ORIGINAL RESEARCH

Association of Bystander and First-Responder Efforts and Outcomes According to Sex: Results From the North Carolina HeartRescue Statewide Quality Improvement Initiative

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***Background*—**The Institute of Medicine has called for actions to understand and target sex-related differences in care and outcomes for out-of-hospital cardiac arrest patients. We assessed changes in bystander and first-responder interventions and outcomes for males versus females after statewide efforts to improve cardiac arrest care.

***Methods and Results*—**We identified out-of-hospital cardiac arrests from North Carolina (2010–2014) through the CARES (Cardiac Arrest Registry to Enhance Survival) registry. Outcomes for men versus women were examined through multivariable logistic regression analyses adjusted for (1) nonmodifiable factors (age, witnessed status, and initial heart rhythm) and (2) nonmodifiable plus modifiable factors (bystander cardiopulmonary resuscitation and defibrillation before emergency medical services), including interactions between sex and time (ie, year and year^2). Of 8100 patients, 38.1% were women. From 2010 to 2014, there was an increase in bystander cardiopulmonary resuscitation (men, 40.5%–50.6%; women, 35.3%–51.8%; P for each <0.0001) and in the combination of bystander cardiopulmonary resuscitation and first-responder defibrillation (men, 15.8%–23.0%, P=0.007; women, 8.5%–23.7%, P=0.004). From 2010 to 2014, the unadjusted predicted probability of favorable neurologic outcome was higher and increased more for men (men, from 6.5% [95% confidence interval (CI), 5.1–8.0] to 9.7% [95% CI, 8.1–11.3]; women, from 6.3% [95% CI, 4.4–8.3] to 7.4% [95% CI, 5.5–9.3%]); while adjusted for nonmodifiable factors, it was slightly higher but with a nonsignificant increase for women (from 9.2% [95% CI, 6.8–11.8] to 10.2% [95% CI, 8.0–12.5]; men, from 5.8% [95% CI, 4.6–7.0] to 8.4% [95% CI, 7.1–9.7]). Adding bystander cardiopulmonary resuscitation and defibrillation before EMS (modifiable factors) did not substantially change the results.

***Conclusions*—**Bystander and first-responder interventions increased for men and women, but outcomes improved significantly only for men. Additional strategies may be necessary to improve survival among female cardiac arrest patients. **(*J Am Heart Assoc.* 2018;7:e009873. DOI: 10.1161/JAHA.118.009873.)**

Key Words: bystander cardiopulmonary resuscitation • cardiac arrest • cardiopulmonary resuscitation • first responder • women

In 2015, the Institute of Medicine called for actions to improve care and outcomes for out-of-hospital cardiac arrest patients, including understanding and targeting disparities across demographic subgroups.[1] Multiple studies highlight differences in care between women and men treated for cardiac arrest, with evidence suggesting that women have poorer outcomes.[2–7]

Inherent differences related to patient and cardiac arrest characteristics can help explain these sex-based differences. For example, women with out-of-hospital cardiac arrest are more likely to have advanced age, chronic health comorbidities, noncardiac etiology, unwitnessed cardiac arrest, and initial nonshockable heart rhythm, and to live alone, all of which have

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Accompanying Tables S1 through S3 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009873

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Clinical Perspective

What Is New?

- This study found that following statewide, multifaceted interventions to improve care and outcomes for cardiac arrest patients, women did not enjoy any temporal improvement in outcomes, even though bystander cardiopulmonary resuscitation and the combination of bystander cardiopulmonary resuscitation and first-responder defibrillation increased for both women and men.
- Further, sex differences in outcomes were mainly associated with non-modifiable factors (patient age, sex, first recorded heart rhythm and whether the cardiac arrest was witnessed).

What Are the Clinical Implications?

- In addition to improving bystander cardiopulmonary resuscitation and early defibrillation, other strategies may be necessary to improve survival among female cardiac arrest patients.

been associated with worse outcomes.[2,5,8–11] While these characteristics are important to understand differences in outcomes, they are unlikely to be modifiable. In contrast, sex-related differences in interventions that may highly impact survival, such as bystander or first-responder resuscitation efforts, are presumably modifiable. Recent European studies found that female sex was associated with lower rates of bystander cardiopulmonary resuscitation (CPR) and early defibrillation, even among witnessed cardiac arrests.[2,5,12,13] It is unclear whether such differences also exist in contemporary US cardiac arrest populations. In 2010, the HeartRescue project was initiated in North Carolina to improve care and outcomes for out-of-hospital cardiac arrest patients. The project included statewide efforts targeting the full spectrum of the links in the chain of survival.[14,15] These interventions were associated with increased bystander CPR, first-responder defibrillation, and overall survival. However, it is unknown if these changes have translated into improved bystander and first-responder interventions and outcomes for both women and men.[16]

The aim of this study was to examine temporal changes in bystander and first-responder intervention and how these changes were associated with survival in men compared with females in North Carolina from 2010 to 2014.

Methods

Data Source

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of data protection rules.

The CARES (Cardiac Arrest Registry to Enhance Survival) registry is a voluntary, prospective clinical registry of patients with out-of-hospital cardiac arrest in the United States, established by the Centers for Disease Control and Prevention and Emory University for public health surveillance and continuous quality improvement.[17,18] The registry includes all patients with a confirmed out-of-hospital arrest (defined as pulseless and unresponsive) for whom resuscitation is attempted, including those with termination of resuscitation before hospital arrival. Data are collected prospectively from emergency medical services (EMS) agencies and receiving hospitals and entered in the database. Every record is reviewed for completeness and accuracy by a CARES analyst.[17] In North Carolina, participating EMS agencies receive training, quality control, and data feedback, and establishing this process was one of the HeartRescue interventions. The physical location of each cardiac arrest was assigned on the basis of the address of the cardiac arrest, and ArcGIS 10.2 software (ESRI, Redlands, CA) was used to geocode each incident location to the street address level. The geocoding process assigns a latitude and longitude coordinate to each address. A 97% geocoding rate was achieved. Nongeocoded records included post office boxes and other nonphysical locations. This process verified the county in which each cardiac arrest occurred.

