Paradoxical lower postmyocardial infarction mortality among veteran women – does a sex bias exist in the Veterans Affairs medical system?

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BACKGROUND: Outcomes after acute coronary disease are reportedly worse among women in general and more so among women with diabetes compared with men. Sex differences were evaluated in postmyocardial infarction (MI) mortality among veterans (who are predominantly male) to determine whether evaluation and treatment in Veterans Affairs hospitals amplifies sex differences in outcome.

METHODS: All patients discharged with the primary diagnosis of acute MI from any Veterans hospitals in the United States between October 1990 and September 1997 were identified. Demographic, comorbidity, inpatient, outpatient, mortality and readmission data were extracted. Mortality, revascularization and readmissions were compared between male and female patients using Cox regression models.

RESULTS: The authors identified 67,889 patients with MI, 17,756 (26%) of whom had diabetes. There were 951 women, 280 (29%) of whom had diabetes, and 66,938 men, 17,476 (26%) of whom had diabetes. Over the entire follow-up period, adjusted mortality was higher in men than women (hazard ratio [HR] 1.5, 95% CI 1.3 to 1.7). Cardiac procedures were significantly higher among men: HR for coronary bypass surgery was 2.1 (95% CI 1.6 to 2.8; $P<0.001$) for all men, while HR for catheterization and percutaneous coronary intervention were higher for men among non-diabetics only – 1.5 (95% CI 1.2 to 1.8; $P<0.001$) and 2.0 (95% CI 1.4 to 2.9; $P<0.001$). Interaction between sex and diabetes was not significant.

CONCLUSIONS: Contrary to previous observations in the nonveteran population, long-term mortality post-MI was lower among veteran women, despite higher procedure rates in men. The present study also failed to show increased mortality in women with diabetes.

Key Words: Diabetes; Mortality; Myocardial infarction; Sex

Despite the substantial improvement in mortality from acute coronary artery disease (CAD) in the overall population, women in general, and diabetic women in particular, reportedly have worse prognoses following myocardial infarction (MI) than men (1-9). Several reasons (1) have been proposed to explain this, including a sex bias in treatment.

The Veterans Affairs (VA) health care system is the largest health care system in the United States and is unique in several aspects. It treats predominantly male patients, covers all geographic areas of the country and offers uniform care without regard to patient financial constraints. Access to care may be affected by health insurance status,

Mortalité post-infarctus du myocarde paradoxalement moindre chez les anciennes combattantes – le système de santé des vétérans comporterait-il un biais lié au sexe?

HISTORIQUE : Selon les rapports, l'issue d'un épisode coronarien aigu est plus sombre chez les femmes en général et davantage chez les femmes atteintes de diabète, comparativement aux hommes. Les auteurs ont voulu vérifier la différence de la mortalité post-infarctus du myocarde (IM) entre les hommes et les femmes chez les vétérans (en majeure partie des hommes) afin de déterminer si les examens et traitements fournis dans les hôpitaux pour anciens combattants amplifient les différences pronostiques liées au sexe.

MÉTHODES : Tous les patients ayant reçu leur congé avec un diagnostic principal d'IM aigu dans un hôpital des États-Unis pour anciens combattants entre octobre 1990 et septembre 1997 ont été recensés. Les auteurs ont extrait les données démographiques et les données sur les comorbidités, l'hospitalisation, les soins ambulatoires, la mortalité et les réadmissions. La mortalité, la revascularisation et les réadmissions ont été comparées entre les hommes et les femmes au moyen de modèles de régression de Cox.

RÉSULTATS : Les auteurs ont relevé 67 889 cas d'IM dont 17 756 (26 %) sur fond de diabète. En tout, le groupe comprenait 951 femmes et 66 938 hommes dont 280 (29 %) et 17 476 (26 %) respectivement souffraient de diabète. Au cours de l'entière période de suivi, la mortalité ajustée a été plus élevée chez les hommes que chez les femmes (risque relatif [RR] 1,5, IC à 95 %, 1,3 à 1,7). Les interventions cardiaques ont été significativement plus nombreuses chez les hommes. Le RR pour les pontages coronariens a été de 2,1 (IC à 95 %, 1,6 à 2,8; $P<0,001$) pour tous les hommes, tandis que le RR pour le cathétérisme et les interventions coronariennes percutanées a été plus élevé pour les hommes chez les sujets non diabétiques seulement, 1,5 (IC à 95 %, 1,2 à 1,8; $P<0,001$) et 2,0 (IC à 95 %, 1,4 à 2,9; $P<0,001$). L'interaction entre le sexe et le diabète s'est révélé non significatif.

