Sex Differences in Ventricular Arrhythmias and Adverse Outcomes Following Acute Myocardial Infarction

1. SPACE:THE SAUDI PROJECT FOR ASSESSMENT OF CORONARY EVENTS
2. GRACE:THE GLOBAL REGISTRY OF ACUTE CORONARY EVENTS
3. FAST-MI:The French registry of acute ST elevation or non ST elevation MI
4. HCUP:Healthcare cost and utilization project
5. NIS:National inpatient sample

Ventricular arrhythmias (VAs), including ventricular tachycardia (VT) and ventricular fibrillation (VF) occur following 10 to 20% of acute myocardial infarction (AMI) cases and are associated with an increased risk of poor hospital outcomes

Data from the (SPACE) registry have shown that patients with AMI who develop VAs are more likely to experience reinfarction, cardiogenic shock, congestive heart failure, stroke, and in-hospital mortality.

Congruently, a study using data from the (GRACE) registry showed similar outcomes in patients with AMI who develop VAs, with in-hospital mortality rates as high as 52% as compared to 1.6% in those who did not develop VAs

Previous studies have explored the sex specific differences in AMI outcomes, including a higher incidence of VAs in men.

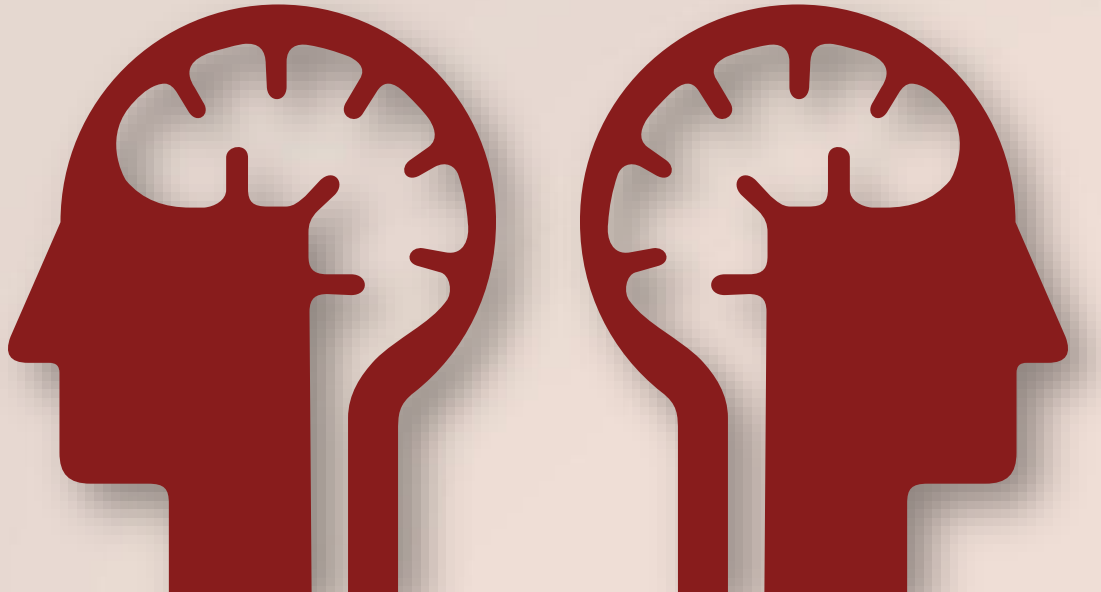
The (FAST-MI) found that women with VAs had higher 1-year mortality but were less likely to receive cardiac interventions.

Given these findings, using a national representative sample of the United States, we sought to determine whether sex differences exist in VA incidence and in-hospital outcomes in patients admitted for AMI.

METHODOLOGY

STUDY DESIGN AND DATA SOURCE. This study is reported following the (STROBE) reporting guidelines.

We analyzed hospitalizations between January 1,2016, and December 31, 2020, in the U.S. National Inpatient Sample (NIS).

