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**ORIGINAL ARTICLE**
*Interventional cardiology and cardiac surgery*

# Five years of a comprehensive ST-elevation myocardial infarction protocol and its association with sex disparities

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**Aims** To determine whether a comprehensive ST-elevation myocardial infarction (STEMI) protocol is associated with reduced sex disparities over 5 years.

**Methods and results** This was an observational cohort study of 1833 consecutive STEMI patients treated with percutaneous coronary intervention (PCI) before (1 January 2011–14 July 2014, control group) and after (15 July 2014–15 July 2019, protocol group) implementation of a protocol for early guideline-directed medical therapy (GDMT), rapid door to balloon time (D2BT), and use of trans-radial PCI. In the control group, females had less GDMT (77.1% vs. 68.1%, $P = 0.03$), similarly low trans-radial PCI (19.0% vs. 17.6%, $P = 0.73$), and longer D2BT [104 min (79, 133) vs. 112 min (85, 147), $P = 0.02$] corresponding to higher in-hospital mortality [4.5% vs. 10.3%, odds ratio (OR) 2.44 (1.34–4.46), $P = 0.004$], major adverse cardiac and cerebrovascular events [MACCE, 9.8% vs. 16.3%, OR 1.79 (1.14–2.84), $P = 0.01$], and net adverse clinical events [NACE, 16.1% vs. 28.3%, OR 2.06 (1.42–2.99), $P < 0.001$]. In the protocol group, no significant sex differences were observed in GDMT (87.2% vs. 86.4%, $P = 0.81$) or D2BT [85 min (64–106) vs. 89 min (65–111), $P = 0.06$], but trans-radial PCI was used less in females (77.6% vs. 71.2%, $P = 0.03$). In-hospital mortality [2.5% vs. 4.4%, OR 1.78 (0.91–3.51), $P = 0.09$] and MACCE [9.0% vs. 11.1%, OR 1.27 (0.83–1.92), $P = 0.26$] were similar between sexes, but higher NACE in females approached significance [14.8% vs. 19.4%, OR 1.38 (0.99–1.92), $P = 0.05$] due to higher bleeding risk [7.2% vs. 11.1%, OR 1.60 (1.04–2.46), $P = 0.03$].

**Conclusions** A comprehensive STEMI protocol was associated with sustained reductions for in-hospital ischaemic outcomes over 5 years, but higher bleeding rates in females persisted.

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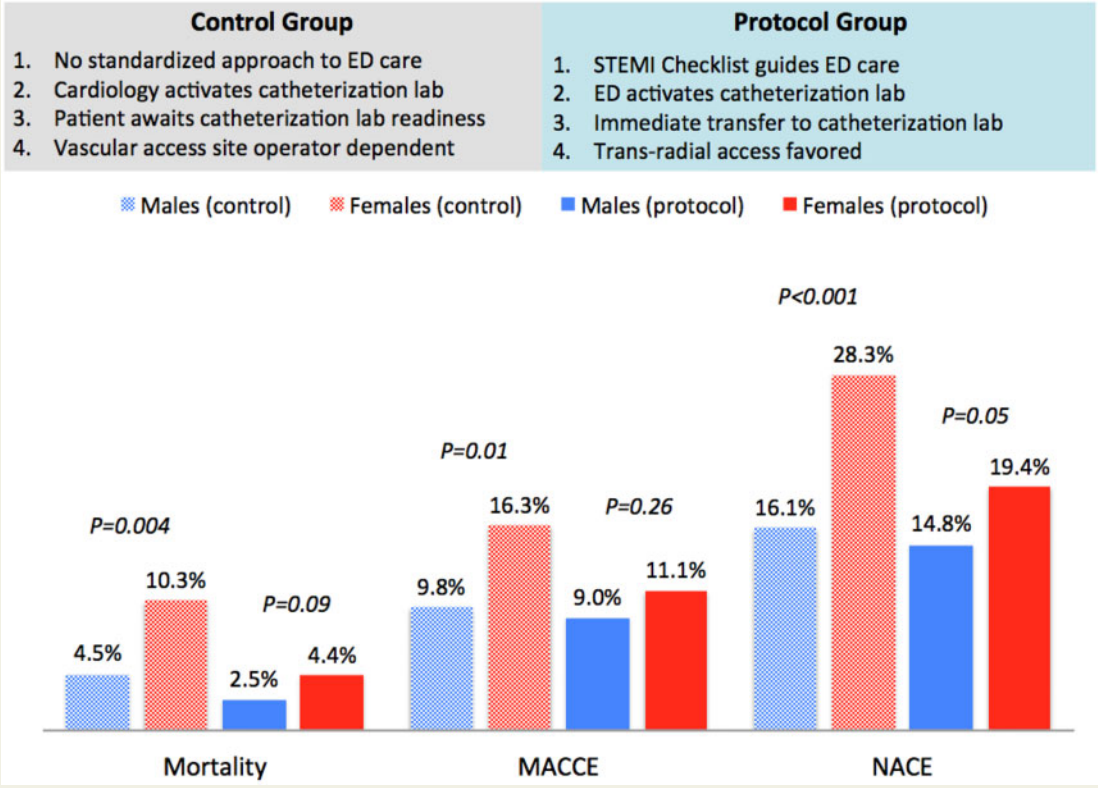
## Graphical Abstract