CONCLUSION : Contrairement aux observations antérieures dans la population générale (vs anciens combattants), la mortalité post-IM à long terme a été moindre chez les anciennes combattantes malgré un taux d'interventions plus élevé chez les hommes. La présente étude n'a pas non plus réussi à démontrer une mortalité accrue chez les femmes atteintes de diabète.

lower socioeconomic status, lower levels of literacy and lack of cultural sensitivity by physicians (Smedley et al 10). Equal access to care in the VA health care system may impact sex differences in CAD mortality. Given the background of these peculiarities to the VA health system, whether sex differences in CAD mortality post-MI exist in the veteran population is not known. Furthermore, determining recent trends in the outcomes of patients with diabetes and CAD assumes greater importance, given the increasing prevalence of diabetes worldwide (11,12).

We hypothesized that if a true sex bias existed, the differences in post-MI mortality among men and women should be amplified in the

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TABLE 1
Baseline subject characteristics

	Women (n=951)	Men (n=66,938)	P*
Age in years	65.8±12.3	65.0±10.8	0.028
Caucasian	773 (82)	64,958 (97)	0.240
Number of diagnoses	5.6±2.6	5.6±2.6	0.774
Diabetes	280 (29)	17,476 (26)	0.020
Hypertension	425 (45)	29,830 (45)	0.938
Hyperlipidemia	166 (18)	9675 (15)	0.009
History of atrial fibrillation	74 (8)	6036 (9)	0.186
History of stroke	16 (2)	724 (1)	0.076
Congestive heart failure	189 (20)	14,569 (22)	0.160
Chronic obstructive pulmonary disease	139 (15)	13,004 (19)	<0.001
Charlson Index >2	270 (28)	23,299 (35)	<0.001
Region			<0.001
Midwest	183 (19)	15,448 (23)	
Northeast	144 (15)	9161 (14)	
South	390 (41)	29,913 (45)	
West	234 (25)	12,416 (19)	

*Age and number of diagnoses are shown as mean ± SD, with comparisons using t tests. All other characteristics shown as n (%), with comparisons using χ^2 tests

setting of VA hospitals, given the predominantly male population treated in these hospitals. We tested this hypothesis in a large veterans post-MI dataset.

METHODS

Study population

The patient treatment file (PTF) portion of the medical record was used to identify all female patients discharged from any VA medical centre in the United States between October 1990 and September 1997 with a diagnosis of acute MI (*International Classification of Diseases*, ninth revision, clinical modification [ICD-9-CM] code 410) listed as the primary discharge diagnosis. The validity of this strategy to identify patients with acute MI has been previously established (13,14). For veterans with more than one admission with an eligible ICD-9-CM code during the study period, the first admission was considered to be the index admission. Patients who were discharged and readmitted the same day were assumed to have been transferred from one medical centre to another (a common practice in the VA medical system), and their admissions were considered to represent a single hospitalization. Patients whose length of stay exceeded one year were excluded from the analysis. These patients had comorbid conditions causing long-term disability or were mental health care patients who have a different postinfarction course and health care resource use than those without these conditions. The study was approved by the institutional review board of Indiana University School of Medicine (Indianapolis, USA).

Data on hospitalization, follow-up and mortality

Data were extracted from the central VA administrative data centre in Austin, USA. Data regarding VA inpatient utilization throughout the index hospitalization were extracted from PTFs. There is high agreement between PTF data and data extracted from paper patient medical charts (15). Demographic, in-hospital and follow-up data were recorded for each patient. Each hospitalization record in the PTF contains up to 10 discharge diagnoses. Discharge diagnoses 2 through 10 from the index admission were used to identify comorbid conditions. The severity of a patient's acute MI and medication profile were not available in the PTF.

All readmissions and readmissions due to cardiac causes (first listed diagnosis of acute MI, angina and congestive heart failure) to any VA

medical centre were assessed at one year and ever following discharge from the index hospitalization. Readmissions within 30 days of the index admission were considered to be part of the index admission, and these were excluded from the readmission analysis. However, these patients were included in the mortality analysis.

For outpatient services, utilization data were extracted from the VA outpatient clinic file identifying visits to primary care, cardiology clinic, emergency units and cardiac surgery clinics. Data regarding diagnostic tests and procedures were also extracted for cardiac catheterization, coronary artery bypass graft surgery, percutaneous coronary revascularization (percutaneous coronary intervention [PCI]) and pacemaker or defibrillator implantation. Time to cardiac procedures within one year was assessed.

