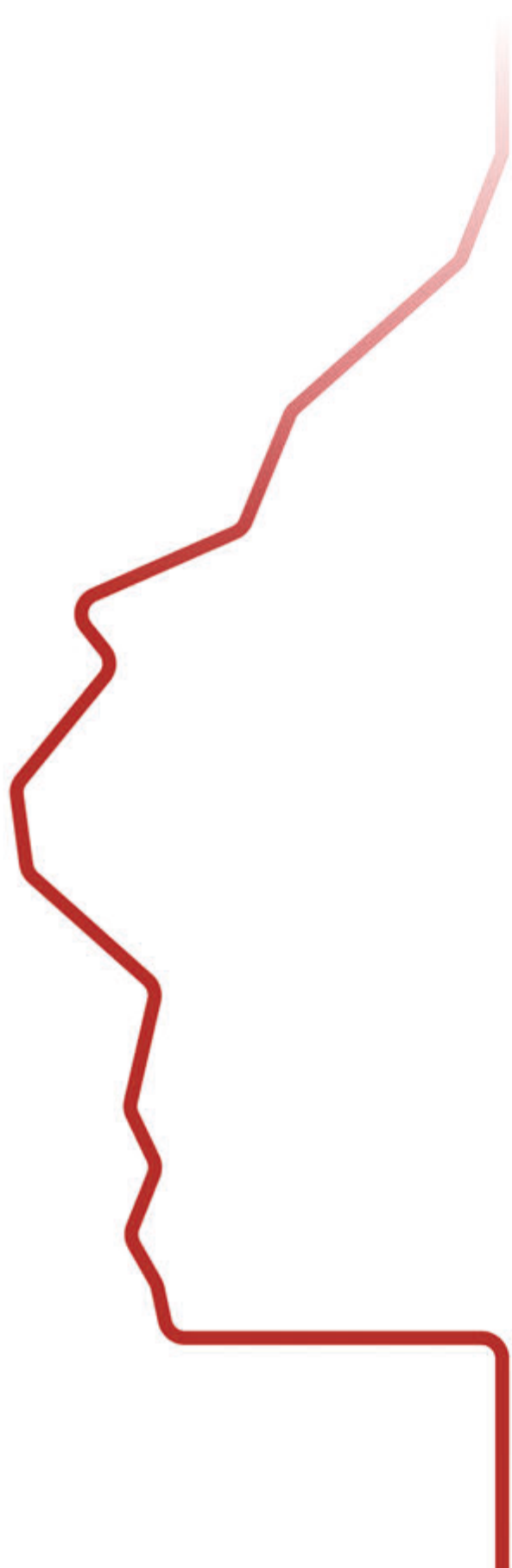
Primary outcome, composite recurrent stroke, myocardial infarction and cardiovascular mortality; Ref., reference group; PY, patient–years; IR, incidence ratio; HR, hazard ratio; adj, adjusted. Values are number (percentages) unless stated otherwise; CCI, Charlson comorbidity index.

Supplementary figure S1. Inclusion flowchart



3

Short term clinical outcomes in geriatric patients after transcatheter aortic valve implantation



3.1

Predictors of clinical outcome following transcatheter aortic valve implantation: a prospective cohort study.

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Abstract

Objective: In recent years, transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with symptomatic aortic valve stenosis considered to be at increased or high surgical risk. The aim of this study was to identify predictors of postoperative adverse events in older adults undergoing TAVI.

Methods: A prospective observational cohort study of patients who were referred to a geriatric outpatient clinic for a geriatric assessment prior to TAVI was conducted. The outcomes were mortality and hospital readmission within 3 months of TAVI and the occurrence of major postoperative complications during hospitalisation according to the Clavien-Dindo classification. These three outcomes were also combined to a composite outcome. Univariate and multivariate logistic regression analyses were performed to identify predictors of the outcomes and composite outcome of adverse events.

Results: This cohort included 490 patients who underwent TAVI (mean age 80.7±6.2 years, 47.3% male). Within 3 months of TAVI, 19 (3.9%) patients died and 46 (9.4%) patients experienced a hospital readmission. A total of 177 (36.1%) patients experienced one or more major complications according to the Clavien-Dindo Classification during hospitalisation and 193 patients (39.4%) experienced the composite outcome of adverse events. In multivariate analyses, cognitive impairment was identified as an independent predictor of major postoperative complications (OR 2.16; 95% CI 1.14 to 4.19) and the composite outcome of adverse events (OR 2.40; 95% CI 1.21 to 4.79). No association was found between the other variables and the separate outcomes and composite outcome.

Conclusion: Cognitive impairment is associated with postoperative adverse events in older patients undergoing TAVI. Therefore, it is important to screen for cognitive impairment prior to TAVI and it is recommended to include this in current TAVI guidelines.

Introduction

Stenosis of the aortic valve is one of the most common cardiovascular diseases in the Western population.(1,2) It is associated with ageing and affects one in eight individuals aged 75 years and above.(1–3) In recent years, transcatheter aortic valve implantation (TAVI) has become the treatment of choice for patients with symptomatic aortic valve stenosis, considered to be at increased or high surgical risk.(1–3) Common surgical risk scores, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) score, are widely used to guide treatment options based on the predicted risk of poor outcomes.(3) These models were created and validated in a standard surgical risk population.(3,4) Therefore, these models do not include relevant risk factors that are specifically prevalent in the geriatric population. (1–3) In recent years, the evidence has grown that frailty can help identify patients who are at increased risk of mortality after a TAVI procedure.(3,4) Therefore, the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease and the guidelines of the American College of Cardiology (ACC) recommend to use frailty scores to determine a patients' suitability for TAVI.(1,2) Previous studies aimed to identify preoperative factors predictive of postoperative adverse outcomes in older patients undergoing TAVI.(3,4) Several predictors of 1-year mortality in older patients has been found, including the presence of frailty, a reduced gait speed and dependence in Activities of Daily Living (ADL). With regard to predictors of short-term outcomes (e.g. 30-day mortality), there have been conflicting results, in particular with respect to frailty. (5–7) The majority of recently created prediction models in older patients focused on the occurrence of long term mortality. (8–10) Since the occurrence of postoperative complications results in substantial burden for patients and health care systems, it is necessary to focus both on postoperative mortality and morbidity and the overall occurrence of these negative outcomes. (11,12)

In this study, we aimed to identify predictors of postoperative adverse events, including mortality, hospital readmissions, major postoperative complications and the composite of these outcomes in older patients undergoing TAVI.

Methods

Study design and population

This prospective, single-centre cohort study was conducted at the University Medical Centre Utrecht, a tertiary hospital in the Netherlands. All consecutive patients who visited the geriatric outpatient clinic for a geriatric assessment prior to TAVI between January 2014 and June 2020 were included. Patients were excluded if a) they were referred for a preoperative geriatric assessment prior to another operation than TAVI, b) the TAVI operation was cancelled, or c) the 3-month follow-up appointment was planned after 30

June 2020. Data was collected from patients' electronical medical records during the outpatient clinic visit prior to TAVI, during the TAVI admission and three months post-TAVI.

The study involved data obtained from usual care and ethical approval was waived by the local Ethics Committee of the University Medical Centre Utrecht. According to Dutch national regulations, in case of file research, there is no obligation to obtain informed consent. An anonymized data set was used in this study.

TAVI-procedure

A multidisciplinary heart team consisting of at least one interventional cardiologist and one cardiac surgeon evaluated the patients' suitability for a TAVI-procedure according to current guidelines. A preoperative complete cardiac assessment was performed. The preferred access site was the transfemoral artery. Procedures were performed under local or general anaesthesia. After the TAVI procedure, patients had to take six hours bedrest.

Preoperative geriatric assessment

The preoperative geriatric assessment was performed by a geriatric nurse practitioner under supervision of a geriatrician and involved a comprehensive geriatric assessment (CGA) in which the following domains were assessed: somatic, psychological, social and functional. An anamnesis was performed and data were collected on medical history, medication use (in particular the presence of (hyper)polypharmacy), smoking status, alcohol use, living situation, dependence in (instrumental) activities of daily living ((i)ADL), nutritional status, the presence of a fall in the previous six months and the presence of a delirium in the past. With regard to the medical history, the Charlson Comorbidity Index (CCI) score was calculated. (13) An adjusted CCI score without scoring points for age-category was used. A cut-off value of ≥3 was defined as multimorbidity. Polypharmacy was defined as the use of five or more medications, excluding food supplements without prescription, medication only taken when necessary, dermal creams and eye drops. Hyperpolypharmacy was defined as the use of ten or more medications. With regard to alcohol use and smoking status patients scored positive if they were current users, regardless of the amount. Patients lived dependent when they lived in a skilled nursing or assisted nursing facility. Patients lived independent when they lived in their own house, with or without homecare. To assess the dependence in (i)ADL the KATZ-15 questionnaire was conducted.(14) Dependence in (i)ADL was defined as a KATZ-15 score ≥2. The nutritional status was assessed using the Malnutrition Universal Screening Tool (MUST).(15) Malnutrition was suspected when the MUST score was ≥1. In addition, the American Society of Anaesthesiologists (ASA) score, determined by an anaesthesiologist, was obtained from the patients' electronical medical records.(16)

Furthermore, a psychical examination was performed, which consisted of measurement of vital signs, gait speed and handgrip strength and a neurological - and functional examination. A decreased gait speed was defined as a gait speed of ≤0.80 meters per second and a decreased handgrip strength was defined as ≤20 kilograms for women

and ≤30 kilograms for men.(17) In addition, a minimal mental state examination (MMSE) or Montreal Cognitive Assessment (<5% of the cases, MoCA) was conducted to assess cognitive function.(18,19) A MMSE score ≤24 or MoCA score <26 was indicative for cognitive impairment. To assess the possible presence of a depression, the Geriatric Depression Scale (GDS) questionnaire was conducted. A GDS-15 score ≥6 was suggestive of a depression.(20)

Frailty was assessed according to the Groningen Frailty Indicator (GFI).(21) This is an internationally applied, validated frailty instrument which offers a multidomain view on the degree of frailty. The GFI questionnaire consists of 15 questions, covering all domains of the CGA. Frailty was present in case of a GFI score of ≥4. Due to varying standard instruments to determine frailty in recent years, the GFI score was not reported in all patients by the geriatric nurse practitioner. In these cases, the GFI score was determined by the authors based on information collected during the preoperative geriatric assessment. A few questions of the GFI could not be filled in retrospectively. Therefore, the answers to these questions were rated as missing and the total GFI score was calculated, excluding these questions. Based on the results of the CGA, advice was provided on perioperative delirium prevention including both non-pharmacologic interventions and pharmacological interventions if indicated. Furthermore, advice was provided concerning fall-prevention, medication management, mobility, optimising nutritional status and reducing alcohol use and smoking. In some cases, it was recommended to cancel or postpone the TAVI procedure, for example in case of multimorbidity or severe functional or cognitive impairment. Nonetheless, the cardiologist made the ultimate decision.

Postoperative geriatric involvement

One day after the TAVI procedure, a geriatric nurse practitioner visited the patient on the cardiac ward to assist in the prevention or treatment of complications prevalent in the geriatric population (e.g. falls, delirium, stroke). Nurses from the cardiac ward observed the patients during the hospital stay and in case a postoperative delirium was suspected, the Delirium Observation Screening Scale (DOSS) was assessed three times a day. The DOSS is an early recognition tool for delirium, based on observations by nurses. A score of three and higher indicates a delirium.(22) A postoperative delirium was confirmed by the geriatric consulting team, based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).(23) A postoperative delirium was treated by non-pharmacological interventions and if indicated, by pharmacological treatment like haloperidol.

Follow-up

Three months after the TAVI procedure there was a follow-up appointment with a geriatric nurse practitioner, mostly by phone. Patients were asked about their general well-being and physical complaints compared to the situation before the procedure. Data was collected on the occurrence of postoperative complications. Patients were also followed by their cardiologist six and twelve months after TAVI.

Outcomes

The outcomes were mortality and hospital readmissions within three months of TAVI and major postoperative complications during hospitalisation according to the Clavien-Dindo classification (Supplement Table 1).(24,25) The Clavien-Dindo classification was already successfully implemented as outcome classification method in other surgical specialties (e.g. noncardiac thoracic surgery, colorectal surgery and urologic surgery) (26–30) and a recent study proved that this classification adequately measures the quantity and severity of postoperative complications in adult cardiac surgery.(31) The Clavien-Dindo classification consists of five categories, each category represents the type of therapy which was required to correct the complication. The need for pharmacological treatment is reflected in category I and II. Category III to IV range from a complication requiring a surgical, endoscopic or radiological intervention to a life-threatening complication requiring intensive care (unit) management. For example, an arrhythmia requiring the placement of a pacemaker is a Clavien-Dindo grade III complication. Category V reflects the death of a patient.(24,25) A composite outcome was created in which the three outcomes were combined. A Clavien-Dindo grade of II and higher was considered a major postoperative complication. When a patient suffered from two or more complications in different grade categories, the highest grade was used in the analysis.

