

openheart Statins are associated with a large reduction in all-cause mortality in women from a cardiac outpatient population

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ABSTRACT

Objectives Uncertainty about the benefit of (high-intensity) statins for women remains due to under-representation of women in primary prevention trials and scarcity of sex-stratified data. This study evaluates the sex-specific relation between statin treatment and survival and the additional benefit of high-intensity statins.

Methods Electronic health record data from 47 801 patients (17 008 statin users and 30 793 non-users) without prior cardiovascular disease were extracted from thirteen Dutch outpatient cardiology clinics. Patients prescribed statins at baseline were propensity-score matched to those eligible for statin therapy (low-density lipoprotein >2.5 mmol/L) without a statin prescription. Statins were divided into low-intensity and high-intensity according to Dutch guidelines. Mortality data were obtained via linkage to the national mortality registry. Cox regression was used to evaluate the relationship between statin prescription and intensity and all-cause and cardiovascular mortality.

Results Propensity score matching created a cohort of 8631 statin users and 8631 non-users. 35% of women and 28% of men received a low-intensity statin. The beneficial effect of statins on both all-cause and cardiovascular mortality was stronger in women (HR 0.66, 95% CI 0.58 to 0.74 and HR 0.55, 95% CI 0.39 to 0.71, respectively) than in men (HR 0.89, 95% CI 0.81 to 0.95 and HR 0.93, 95% CI 0.77 to 1.08, respectively). High-intensity statins conferred modest protection against all-cause mortality (HR 0.94, 95% CI 0.88 to 1.00) and cardiovascular mortality (HR 0.86, 95% CI 0.74 to 0.98) in both sexes.

Conclusions The protective effect of primary prevention statins was stronger in women than men for both all-cause and cardiovascular mortality. High-intensity statins conferred a modest additional benefit in both sexes. Statins seem to be effective regardless of treatment intensity, especially in women.

INTRODUCTION

Statins have been shown to effectively lower the risk of cardiovascular events by reducing low-density lipoprotein (LDL) levels, with

Key questions

What is already known about this subject?

- Women more often receive low-intensity statin therapy than men despite evidence that statin therapy lowers cardiovascular disease risk in a dose-dependent manner.
- It remains unclear whether statin treatment is equally effective in women and men due to under-representation of women in primary prevention trials and scarcity of sex-stratified data.
- This study evaluates the sex-specific relation between statin treatment and survival, and explores whether high-intensity statins confer additional benefit.

What does this study add?

- Statins were effective in lowering cardiovascular disease risk, especially in women, and high-intensity regimens conferred only marginal additional benefit in both sexes.

How might this impact on clinical practice?

- The current trend of preferentially prescribing women low-intensity statins does not seem to reduce the potential benefit of treatment. Future studies are needed to evaluate whether lower dosages are appropriate if higher dosages lead to side effects or otherwise negatively influence quality of life.

high-intensity regimens being more effective than low-intensity variants.¹ This effect is seen independently of baseline mortality risk,² suggesting that all people at risk of cardiovascular events benefit from treatment. However, women are less likely to receive guideline-recommended statin therapy than men in both primary and secondary prevention.^{3–5} It has been shown that women are more likely to refuse or stop statin therapy^{3,6} and that healthcare professionals are also less likely to prescribe (high-intensity) statins for women.^{3,5} This careful approach may stem

from remaining uncertainty about the benefit of statin therapy as primary prevention strategy for women due to the low number of women in primary prevention trials.⁷

There is some evidence to suggest that women and men may benefit equally from statin treatment.^{8,9} The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin trial showed that rosuvastatin reduced the risk of cardiovascular events and cardiovascular mortality in both women and men.¹⁰ In addition, data from a primary care cohort of new statin users showed that improved adherence to statins reduced the risk of hospitalisation for cardiovascular events in both men and women to a similar extent.⁶ While some meta-analyses of primary prevention trials confirmed that statin treatment benefits both sexes,^{2,10} others failed to find such positive effects.^{11,12} Moreover, it remains unclear whether the intensity of therapy influences outcomes. Therefore, we used regular care data from cardiac outpatient clinics to study whether receiving a statin prescription for primary prevention affects long-term prognosis in women and men without a history of cardiovascular disease. We also explored whether high-intensity statins confer additional protection over low-intensity regimens.

METHODS

Study population

The Cardiology Centers of the Netherlands regular care database contains data from 109 151 unique patients that were referred for a full cardiac workup by their general practitioner on suspicion of cardiac disease between 2007 and 2018. During the first visit, information was collected on anthropometric measurements, cardiovascular risk factors, medical history, comorbidities and medication use. All patients underwent transthoracic echography and electrocardiography at rest. Stress electrocardiography and laboratory measurements were performed in approximately 75% of patients. Passive follow-up was obtained for 95.9% of the study population via linkage to the national mortality registry.

For the current study, all patients with a history of coronary heart disease, heart failure, cerebrovascular disease or congenital heart disease, or a prior or ongoing statin prescription were excluded.

Selection of statin users and non-users

Medication prescriptions were identified using pattern matching based on a combination of generic compound names and brand names. The search term was based on brand names of statins available in the Netherlands tailored to those that were prescribed within the study population. It contained the words *statin*, *crestor*, *lipitor*, *selektine*, *zocor* and *tahor*. Medication dose was extracted from the text fields and multiplied by daily frequency and dosage to obtain the daily dose per prescription. The *grep* and *gsub* functions from the R *grep* package were used for the name and dose pattern matching, respectively. Statin prescription entries missing information on dose

or daily frequency, prescriptions with a negative duration and one-off prescriptions were excluded. Combination preparations with ezetimibe or fenofibrate were also excluded because Dutch guidelines recommend these when prior statin-only therapy was not effective enough, so these prescriptions are unlikely to be a patient's first statin prescription.

Statin users were defined as patients who received their first statin prescription within 31 days prior to or after their baseline visit. The 31-day window was chosen to both allow for small delays in data entry and include people prescribed statins shortly before or after their visit at the cardiac outpatient clinic, because labelling these people as non-users would introduce misclassification. Non-users were defined as patients eligible for statin therapy according to the Dutch primary prevention guidelines (LDL > 2.5 mmol/L) who did not receive a statin prescription within the 31-day period.

