

# openheart Sex disparities in the presentation, management and outcomes of patients with acute coronary syndrome: insights from the ACS QUIK trial

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## ABSTRACT

**Aims** Our aim was to explore sex differences and inequalities in terms of medical management and cardiovascular disease (CVD) outcomes in a low/middle-income country (LMIC), where reports are scarce.

**Methods** We examined sex differences in presentation, management and clinical outcomes in 21 374 patients presenting with acute coronary syndrome (ACS) in Kerala, India enrolled in the Acute Coronary Syndrome Quality Improvement in Kerala trial. The main outcomes were the rates of in-hospital and 30-day major adverse cardiovascular events (MACEs) defined as composite of death, reinfarction, stroke and major bleeding. We fitted log Poisson multivariate random effects models to obtain the relative risks comparing women with men, and adjusted for clustering by centre and for age, CVD risk factors and cardiac presentation.

**Results** A total of 5191 (24.3%) patients were women. Compared with men, women presenting with ACS were older (65±12 vs 58±12 years;  $p<0.001$ ), more likely to have hypertension and diabetes. They also had longer symptom onset to hospital presentation time (median, 300 vs 238 min;  $p<0.001$ ) and were less likely to receive primary percutaneous coronary intervention for ST-elevation myocardial infarction (45.9% vs 49.8% of men,  $p<0.001$ ). After adjustment, women were more likely to experience in-hospital (adjusted relative risk (RR)=1.53; 95% CI 1.32 to 1.77;  $p<0.001$ ) and 30-day MACE (adjusted RR=1.39; 95% CI 1.23 to 1.57,  $p<0.001$ ).

**Conclusion** Women presenting with ACS in Kerala, India had greater burden of CVD risk factors, including hypertension and diabetes mellitus, longer delays in presentation, and were less likely to receive guideline-directed management. Women also had worse in-hospital and 30-day outcomes. Further efforts are needed to understand and reduce cardiovascular care disparities between men and women in LMICs.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in women worldwide, claiming an estimated 6 million lives each year.<sup>1,2</sup> The burden of CVD has shifted globally toward

## Key questions

### What is already known about this subject?

► Reports from high-income countries demonstrate gender disparities in acute coronary syndrome (ACS) presentation and management with women being disadvantaged. However, conflicting data exist in regards to short-term and intermediate-term outcomes. Scarce reports are available on sex disparities in low/middle-income countries (LMICs).

### What does this study add?

► Limited evidence from LMICs demonstrates gender disparities in the presentation and management for women with ACS. However, prior studies have reported conflicting data regarding gender disparities in the incidence of adverse clinical outcomes including major adverse cardiovascular events, in-hospital mortality and long-term prognosis. In this large study of patients with ACS from Kerala, India, we now show that women had higher in-hospital and 30-day mortality even after adjusting for possible confounders, such as age, cardiac risk factors and hospital of presentation.

### How might this impact on clinical practice?

► These results are important for clinicians, cardiologists and global health experts. Improved awareness, research, advocacy and guidelines related to women's heart health are needed, especially in LMICs, where the gap is larger.

low/middle-income countries (LMICs), which disproportionately carry 80% of the burden of CVD. The burden of CVD in LMICs is only expected to rise as these countries progress through the epidemiological transition.<sup>3,4</sup> Studies predominantly from high-income countries (HICs) have shown that women with acute coronary syndromes (ACS) are less likely to receive guideline-recommended pharmacotherapy and undergo invasive angiography and

percutaneous coronary intervention (PCI) compared with men.<sup>5–8</sup> These diagnostic and therapeutic disparities in cardiovascular care are associated with worse outcomes and represent opportunities for quality improvement initiatives to narrow the sex gap in ACS outcomes.<sup>9</sup>

India has one of the highest burden of atherosclerotic CVD in the world where women account for 40% of all CVD deaths.<sup>4 10 11</sup> Studies evaluating sex differences in CVD in India are limited but indicate an alarming steady increase in death rates in women and a consistent pattern of sex-associated differences in presentation and management.<sup>12–15</sup> However, inconsistent data exist on whether those differences ultimately impact in-hospital and long-term outcomes among Indian women with ACS.<sup>1 13 14</sup> Using data from the Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK) randomised clinical trial, we aimed to examine the impact of sex on the clinical presentation, management and outcomes in a contemporary, large population of patients with ACS in an LMIC.

