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Sex-based utilization of guideline recommended statin therapy and cardiovascular disease outcomes: Data from a multisite healthcare network primary prevention cohort

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ABSTRACT

Background: In the US, women have similar cardiovascular death rates as men. However, less is known about sex differences in statin use for primary prevention and associated atherosclerotic cardiovascular disease (ASCVD) outcomes.

Methods: Statin prescriptions using electronic health records were examined in patients without ASCVD (myocardial infarction (MI), revascularization or ischemic stroke) between 2013 and 2019. Guideline-directed statin intensity (GDSI) at index (at least moderate intensity, defined per pooled-cohort equation) and follow-up visits were compared between sexes across ASCVD risk groups, defined by the pooled-cohort equation. Cox regression hazard ratios were calculated for statin use and outcomes (myocardial infarction, stroke/transient ischemic attack (TIA), and all-cause mortality) stratified by sex. Interaction terms (statin and sex) were applied.

Results: Among 282,298 patients, (mean age ~ 50 years) 17.1 % women and 19.5 % men were prescribed any statin at index visit. Time to GDSI was similar between sexes, but the proportion of high-risk women on GDSI at follow-up were lower compared to high-risk men (2-years: 27.7 vs 32.0 %, and 5-years: 47.2 vs 55.2 %, $p < 0.05$). When compared to GDSI, no statin use was associated with higher risk of MI and ischemic stroke/TIA among both sexes. High-risk women on GDSI had a lower risk of mortality (HR=1.39 [1.22–1.59]) vs. men (HR=1.67 [1.50–1.86]) of similar risk (p value interaction=0.004).

Conclusion: In a large contemporary healthcare system, there was underutilization of statins across both sexes in primary prevention. High-risk women were less likely to remain on GDSI compared to high-risk men. GDSI significantly improved the survival in both sexes regardless of ASCVD risk group. Future strategies to ensure continued use of GDSI, specifically among women, should be explored.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the number one cause of cardiovascular death in both women and men in the United States [1]. Since the 1990s, there has been a steady decline in the number of cardiovascular deaths [1]. This may be, in part, due to improved care of patients with acute coronary syndrome as well as to greater effort at primary and secondary prevention of ASCVD [2]. An integral part of ASCVD prevention is the use of statin therapy to treat hyperlipidemia [2–5]. However, underutilization of statin therapy

Abbreviations: atherosclerotic cardiovascular disease, (ASCVD); American Heart Association, (AHA); electronic health record, (EHR); guideline-directed statin intensity, (GDSI); myocardial infarction, (MI).

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remains prevalent in everyday practice leading to increased ASCVD and mortality [6].

The decline in cardiovascular disease death over the past several decades has, not been equally shared between women and men, and since 1984 ASCVD mortality had been higher in women [7]..

Not until recently were total cardiovascular deaths similar among women and men (for women n = 441,525 (46 %) and for men n = 487,188 (45 %) in the 2020), with recent upward trend in cardiovascular death for both men and women

As detailed by two recent American Heart Association (AHA) Scientific Statements, there are distinct differences in the pathophysiology, presentation, and outcome of cardiovascular disease between women and men [7,8]. Women also have sex-specific risk factors including use of polycystic ovary syndrome, preeclampsia, gestational diabetes, premature menopause, postmenopausal hormone therapy, as well as greater prevalence of implicated autoimmune diseases [8]. Several of these risk factors have been incorporated in the American College of Cardiology/American Heart Association (ACC/AHA) 2018 Cholesterol Management Guideline as ASCVD risk enhancers [9].

In spite of sex-specific risk enhancers, the use of statins have been shown to be equally effective and safe in women and men, resulting in similar reductions in coronary events, coronary revascularization, and stroke [10]. Nevertheless, several prior studies have shown that women with established ASCVD are less likely to be on statins, to stay adherent to statins, and to achieve low-density lipoprotein (LDL) cholesterol goals while on statins. This likely contributes to the difference in decline of cardiovascular disease between sexes [11–15]. Data regarding sex-differences across longitudinal follow-up with statin use in primary prevention and its relationship to outcomes has not prior been reported.

