**Title:** Healthcare disparities for women hospitalised with myocardial infarction and angina

**Short title:** Sex disparities in MI

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# Introduction

Ischaemic heart disease persists as the leading global cause of death.[1] Myocardial infarction (MI) accounts for a large proportion of death due to cardiovascular disease. Between 2007 and 2016, age-sex standardised mortality for MI in Scotland has fallen by 42.5% from 129 to 74 per 100,000 population[2] – a trend also apparent in other countries.[3] [4] Despite improvements in survival, considerable disparities exist according to sex in terms of delivery of guideline-recommended treatments and outcomes following MI suggesting women may be disadvantaged.[5]

Use of high-sensitivity troponin assays with sex-specific thresholds increases the detection of MI in women.[6] However, women are less likely to undergo percutaneous coronary revascularisation (PCI) and are more often subject to underutilisation of evidence-based secondary preventative pharmacotherapy.[5] [7] [8] Differences in adoption of invasive management may, in part, be explained by a perception held by clinicians and patients that outcomes are worse for women receiving PCI, as well as differences in symptoms and baseline risk profile which may impact clinical decision-making.[9] Adverse events post-MI, including cardiogenic shock, heart failure and death, remain more common in women than in men, most notably in those with ST-elevation myocardial infarction (STEMI).[10] [11] Whether sex remains an independent predictor of adverse events despite adjustments for the higher risk-profile of women, notably age, is less clear.

We hypothesised that sex-related differences in demographics and comorbidity underpin disparities in management and outcomes of women and men hospitalised with MI or angina. We investigated this hypothesis by analysis of a contemporary secondary care electronic registry (e-Registry) using electronic patient records (EPRs) for patients admitted to a complex regional healthcare network.[12]

# Methods

## Setting

Seven acute hospitals in the National Health Service (NHS) in Glasgow and the West of Scotland provide a complex healthcare system serving a population of approximately 1.2 million. The Golden Jubilee National Hospital is a regional cardiothoracic centre that provides invasive cardiology services for this population. EPRs were implemented across all secondary care clinical and administration systems in NHS Greater Glasgow and Clyde (GGC) and the Golden Jubilee National Hospital by June 2012 enabling capture of key components of hospital care. These EPRs have been combined into an e-Registry for quality improvement and research.[12]

The Information Services Division is part of NHS National Services Scotland and holds a range of health-related administrative data, including information relating to medicines dispensed in the community within its Prescribing Information System (PIS) database, morbidity collected from all hospital admissions in the Scottish Morbidity Record 01 (SMR01) database and all deaths registered by National Records of Scotland (NRS). Once data were extracted, identifiers were removed and replaced with a pseudonymous identifier. The research team accessed these pseudonymised datasets within a Safe Haven analytical platform.[13]

## Ethics and governance

The project was supported by the National Advisory Committee for Coronary Heart Disease on behalf of the Scottish Government. The Joint Working Project received ethical approval from the NHS GGC Local Privacy Advisory Committee and was approved by hospital management and the Caldicott Guardian for clinical governance in each health board.

## Design and methodology

Data were extracted from EPRs for all admissions (01/10/13-30/06/16) with an International Statistical Classification of Diseases (ICD-10) diagnosis of angina (I200-I209), MI (I210-I229), other ischaemic heart disease (I240-I249), or heart failure (I50) to ensure complete capture of events. Data were deposited within an existing repository for electronic health data and linked to electronic referrals for cardiovascular procedures performed in the invasive centre. An executable system was developed to identify, link and classify these records into episodes of care as detailed in a previous project.[12] Patients with a final diagnosis of MI or angina were isolated and linked to PIS prescribing data, SMR01 data for comorbidities and mortality data from NRS. This linked dataset was analysed to look at patient characteristics, invasive cardiovascular procedures, service delivery metrics, drug treatment and mortality. The pre-specified primary outcomes were 30 day and 1 year all-cause mortality (from date of admission). The receipt of cardiac interventions and medical therapy at discharge, 6 months and 1 year post-discharge were the pre-specified secondary outcomes.