Study Population and Setting

To reduce the chance that our results were driven by changes in reporting, we included only counties with complete registry enrollment and thus complete county-wide case ascertainment during 2010–2014 (counties where cases were reported to CARES during the whole study period), as done previously.[16,19] Thus, the study population included all out-of-hospital cardiac arrests from 16 counties in North Carolina, covering a total population of ≈3 million inhabitants (30% of the total state population) with demographics varying from urban to rural areas. Following the Utstein guidelines for reporting cardiac arrest, the study population included cases of cardiac arrest with presumed cardiac cause and ≥18 years of age during 2010–2014 and excluded cases witnessed by a 911 responder or with “do not resuscitate” orders.[20] Because patient sex was the main interest in this study, we excluded cases with missing sex. All EMS agencies included in this study had 2-tiered response systems with first-responders equipped with automated external defibrillators.[21]

The HeartRescue Project in North Carolina

As part of a multistate initiative, the North Carolina HeartRescue project initiated a multifaceted, statewide quality-improvement program in 2010.[15] The protocol is publicly available and the project has previously been described in detail.[16,22] In short, it included interventions for community members (widespread compression-only CPR training and automated external defibrillator use), EMS medical dispatchers (training in recognition of cardiac arrest, dispatch-assisted CPR, and implementation of protocols to transport certain patients to specialized centers), first responders (in team-based CPR, including automated external defibrillator use and high-performance CPR), and hospital administrators and staff (establishment of protocols for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, target temperature and hypothermia management, and goal-directed intensive unit care neurorehabilitation).

Definitions

First responders were defined as personnel who responded to the medical emergency in an official capacity as part of an organized medical response team, but who were not the designated transporter of the patient to the hospital, in accordance with the CARES registry.[21] First responders in this study were mainly firefighters and also could include police officers and rescue squad or lifesaving crew dispatched by emergency dispatch centers and trained to perform basic life support until arrival of the EMS. As defined by the Utstein guidelines, bystanders were other people who were present and intervened but not dispatched by the emergency dispatch center.[20] Favorable neurological outcome was measured by cerebral performance category 1 or 2, with 1 representing full recovery or mild disability and 2, moderate disability but independent in activities of daily living.[23] Modifiable factors were defined as factors that, in theory, could be altered by public health or organizational initiatives/interventions to improve care and outcomes for out-of-hospital cardiac arrest patients. In this study, we chose to focus on bystander and first-responder intervention (CPR and/or defibrillation). Nonmodifiable factors were defined as patient/arrest characteristics that cannot be altered by any public health interventions or improvements in systems of care (age, witnessed status, initial heart rhythm).

Outcome Measures

The main outcome measures were survival and survival with favorable neurologic outcome.

Statistics

For continuous data, mean and standard deviation, or median and interquartile range, were calculated, as appropriate. Proportions were calculated for categorical data. The Fisher exact test or χ^2 was used to test for statistical significance for categorical data. Temporal trends for categorical data were assessed using the Cochran-Armitage trend test for trends across ordered groups (by year). Analyses regarding the combination of efforts from bystanders, first responders, and EMS (CPR and defibrillation) included only patients who were defibrillated before hospital arrival.

Logistic regression models were used to examine how differences in prehospital interventions were associated with survival and favorable neurologic outcome for men and women from 2010 to 2014. Interaction terms were included to assess whether changes in outcomes significantly differed for men and women. Preliminary analyses showed that change in outcomes across years (2010–2014) was best captured as a quadratic function. To account for the greater increase in survival for men compared with women over time, all logistic regression models included interactions between sex and time (ie, year and year^2). All results are presented as predicted probabilities with 95% confidence intervals (CIs). Logistic regression analyses were performed in 3 steps: (1) unadjusted; (2) adjusted for nonmodifiable factors (age, witnessed status, and rhythm); and (3) adjusted for nonmodifiable and modifiable factors (bystander CPR and defibrillation before EMS). To examine these changes in a more homogenous population, we included an additional analysis subsetting on patients with a first recorded shockable heart rhythm.

A P value of <0.05 was considered statistically significant; all statistical tests were 2-sided; adjusted results should be interpreted in context of lack of adjustment for multiple comparisons and, thus, are exploratory rather than confirmatory. P values were reported for linear and quadratic terms when appropriate. All analyses were performed using SAS versions 9.2 and 9.4 (SAS Institute, Cary, NC) and Stata version 13.0 (StataCorp, College Station, TX).

Ethics

The Duke University Medical Center Institutional Review Board for analyses and publication of the findings approved the current study. A waiver of the requirement for written informed consent and Health Insurance Portability and Accountability Act authorization was granted on the basis of (1) using existing central CARES registry data and under existing waivers of consent for CARES under the HeartRescue project and (2) using aggregated and limited data.