Mortality was assessed at 30 days, 60 days and one year from the index admission. To determine mortality, the Beneficiary Information and Resource Locator was used (16,17). This contains dates of death, but not causes of death. Hence, all-cause mortality was used as an end point.

Statistics

All analyses were performed using SAS version 9.1 (SAS Institute Inc, USA). For discrete variables, frequencies and proportions were calculated and χ^2 tests were used to test for differences between sexes. For continuous variables, mean ± SD were calculated, and two-sample t tests were used to test for differences between sexes.

Male and female patients were compared for differences in the percentages who died within 30 days, 60 days and one year of the index admission using logistic regression; ORs were used to summarize the male versus female comparisons. Because of different follow-up times and censored observations, total time to death, and the numbers of coronary artery bypass graft, PCI and cardiac catheterization procedures were compared between men and women using Cox proportional hazards survival analysis; hazard ratios (HR) were used to summarize the men versus women comparisons. All analyses were adjusted for the following demographic and comorbid conditions: age, race, diabetes, hypertension, congestive heart failure, hyperlipidemia, atrial fibrillation, chronic obstructive pulmonary disease, stroke, and number of discharge diagnoses, Charlson Index (categorized as higher than 2, or 2 or lower) and geographical region (midwest, northeast, west or south). These variables were determined a priori to be possible predictors of the outcomes and were not evaluated here for significance (18). The interactions between sex and diabetes were examined for all outcomes.

To evaluate how the large sample size difference between men and women affected the conclusions, analyses were repeated using a subset of men, so that equal numbers of men and women were used. Men were selected randomly with replacement, and the selected men and all women were used in the same analyses as described above. These bootstrap analyses (19) were repeated 500 times to provide estimates of the OR or HR, and P values. This sensitivity analysis was performed to ensure that any significant differences found when analyzing all subjects were 'real' and not due to being overpowered for testing the sex differences due to the large number of men.

RESULTS

A total of 67,889 patients with MI were identified, 17,756 (26%) of whom had diabetes. There were 951 women, 280 of whom (29%) had diabetes, and 66,938 men, 17,476 of whom (26%) had diabetes. The baseline characteristics of male and female subjects are shown in Table 1. Women were slightly older (66 versus 65 years of age), were more likely to have diabetes and hyperlipidemia, and were less likely to have chronic obstructive pulmonary disease or a Charlson Index higher than 2. The geographic distribution of the patients was also significant, with a higher percentage of women from the west region, and lower percentages from the midwest and south regions.

Adjusted OR for death within 30 days or 60 days showed no significant sex effects, although men were more likely to die within one year (Table 2). Over the entire follow-up period, death was higher

TABLE 2
OR for death within 30 days, 60 days and one year for men versus women

	Events, n (women)	Events, n (men)	OR (95% CI)	P
Death within 30 days	100	7626	1.13 (0.90 to 1.40)	0.295
Death within 60 days	115	8964	1.15 (0.93 to 1.42)	0.191
Death within 1 year	165	14,344	1.33 (1.10 to 1.59)	0.003

OR were adjusted for age, race, diabetes, hypertension, congestive heart failure, hyperlipidemia, atrial fibrillation, chronic obstructive pulmonary disease, stroke, number of discharge diagnoses, Charlson Index and geographical region

TABLE 3
Hazard ratios for death, invasive procedures and readmissions for men versus women

	Events, n (women)	Events, n (men)	Hazard ratio (95% CI)	P
Death, ever	250	25,056	1.51 (1.33 to 1.72)	<0.001
Coronary artery bypass graft within 1 year	50	7551	2.11 (1.60 to 2.80)	<0.001
PCI within 1 year, diabetics	24	1359	0.96 (0.63 to 1.47)	0.862
PCI within 1 year, nondiabetics	32	4640	2.01 (1.41 to 2.88)	<0.001
Catheterization within 1 year, diabetics	68	4504	1.04 (0.82 to 1.33)	0.755
Catheterization within 1 year, nondiabetics	121	13,409	1.49 (1.24 to 1.79)	<0.0001
Readmission				
Any, within 1 year	383	32,566	1.30 (1.17 to 1.44)	<0.001
CV, within 1 year	292	24,254	1.24 (1.10 to 1.39)	<0.001
Any, ever	453	40,903	1.48 (1.35 to 1.63)	<0.001
CV, ever	355	31,938	1.40 (1.26 to 1.56)	<0.001

