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CLINICAL INVESTIGATIONS

Sustained sex-based treatment differences in acute coronary syndrome care: Insights from the American Heart Association Get With The Guidelines Coronary Artery Disease Registry

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Background: Sex-based differences in acute coronary syndrome (ACS) mortality may attenuate with age due to better symptom recognition and prompt care.

Hypothesis: Age is a modifier of temporal trends in sex-based differences in ACS care.

Methods: Among 104 817 eligible patients with ACS enrolled in the AHA Get With the Guidelines–Coronary Artery Disease registry between 2003 and 2008, care and in-hospital mortality were evaluated stratified by sex and age. Temporal trends within sex and age groups were assessed for 2 care processes: percentage of STEMI patients presenting to PCI-capable hospitals with a DTB time ≤ 90 minutes (DTB90) and proportion of eligible ACS patients receiving aspirin within 24 hours.

Results: After adjustment for clinical risk factors and sociodemographic and hospital characteristics, 2276 (51.7%) women and 6276 (56.9%) men with STEMI were treated with DTB90 (adjusted OR: 0.85, 95% CI: 0.80–0.91, $P < 0.0001$ for women vs men). Time trend analysis showed an absolute increase ranging from 24% to 35% in DTB90 rates among both men and women (P for trend <0.0001 for each group), with consistent differences over time across the 4 age/sex groups (3-way P-interaction = 0.93). Despite high rate of baseline aspirin use (87%–91%), there was a 9% to 11% absolute increase in aspirin use over time, also with consistent differences across the 4 age/sex groups (all 3-way P-interaction ≥0.15).

Conclusions: Substantial gains of generally similar magnitude existed in ACS performance measures over 6 years of study across sex and age groups; areas for improvement remain, particularly among younger women.

KEYWORDS

Acute Coronary Syndrome, Epidemiology, Quality of Care, Women

1 | INTRODUCTION

Women have an observed increased mortality risk after myocardial infarction (MI) compared with their male counterparts.[1–3] A potential contributor to this risk may be that women, particularly younger women, present more frequently with atypical chest pain during an acute coronary syndrome (ACS), making the physician recognition of MI risk and diagnosis more challenging, with resultant delays in prompt treatment.[4,5] There are other sex-based factors that may be associated with observed gaps in timely revascularization and outcomes between women and men.[3,6,7] Disparities in access to care, delays in timing of presentation, differences in comorbidities and features of coronary heart disease (CHD), and delays in initiation of optimal medical therapy may all play a role.[2,8–12] Sex-based differences in ACS presentation and mortality may attenuate with increasing age, resulting in a reversal in mortality risk and poorer prognosis among men age ≥ 65 years compared with similarly aged women.[1,13] The translation of these observations into better symptom recognition by patients and physicians, and more equitable care among the sexes by providers, may potentially be reflected in temporal trends toward diminishing sex differences in early ACS treatment and outcomes.[14–18]

The American Heart Association (AHA) Get With the Guidelines Coronary Artery Disease (GWTG-CAD) Registry provided a unique opportunity to evaluate whether differences in early acute ACS therapy and mortality have narrowed among the sexes in the United States, and whether age was an important modifier of sex-based differences in ACS care.

2 | METHODS

2.1 | Study population

We studied participants in the national AHA GWTG-CAD database, a multicenter, prospective, observational registry and quality-improvement initiative established by the AHA in collaboration with researchers, professional organizations, and hospitals to improve the care of patients with CAD with continuous performance feedback and care strategies. Details of the program, including the design, methods, inclusion and exclusion criteria, and data definitions, have been described previously.[19,20] Briefly, the registry utilized a standardized clinical reporting system and data definitions, allowing for uniform data entry and transmission by participants, who were subject to regular data quality checks and feedback. All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule.

This study was prepared in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The current report considered 159 148 consecutive patients with an initial clinical diagnosis of ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndrome (NSTE-ACS) admitted to 406 participating hospitals with percutaneous coronary intervention (PCI) capabilities between 2003 and 2008, in whom complete patient demographic details were available. Patients were excluded if they had missing or incomplete follow-up details if transferred in (n = 38 066) or transferred out of participating hospitals, if they left against medical advice or were discharged to hospice care (n = 14 366), or if they had missing demographic information for classification (n = 1899). This yielded a final study population of 104 817 patients from 397 hospitals with PCI capabilities between January 1, 2003, and December 31, 2008.

2.2 | Data definitions

Data on patient demographics, medical history, signs and symptoms on presentation, acute therapy, in-hospital clinical events, discharge therapy, counseling, and disposition were collected from chart review and entered into the web-based patient database.

