Statins for secondary prevention and major adverse events after coronary artery bypass grafting

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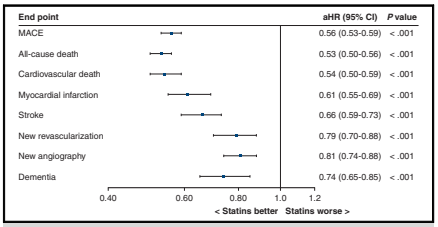
ABSTRACT

Objective: The objective of this study was to evaluate the association of statin use after coronary artery bypass grafting (CABG) and long-term adverse events in a large population-based, nationwide cohort.

Methods: All 35,193 patients who underwent first-time isolated CABG in Sweden from 2006 to 2017 and survived at least 6 months after surgery were included. Individual patient data from the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) and 4 other nationwide registries were merged. Multivariable Cox regression models adjusted for age, sex, comorbidities, and time-updated treatment with other secondary preventive medications were used to evaluate the associations between statin treatment and outcomes. The primary end point was major adverse cardiovascular events (MACE). Median follow-up time to MACE was 5.3 (interquartile range, 2.5-8.2) years.

Results: Statins were dispensed to 95.7% of the patients six months after discharge and to 78.9% after 10 years. At baseline, 1.4% of patients were prescribed low-, 57.6% intermediate-, and 36.7% high-dose statins. Ongoing statin treatment was associated with markedly reduced risk of MACE (adjusted hazard ratio [aHR], 0.56 [95% CI, 0.53-0.59]), all-cause mortality (aHR, 0.53 [95% CI, 0.50-0.56]), cardiovascular death (aHR, 0.54 [95% CI, 0.50-0.59]), myocardial infarction (aHR, 0.61 [95% CI, 0.55-0.69]), stroke (aHR, 0.66 [95% CI, 0.59-0.73]), new revascularization (aHR, 0.79 [95% CI, 0.70-0.88]), new angiography (aHR, 0.81 [95% CI, 0.74-0.88]), and dementia (aHR, 0.74 [95% CI, 0.65-0.85]; all $P < .01$), irrespective of the statin dose.

Conclusions: Ongoing statin use was associated with a markedly reduced incidence of adverse events and mortality after CABG. Initiating and maintaining statin medication is essential in CABG patients. (J Thorac Cardiovasc Surg 2021;■:1-12)



Interaction analyses depicting the effect of statin use on MACE for selected subgroups.

CENTRAL MESSAGE

Ongoing use of statins was associated with a markedly reduced incidence of adverse events and mortality after CABG. Initiating and maintaining statin medication are essential in CABG patients.

PERSPECTIVE

This large, nationwide, population-based registry study shows that statin use was associated with a reduced risk for several important long-term complications after CABG, including MACE, myocardial infarction, stroke, and dementia. The use of statins was high early after the CABG but gradually declined over time. Initiation and continuation of statins remain essential in CABG patients.

See Commentary on page XXX.

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Abbreviations and Acronyms

aHR = adjusted hazard ratio
CABG = coronary artery bypass grafting
CVD = cardiovascular disease
eGFR = estimated glomerular filtration rate
HR = hazard ratio
ICD = International Classification of Diseases
IQR = interquartile range
LDL = low-density lipoprotein
LVEF = left ventricular ejection fraction
MACE = major adverse cardiovascular events
OR = odds ratio
STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

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For decades, cardiovascular diseases (CVDs) have been the leading cause of premature mortality worldwide, and the burden is still growing.[1] Primary prevention for coronary artery disease includes lifestyle modifications, treatment of elevated low-density lipoprotein (LDL) cholesterol levels, and controlling other cardiovascular risk factors.[2] Secondary prevention is essential when a cardiovascular event has occurred or when the patient has undergone a revascularization procedure, such as coronary artery bypass grafting (CABG), to improve long-term survival and decrease the risk of subsequent cardiac events.

According to current guidelines, unless contraindicated, optimal secondary prevention medical therapy after CABG includes statins and antiplatelet agents for all patients, renin-angiotensin-aldosterone system inhibitors selectively for patients with reduced left ventricular ejection fraction (LVEF), hypertension, or previous myocardial infarction, and β-blockers for patients with previous myocardial infarction or reduced LVEF.[3-6] Observational studies have shown that statin use is independently associated with a reduction in all-cause mortality and major adverse cardiovascular events (MACE) after CABG.[7-9] However, most of these studies were published decades ago, are limited to single-center investigations, or have limited information on medication adherence over time. More recently, in a study based, in part, on the same cohort as the present study, our group reported that ongoing treatment with statins was associated with better long-term survival.[10]

There is recent evidence suggesting that younger CABG patients and myocardial infarction survivors have an increased risk to develop dementia compared with the general population.[11,12] It has been suggested that statins might also be beneficial in preventing dementia.[13,14] However, no previous studies have investigated the association between statin use and dementia among post-CABG patients.

The purposes of this contemporary, large, nationwide cohort study were: (1) to examine the longitudinal statin use after CABG, (2) to assess the association between the use of statins and occurrence of MACE as a primary end point, and separately for all-cause mortality, CVD-related death, myocardial infarction, stroke, new revascularizations, new angiography, and dementia as secondary end points, and (3) to investigate the associations between low, intermediate, and high doses of statins and the primary and secondary end points.

METHODS

Study Population and Data Sources

All consecutive patients older than 18 years of age who underwent first-time isolated CABG in Sweden between January 1, 2006, and December 31, 2017, were identified in the Swedish Cardiac Surgery Registry, a subregister of the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.[15] Because the objective was to study the long-term effects of statin treatment, patients who did not complete at least 6 months of follow-up after discharge were excluded (ie, they died, were discharged after June 30, 2017, or emigrated within 6 months after discharge). All included patients were followed-up until death, emigration, or until December 31, 2017, whichever occurred first. A flow chart of included and excluded patients is depicted in Figure 1.

Individual patient data were collected from 5 mandatory national registries, as previously described,[10] and merged for the study using the unique identification number allocated to all Swedish residents. The Swedish Cardiac Surgery Registry contains data on all cardiac surgery procedures performed in Sweden since 1992.[16] The National Patient Register covers all International Classification of Diseases (ICD), ninth or 10th revision codes from all hospital admissions, for out- and inpatients in Sweden since 1987.[17] Taken together, the registers provide data on the CABG procedure, comorbidities, and postoperative complications and events. The National Cause of Death Register, from which the mortality data were obtained, contains information on the date and the ICD-coded cause of death of all Swedish citizens. Data on the date of emigration, where applicable, were collected from the Swedish Population Register. The data on medical prescriptions dispensed from pharmacies were retrieved from the Swedish Prescribed Drug Register, which includes all prescriptions dispensed from Swedish pharmacies since July 2005.[18] The exposure status during the first 6 months was set as baseline. Information about medication was updated every third month during the follow-up, as previously described.[10]

This report was composed according to recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19] The study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Regional Research Ethics Committee in Gothenburg (registration number 139-16, approved April 4, 2016; addendum registration number T595-18, approved July 2, 2018). Need for individual informed consent was waived by the committee.

