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REVIEW ARTICLE

Are Sex Differences in Outcomes of Patients with ACS from Observational Registries Similar to the Findings from Randomized Clinical Trials?

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Abstract: ***Background:*** The incidence of acute coronary syndrome is reported to be higher for males than females, yet clinical outcomes following acute myocardial infarction are worse among females. Information about acute coronary syndrome outcomes is obtained from randomised and cohort data. However, randomised controlled trials which are designed to evaluate the efficacy of clinical interventions often have limited external validity, and observational studies which draw inferences from the effect of an exposure whilst being more generalizable are limited by confounding. ***Methods:*** We undertook a structured literature review of research manuscripts published between 2000 and 2015 to examine whether reported sex-dependent outcomes following acute coronary syndrome differed between randomised control trials and observational registries. ***Results:*** Of 56 manuscripts, we found consistency between the two types of study designs – each type of study describing worse clinical outcomes for females with acute coronary syndrome. We also found a reduction in the use of guideline recommended therapy in females. ***Conclusion:*** Further research is needed to understand at a mechanistic and health services level why such a discrepancy in clinical outcomes exists.

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INTRODUCTION

It is well recognised that the incidence of ischaemic heart disease is higher for males than females, and that males have a higher mortality rates from ischaemic heart disease [1]. For acute myocardial infarction (AMI), however, a number of studies suggest that mortality rates are higher among females than males [2,3]. Information about acute coronary syndrome (ACS) outcomes is obtained from randomised and cohort data. Randomised controlled trials (RCT) are designed to evaluate the efficacy of clinical interventions, but often have limited external validity. Observational studies draw inferences from the effect of an exposure and, whilst being more generalizable, are limited by confounding [4,5]. Therefore, we aimed to examine whether reported sex-dependent outcomes following ACS differed between RCTs and observational registries. We focus initially on the results of RCTs, then observational registries and finally compare and contrast the results from the two types of study design.

METHODS

We followed the PRISMA guidelines to conduct a structured literature review [6]. A Medline search strategy was developed and adapted for CINAHL, EMBASE, Web of Science and AMED. All databases were searched from 1st January, 2000 to the 18th September, 2015. The search was restricted to English language publications. A full search strategy can be found in Appendix **1**.

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Eligibility Criteria

All abstracts were reviewed and potentially eligible studies selected (OB). Eligible studies were those, which assessed patients with ACS, included females in their cohort, were either based on registry or randomised data and provided outcomes with respect to sex. Meta-analyses were reviewed if they met the above criteria. Manuscripts were restricted to those where the full text was available in English; posters and conference abstracts were excluded. Eligible manuscripts were reviewed in full and their references used to identify additional manuscripts. Whenever possible, supplementary data specifically concerning subgroup analyses were sought and reviewed where available. When reviewing eligible manuscripts for further manuscripts, the time restrictions were not applied. Fig. (**1**) shows the flow of selection of manuscripts from the search engines.

RESULTS

In total 56 manuscripts fulfilled the inclusion criteria (Fig. **1**). There were 29 manuscripts about RCTs and 27 observational registries. There were seven RCTs and seven observational registry manuscripts that focussed on reperfusion strategies. Twenty one manuscripts considered the utilisation of medications (fourteen RCTs and one observational registry). Eleven manuscripts considered an invasive strategy as the primary focus of the article, of which eight manuscripts were about RCTs (concerning three different trials) compared with three observational registry studies.

Twelve registry manuscripts primarily focussed on outcomes whilst four considered the incidence of acute myocardial infarction (AMI) or its risk factors.

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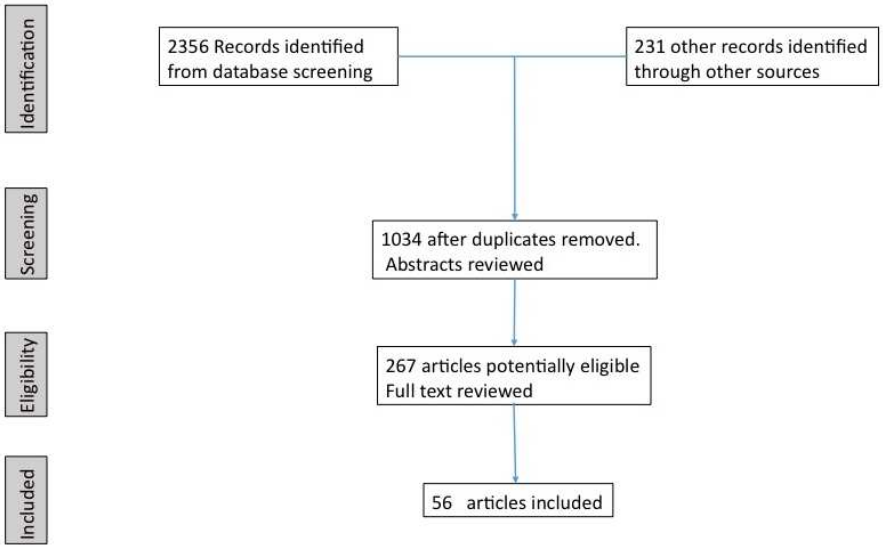

Fig. (1). Flow chart of article selection.

The total number of patients across all included studies was 2,538,327 of which 308,781 patients were in RCT and 2,229,546 in observational registries.

The proportion of females in the selected manuscripts was, on average, 31.5%, being 28%, range 18% to 38% for RCTs and 35%, range 24% to 52% for observational registries.

