Five Years of a Comprehensive ST Elevation Myocardial Infarction Protocol and its Association with Sex Disparities

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Abstract [250 words]

Aims: To determine whether a comprehensive 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 (1/1/2011-7/14/2014, control group) and after (7/15/2014-7/15/2019, 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%, 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. 11.0%, 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 ischemic outcomes over 5 years, but higher bleeding rates in females persisted.

Key Words: 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 multi-hospital regional health system from 1/1/2011 to 7/15/2019 (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 7/15/2014 a comprehensive STEMI protocol was instituted within the health system to standardize STEMI care. For the purposes of this study, the population was divided into control (1/1/2011 – 7/14/2014) and protocol groups (7/15/2014-7/15/2019). 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.

STEMI Protocol

The details of the comprehensive STEMI protocol implemented on 7/15/2014 have been previously published.[14, 16] In brief the protocol entailed 4 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 Figures 1-3. 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

STEMI 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 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. D2BT was defined as the time from first ED arrival to first device activation during PCI. For in-hospital STEMI, the time of first ECG showing STEMI was used instead of time of first ED arrival. D2BT was analyzed overall and also stratified by STEMI presenting location (primary ED, in-hospital, inter-hospital transfer). STEMI clinical outcomes assessed were in-hospital mortality, major adverse cardiovascular and cerebrovascular events (MACCE; composite of death, reinfarction, 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 (25^{th}, 75^{th} percentile) and compared with a Mann Whitney U test. Baseline categorical variables are presented as number (%) and compared with Chi-squared 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 favor 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) 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 Table 1). 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.

STEMI Process Outcomes

In the control group, GDMT was administered prior to arterial sheath insertion for PCI significantly less in females (77.1% [378/490] 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 minutes in females, a difference which approached statistical significance (96 min [81, 114] vs. 100 min [84, 117], p=0.05).

STEMI 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 reinfarction, 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 Table 2 and Supplementary Figure 1).

Discussion

Principal Findings

In this observational cohort study of consecutive STEMI patients treated with PCI before and after implementation of a comprehensive STEMI protocol, the following principal findings were observed. First, use of GDMT and D2BT were similar between sexes for 5 years after 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 implementation of a STEMI protocol including promotion of trans-radial PCI.

Reduction of Sex Disparities in STEMI

In a previous study by Wei et al., the authors observed no significant sex difference in age-adjusted long-term survival after STEMI in a regional STEMI system.[17] However,

despite the impressive findings of that analysis, sex disparities in both 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 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 STEMI 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 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 minutes). 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 >4 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 United States,[22] and as a significant predictor of trans-radial PCI failure (OR 3.2, 95% confidence interval 2.0 to 5.3, $p<0.001$).[23] This may be due to smaller radial artery caliber 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 higher risk for severe bleeding and access related complications.[26] In that study, use of trans-radial access had a relatively greater benefit in reducing MACE and NACCE 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 center 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, 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 ischemic 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 five-year follow-up, a comprehensive STEMI protocol was associated with reduced sex disparities in GDMT, D2BT, in-hospital mortality, and ischemic in-hospital events. STEMI protocols modeled after the comprehensive STEMI protocol described in this study may offer the potential to improve the cardiovascular outcomes of women with STEMI.

Supplementary Data

An on-line supplementary appendix is provided with the following data.

Supplementary Table 1 - Baseline Characteristics by Sex in Control and Protocol Groups.

Supplementary Table 2 - Annual In-Hospital Mortality by Sex

Supplementary Figure 1 - Annual In-Hospital Mortality by Sex

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Disclosures

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References

1. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation 2016;**133**(9):916-47.
2. Stevens GA, Mathers CD, Beard JR. Global mortality trends and patterns in older women. Bull World Health Organ 2013;**91**(9):630-9.
3. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L. Sex differences in medical care and early death after acute myocardial infarction. Circulation 2008;**118**(25):2803-10.
4. Dreyer RP, Beltrame JF, Tavella R, Air T, Hoffmann B, Pati PK, Di Fiore D, Arstall M, Zeitz C. Evaluation of gender differences in Door-to-Balloon time in ST-elevation myocardial infarction. Heart Lung Circ 2013;**22**(10):861-9.
5. Hinohara TT, Al-Khalidi HR, Fordyce CB, Gu X, Sherwood MW, Roettig ML, Corbett CC, Monk L, Tamis-Holland JE, Berger PB, Burchenal JEB, Wilson BH, Jollis JG, Granger CB. Impact of Regional Systems of Care on Disparities in Care Among Female and Black Patients Presenting With ST-Segment-Elevation Myocardial Infarction. J Am Heart Assoc 2017;**6**(10).
6. Cenko E, van der Schaar M, Yoon J, Manfrini O, Vasiljevic Z, Vavlukis M, Kedev S, Milicic D, Badimon L, Bugiardini R. Sex-Related Differences in Heart Failure After ST-Segment Elevation Myocardial Infarction. Journal of the American College of Cardiology 2019;**74**(19):2379-2389.

7. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. JAMA Intern Med 2014;**174**(11):1822-30.

8. Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. Time trends in STEMI--improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register. BMJ Open 2012;**2**(2):e000726.

9. Johnston N, Bornefalk-Hermansson A, Schenck-Gustafsson K, Held C, Goodman SG, Yan AT, Bierman AS. Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada? Eur Heart J Acute Cardiovasc Care 2013;**2**(4):350-8.

10. Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, Caussin C, Teiger E, Garot P, Lambert Y, Jouven X, Spaulding C. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. EuroIntervention 2011;**6**(9):1073-9.

11. Kosmidou I, Redfors B, Selker HP, Thiele H, Patel MR, Udelson JE, Magnus Ohman E, Eitel I, Granger CB, Maehara A, Kirtane A, Genereux P, Jenkins PL, Ben-Yehuda O, Mintz GS, Stone GW. Infarct size, left ventricular function, and prognosis in women compared to men after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: results from an individual patient-level pooled analysis of 10 randomized trials. Eur Heart J 2017;**38**(21):1656-1663.

12. Hvelplund A, Galatius S, Madsen M, Rasmussen JN, Rasmussen S, Madsen JK, Sand NP, Tilsted HH, Thayssen P, Sindby E, Hojbjerg S, Abildstrom SZ. Women with

acute coronary syndrome are less invasively examined and subsequently less treated than men. Eur Heart J 2010;**31**(6):684-90.

13. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;**39**(2):119-177.

14. Huded CP, Johnson M, Kravitz K, Menon V, Abdallah M, Gullett TC, Hantz S, Ellis SG, Podolsky SR, Meldon SW, Kralovic DM, Brosovich D, Smith E, Kapadia SR, Khot UN. 4-Step Protocol for Disparities in STEMI Care and Outcomes in Women. J Am Coll Cardiol 2018;**71**(19):2122-2132.

15. Moussa I, Hermann A, Messenger JC, Dehmer GJ, Weaver WD, Rumsfeld JS, Masoudi FA. The NCDR CathPCI Registry: a US national perspective on care and outcomes for percutaneous coronary intervention. Heart 2013;**99**(5):297-303.

16. Huded CP, Kumar A, Johnson M, Abdallah M, Ballout JA, Kravitz K, Menon V, Gullett TC, Hantz S, Ellis SG, Podolsky SR, Meldon SW, Kralovic DM, Brosovich D, Smith E, Kapadia SR, Khot UN. Incremental Prognostic Value of Guideline-Directed Medical Therapy, Transradial Access, and Door-to-Balloon Time on Outcomes in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv 2019;**12**(3):e007101.

17. Wei J, Mehta PK, Grey E, Garberich RF, Hauser R, Bairey Merz CN, Henry TD. Sex-based differences in quality of care and outcomes in a health system using a standardized STEMI protocol. Am Heart J 2017;**191**:30-36.

18. Joshi S, Nuckols T, Escarce J, Huckfeldt P, Popescu I, Sood N. Regression to the Mean in the Medicare Hospital Readmissions Reduction Program. JAMA Intern Med 2019.

19. Girbes AR, Robert R, Marik PE. Protocols: help for improvement but beware of regression to the mean and mediocrity. Intensive Care Med 2015;**41**(12):2218-20.

20. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW, Fdn ACC, Force AHAT. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2013;**61**(4):485-510.

21. Lewis WR, Ellrodt AG, Peterson E, Hernandez AF, LaBresh KA, Cannon CP, Pan W, Fonarow GC. Trends in the use of evidence-based treatments for coronary artery disease among women and the elderly: findings from the get with the guidelines quality-improvement program. Circ Cardiovasc Qual Outcomes 2009;**2**(6):633-41.

22. Valle JA, Kaltenbach LA, Bradley SM, Yeh RW, Rao SV, Gurm HS, Armstrong EJ, Messenger JC, Waldo SW. Variation in the Adoption of Transradial Access for ST-Segment Elevation Myocardial Infarction: Insights From the NCDR CathPCI Registry. JACC Cardiovasc Interv 2017;**10**(22):2242-2254.

