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Lower Post Myocardial Infarction Mortality among Women Treated at Veterans Affairs Hospitals Compared to Men

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Abstract

Background: There is conflicting evidence about whether mortality after myocardial infarction (MI) is higher among women than among men. This study aimed to compare sex differences in post myocardial infarction mortality in the Veterans Affairs system, a setting where the predominant subjects are men.

Methods: The Veterans Affairs Corporate Data Warehouse inpatient and laboratory chemistry databases were used to identify patients diagnosed with acute myocardial infarction from inpatient records from January 1st, 2005 to April 25th, 2015. Mortality data was obtained through the VA's death registry.

Results: A total of 130,241 patients were identified; 127,711 men (98%) and 2,530 women (2%). Men typically had more comorbidities including congestive heart failure (54% vs 46%, *p* value <0.001), diabetes mellitus (54% vs 48%, *p* value <0.001), and chronic kidney disease (39% vs 28%, *p* value <0.001). The peak troponin-I was significantly higher among men (16.0 vs 10.7 ng/mL, *p* value = 0.03). The mean follow-up time was 1490.67 ± 8 days. After adjusting for differences in demographics and comorbidities, women had a significantly lower risk of mortality (hazard ration [HR]: 0.747, *p* value <0.0001) as compared to men.

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Conclusions: In a health care system where the predominant subjects are men, women had better short- and long-term survival than men after an acute myocardial infarction. Further investigation is warranted to determine the reasons behind the improved outcomes in women post-MI in the veteran population.

Keywords

Cardiology; Myocardial Infarction; Mortality

INTRODUCTION

Despite advances in management of myocardial infarction (MI) with reduction in mortality, a review of the literature suggests that post MI mortality in the U.S. and abroad remains higher among women than men.[1–4] A variety of reasons have been suggested to explain this including atypical presentation among women, delay in presentation, delay in recognition of MI, delay in treatment, and lower a procedure rate among women.[1–4]

The Veterans Affairs medical system serves a predominantly male patient population and provides equal access to care to all veterans. It is not clearly known whether a sex difference in post MI prognosis exists, or if it is even greater in the veteran population. Contrary to prior reports[5], our prior attempt to address the question of differences of post-MI outcomes based on sex\ showed that despite a greater number of procedures performed on men, women fared better post MI in the veterans hospitals in long term follow up. Our initial study had several limitations, including lack of information on pharmacotherapy and size of infarct. Our new analysis utilizes one of the largest databases to address the sex difference in post MI prognosis among veterans. The updated database includes a greater number of patients, longer follow-up to 10 years, and information on drug use, procedures, and infarct size.

METHODS

Study Population

The Veterans Affairs (VA) administration provides care for 9 million veterans and their families in the United States. The study was approved by an institutional review committee. We queried the VA's Corporate Data Warehouse (CDW) inpatient and laboratory chemistry databases. All hospital discharges of veterans with a primary ICD-9 code diagnosis of type 1 MI recorded, which have been shown previously to have excellent positive predictive value, were studied.[6] Our sample contains patients who were discharged between January 1, 2005 and April 25, 2015 (Figure 1). For veterans with an eligible ICD-9 code during the study period who had multiple admissions, the first admission was considered to be the index admission. Patients without a VA measurement of troponin at any time were excluded (3%). Follow-up duration was defined as the time from the first inpatient diagnosis of myocardial infarction to death or to the end of the study.

Comorbidities were defined by inpatient or outpatient ICD-9 code diagnoses. All-cause mortality data was obtained through the VA's death registry. Other patient characteristics

considered as variables in our risk-adjustment models included age and sex. We chose not to include race in the models due to a large number of missing values.

Statistical Analysis

Using chi-square test and Student's t-test, for categorical and continuous variables, respectively, men and women were compared in terms of demographics, medications, and comorbidities. The mortality rate difference by sex at 30 days, 60 days, and 1 year after admission was assessed using chi-square test, and the odds ratios (OR) were calculated. In order to consider the follow-up time and censored observations, Cox proportional hazards survival analysis was utilized to compare survival between men and women, and the hazard ratio (HR) was reported. The survival analysis was adjusted for the following variables: age, insurance status, peak serum troponin, ST elevation (STE) diagnosis, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), comorbidities previously mentioned, and medications that patient was discharged on. As a robustness test, we also performed propensity score matching of sex based on observed patient characteristics and comorbidities, and they were re-analyzed to test the consistency of results after matching.

