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Research paper

## Narrowing disparities in PCI outcomes in women; From risk assessment, to referral pathways and outcomes

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### ABSTRACT

This review evaluates published data regarding outcomes for women with ACS undergoing PCI. Data is discussed from a patient centred perspective and timeline, beginning with sex-based differences in perception of risk, time to presentation, time to treatment, access to angiography, access to angioplasty, the impact of incomplete revascularization, prescribing practices, under-representation of women in randomized controlled trials and in cardiology physician workforces. The objective of the review is to identify factors contributing to outcome disparities for women with ACS, and to discuss potential solutions to close this outcome gap.

### 1. Overview

Cardiovascular disease is the leading cause of death for women, in 2019 it was responsible for 35 % of all deaths in women [1]. Ischemic heart disease was the primary cause of cardiovascular disease mortality [1]. Outcomes for women with acute coronary syndrome (ACS), are worse than those for men, significant differences persist post risk adjustment for age and comorbidities [1–8] particularly for women with ST-elevation myocardial infarction (STEMI) [2–4,8]. Women are more likely to underestimate their risk of death from heart disease and are often more aware of breast cancer risks, but up to eight times more women die from ischemic heart disease than from breast cancer.

Closing this outcome gap for women has been challenging [1,5,9]. Disparities in referral for percutaneous coronary intervention (PCI) and its associated outcomes for women have been clearly demonstrated for many years. Solutions should target each factor contributing to these outcome disparities. Sex-based differences have been documented at all timepoints of ACS presentations starting at perception of risk, and time to presentation, and continuing through time to treatment, referral for angiography and angioplasty, completeness of revascularization, prescription of potent P2Y12 agents, and disparities in post PCI care (see Fig. 1). The under-representation of women as patients in randomized controlled trials may contribute to evidence gaps in treatment efficacy/safety and as physicians result in unconscious biases thereby potentiating poorer outcomes in women.

Sex based outcome disparities have been well documented, what is needed now are successful solutions to close these outcome gaps.

Addressing these complex issues is challenging and made more so by the question often asked either covertly or overtly when discussing this topic. Are we really treating women differently? Or are we appropriately more conservative when treating women, in response to risk? These discussions can be difficult and polarising, and sex-based biases must be objectively considered.

### 2. Perception of risk

Management of acute coronary syndromes begins with risk assessment and perception of risk both at the patient and healthcare professional level. Sex based differences in perception of risk contribute to contemporary sex-based outcome disparities; women with coronary disease are less likely than men to believe they are at risk [10,11]. Women are more likely to overestimate their risk of cancers such as breast cancer and underestimate their risk of heart disease [10,12,13]. Women with ACS have been shown to take 13 %–36 % more time to present to hospital with an event following the onset of symptoms [4,11,14,15]. In particular data shows young women, non-white women and women with hypertension, underestimate their risk of heart disease [10,11]. Unfortunately, misconceptions regarding risk of heart disease in women are not limited to patients, health providers have also been found to underestimate risk in women [4,11,13]. The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, evaluating patterns of presentation in patients under 55 with ACS found among those presenting with symptoms prior to their MI, 53 % of women reported that their provider did not think these symptoms were

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## Factors contributing to Disparities in PCI outcomes for women