Results

Cardiac Arrests

The final study population comprised 8100 cardiac arrests (Figure 1) and 38.1% were women. The proportion of women

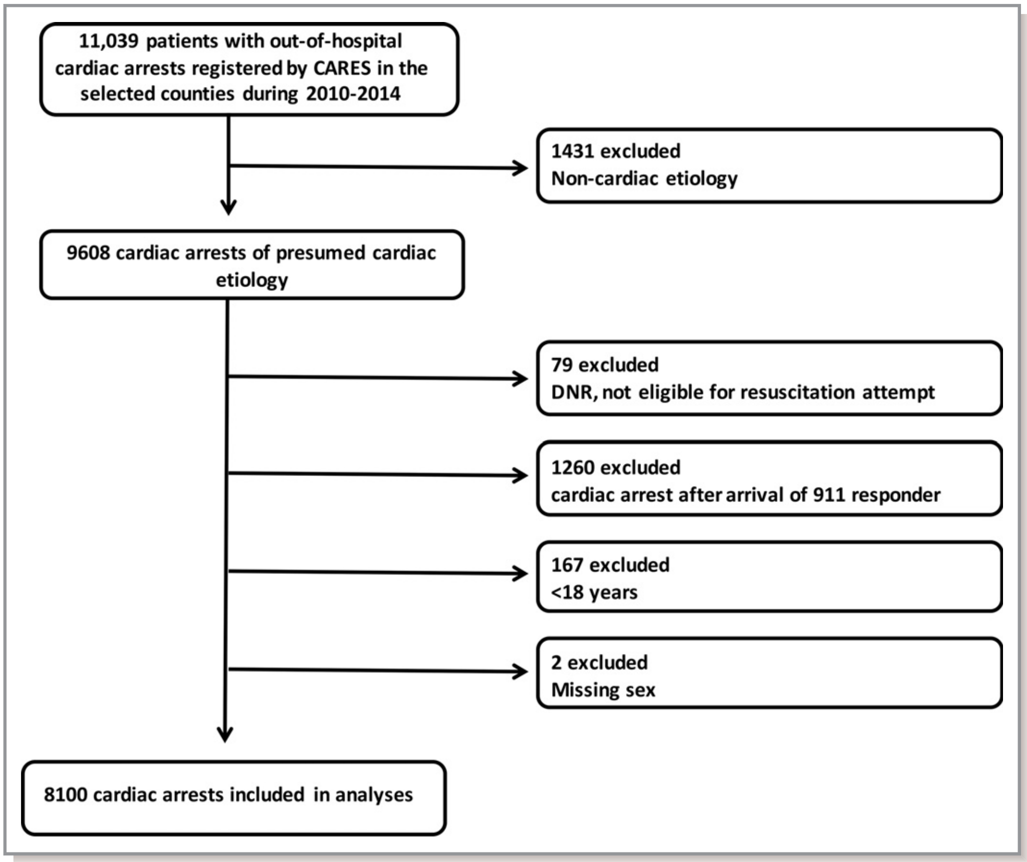

Figure 1. Population selection.

versus men was stable throughout the study period. Women were older and less likely to have an initial shockable heart rhythm or witnessed arrest. During 2010–2014, patient and cardiac arrest characteristics did not change significantly for men or women, except for a decrease in age for women (from 71 to 69 years, P=0.04) and an increase in the proportion of cardiac arrests in public for both sexes (P<0.0001 for women, and P=0.002 for men; see Table S1).

Overall Sex-Related Differences in Shockable Heart Rhythm According to Witnessed Status and Bystander CPR

A total of 28.1% (n=1411) males and 14.6% (n=450) females had shockable rhythm as first recorded rhythm. Among men who experienced a witnessed cardiac arrest (n=2383), those who received bystander CPR (n=1233) were more likely to have an initial shockable heart rhythm (56.5% [572/1233] versus 43.6% [442/1150], P<0.0001) compared with those who did not receive bystander CPR. This was not observed in the female population: among women who suffered a witnessed arrest (n=1271), those who received bystander CPR (n=637) had similar rates of shockable and nonshockable heart rhythm (51.3% [160/637] versus 48.7% [152/634], P for difference 0.64). Among 1870 patients (1233 males and 637 females) who had a witnessed cardiac arrest and received bystander-initiated CPR, men were more likely to have a shockable heart rhythm (46.4% [572/1233] versus 25.1% [160/637], P for difference <0.0001).

Changes in Prehospital Interventions According to Sex, 2010–2014

Table 1 shows prehospital interventions according to sex during the study period. From 2010 to 2014, bystander CPR increased for both patient groups: for men from 40.5% to 50.6% and for women from 35.3% to 51.8%, P for each <0.0001. From 2010 to 2014, the combination of bystander CPR and first-responder defibrillation increased for both men (from 15.8% to 23.0%, P=0.007) and women (from 8.5% to 23.7%, P=0.004). Among those who were defibrillated, women had overall longer median time from collapse to defibrillation (13.4 versus 11.1 minutes, P<0.0001) compared with men. Women were also more likely to be defibrillated by EMS (53.1% versus 47.5%, P for difference 0.007) compared to first-responder defibrillation, and this did not change significantly across years.

