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Sex Disparities In St-Elevation Myocardial Infarction Care And Outcomes: A Global Systematic Metaanalysis

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Sex Disparities in ST-Elevation Myocardial Infarction Care and Outcomes:

A Global Systematic MetaAnalysis

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Abstract

Background: Cardiovascular disease is the leading cause of death worldwide. Outcomes of patients with ST-segment–elevation myocardial infarction (STEMI) have improved through widespread implementation of systems-of-care, yet sex disparities continue to be reported. A comprehensive, *global* study of sex disparities in contemporary STEMI care and outcomes has not been undertaken.

Objective: To examine whether sex differences in STEMI management and mortality outcomes persist worldwide and by geographic region.

Methods: A systematic PubMed literature search was performed using search terms "sex" or "gender" and "STEMI" for studies in English from 2000 to present reporting sex-based STEMI mortality. Articles with primary data on sex-based STEMI mortality were included. Data collected prior to 2000, sub-categorized data, and studies with less than 50 women were excluded. Meta-analyses were conducted using random effects models and are reported overall and by geographic region. Heterogeneity was assessed via Cochran's Q statistic. Sex differences were evaluated in baseline characteristics, door-to-balloon times, and mortality (in-hospital, 30-day, 6 months, and 1 year).

Main Outcome and Measure: The primary outcome is in-hospital to 12-month mortality. Secondary outcome is Door-to-Balloon/Door-to-Reperfusion time.

Results: 613 published manuscripts were reviewed and ultimately 75 studies included in the meta-analysis, representing 29 countries in 6 geographic regions and 731,990 patients (32% female). Women were older and had more diabetes and hypertension. Overall, unadjusted in-hospital mortality was 2-fold higher in women compared to men (2.09 OR, 95%CI 1.91-2.08; $p<0.0001$), with excess mortality in all regions and time-points.

Adjusting for age alone did not alter the mortality discrepancy. After adjustment for hypertension and diabetes the difference in sex-based mortality was no longer significant. Additionally, reperfusion therapy was less common in women, door-to-reperfusion time was longer in all countries with a mean delay of 5.3 minutes (p<0.0001).

Conclusions: This study demonstrates concerning global sex disparities in risk factors, time to treatment, STEMI care and a doubling of unadjusted mortality in women. Adjustments for comorbidities suggest that modifiable risk factors, rather than difference in reperfusion therapy, account primarily for the difference in mortality. This highlights the need for a global call-to-action to elucidate critical factors and barriers to preventive care to reduce the observed sex gap in STEMI outcomes worldwide.

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Table of Contents

Introduction

Background

Acute myocardial infarction (AMI) is the leading cause of death worldwide[1-3]. Although historically perceived as predominantly an ailment of men, it is the principal cause of death for women, both in the United States and globally[1,4]. ST-segment Elevation Myocardial Infarction (STEMI), its deadliest form[5,6], requires emergent reperfusion and revascularization with primary percutaneous coronary intervention (PPCI) to reduce the high rates of morbidity and mortality[7-9]. "Time is myocardium", the old cardiology maxim goes, asserting that successful intervention is dependent on minimizing time of ischemia. That is, the time from symptom onset to the restoration of coronary blood flow. Current guidelines have set this optimal golden window, now known as door-to-balloon (D2B) time, at less than 90 minutes[10-12].

Over the past decade, organizations such as Mission Lifeline[13-15] (2007, American Heart Association) and Stent-for-Life[16,17] (2009, European Society of Cardiology) were established to meet these goals on a national and international level. These initiatives not only tackled the root causes behind system-barriers to timely reperfusion, but also revolutionized the approach to STEMI care in the U.S. and Europe. This involved implementing essential core measures, generating robust national data registries, instituting standardized protocols to decrease reperfusion times, and establishing efficient and reliable networks of care[10,11,18-20].

These US and EU based initiatives have resulted in dramatic improvements in STEMI mortality rates[21-23], but at the same time accentuated the gap in STEMI mortality in

other regions of the world – many of which face an increasing AMI burden[20,24]. It also revealed previously under-recognized discrepancies in treatment times associated with sex, age, race, and socioeconomic status[25-28]. Underprivileged and traditionally marginalized social groups, including women, combined with insufficient regional resources and infrastructure, historically has lead to a pervasive sex gap in STEMI care and outcomes. Whether this sex gap persists with the current widespread adoption of systems of care, remains unknown.

Epidemiology

For decades, coronary heart disease (CHD) has been a leading cause of morbidity and mortality for women worldwide. Moreover, since the 1980's, the annual mortality rate of AMI in the US has been higher for women than for men. Today, despite a decade of considerable improvement in systems of care and reduction in mortality rates in developed countries, AMI remains the number one killer of women both in the US, and globally[1]. Furthermore, the lifetime risk for CHD at age 70 in American women is a staggering 1 in 3, fivefold higher than the infamous 1 in 8 statistic often cited for breast cancer[29]. Annually, 6.6 million women in the US suffer from CHD. Of these, 2.7 million had an AMI, over 50,000 died as a result of their MI, and approximately 262,000 were admitted for ACS (AMI and unstable angina)[1]. These statistics are, of course, much worse in lower-income countries[20,24].

Still, despite mounting evidence throughout the years, the risk of cardiovascular disease (CVD) in general, and CHD in particular, is frequently underestimated in women. It has been suggested that at the core of this misperception is an anachronistic fallacy that females, particularly at younger ages, are 'protected' from CVD, and as an extension CHD. Debunking this misconception, are ample data, most recently from the National Health and

Nutrition Examination Surveys that demonstrate that over the past two decades the prevalence of myocardial infarctions has increased in premenopausal women of ages 34-54 years[30-32].

Globally, similar trends are slowly starting to emerge[33]. Research from various developing regions of the world shows higher comorbidity burden (mainly, DM and hypertension) in women as compared to men, as well as an accompanying higher CHD and STEMI mortality rates[20,24]. This is seen in research from South Asia (e.g., India, Pakistan, Sri Lanka)[34,35], China[36] and Taiwan[37], the Middle East (e.g., Bahrain, Kuwait, Qatar and Yemen)[38], and Latin America (e.g., Brazil and Mexico)[39].

A Question of Representation
As already established, CVD and CHD are equal opportunity killers. Nevertheless, when it comes to cardiovascular research, particularly clinical trials, women have historically been, and continue to be, underrepresented[40-42]. Perhaps the most absurd example is that of the Coronary Drug Project[43]. This first large clinical trial, launched by the National Heart, Lung, and Blood Institute, included a randomized controlled trial that, in light of Framingham data demonstrating a 10-year lag in female cardiovascular mortality relative to men[44], evaluated the effects of estrogen for the secondary prevention of CHD exclusively in men post-myocardial infarction. Suffice it to say that, although the study was stopped early due to higher mortality in the treatment arm, the administration of supplemental estrogen to postmenopausal women continued for years, solely based on observational data in women[45,46]. No words describe this historical folly more aptly than the words of cardiologist Dr. Wenger of Emory: "For many years, the medical community has viewed women's health with a bikini approach, focusing essentially on the breast and

reproductive system. The rest of the woman was virtually ignored in considerations of women's health"[47].

Surely such grave historical imbalances have been sufficiently addressed, one might conclude. Unfortunately, the historical, routine underrepresentation of women in cardiovascular clinical trials and registries is alive and well. Two relatively recent and major studies from the Institute of Medicine[48,49] and one from the European Heart Health Strategy[50], emphasize that although significant strides have been made in medical care and outcomes of women with CHD, aside from reproductive care, medical research had mostly neglected women's health needs. Female subjects rarely represent more than 20-30% of subjects in clinical trials and ~40% of most patient registries[41,42,51]. As a result, an accurate epidemiologic snapshot of regional and global data on CHD and their dissection by geographic region, clinicopathologic subtype, temporal trends, and especially biosocial parameters (e.g., sex and gender) remains lacking and inaccurate[52]. This is further bolstered by that fact that robust population-based studies do not exist in large swaths of the developing world, where registries and clinical trials are much less common in the first place.

Consequently, significant knowledge gaps undermine our ability to accurately assess whether our treatment and prevention efforts have culminated in significant local and global changes in the incidence and prevalence of CHD in women. A testament to this challenge is the discrepancy between studies suggesting a temporal stagnation or increase in MI incidence (e.g., Framingham Heart Study and ARIC), and those suggesting a temporal decrease (e.g., Minnesota Heart Survey and Rochester Epidemiology Project)[52].

Despite this gloomy backdrop, the progress that has been made by research focused on women's health and CHD over the past decade has improved our understanding of the unique female pathophysiology, sex differences in clinical presentation, and contribution of biopsychosocial factors.

Biosocial Trends: The Influence of Age and Race

First presentation of MI in women, particularly STEMI, occurs at an older average age of 71.8 years as compared to 65 years of age in men[31]. This "delay" is hypothesized to be the result of the protective effect of estrogen on the vascular endothelium[53]. In the last decade, the annual death rate for both men and women older than 65 years of age has fallen dramatically, partially reflecting the large reduction in STEMI incidence and mortality[54].

CHD in young women (under age 55) is rare. Annually, in the United States, ~30,000 women under the age of 55 are admitted for AMI[55]. However, compared to men less than 65 years of age, current data indicates that women of the same age group have almost 2-fold higher readmission rates after STEMI[56]. While CHD death rates fell dramatically among all US women between 2001-2010, when stratifying by age for the 35-54 year old group, this decline is absent or in some cases turns to an increase[57]. Additionally, there exist concerning evidence that young women in the US have a higher risk of death after AMI, even when adjusting for other parameters[58,59]. To date, STEMI-specific data on mortality in young women is deficient.

