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Sex related inequalities in the management and prognosis of acute coronary syndrome in Switzerland: cross sectional study

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ABSTRACT

OBJECTIVES To assess the differences in the management and prognosis of acute coronary syndrome in men and women who were admitted to hospital for acute coronary syndrome.

DESIGN Cross sectional study.

SETTING Discharge data from Swiss hospitals linked at the hospital and patient levels.

PARTICIPANTS 224 249 adults (18 years and older) were admitted to hospital for acute coronary syndrome between 1 January 2009 and 31 December 2017 in any Swiss hospital, of which 72 947 (32.5%) were women. People who were discharged against medical advice were excluded.

RESULTS Women admitted to hospital with acute coronary syndrome were older than their male counterparts (mean age 74.9 years (standard deviation 12.4) *v* 67.0 years (13.2)). Irrespective of acute coronary syndrome type, women were less likely to undergo diagnostic procedures, such as coronary angiography (adjusted odds ratio 0.79 (95% confidence interval 0.77 to 0.82) for non-ST-segment elevation myocardial infarction *v* 0.87 (0.84 to 0.91) for ST-segment elevation myocardial infarction)) and ventriculography (0.84 (0.82 to 0.87) *v* 0.90 (0.87 to 0.91)). Women were also less likely to receive treatments, such as percutaneous coronary intervention (0.67 (0.65 to 0.69) *v* 0.76 (0.73 to 0.78)) and coronary artery bypass graft (0.57 (0.53 to 0.61) *v* 0.79 (0.72 to 0.87)). Women had a poorer prognosis than men, with a higher likelihood of healthcare related complications (1.10 (1.06 to 1.15) *v* 1.14 (1.09 to 1.21)) and of a longer hospital stay (1.24 (1.20 to 1.27) *v* 1.24 (1.20 to 1.29)). In non-adjusted models, the likelihood of death in hospital was higher among women (odds ratio 1.30 (95% confidence interval 1.24 to 1.37) for non-ST-segment elevation myocardial infarction *v* 1.75 (1.66 to 1.85) for ST-segment elevation myocardial infarction), but the association was reversed for ST-segment elevation myocardial infarction (adjusted odds ratio 0.87 (0.82 to 0.92)) or was non-significant for non-ST-segment elevation myocardial infarction (1.00 (0.94 to 1.06)) after adjustment for confounding variables. The main effect modifier was age: younger women were more likely to die than men of the same age and older women were less likely to die than men of the same age. For example, women who were younger than 50 years had a 38% increased likelihood of dying compared with men of the same age range (adjusted odds ratio 1.38 (1.04 to 1.83)).

CONCLUSIONS Sex inequalities were reported in the management of heart disease in this population of patients from a high income country with good healthcare coverage. These differences affect mortality and morbidity, especially in younger women. Efforts are needed to overcome these inequalities, including educational programmes aimed at healthcare professionals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Women are at risk of a higher mortality than men after an acute coronary syndrome event, however, most studies are done with small samples compared with the total number of acute coronary syndrome events that occur in a country

⇒ Data at the national level are needed to identify the extent of inequalities related to sex in the management and prognosis of acute coronary syndromes

WHAT THIS STUDY ADDS

⇒ Sex inequalities in heart disease care are shown in a population of patients from a high income country with good healthcare coverage

⇒ Younger women are particularly at risk of poor prognosis, with 38% higher odds of death for women younger than 50 years old compared with men who are the same age and 25% higher odds of death for women aged 50-65 years compared with men of the same age

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Efforts must be continued to educate healthcare professionals to allow for better equity in the management of patients

Introduction

Cardiovascular diseases are the leading cause of death in men and women in middle and high income countries.[1] In Switzerland, cardiovascular diseases were responsible for 9114 deaths in men and 10 787 in women in 2019, according to the Swiss Federal Statistical Office.[2] Of these, 3788 (41.6%) deaths in men and 2997 (27.8%) in women were attributable to coronary artery diseases. Globally, coronary artery diseases develop 7-10 years later in women than in men. Men represent the largest proportion of people who have an acute coronary syndrome before 60 years of age, whereas women represent the largest proportion of those having an acute coronary syndrome after 75 years of age.[3 4] Moreover, mortality[5] and recurrence after an acute coronary syndrome are higher in women, especially in younger age groups.[4 6] Female sex is considered an independent risk factor for mortality in acute coronary syndrome,[6] therefore, numerous studies have investigated the possible causes of this excess mortality related to sex. Firstly, age can partly explain the difference observed; women are older than men when presenting with acute coronary syndrome events and thus have more comorbidities.[3 4 6] However, this factor does not

explain the higher mortality among younger women compared with men of the same age.[4 6] Secondly, women with cardiovascular risk factors might be more susceptible to developing cardiac complications than men.[7] Differences in clinical presentation is often used as an explanation. Women's symptoms are more often described as atypical, leading to late diagnosis or misdiagnosis and delays in management of the disease.[3 8 9] However, studies have challenged this hypothesis, arguing that women are misdiagnosed even with a similar initial presentation.[10 11] Finally, non-invasive diagnostic procedures with electrocardiograms and troponin dosages are less sensitive in female patients, because the diagnostic criteria and thresholds have been determined mainly on male cohorts, and might influence or delay an acute coronary syndrome diagnosis.[8 9 12] Cardiovascular disease has long been perceived as a problem related to men by general society and among healthcare providers.[13] Because of greater exposure to risk factors such as smoking, men have been more affected by cardiovascular disease. Epidemiological factors have now shifted but knowledge transfer has not. When presenting with symptoms of acute coronary syndrome, women took more time to seek medical care because generally they wrongly believed that being a woman made them less prone to having cardiovascular disease.[8 9] The same knowledge bias applies to healthcare providers; women with acute coronary syndrome were less likely than men to be referred for catheterisation,[4 9 14 15] and female sex was a statistically significant predictor of delayed so-called door-to-balloon time, even after adjustment for clinical variables.[8 9 15] In ambulatory care, despite presenting similarly to men, women with chest pain were less often referred to a cardiologist.[12]

