Quantifying Sex Differences in Cardiovascular Care Among Patients Evaluated for Suspected Ischemic Heart Disease

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Abstract

Background: Cardiovascular care sex differences are controversial. We examined sex differences in management and clinical outcomes among patients undergoing noninvasive testing for ischemic heart disease (IHD).

Methods: In a rural integrated healthcare system, we identified adults age 40–79 without diagnosed IHD who underwent initial evaluation with a cardiac stress test with imaging or coronary computed tomographic angiography (CTA), 2013–2014. We assessed sex differences in statin/aspirin therapy, revascularization, and adverse cardiovascular events. The 2013 American College of Cardiology/American Heart Association statin guidelines and U.S. Preventive Services Task Force aspirin guidelines were applied.

Results: Among 2213 patients evaluated for IHD, median age was 57 years, 48.8% were women, and 9% had a positive stress test/CTA. Women were more likely to be missing lipid values than men ($p < 0.001$). Mean ASCVD risk score at baseline was 7.2% in women versus 12.4% in men ($p < 0.001$). There was no significant sex difference in statin therapy at baseline or 60-day follow-up. Women were less likely than men to be taking aspirin at baseline (adj. diff. = -8.5% ; 95% CI, -4.2 to -12.9) and follow-up (adj. diff. = -7.7% ; 95% CI, -3.3 to -12.1). There were no sex differences in revascularization after accounting for obstructive CAD or adverse cardiovascular outcomes during median follow-up of 33 months.

Conclusion: In this contemporary cohort of patients with suspected IHD, women were less likely to receive lipid testing and aspirin therapy, but not statin therapy. Women did not experience worse outcomes. Sex differences in statin therapy reported by others may be due to inadequate accounting for baseline risk.

Keywords: cardiac stress testing, sex differences, statins, aspirin, disparities

Introduction

SEX DIFFERENCES IN CARDIOVASCULAR care have been the source of considerable controversy.¹ Debates over whether women are less likely than men to receive life-saving cardiovascular medications and procedures span decades, and researchers have found evidence to both support and refute these concerns.^{2–11} During this time period, significant advances have been made in the prevention of cardiovascular disease, including broader availability of inexpensive and potent statins, an expansion of antiplatelet therapy options, advances in revascularization technology, and refinements in our ability to risk stratify patients using clinical and imaging information.^{12,13} In addition, some important risk factors, such as diabetes, have increased markedly in prevalence,

while others, such as tobacco use, have fallen.¹⁴ Among patients with suspected ischemic heart disease (IHD), preventive cardiovascular care is particularly important, as these patients often have multiple risk factors, and their encounter with the healthcare system for cardiovascular testing can serve as a “teachable moment” and an opportunity to reduce gaps in cardiovascular care.^{15,16} There are few recent evaluations focusing on sex differences in care within this population of patients.

In this study, we aimed to examine sex differences in patient management—as measured by changes in guideline-recommended medical therapy and revascularization within 60 days—among patients undergoing noninvasive testing for suspected IHD. We also assessed sex differences in clinical outcomes during long-term follow-up.

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Methods

Data and study population

We identified adults age 40–79 without diagnosed IHD who underwent initial evaluation for suspected IHD with a cardiac stress test with imaging or coronary computed tomographic angiography (CTA) between November 1, 2013 and November 26, 2014 with follow-up through February 12, 2016 at Geisinger Health System, a rural integrated healthcare system. Geisinger Health System is located in northeastern and central Pennsylvania. The institutional review boards at Geisinger Health System and UCLA approved the study. Additional inclusion criteria, based on prior work with Geisinger Health System's EHR and other research,¹⁷ included at least 2 years duration between the first and last Geisinger Health System encounter, with at least one primary care visit during this interval. Exclusion criteria included a history of IHD; index testing performed in an inpatient or emergency department setting; or indeterminate index test result.