23. Abdelaal E, Brousseau-Provencher C, Montminy S, Plourde G, MacHaalany J, Bataille Y, Molin P, Dery JP, Barbeau G, Roy L, Larose E, De Larochelliere R, Nguyen CM, Proulx G, Costerousse O, Bertrand OF. Risk score, causes, and clinical impact of failure of transradial approach for percutaneous coronary interventions. JACC Cardiovasc Interv 2013;**6**(11):1129-37.

24. Hermanides RS, Ottervanger JP, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT, Suryapranata H, van 't Hof AW. Incidence, predictors and prognostic importance of bleeding after primary PCI for ST-elevation myocardial infarction. EuroIntervention 2010;**6**(1):106-11.

25. Kikkert WJ, van Geloven N, van der Laan MH, Vis MM, Baan J, Jr., Koch KT, Peters RJ, de Winter RJ, Piek JJ, Tijssen JG, Henriques JP. The prognostic value of bleeding academic research consortium (BARC)-defined bleeding complications in ST-segment elevation myocardial infarction: a comparison with the TIMI (Thrombolysis In Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and ISTH (International Society on Thrombosis and Haemostasis) bleeding classifications. Journal of the American College of Cardiology 2014;**63**(18):1866-75.

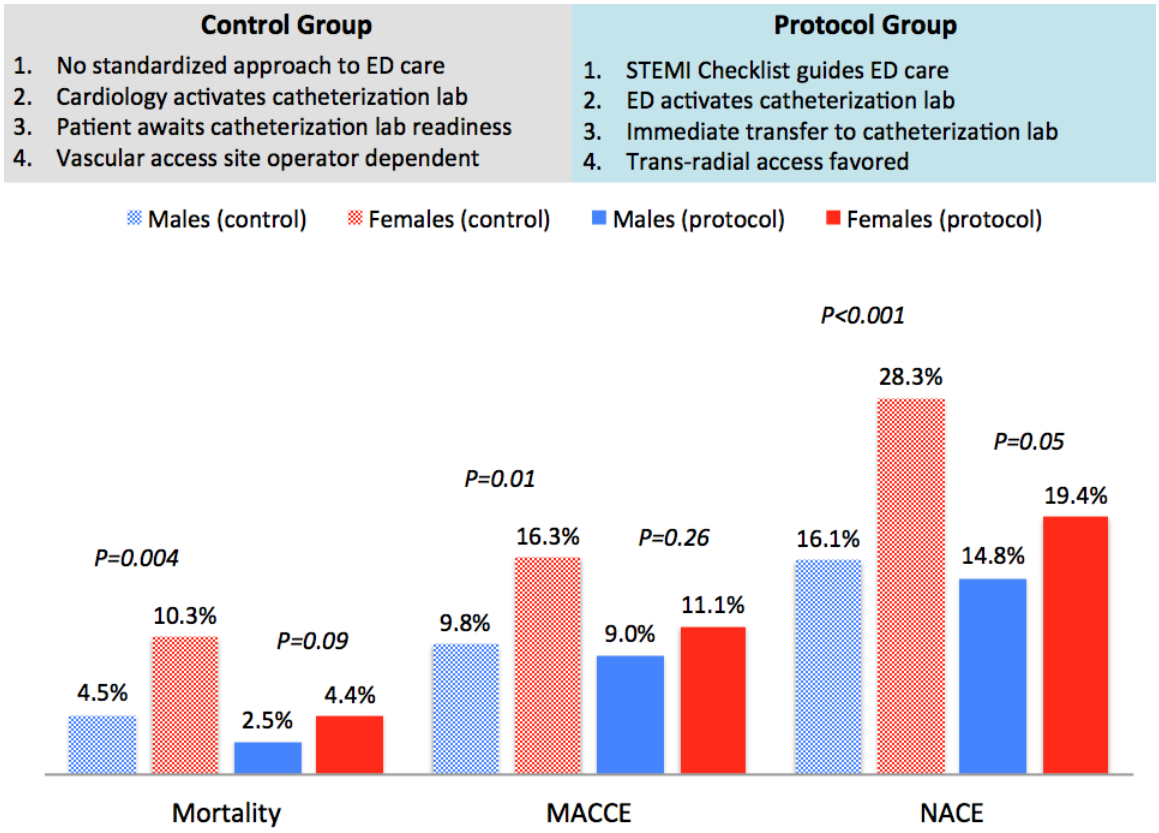
26. Gargiulo G, Ariotti S, Vranckx P, Leonardi S, Frigoli E, Ciociano N, Tumscitz C, Tomassini F, Calabro P, Garducci S, Crimi G, Ando G, Ferrario M, Limbruno U, Cortese

