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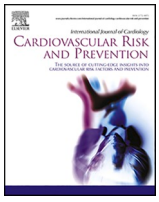

Statins for secondary prevention in women with atherosclerotic vascular disease: A nation-wide analysis of 24,665 women hospitalized for coronary, cerebrovascular or peripheral artery disease

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ABSTRACT

Background: Statin therapy is recommended for secondary prevention of atherosclerotic vascular disease (ASCVD) based on randomized trials, which enrolled mostly men with coronary artery disease (CAD), whereas women and patients with cerebrovascular (CVD) and peripheral artery disease (PAD) were under-represented. We analyzed the effectiveness of statin therapy uptake in a nation-wide cohort of women hospitalized for ASCVD.
Methods: Women hospitalized for CAD, CVD, or PAD, including aortic disease, between 2015 and 2021 were retrospectively identified by linking the national hospital database, medicines reimbursement claims, and national mortality registry. The association of statin uptake within 30 days post-discharge with clinical outcomes (all-cause mortality and cardiovascular hospitalizations) was assessed by Kaplan-Meier curves and Cox proportional hazards regression model with propensity score-derived inverse probability of treatment weights and a 30-day landmark period.
Results: We included 24,665 women with ASCVD – 14,419 with CAD, 5,427 with CVD, and 4,819 with PAD. Overall, the median age was 73 (64–81) years. The rates of statin uptake were 50 % for women with CAD, 60 % for CVD and 28 % for PAD. Statin therapy uptake was associated with a reduction in all-cause mortality and cardiovascular hospitalizations across all three major types of ASCVD: hazard ratio (HR) 0.88, 95 % confidence interval (CI) 0.83–0.93, $p = 0.001$ for CAD, HR 0.87, 95 % CI 0.80–0.94, $p = 0.006$ for PAD, and HR 0.72, 95 % CI 0.66–0.78, $p < 0.001$ for CVD.
Conclusion: Statin therapy is associated with reduced all-cause mortality and cardiovascular hospital readmissions in women with all major types of ASCVD.

1. Introduction

Cardiovascular (CV) diseases are the leading cause of morbidity and mortality in women [1]. Atherosclerotic vascular disease (ASCVD) represents the single most important subset of CV diseases — both in terms of ASCVD-driven events, such as myocardial infarction and stroke [2], and in terms of ASCVD representing a major target for risk management and disease-modifying therapies [3,4]. Therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors – i.e., statins — represents the cornerstone of lipid-lowering and—by extension—risk management in ASCVD [5]. Several randomized trials have established the efficacy of statin therapy for secondary prevention of ASCVD, especially in patients with coronary artery disease (CAD); selected trial populations (mostly men with CAD) and rigorous intervention protocols may, however, challenge the generalizability of statin effectiveness, especially in under-represented populations, such as

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women and/or patients with non-coronary ASCVD, namely peripheral artery disease (PAD) and cerebrovascular disease (CVD) [6–10]. Dedicated randomized controlled trials of statin therapy in women with ASCVD are lacking and very unlikely to be performed in the future. Women with ASCVD — and especially with PAD — thus remain under-represented and under-studied in evidence-generating trials and observational studies. Our goal was to assess the comparative effectiveness of statin therapy uptake in women across all three major types of atherosclerotic vascular disease – CAD, CVD and PAD.

2. Methods

This was an observational longitudinal study with retrospective design. The study protocol was approved by the Medical Ethics Committee of the Republic of Slovenia (KME No. 0120–223/2021/7, approval date September 8th, 2021), and the analysis was conducted in compliance with Slovenian and European Union regulations and legislative frameworks. The study was performed on registry-based data, so individual subjects' informed consent was not required.