Definition of statin intensity

The intensity of statin treatment was categorised as lower, equal or higher based on how much it lowered LDL cholesterol levels compared with the Dutch primary prevention guideline-recommended dose of 40 mg simvastatin (online supplemental table 1).^{13–15} We compared patients on lower intensity statin regimens (low intensity) with patients on equal and higher intensity regimens (high intensity).

Outcome

Passive follow-up for all-cause mortality was available for 95.9% of the study population via linkage to the national mortality registry from Statistics Netherlands. This registry continuously collects all official cause of death reports submitted by medical doctors and coroners in the Netherlands and is updated quarterly throughout the year and at the end of each year. The cause of death is coded according to the guidelines of the WHO using the International Classification of Diseases and related Health Problems edition 10 (ICD-10). For the current analyses, all-cause mortality was available until 12 February 2020 and cause-specific mortality was available until 1 January 2020. Follow-up time for patients who were still alive was censored on 12 February 2020. All-cause mortality was defined as having a date of death recorded in the mortality registry. Cardiovascular mortality was defined as any mortality entry that was labelled with an ICD-10 code from the diseases of the circulatory system chapter (I00–I99).

Propensity score matching

We created propensity-score matched cohorts for our analyses to account for confounding by indication. We first imputed missing data on components of the propensity score using the *mice* ¹⁶ package, resulting in five imputed datasets. We subsequently calculated the propensity score in each imputed dataset based on a set of confounding variables (online supplemental table

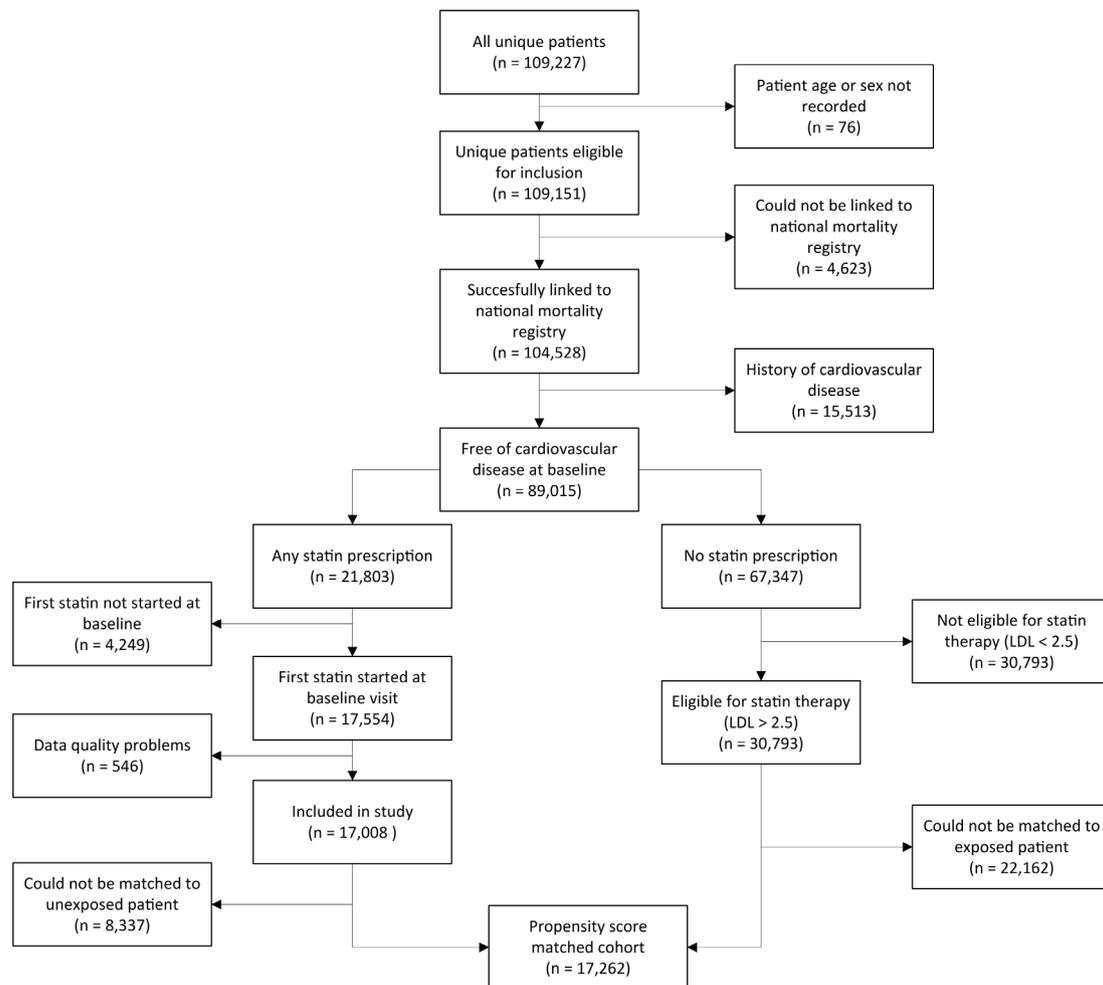


Figure 1 Flow chart describing the study population selection process. LDL, low-density lipoprotein.

2) and matched one-on-one to create five new cohorts where all confounders were balanced between the two groups. We used the *MatchIt*¹⁷ package to calculate the propensity score and perform the matching, applying the nearest neighbours approach with a calliper width of 0.1. We assessed whether covariates were properly balanced based on the mean difference using the *cobalt* package. We then ran our survival analyses in each imputed matched dataset and pooled the results using the *meta* package.

For the analyses exploring the relationship between statin use and long-term prognosis, we propensity-score matched statin users with statin non-users. For the analyses exploring the relationship between statin intensity and long-term prognosis, we propensity-score matched low-intensity statin users with high-intensity statin users.