All data analyses were performed using STATA 15.1. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 130,241 patients were identified; 127,711 men (98%) and 2,530 women (2%). Table 1 summarizes the demographics and comorbidities of the two groups.

Women were slightly younger (mean age 70 vs 73 years old). They were less likely to have significant comorbidities including atrial fibrillation, coronary artery disease history, congestive heart failure, diabetes mellitus, obstructive sleep apnea, peripheral artery disease, cirrhosis, chronic kidney disease, and chronic obstructive pulmonary disease. The peak troponin-I was significantly higher among men (16.0 vs 10.7 ng/mL). The rate of STEMI was comparable, but men were more likely to undergo CABG or PCI. Furthermore, men were prescribed more cardiac medications (Table 1).

Women had lower unadjusted mortality at 30 days, 60 days, and 1 year from their initial MI (Table 3). The mortality rate was also lower among women over the entire follow-up period (1.5% vs 2.3%). In the 10-year follow-up period, women had higher survival rates compared to men (Figure 2). The mean follow-up time was 1490.67 ± 8 days, and there was no significant difference in follow-up time between men and women.

Two models were included for a patient's risk of mortality due to MI using Cox proportional hazard survival analysis (Table 2). Model 1 controls for patient characteristics, presentation, interventions, and comorbidities of patients. Even after adjusting for differences in demographics and comorbidities, women had a significantly lower risk of death (HR: 0.747, p value <0.0001). In addition, to account for the differences in mortality due to specific medications, in Model 2 we controlled for medications prescribed and found that the results of sex remain robust to their inclusion in the model.

Further, robustness tests with propensity score matched sample also yielded consistent results using Cox proportional hazard survival analysis (HR: 0.782, *p* value <0.0001). Table 4 compares the hazard ratio of men and women across various parameters of the Cox proportional survival model. All variables were included as independent predictors of mortality for a time period of 10-year post-MI follow up.

DISCUSSION

This study analyzed data from a national database in the setting in which predominantly male patients are treated and found that women had a better survival compared to men after acute myocardial infarction despite a greater number of cardiac procedures performed among men. Our findings provide unexpected results in disagreement with prior studies,[1–4] but are similar to our previous investigation and in a larger and more recent data set with more complete information including therapy and size of myocardial infarction.[5]

Better survival in women may be associated with a variety of reasons. First, women seem to have smaller sized infarcts as determined by peak troponins. This could translate to better survival. Second, men were more aggressively treated both pharmacologically and with PCI and CABG procedures. Although this may suggest better management for men, it may also represent more comorbidities not accounted for in our analysis that could result in a worse prognosis.

The literature on sex differences in post MI survival has conflicting information. A number of older studies have reported lower post MI survival in women.[1–3, 7–11] Recently in comparable sized studies, Swedish and British reports also suggested this trend on long term follow up with another report from the United States showing that risk of readmission after MI is higher for women than men.[12, 1314] In contrast, Nauta and colleagues reported that adjusted mortality rates for men and women were similar in the intensive care unit in the Netherlands.[15]

In general, men have more risk factors for coronary disease making them higher risk for poor outcomes. The large US study by Dreyer and colleagues confirmed our findings that invasive procedures were higher among men.[14] Many reasons have been put forward for worse survival among women post MI including differences in presentation with more atypical presentation in women, delay in diagnosis, and less use of invasive procedures among women.[16] Irrespective of the cause of the MI, there is disparity in diagnostic evaluation between the sexes, and our study confirms fewer invasive procedures were performed on women. However, despite this, survival was better among women.

Men also have higher coronary atherosclerotic burden than women in the setting of acute coronary syndrome when referred for percutaneous coronary intervention.[7, 17–19] It has been hypothesized that endothelial and microvascular dysfunction is one potential mechanism to explain why women frequently have non-obstructive coronary artery disease. Female cardiomyocytes has been demonstrated to be more protected against apoptosis and cell death as compared to male cardiomyocytes,[20] even in mice models which demonstrated a delay in myocardial healing and higher infarct re-expansion and increased risk of cardiac

rupture.[20, 2122] Decreased apoptosis were linked to 17-B-estradiol which is significantly higher in women. [23, 24]

Better outcomes in women do not appear to be related as a result of varying access to care, given uniform access to the VA health system among veterans. Consistent with previous observations and reports,[1–4, 25–28] women underwent fewer invasive cardiac procedures in our study without an effect on outcomes. The female population is significantly smaller compared to men that are treated in the veteran's system, and it may translate to increase focus and improved overall quality of care.