Data were obtained by merging the national Healthcare Insurance Institute databases for hospital management and medication reimbursement claims, and the national mortality registry by using unique patient specific identifiers. The Healthcare Insurance Institute provides mandatory universal healthcare coverage for all 2.1 million residents in Slovenia and has been electronically collecting data on hospital episodes (disease-related group payment) and medication reimbursement (e-prescriptions) since 2015. Patients without National Healthcare Insurance coverage (e.g., tourists and non-residents) could not be included. After linkage (DG), datasets were de-identified for research analysis purposes and restricted to the core research group (BJ, PDB).

Women hospitalized in Slovenia between January 1st, 2015 and June 30th, 2021 for either CAD, CVD, PAD or aortic disease were included (Fig. 1; disease specific International Classification of Disease 10 (ICD-10) codes are listed in Supplement Table S9). We excluded women with high in-hospital mortality risk unstable aortic disease (i.e., aortic dissection and/or rupture) and primarily non-ASCVD related CVD (i.e., embolic CVD/stroke).

In addition to the primary diagnosis of CAD, PAD or CVD (index hospitalization), we collected the following information/co-variates: ASCVD type (i.e., for CAD: ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina, other myocardial infarction, chronic coronary syndromes; for PAD: intermittent claudication, chronic limb-threatening ischemia, aortic aneurysm, other PAD; for CVD: thrombotic CVD event, carotid atherosclerosis, other non-embolic CVD), patients' age, recorded co-morbidities (i.e., diabetes mellitus, arterial hypertension, presence of ASCVD other than index diagnosis (e.g., presence of PAD and/or CVD in patients with CAD), heart failure, chronic obstructive pulmonary disease (COPD) and/or asthma, dementia, depression, chronic kidney disease, cancer), revascularization procedures performed, total number of diagnoses, total number of procedures during index hospitalization, length of stay, socioeconomic status (obtained using postal code information for patients' residence, and categorized into quartiles). Medication uptake were adjudicated from e-prescription reimbursement claims within 30 days from discharge based on ATC codes for statins and antithrombotic therapy (i.e., acetyl-salicylic acid, P2Y12 antagonists, and/or anticoagulant therapy, Table S9).

For the purpose of the study, the analytic cohort was divided in three groups according to index diagnosis – CAD, PAD (including aortic diseases) or CVD – and further subdivided according to statin therapy uptake within 30 days from discharge. The primary outcome of interest was time to a composite endpoint of death from any cause and cardiovascular hospitalization – defined as hospitalization for CAD, heart failure, CVD, PAD or aortic disease. Secondary outcomes included time to death from any cause and time to first cardiovascular hospitalization. Other outcomes of interest were the proportion of female patients with