Health equity is defined by the World Health Organisation as "the absence of avoidable, unfair, or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other means of stratification." However, health is not equitable between men and women in managing cardiovascular disease. Many studies, in countries such as the USA, have assessed health inequalities by using hospital discharge data.[16] Because these data sources include a large number of patients, investigators can form a comprehensive overview of one population. To our knowledge, inequalities related to sex in the management and prognosis of coronary artery disease have not been investigated nationally in Switzerland.

Our main objective for this study was to compare the management of acute coronary syndrome and its prognosis in male and female inpatients using Swiss hospital discharge data. We also aimed to compare patient age and mortality related to a diagnosis of acute coronary syndrome, stratified by sex, over a decade.

Methods

Study design

We conducted a cross sectional study based on Swiss hospital discharge data linked at the individual and hospital levels for the period 1 January 2009 to 31 December 2017. Hospital discharge data contained standardised information on patient demographics, hospital stay characteristics, treated health conditions, and surgical or interventional procedures performed during the patient's hospital stay. In Swiss inpatient data, up to 50 health conditions can be coded as diagnoses, and up to 100 procedures can be coded according to the International Statistical Classification of Diseases and Related Problems, 10th revision, German Modification (ICD-10-GM)[17] and the Swiss Classification of Operations (known as CHOP).[18]

Population

We selected all stays that included a code for acute coronary syndrome as a primary diagnosis (most severe or resource intensive diagnosis during the hospital stay) or secondary diagnosis (conditions that coexist at the time of admission or develop subsequently). ICD-10-GM codes used for selection were as follows: I20.0 for unstable angina, I21.4 for non-ST-elevation myocardial infarction (NSTEMI), and I21.0, I21.1, I21.2, and I21.3 for ST-elevation myocardial infarction (STEMI). All the ICD-10-GM or Swiss Classification of Operations corresponding codes are detailed in the online supplemental data 1. We selected these cardiovascular diseases because they share the same pathophysiology (ischaemia secondary to atheromatous plaques or type one myocardial infarction).[19] Cardiovascular diseases with different pathophysiology (eg, Takotsubo syndrome or spontaneous coronary artery dissection) were excluded. We excluded patients younger than 18 years and people who were discharged against medical advice.

Patient data included age in five categories (≤50, >50 to ≤65, >65 to ≤75, >75 to ≤85, >85 years), nationality (Swiss *v* non-Swiss), class of stay (common, semi-private, private), type of acute coronary syndrome event (unstable angina, NSTEMI, or STEMI), and personal history of acute coronary syndrome (no/yes). We chose this age categorisation to roughly differentiate between premenopausal and postmenopausal women (ie, with and without the relative protective effect of oestrogen) and to align with the commonly accepted age categorisation in Switzerland. Patient's data for sex were from assigned sex rather than self-reported gender. We also extracted cardiovascular somatic comorbidities (ie, diabetes, obesity, hypertension, dyslipidaemia, alcohol or tobacco dependence, and positive family history of cardiovascular diseases) and psychiatric comorbidities (diagnoses of psychotic, mood, or neurotic disorders by the ICD-10-GM codes) when coded in the index stay.

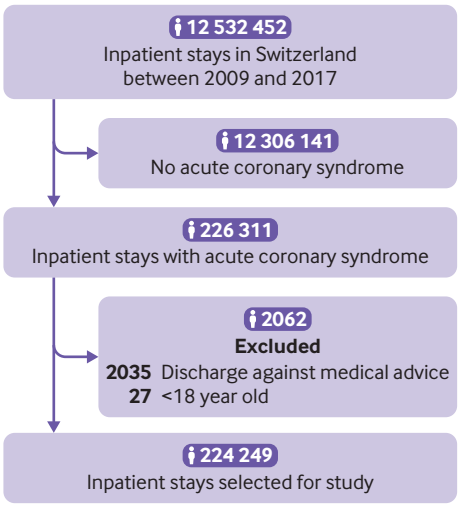

Figure 1 | Selection process of the population

Outcome variables

Studied outcomes covered the following four domains: (1) diagnostic procedures of coronary angiography and ventriculography; (2) treatments of thrombolysis, percutaneous coronary intervention, and coronary artery bypass graft; (3) complications of the acute coronary syndrome event (ie, haemopericardium, atrial septal defect, ventricular septal defect, rupture of the cardiac wall, rupture of chordae tendineae, rupture of papillary muscle, and thrombosis of the atrium, auricular appendage, or ventricle) and all complications of medical and surgical care; (4) morbidity and mortality by intensive care unit stay, longer hospital stay (longer than five days), one or more readmissions, state at discharge, and death in hospital.

Statistical analyses

Continuous variables were summarised as means and standard deviations, and the differences between the sexes were compared using the Student's t test with equal variance. Categorical variables were summarised as absolute numbers and proportions and the differences between the sexes were compared by using Pearson's χ^2 test.