Moreover, stratification of American women with AMI by race and ethnicity, unveils substantial differences in prevalence, presentation, medical care, and outcome. First, black

women have the highest MI prevalence compared to all other ethnic and racial women groups[1,60]. Additionally, over one third of Indian American women have three or more cardiac risk factors, and their AMI rates are now 2-fold higher than the general US population[61]. At time of presentation, black and Hispanic women have more comorbidities (DM, HTN, physical inactivity, higher lipid levels, and obesity) compared to white women, which is thought to partially explain their higher AMI rates and inferior long-term outcomes[62,63]. The same trend exists also in black women younger than 55, who suffer from higher AMI mortality rates than white women in the same age group, even after adjusting for socioeconomic parameters such as access to medical insurance[62,63].

Finally, although women of all ethnicities are less likely to be referred to PCI and CABG compared to men, black women are at the bottom of the totem pole when measuring referrals to PCI and coronary angiography, even after controlling for baseline differences [64].

Pathophysiology Through the Gender Lens

The overwhelming majority of AMI cases, in both men and women, begin with an obstructive atherosclerotic disease in an epicardial vessel, generally followed by superimposed thrombosis. STEMI, its most dreadful form, is most often precipitated by the disruption of a previously stable atherosclerotic plaque in an already narrowed coronary vessel. Such a disruption exposes the vascular endothelium with its underlying thrombogenic milieu, which in turn promotes platelet aggregation, activation of the coagulation cascade, and ultimately thrombus formation[65]. The final result is an abrupt and persistent occlusion of the affected vessel, culminating in a complete cessation of blood flow to the associated myocardium. It has long been established that the duration of vessel occlusion (ischemic time) is directly proportional to infarct size, a phenomenon

characterized as "a wave front of necrosis" [66], which is in turn associated with poorer clinical outcomes[12,67].

Current evidence supports sex-based differences in the pathophysiological mechanisms underlying the aforementioned events[68,69]. These indicate that women have different plaque characteristics, pathogenicity, burden, and distribution, as well as an increased incidence of the more rare syndromes giving rise to STEMI such as coronary artery spasm (CAS)[70] and spontaneous coronary artery dissection (SCAD)[71,72]. Of note, this pathophysiological variability is accentuated in young women, as was recently demonstrated by the VIRGO trial, where 1 out of 8 women with AMI did not fit current classification schemes[58]. Still, gender differences in the pathophysiology and progression of CHD (mainly atherosclerosis) remain elusive, and require additional research before they can be translated into clinical practice.

Hormone-Vessel Interplay
As previously discussed, on average CHD develops ~7 years later in women than in men. This time lag in female morbidity and mortality was first demonstrated in the Framingham Population[44], and was punctuated by the age of menopause, hinting at the atheroprotective effects of endogenous estrogen[53]. Strengthening this hypothesis further are evidence from the Women's Ischemia Syndrome Evaluation (WISE) study, showing that young women with endogenous estrogen deficiency have a sevenfold increased risk for coronary artery disease[71].

Although the exact mechanisms are not completely elucidated, estrogen was demonstrated to inhibit smooth muscle proliferation[73], and to increase nitric oxide levels leading to vasodilation[74,75]. Decline in the levels of estrogen at menopause was shown to

promote endothelial dysfunction and vascular lipid deposition, both of which serve as a preamble to AMI[76,77]. Interestingly, exogenous estrogen supplementation in postmenopausal women did not exhibit any efficacy in halting the progression of atherosclerosis or in preventing CHD. Rather, it may precipitate acute cardiovascular events in postmenopausal women[45,78]. Consequently, systemic estrogen supplementation is not recommended for either the primary or secondary prevention of CHD.

Plaque Rupture vs. Plaque Erosion
Plaque rupture/disruption is the culprit event in 76% of men and 55% of women with lethal MI[79]. It occurs when the thin fibrous cap encasing a lipid-rich, centrally necrotic atherosclerotic plaque is disrupted. This newly exposed plaque is subsequently infiltrated by macrophages, matrix metalloproteases, and lymphocytes, whose digestive actions expose an otherwise concealed tissue factor to the blood stream[80]. This interaction leads to the activation of the coagulation cascade, and quickly culminates in the formation of an obstructive thrombus.

Evidence suggests that although plaque rupture is responsible for the lion share of MIs in men, plaque erosion is quite common in women, particularly of young age[68], with some studies suggesting it accounts for 27% of patients with STEMI and 31% of NSTEMI[81]. In fact, the only two risk factors predicting the type of coronary vessel occlusion are female sex and premenopausal status. This is of particular interest since MI with non-occlusive CAD is also more prevalent in young women[82,83].

Erosions are characterized by denuded endothelium covering a plaque composed of copious proteoglycans and larger proportions of proliferating smooth muscle cells than inflammatory cells. Studies suggest that activated macrophages close to the endothelium

are responsible for endothelial apoptosis and disruption by proteases[65]. Coronary vessel obstruction and AMI develop when thrombi form on the surface of plaque erosions, where the dysfunctional endothelium is unable to keep the coagulation cascade in check. Microthrombi can then embolize, a phenomenon more commonly associated with plaque erosion than with plaque rupture, causing downstream vessel occlusion and tissue infarction[84,85].

The clinical significance of the differences between rupture and erosion has yet to be fully explored. The gold standard imaging modality that allows for plaque characterization is optical coherence tomography (OCT), which is rarely performed due to limited availability and unknown clinical utility. Still, some studies suggest the possibility that optimal treatment may differ based on plaque type. Namely, replacing the stent, the successful workhorse in treatment of plaque rupture, with aspiration thrombectomy and transcatheter thrombolysis for plaque erosion. Thus far, minimal data supports this hypothesis[86]. Finally, the interplay between plaque type and common comorbidities such as hypertension, DM, hypercholesterolemia, and smoking has proven inconclusive[87,88].

Coronary Artery Spasm
Although considered a rare mechanism of MI, CAS is known to be associated with stable angina and transient ST–segment elevations on ECG[70,89]. Common triggers include sudden changes in autonomic activity and tone[90], use of ephedrines[91] and other drugs[92], and cigarette smoke[93]. Although data on sex differences in CAS is limited, one study showed that, compared to men, women with CAS were older, smoked less, and had less coronary vessel obstruction[94].

Spontaneous Coronary Artery Dissection

SCAD is an exceedingly rare cause of AMI, with a reported prevalence ranging from 0.2% to 4%[95-97] of patients undergoing cardiac catheterization. Its clinical presentation and EKG findings often mimic STEMI. Similar to other less common etiologies of MI, its incidence is higher in women, and clinical suspicion should be particularly high in young females presenting with ACS in the absence of typical risk factors[98]. Although the accurate prevalence of SCAD is unknown, reports suggest that it is identified in 10.8% of women <50 years of age who present with ACS[97]. It is also associated with oral contraceptive use, pregnancy and postpartum status, connective tissue disorders (e.g., Ehlers-Danlos syndrome), and vasculitides (e.g., fibromuscular dysplasia)[99].

Diagnosis with Gender in Mind

Symptomology and Clinical Presentation

It is well established that apart from the classical AMI presentation of crushing chest pain and pressure typical of both sexes, women often have an atypical presentation with less severe pain and more symptoms[100]. Namely, they present with atypical chest pain patterns (e.g., burning and reproducible pain), indigestion, nausea/vomiting, dyspnea, fatigue, flu-like symptoms and generalized anxiety[101-108]. In STEMI, both men and women tend to have symptoms of chest pain. However, in women, especially at younger ages, these symptoms are often accompanied by a vaso-vegetative state that tends to attenuate or even mask the pain, as well as lead to less conspicuous ST-T elevations[109-111].

Additionally, one qualitative study found that young women reported experiencing subtle symptoms that would wax and wane over months prior to MI[112]. Yet, the fear of being characterized as anxious precluded them from communicating their worries that

such symptoms could represent CHD[113]. Interestingly, symptoms of ACS (especially classic) are an independent MI predictor in women, even with healthy appearing coronaries[69,114]. For example, referred shoulder pain, when present, is 2-fold more likely to predict ACS in women than in men[115].

For women to act on atypical CHD and MI symptoms they must be aware of their significance, quality, and urgency. Tragically, a national survey of 1000 women conducted in 2000, meant to assess knowledge, awareness, and perception of heart disease, discovered a profound lack of awareness of gender-specific MI warning signals[116]. Whereas 67% of the women could recognize "classic" signals of MI (e.g., chest pain and tightness, arm pain), only 10% had knowledge of the symptoms common in women (e.g., nausea, indigestion, fatigue). Worse, 7% of the women could not provide any answer. The survey also uncovered an even more worrisome statistic: only 18% of women learned about MI symptoms from their own physician (18%), and although 90% reported feeling comfortable discussing CHD prevention with their provider, 70% never did.

These sex-based differences in presentation and awareness contribute to missed or delayed diagnoses, decreased rates of timely reperfusion, and subsequent worse outcomes in women in general, and young women in particular[117,118].

Diagnostic Armamentarium
The seemingly favorable pathologic profile in women of all ages—less obstructive CAD (particularly triple vessel and left main disease)—results in a decreased diagnostic accuracy, namely an increased false-positive rate with most diagnostic tests. In addition, the lesser extent of obstructive disease on angiography combined with similar or worse

prognosis than men renders noninvasive diagnostic methods the fulcrum of CHD and AMI workup in women.

Over the past two decades, the use of myocardial revascularization procedures for the treatment of diagnosed AMI, particularly STEMI, in developed countries has finally become standardized, and essentially gender neutral[119-121]. As previously discussed, in women the proper implementation of such therapeutic interventions relies heavily on the accuracy of noninvasive tests. When such tests are abnormal, women are now more likely to be referred to PCI than ever before[119,122]. Yet, the underrepresentation of women in studies of noninvasive testing prevents an optimal evidence-based approach to clinical decision-making[123,124]. These data suggest that a gender-based recalibration of common noninvasive tests is essential.