The strengths of our study include having a nationwide analysis, large number of patients, uniform access of care among veterans, long follow up, and involvement of all patients who receive their care through the VA. This study has several limitations that affect its generalizability. Although we adjusted for baseline characteristics, not all confounders can be adjusted in a retrospective study and is therefore subject to residual confounding. In addition, patients were identified by ICD codes along with troponins, however electrocardiographic and cardiac catheterization information were not provided. We were unable to classify the cause of MI and to assess cardiovascular mortality. Being a VA study, women were underrepresented.

CONCLUSIONS

Our study showed that in the predominantly male veteran population, post-MI mortality is significantly lower in women even after adjusting for comorbidities. Further investigation is warranted to determine the reasons behind the improved survival in women post-MI in the veteran population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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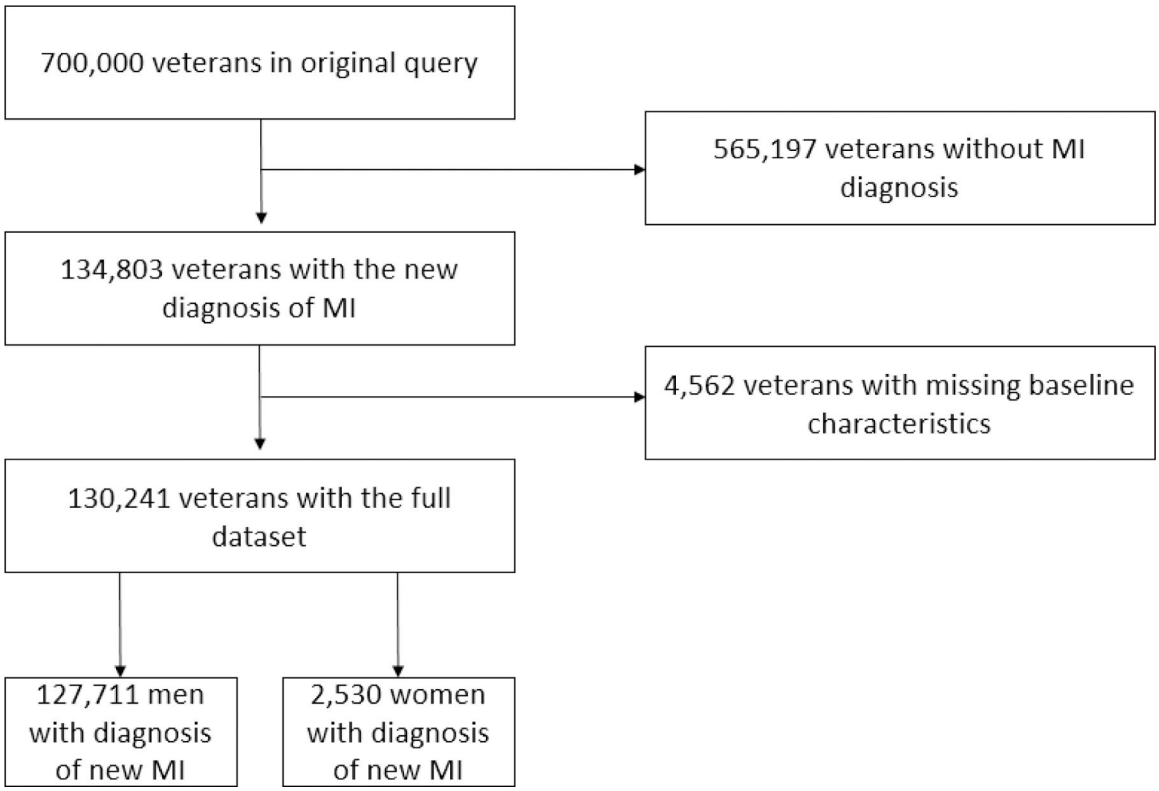

Figure 1:
Consort diagram for retrospective data analysis. Abbreviation: MI, myocardial infarction.

