Meta-Analysis of Gender Disparities in In-hospital Care and Outcomes in Patients with ST-Segment Elevation Myocardial Infarction

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Gender disparities in ST-segment elevation myocardial infarction (STEMI) outcomes continue to be reported worldwide; however, the magnitude of this gap remains unknown. To evaluate gender-based discrepancies in clinical outcomes and identify the primary driving factors a global meta-analysis was performed. Studies were selected if they included all comers with STEMI, reported gender specific patient characteristics, treatments, and outcomes, according to the registered PROSPERO protocol: CRD42020161469. A total of 56 studies (705,098 patients, 31% females) were included. Females were older, had more comorbidities and received less antiplatelet therapy and primary percutaneous coronary intervention (PCI). Females experienced significantly longer delays to first medical contact (mean difference 42.5 min) and door-to-balloon time (mean difference 4.9 min). In-hospital, females had increased rates of mortality (odds ratio [OR] 1.91, 95% confidence interval [CI] 1.84 to 1.99, p <0.00001), repeat myocardial infarction (MI) (OR 1.25, 95% CI 1.00 to 1.56, p=0.05), stroke (OR 1.67, 95% CI 1.27 to 2.20, p <0.001), and major bleeding (OR 1.82, 95% CI 1.56 to 2.12, p <0.00001) compared with males. Older age at presentation was the primary driver of excess mortality in females, although other factors including lower rates of primary PCI and aspirin usage, and longer door-to-balloon times contributed. In contrast, excess rates of repeat MI and stroke in females appeared to be driven, at least in part, by lower use of primary PCI and P2Y12 inhibitors, respectively. In conclusion, despite improvements in STEMI care, women continue to have in-hospital rates of mortality, repeat MI, stroke, and major bleeding up to 2-fold higher than men. Gender disparities in in-hospital outcomes can largely be explained by age differences at presentation but comorbidities, delays to care and suboptimal treatment experienced by women may contribute to the gender gap. **(Am J Cardiol 2021;147:23−32)**

Worldwide, acute myocardial infarction is the leading cause of death for males and females.[1] Over the past 2-decades, worldwide initiatives to increase public awareness have led to the implementation of reliable medical systems and generated guidelines to reduce morbidity and mortality associated with ST-segment elevation myocardial infarction (STEMI).[2-7] As the care for STEMI patients has continued to improve globally, gender disparities in quality of care and outcomes have become more apparent. While some studies have showed that the higher mortality in women is largely due to differences in age, comorbidities, treatment strategy, and reperfusion delays,[8-12] others have found that the differences persist despite adjustment for these variables, especially in younger patients.[13-15] Whether the gender disparities persist at a global level with the current widespread adoption of care systems for STEMI patients remains unknown. The aim of this global meta-analysis was to identify differences in patient characteristics, delays to care, treatment strategies, and outcomes by gender, in order to raise awareness of gender disparities and to inform future initiatives for improvement of care.

Methods

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[16] and was prospectively registered in PROSPERO (CRD42020161469). PubMed was searched using the following search terms: STEMI, sex, gender, mortality, and outcome. The search was restricted to studies published in the English language between January 2000 and December 2019. Two authors (TS and SG) independently screened titles/abstracts for mention of patient characteristics and gender-based STEMI

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See page 30 for disclosure information.

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outcomes to identify eligible articles. The studies were selected if they included all-comer STEMI patients and reported patient characteristics and relevant prespecified clinical endpoints by gender. Studies were excluded if they reported data for only thrombolysis therapy, included less than 100 patients of any gender, or only patients from certain cohorts of STEMI patients (e.g., diabetics, cardiogenic shock, or narrow age ranges), or based on major shortcomings (e.g., improper data, different endpoints or timepoints). When overlapping data were identified only the study with the most relevant data was selected and the other publications were discarded. Bibliographies of selected studies were examined to identify potentially relevant studies.

Three authors (TS, SG, and RT) independently abstracted data on prespecified patient demographics/characteristics, delays to care, treatment strategies and outcomes from selected studies and crosschecked for accuracy. Data on treatment strategies included proportion of primary PCI (as the initial treatment strategy before fibrinolysis or GpIIb/IIIa inhibitor usage) and medication usage. Prespecified delays to care included time to first medical contact (FMC), door-to-balloon (DTB), and door-to-needle (DTN). Prespecified clinical outcomes included in-hospital mortality, repeat MI (site defined), stroke (site defined), and major bleeding (definition varied by study, generally including bleeding requiring transfusion or repeat procedure).

Odds ratios were calculated using the DerSimonian and Laird inverse variance random-effects model and were performed using the Review Manager version 5.3 (Nordic Cochrane Center, Copenhagen, Denmark). The I^2 statistic and heterogeneity p-value were used as a measure of variability in observed effect estimates attributable to heterogeneity between studies. For the I^2 statistic, heterogeneity was defined as low (25% to 50%), moderate (50% to 75%), or high (>75%). Estimates for pooled analyses per geographic regions and combined were displayed in Forest plots. R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for demographic and clinical characteristics analyses. Two sample *t*-test was used for analyzing the continuous variable of age, expressed as mean and standard deviation. Categorical variables were evaluated by two-sample test for equality of proportions and reported as percentages. Simple and multiple logistic regression models were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina) to identify significant moderator variables.