Reperfusion Therapy for AMI - RCTs

The long-term outcomes for 30-day survivors of AMI who were in the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO 1) trial of four different thrombolytic strategies (Streptokinase and intravenous heparin, streptokinase and subcutaneous heparin, tissue plasminogen activator (t-PA) and intravenous heparin and a combination of streptokinase, t-PA and intravenous heparin were worse among females. The Kaplan Meier estimated mortality rates were 36.2% for females vs. 29.5% for males (P<0.0001) [7]. A higher proportion of females had cardiogenic shock 33.9% vs. 25.6%. Multivariable regression estimated a hazard ratio of 1.21 - suggesting that, on average, the risk of death was 21% higher for females. The International Studies of Infarct Survival (ISIS2) trial investigated the efficacy of aspirin and streptokinase both individually and combined on 35-day mortality for AMI. The proportion of females was 23%. Survival was greatest for the combination of aspirin and streptokinase and, although evident across both sexes, males gained more from the intervention than females. Moreover, females fared worse across all groups – mortality rates being 14.6% among females compared with 9.4% among males [8].

The ISIS 1 trial of intravenous atenolol among patients hospitalised with AMI reported higher rates of mortality at 7 days for females in both the intervention 5.2% vs. 3.5% and control groups 7.5% vs. 3.7% [9]. The Should We Emergently Revascularise Occluded Coronaries for Cardiogenic Shock (SHOCK) trial comparing emergency revascularisation (angioplasty or bypass surgery) vs. medical stabilisation (which could include intra-aortic balloon pump and thrombolysis) at up to 11 years follow-up among patients with AMI complicated by cardiogenic shock comprised 32% females. The study demonstrated improved survival with early revascularisation, but did not demonstrate any interaction between the treatment assigned and sex, or that sex was an independent risk factor [10]. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trial investigated the use of streptokinase in AMI patients. It demonstrated improved outcomes among those who received streptokinase across both sexes. Even so they demonstrated higher mortality rates for females compared with males in both those who received streptokinase and in the control group (28.3% vs. 14.5% and 31.3% vs. 16%, respectively). Although statistical significance was only reached for males, the trial described the same results for those discharged alive. For patients discharged alive, there was no difference between those in the streptokinase arm and the control arm– females had worse outcomes. (female mortality rate 11.6% streptokinase) vs. 11.5% control, male mortality rate 6.3% for both the streptokinase and the control arms) [11].

In the Danish Trial in Acute Myocardial Infarction-2 (DANAMI2) trial, patients with ST elevation myocardial infarction (STEMI) were randomised to either percutaneous coronary intervention (PCI) or thrombolysis. The trial examined patients who presented to hospitals without the availability of PCI on site as well as those who presented to PCI-capable hospitals. The primary end point was 30-day mortality, clinical evidence of re-infarction or disabling stroke. The proportion of females was 27%, with no difference in the proportion of females between the two arms. The investigators demonstrated no difference in rates of mortality or stroke by intervention or control. There was, however, a reduction the in the rate of reinfarction (1.6% in the PCI group compared with 6.3% in the thrombolysis group; P<0.001). Moreover, females who received PCI had better outcomes compared with females who received thrombolysis and, notably, received a greater benefit than males (odds ratio (OR) for female 0.47 (95%CI 0.27-0.81 P=0.005) vs. male 0.59 (95% CI 0.39-0.90, P=0.01) [12].

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial considered the addition of clopidogrel to aspirin and fibrinolytic therapy for patients with STEMI. The primary outcome was a composite of an occluded infarct-related artery at angiography, death or recurrent myocardial infarction prior to angiography. The proportion of females in the trial was 20%. The investigators found that the addition of clopidogrel resulted in an absolute risk reduction of 6.7% for the primary endpoint. Additionally, there was a higher incidence of the primary endpoint among females who received clopidogrel or placebo compared with males (16.9% vs. 14.5% and 24.7% vs. 20.8%, respectively) [13].

Reperfusion Therapy for AMI – Observational Registries

The SHOCK registry comprised patients who were not randomised to a treatment arm of the SHOCK trial. There were more fe-

males in the registry than in the trial (36% vs. 32%, respectively). A higher proportion of females underwent PCI than medical therapy (37% vs 27%). There was a survival benefit for males who received revascularisation, though this benefit was not apparent among females [14].

Boucher *et al.* used the Quebec hospital registry to look at use of thrombolysis and outcomes with respect to age. Here the proportion of females was 30%, who were older than males. Being female carried an adjusted OR of 1.36 (95% CI 1.04 -1.79) for in hospital mortality [15].

In the Acute Myocardial Infarction in Switzerland (AMIS) Plus registry the proportion of females was 28%. Females more frequently than males had cardiogenic shock (10% vs. 8%). However, females tended to develop cardiogenic shock during their admission rather than present with it (77% vs. 23%). Being female was a predictor for both in-hospital mortality and the development of cardiogenic shock, although neither were statistically significant. When the temporal trends were examined then the incidence of cardiogenic shock is decreasing. This is being driven by a reduction in the development of cardiogenic shock during admission [16].

The Myocardial Ischaemia National Audit Project (MINAP) was studied to look at age dependent in-hospital mortality. The prevalence of females within the study population was 35%. They modelled their groups by sex, as there was significant interaction between age, in-hospital mortality and sex for both STEMI and NSTEMI (P<0.001). As age increased so did the OR for all cause in-hospital mortality. Being male conferred a higher adjusted OR in all age groups for both STEMI and NSTEMI [17].

The Vienna STEMI Registry examined the impact of updated guidelines on clinical outcomes; in their cohort 28% of patients were female. In-hospital mortality rates for females were double that of males (14.7% vs. 7.4%, P<0.001). The worst outcomes were seen in females who did not undergo reperfusion; who had in-hospital mortality rates of 21.2%. Even so, sex was not found to be an independent predictor of death [18].

The Swedish RIKS-HIA registry was used to report long-term outcomes for patients with STEMI who underwent reperfusion. The proportion of females was 30%, with a higher frequency of females in the hospital thrombolysis group compared to pre-hospital thrombolysis and primary PCI (PPCI). Although the authors did not comment on sex-specific outcomes, it did not appear a significant factor in the regression models [19].

Valente *et al.* investigated gender differences in patients with STEMI treated with PCI. Females comprised 26% of the cohort. There was no significant difference in the angiographic characteristics of patients. Females were more likely to die in hospital and also more likely have major bleeding, but neither was significant when multilevel regression analysis was performed [20].

