Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada?

European Heart Journal: Acute Cardiovascular Care
2(4) 350–358

© The European Society of Cardiology 2013

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/2048872613496940

acc.sagepub.com

Nina Johnston^{1,2}, Anna Bornefalk-Hermansson³,
Karin Schenck-Gustafsson¹, Claes Held^{2,3}, Shaun G Goodman^{4,5},
Andrew T Yan^{4,5} and Arlene S Bierman^{5,6}

Abstract

Aims: This study examined clinical factors associated with sex differences in the use of acute reperfusion therapy (fibrinolysis or primary percutaneous coronary intervention) in ST-elevation myocardial infarction (STEMI) patients, and the interaction between sex and these factors in Sweden and Canada.

Methods: Patients with STEMI in Sweden ($n=32,676$ from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions) were compared with similar patients in Canada ($n=3375$ from the Canadian Global Registry of Acute Coronary Events) for the period 2004–2008.

Results: Unadjusted vs. age-adjusted odds ratios (OR) for no reperfusion (women vs. men) were for Sweden 1.57 (95% CI 1.49–1.64) vs. 1.14 (95% CI 1.08–1.20), and for Canada 1.61 (95% CI 1.39–1.87) vs. OR 1.18 (95% CI 1.01–1.39). Sex differences persisted after multivariable adjustments (including prehospital delay, atypical symptoms, diabetes), factors for which no interaction with sex was found. Among women <60 years, adjusting for atypical symptoms in Canada and angiographic data in Sweden made the greatest contribution to explaining observed sex differences.

Conclusions: In both countries, acute reperfusion therapy in STEMI was used less often in women than in men. Factors associated with these sex differences appear to differ between older and younger women. Targeted interventions are needed to optimize care for women with STEMI, as well as sex- and age-stratified reporting of quality indicators to assess their effectiveness.

Keywords

Myocardial infarction, reperfusion therapy, sex differences

Received: 26 March 2013; accepted: 14 June 2013

Introduction

International guidelines recommend the use of acute reperfusion therapy (fibrinolysis or primary percutaneous coronary intervention (PCI)) in ST-elevation myocardial infarction (STEMI) for both men and women.^{1,2} While the benefits of reperfusion therapy do not differ by patient sex, multiple previous studies have found women to be at increased risk of not receiving guideline-concordant care for STEMI.^{3–6} Recent studies from Canada and Sweden have raised concerns that the sex disparities in utilization of evidence-based therapies, including reperfusion in acute coronary syndromes (ACS) persist.^{5,6}

¹Karolinska Institutet, Stockholm, Sweden

²Uppsala University, Uppsala, Sweden

³Uppsala Clinical Research Center, Uppsala, Sweden

⁴Canadian Heart Research Centre, Toronto, Canada

⁵Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

⁶Faculties of Nursing, Medicine, and Public Health University of Toronto, Toronto, Canada

Corresponding author:

Nina Johnston, Centre for Gender Medicine, Department of Medicine, Karolinska Institutet 171 76 Stockholm, Sweden.

Email: nina.johnston@ki.se

While higher age and associated comorbidities in women with myocardial infarction (MI) have been suggested as explanations for this sex difference in management, reasons in younger patients have been less well studied.⁷ Accordingly, in order to eliminate sex disparities in STEMI care, studies performing age-stratified analysis on the effect of contributing factors are needed. For this purpose, use of registry data has advantages over clinical trial data as registries provide a more representative spectrum of patients seen in clinical practice. Comparing the delivery of care in different healthcare systems provides an opportunity to better understand factors that can lead to interventions aimed at optimizing patient care. The aim of the study was to investigate how common clinical confounders are associated with provision of reperfusion therapy in STEMI and whether sex has a residual explanatory effect after adjustment for these confounders when stratifying by age.