Table 1. Prehospital Intervention According to Sex From 2010 to 2014

	2010	2011	2012	2013	2014	Total	*P* for Trend (change over time)	*P* for Interaction*
Cardiac arrests, n	1489	1457	1621	1712	1821	8100		
Men	958	887	987	1032	1152	5016	...	...
Women	531	570	634	680	669	3084	...	...
CPR initiated, % (n)[†]								
Bystander								
Men	40.3 (363)	40.9 (355)	48.3 (472)	48.2 (490)	50.5 (569)	46.0 (2249)	<0.0001	0.32
Women	35.3 (170)	47.7 (264)	43.8 (274)	51.7 (345)	51.8 (339)	46.7 (1392)	<0.0001	
First responder								
Men	44.1 (397)	43.3 (376)	37.7 (368)	40.7 (413)	38.3 (431)	40.6 (1985)	0.006	0.83
Women	43.0 (207)	36.6 (203)	42.4 (265)	36.7 (245)	37.0 (242)	39.0 (1192)	0.08	
EMS								
Men	15.6 (141)	15.9 (138)	14.0 (137)	11.1 (113)	11.2 (126)	13.4 (665)	<0.0001	0.11
Women	21.6 (104)	15.7 (87)	13.8 (86)	11.7 (78)	11.3 (74)	14.4 (429)	<0.0001	
Men	37.4 (358)	42.6 (378)	41.1 (406)	40.9 (422)	41.8 (482)	40.8 (2046)	0.15	0.81
Women	22.6 (120)	28.5 (162)	26.5 (168)	25.8 (175)	26.3 (176)	26.0 (801)	0.45	
Median time to defibrillation, min (25th, 75th)[§]								
Men	12.0 (8.0, 21.7)	11.5 (7.8, 20.5)	12.0 (8.0, 19.3)	10.4 (7.6, 18.1)	10.5 (7.5, 17.6)	11.1 (7.7, 19.4)	0.006	
Women	14.0 (8.7, 25.7)	14.2 (9.5, 24.0)	13.8 (9.9, 22.9)	14.0 (8.8, 23.0)	12.1 (7.6, 22.3)	13.4 (8.6, 23.1)	0.04	
Who first performed defibrillation, % (n)[‖]								
Bystander								
Men	8.4 (30)	4.8 (18)	4.7 (19)	6.2 (26)	7.7 (37)	6.4 (130)	0.83	0.52
Women	10.0 (12)	8.6 (14)	4.8 (8)	7.4 (13)	7.9 (14)	7.6 (61)	0.53	
First responder								
Men	41.5 (148)	48.7 (184)	41.4 (168)	51.8 (218)	46.9 (226)	46.2 (944)	0.09	0.50
Women	32.5 (39)	38.3 (62)	41.1 (69)	38.3 (67)	44.3 (78)	39.3 (315)	0.08	
EMS								
Men	50.1 (179)	46.6 (176)	53.9 (219)	42.0 (177)	45.4 (219)	47.5 (970)	0.07	0.78
Women	57.5 (69)	53.1 (86)	54.2 (91)	54.3 (95)	47.7 (84)	53.1 (425)	0.16	
CPR and defibrillation, % (n)[#]								
EMS-initiated CPR and EMS defibrillation								
Men	15.0 (53)	15.4 (58)	12.9 (52)	9.3 (39)	11.0 (53)	12.6 (255)	0.09	0.43
Women	19.5 (23)	15.0 (24)	14.4 (24)	13.8 (24)	15.6 (27)	15.4 (122)	0.41	
First-responder–initiated CPR and EMS defibrillation								
Men	15.5 (55)	15.7 (59)	16.9 (68)	10.8 (45)	10.8 (52)	13.7 (279)	0.07	0.93
Women	22.0 (26)	18.8 (30)	18.0 (30)	13.2 (23)	10.4 (18)	16.0 (127)	0.002	
First-responder–initiated CPR and first-responder defibrillation								
Men	26.0 (92)	27.9 (105)	21.1 (85)	27.5 (115)	23.9 (115)	25.2 (512)	0.50	1.0
Women	22.9 (27)	18.8 (30)	20.4 (34)	17.8 (31)	20.8 (36)	20.0 (158)	0.70	

Continued

Table 1. Continued

	2010	2011	2012	2013	2014	Total	*P* for Trend (change over time)	*P* for Interaction*
Bystander-initiated CPR and EMS defibrillation								
Men	20.1 (71)	15.7 (59)	24.4 (98)	21.8 (91)	23.7 (114)	21.3 (433)	0.04	0.69
Women	17.0 (20)	19.4 (31)	22.2 (37)	27.6 (48)	22.5 (39)	22.1 (175)	0.07	
Bystander-initiated CPR and first-responder defibrillation								
Men	15.8 (56)	20.7 (78)	20.7 (83)	24.6 (103)	23.0 (111)	21.2 (431)	0.007	0.29
Women	8.5 (10)	19.4 (31)	21.0 (35)	20.1 (35)	23.7 (41)	19.2 (152)	0.004	
Bystander-initiated CPR and bystander defibrillation								
Men	7.6 (27)	4.5 (17)	4.0 (16)	6.0 (25)	7.7 (37)	6.0 (122)	0.51	0.29
Women	10.2 (12)	8.8 (14)	4.2 (7)	7.5 (13)	6.9 (12)	7.3 (58)	0.29	

CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services.
**P* values reported for linear and quadratic terms when appropriate. Interaction denotes interaction between sex and year (difference in change in survival for men vs women across years).
[†]Missing value, n (%): all patients 231 (2.8).
[‡]Missing value, n (%): women2 (0.06).
[§]Missing value, n (%): men 328 (16.0), women121 (15.1).
[||]Missing value, n (%): all patients 127 (2.5).
[#]Missing value, n (%): men 14 (0.68), women9 (1.1).

Changes in Outcomes According to Sex, 2010–2014

Table 2 shows observed outcomes according to sex from 2010 to 2014. A substantial and similar increase in return of spontaneous circulation was observed for both men and women, while hospital admission increased significantly only for men. From 2010 to 2014, the increase in observed survival and favorable neurologic outcome was significant only for men (*P* for interaction: survival to discharge=0.002, favorable neurologic outcome=0.009).