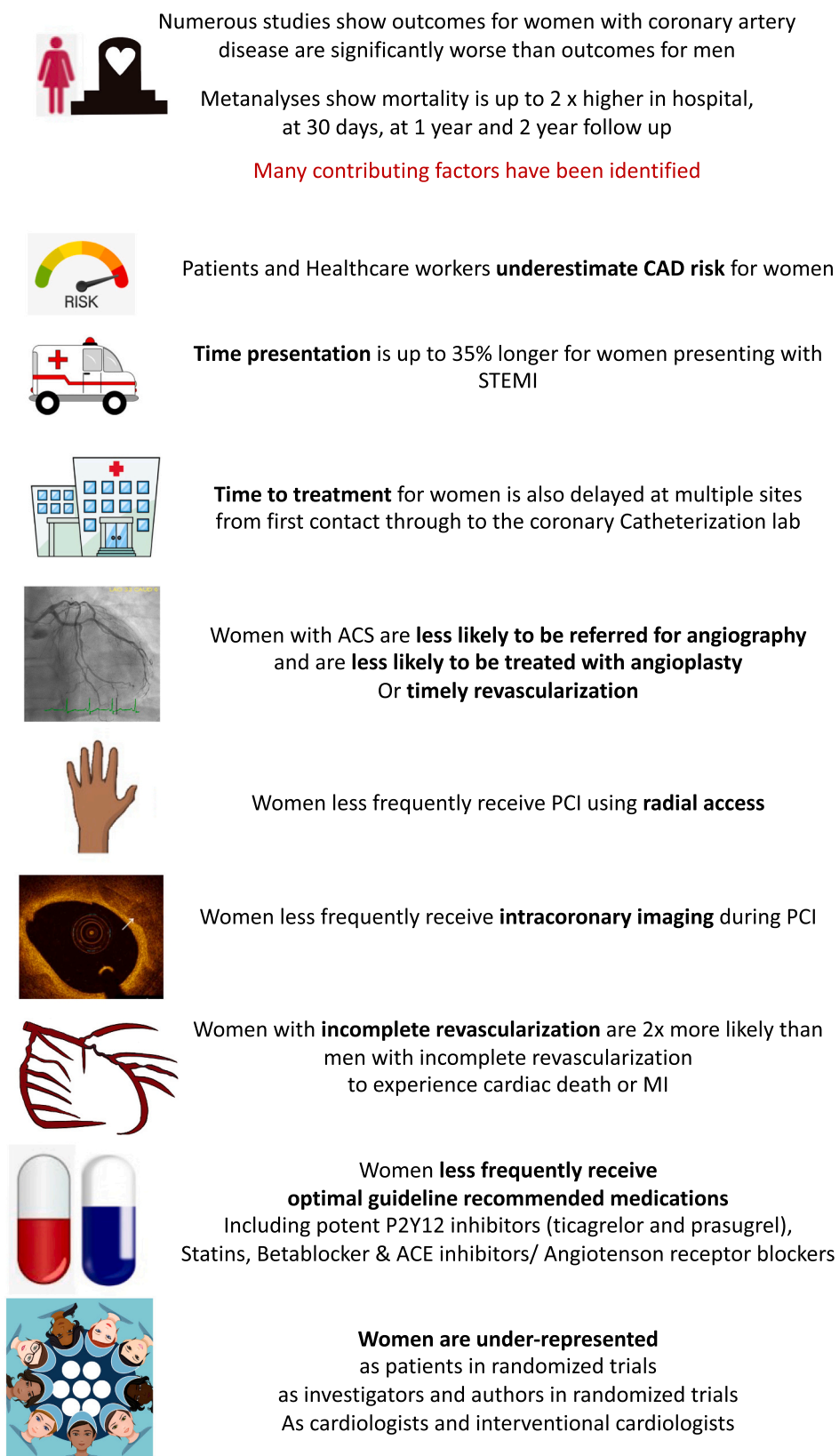


Fig. 1. Illustrates factors contributing to disparities in PCI outcomes from symptom recognition through hospital care and follow up. All factors need to be addressed to minimise the outcome disparities evident for women with cardiovascular disease

cardiac in comparison with 37 % of men ( $P < 0.001$ ). Issues with risk perception are not limited to women under the age of 55. Mosca et al. [16] when studying 2302 American women found women in all age groups demonstrated poor or suboptimal perception of cardiovascular risk.

### 3. Time to presentation

Perception of risk impacts significantly on time to presentation. Sex based differences in time to presentation are evident [4,11,14,15]. The VIRGO study [11] found women (under 55 years of age) with ACS take an average of 48 min (30 %) longer to present during an AMI than men of the same age. Median times from symptom onset to hospital presentation in women in the VIRGO study were 3.2 h [IQR 0.8–21.2] for women versus 2.4 h [IQR 0.7–13.0] for men, ( $p < 0.004$ ). An Australian state wide study of 13,451 ACS patients similarly reported symptom to hospital door times 13 % (29 min) longer in women with STEMI than in men than men (198.0 versus 169.2 min;  $p < 0.001$ ), but no differences for time to presentation NSTEMI patients [4]. A similar study in Sweden [14] found women with STEMI had delays to first medical contact of 24 min when compared to men (90 min [IQR 39–221] vs 66 [28–161] min;  $p = 0.04$ ). A Korean 14,253 patient nationwide multicentre prospective registry [15] found a 56 min ( $p < 0.001$ ) difference in symptom to presentation time between men and women, with women taking 35 % longer to present than men.