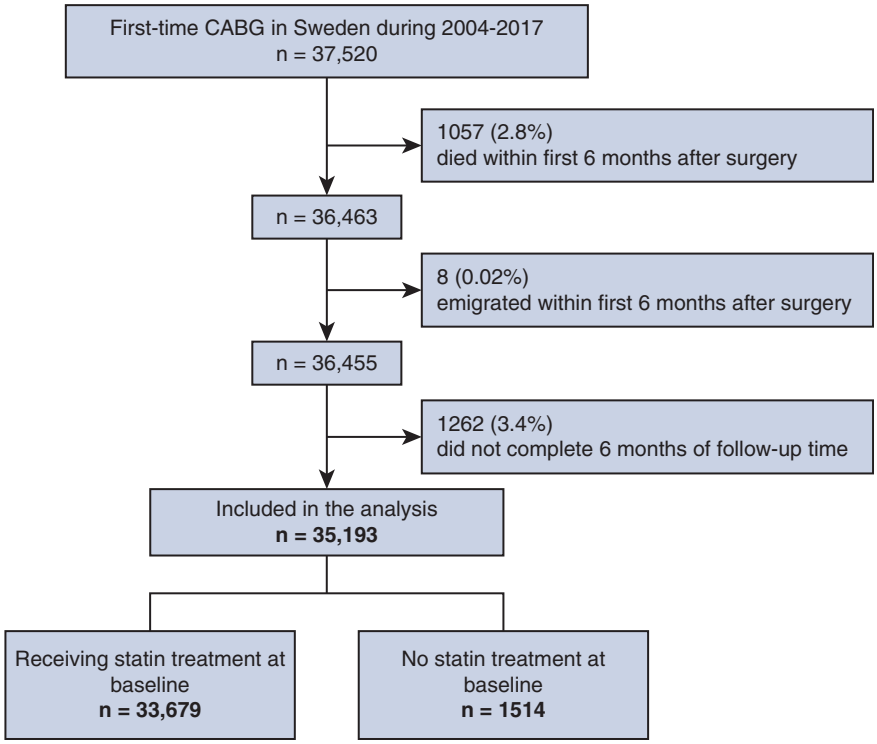

FIGURE 1. Patient selection and exclusion criteria. *CABG*, Coronary artery bypass grafting.

Definitions

The primary end point was MACE, defined as all-cause mortality, myocardial infarction, and/or stroke during follow-up. The secondary end points were all-cause mortality, CVD-related death, myocardial infarction, stroke, new revascularization, new angiography, and dementia. The ICD codes used are listed in Table E1. Low, moderate, and high doses of statins were determined on the basis of the prescription that was dispensed to a patient and defined as presented in Table E2, which is modified from the 2018 American College of Cardiology/American Heart Association classification of statin intensity.[20]

Statistical Analysis

For the baseline characteristics, continuous variables are presented as mean with SD or median with interquartile range (IQR). Categorical variables are reported as frequencies with percentages. Fisher exact test was used for dichotomous variables; χ^2 or Mantel–Haenszel χ^2 test, as appropriate, was used for categorical variables, and Mann–Whitney *U* test was used for continuous variables, when 2 groups were compared.

The crude incidence rates were calculated by dividing the number of events by follow-up years; and the time-updated statin data were estimated using Poisson regression with the logarithm of follow-up time as the offset parameter. The trend for dispense of statins over time, overall, and according to sex and age category, was expressed as odds ratios (ORs) with 95% CIs per 1 year increase obtained using generalized estimating equations with binomial distribution and logit link function. The intensity of statins was on the basis of dispensed prescriptions that were updated every third month and evaluated as a time-updated categorical variable (none/low/intermediate/high) using Cox time-updated regression models, allowing patients to switch category over time. Hazard ratios (HRs) are reported with 95% CIs. In the first model, HRs were adjusted for age and sex. The second model additionally adjusted for body mass index, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, ST-segment elevation myocardial infarction/non–ST-segment elevation myocardial infarction/unstable angina/stable angina as indication for CABG, LVEF, estimated glomerular filtration rate (eGFR) on the basis of the Chronic Kidney Disease-Epidemiology Collaboration formula,[21] and year of CABG. Model 3 was further adjusted for other time-updated secondary prevention medications (renin-angiotensin-aldosterone system inhibitors, β-blockers, platelet inhibitors). The interaction analyses were performed for predefined subgroups (age younger than 75 years or 75 years of age and older, sex, hypertension, hyperlipidemia, diabetes, myocardial infarction, heart failure, and eGFR) to evaluate the effect of statin use and intensity of statins on MACE. The results are shown as forest plots.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). All tests were 2-tailed. The primary and the secondary analyses (model 3, with vs no treatment; 32 tests) were adjusted for multiple comparison using a Bonferroni–Holm step down procedure.

RESULTS

Patients

In total, 37,520 patients underwent isolated first-time CABG surgery in Sweden during 2006 to 2017. Altogether 1057 (2.8%) patients did not survive the first 6 months after surgery, 1262 (3.4%) did not complete 6 months of follow-up time, and 8 (0.02%) emigrated from Sweden within 6 months after surgery, and were excluded, leaving 35,193 (93.8%) for the final analysis (Figure 1). Median follow-up time to the primary end point was 5.3 years (IQR, 2.5-8.2 years). Mean age was 68.1 (median, 69.0; IQR, 62.0-75.0) years; 80.3% of patients were male and

19.7% were female. During the entire follow-up, MACE occurred in 8787 (25.0%) patients, a total of 6368 patients (18.1%) died; 2940 (8.4%) died from cardiovascular causes, 1928 (5.5%) had a myocardial infarction, 2138 (6.1%) had a stroke, 2376 (6.8%) were re-revascularized, 4415 (12.5%) underwent a new angiography, and 1165 (3.3%) were diagnosed with dementia.

Statin Use at Baseline

At baseline, statins were dispensed to 33,679 (95.7%) patients. Baseline characteristics among statin users and nonusers are presented and compared in Table 1. Statin users were significantly younger, less often had reduced ejection fraction (LVEF <50%), had better eGFR, higher body mass index, fewer comorbidities, and were more

TABLE 1. Patient characteristics of CABG patients at baseline according to statin use

	No statin use at baseline (n = 1514)	Statin use at baseline (n = 33,679)	*P* value
Sex			.022
Male	1180 (77.9)	27,075 (80.4)	
Female	334 (22.1)	6604 (19.6)	
Mean age (SD), y	70.3 (9.4)	68.0 (9.1)	<.0001
Left ventricular ejection fraction			<.0001
Normal	942 (62.2)	23,237 (69.0)	
<50%	555 (36.7)	10,186 (30.2)	
Missing	17 (1.1)	256 (0.8)	
BMI category			<.0001
<18.5	10 (0.7)	110 (0.3)	
18.5-25	485 (32.0)	8814 (26.2)	
>25-30	600 (39.6)	14,655 (43.5)	
>30-35	246 (16.2)	5762 (17.1)	
>35	70 (4.6)	1538 (4.6)	
Missing	103 (6.8)	2800 (8.3)	
eGFR (CKD-EPI) category, mL/min			<.0001
≥90	273 (18.0)	8509 (25.3)	
60 to <90	800 (52.8)	18,670 (55.4)	
30 to <60	345 (22.8)	5505 (16.3)	
15 to <30	29 (1.9)	312 (0.9)	
<15	41 (2.7)	193 (0.6)	
Missing	26 (1.7)	490 (1.5)	
Comorbidities at baseline			
Atrial fibrillation (including postoperative atrial fibrillation)	575 (38.0)	10,063 (29.9)	<.0001
Chronic respiratory disease	202 (13.3)	3355 (10.0)	<.0001
Chronic obstructive pulmonary disease	129 (8.5)	1883 (5.6)	<.0001
Dementia	11 (0.7)	91 (0.3)	.001
Diabetes	553 (36.5)	10,240 (30.4)	<.0001
Heart failure	516 (34.1)	7231 (21.5)	<.0001
History of cancer	236 (15.6)	4713 (14.0)	.091
History of stroke	191 (12.6)	2939 (8.7)	<.0001
Hyperlipidemia	596 (39.4)	17,290 (51.3)	<.0001
Hypertension	1075 (71.0)	23,930 (71.1)	.99
Myocardial infarction	760 (50.2)	18,141 (53.9)	.0056
Renal failure	161 (10.6)	1693 (5.0)	<.0001
Peripheral vascular disease	208 (13.7)	3324 (9.9)	<.0001
Statin intensity at baseline			
Low	0	505 (1.5)	
Intermediate	0	20,147 (60.2)	
High	0	12,828 (38.3)	
Missing	0	199	
None	1514 (100.0)	0	

Data are presented as n (%), except where otherwise noted. *CABG*, Coronary artery bypass grafting; *BMI*, body mass index; *eGFR (CKD-EPI)*, estimated glomerular filtration rate (Chronic Kidney Disease-Epidemiology Collaboration).

frequently dispensed with other cardiovascular medications. Among men and women statins were dispensed for 95.8% and 95.2%, respectively. Overall, 12,828 (36.7%) patients were prescribed high-dose statins, 20,147 (57.6%) received intermediate-dose statins, and 505 (1.4%) were prescribed low-dose statins at baseline.