The primary quality-of-care process outcome of this analysis was adherence to evidence-based primary therapy, which was evaluated with 2 measures. First, among patients presenting with STEMI, the proportion of women with door-to-balloon time ≤ 90 minutes (DTB90) who underwent primary PCI without concomitant thrombolytic therapy or missing data was compared with men. Second, among all patients with ACS, the percentage of women receiving aspirin (acetylsalicylic acid, ASA) treatment within the first 24 hours of presentation (ASA24) was compared with men. In addition, the relative rates of in-hospital mortality post-ACS were compared between women and men.

2.3 | Statistical analysis

Patients were categorized by sex and divided into age groups (4 age groups of <55, 55–64.9, 65–74.9, and ≥ 75 years and dichotomized at age < 65 years and ≥ 65 years) with analyses conducted among patients according to presenting acute coronary diagnosis (STEMI or NSTE-ACS). Baseline characteristics were compared across sex and age groups using the Pearson χ^2 test for categorical variables (summarized as frequencies/percentages) and the Wilcoxon test for continuous variables (summarized as median values with interquartile ranges).

The percentage of patients treated with DTB90 and ASA24, as well as mortality rates, was reported over time stratified by sex and age groups. Temporal trends were assessed within each sex and age group using a Cochran-Armitage trend test, and general estimating equation logistic regression models (to account for hospital clustering of patients) were used to derive odds ratios (OR) and 95% confidence intervals (CI) after adjustment for sociodemographic variables, clinical risk factors, hospital characteristics, and within-hospital clustering. The covariates in the model were drawn from a previously validated registry mortality model and included age, sex, ethnicity/race, medical insurance type, history of established ischemic heart disease (IHD), MI, coronary revascularization, hypertension, diabetes mellitus, hyperlipidemia, heart failure (HF), stroke, peripheral artery disease, current/recent tobacco use, obstructive airway disease, and history of renal impairment or dialysis-dependent.[21] Hospital characteristics included hospital bed number, region, teaching status, and rural or urban setting.

Multiplicative interaction terms for age and sex, sex and time, and age-sex-time were explored at the $P < 0.10$ level to determine whether temporal trends in risk significantly changed over time between sex and age groups. Additional effect modifications were explored for differences in temporal trends among patients with and without a history of established IHD or prior MI. All other tests for significance were tested at a 2-sided P value <0.05. Statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). Quintiles (Cambridge, MA) served as the registry data collection coordinating center. The Duke Clinical Research Institute (Durham, NC) served as the data-analysis center, and institutional review board approval was granted to analyze aggregate de-identified data for research purposes.

3 | RESULTS

3.1 | Baseline characteristics

Among the overall study population of 104 817 patients, 41 264 (39.4%) women and 63 553 (60.6%) men presented with STEMI (n = 30 409; 29.0%), NSTEMI (n = 63 725; 60.8%), or unstable angina (n = 10 683; 10.2%). The median age of the overall cohort was 67 years (IQR, 56–79 years), with 22 938 (21.9%) patients age < 55 years, 23 155 (22.1%) age 55 to 64.9 years, 22 331 (21.3%) age 65 to 74.9 years, and 36 393 (34.7%) age ≥ 75 years. There were no clinically relevant differences in age, sex, and race/ethnicity over the study period in our study population (see Supporting Information, Table 1, in the online version of this article).

Baseline characteristics stratified by sex and age groups pooled across all years of observation are presented in Table 1. Women with ACS tended to be older and presented more frequently with hypertension, HF, and diabetes compared with men. Women less often had obstructive CAD or prior MI within any age group, and sex-based differences in the prevalence of these CHD conditions rose with age. However, for other risk factors, the ratio of female-to-male patients reversed with age. For example, there was a higher proportion of young women with ACS who were minorities compared with men, a pattern that reversed among the oldest patients with STEMI. Reversals in sex ratios across age groups were also seen for obstructive airway disease, stroke, renal insufficiency, and lipid levels.