Medications - RCTs

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial tested the efficacy of clopidogrel in addition to aspirin in ACS patients without electrocardiographic ST-segment elevation. The primary outcome was death from cardiovascular cause, non-fatal myocardial infarction or non-fatal stroke. The proportion of females in the trial was 39%. Those who received clopidogrel in addition to aspirin had a lower rate of the primary endpoint than those who received aspirin alone (relative risk 0.8, P<0.001). The effect was not reported to be as pronounced in females compared with males, although the exact figures were not provided [21].

The TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel (TRITON) trial compared prasugrel with clopidogrel among patients with ACS scheduled for PCI. The primary endpoint was death from cardiovascular cause, non-fatal myocardial infarction and non-fatal stroke at 15months. The prevalence of females was 25%. The trial showed a reduction in the primary endpoint associated with prasugrel (Hazard Ratio (HR) 0.81, P<0.001). This effect was largely driven by a decrease in the rate of non-fatal myocardial infarction. For females the benefit of prasugrel was not as marked as that in males, with a 12% risk reduction for females as opposed to 21% for males [22].

The PLATelet inhibition and patient Outcomes (PLATO) trial assessed the use of ticagrelor compared with Clopidogrel in patients with ACS. The prevalence of females was 28% and did not differ between the groups. There were similar significant reductions in the primary endpoint of 12 month rates of death from vascular cause, MI or stroke for females and males (HR 0.83 vs. 0.85, respectively) [23].

The PEGASUS trial investigated the impact of the longer-term use of ticagrelor, starting at 12 to 36 months post AMI. The proportion of female patients was 24% across the three groups of ticagrelor 90 mg bid, ticagrelor 60 mg bid and placebo. They showed a statistically significant reduction in the event rate for both ticagrelor groups compared to placebo, but no difference between the two ticagrelor groups. There was no difference when they examined the outcomes with respect to sex, however, better outcomes were evident in females compared with maleswho received the 90 mg ticagrelor dose (HR 0.74 vs. 0.98) [24].

The ATLAS ACS2-TIMI 51 trial added rivaroxaban to standard ACS (acute coronary syndrome) treatment and compared its effects on death from cardiovascular cause, myocardial infarction or stroke. In their subgroups the prevalence of females was 25.1%, 25.6% and 25%. They demonstrated a significant reduction in their primary end point for rivaroxaban and interestingly showed a greater benefit for females than males (HR 0.77 (95% CI 0.60-0.99) vs. 0.87 (95% CI 0.75-1.01) P=0.40). There was a higher bleeding rate in females in comparison to males (HR 6.41 (95% CI 1.52-27.09) vs. 3.66 (95% CI 2.21-6.09) P=0.47) [25].

GISSI3 considered the use of lisinopril and transdermal GTN in patients with AMI. The primary outcome was death at 6-weeks; 22% of the participants were female. The trial showed an improvement for all the interventions, although GTN on its own was not significant. For females, compared with males, there was a reduction in the primary endpoint of 11% for lisinopril (20.8% *vs.* 23.4% 2P=0.039), 10% with GTN (20.9% *vs.* 23.3% 2P=0.048) and 21% reduction when used in combination (19% *vs* 24%.2P=0.005) [26].

The Survival and Ventricular Enlargement (SAVE) trial assessed the impact of captopril versus placebo on mortality from all causes. The proportion of females was 18%. It demonstrated a 21% risk reduction for captopril (P=0.014). The benefit for females was much less than males (risk reduction for death from all causes for females 2% (95% CI -53 to 37) vs. males 22% (95% CI 2 to 36); cardiovascular death and morbidity females 4% (95% CI -32 to 30) vs. males 28%(95% CI 16 to 38)) [27].

The Valsartan in acute myocardial infarction (VALIANT) trial investigated the use of valsartan or valsartan plus captopril against captopril for patients with AMI and either heart failure or left ventricular dysfunction. The proportion of females was 31%. There was no statistical benefit seen and indeed the trial was discontinued due to adverse effects. However, it demonstrated a non-significant trend among females for a reduction in death from any cause and combined cardiovascular end point with valsartan versus captopril [28].

The Metoprolol in Acute Myocardial Infarction (MIAMI) trial studied the efficacy of metoprolol versus placebo on death at 15-days. The proportion of females was 22%. It demonstrated a non-significant improvement in survival with metoprolol. This difference persisted and was similar for females and males (4.4% vs. 4.2%), however, females in the placebo arm had worse outcomes than males (6.2% vs. 4.5%) [29].

Table 1. Included studies.