To study the association between the various outcomes and sex, we performed single level logistic regression models. The number of patients with multiple stays for acute coronary syndrome over the nine year period was small (n=1354; 0.6% of the study sample) and became non-existent for multiple stays in the same year. Therefore, we decided not to account for potential clustering effects and treat the stays as independent observations. NSTEMI and STEMI can have differences in clinical manifestations, diagnostic procedures, and treatments, therefore, we performed stratified analyses on the type of acute coronary syndrome (ie, NSTEMI and STEMI). The models were built with and without adjusting for potential confounders: age, nationality, class of stay, history of an older acute coronary syndrome event, somatic comorbidities, and psychiatric comorbidities. The covariates of the models were preselected, based on the scientific literature, because they were estimated to be at high risk of being confounders for the associations between sex and the studied outcomes. Our preliminary analysis showed age to be an effect modifier. We then performed an age stratified analysis for each of the outcomes with adjustment for nationality, class of stay, presence of an older acute coronary syndrome event, somatic comorbidities, and presence of psychiatric comorbidities. We did not find other variables, beyond age, that were effect modifiers. We estimated odds ratios, adjusted odds ratios, and their 95% confidence interval for each variable of the models.

We also performed non-parametric Jonckheere-Terpstra tests (P value calculated with an exact test) to identify potential temporal trends in the number of acute coronary syndrome events, mean age at admission for an acute coronary syndrome, and mortality in hospital in patients with acute coronary syndrome.

All analyses were performed with Stata version Basic Edition 17.0 for Macintosh (StataCorp 2019, College Station, TX).

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. We used administrative data (hospital discharge data), which explains why patients and the public were not involved in the design, conduct, or reporting of the data. Our findings potentially concern all people who were admitted to hospital in Switzerland between 2007 and 2017 with a primary or secondary diagnosis of acute coronary syndrome. We plan to disseminate our results to the population through various Swiss media to inform the population affected by these results. A press release will be prepared.

Results

The original database contained 12 532 452 inpatient stays. After study exclusions, our final sample consisted of 224 249 inpatient stays (figure 1). Women represented 32.5% of the population with 72 947 inpatient stays out of 224 249 (table 1).

Women were, on average, eight years older than their male counterparts. The proportion of women with unstable angina and NSTEMI was higher than in men, whereas men had a higher proportion of STEMI than women (table 1). Regarding cardiovascular risk factors, men were more likely than women to have a diagnosis of dyslipidaemia, alcohol dependence, or tobacco dependence, and to have a previous acute coronary syndrome documented at the index stay.

Table 1 | Baseline characteristics of the study population stratified by sex. Data are number (%), unless otherwise specified

	Men (n=153 302)	Women (n=72 947)	Total (n=224 249)	P value
Mean (SD) age (years)	67.0 (13.2)	74.9 (12.4)	69.6 (13.5)	<0.001*
Age group (years):				
≤50	18 020 (11.9)	3366 (4.6)	21 386 (9.5)	<0.001
>50 to ≤65	50 300 (33.2)	12 608 (17.3)	62 908 (28.1)	<0.001
>65 to ≤75	38 247 (25.3)	16 541 (22.7)	54 788 (24.4)	<0.001
>75 to ≤85	33 111 (21.9)	25 321 (34.7)	58 432 (26.1)	<0.001
>85	11 624 (7.7)	15 111 (20.7)	26 735 (11.9)	<0.001
Nationality:				
Swiss	122 667 (81.1)	64 620 (88.6)	187 287 (83.5)	<0.001
Non-Swiss	28 582 (18.9)	8314 (11.4)	36 896 (16.5)	<0.001
Missing	53 (0.0)	13 (0.0)	66 (0.0)	0.026
Class of stay:				
Common	118 837 (78.6)	56 559 (77.5)	175 396 (78.2)	<0.001
Semi-private	21 526 (14.2)	11 675 (16.0)	33 201 (14.8)	<0.001
Private	10 929 (7.2)	4709 (6.5)	15 638 (7.0)	<0.001
Unknown	10 (0.0)	4 (0.0)	14 (0.0)	0.752
Type of acute coronary syndrome event:				
Unstable angina	23 277 (15.4)	11 684 (16.0)	34 961 (15.6)	<0.001
NSTEMI	71 457 (47.2)	38 099 (52.2)	109 556 (48.8)	<0.001
STEMI	56 568 (37.4)	23 164 (31.8)	79 732 (35.6)	<0.001
History of older acute coronary syndrome events	47 420 (31.3)	17 718 (24.3)	65 138 (29.0)	<0.001
Mean (SD) No of somatic comorbidities	1.0 (0.9)	1.0 (0.9)	1.0 (0.9)	0.061*
Somatic comorbidities:				
Diabetes	31 380 (20.7)	15 289 (21.0)	46 669 (20.8)	0.0231
Obesity	6545 (4.3)	3208 (4.4)	9753 (4.3)	0.434
Hypertension	75 078 (49.6)	41 999 (57.6)	117 077 (52.2)	<0.001
Dyslipidaemia	23 415 (15.5)	9351 (12.8)	32 766 (14.6)	<0.001
Alcohol dependence	4133 (2.7)	684 (0.9)	4817 (2.1)	<0.001
Tobacco dependence	11 690 (7.7)	2404 (4.7)	15 094 (6.7)	<0.001
Presence of CVD family history	782 (0.5)	333 (0.5)	1115 (0.5)	0.057
Psychiatric comorbidities	6548 (4.3)	6072 (8.3)	12 620 (5.6)	<0.001

P values compare the characteristics between men and women and are by Pearson's x^2 test, unless otherwise indicated. CVD=cardiovascular disease; NSTEMI=non-ST-segment elevation myocardial infarction; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction.

*Two sample t test with equal variance.