Figure 2, Table 3, Figure S1, and Tables S2 and S3 show results from multivariable logistic regression models assessing the association between outcomes and year (2010–2014)

Table 2. Observed Outcomes According to Sex, 2010–2014

	2010	2011	2012	2013	2014	Total	*P* for Trend (change over time)	*P* for Interaction*
Men	64.3 (616)	68.7 (609)	60.7 (599)	52.7 (544)	55.4 (638)	59.9 (3006)	<0.0001	0.83
Women	62.0 (329)	62.3 (355)	58.8 (373)	50.2 (341)	52.2 (349)	56.7 (1747)	<0.0001	
Return of spontaneous circulation, % (n)[†]								
Men	19.7 (188)	28.9 (256)	27.4 (269)	30.6 (315)	32.9 (379)	28.1 (1407)	<0.0001	0.10
Women	25.7 (136)	26.0 (148)	32.8 (206)	27.7 (188)	33.3 (223)	29.3 (901)	0.003	
Admitted to hospital ward, % (n)								
Men	17.6 (169)	26.9 (239)	26.3 (260)	27.9 (288)	28.7 (330)	25.6 (1286)	<0.0001	0.03
Women	23.2 (123)	23.3 (133)	28.4 (180)	22.4 (152)	27.5 (184)	25.0 (772)	0.19	0.08
Survival to discharge, % (n)[†]								
Men	7.0 (66)	10.8 (95)	11.7 (114)	12.4 (127)	11.3 (130)	10.7 (532)	0.001	0.002
Women	7.6 (40)	7.9 (45)	7.3 (46)	6.3 (43)	9.9 (66)	7.8 (240)	0.33	0.003
Favorable neurologic outcome, %[†] (n)								
Men	6.2 (59)	10.2 (89)	10.7 (105)	11.2 (115)	9.8 (113)	9.7 (481)	0.007	0.009
Women	6.3 (33)	6.0 (34)	6.0 (38)	6.2 (42)	7.5 (50)	6.4 (197)	0.36	0.012

Missing values are 0 unless otherwise indicated.
**P* values reported for linear and quadratic terms when appropriate. Interaction denotes interaction between sex and time (difference in change in survival for men vs women across years).
[†]Missing values < 1%.

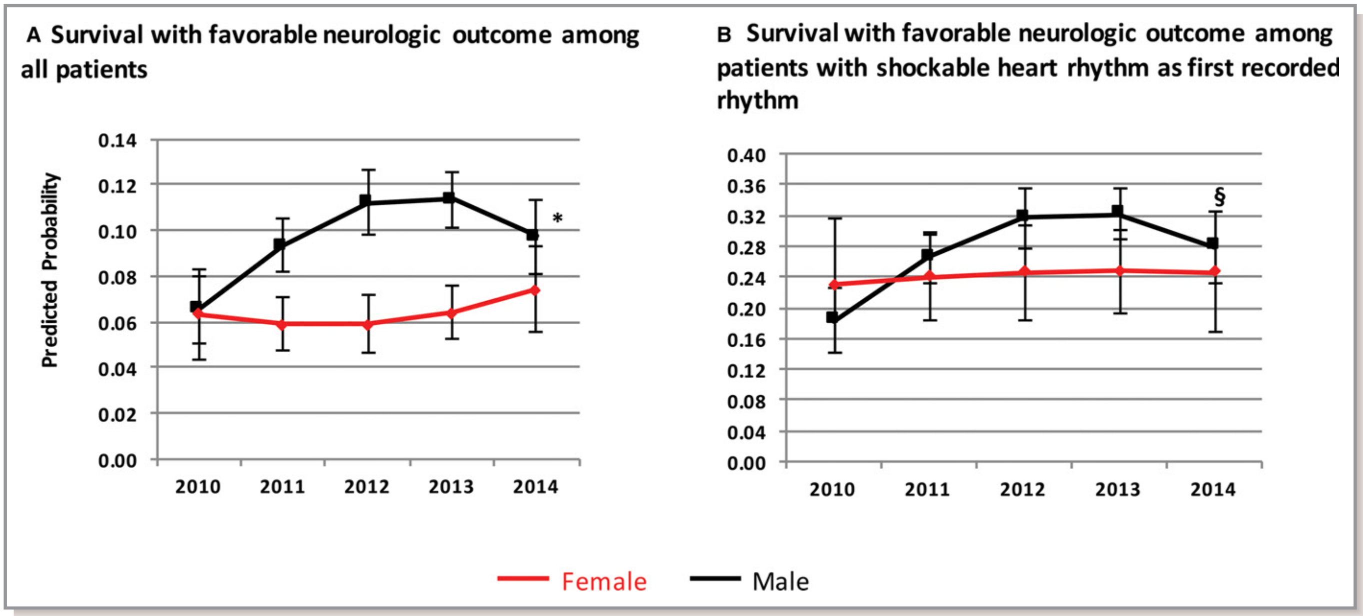

Figure 2. Predicted probabilities of survival with favorable neurologic outcome according to sex, 2010–2014. Results from logistic regression models assessing survival from 2010 to 2014 according to sex. Results are presented as predicted probabilities including this interaction. A, Results from analysis including all patients. B, Only included patients with shockable heart rhythm as first recorded rhythm. *P* value indicates interaction between sex and year (significant difference in change in survival for men vs women). The change in outcomes over time was best captured as a quadratic function and thus 2 *P* values are reported when appropriate. The error bars show standard error bars on 95% confidence intervals. **P*=0.009 and 0.012. §*P*=0.13 and 0.18.

for men compared with women. Results are presented unadjusted and adjusted for modifiable factors and nonmodifiable factors. The predicted probability of return of spontaneous circulation increased similarly for men and women. Unadjusted, return of spontaneous circulation was initially lower for men, but the gap was narrowed during the study period and was consistently higher for women in adjusted models. The predicted probability of survival to discharge increased significantly only for men and was lower for women in unadjusted models. After adjusting for nonmodifiable factors, the predicted probability of survival to discharge was higher for women, and adjusting for modifiable factors did not substantially change the results.