3.2 | Temporal trends in early reperfusion, ASA treatment, and outcomes

Among patients with STEMI, 15436 patients from 238 sites underwent primary PCI and had times available for evaluation of door-to-balloon time adherence within 90 minutes (DTB90). In addition, 8958 STEMI patients were medically managed, 1200 received thrombolytic therapy, and 4815 had missing or imprecise data on arrival time or PCI. Among eligible patients, 8552 (55.4%) achieved DTB90 (Table 2), with a larger sex-based gap unfavorable to women among patients younger vs older than 65 years (Tables 2 and 3). For instance, 54.1% of women age < 55 years were treated with a DTB90 compared with 58.7% similar-aged men, resulting in a 4.6% absolute lower achievement in this performance metric (adjusted OR: 0.80, 95% CI: 0.69–0.93, $P = 0.0025$). Similar results were observed for women compared with men age 55 to 64.9 years (52.1% vs 58.6%; adjusted OR: 0.81, 95% CI: 0.70–0.92, $P = 0.002$). Among patients age 65 to 74.9 years (53.5% vs 54.5%; adjusted OR: 0.93, 95% CI: 0.79–1.10, $P = 0.41$) and ≥ 75 years (48.4% vs 49.7%; adjusted OR: 0.97, 95% CI: 0.83–1.14, $P = 0.73$), the treatment gap narrowed and was no longer significant. After multivariable adjustment, there appeared to be potential heterogeneity in sex-based differences in DTB90 between younger and older patients (2-way P-interaction for sex/dichotomous age at 65 = 0.06), with achievement of DTB90 significantly lower among women age < 65 years (adjusted OR: 0.81, 95% CI: 0.73–0.89) but not older patients age ≥ 65 years (adjusted OR: 0.92, 95% CI: 0.83–1.01).

Between 2003 and 2008, the rate of DTB90 achievement improved (range, 24%–35%) for both men and women across all age groups (P-trend for all <0.0001; see Supporting Information, Table 2, in the online version of this article). After multivariable adjustment, no significant heterogeneity was detected, suggesting consistent improvement over time in sex differences in DTB90 achievement across age/sex groups (3-way P-interaction for sex/age/time = 0.93; Figure 1).

Similarly, despite a high rate of ASA use at baseline (ranging from 87% to 91%), there was a 9% to 11% absolute increase in prompt ASA therapy within 24 hours of presentation (ASA24) with STEMI (n = 28 491) or NSTE-ACS (n = 68 020) over time among men and women across age groups (P-trend <0.0001 for all; see Table 3 and Supporting Information, Table 3, in the online version of this article). After adjustment for clinical risk factors, temporal improvements in prompt ASA treatment appeared consistent across age/sex groups (3-way P-interaction = 0.15 for STEMI and 0.54 for NSTE-ACS).

A total of 2071 STEMI patients (6.8%) and 4093 NSTE-ACS (5.5%) patients died in-hospital, with significantly higher fatality rates among women compared with men (Table 2). A sex difference in mortality was particularly evident among younger women, age < 55 years (Table 3), presenting with STEMI (adjusted OR: 1.49, 95% CI: 1.12–1.98, $P = 0.006$) and NSTE-ACS (adjusted OR: 1.47, 95% CI: 1.22–1.77, $P < 0.0001$). Among patients age 55 to 64.9, 65 to 74.9, and ≥ 75 years, the mortality gap narrowed and was no longer significant (Table 3). Over time there was either modest or no significant change in survival among men and women stratified by age, except for a lower mortality risk over time seen among younger women presenting with NSTE-ACS (P-trend = 0.004; see Supporting Information, Table 4, in the online version of this article). Specifically, the temporal trend that was most pronounced was the 2.7% absolute lower risk among women age 55 to 65 years (P-trend = 0.009; Table 4). However, after multivariable adjustment, temporal trends in survival improvement were consistent across the age/sex groups for both STEMI and NSTE-ACS (STEMI 3-way P-interaction for sex/age/time = 0.63; NSTE-ACS 3-way P-interaction = 0.28; see Supporting Information, Figure, in the online version of this article).

Temporal trends across age and sex groups in achievement of DTB90, ASA24 therapy, and in-hospital mortality were generally consistent among patients with and without a history of established IHD and prior MI (see Supporting Information, Tables 5–7, in the online version of this article).

TABLE 1 Baseline characteristics by index diagnosis and sex and age groups among patients presenting with ACS