Dispensed Prescriptions Over Time

The total statin use decreased over time (OR per 1 year increase, 0.89 [95% CI, 0.89-0.90]; $P < .0001$). The proportion of patients who were prescribed statins decreased from 95.7% at 6 months to 89.0%, 82.8%, 80.4%, and 78.9% at 1, 5, 8, and 10 years, respectively, after CABG. In general, the dispense of statins over time decreased more among women than men (OR per 1 year increase, 0.87 [95% CI, 0.86-0.88] and 0.90 [95% CI, 0.89-0.90], respectively; P for interaction $< .0001$), and decreased more among patients 75 years of age and older, than among patients younger than 75 years (OR per 1 year increase, 0.84 [95% CI, 0.83-0.85] and 0.91 [95% CI, 0.90-0.91], respectively; P for interaction $< .0001$; Figure 2).

The time-updated statin use according to dose in the different subgroups is presented in Figure 3, *A*, and Table E3. The proportion over time of patients who were dispensed high-dose statins decreased from 36.7% at baseline to 31.9%, 21.5%, 22.3%, and 24.3% at 1, 5, 8, and 10 years, respectively. The proportion of patients with an intermediate dose was stable, at between 55% and 60%, during the follow-up, whereas the proportion receiving a low dose slightly increased, from 1.4% at baseline to 1.7%, 2.1%, and 2.2% at 1, 5, and 8 years after baseline,

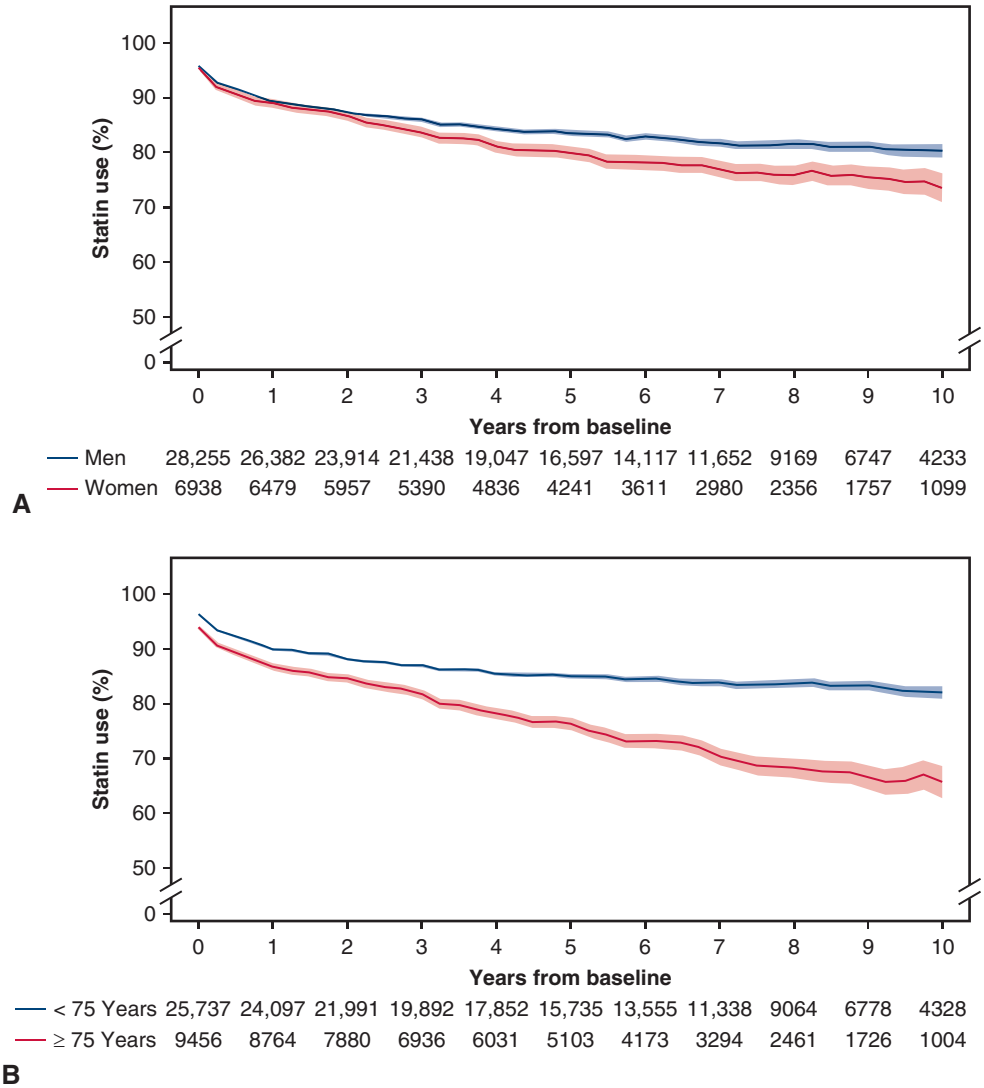

FIGURE 2. The time-updated overall statin use on the basis of dispensed prescriptions (A) according to sex and (B) age category. *Shaded area* denotes 95% confidence interval.