We evaluated sex differences in guideline-recommended statin and aspirin therapy across the entire cohort of patients with suspected IHD. We applied the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for statin therapy and the U.S. Preventive Services Task Force (USPSTF) guidelines for aspirin therapy. Specifically, the 2013 ACC/AHA guidelines recommend statin therapy for patients 40–75 years old with cardiovascular disease (CVD), low-density lipoprotein cholesterol (LDL) ≥ 190 , diabetes and LDL ≥ 70 , or 10-year CVD risk $\geq 7.5\%$. The USPSTF recommends aspirin/antiplatelet therapy for primary or secondary prevention of CVD in patients at increased risk (men age 45–79, women age 55–79, or any patient with prior CVD).^{18–20} We considered treatment with clopidogrel, ticagrelor, or prasugrel to be equivalent to aspirin therapy. We excluded adults with a history of liver disease from our assessment of statin therapy and adults with a history of gastrointestinal bleeding, peptic ulcer disease, or cerebral hemorrhage from our assessment of aspirin therapy.

Demographic and clinical characteristics

We used Geisinger Health System's EHR to collect baseline demographic and clinical information on comorbidities, smoking status, statin and aspirin therapy, and incidence of major adverse cardiovascular events (death from any cause, myocardial infarction, hospitalization for unstable angina, and hospitalization for stroke). Comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). A patient was required to have at least two outpatient diagnoses or one inpatient diagnosis to be considered to have a comorbidity, similar to prior work.^{21,22} We used Current Procedural Terminology codes and Geisinger-specific codes to identify patient receipt of cardiac tests and procedures. As described in our prior work, a subset of these patients participated in a survey study ($N=351$, of which 313 met inclusion criteria for this analysis) and provided information about self-reported angina.¹⁷

Initial test results

We categorized initial test results as positive, negative, or indeterminate based on an adaption of previously published

criteria.^{23,24} CTA was positive if there was a $\geq 70\%$ stenosis in the left anterior descending, left circumflex, or right coronary artery or a $\geq 50\%$ stenosis in the left main coronary artery. Stress nuclear imaging was positive if there was a reversible perfusion defect (inducible ischemia), mixed defect (infarct and ischemia), or fixed defect during stress in at least one territory; negative if perfusion was normal; and indeterminate if test results were uninterpretable. Stress echocardiography was positive if there was a reversible or mixed wall motion abnormality during stress in at least one territory (ischemia) or a fixed wall motion abnormality; negative if wall motion was normal; and indeterminate if test results were uninterpretable. Exercise electrocardiography was positive if there were significant ST-segment changes consistent with ischemia.

Statistical analysis

We performed descriptive data analysis and used simple logistic regressions, including ordinal and multinomial models, to compare the characteristics of women and men evaluated for suspected IHD. We also estimated linear probability models with robust standard errors to examine the association between sex and statin or aspirin therapy by 60 days after the index test (as defined by any medication order within 60 days of testing) while controlling for age, physician specialty, initial test type, initial test result, early revascularization (before 60 days), and presence of obesity, smoking history, dyslipidemia, diabetes mellitus, hypertension, and non-IHD CVD. We used linear probability models rather than nonlinear models to more easily facilitate post-estimation analyses with multiple imputation. Moreover, the probabilities were in a range where linear approximation performs well, and findings of significance did not differ when logistic models were executed.²⁵ One set of models assessed overall sex differences in statin or aspirin therapy at baseline and follow-up. A second set of models adjusted for baseline use of statin or aspirin and assessed whether changes in statin or aspirin therapy at follow-up differed by sex. Medication therapy analyses were limited to patients who met guideline-recommended criteria for statin or aspirin therapy.^{18–20} This requirement was relaxed in a sensitivity analysis in which we used a method similar to other studies and did not limit the study population to patients meeting guideline-recommended criteria for therapy.^{16,23,26} In analyses of sex differences in revascularization, we adjusted for the presence of obstructive coronary artery disease (CAD), which we defined as $\geq 50\%$ stenosis in any coronary artery at the time of cardiac catheterization.