Characteristic	STEMI											
	Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y		
	Men, n = 7241	Women, n = 1864	*P* Value	Men, n = 5924	Women, n = 1984	*P* Value	Men, n = 3697	Women, n = 2081	*P* Value	Men, n = 3448	Women, n = 4170	*P* Value
Demographics												
Age, y	48 (44–51)	48 (43–51)	0.08	59 (57–62)	60 (57–62)	<0.0001	69 (67–72)	70 (67–72)	<0.0001	81 (77–85)	83 (79–87)	<0.0001
White race/ethnicity	71.2	66.9	<0.0001	75.0	72.2	<0.0001	76.5	74.1	0.0085	78.9	80.3	0.01
Medical history												
HTN	48.0	53.9	<0.0001	56.8	66.2	<0.0001	63.1	72.4	<0.0001	65.0	74.8	<0.0001
DM	7.3	11.7	<0.0001	9.3	11.8	0.001	10.2	12.7	0.004	8.6	9.0	0.52
Hypercholesterolemia	43.9	39.3	<0.001	46.7	50.2	0.01	48.4	47.9	0.72	39.2	37.4	0.12
Current/recent tobacco use	62.2	66.8	<0.001	45.7	47.5	0.13	27.0	28.7	0.19	11.4	9.1	<0.001
Prior MI	15.3	14.4	0.36	17.1	14.1	0.003	18.6	16.4	0.04	21.1	16.9	<0.0001
Prior CAD	8.8	8.3	0.52	10.7	9.2	0.07	12.2	10.5	0.06	14.1	11.1	<0.0001
Stroke	1.6	3.1	<0.0001	3.7	6.1	<0.0001	6.8	8.7	0.007	12.1	11.5	0.45
HF	2.7	4.5	0.0001	4.7	7.7	<0.0001	7.3	11.6	<0.0001	17.0	19.3	0.009
Renal insufficiency	1.8	2.5	0.06	3.2	4.8	0.0014	5.6	6.6	0.13	13.2	9.9	<0.0001
Obstructive airway disease	4.2	8.5	<0.0001	8.0	12.8	<0.0001	12.2	17.2	<0.0001	15.1	13.4	0.04
Other baseline findings												
BMI, kg/m^2	29.1 (25.9–32.7)	30.1 (25.3–35.0)	0.009	28.4 (25.5–32.0)	29.3 (25.1–34.4)	0.003	27.5 (24.9–30.8)	28.0 (24.1–32.3)	0.17	25.3 (22.9–28.2)	25.0 (21.8–29.0)	0.052
HR, bpm	78 (68–92)	80 (69–93)	0.20	76 (65–90)	78 (67–91)	0.12	77 (65–90)	77 (65–92)	0.76	78 (64–94)	81 (69–97)	<0.001
SBP, mm Hg	135 (118–153)	131 (112–152)	0.002	134 (116–155)	133 (114–154)	0.66	132 (114–155)	132 (113–153)	0.61	130 (110–150)	134 (112–155)	0.005
LDL-C, mg/dL	114 (89–141)	108 (84–135)	<0.0001	105 (82–130)	111 (85–141)	<0.0001	94 (74–119)	100 (77–126)	<0.0001	86 (67–108)	96 (73–122)	<0.0001
	NSTE-ACS											
	Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y		
Characteristic	Men, n = 9818	Women, n = 4015	*P* Value	Men, n = 10 256	Women, n = 4991	*P* Value	Men, n = 9940	Women, n = 6613	*P* Value	Men, n = 13 229	Women, n = 15 546	*P* Value
Demographics												
Age, y	48 (44–52)	49 (44–52)	0.23	60 (57–62)	60 (57–62)	<0.0001	69 (67–72)	70 (67–72)	<0.0001	81 (78–86)	83 (79–88)	<0.0001
White race/ethnicity	68.5	60.7	<0.0001	73.1	66.7	<0.0001	75.0	68.7	<0.0001	78.7	77.5	<0.0001
Medical history												
HTN	59.1	65.0	<0.0001	68.5	72.3	<0.0001	72.6	77.6	<0.0001	71.8	78.6	<0.0001
DM	9.4	14.3	<0.0001	13.2	17.1	<0.0001	14.6	16.3	0.006	13.2	13.2	0.98
Hypercholesterolemia	50.3	44.2	<0.0001	55.5	53.8	0.002	54.3	52.6	0.04	45.1	41.4	<0.0001

TABLE 1 (Continued)