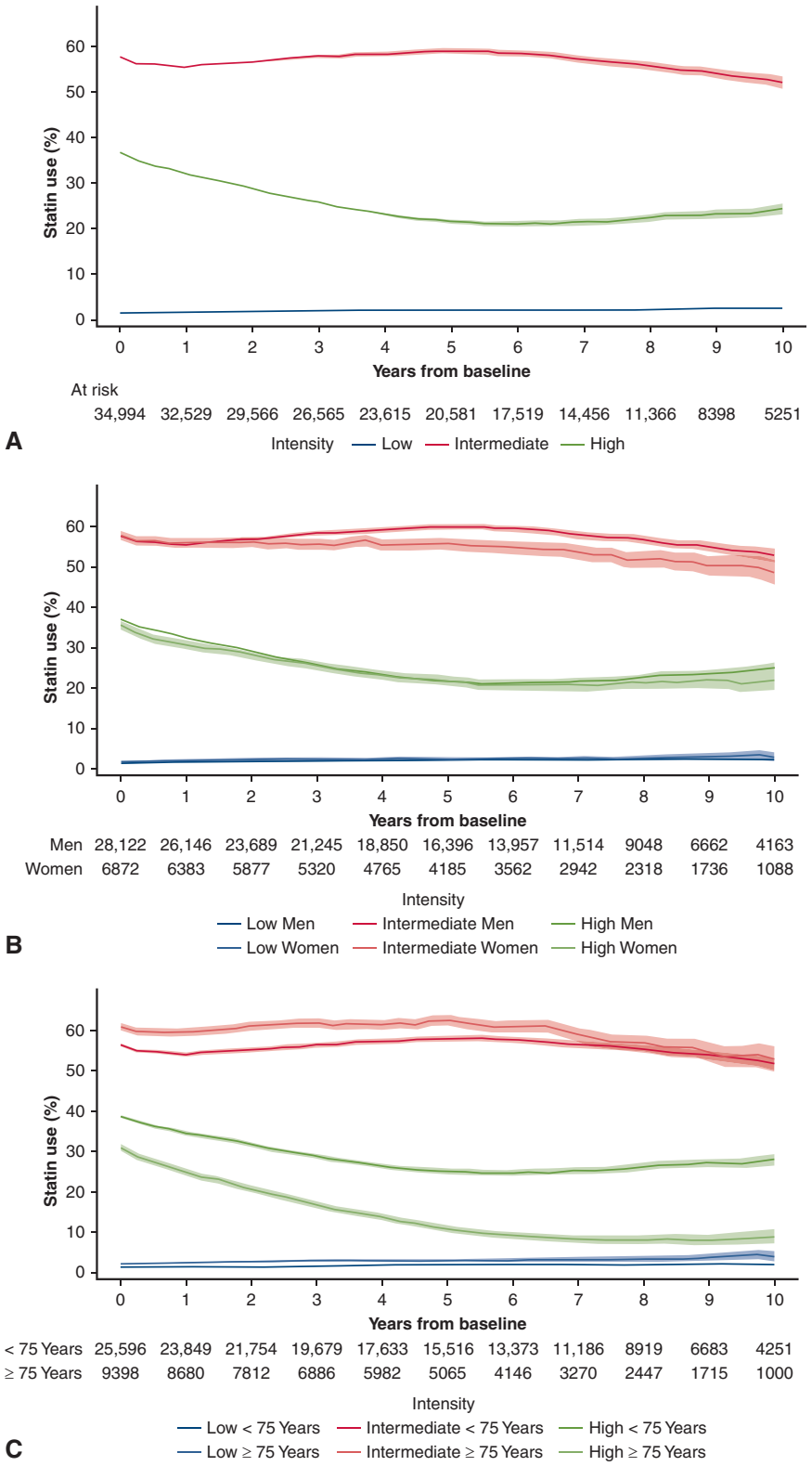

FIGURE 3. Percentage of patients with time-updated statin prescriptions according to the intensity of the statin dose (A), then grouped according to sex (B) and age categories (C). *Shaded area* denotes 95% confidence interval.

respectively. Men were more often dispensed intermediate-intensity statins than women, particularly for later follow-up, but no differences could be seen between the sexes in the low- or high-dose groups (Figure 3, *B*). Younger (younger than 75 years) patients were more often dispensed a high statin dose than the older (75 years or older) patients (Figure 3, *C*).

Outcomes

A total of 46.2% of all baseline statin non-users and 24.0% of baseline statin users had a MACE during follow-up, and respectively, 38.2% of baseline statin non-users and 17.2% of baseline statin users died. The crude event rates with 95% CIs for statin use versus no statin use, over time, are presented in Table 2.

Ongoing statin use was associated with reduced MACE events in all 3 statistical models. The adjusted hazard ratio (aHR) for model 3 (adjusted for age, sex, year of CABG, co-morbidities, and the use of other secondary prevention medication) was 0.56 (95% CI, 0.53-0.59) for MACE. Ongoing treatment with statins was also associated with a reduction in all-cause mortality, CVD-related death, myocardial infarction, stroke, new revascularization, new angiography, and dementia, all $P < .0001$ (Table 2 and Figure 4).

Outcome in Relation to Statin Intensity

Ongoing use of low-, intermediate-, and high-intensity of statins, compared with no statin use, was associated with reduced adjusted risk for MACE (model 3; aHR, 0.60 [95% CI, 0.52-0.69], aHR, 0.56 [95% CI, 0.53-0.59], and aHR, 0.56 [95% CI, 0.53-0.60], respectively), as well as with a reduction in the risk for all-cause mortality, CVD death, myocardial infarction, and stroke. Intermediate- and high-intensity statin use, compared with no statin use, were also associated with reduced risk of dementia (Table E4). Moreover, high-dose statin users had increased risk of CVD death, new revascularization, and new angiography compared with intermediate-dose users, as well as increased risk of new angiography compared with low-dose statin users (Table E5).

Subgroup Analyses

Forest plots of aHRs for MACE and interaction *P* values in predefined subgroups are presented in Figure 5. Ongoing treatment with statins was associated with reduced incidence of MACE in all subgroups. Interaction analyses indicated lower HRs (greater risk reduction of event) in male patients, and in patients with hyperlipidemia, patients without diabetes, patients without heart failure, and patients with normal left ventricular function. There was no interaction with age, hypertension, previous myocardial infarction, or renal function.

DISCUSSION

There are 3 main findings in this nationwide, population-based cohort study in CABG patients. First, the use of statins after CABG was high early after the operation, but gradually declined over time. Second, ongoing statin use was significantly and independently associated with a

TABLE 2. Crude event rates per 100 person-years with 95% CI for patients receiving statins versus no statins, and aHRs for on- versus off-treatment in different models

End point	Crude event rate per 100 person-years (95% CI) without treatment	Crude event rate per 100 person-years (95% CI) with treatment	Model 1, treatment vs no treatment aHR (95% CI); *P* value	Model 2, treatment vs no treatment aHR (95% CI); *P* value	Model 3, treatment vs no treatment aHR (95% CI); *P* value*
MACE (all-cause mortality, myocardial infarction, stroke)	9.26 (8.90-9.64)	3.86 (3.76-3.96)	0.50 (0.48-0.53); < 0.0001	0.52 (0.50-0.55); <.0001	0.56 (0.53-0.59); <.0001
All-cause mortality	7.17 (6.86-7.49)	2.49 (2.42-2.56)	0.47 (0.44-0.49); <.0001	0.49 (0.46-0.52); <.0001	0.53 (0.50-0.56); <.0001
Cardiovascular death	3.27 (3.06-3.49)	1.16 (1.11-1.21)	0.49 (0.45-0.53); <.0001	0.51 (0.47-0.56); <.0001	0.54 (0.50-0.59); <.0001
Myocardial infarction	1.55 (1.40-1.70)	0.89 (0.84-0.93)	0.59 (0.53-0.66); <.0001	0.61 (0.55-0.68); <.0001	0.61 (0.55-0.69); <.0001
Stroke	1.78 (1.62-1.95)	0.98 (0.93-1.03)	0.62 (0.56-0.69); <.0001	0.63 (0.57-0.70); <.0001	0.66 (0.59-0.73); <.0001
New revascularizations	1.29 (1.16-1.43)	1.21 (1.16-1.27)	0.82 (0.73-0.92); .0007	0.82 (0.73-0.91); .0005	0.79 (0.70-0.88); <.0001
New angiography	2.54 (2.35-2.74)	2.34 (2.27-2.42)	0.83 (0.76-0.90); <.0001	0.83 (0.76-0.90); <.0001	0.81 (0.74-0.88); <.0001
Dementia	1.12 (1.00-1.26)	0.50 (0.46-0.53)	0.66 (0.58-0.75); <.0001	0.67 (0.58-0.76); <.0001	0.74 (0.65-0.85); <.0001

Confidence interval for event rates per 100 person years are obtained from exact Poisson confidence limits. Model 1 is adjusted for: age and sex; model 2 is additionally adjusted for: BMI category, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, and ACS, (STEMI/NSTEMI/unstable/stable) as indication for CABG, LV function, CKD-stages (CKD-EPI for eGFR), year of CABG; model 3 is additionally adjusted for other time-updated secondary prevention medications (RAAS inhibitors, β-blockers, platelet inhibitors). *aHR*, Adjusted hazard ratio; *MACE*, major adverse cardiovascular events. *All *P* values are < .05 also after adjustment for multiple comparisons using the Bonferroni–Holm step down procedure.