Methods

Patient population and data collection

Data from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) and the Canadian Global Registry of Acute Coronary Events (GRACE) were used.⁸ RIKS-HIA includes all patients admitted to coronary care units of all hospitals in Sweden. Patients with ACS and admitted to general medical wards are not included. Information for each MI is kept on electronic case record forms, including over 100 variables, such as demographic data, clinical characteristics at admission, in-hospital treatment, and medications at admission and discharge. The data collection and details of GRACE methodology have been previously published.⁹

Briefly, GRACE was a prospective multinational registry initiated in 1999 designed to provide a sample population of patients presenting with acute coronary syndromes across numerous geographic regions. Beginning in 2003, an expanded GRACE (GRACE2) enabled enrolment of patients with ACS by additional hospitals and countries, including Canada.¹⁰ After enrolment in the main and expanded GRACE registries were completed in 2007, Canadian recruitment continued until the end of 2008 (Canadian Registry of Acute Coronary Events (CANRACE)). Entry criteria were identical for GRACE, GRACE2, and CANRACE: patients eligible for enrolment into the registries were ≥ 18 years presenting with a presumed diagnosis of ACS requiring hospital admission. Patients with a secondary cause (e.g. bleeding, trauma, post-operative) for an ACS were excluded. The presumed diagnosis of ACS was based on symptoms consistent with ACS and at least one of the following: a documented history of coronary artery disease, ischaemic electrocardiographic (ECG) changes consistent with ACS, or positive

biomarkers indicative of myocardial necrosis. Using predefined criteria, ACS diagnoses were classified as STEMI, non-STEMI, and unstable angina. At all registry sites, trained personnel were instructed to enrol the first 10–20 consecutive patients each month to assemble an unselected study population, and data were recorded by means of a standardized case report form. Patient demographics, medical history, clinical presentation, laboratory findings, treatment, and outcomes were recorded.

In the current analysis, we included patients receiving a final discharge diagnosis of STEMI (ICD10 I21) between 1 January 2004 and 31 December 2008 from these Swedish and Canadian registries. By definition, our cohort includes patients with symptoms and ECG changes (i.e. ≥ 0.1 mV of ST-segment elevation in two or more contiguous leads, or new/presumed new left bundle branch block (LBBB)) consistent with acute cardiac ischaemia. For RIKS-HIA, only patients with their first recorded admission for MI during the registration period were included ($n=32,676$). For GRACE, all MI admissions were included but due to the systematic sampling procedure multiple visits were unlikely to occur ($n=3375$).

The study complies with the Declaration of Helsinki. All patients included in the registries were informed of their participation. The RIKS-HIA registry was approved by the Swedish National Board of Health and Welfare and Swedish Data Inspection Board. In the case of GRACE, study approval was provided by the local hospital ethics committee/institutional review boards.

Definitions and study variables

Acute reperfusion was defined as fibrinolysis or primary PCI. The acute reperfusion variable does not include catheterization without revascularization as the definition differed between the two countries; in RIKS-HIA there is a variable for catheterization without revascularization as a method of primary reperfusion, whereas for Canada this variable includes all cases of in-hospital catheterizations. A subgroup analysis was therefore only performed for Sweden.

Candidate variables associated with acute reperfusion were based on clinical importance and included: age (18–59, 60–74, 75–89 years); Killip class; LBBB; presentation without chest pain; time from symptom onset to first ECG exceeding 12 hours; kidney function; chronic warfarin usage; contraindication for fibrinolysis; diabetes mellitus; prior MI; prior cerebrovascular accident (CVA); prior congestive heart failure (CHF); prior PCI; prior coronary bypass surgery (CABG).⁷ On-site cardiac catheterization capability as a variable was only obtainable for Canada.

As not all variables were identical in the two databases, construction of the following variables was done. Killip class in RIKS-HIA was constructed using a combination of the degree of pulmonary rales on lung auscultation at admission and cardiogenic shock. In RIKS-HIA,

presentation without chest pain has been constructed from the reason for admission variable and refers to all symptoms other than chest pain. Presentation without chest pain for the Canadian data was estimated as any presumptive admission diagnosis other than ACS. Glomerular filtration rate (GFR) was estimated from serum creatinine using the Modification of Diet in Renal Disease equation. Kidney function was classified according to the American National Kidney Foundation.¹¹

Statistical methods

Data were tabulated using frequencies and percentages stratified by age group, sex, and country. Simple comparisons of median age were made using a one-sided Mann–Whitney test. Two multiple logistic regression models, one per country, were used to determine if female sex was associated with not receiving acute reperfusion, while controlling for the effect of relevant confounders. The effect of including in-hospital death as an explanatory variable was tested for each model. The final parameter estimates for the two countries were converted to odds ratios (OR) with a corresponding Wald CI. For the younger age group (<60 years), the basic data for Canada is sparse for women. Considering the large number of possible confounders, a subgroup analysis was therefore performed for both countries. Receiver operating characteristic (ROC) curve analysis based on the two main models was performed within each age–sex group. Country differences were tested separately in an aggregated model that included the same variables and interactions as the two separate models. A two-sided type I error of 0.05 was used to indicate statistical significance. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA).