Electrocardiogram
Current evidence suggests that the most cost-effective diagnostic approach to the evaluation of chest pain in women is sequential testing[119,125]. For both practical and clinical reasons electrocardiogram (ECG) is often the first step. In the National Hospital Ambulatory Medical Care Survey, conducted by the CDC, younger women (<55 years) presenting to the emergency room with chest pain were less likely to undergo ECG than younger white men[126]. This trend was not detected for older patients. Guidelines issued by the American College of Cardiology (ACC) require that, independent of gender or age, all ED comers with chest pain should undergo a rapid electrocardiographic evaluation to rule out AMI. Extra attention should be given to young women, whose ST-T changes tend to be less obvious[111].

Biochemical Markers

The use of cardiac troponin assays has become a part and parcel of the universal definition of AMI, with an increase above the upper reference limit being diagnostic of MI in patients with signs and symptoms of myocardial ischemia[127]. The universal definition set the upper reference limit as the 99th percentile of a normal reference population, consisting mostly of male subjects. In recent years, both the accuracy of common troponin assays and the reference limit were shown to be suboptimal[128].

Recently, new high-sensitivity troponin assays have shown promise not only in improving the diagnosis of myocardial infarction[129] and leading to reductions in post-MI deaths[130,131], but also in uncovering important sex differences, with the upper reference limit being two-fold higher in men than in women[132]. Recent studies demonstrated that the use of high sensitivity troponin assay in conjunction with sex-specific diagnostic thresholds doubled the diagnosis of MI in women (13% to 23% and 11% to 22%), with a negligible effect in men (23% to 24% and 19% to 21%)[130,133]. These data may prove particularly important not only for the traditional exclusion of NSTEMI, but also for young women or diabetic women with STEMI, whose ECG can be deceivingly normal despite imminent catastrophe.

Stress/Exercise Testing

Ideally, stress testing should not have any role in the diagnosis of STEMI. However, its use or misuse has serious implications on prevention, risk stratification, resolution, and treatment.

Exercise ECG is less sensitive in women due to the lower prevalence of atherosclerotic obstruction. Moreover, many women do not have the exercise capacity to

attain the necessary intensity that maximizes diagnostic value. Consequently, the sensitivity and specificity of exercise ECG in women are 61% and 70% respectively, as compared to 68% and 77% in men[134]. Furthermore, the rate of false positive ST-segment changes in women has been quoted anywhere from 5- to 20-fold higher compared with men. To improve the accuracy of exercise testing in women, the ACC Task Force on Exercise Testing recommends myocardial perfusion imaging or stress echocardiography as better initial choices[135]. The accuracy of exercise myocardial perfusion imaging for the diagnosis of CHD does not differ between women and men, with a sensitivity and specificity >80% and >70%, respectively[134]. Exercise echocardiography was shown to outperform both exercise ECG and exercise radionuclide scans in identifying CHD in women[135], with the major limitation being the ability to capture adequate sonographic windows. Compared with exercise ECG, stress echocardiography has shown superior average sensitivity (84%) and specificity (76%)[119,136,137].

Management of ST-Elevation Myocardial Infarction

At the core of the successful revolution in STEMI care and outcomes that has swept across most of the developed world over the past two decades is the translation of clinical and basic research into guidelines, and their implementation and optimization in the form of STEMI systems of care. That is, the design of a streamlined algorithm with assembly line efficiency that hinges on several key principles: patient education (e.g., quick symptom recognition and early contact with emergency medical services [EMS]); synchronization of destination and treatment protocols for EMS personnel (e.g., merging the fastest route philosophy with choosing the most capable hospital); effective protocols in emergency departments to minimize door-to-reperfusion times (e.g., rapid assessment and activation

of the cath lab); and finally prompt deployment of the most suitable reperfusion strategy (e.g., D2B < 90min or thrombolysis < 30min) by a capable team[9,10,14,138]. These are also collectively known as the STEMI chain of survival.

The next breakthrough in STEMI care, both in developed countries and most certainly in lower-income countries, will most likely result from further implementation and optimization of the assembly line to shorten total ischemic time (i.e., Time to Treatment), and tailoring reperfusion strategies to specific patient populations[139-141]. As in the realms of epidemiology, pathophysiology, and diagnosis, previously discussed, sex differences also exist in the management of STEMI. These manifest both in metrics evaluating the efficiency of the chain of survival, as well as in clinical response to the different reperfusion strategies.

Time-to-Treatment
Given the importance of time to reperfusion[67], the medical community has set benchmarks for STEMI systems of care[10]. These include limiting ischemic time < 120 minutes, and maintaining are a door-to-needle (i.e., fibrinolysis) time <= 30 minutes and a D2B time (i.e., PPCI) of <= 90 minutes[10,18,142].

Delay in seeking medical attention after the onset of STEMI symptom is a problem afflicting both men and women. Many studies have found that the median delay time in seeking care ranges from 2 to 5 hours[143], with an overall range of up to 53.7 hours[144,145]. Although some data indicates that upon recognition of cardiovascular symptoms women tend to call 9-1-1 more often than men[146], multiple studies have found that women with AMI tend to present to medical care later than men[143,147,148]. One study found that while the median symptom-to-presentation time was 15.6 hours for men, it was 53.7 hours in

women[149] (both significantly exceeding guidelines of total ischemic time <120 min). Most recently, the VIRGO trial showed that compared to young man, young women who were diagnosed with STEMI and received reperfusion therapy, were more likely to present >6 hours after symptom onset (35% versus 23%; *P*=0.002)[26].

Many factors were found to be associated with delay in seeking treatment for STEMI symptoms. These include barriers to self-care, inadequate understanding of health risk, and incorrect attribution of symptoms[113,150]. In the US, older age, being black or Hispanic, lack of education, and lower socioeconomic status were also associated with delays in seeking medical attention[143]. Lastly, having a history of specific comorbidities (e.g., DM, hypertension and dyslipidemia), living alone, confiding in a family member instead of a physician, and fear and feelings of shame were all associated with delays in pursuing treatment options after the onset of symptom[143].

Although data from various regions of the world, particularly lower-income countries, is often lacking, it stands to reason that in addition to region specific obstacles for women[24] (e.g., cultural and societal differences, poor infrastructure, or patriarchal family dynamics), the factors described above paly a large role in perpetuating this delay in women[4].

Thrombolysis

Thrombolytic agents, most commonly tissue plasminogen activator (t-PA) and its synthetic variants, work by dissolving occlusive thrombi, thus recanalizing culprit vessels, restoring coronary blood flow, and minimizing infarct size[65]. In STEMI patients, timely intravenous fibrinolysis (door-to-needle <30 minutes) improves survival over both the short and long term[10,151,152], an effect that is independent of sex[153]. The most dramatic

mortality benefits are seen when fibrinolysis is initiated <120 minutes after symptom onset[154]. Consequently, the ACC/AHA STEMI guidelines recommend thrombolytic therapy for both men and women with no contraindications, who cannot be transported to PCI-capable hospitals or have an anticipated delay in symptom-to-PCI time of >120 minutes[155].

Compared to men, women who receive thrombolytic therapy have higher morbidity and mortality rates[59,109,143,156]. These may be related to higher rates of reinfarction, shock, heart failure, stroke, and bleeding[156-158]. The elevated risk of reinfarction was reduced in women when enoxaparin was used in conjunction with thrombolytics, however at the unintended cost of increased bleeding risk[159]. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial found that while 90-minute vessel patency rates and global ejection fraction results were similar for men and women, the thrombolysis-associated bleeding risk was 1.43-fold higher in women[160].

Reported mortality benefits of thrombolysis vary considerably, based on the patient population and the use of adjunctive therapies. For example, in women, who tend to present with STEMI at significantly older ages, the effect of age on successful thrombolysis is amplified. Data shows that older patients with STEMI have the following barriers to timely administration of thrombolytic therapy: prolonged delay in seeking medical care, lower incidence of classic ischemic symptoms and higher incidence of atypical symptoms, more comorbidities, presence of relative contraindications, and non-diagnostic ECGs[65,161].

The risks and complications associated with thrombolysis together with data on the superiority and widespread implementation of PCI have significantly decreased the use of fibrinolysis in the majority of developed nations. Nevertheless, in many regions of the

developing world, where barriers such as infrastructure, funding, and training prevent the establishment of an efficient PCI-capable system, thrombolysis continue to be mainstay therapy. In these regions, understanding the interplay between thrombolysis and sex remains relevant.

Primary Percutaneous Coronary Intervention

Today, PCI is an umbrella term for a wide array of procedures: balloons, stents, adjunct devices, thrombectomy, and pharmacologic agent delivery, all necessary for a safe and effective navigation of a complex coronary geography[65]. When performed rapidly and in an experienced center, primary PCI was proven superior to intravenous thrombolytic therapy for both men and women with STEMI[162,163]. Consequently, the use of primary PCI has expanded dramatically over the past two decades, and in the absence of complex multi-vessel CAD, has become the modality of choice for emergent revascularization in the United States and most of the developed world[10]. ACC/AHA and ESC guidelines for STEMI care define timely reperfusion with PCI as hospital D2B time <90 minutes for patients who self-transport and EMS-to-balloon time <90 minutes for patients arriving by ambulance. Still, controversy exists as to whether PCI remains the superior modality in cases of substantial delay; as in places where 24-hour primary PCI is unavailable[10].

In women, primary PCI was found to have a significant mortality benefit as compared to thrombolysis, which, as previously discussed, has a very high complication rate. In the GUSTO II-B trial primary PCI prevented 56 deaths per 1000 treated patients in women as compared to 42 deaths in men[164]. Despite almost eliminating the risk of intracranial bleeding associated with thrombolytic therapy[165], women undergoing PCI still had higher rates of vascular complications requiring transfusions[166,167]. Use of early-

generation stents for AMI was initially associated with higher mortality rates in women[168], however, later studies found that compared to angioplasty alone, bare-metal stenting was associated with reduced major adverse cardiac events (MACE) and reinfarction rates[166]. A recent patient-level pooled analysis of randomized trials in women undergoing coronary stenting found that compared to bare metal stents and early generation drug eluting stents (DES), women receiving new-generation DES had lower rates of death, MI, and target vessel revascularization[169].