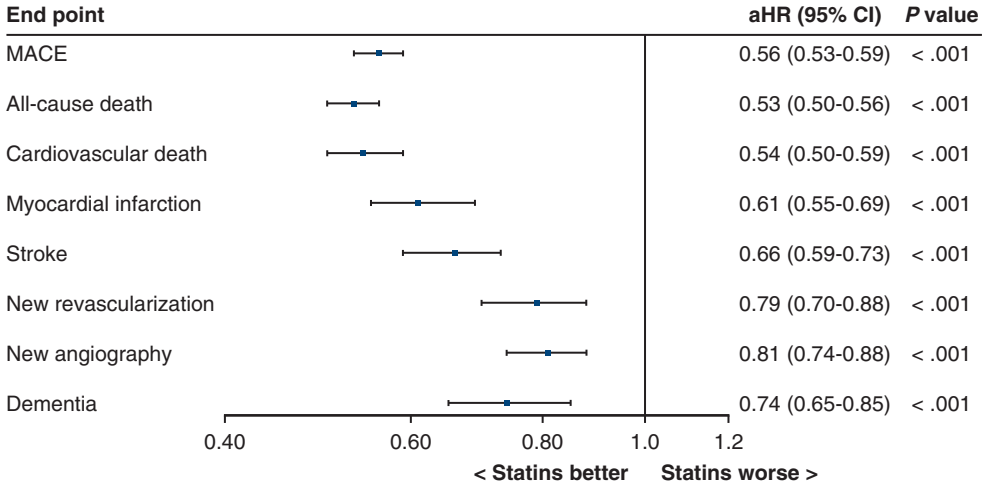

FIGURE 4. Forest plots illustrating the associations between time-updated statin use and MACE, all-cause mortality, cardiovascular death, myocardial infarction, stroke, new revascularization, new angiography, and dementia. The model is adjusted for: age, sex, BMI category, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, ACS (STEMI/NSTEMI/unstable/stable) as indication for CABG, LV function, CKD-stages (CKD-EPI for eGFR), year of CABG, and other time-updated secondary prevention medications (RAAS, β-blockers, platelet inhibitors). *aHR*, Adjusted hazard ratio; *MACE*, major adverse cardiovascular event.

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reduction in MACE, all-cause mortality, CVD death, myocardial infarction, stroke, new revascularization, new angiography, and dementia for all CABG patients. Last, most of the associations with outcome variables did not differ significantly between low-, intermediate-, and high-dose of statins compared with no statin use (Figure 6 and Video 1).

Statins are effective in reducing serum LDL levels in patients with hyperlipidemia and risk of complications in patients with established coronary artery disease.[22] In

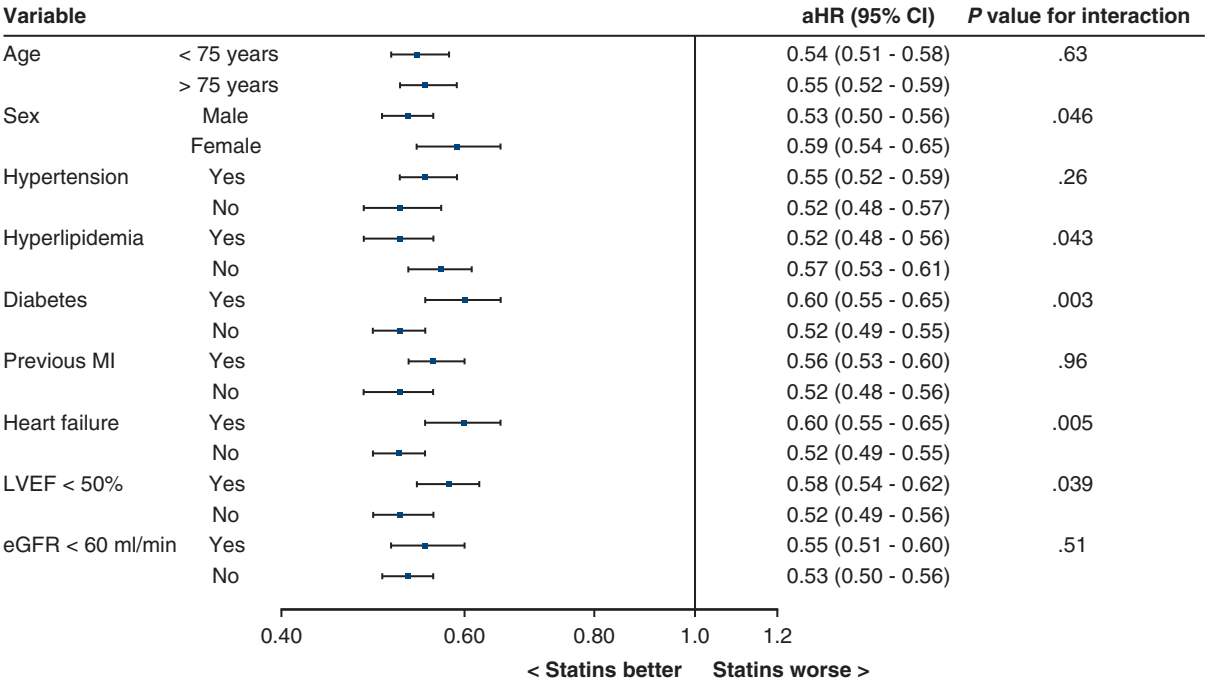


FIGURE 5. Forest plots showing the results from the interaction analyses of the effect of statin use on MACE for selected subgroups. The model is adjusted for: age, sex, BMI category, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, ACS (STEMI/NSTEMI/unstable/stable) as indication for CABG, LV function, CKD-stages (CKD-EPI for eGFR), year of CABG, and other time-updated secondary prevention medications (RAAS, β-blockers, platelet inhibitors). *aHR*, Adjusted hazard ratio; *MI*, myocardial infarction; *LVEF*, left ventricular ejection fraction; *eGFR*, estimated glomerular filtration rate.