Statistical analyses

Continuous variables were reported as mean (SD) or median (IQR), depending on their distribution. Categorical variables were reported as number and percentage. The effect of statin prescription on long-term prognosis and the effect of statin intensity on long-term prognosis were evaluated using Cox

regression in the whole propensity-matched cohort and stratified by sex. We calculated robust confidence intervals to account for the matched nature of the dataset. The presence of sex differences in treatment effect was tested using an interaction term.

Sensitivity analysis

We excluded participants with a history of cardiovascular disease, which was defined as having a cardiovascular diagnosis before baseline. However, 2000 patients (12%) were diagnosed with cardiovascular disease at baseline. To test the robustness of our findings, we repeated the main analysis excluding these 2000 patients. A new propensity score matched cohort was created with the same set of variables used in the main analysis except those related to cardiovascular disease diagnosis. We based our definition of high-intensity statin on Dutch guidelines, which resulted in a different classification than what is internationally used. To check generalisability of our results, we repeated the main analysis defining high-intensity statins as those that reduce LDL cholesterol by 50% or more (atorvastatin 40 mg or higher, rosuvastatin 20 mg or higher and simvastatin 80 mg or higher).

Table 1 Baseline characteristics of statin users and non-users after propensity score matching

	Statin users (n=8631)	Statin non-users (n=8631)
General characteristics		
Age (years)	61 (11)	61 (13)
Women (n, %)	4482 (52)	4499 (52)
Ethnicity (n, %)		
Native Dutch	6753 (78.2)	6841 (79.3)
First generation immigrant	1297 (15.0)	1200 (13.9)
Second generation immigrant	581 (6.7)	590 (6.8)
Annual personal income (€)	€27 860 (€14 647–€48 390)	€28 261 (€14 956–€47 613)
Current smoker (n, %)	3543 (41.0)	3540 (41.0)
10-year cardiovascular mortality risk (SCORE)		
0%–4%	4757 (55.1)	4562 (52.9)
5%–9%	2380 (27.6)	2175 (25.2)
≥10%	1493 (17.3)	1887 (21.9)
Complaints (n, %)		
No of complaints	3451 (40.0)	3389 (39.3)
0	4925 (57.1)	5014 (58.1)
1	235 (2.7)	216 (2.5)
2	20 (0.2)	12 (0.1)
≥3		
Chest pain	3176 (36.8)	3158 (36.6)
Dyspnoea	778 (9.0)	759 (8.8)
Fatigue	277 (3.2)	273 (3.2)
Heart murmurs	77 (0.9)	75 (0.9)
Palpitations	1088 (12.6)	1141 (13.2)
Collapse	63 (0.7)	76 (0.9)
Comorbidities (n, %)		
Hypertension	3386 (39.2)	3310 (38.4)
Diabetes mellitus	843 (9.8)	686 (7.9)
Dyslipidaemia	2078 (24.1)	1957 (22.7)
Cardiovascular diagnosis at baseline	1061 (12.3)	939 (10.9)
Clinical characteristics		
Body mass index (kg/m ²)	27.0 (4.5)	27.0 (4.7)
Systolic blood pressure (mmHg)	146 (21)	146 (22)
Total cholesterol (mmol/L)	5.53 (1.29)	5.62 (0.86)
Low-density lipoprotein cholesterol (mmol/L)	3.30 (2.50–4.20)	3.30 (2.90–3.80)
High-density lipoprotein cholesterol (mmol/L)	1.40 (1.10–1.80)	1.40 (1.10–1.80)
Triglycerides (mmol/L)	1.50 (1.00–2.20)	1.50 (1.00–2.20)
Estimated glomerular filtration rate (mL/min/1.73 m ²)	82 (27)	82 (28)
History of cardiovascular medication use	970 (11.2)	971 (11.3)

Continued

Table 1 Continued

	Statin users (n=8631)	Statin non-users (n=8631)
Cardiovascular medication prescribed at baseline	5798 (67.2)	5807 (67.3)
No of cardiovascular medications		
0	2256 (26.1)	2240 (26.0)
1–3	5316 (61.6)	5457 (63.2)
4–7	1048 (12.1)	924 (10.7)
8–10	11 (0.1)	10 (0.1)
Blood pressure lowering medication	5388 (62.4)	5352 (62.0)
Antiplatelet or anticoagulant medication	3086 (35.8)	3032 (35.1)
Other lipid-lowering medication	187 (2.2)	191 (2.2)
Diabetes mellitus medication	728 (8.4)	572 (6.6)
Nitrates	859 (10.0)	803 (9.3)
Antiarrhythmic medication	108 (1.3)	121 (1.4)
Digoxin	62 (0.7)	65 (0.8)
Statin prescriptions at baseline (n, %)		
Statin name		
Atorvastatin	1859 (21.5)	
Fluvastatin	42 (0.5)	
Pravastatin	643 (7.4)	
Rosuvastatin	889 (10.3)	
Simvastatin	5198 (60.2)	
Statin intensity		
Lower than guideline recommended	2805 (32.5)	
Equal to guideline recommended	3473 (40.2)	
Higher than guideline recommended	2353 (27.3)	

SCORE, Systematic COronary Risk Evaluation.

All analyses were performed in R (R Core Team, Vienna, Austria). A $p < 0.05$ was considered statistically significant.

Patient and public involvement

Patients or public were not involved in any stage of the research process.

RESULTS

Propensity score matching

We extracted data from 17 008 statin users (48% women) and 30 793 patients (57% women) eligible for statin therapy who did not receive any statins (non-users) (figure 1; online supplemental table 3). Statin users were on average older (62 ± 11 vs 55 ± 13 years), more often men (52% vs 43%) and had a higher median 10-year cardiovascular mortality risk (3.94 (1.68–8.36) vs 1.66 (0.45–4.77)) compared with non-users. They also more often presented with comorbidities such as hypertension (46%

vs 23%) and dyslipidaemia (39% vs 7%), and were more often prescribed cardiovascular medication other than statins at baseline (80% vs 34%) compared with non-users (online supplemental table 3). Due to these pronounced differences between statin users and non-users, it was not possible to match each statin user to a non-user with a similar propensity score and individuals that could not be matched were excluded from analyses. Propensity-score matching resulted in a cohort consisting of 8631 statin users and 8631 non-users who were highly similar on all baseline characteristics (table 1).