Hazard ratios were adjusted for age, race, diabetes, hypertension, congestive heart failure, hyperlipidemia, atrial fibrillation, chronic obstructive pulmonary disease, stroke, number of discharge diagnoses, Charlson Index and geographical region. CV Cardiovascular; PCI Percutaneous coronary intervention

among men than women (Table 3) (HR of 1.51 [95% CI 1.33 to 1.72]) ($P<0.001$). Interactions between sex and diabetes were not significant, indicating that the presence of diabetes does not affect the relationship between sex and death in this population. Survival curves for men and women are shown in Figure 1.

Among procedures, men had significantly higher coronary bypass surgery procedures by one year compared with women (Table 3). However, the numbers of PCI and catheterization procedures were significantly higher in men only among nondiabetics. Readmissions for any reason or cardiovascular reason were significantly higher in men over the entire duration of follow-up.

The results of the bootstrap analyses (OR or HR and significance tests) were similar to the results when using data from all men (Table 4). Table 5 provides the actual numbers of events in male and female subjects according to their diabetes status.

DISCUSSION

The main conclusions of our study are that in a setting in which predominantly male patients are treated, women had a better long-term post-MI outcome than men despite a greater number of cardiac procedures performed among men, and that the diabetes status had no effects on sex differences in post-MI mortality. Survival curves reveal that on long-term follow up, diabetic women have long-term outcomes similar to nondiabetic men. These results are unique and are being reported for the first time among a veteran population. They present a unique

Figure 1) Survival functions for men and women for time to death from the multiple-variable Cox proportional hazards model

TABLE 4
Bootstrap analysis OR and hazard ratio (HR) for death for men versus women

	OR or HR (95% CI)	P
Death within 30 days	1.13 (0.83 to 1.53)	0.307
Death within 60 days	1.16 (0.87 to 1.56)	0.176
Death within 1 year	1.31 (1.02 to 1.69)	0.004
Death, ever	1.49 (1.26 to 1.76)	<0.001

OR and HR adjusted for age, race, diabetes, hypertension, congestive heart failure, hyperlipidemia, atrial fibrillation, chronic obstructive pulmonary disease, stroke, number of discharge diagnoses, Charlson Index and geographical region

TABLE 5
Actual number of events in men (M) and women (W) by diabetes status

	No DM, W	No DM, M	DM, W	DM, M
Death within 60 days	76	6412	39	2552
Death within 1 year	103	10,045	62	4299
Death, ever	158	17,472	92	7584
CABG within 1 year	32	5498	18	2053
PTCA within 1 year	32	4640	24	1359
Catheterization within 1 year	121	13,409	68	4504
Readmission				
Any, within 1 year	257	23,372	126	9194
Cardiovascular, within 1 year	193	17,298	99	6956
Any, ever	306	29,819	147	11,084
Cardiovascular, ever	237	23,070	118	8868

CABG Coronary artery bypass graft; DM Diabetes mellitus; PTCA Percutaneous transluminal coronary angioplasty

perspective on sex differences in post-MI outcomes and add an interesting dimension to the conundrum regarding a sex bias in treatment.

At baseline, there were higher numbers of diabetic and hyperlipidemic patients among women, while chronic obstructive pulmonary disease was more common among men. In addition, comorbidities, as measured by the Charlson Index, were higher among men. The number of cardiac procedures was higher in men. The mortality difference in our study became significant only after the first year.

It is interesting to note that a number of trials of acute coronary syndromes have reported higher mortality and morbidity among women, and more so in subjects with diabetes (1-9,20). Several possible explanations have been put forward to explain this, including differences in presentation, and sex bias in diagnosis and in management

of acute coronary syndromes in women (1-9,20). However, from our study, it appears that despite the fact that the VA health care system cares predominantly for male patients, the post-MI prognosis of veteran women is better, even among diabetic women. The reasons for this paradoxical finding are not immediately obvious. If a true sex bias existed, one would have expected to find worse outcomes among women, in line with other previous reports (1-9). Although in this dataset we cannot directly correlate outcomes to access to care (which is uniform among all veterans), access to care is clearly an important issue affecting outcomes (21). Furthermore, although the demographics of our patient population are comparable with those included in previous reports (1-9), unknown and unmeasured confounders in the veteran population accounting for these results cannot be ruled out. Consistent with previous observations and reports (1-9), women underwent lower numbers of invasive cardiac procedures in our study. However, this did not translate into poorer outcomes, raising the possibility of increased procedure-related effects on long-term mortality. This has been noted by previous investigators who have reported that despite a strikingly greater number of invasive procedures post-MI in the United States compared with Canada, the outcomes were not different (22).