Finally, in an analysis of 22 trials randomizing 6,763 STEMI patients to either primary PCI or thrombolysis, women had a lower 30-day mortality with PCI, irrespective of time to reperfusion[170]. Mortality rates were 7.7% versus 9.6% for women presenting within the first 2 hours of symptom onset, and 8.5% versus 14.4% when presenting after a delay >2 hours. Notably, the highest mortality was observed in women with a delayed presentation who were treated with thrombolytic therapy.

Coronary Artery Bypass Graft

Emergency CABG as a treatment modality for STEMI is exceedingly rare. Even in patients with triple-vessel disease, it usually reserved to the post PCI period, after initial vessel patency had already been achieved. Several outcomes studies, with data stratified by sex, show, that post CABG, women tend to have higher in-hospital mortality rates. Although women presenting for CABG were on average older and sicker, adjustments for such baseline characteristics only attenuated, but did not eliminate this outcome discrepancy[171,172].

Prognostic Factors and Adverse Outcomes

Although several risk prediction models for adverse events post AMI, such as Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI), are often used in patients with ACS, women account for only one third of the population studied to create these models. Consequently, their ability to accurately predict and stratify risk in women is questionable[173,174]. A recent study that used prognostic values such as left ventricular ejection fraction and certain ECG measures was able to stratify 5-year mortality risk in both men and women, but the prediction strength and accuracy varied between the sexes. For example, lack of sinus rhythm was associated with a 2–fold increased hazard ratio in women than in men. The study concluded that sex-specific models provided more accurate risk stratification than their traditional, sex-neutral counterparts[175].

Creating sex-specific models requires taking into account the previously described variations in presentation and baseline characteristics, traditional coronary risk factors, and psychosocial effects. For example, women with STEMI that present without chest pain have an increased risk of in-hospital mortality regardless of age group[117,176]. Such lack of pain on presentation is independently associated with increased mortality in women more so than in men[117]. Additionally, DM nearly doubles the long-term mortality risk in women after MI, an effect that is, once again, more pronounced in women. As previously discussed, other coronary risk factors such as hypertension, smoking, and obesity have high prevalence in women admitted with AMI, especially in developing countries. A study that followed 19 centers indicated that while among all AMI patients over two thirds had ≥2 risk factors and over one third had ≥3 risk factors, black women had the highest amount of

risk factors among the different sub-populations. Two thirds of older and half of younger black women had ≥3 risk factors[62].

Finally, there is increasing evidence that negative psychosocial factors, particularly depression, are associated with poorer ACS outcomes[177]. In patients with ischemic heart disease mental stress-induced ischemia increases mortality and recurrence of cardiac events by 50%[178]. These data are especially relevant when assessing prognosis in women, who bear a higher burden of psychosocial risk factors compared to men at all age groups[179,180]. Approximately one fifth of post MI patients suffer from depression, and depression rates in women with MI are two fold higher than in men[177]. Half of women with AMI younger than fifty and over 40% of women 50-60 years old suffer from clinical depression[180]. This increases their risk of death or additional MACE by almost 3-fold[181-183]. Furthermore, social support was found to be a positive prognostic factors in post MI women, and is associated with better psychological function, higher quality of life, and reduced rates of depression one-year post MI[184]. The significance of psychosocial stress in women with AMI was also demonstrated in experimental studies where emotional stress was induced in women with prior ischemic heart disease or MI, and was shown to cause myocardial ischemia. These studies found higher rates of stress induced myocardial ischemia in women than in men[185].

Statement of Purpose

Over the past decade, the United States and most European countries have seen, for the first time, a significant reduction in ACS mortality in women. These encouraging trends are, in part, the result of growing awareness to long-lasting sex disparities, increased attention to specific cardiovascular risk factors and pathophysiology in women, and the implementation of evidence-based guidelines and systems of care for AMI patients as a whole (i.e., SFL and Mission: Lifeline).

Nevertheless, ACS in general, and STEMI in particular, remain a leading cause of morbidity and mortality afflicting millions of women both in the US and worldwide. While the reasons for the increased incidence of AMI among women are numerous and may be related the increased prevalence of comorbidities, age, race, ethnicity, and socioeconomic trends one thing seems clear—women are late to reap the full benefits of the STEMI revolution that has swept most of the developed world over the past two decades. What is more, women in developing countries and underprivileged women in more developed nations bear the brunt of this persistent gender gap in STEMI care and outcomes.

With the constant trickle of sporadic data on sex-based disparities in STEMI care and outcomes, the once considered mythical gender-gap has been receiving increasing amounts of attention. Nevertheless, to date, a comprehensive, global analysis of gender-based outcome has never been performed. We believe that the first step in addressing any such problem is evaluating the quality of existing data (e.g., amount, connectedness), gauging the magnitude of the problems, and taking an initial stab at unveiling regional

and global trends. This meta-analysis aims to provide partial answers to these questions, as well as to invigorate others to collaborate and tackle these same topics. Every conversation needs an intermittent stimulus to remain relevant; hopefully our data will serve as a spark.

Methods

Data Sources and Search Strategy

A systematic literature search in PubMed of all studies published from 2000 to present was performed according to the Preferred Reporting Items for Systematic Reviews as detailed in the checklist in *Table 3*. Two independent reviewers (HL and IH) performed the search, selected the studies and validated the selection process as detailed in *Figure 1*. Using the search terms "sex", "gender" and "STEMI," 613 studies were initially identified by one of the co-primary authors. Each study written in English was manually reviewed, and only studies reporting sex-based STEMI mortality outcomes were included. After the exclusion of 505 studies based on these initial search criteria, 108 studies remained. Of these, 17 studies were excluded because they spanned data preceding the year 2000. An additional 10 studies were excluded because they were reviews or meta-analyses and did not include primary data, 5 studies were excluded because the sex-based mortality data were reported as sub-stratified or fragmented data, and 1 study was excluded due to the small sample size of included women (below 50). These selection criteria yielded 75 studies for inclusion in the meta-analysis (*Table 4*). The second co-primary author replicated the search in a blinded manner to validate the search criteria and demonstrate reproducibility.

Endpoint Selection

The primary clinical endpoints were in-hospital and 12-month mortality; other time points included 30 days and 6 months. In addition, as secondary endpoints, we evaluated sex differences in baseline characteristics and D2B times.

Statistical Analysis

Meta-analyses were conducted using random effects models. Heterogeneity was assessed via Cochran's Q statistic. Odds ratios and 95% confidence intervals from the random effects models are displayed grouped by region and overall. All available data was used at each reported time point, there was no imputation of missing data. Bias was assessed via visual assessment of funnel plots of the effect differences versus study size. Sensitivity analyses were conducted by excluding studies under various conditions including (1) studies in which all patients underwent reperfusion therapy, and (2) studies that included only patients presenting within a pre-specified time-frame following onset of symptoms. All analyses were performed using NCSS 2007 [186].

Meta regressions were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Models to examine the impact of moderator variables on study effect sizes for in hospital and 12-month mortality were run adjusting for the normalized mean age (mean/standard deviation), the percent of men and women with hypertension and the percent of men and women with diabetes, within each study.

Contributions

Data collection, refinement, and selection were done in collaboration with Dr. HyonJae Lee. I devised the initial searching algorithm and data collection methodology, and these were further improved and optimized by Dr. Lee. Dr. Lee and I also collaborated on preparing and "cleaning" the data for statistical analysis. I performed preliminary statistical analysis (on a smaller scale study as a proof of concept). Helen Parise, a statistician working with Dr. Lansky and the Yale Cardiovascular Research Group, performed the comprehensive statistical analysis presented in this work.

Results

Of the original 613 citations identified, a total of 75 studies qualified for inclusion in the meta-analysis (*Figure 1*). There were a total of 731,990 patients comprised of 233,310 (32%) women and 499,697 (68%) men (*Table 4, and Figure References* section*).* The studies represent 29 countries, grouped into 6 geographic regions: North America, Europe, Eastern Europe, Nordic Countries, Middle East/Israel, Australasia, and mixed multi-regional countries (*Table 5*). Of the 75 included studies, 31 studies included only patients undergoing reperfusion therapy (N=189,791; 28.7% men and 20% women, p<0.001) and 18 studies excluded patients presenting after a pre-specified period of time (range 12-72 hours) following onset of symptoms (*Table 6*). One U.S. study included only patients presenting with STEMI in cardiogenic shock and 1 study from the Netherlands excluded patients with cardiogenic shock. One study included only patients with diabetes, 2 studies excluded patients with chronic kidney disease, 1 study excluded patients with contraindication to anticoagulation. Three studies included only patients with anterior STEMI, 3 studies included only patients with first-time STEMI, 1 study included only patients with multi-vessel disease. Overall, women presenting with STEMI were older than men and had a higher prevalence of hypertension and diabetes, but were less likely to be active smokers or have a history of prior myocardial infarction (MI) (*Table 1*).