Table 1 Baseline characteristics

		N	%
All patients		490	
Demographics			
Age	Years [Mean ±SD]	80.7 ±6.2	
	Age ≥80 years	319	65.1
Sex	Male	232	47.3
Smoking	Current smoker	31	6.3
	Ex-smoker	198	40.4
Alcohol use	Current alcohol user	241	49.2
Frailty			
GFI[a]	≥4	170	34.7
Somatic status			
ASA class[b]	≥3	456	93.1
CCI[c]	≥3*	258	52.7
Medication use	Number [Mean ±SD]	8.4 ±4.5	
	Polypharmacy (≥5 medications)	408	83.3
	Hyperpolypharmacy (≥10 medications)	163	33.3

Table 1 Continued

		N	%
Cognitive and psychological status			
MMSE[d]	[Mean ±SD]	27.5 ±2.5	
	MMSE ≤24	47	9.6
MOCA[d]	[Mean ±SD]	26 ±3.4	
	MOCA <26	8	1.6
Impaired cognition	MMSE ≤24 or MOCA <26	55	11.2
GDS[a]	≥6	17	3.5
Delirium	In past	48	9.8
Social status			
Living situation	Dependent	22	4.5
Functional status			
Dependence in ADL[e]	KATZ6 ≥1	114	23.3
Dependence in iADL[f]	KATZ9 ≥1	287	60.5
Dependence in (i)ADL[a]	KATZ15 ≥2	225	45.9
(At risk of) malnutrition[e]	MUST ≥1	75	15.3
Gait speed	<0.8 m/s	98	20
Handgrip strength	≤20 kg female / ≤30 kg male	246	50.2
Falls	≥1 in previous 6 months	93	19.1

* Points for age category not included
SD: standard deviation GFI: Groningen Frailty Indicator, ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Index, MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment, GDS: Geriatric Depression Scale, (i)ADL: (Instrumental) Activities of Daily Living, MUST: Malnutrition Universal Screening Tool, m/s: meters per second, kg: kilograms
[a]Score range from 0 to 15, [b]score range from 1 to 5, [c]score range from 0 to 24, [d]score range from 0 to 30, [e]score range from 0 to 6, [f]score range from 0 to 9.

Statistical analysis

The prevalence of dichotomized baseline variables is presented as numbers and corresponding percentages. Continuous baseline variables are expressed as mean and standard deviation. In case there were more than 10% missing values for a variable (which holds for the GDS), the Little's MCAR test was performed to determine whether missing values were completely at random or not. Since the results of the Little's MCAR test showed no significance ($p>0.05$), multiple imputation methods were not indicated. Univariate logistic regression analyses were performed to identify potential predictors of the outcomes and the composite outcome. Before entering continuous variables into

the univariate logistic regression analysis, we first performed the Box-Tidwell procedure to assess whether the continuous variables were linearly related to the logit of the dependent variable. All variables with p-value ≤0.10 in univariate analyses were entered into a stepwise multivariate analysis. Odds Ratios (OR) with a 95% Confidence Interval (CI) were calculated. Analyses were performed using IBM Statistical Package for the Social Sciences, version 25 (SPSS Inc., Chicago III, United States).

Results

Patient inclusion and baseline characteristics

A total of 555 patients visited the geriatric outpatient clinic for a geriatric assessment prior to TAVI between January 2014 and June 2020. 65 patients were excluded from this study. Reasons for exclusion were referral to the geriatric outpatient clinic because of a preoperative assessment for an intervention other than TAVI (n=31), no three-month follow-up data available because the follow-up appointment was scheduled after 30 June 2020 (n=20), insufficient information collected during preoperative assessment (n=10) and cancellation of the TAVI procedure (n=4). Operations were mostly cancelled due to severe comorbidities. Finally, 490 patients were included in the study. The baseline characteristics of the study population are outlined in Table 1. Mean age was 80.7 ± 6.2 years. 5 percent were between the age of 50 and 70 and 28% 85 years or older. 232 patients (47.3%) were male. A total of 170 patients (34.7%) were frail. The mean logistic EuroSCORE was 14.8%.

Mortality and hospital readmissions within three months of TAVI

Occurrence of outcome measures are displayed in Table 2. Twelve patients (2.4%) died during hospital admission and 19 patients (3.9%) died within three months of TAVI. In total, there were 46 readmissions (9.4%), of which 22 (48%) were cardiac, 23 (50%) non-cardiac and for one readmission (2%) the reason could not be traced in the patient file. Cardiac reasons for readmission were often arrhythmias requiring pacemaker implantation or acute decompensated heart failure. Non-cardiac reasons were among others infections (requiring intravenous antibiotics) or cerebrovascular events. Due to the limited number of outcome events within three months of TAVI, logistic regression analyses to identify independent predictors were not feasible.

Occurrence of major postoperative complications during hospitalisation

A total of 177 (36.1%) patients experienced one or more major postoperative complications (Clavien-Dindo Grade ≥II) during hospital admission. Results of the univariate and multivariate analysis are displayed in Table 3. Univariate analysis showed that cognitive impairment (OR 2.30; 95% CI 1.30-4.07), dependence in (i)ADL (OR 1.57; 95% CI 1.08-2.30), and a decreased gait speed (OR 1.64; 95% CI 1.04-2.60) were significantly associated with a higher risk of a major postoperative complication during hospitalisation. Multivariate

analysis showed that cognitive impairment was independently associated with a higher risk of a major postoperative complication during hospital admission (OR 2.16; 95% CI 1.14-4.19).

Table 2 Occurrence of outcome measures

	N	%
Mortality within three months of TAVI	19	3.9
Hospital readmission within three months of TAVI	46	9.4
Complications according to Clavien-Dindo during admission	177	36.1
Clavien-Dindo Grade I	144	29.4
Clavien-Dindo Grade II	69	14.1
Clavien-Dindo Grade IIIa	66	13.5
Clavien-Dindo Grade IIIb	15	3.1
Clavien-Dindo Grade IVa	14	2.9
Clavien-Dindo Grade IVb	2	0.4
Clavien-Dindo Grade V	12	2.4
Composite outcome*	193	39.4

*Including mortality and hospital readmission within three months of TAVI and the occurrence of major postoperative complications (Clavien-Dindo Grade ≥II) during hospitalisation

Composite outcome of adverse events

A total of 193 (39.4%) patients experienced the composite outcome consisting of mortality or hospital readmission within three months of TAVI and occurrence of major postoperative complications (Clavien-Dindo Grade ≥ II) during hospitalisation. Results from the univariate and multivariate analyses of the composite outcome are presented in Table 4. Cognitive impairment was statistically significant associated with an increased risk of the composite outcome in both univariate (OR 2.56; 95% CI 1.41-4.65) and multivariate analysis (OR 2.40; 95% CI 1.21-4.79). Univariate analysis showed that current alcohol use was associated with a lower risk (OR 0.62; 95% CI 0.43-0.90) and living dependently (OR 2.49; 95% CI 1.01-6.13), dependence in (i)ADL (OR 1.74; 95% CI 1.20-2.54) and a decreased gait speed (OR 1.62; 95% CI 1.02-2.56) with a higher risk of the composite outcome. In the multivariate analysis, these factors were not identified as independent predictors of the composite outcome.

Table 3 Variables associated with major postoperative complications* during hospitalisation

Demographics	Univariate OR [95% CI]	p value	Multivariate OR [95% CI]	p value
Age	1.00 [0.97-1.03]	0.91		
Sex (male)	1.37 [0.94-1.98]	0.10	0.91 [0.59-1.40]	0.66
Current smoker	1.12 [0.53-2.37]	0.76		
Alcohol user	0.62 [0.42-0.89]	0.01	0.78 [0.50-1.21]	0.26
Frailty				
GFI ≥4[a]	1.43 [0.96-2.13]	0.08	0.73 [0.42-1.24]	0.24
Somatic status				
ASA class ≥3[b]	0.91 [0.44-1.86]	0.79		
CCI ≥3**[c]	1.37 [0.94-1.98]	0.10	1.22 [0.80-1.87]	0.35
Polypharmacy	1.11 [0.67-1.83]	0.68		
Hyperpolypharmacy	1.27 [0.86-1.88]	0.22		
Cognitive and psychological status				
MMSE ≤24 or MOCA <26[d]	2.30 [1.30-4.07]	<0.01	2.16 [1.14-4.19]	0.02
GDS ≥6[a]	0.57 [0.18-1.77]	0.33		
Delirium in past	1.06 [0.57-1.96]	0.85		
Social status				
Living dependent	2.20 [0.93-5.21]	0.07	1.59 [0.60-4.23]	0.35
Functional status				
Katz15 ≥2[a]	1.57 [1.08-2.30]	0.02	1.20 [0.73-1.97]	0.47
MUST ≥1[e]	1.06 [0.64-1.77]	0.81		
Gait speed < 0.8m/s	1.64 [1.04-2.60]	0.03	1.47 [0.85-2.55]	0.17
Handgrip strength ≤20 kg/≤30 kg***	1.00 [0.68-1.47]	>0.99		
Falls in previous 6 months	1.37 [0.86-2.17]	0.18		

*Clavien-Dindo Grade ≥II
** Points for age category not included
***≤20 kg female / ≤30 kg male
GFI: Groningen Frailty Indicator, ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Index, MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment, GDS: Geriatric Depression Scale, MUST: Malnutrition Universal Screening Tool, m/s: meters per second, kg: kilograms
[a]Score range from 0 to 15, [b]score range from 1 to 5, [c]score range from 0 to 24, [d]score range from 0 to 30, [e]score range from 0 to 6.

Table 4 Variables associated with the composite outcome consisting of mortality or hospital readmission within three months of TAVI and occurrence of major postoperative complications (Clavien-Dindo Grade ≥ II) during hospitalisation

Composite outcome: postoperative adverse events	Univariate OR [95% CI]	p value	Multivariate OR [95% CI]	p value
Demographics				
Age	1.01 [0.98-1.04]	0.51		
Sex (male)	0.87 [0.60-1.25]	0.45		
Current smoker	1.13 [0.54-2.38]	0.75		
Alcohol user	0.62 [0.43-0.90]	0.01	0.77 [0.50-1.19]	0.23
Frailty				
GFI ≥4[a]	1.47 [0.99-2.19]	0.06	0.67 [0.39-1.15]	0.14
Somatic status				
ASA class ≥3[b]	1.11 [0.54-2.27]	0.78		
CCI ≥3*[c]	1.38 [0.96-2.00]	0.09	1.23 [0.81-1.86]	0.34
Polypharmacy	1.18 [0.72-1.95]	0.52		
Hyperpolypharmacy	1.27 [0.86-1.87]	0.23		
Cognitive and psychological status				
MMSE ≤24 or MOCA <26[d]	2.56 [1.41-4.65]	<0.01	2.40 [1.21-4.79]	0.01
GDS ≥6[a]	0.46 [0.15-1.45]	0.19		
Delirium in past	1.20 [0.66-2.21]	0.55		
Social status				
Living dependent	2.49 [1.01-6.13]	0.05	1.85 [0.66-5.19]	0.24
Functional status				
Katz15 ≥2[a]	1.74 [1.20-2.54]	<0.01	1.42 [0.87-2.31]	0.16
MUST ≥1[e]	1.03 [0.62-1.71]	0.90		
Gait speed < 0.8m/s	1.62 [1.02-2.56]	0.04	1.32 [0.76-2.28]	0.32
Handgrip strength ≤20 kg/≤30 kg***	1.11 [0.76-1.63]	0.58		
Falls in previous 6 months	1.39 [0.88-2.19]	0.16		

* Points for age category not included
**≤20 kg female / ≤30 kg male
GFI: Groningen Frailty Indicator, ASA: American Society of Anaesthesiologists, CCI: Charlson Comorbidity Index, MMSE: Mini-Mental State Examination, MOCA: Montreal Cognitive Assessment, GDS: Geriatric Depression Scale, MUST: Malnutrition Universal Screening Tool, m/s: meters per second, kg: kilograms
[a]Score range from 0 to 15, [b]score range from 1 to 5, [c]score from range 0 to 24, [d]score range from 0 to 30, [e]score range from 0 to 6.

Discussion

The aim of this study was to identify predictors of postoperative adverse outcomes in older patients undergoing TAVI. Cognitive impairment was identified as an independent predictor of major postoperative complications during hospitalisation and the composite outcome of major complications, hospital readmissions and mortality. No association was found between the other variables and the composite and separate outcomes.

The finding of cognitive impairment as an independent predictor of worse outcomes in older patients is in line with previous studies conducted in patients undergoing TAVI. Yanagisawa et al. evaluated if the presence of preoperative cognitive impairment was associated with postoperative adverse outcomes, in particular 1-year cumulative mortality. (32) They included TAVI patients aged 70 or higher, whose cognitive performance was assessed using the MMSE. They found that patients with cognitive impairment had more in-hospital adverse outcomes (major bleeding, vascular complications, acute kidney injury, prolonged hospital stay) and that cognitive impairment was an independent predictor of 1-year all-cause mortality.(32)

Khan et al. included TAVI patients who were screened on the presence of geriatric risk factors.(33) They found that the presence of cognitive deficits (according to the Mini-Cog test) was associated with the occurrence of a postoperative delirium and 30-day mortality.(33)

A possible explanation for this finding could be that patients with cognitive impairment are more prone to develop a postoperative delirium and that this is reflected in our outcome 'major postoperative complications during hospitalisation according to the Clavien-Dindo classification' and the composite outcome. However, only a minority (11.3%) of all patients with a Clavien-Dindo grade II complication experienced a delirium for which pharmacological treatment was necessary. Another explanation, as stated by Yanagisawa et al., could be that a part of the patients with cognitive deficits are known to suffer from vascular cognitive impairment caused by systemic vascular risk factors.(32) The presence of these vascular risk factors might explain the increased risk of postoperative morbidity in patients with cognitive impairment. In contrast to previous studies conducted in TAVI patients(3,4), we did not find an association between other variables, like frailty, and postoperative adverse outcomes. A possible explanation for this finding could be that all TAVI patients included in our study had a preoperative CGA. Based on the results of the CGA, an extensive advice was given with regard to identified risk factors. Therefore, our study population differs from the study population in previous studies, since all patients in our study had a preoperative intervention consisting of a CGA and the subsequent advice for appropriate treatment to prevent/reduce postoperative adverse outcomes.