## METHODS

### Study population

The ACS QUIK trial was a large pragmatic, cluster-randomised, stepped-wedge clinical trial examining the effect of a quality improvement toolkit intervention on major adverse cardiovascular events (MACEs) in patients with ACS. The design and primary results of the trial were published elsewhere.<sup>16 17</sup> Briefly, 63 hospitals in Kerala, India participated in a cluster-randomised, stepped-wedge clinical trial to evaluate the impact of a locally adapted quality improvement toolkit to improve ACS outcomes.<sup>18</sup> The trial included 21 374 patients with acute myocardial infarction (AMI) (ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI)) enrolled between 10 November 2014 and 9 November 2016. Patients with unstable angina were excluded. In this analysis, we examined differences between women versus men presenting with AMI, in terms of baseline characteristics, management and relevant clinical outcomes.

The current analysis was approved by the Partners Healthcare Institutional Review Board, Boston, Massachusetts, USA and Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC; National Heart, Lung and Blood Institute, Bethesda, Maryland, USA). HK and BA had full access to data in the study and take responsibility for its integrity and the data analysis.

### Outcomes

The main outcome of ACS QUIK was 30-day MACE, defined as a composite of death, reinfarction, stroke and major bleeding. For this analysis, the main outcomes were the rates of in-hospital and 30-day mortality and MACE (as defined above). Major bleeding was defined according to the Global Utilization of Streptokinase and

Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.<sup>19</sup> Other outcomes assessed included in-hospital-incident heart failure and cardiac arrest.

### Covariates

The choice of covariate adjustment in the models was based on parsimony and a priori clinical hypotheses to control for confounding. In all our models we adjusted for age (linearly), smoking or tobacco use (yes/no), hypertension and diabetes on presentation (yes/no), cardiac presentation status (STEMI)/NSTEMI, and whether PCI was done (yes/no). We also evaluated potential confounding by differences in cardiac care in the 63 hospitals and centres in a fixed effects model.

### Data analysis

Continuous variables are summarised as mean±SD if normally distributed, and as median and IQR if not normally distributed. We used Student's t-test and Mann-Whitney U test to compare groups accordingly. Categorical variables are reported as numbers and percentages and were compared between groups using  $\chi^2$  or Fisher's exact test as appropriate.

Multivariable log Poisson regression models were used to assess the association between sex and in-hospital or 30-day outcomes and adjust for possible confounders. Associations were summarised using adjusted and unadjusted relative risks (RRs) and 95% CIs. We reported both unadjusted (crude) and adjusted RRs for all outcomes. For the adjusted RRs, we applied generalised linear mixed-effects models with multivariable normal random effects, using penalised quasi-likelihood. This function enabled us to fit models with different family distributions and link functions (log Poisson) that are non-parametric, as compared with the linear mixed-effects that offer parametric estimates. We accounted for within-hospital clustering by fitting random intercepts for different hospitals. We reported the fixed coefficients which are interpreted as the overall RR comparing women with men. In a sensitivity analysis, we also report fixed effects (with dummy variables) to understand the effect of measured and unmeasured confounding by hospitals.

We examined effect measure modification by a number of variables. This was made possible by dichotomising continuous variables and looking at the RRs of in-hospital MACE comparing women with men within each category. The interaction was tested using the p value from the Wald test that corresponds to the interaction term coefficient in the full sample size.