A comprehensive STEMI protocol was associated with reduced STEMI sex disparities in care and outcomes for 5 years after protocol implementation. Key aspects of the protocol and in-hospital outcomes are summarized. MACCE, major adverse cardiovascular and cerebrovascular events; NACE, net adverse clinical events.

**Keywords** Acute myocardial infarction • STEMI • Disparities • Bleeding • Trans-radial PCI

# Introduction

Cardiovascular disease is the leading cause of death in females worldwide.[1,2] However, compared with males, females with ST-elevation myocardial infarction (STEMI) receive less guideline-directed medical therapy (GDMT), and door to balloon times (D2BT) are significantly longer.[3–5] Rates of in-hospital adverse events, *de novo* heart failure, and mortality from STEMI are also significantly higher in females.[6,7] Sex disparities in STEMI care and outcomes have been widely reported internationally and in randomized clinical trials, highlighting the magnitude of this problem.[8–12]

Recent publications from the American Heart Association and the European Society of Cardiology identify reducing sex disparities in STEMI as a public health priority.[1,13] The 2017 European STEMI guidelines 'highlight the fact that women and men receive equal benefit from reperfusion strategy and STEMI-related therapy, and that both genders must be managed in a similar fashion'.[13] In order to improve the cardiovascular health of females, strategies to achieve the long-term equal management of STEMI are needed. We have previously shown promising results of a STEMI protocol that reduced STEMI sex disparities in short-term follow-up.[14] However, it remains unclear whether this protocol can be sustained long-term to consistently achieve the similar management and outcomes of STEMI between sexes. The purpose of this study was to evaluate the association of a comprehensive STEMI protocol with sex disparities in STEMI care and outcomes for 5 years after protocol implementation.

# Methods

## Study population

This was an observational cohort study of consecutive patients with STEMI treated with primary PCI at a tertiary care hospital within a multihospital regional health system from 1 January 2011 to 15 July 2019 (*Figure 1*). No patients were excluded. Data were collected prospectively as part of institutional reporting for the National Cardiovascular Data Registry CathPCI database.[15] On 15 July 2014 a comprehensive STEMI protocol was instituted within the health system to standardize STEMI

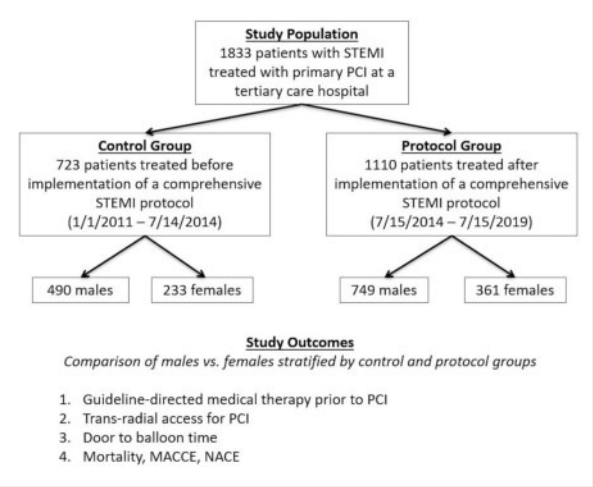



**Figure 1** Study population. MACCE, major adverse cardiovascular and cerebrovascular events; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

care. For the purposes of this study, the population was divided into control (1 January 2011–14 July 2014) and protocol groups (15 July 2014–15 July 2019). The care and outcomes of male vs. female patients with STEMI were compared in the control and protocol groups separately. This study was approved by the Cleveland Clinic Institutional Review Board with a waiver of informed consent. The data underlying this article cannot be shared publically to protect the privacy of individuals that participated in the study.