#### 3.1. Solutions (for perception of risk and time to presentation)

Campaigns targeting heart disease prevention and awareness messages aimed at women in are needed and have become more common globally. Campaigns such as the American heart foundations “red dress” campaign for heart disease, and the Australian heart foundations “make the invisible visible” campaign address this. These risk messages need to be routinely embedded in heart health messaging by all health professions to address misconceptions. Efforts by healthcare professionals should be made to avoid falsely reassuring women with symptoms or significant risk profiles, objective testing is important in this setting as is early screening and mitigation by risk factor modification.

Avoidance of the phrase ‘atypical symptoms’ is also recommended. Women are more likely to report symptoms which would be historically described as atypical in the presence of an MI, meaning symptoms not fitting the classic description of a heart attack (central crushing chest pain radiating to the left arm with associated dyspnoea and sweating). The labelling of symptoms of typical or atypical can result in delays to presentation and to diagnosis and can contribute to perception of risk issues within the community.

### 4. Time to treatment

Perception of risk also delays time to treatment as healthcare workers also underestimate the risk of ACS in women [1,4,5,11,17]. An Australian state wide study of 13,451 ACS patients found door to treatment times in STEMI patients were 8 min longer (9 % longer) in women than men [4]. The Lancet women and cardiovascular disease commission [1] reported women with cardiovascular disease were under-recognised by physicians and allied health care professionals, with evidence for delays at multiple sites from first contact through to the coronary catheterization laboratory [2,18–20]. Causes of these delays to treatment can be unexpected and, in some cases, embedded in inappropriate policy and treatment algorithms. For example, a European study [20] of gender specific ambulance prioritization policies found that some emergency ambulance services place a lower priority on transporting women who present with possible STEMI than men. An analysis of the UK national heart attack registry has shown that women admitted with an NSTEMI were less likely to be admitted in the first 24 h under a cardiologist and are less likely to be managed on a cardiology

ward [21]. Such structural biases and reduced access to specialist care serve only to magnify delays in treatment and appropriate risk assessment [22].

#### 4.1. Solutions

Educational programs are needed to inform healthcare providers at all levels about the risk and symptom profile and presentation of cardiovascular disease in women to decrease missed diagnoses and delays to treatment. Early detection in primary care is needed. Timely in-hospital escalation of care should also be prioritised. Any policies inappropriately delaying care for women should identified and removed. Policies and strategies aimed at narrowing outcome disparities should be funded rather than dependant on advocacy groups or individuals. Policies and strategies are needed to ensure healthcare workers and hospitals in socioeconomically deprived areas are also included. Comprehensive standardized STEMI protocols have been shown to reduce sex disparities and should be used [18,19].

### 5. Referral for angiography and angioplasty

Women with ACS are less likely to receive acute reperfusion therapy, women are less likely to be referred for angiography, and are less likely to be treated with angioplasty [1,2,19,23,24]. These sex-based differences in use of angiography angioplasty and/or thrombolysis persist post multivariate risk analysis adjusting for differences in age, comorbidities and acuity of presentation in several studies [2,4,19,23,24], many of these studies also demonstrate higher risk and age adjusted death rates and MACE rates for women within these cohorts [2,4,19,24]. Previous studies have suggested that women with high GRACE ACS risk score (>140) are 50 % less likely to be referred for cardiac catheterization within 24 h in the setting of an NSTEMI as man with a low risk GRACE score [25].

A large study from the United Kingdom assessing quality indicator attainment in 691,290 women and men found women less frequently received 13 out of 16 quality indicators of ESC guideline indicated care including timely reperfusion. Timely reperfusion therapy was given to 76.8 % of women and 78.9 % of men;  $p < 0.001$ , and timely coronary angiography for non-STEMI was performed in 24.2 % of women and 36.7 % of men;  $p < 0.001$ , 30 day adjusted mortality was more than double for women than men 5.2 % (IQR 1.8–13.1 %) vs 2.3 % (IQR 0.8–7.1 %),  $p < 0.001$ . Significant differences in prescribed post PCI medications were also noted. Authors found an estimated 8243 (95 % CI 8111–8375) deaths among women over the 10 year time period could have been prevented if quality attainment in women had been equal to that attained for men [19].