Primary Endpoints

Primary PCI was reported in 23.2% of men and 16.3% of women, (p<0.001). Overall unadjusted in-hospital mortality was 2-fold higher in women compared to men and consistently higher in all regions evaluated (OR 2.09; 95% CI 1.91-2.28; p<0.0001) (*Figure 2*). Overall unadjusted mortality rates for women were at least 70% higher at all follow-up time points including 1-year (OR 1.76; 95% CI 1.63-1.90; p<0.0001) (*Figure 3*), 6-month

(OR 1.72; 95% CI 1.38-2.14; p<0.0001), and 30-day (OR 1.74; 95% CI 1.65-1.84; p<0.0001) (*Figure 4*). The greatest sex-disparity in mortality was reported in the Middle East, where women had a 10-fold higher in-hospital mortality and a greater than 2 fold higher mortality at 30 days and 1 year. The highest absolute in-hospital mortality rates for women were reported in North America due to the inclusion of a large study of cardiogenic shock, and the highest absolute out-of-hospital mortality at 30-day, 6-month, and 1-year follow-up were reported in Eastern Europe. Review of the funnel plots indicated minimal publication bias (*Figure 6*).

Sub-analysis excluding studies in which all patients underwent reperfusion therapy (32 studies, N=189,791) did not significantly change overall relative mortality outcomes in-hospital (2.12 OR, 95%CI 1.90-2.37; p<0.0001), at 30 days (1.80 OR, 95%CI 1.61-2.02; p<0.0001), or at 1 year (1.87 OR, 95%CI 1.69-2.07; p<0.0001). Sub-analysis excluding studies that included only patients presenting within a pre-specified time-frame following onset of symptoms also did not significantly change overall relative mortality outcomes in-hospital (2.09 OR, 95%CI 1.90-2.30; p<0.0001), at 30 days (1.78 OR, 95%, CI 1.56-2.03; p<0.0001), or at 1 year (1.80 OR, 95%CI 1.63-1.98; p<0.0001).

Adjusting for age alone (N=233,039) in the meta-regression did not affect the observed differences in mortality between men and women at any time point (OR 1.92; p=0.0002 for in-hospital mortality, and OR 1.71; p=0.014 for 12 month mortality). After adjusting for age and differences in hypertension and diabetes (the two most frequently reported comorbidities; N=164,815), the difference in outcomes both in-hospital and at 12 months though still favoring outcomes in men, were no longer statistically significant, (OR

1.71; p=0.34 for in-hospital mortality and OR 1.51; p=0.51 for 12-month mortality) (*Table 2*).

Secondary Endpoints

As previously described, Primary PCI was reported in only 16.3% of women, limiting our ability to accurately and comprehensively assess D2B times. Furthermore, there exists a rather large region-based variability in reporting practices, as well as in common types of interventions (i.e., PPCI vs. thrombolysis). Nevertheless, D2B time for women, compared to men, was longer in all countries with a mean delay of 5.3 minutes (range: 0-10; p<0.0001) (*Figure 5*). Interestingly, the largest delays were observed in Australasia (9.94 min, 95%CI -1.64-21.52), Europe (7.11 min, 95%CI 3.41-10.80), North America (6.52 min, 95%CI 1.79-11.25), and in the Mixed group (4.0 min, 95%CI 0.50-7.50).

The large delays in North America and Europe should be interpreted with the understanding that these regions collect and report the most robust data both quantitatively and qualitatively, thus allowing for a more meaningful statistical analysis with significantly less heterogeneity. This discrepancy between observed delays in D2B times and clinical outcomes is highlighted when looking at data from the Middle East. There, we detect a minimal delay in D2B time (5 min, 95% -3.65-3.75), which is not statistically significant, but at the same time we observe the largest sex-disparity in mortality (10-fold higher in-hospital mortality and a >2 fold higher mortality at both 30 days and 1 year).

Discussion

This systematic meta-analysis represents a comprehensive contemporary study that examines sex-based STEMI outcomes on a global scale. When evaluating the data globally (Table 2), this work demonstrates that, compared to men, women have more coronary risk factors, undergo less reperfusion therapy, and experience a mortality excess of more than two-fold in-hospital and more than 70% at 12-month following hospitalization for AMI.

A region-by-region analysis shows consistent excess in women's mortality compared to men (Fig. 2, 3). This discrepancy did not spare the U.S. or Europe, where STEMI systems of care are already well established. Overall delays in reported D2B times for women, while statistically significant, were relatively small (Fig. 5). Additionally, the largest D2B delays, detected in the most developed regions (e.g., North America and Western Europe), merit a closer look. A careful observation reveals a rather consistent discordance between delays in D2B times and mortality rates. Regions like Eastern Europe and the Middle East exhibit the smallest delays in D2B times (not statistically significant), while at the same time these same regions suffer from the highest in-hospital and 1-year mortality rates. This trend is reversed when observing the more developed regions (e.g., North America), where much longer delays in D2B times are recorded, but mortality rates are much lower (Fig 2, 3). We believe that this is the result of a lower signal-to-noise ratio in developing nations, which results from the scarcity of standardized registries, lack of clinical trials, more homogeneous patient populations, heterogeneity of treatment strategies, and less resources to implement efficient PCI networks.

Consequently, delays in D2B times are unlikely to be the principal driver of the mortality difference. In fact, among Medicare patients suffering AMI (STEMI and NSTEMI),

Guideline Determined Medical Therapy (GDMT) explains only 7% of the variation in outcomes. This not only highlights both the magnitude and multifactorial nature of the problem, but also implicates other underlying causes. Specifically, our data suggest that despite improved systems of care, women's higher mortality persists, and is probably in large part the result of upstream modifiable risk factors.

Indeed, our study confirms differences in risk profile previously reported in other studies, with women typically presenting at an older age and with more comorbidities than men[187-190]. Moreover, previous data suggest that the sex discrepancy in comorbidity burden is even more pronounced in developing, lower-income countries[3,20,24]. The significance of modifiable risk factors on mortality is emphasized when our analysis is adjusted for differences in age, hypertension, and diabetes (the most prevalent and consistently reported covariates). Such an adjustment eliminates both the in-hospital and 12-month disparity in mortality (Table 2).

Our findings are consistent with published data suggesting that, at least in the US, the higher STEMI mortality rate in women is largely due to comorbidities and the prevalence of risk factors rather than treatment discrepancies[191,192]. This meta-analysis suggests that risk factors may be pivotal upstream contributors to the sex mortality gap in developed countries—both acutely and at 1 year. It is important to note that although some data exist to suggest that women face additional upstream challenges in access to care, they are limited in scope, accuracy, and depth particularly. This is especially true in many parts of the developing world, where systematic, standardized data collection is frequently not practiced.

As previously discussed, women's underrepresentation in cardiovascular clinical trials (~20% of enrolled patients) and in longitudinal studies and registries (~40% of enrolled patients) is of historic magnitude. To add insult to injury, even clinical trials that were conducted with equal representation, often were not sub-stratified by sex. The effect of this marginalization echoes even louder in the era of evidence-based medicine, as it limits the quantity and quality of sex-specific data available to both providers and patients[42].

Consequently, 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 face in accessing care. This critical information gap masks upstream barriers to care, which often affect vulnerable populations, including women, more profoundly. These barriers may include lack of awareness and recognition of STEMI symptoms[28], variations in threshold for seeking medical attention, insufficient management of modifiable risk factors, region-specific transportation, and financial, social, religious and cultural impediments to care [11,20].

This global analysis reveals the latitude and magnitude of widely recognized sex disparities in STEMI care and outcomes. However, its most powerful function is exposing our global ignorance of the epidemiological, clinical, and social barriers to high-quality STEMI care for women. The major impediment to the improvement of STEMI care and outcomes for women is the lack of comprehensive and accurate data.

Closing this information gap requires a rigorous reevaluation of sex-specific differences and their clinical implications. This long overdue task should consist of a two-pronged approach: 1. Expanding basic science and translational research to further

characterize differences in coronary pathophysiology, optimize diagnostic modalities with gender in mind, and evaluate pharmacotherapies and invasive treatment strategies in light of new data at the subpopulation level (e.g., young vs. older women, women of certain races and income levels etc.). An example of one such practical step would be changing the practice of excluding elderly patients from clinical trials, a "tradition" that works to the detriment of women, whose CHD develops predominantly at older ages. 2. Implementing public health initiatives to tackle economic, political, regulatory, cultural, environmental, health systems, and policy challenges both locally and globally[193]. A desperately needed first step in improving treatment availability and outcomes for women with STEMI is the creation of large, uniform, global registries with reliable data on demographic risk factors, use of reperfusion, and patient outcomes.

As we enter the age of personalized medicine, attention to sex-specific characteristics and disparities will become inescapable. It will improve prevention, recognition, treatment, and outcomes for women with STEMI. The remaining questions are what will the rate of change be? And, how do we make sure developing nations do not stay behind for yet another two decades? We cannot answer these questions when in the US, the hub of innovation and cutting edge medicine, women constituted ~1/3 of all participants in the 78 cardiovascular device trials between 2002 and 2007[194]. How can we instigate global change, when the Food and Drug Administration does not mandate, sex-specific data in device studies despite mounting evidence that the safety and efficacy of cardiovascular devices vary by sex[194,195]? Enough said.

Limitations

      This meta-analysis is intended to be comprehensive and systematic, but inherently has several unavoidable limitations. Most importantly, many of the studies included in this analysis come from larger hospitals with PPCI capabilities and individual data-storage systems, resulting in a reporting bias and likely representing a best-case scenario. Thus, it is likely that our analysis under-estimates mortality rates and delays-to-reperfusion, particularly when accounting for the paucity of data from more rural, resource scarce regions. There are also limitations intrinsic to a meta-analysis, including a heterogeneity of studies with varying inclusion and exclusion criteria, selection bias within studies that may not be necessarily representative of a general population of patients, and the potential for regional under-reporting. For example, the highest in-hospital absolute mortality rates were in North America because the North American mortality data incorporates a large study including only patients with cardiogenic shock. Additionally, the difference in absolute mortality rates raises concerns over systematic under-reporting of mortality events in many regions of the world – potentially from lack of access to care and loss to follow-up. However, an adequately powered study with the inclusion of a large number of studies decreases the likelihood that the overall results are significantly affected by subsets of patients. Furthermore, assessment of bias by funnel plots of the effect differences versus study size confirms minimal variability in outcomes between studies for both in-hospital and 12 month mortality outcomes and D2B times (*Figure 5*). In addition, analysis of sub-groups (1. Inclusion of only patients undergoing reperfusion; 2. Inclusion of only patients presenting within a specified time frame following symptoms) did not significantly impact the results.