Authors	Year	Type	ACS group	Number patients	Prevalence Females	Primary Outcome
Reperfusion Therapy for AMI – RCTS						
GUSTO investgators [7]	1997	RCT	STEMI	1641	25%	Death, non-fatal disabling stroke or non-fatal reinfarction at 30 days
ISIS 2 investigators [8]	1988	RCT	AMI	17187	23%	Mortality at 35 days
ISIS investigators [9]	1986	RCT	AMI	16027	23%	7 day mortality
Hochman *et al.* [10]	2006	RCT	STEMI	302	32%	Mortality
GISSI Authors [11]	1987	RCT	AMI	11696	20%	Mortality at 12 months
Anderson *et al.* [12]	2003	RCT	STEMI	1572	27%	Death, non-fatal disabling stroke or non-fatal reinfarction at 30 days
Sabatine *et al.* [13]	2005	RCT	STEMI	3491	20%	Occluded infarct related artery on angiography, death or recurrent myocardial infarction prior to angiography
Reperfusion Therapy for AMI – Observational Registries						
Hochman *et al.* [14]	1999	Registry	STEMI	302	32%	Mortality at 30 days
Boucher *et al.* [15]	2001	Registry	AMI	3741	30%	Use of thrombolysis and outcomes
Jeger *et al.* [16]	2008	Registry	ACS	23696	28%	Treatment and outcomes
Gale *et al.* [17]	2011	Registry	ACS	2229546	35%	In-hospital mortality
Kalla *et al.* [18]	2006	Registry	STEMI	1053	28%	Outcomes
Stenestrand *et al.* [19]	2006	Registry	STEMI	26205	30%	Long term outcomes
Valente *et al.* [20]	2010	Registry	STEMI	1127	26%	Gender differences in STEMI patients
Medications – RCT						
Yusef *et al.* [21]	2001	RCT	UA/NSTEMI	12562	38%	CV mortality, non-fatal MI, or non-fatal stroke
Wiviott *et al.* [22]	2007	RCT	ACS	13608	25%	CV mortality, non-fatal MI, or non-fatal stroke
Wallentin *et al.* [23]	2009	RCT	ACS	18624	28%	CV mortality, non-fatal MI, or non-fatal stroke
Bonaca *et al.* [24]	2015	RCT	12-36 months post MI	21162	24%	CV mortality, non-fatal MI, or non-fatal stroke
Mega *et al.* [25]	2012	RCT	ACS	15342	25%	CV mortality, MI, or stroke
Devita *et al.* [26]	1994	RCT	AMI	19394	22%	6 week mortality
Pfeffer *et al.* [27]	1992	RCT	MI and either impaired LV or HF	2231	18%	All cause mortality
Pfeffer *et al.* [28]	2003	RCT	MI and either LVSD or HF	14703	31%	All cause mortality
Herlitz *et al.* [29]	1985	RCT	AMI	5778	22%	Mortality at 15 days
Chen *et al.* [30]	2005	RCT	AMI	45852	28%	Death, reinfarction, cardiac arrest at 28days
Pitt *et al.* [31]	2003	RCT	MI and either LVSD or HF	6642	29%	Time to death from any cause, time to death from CV cause and hospitalisation for CV event
Schwartz *et al.* [32]	2001	RCT	UA/NSTEMI	3086	36%	All cause mortality, nonfatal MI, cardiac arrest with resuscitation, rehospitalisation for ACS

(Table 1) Contd….

Authors	Year	Type	ACS group	Number patients	Prevalence Females	Primary Outcome
Cannon *et al.* [33]	2004	RCT	ACS	4162	22%	Death, MI, UA requiring hospitalization, revascularization at ≥30 days, or stroke
Cannon *et al.* [34]	2015	RCT	ACS	18144	24%	CV mortality, major CV event, or non-fatal stroke
Medications – Observational Registries						
Dziewierz *et al.* [35]	2007	Registry	NSTEACS	807	46%	Use of medication and outcomes
Invasive Strategy – RCT						
Fox *et al.* [36]	2010	MA	NSTEACS	5467	32%	5 year mortality
Ragmin *et al.* [37]	1999	RCT	NSTEACS	2457	30%	Death or MI at 6 months
Lagerqvist *et al.* [38]	2006	RCT	NSTEACS	2457	30%	5 year mortality
de Winter *et al.* [39]	2005	RCT	NSTEACS	1200	27%	Death, MI or rehospitalisation for angina within 12months of randomisation
Fox *et al.* [40]	2002	RCT	NSTEACS	1810	38%	Death or non fatal MI at 12months, and Death, non fatal MI or refractory Angina at 4 months
Fox *et al.* [41]	2005	RCT	NSTEACS	1810	38%	5 year mortality
Henderson *et al.* [42]	2015	RCT	NSTEACS	1810	38%	10 year mortality
Invasive Strategy – Observational Registries						
Anderson *et al.* [43]	2012	Registry	Post PCI	426996	42%	Outcomes
Roe *et al.* [44]	2009	Registry	NSTEACS	19336	42%	Long term outcomes
Ryan *et al.* [45]	2005	Registry	NSTEACS	56352	39%	Timing of intervention
Mortality and Outcomes – Observational Registries						
Collart *et al.* [46]	2012	Registry	AMI	2936	25%	Patient characteristics
Taneja *et al.* [47]	2004	Registry	NSTEACS	653	39%	4 year outcomes
Gulliksson *et al.* [48]	2009	Registry	AMI	589341	36%	Risk recurrent MI
Gurjeva *et al.* [49]	2005	Registry	NSTEACS	2948	46%	Characteristics and outcomes
Hansen *et al.* [50]	2012	Registry	AMI	1595	52%	All cause mortality, recurrent MI, discharge medication prescription
Jneid *et al.* [51]	2008	Registry	AMI	78254	39%	Outcomes and medical care
Langorgen *et al.* [52]	2009	Registry	First AMI	11878	36%	Short and long term outcomes
Lopez de Sa *et al.* [53]	2002	Registry	NSTEACS	4115	33%	Outcomes at 90 days
Montaye *et al.* [54]	2013	Registry	ACS	1960	24%	Mortality and patient characteristics
Shah *et al.* [55]	2012	Registry	AMI	187803	33%	Risk HF
Steg *et al.* [56]	2004	Registry	ACS	16166	35%	Risk HF
Kyto *et al.* [57]	2015	Registry	NSTEMI	48584	45%	Incidence NSTEMI
Bahler *et al.* [58]	2011	Registry	AMI	15711	27%	Age at first mi
Radomska *et al.* [59]	2013	Registry	STEMI	26035	35%	Outcomes and treatments with special consideration for diabetes
Rasmussen *et al.* [60]	2005	Registry	First AMI	64321	38%	Outcome 28 and 365 days

Abbreviations:
RCT; Randomised Control Trial, ACS; Acute Coronary Syndrome, UA; Unstable Angina, CV; cardiovascular, HF; Heart Failure, STEMI; ST elevation myocardial infarction, MI; Myocardial Infarction, NSTEMI; non ST elevation myocardial infaction, NSTEACS; non ST elevation acute coronary syndrome, AMI; acute myocardial infarction, LVSD; left ventricular systolic dysfunction.

The Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial investigated metoprolol versus placebo in patients with AMI. The primary outcome was a composite of death, re-infarction or cardiac arrest at 28 days. The proportion of females in the study was 28%. The trial found no improvement in the primary outcome from the use of early metoprolol, although it was felt this might be due to higher rates of cardiogenic shock in the metoprolol arm. Interestingly, both the incidence of death and cardiogenic shock were increased in females compared with males (death females 11.8% vs. males 6.3%;cardiogenic shock females 6% vs. males 4.8%) [30].

