Accounting for Clinical Action Reduces Estimates of Gender Disparities in Lipid Management for Diabetic Veterans

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BACKGROUND: Women with diabetes have higher low-density lipoprotein (LDL) levels than men, resulting in apparent disparities between genders on quality indicators tied to LDL thresholds.

OBJECTIVE: To investigate whether gender disparities persist when accounting for clinical action with statins or cardiovascular risk.

DESIGN: Retrospective cohort study.

PARTICIPANTS: Veterans Health Administration patients (21,780 women and 646,429 men) aged 50–75 with diabetes.

MAIN MEASURES: Threshold measure: LDL < 100 mg/dL; clinical action measure: LDL < 100 mg/dL; or LDL ≥ 100 mg/dL and the patient was prescribed a moderate or high-dose statin at the time of the test; or LDL ≥ 100 mg/dL and the patient received other appropriate clinical action within 90 days; adherence: continuous multiple interval measure of gaps in dispensed medication (CMG).

KEY RESULTS: Women were much less likely to have LDL < 100 mg/dL than were men (55 % vs. 68 %). This disparity narrowed from 13 % to 6 % for passing the clinical action measure (79 % vs. 85 %). These gender differences persisted among those with ischemic heart disease (IHD). Women had a lower odds of passing the clinical action measure (odds ratio 0.68, 95 % confidence interval 0.66–0.71). Among those with IHD, the gender gap increased with age. Differences in pass rates were explained by women's higher LDL levels, but not by their slightly worse adherence (3 % higher CMG).

CONCLUSIONS: Women and men veterans receive more similar quality of care for lipids in diabetes than previously indicated. Less reassuringly, the remaining gender differences appear to be as common in women at high cardiovascular risk as in those at low risk. Rather than focus on simply improving LDL levels in all women with diabetes, future efforts should ensure that patients with high cardiovascular risk are appropriately treated with statins when clinically indicated, feasible, and concordant with patient preferences.

KEY WORDS: women; disparities; statins; quality of care; diabetes.
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INTRODUCTION

Large gender differences in achievement of target low-density lipoprotein (LDL) levels are reported consistently in diabetic populations.[1–7] However, there are relatively small differences by gender in initiation and provision of lipid lowering treatment.[1,2,8] It is not yet clear whether these observations reflect less aggressive treatment intensification in women on the part of providers, poorer adherence to treatment on the part of women, or some combination of the two. Furthermore, if women are treated less aggressively than men, it is unknown whether this appropriately reflects their lower overall cardiovascular risk once other risk factors are taken into account.

Nevertheless, the obvious consequence of the higher LDL levels seen in diabetic women is that existing LDL < 100 mg/dl quality measures are attained less frequently in women than in men. For example, among patients using Department of Veterans Affairs (VA) medical facilities in fiscal year (FY) 2011, the gender difference was 14 % for those with diabetes, and 16 % for those with ischemic heart disease (IHD), suggesting significant quality gaps between women and men.[9] This difference occurs even as the VA exceeds the private sector on many measures of performance for both gender-specific and gender-neutral care,[5,10,11] and provides comparable quality of care to women and men veterans by most measures.[12] The utility of this LDL target quality measure has come under serious scrutiny, however.[13] Recent literature suggests that the method of treatment for hyperlipidemia may be as or more important than attainment of an LDL target,[14,15] and

professional society treatment guidelines now credit use of a statin in addition to achievement of low LDL levels.[16–18] In 2012, in light of the shifting paradigm and evolving definition of high-quality care, the VA adopted a new quality measure for lipid management in diabetes that was developed by a workgroup of clinical and measurement experts and accounts for clinical action in addition to LDL levels (personal communication, Kerr 2011). Development of this measure followed similar work developing a clinical action performance measure for blood pressure management in the VA.[19] Including the focus on clinical action deemphasizes target attainment and acknowledges the effectiveness of appropriate therapy—in this case, use of statins in diabetes.