Handling of missing data

Variables used in the modelling with more than about 5% missing observations were for Sweden Killip class, kidney dysfunction, fibrinolytic contraindication, prior CVA, and prior CHF, and for both countries, time from symptom onset. Age differences were apparent for time from symptom onset, fibrinolytic contraindication, prior CVA, and prior CHF. Overall, missing observations were more common in older compared to younger patients and were randomly distributed over sex. Missing data was generally not imputed but set to ‘No’. The effect of this was carefully monitored during the modelling process.

Results

Study population

Baseline demographic data and clinical admission characteristics are presented in Table 1. Women represented 29%

of patients in Canada and 34% in Sweden. In general, Canadian patients were younger than Swedish patients, which may reflect differences in the prevalence of risk factors. In Canada and Sweden, 46 vs. 28% of the men and 25 vs. 13% of the women, respectively, were under the age of 60 years. Women compared to men in both countries were older and had more risk factors, including hypertension, diabetes mellitus, CHF, and previous CVA, whereas more men had a previous history of MI and prior revascularization. Similar trends in sex differences of admission characteristics between women and men were observed in both countries.

In both countries, in patients younger than 60 years, a higher proportion of women than men were current smokers, had diabetes mellitus, and presented with a higher Killip class, LBBB, and kidney dysfunction. Presentation without chest pain occurred in 8.8% of women and 3.8% of men in Canada, compared to 4.7% in women and 3.5% in men in Sweden. Time from symptom onset to first ECG >12 hours was prevalent in 13% of women and 9% of men in Canada and in 11% of women and 11% of men in Sweden. Coronary angiography without revascularization was performed in 4.8% of women and 2.3% of men in Sweden.

Sex, age, clinical confounders, and reperfusion

Female sex was associated with less use of reperfusion in both countries. Overall crude ORs for no reperfusion (women vs. men) were for Sweden 1.57 (95% CI 1.49–1.64) and for Canada 1.61 (95% CI 1.39–1.87). Adjusting for age reduced the ORs to 1.14 (95% CI 1.08–1.20) in Sweden and 1.18 (95% CI 1.01–1.39) in Canada. No reperfusion was more common in older compared to younger women in both countries.

The ORs adjusted for sex and clinical confounders are shown in Table 2. The magnitude of the sex difference was similar in patients ≥60 years for the two countries. In Sweden the largest sex difference was observed for patients <60 years; in Canada the number of patients included for this age group was smaller. In the overall sample no interaction between sex, age, and country was observed ($p=0.450$). The three factors independently associated with the highest likelihood of no reperfusion therapy in both countries were LBBB on admission ECG, time from symptom onset to first ECG >12 hours, and atypical symptoms at presentation. For these three factors no interaction was found with sex, and country interactions were only found for LBBB ($p<0.001$) for which rates of reperfusion were higher in Canada. In both countries diabetes was associated with less use of reperfusion but there was no significant interaction with sex. The ROC curves for the models in Table 2 (Figure 1) show that the confounding variables become more important the older a patient is.

Table 1. Characteristics of women and men with STEMI in Canada and Sweden by age.