Women, however, were more likely than men to have a diagnosis of hypertension or reported psychiatric comorbidity. No difference was noted between the sexes for diabetes, obesity, the presence of a family history of heart disease, and overall number of somatic comorbidities.

Our preliminary analyses on the outcomes stratified by sex (online supplemental data 2) showed a significant difference between men and women for all diagnostic procedures and cardiac treatments, women had a systematically lower proportion of procedures and treatments (for men *v* women, 30.4% *v* 23.6% for coronary angiography; 26.5% *v* 21.2% for ventriculography; 4.9% *v* 4.2% for thrombolysis; 42.6% *v* 30.6% for percutaneous coronary intervention; 6.0% *v* 3.4% for coronary artery bypass graft; all P<0.001). The burden of morbidity was also higher on women because they were more likely to have complications of medical and surgical care than men (9.8% for men *v* 11.8% for women, P<0.001); no significant difference was observed for complications of the acute coronary syndrome. Women were less likely than men to be admitted to the intensive care unit (36.0% for men *v* 29.8% for women, P<0.001) and more likely to have a longer hospital stay (39.9% for men *v* 51.2% for women, P<0.001). Overall, men were in better health at discharge than women; men were more likely to recover without the need for follow-up after hospitalisation (22.5% for men *v* 21.0% for women, P<0.001). If men did need a follow-up, they were more likely to need ambulatory care (29.4% for men *v* 24.8% for women), whereas women were more likely to require home care (1.7% for men *v* 4.2% for women) or inpatient care (25.5% for men *v* 26.2% for women), all P<0.001. We observed no difference between men and women in the use of rehabilitation care after discharge. During the duration of the hospital stay for acute coronary

Table 2 | Unadjusted and adjusted association, between sex (women compared with men) and diagnostic procedures, treatments, and complications of acute coronary syndrome event, stratified by NSTEMI and STEMI type of event

	Unadjusted models OR (95% CI)		Adjusted models*, OR (95% CI)	
	NSTEMI	STEMI	NSTEMI	STEMI
Diagnostic procedures				
Coronary angiography	0.66 (0.64 to 0.68)	0.80 (0.77 to 0.83)	0.79 (0.77 to 0.82)	0.87 (0.84 to 0.91)
Ventriculography	0.70 (0.68 to 0.72)	0.82 (0.79 to 0.86)	0.84 (0.82 to 0.87)	0.90 (0.87 to 0.91)
Treatments				
Thrombolysis	0.94 (0.88 to 1.01)	0.79 (0.74 to 0.85)	0.96 (0.89 to 1.03)	0.84 (0.79 to 0.90)
Percutaneous coronary intervention	0.55 (0.54 to 0.57)	0.69 (0.67 to 0.71)	0.67 (0.65 to 0.69)	0.76 (0.73 to 0.78)
Coronary artery bypass graft	0.48 (0.45 to 0.51)	0.74 (0.68 to 0.81)	0.57 (0.53 to 0.61)	0.79 (0.72 to 0.87)
Complications				
Acute coronary syndrome event	0.98 (0.75 to 1.28)	.11 (0.97 to 1.28)	1.05 (0.80 to 1.39)	1.03 (0.89 to 1.20)
Medical and surgical care	1.17 (1.13 to 1.22)	1.24 (1.17 to 1.30)	1.10 (1.06 to 1.15)	1.14 (1.09 to 1.21)
Morbidity and mortality				
Intensive care unit stay	0.72 (0.70 to 0.74)	0.82 (0.80 to 0.85)	0.82 (0.79 to 0.84)	0.90 (0.87 to 0.93)
Longer stay in hospital (>5 days)	1.63 (1.59 to 1.68)	1.53 (1.49 to 1.58)	1.24 (1.20 to 1.27)	1.24 (1.20 to 1.29)
Readmission	1.06 (1.00 to 1.13)	1.01 (0.93 to 1.09)	1.13 (1.06 to 1.20)	1.06 (0.97 to 1.16)
State at discharge				
Healed without follow-up	0.88 (0.86 to 0.91)	0.85 (0.81 to 0.88)	0.99 (0.96 to 1.02)	0.96 (0.92 to 1.00)
Ambulatory care or treatment	0.78 (0.76 to 0.80)	0.77 (0.75 to 0.80)	0.88 (0.85 to 0.91)	0.90 (0.87 to 0.93)
Care at home	2.27 (2.12 to 2.42)	3.05 (2.72 to 3.41)	1.63 (1.54 to 1.72)	1.75 (1.55 to 1.97)
Stationary care or treatment	1.07 (1.04 to 1.10)	1.00 (0.97 to 1.04)	1.03 (1.01 to 1.05)	1.01 (0.97 to 1.04)
Ambulatory or stationary rehabilitation	1.02 (0.98 to 1.06)	1.03 (0.98 to 1.07)	1.00 (0.96 to 1.04)	1.03 (0.99 to 1.09)
Death in hospital	1.30 (1.24 to 1.37)	1.75 (1.66 to 1.85)	0.87 (0.82 to 0.92)	1.00 (0.94 to 1.06)

Men are the reference group. CI=confidence interval; NSTEMI=non-ST-segment elevation myocardial infarction; OR=odds ratio; STEMI=ST-segment elevation myocardial infarction.

*Adjustment variables: age, nationality, class of stay, presence of an older acute coronary syndrome event, and somatic and psychiatric comorbidities.

syndrome, mortality was significantly higher in women than in men (7.5% *v* 5.2%, P<0.001).

Unadjusted and multivariable-adjusted logistic regression models for each outcome, stratified by NSTEMI and STEMI, showed similar adjusted estimates for both types of events on most outcomes, except for thrombolysis, the need for stationary care and death in hospital (table 2).

