Sex Disparities in Treatment of Cardiac Risk Factors in Patients With Type 2 Diabetes

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OBJECTIVE — Diabetes eliminates the protective effect of female sex on the risk of coronary heart disease (CHD). We assessed sex differences in the treatment of CHD risk factors among patients with diabetes.

RESEARCH DESIGN AND METHODS — A cross-sectional analysis included 3,849 patients with diabetes treated in five academic internal medicine practices from 2000 to 2003. Outcomes were stratified by the presence of CHD and included adjusted odds ratios (AORs) that women (relative to men) were treated with hypoglycemic, antihypertensive, lipid-lowering medications or aspirin (if indicated) and AORs of reaching target HbA1c, blood pressure, or lipid levels.

RESULTS — Women were less likely than men to have HbA1c <7% (without CHD: AOR 0.84 [95% CI 0.75–0.95], P = 0.005; with CHD: 0.63 [0.53–0.75], P < 0.0001). Women without CHD were less likely than men to be treated with lipid-lowering medication (0.82 [0.71–0.96], P = 0.01) or, when treated, to have LDL cholesterol levels <100 mg/dl (0.75 [0.62–0.93], P = 0.004) and were less likely than men to be prescribed aspirin (0.63 [0.55–0.72], P < 0.0001). Women with diabetes and CHD were less likely than men to be prescribed aspirin (0.70 [0.60–0.83], P < 0.0001) or, when treated for hypertension or hyperlipidemia, were less likely to have blood pressure levels <130/80 mmHg (0.75 [0.69–0.82], P < 0.0001) or LDL cholesterol levels <100 mg/dl (0.80 [0.68–0.94], P = 0.006).

CONCLUSIONS — Women with diabetes received less treatment for many modifiable CHD risk factors than diabetic men. More aggressive treatment of CHD risk factors in this population offers a specific target for improvement in diabetes care.

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Diabetes confers a markedly increased risk of coronary heart disease (CHD) events in both women and men (1) and eliminates the protective effect of female sex on the risk of CHD. In women with and without diagnosed heart disease, diabetes raises the relative risk of heart disease mortality 3- to 10-fold relative to that of women without diabetes (2–6). Despite declining CHD mortality over the last 30 years in the U.S. population overall and in men with diabetes, women with diabetes appear to have experienced an increase in age-adjusted CHD mortality (7).

Several pathophysiological mechanisms may contribute to the increased risk of CHD mortality in men and women with diabetes. Patients with type 2 diabetes have an increased incidence of conventional and unconventional CHD risk factors (8,9). Women with diabetes may be subject to even more adverse changes in coagulation, vascular function, and CHD risk factor levels than diabetic men (10–13).

In addition to sex-based physiologic differences, there may also be differences in treatment of CHD risk factors that contribute to increased risk in women with diabetes. Several studies of patients without diabetes have demonstrated disparities in treatment of heart disease and CHD risk factors among women and men in primary care (14,15) and hospital settings (16,17). Treatment disparities have been shown to be related to differences in patient risk factors (18) and physician behavior (19). These differences may persist even after a problem is identified: when women receive treatment, they are often treated less aggressively (20).

Treating modifiable CHD risk factors (such as blood pressure and lipids) and using ACE inhibitors and aspirin reduce mortality in diabetes (21–25), which is now considered a CHD equivalent (26). The Heart Protection Study showed an ~25% reduction in vascular event rates in all subgroups treated with simvastatin, including patients with diabetes and women, regardless of initial levels of LDL and HDL cholesterol (27). In 2000, the American Diabetes Association (ADA) recommended statin therapy for patients with LDL cholesterol >100 mg/dl if CHD or multiple risk factors were present, as well as prophylactic use of aspirin and blood pressure control with an ACE inhibitor to delay progression to microalbuminuria (28). Subsequent recommendations are more stringent (29). The American Heart Association, concordant with the latest ADA guidelines, has endorsed an HDL target of >50 mg/dl and recommends that statins be initiated in women with diabetes, even if LDL is <100 mg/dl (30).
In light of these recommendations and the possibility of sex disparities in CHD risk factor control in the high-risk diabetic state, we sought to determine whether there were differences in the treatment of CHD risk factors in women compared with men in a large primary care cohort of patients with diabetes, stratified by presence of diagnosed CHD.