Propensity-score matched study population

Female statin users were on average older than male statin users (62±10 vs 59±11 years) and more often had a low (0%–4%) cardiovascular mortality risk (61% vs 49%). They less often presented without cardiovascular complaints (36% vs 45%) and had a lower estimated glomerular filtration rate (76±24 vs 89±28 mL/min/m³). Similar differences between the sexes were seen for the statin non-users. The prevalence of comorbidities and medication use was similar between the sexes for both statin users and non-users (table 2).

Statin use and mortality risk

Median follow-up in the matched cohort was 5.8 (3.5–7.9) years, during which 1035 patients (50% women) died. Cardiovascular deaths accounted for a total of 270 events (26% of total). In the whole cohort, statin use reduced the risk of all-cause mortality by 24% (HR 0.76, 95% CI 0.71 to 0.82) and the risk of cardiovascular mortality by 28% (HR 0.72, 95% CI 0.61 to 0.83). This protective effect was stronger in women, with a 34% lower all-cause mortality risk (HR 0.66, 95% CI 0.58 to 0.74) and a 45% lower cardiovascular mortality risk (HR 0.55, 95% CI 0.39 to 0.71) in statin users compared with non-users. A similar but weaker trend was seen for men, with an 11% reduction in all-cause mortality (HR 0.89, 95% CI 0.81 to 0.96) and a non-significant 7% reduction in cardiovascular mortality (HR 0.93, 95% CI 0.77 to 1.08) in statin users compared with non-users (table 3). The interaction term for sex was statistically significant for both all-cause mortality (p value for interaction=0.040) and cardiovascular mortality (p value for interaction=0.035).

Statin intensity and mortality risk

Thirty-six per cent of women who were prescribed statins (n=8171) received a low-intensity statin and 26% received a high-intensity statin, compared with 29% and 28% of men who were prescribed statins (n=8837), respectively. The remainder received a statin prescription at guideline-recommended dose (38% of women vs 42% of men).

Propensity score matching resulted in a cohort of 10688 patients (52% women) with a balanced confounder distribution (online supplemental table 4). The total number of deaths was 820 in this cohort, of which 224 were cardiovascular. Higher intensity statins conferred a small protective effect against all-cause mortality (HR 0.94,

95% CI 0.88 to 1.00) and cardiovascular mortality (HR 0.86, 95% CI 0.74 to 0.98) compared with lower intensity statins. The results were similar for women (HR 0.91, 95% CI 0.82 to 1.00 and HR 0.88, 95% CI 0.70 to 1.05, respectively) and men (HR 0.96, 95% CI 0.88 to 1.05 and HR 0.85, 95% CI 0.69 to 1.01, respectively) although not statistically significant (table 4). There was no significant interaction between sex and statin intensity for neither all-cause mortality (p value for interaction=0.73) nor cardiovascular mortality (p value for interaction=0.76).

Sensitivity analysis

Repeating our analyses in those without a cardiovascular diagnosis at baseline resulted in a matched cohort of 15180 people (52% women). Results for all-cause mortality were similar to the main analysis in both sexes, but the protective effect of statins for cardiovascular mortality was no longer present in men (HR 1.02, 95% CI 0.86 to 1.18) when restricted to this subgroup (online supplemental table 5). Repeating our analyses with the adapted definition of high-intensity statin did not change our results (data not shown).

DISCUSSION

This study shows that fewer women eligible for statin therapy received statins compared with men, and when they did, they more often received a low-intensity statin. Statin prescription for primary prevention reduced the risk of all-cause and cardiovascular mortality to a greater extent in women compared with men. High-intensity statins conferred modest additional protection against both mortality outcomes and this effect was similar for women and men.

The main strength of our study was the use of a clinical care database that closely reflects the current situation in clinical care, both regarding statin prescription practices and patients that are seen at such outpatient clinics. Women were well represented (52%) and the majority of patients (55%) had a low (<5%) 10-year risk of cardiovascular mortality, which is exactly the patient population for whom more evidence regarding statin efficacy is warranted. The main limitation of our study is that data collection was driven by medical need and thus not performed systematically. Residual confounding may remain despite our efforts to control for confounding by indication. This may have biased our findings towards the null because patients with a higher mortality risk have a higher chance of being prescribed (high-intensity) statins, which would reduce the difference in survival between statin users and non-users and low-intensity and high-intensity statin users. We were also unable to evaluate more short-term outcomes that may be relevant in this low-risk population such as cardiovascular events and hospitalisations, and lacked good-quality data on adverse drug reactions. We were unable to

Table 2 Baseline characteristics of statin users and non-users after propensity-score matching stratified by sex