Lipid values were more likely to be missing among women than men (38% vs. 32%; $p < 0.001$). Because differential rates of lipid testing could bias our assessment of sex differences due to the inability to calculate ASCVD scores for patients with missing data, we imputed these missing data with multiple imputation, a robust method for dealing with missing data.²⁷ Patients currently receiving statin therapy were also included in our analysis; for these patients, we estimated their off-statin lipid values based on prior studies showing that statins reduced total cholesterol by 21.18% and raised high-density lipoprotein cholesterol by 3.57%.^{28,29}

Imputing missing lipid values to calculate ASCVD does not fully account for physician decision-making, since

physicians caring for patients in our cohort would not have had the opportunity to treat patients based on these values. However, our methodology does address sex differences, since sex differences in care could be due to differences at various points along the care pathway, including differences in lipid testing and risk stratification. Blood pressure was missing in 1% of patients, and these values were also imputed with multiple imputation.

Survival analysis was performed with Cox regression modeling. The primary outcome was time to occurrence of any major cardiovascular event (death from any cause, myocardial infarction, hospitalization for unstable angina, and hospitalization for stroke). We used mean imputation for missing values of body mass index (<1%). All analyses were performed in Stata (version 14, College Station, TX).

Results

Patient characteristics

Among 2213 patients who were evaluated for IHD between November 1, 2013 and February 12, 2016, median age was 57 years (interquartile range, 50–64), 48.8% were women, and 9% had a positive stress test/CTA. Mean ASCVD

risk score at baseline was 7.2% in women versus 12.4% in men ($p < 0.001$). Baseline characteristics are presented in Table 1. Initial stress test or CTA results were positive in 9%, and 2% of patients underwent revascularization.

Statin and aspirin therapy in eligible patients

Lipid values were more likely to be missing among women than men (38% vs. 32%; $p < 0.001$). Of the overall cohort, 923 patients were considered eligible for statin therapy by ACC/AHA criteria, and 1624 patients were considered eligible for aspirin therapy. At baseline, 53% and 51% of women and men were prescribed a statin, and 23% and 28% of women and men were prescribed an aspirin, respectively (Fig. 1). By 60 days after testing, this changed to 55% and 56% among women and men for statins and 25% and 31% among women and men for aspirin, respectively. There was no significant sex difference in statin therapy at baseline (adjusted difference = -3.9% ; 95% CI, -9.8 to 1.9) or follow-up (adjusted difference = -3.0% ; 95% CI, -8.8 to 2.8) (Fig. 2). Women were less likely than men to be taking aspirin at baseline (adjusted difference = -8.5% ; 95% CI, -4.2 to -12.9) and follow-up (adjusted difference = -7.7% ; 95% CI, -3.3 to -12.1). After accounting for baseline statin or aspirin therapy, there was no significant

TABLE 1. CHARACTERISTICS OF WOMEN AND MEN WITH SUSPECTED ISCHEMIC HEART DISEASE REFERRED FOR STRESS TESTING OR CORONARY CTA

	All patients (n=2213)	Percent, %	Women (n=1196)	Percent, %	Men (n=1017)	Percent, %	p value
Sex							
Male	1017	46	0	0	1017	100	
Female	1196	54	1196	100	0	0	—
Age, yrs.							
40–49	515	23	257	22	258	25	
50–59	747	34	396	33	351	35	
60–69	635	29	364	30	271	27	
70–79	316	14	179	15	137	14	0.009
Initial test							
Stress echocardiography	1658	75	902	75	756	74	
Stress MPI	473	21	254	21	219	22	0.787
Coronary CTA	82	4	40	3	42	4	0.319
Initial test result positive							
No	2007	91	1122	94	885	87	
Yes	206	9	74	6	132	13	<0.001
Baseline medical history							
Obese (BMI ≥ 30)	1179	53	637	53	542	53	0.988
Smoker (current/former)	1142	52	549	46	593	58	0.363
Dyslipidemia	1192	54	636	53	556	55	0.483
Diabetes	388	18	198	17	190	19	0.864
Hypertension	1044	47	567	47	477	47	0.812
Stroke/TIA	107	5	56	5	51	5	0.716
Baseline medications							
Aspirin	488	22	216	18	272	27	<0.001
Statin	784	35	390	33	394	39	0.003
Physician specialty ^a							
Cardiology	420	19	236	20	184	18	
Primary care/Other	1793	81	960	80	833	82	0.327

Values are given as percent of patients within each group and may not sum to 100 because of rounding. p values calculated with Wald chi-square test from simple ordinal (age) or binomial (all other variables) logistic regression models comparing women to men.