Characteristic	NSTE-ACS											
	Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y		
	Men, n = 9818	Women, n = 4015	*P* Value	Men, n = 10 256	Women, n = 4991	*P* Value	Men, n = 9940	Women, n = 6613	*P* Value	Men, n = 13 229	Women, n = 15 546	*P* Value
Current/recent tobacco use	54.3	51.3	<0.001	36.2	35.6	0.37	20.7	19.5	0.048	8.3	6.4	<0.0001
Prior MI	20.2	17.3	<0.001	23.2	19.8	<0.0001	26.7	19.6	<0.0001	27.1	21.3	<0.0001
Prior CAD	13.3	12.5	0.23	17.0	16.1	0.16	19.1	15.7	<0.0001	21.1	17.7	<0.0001
Stroke	2.9	4.3	<0.0001	6.5	7.8	0.003	9.8	10.6	0.12	14.7	14.6	0.95
HF	6.0	8.8	<0.0001	10.0	14.5	<0.0001	15.4	18.1	<0.0001	25.1	28.2	<0.0001
Renal insufficiency	4.2	6.7	<0.0001	7.3	8.4	0.03	12.7	11.4	0.02	18.9	14.0	<0.0001
Obstructive airway disease	6.8	12.2	<0.0001	11.4	17.6	<0.0001	16.4	20.6	<0.0001	19.2	16.8	<0.0001
Other baseline findings												
BMI, kg/m^2	30.0 (26.5–34.8)	31.3 (26.2–37.0)	<0.0001	29.4 (25.9–33.6)	30.1 (25.7–35.7)	<0.001	28.3 (25.1–32.0)	29.0 (24.8–34.0)	<0.001	25.6 (22.9–28.7)	25.2 (21.6–29.2)	<0.0001
HR, bpm	79 (68–92)	82 (71–96)	<0.0001	78 (66–92)	81 (69–95)	<0.0001	78 (66–94)	81 (69–97)	<0.0001	82 (69–98)	84 (71–101)	<0.0001
SBP, mm Hg	138 (121–157)	137 (118–159)	0.32	139 (121–158)	142 (122–162)	<0.001	139 (120–157)	140 (121–161)	0.009	134 (116–155)	138 (118–160)	<0.0001
LDL-C, mg/dL	112 (87–141)	109 (83–137)	<0.001	101 (77–128)	106 (80–134)	<.0001	89 (70–115)	97 (74–127)	<0.0001	83 (64–107)	92 (70–119)	<0.0001

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; HR, heart rate; HTN, hypertension; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction. Data are presented as % or median (IQR).

TABLE 2 Overall treatment performance after ACS by sex and age groups

In-Hospital Care Metric	Overall, N = 15 436	Eligible STEMI Patients											
		Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y		
		Women, n = 998	Men, n = 4391	*P* Value[a]	Women, n = 1028	Men, n = 3420	*P* Value[a]	Women, n = 957	Men, n = 1939	*P* Value[a]	Women, n = 1420	Men, n = 1283	*P* Value[a]
DTB/PCI time, min	85 (61–123)	87 (62–131)	83 (59–115)	<0.001	88 (63–128)	82 (58–116)	<0.0001	87 (63–131)	85 (61–125)	0.33	93 (65–143)	91 (65–132)	0.13
DTB ≤90 min	55.4	54.1	58.7	0.008	52.1	58.6	<0.001	53.5	54.5	0.63	48.5	49.7	0.51
	Overall, n = 30 409	Women, n = 1864	Men, n = 7241	*P* Value[a]	Women, n = 1984	Men, n = 5924	*P* Value[a]	Women, n = 2081	Men, n = 3697	*P* Value[a]	Women, n = 4170	Men, n = 3448	*P* Value[a]
In-hospital mortality	6.8	3.3	2.1	0.001	4.2	3.2	0.04	8.0	6.8	0.08	15.5	15.1	0.60
	Overall (n = 74 408)	Eligible NSTE-ACS Patients											
		Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y		
		Women, n = 4015	Men, n = 9818	*P* Value[a]	Women, n = 4991	Men, n = 10 256	*P* Value[a]	Women, n = 6613	Men, n = 9940	*P* Value[a]	Women, n = 15 546	Men, n = 13 229	*P* Value[a]
In-hospital mortality	5.5	2.1	1.2	<0.0001	2.8	2.2	0.03	4.4	4.5	0.69	9.6	9.8	0.51
	Overall (n = 104 817)	All Eligible ACS Patients											
		Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y		
		Women, n = 5879	Men, n = 17 059	*P* Value[a]	Women, n = 6975	Men, n = 16 180	*P* Value[a]	Women, n = 8694	Men, n = 13 637	*P* Value[a]	Women, n = 19 716	Men, n = 16 677	*P* Value[a]
ASA24	93.8	94.5	95.6	0.002	93.9	95.2	<0.0001	93.3	93.8	0.11	92.2	92.4	0.66
In-hospital mortality	5.9	2.5	1.5	<0.0001	3.2	2.6	0.01	5.3	5.1	0.67	10.9	10.9	0.84

Abbreviations: ACS, acute coronary syndrome; ASA24, acetylsalicylic acid (aspirin) within first 24 hours; DTB, door-to-balloon; DTB90, door-to-balloon time within 90 minutes; IQR, interquartile range; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction. Data are presented as % or median (IQR).