The Eplerenone post-acute myocardial infarction heart failure efficacy and survival (EPHESUS) trial assessed the use of eplerenone in patients with left ventricular dysfunction after AMI. The proportion of females was 28% in the intervention arm and 30% in the placebo arm. It found a statistically significant reduction in deaths from any cause and cardiovascular mortality or hospitalisation. There was a non-significant trend to reduced death from any cause for females, however, males on eplerenone were less likely to die from a cardiovascular cause or be hospitalized [31].

The Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial investigated whether atorvastatin reduced early cardiovascular events among patients with unstable angina and non ST-elevation myocardial infarction (NSTEMI). The proportion of females was 36%. It demonstrated a reduction in mortality associated with atorvastatin. There was no significant interaction between treatment assignment and sex [32].

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial compared outcomes for ACS patients treated with either high intensity statins (i.e. atorvastatin 80mg) or moderate dose statin (i.e. pravastatin 40mg). The primary outcome was death from any cause, myocardial infarction, unstable angina requiring rehospitalisation, revascularisation within 30 days and stroke. The mean follow up was 24 months. The proportion of females was 22%. It showed that those on high intensity statins had better outcomes than those on a moderate dose statins (16% reduction in the HR P=0.005). The trial found that females on high intensity statins had a greater benefit than males.

The two year event rate for females on high intensity statins was 20.3% and for males 23% [33].

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial considered the addition of ezetimibe to simvastatin versus simvastatin alone. The primary endpoint was cardiovascular death, major cardiovascular event (non-fatal AMI, hospitalisation for unstable angina, revascularisation within 30 days). It demonstrated a significant improvement for the group who received ezetimibe plus simvastatin (HR 0.936, P=0.016). There was a non-significant trend towards a greater benefit for females than males (HR 0.885 (95% CI 0.791 to 0.991) vs. 0.952 (95% CI 0.895 to 1.012) [34].

Medications - Observational Registries

The Malopolska registry was interrogated to look at the treatment of non ST-elevation ACS (NSTEACS). The proportion of females was 46%. The investigators assigned points for the use of guideline recommended therapies. Mortality decreased as the use of guideline directed therapy in hospital increased. In individual analysis, statin use had the greatest effect (OR 0.11, 95% CI 0.058-0.208, P<0.0001). The prescription of aspirin, β blocker and ACEi/ARB all significantly reduced in-hospital mortality. The authors did not consider the prescription of medications by sex. In this study male sex was a predictor of raised in-hospital mortality, male sex conferred an OR of 1.46 (95% CI 0.74-2.90 P=*0.280*) [35].

Invasive Strategy -RCTs

There have been three randomised control trials of invasive strategies for patients with ACS that have presented five year outcome data. Fox *et al.* published the FRISC2, ICTUS and RITA3 trials' long-term outcomes as a meta-analysis. This showed a reduction in the composite endpoint of death and myocardial infarction for those who routinely underwent an invasive strategy compared with those who received a selective invasive strategy (HR 0.81 P=0.002). Females had slightly better outcomes than males (mortality 15% vs. 16.2%, respectively; OR 1.1, P=0.2) [36].

The Fast Revascularization During Instability in Coronary Artery Disease (FRISC)-II trial investigated patients with NSTEACS – assigning them to either an invasive or non-invasive strategy. The primary endpoint was death or AMI at 6 months. The investigators demonstrated a reduction in the primary endpoint among those who received a routine invasive strategy. In the subgroup analysis for the primary endpoint, however, females did better with a non-invasive strategy (8.3% vs. 10.5%, risk ratio 1.26). Males had better outcomes when an invasive strategy was employed. When the investigators considered the effect on angina symptoms at 6 months, an invasive strategy was found to be superior among females (risk ratio 0.64) [37]. The five-year outcomes for FRISC-II showed a significant improvement in the primary endpoint for all groups, mostly driven by a reduction in rates of AMI. Females continued to have better outcomes when a non-invasive strategy was employed (relative risk for an invasive strategy 1.12, 95% CI0.83-1.5, P=0.01) [38].

The Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial assessed the merits of an invasive strategy in patients with NSTEACS; the primary endpoint was a composite of death, AMI or rehospitalisation for angina within 12 months of randomisation. The proportion of females was 27%. There was no benefit associated with an early invasive strategy over optimal medical therapy plus selective invasive strategy. In the subgroup analysis, there was a trend for females to favour an early invasive strategy when compared to males, although females had worse outcomes than males regardless of the strategy that was used (primary end point 25.7% vs. 20.3%) [39].

The Randomised Treatment of Angina (RITA 3) trial randomised patients to early intervention versus conservative management. The study had co-primary endpoints of death or non-fatal AMI at 12 months and death, non-fatal AMI and refractory angina at 4 months. The proportion of females was 38%, with a slightly higher proportion in the intervention group 39% vs. 36%. There was a reduction in the primary end point at both 4 months (risk ratio 0.66 95 % CI 0.51-0.85 P=0.001) and 12 months (risk ratio 0.72, 95% CI 0.58-.090, P=0.003) and driven by a reduction in rates of refractory angina. At 12 months females in the conservative group had a lower incidence of death or AMI (5.1% vs. 8.6%). Males in whom an invasive strategy was employed had better outcomes at both 4 and 12 months. (40) The five-year outcomes show the benefit accrued by an early invasive strategy over a conservative one. Being male carried a greater risk of primary outcome (OR 1.44 95% CI 1.09-1.89, P=0.0099). (41) The recently published 10 year outcomes for RITA 3 demonstrated no difference in mortality between the groups. Male, however, continued to carry an increased risk of death (OR 1.3, 95% CI 1.00-1.68, P=0.051) [42].