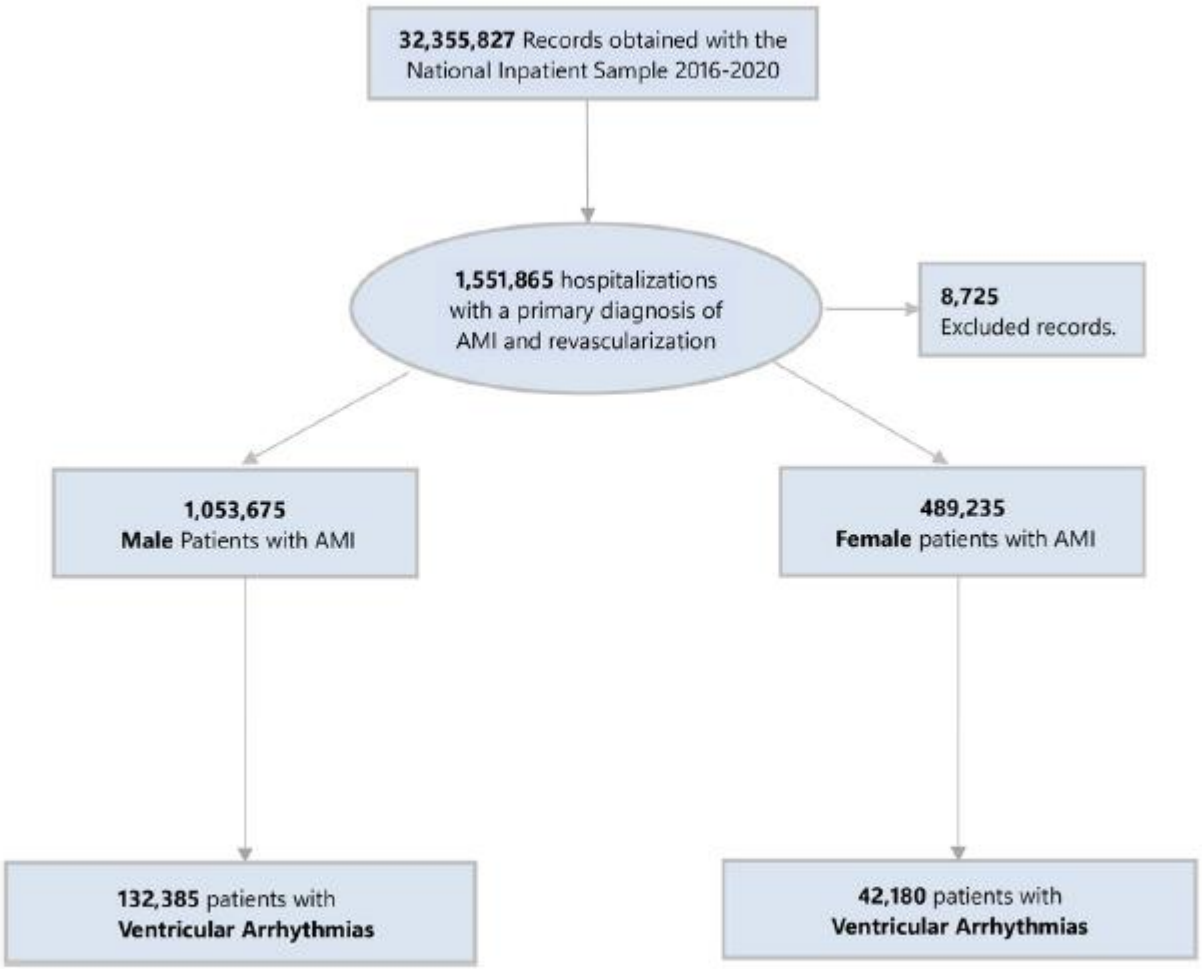


STUDY SAMPLE. The study population consisted of all inpatient hospitalizations with a primary diagnosis of type 1 AMI who underwent revascularization (percutaneous coronary intervention or coronary artery bypass grafting) and had a secondary diagnosis of VAs (VT or VF).

Diagnoses were identified using ICD-10-CM codes .

We excluded patients less than 18 years and those who had infiltrative cardiac diseases (amyloidosis,sarcoidosis), Lyme disease, or long QT syndrome .

FIGURE 1 Flow Chart of Our Study Population



The flow chart displays the selection of patients with acute myocardial infarction and ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) from year January 1, 2016, to December 31, 2020. AMI = acute myocardial infarction.

VARIABLES. The study population was divided into 2 subgroups based on the gender/sex. In the NIS, the sex of the patient was recorded as binary, either “female or male,” with all nonfemale and nonmale (eg, “other”) values set to missing.

Hence to maintain uniformity, we consistently used “sex’’ instead of “gender” throughout this article. Baseline demographic variables including age, sex, race, hospital characteristics, and medical comorbidities (computed from Charlson index for comorbidities) were identified as variables present in the data set. Other comorbidities were obtained using ICD-10-CM and ICD-10-PCS codes .