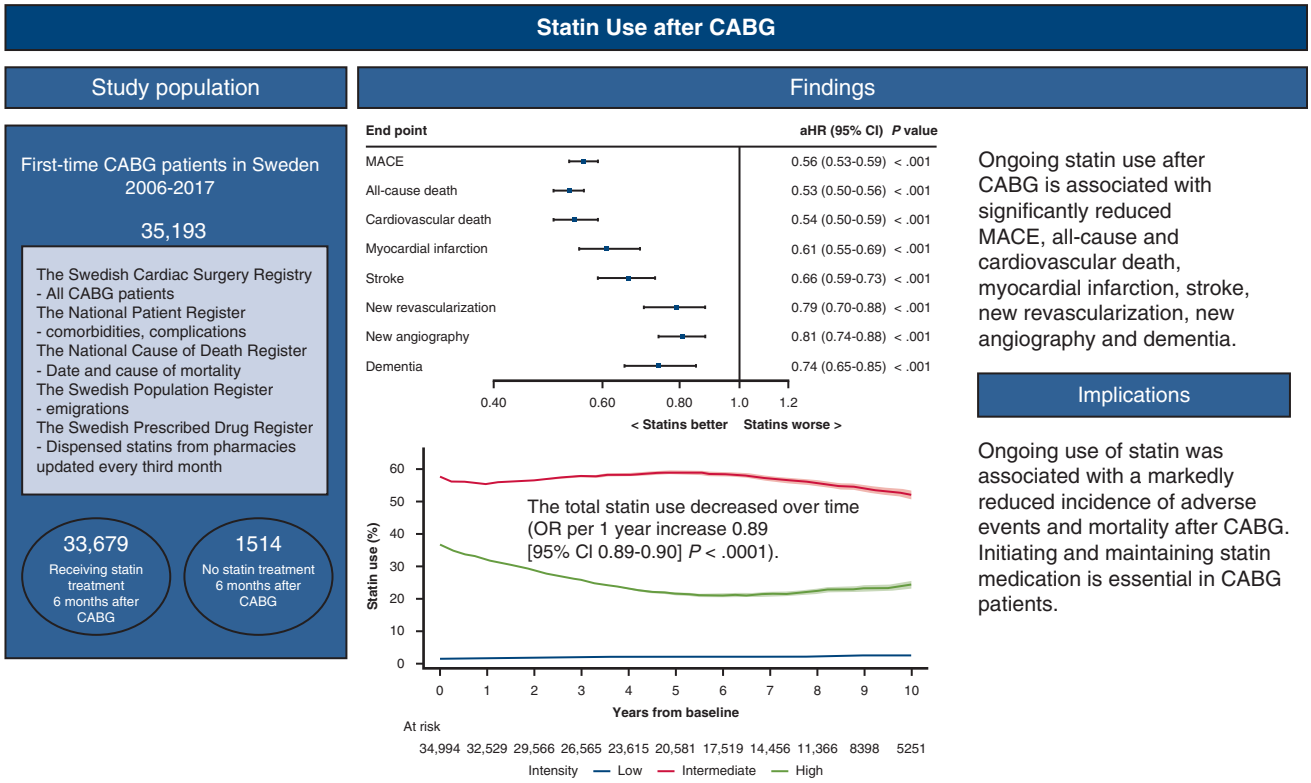
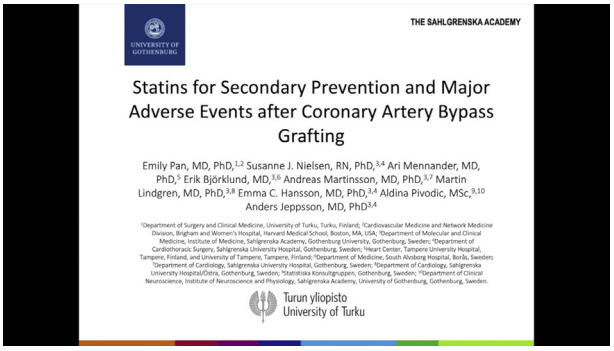


FIGURE 6. Summary of study design and main results of the report. The model is adjusted for: age, sex, BMI category, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, ACS (STEMI/NSTEMI/unstable/stable) as indication for CABG, LV function, CKD-stages (CKD-EPI for eGFR), year of CABG, and other time-updated secondary prevention medications (RAAS, β-blockers, platelet inhibitors). *aHR*, Adjusted hazard ratio; *MACE*, major adverse cardiovascular event; *OR*, odds ratio; *ACS*, acute coronary syndrome; *STEMI*, ST-elevation myocardial infarction; *NSTEMI*, non-ST–elevation myocardial infarction; *CKD*, chronic kidney disease; *CKD-EPI*, Chronic Kidney Disease-Epidemiology Collaboration; *eGFR*, estimated glomerular filtration rate.

CABG patients, the use of statins has consistently been associated with improved survival and a reduction of MACE in observational studies.[7,9,23] Accordingly, in all guidelines, statins are recommended as a secondary preventive medication for all CABG patients without contraindications.[2,6] However, the use of statins after CABG varies considerably in most observational, real-world studies.[24,25]



VIDEO 1. The author discussing main findings and the importance of the study. Video available at: https://www.jtcvs.org/article/S0022-5223(21)01536-1/fulltext.

In the present study with full coverage of dispensed medications, statins were dispensed to 95.7% of all CABG patients at baseline and 78.9% at 10 years, which is markedly higher than reported in most previous registry studies.[9,23,25-27] We observed a significant and independent association between statin use, irrespective of intensity, and reduced incidence not only of MACE, but also for each of the secondary end points. This suggests that CABG patients might benefit from statins even more than has previously been thought.

The statins can be grouped, on the basis of their type and dose, into low-, intermediate-, and high-dose statin treatment, as illustrated in Table E2. The choice of intensity for an individual patient is typically on the basis of the effect on LDL levels; if the target LDL levels are reached with intermediate- or low-intensity, this is generally considered sufficient, although there are data supporting a strategy aiming for as low an LDL level as possible.[28] Most patients in the present study were prescribed an intermediate or high dose of statin, and only 1% to 2% received low-dose statins. The current study shows that low-, intermediate-, and high-dose groups were all independently associated with reduced incidence of MACE compared with the

no-treatment group, but we were unable to detect any significant difference between the intensities regarding the risk of MACE, myocardial infarction, stroke, and dementia in adjusted models. This suggests that unadjusted higher crude event rate in low statin dose patients is likely to be caused by higher comorbidities and/or other factors that increase the mortality risk. However, considering the limitations of an observational study and the risk of errors when multiple secondary analyses are performed, these data need to be interpreted cautiously. Moreover, the present study shows that high-intensity statin use seems to increase the risk for CVD death and new catheter-based interventions compared with intermediate statin intensity. The reason is unclear, but high-dose statins may be prescribed to patients at higher risk of cardiovascular events, and as Figure 3, *C*, shows, younger (younger than 75 years) patients were prescribed higher doses than elderly patients, which might partly explain the higher rate of new interventions. Our findings, however, are at odds with a recent study in CABG patients by Poorhosseini and colleagues,[29] who reported that the rate of MACE was significantly reduced when high-intensity statins were used, compared with low-intensity statins.

To our knowledge, no previous study has investigated the association between statin treatment and dementia in CABG patients. Giang and colleagues[11] recently reported an observational study in which younger CABG patients had an increased risk of all types of dementia compared with the general population. Sundbøll and colleagues[12] reported that myocardial infarction survivors had an increased risk of vascular dementia, which is related to small vessel infarctions and perivascular inflammation. Alzheimer's disease, however, is associated with cholesterol metabolism, especially apolipoprotein E4, which transports cholesterol in the brain.[30] Moreover, high total cholesterol is associated with increased risk of dementia and cognitive impairment in later life.[31] Therefore, it has been suggested that statins might reduce the risk for dementia because they decrease cholesterol levels, as well as having pleotropic effects.[13,14] However, there are contradictory results regarding the benefit of statin use in primary prevention of dementia.[32,33] This population-based study shows that, as secondary prevention, statins are associated with a reduction in the risk of dementia in CABG patients after adjustment for comorbidities.

Strengths and Limitations

The strengths of this study include its large, population-based cohort in a real-world setting. Furthermore, the registry has full national coverage and a complete follow-up and uses time-updated data regarding medications in the statistical models. The time-updated data on dispensed statin prescriptions compared all patients receiving statins with all patients not receiving statins, at each time point. This means that it is possible for an individual to have some periods of statin treatment and other periods not receiving statin treatment, because this can change over time. The patients needed to have two 3-month periods without dispensed medication to be counted as no statin treatment, hence the increased mortality risk in patients without statins is not caused by discontinuation of medication in terminally ill patients.