Adjustment for possible confounding factors (ie, age, nationality, class of stay, presence of an older acute coronary syndrome, and comorbidities) slightly decreased the associations between sex and diagnostic procedures without modifying their statistical significance. Women were 21% less likely than men to undergo a coronary angiography for NSTEMI and 13% less likely for STEMI (adjusted odds ratio 0.79 (95% confidence interval 0.77 to 0.82) *v* 0.87 (0.84 to 0.91)), and 16% less likely to undergo ventriculography for NSTEMI and 10% less likely for STEMI (0.84 (0.82 to 0.87) *v* 0.90 (0.87 to 0.91)) (table 2). Regarding treatments, no significant difference was noted in the unadjusted and adjusted models for thrombolysis in NSTEMI. In STEMI, women were 16% less likely to receive thrombolysis than men (0.84 (0.79 to 0.90)). For other cardiac treatments, women were 33% less likely in NSTEMI versus 24% less likely in STEMI to receive percutaneous coronary intervention (0.67 (0.65 to 0.69) *v* 0.76 (0.73 to 0.78)), and 43% less likely in NSTEMI and 21% less likely in STEMI to receive a coronary artery bypass graft (0.57 (0.53 to 0.61) *v* 0.79 (0.72 to 0.87)). For complications of medical and surgical care, women had a 10% increased likelihood of complications in NSTEMI and a 14% increased likelihood in STEMI (1.10 (1.06 to 1.15) *v* 1.14 (1.09 to 1.21)). Women were less likely than men to stay in the intensive care unit (0.82 (0.79 to 0.84) *v* 0.90 (0.87 to 0.93)), but more likely to have a hospital stay of more than five days (1.24 (1.20 to 1.27) *v* 1.24 (1.20 to 1.29)). No difference was observed for readmission in the unadjusted model. Women were 13% more likely than men to be readmitted after an admission for NSTEMI (1.13 (1.06 to 1.20)); no significant sex difference was noted for STEMI. Patients' state at discharge remained less favourable for women in the adjusted models: women, compared with men, were 63% more likely to need home care for NSTEMI (1.63 (1.54 to 1.72)) and 75% more likely for STEMI (1.75 (1.55 to 1.97)). Finally, in the adjusted model, the female sex was no longer associated with higher mortality in hospital. Indeed, women became 13% less likely than men to die for NSTEMI (0.87 (0.82 to 0.92)), and no significant association was noted for STEMI. These results were consistent with the models we built with the type of event as a confounding factor (online supplemental file 3).

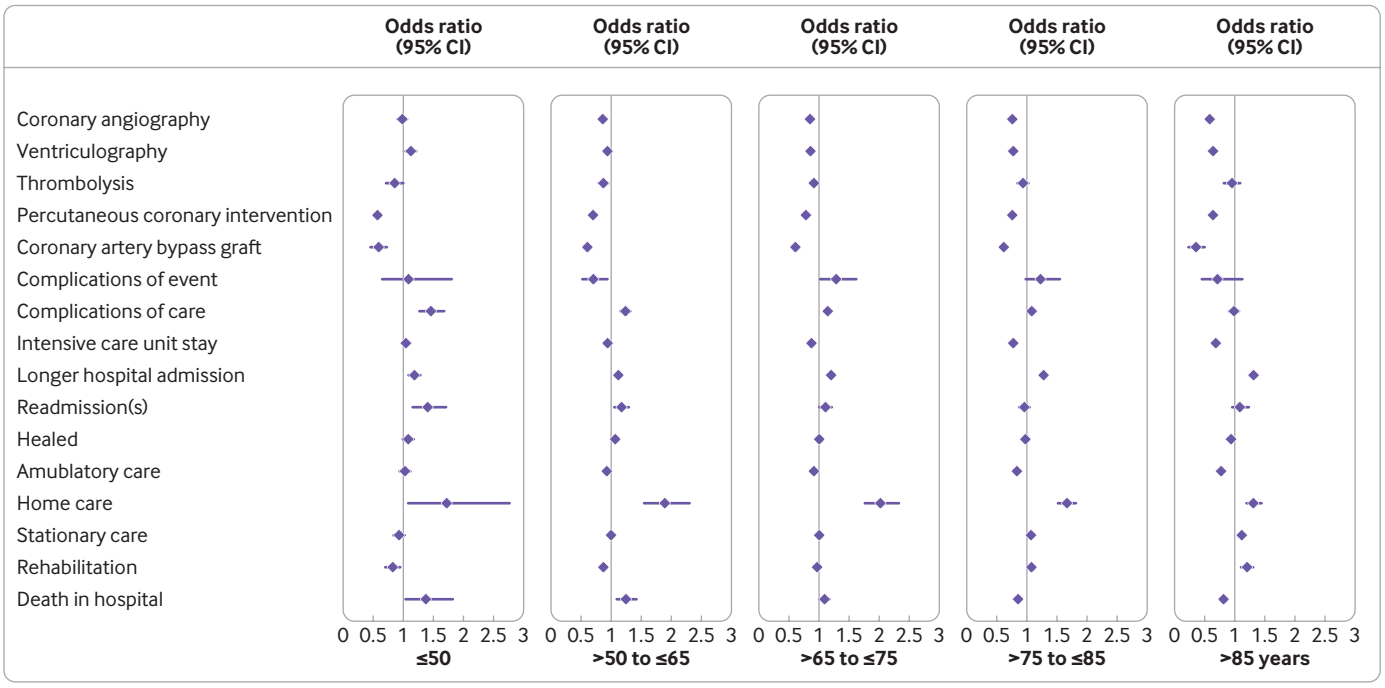

Figure 2 | Adjusted association between sex and diagnostic procedures, treatments, or complications of acute coronary syndrome event, stratified by age group. The data for this forest plot can be found in online supplemental data 4. CI=confidence interval. *Adjustment variables: nationality, class of stay, type of acute coronary syndrome event, previous older acute coronary syndrome event, and somatic and psychiatric comorbidities