B, Sganzerla P, Lupi A, Russo F, Garbo R, Ausiello A, Zavalloni D, Sardella G, Esposito G, Santarelli A, Tresoldi S, Nazzaro MS, Zingarelli A, Petronio AS, Windecker S, da Costa BR, Valgimigli M. Impact of Sex on Comparative Outcomes of Radial Versus Femoral Access in Patients With Acute Coronary Syndromes Undergoing Invasive Management: Data From the Randomized MATRIX-Access Trial. JACC Cardiovasc Interv 2018;**11**(1):36-50.

27. Kikkert WJ, Delewi R, Ouweneel DM, van Nes SH, Vis MM, Baan J, Jr., Koch KT, Dangas GD, Mehran R, de Winter RJ, Peters RJ, Piek JJ, Tijssen JG, Henriques JP. Prognostic value of access site and nonaccess site bleeding after percutaneous coronary intervention: a cohort study in ST-segment elevation myocardial infarction and comprehensive meta-analysis. JACC Cardiovasc Interv 2014;**7**(6):622-30.

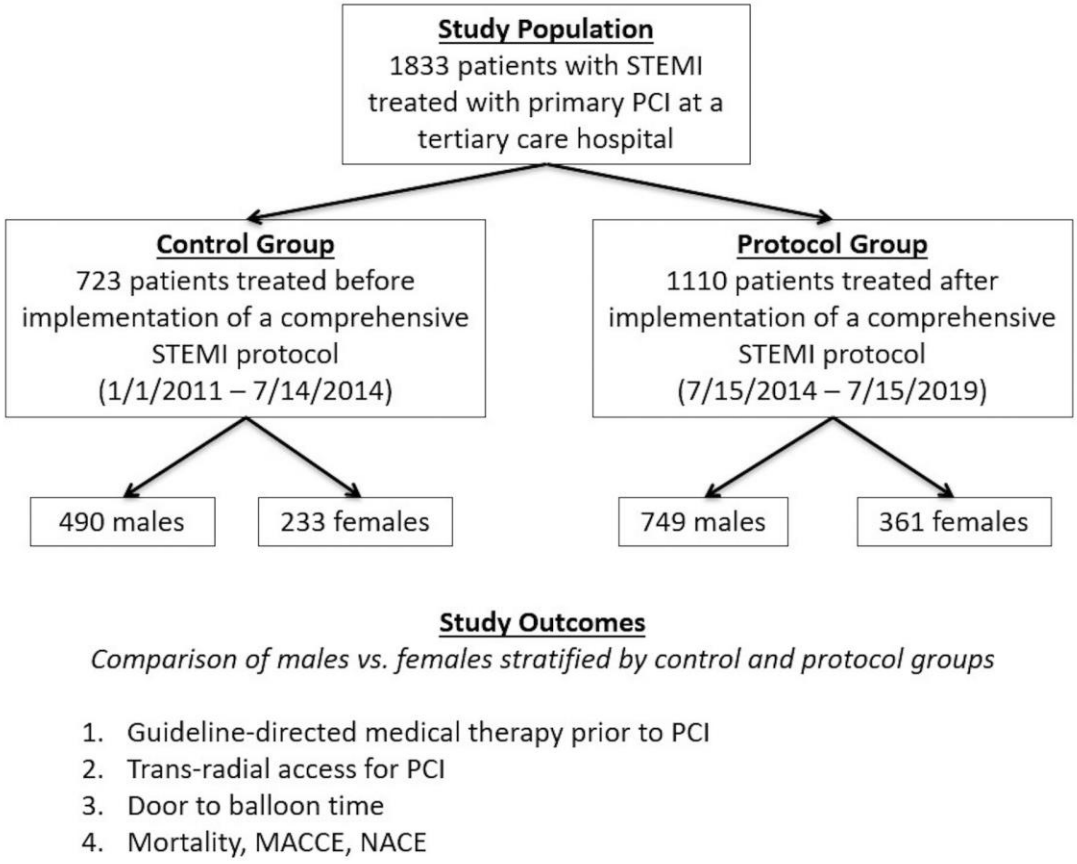
Figures and Legends

Graphical Abstract



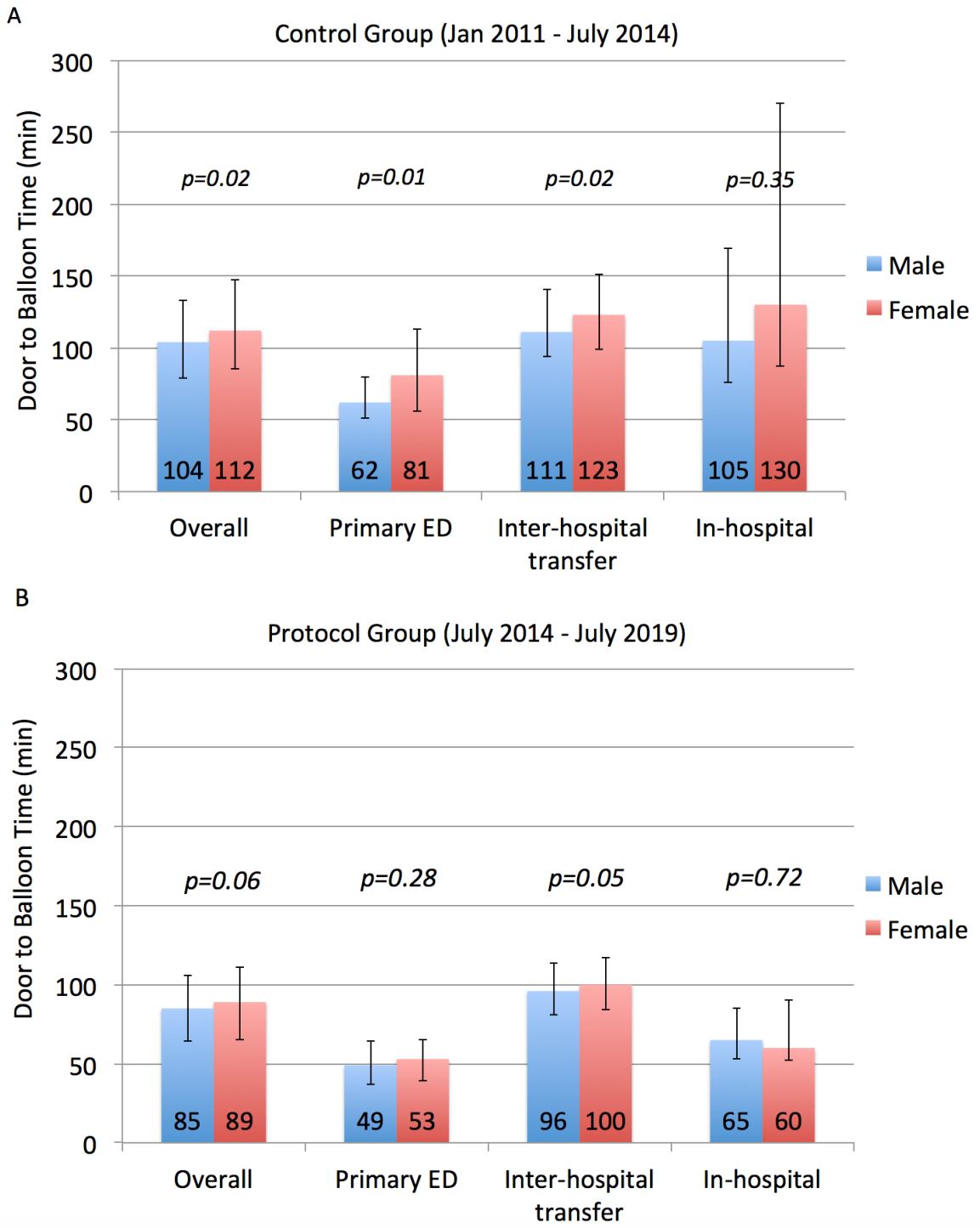
A comprehensive STEMI protocol was associated with reduced STEMI sex disparities in care and outcomes for 5 years after protocol implementation. Key aspects of the protocol and in-hospital outcomes are summarized. MACCE = major adverse cardiovascular and cerebrovascular events. NACE = net adverse clinical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

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.

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.

Table 1 – Baseline Characteristics

Variable	Male (n=1,239)	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
Dyslipidemia	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.

Table 2 – In-Hospital Clinical Outcomes by Sex in Control and Protocol Groups

A. Control Group (1/1/2011 – 7/14/2014)				
Outcome	Male events (N, % [95% CI])	Female events (N, % [95% CI])	OR (95% CI) for females vs. males	P
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 (7/15/2014 – 7/15/2019)				
Outcome	Male events (N, % [95% CI])	Female events (N, % [95% CI])	OR (95% CI) for females vs. males	P
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

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