Comparison of Long-Term Survival Following Sudden Cardiac Arrest in Men Versus Women

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Sudden cardiac death (SCA) is a major cause of mortality with estimates of 450,000 deaths annually in the United States. The incidence of SCA differs between the sexes. Data regarding survival of women compared with men after SCA are, however, conflicting. We, therefore, examined the long-term survival of women versus men after SCA. A total of 1,433 (41% women; 44% out-of-hospital) survivors of SCA at our institution between 2002 and 2012 were followed to the primary end point of death through February 20, 2017. Women in our cohort were older ($p = 0.02$), were less likely to be white ($p = 0.01$), or to have suffered an acute myocardial infarction at the time of SCA ($p < 0.001$). They also had significantly shorter PR ($p < 0.001$) and QRS ($p < 0.001$) durations on their surface electrocardiogram, were more likely to present with an initial ventricular rhythm other than ventricular tachycardia or ventricular fibrillation (29% vs 22%, $p = 0.001$) and less likely to receive an implantable cardioverter defibrillator (22% vs 31%, $p < 0.001$). Over a median follow-up of 3.6 years, 674 (45%) patients died (53% women vs 43% men, $p < 0.001$). After adjusting for unbalanced baseline covariates, the sex difference in survival disappeared (hazard ratio 1.05; 95% confidence interval 0.85 to 1.29, $p = 0.66$). In conclusion, our results demonstrate comparable long-term mortality after SCA for men and women. Differences in unadjusted mortality are mainly due to older age, different risk profiles at the time of index event, and differential treatment with implantable cardioverter defibrillator. **(Am J Cardiol 2019;124:362−366)**

Sudden cardiac death (SCA) is a major cause of mortality in the United States with estimates accounting for upward of 20% of all deaths or >450,000 fatalities annually.[1−6] The incidence of SCA differs between the sexes and women are less likely to suffer SCA at every age.[7] Previous studies have evaluated whether mortality differed for women, however these data remain conflicted. Some studies found better survival for women following SCA in general,[8] if the presenting rhythm was shockable (i.e., ventricular tachycardia [VT] or ventricular fibrillation [VF] arrest),[9] at 1 month,[10,11] or at hospital discharge.[12] Others, however, have demonstrated worse survival for women,[13,14] particularly if the presenting rhythm is shockable.[15] To further complicate matters, yet other studies found no difference in mortality by sex before[16] or after adjusting for differences in baseline covariates.[17−19] Not only are the existing data regarding the correlation between sex and mortality following SCA conflicting, but also the majority of the current literature is based exclusively on out-of-hospital cardiac arrest with limited follow-up. Our present study was designed to address these limitations by following a large cohort of men and women who suffered a SCA in both the outpatient and in-hospital settings over several years from the time of the index event.

Methods

The study population consists of patients who presented to the hospitals of the University of Pittsburgh Medical Center after in-hospital or out-of-hospital SCA between 2002 and 2012, excluding those who have previously received an ICD, who survived to hospital discharge. The study was approved by the internal review board of the University of Pittsburgh. Patients were followed to the primary outcome of all-cause mortality, through February 20, 2017. Clinical and demographic data were collected on all patients upon presentation with SCA. Details of the SCA were collected, including location of the event, the initial documented rhythm, as well as the presence of a potentially reversible cause for the ventricular arrhythmia such as acute myocardial infarction or severe metabolic abnormalities, as previously described.[20] SCA was defined as any patient with a primary ICD-9-CM code of VF (427.41), ventricular flutter (427.42), VT (427.1), or cardiac arrest (427.5).

Patients' baseline characteristics were expressed as mean ± standard deviation for continuous variables and as number and percentages for categorical variables. They were compared between sex groups using the student *t* Test for continuous variables and the chi-squared test for categorical variables. Survival was examined using the Kaplan-Meier method. Survival was compared between sex groups using the log rank test and a Cox proportional hazards multivariable model was used to adjust for unbalanced baseline covariates. All statistical analyses were performed on SPSS

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See page 365 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.04.051