## ST-elevation myocardial infarction *protocol*

The details of the comprehensive STEMI protocol implemented on 15 July 2014 have been previously published.[14,16] In brief, the protocol entailed four steps intended to standardize STEMI care. First, Emergency Department (ED) physicians were authorized to activate the cardiac catheterization lab without delay for cardiac consultation. Second, a checklist was used to streamline critical tasks and provide real-time clinical decision support prior to PCI (medication administration, clinical assessments, identification of high-risk alerts). The checklists used for patients presenting to the primary ED, for patients transferred for PCI, and those with in-hospital STEMI are provided in Supplementary material online, *Figures S1–S3*. Third, a policy of immediate transfer to an immediately available catheterization lab was implemented. Patients were not held in the ED awaiting catheterization lab readiness. Instead, the catheterization lab was prepared at all times to accept a patient with STEMI. Finally, the protocol standardized trans-radial access as the preferred initial arterial access site for PCI, but the final decision on arterial access site was left to the attending interventional cardiologist.

## Study outcomes

ST-elevation myocardial infarction process outcomes assessed were the use of GDMT prior to arterial sheath insertion for PCI, the use of trans-radial access for PCI, and D2BT. GDMT was defined as the administration of aspirin, a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor), and an anticoagulant (low-molecular weight, unfractionated heparin, or bivalirudin). Medication administration data was retrieved from the medication administration record and emergency medical services records. Door to balloon time was defined as the time from first ED arrival to first device activation during PCI. For in-hospital STEMI, the time of first electrocardiogram showing STEMI was used instead of time of first ED arrival. Door to balloon time was analysed overall and also stratified by STEMI presenting location (primary ED, in-hospital, and inter-hospital transfer). ST-elevation myocardial infarction clinical outcomes assessed were in-hospital mortality, major adverse cardiovascular and cerebrovascular events (MACCE; composite of death, re-infarction, stroke, cardiogenic shock), and net adverse clinical events (NACE: composite of MACCE and bleeding). Definitions for re-infarction (myocardial infarction after index PCI), stroke, cardiogenic shock, and bleeding were based on the specifications of the coder's data dictionary for the NCDR CathPCI Registry. These events were adjudicated and recorded prospectively by trained data abstractors for purposes independent of this research study.

## Data analysis

Continuous variables are presented with median (25th, 75th percentile) and compared with a Mann–Whitney *U* test. Baseline categorical variables are presented as number (%) and compared with $\chi^2$ test or Fisher's exact tests as appropriate. The process and clinical outcomes enumerated above were compared between sexes in the protocol and control groups separately. In-hospital outcomes were compared between sexes using logistic regression. Models were carried out separately for control and protocol groups. Number of events, event rates (95% confidence interval), odds ratios (95% confidence interval), and *P*-values of regression models are presented. No risk adjustment was performed. Despite the known higher risk profile of females, the *a priori* analysis plan was to evaluate the association of the STEMI protocol with sex disparities without risk adjustment to minimize potential bias in favour of the STEMI protocol. All *P*-values are two sided and considered statistically significant if <0.05. Analysis was performed with SPSS version 26 software (IBM Corporation; Armonk, NY, USA) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Dr Huded and Dr Khot had full access to all of the data and take responsibility for its integrity and the data analysis.

# Results

## Baseline characteristics

The study population included 1833 consecutive patients with STEMI treated with primary PCI. Females comprised 32.2% (233/723) of the control group and 32.5% (361/1110) of the protocol group. Compared with males, females were significantly older with higher rates of hypertension, cerebrovascular disease, peripheral artery disease, chronic lung disease, and diabetes (*Table 1*). Differences between males and females were fairly consistent in both the control and protocol groups (Supplementary material online, *Table S1*). Females were older, more likely to be of black race, and had higher rates of hypertension, cerebrovascular disease, and diabetes in both the control and protocol groups. In the control group, females were more likely to have a non-system delay prior to PCI, while in the protocol group females were more likely to have peripheral artery disease and chronic lung disease.