TABLE 1 *Gender Differences in the Sociodemographic and Comorbid Characteristics of AMI Patients With Ventricular Arrhythmias*

	All Ventricular Arrhythmias (11.3%) 174,565		
	Male 132,385 (75.8%)	Female 42,180 (24.2%)	P Value
Age (y)	62 0.2	66 0.3	<0.001
Race			<0.0001
White	78.4	77.3	
Blacks	7.76	11.7	
Hispanics	6.99	6.2	
Asians	2.63	1.6	
Native Americans	0.6	0.5	
Others	3.7	2.7	
Median household income			<0.0001
1	25.8	29.1	
2	26.4	29.0	
3	25.4	23.8	
4	22.3	18.1	
Primary insurance payer			<0.0001
Medicaid	40.84	56.5	
Medicare	10.03	10.86	
Private pay	37.78	25.98	
Self-pay	6.86	4.83	
No-charge	0.54	0.3	
Others	3.95	1.53	
Hospital bed size			0.623
Small	15.49	15.85	
Medium	29.78	29.34	
Large	54.73	54.81	
Hospital location/teaching status			0.093
Rural	5.08	5.69	
Urban nonteaching	20.57	20.41	
Urban teaching	74.36	73.9	
Hospital region			<0.0001
Northeast	16.62	16.39	
Midwest	24.53	26.67	
South	37.93	38.8	
West	20.91	18.14	
Old MI	14.3	11.2	<0.0001
Old PCI	1.1	0.9	0.056
Old CABG	5.6	3.8	<0.0001
Old pacemaker	1.4	1.6	0.145
Old catheter ablation	2.7	1.6	<0.0001
Hypertension	39.9	39.4	0.379
Diabetes mellitus	11.2	12.2	0.013
Peripheral vascular disease	3.6	5.1	<0.0001
Smoking	25.9	21.2	<0.0001
Obesity	16.6	20.5	<0.0001
Cocaine use	1.0	0.6	0.0005
CHF	34.6	39.5	<0.0001
Elixhauser comorbidity categories			<0.0001
1	5.67	3.57	
2	13.96	8.88	
>/¼3	80.37	87.55	
Dyslipidemia	63.3	61.9	0.025
Prior catheter ablation	7.3	2.7	<0.0001
Atrial fibrillation	19.5	21.5	0.0001
Palliative care	4.5	5.9	<0.0001

TABLE 1 Continued

	All Ventricular Arrhythmias (11.3%) 174,565		
	Male 132,385 (75.8%)	Female 42,180 (24.2%)	*P* Value
DNR	6.8	10.0	<0.0001
ADPRG severity scale			
1	1.5	2.1	
2	34.4	26.9	
3	24.7	25.6	
4	39.4	45.4	

Values are expressed in percentage unless otherwise indicated. Estimated median household incomes are ZIP code-specific, updated annually and are classified into 4 quartiles indicating the poorest to wealthiest populations.

ADPRG ¼ All-Payer Refined Diagnostic Related Group; AMI ¼ acute myocardial infarction; CABG ¼ coronary artery bypass grafting; CHF ¼ congestive heart failure; DNR ¼ do-not-resuscitate; MI ¼ myocardial infarction; PCI ¼ percutaneous coronary intervention.

STUDY OUTCOMES. The primary end point of this study was to determine the sex differences in the rates of VAs among patients with AMI, while the secondary outcomes were sex differences in rates of in-hospital mortality, cardiogenic shock, cardiac arrest, implantable cardiac defibrillator insertion, palliative care consultation, catheter ablation, and length of hospitalization. We also performed a sub- analysis to assess the sex differences in the outcomes of patients with AMI and either VT or VF, and the VA outcomes in patients with NSTEMI or STEMI

STATISTICAL ANALYSIS. Data analysis was per- formed using the HCUP STATA package, which in- corporates the NIS-specific variables, including hospital identifiers, stratum, and discharge weights to account for clustering and large survey-weighted data analysis according to HCUP recommendations.

RESULT

BASELINE CHARACTERISTICS. From 2016 to 2020, there were 3,191,049 admissions for AMI. After applying exclusions, our final cohort comprised of 1,542,910 patients with AMI. Of these, 174,565 (11.3%) patients had VAs. Among patients with AMI and VAs 132,385 (75.8%) were men.