Table 1
Baseline characteristics of study cohort stratified by sex

Variable	Total (n = 1,433)	Men (n = 845)	Women (n = 544)	p Value
Age (years), mean ± standard deviation	62 ± 16	62 ± 16	64 ± 15	0.021
Race				0.014
White	1179 (82%)	714 (85%)	465 (79%)	
Black	172 (12%)	84 (10%)	88 (15%)	
Other	82 (6%)	47 (6%)	35 (6%)	
Atrial fibrillation	437 (31%)	254 (30%)	183 (31%)	0.68
Myocardial infarction at time of sudden cardiac arrest	546 (38%)	366 (43%)	180 (31%)	<0.001
Stent placement	303 (21%)	206 (24%)	97 (18%)	<0.001
Coronary artery bypass graft surgery	148 (10%)	103 (12%)	45 (8%)	0.005
Myocardial infarction at anytime	698 (49%)	460 (54%)	238 (41%)	<0.001
New York Heart Association heart failure class				0.17
I	58 (4%)	28 (3%)	30 (6%)	
II	43 (3%)	22 (3%)	21 (4%)	
III	50 (3%)	32 (4%)	18 (3%)	
IV	6 (<1%)	3 (<1%)	3 (1%)	
Total	157 (11%)	85 (10%)	72 (13%)	
Left ventricular ejection fraction (%)	45 ± 16	44 ± 16	47 ± 16	0.002
Pre-sudden cardiac arrest beta-blocker	563 (41%)	325 (39%)	238 (42%)	0.28
Pre-sudden cardiac arrest aspirin	587 (41%)	346 (41%)	241 (41%)	0.99
Charlson comorbidity index	2.7 ± 2.3	2.7 ± 2.4	2.7 ± 2.2	0.787
Diabetes mellitus	465 (32%)	262 (31%)	203 (35%)	0.17
Chronic obstruct pulmonary disease	465 (32%)	247 (29%)	218 (37%)	0.002
Chronic kidney disease	230 (16%)	143 (17%)	87 (15%)	0.31
Metastatic neoplasm	49 (3%)	30 (4%)	19 (3%)	0.77
Hypertension	885 (62%)	516 (61%)	369 (63%)	0.54
Cardiac arrest				
Location				0.55
In-hospital	807 (56%)	470 (56%)	337 (57%)	
Out-of-hospital	626 (44%)	375 (44%)	251 (43%)	
Initial rhythm				0.001
Ventricular tachycardia/ventricular fibrillation	768 (54%)	497 (59%)	271 (46%)	
Asystole/pulseless electrical alternans	355 (25%)	186 (22%)	169 (29%)	
Unknown	310 (22%)	162 (19%)	148 (25%)	
Body mass ondex (kg/m^2)	30 ± 8	30 ± 7	30 ± 9	0.291
Systolic blood pressure (mm Hg)	127 ± 31	126 ± 31	128 ± 32	0.337
Diastolic blood pressure (mm Hg)	71 ± 26	71 ± 21	70 ± 32	0.558
Troponin (μg/L)	10 ± 41	12 ± 44	6 ± 36	0.013
Creatinine kinase-muscle/brain (μg/L)	376 ± 55	58 ± 146	143 ± 48	0.462
Potassium (mEq/L)	4.2 ± 1.2	4.3 ± 1.3	4.1 ± 1.0	0.058
Magnesium (mEq/L)	2.0 ± 0.5	2.0 ± 0.5	2.0 ± 0.5	0.191
Bicarbonate (mmol/L)	24 ± 5	24 ± 5	24 ± 6	0.332
Ventricular Rate (bpm)	89 ± 26	89 ± 26	89 ± 26	0.7
P-R interval (ms)	167 ± 41	172 ± 43	160 ± 36	<0.001
QRS duration (ms)	106 ± 31	110 ± 31	101 ± 23	<0.001
QT interval (ms)	400 ± 71	398 ± 66	401 ± 77	0.512
QTc interval (ms)	473 ± 54	471 ± 53	476 ± 56	0.093
R axis (deg)	19 ± 58	19 ± 57	20 ± 59	0.677
Bundle branch block	181 (13%)	111 (13%)	70 (13%)	0.49
Reversible causes of sudden cardiac death	792 (55%)	478 (57%)	314 (58%)	<0.001
Myocardial infarction/ischemia	441 (31%)	302 (36%)	139 (26%)	
Electrolyte abnormalities	160 (11%)	82 (10%)	78 (14%)	
Metabolic abnormalities	103 (7%)	52 (6%)	51 (9%)	
Anti-arrhythmic drugs	27 (2%)	9 (1%)	18 (3%)	
Drug abuse	61 (4%)	33 (4%)	28 (5%)	
Admission duration (days)	16 ± 16	15 ± 17	16 ± 16	0.906
Post-sudden cardiac arrest implantable cardioverter defibrillator	389 (27%)	260 (31%)	129 (22%)	<0.001

version 25 (IBM, Armonk, New York). Two-sided p values <0.05 were considered statistically significant.