In this study, we assessed whether sex-based differences exist in statin utilization for primary prevention across the ACC/AHA risk-based categories in a large health care network at the University of Pittsburgh Medical Center (UPMC) across longitudinal follow-up. Using electronic health record (EHR) data, we assessed the effects of statin use and guideline-directed statin intensity (GDSI) and the association with ASVCD outcomes (myocardial infarction (MI), stroke, and mortality) in men and women.

2. Methods

Detailed description of the methods and definitions used to create primary prevention cohort from the mutual EMR across our healthcare system have been published previously [6]. Briefly, the primary prevention cohort consisted of men and women ages 20 to 79 years. Participants were evaluated in at least two health care interactions between January 2013 and December 2017 in the University of Pittsburgh Medical Center (UPMC) health care system, a large multihospital network based in Pittsburgh, PA. All included patients had at least one lipid profile drawn within 180 days of the first interaction. Data was collected via review of the patients' EHR records. Exclusion criteria included prior coronary artery disease (ICD-9: angina, myocardial infarction, revascularization, and ischemic cardiomyopathy), cerebrovascular disease or stroke (ICD-9 and ICD-10: transient ischemic stroke, ischemic stroke, and peripheral artery disease), history of rhabdomyolysis, and being in a skilled nursing facility or hospice. A total of 2348,822 patients were evaluated in the UPMC health care system during the study period, and 282,298 patients (12 %) met criteria for the study.

Eligible patients in this primary prevention cohort[6] were divided at their index visit based on their biologic sex, pooled-cohort equations estimated 10-year ASCVD risk (low: <5 %, borderline: 5 %−7.4 %, intermediate: 7.5 %−19.9 %, and high: ≥20 %), [16] and statin prescription. Guideline-directed statin intensity (GDSI) was as defined by the 2013 and 2018 ACC/AHA cholesterol guidelines [9,17]. Specifically, GDSI was defined as being on at least moderate intensity statin for intermediate risk patients and being on high intensity statin for high-risk patients. Cardiovascular risk was defined by the pooled-cohort equation. Less than GDSI (<GDSI) was defined as statin use of lower intensity than appropriate by cardiovascular risk, similarly, defined by the pooled-cohort equation [9,17]. Statin intensity was further defined as low (simvastatin 10 mg, lovastatin 20 mg, fluvastatin 20 and 40 mg), moderate (atorvastatin 10 and 20 mg, rosuvastatin 5 and 10 mg, simvastatin 20 and 40 mg, lovastatin 40 and 80 mg), or high (atorvastatin 40 and 80 mg, rosuvastatin 20 and 40 mg). Of note, patients on pravastatin represented less than 0.001 % of the cohort, so they were excluded from the study. Time to GDSI was defined as years from first health care encounter to achieving GDSI.

The incident ASCVD events assessed were ischemic stroke/transient ischemic attack (TIA), myocardial infarction (MI), and mortality. Events until March 2020 were included. All outcomes were surveyed and included as defined per the ICD-9 and ICD-10 coding in the EHR. Mortality was assessed using the United States Social Security Death Index. Our health care system is exempt from the 3-year delay period by the Social Security Administration.