The Framingham Study (20) reported 5209 men and women who were followed biennially. In the course of follow-up, 414 men and 195 women survived an initial MI and were followed for recurrent MI or a fatal coronary event. Among this group, 55 men and 37 women had diabetes. The recurrent MI rate was 17.7% in diabetic women compared with 9.6% in diabetic men, while the fatal CAD rate was 14.0% in diabetic women and 14.1% in diabetic men. The risk conferred by diabetes was much higher for women than for men compared with the nondiabetic population. They concluded that while in the nondiabetic population women had a significant survival advantage compared with men post-MI, this was lost in the setting of diabetes. This excessive event rate in women could not be explained on the basis of baseline characteristics. More recently, Natarajan et al (23) analyzed pooled data of 5243 patients in the Framingham Study and the Framingham Offspring Study, with a follow-up of 20 years. At baseline, 134 men and 95 women had diabetes. They compared the risk for CAD mortality associated with diabetes versus established CAD. Among women with diabetes, the HR for coronary death was 3.8 (95% CI 2.2 to 6.6), while among women with known CAD, it was 1.9 (95% CI 1.1 to 3.4). Thus, they concluded that in women, diabetes confers an even greater risk for coronary mortality than established coronary disease, while the reverse was true for men. On the other hand, Miettinen et al (24) were unable to demonstrate higher mortality for female diabetics post-MI. However, their follow-up lasted up to one year, as opposed to our study, in which the follow-up was much longer. It is also noteworthy that in their study, among hospitalized diabetic patients, the 28-day mortality was markedly higher in women than in men.

Our study has several strengths. It is one of the largest studies to date to investigate long-term post-MI mortality in the 1990s, when substantial changes occurred in the management of acute MI. The data were collected all over the country, as opposed to certain regions or medical centres, providing a homogenous and unbiased population. Hospitals treating the patients included both community hospitals and tertiary care referral centres. There was a good mix of white and black population, with 13% of the population being black. We used all-cause mortality as an end point, which has previously been used and accepted in such investigations. Despite the fact that the VA medical centres predominantly treat male subjects, our dataset of female subjects was sufficiently large to be analyzed for the study. In fact, the absolute sample size of female subjects was larger than some recently published trials (20,23,24).

Certain methodological considerations merit discussion. The diagnoses of diabetes and MI were based on ICD9-CM codes, and the diagnoses of a random sample was not validated. However, previous data revealed a greater than 88% correlation of database coding information for acute MI, with actual review of medical records in VA patients (17).

Previous administrative database studies have shown good validity using ICD-9 codes for MI (25,26) and diabetes mellitus. Because medication histories were not available, treatment with hypoglycemic agents could not be confirmed. Data on the duration of diabetes, glycosylated hemoglobin levels and classification of diabetes as type 1 or type 2 were not available. However, because both diabetes and MI are diagnosed on the basis of objective tests (blood tests), the possibility of misclassification is lower than some other clinical situations, such as a congestive heart failure diagnosis (25). It needs to be mentioned that many of the studies we have referred to have used similar administrative databases (25,26). The absolute number of patients with diabetes may be higher; a recent report showed that undiagnosed diabetes is common in patients admitted with acute MI (27). Moreover, we used the index admission to classify patients as having or not having diabetes. Therefore, patients who had been diagnosed subsequent to their index admission might have been misclassified. It is possible that during the period of the study, some patients in the group without diabetes might have developed diabetes. This could potentially narrow the mortality difference between the two groups. Although in terms of absolute numbers our study had more diabetic women than any of the previous studies, the relative proportion of women, compared with men, was markedly lower (given the fact that the study was performed in a veteran hospital setting). Bootstrap analyses of the data sample were performed to assess the impact of this on the conclusions, and these analyses showed no effects on the final results.

CONCLUSIONS

Our study showed that in the veteran population, post-MI mortality is significantly lower in women in general, and particularly in women with diabetes. These results are unique and in contrast to what has been reported in the literature. Further investigation is needed to determine the reasons behind the increased survival in women post-MI in the veteran population, especially among diabetics.

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