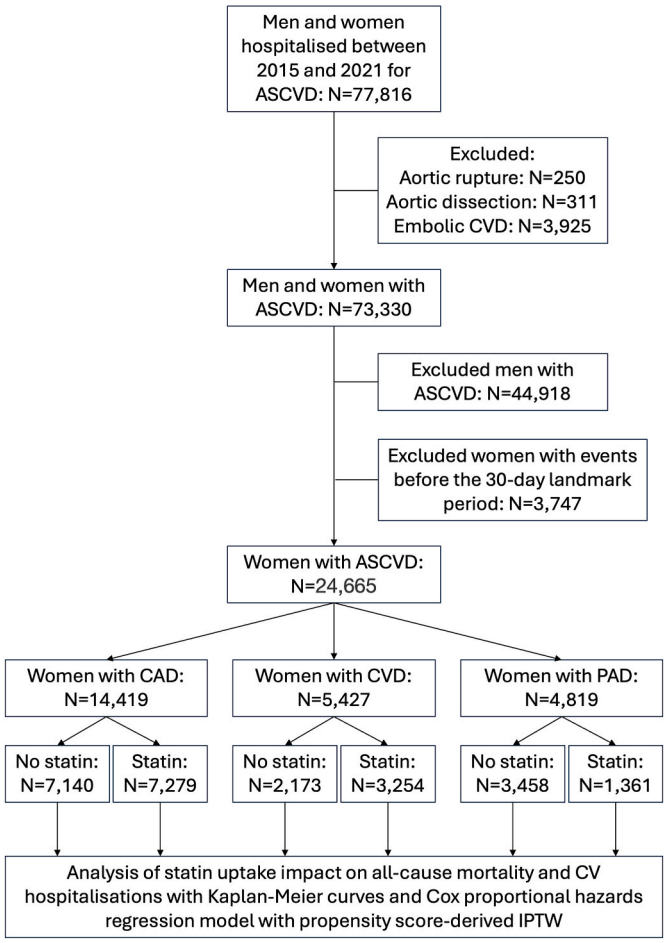

Fig. 1. Study outline.
Abbreviations: ASCVD – atherosclerotic vascular disease, CAD – coronary artery disease, CV – cardiovascular, CVD – cerebrovascular disease, IPTW - inverse probability of treatment weights, PAD – peripheral artery disease.

atherosclerotic vascular disease with statin therapy and predictors of statin therapy uptake.

Continuous variables are presented with median and interquartile range (IQR), nominal variables are presented with number and percentage. Pearson's Chi-squared and Kruskal-Wallis rank sum tests were used for comparison of baseline patient characteristics between different types of ASCVD, whereas Pearson's Chi-squared and Wilcoxon rank sum tests were used for comparison of baseline patient characteristics between women with and without statin therapy. Predictors of statin therapy uptake were assessed using multivariate logistic regression.

The association of statin therapy uptake with clinical outcomes (all-cause mortality and/or cardiovascular hospitalizations) was assessed by survival analysis with inverse probability of treatment weights, calculated using propensity scores. Propensity scores (i.e., the probability of statin treatment assignment) were calculated separately for CAD, PAD and CVD with baseline covariates (ASCVD type, age, co-morbidities, revascularization, total number of diagnoses, total number of procedures, antithrombotic therapy and PPI therapy) using covariate-balancing propensity score [11]. Weights (the inverse probability of receiving treatment that was indeed received) were calculated with average treatment effect (ATE) as target estimand. Covariate balancing diagnostics was assessed using standardized mean differences (SMDs) and Kolmogorov-Smirnov statistics. After weights were applied, baseline characteristics of the generated pseudo-populations were compared with the Chi-squared test with Rao and Scott's second-order correction and Wilcoxon rank-sum test. A landmark period of 30-days

post-discharge was used to address survival bias.

Treatment effects were assessed by fitting a 'double-robust' Cox proportional hazard regression model (i.e., weighted for inverse probability of treatment and adjusted for all covariates, with robust standard errors estimation) and by adjusted Kaplan-Meyer curves [12]. Survival time (in days) was defined by a minimum (landmark) period of 30 days. Proportional hazards assumption was assessed by Schoenfeld residuals.

3. Results

Between 2015 and 2021, 77,816 patients were hospitalized in Slovenia for ASCVD. We excluded 250 patients because the presenting diagnosis was aortic rupture, 311 because of aortic dissection, and 3,925 because of embolic CVD. Of the remaining 73,330 patients, 28,412 (38.7 %) were women. After excluding 3,747 women with events before the 30-day landmark period, a total of 24,665 women with ASCVD were included in the analysis — 14,419 with CAD, 4,819 with PAD, and 5,427 with CVD (Fig. 1).

Overall median age was 73 (IQR 64–81) years: 70 (IQR 62–78) years for women with CAD, 76 (IQR 67–83) years for women with PAD, and 77 (IQR 69–84) years for women with CVD ($p < 0.0001$). The rate of statin therapy uptake was 48 % overall, and 50 %, 28 %, and 60 % for women with CAD, PAD and CVD, respectively ($p < 0.0001$). Overall, 20 % of women had diabetes mellitus, 53 % arterial hypertension, 13 % other concomitant ASCVD, 10 % heart failure, 4.3 % dementia, 5.9 % chronic kidney disease and 11 % depression; the differences were expectedly significant across ASCVD type (Table 1) and statin uptake (Supplement Table S1).