Other studies have also demonstrated disparity in use of reperfusion therapies [2,4], the CONCORDANCE study including data from 41 Australian centres and 2898 STEMI patients found less women received coronary angiography (adjusted odds ratio [aOR], 0.53; 95 % CI, 0.41–0.69), revascularization (aOR = 0.42; 95%CI, 0.34–0.52), timely revascularization (aOR = 0.72; 95%CI, 0.63–0.83) or primary PCI (aOR = 0.76; 95 % CI, 0.61–0.95) in this study MACE rates at 6 months were higher in women (aOR = 2.68; 95 % CI, 1.76–4.09) as was mortality (aOR, 2.17; 95 % CI, 1.24–3.80). A Scottish study also found less immediate invasive management was provided to women than men with myocardial infarction or angina, and men were more likely to receive coronary angiography, (aOR = 1.52; 95%CI 1.37–1.68) and PCI (aOR 1.68, CI 1.52–1.86) [24]. Similar sex-based disparities are reported in China [23] when evaluating data from CCC-ACS project (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) studying 82,196 patients admitted for ACS at 192 hospitals in China from 2014 to 2018. Authors report reperfusion therapy for ST-segment-elevation myocardial infarction was provided less frequently to women than men (50.2 % versus 59.5 %,  $P < 0.001$ ), differences persisted post risk adjustment, and women with NSTEMI-ACS were less likely to undergo

timely PCI than men (30.5 % versus 34.2 %,  $P < 0.001$ ).

Sex-based differences in risk do not adequately explain all demonstrated disparities in use of angioplasty, angiography, or thrombolysis for women. Careful multivariate risk adjustment using age, comorbidities, acuity of presentation and GRACE scores still show sex-based differences persist [2,4,19,23,24]. These differences are associated with poorer outcomes for women including higher mortality [2,4,19,24].

### 5.1. Solutions

All institutions should be using comprehensive standardized STEMI protocols to reduce sex disparities in revascularization rates, and time to revascularization [18,19], objective rather than subjective assessment of frailty or eligibility for revascularization is advised. Age alone as an assessment of frailty should be avoided, as should body size alone. Patients at the highest risk for PCI are often those who will also benefit the most from revascularization [26]. Quality improvement efforts should promote equity of access to treatment.

## 6. PCI outcomes

Numerous studies have shown worse outcomes following PCI in women compared to men. A meta-analysis of 49 studies involving 1,032,828 patients with coronary artery disease reported that the odds of in-hospital mortality (OR 0.58 95 % CI 0.52–0.63,  $P < 0.001$ ), 30-day mortality (OR 0.64, 95 % CI 0.61–0.66,  $P = 0.04$ ), 1-year mortality (OR 0.67, 95 % CI 0.60–0.75,  $P < 0.001$ ), and at least 2-year mortality (OR 0.71, 95 % CI 0.63–0.79,  $P = 0.005$ ) was lower in men compared to women following PCI [27]. A pooled individual patient-level meta-analysis of data from 10 randomized primary PCI trials reported that women had significantly higher unadjusted as well as adjusted risk of all-cause death or HF hospitalization compared to men, even though infarct size was similar [8]. Similarly, an analysis of pooled data from 21 randomized controlled trials including 32,877 patients (9141 (27.8 %) were women) reported that women were older, had higher body mass index and more prevalent hypertension and diabetes, and less frequent history of percutaneous revascularization compared to men [28]. Lesions in women had smaller reference vessel diameter and shorter lesion length by angiographic core lab analysis. At 5 years, women had a higher unadjusted rate of MACE (18.9 % vs. 17.7 %;  $p = 0.003$ ), all-cause death (10.4 % vs. 8.7 %;  $p = 0.0008$ ), cardiac death (4.9 % vs. 4.0 %;  $p = 0.003$ ) and ischemia driven-TLR (10.9 % vs. 10.2 %;  $p = 0.02$ ) compared with men. Even following adjustment for differences in clinical and lesion characteristics, female sex was an independent predictor of MACE (hazard ratio [HR]: 1.14; 95 % confidence interval [CI]: 1.01 to 1.30;  $p = 0.04$ ) and ischemia driven target lesion revascularization (HR: 1.23; 95 % CI: 1.05 to 1.44;  $p = 0.009$ ). Many of the disparities in PCI outcomes reported between women and men have not narrowed over time. An analysis of administrative data including 6,601,526 PCI procedures performed over a decade (2004–2014) from the United States revealed that women had higher in-hospital crude mortality (2.0 % vs 1.4 %) and complication rates compared to men (11.1 % vs 7.0 %) [29]. Even when baseline differences were adjusted for, women had an increased odds of in-hospital mortality (OR 1.20 (95 % CI 1.16,1.23)) and major bleeding (OR 1.81 (95 % CI 1.77,1.86)), and these disparities persisted over the 10 years of the study. Sex-based differences in clinical outcomes have also been reported in several meta-analyses for PCI procedures undertaken in unprotected left main PCI [30] and CTO procedures [31] and more recently from UK data in complex high-risk but indicated coronary interventions (CHiP) [32]. Whilst many of these studies are either observational studies or post-hoc analyses of randomized trials in which sex is not randomly allocated and therefore unmeasured confounders including frailty may contribute to the worse outcomes in women, there is a large body of literature highlighted below that suggests women do not receive optimal evidence-based guideline