**RESEARCH DESIGN AND METHODS** — We conducted a cross-sectional observational study of outpatients with diabetes in five internal medicine practices—two hospital based and three community based—affiliated with an academic medical center between 1 January 2000 and 31 July 2003. Data were collected from the hospital Central Data Repository (laboratory test dates and results), billing claims (hospitalizations and hospital discharge diagnoses), administrative records (patient demographics and insurance status), and directly from the electronic medical record or written medical record (problem lists and prescribed medications at the end of the study period). In addition, we performed manual chart reviews at one community-based health center and one hospital-based clinic to assess changes in blood pressure and medication prescription.

We generated lists of potentially eligible patients using billing claims for non-gestational diabetes (ICD-9 codes 250.00–250.90) over a 3-year period. For the two clinics that underwent manual chart review, trained research nurses created diabetes registries. Diabetes was defined based on the diagnosis being listed in the problem list, diabetes-specific medicine listed in the medication list (e.g., sulfonylurea, metformin, insulin, or equipment for insulin injection or home glucose monitoring), or diabetes diagnosis discussed in a progress note. Using these registries as a gold standard, we developed an automated algorithm to identify patients with diabetes using billing claims, laboratory testing, and problem lists and medications from the electronic medical record. Compared with the gold standard chart review, the algorithm had a sensitivity of 98% and specificity of 98% for diabetes. We then used this validated algorithm to develop diabetes registries for the additional clinics. Determination of the type of diabetes was not possible in ~50% of the sample; in the remainder, 97% of patients were recorded as having type 2 diabetes. We limited our analysis to patients who had at least one visit early (1 January 2000 to 31 August 2001) and one visit late (1 December 2001 to 31 July 2003) in the observation period to capture a population of patients who were attending regular follow-up visits at the practices.

Forty-four percent of the patients in the study cohort were treated at hospital-based primary care practices; the rest were treated at health centers located in different neighborhoods in and around Boston. The population represented a broad sociodemographic sample of outpatients with type 2 diabetes.

Patients with missing values for HbA₁c, total cholesterol, HDL, or LDL (n = 382) were excluded from the original sample of 4,231, leaving a population of 3,849 for analysis (91%). The excluded patients were of similar age, sex, and race as the included patients, but fewer spoke English (81 vs. 87%, P = 0.002).

Demographic variables examined included age, race (white, African American, Hispanic, or other) and whether the patient spoke English (yes/no). All co-morbidity and treatment variables were determined at the end of the study period. Active treatment for diabetes and CHD risk factors was defined as follows: treatment for hyperglycemia (prescription of α-glucosidase inhibitors, biguanides, insulin, glitazones, sulfonylureas, or thiazolidinediones); treatment for hypertension (ACE inhibitors, angiotensin receptor blocker [ARB], α-blocker, β-blocker, calcium-channel blocker, or thiazide); and treatment for hyperlipidemia (hydroxy-methylglutaryl-CoA reductase inhibitors, cholestyramine, colestipol, fenofibrate, gemfibrozil, or niacin). We also determined whether the nonprescription medications aspirin, acetaminophen, and ibuprofen were listed in the medical record.

Hypertension was present if listed on the problem list or if an antihypertensive medication was listed on the medication list. CHD was defined by having CHD (or synonyms) on the problem list or CHD-specific medications such as sublingual nitroglycerin on the medication list. Dyslipidemia was defined as present if listed on the problem list, if a lipid-lowering drug had been prescribed, or if the subject was not taking a lipid-lowering drug and LDL was >100 mg/dl and HDL was <40 mg/dl in men and <50 mg/dl in women. Over 80% of patients identified using these algorithms had hypertension, CHD, or dyslipidemia recorded in the problem list. Current smoking was determined by inclusion on the problem list.