[a] *P* values are computed with the Wilcoxon test for DTB time and the Pearson χ^2 test for DTB90, ASA24, and in-hospital mortality.

TABLE 3 Adjusted ORs of women vs men achieving DTB90, ASA24, and mortality by ACS diagnosis and age

	Age < 55 y			Age 55–64.9 y			Age 65–74.9 y			Age ≥ 75 y			
Eligible STEMI Patients	**OR**	**95% CI**	***P* Value[a]**	**OR**	**95% CI**	***P* Value[a]**	**OR**	**95% CI**	***P* Value[a]**	**OR**	**95% CI**	***P* Value[a]**	**$P_{interaction}$**
DTB90	0.80	0.69–0.93	0.003	0.81	0.70–0.92	0.002	0.93	0.79–1.10	0.41	0.97	0.83–1.14	0.73	0.12
ASA24	0.95	0.83–1.10	0.52	0.94	0.79–1.12	0.49	0.94	0.78–1.14	0.53	0.94	0.82–1.07	0.34	1.00
In-hospital mortality	1.49	1.12–1.98	0.006	1.24	0.95–1.60	0.11	1.13	0.93–1.38	0.22	1.04	0.92–1.19	0.52	0.10
Eligible NSTE-ACS Patients	**OR**	**95% CI**	***P* Value[a]**	**OR**	**95% CI**	***P* Value[a]**	**OR**	**95% CI**	***P* Value[a]**	**OR**	**95% CI**	***P* Value[a]**	**$P_{interaction}$**
ASA24	0.91	0.81–1.02	0.10	0.86	0.77–0.96	0.007	0.93	0.84–1.03	0.17	0.93	0.87–1.00	0.06	0.70
In-hospital mortality	1.47	1.22–1.77	<0.0001	1.12	0.93–1.35	0.25	0.93	0.81–1.08	0.35	0.97	0.90–1.06	0.53	0.0001

Abbreviations: ACS, acute coronary syndrome; ASA24, acetylsalicylic acid (aspirin) within first 24 hours; CI, confidence interval; DM, diabetes mellitus; DTB90, door-to-balloon time ≤ 90 minutes; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; OR, odds ratio; PAD, peripheral arterial disease; STEMI, ST-segment elevation myocardial infarction. Multivariate ORs and 95% CIs were computed with general estimating equation logistic regression models to account for clustering within hospitals and adjustment for sociodemographic variables (ethnicity/race, medical insurance type), clinical risk factors (history of IHD [MI, coronary revascularization], HTN, DM, hyperlipidemia, HF, stroke, PAD, current/recent tobacco use, obstructive airway disease, and history of renal impairment or dialysis-dependent), and hospital characteristics (hospital bed number, region, teaching status, and rural or urban setting).

$P_{interaction}$ were computed using Wald tests.

[a] *P* values were computed using Wald tests.

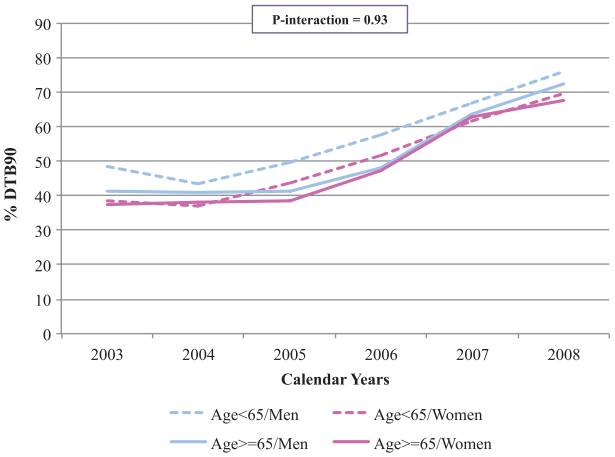

FIGURE 1 Temporal trends in DTB90 by sex and age groups among eligible patients with STEMI. No significant heterogeneity was detected for the change over time in achievement of DTB90 between women and men across age groups (adjusted 3-way *P*-interaction = 0.93). Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DTB90, door-to-balloon time within 90 minutes; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; PAD, peripheral arterial disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack

4 | DISCUSSION

Among hospitals participating in the AHA GWTG registry of ACS, there were large and equitable gains seen in 2 major ACS care performance measures over 6 years of study of a generally consistent magnitude across sex and age groups. There were modest but consistent temporal trends in improvement in survival across sex/age groups as well, though a ≈ 1% mortality gap between the sexes remained across age groups.