Results

The literature search resulted in a total of 1,234 articles. After screening and eligibility assessment for inclusion criteria a total of 56 studies were selected and included in the global meta-analysis (Figure 1). A total of 705,098 patients (31% females) from more than 30 countries, grouped into 6 regions: Asia, Australia, Europe, Middle East, mixed regional population, and North America were included in the meta-analysis (Supplemental Table 1). The mixed regional population included patients for which regional separation was not possible. The studies consisted mostly of observational studies and registries, but also included one randomized controlled trial[17] (Supplemental Table 2).

The pooled baseline characteristics by gender demonstrated that females with STEMI were older than males (70.2 ± 3.1 vs 61.1 ± 2.2 years) and were more likely to have diabetes mellitus (27.4% vs 21.0%), hypertension (61.1% vs. 50.6%), a prior stroke (8.1% vs 7.4%), and cardiogenic shock at presentation (6.9% vs 5.5%) (Table 1). Males were more likely to be smokers (44.2% vs 27.2%) and to have had a prior MI (16.2% vs 14.7%) (Table 1).

Gender differences in time to FMC and DTB were calculated for regions with available data. Time to FMC, determined for Asia, Australia and Europe was significantly longer for females, both per regions and combined, with a mean delay of 42.5 min (95% CI 28.4 to 56.6, p <0.00001) (Supplemental Figure 1A). In a combined analysis, DTB time was significantly longer for females with a mean delay of 4.9 min (95% CI 3.8 to 6.1, p <0.00001) (Supplemental Figure 1B). However, there was a high variability in reported DTB time per regions with longer delays, more than 5 min for females in Asia, Australia, North America and the mixed region. Shorter delays were in Europe (mean 2.1 min) and in the Middle Est (mean 1.1 min).

While it was not feasible to determine gender differences in DTN time and total ischemic time (defined from the symptom onset to balloon time) per regions due to limited data, it was possible by pooling all available data, regardless of region. As shown in Supplemental Table 3, there were significant delays for females in DTN times (mean 0.9 min) and ischemic times (mean 21.3 min).

Female patients with STEMI received less optimal therapy during hospitalization, compared with their male counterparts, including: primary PCI (59.5% vs 68.2%), aspirin (89.5 vs 92.1%), P2Y12 inhibitors (67.6% vs 75.4%), GpIIb/IIIa inhibitors (22.7% vs 29.3%), beta blockers (75.1% vs 76.1%) and ACE inhibitors (55.6% vs 59.4%) (Table 1). Of note, patients not receiving primary PCI often received PCI at some point during their hospital stay in most included studies. The proportion of primary PCI varied significantly across regions with >80% of patients from studies in North America and Europe receiving primary PCI while only 50% to 60% received primary PCI in studies from Asia and the Middle East.

In combined analysis, the unadjusted rate of in-hospital mortality was higher in females compared with males (N=669,358; OR 1.91, 95% CI 1.84 to 1.99, p <0.00001, I^2=58%) (Figure 2). Consistently, females had higher in-hospital mortality rates across all regions (OR varying from 1.54 to 2.57, p <0.00001, I^2 varying 0-65%) (Figure 2). Furthermore, gender disparities in mortality rates did not significantly change in the last 20 years, since the implementation of care systems for STEMI (Supplemental Figure 2).

For the other in-hospital outcomes, repeat MI, stroke and major bleeding, significant differences between genders were not identified in all regions, although the combined results showed worse outcomes for females. The unadjusted rate of repeat MI for females was higher compared with males in combined analysis (N=70,408; OR 1.25, 95% CI 1.00 to 1.56, p = 0.05, I^2=57%), however there were no significant differences between females and males per regions (Figure 3). The risk of stroke was higher in females