## ST-elevation myocardial infarction *process outcomes*

In the control group, GDMT was administered prior to arterial sheath insertion for PCI significantly less in females [77.1% (378/

**Table 1 Baseline characteristics**

| Variables | Male (*n* = 1239) | Female (*n* = 594) | *P* |
|---|---|---|---|
| Age (years) | 60.1 (52.2, 67.9) | 65.0 (55.0, 74.6) | <0.001 |
| White race | 881 (71.1%) | 391 (65.8%) | 0.02 |
| Black race | 296 (23.9%) | 183 (30.8%) | 0.002 |
| Hypertension | 887 (71.1%) | 477 (80.3%) | <0.001 |
| Dyslipidaemia | 873 (72.0%) | 442 (76.3%) | 0.05 |
| Prior heart failure | 171 (13.8%) | 92 (15.5%) | 0.34 |
| Prior PCI | 276 (22.3%) | 130 (21.9%) | 0.85 |
| Prior CABG | 18 (1.5%) | 9 (1.5%) | 0.92 |
| Current dialysis | 18 (1.5%) | 11 (1.9%) | 0.52 |
| Prior cerebrovascular disease | 125 (10.1%) | 95 (16.0%) | <0.001 |
| Prior peripheral artery disease | 102 (8.2%) | 74 (12.5%) | 0.004 |
| Chronic lung disease | 122 (9.8%) | 106 (17.9%) | <0.001 |
| Diabetes mellitus | 347 (28.0%) | 231 (38.9%) | <0.001 |
| Non-system delay for PCI | 288 (23.2%) | 158 (26.6%) | 0.12 |
| Presenting location | | | |
| Main campus ED | 292 (23.6%) | 148 (24.9%) | 0.40 |
| Transfer from non-PCI facility | 864 (69.7%) | 398 (67.0%) | |
| In-hospital | 83 (6.7%) | 48 (8.0%) | |

CABG, coronary artery bypass grafting; ED, emergency department; PCI, percutaneous coronary intervention.

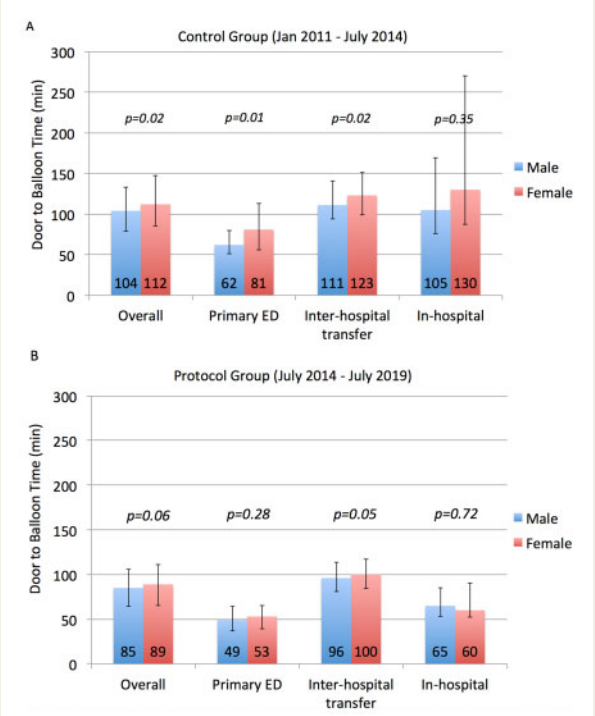



**Figure 2** Door to balloon times. D2BT in males vs. females overall and stratified by STEMI presenting location in the (*A*) control group and (*B*) protocol group. Error bars show interquartile range. D2BT, door to balloon time; ED, emergency department; STEMI, ST-elevation myocardial infarction.

490) vs. 68.1% (161/233), $P = 0.03$]. In the protocol group, GDMT administration was similar in both sexes [87.2% (652/749) vs. 86.4% (312/361), $P = 0.81$]. Trans-radial access for PCI was used infrequently in both males and females in the control group [19.0% (93/490) vs. 17.6% (41/233), $P = 0.73$]. There was a major increase in trans-radial PCI adoption in both males and females after protocol implementation ($P < 0.001$ for both), although the absolute trans-radial PCI use in males was higher than females in the protocol group [77.6% (581/749) vs. 71.2% (257/361), $P = 0.03$].