We stratified all analyses by the presence or absence of diagnosed CHD as indicated by CHD entry in the medical record, but we present some collapsed results for analyses where results did not differ by CHD status. Descriptive statistics included tests for means and the χ² test for proportions comparing differences between women and men. We used logistic regression models to estimate adjusted odds ratios (AORs) and 95% CIs that women, using treatment in men as the referent, were prescribed specific treatments. The models were adjusted for sociodemographic variables that differed by sex in the bivariate analysis including age, racial/ethnic group, language, and smoking status and included a term for clinic site as a random effect to account for possible within-site correlation of treatment patterns.

Evaluation of treatment appropriateness included use of hypoglycemic medicines in all patients and those with HbA₁c >7%, an ACE inhibitor or ARB in all patients, antihypertensive medicine in patients with hypertension, lipid-lowering therapy in patients with dyslipidemia, and aspirin in all patients. Using the same modeling strategy, we also estimated the odds of treatment effectiveness in patients who were prescribed medications for hyperglycemia, hypertension, and hyperlipidemia. Treatment effectiveness was defined as meeting recommended risk factor treatment goals defined by the ADA, the National Cholesterol Education Program, and the American Heart Association guidelines or quality-of-care benchmarks established by the National Committee on Quality Assurance (NCQA) (31). Analysis of antihypertensive treatment effectiveness was limited to the subset of patients (n = 1,817, 47% of cohort) for whom blood pressure data were available. All analyses were conducted using the SAS System for Windows, version 8.2 (32). Statistical significance was defined as a two-tailed P value <0.05.

**RESULTS** — Of 3,849 patients with diabetes in our analysis cohort, about one-half were women. Thirty percent...
Sex disparities in cardiac risk treatment

Table 1—Population characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without CHD</th>
<th>Patients with CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>n (%)</td>
<td>2,699 total</td>
<td>1,150 total</td>
</tr>
<tr>
<td>Sociodemographic (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>English-speaking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD risk factors (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>87%</td>
<td>91%</td>
</tr>
<tr>
<td>Hyperlipidemia‡</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>17%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise noted. Columns may not sum to 100% due to rounding error. *Men versus women by t test for continuous variables and χ² for categorical variables; †identified by problem list or condition-specific medication; ‡identified by problem list, condition-specific medication, or LDL/HDL subfractions. The cohort had CHD. Table 1 shows the baseline characteristics for men and women, stratified by CHD status. In general, women were more likely than men to be older, non-white, and non-English speaking and to be treated at a community health center. Women with CHD had significantly higher systolic blood pressure than their male counterparts. Women with and without CHD had higher total HDL and LDL levels than the men.

Table 2—Levels of blood pressure, HbA₁c, and cholesterol

<table>
<thead>
<tr>
<th>BP (n)†</th>
<th>Male</th>
<th>Female</th>
<th>P*</th>
<th>Male</th>
<th>Female</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129 ± 16</td>
<td>131 ± 17</td>
<td>0.37</td>
<td>129 ± 18</td>
<td>133 ± 19</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77 ± 10</td>
<td>74 ± 10</td>
<td>&lt;0.0001</td>
<td>72 ± 10</td>
<td>71 ± 11</td>
<td>0.11</td>
</tr>
<tr>
<td>BP &lt;140/90 (%)</td>
<td>28 ± 31</td>
<td>104 ± 104</td>
<td>0.065</td>
<td>40 ± 34</td>
<td>34 ± 34</td>
<td>0.12</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>7.6 ± 1.7</td>
<td>7.6 ± 1.6</td>
<td>0.62</td>
<td>7.5 ± 1.5</td>
<td>7.7 ± 1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>HbA₁c &lt;7.0% (%)</td>
<td>41 ± 40</td>
<td>40 ± 40</td>
<td>0.44</td>
<td>41 ± 34</td>
<td>34 ± 34</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL &lt;100 mg/dl (%)</td>
<td>67 ± 69</td>
<td>62 ± 62</td>
<td>0.25</td>
<td>69 ± 62</td>
<td>62 ± 62</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise noted. Columns may not sum to 100% due to rounding error. *Men versus women by t test for continuous variables and χ² for categorical variables; †blood pressure (BP) data for community health center 3 and hospital-based practice 2 only (n = 1,817).
Table 3—Comparison of diabetes and CHD treatments in men and women