Figure Legends

Figure 1.
Title: Search criteria and methodology for selecting included studies
Caption: A systematic literature search in PubMed of all studies published from 2000 to present was performed using the search terms "sex", "gender" and "STEMI." All studies written in English were manually reviewed, and only studies reporting sex-based STEMI mortality outcomes were included. Studies were also excluded if they did not include primary data or due to the small sample size. These selection criteria yielded 75 studies for inclusion.

Figure 2.
Title: In-hospital STEMI mortality by region
Caption: In-hospital mortality was 2-fold higher in women compared to men, and consistently higher in all regions evaluated.

Figure 3.
Title: 1 year STEMI mortality by region
Caption: 1 year mortality rates were at least 70% higher in women compared to men, and consistently higher in all regions evaluated.

Figure 4.
Title: 30 day STEMI mortality by region
Caption: 30-day mortality rates were at least 70% higher in women compared to men, and consistently higher in all regions, with the exception of North America.

Figure 5.
Title: Delay in door to balloon times by region
Caption: Door-to-reperfusion time for women was longer in all countries with a mean delay of 5.3 minutes. Not all regions demonstrated statistical significance.

Figure 6.
Title: Funnel plots for study variability in mortality and D2B times
Caption: While clinical heterogeneity is present to some degree in all meta-analyses, the large scale of this meta-analysis, the geographic variability, and the relatively large time span require an assessment of statistical heterogeneity. Bias was assessed via visual assessment of funnel plots of the effect differences versus study size

Figures

Figure 1. Search criteria and methodology for selecting included studies.
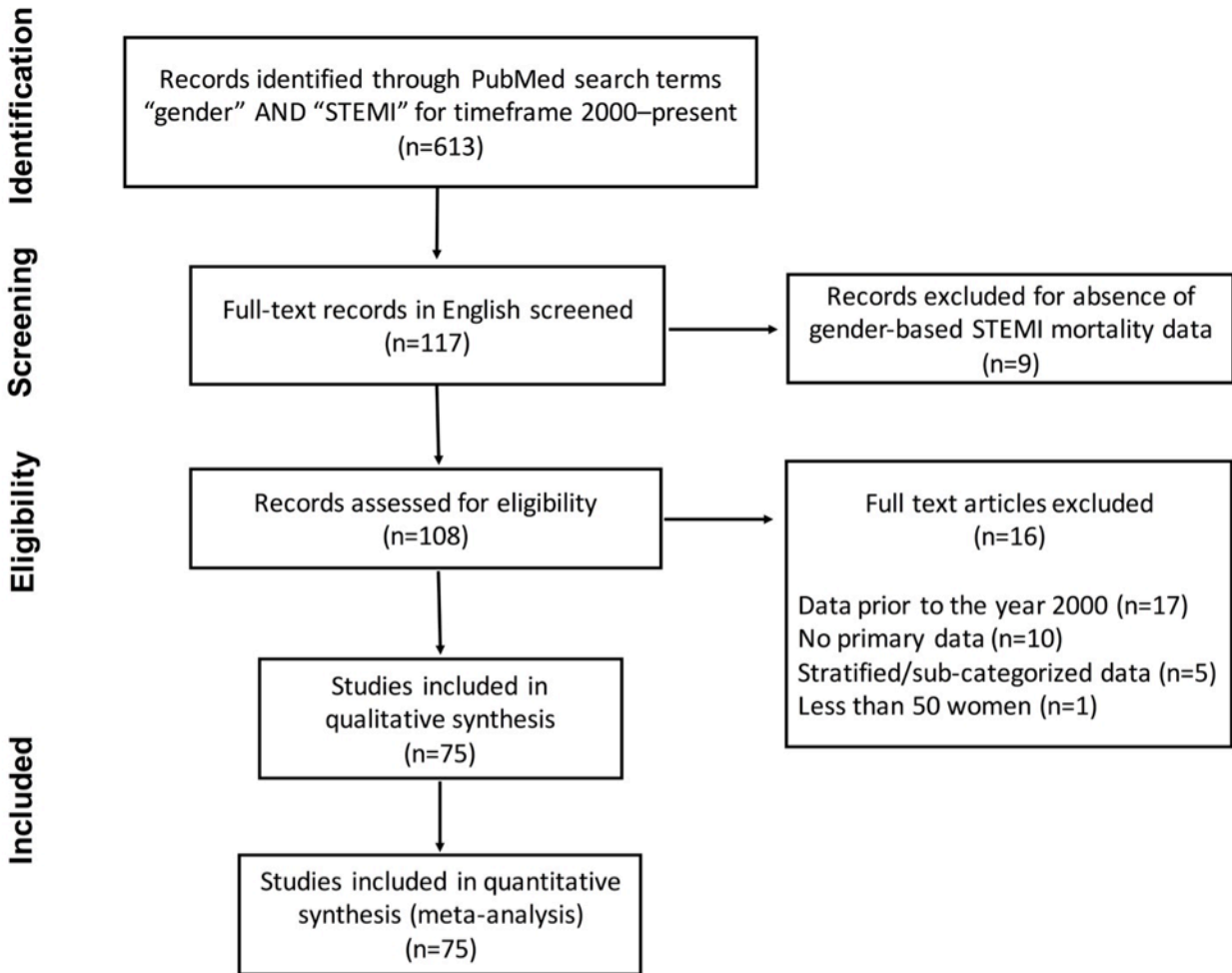
Figure 2. In-hospital STEMI mortality by region

Region	Mortality rate Women	Men	OR	Lower limit	Upper limit	
Australasia *	1078/8212 (13%)	1683/24997 (7%)	2.02	1.75	2.33	
Eastern Europe †	2050/17262 (12%)	2186/32668 (7%)	1.77	1.66	1.89	
Europe ‡	7089/62264 (11%)	8649/167531 (5%)	2.24	2.05	2.44	
Middle East §	59/327 (18%)	36/1772 (2%)	10.54	6.85	16.23	
Mixed ‖	40/982 (4%)	71/3089 (2%)	1.74	1.17	2.58	
Nordic #	3848/29085 (13%)	3585/56814 (6%)	2.25	2.06	2.45	
North America **	30911/96304 (32%)	38138/168269 (23%)	1.80	1.52	2.14	
Combined	45075/214436 (21%)	54348/455140 (12%)	2.09	1.91	2.28	

Favors women   Favors men

* [34, 37, 39, 45, 47, 61, 62, 72, 73, 75]; † [28, 41, 50, 55, 56, 59, 70]; ‡ [1, 2, 4, 5, 6, 8, 11, 12, 13, 14, 16, 18, 21, 27, 30, 33, 36, 46, 52, 54, 65, 66]; § [20] ‖ [30, 69]; # [19, 29, 32, 57, 58]; ** [23, 24, 26, 48, 51, 74] (Reference List in Appendix)

Figure 3. 1 year STEMI mortality by region

Region	Mortality rate Women	Men	OR	Lower limit	Upper limit	
Australasia *	113/561 (20%)	158/1603 (10%)	2.27	1.74	2.96	
Eastern Europe †	5144/24585 (21%)	6218/47074 (13%)	1.61	1.49	1.75	
Europe ‡	160/926 (17%)	306/2615 (12%)	1.53	1.04	2.25	
Middle East §	63/411 (15%)	101/1404 (7%)	2.31	1.65	3.24	
Nordic ‖	3699/20001 (18%)	4078/40029 (10%)	1.95	1.79	2.12	
North America **	129/885 (15%)	200/2394 (8%)	1.79	1.13	2.85	
Combined	9308/47369 (20%)	11061/95119 (12%)	1.76	1.63	1.90	

Favors women   Favors men

* [10, 71]; † [44, 50, 53, 55, 56, 59]; ‡ [1, 5, 18, 27, 54]; § [42, 67]; ‖ [22, 32, 57, 58]; ** [2, 60] (Reference List in Appendix)

Figure 4. 30-day STEMI mortality by region

Region	Mortality rate		OR	Lower limit	Upper limit	
	Women	Men				
Australasia *	245/3145 (8%)	365/9371 (4%)	1.89	1.51	2.37	
Eastern Europe †	2200/16113 (14%)	2493/31307 (8%)	1.70	1.60	1.81	
Europe ‡	52/395 (13%)	69/1027 (7%)	2.12	1.45	3.09	
Middle East §	41/518 (8%)	62/1854 (3%)	2.39	1.60	3.59	
Mixed ‖	38/960 (4%)	68/3094 (2%)	1.85	1.24	2.76	
Nordic #	272/3107 (9%)	462/8660 (5%)	1.71	1.46	1.99	
North America **	3/57 (5%)	8/120 (7%)	0.85	0.23	3.08	
Combined	2851/24295 (12%)	3527/55433 (6%)	1.74	1.65	1.84	

0.5 1 5

← Favors women   Favors men →

* [9, 10, 34, 35, 49, 71, 73] † [25, 43, 44, 50, 53, 55, 56, 59] ‡ [11, 63] § [31, 42] ll [64, 69] # [7, 22, 40] ** [51] (Reference List in Appendix)

Figure 5. Delay in door to balloon times by region

Region	Delay in DTB	Lower limit	Upper limit
Australasia *	9.94	-1.64	21.52
Eastern Europe †	1.10	0.11	2.09
Europe ‡	7.11	3.41	10.80
Middle East §	0.05	-3.65	3.75
Mixed ‖	4.00	0.50	7.50
Nordic #	0.08	-1.23	1.40
North America **	6.52	1.79	11.25
Combined	5.33	3.39	7.26