Figure 1 shows the unadjusted predicted probability of survival with favorable neurologic outcome for all patients (Figure 1A) and including only patients with a shockable heart rhythm as first recorded rhythm (Figure 1B). Overall, the predicted probability of survival with favorable neurologic outcome increased more markedly for men compared to women from 2010 to 2014. Unadjusted, the predicted probability of survival with favorable neurologic outcome was higher for men (from 6.5% [95% CI, 5.1–8.0] to 9.7% [95% CI, 8.1–11.3]) compared with women (from 6.3% [95% CI, 4.4–8.3] to 7.4% [95% CI, 5.5–9.3%]), *P* for interaction 0.009 and 0.012. After accounting for differences in age, witnessed status, and first recorded heart rhythm (non-modifiable factors), survival with favorable neurologic outcome for women was slightly higher but with a limited increase (from 9.2% [95% CI, 6.8–11.8] to 10.2% [95% CI, 8.0–12.5]) compared with men (from 5.8% [95% CI, 4.6–7.0] to 8.4% [95% CI, 7.1–9.7]), *P* for interaction 0.003 and 0.004. Adding modifiable factors to the model did not substantially change the results.

When subsetting the analysis to a more homogenous population of patients with a shockable heart rhythm as the first recorded rhythm, outcomes were largely unchanged for females but improved for males (although the difference in increase was not statistically significant).

Discussion

This study of out-of-hospital cardiac arrest patients in urban and rural areas in North Carolina aimed to assess sex-related differences in bystander and/or first-responder intervention from 2010 to 2014 and how these differences related to outcomes. The study had 4 main findings: (1) rates of bystander-initiated CPR and the combination of bystander-initiated CPR and first-responder defibrillation increased for both men and women; (2) observed rates of survival and favorable neurologic outcome were consistently higher and increased more for men than women; (3) after taking nonmodifiable sex-related differences into account (age,

Table 3. Adjusted Predicted Probabilities of Survival With Favorable Neurologic Outcome According to Year

Patient Groups	Adjusted Predicted Probabilities of Survival With Favorable Neurologic Outcome by Year (95% CI)				
	2010	2011	2012	2013	2014
All patients					
Adjusted for nonmodifiable factors: age, witnessed status, and first recorded heart rhythm*					
Women	9.29 (6.80–11.8)	8.06 (6.68–9.44)	7.81 (6.30–9.32)	8.48 (7.11–9.86)	10.2 (8.04–12.5)
Men	5.78 (4.57–6.99)	7.96 (7.06–8.85)	9.34 (8.25–10.43)	9.52 (8.57–10.47)	8.43 (7.13–9.72)
Adjusted for nonmodifiable and modifiable factors: factors age, witnessed status, first recorded heart rhythm, bystander cardiopulmonary resuscitation*					
Women	9.82 (7.20–12.46)	8.35 (6.92–9.78)	7.99 (6.44–9.53)	8.63 (7.23–10.03)	10.47 (8.21–12.71)
Men	6.04 (4.78–7.30)	8.19 (7.27–9.11)	9.53 (8.42–10.64)	9.66 (8.69–10.6)	8.55 (7.23–9.87)
Patients with a shockable heart rhythm					
Adjusted for nonmodifiable factors: age and witnessed status					
Women	26.7 (16.3–35.0)	24.2 (18.8–29.5)	24.0 (18.0–30.0)	25.2 (19.8–30.6)	27.8 (19.6–36.0)
Men	19.2 (14.8–23.5)	26.3 (23.2–29.4)	30.6 (26.9–34.3)	31.0 (27.8–34.2)	28.5 (23.0–31.9)
Adjusted for nonmodifiable and modifiable factors: age, witnessed status, bystander cardiopulmonary resuscitation, defibrillation before ambulance					
Women	26.0 (17.6–35.5)	24.4 (19.0–29.8)	24.2 (18.1–30.2)	25.3 (19.9–30.7)	28.0 (19.8–36.3)
Men	19.4 (15.0–24.9)	26.2 (23.1–29.4)	30.3 (26.6–34.0)	30.7 (27.5–33.9)	27.3 (22.8–31.7)

CI indicates confidence interval.
**P* value for significant interaction between sex and year <0.05 (significant difference in change in survival for men vs women across years).

witnessed status, and initial heart rhythm), survival was slightly higher for women compared with men, but increased substantially more over time for men compared with women; and (4) modifiable prehospital factors (bystander CPR and defibrillation before EMS arrival) did not seem to explain the sex-related differences in outcomes. Taken together, these findings indicate the lower survival observed in women may mainly be related to nonmodifiable prehospital factors, and thus increasing survival for female patients may require alternative treatments to those in current use (including bystander CPR and early defibrillation).

Our novel findings may contribute to better understanding differences in outcomes between women and men suffering a cardiac arrest. In particular, our results may have implications for how to address sex-related differences in order to increase survival for both men and women. It has previously been suggested that lower rates of survival in women could be attributable to lower rates of bystander CPR, which our study does not support.[2,12] The limited increase in overall survival in women compared with men despite the significant increase in bystander CPR and the combination of bystander CPR and first-responder defibrillation may be partly attributable to the substantial proportion of female patients with nonshockable heart rhythm. However, even among women with a shockable heart rhythm, survival was largely unchanged for women but increased for men. The limited increase in survival among women may also be related to different underlying pathophysiology of cardiac arrest. In our study, women were less likely to have a shockable heart rhythm even when subsetting the analysis to patients with a witnessed arrest and bystander CPR, indicating a different underlying pathophysiology of cardiac arrest. The vast majority of men suffer cardiac arrest because of coronary artery disease and acute myocardial infarction, whereas women are more likely to have other underlying pathophysiology such as cardiomyopathies.[9] The mechanism of cardiac arrest in the absence of an acute myocardial infarction is believed to be an electric event caused by ventricular arrhythmia in the setting of a chronically diseased heart, which is more likely to occur among women who are typically older and have more comorbidities.[2] This is supported by our finding that even among those with an initial shockable heart rhythm, the increase in survival was more limited for women compared with men (although this difference was not statistically significant).