All p values were two-sided with a significance level of <0.05. Data analyses were conducted using R V.3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata/IC V.15.0 (StataCorp). Mixed-effects models were fitted using the 'nlme' R package and 'glmmPQL' function.

**Table 1** Baseline characteristics of ACS QUIK patients stratified by sex

	Total (n=21 374)	Women (n=5191)	Men (n=16 183)	P value
Age, mean (SD)	60 (12)	65 (12)	58 (12)	<0.001
Transferred from another facility, no (%)	8401 (39.3)	1932 (37.2)	6469 (40.0)	<0.001
No insurance, no (%)	15 542 (72.7)	3814 (73.5)	11 728 (72.5)	0.16
ST-elevation myocardial infarction, no (%)	13 689 (64.0)	2846 (54.8)	10 843 (67.0)	<0.001
Symptom-to-door time, median (IQR), min	246 (118–830.5)	300 (127.5–990)	238 (115–780)	<0.001
Body weight, mean (SD), kg	63.0 (10.0)	59.0 (10.0)	65 (9)	<0.001
Systolic blood pressure, mean (SD), mm Hg	139 (29)	141 (30)	138 (29)	<0.001
Heart rate, mean (SD), /min	80 (19)	83 (20)	79 (19)	<0.001
Initial troponin, median (IQR), ng/mL	1.32 (0.29–5.82) (n=9049)	1.05 (0.26–4.02) (n=2299)	1.44 (0.3–6.58) (n=6750)	<0.001
Low-density lipoprotein cholesterol, mean (SD), mg/dL	123 (41) (n=14 830)	127 (43) (n=3578)	121 (40) (n=11 252)	<0.001
Triglycerides, median (IQR), mg/dL	121 (90–165) (n=14 860)	122 (91–161) (n=3578)	121 (89–166) (n=11 282)	0.98
Serum creatinine, median (IQR), mg/dL	1.0 (0.9–1.2) (n=13 835)	0.92 (0.8–1.2) (n=3361)	1.1 (0.9–1.3) (n=10 474)	<0.001
Fasting glucose, median (IQR), mg/dL	127 (102–176) (n=13 398)	134 (106–188) (n=3286)	125 (100–172) (n=10 112)	<0.001
Haemoglobin, mean (SD), mg/dL	13 (2) (n=20 842)	12.0 (2.0) (n=5064)	14.0 (2.0) (15 778)	<0.001
Killip class, n (%)				
I	18 459 (86.4)	4266 (82.2)	14 193 (87.7)	<0.001
II–IV	2914 (13.6)	925 (17.8)	1989 (12.3)	
Risk factors, n (%)				
Hypertension	10 042 (47.0)	3179 (61.2)	6863 (42.4)	<0.001
Diabetes mellitus	9484 (44.4)	2783 (53.6)	6701 (41.4)	<0.001
History of tobacco use, no (%)	6614 (30.9)	168 (3.2)	6446 (39.8)	<0.001
Peripheral arterial disease	211 (1.0)	50 (1.0)	161 (1.0)	1.00
History of stroke	470 (2.2)	137 (2.6)	333 (2.1)	0.014
Hospital type				
Government (n=9)	7133 (33.4%)	1618 (31.2%)	5515 (34.1%)	<0.001
Non-profit/charity (n=12)	5749 (26.9%)	1478 (28.5%)	4271 (26.4%)	
Private (n=42)	8492 (39.7%)	2095 (40.4%)	6397 (39.5%)	
Hospital size				
Extra large (>1000) (n=5)	3560 (16.7%)	730 (14.1%)	2830 (17.5%)	<0.001
Large (501–1000) (n=15)	8523 (39.9%)	2089 (40.2%)	6434 (39.8%)	
Medium (201–500) (n=24)	7415 (34.7%)	1779 (34.3%)	5636 (34.8%)	
Small (≤200) (n=19)	1876 (8.8%)	593 (11.4%)	1283 (7.9%)	
Presence of onsite cath lab				
Installed during study (n=3)	496 (2.3%)	136 (2.6%)	360 (2.2%)	<0.001
No (n=17)	3552 (16.6%)	976 (18.8%)	2576 (15.9%)	
Yes (n=43)	17 326 (81.1%)	4079 (78.6%)	13 247 (81.9%)	

ACS QUIK, acute coronary syndrome quality improvement in Kerala; IQR, interquartile range; SD, standard deviation.