Invasive Strategy - Observational Registries

Anderson *et al.* investigated the short and long term outcomes of coronary stenting with respect to sex using the NCDR Cath PCI registry. The proportion of females was 42%. All patients were aged >65 with females being, on average, older than males (mean age 76 vs. 74 years). Females had a higher unadjusted risk of death (HR 1.06, 95% CI 1.04-1.07) and lower adjusted risk of death at 30

months (HR 0.92, 95% CI 0.9-0.94, P=0.002). They did however, have a higher risk of in-hospital death. For both males and females drug-eluting stents) were associated with better outcomes than bare metal stents [43].

Roe *et al.* used the CRUSADE registry to assess long-term outcomes in older patients with NSTEMI. The proportion of females was 42%. Patients were split according to treatment strategy; medical management, PCI and CABG. Females were less likely to be in the CABG group than any other (P<0.0001). The group who received CABG had the best outcomes at five years; those who underwent medical management had the worst outcomes [44].

The Can Rapid risk Stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) registry investigate the optimal timing of intervention in patients with NSTEACS. The investigators divided patients into groups based on the day of admission to hospital. The proportion of females was 39% which did not differ between weekday or weekend hospitalisation. There was an increase in the time to catheterisation for those admitted at the weekend compared with a weekday (46.3 hrs vs. 23.4 hrs). There was no significant difference in mortality rates for females between those admitted on a weekend (4.7%) and those on a weekday (4.7%). The authors found a difference between those admitted on a weekend and weekday for males (4.2% vs. 3.7%). Females had a higher mortality rate than males [45].

Mortality and Outcomes Registries

The Charleroi registry in Belgium examined 25-69 year olds with AMI between 1998 and 2007 in biennial periods. The proportion of females was 25% and did not change over the study period. Females were older (58 vs. 55 years) and more frequently had diabetes and hypertension, and less frequently smoked or had previous AMI (P<0.001 for all values). There was an increase in the utilisation of therapies over time; males were more likely to have reperfusion therapy than females (Odds ratio for thrombolysis 1.65 P<0.001; PTCA OR 1.32 P=0.022). Receiving thrombolysis resulted in a reduction in mortality for males (OR 0.39 P<0.001), this however, was not seen in females in whom receiving thrombolysis resulted in no improvement in mortality (OR 1.07 P=0.846). There was no statistically significant difference in the use of antiplatelets or β blockers by sex, though ACE inhibitors were more frequently prescribed for males. The authors did look at 28 day mortality and reported no significant difference with regard to sex, they did note being male carried a slightly higher risk than being female (OR 1.15 P=0.648) [46].

The Prospective Registry of Acute Ischaemic Syndromes (PRAIS) UK registry assessed long-term outcomes following NSTEMI. It reported a higher rate of death among males (HR 1.78, 95% CI 1.22 – 2.59, P=0.003) [47].

Gulliksson *et al.* analysed 775,901 events in patients aged between 20 and 84 years from 1972 to 2001 to look at the risk of recurrent AMI. The proportion of females was 36%, who were more likely than males to die within 28 days after both the index AMI (23.8% vs. 19.3% P<0.0001) and recurrent AMI (23.2% vs. 21.3% P<0.0001). There was a reduction in the mortality rate for both males and females from 1972 to 2001. Females were also more likely to have recurrent AMI than males (average recurrent AMI per patient 1.48 for females vs. 1.42 for males) [48].

Gurjeva *et al.* used the Global Unstable Angina Registry and Treatment Evaluation (GUARANTEE) registry to look at the impact of both gender and age on patients with NSTEACS. The proportion of females in the cohort was 46% although females tended to be older; 55% were >75 as opposed to 36% <75 (P<0.001). Although older females were more likely to be diagnosed with AMI on admission, they were less likely to be cared for by a cardiologist. PCI was performed more frequently in males than females and also younger females as opposed to older females (13.7% vs. 8.1%). In addition to not receiving PCI, females were less likely to be discharged on aspirin or β blockers compared to males despite having similar rates of use to males prior to admission. Overall the use of medications was low for all groups. The study demonstrated that with respect to in hospital outcomes; the group that had the worst outcomes (death or MI) were elderly females [49].

Hansen *et al.* used the Danish registries from 2005-07 to identify patients with AMI and assess their prognosis and treatment in those without significant coronary stenoses. The proportion of females was 52%. Females were more likely to die within three years than males (HR 1.22, 95% CI 0.86-1.72) although less likely to have a recurrent event (HR 0.84, 95% CI 0.50-1.43) [50].

Jneid *et al.* studied medical care and early death following AMI with respect to sex using the Get With the Guidelines – Coronary Artery Disease database. The proportion of females was 39%. Females were older than males (mean age 73 vs. 65). Females with STEMI were less likely to receive acute reperfusion (56.3% vs. 73% *P*<0.0001). This discrepancy was also seen in other invasive procedures – angiography (45.6% vs. 56.2% P<0.0001) PCI (36.1% vs. 52.3% P<0.0001) CABG (5.4% vs. 9.2% P<0.0001). These differences persisted after multivariable adjustment. The unadjusted mortality rate was higher for females than males (8.2% vs. 5.7%, P<0.0001) and also for those with STEMI (10.2% vs. 5.5% P<0.0001), but after multivariable adjustment was only significant for STEMI (OR 1.12, 95% CI 1.02 – 1.23, P=0.015) [51].

The Western Norway cardiovascular registry studied short- and long-term mortality in patients who were hospitalised with first AMI from 1979 – 2001. The proportion of females was 36%. The investigators considered mortality at 28 days, one year and 10 years across three time periods, 1979-1985, 1986-1993 and 1994-2001. They demonstrated consistent higher crude mortality rates for females when compared to males. For both males and females the mortality rate declined as time advanced. There was no significant age and sex-adjusted differences in mortality for those under 60 years, but for those over 60 years mortality rate were significantly lower at each time point [52].

The Proyecto de Estudio del Pronostico de la Angina (PEPA) registry focused on patients with NSTEACS, 90-day mortality and predictors of this. A third of the patients were female. The rates of cardiovascular mortality were 4.3% and cardiovascular death or AMI 6.9%. Whilst females were more likely to die than males (5.2% vs. 3.3%, P=0.005), sex was not an independent predictor [53].