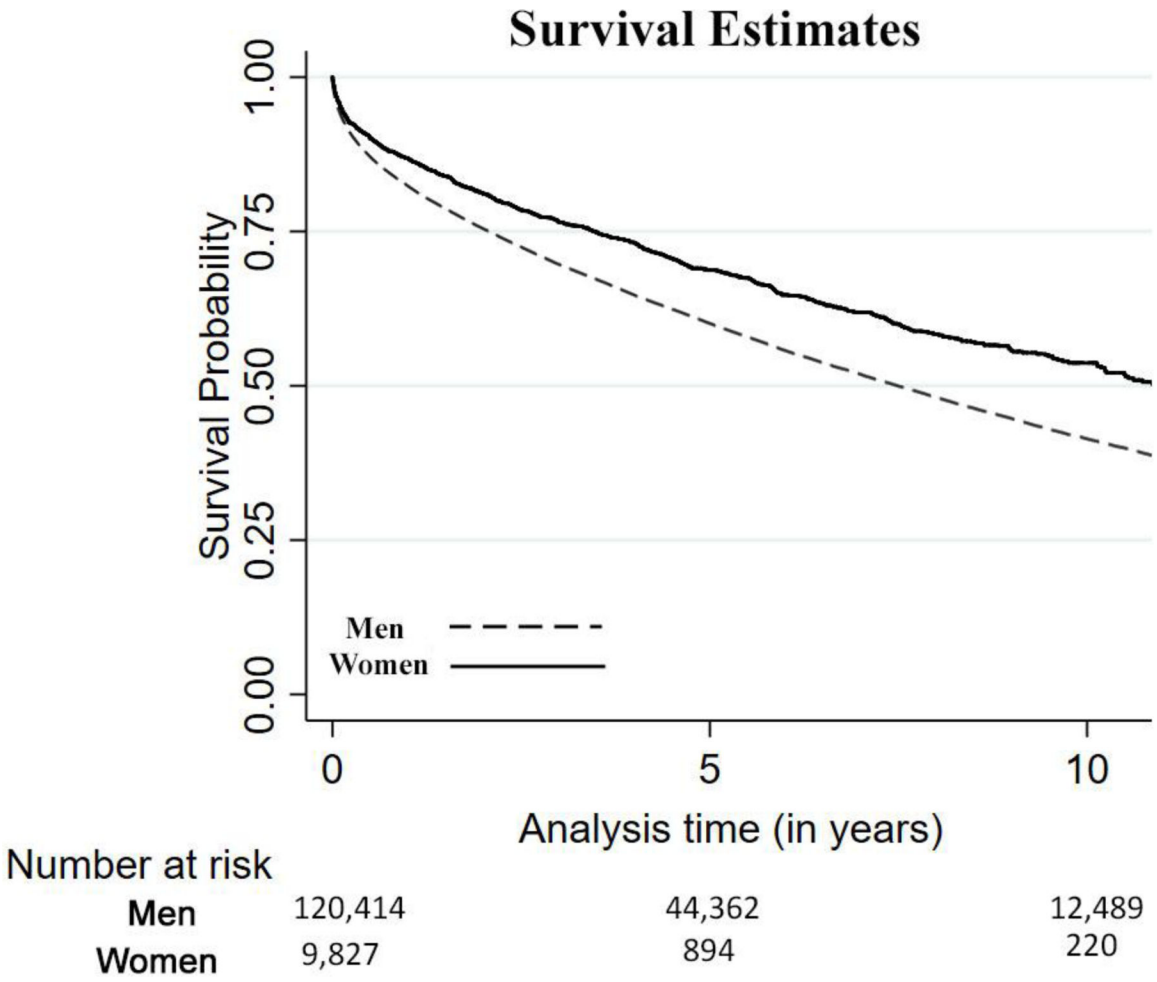

Figure 2:
Kaplan-Meier survival estimates of men vs women.

TABLE 1

Summarizes the demographics and comorbidities of the two groups.

	Men	**Women**	***P* Value**
	***n* = 127,711**	***n* = 2,530**	
Age, years (mean)	72.89	70.17	<0.001
Comorbidities			
Smoking	30.7%	33.4%	0.003
Atrial fibrillation	30.6%	23.6%	<0.001
Coronary artery disease	88.8%	80.6%	<0.001
Congestive heart failure	53.7%	45.9%	<0.001
Diabetes	54.1%	47.8%	<0.001
Hypertension	82.5%	81.9%	0.47
Obstructive sleep apnea	12%	10.3%	0.009
Peripheral artery disease	27.7%	18.6%	<0.001
Deep vein thrombosis	6.2%	5.9%	0.56
Pulmonary emboli	3.4%	3.8%	0.22
Cirrhosis	2.6%	1.9%	0.03
Chronic kidney disease	39.4%	28%	<0.001
Chronic obstructive pulmonary disease	38.1%	32.3%	<0.001
Cerebrovascular accident	20.5%	19.3%	0.16
Presentation			
Peak troponin levels (normal < 0.05 ng/mL)	16.00	10.70	0.03
STE-MI	24.2%	24.3%	0.91
Medications [a]			
Aspirin	88.4%	84%	<0.001
Digoxin	15.3%	10.4%	<0.001
Hydralazine	1%	1%	0.85
Beta blockers	88.1%	82.5%	<0.001
$P2Y_{12}$ inhibitors	67.2%	59.4%	<0.001
Loop diuretics	59.3%	54.2%	<0.001
Non-dihydropyrdines Ca blockers	18.3%	19.8%	0.05
Dihydropyridine Ca Blockers	38.9%	41.4%	0.01
Statin	91.7%	87.3%	<0.001
Nitrates	42.6%	36.8%	<0.001
ACE inhibitor and ARB	87.8%	81.5%	<0.001
Interventions			
CABG	4.30%	2.1%	<0.0001
PCI	32.0%	28.1%	<0.0001