We show the adjusted association between sex and outcomes, stratified by age (figure 2). Women who were younger than 50 years had a 38% increased likelihood of dying compared with men of the same age (odds ratio 1.38 (95% confidence interval 1.04 to 1.83)), and a 25% increased likelihood compared to men of the same age when women were of an age between 50 years and 65 years (1.25 (1.09 to 1.42)). The result was not significant in the more than 65 years to 75 years age group, and the trend reversed for older women. The two older age groups showed a decreased likelihood for women to die compared with men (0.86 (0.81 to 0.91) for the >75 to ≤85 years group and 0.81 (0.76 to 0.87) for the >85 years group). The other significant interactions were ventriculography, intensive care unit stay, and readmissions. In the younger than 50 years group, women were more likely than men to receive ventriculography (1.12 (1.03 to 2.21)). In all the other age groups, women were less likely to receive diagnostic procedures (both coronary angiography and ventriculography) than men. Regarding stays in an intensive care unit, no differences were noted between men and women for the younger than 50 years age group, but in every other age group, women were less likely to be admitted to the intensive care unit compared with men. Women were more likely to be readmitted in the younger than 50 years group (1.41 (1.15 to 1.72)), the older than 50 years to 65 years or younger group (1.17 (1.05 to 1.30)), and the the older than 65 years to 75 years or younger group (1.10 (1.01 to 1.21)). The results were not significant for the other older age groups. The other outcomes roughly stayed the same compared with the non-age stratified analyses, with age emphasising differences previously observed between men and women.

The proportions of the different types of events roughly did not change throughout the nine years of observations (figure 3). The absolute number of events has also continuously increased over time

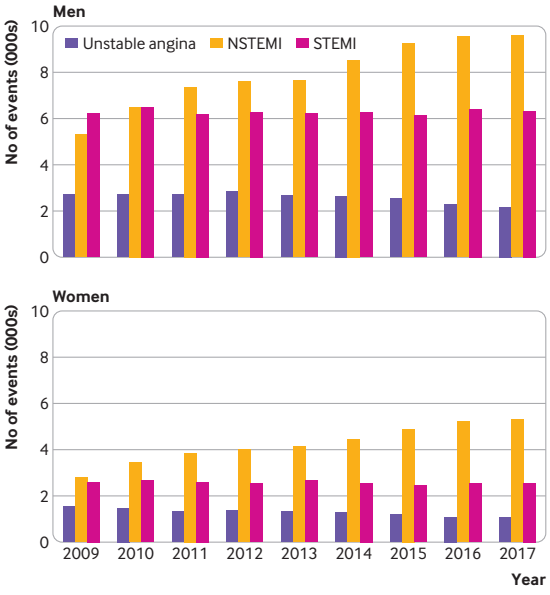

Figure 3 | Number of events and type of acute coronary syndrome by year and sex. NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction

(P for trend<0.001 for both women and men), with 21 218 events in 2009 and 27 021 events in 2017, mainly driven by the increase of NSTEMIs.

Throughout the years, the eight year age gap between men and women remained, with a steady increase in mean age for both men and women. Overall, women were a mean of 74.3 years old in 2009 and 75.8 years old in 2017. Men were, on average, 66.2 years old in 2009 and 67.8 years old in 2017 (P for trend<0.001 for both sexes). Mortality decreased over the years for both sexes but an important gap remained between men and women, with mortality for women at 8.0% in 2009 and 7.5% in 2017, whereas for men, mortality was 5.8% in 2009 and 5.3% in 2017 (P for trend<0.001 for both sexes).

Discussion

Principal findings

Our study shows that after an acute coronary syndrome, whether suffering from a NSTEMI or STEMI, women were less likely than men to undergo cardiac diagnostic procedures (ie, coronary angiography and ventriculography) or to undergo treatments and interventions such as percutaneous coronary intervention and coronary artery bypass graft. We also observed a poorer prognosis among women than men; women were more likely to have complications of medical and surgical care, have a long stay in hospital, and have worse health status at discharge. Death in hospital was more likely among women than men, but the difference disappeared after adjusting for confounding factors. Of note, age was an important effect modifier and when stratified by age, younger women (≤65 years) were more likely to die than men, whereas older women (>75 years) were less likely to die. Additionally, the mean age for an acute coronary syndrome event was shown to steadily increase for both sexes, with an eight year difference between men and women remaining constant over time. Likelihood of death in hospital reduced for both sexes throughout the years but an inequity between men and women remained constant over time.

Baseline characteristics

At baseline, as expected, women were on average older than men, our population contained more Swiss people than non-Swiss people, and most patients had standard insurance. However, what was more surprising was, on the one hand, the almost balanced risk factors burden between men and women and, on the other hand, the high prevalence of hypertension in both sexes.

The scarcity of difference between men and women for some comorbidities (eg, obesity, alcohol or tobacco dependence, and family history of cardiovascular disease) could be explained by their low prevalence because for these conditions to be coded in the database, the information must be present in patients' discharge letters. This incomplete reporting can lead to a clear underreporting of these comorbidities (discussed later in the limitations section). Comorbidities that were treated during patients' stay in hospital (eg, diabetes, hypertension, and dyslipidaemia) should be rightfully coded.