2.1. Statistical analysis

Baseline descriptive statistics of the study sample for each continuous variable and frequency tables for each categorical variable were initially analyzed to detect outliers and missing values. Missing data were uncommon and, where applicable, replaced by the simple mean imputation across the risk groups. Descriptive characteristics were normally distributed and were presented as mean and standard deviation (SD) for continuous variables, and frequencies and proportions for categorical variables. The difference of means across the ASCVD groups was assessed by 1-way ANOVA, while the difference of frequencies was compared using the $\chi 2$ test. All analyses were completed using SAS version 9.4 software (SAS Institute). Statistical significance was set at $\alpha = 0.05$. All tests of statistical significance were 2-tailed. SAS was used to calculate mean time to GDSI amongst each group. The primary and composite outcomes incident rates (IRs) and mortality were calculated as event rates per 1000 person-years across risk categories stratified by statin utilization. The 95 % CIs were estimated using a generalized linear model with the Poisson distribution. Further, Cox proportional hazards regression models were used to compare the hazard ratios of primary outcomes among each risk category and between use of GDSI versus no statin use before the first event. The survival curves for cardiovascular outcomes and mortality comparing the statin therapy groups were plotted after Cox proportional hazards regression adjusted for mean values of age, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic blood pressure at index visit, and reference groups of categorical variables (white self-identified race, men, current smoker and no diabetes). The GDSI variable was treated as a time invariant, and classification of GDSI was based on the statin status before each outcome. Individuals without the primary outcome (composite ASCVD events and mortality) were censored between 2 and 7 years after baseline in the corresponding analysis. The time to GDSI across the ASCVD risk groups was estimated using Kaplan-Meier method.

3. Results

3.1. Baseline demographics

The baseline characteristics for women (n = 159,100) and men (n = 123,198) (mean age ~ 50 years) are shown in Table 1. In general, fewer women were noted to have underlying diabetes (9.6 vs. 11.0 %), have hypertension (22.5 vs 27.8 %), and be smokers (22.4 vs 26.0 %) compared to men. However, women were marginally older (50.6 vs 49.5 years) and more likely to self-identify as Black (7.7 vs 6.7). The LDL-c (114 ± 32.4 mg/dL in women, 115 ± 31.5 mg/dL in men) and total cholesterol (196 ± 36.9 mg/dL in women and 191 ± 36.1 mg/dL in

Table 1
Sex differences in baseline demographics.

Baseline characteristics	Men (n = 123,198)	Women (n = 159,100)	P-value
Age	49.5 ± 13.7	50.6 ± 14.4	<0.001
Age ≥ 75	2765 (2.2)	5349 (3.4)	<0.001
Race*			<0.001
White	108,800 (88.3)	140,802 (88.5)	
Black	8236 (6.7)	12,241 (7.7)	
Other	6162 (5.0)	6057 (3.8)	
BMI	30.4 ± 6.32	30.3 ± 7.80	0.02
Current smoking	31,957 (26.0)	35,553 (22.4)	<0.001
Diabetes	13,545 (11.0)	15,262 (9.6)	<0.001
ELIX comorbidity score	0.45 ± 3.46	0.14 ± 3.65	<0.001
Index Visit			
Heart rate	76.3 ± 11.7	77.4 ± 11.6	<0.001
Systolic BP	129 ± 15.6	125 ± 16.1	<0.001
Hypertension treated	34,182 (27.8)	35,788 (22.5)	<0.001
Aspirin	22,218 (18.3)	22,620 (14.2)	<0.001
Statin	24,027 (19.5)	27,231 (17.1)	<0.001
Ezetimibe	1173 (1.0)	1494 (0.9)	0.72
PCSK-9 inhibitor	3 (<0.1)	8 (<0.1)	0.27
Lipid profile			
Cholesterol	191 ± 36.1	196 ± 36.9	<0.001
HDL-c	46.6 ± 13.1	57.0 ± 15.6	<0.001
LDL-c	115 ± 31.5	114 ± 32.4	<0.001
ASCVD risk			<0.001
Low	56,511 (45.9)	106,667 (67.0)	
Borderline	13,981 (11.4)	15,153 (9.5)	
Intermediate	36,602 (29.7)	26,697 (16.8)	
High	16,104 (13.1)	10,583 (6.7)	
Clinician specialty			<0.001
Cardiology	6667 (5.4)	8065 (5.1)	
Primary care	116,531 (94.6)	151,035 (94.9)	

Data are presented as n (%) or mean ± standard deviation where appropriate.
* Race is self-reported. *Abbreviations*: ASA: aspirin, ASCVD: atherosclerotic cardiovascular disease, BMI: body mass index, BP: blood pressure, ELIX: Elixhauser, PCSK-9: Proprotein convertase subtilisin/kexin type 9 serine protease, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol.

men) levels were comparable between sexes. A lower percentage of women were prescribed any statin compared to men (17.1 vs. 19.5 %) overall.