## Statistical analysis

Baseline characteristics were described using means with standard deviations, total numbers with percentages, or medians with interquartile ranges. Where all patients were analysed, this included unspecified MI. Comparisons between men and women were made using appropriate statistical tests (t-test/Mann-Whitney/chi-squared/Fisher's exact). Deprivation status was identified based on home postcode and measured using quintiles of the Scottish Index of Multiple Deprivation (SIMD) 2012 measure.[14] Quintile 1 represents the highest level of deprivation with quintile 5 representing the least deprived. The top 20% most deprived data zones in Scotland are in quintile 1, and the distribution of Glasgow's data zones is 49%, 19%, 13%, 10.5%, 8.5% (Q1-Q5).[15] A Charlson comorbidity score was derived using standard procedures and ICD-10 codes included the hospital admission records.[16] Pre-admission medical therapy and medical therapy at discharge were defined as fulfilment of prescription within 90 days pre-admission and post-discharge, respectively. Medical therapy at 6 months and at 1 year were defined as fulfilment of prescription at 6 months or 1 year post-discharge +/- 45 days.

To analyse the relationship between sex and medical treatment, three analyses using mixed effects logistic models were performed for each drug and drug combination: (1) for patients alive at discharge, fulfilling a prescription claim within 90 days of discharge, (2) for patients discharged with treatment and alive at 6 months post-discharge, fulfilling a prescription claim at 6 months post-discharge, (3) for patients discharged with treatment and alive at 1 year post-discharge, fulfilling a prescription claim at 1 year post-discharge. Analyses were adjusted for age, SIMD, use of the respective drug within 90 days pre-admission, comorbidities and PCI. Furthermore, we adjusted for clustering at the discharge hospital level. When analysing the association of sex with use of drug combinations, pre-admission drug use was not adjusted for. Multivariable logistic regression was used to evaluate the association of sex and baseline factors with invasive management. Cox proportional hazards regression was used to evaluate the association of sex with all-cause mortality. Kaplan-Meier survival curves were generated for all-cause death and sex differences were assessed using a log rank test. Analyses were conducted using SAS Enterprise Guide (v5.1).

## Results

### Baseline characteristics

There were 7878 patients admitted with MI or angina between 1 October 2013 and 30 June 2016, including 3161 (40.1%) women (Table 1). Diagnosis of STEMI was made in 2042 (25.9%) patients, non-ST-elevation myocardial infarction (NSTEMI) in 3957 (50.2%) patients, hospitalised angina in 1425 (18.1%) patients, and in 454 (5.8%) patients the MI type was unspecified. Women were older than men (69.7 years vs 64.0 years, p<0.0001) and were relatively more deprived (75.7% vs 72.5% in SIMD Q1-3, p=0.0016). Diagnosis of STEMI was less common in women than men (20.3% vs 29.7%, p<0.0001), but women had a higher proportion of NSTEMI (51.7% vs 49.2%, p <0.001) and hospitalised angina (21.4% vs 15.9%, p<0.0001). Comorbidity differed according to sex both in terms of higher Charlson scores and an increased proportion of individual comorbid diseases in women, who more frequently had hypertension, atrial fibrillation, renal failure, respiratory disease, cerebrovascular disease, stroke, heart failure, dementia and depression. Compared to men, women were more often treated with statins (46.9% vs 43.2%, p=0.0013), beta-blockers (34.9% vs 30.5%, p<0.0001) and anticoagulants or antiplatelets (48.5% vs 42.1%, p<0.0001) pre-admission.

### Invasive management

Approximately 16% fewer women than men underwent coronary angiography (52.1% vs 68.2%, p<0.001) and PCI (30.3% vs 46.5%, p<0.001) (Table 1). Amongst those who had a coronary angiogram, women received PCI 10% less frequently than men (58.1% vs 68.1%, p<0.001). The difference in median duration of hospital stay was 1 day (5 days for women vs 4 days for men, p<0.001). In patients with STEMI, 6.2% fewer women than men were transferred for immediate invasive management (63.6% vs 69.8%, p=0.0117) and the median door-to-balloon time was longer for women (23mins vs 21mins, p<0.0001) (Supplementary Table 1a). We also examined the effect of age on door-to-balloon time; in those above 65 years, the median time was 3 minutes longer for women than for men (24mins vs 21mins, p<0.0001), whereas no difference existed in those under 65 years (21mins vs 21mins, p=0.2287).

The sex differences in demographic characteristics were similar for patients with STEMI and NSTEMI (Supplementary Tables 1a and 1b). In patients hospitalised with angina, there were fewer differences although women were older and less frequently received invasive management (Supplementary Table 1c).