In this study, we hypothesize that taking appropriate clinical action for lipid management into account will reduce estimates of gender disparities based on LDL thresholds alone among veterans with diabetes. If providers are appropriately using cardiovascular risk to tailor treatment, we also expect to see further narrowing of any gender differences among those with increased levels of cardiovascular risk, such as those patients with IHD and diabetes or with increasing age. Finally, we hypothesize that any persistent disparities with use of the clinical action measure will be explained in part by worse adherence among women.

METHODS

Subjects and Study Design

We used data from the VA Corporate Data Warehouse (CDW), a national repository comprising data from multiple VA clinical and administrative systems. Data included information on outpatient encounters; vital signs; ICD-9 diagnoses; prescription medication fills, doses, quantities and days' supply; and laboratory values. We conducted a retrospective cohort study of data from women and men aged 50–75 with diabetes active in primary care at a VA medical center (VAMC) or community-based outpatient clinic (CBOC) during July 1, 2010 to June 30, 2011. We identified patients with diabetes on the basis of two outpatient visits with ICD-9 codes for diabetes, or a total of ≥ 31 days of prescription diabetes medications filled in the 24 months prior to the study period. For the patient to be included in the study, one of these visits or fills needed to be in the 12 months prior to the start of the study period. Active patients were defined as those with ≥ two primary care clinic visits in the 24 months prior to the study period and ≥ one primary care clinic visit during the study period. Patients were assigned to a facility based upon the location of most primary care visits during the study period. We found 881 unique facilities.

We excluded those with ICD-9 codes for dialysis; pregnancy; liver, esophageal, or pancreatic cancer; death during the study period; or with limited life expectancy recorded in response to clinical reminders in the electronic medical record. The VA Ann Arbor Healthcare System's Subcommittee on Human Studies approved this study.

Patient Data

Body mass index (BMI) was calculated from weight and height. We reported mean blood pressure and LDL and most recent hemoglobin A1C from the year prior to the study period. Comorbidities were identified using ICD-9-CM codes.[20] We classified certain conditions as concordant, meaning that treatments for these conditions are generally related to and/or overlap with diabetes care.[21,22] These included hypertension, hyperlipidemia, obesity, heart failure, ischemic heart disease, peripheral vascular disease, renal disease, and cerebrovascular disease. All other conditions were considered non-concordant.

Clinical Action Quality Measure

The clinical action measure[23] is intended to account for LDL target achievement as well as processes that are associated with positive results irrespective of intermediate outcomes.[14,18,24] The measure was considered met in those instances where: index LDL < 100 mg/dL; or LDL ≥ 100 mg/dL and the patient was prescribed a moderate-dose or high-dose statin at the time of the test or within 90 days; or index LDL ≥ 100 mg/dL and the patient received other appropriate clinical action within 90 days. The last LDL value of the study period was the index LDL. Those with no LDL test recorded but who were prescribed a moderate or high dose statin passed the measure on the basis of the prescription. "Other appropriate clinical action" included starting, changing, or intensifying low-dose statin therapy, or finding an LDL < 100 mg/dL upon repeat testing. The measure limits credit for lipid-lowering medication use to statins only; other lipid-lowering medications are not definitively associated with reduced cardiovascular disease (CVD) events. The measure also focuses on statins at a moderate dose, which have strong evidence for cardiovascular event reduction and total mortality.[25–30] Moderate-dose statins are those that produce a 30–40 % decrease in LDL levels. Statins at low dose appear to be of limited benefit in reducing CVD risk, but because many patients may be unable to tolerate moderate dose statins, the measure credits starting a low dose statin as evidence of a reasonable provider attempt to improve lipid control. The definitions of low-dose, moderate-dose and high-dose statins are based on the relative potency

of each statin in lowering LDL levels and are presented in the Appendix.

Statistical Analysis

We calculated the proportions of women and men who met the LDL < 100 mg/dL threshold measure and the clinical action measure, both for the entire identified population and for those with IHD. Using multilevel logistic regression models controlling for age and with facility as a random effect, we examined the association of gender with the likelihood of passing the LDL < 100 mg/dL threshold measure. We used sequential models to control for utilization factors, including the number of primary care visits and type of facility (VAMC or CBOC). We then further adjusted for indicators of cardiovascular risk: presence of IHD and BMI. These analyses were repeated using the clinical action measure as the outcome variable. We tested interactions between gender and both age and IHD for the clinical action measure. We compared the distribution of statin dose levels and examined LDL control by statin dose in women and men.