Regarding predictors of statin therapy uptake at 30 days from discharge (Supplement Table S8), women with CVD were more likely prescribed and dispensed with a statin than women with CAD (odds ratio (OR) 1.56, 95 % CI 1.42–1.72, $p < 0.001$), whereas PAD was associated with a lower likelihood of statin therapy uptake (OR 0.55, 95 % CI 0.51–0.60, $p < 0.001$). With respect to comorbidities, statin therapy uptake was more likely in women with arterial hypertension (OR 1.32, 95 % CI 1.23–1.42, $p < 0.001$), other concomitant ASCVD (OR 1.48, 95 % CI 1.35–1.62, $p < 0.001$) or depression (OR 1.29, 95 % CI 1.17–1.42, $p < 0.001$), and also in those, who were receiving other key preventive medication, such as acetylsalicylic acid (OR 4.69, 95 % CI 4.40–5.00, $p < 0.001$), P2Y12 antagonist (OR 2.15, 95 % CI 2.00–2.31, $p < 0.001$) or anticoagulation (OR 1.63, 95 % CI 1.48–1.80, $p < 0.001$). Conversely, statin therapy uptake was lower in women with heart failure (OR 0.85, 95 % CI 0.76–0.95, $p = 0.003$), atrial fibrillation (OR 0.77, 95 % CI 0.69–0.85, $p < 0.001$), chronic obstructive pulmonary disease/asthma (OR 0.88, 95 % CI 0.78–0.98, $p = 0.024$), dementia (OR 0.59, 95 % CI 0.51–0.69, $p < 0.001$), chronic kidney disease (OR 0.63, 95 % CI 0.55–0.73, $p < 0.001$) and cancer (OR 0.81, 95 % CI 0.67–0.97, $p = 0.025$).

Statin therapy was associated with a reduction in the composite outcome of all-cause mortality and CV hospitalizations by 12 % in women with CAD (hazard ratio (HR) 0.88, 95 % confidence interval (CI) 0.83–0.93, $p = 0.001$), 13 % in women with PAD (HR 0.87, 95 % CI 0.80–0.94, $p = 0.006$), and 28 % in women with CVD (HR 0.72, 95 % CI 0.66–0.78, $p < 0.001$) (Fig. 2 , Supplement Tables S3, S5, S7). With regard to secondary outcomes, statin therapy was associated with a reduction of mortality for any cause in women with all three major types of atherosclerotic vascular disease (HR 0.79, 95 % CI 0.72–0.86, $p < 0.001$ for women with CAD; HR 0.72, 95 % CI 0.64–0.81, $p < 0.001$ for women with PAD; HR 0.67, 95 % CI 0.61–0.73, $p < 0.001$ for women with CVD). Conversely, statin therapy was associated with a reduction of cardiovascular hospitalizations only in women with CVD (HR 0.80, 95 % CI 0.70–0.91, $p = 0.004$); the effectiveness of statin therapy uptake on cardiovascular hospitalizations in women with CAD or PAD was not significant. Outcomes with respect to the presence of co-morbidities and prescription of other key secondary preventive medication are presented in the Supplementary material (Tables S3, S5, S7).

4. Discussion

Our study represents one of the largest analyses of the effectiveness of statin therapy uptake in women with different types of ASCVD — CAD, PAD or CVD. Across all major types of ASCVD, statin therapy uptake was associated with a significant reduction of all-cause mortality and CV hospitalizations. Overall, our study complements the existing evidence of risk reduction with statin therapy in patients with ASCVD, providing robust real-life observational evidence on statin therapy effectiveness in populations that have traditionally been underrepresented in statin trials, namely women with CAD and CVD, but especially PAD.