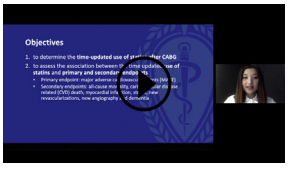
A major limitation is the missing data on blood cholesterol levels, which most likely dictates the intensity of the statin dose that had been dispensed. In addition, we do not know whether the reasons for discontinuing the medication were patient nonadherence or whether there were other reasons that might confound the studied associations. The present study included only statins, and not any of the new lipid-lowering medications, and therefore, the inability to adjust for therapy switches among statin non-user patients could constitute a source of residual confounding. This could have led to underestimation of the studied associations, due to regression to the mean, and it could, at least in part, explain the fact that no observed difference could be found for different statin dose regimens. Finally, as an inherent limitation of a retrospective study, selection bias and residual confounding might be present.

CONCLUSIONS

The use of statins was high early after CABG surgery but decreased markedly over time. Statin use was associated with a reduced risk of a number of important long-term complications after CABG, including mortality, stroke, and dementia. Initiation and continuation of statins in CABG patients is essential.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/21%20AM/AM21_A27/AM21_A27_06.mp4.



Conflict of Interest Statement

A.J. has received fees for consultancy or lectures from Werfen, Boehringer-Ingelheim, Portola, Baxter, and Laboratoire Français du Fractionnement et des Biotechnologies unrelated to the present work. E.C.H. has received speaker's honorarium from AstraZeneca and Boehringer-Ingelheim. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict

of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: coronary artery bypass grafting, secondary prevention medication, statin, outcome

Discussion

Presenter: Dr Emily Pan

Dr Paul Kurlansky (*New York, New York*). My name is Dr Paul Kurlansky from Columbia University and I have no disclosures. Dr Pan, this is a fascinating study, and the authors are to be congratulated for elegantly modeling and beautifully presenting a wealth of data from an entire country to address an issue of serious clinical importance to anyone taking care of patients undergoing coronary

artery bypass surgery.

Moreover, I think you're to be congratulated. Medication compliance is an extremely difficult and complex topic to try to study and I think you should be congratulated for taking it on. The fact that you use data on the medication that was dispensed, rather than prescriptions that were actually given, further strengthens the power of your study or the significance of your study. I have 4 questions for the authors.

The first question is: since about 2011, the American College of Cardiology/American Heart Association Guidelines have recommended statin prescription for patients undergoing CABG surgery, as a class 1A recommendation. And the Society of Thoracic Surgeons has incorporated this as a quality metric in CABG surgery. Your study actually preceded that recommendation, beginning in 2006 and going through 2017. I was wondering if you had any information regarding any change in the pattern of statin prescription or statins dispensed for CABG patients during the course of your study?

The second question is that the authors have chosen a 6-month postoperative time point to emphasize the effect of statins on the long-term rather than perioperative outcomes. Therefore, time 0 is actually 6 months postoperatively. I wonder if the authors considered including other potentially important factors such as operative and postoperative variables like arterial grafting, completeness of revascularization, postoperative atrial fibrillation, or other factors that might affect their modeling of long-term outcomes?

The third question was whether or not the author's considered adding medical center where the surgery was performed as a random event into your modeling? The reason why is it might well be that centers that prescribe statins actually take more thorough and careful care of their patients, and that what we are seeing here is actually a measure of the intensity or quality of care in general, rather than the effect of the statins themselves. Introducing center effect in the model might be one way to try to distinguish this.

The final question is regarding the data that you alluded to regarding dementia is fascinating and quite provocative. I was wondering if the authors have any data regarding postoperative dementia or underlying neurocognitive status that would enable them to distinguish the new incidence of dementia from a preexisting or chronic phenomena?

I thank the authors for providing me with a copy of the manuscript before the presentation. And I thank the association for the privilege of discussing this important work. Thank you.

Dr Emily Pan (*Jyväskylä, Finland*). Thank you very much, Dr Kurlansky, for your comments and questions. I'll start one by one. So first, you asked about the patterns about dispensed statins, that's a very interesting point and there's actually a slight increase of dispensed statins. In 2006, it was some 92% and it increased to 96% or 97% in 2017 and the trend is still growing.

And the second question was regarding the other postoperative variables. We do have information on perioperative procedures and the complications, but we decided not to include those because some variables are quite hard to define such as completeness of revascularization and might be related to statin induction and statin use before CABG instead of our focus, which was long-term use of statins after CABG. But it is a very interesting point and maybe we should take a look at those variables separately in another study.

And then you asked about the different centers. In Sweden we have 8 cardiothoracic centers. The thing is, the cardiologist actually refers, and they also follow-up those patients 6 months after CABG surgery, but after that, they are followed by their GPs. They are family physicians in primary health care centers, which means there are many of those health centers and we don't think it's appropriate to compare those because the follow-up goes to primary health care after 6 months.

And the last question, you asked about the dementia. It is a limitation that we unfortunately do not have preoperative or early postoperative neurocognitive status. However, we do know that at baseline, we have 63 patients who were with dementia diagnosis—at baseline—so it's less than 0.00-something in our data, which should not affect the results. So, these are new dementias that were diagnosed afterward.

Dr Kurlansky. Thank you very much. Particularly the information about dementia might have implications well beyond cardiac surgery and thank you for bringing it up.

TABLE E1. ICD codes used for comorbid conditions and events and ATC classification codes for medications

	ICD-ninth revision 1986-1996	ICD-10th revision 1997-Present
Comorbid condition or event		
Myocardial infarction	410	I21.0-I21.4
Diabetes	250	E10-E14
Hypertension	401-405	I10.0-I15.9
Heart failure	428	I50, I42-143.8, I11.0, I13.0, I13.2, I50, I25.5
Atrial fibrillation	427D	I48
Stroke	431-434, 436	I61.0-I64
Chronic respiratory disease	490-496	J40-J47
Renal failure	584-586	N17-N19
Malignancy	140-208	C00-C97
Congenital heart disease	745-747	Q20-Q26
Hyperlipidemia	272.0, 272.01, 272.09	E78
Peripheral artery disease	440, 443X, 444, 447	I70, I73.9, I74, I77
Dementia	290	F00- F03, G30, G31
Left ventricular ejection fraction	Collected from SWEDEHEART	
Medication	ATC code	
β-Blockers	C07 (excluding C07AA07)	
RAS inhibitors	C09	
Statins	C10AA, C10BA02, C10BX06	
Platelet inhibitors	B01AC	
Oral anticoagulants	B01AA, B01AE, B01AF	

ICD, International Classification of Diseases; *ATC*, Anatomical Therapeutic Chemical Classification System; *SWEDEHEART*, Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies; *RAS*, renin-angiotensin system.