Variable	Canada (n=3375)		Sweden (n=32,676)	
	Women (n=988)	Men (n=2387)	Women (n=10,998)	Men (n=21,678)
Overall				
18–59	250 (25)	1106 (46)	1412 (13)	5973 (28)
60–74	312 (32)	802 (34)	3456 (31)	8804 (41)
75–89	426 (43)	479 (20)	6130 (56)	6901 (32)
Current smoker				
18–59	161 (64)	594 (54)	831 (59)	2894 (48)
60–74	107 (34)	254 (32)	1149 (33)	2338 (27)
75–89	64 (15)	71 (15)	551 (9.0)	637 (9.2)
Hypertension				
18–59	100 (40)	380 (34)	498 (35)	1555 (26)
60–74	211 (68)	413 (52)	1540 (45)	3336 (38)
75–89	295 (69)	282 (59)	3145 (51)	2819 (41)
Diabetes				
18–59	43 (17)	156 (14)	267 (19)	896 (15)
60–74	90 (29)	206 (26)	782 (23)	1756 (20)
75–89	124 (29)	137 (29)	1429 (23)	1574 (23)
Prior MI				
18–59	30 (12)	154 (14)	92 (6.5)	594 (9.9)
60–74	59 (19)	231 (29)	419 (12)	1467 (17)
75–89	125 (29)	200 (42)	1336 (22)	2103 (30)
Prior CABG				
18–59	8 (3.2)	26 (2.4)	22 (1.6)	140 (2.3)
60–74	16 (5.1)	78 (9.7)	102 (3.0)	554 (6.3)
75–89	22 (5.2)	71 (15)	209 (3.4)	669 (9.7)
Prior PCI or fibrinolysis				
18–59	22 (8.8)	122 (11)	68 (4.8)	482 (8.1)
60–74	41 (13)	161 (20)	250 (7.2)	1095 (12)
75–89	59 (14)	116 (24)	387 (6.3)	982 (14)
Prior CVA				
18–59	3 (1.2)	11 (1.0)	28 (2.0)	102 (1.7)
60–74	23 (7.4)	45 (5.6)	164 (4.8)	460 (5.2)
75–89	65 (15)	89 (19)	614 (10)	775 (11.2)
Prior CHF				
18–59	2 (0.8)	8 (0.7)	18 (1.3)	69 (1.2)
60–74	33 (11)	70 (8.7)	163 (4.7)	367 (4.2)
75–89	77 (18)	93 (19)	795 (13)	909 (13)
Killip class				
I				
18–59	225 (90)	1022 (92)	1211 (86)	5083 (85)
60–74	237 (76)	660 (82)	2681 (78)	7072 (80)
75–89	286 (67)	309 (65)	3973 (65)	4727 (68)
II				
18–59	12 (4.8)	45 (4.1)	51 (3.6)	201 (3.7)
60–74	36 (12)	81 (10)	301 (8.7)	642 (7.3)
75–89	76 (18)	91 (19)	1148 (19)	1195 (17)
III				
18–59	5 (2.0)	13 (1.2)	6 (0.4)	28 (0.5)
60–74	29 (9.3)	38 (4.7)	69 (2.0)	113 (1.3)
75–89	58 (14)	64 (13)	302 (4.9)	225 (3.3)
IV				
18–59	1 (0.4)	8 (0.7)	33 (2.3)	103 (1.7)
60–74	4 (1.3)	6 (0.7)	100 (2.9)	215 (2.4)
75–89	3 (0.7)	5 (1.0)	175 (2.9)	216 (3.1)

(Continued)

Table 1. (Continued)