When stratified by the ASCVD 10-year risk score, there were more women in the low-risk group compared to men (67.0 vs 45.9 %) (Table 1). Conversely, there were more men in the borderline (11.4 vs 9.5 %), intermediate (29.7 vs 16.8 %), and high (13.1 vs 6.7 %) risk groups compared to women.

Although there were less women in the high-risk group, the percentage on any statin as well as GDSI was greater at index visit as compared to men (high risk, any statin: 45.6 vs 41.6 %, high risk, GDSI: 41.7 vs 38.8 %; Table 2). However, at follow-up visits, the percentage of high-risk women on GDSI was significantly lower compared to men (high risk GDSI: 63.8 vs. 66.9 %). A total of 5654 individuals within our database had severe LDL-c elevations (LDL-c > 190 mg/dl), among which 58.7 % (3319) were women and 41.3 % (2335) were men. Among women, only 21 % (697) were on any statin.

3.2. Statin use by sex and time to GDSI

Evaluating the patients over time, the mean times to GDSI for women and men in both the intermediate and high-risk groups were not different (Table 3). However, based on the Kaplan-Meier probability estimates, high-risk women were persistently less likely to be on GDSI compared to high risk-men both at 2- and 5-years follow-ups (2-years: 27.7 vs 32.0 %, and 5-years: 47.2 vs 55.2 %, $p < 0.05$) (Supplemental Table 1) (Fig. 1).

3.3. Hazard ratio of event by sex and statin use

Over a median follow-up of 6 years, no statin use was associated with a significantly higher risk of adverse cardiovascular events as compared to GDSI (MI: HR_{Women} = 1.32 [1.07–1.62] vs HR_{Men} = 1.46 [1.25–1.72]), stroke/TIA: (HR_{Women} = 1.61 [1.31–1.98] vs HR_{Men} = 1.63 [1.36–1.96]) amongst both high-risk men and women. Further, GDSI use (compared to no GDSI) in high-risk women had lower incident all-cause mortality (HR_{Women} = 1.39 [1.22–1.59]) compared with men (HR_{Men} = 1.67 [1.50–1.86]) (*p-value interaction = 0.004*). (Table 4). Similarly, in the intermediate risk group, patients of both sexes on no statin had a higher risk of MI, stroke, and mortality compared to those on GDSI.

Table 3
Time to guideline directed statin intensity initiation during follow-up.

ASCVD risk	Statin	Time to GDSI (months)		
		Men	Women	P value
Intermediate	Moderate	20.7 ± 20.8	20.8 ± 20.4	0.04*
	High	27.3 ± 21.7	26.8 ± 21.6	0.3
High	Moderate	19.1 ± 19.6	19.5 ± 19.6	0.3
	High	24.8 ± 21.0	24.8 ± 21.7	0.7

Data are presented as mean ± SD. *P = 0.05. ASCVD: atherosclerotic cardiovascular disease, GDSI: guideline-directed statin intensity. The ASCVD risk categories are defined per the pooled-cohort equations based on 10-year ASCVD risk calculator as intermediate risk (7.5 %–19.9 %), and high risk (≥20 %). *P < 0.05. Data shown are mean (SD) time (in months) to initiation of intermediate or high intensity statin therapy for men and women without statin prescription at index visit.

Table 2
Proportion of statin therapy utilization on index and follow-up visits across intermediate and high ASCVD risk categories.