This study has several strengths. The study design was prospective and a relatively large number of patients was included. Whereas previous studies mostly focused on separate

outcomes, in particular mortality, this study also assessed a composite outcome, including mortality and hospital readmission within three months of TAVI and the occurrence of major postoperative complications during hospitalisation, assessing both postoperative mortality and morbidity. Therefore, an advantage of this composite outcome is that it reflects the overall course following TAVI. Furthermore, we included a wide variety of potential preoperative predictive factors, covering all the different domains of the CGA. In this study, frailty was assessed by a validated frailty instrument that includes all domains of the CGA and therefore it offers a broad assessment of frailty in comparison to other frailty instruments that cover less domains of the CGA.(21)

This study has some limitations. Due to the limited number of events for mortality and hospital readmission within 3 months of TAVI, planned logistic regression analyses were not feasible. Furthermore, during the study period, the local guidelines regarding frailty instruments were changing. Therefore, for a number of patients, the GFI score was not reported by the geriatric nurse practitioner and had to be calculated by the authors. However, some questions of the GFI are subjective and could not be filled in retrospectively. The answers for these questions were rated as missing, and the total GFI score was calculated, excluding these questions. This might have resulted in an underestimation of the number of frail patients. However, the frailty prevalence in this study corresponded to the prevalence range (29 to 63%) of frailty in patients undergoing TAVI that was found in a recent meta-analysis.(34) Lastly, during the 3-month follow-up appointment with the geriatric nurse practitioner, patients were often not explicitly asked if they had been readmitted to a hospital within three months of TAVI. This may lead to an underestimation of the number of participants with a readmission if a patient was admitted to a hospital other than the University Medical Centre Utrecht.

Clinical implications

The results of this study have some important clinical implications. We found cognitive impairment to be independently associated with a higher risk of postoperative adverse events. Screening for cognitive impairment with a screening tool like the MMSE or MoCA could help identify patients who are at increased risk of unfavourable outcomes and will provide additional information on the potential risks of TAVI, which improves shared-decision making. Therefore, we advise to include screening for cognitive impairment in the current local and international guidelines.(1) The 2017 ACC expert consensus on a decision pathway for TAVI in the management of adults with aortic stenosis, is innovative by advising to assess cognition by means of the MMSE, however, cognitive function is not yet included in their four proposed risk categories.(2) In addition, if a patient is suspected of cognitive decline or impairment after screening for cognitive impairment, he or she could be monitored more closely during admission and afterwards, especially by a geriatric team in order to detect and anticipate on problems in an early stage.

Conclusion

This study identified cognitive impairment as an independent predictor of postoperative adverse events in older patients undergoing TAVI. Therefore, it is important to screen for cognitive impairment prior to TAVI, as this can identify patients who are at increased risk to develop a postoperative adverse event. It is recommended to include screening for cognitive impairment in current TAVI guidelines.

Author contributions*:

Study concept and design: ME-V, HLK. Acquisition of data: JEMP, MA. Analysis and interpretation of data: LD, JEMP, PRS, HLK. Drafting of the manuscript: LD, JEMP. Critical revision of the manuscript: PRS, ME-V, MA, HLK. All authors critically reviewed and approved the final manuscript.

Competing interests:

There are no competing interests for any author

Funding:

None

Ethical approval information:

The study involved data obtained from usual care and the local Ethics Committee of the University Medical Centre Utrecht confirmed that this study did not fall under the scope of The Medical Research Involving Human Subjects Act. Therefore, patient consent was not required.

Data sharing statement:

Data are available upon reasonable request.

* In the original article, GL's authorship contribution was inadvertently omitted. GL established care pathways, including the perioperative care for TAVI patients, enabling the automatic acquisition of quality assured data within the research data platform. Utilizing this data, he generated a subset of the dataset for this study, while validating the manually obtained data. He contributed to both the design, data acquisition and critical revision of the manuscript.

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Supplementary data chapter 3.1

Supplementary Table S1 Clavien-Dindo Classification of surgical complications[1,2]

Grade		Definition
I		Any deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetic's, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III		Complication requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention not under general anesthesia	
IIIb	Intervention under general anesthesia	
IV		Life-threatening complication (including central nervous system complications) requiring intensive care unit management
IVa	Single organ dysfunction (including dialysis)	
IVb	Multi-organ dysfunction	
V		Death of a patient

References supplementary table S1

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3.2

The association between perioperative statin treatment and short-term clinical outcomes following transcatheter aortic valve implantation: a retrospective cohort study

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What is already known about this subject?

Some studies found that statin treatment is associated with improved long-term outcomes after trans aortic valve implantation (TAVI).Recent literature suggests that perioperative pleiotropic effects of statin treatment during and direct after TAVI might in part explain the improved long-term outcomes after TAVI

What does this study add

We found no association between continued statin treatment and postoperative complications after TAVI, including mortality, rehospitalisation, and post operative major complications according to the Clavien-Dindo classification.

How might this impact on clinical practice

Initiation of statin treatment is not advised specifically to improve short-term outcomes after TAVI

Abstract

Background:
Studies have found statin treatment to be associated with improved one-year survival after transcatheter aortic valve implantation (TAVI), suggesting pleiotropic effects of statins on preventing perioperative complications. Statin treatment is not associated with postoperative cardiovascular complications or mortality, however, other postoperative complications have not been investigated.

Aim: To explore whether preoperative statin treatment is associated with a lower short-term risk of mortality, readmission, and major postoperative complications in older patients undergoing TAVI.

Methods: A retrospective cohort study including patients aged 65 years and older who had undergone a comprehensive geriatric assessment prior to TAVI between January 2014 and January 2021. The primary outcomes were 90-day mortality, 90-day readmissions, and major postoperative complications according to the Clavien-Dindo classification. Multivariable logistic regression was performed with adjustment for potential confounders, namely age, gender, comorbidity, body-mass index, smoking, diminished renal function, alcohol use and falls .

Results: This study included 584 patients, of whom 324 (55.5%) were treated with a statin. In the statin treated group, 15 (4.6%) patients died within 90 days of TAVI compared with 10 (3.8%) patients in the non statin group (adjusted OR 1.17; 95% CI 0.51 to 2.70). The number of 90-day readmissions was 39 (12.0%) and 34 (13.1%) (adjusted OR 0.91; 95% CI 0.54 to 1.52), respectively. In the statin treated group, 115 (35.5%) patients experienced a major complication compared to 98 (37.7%) in the non-statin group (adjusted OR 0.95; 95% CI 0.67 to 1.37).

Conclusion: Preoperative statin treatment is not associated with improved short-term outcomes after TAVI. A randomized controlled trial with different statin doses may be warranted to investigate whether initiating statin treatment before TAVI improves both post-operative outcomes and long term survival.

Introduction

Aortic valve stenosis is the most common valvular heart disease in developed countries and becomes more prevalent with age. In people aged 75 years and older, the prevalence is 12.4% (1). Due to the poor prognosis of untreated symptomatic aortic valve stenosis, even in the absence of severe comorbidities, early treatment is recommended. Transcatheter aortic valve implantation (TAVI) is recommended in patients who are unsuitable for surgical aortic valve replacement. The criteria for TAVI include increased surgical risk, age ≥75 years and frailty (2). Although TAVI is a well-established therapy in older patients, especially in more frail patients, the five year survival rate after TAVI is only 48% (3).

Periprocedural statin treatment, among other treatments, has been the subject of investigations to improve patients'survival after TAVI. In a meta-analysis of observational studies on statin treatment at the time of TAVI, statin treatment was found to be associated with reduced all-cause mortality two years after TAVI (4). Since this meta-analysis, three more observational studies have been published, the results of which were in line with the original meta-analysis (5–7). In two of these studies, the observed association was strongest in patients without coronary artery disease and within the first months after TAVI (5,7). One could discuss whether this association was caused by residual confounding or by direct, pleiotropic effects of statin treatment on post-TAVI complications. Suggested pleiotropic effects include anti-inflammatory effects, the inhibition of cytokine-mediated induction of proadhesive and procoagulant substances, the reduction of neointimal thickening and the induction of endothelial nitric oxide synthase leading to improved vascular remodelling (8–10). However in studies on short-term cardiovascular outcomes after TAVI, no association has been found between statin treatment and periprocedural cardiovascular outcomes or 30 day mortality (11,12). This finding is in line with two randomised controlled trials (RCTs) that have indicated no effect of statin treatment in preventing perioperative myocardial injury in cardiothoracic surgery (13,14). Furthermore, the available studies on short-term outcomes have focused on cardiovascular outcomes and mortality, not on other post-operative complications. Therefore, in the present study, we aimed to determine whether statin treatment is associated with a short-term risk of mortality and readmissions, as well as with major postoperative complications in older patients undergoing TAVI.

Methods

Study design

This retrospective cohort study was conducted at the University Medical Center Utrecht, a tertiary teaching hospital in the Netherlands. All patients aged 65 years and older who had undergone a comprehensive geriatric assessment (CGA) within 90 days prior to TAVI between January 2014 and January 2021 were included. Patients were excluded if no CGA was performed or if they declined permission for their healthcare data to be re-use

for research. Due to the retrospective nature of this study, it did not fall within the scope of the Medical Research Involving Human Subjects Act, which was confirmed by the local Ethics Committee (reference number WAG/mb/18/019289).

Data collection

Baseline

Patients visited the geriatric outpatient clinic for a CGA prior to TAVI. During this visit, the patients' somatic, psychological, functional and social domains were assessed as described in an earlier study (15). After the CGA had been performed, the patients were advised regarding the feasibility of TAVI, how to optimise their health prior to the intervention, and how to reduce the risk of complications. Data from the CGA (Supplementary table I) were collected from electronic medical charts. The Charlson comorbidity index at baseline was calculated for each patient., A score of 3 or higher was defined as multimorbid. Moreover, statin treatment was determined based on structured medication reconciliation at hospital admission and actual statin treatment at hospital admission before and after TAVI. Furthermore, the intensity of statin treatment was divided into low-to-moderate intensity statin (LMIS) and high intensity statin (HIS) therapy (16). HIS therapy was defined as daily dosage of atorvastatin ≥40 mg or rosuvastatin ≥20 mg. Lower daily doses of these medications and the use of other types of statins were defined as LMIS therapy.

Follow-up

During hospitalisation for TAVI (index hospitalisation), a geriatric nurse practitioner performed patient follow-up to diagnose and treat geriatric complications such as falls, delirium, functional decline, and stroke. During a follow-up appointment three months after TAVI, a geriatric nurse practitioner checked whether rehospitalisation had occurred. This practitioner was supervised by a geriatrician.

Outcomes

The primary outcomes were 90-day mortality, 90-day readmissions and major postoperative complications during hospitalisation. The Clavien-Dindo classification system was used to classify of postoperative complications through reviewing patient charts of all patients (17,18). All complications that occurred during index hospitalization were collected and classified according to the treatment needed for the complication. Grades I complications require no intervention or mainly basic pharmacological treatment; Grade II complications require more advanced pharmacological treatment; Grade III complications require surgical, endoscopic, or radiological intervention; Grade IV complications require intensive care; and Grade V indicates death. This study considered a Clavien-Dindo grade II complications or higher to be major postoperative complications (Supplement Table II). For secondary outcomes, we divided these major postoperative complications, into cardiovascular complications, respiratory complications, neurologic

complications, renal complications, and complications with other organ systems. Cardiovascular complications encompassed various conditions such as arrythmia requiring medication or pacemaker insertion, tamponade, myocardial infarction, and resuscitation; pulmonary complications were mainly pneumonia; neurologic complications included delirium, transient ischaemic attacks and stroke; renal complications primarily consisted of urinary tract infections; and other complications included post-procedural bleeding or anaemia requiring transfusion. Furthermore, acute kidney injury (AKI) was evaluated as a postoperative complication, as it is often only a Clavien-Dindo Grade I complication according to the Clavien-Dindo classification. AKI was defined as an increase in serum creatinine of ≥26.5 µmol/l from baseline or to ≥1.5 times the baseline value(19).

Statistical analysis

Categorical baseline variables were expressed as numbers and corresponding percentages. Continuous baseline variables were presented as means and standard deviations. Between-group differences for categorical variables were determined using Pearson's chi square and Fisher's exact test where appropriate. For continuous variables, an independent two-sample *t*-test was used to test for group differences. In the case of more than 10% missing values for a variable, we performed Little's Missing Completely At Random test to determine whether the missing values were missing completely at random. Since no variables were missing in more than 10% of patients, multiple imputation methods were not indicated. Furthermore, we performed a logistic regression analysis to assess the association between statin treatment and the various outcomes. For the multivariate analysis, the number of independent variables included was limited to 1 per 10 outcomes. The selected variables were age, gender, a Charlson Comorbidity Index three or higher, BMI≥30, smoking, eGFR<60, alcohol use and falls in the previous 6 months. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Additional analyses were performed to assess for effect modification by LMIS or HIS therapy, and age (<80 years and ≥ 80 years). All analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software version 26.0 (SPSS Inc., Chicago Ill, United States).