TABLE E2. Intensity of statins

Statin	Low intensity	Moderate intensity	High intensity
Atorvastatin	N/A	10-20 mg	40-80 mg
Fluvastatin	20-40 mg	80 mg	N/A
Lovastatin	20 mg	40-80 mg	N/A
Pitavastatin	N/A	1-4 mg	N/A
Pravastatin	10-20 mg	40-80 mg	N/A
Rosuvastatin	N/A	5-10 mg	20-40 mg
Simvastatin	10 mg	20-40 mg	N/A

N/A, Not available. Adapted from Grundy and colleagues.[20]

TABLE E3. The time-updated statin use compared with non-users, and according to the intensity of the dose

Statins	At baseline (n = 35,193)	At 6 mo postbaseline (n = 34,422)	At 1 y postbaseline (n = 32,861)	At 2 y postbaseline (n = 29,871)	At 3 y postbaseline (n = 26,828)	At 4 y postbaseline (n = 23,883)	At 5 y postbaseline (n = 20,838)	At 6 y postbaseline (n = 17,728)	At 7 y postbaseline (n = 14,632)	At 8 y postbaseline (n = 11,525)	At 9 y postbaseline (n = 8504)	At 10 y postbaseline (n = 5332)	*P* value
No treatment	1514 (4.3%)	2954 (8.6%)	3610 (11.0%)	3832 (12.8%)	3881 (14.5%)	3922 (16.4%)	3589 (17.2%)	3217 (18.1%)	2818 (19.3%)	2263 (19.6%)	1712 (20.1%)	1126 (21.1%)	
Treatment	33,679 (95.7%)	31,468 (91.4%)	29,251 (89.0%)	26,039 (87.2%)	22,947 (85.5%)	19,961 (83.6%)	17,249 (82.8%)	14,511 (81.9%)	11,814 (80.7%)	9262 (80.4%)	6792 (79.9%)	4206 (78.9%)	<.0001
Statin intensity													<.00001
None	1514 (4.3%)	2954 (8.7%)	3610 (11.1%)	3832 (13.0%)	3881 (14.6%)	3922 (16.6%)	3589 (17.4%)	3217 (18.4%)	2818 (19.5%)	2263 (19.9%)	1712 (20.4%)	1126 (21.4%)	
Low	505 (1.4%)	515 (1.5%)	546 (1.7%)	526 (1.8%)	524 (2.0%)	493 (2.1%)	434 (2.1%)	390 (2.2%)	311 (2.2%)	250 (2.2%)	206 (2.5%)	123 (2.3%)	
Intermediate	20,147 (57.6%)	19,105 (56.0%)	18,002 (55.3%)	16,706 (56.5%)	15,332 (57.7%)	13,737 (58.2%)	12,134 (59.0%)	10,236 (58.4%)	8229 (56.9%)	6322 (55.6%)	4532 (54.0%)	2726 (51.9%)	
High	12,828 (36.7%)	11,546 (33.8%)	10,371 (31.9%)	8502 (28.8%)	6828 (25.7%)	5463 (23.1%)	4424 (21.5%)	3676 (21.0%)	3098 (21.4%)	2531 (22.3%)	1948 (23.2%)	1276 (24.3%)	
Missing	199	302	332	305	263	268	257	209	176	159	106	81	

For categorical variables data are presented as n (%). For comparison between groups the Mantel–Haenszel χ^2 test was used for ordered categorical variables.

TABLE E4. The aHRs for each end point in model 3 for low-intensity versus no statin treatment, intermediate-intensity versus no statin treatment, and high-intensity versus no statin treatment

End point	Low-intensity vs no statin treatment	Intermediate-intensity vs no statin treatment	High-intensity vs no statin treatment
MACE (all-cause mortality, myocardial infarction, stroke)	0.60 (0.52-0.69); <.0001	0.56 (0.53-0.59); <.0001	0.56 (0.53-0.60); <.0001
All-cause mortality	0.63 (0.54-0.74); <.0001	0.53 (0.50-0.56); <.0001	0.55 (0.50-0.59); <.0001
Cardiovascular death	0.70 (0.56-0.87); .0015	0.52 (0.47-0.56); <.0001	0.60 (0.53-0.68); <.0001
Myocardial infarction	0.61 (0.44-0.86); .0042	0.59 (0.53-0.67); <.0001	0.66 (0.57-0.77); <.0001
Stroke	0.61 (0.45-0.83); .0018	0.65 (0.59-0.73); <.0001	0.66 (0.57-0.76); <.0001
New revascularizations	0.82 (0.59-1.13); .22	0.73 (0.65-0.83); <.0001	0.88 (0.77-1.01); .076
New angiography	0.60 (0.46-0.78); .0002	0.77 (0.71-0.85); <.0001	0.89 (0.80-0.99); .025*
Dementia	0.90 (0.63-1.27); .54	0.74 (0.64-0.85); <.0001	0.74 (0.60-0.91); .0037

Model 3 data are presented as aHR (95% CI); *P* value. Model 3 is adjusted for: age, sex, BMI category, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, ACS (STEMI/NSTEMI/unstable/stable) as indication for CABG, LV function, CKD stages (CKD-EPI for eGFR), year of CABG and other time-updated secondary prevention medications (RAAS, β-blockers, platelet inhibitors). *aHR*, Adjusted hazard ratio; *MACE*, major adverse cardiovascular event. *All *P* values are < .05 also after adjustment for multiple comparisons using the Bonferroni–Holm step down procedure, except for the indicated *P* value for high-intensity statin dose versus no statin in relation to the end point, new angiography.

TABLE E5. The crude event rate per 100 person-years with 95% CI for patients with low-, intermediate-, and high-dose statin intensity, and the aHRs with 95% CI for model 3 for high versus low, intermediate versus low, and high versus intermediate statin doses

	Crude event rate (95% CI)			Model 3 aHR (95% CI)		
End point	Low-intensity	Intermediate-intensity	High-intensity	High- vs low-intensity	Intermediate- vs low-intensity	High- vs intermediate-intensity
MACE (all-cause mortality, myocardial infarction, stroke)	5.41 (4.69-6.20)	4.06 (3.95-4.18)	3.26 (3.10-3.42)	0.94 (0.81-1.09); $P = .40$	0.93 (0.81-1.07); $P = .30$	1.01 (0.95-1.08); $P = .76$
All-cause mortality	4.23 (3.61-4.92)	2.66 (2.57-2.75)	1.99 (1.87-2.12)	0.86 (0.73-1.02); $P = .086$	0.84 (0.71-0.98); $P = .023$	1.03 (0.961.12); $P = .38$
Cardiovascular death	2.21 (1.78-2.73)	1.21 (1.15-1.27)	0.96 (0.88-1.05)	0.86 (0.68-1.09); $P = .20$	0.74 (0.59-0.92); $P = .0057$	1.17 (1.04-1.30); $P = .0063$
Myocardial infarction	0.97 (0.69-1.34)	0.86 (0.81-0.92)	0.92 (0.84-1.01)	1.08 (0.77-1.51); $P = .66$	0.96 (0.70-1.34); $P = .83$	1.12 (0.99-1.26); $P = .074$
Stroke	1.14 (0.83-1.53)	1.04 (0.98-1.10)	0.82 (0.75-0.91)	1.08 (0.79-1.49); $P = .63$	1.07 (0.79-1.45); $P = .65$	1.01 (0.89-1.14); $P = .87$
New revascularizations	1.08 (0.78-1.46)	1.04 (0.98-1.10)	1.62 (1.50-1.73)	1.08 (0.79-1.48); $P = .64$	0.90 (0.66-1.22); $P = .48$	1.20 (1.09-1.33); $P = .0004$
New angiography	1.53 (1.16-1.98)	2.09 (2.00-2.18)	2.97 (2.82-3.14)	1.49 (1.14-1.94); $P = .0036$	1.29 (0.99-1.68); $P = .055$	1.15 (1.07-1.24); $P = .0003$
Dementia	0.93 (0.65-1.28)	0.56 (0.51-0.60)	0.34 (0.29-0.39)	0.82 (0.57-1.19); $P = .30$	0.83 (0.59-1.16); $P = .27$	1.00 (0.83-1.19); $P = .96$

Model 3 data are presented as aHR (95% CI); *P* value. Model 3 is adjusted for: age, sex, BMI category, hypertension, diabetes, hyperlipidemia, previous stroke, atrial fibrillation, heart failure, previous myocardial infarction, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, ACS (STEMI/NSTEMI/unstable/stable) as indication for CABG, LV function, CKD stages (CKD-EPI for eGFR), year of CABG and other time-updated secondary prevention medications (RAAS, β-blockers, platelet inhibitors). *aHR*, Adjusted hazard ratio; *MACE*, major adverse cardiovascular event.