## RESULTS

### Baseline characteristics

Of 21 374 patients with ACS enrolled in the ACS QUIK trial, 5191 (24.3%) were women. **Table 1** shows the baseline characteristics of the study population by sex. Compared with men with ACS, women with ACS were older (mean±SD, 65±12 vs 58±12 years;  $p<0.001$ ), more

likely to have hypertension (61.2% vs 42.4%;  $p<0.001$ ), diabetes mellitus (53.5% vs 41.4%;  $p<0.001$ ), and higher low-density lipoprotein cholesterol levels (127±43 vs 121±40 mg/dL;  $p<0.001$ ). After symptom onset, women tended to present later to the hospital (median (IQR) time, 300 (127.5–990) vs 238 (115–780) min;  $p<0.001$ ). Compared with men, women were less likely to present

**Table 2** In-hospital and on-discharge treatment patterns stratified by sex

	No/total no (%)			P value
	Total (n=21 374)	Women (n=5191)	Men (n=16 183)	
<b>Medications</b>				
Prehospital aspirin	3796/21 352 (17.8)	948/5186 (18.3)	2848/16 166 (17.6)	0.28
In-hospital aspirin	20 885/21 328 (97.9)	5044/5171 (97.5)	15 841/16 157 (98.0)	0.033
In-hospital second antiplatelet	20 973/21 347 (98.2)	5071/5180 (97.9)	15 902/16 167 (98.4)	0.028
In-hospital $\beta$ -blocker	8314/20 759 (40.1)	2049/5009 (40.9)	6265/15 750 (39.8)	0.16
In-hospital anticoagulant	18 256/21 332 (85.6)	4421/5177 (85.4)	13 835/16 155 (85.6)	0.67
<b>Studies and procedures</b>				
Echocardiography	19 725 (92.3)	4777/5191 (92.0)	14 948/16 183 (92.4)	0.42
Diagnostic angiography	12 681 (59.3)	2638/5191 (50.8)	10 043/16 183 (62.1)	<0.001
PCI	10 553 (49.4)	2067/5191 (39.8)	8486/16 183 (52.4)	<0.001
Primary PCI (STEMI)	6710/13 689 (49.0)	1307/2846 (45.9)	5403/10 843 (49.8)	<0.001
Door-to-balloon time (STEMI), median (IQR), min	83 (57–190) (n=9462)	90 (60–270) (n=1874)	80 (55–180) (n=7588)	<0.001
Thrombolysis (STEMI)	3167/13 689 (23.1)	635/2846 (22.3)	2532/10 843 (23.4)	0.25
Door-to-needle time (STEMI), median (IQR), min	44 (30–70) (n=2888)	45.5 (30–75) (n=594)	43 (29–70) (n=2294)	0.001
Any reperfusion (STEMI)	9872/13 689 (72.1)	1942/2846 (68.2)	7930/10 843 (73.1)	<0.001
Rescue PCI	1675/13 659 (12.3)	308/2841 (10.8)	1367/10 818 (12.6)	0.009
<b>Discharge treatment and counselling</b>				
Discharge aspirin	19 137/19 557 (97.9)	4448/4603 (96.6)	14 689/14 954 (98.2)	<0.001
Discharge second antiplatelet agent	19 201/19 591 (98.0)	4509/4620 (97.6)	14 692/14 971 (98.1)	0.026
Discharge $\beta$ -blocker	12 607/19 072 (66.1)	2963/4470 (66.3)	9644/14 602 (66.0)	0.77
Discharge statin	18 989/19 585 (97.0)	4460/4625 (96.4)	14 529/14 960 (97.1)	0.019
Discharge ACE inhibitor or ARB	9232/19 193 (48.1)	2182/4516 (48.3)	7050/14 677 (48.0)	0.75
Cardiac rehabilitation referral	5684/20 019 (28.4)	1363/4711 (28.9)	4321/15 308 (28.2)	0.36

ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

with STEMI (67.0% vs 54.8%;  $p<0.001$ ), but more likely to present with a Killip class II or greater (17.8% vs 12.3%;  $p<0.001$ ). More women presented to small hospitals (<200 beds) (11.4% vs 7.9% of men;  $p<0.001$ ), and women were less likely to present to extra-large hospitals (>1000 beds) (14.1% vs 17.5% of men,  $p<0.001$ ).

### In-hospital and on-discharge management

Among eligible individuals with no contraindications, the rates of in-hospital and discharge aspirin, adjuvant antiplatelet therapy (clopidogrel, prasugrel or ticagrelor), and statin prescription were high (>95% for all) and similar in men and women (table 2). The rate of in-hospital  $\beta$ -blockers, ACE inhibitors or angiotensin receptor blockers, or anticoagulant use did not differ by sex. Compared with men with ACS, women were less likely to undergo diagnostic coronary angiography (50.8% vs 62.1% of men,  $p<0.001$ ) or PCI (39.8% vs 51.4% in men,  $p<0.001$ ) during hospitalisation. Women presenting with STEMI were less likely to receive primary PCI (45.9% vs 49.8% of men,  $p<0.001$ ) and had longer median

door-to-balloon times (90 (60–270) vs 80 (55–180) min for men;  $p<0.001$ ).

### Outcomes

In the overall cohort, a total of 835 in-hospital MACE and 1247 30-day MACE events occurred among study participants (table 3). Compared with men, women were 53% more likely to experience in-hospital MACE (adjusted RR=1.53; 95% CI 1.32 to 1.77;  $p<0.001$ ), and 67% more likely to die during their hospitalisation (adjusted RR=1.67; 95% CI 1.42 to 1.97;  $p<0.001$ ), even after taking into account age and potential confounders. Women were also more likely to experience in-hospital heart failure, stroke and cardiac arrest. Likewise, women had 39% higher risk of 30-day MACE (adjusted RR=1.39; 95% CI 1.65 to 2.07,  $p<0.001$ ), 48% higher risk of 30-day mortality (adjusted RR=1.48; 95% CI 1.29 to 1.70;  $p<0.001$ ) and a 50% higher risk of CVD mortality (adjusted RR=1.50; 95% CI 1.30 to 1.72).

Subgroup analyses consistently showed worse MACE in women compared with men within the strata of age,