In order to explore the effect of adherence to statins in women and men, we used automated VA pharmacy data to calculate the continuous, multiple interval measure of gaps in therapy (CMG).[31,32] The CMG has been shown to be a reliable estimate of patient adherence[33] and is defined as: total number of days without medication/total number of days the patient should have been taking medication, expressed as a percentage. The larger the percent, the larger the refill gaps and presumed worse adherence. We calculated the CMG based on prescription fills over the 12 months preceding the index LDL to account for medication stockpiling from previous prescriptions. Medications which were not filled for ≥ 180 days were considered discontinued rather than counted as missing medication supply. We examined whether controlling for adherence in the full model would change the association between gender and having an LDL < 100 mg/dL.

RESULTS

The study included 21,780 women and 646,429 men (Table 1). While A1C and blood pressure levels were similar between women and men, women were younger (59.6 years vs. 63.9 years), had a higher BMI (34.2±7.2 kg/m^2 vs. 32.6± 6.3 kg/m^2), higher mean LDL level (102±34 mg/dL vs. 89± 29 mg/dL), and more non-concordant conditions. Women had a lower prevalence of IHD (16 % vs. 23 %), were less likely than men to be on either a moderate or a high dose statin (52 % vs. 57 %) and were less likely to be seen in a community-based outpatient center (CBOC).

Table 1. Demographic and Clinical Characteristics*

	Women (*n*=21,780)	Men (*n*=646,429)	P value
Age (yrs)	59.6 (6.1)	63.9 (6.1)	< 0.0001
A1C (%)†	7.3 (1.6)	7.3 (1.4)	< 0.0001
BMI (mg/kg2)†	34.2 (7.2)	32.6 (6.3)	< 0.0001
Mean SBP (mmHg) ‡	132 (14)	132 (14)	0.27
Mean DBP (mmHg) ‡	74 (9)	75 (9)	< 0.0001
Mean LDL (mg/dl)‡	102 (34)	89 (29)	< 0.0001
Comorbidities (no.)§	4.5 (2.2)	4.3 (2.1)	< 0.0001
Non-concordant conditions (no.)‖	2.7 (1.9)	2.2 (1.8)	< 0.0001
Moderate dose statin use (%)	29	32	0.04
High dose statin use (%)¶	23	25	0.17
Ischemic heart disease (%)§	16	23	< 0.0001
Care received in community based clinic (%)	39	49	< 0.0001

A1C hemoglobin A1C, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LDL low-density lipoprotein
**Values are mean (SD) unless otherwise indicated.* †*Mean value in year prior to study year.* ‡*Most recent value from year prior to study year.* §*Comorbidities were identified on the basis of ICD-9 codes listed in the two years prior to the study year.* ‖*Concordant conditions included those whose treatment is generally related to, or overlaps with, diabetes care and include hypertension, hyperlipidemia, obesity, heart failure, ischemic heart disease, peripheral vascular disease, renal disease, and cerebrovascular disease. All others are considered non-concordant.* ¶*Based on the statin dose at start of study year*

Women were less likely than their male counterparts to meet either the LDL threshold measure or the clinical action measure (Table 2). Fifty-five percent of women and 68 % of men met the LDL threshold measure (difference=13 %). Among those with IHD, women were still less likely than men to meet the LDL threshold measure (67 % vs. 81 %, difference=14 %). Women were also less likely to meet the clinical action measure, although the difference was smaller (79 % vs. 85 %, difference=6 %). Among those with IHD, the gender difference remained (84 % vs. 89 %, difference=5 %).