Results

Patient inclusion and baseline characteristics

During the study period, 620 patients underwent TAVI. Seven patients did not permit their data to be reused for clinical research, while 29 patients did not receive a CGA prior to TAVI. A total of 584 patients were included in this study, of whom 324 were treated with a statin before TAVI (55.5%). Moreover, 65 patients were treated with HIS (20% of the statin users). Table 1 presents the patients' baseline characteristics. Compared with non-users, statin users were younger (79.8 vs 81.7 years); were more often male (53.7% vs 38.5%); had a higher BMI (27.1 vs 26.3); were more often multimorbid (51.2% vs 35.8%) including prior stroke (21.9% vs 13.1%), prior myocardial infarction (18.8% vs 6.9%), and diabetes (29.6% vs 12.3%); used more medications (10.6 vs 7.5), and were less often at

risk of malnutrition (14.8% vs 21.9%). The statin treatment status did not change for any patient during their hospital stay.

Table 1 Baseline characteristics

		Statin (n=324)	No statin (n=260)	P-value
Demographics				
Age	Years [Mean ±SD]	79.8 ±6.2	81.7 ±5.9	<0.001
	Age ≥80 years	187 (57.7)	190 (73.1)	<0.001
Gender	Male	174 (53.7)	100 (38.5)	<0.001
BMI	Kg/m2 [Mean ±SD]	27.1 ±4.8	26.3 ±4.8	0.05
Smoking	Current smoker	28 (8.6)	17 (6.5)	0.38
	Missing	4 (1.2)	8 (3.1)	
Alcohol use	Current alcohol user	163 (50.3)	128 (49.2)	0.99
	Missing	4 (1.2)	9 (3.5)	
Frailty				
EFS [a] or GFI [b]	≥6 or ≥4, respectively	81 (25.0)	64 (24.6)	0.936
	Missing	20 (6.2)	17 (6.5)	
Somatic status				
CCI [c*]	≥3	166 (51.2)	93 (35.8)	<0.001
- Diabetes	n (%)	96 (29,6)	32 (12,3)	<0.001
- Stroke	n (%)	70 (21,9)	34 (13,3)	0.008
- Myocardial infarction	n (%)	61 (18,8)	18 (6,9)	<0.001
- Any malignancy	n (%)	41 (12,7)	29 (11,2)	0.58
Medication use	Number [Mean ±SD]	10.6 ±4.2	7.5 ±4.0	<0.001
	Polypharmacy (≥5 medications)	312 (96.3)	196 (75.4)	<0.001
	Hyper polypharmacy (≥10 medications)	175 (54.0)	73 (28.1)	<0.001
eGFR	< 60 ml/min/1.73m2	109 (33.6)	78 (30.0)	0.35
Cognitive and psychological status				
Impaired cognition	MMSE [e] ≤24, MOCA [e] <26, 6-CIT≥8 [f]	5 (1.5)	3 (1.2)	0.68
	Missing	33 (10)	24 (9.2)	
GDS-15[b]	≥6	14 (4.3)	10 (3.8)	0.77
Delirium in past		41 (12.7)	23 (8.8)	0.14
	Missing	3 (0.9)	2 (0.8)	
Functional status				

Table 1 Continued

		Statin (n=324)	No statin (n=260)	P-value
Dependence in (i)ADL	KATZ-15 [b] ≥2	154 (47.5)	122 (46.9)	0.81
	Missing	21 (6.5)	15 (5.8)	
At risk of malnutrition	MNA [g] ≤11, MUST [h] ≥1	48 (14.8)	57 (21.9)	0.03
	Missing	7 (2.2)	5 (1.9)	
Falls	≥1 in previous 6 months	63 (19.4)	45 (17.3)	0.55
	Missing	10 (3.1)	11 (4.2)	
Social status				
Living situation	Living dependent	15 (4.6)	8 (3.1)	0.37
	Missing	27 (8.3)	28 (10.8)	

Values are number (percentages) unless stated otherwise.
* not adjusted for age
BMI: Body Mass Index; EFS: Edmonton Frail Scale; GFI: Groningen Frailty Indicator; ASA: American Society of Anaesthesiology; CCI: Charlson Comorbidity Index; eGFR: estimated glomerular filtration rate; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; 6-CIT: six item cognitive impairment test; GDS: Geriatric Depression Scale; (i)ADL: (Instrumental) Activities of Daily Living; MNA: Mini Nutritional Assessment; MUST: Malnutrition Universal Screening Tool.
[a] Score range from 0 to 17, [b] Score range from 0 to 15, [c] Score range from 0 to 33, [d] Score range from 0 to 30, [e] Score range from 0-28, [f] Score range from 0 to 14, [g] Score range from 0 to 6

Primary outcomes

Statin treatment was found not to be associated with a decreased short-term risk of mortality, readmissions, or major complications (Table 2). The 90-day mortality rate was 4.6% among statin users compared with 3.8% among non-users (adjusted OR 1.17; 95% CI 0.51–2.70). Furthermore, readmission risks at 90 days was 12.0% (39) in statin users and 13.1% (34) in non-users (adj. OR 0.91; 95% CI 0.54–1.52). Of the statin users, 35.5% experienced a major complication compared with 37.7% of non-users (adjusted OR 0.95; 95% CI 0.67–1.37). The effect of statin use on the short-term risks of mortality, readmissions, or postoperative complications was not significantly modified by the intensity of statin treatment (i.e. LIMS or HIS) or age (Table 3).

Table 2. The association between statin treatment and short-term outcomes after TAVI.

Outcomes	Statin	No statin	OR [95% CI]	P-value	adj OR [95% CI]	P-value
Primary outcomes	**n=324**	**n=260**				
90-day mortality	15 (4.6%)	10 (3.8%)	1.21 [0.54-2.75]	0.64	1.17 [0.51-2.70][c]	0.71
90-day readmission	39 (12.0%)	34 (13.1%)	0.91 [0.56-1.49]	0.71	0.91 [0.54-1.52][d]	0.70
Major postoperative complications[a]	115 (35.5%)	98 (37.7%)	0.91 [0.65-1.28]	0.58	0.95 [0.67-1.37][e]	0.79
Secondary outcomes						
Cardiovascular complications	59 (18.2%)	52 (20.0%)	0.93 [0.621.41]	0.74	1.05 [0.67-1.63][e]	0.84
Respiratory complications	8 (2.5%)	8 (3.1%)	0.80 [0.30-2.15]	0.66	0.86 [0.32-2.36][f]	0.77
Neurologic complications	23 (7.1%)	20 (7.7%)	0.92 [0.49-1.71]	0.78	1.05 [0.55-2.01][g]	0.87
Renal complications	12 (3.7%)	6 (2.3%)	1.63 [0.60-4.40]	0.34	1.60 [0.59-4.36][f]	0.36
Other complications	49 (15.1%)	36 (13.8%)	1.11 [0.70-1.77]	0.66	1.01 [0.61-1.66][e]	0.97
Acute kidney injury[b]	15 (4.6%)	14 (5.4%)	0.88 [0.41-1.85]	0.73	0.86 [0.40-1.85][c]	0.70
- Missing	19 (5.9%)	9 (3.5%)	-			

[a] Clavien-Dindo Grade ≥II
[b] increase in serum creatinine of ≥26.5 µmol/l from baseline or an increase in serum creatinine to ≥1.5 times the baseline value
[c] Adjusted for age and gender
[d] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60 and alcohol use
[e] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60, alcohol use and falls in previous 6 months
[f] Adjusted for age
[g] Adjusted for age, gender, a CCI three or higher and BMI≥30

Table 3. The association between statin treatment and short-term outcomes after TAVI, stratified by age and intensity of statin therapy

	Statin	No statin	OR [95% CI]	P-value	adj OR [95% CI]	P-value
Age <80 years (n=207)	**n=137**	**n=70**				
90-day mortality	4 (2.9%)	4 (5.7%)	0.50 [0.12-2.05]	0.33	na.[b]	
90-day readmission	19 (13.9%)	7 (10.0%)	1.45 [0.58-3.63]	0.43	1.45 [0.57-3.69][c]	0.43
Major postoperative complications[a]	48 (35.0%)	23 (32.9%)	1.10 [0.60-2.03]	0.76	0.88 [0.45-1.70][d]	0.69
Age ≥80 years (n=377)	**n=187**	**n=190**				
90-day mortality	11 (5.9%)	6 (3.2%)	1.92 [0.69-5.29]	0.21	1.91 [0.89-5.29][e]	0.21
90-day readmission	20 (10.7%)	27 (14.2%)	0.72 [0.39-1.34]	0.30	0.72 [0.38-1.36][f]	0.31
Major postoperative complications[a]	67 (35.8%)	75 (39.5%)	0.86 [0.56-1.30]	0.47	0.91 [0.59-1.42][g]	0.69
LMIS (n=519)	**n=259**	**n=260**				
90-day mortality	14 (5.4%)	10 (3.8%)	1.43 [0.62-3.28]	0.40	1.37 [0.59-3.19][c]	0.46
90-day readmission	32 (12.4%)	34 (13.1%)	0.94 [0.56-1.57]	0.81	0.93 [0.54-1.58][h]	0.78
Major postoperative complications[a]	95 (36.7%)	98 (37.7%)	0.96 [0.67-1.37]	0.81	1.02 [0.70-1.48][g]	0.94
HIS (n=325)	**n=65**	**n=260**				
90-day mortality	1 (1.5%)	10 (3.8%)	0.39 [0.05-3.11]	0.37	0.35 [0.04-2.86][e]	0.33
90-day readmission	7 (10.8%)	34 (13.1%)	0.80 [0.34-1.90]	0.62	0.70 [0.28-1.74][f]	0.45
Major postoperative complications[a]	20 (30.8%)	98 (37.7%)	0.74 [0.41-1.32]	0.30	0.69 [0.37-1.29][g]	0.24

LMIS: Low-moderate intensity statin; HIS: High intensity statin (atorvastatin ≥40mg or rosuvastatin ≥20 mg).
[a] Clavien-Dindo Grade ≥II
[b] not applicable, less than 10 outcomes
[c] Adjusted for age and gender
[d] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60 and alcohol use
[e] Adjusted for age
[f] Adjusted for age, gender, a CCI three or higher, BMI≥30
[g] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking, eGFR<60, alcohol use and falls in previous 6 months
[h] Adjusted for age, gender, a CCI three or higher, BMI≥30, smoking and eGFR<60

Secondary outcomes

No significant associations were observed between statin treatment and the risk of postoperative complications in any specific organ system, including major cardiac or neurologic complications or AKI (Table 2). The rate of cardiovascular complications was 18.2% among statin users compared with 19.6% among non-users (adjusted OR 0.95; 95% CI 0.62–1.45). Pulmonary complications occurred in 2.5% of statin users and 3.1% in non-users (adjusted OR 0.84; 95% CI 0.30–2.32), while neurological complications were found in 7.1% of statin users compared with 7.7% in non-users (adjusted OR 1.05; 95% CI 0.56–2.00). Renal complications were seen in 3.7% of statin users compared with 2.3% of non-users (adjusted OR 1.54; 95% CI 0.56–4.23) and other complications occurred in 15.1% of statin users compared with 18.8% of non-users (adjusted OR 1.05; 95% CI 0.65–1.68). Acute kidney injury occurred in 5.9% of statin users and 3.5% of non-users (adjusted OR 0.88; 95% CI 0.40–1.85).

Discussion

This study found no association between statin treatment before TAVI and a decreased risk of negative short-term outcomes, including 90-day mortality, 90-day readmissions, and major postoperative complications. Although several studies have suggested a direct pleiotropic effect of statins during the postoperative period after TAVI, we found no association between statin treatment and any postoperative complications.

The difference between our study and the two previous studies that have suggested a direct pleiotropic effect directly after TAVI is that they were propensity score matched (5,7). In the first study, which included 3,956 patients, a total of 626 matched pairs were formed, accounting for 31% of the initial cohort (5). In the second study which included 2,588 patients, 936 matched pairs were created, accounting for 72% of the initial study population(7). In both studies, 40% of patients who were not using statins could not be successfully matched. It is important to consider that propensity score matching might have led to the exclusion of patients without an indication for statin treatment while including patients with a high cardiovascular risk who were not using statin treatment. This could have led to higher mortality risks in the included non-users compared to the included users. This could have potentially accounted for the observed positive effect of statin use on mortality in these two studies, as matching was performed based on variables such as prior cardiovascular events, cholesterol levels, and other coexisting medical conditions.

In addition, the finding that statin treatment was not significantly associated with short-term outcomes after TAVI is consistent with previous observational studies on short-term cardiovascular complications and short-term mortality. Merdler et al. found no significant effect of statin treatment on one-month mortality and postoperative cardiologic complications (11). Moreover, Huded et al. found no significant effect of statin treatment

on post-TAVI myocardial infarction, AKI, in-hospital mortality and 30-day mortality (12). Furthermore, Klinkhammer et al. demonstrated no effect of statin treatment on postoperative cardiological complications or mortality one and six months after TAVI (20). In all studies, including our study, statin non-use in patients with an indication for statins treatment was highly prevalent. Therefore, matching on covariates indicative of high cardiovascular risk, including prior cardiovascular events, diabetes, hypercholesterolemia and hypertension, poses a risk of overestimating statin treatment after TAVI by selecting high-risk patients already known to benefit from statin treatment. Our outcomes are in line with RCTs on statin treatment during coronary artery bypass grafting surgery, which revealed no association with short-term mortality and postoperative complications (21).