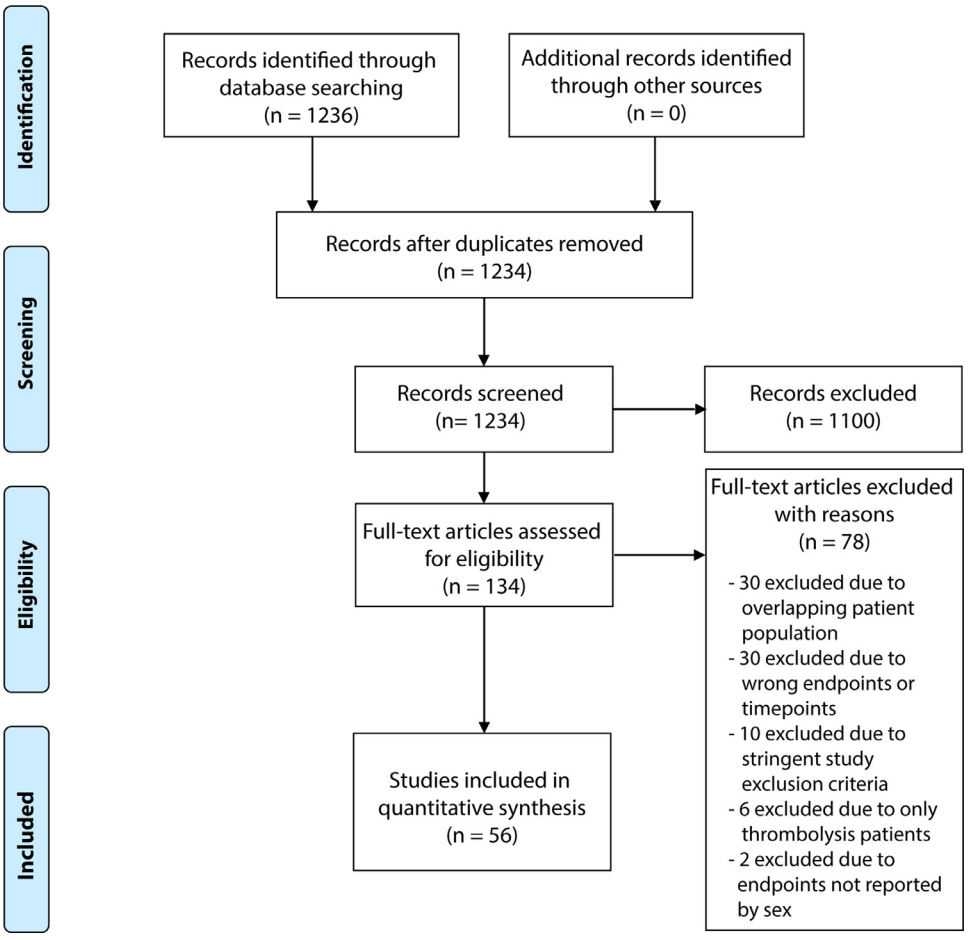

Figure 1. Prisma flow diagram.

Table 1
Baseline demographics and clinical characteristics of global study population

Variable	Women		Men		P-value
	N	% of N	N	% of N	
Mean Age (SD)	187,764	70.2 (3.1)	422,202	61.1 (2.2)	<0.0001
Diabetes mellitus	214,320	27.4	478,751	21.0	<0.0001
Hypertension	200,018	61.1	438,495	50.6	<0.0001
Smoker	164,239	27.2	360,768	44.2	<0.0001
Prior MI	156,869	14.7	339,566	16.2	<0.0001
Prior stroke	137,121	8.1	302,162	7.4	<0.0001
Cardiogenic shock	156,510	6.9	344,128	5.5	<0.0001
Treatment					
Primary PCI	213,296	59.5	478,335	68.2	<0.0001
Aspirin	83,441	89.5	217,489	92.1	<0.0001
P2Y12 inhibitor	73,926	67.6	193,405	75.4	<0.0001
GpIIb/IIIa inhibitor	71,929	22.7	162,396	29.3	<0.0001
Beta Blocker	79,099	75.1	202,210	76.1	<0.0001
ACE inhibitor	55,072	55.6	144,422	59.4	<0.0001

Smoker includes all current and former smokers. Medication usage was up to discharge except for GpIIb/IIIa inhibitors which were used exclusively during PCI.

Abbreviations: ACE=Angiotensin-converting Enzyme; Gp= Glycoprotein; MI= Myocardial Infarction; PCI= Percutaneous Coronary Intervention.

compared with males (N = 60,881; OR 1.67, 95% CI 1.27 to 2.20, p <0.001, I^2=41%) with significant differences disfavoring females in the Middle Est and North America (Figure 4). The rate of major bleeding was higher in females (N = 208,201; OR 1.82, 95% CI 1.56 to 2.12, p <0.00001, I^2=80%) with significantly increased rates in Asia, Europe, mixed region and North America (Figure 5).

The odds ratio by gender (females vs. males) for in-hospital mortality was adjusted at the study level for various individual variables including age, comorbidities, treatments, and delays to care (Supplemental Table 4). When adjusting for age alone, females no longer had a significantly increased mortality rate (adjusted OR 0.934, 95% CI 0.898 to 0.971, p <0.0001). However, to a lesser degree, the mortality risk in females was significantly reduced in the univariate analysis by: smoking (adjusted OR 1.475, 95% CI 1.434 to 1.516), primary PCI (adjusted OR 1.898, 95% CI 1.864 to 1.933), DTB time (adjusted OR 1.795, 95% CI 1.705 to 1.890), time to FMC (adjusted OR 1.796, 95% CI 1.734 to 1.862), and ischemic time (adjusted OR 1.690, 95% CI 1.534 to 1.860) (Supplemental Table 4).