Results

Our cohort consisted of a total of 1,433 SCA survivors including 41% women. Out-of-hospital SCA accounted for 44%, whereas in-hospital SCA accounted for 56% of events. A total of 563 (42% of women vs 39% of men, p = 0.28) patients were on a β-blocker and 587 (41% of women vs 41% of men, p = 99) patients were on aspirin before SCA. Table 1 shows baseline characteristics of our cohort, stratified by sex. Women compared with men were older (64 ± 15 years vs 62 ± 16 years, p = 0.02), were less likely to be white (79% vs 84%, p = 0.01), or to have suffered an acute myocardial infarction at the time of SCA (40% vs 54%, p < 0.001). They also had significantly shorter PR (160 ± 36 ms vs 172 ± 43 ms, p < 0.001) and QRS (101 ± 23 ms vs 110 ± 31 ms, p < 0.001), but nonsignificantly different QT (401 ± 77 ms vs 398 ± 66 ms, p = 0.51) intervals on their surface electrocardiogram, and were more likely to present with an initial ventricular rhythm other than VT or VF (29% vs 22%, p = 0.001). Following SCA, women were less likely to receive an implantable cardioverter defibrillator (ICD) (22% vs 31%, p < 0.001). Of the patients with a shockable SCA rhythm (VT or VF), women were however equally likely to men to receive an ICD (41% vs 45%, p = 0.23).

Over a median follow-up of 3.6 years, 674 patients died including a larger proportion of the women than men (53% vs 43%, p = 0.001). Survival curves stratified by sex were constructed and are shown in Figure 1. After adjusting for unbalanced baseline covariates which included patients' age at SCA, race, presence of a shockable rhythm, presence of acute myocardial infarction at the time of the arrest, left ventricular function, presence of an ICD, PR duration, QRS and QTc intervals, and the presence of chronic obstructive pulmonary disease, the sex difference in survival could no longer be demonstrated (hazard ratio 1.05; 95% confidence interval 0.85 to 1.29, p = 0.66; Table 2).

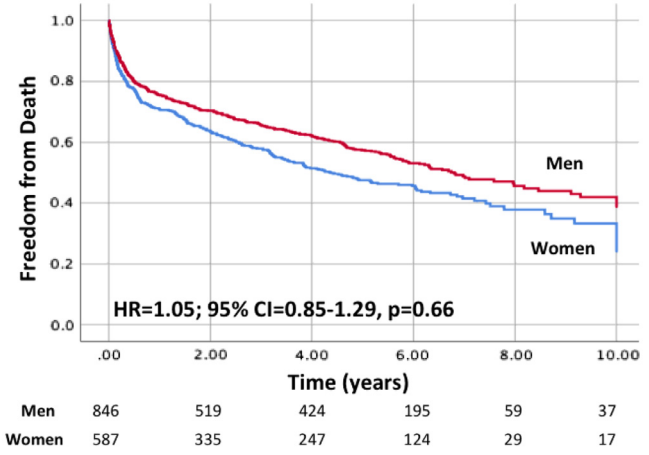

Figure 1. Kaplan-Meier curves for all-cause mortality of survivors of sudden cardiac arrest, stratified by sex.

Discussion

Men and women who suffer an SCA are different at baseline, however, there is no difference in their mortality. The baseline differences between the sexes include demographics traits, presenting SCA rhythms, baseline surface electrocardiographic characteristics, incidences of myocardial infarctions and post SCA ICD implantations. These differences likely account for a seemingly worse survival for women. This finding is significant given the conflicting data on sex and mortality in previous studies. Furthermore, our data includes both in-hospital and out-of-hospital SCA and focuses on a longer follow-up period, which were the areas of weakness in the literature.