Baseline sociodemographic, hospital, and clinical characteristics of patients with AMI who had VAs are summarized by sex in .

Overall, women were older, more likely to have congestive heart failure, diabetes mellitus,obesity, atrial arrhythmia, and had higher index of illness severity by the All-Payer Refined Diagnostic Related Group severity of illness scale, and more likely to have do-not-resuscitate status.

SEX DIFFERENCES IN IN-HOSPITAL OUTCOMES. Compared with men, women were found to have a lower incidence of VAs following AMI (8.6% for women vs 12.6% for men)

However, women had worse secondary outcomes with higher rates in hospital mortality , cardiogenic shock, and cardiac arrest.

12/6%

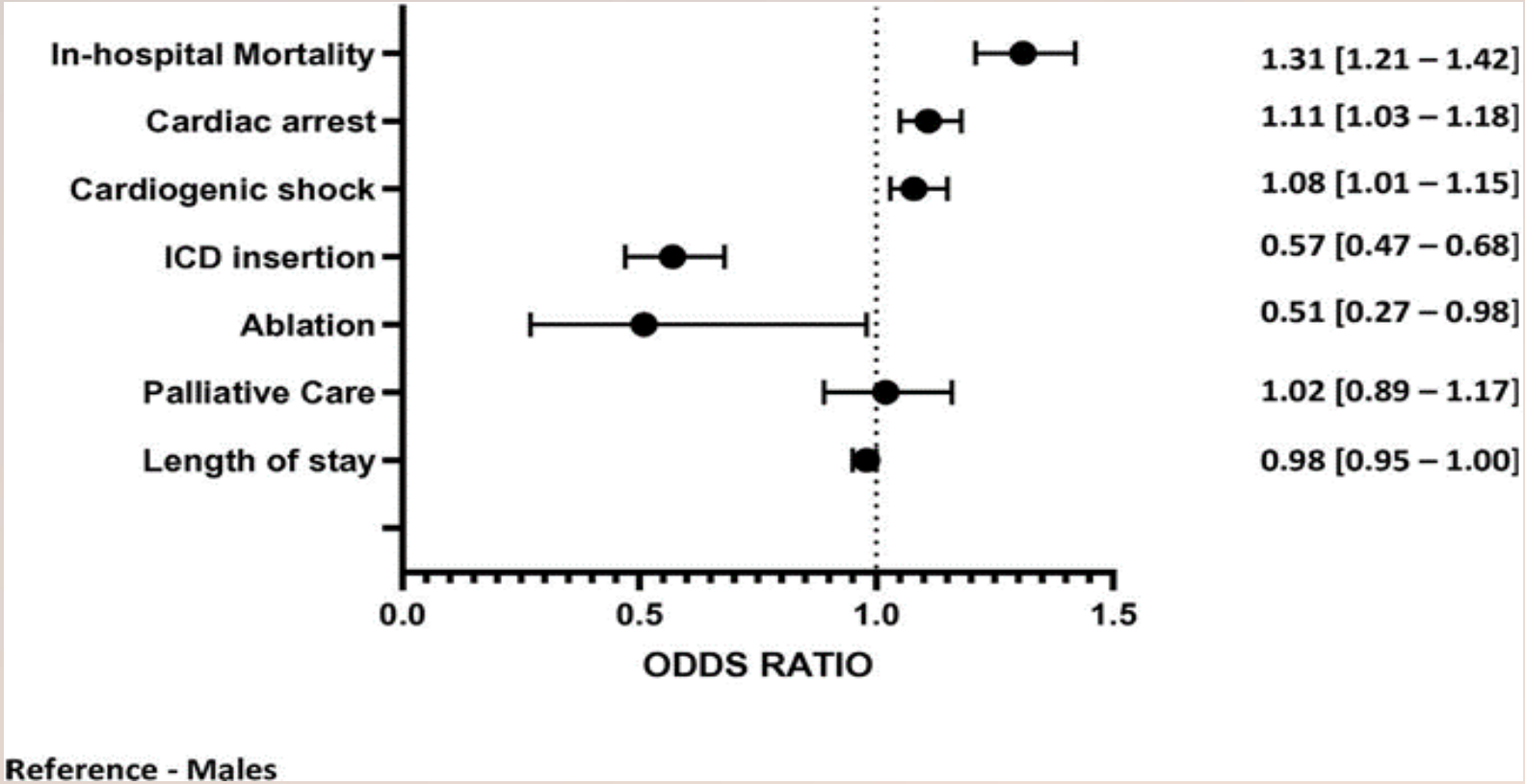
8/6%

. Women were also found to have lower rates of ICD insertion and less likely to receive ablative therapies following VAs, as compared to men .