-5 0 5 10 15 20

Delays in door to balloon time (minutes)
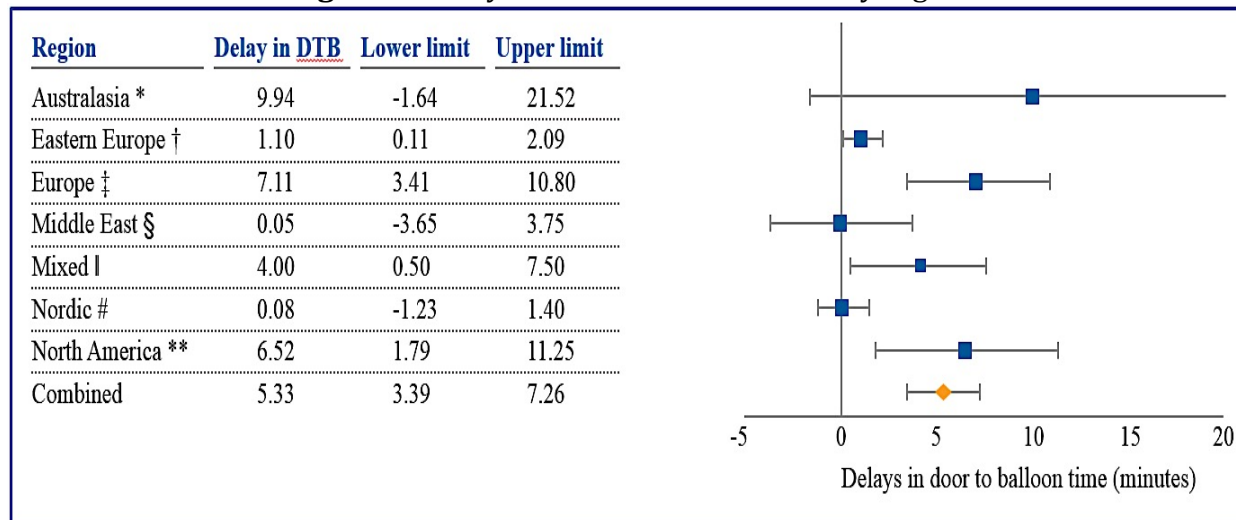
* [9, 10, 34, 38, 39, 47, 62, 71] † [25, 53, 55] ‡ [4, 6, 8, 11, 33, 62, 63, 65] § [31, 42, 67] ll [69] # [15, 19, 40, 68] ** [2, 23, 51] (Reference List in Appendix)

Figure 6. Funnel plots for study variability in mortality (a,b) and D2B time (c)
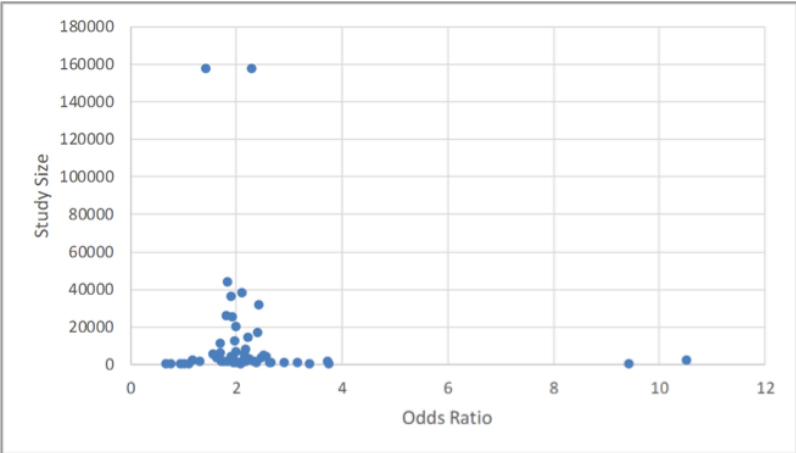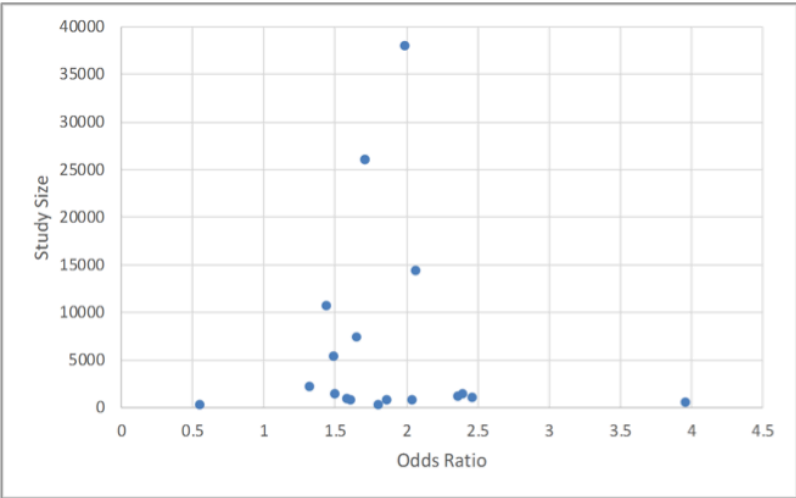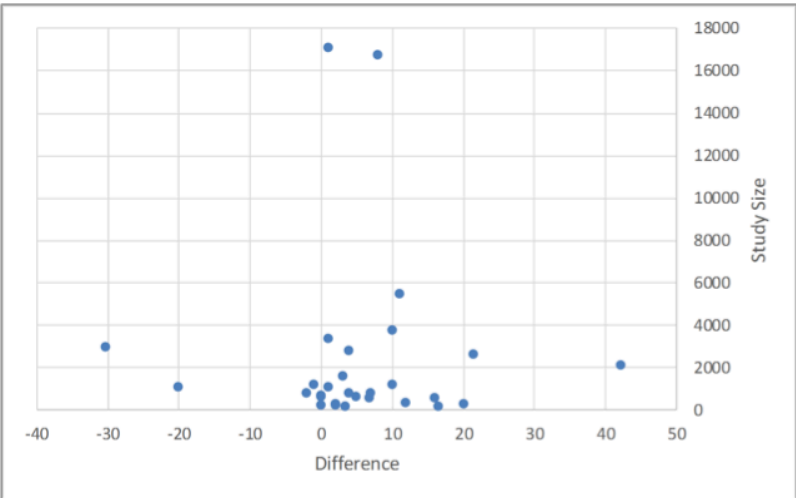

(a) In-Hospital Mortality

(b) 12-M Mortality

(c) Door-to-Balloon Time

Tables

Table 1. Demographics of patients included in the meta- analysis

	Women n = 233,310*	**Men** n = 499,697*	**p-value**
Clinical Characteristics			
Age, mean (SD), years	68.7 (11.9)	62.3 (10.8)	<0.001
Hypertension	57.0%	43.9%	<0.001
Diabetes	22.1%	16.3%	<0.001
Active Smoking	22.8%	40.5%	<0.001
Prior MI [a]	11.7%	12.8%	<0.001

(a) MI = Myocardial Infarction; * Percentages reflect the studies that report the specified clinical characteristic

Table 2. Odds ratio of death adjusted to clinical variables Give N for each group

In-Hospital Mortality	**Sex Alone**	**Age Adjusted Only**	**HTN[a] Adjusted Only**	**DM[b] Adjusted Only**	**Fully Adjusted***
OR[c] for Sex	2.09	1.92	1.64	1.81	1.71
p-Value for Sex	<.0001	0.0002	0.26	0.043	0.34
Number of Studies Included	52	37	33	35	27

12-Month Mortality	**Sex Alone**	**Age Adjusted Only**	**HTN Adjusted Only**	**DM Adjusted Only**	**Fully Adjusted***
OR for Sex	1.76	1.71	1.42	1.60	1.51
p-Value for Sex	<.0001	0.014	0.39	0.86	0.51
Number of Studies Included	21	19	19	18	16

(a) HTN = Hypertension; (b) DM = Diabetes; (c) OR = Odds Ratio; * Adjusted for age, HTN and DM simultaneously.

Table 3. MOOSE Checklist

Section/topic	No.	Checklist item	Reported on page no.
Background	1	Problem definition	22
	2	Hypothesis statement	ii, 22
	3	Description of study outcomes	26-28
	4	Type of exposure or intervention used	26
	5	Type of study designs used	24-25
	6	Study population	24, Table 1
Reporting of search strategy	7	Qualifications of searchers (eg. librarians and investigators)	24-25
	8	Search strategy, including time period included in the synthesis and keywords	24, Figure 1
	9	Effort to include all available studies, including contact with authors	24
	10	Databases and registries searched	24
	11	Search software used, name and version, including special features used	25, Figure 1
	12	Use of hand searching (eg. reference lists of obtained articles)	N/A
	13	List of citations located and those excluded, including justification	24, Figure 1
	14	Method of addressing articles published in languages other than English	24, Figure 1
	15	Method of handling abstracts and unpublished studies	24, Figure 1
	16	Description of any contact with authors	N/A
Reporting of methods	17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	24
	18	Rationale for the selection and coding of data (eg. sound clinical principles or convenience)	24
	19	Documentation of how data were classified and coded (eg. multiple raters, blinding, and interrater reliability)	24-25
	20	Assessment of confounding (eg. comparability of cases and controls in studies where appropriate)	25, Table 5
	21	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	24
	22	Assessment of heterogeneity	25, Figure 6
	23	Description of statistical methods (eg. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	25
	24	Provision of appropriate tables and graphics	Figure 1, Table 3
Reporting of results	25	Graphic summarizing individual study estimates and overall estimate	Figure 2-3, Table 2, Figure 3-4
	26	Table giving descriptive information for each study included	Table 3-5
	27	Results of sensitivity testing (eg. subgroup analysis)	25-26, Table 3-4
	28	Indication of statistical uncertainty of findings	25, 31
Reporting of discussion	29	Quantitative assessment of bias (eg. publication bias)	31, Figure 6
	30	Justification for exclusion (eg. exclusion of non-English-language citations)	9
	31	Assessment of quality of included studies	24-25, Table 5
Reporting of conclusions	32	Consideration of alternative explanations for observed results	30-31
	33	Generalization of the conclusions (ie. Appropriate for the data presented and within the domain of the literature review)	29-31
	34	Guidelines for future research	29-31
	35	Disclosure of funding source	N/A