recommended treatments during PCI that may contribute to the disparities that we highlight above. Below we focus on some of these areas and how these disparities may be actioned.

## 7. Radial access

The benefits of radial access for angiography and PCI are well proven particularly in ACS patients and patients at higher bleeding risk [33–37], with the magnitude of benefit related to baseline bleeding risk [38]. The mortality benefit demonstrated by major RCTs has led to a Class 1A guideline recommendations for transradial access in patients presenting with ACS from the European Society of Cardiology 2020 NSTEMI guidelines [39] and the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization [40], however women less frequently receive radial access, and are exposed to high bleeding risk and risks of death as a result.

Data from the Mayo Clinic PCI Registry (2006–2016) studying 21,123 patients found women received radial access in 23.6 % of cases compared to men with 26.4 % radial access ( $p < 0.001$ ), differences persisted post multivariable risk adjustment (aOR 0.78, 95 % CI 0.72–0.84;  $p < 0.0001$ ), overall women experienced more bleeding (6.3 vs. 3.0 %;  $p < 0.0001$ ) but bleeding was less likely in those with radial access (OR 0.45, 95 % CI 0.36–0.56;  $p < 0.0001$ ). Similar results were found in a 16,330 patient study of ACS patients evaluating data from a state-wide Australian registry [36], authors found radial access was used in 41.6 % of women and 51.0 % of men, ( $p < 0.001$ ) and female sex independently predicted lower radial use (aOR 0.75, 95%CI 0.68–0.83). Radial access was associated with lower mortality and major bleeding, and authors of this study found lower use of radial access in women persisted independent of body size and comorbidities. Similarly, an analysis of 412,122 patients who underwent PCI between 2007 and 2012 across all indications for PCI in the United Kingdom found radial access was used in 45.5 % of men and 40.7 % of women ( $P < 0.001$ ) [41]. The use of TRA increased in both genders across all indications (Elective and ACS) over time, although this lagged behind in women compared with men. Even though women were less likely to receive radial access, the magnitude of benefits were similar and radial access was independently associated with a lower in-hospital major adverse cardiovascular event (odds ratio men [OR] 0.82, 95 % CI 0.76–0.90; OR women 0.75, 95 % CI 0.66–0.84) and 30-day mortality (OR men 0.80, 95 % CI 0.73–0.89; OR women 0.82, 95 % CI 0.71–0.94) in men and women respectively. Interestingly the effect size for the reduction in hospital major bleeding associated with radial access in women (OR 0.26, 95 % CI 0.20–0.33) was greater than that for men (OR 0.54, 95 % CI 0.44–0.66) suggesting that women may have a great benefit for this endpoint.

These data demonstrate in countries with high and low radial access use, sex-based differences in the way PCI is performed impacts on treatment and outcomes for women with coronary artery disease and ACS. Women receive less radial access and have higher mortality when being treated for STEMI. Radial access is also associated with more frequent use of potent P2Y12 inhibitors. Depriving female patients of equitable use of radial access not only limits their ability to benefit from the safer risk profile of transradial access, it also decreases their chances of being treated with more potent guideline recommended medical therapy [42].

### 7.1. Solutions

Improving rates of radial access may decrease outcome disparities for women presenting with ACS, and concurrently allow for more potent P2Y12/antithrombotic use. Whilst case volume and learning curves for radial access can limit initial progress in learning radial access skills the majority of patients, women and men can be accessed radially for PCI and benefit from lower complication and mortality rates as a result. Investing time in developing radial access skills, radial workshops (for early mid and late career proceduralists), and radial first strategies are

essential to improve patient outcomes in ACS PCI.