Regarding the surprisingly high prevalence of hypertension in our population (around 50%), we believe the data reflect the importance of this risk factor for acute coronary syndrome. For example, another Swiss study of 4360 patients with acute coronary syndrome over a 17 year period (2000-16) reported a prevalence of hypertension of 67% for women and 52% for men.[8]

Sex differences in management

One argument to explain the sex difference in diagnostic procedures and treatments could be because women present statistically more NSTEMIs than men. However, our results showed no difference between NSTEMI and STEMI, except for thrombolysis in NSTEMI, which was not significantly different between men and women. Furthermore, the 2020 European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[19] are clear on that matter and recommend that "Women who present with NSTE-ACS [non ST-elevation-acute coronary syndrome] should be provided with equal access to care, a prompt diagnosis, and treatments at the same rate and intensity as their male counterparts". The 2017 European Society of Cardiology guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[20] also states that "it is important to highlight that women and men receive equal benefit from a reperfusion and other STEMI-related therapies, and so both genders must be managed equally". Therefore, clear and unwarranted inequality in the management of acute coronary syndrome has been observed between men and women, with women being undertreated.

Sex differences in morbidity

The two most surprising results we found about morbidity after an acute coronary syndrome in our study were the lower rate of admission to intensive care units for women and that nearly half of women stay in hospital longer than five days.

The lower chance of admission to an intensive care unit for women has already been described in medical literature. In one study, the authors speculated that as demand for beds in intensive care exceeds availability, patients presenting with symptoms other than chest pain were more likely to be admitted to medical wards.[21] This finding correlates with the assumption that women more often present with atypical symptoms and are therefore less likely to be admitted to the intensive care unit than men.

Regarding the longer duration in hospital for women than men, we hypothesised mainly two reasons for this finding. The first assumption is that, because women were older in our study, they needed longer stays in hospital to recover from their acute coronary syndrome, and more time to organise their discharge because home care is more often needed. Our other hypothesis is that we defined a long hospital stay as more than five days, based on the mean length of stay according to the SwissDRG (the body that sets hospital tariffs in Switzerland)[22]; however, the literature describes the average length of a stay after an acute coronary syndrome between seven and nine days.[23 24] This difference could mean an artificial increase in the proportion of patients who stayed longer in hospital in our population.

Sex differences in prognosis

Women are deemed to be more likely to die because of their older age after an acute coronary syndrome event.[3 5] This hypothesis correlates to women often having more comorbidities than their male counterparts. In our study, we did not have concordant findings because women, although older than the men, had fewer risk factors and somatic comorbidities overall compared with men.

However, women were more likely to have psychiatric comorbidities, which could partially explain the worse outcomes after an acute coronary syndrome. We recognise that our data probably do not reflect the true prevalence of psychiatric comorbidities in our study population. Indeed, as for the other comorbidities, the condition had to be included in the discharge letter to be coded, thereby leading to a risk of underreporting. We compared our results to data from the general population; yet, capturing the prevalence of psychiatric disorders can be difficult because some can be episodic. However, as an example, the latest report on psychological health in Switzerland states that 6.6% of people in Europe reported mood symptoms in the last two weeks (7.9% of women and 5.2% of men).[25] Our study encompasses more than mood disorders but shows a similar prevalence to that of the general population. The observed sex difference, with women being more likely to be diagnosed with mental disorders compared with men, has often been described in the literature.[26 27] The reasons for these differences are multifactorial and not fully understood; explanations include the influence of sex hormones, the association with lived experience of violence, sexual abuse, or gender harassment among women, lower sensitivity of diagnostic criteria for men, and higher likelihood for women to report a mental health problem and to consequently seek help.[28–31] Concerning the outcomes, regardless of sex, one study showed that patients with psychotic disorders had a higher 30 day and one year mortality rate after an acute myocardial infarction and were less likely to receive coronary revascularisation.[32] In this specific population, the confounding factor of the increased cardiovascular risk conferred by neuroleptics must be taken into account.[33] However, another study, which included depressive disorders, anxiety disorders, post-traumatic stress disorders, bipolar disorders, and psychotic disorders, also reported a higher 30 day and 365 day mortality after an acute myocardial infarction among patients with psychiatric disorders.[34] In brief, women are more likely to suffer from psychiatric comorbidities due to various reasons and these comorbidities, besides additional cardiovascular disease risks associated with neuroleptics, can be associated with bias in management and thus higher mortality.

As such, the assumption that women have acute coronary syndromes at an older age and thus undergo fewer cardiac treatments and are more at risk of death is not always founded. For example, one study showed that, in a cohort of nonagenarians, women who presented with a STEMI were less likely to undergo percutaneous coronary intervention than men but had better clinical outcomes.[35]

Age as the sole explanation does not match with our age stratified analyses, which showed that younger women were relatively more likely to die compared with men of the same age. This finding has already been described in the literature, and no unique explanation has been found to date. Firstly, some authors speculated that men die more frequently than women before reaching the hospital, thus explaining the lower mortality in hospital.[36] Secondly, the poor awareness of women and physicians regarding women's cardiovascular risk,[37] especially in younger age groups, could explain the longer delays, whether to first medical contact or to get to the revascularisation.[8 9 15] Additionally, some more pathophysiological aspects were suggested, such as the different impact of the risk factors on endothelial and microvascular dysfunction[38] or the tendency to have more plaque erosion in younger women than plaque rupture in older women.[39]

Change over time

Over the years studied, we observed a steady decrease in the number of unstable anginas for both men and women, while NSTEMI increased. Unstable angina is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury or necrosis.[19] As measurements of biomarkers, such as troponins, gained in sensitivity, diagnosis of unstable angina has shifted through to NSTEMI over time.