	Index visit				Follow-up			
ASCVD risk	Intermediate		High		Intermediate		High	
Sex (n)	Men (36,602)	Women (26,997)	Men (16,104)	Women (10,583)	Men (36,602)	Women (26,997)	Men (16,104)	Women (10,583)
No statin	26,661 (72.9)	17,597 (65.9)	9403 (58.4)	5760 (54.4)	16,627 (45.4)	10,731 (40.2)	4882 (30.3)	3418 (32.3)
< GDSI	730 (2.0)	730 (2.7)	449 (2.8)	408 (3.9)	773 (2.1)	890 (3.3)	457 (2.8)	411 (3.9)
GDSI	9621 (25.3)	8370 (31.4)	6252 (38.8)	4415 (41.7)	19,202 (54.5)	15,076 (56.5)	10,765 (66.9)	6754 (63.8)

Proportions (percentage) of patients on targeted treatment based on initial risk group at index visit and the highest treatment they ever received during follow-up period. Statins were defined as high intensity: atorvastatin 40 and 80 mg, rosuvastatin 20 and 40 mg; moderate intensity: atorvastatin 10 and 20 mg, rosuvastatin 5 and 10 mg, simvastatin 20 and 40 mg, pravastatin 40 and 80 mg, lovastatin 40 and 80 mg; low intensity: simvastatin 10 mg, pravastatin 10 and 20 mg, lovastatin 20 mg, fluvastatin 20 and 40 mg. Data are presented at n (%). *P < 0.05. Abbreviations: ASCVD- atherosclerotic cardiovascular disease, GDSI- guideline-directed statin intensity.

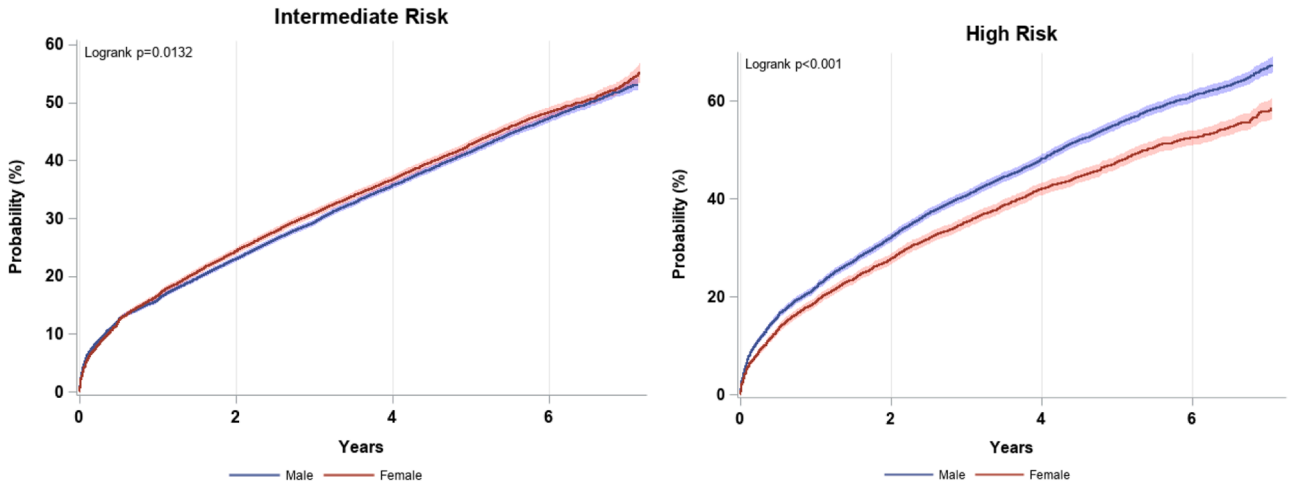

Fig. 1. Probability of GDSI use over follow-up period.
The projected percentage of men and women to achieve guideline-directed statin intensity in the (right panel) intermediate risk and (left panel) high risk patient groups based on the calculated 10-y atherosclerotic cardiovascular disease risk over the study follow-up period.

Table 4
Sex differences in adverse outcomes comparing on no statin among intermediate and high-risk individuals.