After full adjustment analysis by multiple logistic regression models (including 52,070 patients) using important identified variables: age, diabetes, aspirin use, primary PCI, and DTB time, female gender was no longer a

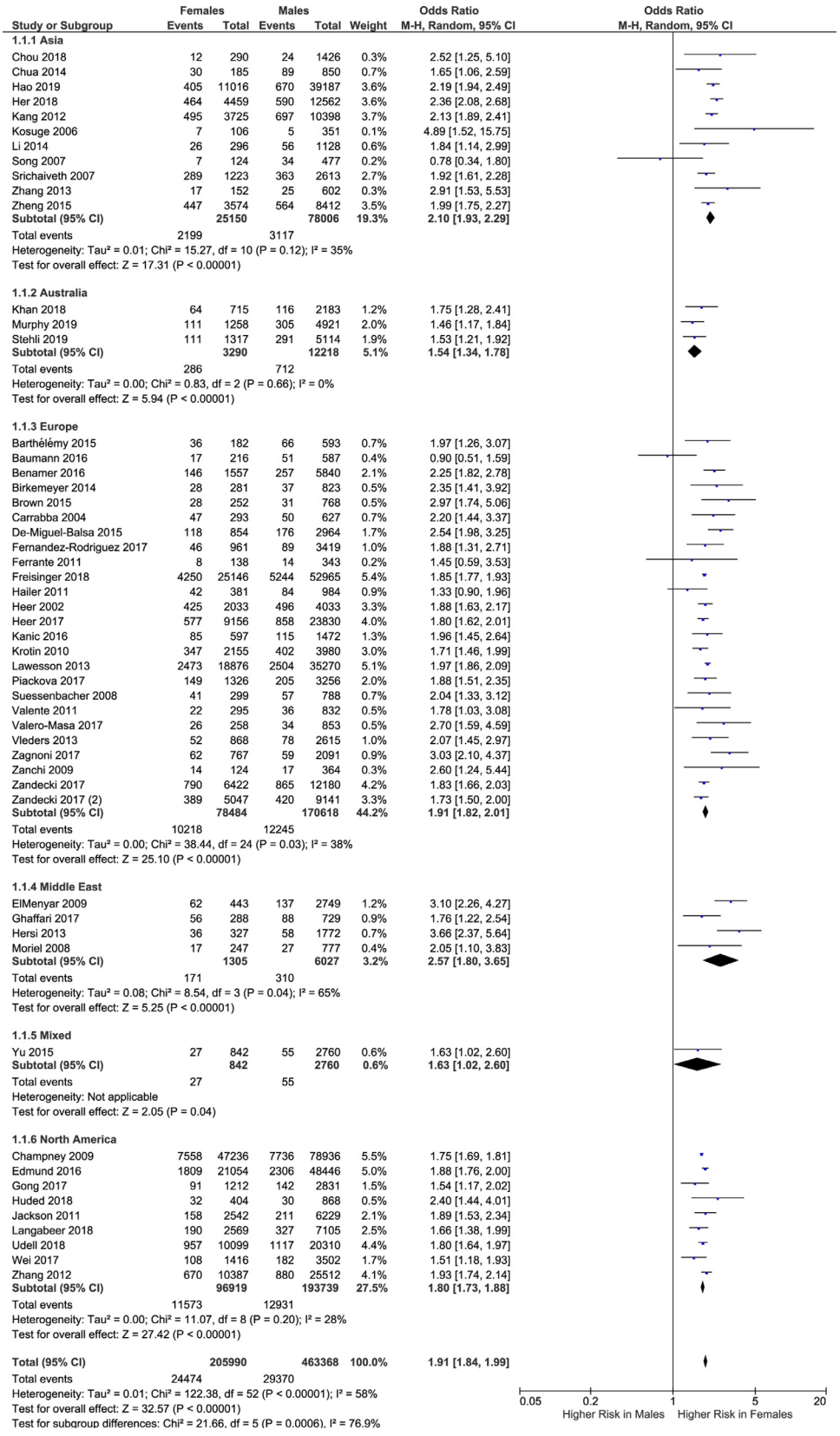

Figure 2. In-hospital mortality in females vs. males. Forest plots of unadjusted odd ratios by gender (odds in females/odds in males) for in-hospital mortality per regions and combined. Statistical pooling was performed using the random effects model with inverse-variance weighting.