Strengths and limitations

This study has several strengths. First, the data were collected from a relatively large cohort that included patients over a long period of time. Together with the broad inclusion criteria, this has probably resulted in a high representation of the study population for the total older population of TAVI patients and thus good external validity of the outcomes. Second, this study examined the effect of statin treatment on the overall risk of short-term negative outcomes using both short-term mortality and morbidity. Third, all postoperative complications occurring after TAVI were classified according to the Clavien-Dindo classification, therefore, in addition to the standard reported complications, such as myocardial infarction, stroke, and AKI, all other postoperative complications were included as relevant clinical outcomes. However, due to the retrospective nature of the study, we were not able to report on all endpoints specified by the Valve Academic Research Consortium (22).

This study also has several limitations. First, the number of events was relatively low, which could have led to residual confounding in the analyses, as only a limited number of possible confounding variables could be included. Second, due to the retrospective nature of the study, a possibility of residual confounding also exists, since reasons for non-use were not available. Third, we only had information on statin treatment before hospitalisation from a structured medication review and on statin exposure during the hospital stay for the TAVI procedure. Fourth, we did not have access to public pharmacy outpatient dispensing records; therefore, we did not have information on the duration of statin treatment before the procedure or its continuation after TAVI. Lastly, the HIS subgroup was small, which could have resulted in insufficient power to demonstrate significant associations between HIS and the outcomes.

Clinical implications and recommendations for future research

Based on the lack of an association between statin treatment and short-term outcomes post-TAVI in this study as well as in previous studies, the initiation of statin treatment is not specifically advised for improving short-term outcomes after TAVI. Yet, statins are often indicated to improve long-term negative outcomes, as atherosclerotic comorbidity is

common in these patients. A clinical trial could answer critical questions about the short-term effects of statin treatment after TAVI as well as whether initiating statin treatment before TAVI improves long-term outcomes. Furthermore, because our study included a relatively small number of patients treated with HIS, different statin dosages could be incorporated into a trial as well to determine whether HIS treatment has an effect on short-term outcomes in patients who can tolerate high statin dosages.

Conclusion

This study demonstrated that preoperative statin treatment is common in TAVI patients, but is not associated with decreased risks of negative short-term outcomes after a TAVI, including 90-day mortality, 90-day readmissions, and major postoperative complications. Given the magnitude of statin non-use in all observational TAVI statin studies, an RCT with different statin doses could be warranted for investigating whether initiating statin treatment before TAVI improves both post-operative outcomes and long-term survival.

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Disclosures:

None.

Supplemental Materials

Supplementary Table S1. Individual elements of the applied comprehensive geriatric assessment stratified by the somatic, psychological, functional, and social domains.

Supplementary Table S2. Clavien-Dindo classification of surgical complications.

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Supplementary data chapter 3.2

Supplementary table S1 Individual elements of the applied comprehensive geriatric assessment stratified by the somatic, psychological, functional and social domains

Elements of the CGA	Instrument/test	Cut-off score	Interpretation
Somatic domain			
Medical history			
Comorbidity	Charlson Comorbidity Index[1]	≥3	Multimorbidity
Medication use		1. ≥5 drugs 2. ≥ 10 drugs	1. Polypharmacy 2. Hyperpolypharmacy
Smoking status			Current smoker
Alcohol use			Current alcohol user
BMI	Kg/m^2		
Renal function	Estimated glomerular filtration rate	< 60 ml/min/1.73m^2	Impaired kidney function
Psychological domain			
Cognition	Mini-Mental State Examination[2]	≤24	Cognitive impairment
Cognition	Montreal Cognitive Assessment[3]	<26	Cognitive impairment
Cognition	Six item cognitive impairment test[4]	≥8	Cognitive impairment
Mood	Geriatric Depression Scale[5]	≥6	Depression
Previous delirium		Yes	Increased risk of delirium
Functional domain			
(Instrumental) activities of daily living	KATZ-15[6]	≥2	Dependence
Nutritional status	Malnutrition Universal Screening Tool[7]	≥1	Increased risk of malnutrition
Nutritional status	Mini Nutritional Assessment[8]	≤11	Increased risk of malnutrition
History of falling		≥1 in previous 6 months	Increased risk of falling
Gait speed	4 meter walk gait speed test[9]	≤0.80 meters per second	Decreased gait speed
Handgrip strength	Hand dynamometer[9]	≤20 kilograms for women and ≤30 kilograms for men	Decreased handgrip strength

Supplementary table S1 Continued

Elements of the CGA	Instrument/test	Cut-off score	Interpretation
Social domain			
Living situation		1. At home 2. At a skilled nursing or assisted nursing facility	1. Independent 2. Dependent
Frailty			
Frailty status	Edmonton Frail Scale[10]	≥6	Frail
Frailty status	Groningen Frailty Indicator[11]	≥4	Frail

References supplementary table S1

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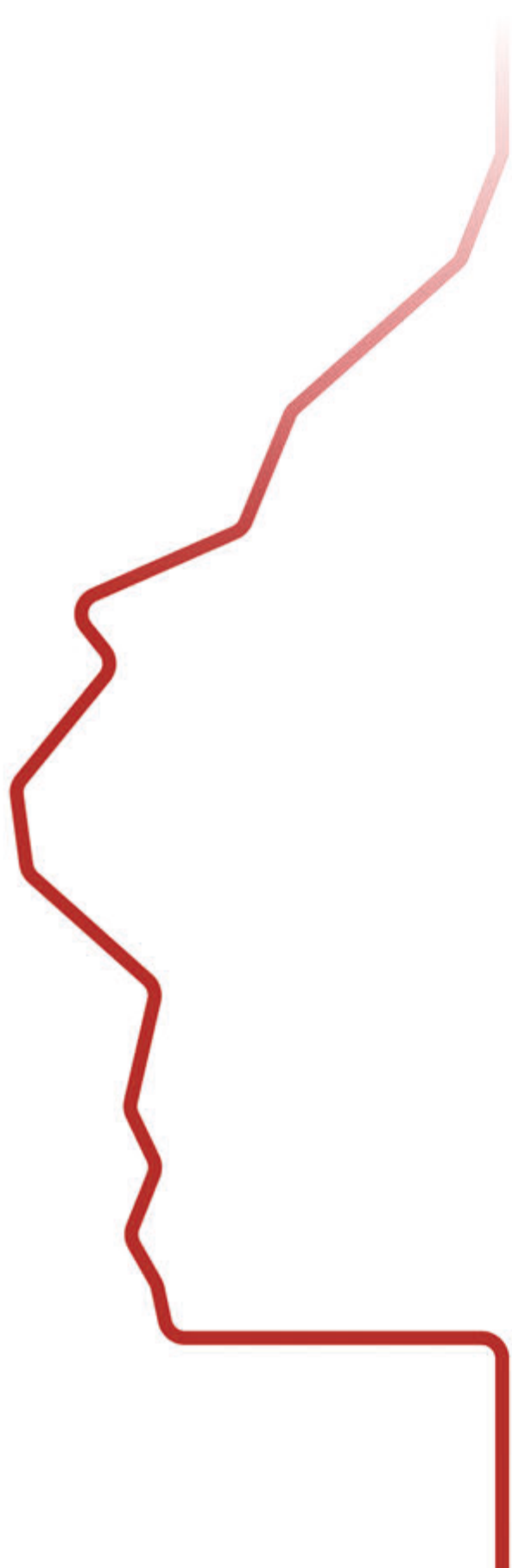
Supplementary Table S2 Clavien-Dindo Classification of surgical complications.

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drug as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complications (including central nervous system complications)* requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis)
- IVb	Multiorgandysfunction
Grade V	Death of a patient

* Brain hemorrhage, ischemic stroke, subarachnoid haemorrhage, but excluding transient ischemic attacks; IC: intermediate care; ICU: intensive care unit

4

General discusion



Introduction

The focus of this thesis was to investigate the association between initiation and discontinuation of statin treatment and the recurrence of cardiovascular events after a first myocardial infarction (MI) or stroke as well as short-term complications following transcatheter aortic valve implantation (TAVI) in patients aged 80 years or older. Our aim was to address statin treatment questions that arise in daily practice but have not yet been answered for this age group by previous studies.

Up to 89% of men and 92% of women aged 80 years and older suffer from cardiovascular disease, with one in 10 developing aortic valve stenosis (1,2). While statin treatment is effective in reducing cardiovascular risk in younger patients, evidence for its effectiveness in patients aged 80 years and older is limited (3,4). Additionally, up to 49% of patients over the age of 80 are statin naïve, and every year, 3% of these patients receive their first statin prescription (5). Furthermore, every year, one in 20 statin users discontinues statin treatment. Results of recent studies in older high-surgical-risk patients have suggested that statin treatment may reduce short-term negative outcomes following TAVI (6,7).

In this chapter, we first summarise our main findings. Subsequently, we discuss the most important methodological issues we encountered in our studies. We also discuss the clinical implications of our findings from the perspectives of patients, prescribers, pharmacists, and society. Finally, this chapter offers a discussion of future perspectives in this field.

Main findings

In Chapter 2, we reveal that initiating statin treatment both after a first MI (Chapter 2.1) or stroke (Chapter 2.2) in patients aged 80 years and older was associated with a reduced risk of both cardiovascular event recurrence and all-cause mortality after two years of cumulative statin treatment. The number of patients needed to treat with statins after MI, corrected for the 36% of deaths that occur during the first two years after the initial event, was 83 for prevention of new cardiovascular events and 61 for all-cause mortality during a median follow-up of 4.5 years. The number of patients needed to treat with statins after stroke, corrected for the 24% of deaths that occur during the first two years after the initial event, was 64 for prevention of new cardiovascular events and 19 for all-cause mortality during a median follow-up of 3.9 years. The results in patients aged 80 years and older align with the results we found for patients between the ages of 65 and 80 and were comparable to results from a large meta-analysis of statin trials in patients between the ages of 65 and 80 (4).

In Chapter 2.3, we found that discontinuing statin treatment that was initiated after a cardiovascular event was associated with a higher risk of recurrent cardiovascular events,

leading to 7.0 cardiovascular events per 100 patient years after discontinuation versus 3.7 events per 100 patient years in patients who continued statin treatment. This higher risk was found both in patients receiving statin treatment after an MI and after a stroke and in patients between the ages of 65 and 80 as well as in those 80 years of age and older. After stratifying for frailty, the association persisted in both fit patients, with 5.4 events per 100 patient years after discontinuation versus 2.4 events per 100 person years in patients who continued statin treatment, and in severely frail patients, with 14.3 events per 100 patient years after discontinuation versus 10.6 events per 100 person years in patients who continued statin treatment. This higher risk of cardiovascular events primarily occurs within three months of statin discontinuation.

In Chapter 3, we reported that, in patients who received a comprehensive geriatric assessment (CGA) before TAVI, cognitive impairment was associated with an increased risk of major complications with an odds ratio (OR) of 2.16 (95% CI: 1.14 to 4.19) and a composite outcome of major complications, 90-day readmissions, and 90-day mortality after TAVI with an OR of 2.40 (95% CI: 1.21 to 4.79)(Chapter 3.1). We furthermore indicated that perioperative statin treatment was not associated with a reduction in the risk of any of these short-term outcomes after TAVI (Chapter 3.2).

Methodological considerations

Various methodological challenges arise while studying statin treatment in older patients. The most important issues we encountered in the studies presented in this thesis relate to the study design, the study population, and the exposure to statins.

Study design

Ideally, studies of treatment effects on outcomes use a randomised controlled design, as randomised controlled trials (RCTs) allow direct comparison between intervention and comparator treatment on the effect of a prespecified outcome. Additionally, this design minimises confounding and bias (8). The prespecified outcome of previous statin trials is often defined as all-cause mortality or cardiovascular events. Four of the five studies in this thesis focus on treatment effects, an RCT would have been the most favourable design. However, for statin treatment, current guidelines generally recommend statin treatment after the age of 80, so prescribing placebo as a comparator to statin treatment, much less discontinuing statin treatment, does not comply with ethical rules and may conflict with the Helsinki declaration of research ethics (3,9). Both in real life and in RCTs, medication adherence is difficult. In recent statin trials, 15%–25% of patients who initiated statin treatment discontinued their treatment during follow-up, whereas 10%–21% of patients in the placebo group initiated statin treatment after study initiation (10–12). In most drug trials, age limits and frailty are used as exclusion criteria (13). Although increasing age is predictive of limited life expectancy, multimorbidity and frailty are more accurate predictors of limited life expectancy and increased susceptibility to adverse

events. Older patients are not often included in RCTs, as doing so may lead to decreased benefits or a lack of benefits for the total study population because of the increased adverse events prevalent in this population. The NHS, to stimulate and facilitate the further inclusion of older patients and to integrate more patient-centred treatment goals as outcomes in RCTs, developed the Inclusion Across the Lifespan policy (14). However, this policy has not led to inclusion of additional older patients or patient-centred treatment outcomes (15). Furthermore, researchers conducting clinical trials find it challenging to recruit and retain a representative sample of the older population including those who are frail or unwilling to commit to treatment. If older patients are to be included in RCTs, then exclusion criteria such as frailty should be abandoned to allow the generalisability of results to the community dwelling older population. Alternatively, observational studies that include older patients may be more informative because such studies are more representative of the general older population (16,17). We therefore chose to perform observational studies, although this design presents other methodological issues related to the study population, including availability of data and to the exposure definition of statin treatment. In the following sections, we discuss these methodological issues in more detail. Well-designed observational studies can be the optimal alternative if an RCT is not feasible (18). The advantages of observational studies are the ability to include a substantial number of patients with less effort than RCTs, the freedom to allow more flexible inclusion and exclusion criteria as well as fewer ethical considerations, the opportunity to reflect more complex real-life situations, and the accumulation of fewer expenses if previously collected data can be used. The main disadvantages of observational studies compared to RCTs are the lack of randomisation, the possibility of missing data, and the potential presence of bias and confounding for multiple reasons.