[a] Medications listed were prescribed on discharge.

Table 2.

Two models were included for a patient's risk of mortality due to MI using Cox proportional hazard survival analysis.

Parameter	Model 1: baseline model			Model 2: with medications		
	Hazard ratio	***P* Value**	**CI**	**Hazard Ratio**	***P* Value**	**CI**
Patient Characteristics						
Women	0.747	<0.0001	0.696–0.801	0.682	<0.0001	0.636–0.732
Age	1.011	<0.0001	1.01–1.012	1.008	<0.0001	1.007–1.009
Presentation						
Log-peak troponin	1	<0.0001	0.999–1	1	<0.0001	0.999–1
STE+MI	0.693	<0.0001	0.679–0.708	0.686	<0.0001	0.672–0.7
Interventions						
CABG	0.462	<0.0001	0.432–0.494	0.481	<0.0001	0.449–0.514
PCI	0.613	<0.0001	0.601–0.626	0.712	<0.0001	0.696–0.728
Comorbidities						
Smoking	0.814	<0.0001	0.797–0.831	0.826	<0.0001	0.809–0.844
Atrial fibrillation	1.123	<0.0001	1.103–1.144	1.074	<0.0001	1.053–1.095
Chronic artery disease	0.466	<0.0001	0.454–0.48	0.637	<0.0001	0.618–0.657
Congestive heart failure	1.684	<0.0001	1.65–1.718	1.643	<0.0001	1.607–1.679
Deep vein thrombosis	1.103	<0.0001	1.067–1.139	1.079	<0.0001	1.045–1.115
Diabetes mellitus	1.021	0.025	1.003–1.039	1.075	<0.0001	1.055–1.095
Hypertension	0.804	<0.0001	0.785–0.823	0.892	<0.0001	0.871–0.914
Obstructive sleep apnea	0.699	<0.0001	0.679–0.72	0.722	<0.0001	0.701–0.743
Peripheral artery disease	1.182	<0.0001	1.16–1.205	1.234	<0.0001	1.21–1.257
Pulmonary emboli	1.094	<0.0001	1.047–1.143	1.059	0.01	1.014–1.107
Cirrhosis	1.316	<0.0001	1.255–1.379	1.179	<0.0001	1.124–1.236
Chronic kidney disease	1.134	<0.0001	1.111–1.157	1.217	<0.0001	1.192–1.242
Chronic obstructive pulmonary disease	1.274	<0.0001	1.252–1.297	1.237	<0.0001	1.215–1.2
Cerebrovascular accident	1.109	<0.0001	1.087–1.131	1.166	<0.0001	1.143–1.19
Medications						
Aspirin	–	–		0.823	<0.0001	0.799–0.848
Digoxin	–	–		1.077	<0.0001	1.053–1.101
Hydralazine	–	–		0.99	0.771	0.922–1.062
Beta blocker	–	–		0.677	<0.0001	0.658–0.698
P2y12 inhibitor	–	–		0.8	<0.0001	0.784–0.817
Loop diuretics				1.191	<0.0001	1.164–1.218
Non-dihydropyrdines Ca blockers	–	–		1.023	0.031	1.002–1.045
Dihydropyridine Ca blockers	–	–		0.738	<0.0001	0.724–0.752
Statin	–	–		0.609	<0.0001	0.59–0.629
Nitrates	–	–		0.961	<0.0001	0.943–0.979

Parameter	Model 1: baseline model			Model 2: with medications		
	Hazard ratio	*P* Value	CI	Hazard Ratio	*P* Value	CI
Patient Characteristics						
ACE inhibitor/ARB	–	–		0.795	<0.0001	0.772–0.819