Table 4. Characteristics of studies included for analysis

Study	Region/Country	Total, n	Men, n	Women, n	Women (%)
Barthelemy, O., et al. 2015[1]	France	775	593	182	23.48
Bataille, Y., et al. 2013[2]	Canada	2020	1540	480	23.76
Benamer, H., et al. 2011[3]	France	16760	13096	3664	21.86
Biava, L.M., et al. 2015[4]	Italy	325	250	75	23.08
Birkemeyer, R., et al. 2014[4]	Germany	1104	823	281	25.45
Brown, R.A., et al. 2015[6]	U.K.	1020	768	252	24.71
De Boer, S.P., et al. 2014[7]	Netherlands	4229	3134	1095	25.89
De-Miguel-Balsa, E., et al. 2015[8]	Spain	4816	3752	1064	22.09
Dreyer, R.P., et al. 2013[9]	Australia	470	335	135	28.72
Dreyer, R.P., et al. 2013[10]	Australia	735	562	173	23.54
Eitel, I., et al. 2012[11]	Germany	335	239	96	28.66
Gale, C.P., et al. 2012[12]	U.K.	157543	112476	45067	28.61
Gevaert, S.A. 2014[13]	Belgium	8073	6153	1920	23.78
Gevaert, S.A., et al. 2013[14]	Belgium	1638	1300	338	20.63
Ghauharali, S., et al. 2015[15]	Netherlands	832	611	221	26.56
Gnavi, R., et al. 2014[16]	Italy	3506	2296	1210	34.51
Guo, R.W., et al. 2014[17]	China	202	134	68	33.66
Hailer, B., et al. 2011[18]	Germany	1365	984	381	27.91
Halvorsen, S., et al. 2009[19]	Norway	1565	1169	396	25.30
Hersi, A., et al. 2013[20]	Saudi Arabia	2099	1772	327	15.58
Isorni, M.A., et al. 2015[21]	France	19956	15306	4650	23.30
Jakobsen, L., et al. 2012[22]	Denmark	7385	5405	1980	26.81
Jneid, H., et al. 2008[23]	U.S.A.	25353	16694	8659	34.15
Kaul, P., et al. 2011[24]	Canada	2067	1187	880	42.57
Kawecki, D. 2009[25]	Poland	746	541	205	27.48
Kolte, D., et al. 2014[26]	U.S.A.	157657	96132	61525	39.02
Kralev, S., et al. 2010[27]	Germany	297	215	82	27.61
Krotin, M., et al. 2010[28]	Serbia	6135	3980	2155	35.13
Kyto, V., et al. 2015[29]	Finland	31689	21021	10668	33.66
Lanaro, E., et al. 2014[30]	Brazil	469	329	140	29.85
Laufer-Perl, M., et al. 2015[31]	Israel	1346	1075	271	20.13
Lawesson, S.S., et al. 2012[32]	Sweden	14380	9386	4994	34.73
Lazzeri, C., et al. 2011[33]	Italy	357	200	157	43.98
Lee, C.Y., et al. 2013[34]	Malaysia	2357	2050	307	13.03
Lee, K.H., et al. 2008[35]	Korea	5624	3925	1699	30.21
Leurent, G., et al. 2014[36]	France	5000	3826	1174	23.48
Li, Z.Y., et al. 2014[37]	China	1424	1128	296	20.79
Liu, Y., et al. 2008[38]	China	259	143	116	44.79
Lu, H.T., et al. 2014[39]	Malaysia	6378	5433	945	14.82
Melberg, T., et al. 2013[40]	Norway	244	179	65	26.64
Miric, D., et al. 2013[41]	Croatia	637	481	156	24.49
Moriel, M., et al. 2008[42]	Israel	1026	779	247	24.07
Motovska, Z., et al. 2008[43]	Czech Republic	679	526	153	22.53
Mrdovic, I., et al. 2013[44]	Serbia	2096	1533	563	26.86
Oqueli, E., et al. 2008[45]	Australia	147	107	40	27.21
Pain, T.E., et al. 2013[46]	U.K.	2467	1918	549	22.25
Park, J.S., et al. 2010[47]	Korea	4037	2954	1083	26.83
Pathak, E.B., et al. 2010[48]	U.S.A.	43849	28624	15225	34.72
Pu, J., et al., 2011[49]	China	594	446	148	24.92
Radomska, E., et al. 2013[50]	Poland	5346	2826	2520	47.14
Rezaee, M.E., et al. 2013[51]	U.S.A.	177	120	57	32.20
Roncalli, J., et al. 2010[52]	France	1753	1343	410	23.39
Sadowski, M., et al. 2010[53]	Poland	26035	17046	8989	34.53
Sadowski, M., et al. 2011[54]	Poland	26035	17046	8989	34.53
Sadowski, M., et al. 2011[55]	Poland	10707	7493	3214	30.02
Sadowski, M., et al. 2013[56]	Poland	528	463	65	12.31
Sederholm, L.S., et al. 2015[57]	Sweden	37991	25062	12929	34.03
Sederholm L.S., et al.2011[58]	Sweden	274	176	98	35.77
Sinkovic, A., et al. 2015[59]	Slovenia	913	668	245	26.83
Skelding, K.A., et al. 2013[60]	U.S.A.	1259	854	405	32.17
Song, X.T., et al. 2007[61]	China	248	124	124	50.00
Srichaiveth, B. 2007[62]	Thailand	3836	2613	1223	31.88
Suessenbacher, A., et al. 2008[63]	Austria	1087	788	299	27.51
Tomey, M.I., et al. 2015[64]	U.S.A, Germany, U.K.	452	334	118	26.11
Trigo, J., et al. 2010[65]	Portugal	1578	1161	417	26.43
Valente, S., et al. 2012[66]	Italy	1127	832	295	26.18
Weissler-Snir, A., et al. 2014[67]	Israel	789	625	164	20.79
Wijnbergen, I., et al. 2013[68]	Netherlands	870	668	202	23.22
Yu, J., et al. 2015[69]	U.S.A, Australia, Argentina, Israel, Germany	3602	2760	842	23.38
Zanchi, J., et al. 2009[70]	Croatia	488	364	124	25.41
Zhang, B., et al. 2012[71]	China	1429	1041	388	27.15
Zhang, B., et al.2013[72]	China	754	602	152	20.16
Zhang, Q., et al. 2010[73]	China	2042	1574	468	22.92
Zhang, Z., et al. 2012[74]	U.S.A.	35899	25512	10387	28.93
Zheng, X., et al. 2015[75]	China	11986	8412	3574	29.82

* See *Figure References* section for citation list of included studies

Table 5. Studies by geographic region

Geographic Region	Studies, n	Total Patients, n	Women, n (%)	Men, n (%)
North America [2, 23, 24, 26, 48, 51, 60, 74]	8	267,852	97,189 (36.3%)	170,663 (63.7%)
Europe [1, 3-6, 8, 11-14, 16, 18, 21, 27, 30, 33, 36, 46, 52, 62, 65, 66]	22	232,924	63,012 (27.1%)	169,912 (72.9%)
Eastern Europe [25, 28, 41, 43, 44, 50, 53-56, 59, 70]	12	80,715	27,537 (34.1%)	53,178 (65.9%)
Nordic Europe [7, 15, 19, 22, 29, 32, 40, 57, 58, 68]	10	99,459	32,648 (32.8%)	66,811 (67.2%)
Middle East/Israel [20, 31, 42, 67]	4	5,260	1,009 (19.2%)	4,251 (80.8%)
Australasia [9, 10, 17, 34, 35, 37-39, 47, 49, 61, 62, 71-73, 75], (a)	16	42,274	10,815 (25.6%)	31,459 (74.4%)
Mixed/Multi-regional [30, 64, 69]	3	4,523	1,100 (24.3%)	3,423 (75.7%)
TOTAL	75	731,990	233,310 (32%)	499,697 (68%)

(a) Australasia = Australia and Asia * See *Figure References* section for citation list of included studies

Table 6. Significant Inclusion and Exclusion Criteria of Included Studies

	Study Population	Number of Studies
Clinical Characteristics		
Inclusion	Only patients undergoing reperfusion therapy [1, 2, 4, 6-7, 10, 11, 13-15, 17, 21-22, 27, 30, 31, 33, 41, 43-44, 46, 49, 51, 55, 64, 66-69, 72-73]	31
Inclusion	Only patients presenting with STEMI [a] and cardiogenic shock [26]	1
Exclusion	Patients with cardiogenic shock [15]	1
Exclusion	Patients presenting after pre-specified time period after onset of symptoms [2, 11, 22, 30, 36, 38, 43, 44, 47, 49, 53, 55, 63, 64, 66, 69-71]	18
Patient Characteristics		
Inclusion	Only patients with diabetes [50]	1
Exclusion	Patients with chronic kidney disease [37, 38]	2
Exclusion	Patients with contraindication to anticoagulation [66]	1
STEMI Categorization		
Inclusion	Only patients with anterior STEMI [17, 64, 67]	3
Inclusion	Only patients with first-time STEMI [16, 64, 67]	3
Inclusion	Only patients with multi-vessel disease [71]	1

(b) STEMI = ST-elevation Myocardial Infarction * See *Figure References* section for citation list of all studies

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Appendix

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