^aSpecialty of physician who ordered stress test/CTA.

CTA, computed tomographic angiography; MPI, myocardial perfusion imaging; TIA, transient ischemic attack.

FIG. 1. Cardiovascular care at baseline and 60-day follow-up among patients with suspected ischemic heart disease referred for stress testing or coronary CTA. CTA, computed tomographic angiography.

difference in the likelihood of a change in statin or aspirin therapy at 60 days between women and men ($p=0.99$ for statin therapy, $p=0.39$ for aspirin therapy).

Sensitivity analysis for statin and aspirin therapy in eligible patients

In a sensitivity analysis, we used a method similar to other studies and expanded our analysis of sex differences to the entire population of patients, rather than limiting it to patients for whom treatment is recommended.^{16,26} In contrast to our primary analyses, this sensitivity analysis found that women were less likely to be taking statin therapy at baseline (adjusted difference = -5.7% ; 95% CI, -2.2 to -9.1) and follow-up (adjusted difference = -4.9% ; 95% CI, -1.4 to -8.4). Our findings for sex differences in aspirin therapy were similar.

In another sensitivity analysis, we examined sex differences among patients with a positive initial stress test or CTA. In this

group, at baseline, 54% and 53% of women and men were prescribed a statin, and 28% and 36% of women and men were prescribed aspirin, respectively. By 60 days after testing, this changed to 62% and 74% among women and men for statin therapy and 43% and 60% among women and men for aspirin therapy, respectively. These differences by sex were not significant in this small subset of patients with positive initial stress test or CTA results. However, compared to patients with a negative initial stress test or CTA result, a positive result increased the absolute adjusted probability of statin or aspirin therapy at 60 days by 12% and 16%, respectively.

Revascularization

Cardiac catheterization was performed in 5% of women (68% after a positive test, 1% after a negative test) and 10% of men (67% after a positive test, 1% after a negative test), with no significant sex difference after accounting for initial

FIG. 2. Adjusted sex differences in cardiovascular care at baseline and 60-day follow-up among patients with suspected ischemic heart disease referred for stress testing or coronary CTA. Aspirin category includes other antiplatelet agents (clopidogrel, ticlopidine, and prasugrel). Models adjust for clinical risk factors and demographics; models for cardiovascular care at follow-up also adjust for stress test/CTA results and revascularization. Sex differences in cardiac catheterization only evaluated at 60-day follow-up. $p < 0.001$ for aspirin and $p < 0.01$ for statins at baseline and follow-up; $p = 0.10$ for cardiac catheterization.

test results. Revascularization by percutaneous coronary intervention or cardiac surgery was performed in 1.0% of women and 3.8% of men. Stratified by initial test results, revascularization was performed in 14% and 28% of women and men with a positive stress test or CTA versus 0.2% and 0.2% of women and men with a negative stress test or CTA, respectively. At the time of cardiac catheterization, obstructive CAD was seen in 33% of women versus 56% of men ($p=0.004$). There was no significant sex difference in revascularization rates after accounting for clinical risk factors, initial test results, and presence of obstructive CAD.

Cardiovascular events during follow-up

The median duration of follow-up was 33 months (interquartile range, 29–36 months). Adverse cardiovascular events occurred in 5% (5% in women, 5% in men). In multivariate models, there was no significant sex difference in rates of cardiovascular events during follow-up (hazard ratio 1.30; 95% CI 0.89–1.90).

Discussion

We found that women with suspected IHD were less likely to receive lipid testing and aspirin therapy compared to men, but there were no sex differences in statin therapy or clinical outcomes. Patients of both sexes were often not prescribed recommended medication, although some physicians may not have yet adopted 2013 ACC/AHA statin guidelines during our study period. Because of the high prevalence of cardiovascular risk factors in the U.S. population, optimal use of cardiovascular care is an issue of substantial public health and economic relevance.³⁰

This study contributes to our understanding of sex differences in cardiovascular care because it demonstrates that lower use of aspirin therapy among women compared to men persists in a contemporary cohort of patients with suspected IHD. Another contribution is our finding that sex differences in statin prescription were only present when the overall population was examined rather than just the subpopulation recommended to receive therapy. It is possible that other studies that have found worse care in women might reach different conclusions using more granular patient-level data on risk and lipids, but this is uncertain.^{16,23,26} In addition, while baseline ASCVD risk was substantially lower in women compared to men (7.2% vs. 12.4%), the rate of adverse CVD events was not significantly different. The absence of a difference may be attributable to the relatively short time horizon of our study, compared to the 10-year time horizon used to estimate ASCVD risk.