A subanalysis considering VT and VF patients separately found the disparity to apply to both types of VAs: for VT and for VF.

Similarly, women were less likely to undergo catheter ablation during the index hospitalization as compared to men .

FIGURE 2 Sex Differences in the In-Hospital Outcomes of Patients With AMI Complicated by Ventricular Arrhythmias



The Forest plot shows the in-hospital outcomes of ventricular arrhythmias in women compared to men, represented with adjusted odds ratios and their 95% confidence intervals. AMI ¼ acute myocardial infarction; ICD ¼ implantable cardiac defibrillator.

SUBANALYSIS OF OUTCOMES IN NSTEMI VS STEMI PATIENTS. Subgroup analysis on the sex differences in outcomes of STEMI patients revealed that women were less likely to experience VAs post-STEMI , but they had worse in-hospital mortality and were less likely to receive an ICD . Similar findings were also observed in the NSTEMI subgroup of patients as shown in .

TABLE 2 Sex Differences in the Outcomes of Patients With STEMI and Ventricular Arrhythmias

	Males[a]	Females	Odds Ratio (CI)	*P* Value
In-hospital mortality	12.5	17.9	1.24 [1.13-1.35]	<0.001
Cardiogenic shock	26.4	30.8	1.03 [0.95-1.11]	0.435
Cardiac arrest	21.8	23.4	1.05 [0.97-1.13]	0.209
ICD insertion	2.0	1.30	0.57 [0.43-0.72]	<0.001
Ablation	0.1	0.01	0.49 [0.18-1.33]	0.165

[a]In males represent "reference variable".

TABLE 3 Sex Differences in the Outcomes of Patients With NSTEMI and Ventricular Arrhythmias

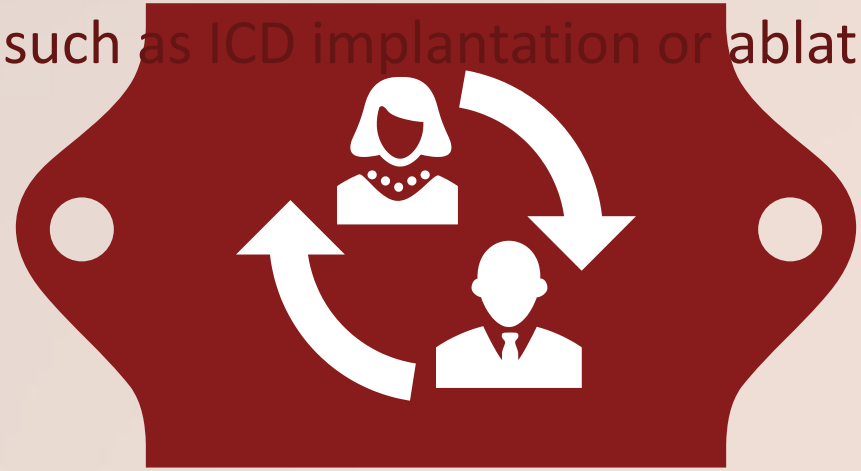
	Males[a]	Females	Odds Ratio (CI)	*P* Value
In-hospital mortality	8.5	13.4	1.48 [1.27-1.74]	<0.001
Cardiogenic shock	14.7	17.7	1.15 [1.01-1.32]	0.04
Cardiac arrest	13.3	17.3	1.28 [1.12-1.46]	<0.001
ICD insertion	4.9	3.1	0.61 [0.47-0.78]	<0.001
Ablation	0.5	0.3	0.57 [0.26-1.25]	0.163

[a]In males represent "reference variable".

DISCUSSION

Our study set out to explore the sex differences in the incidence and in-hospital outcomes of VAs following an AMI using a nationally representative sample of patients admitted for AMI in the United States.

The salient findings of this study are that while women were less likely to have VAs following AMI, they suffered worse in-hospital outcomes in terms of in- hospital cardiogenic shock, cardiac arrest, and in- hospital mortality, and were less likely to receive procedural care such as ICD implantation or ablation therapy



VAs are known complications of AMI. However, to the best of our knowledge, this study represents the largest study to date to examine sex differences in the incidence and in-hospital outcomes of VAs in patients admitted with AMI. Consistent with the findings of other studies, our work confirms observations that women are less likely to experience VAs after AMI.