Variable	Canada (n=3375)		Sweden (n=32,676)	
	Women (n=988)	Men (n=2387)	Women (n=10,998)	Men (n=21,678)
LBBB				
18–59	9 (3.6)	31 (2.8)	95 (6.7)	353 (5.9)
60–74	49 (16)	104 (13)	496 (14)	1255 (14)
75–89	118 (28)	143 (30)	1580 (26)	2138 (31)
Presentation without chest pain				
18–59	22 (8.8)	42 (3.8)	66 (4.7)	210 (3.5)
60–74	33 (11)	81 (10)	353 (10)	602 (6.8)
75–89	68 (16)	83 (17)	1192 (19)	1097 (16)
Time from symptom onset to first ECG >12 h				
18–59	33 (13)	100 (9.0)	151 (11)	654 (11)
60–74	41 (13)	68 (8.5)	484 (14)	1082 (12)
75–89	51 (12)	60 (13)	907 (15)	978 (14)
Kidney function				
GFR ≥60 ml/min/1.73 m ²				
18–59	205 (82)	970 (88)	1197 (85)	5390 (90)
60–74	155 (50)	548 (68)	2450 (71)	7080 (80)
75–89	147 (35)	206 (43)	2731 (45)	3727 (54)
GFR 30–59 ml/min/1.73 m ²				
18–59	36 (14)	97 (8.8)	128 (9.1)	236 (4.0)
60–74	134 (43)	213 (27)	731 (21)	1147 (13)
75–89	218 (51)	213 (44)	2559 (42)	2398 (35)
GFR <30 ml/min/1.73 m ²				
18–59	3 (1.2)	14 (1.3)	27 (1.9)	49 (0.8)
60–74	17 (5.4)	21 (2.6)	128 (3.7)	185 (2.1)
75–89	46 (11)	47 (9.8)	491 (8.0)	446 (6.5)
Use of warfarin at admission				
18–59	3 (1.2)	6 (0.5)	19 (1.4)	60 (1.0)
60–74	15 (4.8)	42 (5.2)	84 (2.4)	308 (3.5)
75–89	37 (8.7)	55 (11)	288 (4.7)	514 (7.4)
Fibrinolytic contraindication				
18–59	10 (4.0)	70 (6.3)	24 (1.7)	78 (1.3)
60–74	24 (7.7)	52 (6.5)	88 (2.6)	160 (1.8)
75–89	40 (9.4)	55 (11)	216 (3.5)	235 (3.4)
Cath without action ^a				
18–59			67 (4.8)	136 (2.3)
60–74			150 (4.3)	263 (3.0)
75–89			174 (2.8)	177 (2.6)
On-site cathlab ^a				
18–59	79 (32)	347 (31)		
60–74	62 (20)	233 (29)		
75–89	88 (21)	101 (21)		
No reperfusion				
18–59	77 (31)	303 (27)	368 (26)	1173 (20)
60–74	146 (47)	319 (40)	1191 (34)	2616 (30)
75–89	279 (65)	310 (65)	3460 (56)	3779 (55)
In-hospital death				
18–59	1 (0.4)	10 (0.9)	30 (2.1)	73 (1.2)
60–74	16 (5.1)	32 (4.0)	178 (5.2)	329 (3.7)
75–89	47 (11)	55 (11)	900 (15)	898 (13)

Values are n (%).

^aInformation not available.

CABG, coronary artery bypass grafting; CHF, congestive heart failure; CVA, cerebral vascular accident; ECG, electrocardiogram; GFR, glomerular filtration rate; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Multivariable model for no acute reperfusion in Canada and Sweden.

Effect	Canada (n=3375)	p-value	Sweden (n=32,676)	p-value	Country interaction p-value
Men 18–59 vs. 60–74	0.85 (0.68–1.06)	0.155	0.80 (0.73–0.87)	<0.001	
Men 75–89 vs. 60–74	1.73 (1.31–2.28)	<0.001	1.93 (1.78–2.09)	<0.001	
Age 18–59 women vs. men	1.03 (0.74–1.42)	0.883	1.48 (1.27–1.71)	<0.001	
Age 60–74 women vs. men	1.23 (0.90–1.67)	0.191	1.24 (1.12–1.37)	<0.001	
Age 75–89 women vs. men	1.22 (0.89–1.68)	0.217	1.20 (1.10–1.30)	<0.001	0.450
Presentation without chest pain and with ST-elevation on ECG	8.20 (5.64–11.92)	<0.001	6.29 (5.63–7.03)	<0.001	
LBBB vs. ST-elevation on ECG (presentation with chest pain)	5.11 (3.67–7.11)	<0.001	8.45 (7.77–9.20)	<0.001	
Additional effect (given LBBB) of presentation without chest pain	1.74 (0.88–3.47)	0.113	3.79 (2.99–4.80)	<0.001	<0.001 ^a
Time from symptom onset to first ECG >12 h vs. ≤12 h	3.40 (2.62–4.40)	<0.001	3.56 (3.29–3.85)	<0.001	0.768
Killip class III or IV vs. I or II	1.82 (1.27–2.61)	0.001	0.83 (0.73–0.95)	0.008	0.001
On-site cath lab vs. not	0.73 (0.61–0.88)	0.001	–	–	
GFR 30–59 vs. ≥60 ml/min/1.73 m ²	1.01 (0.83–1.23)	0.942	1.10 (1.03–1.18)	0.008	
GFR ≤29 vs. >60 ml/min/1.73 m ²	2.12 (1.31–3.42)	0.002	1.52 (1.31–1.76)	<0.001	0.312
Warfarin treatment vs. none	1.84 (1.17–2.90)	0.009	1.56 (1.35–1.81)	<0.001	0.647
Fibrinolytic contraindication vs. none	4.58 (3.26–6.42)	<0.001	2.45 (2.07–2.89)	<0.001	<0.001
Diabetes mellitus vs. none	1.23 (1.01–1.50)	0.044	1.20 (1.12–1.29)	<0.001	0.594
Prior MI vs. none	1.40 (1.13–1.74)	0.002	1.62 (1.50–1.75)	<0.001	0.568
Prior CABG vs. none	2.17 (1.48–3.19)	<0.001	1.59 (1.39–1.82)	<0.001	0.316
Prior CVA vs. none	1.72 (1.22–2.43)	0.002	1.24 (1.11–1.39)	<0.001	0.088
Prior CHF vs. none	1.26 (0.86–1.83)	0.239	2.10 (1.84–2.38)	<0.001	0.026
C-statistic	0.799		0.816		