**Table 3** Risk of adverse clinical outcomes among patients with ACS for women compared with men

	No/total no (%)		Unadjusted RR (95% CI)	P value	Adjusted* RR (95% CI)	P value
	Women (n=5191)	Men (n=16 183)				
<b>In-hospital outcomes</b>						
MACE	327 (6.3)	508 (3.1)	2.01 (1.75 to 2.30)	<0.001	1.53 (1.32 to 1.77)	<0.001
Death	276 (5.3)	376 (2.3)	2.29 (1.97 to 2.67)	<0.001	1.67 (1.42 to 1.97)	<0.001
Reinfarction	41 (0.8)	126 (0.8)	1.01 (0.71 to 1.44)	0.936	1.03 (0.75 to 1.42)	0.850
Blood transfusion	93 (1.8)	142 (0.9)	2.04 (1.57 to 2.65)	<0.001	1.26 (0.97 to 1.64)	0.081
Stroke	35 (0.7)	58 (0.4)	1.89 (1.23 to 2.86)	0.003	1.59 (1.05 to 2.42)	0.028
Heart failure	483 (9.3)	982 (6.1)	1.28 (1.04 to 1.58)	0.018	1.11 (1.00 to 1.23)	0.048
Cardiac arrest	178 (3.4)	254 (1.6)	2.109 (1.74 to 2.53)	<0.001	1.49 (1.26 to 1.75)	<0.001
Major bleeding	9 (0.2)	296 (1.8)	1.56 (0.70 to 3.47)	0.277	1.06 (0.54 to 2.06)	0.865
<b>30-day</b>						
MACE	463 (9.1)	784 (4.9)	1.85 (1.65 to 2.07)	<0.001	1.39 (1.23 to 1.57)	<0.001
Death	382 (7.4)	572 (3.6)	2.09 (1.83 to 2.38)	<0.001	1.48 (1.29 to 1.70)	<0.001
CVD death	376 (7.4)	552 (3.5)	2.13 (1.87 to 2.43)	<0.001	1.50 (1.30 to 1.72)	<0.001

RR=relative risk from multivariate regression, multilevel analysis for women compared with men (reference). MACE included a composite of death, reinfarction, major bleeding and stroke.

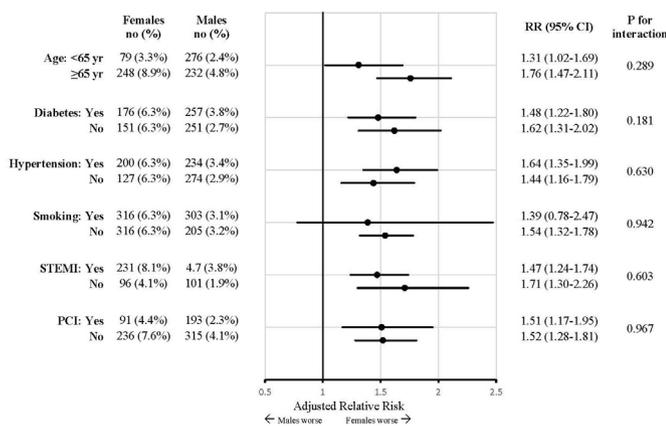
\*Models adjusted for age, smoking, diabetes, hypertension, MI subtype (STEMI vs NSTEMI) and PCI with random intercepts for centres. ACS, acute coronary syndrome; CVD, cardiovascular disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

diabetes, hypertension and smoking (figure 1). Compared with men, women also had worse in-hospital MACE whether or not they presented with STEMI or received PCI during their hospitalisation. The interaction terms in the full models between sex and these factors did not show statistical significance. In a sensitivity analysis using fixed effects model with dummy variables for 63 hospitals and centres, no appreciable difference was detected with the main model that had random intercepts, indicating a low risk of unmeasured confounding by different care providers (results not shown).

**DISCUSSION**

Our study examined sex differences in ACS outcomes in an LMIC (India) using data from the ACS QUIK trial, which included 21 374 patients with ACS who presented to 63 hospitals in Kerala between 10 November 2014 and 9 November 2016. In this analysis, women presenting with ACS were older and more likely to have diabetes, hypertension and a history of stroke, but less likely to smoke compared with men. Women were also less likely to present with STEMI and more likely to present later after symptom onset and have heart failure on presentation. In-hospital and discharge medical management were similar for men and women; however, significant sex differences were evident in using potentially life-saving procedures such as primary PCI which was provided less often and with greater door-to-balloon time delays in women with STEMI compared with men. We also observed that women were more likely to experience in-hospital and 30-day MACE, even after adjustment for age, CVD risk factors, MI subtype, performance of PCI and other potential confounders. Additionally, significant sex disparities were evident after adjustment for these same covariates for in-hospital mortality, cardiac arrest and heart failure.