Despite a tremendous decline in CHD mortality among most demographics in the past 40 years, improvement in outcomes among younger patients, particularly women, has stagnated.[22] The causes for this observation are multifactorial, including an increased incidence in traditional and emerging risk factors among young women.[12,23] It is also apparent that there is a wider gap in treatment performance and outcomes among younger patients presenting with MI in routine clinical practice compared with older individuals.[15] The potential reasons for younger women receiving lower quality of care are complex, and they likely include differences in presentation and/or physician recognition of ACS in younger women, with resultant delays in care decisions that factor into delays in timing of coronary angiography and revascularization, as well as a potential sex differential in troponin elevation thresholds.[24] Other factors such as differences in clinical symptoms,[4] timing of presentation,[8,25] baseline comorbidities,[26] sociodemographic circumstances,[27] quality of life,[28] and rates of non-obstructive acute coronary syndromes[29] interact to result in treatment delays particularly among young women.

We hypothesized that increasing recognition of this phenomenon in concert with secular trends of increased knowledge dissemination through media campaigns,[30–32] national cardiovascular treatment

TABLE 4 Temporal trends in in-hospital mortality by sex and age groups

STEMI	Total (N)	2003	2004	2005	2006	2007	2008	P_{trend}[a]
	Age < 55 y							
Men	7241	2.0	2.2	2.3	1.3	2.0	2.5	0.79
Women	1864	3.6	4.1	3.1	3.7	3.1	2.6	0.37
	Age 55–64.9 y							
Men	5924	4.7	2.9	2.4	3.5	3.86	2.5	0.24
Women	1984	7.1	3.75	2.84	5.0	3.0	4.4	0.25
	Age 65–74.9 y							
Men	3697	6.4	7.3	6.3	6.3	7.5	6.9	0.73
Women	2081	8.1	7.4	7.7	6.0	9.6	9.8	0.30
	Age ≥ 75 y							
Men	3448	12.6	16.2	13.3	17.4	16.0	15.6	0.15
Women	4170	15.7	15.6	14.2	16.5	17.8	13.8	0.95

NSTE-ACS	Total (N)	2003	2004	2005	2006	2007	2008	P_{trend}[a]
	Age < 55 y							
Men	9818	1.2	1.6	1.4	0.9	0.9	0.9	0.052
Women	4015	2.8	2.1	2.1	2.1	1.8	1.6	0.16
	Age 55–64.9 y							
Men	10 256	1.8	2.0	2.2	2.6	2.7	1.9	0.32
Women	4991	4.4	2.7	2.8	2.8	2.6	1.8	0.009
	Age 65–74.9 y							
Men	9940	4.9	5.0	4.2	5.0	3.8	4.3	0.16
Women	6613	4.7	4.1	5.2	4.2	3.9	4.0	0.33
	Age ≥ 75 y							
Men	13 229	9.8	10.3	10.5	10.6	8.1	9.5	0.14
Women	15 546	9.2	10.4	9.3	10.2	8.8	9.8	0.83

Abbreviations: NSTE-ACS, non–ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

[a] *P* values are computed with Cochran-Armitage trend tests.

guidelines,[33] education and training,[34] and standardization of treatment protocols would translate over time into improvements in care and diminishing sex-based differences in early treatment and outcomes among patients with ACS, particularly younger patients. However, although we did observe substantial and consistent improvements in 2 major care processes across sex/age groups, modest gaps in treatment and outcomes across sex/age groups persist. Our findings are consistent with those seen in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Event Outcomes With Early Implementation of the ACC/AHA Guidelines? (CRUSADE) and National Cardiovascular Data Registry (NCDR) ACTION registries, where no significant impact was seen over time in women in regard to timing of MI presentation after the introduction of a national women's cardiovascular awareness campaign.[35] A significant sex-based gap in the timing of presentation remained after adjustment for differences in baseline comorbidities.[35] Moreover, in ACTION, women with ACS had higher rates of in-hospital complications despite fewer high-risk angiographic features.[36] One possible explanation for these observations is the potential that knowledge translation and education campaigns aimed at improving symptom recognition and risk assessment of younger women have been inadequate, and undertreatment persists. Targeting knowledge translation efforts in young women, and their physicians, of racial/ethnic minorities or low-income neighborhoods may be an area for potential improvement.[32,37,38]

Our data also incrementally complement those of previous research into sex differences in early MI treatment and outcomes within the AHA-GWTG CAD program. Jneid et al and Li et al evaluated sex differences in care and outcomes in aggregate; however, an evaluation for changes over time was not conducted.[14,18] Lewis et al evaluated sex differences in adherence to performance measures over time among patients with various forms of CHD (not only ACS), with a particular focus on older patients (age ≥ 75 years).[16] Bangalore et al focused on time trends in quality of care and outcomes between young and older patients with STEMI, and subgroup results by sex were explored.[17] In contrast, the present analysis included patients with NSTE-ACS and further evaluated whether age was a modifier of sex-based differences in ACS care over time.