## 8. Intravascular imaging

Intracoronary imaging (ICI) in the form of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are essential adjunct procedural tools used to optimise PCI results, with current guidelines recommending their use in selected groups of patients undergoing complex PCI including those undergoing PCI for left main stem disease, complex bifurcation lesions or long lesions, and chronic total occlusions [43,44]. The clinical value of ICI in optimising procedural outcomes and reduction of MACCE, target vessel revascularization (TVR) has been well-established in several randomized controlled trials and subsequent meta-analyses, [45–48] and may be of greater value in women who have a higher incidence of non-obstructive CAD and spontaneous coronary artery dissection than men. In a UK analysis of 994,478 PCI procedures undertaken between 2006 and 2019, 8.4 % of 738,616 men received ICI, whereas only 7.9 % of 255,862 women received ICI ( $P < 0.001$ ) with the absolute rates of ICI use approximately 5 % lower in women than men (women 14.5 % vs men 19.6 %;  $P < 0.001$ ) in 2019 [49]. Even after differences in baseline characteristics, female sex was independent negative predictor (OR 0.93; 95 % CI: 0.91–0.96) for the receipt of ICI. Furthermore, utilisation of ICI was lower for all EAPCI recommended indications including acute coronary syndrome (11.6 % vs 12.3 %;  $P < 0.01$ ), chronic total occlusions (16.2 % vs 18.3 %;  $P < 0.01$ ), long lesions (13.1 % vs 16.3 %;  $P < 0.01$ ), LMS PCI (55.1 % vs 57.5 %;  $P < 0.01$ ), in-stent restenosis (28.0 % vs 30.7 %), calcified lesions (36.6 % vs 40.1 %;  $P < 0.01$ ) and stent thrombosis (30.9 % vs 34.9 %;  $P < 0.01$ ) in women compared to men. The authors reported that women gain as much benefit from ICI as men, with the use of ICI associated with a similar lower odds of adjusted in-hospital mortality and MACCE in women and men.

### 8.1. Solution

Studies such as those highlighted above consistently show that intravascular imaging is under-utilised in contemporary practice, even with several RCTs showing an association with better outcomes. This under-utilisation seems particularly evident in women. Some of the barriers to use of imaging relate to operator training/expertise in interpretation of the images as well as funding in many healthcare systems. More equitable access to training programs and emerging technologies may in part narrow these disparities and ensure that those that derive the greatest benefit from ICI are more likely to receive it.

## 9. Completeness of revascularization

Both sex, and incomplete revascularization are independently associated with poorer outcomes for patients with ACS [50–53]. A meta-analysis [54] of 38 studies including 156,240 patients reported that the odds of death (OR 0.69, 95 % CI 0.61–0.78), myocardial infarction (OR 0.64, 95 % CI 0.50–0.81), and major adverse cardiac events (OR 0.63, 95 % CI 0.50–0.79) were significantly lower in the patients who underwent complete revascularization. Incomplete revascularization in women is associated with poorer outcomes and higher cardiac death rates [3]. Burgess et al. [3] studied consecutive STEMI patients and found women with incomplete revascularization (quantified by a residual SYNTAX score (rSS)  $> 8$ ) were more likely to experience cardiac death or MI at long term follow up than men with incomplete revascularization (rSS  $> 8$ ) (OR 2.14; 95%CI 1.17–3.91), these sex based differences persisted with risk adjustment for multiple comorbidities including diabetes, shock at presentation, renal dysfunction and age, and were seen in a real-world population which excluded those patients not considered suitable for angiography or angioplasty. Baseline SYNTAX scores at presentation were 15.0 (IQR 9–20) in women, and 16.0 in men (IQR 9–20;  $p = 0.02$ ). At a mean follow up of 3.6 years 43 % of

women with incomplete revascularization (rSS  $> 8$ ) had experienced cardiac death or MI, compared to 23 % of men with IR ( $p = 0.001$ ), 17 % of women with complete or near complete revascularization (rSS 0–8), and 10 % of men with complete or near complete revascularization (rSS 0–8;  $p = 0.10$ ).