Events	Men		Women	
	Intermediate risk	High risk	Intermediate risk	High risk
MI	1.59 (1.38 – 1.84) ***	1.46 (1.25 – 1.72) ***	1.54 (1.30–1.84) ***	1.32 (1.07–1.62) **
Stroke-TIA	1.32 (1.09–1.60) **	1.63 (1.36–1.96) ***	1.72 (1.42–2.08) ***	1.61 (1.31–1.98) ***
Mortality	1.67 (1.50–1.86) ***	1.67 (1.50–1.86) ***	1.65 (1.47–1.85) ***	1.39 (1.22–1.59) ***

Hazard Ratios using guideline-directed statin intensity as reference. Data presented as median (IQR). Values expressed as hazard ratio (95 % CI). *$P < 0.05$, ** $P < 0.01$, ***$P < 0.001$. TIA: transient ischemia attack.

4. Discussion

In this study of sex-based assessment of statin utilization and ASCVD outcomes in a contemporary primary prevention cohort, stratified by 10-year ACC/AHA risk, we present three key findings; 1) high risk women were statistically less likely, albeit with small differences, to be on GDSI compared with high-risk men both at 2- and 5-years follow-up (2-years: 27.7 vs 32.0 %, and 5-years: 47.2 vs 55.2 %). This was despite comparable risk and higher proportion of GDSI at baseline, 2) both intermediate and high risk women and men had lower risk of MIs, stroke and mortality when on GDSI compared to when on no statin and 3) GDSI significantly improved the survival in both sexes across all ASCVD risk groups.

Several prior studies have shown disparities in statin utilization among women compared with men for secondary prevention of ASCVD events [11–15,18]. Our study is additive to existing literature in evaluating sex-based disparities in statin use and ASCVD outcomes in a purely primary prevention cohort from large contemporary healthcare systems in the United States. In limited studies evaluating primary prevention patients, differences in statin use are less clear with mixed results [19,20]. Navar et al. have previously reported that women were less likely than men to receive guideline-recommended statin therapy in the PALM registry [21]. Although the PALM registry is also a contemporary sample, the number and percentage of patients in primary prevention were far less than this study. Further, our study examined longitudinal outcomes including Social Security Index verified all cause mortality. Recall bias in the survey-based registry as well as a shorter duration of enrollment (all within 2015 in PALM versus 2013–2017 in the current study) may be implicated in differing results. Further, our data were strengthened by statin associated ASCVD outcomes as well as social security death index adjudicated mortality.

We found that the probability of high-risk women being on GDSI was lower as compared with high-risk men persistently at 2- and 5-year follow-up. Prior data evaluating reasons for statin therapy have shown there are both clinician and patient driven factors leading to decreased use of guideline-directed statin initiation in women [21]. Our data suggest that despite the introduction of the 10-year risk estimation in 2013, high-risk women had comparatively lower initiation of guideline-concordant statin intensity over time as compared to high-risk men [22]. This is illustrated by a larger proportion of high-risk women on less than guideline-directed statin therapy compared to men during the course of the follow up period. It is also important to note that the ASCVD risk calculation may not fully capture sex-specific risk factors which are now emphasized as risk-enhancers in the most recent guidelines [9]. Therefore, there may be an overall underestimation of women's risk when looking at ASCVD calculations in isolation.

Although we did not evaluate the reasons for differences in sex-associated differences in our data, prior studies have shown that both clinician-driven and patient-driven factors may contribute to this disparity in statin utilization [21]. Clinician-driven factors may include clinicians' sex-specific biases as well as an under appreciation of women's true ASCVD risk. In the PROMISE trial, diagnostic workup for possible coronary artery disease (CAD) was shown to be biased by the patient's sex [23]. Another study showed clinicians were more likely to consider men to be of higher risk compared women with an identical clinical scenario and consequently were more likely to prescribe lipid-lowering medications to men [22]. Incidence of cardiovascular risk factors contributing to clinical ASCVD increase in the post-menopausal period. As a result, cardiovascular event rates among women increase to match that of their men counterparts in later life. A lack of knowledge about increases in risk status following menopause may lead to under prescribing of GDSI. From the patient's perspective, women of child-bearing status may have concerns about statins and teratogenicity. In addition, women have tended to report more adverse effects to statin [15,24]. Prior studies have hypothesized this could be due to exposure to public warnings affecting patients' perceptions as well as possible drug-drug interactions [15].