| Medications (n)† | Male 2,699 total | Female 1,150 total | P*  
|------------------|------------------|------------------|-----
| Aspirin (%)      | 46               | 37               | <0.0001  
| Acetaminophen (%)| 6                | 9                | 0.002  
| Ibuprofen (%)    | 10               | 15               | 0.0002  
| Glycemic management (%)† | 87               | 85               | 0.16  
| HbA1c of patients taking hypoglycemic medication (%)† | 7.8 ± 1.7 | 7.8 ± 1.6 | 0.82  
| HbA1c (%)        | 2,310 total      | 1,016 total      |  
| HbA1c <7.0% (%)  | 75               | 75               |  
| HbA1c <8.0% (%)  | 1,419 total      | 1,113 total      |  
| Lipid management (%)† | 54               | 51               | 0.09  
| Levels of patients on lipid lowering therapy (%)  
| Total cholesterol (mg/dl) | 171 ± 41 | 184 ± 39 | <0.0001  
| Total cholesterol <200 mg/dl (%) | 81 | 70 | 0.0002  
| HDL (mg/dl)      | 42 ± 11          | 50 ± 14          | <0.0001  
| LDL (mg/dl)      | 94 ± 33          | 101 ± 34         | 0.0003  
| LDL <100 mg/dl (%) | 62             | 56               | 0.02   
| LDL <130 mg/dl (%) | 87             | 81               | 0.002  
| Cardiac risk ratio <5 (%)‡ | 75               | 83               | 0.0004  
| BP management (%)† | 2,699 total      | 1,150 total      | 1,016 total  
| BP for patients taking antihypertensive medication (%)  
| Systolic BP (mmHg) | 132 ± 17 | 133 ± 16 | 0.13  
| Diastolic BP (mmHg) | 77 ± 11 | 74 ± 11 | <0.0001  
| BP <130/80 (%)  | 27               | 27               | 0.75  
| BP <140/90 (%)§ | 62               | 61               | 0.56  

Data are means ± SD unless otherwise noted. *Men vs. women by t test for continuous variables and χ² for categorical variables; †as listed in the medical record; ‡blood pressure (BP) data for community health center 3 and hospital-based practice 2 only, n = 1,817; §cardiac risk ratio = total cholesterol/HDL cholesterol.

CONCLUSIONS — In this large cohort of patients with diabetes seen in five academically affiliated primary care clinics, one-third of whom had diagnosed CHD, women were significantly less likely than men to receive recommended treatments for several major modifiable CHD risk factors and, when treated, were less likely to achieve recommended goals of therapy. Even though all of the patients received, on the whole, above-average quality of care by NCQA standards, women did not uniformly receive as good care as men in unadjusted analyses and after adjusting for differences in age, race, clinic site, and other variables. Among patients without CHD, women were less likely than men to be prescribed lipid-lowering medications and aspirin and were less likely to have HbA1c and LDL at goal levels. Among patients with CHD (and likely to reap the greatest benefits from treatment of CHD risk factors), women were less likely than men to be taking aspirin or to have their HbA1c, <140/90 mmHg (AOR 0.88 [95% CI 0.85–0.91], P < 0.0001, n = 587, Fig. 1B).

In unadjusted analyses of patients with diabetes, aspirin was listed less frequently in the medication lists of women than men without CHD (37 vs. 46%, P < 0.0001) and of women than men with CHD (72 vs. 79%, P < 0.01). In contrast, two other nonprescription medicines, acetaminophen and ibuprofen, were listed with equal frequency for women and men with diagnosed CHD and more frequently for women without CHD (Table 3). In multivariable analyses adjusted for age, sociodemographic variables, and clinic site (Fig. 1A), women without CHD were less likely to have aspirin on their medication list than men (AOR 0.63 [0.55–0.72], P < 0.0001, n = 2,699). The results among patients with diagnosed CHD were similar to those for patients without diagnosed CHD: women with diagnosed CHD were 30% less likely than men to have aspirin listed in their medical records.
blood pressure, or lipids controlled to recommended levels.