While the reasons for sex differences in the risk of VAs post AMI is not entirely understood, our study showed a higher rate of prior MI and ischemic heart disease (IHD) among men, which might result in a greater myocardial scar burden as a substrate for potential re-entrant circuits.

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Our findings are supported by reports from the landmark Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy Trial (MADIT-CRT), which also reported higher rates of IHD in men. They also noted that the probability of ICD shocks due to VT/VF among women was half that observed in men .

In addition to a greater burden of proarrhythmic substrate, other sex-dependent characteristics due to hormonal influences on ion channel expression and action potential may also help explain our findings

Although women had a lower likelihood of VAs following AMI, women had higher odds of in-hospital mortality, cardiogenic shock, and cardiac arrest among those with VAs. These findings can be partly explained by the general comorbid profile of women with AMI, as they were older, had higher rates of congestive heart failure, diabetes mellitus and worse Charlson comorbidity index scores.

However, this excess risk was observed even after accounting for these differences. In a similar study by Shih et al,24 as compared to men, women had higher mortality rates despite equivalent rates of VAs with primary drivers of these higher rates being older age, post-MI Heart Failure, and less frequent utilization of guideline-directed therapies. We noted persistence of these worse outcomes in women with VAs even after subdivision into AMI groups (STEMI and non-STEMI)

In addition, women were less likely to receive ICDs or catheter ablation therapies during hospital admission.

While ICD is recommended as a secondary prevention therapy for women as it is for men with ventricular tachyarrhythmias in the setting of AMI, there continue to be sex differences in the recruitment to ICD trials and implantation in women as previously demonstrated.

Whether the difference in implantation is related to suggestions of higher complications of ICD implantation in women or a greater benefit in men, as suggested in some trials.

The available data indicate an underrepresentation of women in these studies, with no definite sex differences in mortality and an equivocal benefit of ICD therapy post implantation.

Therefore, future efforts should be directed toward minimizing the sex disparities in ICD implantation in AMI patients with VAs.

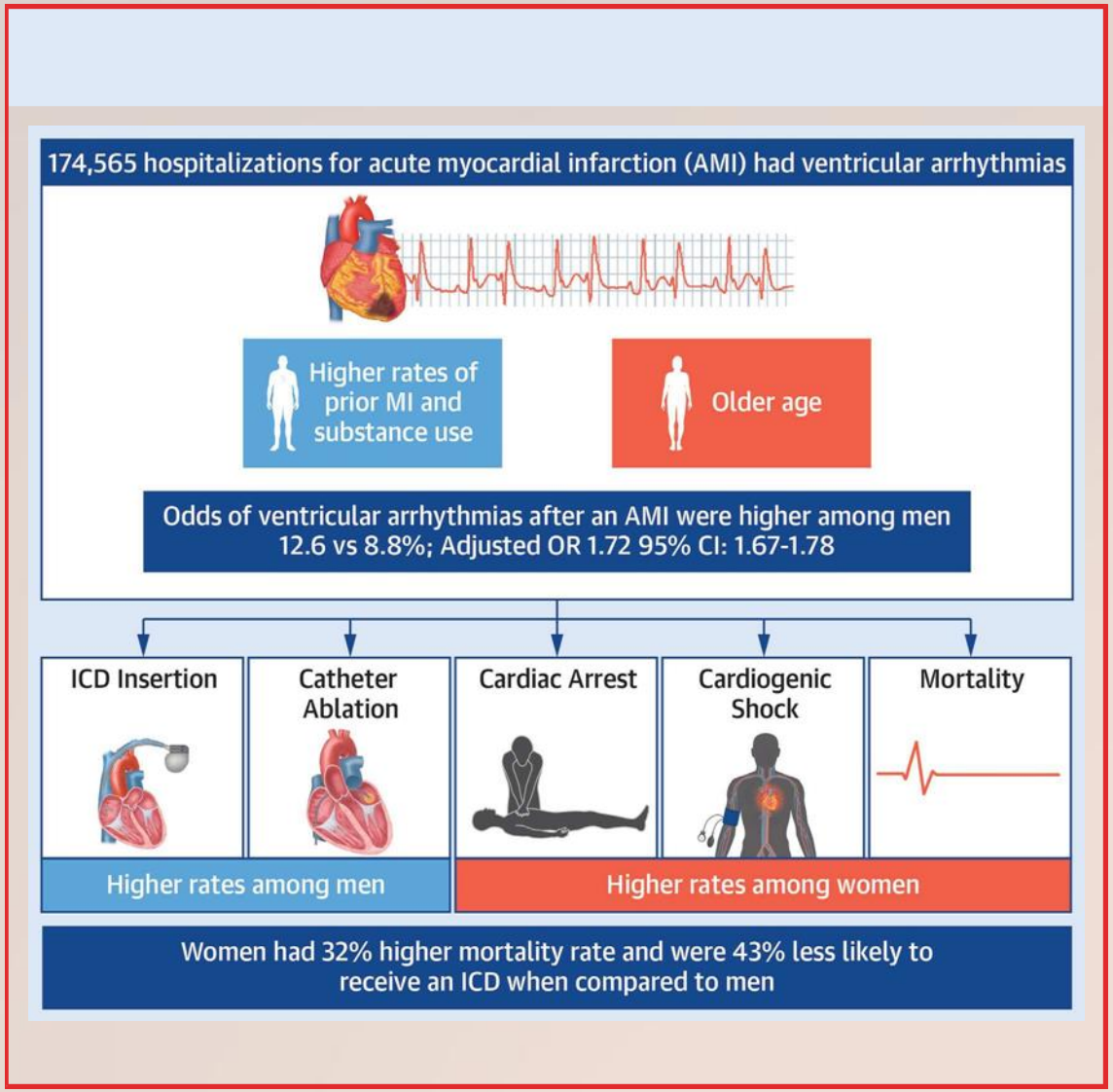
This study should be interpreted in the context of some limitations.