D2BT was significantly longer in females in the control group [104 min (79, 133) vs. 112 min (85, 147), $P = 0.02$; *Figure 2*]. D2BT was significantly longer in females both among patients presenting to the primary ED [62 min (51, 80) vs. 81 min (56, 113), $P = 0.01$] and those transferred for PCI [111 min (94, 141) vs. 123 min (99, 151), $P = 0.02$]. Among those with in-hospital STEMI, D2BT were statistically similar in males and females in the control group [105 min (76, 169) vs. 130 (87, 270), $P = 0.35$].

In the protocol group, D2BT was not statistically different between males and females overall [85 min (64, 106) vs. 89 min (65, 111), $P = 0.06$], in those presenting to the primary ED [49 min (37, 64) vs. 53 min (39, 65), $P = 0.28$], and in those with in-hospital STEMI [65 min (53, 85) vs. 60 (52, 90), $P = 0.72$]. In patients transferred for PCI, D2BT remained longer by 4 min in females, a difference which approached statistical significance [96 min (81, 114) vs. 100 min (84, 117), $P = 0.05$].

### ST-elevation myocardial infarction *clinical outcomes*

In the control group, females had higher rates of in-hospital mortality, MACCE, and NACE (*Table 2*). In-hospital stroke and bleeding were also significantly higher in females in the control group. In the protocol group, there were no sex differences in the rates of mortality, MACCE, or stroke. The rate of bleeding in females fell from 19.0% in the control group to 11.1% in the protocol group, but a sex disparity in bleeding persisted in the protocol group with a statistically higher risk of bleeding in females. The higher rate of bleeding in females contributed to a 4.6% higher absolute risk of NACE in females compared with males in the protocol group that approached statistical significance. Females in the protocol group also had a higher rate of in-hospital re-infarction, a difference that was not observed in the control group.

During the study period, annual male in-hospital mortality was stable, while there was a trend toward reduced annual female in-hospital mortality, which approached statistical significance (Supplementary material online, *Table S2* and *Figure S1*).

## Discussion

### Principal findings

In this observational cohort study of consecutive STEMI patients treated with PCI before and after implementation of a

**Table 2 In-hospital clinical outcomes by sex in control and protocol groups**

| Outcomes | Male events [*N*, % (95% CI)] | Female events [*N*, % (95% CI)] | OR (95% CI) for females vs. males | *P* |
|---|---|---|---|---|
| A. Control Group (1 January 2011–14 July 2014) | | | | |
| Mortality | 22/490 [4.5% (2.8–6.7) | 24/233 [10.3% (6.7–14.9)] | 2.44 (1.34–4.46) | 0.004 |
| MACCE | 48/490 [9.8% (7.3–12.8)] | 38/233 [16.3% (11.8–21.7)] | 1.79 (1.14–2.84) | 0.01 |
| NACE | 79/490 [16.1% (13.0–19.7)] | 66/233 (28.3% (22.6–34.6)] | 2.06 (1.42–2.99) | <0.001 |
| Re-infarction | 6/489 [1.2% (0.5–2.7)] | 2/231 [0.9% (0.1–3.1)] | 0.70 (0.14–3.51) | 0.67 |
| Stroke | 1/489 [0.2% (0.0–1.1)] | 7/231 [3.0% (1.2–6.1)] | 15.25 (1.87–124.69) | 0.01 |
| Cardiogenic shock | 36/489 [7.4% (5.2–10.1)] | 19/231 [8.2% (5.0–12.6)] | 1.13 (0.63–2.01) | 0.68 |
| Bleeding | 42/487 [8.6% (6.3–11.5)] | 44/231 [19.1% (14.2–24.7)] | 2.49 (1.58–3.93) | <0.001 |
| B. Protocol Group (15 July 2014–15 July 2019) | | | | |
| Mortality | 19/749 [2.5% (1.5–3.9)] | 16/361 [4.4% (2.6–7.1)] | 1.78 (0.91–3.51) | 0.09 |
| MACCE | 67/749 [9.0% (7.0–11.2)] | 40/361 [11.1% (8.0–14.8)] | 1.27 (0.83–1.92) | 0.26 |
| NACE | 111/749 [14.8% (12.4–17.6)) | 70/361 [19.4% (15.4–23.9)] | 1.38 (0.99–1.92) | 0.05 |
| Re-infarction | 8/749 [1.1% (0.5–2.1)] | 10/361 [2.8% (1.3–5.0)] | 2.64 (1.03–6.74) | 0.04 |
| Stroke | 8/749 [1.1% (0.5–2.1)] | 5/361 [1.4% (0.5–3.2)] | 1.30 (0.42–4.00) | 0.65 |
| Cardiogenic shock | 46/749 [6.1% (4.5–8.1)] | 20/361 [5.5% (3.4–8.4)] | 0.90 (0.52–1.53) | 0.69 |
| Bleeding | 54/749 [7.2% (5.5–9.3)] | 40/361 [11.1% (8.0–14.8)] | 1.60 (1.04–2.46) | 0.03 |