Women with diabetes have not experienced the same improvement in CHD events and mortality as men with diabetes and as women and men without diabetes over the last 30 years (7). Although there are probably biological and other reasons for these differences, our results suggest that differences in clinical treatment may also contribute to the excess burden of CHD in women with diabetes.

Increasingly, the medical profession and the public have been paying particular attention to heart disease in women (33). The American Heart Association recently launched its “Go Red for Women” campaign, published clinical guidelines focused on women (30), and prioritized sex-specific research goals to improve understanding of the diagnosis and treatment of heart disease in women (34). Women are increasingly aware of their own risk of cardiovascular death (35).

Differences in treatment patterns persist. Lower adherence to treatment guidelines has been demonstrated in patients with diabetes who are older and whose conditions are more medically complicated, but sex-based differences were not examined (36,37). A Swedish study from 2004 examined the treatment of 9,375 patients with diabetes in the primary care setting and found that men had lower blood pressure, HbA1c, and LDL levels (38), but there have been few other studies of this disparity in diabetes. Although the women in our study were older and less likely to be white than the men (differences for which the models adjusted), they had a similar prevalence of CHD risk factors.

Other studies of patients without diabetes have also found that women with dyslipidemia are less likely than men to be

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**Figure 1**—A: Odds of receiving treatment, if indicated, for women relative to men. Indicated treatment: ACE or ARB for all patients, hypoglycemics for all patients on treatment or with Hba1c > 7.0%, lipid-lowering for patients diagnosed with hyperlipidemia or LDL cholesterol > 100 mg/dl and HDL cholesterol < 40 mg/dl in men or < 50 mg/dl in women, and aspirin for all patients. B: Effectiveness of therapy on treatment. Odds ratio, women versus men, of achieving recommended goals of therapy for patients receiving antihypertensive, glucose-lowering, and lipid-lowering medications, stratified by presence of diagnosed CHD. BP, blood pressure; LDL-C, LDL cholesterol.
treated with lipid-lowering agents (39). This may be explained by the fact that women frequently have higher HDL levels. Health care providers in general may disregard elevated LDL levels, assuming a protective effect of elevated HDL levels. Emphasis on the protective effects of elevated HDL levels in patients with diabetes may be misplaced, as some evidence shows that HDL in patients with diabetes may not be as protective as in patients without diabetes (40). Furthermore, results from the Scandinavian Simvastatin Survival Study, the Cholesterol and Recurrent Events (Investigators) Trial (CARE), and the Heart Protection Study have consistently shown a 25–35% reduction in the relative risk of cardiovascular events in patients with diabetes who were treated with statins at all levels of baseline cholesterol. Finally, the consensus recommendations for treating elevated LDL levels are identical for men and women.

No obvious justification can be given to explain the marked differences we observed in aspirin recommendations between diabetic women and men with and without CHD. We have shown in a similar population that hypertension and hyperlipidemia are managed less aggressively than hyperglycemia (41). In this cohort, it appears that female sex may additionally decrease attention to treatment of cardiac risk factors, possibly related to patient preferences or physician perceptions of risk.

Several potential limitations must be addressed. First, the possibility of differential record-keeping by sex cannot be completely eliminated, but the fact that the prevalence of many risk factors and treatments were equal between sexes and without CHD. We have shown in a similar population that hypertension and hyperlipidemia are managed less aggressively than hyperglycemia (41). In this cohort, it appears that female sex may additionally decrease attention to treatment of cardiac risk factors, possibly related to patient preferences or physician perceptions of risk.

In summary, this large, clinic-based cohort of patients with diabetes received generally high-quality diabetes care, yet women were less likely than men to be treated with aspirin and lipid-lowering therapy; also, their lipids, blood pressure, and hyperglycemia tended to be treated less effectively. Sex differences in CHD risk reduction may partially explain the persistent increased risk of CHD events in women with diabetes observed in national surveys. More aggressive treatment of CHD risk in women with diabetes appears to offer a specific target for improvement in diabetes care.

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Sex disparities in cardiac risk treatment

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