While there has been a steady increase in the research investigating sex differences in ACS presentation, management and outcomes in HICs, the evidence from LMICs is limited. Studies from HICs and LMICs demonstrate that women with ACS are older with a greater burden of comorbidities such as hypertension and diabetes mellitus,



**Figure 1** Adjusted relative risk (RR) of in-hospital major adverse cardiac events in selected subgroups comparing women with men (reference). PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

compared with men, which are consistent with the findings of the current study.<sup>5 7 8 20–22</sup> Furthermore, women with ACS tend to present later for medical attention after symptom onset and are less likely to receive optimal pharmacological and reperfusion therapy, even when eligible as seen in our study.<sup>6</sup> However, prior studies have reported conflicting data regarding sex disparity in the incidence of adverse clinical outcomes including MACE, in-hospital mortality and long-term prognosis.<sup>6 23</sup> In this large study of patients with ACS from India, we now show that women have higher rates of in-hospital and 30-day MACE and mortality even after accounting for age and important comorbidities.

Limited resources in LMICs may worsen health disparities experienced by women and vulnerable populations.<sup>24</sup> At a patient level, socioeconomic factors such as limited health literacy, medical insurance or lack of access to transportation may contribute to delays in the care of patients with ACS. ACS-related sex disparities have also been reported in studies from LMICs comparable with those from HICs. In a study of 1204 patients with ACS (253 women) in Egypt, the unadjusted in-hospital mortality was significantly higher in women compared with men (OR: 2.10; 95% CI 1.54 to 2.87).<sup>25</sup> However, no significant difference in mortality was observed after adjusting for CVD risk factors.<sup>25</sup> Another study from the Middle East-Gulf region looked at sex differences and STEMI outcomes.<sup>26</sup> The study included a total of 15 532 patients, 2033 of whom were women. The investigators found that women had higher in-hospital and 1-year mortality even after adjusting for common risk factors.<sup>26</sup> The CRACE Study, which enrolled 1301 patients with ACS from 12 teaching hospitals across China, showed no significant differences in in-hospital mortality between men and women.<sup>27</sup> Similar findings were reported in studies from Thailand and Malaysia.<sup>28 29</sup>

Despite the magnitude of atherosclerotic CVD in India, few studies have explored sex disparities in the management and outcomes of ACS in a large cohort of patients managed with contemporary ACS management strategies. The CREATE registry enrolled 20 468 patients with ACS, of whom 23.6% were women, from 89 hospitals from 10 different regions in India.<sup>30</sup> Similar to our study, women had lower rates of revascularisation and higher unadjusted all-cause mortality at 30 days.<sup>30</sup> Unlike our results, mortality differences were attenuated after adjusting for treatment-related factors such as time-to-hospital presentation, revascularisation rates and utilisation of evidence-based medications.<sup>30</sup> The DEMAT registry included 1565 patients with ACS (334 women) across 10 tertiary care centres in India between 2007 and 2008.<sup>13</sup> Similar to our findings, in-hospital and on-discharge medical management was comparable among men and women, except for clopidogrel. In contrast to our study, no significant differences were noted in 30-day mortality or MACE (composite of death, rehospitalisation and cardiac arrest) after adjustment for potential confounders.<sup>13</sup>

Prior results from the Kerala-ACS<sup>14</sup> registry, which included 125 centres (including the 63 centres involved in the ACS QUIK trial), did not find significant differences between men and women with ACS with respect to in-hospital mortality after adjustment for confounding factors. In the Kerala ACS registry, female patients with ACS were less likely to receive in-hospital aspirin (92.4% vs 93.2%,  $p=0.042$ ) and  $\beta$ -blockers (63.0% vs 66.6%,  $p<0.001$ ), but more likely to receive statins (81.1% vs 78.1%,  $p<0.001$ ) compared with male patients.<sup>14</sup> In addition, female and male patients were equally likely to receive in-hospital PCI, although the low frequency of PCI in both sexes (12.4% in women vs 11.8% in men,  $p=0.202$ ). In comparison, the current study shows a higher proportion of male and female patients receiving aspirin,  $\beta$ -blockers and statins, with persistent sex differences in aspirin prescription. In ACS QUIK, the higher proportion of patients receiving PCI during their hospitalisation enabled for a sex-based comparison and showed a significantly lower likelihood of receiving PCI in women compared with men. These findings may provide potential mechanisms explaining the sex differences in in-hospital outcomes between the two studies. As the number of PCI-capable centres in India increased, the results of Kerala ACS and ACS QUIK highlight a sex-based care gap in coronary revascularisation that became more apparent in the periods 5–7 years separating the two studies. The potential reasons for such gap need to be addressed in future research.