The main finding of our study is a significant reduction in all-cause

Table 1
Baseline patient characteristics of women with atherosclerotic vascular disease.

Characteristic	Overall, N = 24,665[a]	CAD, N = 14,419[a]	CVD, N = 5,427[a]	PAD, N = 4,819[a]	p-value[b]
Age (years)	73 (64–81)	70 (62–78)	77 (69–84)	76 (67–83)	<0.0001
Diabetes Mellitus	5,006 (20 %)	2,926 (20 %)	1,175 (22 %)	905 (19 %)	0.0015
Arterial Hypertension	13,151 (53 %)	7,653 (53 %)	3,634 (67 %)	1,864 (39 %)	<0.0001
Other concomitant ASCVD	3,200 (13 %)	2,906 (20 %)	158 (2.9 %)	136 (2.8 %)	<0.0001
Heart Failure	2,518 (10 %)	1,859 (13 %)	320 (5.9 %)	339 (7.0 %)	<0.0001
Atrial Fibrillation	3,539 (14 %)	1,985 (14 %)	1,069 (20 %)	485 (10 %)	<0.0001
COPD/Asthma	1,907 (7.7 %)	1,230 (8.5 %)	353 (6.5 %)	324 (6.7 %)	<0.0001
Dementia	1,065 (4.3 %)	286 (2.0 %)	596 (11 %)	183 (3.8 %)	<0.0001
Depression	2,719 (11 %)	1,245 (8.6 %)	1,098 (20 %)	376 (7.8 %)	<0.0001
Chronic Kidney Disease	1,467 (5.9 %)	869 (6.0 %)	252 (4.6 %)	346 (7.2 %)	<0.0001
Cancer	633 (2.6 %)	278 (1.9 %)	245 (4.5 %)	110 (2.3 %)	<0.0001
Number of Diagnoses	3 (1–5)	3 (1–5)	4 (3–6)	2 (1–4)	<0.0001
Number of Procedures	7 (2–14)	7 (1–14)	8 (5–14)	7 (2–12)	<0.0001
Revascularization	16,716 (68 %)	12,574 (87 %)	1,243 (23 %)	2,899 (60 %)	<0.0001
Socio-Economic Status	1.04 (0.92–1.19)	1.08 (0.94–1.20)	1.01 (0.88–1.16)	1.02 (0.87–1.18)	<0.0001
Statin therapy	11,894 (48 %)	7,279 (50 %)	3,254 (60 %)	1,361 (28 %)	<0.0001
Acetylsalicylic Acid	12,249 (50 %)	7,224 (50 %)	3,356 (62 %)	1,669 (35 %)	<0.0001
P2Y12 Antagonist	7,806 (32 %)	5,644 (39 %)	590 (11 %)	1,572 (33 %)	<0.0001
Anticoagulation	3,824 (16 %)	1,504 (10 %)	1,446 (27 %)	874 (18 %)	<0.0001
Proton Pump Inhibitor	9,799 (40 %)	6,143 (43 %)	2,467 (45 %)	1,189 (25 %)	<0.0001

Abbreviations: ASCVD – atherosclerotic vascular disease, CAD – coronary artery disease, COPD – chronic obstructive pulmonary disease, CVD – cerebrovascular disease, PAD – peripheral artery disease.

[a] – Median (interquartile range); number (%).

[b] – Kruskal-Wallis rank sum test; Pearson's Chi-squared test.