Study population (and data availability)

Our studies on statin initiation and discontinuation after a cardiovascular event were performed using data from the clinical practice research datalink (CPRD)(19). To validate our results in patients aged 80 years and older, we included patients between the ages of 65 and 80 so that we could compare our results with current evidence from RCTs on statin efficacy. The strengths of this observational data source were the use of real-life data, the breadth of data, the long-term follow-up, and the validated linkages to other information and data systems. The linked systems included the hospital episodes statistics that contain hospital discharge diagnoses and the Office for National Statistics database that provides information on causes of death. For the two studies on short-term outcomes after TAVI, we used data that were prospectively collected in routine care from the collaboration between the geriatric and cardiology departments of UMC Utrecht. The strengths of this database was the prospective nature of data collected during routine care and the opportunity to add missing data if available in the electronic patient file. Another important strength of our study populations over those of earlier studies is that we were able to include frailty, an established independent factor in cardiovascular risk, in all databases (20). In the CPRD database, the frailty index was time varying derived from

a 36-deficit model that is broadly applied in all UK general practitioner systems (20,21). The most important limitation in the CPRD database is the missing data overall, as data are collected during routine care by the general practitioner and we did not have the ability to examine the patient file if specific information was missing. A limitation of the cohort used in our studies on patients undergoing TAVI procedure was the lack of data on long-term follow-up, especially outside the hospital setting. Although we included over 600 patients, which was a larger number than in many earlier studies, we did not have the power to account for all selected covariates. Previous TAVI researchers reported that the perioperative risk for mortality and postoperative complications were much higher than in our cohort. This can be explained by the fact that TAVI was already a mainstream treatment option in our cohort of patients with a lower perioperative risk profile.

Exposure to statins

Most other researchers in observational studies have defined statin treatment as being prescribed a statin at a single time point after a cardiovascular event or TAVI, typically at hospital admission or discharge, which does not accounting for prior statin treatment and initiation or discontinuation of statin treatment after that single time point (22–27). The changes in statin exposure status during follow-up can, however, be significant. In one study on the effect of statin treatment after MI in older patients, within the first two years of follow-up, 42% of statin-treated patients discontinued statin treatment, whereas 43% of patients who were defined as untreated at the study's origination initiated statin treatment (28). The strength of our studies on statin treatment after a first cardiovascular event was that we included statin-naïve patients, which allowed us to investigate both the time until benefit and the time until discontinuation. Moreover, due to the time-varying Cox regression analysis, we accounted for changes in statin exposure and covariates over time. To our knowledge, our studies on initiating statin treatment were the first to use time-varying analysis. Initiation and discontinuation can be influenced by changes in prevalence and severity of covariates over time; therefore, we included information on changes in covariate status over time, such as comorbidities, frailty levels, and comedications (21,29). It is important to note that medication-dispensing data provide limited information on actual medication intake, adherence, and potential side effects.

In previous studies on statin discontinuation, patients were stable long-term statin users, but in our study, all patients had recently begun statin treatment after a cardiovascular event. This fact enables a new perspective on the discontinuation of statins shortly after the onset of treatment; most patients discontinue statin treatment within the first two years after initiation. In the study on statin treatment and short-term outcomes after TAVI, we were not able to account for the duration of statin treatment before TAVI; however, because hospital dispensing records were available, we did know that all statin-treated patients were treated with statins throughout their entire hospital stay.

A limitation in all observational studies on medication use, including our studies on statin treatment, is the lack of information on patients' reasons for deciding to initiate, continue, or discontinue statin treatment. The severity of the MI or stroke might have influenced the decision to initiate statins during the hospital stay (30,31). With time-varying models, it is possible to further investigate this factor by examining different exposure time periods after the initial cardiovascular event. In our studies, we addressed this by investigating different exposure times in our time-varying analysis on the recurrence of cardiovascular events. This could explain the observed risk reduction in less than one year of statin treatment after both MI and stroke, which disappeared after excluding the events during the first six months of follow-up in the MI study. By excluding these events, the possibility that statins were not prescribed due to a predicted limited life expectancy was considered. Healthy user bias may similarly explain the observed risk reduction present after one and two years of statin treatment in the stroke study.

The reasons for discontinuing statin treatment may, of course, be a life-limiting disease. We addressed this by including a lag time of 90 days before the we changed a patient's exposure status to discontinued, and we further investigated an increased lag period of up to 180 days after the last statin prescription, still finding an increased risk on non-cardiovascular mortality and a trend towards an increased risk of cardiovascular recurrence. This aligned with a loss of power due to a declining cardiovascular event rate over time. Moreover, we compared our results to the single RCT that investigated the effect of statin discontinuation. In this study, 381 patients with a life expectancy of less than one year were included (32). In patients who discontinued statin treatment, the 60-day mortality rate was 24% compared to 20% in patients who continued statin treatment. The study was underpowered to demonstrate a statistically significant risk difference; nevertheless, the increased incidence (3.5%) aligns with our findings that indicate a higher risk within the first 90 days after statin discontinuation.

Clinical implications

Patient and (de)prescriber's perspective

Many reasons underscore the decisions of patients who are 80 years or older to use, not use, or stop using statins. These reasons can be influenced by factors at the individual level, by the interaction with healthcare professionals, or by details at an organisational level. In untreated patients who are eligible for statin treatment, 59% reported that they were not offered statin treatment, whereas 31% discontinued statin treatment and 10% declined statin treatment (33). Side effects that patients experienced (55%) were the most common reason for statin discontinuation, and fear of side effects (38%) was the most common reason to decline statin treatment. Of those who declined or discontinued statin treatment, up to 37% of patients felt that statin treatment was safe and up to 69% believed that statin treatment was effective. Up to 50% of patients who were not on statin treatment were willing to initiate or (re)try statin treatment. While patients taking statins

often report side effects, particularly muscle pain, findings from RCTs suggest that this may be more of a nocebo effect than actual statin-related side effects (34). N-of-1 trials have demonstrated that statin therapy is successfully restarted or continued in up to 90% of patients who previously experienced muscle symptoms during statin treatment (35,36). To initiate or restart statin treatment, patients reported that they needed shared decision-making to discuss whether this choice would match their treatment goals; they also desired shared decision-making to manage side effects and wanted to be informed of the risks, benefits, and reasons for their statin prescription (37). Apart from initiation and discontinuation, statin adherence can be challenging for patients as well (38).

For a prescriber, it can be difficult to determine which patients may not benefit from statin treatment. Shared decision-making and exploring patient-centred treatment goals may result in decisions that do not comply with guidelines and may therefore expose the prescriber to medical and legal vulnerabilities. Furthermore, consultation duration may need to be extended (39). In our study, statin treatment initiated after a first stroke or MI and continued for more than two years was associated with similar cardiovascular risk reduction in patients over the age of 80 compared to patients below the age of 80. U-prevent, a decision-support tool for prescribers and patients that prioritises cardiovascular risk management, recently extended the age of the secondary prevention calculator to 90 years (40).

From a deprescriber's perspective, statins are ranked fifth for prescribers overall and second for family physicians as the most important drug to consider for deprescribing in older patients (41). This is not supported by our studies on statin discontinuation: although 37% of general practitioners consider frailty to be a valid reason for statin deprescription, we find that frail patients who discontinued statin treatment had an increased risk of cardiovascular recurrence comparable to fit patients who discontinued statin treatment (20). However, if a patient experiences side effects, if preventing cardiovascular recurrence is no longer a patient-centred goal, or if the patient does not consider the risk reduction to be sufficiently significant to continue taking daily medication and risking potential adverse drug reactions, then discontinuation of statin treatment may be a viable option.

Our study reveals that patients should be aware that cognitive impairment is associated with an increased risk of postoperative complications after TAVI. Patients who experience cognitive impairment their healthcare professionals should make a concrete treatment plan to reduce postoperative complications. According to our results, statin initiation before TAVI is not associated with a reduced risk of postoperative complications. However, we concurrently find that many patients who received TAVI had an indication for secondary prevention with statins but did not receive treatment. In shared decision-making before TAVI, initiating or reinitiating statin treatment in patients who had an indication for secondary prevention may be considered an appropriate healthcare provision.

To optimise statin treatment, prescribers need time, adequate communication skills, knowledge, and interprofessional collaboration that is further aided by the pharmacist.

Pharmacist's perspective

The pharmacist can be a vital factor in coordinating optimal statin treatment, as use and adherence can be significantly improved through several pharmacist-led interventions (42). To our knowledge, no studies regarding the effects of pharmacist-led interventions on statin adherence have been performed in patients over the age of 75; however, it is likely that interventions in patients below the age of 75 could apply to patients over the age of 75. In patients discharged after an MI, statin-use rates improved significantly and was associated with reduced cardiovascular events over a two-year follow-up period when pharmacists prompted physicians on the patients lipid status and statin-use patterns (43). Several other pharmacist-led primary-care interventions resulted in the initiation of statin treatment in up to 50% of untreated patients who met the guideline indication for statin treatment (44,45). The most important factors of success in pharmacist-led interventions include the identification of untreated or non-persistent patients who had an indication for statin treatment in the electronic patient records, a positive prescriber–pharmacist relationship, and most important, the direct contact of the pharmacist with both prescribers and patients: pharmacists counsel patients on the risk reduction by explaining statin treatment effects, potential side effects, and the difficulties patients encounter in daily medication use. Additionally, the hospital pharmacist might prompt the treating physician if statin treatment is omitted in the process of medication reconciliation during hospital admission before TAVI and discharge after MI or stroke.

Societal perspective

The number of older patients continues to increase while the working force decreases, making it important to optimise patients' healthcare utilisation (46). In this respect, initiating statin treatment is warranted when it reduces hospital care for acute cardiovascular events. Discontinuing statin treatment, however, is often not warranted since it is associated with an increased risk of cardiovascular events and thereby may increase the need for acute cardiovascular care. Specialists should consider revising current guidelines regarding cardiovascular risk management and the advice on statin discontinuation in frail patients. Furthermore, persistence of statin use both after initiation and overall should be stimulated. Discontinuation of statin treatment should be restricted to patients who have a life expectancy of less than one year and to patients with serious side effects or after the prescriber's weighing of risks and benefits with the patient when treatment goals no longer comply. Guidelines on aortic valve treatment should recommend cognitive screening before TAVI and the optimisation of cardiovascular risk reduction, including statin treatment.

Future perspective for research

The gold standard in clinical research remains the RCT. Older patients and especially those who are frail are under-represented in RCTs, hampering rational drug prescribing for these patients. Additionally, the time-dependent heterogeneity of older patients regarding characteristics such as frailty, comorbidity, medication use, and individual patient treatment goals further complicate the use of RCT results (47). In light of changing patient-related treatment goals, RCT outcomes such as cardiovascular recurrence and mortality may become less important than older patients' quality of life and the ability to live independently (47). In addition to the individual patient perspective, a societal perspective of healthcare consumption is increasingly relevant. The ageing population leads to an increase in healthcare consumption, which is further complicated by the decreasing availability of healthcare providers (46,48). Independent living, quality of life, and healthcare consumption can be measured both in RCTs and in observational studies. However, population-based observational studies allow researchers to account for time-dependent patient characteristics by using applied statistics such as time-varying analyses. The cornerstone of observational research is structured data gathering during patient care; nevertheless, the Dutch healthcare systems do not sufficiently facilitate structured data collection, and collecting such data is restricted to research. However, if data could be used simultaneously for clinical research and clinical practice, thus allowing pharmacists and prescribers to easily employ data to improve their own practice, then this could aid a commitment to structured patient care documentation. This already occurs in several countries, where nationwide population-based cohorts are continuously filled with patient care data that are used in research (19,49).

With the increase in statin prescriptions over the past years in older patients, researchers may experience difficulty in finding and including the few statin-naïve patients into RCTs. A population study on patients over the age of 80 years in the CPRD database demonstrates that 30% of patients who have an indication for primary prevention and 80% of patients who have an indication for secondary prevention are currently being treated with statins (5). In an observational study, patients without prior statin treatment can be more easily identified and re-examined over time. An advantage of population-based cohorts over RCTs is that they can provide sufficient power to perform subgroup analyses on patient characteristics, such as frailty, which allows observational study results to be used in patient-tailored decision-making.

In exploring the risks of discontinuing statin treatment in patients who have a high cardiovascular risk, an RCT is suitable, as this design would overcome information bias regarding the reasons for statin discontinuation and the observed accompanying risk in our study. We find an increased risk of cardiovascular recurrence and non-cardiovascular mortality in patients who discontinued statin treatment; consequently, conducting an RCT to explore discontinuation may not be ethical in the high-risk older patient. However,

20% of nursing home residents discontinue statin treatment within 30 days of admission, making this a more suitable population in which to compare outcomes of continuation and discontinuation as a prospective observational follow-up study that does not conflict with ethical rules (50). The primary outcome should be patient tailored and include patients' quality of life and degree of independence as well as a societal perspective of healthcare consumption. However, achieving adequate study power is important to allow scholars to examine all-cause mortality as a secondary outcome. The only RCT on statin discontinuation, for example, lacks power to significantly demonstrate an absolute risk difference of 3% on the primary outcome 60 days mortality (28). Two RCTs are being performed on statin discontinuation in the general older population. These trials were initiated before any of the observational studies on statin discontinuation were published (51,52).