	Statin users (women) (n=4482)	Statin non-users (women) (n=4499)	Statin users (men) (n=4149)	Statin non-users (men) (n=4132)
General characteristics				
Age (years)	62 (10)	62 (12)	59 (11)	59 (13)
Ethnicity (n, %)				
Native Dutch	3520 (78.5)	3555 (79.0)	3233 (77.9)	3286 (79.5)
First generation immigrant	685 (15.3)	633 (14.1)	612 (14.8)	567 (13.7)
Second generation immigrant	277 (6.2)	311 (6.9)	304 (7.3)	179 (6.8)
Annual personal income (€)	€17 731 (10 191–31 052)	€18 912 (€10 514–€32 163)	€41 667 (€26 233–€65 118)	€41 515 (€25 110–€63 582)
Current smoker (n, %)	1848 (41.2)	1847 (41.1)	1695 (40.9)	1693 (41.0)
10-year cardiovascular mortality risk (SCORE)				
0%–4%	2712 (60.5)	2601 (57.8)	2045 (49.3)	1961 (47.5)
5%–9%	1085 (24.2)	979 (21.8)	1295 (31.2)	1196 (28.9)
≥10%	684 (15.3)	914 (20.3)	809 (19.5)	973 (23.5)
Complaints (n, %)				
No of complaints				
0	1597 (35.6)	1537 (34.2)	1854 (44.7)	1852 (44.8)
1	2721 (60.7)	2821 (62.7)	2204 (53.1)	2193 (53.1)
2	156 (3.5)	134 (3.0)	79 (1.9)	82 (2.0)
≥3	8 (0.2)	7 (0.2)	12 (0.2)	5 (0.1)
Chest pain	1696 (37.8)	1737 (38.6)	1480 (35.7)	1421 (34.4)
Dyspnoea	457 (10.2)	442 (9.8)	321 (7.7)	317 (7.7)
Fatigue	148 (3.3)	157 (3.5)	129 (3.1)	116 (2.8)
Heart murmurs	41 (0.9)	42 (0.9)	36 (0.9)	33 (0.8)
Palpitations	685 (15.3)	697 (15.5)	403 (9.7)	444 (10.7)
Collapse	30 (0.7)	35 (0.8)	33 (0.8)	41 (1.0)
Comorbidities (n, %)				
Hypertension	1887 (42.1)	1830 (40.7)	1499 (36.1)	1480 (35.8)
Diabetes mellitus	428 (9.5)	387 (8.6)	415 (10.0)	299 (7.2)
Dyslipidaemia	1127 (25.1)	1026 (22.8)	951 (22.9)	931 (22.5)
Cardiovascular diagnosis at baseline	489 (10.9)	487 (10.8)	572 (13.8)	452 (10.9)
Clinical characteristics				
Body mass index (kg/m ²)	26.9 (5.0)	26.9 (5.2)	27.2 (3.9)	27.1 (4.0)
Systolic blood pressure (mm Hg)	146 (22)	146 (23)	147 (20)	147 (21)
Total cholesterol (mmol/L)	5.70 (1.29)	5.73 (0.86)	5.36 (1.27)	5.50 (0.84)
Low-density lipoprotein cholesterol (mmol/L)	3.40 (2.50–4.30)	3.30 (2.90–3.90)	3.20 (2.40–4.10)	3.30 (2.90–3.80)
High-density lipoprotein cholesterol (mmol/L)	1.60 (1.30–2.00)	1.60 (1.30–2.00)	1.20 (1.00–1.50)	1.20 (1.00–1.50)
Triglycerides (mmol/L)	1.40 (1.00–2.00)	1.40 (1.00–2.10)	1.70 (1.10–2.40)	1.70 (1.10–2.40)
Estimated glomerular filtration rate (mL/min/1.73 m ²)	76 (24)	76 (26)	89 (28)	89 (29)
Medication prescriptions at baseline other than statins (n,%)				
History of cardiovascular medication use	518 (11.6)	505 (11.2)	452 (10.9)	467 (11.3)
Cardiovascular medication prescribed at baseline	3017 (67.3)	3081 (68.5)	2781 (67.0)	2726 (66.0)
No of cardiovascular medications				
0	1149 (25.6)	1117 (24.8)	1107 (26.7)	1123 (27.2)

Continued

Table 2 Continued

	Statin users (women) (n=4482)	Statin non-users (women) (n=4499)	Statin users (men) (n=4149)	Statin non-users (men) (n=4132)
1–3	2801 (62.5)	2909 (64.7)	2515 (60.6)	2548 (61.7)
4–7	525 (11.7)	467 (10.4)	523 (12.6)	457 (11.1)
8–10	7 (0.2)	6 (0.1)	4 (0.1)	4 (0.1)
Antiplatelet or anticoagulant medication	1529 (34.1)	1552 (34.5)	1557 (37.5)	1480 (35.8)
Other lipid-lowering medication	89 (2.0)	101 (2.2)	98 (2.4)	90 (2.2)
Diabetes mellitus medication	352 (7.9)	319 (7.1)	376 (9.1)	253 (6.1)
Nitrates	465 (10.4)	488 (10.8)	394 (9.5)	315 (7.6)
Antiarrhythmic medication	47 (1.0)	51 (1.1)	61 (1.5)	70 (1.7)
Digoxin	31 (0.7)	30 (0.7)	31 (0.7)	35 (0.8)
Statin prescriptions at baseline (n, %)				
Statin name				
Atorvastatin	908 (20.3)		951 (22.9)	
Fluvastatin	22 (0.5)		20 (0.5)	
Pravastatin	266 (8.2)		277 (6.7)	
Rosuvastatin	468 (10.4)		421 (10.1)	
Simvastatin	2718 (60.6)		2480 (59.8)	
Statin intensity				
Lower than guideline recommended	1592 (35.5)		1213 (29.2)	
Equal to guideline recommended	1713 (38.2)		1760 (42.4)	
Higher than guideline recommended	1177 (26.3)		1176 (28.3)	

SCORE, Systematic COronary Risk Evaluation.

correct for potential sex differences in adherence, but this is unlikely to change the interpretation of our findings because literature suggests women have poorer adherence than men, which would lead us to underestimate the observed benefit in women.^{3,18}

Our finding that the protective effect of statins was stronger in women compared with men corresponds to findings from previous studies looking at sex differences in statin effectiveness.^{2,10–12} The protective effect of statin was not seen in men after the exclusion of those diagnosed with cardiovascular

disease at baseline. This is in line with findings from a meta-analysis that showed statin use for primary prevention reduced mortality in women but not men, while statin use for secondary prevention did reduce mortality in men.² Literature also suggests low-risk

Table 3 Adjusted HRs with 95% CIs for the risk of all-cause and cardiovascular mortality associated with statin use stratified by sex

	Whole population (n=17262)	Women (n=8981)	Men (n=8281)
All-cause mortality (n _{event} =1035)			
No statin (ref)	1	1	1
Statin	0.76 (0.71 to 0.82)	0.66 (0.58 to 0.74)	0.89 (0.81 to 0.96)
Cardiovascular mortality (n _{event} =270)			
No statin (ref)	1	1	1
Statin	0.72 (0.61 to 0.83)	0.55 (0.39 to 0.71)	0.93 (0.77 to 1.08)

Table 4 Adjusted HRs with 95% CIs for the risk of all-cause and cardiovascular mortality associated with having a statin prescription equal to or higher than guideline-recommended intensity stratified by sex