The gender difference in meeting the clinical action measure was mostly explained by the lower rates of LDL target achievement among women, as clinical action was very similar in women and men with an LDL ≥ 100 mg/dL. Specifically, of those with an LDL above threshold, a similar proportion of women and men were on a moderate or high dose statin either at the time of LDL, within 90 days of the LDL, or in the absence of an LDL test (48 % vs. 50 %). In addition, equal proportions of women and men with LDL ≥ 100 mg/dL had a low-dose statin added or changed (3 %), had a dose increase (0.2 %) or had an LDL < 100 mg/dL on repeat testing (0.3 %).

Table 2. Passing Rates for Quality Measures (%)

	All women (n=21,780)	All men (n=646,429)	Difference	P value
LDL < 100 mg/dL	55	68	13	< 0.0001
Clinical action measure*	79	85	6	< 0.0001
	Women with IHD† (n=3,533)	Men with IHD† (n=192,038)	Difference	
LDL < 100 mg/dL	67	81	14	< 0.0001
Clinical action measure*	84	89	5	< 0.0001

LDL low-density lipoprotein, IHD ischemic heart disease
**Clinical action measure defined as: LDL < 100 mg/dL; or LDL ≥ 100 mg/dL and the patient was prescribed a moderate or high-dose statin at the time of the test; or index LDL ≥ 100 mg/dL and the patient received other appropriate clinical action within 90 days. Those with no LDL test recorded, but who were prescribed a moderate or high dose statin, also passed the measure on the basis of the prescription. †IHD = ischemic heart disease*

In multilevel models, we found that adjustment for age, utilization factors, and cardiovascular risk explained some of the gender difference in meeting the LDL threshold measure, but not in meeting the clinical action measure (Table 3). While the odds ratio (OR) for women of meeting the LDL threshold measure increased from 0.51 [95 % confidence interval (CI) 0.49–0.53] when adjusting for age and facility alone to 0.61 (95 % CI 0.59–0.63) in the fully specified model, the estimate was essentially unchanged for the clinical action measure: 0.68 (95 % CI 0.66–0.71) with adjustment for age and facility alone, and 0.67 (95 % CI 0.65–0.70) in the fully specified model. Increasing age, care at a VAMC (vs. a CBOC), number of primary care practitioner (PCP) visits, and presence of IHD were all positively associated with meeting the clinical action measure, even though adjustment for them did not lead to a change in the odds that women met the measure.

Table 3. Adjusted Odds Ratios for Passing Lipid Management Quality Measures in Women Compared to Men*

	LDL < 100 mg/dL	Clinical action measure†
Age+facility	0.51 (0.49,0.53)	0.68 (0.66,0.71)
Age+facility+number of primary care visits+type of facility‡	0.60 (0.58,0.62)	0.64 (0.62,0.66)
Age+facility+number of primary care visits+type of facility+ IHD§+BMI‖	0.61 (0.59,0.63)	0.67 (0.65,0.70)

LDL low-density lipoprotein, IHD ischemic heart disease, BMI body mass index
**Odds ratios and 95 % confidence intervals †Clinical action measure defined as: LDL < 100 mg/dL; or LDL ≥ 100 mg/dL and the patient was prescribed a moderate or high-dose statin at the time of the test; or index LDL ≥ 100 mg/dL and the patient received other appropriate clinical action within 90 days. Those with no LDL test recorded, but who were prescribed a moderate or high dose statin, also passed the measure on the basis of the prescription. ‡VA medical center or CBOC-community-based outpatient clinic. §IHD-ischemic heart disease. ‖BMI – body-mass index (kg/m^2)*

In addition to adjusting for average age, we examined whether the difference between women and men in meeting the clinical action measure decreased with increasing cardiovascular risk—either advancing age or IHD (Fig. 1). While increasing age and IHD were each positively associated with passing the measure, the effects of each were weaker among women (P for both interactions < 0.001). Among both women and men with IHD, increasing age was associated with decreased rates of meeting the clinical action measure. However, the gender gap actually widened with age in this high-risk group.

The distribution of statin dose levels between women and men was similar (Table 4). At every dose level, however, women had a 12 mg/dL higher mean LDL value than did men. The CMG (i.e. the mean percent of days without medication) among women was 19 %; the mean in men was 16 % (mean difference=3 %). Adjusting for adherence only slightly increased the estimate for the odds of a woman passing the LDL < 100 measure (0.65, 95 % CI 0.62–0.67).