First, this is an observational and nonrandomized study, utilizing an administrative data set.

Secondly, our clinical and procedural variables were defined by ICD-10-CM and PCS codes which are vulnerable to coding errors.

Third, the data available to us lack the granularity necessary to determine the clinical severity on presentation, laboratory, and echocardiographic parameters.

Similarly, lack of data on medications limited our assessment of sex disparities in treatment with guideline medical therapy. Finally, due to the lack of longitudinal data on individual patients, we cannot extrapolate our findings to the posthospitalization period.


174,565 hospitalizations for acute myocardial infarction (AMI) had ventricular arrhythmias
Higher rates of prior MI and substance use
Older age
Odds of ventricular arrhythmias after an AMI were higher among men
12.6 vs 8.8%; Adjusted OR 1.72 95% CI: 1.67-1.78
ICD Insertion
Catheter Ablation
Cardiac Arrest
Cardiogenic Shock
Mortality
Higher rates among men
Higher rates among women
Women had 32% higher mortality rate and were 43% less likely to receive an ICD when compared to men

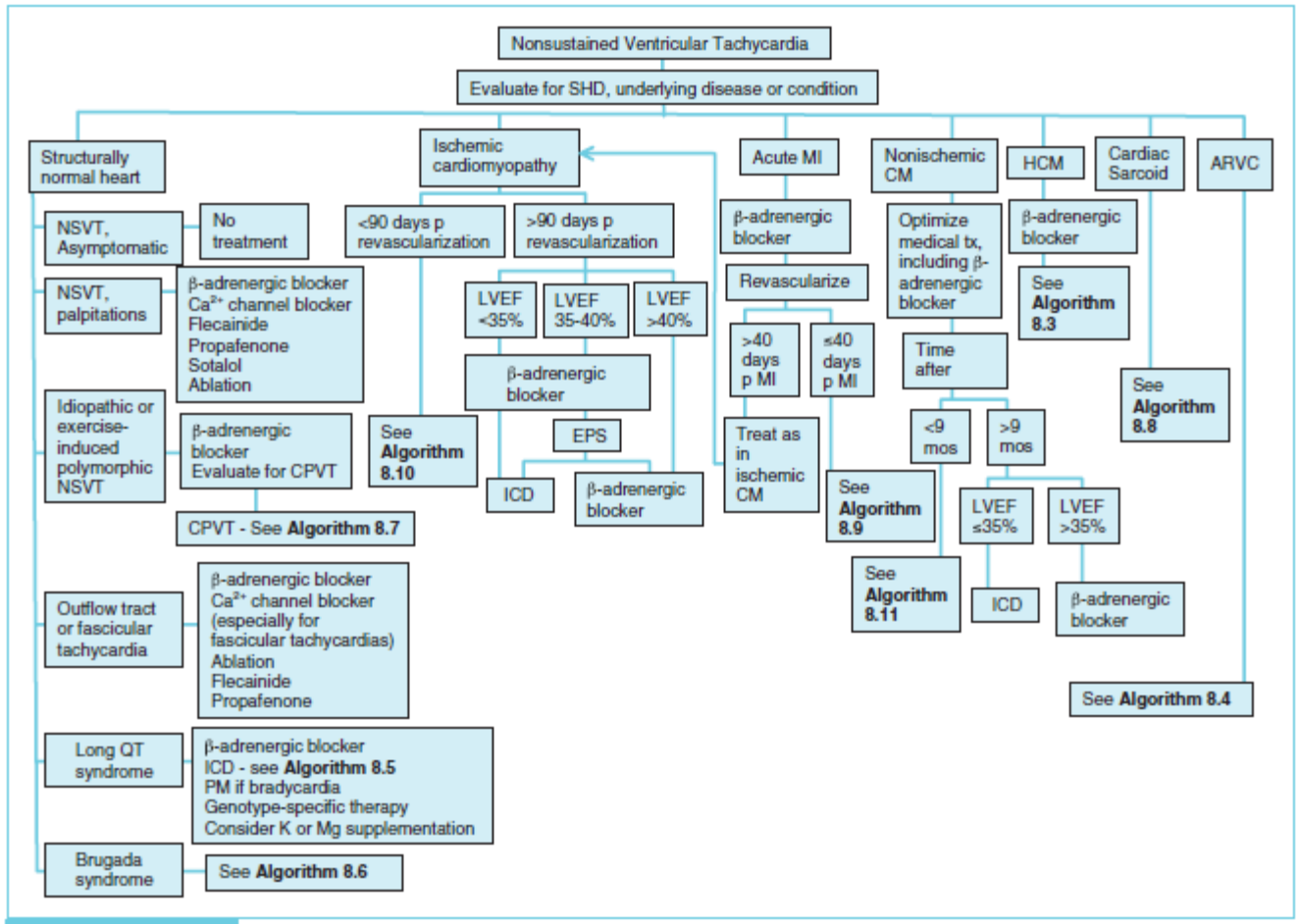
CONCLUSIONS

In this large nationwide analysis of patients with AMI, we found a lower incidence of complicating VAs in women as compared to men. While the lower prevalence of previous IHD might partially explain this, further studies are needed to understand the potential contributions of other factors, such as endocrine and genetic factors to explain this sex difference in VAs following AMI.