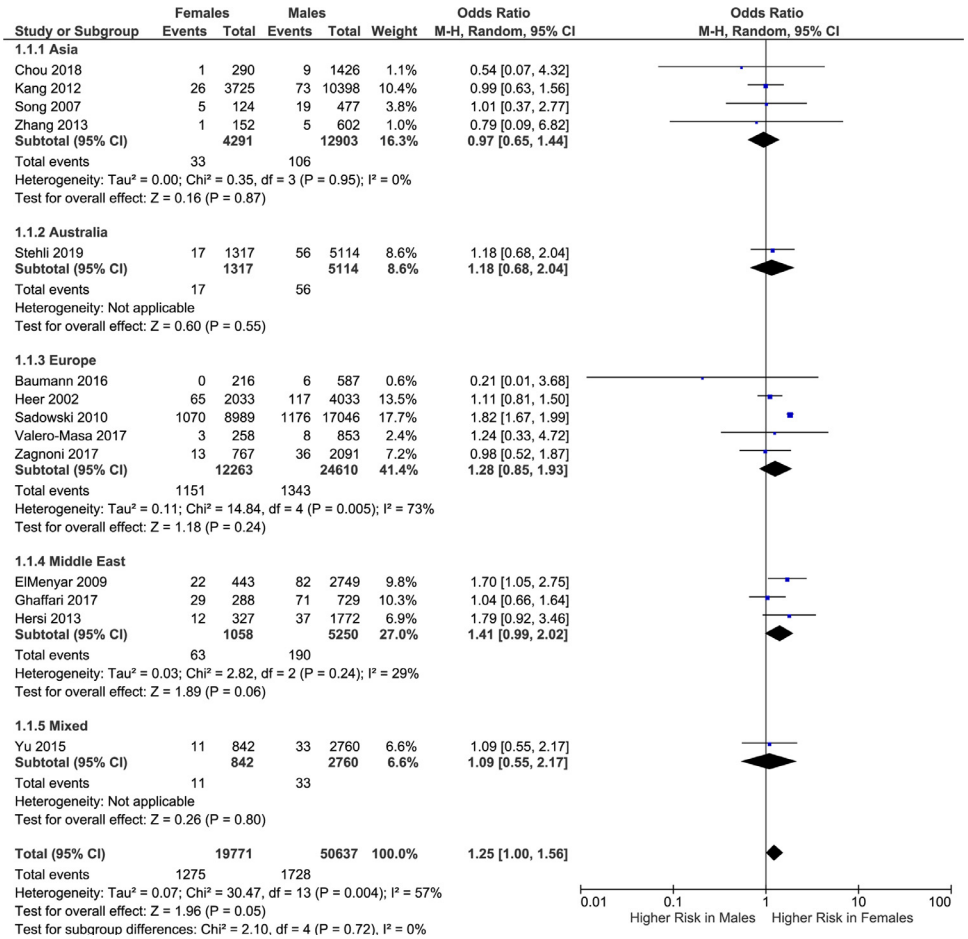

Figure 3. In-hospital repeat MI in females vs. males. Forest plots of unadjusted odd ratios by gender (odds in females/odds in males) for in-hospital repeat MI per regions and combined. Statistical pooling was performed using the random effects model with inverse-variance weighting.

significant predictor of in-hospital mortality (adjusted OR 1.082, 95% CI 0.908 to 1.288, p = 0.378) (Table 2, Model 1). However, even after adjustment, age (OR 1.066, p <0.0001), aspirin use (OR 0.141, p <0.0001), primary PCI (OR 0.334, p <0.0001), and DTB time (OR 1.006, p <0.0001) remained statistically significant, indicating that age, lower aspirin use, lower rate of primary PCI and longer DTB time were all significant predictors of in-hospital mortality. When age was removed from the Model 1 the gender disparity reappeared (adjusted OR for female gender 1.624, 95% 1.480 to 1.782, p <0.0001), but still remained lower compared with unadjusted excess risk (OR 1.992, 95% CI 1.957 to 2.028) (Table 2, Model 2). Age as a significant predictor of in-hospital mortality in females was also observed in a more inclusive multiple regression model analysis including 42 studies (N = 507,641) using age, hypertension and diabetes as covariates. In this model the adjusted OR with age was 0.82, p<0.001, whereas the adjustment without age restored gender disparity to OR 2.10, p <0.001 (Supplemental Table 4, Model 3 and Model 4). Of note, smoking was not included in the full adjustment models despite being a significant predictor in univariate regression analysis because smoking was significantly, negatively correlated with age (Pearson Correlation Coefficient, R = -0.64, p <0.0001 for smoking and age).

Multiple logistic regression analyses for other in-hospital outcomes, repeat MI, stroke and major bleeding were limited, due to fewer number of studies. However, based on these limited analyses the excess risk of repeat MI and stroke experienced by females disappeared after adjusting for age, antiplatelet usage, and/or primary PCI. Adjusted OR for repeat MI was 1.199, 95% CI 0.891 to 1.615, p = 0.231 and primary PCI was still statistically significant after adjustment (OR 0.275, p <0.0001) (Table 2). Adjusted OR for stroke was 0.528, 95% CI 0.311 to 0.897, p = 0.018 and after adjustment, age (OR 1.098, p <0.001) and P2Y12 inhibitor usage (OR 0.040, p <0.0001) remained statistically significant, indicating that age and lower P2Y12 inhibitor usage were significant predictors of in-hospital stroke (Table 2). In contrast, there was no significant change in the excess risk of major bleeding in females after adjustment for age and antiplatelet usage (adjusted OR 1.747, 95% CI 1.556 to 1.962, p <0.0001) (Supplemental Table 5).