Under-recognition of symptoms of ischemia may be more evident among women with a first presentation of ACS compared with patients with established IHD. Yet temporal trends in age/sex-based differences in care performance and mortality were generally consistent among patients with and without a history of CAD or prior MI except in 2 areas. Among STEMI patients age ≥ 75 years achieving a DTB90, temporal trends showed a modestly higher rate of achievement among older women vs men with established IHD; whereas

among patients without a history of CAD/MI, a 9% sex-based achievement gap persisted among older patients. In contrast, in regard to in-hospital mortality among younger patients with NSTE-ACS, a significant temporal trend for lower in-hospital mortality persisted among women without a history of prior CAD/MI but not among patients with established IHD, though both groups achieved >50% reduction in mortality rates over the period of study compared with no notable change among their male counterparts. Importantly, each of these divergent findings may be a result of type I error (ie, a play of chance from multiple testing of groups with small sample size) and warrant confirmation in independent cohorts.

4.1 | Study limitations

We focused on an increased mortality risk among women; however, others have found an increased risk of bleeding complications and HF following MI.[3,14,39] It is unknown to what extent certain care gaps related to patient selection for invasive angiography or antiplatelet therapy may relate to underlying risk differences for major bleeding events. Although our data covered results between 2003 and 2008, these care processes remain key areas for quality improvement for women with ACS in the United States.[40] Thus, our data highlight both the meaningful gains and remaining opportunities for improvement in the care and outcomes of young and older women presenting with ACS and can serve as a benchmark for future temporal analysis comparisons. In addition, future research may investigate the potential for sex- and age-based differences in bleeding risk that impact the selection of ischemic patients for coronary revascularization and antiplatelet therapies. Other limitations inherent to observational studies include the potential influence of confounders such as the timing and severity of symptom presentation, or the distribution and severity of coronary lesions. Our study was also limited to in-hospital outcomes among hospitals participating in this voluntary quality-improvement initiative.

5 | CONCLUSION

Among hospitals participating in the AHA GWTG-CAD registry between 2003 and 2008, there was a substantial improvement over time in 2 major ACS care processes of generally similar magnitude across sex and age groups. Consistent temporal improvements in mortality across sex/age groups were also seen, though modest differences persist. Future studies among patients with ACS should focus on further achievement of quality care and improved outcomes, particularly among women age < 65 years.

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Conflicts of interest

Dr. Udell has served on advisory boards for Boehringer-Ingelheim, Janssen, Merck, and Sanofi Pasteur; received research funding from AstraZeneca and Novartis; and has received honoraria for sponsored symposia from Boehringer-Ingelheim and Janssen. Dr. Peacock has served on advisory boards for Abbott, AstraZeneca, Bayer, Beckman, Boehringer-Ingelheim, Ischemia Care, Dx, ImmunArray, Instrument Labs, Janssen, Ortho Clinical Diagnostics, Relypsa, Roche, and Siemens; received research funding from Abbott, Braincheck, ImmunArray, Janssen, Roche, and ZS Pharma; has provided expert testimony for Johnson & Johnson; and has ownership interests in Comprehensive Research Associates LLC, Emergencies In Medicine LLC, and Ischemia DX LLC. Dr. Bhatt has served on advisory board for Cardax, Elsevier PracticeUpdate Cardiology, Medscape Cardiology, and Regado Biosciences; has served on board of directors of Boston VA Research Institute and the Society of Cardiovascular Patient Care; has been chair of the American Heart Association Quality Oversight Committee; has served on data monitoring committees for Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; has received honoraria from American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor, Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), and WebMD (CME steering committees); has served as deputy editor for *Clinical Cardiology*, chair of the NCDR-ACTION Registry Steering Committee, and chair of the VA CART Research and Publications Committee; has received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Regeneron, Roche, Sanofi Aventis, and The Medicines Company; has received royalties from Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); has served as a trustee of the American College of Cardiology; and reports unfunded research for FlowCo, Merck, PLx Pharma, and Takeda. The authors declare no other potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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