**Predictors of coronary angiography and PCI**

After adjusting for differences in age, deprivation and comorbidities, sex was an independent predictor of both coronary angiography and PCI in all patients (Table 2). For patients with STEMI, men were more likely to receive coronary angiography (adjusted OR:1.44 CI:1.05-1.97) and PCI (adjusted OR:1.62 CI:1.28-2.05). The same was true for patients with NSTEMI (coronary angiography adjusted OR:1.48 CI:1.26-1.75, PCI adjusted OR:1.52 CI:1.32-1.76).

Several baseline characteristics were found to be independently associated with lower use of coronary angiography and PCI in patients with MI including older age, prior MI in STEMI, and heart failure in NSTEMI (Figures 1a and 1b). There were few major sex differences within subgroups; most notably, in those with NSTEMI and renal failure men were less likely than women to receive PCI, and in those with NSTEMI and dementia women were less likely than men to receive coronary angiography and PCI.

**Medical therapy post-MI**

Women were less frequently treated with antiplatelets than men (with no greater treatment with anticoagulants), with a difference at 1 year of 2.8% (p=0.0368) (Figure 2). At 1 year, women were also less often prescribed statins (3.8% difference, p=0.0048) and ACE inhibitors or ARBs (4.3% difference, p=0.003). A similar pattern was seen in the NSTEMI group (Supplementary Figure 1b). In this group, women were also less frequently treated with beta-blockers at 1 year. Drug therapy was similar for men and women at 1 year in the

STEMI and hospitalised angina groups, other than anticoagulants, with which fewer women than men were treated (Supplementary Figures 1a and 1c). In patients with STEMI or hospitalised angina, sex was not an independent predictor of treatment with anticoagulants or antiplatelets, statins, ACE inhibitors or ARBs or beta-blockers at 1 year (Supplementary Table 2). Conversely, in NSTEMI men were 20-32% more likely than women to be treated with statins, ACE inhibitors or ARBs, or beta-blockers at 1 year.

**Death**

Case-fatality at 30 days was 4.9% in all patients, 6.9% in STEMI patients and 2.9% in NSTEMI patients (Table 3). Case-fatality at 1 year was 10.9% in all patients, 10% in STEMI and NSTEMI patients and 5.1% in patients hospitalised for angina. Survival was worse for women than for men, driven by marked differences in outcomes in STEMI (Figure 3); in this group, 6.3% more women than men had died by 1 year (14.3% vs 8.0%, $p<0.0001$). However, after adjustment for baseline demographics, comorbidities and PCI, the association between sex and mortality after STEMI was not significant and male sex emerged as an independent predictor of death in patients with NSTEMI (1 year HR:1.38 CI:1.12-1.69) (Table 3). A subgroup analysis of those patients treated with PCI showed similar results.

# Discussion

In this study of 7878 patients with hospitalised with MI or angina from 2013-2016 we found that women had a higher crude rate of death but, after accounting for baseline risk factors, men were more likely to die following NSTEMI, with no difference for patients with STEMI or hospitalised angina. After taking account of baseline risk factors, there remain sex disparities for patients with MI related to treatment times, invasive management and use of secondary prevention therapies. Our findings highlight the need for renewed focus on achieving health equity for women and men through prioritisation of guideline-directed management.

Our analysis serves evidence of the persistently high crude mortality event rate in women, particularly with STEMI. We found that death from any cause was 2.6% more common amongst women than men at 1 year, driven predominantly by deaths in the STEMI population for whom the crude difference was in excess of 6%. The survival curves for men and women with STEMI separate almost immediately, and this is reflected in the 3.6% mortality difference as early as 30 days. In this study, the crude differences were explained by the older age of women compared to men, greater burden of comorbidity, higher relative degree of deprivation and reduced access to coronary angiography and PCI.

We have included a comprehensive indicator of social deprivation which measures deprivation across seven weighted domains. In our study, women were more often from deprived socioeconomic groups. Socioeconomic deprivation is strongly linked with poorer outcomes in MI and in women the effect is more prominent.[17] In Scotland, rates of coronary revascularisation have increased across all deprivation categories over the past 10 years with the exception of the least deprived.[2]

Important sex differences in cardiovascular risk factors are evident; diabetes and hypertension are more common in women (particularly younger women), and they may increase risk more in women than men.[18] There are a number of other risk factors specific to women, including hypertensive disorders of pregnancy and pregnancy-related diabetes mellitus, which are associated with a higher later cardiovascular risk.[19] We evaluated additional important comorbidities, notably dementia and depression. Although we must interpret the results with caution due to small numbers of patients identified with each condition, the presence of dementia was associated with a lower likelihood of coronary angiography. Dementia likely serves as a disincentive for clinicians and the families of affected patients to adopt invasive management. It's rising prevalence and emergence as a leading cause of death in women in several countries will increase the magnitude of this disparity.[20] [21] Large trials to investigate the appropriate treatment strategy for older patients with MI, including those with dementia, are underway.[22] [23]