### 9.1. Solutions

Current evidence from 5 large RCTs, several real-world observational studies, and meta-analyses strongly support the use of complete revascularization [51–53,55–61], the data that supports this comes from studies where  $>90$  % of all patients assigned to CR completed all PCI within 23 days, and 82 % were treated before hospital discharge from their index event. Timely complete revascularization along with key performance indicators for ACS treatment, such a guideline recommended optimal medical therapy should be a priority. Poorer outcomes for women with incomplete revascularization suggest timely complete revascularization may be even more important in women with a high burden of residual disease [3,60]. To decrease current outcome disparities for these patients efforts should be made to minimise delays to CR and to achieve a residual SYNTAX score as close to 0 as possible in all patients, particularly in women [3,60] and patients with diabetes [60,62,63]. Where delays to CR are unavoidable guideline based prescribing of optimal medical therapy (OMT) including use of potent P2Y12 inhibitors and statins are extremely important for women with a high burden of residual disease [3,19,42,64,65].

## 10. Prescription of guideline based medication-potent P2y12 agents, statins and OMT

Women receive less potent P2Y12 (P-P2Y12) inhibitors, and statins, and have higher mortality when being treated for STEMI [2,3,42,66]. Guidelines strongly recommend the use of (P-P2Y12) inhibitors (ticagrelor and prasugrel) and aspirin for patients with ACS unless they are receiving thrombolysis or oral anticoagulants [67], due to a demonstrated decrease in major adverse cardiac events with use of (P-P2Y12) inhibitors [68–71]. Since 2012 European guidelines have recommended the use of ticagrelor and prasugrel in preference to clopidogrel [72], American guidelines were amended to recommend P-PY12 in preference to clopidogrel (where bleeding risk is not prohibitive) in 2016 [73]. A clear outcome benefit for both women and men prescribed potent P2Y12 inhibitors rather than clopidogrel have been demonstrated by RCT and subsequent meta-analyses [70,74].

Several studies have found women receive less potent P2Y12 inhibitors than men [2,3,42,66]. Unpublished data from an analysis of the British Cardiovascular Intervention Society (BCIS) national percutaneous coronary intervention database studying 43,131 patients enrolled from 2010 to 2020 found women undergoing primary PCI were less likely to receive potent P2Y12 inhibitors (51.2 %) than men (55.2 %;  $P < 0.001$ ) [42]. A higher in hospital mortality in women was reported compared to men, risk adjusted OR = 1.21 (95 % CI 1.14–1.29). Mortality was higher among women treated with clopidogrel (7.57 %), than potent P2Y12 (P-P2Y12) (Prasugrel or ticagrelor) treated women (5.39 %), men treated with clopidogrel (4.60 %) and P-P2Y12 treated men (3.61 %;  $p < 0.001$ ). Baseline patient factors including comorbidities, baseline characteristics and age did not solely explain sex-based differences in rates of prescription of potent P2Y12 inhibitors, but procedural decision making was an important factor in P-P2Y12 selection. Authors found that radial access was the factor most predictive of potent P2Y12 prescription and was significantly lower in women than men. Authors also noted that for male patients, earlier uptake of P-P212 inhibitors was evident, but there was a greater lag time to prescribing of P-P2Y12 for women. Data from the American Chest Pain-Myocardial infarction registry studying 169,505 STEMI patients from 2013 to 2017 registry found predictors of clopidogrel use rather than P-P2Y12 inhibitors included no insurance, insurance with Medicare or Medicaid, and

features associated with higher bleeding risk. Women in this study were less likely to receive P-2Y12 inhibitors (45.5 %) than men (51.6 %;  $P < 0.001$ ). Data from Australia has also demonstrated these sex-based differences in P-2Y12 prescription with 31 % of women receiving P-2Y12 and 43 % of men [3].

Women also are less likely to receive statin therapy, ACE-inhibitor/angiotensin receptor blocker therapy, and betablocker therapy post ACS [1,2,17–19,75]. Physician adherence to guideline based therapy for lipid control is poor in primary and secondary prevention of cardiovascular disease in women [1,75]. An evaluation of commercial health insurance data found after myocardial infarction statin use is significantly lower in women than in men [76], similar data has been when evaluating discharge medications of documented in STEMI patients [2].

### 10.1. Solution

Improving rates of potent P2Y12 use with increased radial access may decrease outcome disparities for women with STEMI, particularly those with multivessel disease or incomplete revascularization where the proinflammatory milieu post STEMI makes non-culprit plaque instability more likely. For patients with multivessel disease treated with PCI (or surgery) the prescription of guideline directed medical therapy is one of the strongest predictors of prognosis [64,65]. To improve outcomes post PCI, we must also improve prescription of guideline recommended medications. Greater attention to the delivery of guideline recommended ACS treatments post PCI is needed, the use of pathways and checklists in ACS treatment and discharge planning may help to close current treatment gaps in sex-based differences in the prescription of optimal medical therapy post ACS and PCI. Access to affordable medications and healthcare are essential to decrease barriers to care and minimise MACE post PCI.