*P* for logistic regression comparison of females vs. males.
CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events (death, re-infarction, stroke, cardiogenic shock); NACE, net adverse clinical events (MACCE + bleeding); OR, odds ratio.

comprehensive STEMI protocol, the following principal findings were observed. First, the use of GDMT and D2BT were similar between sexes for 5 years after the implementation of the STEMI protocol. Second, there were major improvements in the use of trans-radial PCI in both males and females although there was a lower rate of trans-radial PCI use in females after protocol implementation. Third, sex disparities in mortality and MACCE were no longer observed for 5 years after protocol implementation (Graphical Abstract). Finally, a significantly higher rate of bleeding in females persisted despite the implementation of a STEMI protocol including the promotion of trans-radial PCI.

## *Reduction of sex disparities in* ST-elevation myocardial infarction

In a previous study by Wei *et al.*,[17] the authors observed no significant sex difference in age-adjusted long-term survival after STEMI in a regional STEMI system. However, despite the impressive findings of that analysis, sex disparities in both the STEMI process and clinical outcomes persisted. D2BT were significantly shorter in males vs. females while in-hospital mortality (5.2% vs. 7.6%, $P = 0.001$) and 30-day MACE (major adverse cardiac events defined as myocardial infarction, stroke, or death; 7.8% vs. 10.6%, $P = 0.002$) were both significantly higher in females. Additionally, it remains controversial whether STEMI systems of care can truly impact sex disparities even if the system is successful in achieving lower D2BT overall. A recent report from the Mission: Lifeline STEMI accelerator program demonstrated successful improvements in the achievement of guideline-directed D2BT goals in males but no meaningful improvements in females.[5] The present study supports an association of a STEMI protocol with reduced sex disparities and the sustainability of these improvements over a 5-year duration.

## Sustainability of reductions in sex disparities

The comprehensive STEMI protocol in this study previously produced encouraging early results with reduced sex disparities in STEMI care and outcomes in the first 2 years after protocol implementation.[14] Whether these improvements could be sustained over a longer period was the focus of the present analysis. A major challenge of hospital quality improvement work is maintaining early gains in quality for the long-term. The phenomenon of 'regression to the mean' may dictate that early gains in key metrics are lost as performance declines to pre-intervention levels over time.[18,19] The protocol in this study achieved sustained success through the following processes. First, an interdisciplinary team of cardiologists, cardiology fellows, emergency physicians, nurses, and critical care transporters oversaw the STEMI clinical program including protocol adherence. Second, monthly interdisciplinary STEMI committee meetings were conducted to review cases, discuss successes and challenges, and to work through process issues as they arose. Third, new trainees were oriented to the STEMI system workflow and team expectations annually and on an ad hoc basis as appropriate. Fourth, feedback on both positive and negative performance was shared in a constructive and non-punitive manner with the goal of optimizing system performance and patient care.

## *Mechanisms of improved female* ST-elevation myocardial infarction *outcomes*

The observed association of the protocol in this study with reduced sex disparities likely related to its comprehensive nature in targeting prompt GDMT, rapid D2BT, and bleeding avoidance through trans-radial PCI. This protocol fundamentally differs from other protocols that focus solely on D2BT. Current US STEMI guidelines give a Class 1 recommendation for loading doses of aspirin, a P2Y12 inhibitor, and heparin prior to or at the time of PCI.[20] Despite established sex disparities in the use of GDMT,[21] the protocol used in this study was unique in its focus on early antithrombotic and antiplatelet drugs prior to PCI. Many GDMT metrics for STEMI care have traditionally focused on post-PCI medication administration. Undue inter-provider variability in administering prompt antithrombotic and antiplatelet drugs prior to PCI was minimized with a standardized STEMI checklist in the ED.