Values are odds ratio (95% confidence interval). Country differences in effects (or in interaction of effects) are tested separately in an aggregated model.

^aTesting country difference in age-sex pattern and LBBB-lack of chest pain pattern, respectively.

CABG, coronary artery bypass grafting; CHF, congestive heart failure; CVA, cerebral vascular accident; ECG, electrocardiogram; GFR, glomerular filtration rate; LBBB, left bundle branch block.

Subgroup analysis in patients younger than <60 years

In Sweden, women under the age of 60 were more likely to not receive acute reperfusion (OR 1.44, 95% CI 1.25–1.67), even after adjusting for the four most significant factors in this age group (i.e. LBBB, atypical symptoms, late arrival, fibrinolytic contraindication) and for diabetes mellitus as well (Table 3). Including coronary angiography without revascularization in the dependent variable reduced the OR to 1.29 (95% CI 1.10–1.51) in these younger Swedish women (Table 4). In a similar analysis for Canada, adjusting for symptoms other than chest pain at admission had the greatest effect on narrowing the observed sex differences. Angiographic information was not available for Canada.

Discussion

Women were less likely than men to receive acute reperfusion therapy in STEMI in both Sweden and Canada. In patients aged 60 years or older, the magnitude was similar

in both countries even after adjusting for age, comorbidities, LBBB on admission, prehospital delay, and admission symptoms other than chest pain. In a subgroup analysis, even after adjusting for angiographic data, women in Sweden under the age of 60 were 29% more likely not to receive reperfusion compared to men. In Canada for women under the age of 60, adjusting for atypical symptoms made the greatest contribution to reducing observed sex differences.

Two recent papers have been published on the topic including data from Canada and Sweden.^{5,6} The study by Nguyen et al.⁵ included 50,096 patients hospitalized with an ACS (35% STEMI) during the period 1999–2007 from the multinational GRACE registry. In the study by Lawesson et al.,⁶ STEMI patients were included from two different time periods, 1998–2000 (*n*=15,697) and 2004–2006 (*n*=14,380) from the RIKS-HIA register in Sweden. Both studies found sex differences in utilization of evidence-based therapies, including reperfusion for STEMI, with women less likely to receive guideline recommended care. Our study draws on a more recent STEMI population

Figure 1. Performance of the multivariable model for no acute reperfusion by age group and sex in Canada (A) and Sweden (B).

Table 3. Odds for no acute reperfusion in women vs. men <60 years in Canada and Sweden.

	Canada		Sweden	
	OR (95% CI)	c statistic	OR (95% CI)	c statistic
Crude women vs. men	1.18 (0.87–1.59)	0.513	1.44 (1.26–1.65)	0.530
Adjusted for LBBB	1.17 (0.86–1.58)	0.540	1.45 (1.26–1.67)	0.602
Adjusted for presentation without chest pain	1.04 (0.76–1.42)	0.564	1.42 (1.24–1.63)	0.573
Adjusted for time from symptom onset to first ECG >12 h	1.12 (0.82–1.52)	0.579	1.47 (1.28–1.69)	0.602
Adjusted for fibrinolytic contraindication	1.24 (0.92–1.68)	0.563	1.44 (1.26–1.65)	0.532
Adjusted for diabetes	1.17 (0.86–1.58)	0.533	1.42 (1.24–1.62)	0.561
Adjusted for all of the above	1.00 (0.72–1.40)	0.679	1.44 (1.25–1.67)	0.692

ECG, electrocardiogram; LBBB, left bundle branch block.

and adds new insight into possible underlying reasons for these observed sex differences with respect to age.