We found that the proportion of patients achieving return of spontaneous circulation increased similarly for men and women, while the proportion admitted to the hospital increased significantly for men and did not increase significantly for women. Return of spontaneous circulation can be viewed as a proxy measurement of prehospital care, and thus the increase in bystander CPR and first-responder defibrillation may have translated into the observed increase in return of spontaneous circulation. However, for women, these improvements seem to be attenuated in the transition from the prehospital setting to hospital admission. Previous studies have suggested that prehospital treatment strategies (early

CPR and defibrillation) may be more suited to male patients with initial shockable heart rhythm.[24–26] Although bystander CPR has been associated with improved outcomes among patients with nonshockable heart rhythm, survival in this population is markedly lower and limited increase in survival has been shown following improvements in prehospital treatment compared with those having a shockable heart rhythm.[24–26] Thus, as most cardiac arrest patients have a nonshockable heart rhythm and this proportion has been increasing consistently over time, the lack of treatment response in this population poses a challenge for increasing overall survival after cardiac arrest not only in women but in the majority of cardiac arrest populations.[27] Thus, alternative prehospital and hospital therapies may be needed to improve survival in this growing population.

Finally, the lower increase in survival among women could be also partly attributable to longer time to defibrillation compared with men. This may be because women were consistently less likely to be defibrillated by first responders, although there was an increase in the combination of bystander CPR and first-responder defibrillation over time. It is not clear why first responders were less likely to defibrillate female patients. This could be because other diagnoses are more likely considered when women collapse such that the initial dispatch complaint is less often a cardiac arrest. First responders arriving at the scene would then be unprepared and take more time to apply the automated external defibrillator. Wissenberg et al found that women were less likely to receive bystander CPR, even more so in public areas, and hypothesized that this could be attributable to higher hesitation to undress women or because people were less likely to associate female collapse with cardiac arrest.[2] A qualitative research design could provide insight into sex-related differences in treatment and may be considered for future studies seeking to describe such differences.[28]

Limitations

This study has several limitations. The study design requires that inferences based on outcomes must be made with caution and the relationships indicated between factors should be viewed as associations and not cause and effect. Notwithstanding, high data quality was pursued through prospective and uniform data collection through the CARES registry, following Utstein guidelines for reporting cardiac arrest.[20] We included data from only selected counties. Although there may be differences in geographic and cardiac arrest characteristics between the included and excluded counties, we were able to pursue complete case ascertainment, thus reducing the risk of bias because of changes in reporting over time.[16] Also, population and cardiac arrest characteristics in the included counties are similar to other cardiac arrest populations, indicating at least some degree of generalizability.[2,5,8,29] We do not have information on several important factors (also modifiable factors) that may influence outcome such as quality of CPR given, type of CPR (compression-only CPR versus conventional), percentage of dispatcher-identified cardiac arrests, or time from collapse to administration of CPR and defibrillation, as well as other possible modifiable factors that were not specified in the present study. However, our study was not designed to assess causality, and the relationship between bystander and first-responder intervention and outcomes should be viewed as associations and not causal effect.

Conclusion

Bystander CPR and the combination of bystander CPR and first-responder defibrillation increased for men and women, but outcomes improved significantly only for men. Sex differences in survival were mainly associated with nonmodifiable factors (age, witnessed status, and initial heart rhythm). In addition to improving bystander CPR and early defibrillation, other strategies may be necessary to improve survival among female cardiac arrest patients.

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SUPPLEMENTAL MATERIAL

Table S1. Patient and Cardiac Arrest Characteristics According to Sex 2010-2014.

Characteristics	2010	2011	2012	2013	2014	Total	P for trend	P for interaction*
Cardiac arrests, n								
Male	64.3 (958)	60.9 (887)	60.9 (987)	60.3 (1032)	63.3 (1152)	61.9 (5016)	0.55	-
Age, y, median (25th, 75th)†								
Male	64 (54, 75)	66 (54, 76)	64 (54, 76)	64 (53, 75)	64 (54.5, 75)	64 (54, 75)	0.39	0.01 0.02
Female	71 (60, 82)	69 (56, 82)	68 (56, 80)	67 (56, 80)	69 (57, 80)	68 (57, 81)	0.04	
Witnessed, % (n)								
Male	44.4 (425)	51.1 (453)	47.5(469)	48.6 (501)	47.5 (547)	47.8 (2395)	0.45	0.34
Female	37.3 (198)	41.6 (237)	42.9 (272)	41.9 (285)	43.1 (288)	41.5 (1280)	0.08	
Arrest in public								
Male	19.4 (186)	23.8 (211)	21.5 (212)	23.5 (242)	26.0 (300)	23.0 (1151)	0.002	0.02 0.04
Female	9.0 (48)	20.7 (118)	15.5 (98)	20.9 (142)	20.6 (138)	17.6 (544)	<0.0001	
First recorded rhythm VF/pVT, % (n)†								
Male	27.5 (263)	30.2 (268)	27.5 (271)	27.9 (288)	27.9 (321)	28.1 (1411)	0.76	0.89
Female	14.3 (76)	16.2 (92)	13.6 (86)	13.6 (92)	15.6 (104)	14.6 (450)	0.98	
Transported to PCI capable hospital†, % (n)								
Male	70.9 (435)	77.6 (471)	72.3 (433)	80.2 (436)	81.4 (519)	76.4 (2294)	<0.0001	0.14
Female	74.7 (245)	76.6 (271)	78.8 (294)	76.5 (260)	79.7 (278)	77.3 (1348)	0.17	
Received temperature management therapy‡, % (n)								
Male	57.5 (69)	58.7 (132)	63.1 (157)	72.1 (202)	57.9 (187)	62.4 (747)	0.43	0.99
Female	56.0 (47)	56.3 (72)	59.6 (106)	59.6 (90)	59.1 (107)	58.5 (422)	0.51	
Angiography performed§, % (n)								

Characteristics	2010	2011	2012	2013	2014	Total	P for trend	P for interaction*
Male	30.4 (7)	39.8 (47)	46.5 (73)	47.4 (109)	35.7 (107)	41.4 (343)	0.40	0.01 0.01
Female	30.0 (6)	28.8 (21)	20.6 (21)	22.8 (29)	23.3 (37)	23.7 (114)	0.46	

CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range; VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia; PCI, percutaneous coronary intervention.