Despite having less VAs, women were found to have worse in-hospital outcomes (mortality, cardiac arrest, and cardiogenic shock) in the setting of AMI and VAs but were less likely to receive ICD implantation or ablation therapy.

These findings highlight the importance of assessing for sex differences in cardiovascular disease to improve the care of both women and men. Further investigation is needed to determine what treatments can improve the outcomes in women.

دراین تجزیه و تحلیل بزرگ از بیماران مبتلا به AMI ما بروز کمتری از عوارض آریتمی بطنی در زنان در مقایسه با مردان پیدا کردیم.در حالی که شیوع پایین تر IHDاقبلی ممکن است تا حدی این را توضیح دهد، مطالعات بیشتری برای درک نقش بالقوه عوامل دیگر، مانند عوامل غدد درون ریز و ژنتیکی برای توضیح این تفاوت جنسی دراریتمی بطنی به دنبال AMI مورد نیاز است. علیرغم داشتن اریتمی کمتر، زنان نتایج بدتری در بیمارستان (مرگ و میر، ایست قلبی، شوک قلبی)در زمینه AMIو VAداشتند اما احتمال کمتری داشت که ICDیا ABLATIONدریافت کنند.این یافته ها اهمیت ارزیابی تفاوت های جنسیتی در بیماری های قلبی عروقی را برای بهبود مراقبت از زنان و مردان برجسته می کند. تحقیقات بیشتر برای تعیین اینکه چه درمان هایی می توانند نتایج را در زنان بهبود بخشند، مورد نیاز است.



ALGORITHM 6.1

Nonsustained ventricular tachycardia. *ARVC,* Arrhythmogenic right ventricular cardiomyopathy; *CM,* cardiomyopathy; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *EP,* electrophysiologic study; *HCM,* hypertrophic cardiomyopathy; *ICD,* implantable cardioverter defibrillator; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NSVT,* nonsustained ventricular tachycardia; *PM,* pacemaker.