## 11. Under-representation of women in randomized controlled trials as patients and as investigators

Women are also under-represented as patients in randomized controlled trials [3,77–80]. Prevalence corrected estimates evaluating the participation of women as patients acute coronary artery syndrome or coronary artery disease RCTs found significant under-enrolment of women, at 60 % of expected rates based on disease prevalence [79]. Well powered sex-specific data are essential to ensure generalizability of data and to inform guidelines and practice. The recruitment of women to RCT are critical to ensure recommended doses are appropriate for the women, and side effects limiting adherence are minimised. In ACS and PCI trials, in lab decisions regarding timing and completeness of revascularization, the use of tools in the setting of cardiogenic shock such as impella, balloon pumps and ECMO, tools for calcium modification, and imaging all need to have sex specific robust data guiding use, the under enrolment of women in cardiovascular trials also limits our ability to power analysis evaluating sex-based differences. Women are also under-represented as investigators in cardiovascular RCTs [77,78,80,81], and in guideline authorship particularly in interventional cardiology guidelines [82].

### 11.1. Solution

Proactive recruitment of women to RCTs both as patients and as investigators, authors and in leadership positions is needed to address this data gap and provide sex-specific data to narrow disparities in PCI outcomes for women with coronary artery disease. Data shows when women serve as clinical trial leaders trials are more likely to enrol more women, include a broader demographic of recruited patients, include ethnicity data, and information about diverse patient populations [77,78], which improves study validity, generalizability, and subgroup analysis. Well powered sex-specific data are essential to inform guidelines and real-world practice.

## 12. Under-representation of women in cardiology physician workforces

Physician–patient gender concordance is associated with increased patient survival for women with cardiovascular disease [7,83]. Data shows the outcome gap for women with ACS is absent when women patients are treated by women doctors [7,83]. The under-representation of women [84–88] in cardiology physician workforces has an impact on outcomes for women with coronary artery disease [7,83]. Pooled international data shows Cardiology and interventional cardiology have the lowest representation of women of all internal medical specialties [88] only 7 % of all interventional cardiologists, and 15 % of all cardiologists are women [88]. The value of diverse workforces is well established [89,90], diverse [91–97] and gender-balanced physician workforces [7,89,98] are important for patients and patient outcomes [7,83,99]. Women physicians and cardiologists are also more likely to follow guideline based care, with lower morbidity, mortality and readmission rates [7,83,100]. A large ( $n = 581,797$ ) American study [7] found the outcome gap for women with myocardial infarction was not evident when women were treated by women, similar data has reported by Tsugawa et al. [83]. Both studies [7,83] report a survival benefit for women treated by women physicians.

### 12.1. Solution

Addressing the under-representation of women, and lack of diversity in the cardiology physician workforce is complex. Effective solutions are likely to require significant institutional and cultural change. Policies to ensure equity, inclusion, diversity and a sense of belonging in our workplaces [102], and to ensure freedom from bias, discrimination and harassment are needed [102–105], as is audit of these policies to confirm they are successful. The current rate of change is underwhelming, and is an important equity issue not only for cardiologists and trainees, but also for patients and patient outcomes.

## 13. Conclusions

Our review highlights the significant disparities that exist in the management of ACS in women, including biases in referral pathways, delays in the recognition of symptoms and timely referral for coronary revascularization and subsequent provision of evidence based medical therapy. Women undergoing PCI have consistently worse outcomes both in the in-hospital setting and the longer term, which may in part relate to failure of adoption of evidence-based interventions that have been shown to improve PCI clinical outcomes.

Much of the data informing treatment efficacy and clinical outcomes in the practice of PCI is derived from RCTs that consistently under-recruit women and often do not report sex-specific interactions for the primary efficacy and safety endpoints, which may contribute to the under-provision of evidence-based care. There is consistent under-representation of women on many of the guideline committees that inform practice, with a lack of women-centric recommendations within them. Our review highlights potential solutions to narrow these gaps, both at the health system level, procedural level, and importantly in the research generating/guideline level. Whilst biological differences may account for some of the differences in outcomes between men and women, there are many policy, healthcare structural and procedural factors than can be actioned to narrow such sex-based inequalities.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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