*P values reported for linear and quadratic terms when appropriate. Interaction denotes interaction between sex and time (difference in change in survival for males vs. females across years).

Missing values are 0 unless otherwise indicated.

†Missing values < 1 %.

‡Percentages of patients transported to PCI capable hospital are relative to those who were not declared dead in the field (males=3,006, females=1,747). ‡Percentages of patients who received temperature management therapy are relative to patients who were admitted to hospital ward (males=1,197, females=772), missing values n (%), males: 89(6.9), females 50 (6.5). §Percentages of patients who received angiography are relative to patients who were admitted to hospital ward with 24/7 PCI capabilities (males=828, females=481). Missing value, n (%): males 320 (27.9), females 202 (29.6)

Table S2. Interaction Between Sex and Year. Favorable neurologic outcome According to Sex among all patients

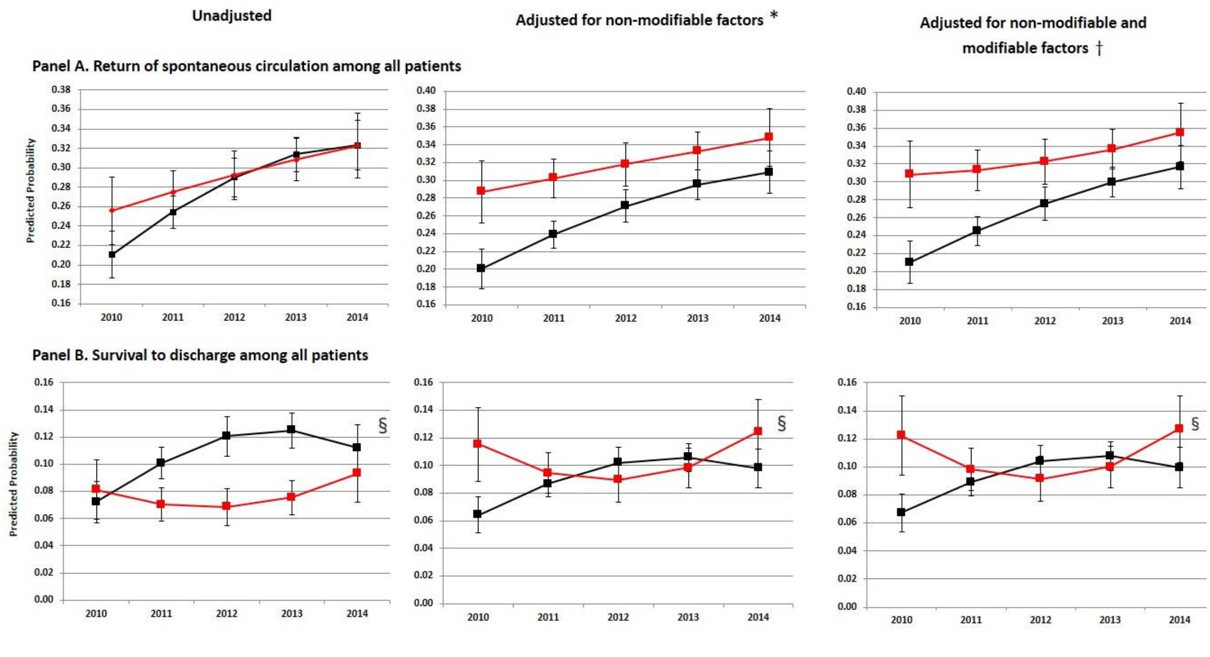
Favorable Neurologic Outcome	**Odds Ratio**	**P>|z|**	**[95% Confidence Interval]**
Male	0.50	0.13	0.21-1.22
Year1	0.83	0.49	0.48-1.42
Year2	1.04	0.38	0.95-1.13
male#c.year1	2.36	0.009	1.23-4.53
male#c.year2	0.88	0.012	0.79-0.97
_cons	0.08	0.000	0.04-0.16

Table S3. Favorable neurologic outcome According to Sex among defibrillated patients.

Favorable Neurologic Outcome	**Odds Ratio**	**P>|z|**	**[95% Confidence Interval]**
Male	0.40	0.16	0.11-1.44
Year1	1.09	0.84	0.48-2.47
Year2	0.99	0.88	0.87-1.13
male#c.year1	2.07	0.13	0.81-5.27
male#c.year2	0.90	0.18	0.78-1.05
_cons	0.28	0.02	0.91-0.84

Results from logistic regression analyses including the interaction between sex and year. Preliminary analyses showed that change in outcomes across years (2010-2014) was best captured as a quadratic function. To account for the greater increase in survival for men compared with women over time, all logistic regression models included interactions between sex and time (i.e., year and $year^2$).

Figure S1. Survival to Discharge and Return of Spontaneous Circulation According to Sex, 2010-2014.



— Female — Male

*age, witnessed status and first recorded heart rhythm

†age, witnessed status and first recorded heart rhythm, bystander cardiopulmonary resuscitation

§ P value for significant interaction between sex and year <0.05 (significant difference in change in survival for males vs. females).

Results from logistic regression models assessing return of spontaneous circulation from 2010-2014 according to sex. Results are presented as predicted probabilities including this interaction. The error bars show standard error bars on 95% confidence intervals.