In our study, we did not find that women had their first acute coronary syndrome event at a younger age across the years[40] because the mean age of both men and women increased over time. One explanation for the difference in age between the patients described in the literature and our population could be the geographical differences

in patient exposure to risk factors. For example, according to the WHO global report on trends in the prevalence of tobacco smoking in 2021, the prevalence of people in France who were 15 years and older and smoked was 28.7% (31.3% for men and 26.3% for women), whereas in Switzerland this number was 23.5% (26.4% and 20.5%).[41] France was chosen as a comparison because this country borders Switzerland, has good healthcare coverage, and has roughly equivalent socioeconomic status. However, men and women had acute coronary syndromes at a younger age compared with people in Switzerland (64.7 years for men and 72.4 years for women in this French study[42] *v* 67.0 years and 74.9 years in our study).

The difference between sexes in cardiovascular disease is one of the milestones in gendered medicine. Therefore, we hypothesise that cardiovascular disease care and prevention for men and women's death has improved because mortality in hospital after an acute coronary syndrome has decreased over the years in both men and women.

Biological or social differences explaining sex inequalities

Ultimately, some of our results cannot be satisfactorily explained by age, comorbidity, or type of event. Despite existing guidelines on sex specific management in patients with acute coronary syndrome, men and women were not treated similarly. Social considerations are a complementary approach to explaining the differences in management and prognosis between men and women with an acute coronary syndrome. As a reminder, gender is defined as the variability between men, women, and gender-diverse people that is attributable to society and culture; sex is defined as the biological characteristics (eg, chromosomes, hormones, and genes) that differentiate men and women.[31] Many gender and society centred explanations are available in the literature that deserve further investigations: gender differences in perception of chest pain,[43] associations between feminine gender scores and cardiovascular risk factors, cardiovascular disease,[44] or higher risk of acute coronary syndrome recurrence,[45] or the direct association between marital status and childcare workload and worse cardiovascular health outcomes.[46]

Limitations and strength

For our study, the most consequential limitation was the paucity of information about pharmacotherapy (eg, acetylsalicylic acid, heparins, and secondary prevention) and medical investigations such as electrocardiograms and troponins. As these treatments and investigations are not expensive, they are not coded in the hospital discharge data. The second important limitation was the lack of precise intervention time, which did not allow us either to assess door-to-balloon delay nor to differentiate between primary percutaneous coronary intervention for STEMI or percutaneous coronary intervention during hospitalisation for NSTEMI. However, we believe that the stratified analysis by acute coronary syndrome type allowed us to select the appropriate treatment for each type of event. Then, as somatic and psychiatric comorbidities had to be coded in the index stay to be included, we could not identify the exact prevalence of these comorbidities nor quantify missing data. Morever, some known cardiovascular risk factors (eg, ethnicity, BMI, and diet) are not coded in the database and are therefore lacking. The fact that these data are from the hospital setting might introduce a selection bias because we have no data for before hospital care and after discharge ambulatory care (eg, change in lifestyle), including long term follow-up and mortality. Variables are missing regarding socioeconomic status and subtle mechanisms, such as professional bias, whether conscious or unconscious, and the reasons behind possible patient or family refusals of some diagnostic procedures or treatments. Finally, some limitations are inherent to the classification system. For example, access site bleeding after coronary angiography or percutaneous coronary intervention is the most common complication after acute coronary syndrome care but the ICD-10-GM does not attribute a specific code for it. Despite the limitations of the hospital discharge data, which are routinely collected for billing purposes, these data are standardised, coded, and available in electronic format for secondary use. They also cover entire inpatient settings for which they provide longitudinal information and have been proven to be reliable and accurate.[47] In Switzerland, these data benefit from yearly quality control.

To our knowledge, this Swiss study was the first of this scale. For example, a multicentre Swiss study published in 2019 that assessed the differences in seeking medical care and management delays after an acute coronary syndrome for men and women had 4360 patients.[8] The AMIS Plus Registry, a nationwide, prospective, multicentre observational study, enrolled 29 620 patients between 2002 and 2012 in one of its studies[48] and 21 620 patients between 1997 and 2011 in another.[49] However, according to the numbers of the Swiss Federal Statistical Office, an average of 15 920 admissions to hospital a year were for acute coronary syndrome events.[50] Therefore, our study is more inclusive and representative of the population admitted to hospital.

Conclusion

Even though clear guidelines exist, important differences remain in the management of acute

coronary syndrome events between women and men in Switzerland. These differences might have an effect on mortality and morbidity (eg, longer stay in hospital and worse health status at discharge). Therefore, efforts must be made to better understand and correct sex inequalities in the management of acute coronary syndrome and to provide equitable and quality healthcare to women and men. This improvement will be possible with better implementation of gender sensitive guidelines and by educating caregivers about sex and gender differences in cardiovascular disease and gender bias in its management.

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Contributors The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors conceived of the presented idea. EH developed the theory and performed the computations. EH wrote the manuscript. All authors discussed the results and contributed to the final manuscript. M-ALP and CC supervised the project. EH is identified as guarantor and is responsible for the overall content. Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Ethics approval As hospitals anonymise their data before transferring them to the Swiss Federal Statistical Office, none of the data in this study allowed patient identification. The local ethics committee (CER-VD) confirmed on 9 April 2021 that this project is outside the scope of the law on human research (Req-2021-00158).

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