Discussion

Our meta-analysis represents the largest and most comprehensive examination of gender-based disparities in STEMI outcomes and possible determinants on a global scale. The global analysis demonstrates that females

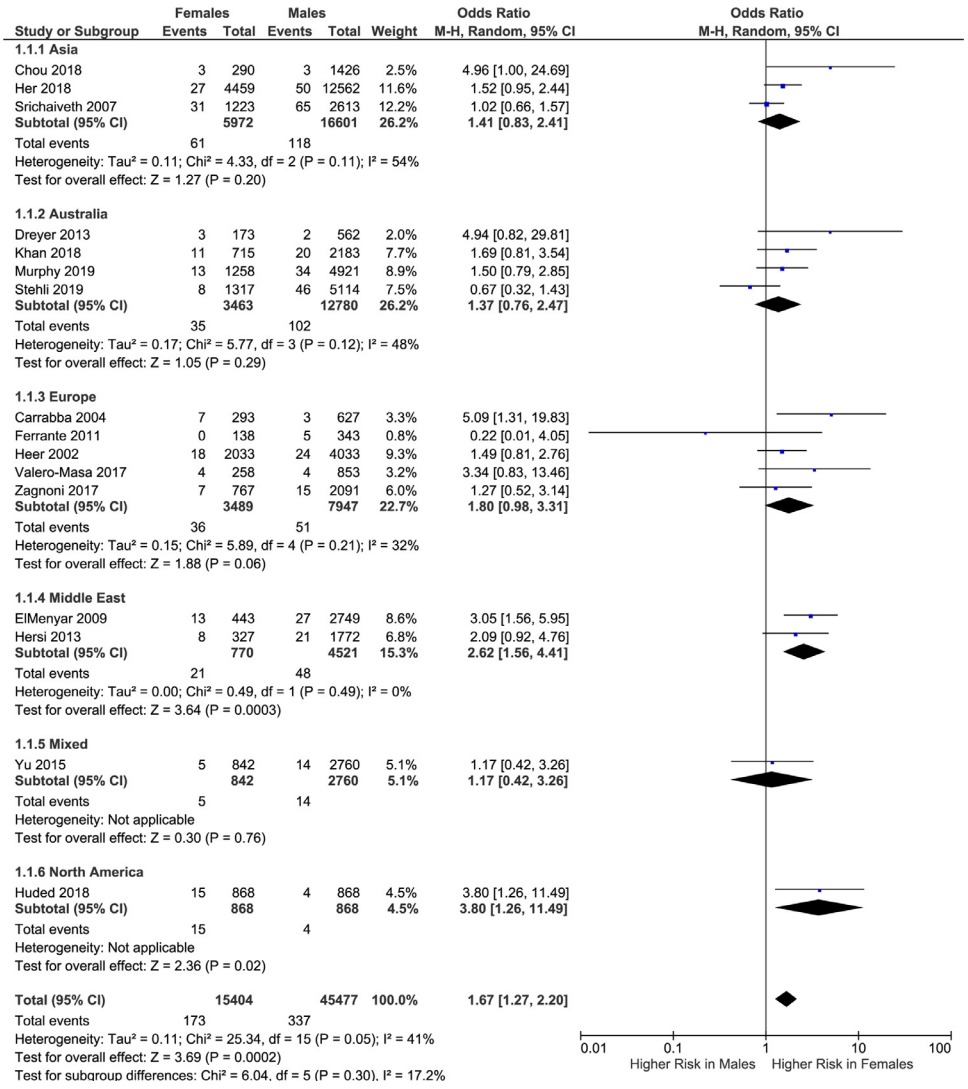

Figure 4. In-hospital stroke in females vs. males. Forest plots of unadjusted odd ratios by gender (odds in females/odds in males) for in-hospital stroke per regions and combined. Statistical pooling was performed using the random effects model with inverse-variance weighting.

consistently have more comorbidities at presentation, receive suboptimal therapy, and have in-hospital rates of mortality, repeat MI, stroke, and major bleeding up to 2-fold higher than males. Overall the global findings were consistent across the regions. Gender-disparities in in-hospital mortality were observed in all regions and did not spare North America or Europe where the systems of care are well-established. Females had higher rates of in-hospital stroke in North America and the Middle East and higher rates of major bleeding in Asia, Europe and North America.

Globally and per region, females experienced significantly longer delays to care than males. There were substantial gender differences in time to FMC and ischemic time (mean delay 42.5 min and 21.3 min, respectively), while the differences in DTB and DTN times were not as noticeable but remained significant (mean delay 4.9 min and 0.9 min, respectively). Per region, delays in DTB time longer than 5 min were reported in Asia, Australia and North America.