DISCUSSION

We found that accounting for appropriate clinical action in addition to achievement of LDL threshold levels decreased gender disparities in appropriate lipid management for diabetes from 13 % to 6 %. Among high-risk individuals with both diabetes and IHD, treatment was better for both

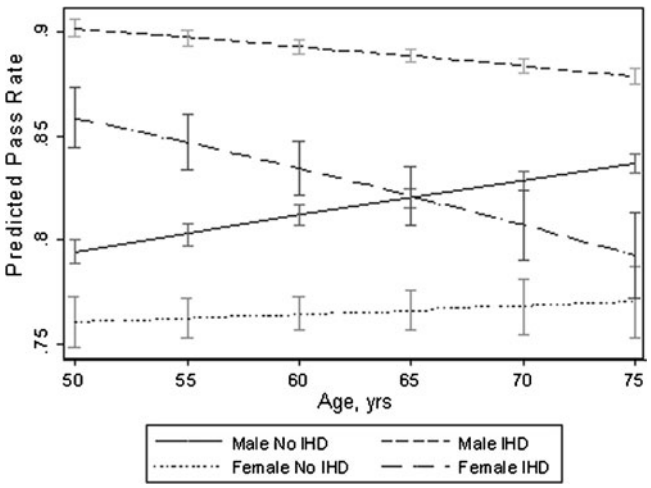

Figure 1. Effects of age and ischemic heart disease on likelihood of passing clinical action measure for lipid management in diabetes, by gender.

Table 4. Statin Dose and LDL Control*†‡§

	Women (n=21,780) (%)	LDL level in mg/dL [mean(SD)]	Men (n=646,429) (%)	LDL level in mg/dL [mean(SD)]
No statin	33	105 (38)	30	92 (32)
Low-dose	8	96 (34)	8	84 (28)
Moderate-dose	32	92 (33)	34	80 (28)
High-dose	27	95 (37)	29	83 (31)

**Based on the statin dose at the time of index LDL. †Percents do not total to 100 due to rounding. ‡Pearson's chi square testing the equality of groups has a P value of < 0.0001. §Mean difference of LDL within each statin dose was significantly different by gender, with a P value < 0.0001*

women and men overall, but the gender gaps did not disappear. For those patients with LDL levels above threshold, clinical action for women and men was similar. Therefore, the persistent difference in the quality of lipid management was driven by women's higher LDL levels at every statin dose level, including among those not on any statin. We did not find that the slightly worse adherence to statins among women fully explained these higher LDL levels. Older women and women with IHD were not treated as aggressively as their male counterparts.

The large difference in LDL levels that we report is similar in magnitude to those reported in other studies among diabetic populations both within and outside of the VA.[1–5,7, 34] However, the relevance of LDL levels alone as a measure of quality has been questioned, with increasing attention paid to appropriate method of treatment.[13] In this study, we found that, among women and men aged 50–75 with diabetes who do not meet LDL targets, provision of statin therapy is very similar. In a previous study using data from the VA Diabetes Epidemiology Cohorts,[8] we noted major lipid treatment disparities among younger veterans with diabetes. Statins are contraindicated in pregnant or breastfeeding women, so such a difference may reflect appropriate clinical decision-making. However, that study found only small differences in provision of lipid-lowering therapy and initiation of statins among older veterans, consistent with our current results. Studies in non-VA populations have reported similarly small gender differences in provision of lipid-lowering therapy among older adults.[1,2,35] The present study extends this literature by applying up-to-date concepts of quality of care for lipid management that account for *both* LDL target achievement and appropriate clinical action. In addition, we focus on statins (the only lipid-lowering medication definitively tied to decreased cardiovascular risk). Recent quality reporting from the VA that applies the clinical action measure found similar results to ours.[9] We confirm that report's findings in a large, national population and explore the effect of multiple indicators of cardiovascular risk as well as adherence on gender differences in treatment.