In our studies on statin treatment and complications following TAVI, we lacked power to investigate the subgroup of those undergoing high-intensity statin treatment. A larger amount of intervention data are needed to perform subgroup analysis. This can be achieved by creating a system of national registries in the Netherlands, such as those currently available in several European countries (53). All TAVI procedures are registered in the Netherlands Heart Registration (54–56). The assessment tools and outcomes of the CGAs performed in most hospitals before TAVI should be incorporated in this registry, as should the PROMIS, the recently selected generic patient-reported outcome measurements for all patients in the Netherlands (57). Data can subsequently be linked to other data that contain insurance declarations and other registries in the Netherlands to allow evaluations of healthcare consumption. In a time when the healthcare system is under pressure, it is unfortunate that this system is not already in place.

As for statin treatment in TAVI patients, performing a expensive operation without optimising the patient's cardiovascular risk does not align with patients or society's perspective. However, we found that up to 20% of patients who underwent TAVI and have a secondary indication for statin treatment were not treated with a statin. Does this warrant a separate trial? TAVI is only indicated in patients whose life expectancy is longer than one year. Therefore, we believe that optimising cardiovascular risk management for patients who have an indication for secondary prevention is important and should already be part of the process before these patients endure expensive TAVI procedures. However, patients who do not have a current indication for statin treatment may be feasible subjects for an RCT that explores how to improve long- and potentially short-term outcomes after TAVI.

Conclusion

In the past two decades, statin treatment for secondary prevention and TAVI for treatment of aortic valve stenosis have been broadly accepted as regular treatment options for patients over the age of 80, which has been based on RCT results in patients under the age of 80. With our research, we add several new findings to the existing body of evidence. We demonstrate that initiating statin treatment after an MI or stroke in patients aged 80 years and older resulted in risk reduction of cardiovascular recurrence comparable to patients below the age of 80 and therefore should be a cornerstone treatment in secondary prevention regardless of age. Discontinuation of statin treatment that is initiated after a first MI or stroke increases the risk of cardiovascular recurrence in both fit and frail patients, which renders it important to stimulate persistent statin use and emphasises that discontinuation should only be considered in the presence of strong arguments. Furthermore, in patients who undergo TAVI, impaired cognition is associated with an increased risk for postoperative adverse events. Cognition should therefore be addressed before TAVI. Statin treatment is not associated with a risk reduction of adverse events after TAVI; however, a lack of statin use in patients who have an indication for statins should be targeted before TAVI is undertaken.

In the coming decades, the challenge is to further confirm, align, and implement these research outcomes for community-dwelling older patients.

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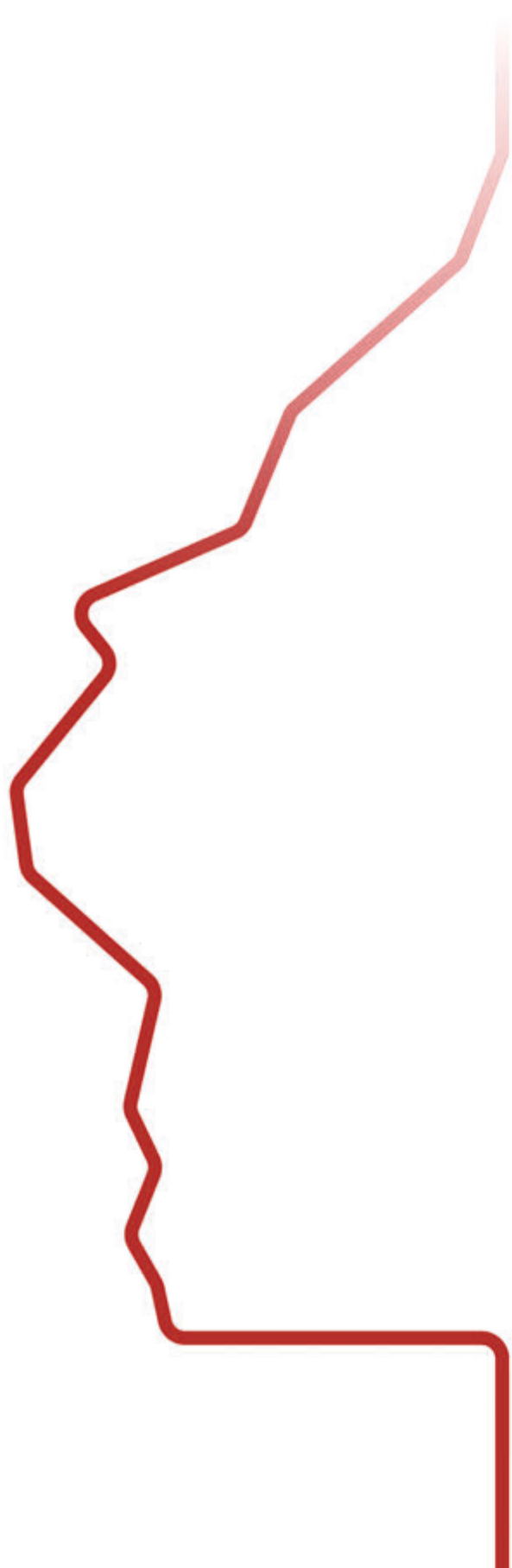
Appendix



Summary

In the upcoming years, the number of people ageing 80 years and older will dramatically increase along with an increase in patients with multiple medical conditions. Up to 90% of those ageing 80 years and older suffer from cardiovascular disease and one out of ten develops aortic valve stenosis.

Treatment with statins to prevent new cardiovascular events is proven effective in patients below the age of 80, however, evidence of effect after the age of 80 is limited. For the treatment of aortic valve stenosis, transcatheter aortic valve implantation (TAVI) has become available around 2003. With this new technique, treatment of aortic valve stenosis has become a viable option even after the age of 80. TAVI has been shown to improve long term survival and associations have been found between statin treatment and further improvement of long term survival. On short term outcomes, little is known with respect to statin treatment and effect in this more frail patient population.

In chapter 2, we focus on both the initiation and discontinuation of statin treatment in the oldest old after a cardiovascular event. Additionally, in chapter 3, we focus on predictors of short term complications for patients with aortic valve stenosis undergoing TAVI and whether statin treatment modifies these short-term complications.

Initiation and discontinuation of statins in the oldest old in secondary prevention

In chapter 2, we investigated the association between initiation and discontinuation of statin treatment using a large cohort from the United Kingdom Clinical Practice Research Datalink (CPRD). The cohort consisted of 9,020 patients hospitalized for a first myocardial infarction (MI) and 5910 patients hospitalized for a first stroke. All patients were statin naïve before hospitalization and aged 65 years and older. We used time varying analysis to account for changes in statin treatment over time.

Initiation of statin treatment after either a first MI (chapter 2.1) or a first stroke (chapter 2.2) in patients aged 80 years and older reduced the risk of both new cardiovascular events and mortality after two years of cumulative statin treatment. The numbers of patients needed to treat with statins after MI, corrected for 36% deaths during the first 2 years, were 93 for prevention of new cardiovascular events and 61 for all-cause mortality during a median follow-up of 4.5 years. The numbers of patients needed to treat with statins after stroke, corrected for 24% deaths during the first 2 years, were 64 for prevention of new cardiovascular events and 19 for all-cause mortality during a median follow-up of 3.9 years. The results in patients aged 80 years and older were in line with the results we found for patients between the age of 65 and 80 years and were comparable to results of a large meta-analysis of statin trials in patients below the age of 80.

In chapter 2.3, we performed a study within 9,680 patients who initiated statin treatment within 90 days after hospital discharge on the effect of discontinuation of statin treatment. Discontinuation of statin treatment, originally initiated after a cardiovascular event, increased the risk of new cardiovascular events in older patients with 3 cardiovascular events per 100 patient years. This higher risk was found both in patients receiving statin treatment after an MI and after a stroke, and in patients between the age of 65 and 80 as well as in those of 80 years and older. Throughout all frailty categories, statin discontinuation was associated with a higher risk of cardiovascular recurrence. This higher risk of cardiovascular events seemed to mainly occur shortly after statin discontinuation.

Clinical outcomes in geriatric patients after transcatheter aortic valve implantation

Chapter 3 focuses on predictors, incorporated in the geriatric assessment, on short term outcomes following TAVI and the possible association of statin treatment with these outcomes. We used continuously prospectively collected data from over 600 patients potentially eligible for TAVI, who were assessed with a standardized comprehensive assessment in the UMC Utrecht from 2014 until 2021.

In chapter 3.1, we assessed predictors of post-operative adverse events after TAVI measured during geriatric evaluation before TAVI. Cognitive impairment doubled the risk of both major complications and the combination of outcome of major complications, 90 days readmissions and 90 days mortality after TAVI. No other independent predictors of an increased risk of short term outcomes after TAVI were found.

Whether statin treatment reduces the risk of short-term outcomes after TAVI was the subject for investigation in Chapter 3.2. We found that perioperative statin treatment did not reduce the risk of short-term outcomes after TAVI.

Conclusion and future perspectives

In chapter 4, we discussed the main findings of this thesis in a broader perspective. Initiating statin treatment after a first MI or stroke, in patients aged 80 years and older, was associated with a reduced risk of cardiovascular event recurrence and all-cause mortality after two years of cumulative statin treatment. Discontinuing statin treatment, originally initiated after a cardiovascular event, was associated with a higher risk of recurrent cardiovascular events, especially within three months after discontinuation in both fit and frail patients. Cognitive impairment in patients, who received a comprehensive geriatric assessment before TAVI, was associated with an increased risk of major complications and adverse outcomes after the procedure. Perioperative statin treatment did not reduce the risk of these short-term outcomes.

We discussed the methodologic strengths and limitations of the observational studies presented in this thesis compared to randomized controlled trials in older patients. We

furthermore evaluated the advantages and challenges of using large population based cohort data from the CPRD compared to the smaller prospectively collected standard care data from the TAVI database. The exposure to statins was another consideration in our research. Previous studies often defined statin treatment at a single time point without accounting for changes in exposure over time. The used time-varying analysis allowed us to examine cumulative statin exposure and discontinuation at different time periods after the initial cardiovascular event.

From a clinical perspective, our findings have important implications for patients, (de) prescribers and pharmacists. Based on our results, we conclude that statin treatment should be initiated after an MI or stroke in patients aged 80 years and older. We emphasize the importance to stimulate persisted statin use and we advise that discontinuation (or not starting) should only be considered in the presence of strong arguments, such as limited life expectancy or (expected) serious side effects. Furthermore, in patients undergoing TAVI, cognition should be addressed in the work up before TAVI. Although statin treatment did not reduce the risk of short term outcomes after TAVI, (re)initiation of statin treatment in patients having an indication for statin treatment could be part of the pre-TAVI work up.

We end chapter 4 with recommendations for future research on statin use in patients aged 80 years and older. With the limitations of randomised controlled trials in older patients, we recommend improving the process of gathering nationwide population based data linkage in the Netherlands by improving methods for continuous data capturing during regular care and linkage between existing data sources. By improving the accessibility of clinical data in large nationwide cohorts, day to day research questions as presented in this thesis can more easily be addressed and simultaneously be used to continuously improve the process of individual patient care.

Samenvatting

In de komende jaren zal het aantal mensen boven de 80 jaar, de oudste ouderen, fors toenemen. Deze mensen hebben vaak meerdere medische aandoeningen tegelijk. Boven de 80 jaar heeft negen op de tien mensen hart- en vaatziekten en één op de tien ontwikkelt een vernauwing van de aortaklep, die tussen het hart en de grote lichaamsslagader zit, waardoor het hart niet meer goed kan pompen. Tot voor kort kon dit alleen opgelost worden met een openhartoperatie.

Statines, geneesmiddelen die het cholesterol verlagen, zijn effectief gebleken om hart- en vaatziekten te voorkomen bij patiënten onder de 80 jaar, maar boven de 80 jaar is dit niet goed onderzocht. Lang was er voor oudere mensen geen goede behandeling van aortaklepstenose, omdat een openhartoperatie vaak te zwaar was. In 2003 veranderde dit met de komst van de transkatheter-aortaklepimplantatie (TAVI), waarbij via de lies met een voerdraad een nieuwe hartklep precies op de juiste plek in het hart gezet kon worden. Hiermee kan de aortaklep dus vervangen worden zonder een openhartoperatie. Met deze nieuwe techniek werd de behandeling van aortaklepstenose een haalbare optie juist voor meer kwetsbare mensen, ook die boven de 80 jaar. Een TAVI verlengt het leven van mensen die dit ondergaan en mogelijk verbeteren statines die overleving nog verder. Er is echter weinig bekend over de korte termijneffecten van statinebehandeling bij deze kwetsbaardere patiëntenpopulatie als zij een TAVI ondergaan.

In hoofdstuk 2 richten we ons zowel op het starten als het stoppen van statinebehandeling bij de oudste ouderen na een hartaanval of beroerte. Daarnaast richten we ons in hoofdstuk 3 op voorspellers van korte termijn complicaties bij patiënten met aortaklepstenose die een TAVI ondergaan. Ook richten we ons op de vraag of statinebehandeling deze korte termijn complicaties kan beïnvloeden.