Montaye *et al.* considered the differences between regions in France in patients who were part of the MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) registry. Females comprised 24% of the entire cohort, who had similar mortality rates at both 28 days and one year to males [54].

Shah *et al.* used the CRUSADE registry to investigate the risk of heart failure complicating acute MI. The proportion of females was 33%, who more frequently had NSTEMI than STEMI (65% vs. 35%). Females were more likely than males to develop heart failure during their index admission (OR 1.25, 95% CI 1.18 – 1.32, P<0.0001) and this remained evident after patients with a history of prior heart failure were excluded (OR 1.26, 95% CI 1.19 – 1.33, P<0.0001) [55].

Steg *et al.* used the Global Registry of Acute Coronary Events (GRACE) registry to study the impact of heart failure on admission among patients with ACS. Females were more likely to present with heart failure than males (OR 0.8, 95% CI 0.72-0.93). Those who presented with heart failure were less likely to undergo invasive treatment and had worse outcomes than those who didn't [56].

Kyto *et al.* used the Finnish Hospital Discharge Registry to calculate the incidence of NSTEMI from 2001 to 2008. Overall males more frequently had an AMI than females (relative risk 1.86,

95% CI 1.60 – 2.16, P<0.0001). However, as age increased so did the frequency of AMI in females. In fact the group most likely to have an AMI were females aged between 80 and 85 years [57].

Bahler *et al.* used the AMIS Plus registry to look at the age of first AMI among smokers; 27% of the patients were females. Smokers had their first AMI at a younger age than their non-smoking counterparts and this was more pronounced in female smokers (13.1 years for female vs. 10.2 for males). When other factors had been adjusted for, female smokers continued to demonstrate this trend. The sex specific difference was 2.1years (P<0.001) [58].

Radomska *et al.* used the Polish Registry of Acute Coronary Syndromes (PL-ACS) registry to look the effect of type 2 diabetes among females with STEMI. The proportion of females was 34% and females more frequently had diabetes. Females with diabetes compared with males with diabetes had worse outcomes, which commenced in-hospital (In-hospital mortality 15.5% vs. 10.3%, P<0.0001) and extended to 12 months (28.5% vs. 21.1%, P<0.0001). Females received an invasive treatment less frequently and were less likely to receive guideline-indicated therapies. Compared with females without diabetes, similar findings were demonstrated (In-hospital mortality 15.5% vs. 10.6%, P<0.0001 and 12 month mortality 28.5% vs. 19.4%, P<0.0001) [59].

Rasmusson *et al.* used the Danish National Hospital Registry to assess outcomes for patients with a first presentation of AMI. The proportion of females was 38%. There was no difference between females and males with regards to mortality at one year. However, at 28 days there was an increase in mortality for females (OR 1.09, 95% CI 1.04 – 1.14, P<0.001) [60].

DISCUSSION

This structured review of 56 papers comprising 2,538,327 patients has found that among RCTs and observational registries alike that females are underrepresented in studies, have high mortality rates following AMI and are less likely to receive guideline-indicated care.

There have been several trials [7-9, 11-13, 61-63] concerning reperfusion and ACS. Five RCTs demonstrated that females did worse than males [7-9, 11,13]. Four manuscripts demonstrated this was across all groups including interestingly the placebo group [8,9, 11, 13]. One trial showed no difference in mortality at 30 days [12].

There have been four registries considering reperfusion and ACS [14, 16, 19, 20]. All three demonstrated worse outcomes for females in comparison to males.

The data from both registries and RCTs, which allow outcomes to be considered with respect to sex for patients receiving reperfusion, suggest that overall females have worse outcomes than males. This may relate to a reduction in the use of guideline driven therapy in females when compared to males [18, 64]. It may relate to the fact that women take longer to present to hospital than men and that in addition there is a delay in the time to make decisions for females in comparison to males [65]. In comparison when the National Registry of Myocardial Infarction data from 1994 to 1998 was interrogated to assess the role of the ambulance as method of transportation to hospital. Using the ambulance resulted in faster reperfusion times females were more likely to use the ambulance service than males. However the results interestingly also revealed worse outcomes in those transported by ambulance despite the fact they received reperfusion faster [66]. The outcomes may be worse in part due to the higher incidence of cardiogenic shock in females [16].

Four RCTs have looked at antiplatelet use. Two showed a superior benefit for males [21, 22] two showed a superior benefit in females [23, 24] though this was for the same drug.

Two RCTs looked at ACE/ARB use [27, 28]. Males did better with prescription of ACEi [27, 28] whilst there was a trend for females to have better outcomes than those on ACEi and also males receiving ARBs [28]. Both studies showed better outcomes for those who received the medication.

Two studies considered beta-blocker use and both focussed on metoprolol [29, 30]. Both studies showed females had better outcomes when on treatment. Females in both placebo groups had worse outcomes than males, one repeated this finding across the study [30].

Three RCTs considered lipid-lowering medication. Two showed females had better outcomes with respect to males within the intervention arm [33, 34]. One registry focussed on lipid lowering medication and showed females were less likely to receive lipid lowering therapy, also those who didn't receive lipid lowering therapy were also less likely to be prescribed other guideline driven therapies [67].

Two registries considered medication prescribing as a whole and this prescribing in relation to guidelines [35, 68]. Those on guideline directed therapy had better outcomes, although only one considered sex as a factor for this prescription and demonstrated no difference.

When considering medication use receiving the medication of interest results in better outcomes. Patients within RCTs that focussed on a specific medication would receive that medication. This allows comparison between treatments. However, registries look at what patients actually use and so reflect the real world where guideline therapy may be contraindicated. Two registries demonstrated that females were less likely to get guideline directed therapy [64, 69].