It is noteworthy that LDL levels in women are higher without statin therapy, and remain significantly higher than those in men in the face of similar provider action and statin doses. The higher LDL levels among women on treatment may reflect higher starting levels before treatment, with providers being less likely to treat women to target due to their own beliefs about lower CVD risk in women,[36, 37] patient preferences[38–40] or drug intolerance.[41] Higher LDL levels may be acceptable if moderate dose statin exposure, rather than LDL target achievement alone, is ultimately a goal of treatment. If women's higher LDL levels reflect worse adherence, however, the lower degree of statin exposure would be of concern. We found that gender differences in statin adherence were slight and did not explain the higher LDL levels. We found a degree of difference in statin adherence that is consistent with other studies,[42] and it suggests that adherence to statins is not a greater problem for women than men in VA.

It is of concern, however, that both age and the presence of IHD had a lesser effect on pass rates among women than men. We also found that among those with IHD, the gender gap widened with increasing age. Greater age and IHD are associated with much higher 10-year risk of CVD in both genders. Statin therapy is similarly effective in women and men, for both primary and secondary prevention,[43–45] and women should not receive a different level of treatment intensity than men. However, as for patients with diabetes as a whole, the reasons for the gender gap in particularly high-risk individuals are unclear and could lie at either the provider or the patient level. Future research and quality improvement efforts should focus on improving lipid management for these high-risk patients.

Our study has several strengths. It examines a national population with large numbers of women, and we were able to adjust for multiple confounders. It is also the first study of which we are aware that applies the newest understandings of quality of care for lipid management in diabetes to an examination of gender disparities. However, our study also has several limitations. The VA often outperforms non-VA settings in meeting quality indicators, and differences in the quality of care between women and men might be smaller than those in the general population.[10,11] Although we used a one-year lookback period to assess adherence, the CMG likely does not fully account for medication stockpiling, especially among those who receive automated mail-order prescriptions. However, our finding of only a small gender difference in statin adherence is consistent with other studies. There are some limitations to CDW data that could affect the validity of measurement of performance on the clinical action measure. For example, we were not able to capture testing or prescriptions provided from outside of the VA system. However, as the measure can be passed in multiple ways, the likelihood of misclassifying an outcome is reduced. In addition, women are more likely to use non-VA care than are men, so that

accounting for statin prescriptions outside of VA would likely decrease our estimates of gender disparities even further. Finally, we were not able to gather information on patient preferences or statin side effects from our administrative data. There is a paucity of data on these issues with respect to women and statins. Some studies have found that women's perception of CVD risk is inaccurately low,[46] and that they prioritize cholesterol screening below gender-specific screening.[47,48] With regard to side effects, one large observational study found that women were less likely than men to develop serious myopathy.[49] However, some have argued that, in general, the quality of data on differences in statin side effects by gender is poor, as meta-analyses of safety data do not disaggregate for women and do not explore gender-specific concerns, such as breast cancer and pregnancy complications.[50] Gender differences in preferences or side effects may explain some differences in treatment approach, however, and should be explored in future studies.

Our results have important implications for policy, practice and research. Significant resources have been directed towards lowering LDL levels in women in VA, based on large and persistent gender disparities in meeting the LDL threshold measure. However, our use of a clinical action measure suggests that the actual quality of care for lipids in diabetic women and men, while not equivalent, is more similar than previously realized. Rather than focus on improving LDL levels in all women with diabetes, future efforts should ensure that patients with high cardiovascular risk are appropriately treated with statins when clinically indicated, feasible, and concordant with patient preferences.

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APPENDIX

Table 5. Definitions of Low-, Moderate-, and High-Dose Statins

Statin	Low-dose (mg/day)	Moderate-dose (mg/day)	High-dose (mg/day)
atorvastatin	< 10	≥ 10 to < 40	≥ 40
fluvastatin	< 80	≥ 80	–
lovastatin	< 40	≥ 40	–
pravastatin	< 40	≥ 40	–
rosuvastatin	< 5	≥ 5 to < 10	≥ 10
simvastatin	< 20	≥ 20 to ≤ 40	> 40

Moderate dose statins are those that produce a 30–40 % reduction in LDL[51–54]