How can we explain less use of reperfusion in older women?

Less use of acute reperfusion therapy among older women compared to men has been consistently reported in other studies.^{3–7} In many of these studies this disparate use is explained by adjusting for age and associated comorbidities in women which raise concerns of an increased treatment risk in relation to benefit or due difficulties in initial diagnosis. The high predictive ability of our models (C-statistic), which include an extensive number of both baseline risk factors and admission characteristics, supports the fact that these factors largely explain the lower use of reperfusion in the elderly. However, what we also found was that, even after controlling for these factors, sex disparities persisted. The lack of interaction of these variables with sex, with the exception of age, may suggest a biased management of older women compared with

men. In a study by Jani et al.,¹² less optimal management of elderly women post MI was potentially related to physician uncertainty as to the benefits of treatment.

How can we explain less use of reperfusion in younger women?

The reasons for younger patients not to be treated according to guidelines is more puzzling than in the elderly. In the Swedish data we adjusted for the greater extent of non-obstructive coronary artery disease found in women compared to men, especially younger women, by including the variable coronary angiography without revascularization (i.e. used as a surrogate for no significant angiographic findings). However, this did not fully explain the sex difference. In the Canadian data, adjusting for atypical symptoms had the greatest effect on narrowing sex differences among younger patients. Atypical symptoms are associated with patient delay in seeking medical attention and belated diagnosis by both emergency department nurses

Table 4. Odds for no acute reperfusion including catheterization without revascularization in women vs. men by age group in Sweden.

Age group	OR (95% CI)
18–59	1.29 (1.10–1.51)
60–74	1.15 (1.04–1.27)
75–89	1.18 (1.09–1.29)
C-statistic	0.827

Adjusted for variables and interactions found in Table 2.

and physicians.¹³ In our study, younger women in Canada more often had a longer prehospital delay than men. Our data may suggest that recognition of atypical symptoms among younger MI patients may be better in Sweden than Canada.¹⁴ Diabetes was also considered among explanatory variables, given findings of a worse outcome in women with diabetes compared to men with MI.¹⁵ In both countries, diabetes was associated with less use of reperfusion therapy but there was no interaction with sex implying similar treatment in men and women.

The lower predictive ability of our models (C-statistic) for younger patients, especially younger women suggests contributions from unmeasured confounders. Such factors could include spontaneous thrombus resolution, vasospastic disease, or microvessel disease and may result in resolution of ST-elevation, which could explain refraining from reperfusion.¹⁶ Our data included the admission ECG evaluation, but the subsequent evolution of the ECG is unknown.

Study implications

In the most recent STEMI guidelines, recommendations read that ‘both genders should be managed in a similar fashion’ and that ‘a high index of suspicion for MI must be maintained in women with atypical symptoms.’¹⁷ Our study provides additional impetus for these recommendations and insight into what needs to be done to eliminate significant sex inequities in STEMI care. As we have shown, commonly cited clinical factors do not entirely explain why reperfusion is being withheld, especially among younger women. Therefore, sex- and age-stratified monitoring of quality indicators and care pathways to standardize management for both sexes should be implemented in routine clinical practice. Sex-specific guidelines may help to support these efforts. The healthcare staff, the patient, and the public sector need to be continuously educated about sex differences in MI, which would help to reduce any bias in the acute management and encourage earlier contact with healthcare services.¹⁸

Strengths and limitations

Strengths include the large real-life patient cohort, inclusion of STEMI patients only, and adjusting for important

clinical confounders that influence decision making. Also, our model estimates were stable to the inclusion of in-hospital death as an explanatory variable. Post-discharge mortality rates were not available to us for either country which does not allow us to draw conclusions as to the net benefit of reperfusion in these patients. However, other studies have shown that in women treated according to guidelines that outcome is similar to that of men, despite older age and greater burden of risk factors.¹⁹ An additional limitation includes the lack of data concerning the whole clinical scenario on which physicians based their decisions. Databases were not identical for all variables and as such a number of new common variables were created, which may not entirely correspond to the actual variable. Inclusion of patients in the two registries was different as well as the sample size. For RIKS-HIA, patients who were not admitted to coronary care units were not included. For GRACE, although only the first 10–20 consecutive patients were included, this selection manner was meant to capture a representative population. Despite these limitations, findings were similar for Canada and Sweden regarding most of the key messages.