Other studies have reported sex differences in cardiovascular care among patients with suspected IHD. However, to the best of our knowledge, ours is the first to focus on patients meeting guideline-recommended criteria for therapy. In the PROMISE trial (PROspective Multicenter Imaging Study for Evaluation of chest pain), women undergoing stress testing/CTA were less likely than men to receive aspirin therapy and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy (ACEi/ARB), but there was no sex difference in statin use.¹⁶ In the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD), women were less likely than men to receive aspirin therapy, and there was a trend toward significantly lower use

of statin therapy.²³ In the international observational longitudinal registry of patients with stable CAD, CLARIFY (ProspeCtive observational Longitudinal RegIStry of patients with stable CAD), women were less likely than men to receive statin or aspirin therapy, although the differences were modest, and there was no difference in outcomes at 1 year.³¹ Women in the Euro Heart Survey of Stable Angina study were also less likely to receive statin and aspirin therapy than men.⁷ However, women in this study were twice as likely to experience death or nonfatal myocardial infarction at 1 year. Overall, these studies suggest that the quality of cardiovascular care that women receive in the United States and in other countries may be comparatively lower compared with men.

The reasons for sex differences in aspirin therapy among women compared to men are unclear. Prior work has shown that physicians may perceive women to be at lower risk for cardiovascular events than men even when their calculated risk is similar.³² Patient preferences for care may also play a role. The clinical implication of our study is that identification and preventive treatment of patients at increased cardiovascular risk remain a challenge, even among patients being actively evaluated for IHD. Another implication of our work is that many patients who may be candidates for statin therapy do not have recent lipid values. Altogether, these are meaningful opportunities for physicians to improve preventive cardiovascular care through increased adherence to guideline-recommended therapy. Future research should inform the extent to which untreated patients are aware they are candidates for statin or aspirin therapy. EHR-based interventions that leverage social networks and provider feedback may also be beneficial for reducing gaps in care. Effective interventions may substantially improve public health and reduce expenditures for acute cardiovascular events.³⁰

While our study accounted for focal coronary atherosclerosis, sex differences in statin or aspirin therapy in the context of microvascular disease is also an important clinical issue. Women with chest pain are more likely than men to have coronary microvascular dysfunction.³³ Patients with coronary microvascular dysfunction are at increased risk of experiencing adverse cardiovascular events, and this risk is further heightened by the observation that coronary microvascular dysfunction may correlate poorly with conventional cardiovascular risk factors.^{33,34} Poor correlation could therefore contribute to undertreatment of patients—and women, in particular—with coronary microvascular dysfunction. In addition, uncertainty remains about optimal treatment for microvascular dysfunction.^{35,36}

Our study has limitations. The data were obtained from a single rural healthcare system, so results may differ in other settings. Most patients were evaluated with stress echocardiography, whereas many centers may primarily use nuclear imaging. We were able to adjust for measured differences between women and men, but unmeasured differences may have influenced decision-making about statin and aspirin therapy. For example, women and men often report differences in clinical presentation (*e.g.*, quality of chest pain) that may influence physicians' recommendations for statin or aspirin therapy. We did not collect data on whether nonobstructive CAD was seen on coronary CTA, but these findings may affect prescribing behavior for statins and aspirin.¹⁶

In this contemporary cohort of patients with suspected IHD in a rural integrated healthcare system, women were less

likely to receive lipid testing and aspirin therapy, but not statin therapy. Women did not experience worse clinical outcomes. Sex differences in statin therapy that have been reported in the literature may be due to inadequate accounting for baseline risk and guideline recommendations. These findings may be relevant to quality improvement initiatives and to payors aiming to reduce sex differences in care.

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Author Disclosure Statement

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