The adjustment of mortality rates demonstrated that the delays to care experienced by females may, at least partly, contribute to their excess in-hospital mortality (Table 2), consistent with earlier studies.[18,19] These delays are likely the result of female STEMI patients being more likely to experience atypical symptoms (i.e., back, shoulder, and/or stomach pain rather than chest pain) and males being more likely to believe that their symptoms are cardiac in nature with bystanders more readily encouraging them to call emergency medical services than females who often attribute symptoms to anxiety, even when they have chest pain.[20-22] Given that women tend to be less reluctant to utilize medical services,[23,24] raising the awareness of the public and health professionals regarding STEMI presentation in females may help to reduce delays to care.

Females tend to present with MI five to ten years later than males because estrogen delays the development of cardiovascular disease in premenopausal females.[25] Based on the multiple logistic regression, the most significant contributor to the gender disparity in mortality by far is age (Table 2, Supplemental Table 4). Although other factors including co-morbidities, primary PCI, antiplatelet usage, and delays to care had an impact to a lesser extent. This is

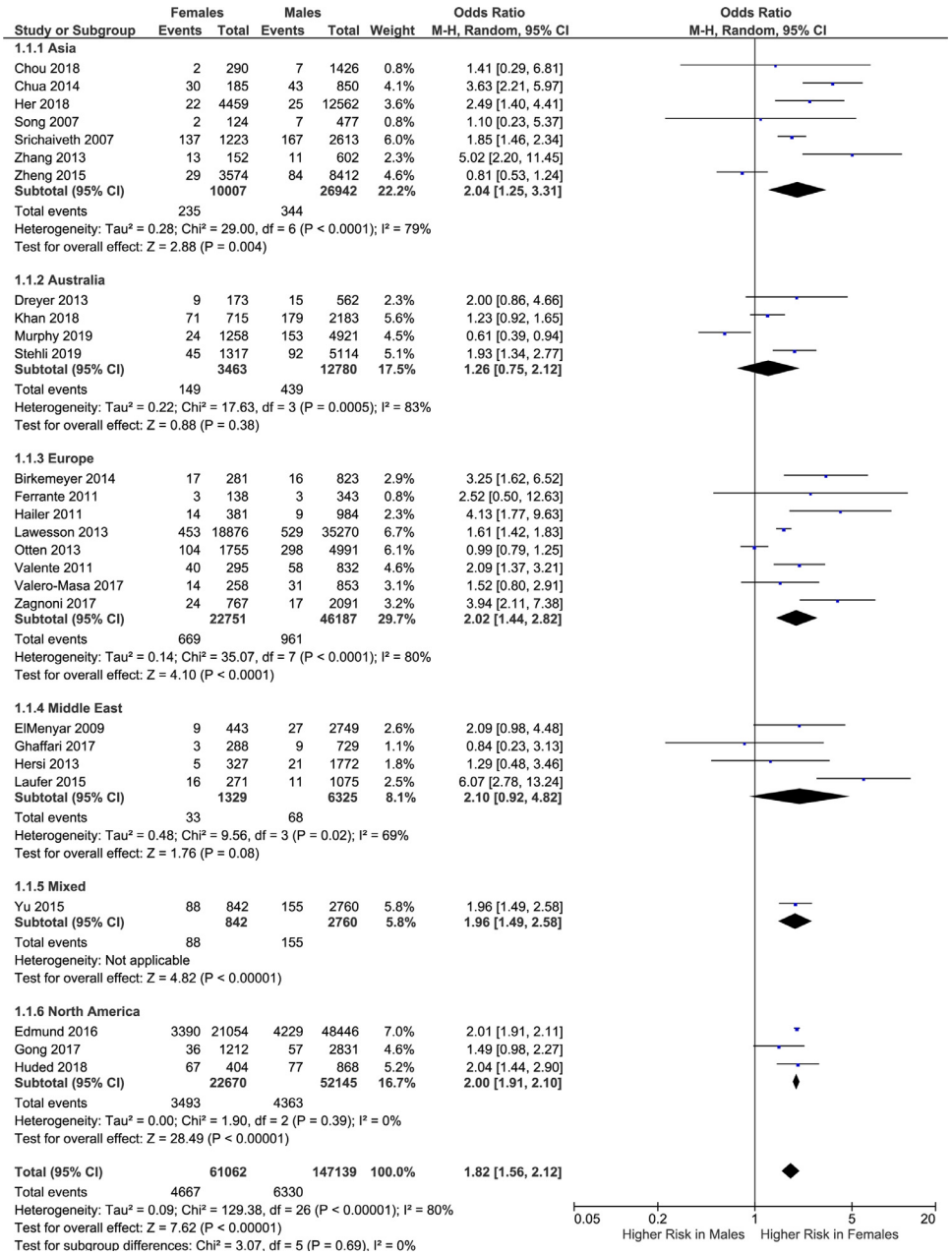

Figure 5. In-hospital major bleeding in females vs. males. Forest plots of unadjusted odd ratios by gender (odds in females/odds in males) for in-hospital major bleeding per regions and combined. Statistical pooling was performed using the random effects model with inverse-variance weighting.