Conclusions

In both countries, acute reperfusion therapy in STEMI was used less often in women than in men even after controlling for important clinical factors. This study underlines the need for routine sex- and age-stratified analyses to guide quality improvement interventions. Future research should make use of mixed methods to better understand the reasons for differences and levers for intervention.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Erica Lederhausen Foundation at the Centre for Gender Medicine, Karolinska Institutet, AFA Insurance, 1.6 Million Club for Women’s Health in Sweden, King Gustav V and Queen Victoria’s Foundation for Freemasons, and the Selander Foundation, Uppsala, Sweden.

References

1. Canadian Cardiovascular Society; American Academy of Family Physicians; American College of Cardiology; American Heart Association, Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008; 51: 210–247.
2. Van de Werf F, Bax J, Betriu A, et al.; ESC Committee for Practice Guidelines (CPG). Management of acute myocardial infarction in patients presenting with persistent

- ST-segment elevation: the Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29: 2909–2945.
3. Cohen M, Gensini GF, Maritz F, et al. The role of gender and other factors as predictors of not receiving reperfusion therapy and of outcome in ST-segment elevation myocardial infarction. *J Thromb Thrombolysis* 2005; 19: 155–161.
 4. Kang SH, Suh JW, Yoon CH, et al.; KAMIR/KorMI Registry. Sex differences in management and mortality of patients with ST-elevation myocardial infarction (from the Korean Acute Myocardial Infarction National Registry). *Am J Cardiol* 2012; 109: 787–793.
 5. Nguyen HL, Goldberg RJ, Gore JM, et al. Age and sex differences, and changing trends, in the use of evidence-based therapies in acute coronary syndromes: perspectives from a multinational registry. *Coron Artery Dis* 2010; 21: 336–344.
 6. Lawesson SS, Alfredsson J, Fredrikson M, et al. Time trends in STEMI – improved treatment and outcome but still a gender gap: a prospective observational cohort study from the SWEDEHEART register. *BMJ Open* 2012; 2: e000726.
 7. Cohen M, Boiangiu C and Abidi M. Therapy for ST-segment elevation myocardial infarction patients who present late or are ineligible for reperfusion therapy. *J Am Coll Cardiol* 2010; 55: 1895–1906.
 8. Stenestrand U and Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA* 2001; 285: 430–436.
 9. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001; 141: 190–199.
 10. Goodman SG, Huang W, Yan AT, et al.; Expanded Global Registry of Acute Coronary Events (GRACE2) Investigators. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. *Am Heart J* 2009; 158: 193–201.
 11. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139: 137–147.
 12. Jani SM, Montoye C, Mehta R, et al.; American College of Cardiology Foundation Guidelines Applied in Practice Steering Committee. American College of Cardiology Foundation Guidelines Applied in Practice Steering Committee. Sex differences in the application of evidence-based therapies for the treatment of acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice Projects in Michigan. *Arch Intern Med* 2006; 166: 1164–1170.
 13. Brieger D, Eagle KA, Goodman SG, et al.; GRACE Investigators. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004; 126: 461–469.
 14. Möllmann H, Liebetrau C, Nef HM, et al. The Swedish paradox: or is there really no gender difference in acute coronary syndromes? *Eur Heart J* 2011; 32: 3070–3072.
 15. Norhammar A and Schenck-Gustafsson K. Type 2 diabetes and cardiovascular disease in women. *Diabetologia* 2013; 56: 1–9.
 16. Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation* 2011; 124: 1414–1425.
 17. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619.
 18. Wenger NK. Gender disparity in cardiovascular disease: bias or biology? *Expert Rev Cardiovasc Ther* 2012; 10: 1401–1411.
 19. Mehilli J, Kastrati A, Dirschinger J, et al. Sex-based analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention. *JAMA* 2002; 287: 210–215.