	Whole population (n=10694)	Women (n=5598)	Men (n=5096)
All-cause mortality (n _{event} =820)			
Low intensity (ref)	1	1	1
Equal/higher intensity	0.94 (0.88 to 1.00)	0.91 (0.82 to 1.00)	0.96 (0.88 to 1.05)
Cardiovascular mortality (n _{event} =224)			
Low intensity (ref)	1	1	1
Equal/higher intensity	0.86 (0.74 to 0.98)	0.88 (0.70 to 1.05)	0.85 (0.69 to 1.01)

patients could gain most benefit from statin treatment.^{2 19} This may explain both why we found such a strong effect of statin treatment in our whole cohort compared with previous trials, and why we found a stronger effect in women compared with men. Our study population had a low median 10-year cardiovascular mortality risk of approximately 3.5%. Women had a lower average mortality risk than men (2.9% vs 4.1%, respectively), and fewer women in both the statin-treated and statin-untreated group had a high mortality risk ($\geq 10\%$) compared with men. Another potential explanation might be that women adhered better to lifestyle recommendations such as dietary advice provided complementary to statin treatment than men, but literature on this topic is scarce.²⁰ In addition, our findings need to be validated. This may be difficult within a trial setting due to the long follow-up time required to accrue sufficient mortality endpoints in these relatively healthy populations. Other observational studies using real-world data may offer valuable insights, provided they are able to properly correct for indication bias. Such studies can also evaluate the generalisability of our findings. Our database only includes Dutch patients located at the unique intersection between primary and secondary care, and we had to exclude the healthiest and least healthy patients because these could not be matched to a counterpart with a sufficiently similar propensity score. It remains unclear how our findings translate to these patient groups.

Women in our dataset more often received low-intensity statins compared with men, confirming previous work.^{3–5} The evidence supporting equal statin prescription strategies for both sexes is growing, but higher rates of side effects in women may be the underlying reason for maintaining this careful approach to statin prescription in women. The topic of statin-related side effects is still debated. Meta-analyses suggesting no differences in adverse events between treatment and placebo arms,^{2 10 21 22} but others argue that statin-related side effects, especially milder ones, are very common and an important challenge in statin treatment.²³ There is also some evidence for sex differences in adverse events,^{2 3 21} but this is not yet conclusive. Our analyses exploring the relationship between statin intensity and long-term prognosis suggested high-intensity regimens only conferred marginal additional benefit. This raises the question whether low-intensity statins could already be sufficiently effective in women, and whether the small additional benefit of high-intensity statins is proportional to the increased risk of potential side effects. These yet unanswered questions underscore the importance of clinical trials providing sex-specific data for both the efficacy of low-intensity versus high-intensity statins and adverse events rates associated with different statin intensities. Dose-finding trials could answer the question which statin dosage best

balances prognosis benefits against possible harms such as side effects.

CONCLUSION

Fewer women received statins than men, and when they did, they were more likely to receive low-intensity regimens. The protective effect of primary prevention statins was stronger in women than men for both all-cause and cardiovascular mortality, but the additional benefit of high-intensity statins was modest and similar for both sexes. Statins seem to be effective regardless of treatment intensity, especially in women.

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Supplementary data

Lower intensity	Equal intensity	Higher intensity
Atorvastatin 5 mg	Atorvastatin 10 mg	Atorvastatin > 10 mg
Fluvastatin any dose		Rosuvastatin > 2.5 mg
Pravastatin any dose		Simvastatin > 40 mg
Rosuvastatin 2.5 mg		
Simvastatin < 40 mg		

Supplementary Table 1 Classification of statin regimens as lower, equal or higher intensity depending on how much they lower low-density lipoprotein cholesterol levels compared to the Dutch guideline recommended 40mg simvastatin (37% lowering)

Variable	Additional sub-classifications
Sex	
Age	
Cardiovascular diagnosis at baseline	Heart failure Coronary heart disease Cardiovascular intervention Cerebrovascular Congenital
Ethnicity	
Personal income	
Height	
Weight	
Body mass index	
Systolic blood pressure	
Diastolic blood pressure	
Complaints at baseline	Chest pain Dyspnoea Fatigue Heart murmur Palpitations Collapse
Number of complaints at baseline	
Comorbidities at baseline	Diabetes mellitus Hypertension Dyslipidaemia
Current smoker	
Total cholesterol	
High-density lipoprotein cholesterol	
Low-density lipoprotein cholesterol	
Creatinine	
Estimated glomerular filtration rate	
Triglycerides	
History of cardiovascular medication	
Cardiovascular medication prescribed at baseline	Blood-pressure lowering Antiplatelet or anticoagulation Lipid-lowering other than statins

	Diabetes mellitus Nitrates Anti-arrhythmic Digoxin
Number of medication prescriptions	
Baseline appointment after 2016	