There is no clear correlation between outcomes and medication use with respect to RCTs and registries, this in part is likely due to the fact that the outcomes they focus on differ. What is clear is that being on guideline directed therapy results in better outcomes. Females in particular should be targeted for high intensity statins. When considering antiplatelet therapy; ticagrelor is probably the best choice for females in comparision to clopidogrel and prasugrel as this was the only antiplatelet agent that demonstrated better outcomes for females than males with in the RCTs.

One study considered anticoagulation for patients post ACS, females received more benefit than males did, although they did have a higher bleeding rate than men, so the net benefit of receiving the rivaroxaban remains unclear [25].

Three RCTs considered outcomes in NSTEACS patients with regards the timing/use of an invasive strategy. Two demonstrated an invasive strategy resulted in better outcomes for males, both of these also showed a trend for females to have better outcomes for mortality with a conservative approach [37, 40]. One in contrast showed that females did better with an invasive approach, although females still had worse outcomes [39].

Three registries have focussed on invasive strategies. Two demonstrated worse outcomes for females [44, 45]. One demonstrated worse short term outcomes, but better long term outcomes (30 months) for females [43].

The registries and RCTs agree that generally females have worse outcomes than males, what is interesting is the trend demonstrated by two of the RCTS that females have better outcomes when managed conservatively for NSTEACS. If you consider a typical female NSTEACS patient they are often elderly and may well have co-morbidities that may prohibit an invasive approach. More work is needed here to determine the optimal strategy for this group of patients.

The registries that have focussed on reporting outcomes have demonstrated that males are more likely to receive an intervention (thrombolysis, medication, or angioplasty) than females [46, 70, 71].

Generally the trend demonstrated was that if you received the specified intervention that was the focus of the article then your outcomes improved.

Two registries considered people who had heart failure in the context of ACS. Females were more likely to both; present or develop heart failure than males. Those with heart failure generally had less invasive treatment and had worse outcomes [55, 56].

Two registries considered at risk groups- smokers and diabetes respectively. In both registries females with these risk factors had poorer outcomes. Those who smoked had their first MI at an earlier year than their male counterparts [58]. Whilst those with diabetes had worse outcomes most likely related to the underuse of guideline directed therapy and intervention [59]. Interestingly the registry concerned with diabetes also showed these trends in females without diabetes.

Strengths and Limitations

This has been a comprehensive systematic review of the available literature, however, given the broad nature of the topic there will inevitably be omissions of manuscripts.

The average proportion of females was 31.5% (18-38%). The proportion of females was higher in observational registries than RCTs, suggesting unequal sex representation between the two study designs. Which may influence outcomes.

For most registries specific gender data was not provided, they often reported with respect to age, the elderly (definition varied between papers) were less likely to receive the intervention of interest. In all the registries included in this review females were older than males, so a higher proportion of females would have been in the elderly group that didn't receive the intervention. Where gender specific data was provided it had been adjusted for age, thereby eliminating the impact of the advanced age on mortality.

CONCLUSION

Females are generally older and not receiving the same care as males, this may be appropriate as they are older and there may be contraindications to therapies. However, when considering RCTs females consistently seemed to have worse outcomes across both the placebo and intervention arms.

When considering longer-term outcomes one registry reviewed 10-year outcomes and females had a higher crude mortality rate than males, and within the older age groups being female was associated with higher risk of mortality [52].

An underlying theme was that females were less likely to receive guideline directed therapy and interventions than their male counterparts [49,51]. One can speculate it reflects the fact females often present in an atypical fashion, which may delay diagnosis. What is clear from the papers analysed if you did not receive the intervention or guideline directed care then your outcomes were worse.

There were some interesting trends from the RCTs which may merit further investigation, one was that females seemed to have better outcomes on ARBs as opposed to ACEi [28] and that females with NSTEACS appear to receive more benefit from a conservative approach than an invasive one with respect to outcomes [37, 40].

The main unanswered question is why females have worse outcomes than males as this was seen across both the RCTs and the registries, be the females in the placebo or the intervention group. The reasons for this are not clear and would merit further investigation.

To improve the care for females the focus needs to shift to ensuring that they receive guideline directed therapy when appropriate and an interventional strategy if this is deemed the correct strategy.

Appendix 1. Search Strategy employed for literature search.

1. Myocardial ischemia/
2. Acute coronary syndrome/
3. myocardial infarction/
4. (coronary adj2 syndrom*).tw.
5. myocard* isch?emia*.tw.
6. isch?emic heart disease*.tw.
7. exp angina, unstable/
8. (unstable adj3 angina).tw.
9. unstable coronary.tw.
10. mi.tw.
11. acs.tw.
12. without st segment.tw.
13. non-Q-wave.tw.
14. NSTEMI.tw.
15. STEMI.tw.
16. or/1-15 [coronory syndrome]
17. Patient Admission/
18. Hospitalization/
19. (readmission or readmitted or re-admission or re-admitted).tw.
20. (rehospitali?ation* or re-hospitali?ation* or rehospitali?ed or re-hospitali?ed).tw.
21. (repeat* hospitali?ation* or repeat* hospitali?ed).tw.
22. recurrent hospitali?ation*.tw.
23. Hospitalization/
24. (hospitali?ation* or hospitali?ed).tw.
25. (hospital adj1 admission*).tw.
26. (admitted adj1 hospital).tw.
27. Inpatients/
28. inpatient*.tw.
29. Mortality/
30. Hospital Mortality/
31. Myocardial Revascularization/
32. exp stroke/
33. exp Heart Failure/
34. outcome*.tw.
35. prognosis/
36. prospective studies/
37. treatment outcome/
38. or/17-37 [outcomes]
39. 16 and 38 [coronary syndrome and outcomes]
40. limit 39 to (english language and yr="2000 - 2015")
41. limit 40 to (full text and human)
42. limit 41 to ovid full text available
43. registry/
44. registry.tw.
45. 43 and 44 [registry]
46. randomi?ed control trial.tw.
47. randomized control trial/
48. RCT.tw.
49. RCT/

50. or/43-44 [registry]

51. or/46-49 [RCT]

52. 50 or 51

53. 42 and 52

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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