Starten en stoppen van statines bij de oudste ouderen na een hartaanval of beroerte

In hoofdstuk 2 hebben we het verband onderzocht tussen het starten en stoppen van statinebehandeling en opnieuw optreden van hartaanvallen of beroerte. Dit hebben we gedaan met behulp van een bestaande, zeer grote database met gegevens van Engelse patiënten (‘United Kingdom Clinical Practice Research Datalink’ (CPRD)). In deze database konden we een groep oudere personen over een langere periode volgen. Wij hebben 9.020 patiënten gevolgd na een opname in het ziekenhuis voor een eerste hartinfarct en 5910 patiënten die waren opgenomen voor een eerste beroerte. Alle patiënten gebruikten geen statine vóór ziekenhuisopname en waren boven de 65 jaar. We gebruikten een tijdafhankelijke analyse om rekening te houden met veranderingen in statinegebruik in de loop van de tijd na de ziekenhuisopname.

Het starten van statinebehandeling na een eerste hartinfarct (hoofdstuk 2.1) of een eerste beroerte (hoofdstuk 2.2) bij patiënten van 80 jaar en ouder verlaagde het risico op nieuwe hartaanvallen of beroertes of overlijden hieraan en op overlijden in het algemeen als mensen minimaal twee jaar statines kregen voorgeschreven. Er moesten 93 patiënten met een hartinfarct behandeld worden met een statine gedurende gemiddeld 4,5 jaar om één hartaanval of beroerte of overlijden hieraan te voorkomen. Dit waren 61 patiënten om één overlijden in het algemeen te voorkomen. Hierbij hebben we in de berekeningen rekening gehouden met de sterfte van 36% van de patiënten gedurende de eerste twee jaar na opname.

Daarnaast moesten 64 patiënten met een beroerte gedurende gemiddeld 3,9 jaar met statines behandeld worden om één hartaanval of beroerte of sterfte hieraan te voorkomen. Dit waren 19 patiënten om één overlijden te voorkomen. Ook hier zijn de berekeningen aangepast voor de sterfte van 24% van de patiënten gedurende de eerste twee jaar na opname.

De resultaten bij patiënten boven de 80 jaar en ouder kwamen overeen met de resultaten die we vonden voor patiënten tussen de 65 en 80 jaar. De resultaten onder de 80 jaar waren vergelijkbaar met de resultaten van een eerder groot onderzoek waarbij een overzicht werd gegeven van alle statine studies bij patiënten onder de 80 jaar.

In hoofdstuk 2.3 onderzochten we 9.680 patiënten die statinebehandeling startten binnen 90 dagen na ontslag uit het ziekenhuis na een hartaanval of beroerte. Bij deze mensen hebben we het effect van het stoppen van statinebehandeling onderzocht. Ten opzichte van doorgebruik verhoogde het stoppen van de statinebehandeling het risico met drie extra hartaanvallen of beroertes of sterfte hieraan per 100 stoppende patiënten per jaar. Dit verhoogde risico werd zowel gevonden bij patiënten die statinebehandeling kregen na een hartaanval of na een beroerte, en bij patiënten tussen de 65 en 80 jaar en die van 80 jaar en ouder. Ook bij kwetsbare patiënten was dit risico op nieuwe hartaanvallen en beroerte in gelijke mate verhoogd. Het risico op nieuwe hartaanvallen en beroerte leek vooral verhoogd tijdens de eerste drie maanden na staken van de statine.

Uitkomsten van transcatheter-aortaklepimplantatie bij geriatrische patiënten

In hoofdstuk 3 maakten we gebruik van verzamelde gegevens van meer dan 600 patiënten in het UMC Utrecht in de periode van 2014 tot 2021. Deze patiënten kwamen mogelijk in aanmerking voor TAVI en zij werden ook beoordeeld door de geriatrie, een medisch specialisme met specifieke kennis van ouderen. We onderzochten of bevindingen bij geriatrisch onderzoek, een onderzoek dat de verschillende problemen (lichamelijk, psychisch, functioneel en sociaal) van een oudere opspoort en beschrijft, voor TAVI een verhoogd risico kunnen voorspellen op korte termijn complicaties na

TAVI. Ook onderzochten we het mogelijke verband tussen statinebehandeling en het voorkomen van deze complicaties.

In hoofdstuk 3.1 onderzochten we voorspellers van complicaties na TAVI, gemeten tijdens de geriatrische medebehandeling vóór TAVI. Geheugenproblemen voorafgaand aan TAVI verdubbelden het risico op ernstige complicaties en het gecombineerde risico op complicaties, heropnames binnen 90 dagen en sterfte binnen 90 dagen na TAVI. Uit de geriatrische analyse kwamen geen andere onafhankelijke voorspellers naar voren die het risico op korte termijn complicaties na TAVI verhoogden.

Of statinebehandeling het risico op korte termijn complicaties na TAVI verlaagd, werd onderzocht in hoofdstuk 3.2. We vonden dat perioperatieve statinebehandeling het risico op korte termijn complicaties na TAVI niet beïnvloedt.

Conclusie en toekomstperspectieven

In hoofdstuk 4 bespreken we de belangrijkste bevindingen van dit proefschrift in een breder perspectief. Het starten van statinebehandeling na een eerste hartaanval of beroerte bij patiënten boven de 80 jaar verlaagt het risico op nieuwe hartaanvallen, beroertes of sterfte hieraan en algemene sterfte als mensen deze minimaal twee jaar kregen voorgeschreven. Het stoppen van statinebehandeling, oorspronkelijk gestart na een hartaanval of beroerte, verhoogde het risico op nieuwe hartaanvallen of beroerte of sterfte hieraan, vooral binnen drie maanden na het stoppen. Dit vonden we bij zowel bij fitte als kwetsbare ouderen. Als bij geriatrische medebeoordeling voor TAVI geheugenproblemen bleken te spelen, werd een verhoogd risico gevonden op ernstige complicaties en andere ongunstige uitkomsten na de ingreep. Statinebehandeling verminderde echter niet het risico op deze korte complicaties na TAVI.

We bespreken ook de methodologische sterke punten en beperkingen van de observationele studies die in dit proefschrift worden gepresenteerd in vergelijking met gerandomiseerde gecontroleerde onderzoeken bij oudere patiënten. In observationeel onderzoek worden patiënten gevolgd zonder dat de onderzoeker een keuze heeft gehad in de behandeling, bij gerandomiseerd onderzoek wijst een onderzoeker patiënten willekeurig toe aan groepen die wel of geen behandeling krijgen om zo het effect van een behandeling te kunnen onderzoeken. We beoordelen ook de voordelen en uitdagingen van het gebruik van grootschalige cohortgegevens uit de CPRD in vergelijking met de kleinschalig prospectief verzamelde standaardzorggegevens uit de TAVI-database. Het goed vaststellen van de blootstelling aan statines was een belangrijk pluspunt in ons onderzoek. Eerdere studies definieerden vaak statinebehandeling op een enkel tijdstip zonder rekening te houden met veranderingen in blootstelling in de loop van de tijd. De gebruikte tijdafhankelijke analyse in ons onderzoek stelde ons in staat om de totale statineblootstelling gedurende de tijd met daarbij rekening houdend met stopzetting

op verschillende tijdstippen na de aanvankelijke eerste hartaanval of beroerte te onderzoeken.

Onze bevindingen leveren een belangrijke bijdrage aan meer inzicht in de behandeling en het beloop van ziekte voor patiënten, voorschrijvers en apothekers. Op basis van onze resultaten concluderen we dat statinebehandeling moet worden gestart na een hartinfarct of beroerte bij patiënten boven de 80 jaar. We benadrukken het belang van het stimuleren van voortgezet gebruik van statines en adviseren dat staken (of het niet starten ervan) alleen moet worden overwogen als hier goede argumenten voor zijn, zoals een beperkte levensverwachting of (verwachte) ernstige bijwerkingen. Bovendien moet bij patiënten die een TAVI ondergaan, rekening worden gehouden met geheugenproblemen als een voorspeller van een verhoogd risico op complicaties. Er is geen indicatie om te starten met een statine bij alle patiënten die een TAVI ondergaan, omdat ons onderzoek aantoonde dat statines het risico op complicaties na TAVI niet lijken te verlagen. Wel adviseren we het starten of herstarten van statines bij de patiënten die een geldende indicatie voor statines hebben, bijvoorbeeld vanwege een eerder hartinfarct of beroerte, maar deze niet gebruiken.

We sluiten hoofdstuk 4 af met aanbevelingen voor toekomstig onderzoek bij patiënten van 80 jaar en ouder. Gezien de beperkingen van gerandomiseerde gecontroleerde onderzoeken bij oudere patiënten, raden we aan het proces van het verzamelen van landelijke populatiegebaseerde gegevenskoppeling in Nederland te verbeteren. Dit kan door continue gegevensregistratie tijdens reguliere zorg en de koppeling tussen bestaande gegevensbronnen te verbeteren. Door de toegankelijkheid van gezondheidsgegevens in grote landelijke cohorten te verbeteren, kunnen onderzoeksvragen zoals gepresenteerd in dit proefschrift gemakkelijker worden aangepakt en tegelijkertijd worden gebruikt om het proces van individuele patiëntenzorg voortdurend te verbeteren.

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Beste Dineke, van de leden van mijn promotieteam gaan wij het langst terug. Aan het einde van mijn opleiding tot klinisch geriater, toen ik naar Apeldoorn ging, gaf ik aan nooit meer in de academie te willen werken. Vier en half jaar later kwamen we elkaar tegen bij de promotie van Erna Beers, waarbij je aangaf dat er een vacature kwam in het UMCU en of dit iets voor mij was. De vacature was management gericht maar, waarvan jij dacht dat het mij wel zou liggen, promoveren hoorde er ook bij, maar daar zouden we wel uit komen. Ons gesprek droeg bij aan mijn vertrouwen om de overstap terug te maken naar de academie. Jou sterker ontwikkelde procedurele en semantische geheugen was een

goede aanvulling op mijn meer episodisch werkend brein. Van jou heb ik veel geleerd over statistiek en methodologie, maar ook zeker over de kunst van het helder schrijven. De komende jaren zullen we naar ik verwacht nog veel samenwerken, waarbij in ons handelen de wederzijdse waardering zichtbaar zal zijn.

Beste Wilma, ook jou sprak ik op de promotie van Erna Beers en ook jij vroeg of ik interesse had om terug te komen naar het UMCU. Op dat moment kenden wij elkaar nog niet zo goed, maar dat is na 9 jaar kamergenootschap wel anders. Jouw motivatie voor klinisch farmacologisch onderzoek in de dagelijkse praktijk is indrukwekkend. Knap vind ik ook hoe je anderen weet te betrekken bij de uitvoering van jouw onderzoek en hoe je van de geëigende banen afwijkt. Voor mijn onderzoek was jouw kennis over het doen van onderzoek naar medicatie bij ouderen zeer waardevol.

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De leden van mijn beoordelingscommissie, prof. dr. O.H. Klungel, prof. dr. P vd Harst, prof. dr. M. Muller, prof. dr. B.C. van Munster, prof. dr. F.L.J. Visseren, wil ik hartelijk danken voor het beoordelen van mijn manuscript.

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Pa en ma, lang geleden met jullie op vakantie, ik meen in Cornwall, heb ik bedacht “allesman” te willen worden. Het “zijn” van allesman is natuurlijk een illusie, maar de reis daar naartoe heeft mij altijd verder geholpen. In opleidingstermen wordt dat tegenwoordig “life-long-learning” genoemd. Naast dat ik nog steeds het gevoel heb (een betere) specialist te worden, werd ik met dit promotietraject nu ook onderzoeker. Daarnaast word ik nog steeds een betere pizzabakker en soms ook chocolatier. Op cruciale momenten in mijn leven hebben jullie mij geholpen de juiste keuzes te maken, tot ik dit zelf wel kon. Mijn streven naar persoonlijke groei is onder jullie dak ontstaan, ik zie dat ook terug bij mijn broers. Dirk heb ik eerder al genoemd in dit dankwoord. Adriaan, mijn oudste broer, ook jij wil ieder jaar een betere versie van jouzelf zijn. Dat zie je terug in dat jij steeds hogere veiligheidskunde wil beheersen en ook telkens beter wil worden

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About the author

Geert Lefeber was born on May 6, 1979, in Lent, near Nijmegen. He grew up in Dordrecht. After graduating from the Johan de Witt gymnasium in Dordrecht, he pursued a degree in medicine at the University Medical Center in Utrecht. He completed his medical studies in 2005 and following an internship at the geriatric ward of the UMC Utrecht he started training as a geriatrician.

His training included rotations in internal medicine at the Gelre hospital in Apeldoorn, under the supervision of Cees Schaar. He also received training in geriatric medicine at the UMCU, under the supervision of Paul Jansen, and in psychiatry at Altrecht in Zeist, under the supervision of Joost Sanders. In 2010, after nearly completing his training as a geriatrician, Geert returned to the UMCU, where he started the training as a clinical pharmacologist under the supervision of Paul Jansen.

In early 2011, Geert began working as a geriatrician at the Gelre hospital in Apeldoorn. During this time, he also completed his training as a clinical pharmacologist. In late 2014, he returned to the UMCU to work as both a geriatrician and clinical pharmacologist. It was during this period that he was given the opportunity to initiate his thesis.

Currently, Geert resides in Utrecht with his partner and two daughters.