Supplementary Table 2

List of variables included in the propensity score

	Statin users (n = 17,008)	Statin non-users (n = 30,793)	Statin users after matching (n =8631)	Statin non-users after matching (n =8631)
General characteristics				
Age (years)	62 (11)	55 (13)	61 (11)	61 (13)
Women (n, %)	8171 (48.0)	17,427 (56.6)	4482 (51.9)	4499 (52.1)
Ethnicity (n, %)				
Native Dutch	13,204 (77.6)	23,740 (77.1)	6753 (78.2)	6841 (79.3)
First generation immigrant	1731 (16.1)	4563 (14.8)	1297 (15.0)	1200 (13.9)
Second generation immigrant	1073 (6.3)	2490 (8.1)	581 (6.7)	590 (6.8)
Annual personal income (€)	26,757 [14,647-46,066]	30,404 [15,679-50,823]	27,860 [14,647-48,390]	28,261 [14,956-47,613]
Current smoker (n, %)	6239 (36.7)	12,207 (39.6)	3543 (41.0)	3540 (41.0)
10-year cardiovascular mortality risk (SCORE)				
0-4%	5560 (32.7)	19,736 (64.1)	4757 (55.1)	4562 (52.9)
5-9%	3237 (19.0)	4883 (15.9)	2380 (27.6)	2175 (25.2)
≥10%	2198 (12.9)	3137 (9.9)	1493 (17.3)	1887 (21.9)
Complaints (n, %)				
Number of complaints				
0	6757 (39.7)	11,015 (35.8)	3451 (40.0)	3389 (39.3)
1	9807 (57.7)	18,809 (61.1)	4925 (57.1)	5014 (58.1)
2	416 (2.4)	906 (2.9)	235 (2.7)	216 (2.5)
≥3	28 (0.1)	63 (0.2)	20 (0.2)	12 (0.1)
Chest pain	6650 (39.1)	10,927 (35.5)	3176 (36.8)	3158 (36.6)
Dyspnoea	1562 (9.2)	2275 (7.4)	778 (9.0)	759 (8.8)
Fatigue	531 (3.1)	1060 (3.4)	277 (3.2)	273 (3.2)
Heart murmurs	158 (0.9)	353 (1.1)	77 (0.9)	75 (0.9)
Palpitations	1697 (10.0)	5924 (19.2)	1088 (12.6)	1141 (13.2)
Collapse	130 (0.8)	274 (0.9)	63 (0.7)	76 (0.9)
Co-morbidities (n, %)				
Hypertension	7888 (46.4)	7096 (23.0)	3386 (39.2)	3310 (38.4)
Diabetes mellitus	3252 (19.1)	806 (2.6)	843 (9.8)	686 (7.9)

Dyslipidaemia	6635 (39.0)	2244 (7.3)	2078 (24.1)	1957 (22.7)
Cardiovascular diagnosis at baseline	3348 (19.7)	1427 (4.6)	1061 (12.3)	939 (10.9)
Clinical characteristics				
Body mass index (kg/m ²)	27.5 (4.7)	26.3 (4.5)	27.0 (4.5)	27.0 (4.7)
Systolic blood pressure (mmHg)	148 (21)	140 (21)	146 (21)	146 (22)
Total cholesterol (mmol/L)	5.23 (1.34)	5.61 (0.86)	5.53 (1.29)	5.62 (0.86)
Low-density lipoprotein cholesterol (mmol/L)	2.90 [2.10-3.80]	3.40 [2.90-3.90]	3.30 [2.50-4.20]	3.30 [2.90-3.80]
High-density lipoprotein cholesterol (mmol/L)	1.40 [1.10-1.80]	1.40 [1.10-1.80]	1.40 [1.10-1.80]	1.40 [1.10-1.80]
Triglycerides (mmol/L)	1.60 [1.10-2.40]	1.40 [0.90-2.00]	1.50 [1.00-2.20]	1.50 [1.00-2.20]
Estimated glomerular filtration rate (mL/min/1.73m ²)	81 (27)	88 (28)	82 (27)	82 (28)
Medication prescriptions at baseline other than statins (n,%)				
History of cardiovascular medication use	1706 (10.0)	2409 (7.8)	970 (11.2)	971 (11.3)
Cardiovascular medication prescribed at baseline	13,556 (79.7)	10,418 (33.8)	5798 (67.2)	5807 (67.3)
Number of cardiovascular medications				
0	2566 (15.1)	18,620 (60.5)	2256 (26.1)	2240 (26.0)
1-3	10,488 (61.7)	11,064 (35.9)	5316 (61.6)	5457 (63.2)
4-7	3892 (22.9)	1099 (3.6)	1048 (12.1)	924 (10.7)
8-10	62 (0.4)	10 (0.0)	11 (0.1)	10 (0.1)
Blood pressure lowering medication	12,436 (73.1)	10,768 (35.0)	5388 (62.4)	5352 (62.0)
Antiplatelet or anticoagulant medication	8552 (50.3)	3432 (11.1)	3086 (35.8)	3032 (35.1)
Other lipid-lowering medication	348 (2.0)	267 (0.9)	187 (2.2)	191 (2.2)
Diabetes mellitus medication	3068 (18.0)	604 (2.0)	728 (8.4)	572 (6.6)
Nitrates	3074 (18.0)	604 (2.0)	859 (10.0)	803 (9.3)
Anti-arrhythmic medication	179 (1.1)	334 (1.1)	108 (1.3)	121 (1.4)
Digoxin	128 (0.8)	133 (0.4)	62 (0.7)	65 (0.8)
Statin prescriptions at baseline (n, %)				
Statin name				
Atorvastatin	3790 (22.3)		1859 (21.5)	
Fluvastatin	90 (0.5)		42 (0.5)	

Pravastatin	1241 (7.3)	643 (7.4)
Rosuvastatin	1735 (10.2)	889 (10.3)
Simvastatin	10,152 (59.7)	5198 (60.2)
Statin intensity		
Lower than guideline-recommended	5356 (31.5)	2805 (32.5)
Equal to guideline-recommended	6924 (40.7)	3473 (40.2)
Higher than guideline-recommended	4728 (27.8)	2353 (27.3)

Supplementary Table 3 Baseline characteristics of statin users and non-users before and after propensity score matching