This study had several limitations. First, standard EMR data-related limitations apply, including but not limited to data entry inaccuracy,

over- and inaccurate coding, misclassifications of medication exposure as well as non-adjudicated endpoints. As reported previously, these should be applied to our study [25]. However, all-cause mortality was reported using a SSI validated measure in our outcomes. Furthermore, racial and ethnic diversity in our patient population was limited which may compromise external validity of our data. Self-identified gender was not effectively documented in the EMR during time period of the study. Women specific risk factors including prior pregnancies, associated pregnancy complications and age of menopause were not assessed as part of this analysis [26]. Since the additions of these risk factors can increase risk for women, we anticipate future studies incorporating these data will further identify sex and gender-based disparities in care for women. Similarly, non-traditional risk factors disproportionately impacting women including certain autoimmune diseases and prior/-current breast cancer treatment were not available for data analysis. In addition, any treatment for ASCVD or statin prescription at outside UPMC sites could not be properly assessed. However, the fact that the UPMC system encompasses over 400 outpatient clinics and nearly 40 hospitals throughout diverse socioeconomic areas of Pennsylvania may offset some of limitations in other single center or single system studies. In addition, given small numbers of patients on ezetimibe (Table 1), we did not include this in our analysis. Finally, we did not have socioeconomic data or insurance status of patients which may have factored into statin non-adherence.

In spite of differences in statin prescriptions, both men and women in intermediate and high ASCVD risk groups were shown to benefit from a reduction in future atherosclerotic cardiovascular events and mortality when on GDSI compared to no statin. This is consistent with prior literature [10,27]. Collectively, these findings underscore the importance for clinicians and patients to be cognizant of both the underutilization of statin in all patients and for continued risk assessment for initiation of statins on follow-up, particularly among women, for optimal prevention of ASCVD events.

5. Conclusion

In summary, this study showed that while women received GDSI comparatively more than men at index visit, fewer high risk women were prescribed GDSI for primary prevention on follow-up. Additionally, although the time to achieving GDSI was comparable between sexes, high-risk women were less likely to be on GDSI at 2- and 5-years of follow up. Lastly, we showed that intermediate and high-risk individuals of both sexes had lower risk of MIs, stroke, and death when on GDSI compared to no statin. Future efforts should focus on initiatives to improve guideline implementation for optimal statin utilization to prevent cardiovascular events in both sexes.

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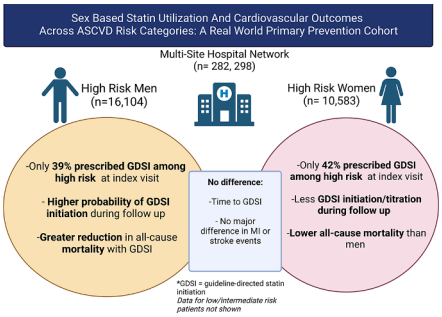

Central Illustration

CRediT authorship contribution statement

Agnes Koczo: Writing – review & editing, Writing – original draft. **Adipong Brickshawana:** Writing – original draft. **Jianhui Zhu:** Writing – review & editing, Formal analysis. **Floyd Thoma:** Methodology, Data curation. **Malamo Countouris:** Writing – review & editing. **Kathryn Berlacher:** Writing – review & editing. **Martha Gulati:** Writing – review & editing. **Erin D Michos:** Writing – review & editing. **Steven Reis:** Writing – review & editing. **Suresh Mulukutla:** Writing – review & editing, Methodology, Investigation, Data curation. **Anum Saeed:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anum Saeed reports article publishing charges was provided by UPMC. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100667.

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