We found that an invasive strategy was used less often in the management of women with MI than it was for men, and this mirrors existing literature.[5] [7] [24] [25] Women were less likely to undergo coronary angiography and PCI. Our analyses suggest that this factor may, in part, explain why crude survival is worse for women than it is for men. There are several reasons why this discrepancy may exist. There were notable differences in route of admission to hospital, with fewer women than men taken directly to the catheterisation laboratory irrespective of MI type. This will incur delays to revascularisation and may reduce the likelihood of coronary angiography altogether. Differences in admission route may be explained by greater diagnostic uncertainty amongst women, who report non-specific or atypical symptoms more often than men.[26] Data on the time between symptom onset and first contact with medical services would highlight delays in presentation, when the benefits of emergent coronary revascularisation are less certain. Finally, emergency care decisions regarding coronary angiography and PCI in women may be influenced by smaller coronary anatomy, more technically challenging vascular access (the excess door-to-balloon time seen in older women in this study may also reflect this), and greater risk of procedure-related complications and post-procedural mortality.[25] Although bleeding complications remain more prevalent in women despite accounting for age, comorbidity and medication use, major adverse cardiac events are largely explained by baseline factors such as these.[25] [27]

A further important finding of our study is that male sex was independently associated with a higher risk of death in patients with NSTEMI. This association has been recognised previously and highlights the importance of evaluating subtypes of MI separately.[28] [29] The reason for this is likely multifactorial. One possible explanation is that women have less obstructive coronary artery disease than men and, in post-menopausal women, more efficient vascular tissue repair.[30] Differences in provision of primary preventative medical therapy may also contribute towards the findings. Finally, we lack data on cigarette smoking. In MI, smoking is not only more prevalent in men than in women[5] [24], but is also thought to be associated with different pathologic mechanisms – predominantly plaque rupture and acute thrombosis in men, and plaque erosion with superimposed thrombosis in women.[31]

Our study has a number of limitations. In addition to those that are inherent to the retrospective design, we were unable to include several important prognostic variables, including haematological and biochemical bloods tests, biomarkers, haemodynamics, left ventricular systolic function, coronary anatomy and extent of disease. We lack information regarding rates of prior PCI, subsequent coronary artery bypass grafting and symptom-burden after the event. However, women are less likely than men to undergo coronary artery bypass grafting and, even in the absence of adjusting for this, the crude association between female sex and death was removed. A further confounder is lack of data on sex of the treating physician; female patients with MI treated by male physicians are less likely to survive than if treated by female physicians, and greater male physician-experience in treating female patients is linked to better outcomes.[32]

## Conclusion

Survival at 30 days and 1 year following STEMI is worse for women than for men. However, this is explained by relative differences in baseline characteristics such as older age, greater deprivation, more prevalent comorbidity and lower rates of coronary angiography and PCI. Differences in the use of evidence-based drug therapy following MI also exist, with women at a disadvantage. Amongst patients with NSTEMI, male sex is an independent predictor of mortality. Efforts to address these sex disparities should be directed towards better understanding the differences in baseline risk and care pathways in order to highlight areas that would benefit from target, sex-specific intervention.

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# Legends

**Table 1.** Baseline demographics and management for all patients according to sex

**Table 2**. Association of sex with coronary angiography and PCI according to diagnosis (odds ratio and 95% confidence interval shown for men vs women)

**Table 3.** All-cause death at 30 days and 1 year according to sex and diagnosis (adjusted hazard ratio[a] and 95% confidence interval shown for men vs women)

**Figure 1a.** Association of baseline characteristics with coronary angiography according to sex for STEMI and NSTEMI (adjusted odds ratio[a] and 95% confidence interval shown for 10-year increase in age, most vs least deprived, presence vs absence of comorbidity)

**Figure 1b.** Association of baseline characteristics with PCI according to sex for STEMI and NSTEMI (adjusted odds ratio[a] and 95% confidence interval shown for 10-year increase in age, most vs least deprived, presence vs absence of comorbidity)

**Figure 2.** Medical therapy at discharge*, at 6 months** and at 1 year** for all patients according to sex and medication

**Figure 3.** Kaplan-Meier curves for all-cause death according to sex and diagnosis