	Low-intensity statin users (n = 5356)	High-intensity statin users (n = 11,652)	Low-intensity statin users after matching (n = 5344)	High intensity statin users after matching (n = 5344)
General characteristics				
Age (years)	63 (11)	62 (10)	64 (11)	63 (10)
Women (n, %)	2861 (53.4)	5310 (45.6)	2850 (53.3)	2732 (51.1)
Ethnicity (n, %)				
Native Dutch	4236 (79.1)	8968 (77.0)	4225 (79.1)	4181 (78.2)
First generation immigrant	784 (14.6)	1947 (16.7)	783 (14.7)	804 (15.0)
Second generation immigrant	336 (6.3)	737 (6.3)	336 (6.3)	359 (6.7)
Annual personal income (€)	24,943 [11,115-43,595]	27,528 [14,940-47,226]	24,968 [14,078-43,619]	25,416 [14,094-44,117]
Current smoker (n, %)	2080 (38.8)	4159 (35.7)	2223 (41.6)	2139 (40.0)
10-year cardiovascular mortality risk (SCORE)				
0-4%	1695 (31.6)	3865 (33.2)	2466 (46.1)	2544 (47.6)
5-9%	1038 (19.4)	2199 (18.9)	1611 (30.1)	1627 (30.4)
≥10%	813 (15.2)	1385 (11.9)	1267 (23.7)	1173 (21.9)
Complaints (n, %)				
Number of complaints				
0	2136 (39.9)	4621 (39.7)	2131 (39.9)	2201 (41.2)
1	3081 (57.5)	6726 (57.7)	3074 (57.5)	3006 (56.2)
2	130 (2.4)	286 (2.5)	130 (2.4)	128 (2.4)
≥3	9 (0.1)	19 (0.1)	9 (0.1)	9 (0.1)
Chest pain	1975 (36.9)	4675 (40.1)	1974 (36.9)	1969 (36.8)
Dyspnoea	554 (10.2)	1018 (8.7)	540 (10.1)	514 (9.6)
Fatigue	162 (3.0)	369 (3.2)	161 (3.0)	158 (2.9)
Heart murmurs	52 (1.0)	106 (0.9)	52 (1.0)	53 (1.0)
Palpitations	583 (10.9)	1114 (9.6)	583 (10.9)	554 (10.4)
Collapse	53 (1.0)	77 (0.7)	52 (1.0)	44 (0.8)
Co-morbidities (n, %)				
Hypertension	2544 (47.5)	5344 (45.9)	2568 (48.1)	2511 (47.0)

Diabetes mellitus	1025 (19.1)	2227 (19.1)	1036 (19.4)	1052 (19.7)
Dyslipidaemia	1952 (36.4)	4683 (40.2)	1972 (36.9)	2016 (37.7)
Cardiovascular diagnosis at baseline	861 (16.1)	2487 (21.3)	861 (16.1)	928 (17.4)
Clinical characteristics				
Body mass index (kg/m ²)	27.3 (4.7)	27.5 (4.6)	27.3 (4.7)	27.4 (4.7)
Systolic blood pressure (mmHg)	148 (21)	147 (21)	148 (21)	148 (22)
Total cholesterol (mmol/L)	5.17 (1.15)	5.26 (1.42)	5.17 (1.14)	5.16 (1.30)
Low-density lipoprotein cholesterol (mmol/L)	2.90 [2.20-3.60]	2.90 [2.00-4.00]	2.90 [2.20-3.70]	2.80 [2.00-3.80]
High-density lipoprotein cholesterol (mmol/L)	1.40 [1.10-1.80]	1.40 [1.10-1.70]	1.40 [1.10-1.80]	1.40 [1.10-1.80]
Triglycerides (mmol/L)	1.60 [1.00-2.30]	1.60 [1.10-2.40]	1.60 [1.10-2.30]	1.60 [1.10-2.30]
Estimated glomerular filtration rate (mL/min/1.73m ²)	79 (27)	83 (28)	78 (27)	79 (27)
Medication prescriptions at baseline other than statins (n,%)				
History of cardiovascular medication use	378 (8.9)	1228 (10.5)	478 (8.9)	500 (9.4)
Cardiovascular medication prescribed at baseline	4303 (80.3)	9253 (79.4)	4292 (80.3)	4268 (79.9)
Number of cardiovascular medications				
0	814 (15.2)	1752 (15.0)	813 (15.2)	820 (15.3)
1-3	3362 (62.8)	7126 (61.2)	3357 (62.8)	3314 (62.0)
4-7	1157 (21.6)	2735 (23.5)	1151 (21.5)	1198 (22.4)
8-10	23 (0.4)	39 (0.3)	23 (0.4)	12 (0.2)
Blood pressure lowering medication	3877 (72.4)	8559 (73.5)	3866 (72.3)	3847 (72.0)
Antiplatelet or anticoagulant medication	2631 (49.1)	5921 (50.8)	2624 (49.1)	2600 (48.7)
Other lipid-lowering medication	80 (1.5)	268 (2.3)	80 (1.5)	100 (1.9)
Diabetes mellitus medication	960 (17.9)	2108 (18.1)	959 (17.9)	980 (18.3)
Nitrates	810 (15.1)	2264 (19.4)	809 (15.1)	824 (15.4)
Anti-arrhythmic medication	59 (1.1)	120 (1.0)	59 (1.1)	54 (1.0)
Digoxin	51 (1.0)	76 (0.7)	47 (0.9)	40 (0.7)
Statin prescriptions at baseline (n, %)				
Statin name				
Atorvastatin	1 (0.0)	3789 (32.5)	1 (0.1)	1722 (32.2)

Fluvastatin	90 (1.7)	0 (0.0)	89 (1.7)	0 (0.0)
Pravastatin	1241 (23.2)	0 (0.0)	1239 (23.2)	0 (0.0)
Rosuvastatin	0 (0.0)	1735 (14.9)	0 (0.0)	788 (14.7)
Simvastatin	4024 (75.1)	6128 (52.6)	4015 (75.1)	2834 (53.0)
Statin intensity				
Lower than guideline-recommended	5356 (100.0)	0 (0.0)	5344 (100.0)	0 (0.0)
Equal to guideline-recommended	0 (0.0)	6924 (59.4)	0 (0.0)	3235 (60.5)
Higher than guideline-recommended	0 (0.0)	4728 (40.6)	0 (0.0)	2109 (39.5)

Supplementary Table 4 Baseline characteristics of low- and high-intensity statin users before and after propensity score matching

	Whole population (n =15,180)	Women (n =7930)	Men (n = 7250)
All-cause mortality			
No statin (ref)	1	1	1
Statin	0.78 (0.72-0.84)	0.68 (0.60-0.77)	0.89 (0.81-0.97)
Cardiovascular mortality			
No statin (ref)	1	1	1
Statin	0.78 (0.66-0.90)	0.58 (0.41-0.75)	1.02 (0.86-1.18)

Supplementary Table 5 Adjusted hazard ratios for the risk of all-cause and cardiovascular mortality associated with statin use stratified by sex in those without a cardiovascular diagnosis at baseline