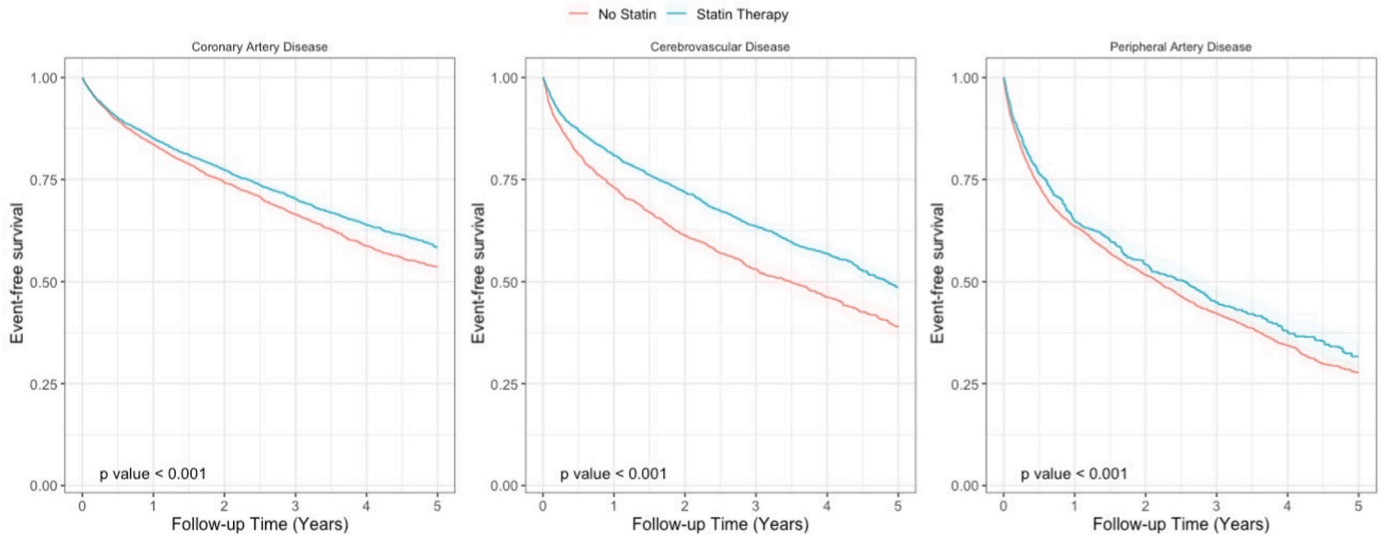

Fig. 2. Event-free survival Kaplan-Meier curves for women with coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD) with respect to statin therapy uptake at 30 days from discharge.

mortality and CV hospitalizations with statin therapy in women with either CAD, PAD or CVD. Our study provides a focused analysis of statin therapy effectiveness in a nation-wide unselected general cohort of women with all three major types of ASCVD, whereas randomized trials of secondary prevention with statin therapy have predominantly included men and patients with CAD. A large meta-analysis of 174,149 participants in primary and secondary prevention (the latter defined by established CAD), of whom 46,675 (27 %) were women, concluded that statin therapy reduces all-cause mortality and major vascular events in both women and men with similar efficacy [13]. Conversely, data on statin therapy efficacy in women with PAD and CVD are limited.

In patients with PAD, no randomized trial has specifically addressed the efficacy of statin therapy in either women or men to date. The Heart Protection Study (HPS) included 6,748 patients with PAD, of whom 26 % were women, and remains one of the largest randomized (subgroup) assessments of reduced vascular outcomes with statin therapy in PAD but did not report on the specific efficacy of statin therapy in women [14]. Conversely, a subgroup analysis of a large Veterans Affairs observational study in PAD patients reported similar effectiveness of high-intensity statin therapy on all-cause mortality reductions in women and men but included a disproportionately small population of women (1,799 vs. 88,459 men) yielding large confidence intervals and non-significance for the effectiveness for low-to moderate-intensity statin therapy [15]. Our results therefore provide much needed, albeit propensity-score adjusted observational evidence on the effectiveness of statin therapy in an unselected nation-wide cohort of 4,819 women with PAD.