The baseline sex disparity in D2BT observed in this study was mitigated in patients presenting to the primary ED, those transferred for PCI, and those with in-hospital STEMI. Among those transferred for PCI, a longer D2BT in females after protocol implementation approached statistical significance, but the absolute difference was small (4 min). Reasons for longer D2BT in women may include atypical symptoms in women and higher rates of medical comorbidities contributing to medical complexity.[1] Use of a comprehensive STEMI protocol with ED physician autonomy, immediate catheterization lab availability, and frequent STEMI team meetings including case reviews offers the potential to improve STEMI management at both PCI-capable and non-PCI-capable hospitals.

Trans-radial PCI for STEMI is now supported by multiple randomized clinical trials demonstrating its benefit and carries a Class 1 indication in the 2017 European STEMI guidelines.[13] In this study, a >four-fold increase in the use of trans-radial PCI was achieved in both sexes. However, a sex disparity was observed with a higher rate of trans-radial PCI in males in the protocol group. Female sex has been previously associated with lower trans-radial PCI use in STEMI in the USA,[22] and as a significant predictor of trans-radial PCI failure (OR 3.2, 95% confidence interval 2.0–5.3, $P < 0.001$).[23] This may be due to smaller radial artery calibre in women, higher rates of vasospasm, or shorter stature, which can contribute to technical challenges due to a short distance between the aortic root and the innominate artery. Further studies are needed to clarify whether an operator learning curve exists such that use of trans-radial PCI in females with STEMI can be improved with experience and adoption of techniques such as ultrasound-guided access, adequate sedation, fewer catheter exchanges, or specific vasodilator cocktails.

## Bleeding events

The relationship between sex disparities in trans-radial access use and bleeding outcomes in the present study is notable and warrants further investigation. Bleeding events in STEMI patients are associated with increased short- and long-term mortality.[24,25] The reasons for persistently higher bleeding events in females in the protocol group in this study may be related to the higher rate of trans-femoral access for PCI in females as discussed above. A recent analysis from the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial demonstrated that females are at higher risk for severe bleeding and access-related complications.[26] In that study, the use of trans-radial access had a relatively greater benefit in reducing MACE and NACE in females. That study highlights the potential importance of operators persisting in using trans-radial access in females with STEMI despite technical challenges. However, non-access site-related causes for bleeding disparities warrant further investigation, as non-access site bleeding in STEMI is particularly associated with long-term outcomes.[27]

## Limitations

First, this was a single-centre study within a multi-hospital regional health system. The majority of patients in this study were transferred for primary PCI. Further work is needed to generalize these findings to varied populations including those with a minority of inter-hospital transfer patients. Second, the sustainability of STEMI systems of care is likely to vary between hospitals. The findings reported in this study may not be similar to the experience of other hospitals. Third, a pre- vs. post-protocol study design was implemented, and bias due to changes in STEMI care provided unrelated to the protocol implementation may influence the observed results. Finally, a higher rate of in-hospital re-infarction in females vs. males was observed in the protocol group while other ischaemic complications including mortality were reduced. This finding may reflect a type 1 error due to multiple comparisons in the present analysis. Re-infarction events were adjudicated based on the definitions set forth by the ACC/NCDR CathPCI Registry, but the clinical importance of these events is uncertain and warrants further investigation.

# Conclusions

With a 5-year follow-up, a comprehensive STEMI protocol was associated with reduced sex disparities in GDMT, D2BT, in-hospital mortality, and ischaemic in-hospital events. ST-elevation myocardial infarction protocols modelled after the comprehensive STEMI protocol described in this study may offer the potential to improve the cardiovascular outcomes of women with STEMI.

# Lead author biography

Dr Chetan Huded earned his B.A. from the University of Chicago and M.D. from Dartmouth Medical School. He completed internal medicine residency, Chief Residency, and a Masters in Clinical Investigation from Northwestern University followed by cardiology and interventional cardiology fellowships at the Cleveland Clinic, where he served as Chief Cardiology Fellow. He joined the faculty at Saint Luke's Mid America Heart Institute where he is an interventional cardiologist and clinical scholar. Dr Huded's work focuses on quality of care, health status, and clinical outcomes of patients treated with coronary and structural heart interventions.

# Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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**Conflict of interest:** Stephen Ellis has served as a consultant for Abbott Vascular, Boston Scientific, and Medtronic. The remaining authors have no conflicts of interest to disclose.

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