consistent with other studies in which the gender gap in mortality was diminished after adjusting for covariates, particularly age.[12,26-31] The gap in age at presentation might also explain the lack in changes in mortality rates by gender in the past 20 years, despite improvements in STEMI care (Supplemental Figure 2). However, the fact that age is the primary driver of the gender disparity in post-STEMI mortality should not lead to complacency because this is a multifactorial problem and there are many modifiable risk factors that also contribute to the observed gender differences. Recent studies showed that the gender gap persists after adjustment, particularly in younger females (< 60 years);[13-15] but, given the lack of patient-level-data, we were not able to include this subgroup in our study and thus requires further investigation. Moreover, although the multiple regressions for other outcomes were limited by sample size, it appears that female gender is not a significant predictor of repeat MI or stroke after adjustment. Rather, the increased rates of repeat MI and stroke in females compared with males are, at least in part, driven by lower rates of primary PCI and in-hospital P2Y12 inhibitor usage, respectively (Table 2). This emphasizes the fact that the suboptimal in-hospital care sometimes received by female patients may contribute to worse outcomes. Despite adjustment, female gender remained a significant predictor of major bleeding; the reasons are unclear and warrant further investigation.

Table 2
Multiple logistic regressions analyses for in-hospital mortality, repeat MI and stroke

A. In-hospital Mortality (13 studies, N=52,070)				
Model 1 with age included as a covariate				
Variable	Odds Ratio Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
Female Gender*	1.082	0.908	1.288	0.3781
Age (years)	1.066	1.042	1.091	<0.0001
Diabetes mellitus	0.484	0.181	1.290	0.1468
Aspirin use	0.141	0.052	0.383	0.0001
Primary PCI	0.334	0.245	0.454	<0.0001
DTB time (min)	1.006	1.003	1.009	<0.0001
Model 2 without age included as a covariate				
Variable	Odds Ratio Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
Female Gender*	1.624	1.480	1.782	<0.0001
Diabetes mellitus	0.920	0.352	2.402	0.8649
Aspirin use	0.608	0.264	1.401	0.2426
Primary PCI	0.200	0.155	0.256	<0.0001
DTB time (min)	1.001	0.999	1.003	0.2638
**unadjusted OR 1.992, 95% CI 1.957-2.028, p<0.0001*				
B. In-hospital Repeat MI (9 studies, N=26,947)				
Variable	Odds Ratio Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
Female Gender*	1.199	0.891	1.615	0.2311
Age	0.991	0.962	1.021	0.5559
Aspirin use	0.051	<0.001	14.483	0.3012
Primary PCI	0.275	0.210	0.359	<0.0001
**unadjusted OR 1.951, 95% CI 1.811-2.102, p<0.0001*				
C. In-hospital Stroke (8 studies, N=27,536)				
Variable	Odds Ratio Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
Female Gender*	0.528	0.311	0.897	0.0182
Age	1.098	1.043	1.155	0.0003
P2Y12 inhibitor use	0.040	0.019	0.083	<0.0001
**unadjusted OR 1.521, 95% CI 1.265-1.829, p<0.0001*				

Abbreviations: CI= Confidence Interval; DTB= Door-to-Balloon; PCI= Percutaneous Coronary Intervention.

Smoking appeared to be associated with lower mortality risk in univariate analysis (Supplemental Table 4). This is most likely because smokers present with STEMI five to ten years earlier than their nonsmoking counterparts.[32-34] Indeed, in our analysis smoking status was negatively correlated with age (the main contributor to mortality in our analysis).

This global meta-analysis is intended to be comprehensive and systematic, but inherently has several unavoidable limitations. This study is a retrospective analysis of heterogenous studies, across geographical regions and therefore differences in healthcare systems, patient demographics, clinical characteristics, choice of therapy, among others were unavoidable. An important limitation is the unavailability of individual patient-level data; which limited the accuracy of adjustments and made analyses examining the impact of age and comorbodities on gender differences in management unfeasible. In addition, the differences in treatment may in part be related to differences in indications or contraindications that cannot be accounted for in our meta-analysis and it is a limitation of the study. High heterogeneity among studies reporting major bleeding was a limitation. Furthermore, this study, which only incorporates data from regions and hospitals with sufficient resources to maintain registries is representative of a best-case scenario and does not adequately capture many of the challenges women might face to access medical care including variations in threshold for seeking medical attention, insufficient management of modifiable risk factors, region-specific transportation, and financial, social, and cultural impediments to care.[35,36] Still, the trend for each endpoint across regions is consistent and the multiple regression models reveal the covariates that explain the variation in clinical outcomes, reinforcing the validity of the results.

In conclusion, this global meta-analysis demonstrates that despite improvements in STEMI care, women have rates of in-hospital mortality, stroke, repeat MI, and major bleeding up to 2-fold higher than men. Gender disparities in in-hospital outcomes can largely be explained by differences in age, but patient comorbidities, delays to care and suboptimal treatment also contribute and are areas in need for improvement at the global level.

Disclosures

The authors have no conflicts of interest to disclose.

Credit Author Statement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.015.

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