In patients with CVD, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial assessed the efficacy of atorvastatin 80 mg in patients with a recent cerebrovascular event, of whom 40 % were women [16]. A dedicated secondary analysis in women showed that statin therapy was associated with a reduced risk for cerebrovascular events, but the results for most other reported outcomes, including all-cause mortality, were not significant [17]. The subgroup analysis, however, included 1,908 women with a mean age of 63 years, reflecting a selected trial population [17]. Conversely, our study included 5,427 women with a median age of 77 years, which represents a higher risk real-life CVD population, wherein vascular risk and absolute risk reductions (i.e., statin effectiveness) expectedly increase with age [18].

Despite its effectiveness, statin therapy uptake remains suboptimal in women with ASCVD in general, and with PAD in particular. Besides primary ASCVD subtype, increasing age, non-cardiovascular co-morbidities (e.g., dementia, chronic kidney disease, and cancer), and lower socio-economic status predicted lower statin uptake in our population of women with ASCVD (Supplement Table S8). While the uptake of statin therapy in women with CAD and CVD in our study was suboptimal (50 % and 60 %, respectively), the uptake was especially meagre in women with PAD — only 28 % women with PAD were prescribed and dispensed a statin within 30 days of hospital discharge. This is in line with previous reports that lipid-lowering medication uptake in PAD is lower than in other forms of ASCVD, which has been attributed to a variety of factors, such lack of awareness, underestimation of risk, specific sub-specialist management setting (surgical vs. medical), and advanced disease at the time of diagnosis [15,19–21].

Our analysis represents a nation-wide population of women hospitalized for ASCVD and provides valuable insight into the real-life effectiveness of statin therapy uptake in women with either CAD, PAD or CVD. However, due to its retrospective observational design based on administrative healthcare datasets, there are several inherent limitations. Firstly, definitions were based on administrative entries (e.g., hospital coding) and propensity score adjustment was limited to recorded covariates, whereas other determinants of CV health could not be adjusted for. This particularly applies to smoking, obesity and elevated levels of atherogenic lipoproteins – all of which are known modifiable risk factors for ASCVD [22]. As a risk factor for ASCVD, smoking is associated with greater detrimental effects in women than men [23,24]. Additionally, women have been shown to be disproportionally affected by lifestyle and social risk factors, as well as adverse metabolic changes after menopause [3]. As these contributors to ASCVD outcomes could not be accounted for, this presents a major limitation of this study.

Secondly, statin therapy was adjudicated based on 30 days post-discharge uptake, whereas long-term non-adherence represents an important determinant of CV risk, which may have impacted recorded outcomes. Overall, the low uptake of statin therapy in women — and especially in women with PAD — was consistent with findings from other studies based on real-life cohorts using administrative data [25]. Significant predictors of lower statin therapy uptake were PAD, increasing age, certain non-cardiovascular co-morbidities, and lower socio-economic status. To mitigate potential treatment selection bias, outcomes were assessed using Kaplan-Meier curves and a “double--robust” Cox proportional hazards regression model with propensity score-derived inverse probability of treatment weights. Nonetheless, the observational design of our analysis provides evidence on the association — not necessarily causation — between statin therapy uptake and

risk reduction for future cardiovascular events in women with ASCVD.

Thirdly, outcomes were limited to all-cause mortality and CV hospital readmissions, while other important outcomes (such as disease-specific mortality or patient-reported outcomes and measures) could not be addressed.

5. Conclusion

Statin therapy uptake is associated with a significant reduction of all-cause mortality and cardiovascular hospitalizations in women with CAD, PAD and CVD. Efforts should be made to improve the rates of statin therapy in women with ASCVD, particularly PAD.

CRediT authorship contribution statement

Gregor Verček: Writing – original draft, Methodology, Investigation, Conceptualization. **Tjaša Furlan:** Methodology, Investigation, Conceptualization. **Dalibor Gavrić:** Methodology, Data curation. **Mitja Lainščak:** Methodology, Investigation. **Jerneja Farkaš Lainščak:** Methodology, Investigation. **Irena Ograjenšek:** Methodology, Investigation. **Petra Došenović Bonča:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Borut Jug:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2025.200415.

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