Both sex (biological differences) and gender (socio-cultural differences) influence cardiovascular outcomes between women and men. Our findings can be partially explained by a higher risk factor profile in women along with late presentation and receiving less guideline-recommended coronary reperfusion, compared with their male counterparts. However, this likely does not fully explain the mortality difference demonstrated in our study. Implicit gender bias towards female patients that precludes the administration of optimal care has been reported as a possible mechanism of gender disparities in cardiovascular care.<sup>31</sup> Significant positive association between implicit bias and lower quality of care has been demonstrated in various studies.<sup>31</sup> Maserejian *et al*<sup>32</sup> conducted a factorial experiment, using videotaped vignette of coronary artery disease with altering patients' sex, age and race. The group found that women, especially middle-aged, were diagnosed with the least confidence.<sup>32</sup> Additionally, female patients were more likely to receive a diagnosis of mental health condition, compared with their male counterparts.<sup>32</sup> In another US study, when compared with similar male patients, female patients with atherosclerotic CVD were also more likely to report that they had poor communication with their healthcare providers, that their doctors did not listen to them or respect them, and they had underutilisation of secondary prevention medications.<sup>33</sup>

The first step towards rectifying sex disparities in health-care, in general, and CVD outcomes, in particular, is identifying and acknowledging the problem. This should

be followed by raising awareness. ‘Go Red For Women’ and ‘Women’s Heart Alliance’ are two campaigns aimed to improve awareness, advocacy and research related to women’s heart health. They have been successful in drawing attention to women’s heart health. We also need to implement delivery care models and specific guidelines to address women’s cardiovascular health.<sup>34 34</sup> Cardiovascular societies have already started to adopt guidelines for women, but this needs to be expanded.<sup>34</sup> Similar efforts should be adopted internationally, especially in LMICs where the gap is even larger.

### Study strengths and limitations

This study has a number of limitations. First, inferences from this study should be interpreted within the local context of the study population. It is likely that the results may not be generalisable to other populations where other factors could modify the nature of the relationship between sex and CVD outcomes. Second, we were unable to obtain information on socioeconomic resources (eg, income, education and others). We cannot rule out the possibility that these or other factors may contribute to the treatment and outcome disparities that we observed. Furthermore, control for smoking was not optimal as we did not have information on long-term use (eg, pack-years) leaving a room for residual confounding. Finally, the interaction analyses were possibly underpowered to detect significant differences in effect estimates. On the other hand, our study had a number of important strengths including a large ACS sample from an LMIC with information on a number of other important confounding comorbidities and details regarding cardiac presentation and clinical management strategies that could be accounted for in our analysis.

### CONCLUSION

Our study confirms a higher CVD risk profile, delayed presentation and suboptimal medical care in women presenting with ACS in Kerala, India. Women were also found to have higher in-hospital and 30-day MACE, even after adjustment for potential confounders. Women around the globe, and especially in LMIC, face sex-based societal and health inequities leading to sex differences in healthcare seeking behaviour and implicit care provider bias. Our study underscores the need to explore and mitigate these gaps through education, research, medical care and broader health policy. A better understanding of these differences is crucial in improving cardiovascular outcomes among women worldwide, especially in LMICs.

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