Our present study has important similarities to previous research on sex and SCA. Similar to our findings, previous studies have shown that women who survive a SCA are older,[9,12,18,19] are more likely to present with nonshockable rhythms,[8,11–13,17] and are less likely to receive an ICD.[21] In addition, women are less likely to have coronary artery disease, structural heart disease or left ventricle dysfunction.[22–25] If any of these features are however present, then these findings predict worse survival.[22,26] When taken together our finding that women who survive a SCA are older and the knowledge that coronary artery disease develops later in life for women compared with men, one could hypothesize that the worse unadjusted survival in women is likely linked to the presence of coronary artery disease and as such may explain why when adjusted, the survival gap between men and women disappears. This hypothesis may be further supported by another study describing a sex-stratified regression model indicating that the adjusted probability of survival for women decreased as age increased.[19]

Our present study focused on ICD implantation as the primary management strategy and on all-cause mortality as the primary end point. Other studies have focused on other important interventions in the context of SCA, such as bystander cardiopulmonary resuscitation (CPR) for out-of-hospital cardiac arrest, which has been shown in recent years to improve short-term and long-term survival.[10] The literature is rich with conflicting data on the likelihood of women versus men to receive CPR, with some reporting more CPR in women,[8,18] while others reporting the exact opposite.[9,11,13,14] Other differential sex applications have included percutaneous interventions, heart catheterizations, and targeted temperature management. For most of these, women were noted to be less likely to receive the therapy and more likely to have a do not resuscitate order placed.[15,19,27]

As far as outcome end points after SCA, many studies did not assess long-term mortality as we did, but rather examined intermediate end points such as neurological recovery, quality of life, and ability to achieve independence in performing tasks of daily activities. Some studies indicate that neurological recovery is worse in women who survive SCA compared with men regardless of age,[27] whereas other studies found comparable cognitive outcomes between sexes when adjusting for confounders.[14] In addition, other factors may affect outcomes for women, as shown in one study which demonstrated that women in the reproductive age group have more neurological impairment

Table 2
Cox multivariable model of independent predictors of mortality after sudden cardiac arrest

Variable	p Value	Hazard Ratio	95% Confidence Interval	
			Lower	Upper
Sex (women vs men)	0.66	1.05	0.85	1.29
Age at sudden cardiac arrest	<0.001	1.03	1.03	1.04
PR interval (per 1 ms)	0.52	0.99	0.99	1.00
QRS duration (per 1 ms)	0.62	0.99	0.99	1.00
QTc duration (per 1 ms)	0.83	1.00	1.00	1.00
Left ventricular ejection fraction (per 1%)	<0.001	0.99	0.98	0.99
Black race (vs white)	0.43	1.13	0.83	1.54
Other races (vs white)	<0.001	2.29	1.58	3.32
Myocardial infarction at sudden cardiac arrest	<0.001	0.60	0.47	0.76
Post-sudden cardiac arrest ICD implantation	<0.001	0.60	0.45	0.80
Chronic obstructive pulmonary disease	0.002	1.38	1.13	1.69
Nonshockable rhythm (vs ventricular tachycardia/ventricular fibrillation)	0.002	1.55	1.17	2.03
Undocumented sudden cardiac arrest rhythm (vs ventricular tachycardia/ventricular fibrillation)	0.016	1.41	1.07	1.86

compared with older women after SCA.[28] These and other unsettled questions deserve further examination.

Our study has limitations. First, it is a single healthcare system, retrospective analysis and therefore our results may be subjected to bias. It is for example unclear what drove the decision to implant or not implant an ICD in patients. Nevertheless, the data were extracted from multiple hospitals within the University of Pittsburgh Medical Center system and we applied appropriate statistical methods to adjust for unbalanced characteristics. Second, we did not know the presenting cardiac arrhythmia in 310 (22%) of the cases. In an effort to minimize exclusions, which amplify selection bias, we elected to include these cases in our present analysis. Finally, we have limited data regarding the immediate post-SCA management including but not limited to targeted temperature monitoring or permissive hypertension. These therapies were unaccounted for and could have influenced long-term survival in our cohort.

There is no difference in mortality between women and men after adjusting for differential baseline covariates. The seemingly worse mortality for women in unadjusted data is likely due to older age, different risk profiles at the time of index event, and differential treatment with ICD. This finding is significant given the conflicting data on sex and mortality in previous studies. Furthermore, our data includes both in-hospital and out-of-hospital SCA and focuses on a longer follow-up period, which were areas of weakness in previous publications.

Acknowledgment

The authors declare there are no acknowledgements.

Disclosures

Samir Saba, MD, receives research support from Boston Scientific and Medtronic and is on the Advisory Board for Boston Scientific. Norman C. Wang, MD, is a consultant for Abbott, received fellowship support from Abbott and Medtronic, and is a research investigator for BostonScientific. Authors have no conflicts of interest to declare.

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