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Sex Differences in Long-term Prognosis, Extent of Myocardial Dysfunction and Acute Ischemic Heart Failure after ST-elevation Myocardial Infarction

Degree Project in Medicine

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Abstract

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Background: Previous studies have shown that women fare worse after ST-elevation myocardial infarction (STEMI) in the short term but that female sex is not associated with a worse long-term prognosis. Whether the short-term prognostic difference in part can be explained by a greater tendency to myocardial stunning in women is unknown.

Aim: To explore sex differences in long-term prognosis in patients with first-time STEMI treated with primary percutaneous coronary intervention (PCI) and to investigate how acute ischemic heart failure (AIHF) contributes to short- and long-term prognosis, as well as how the extent of contractile dysfunction contributes to the development of AIHF in women versus men.

Methods: 960 study patients (26% women) with first-time STEMI admitted to Sahlgrenska University Hospital were collected through Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Echocardiographic data was reviewed in a subgroup of study patients (N=166). Killip class on admission, and percentage akinesia and percentage akinesia and hypokinesia was analyzed as independent variables in multiple logistic regression analysis for the outcomes AIHF and death, respectively.

Results: Women had a higher crude risk of death within 72 hours and within 1 year compared to men, but female sex was not an independent predictor of death within 1 year in

multivariable analysis (OR 1.12, 95% CI 0.602-2.07, p=0.725). AIHF predicted death similarly in both sexes. Women were found to have higher percentage left ventricular akinesia compared to men, but percentage akinesia and hypokinesia was found to be a significant predictor of AIHF only in men.

Conclusions: Women had more widespread contractile dysfunction compared to men, but female sex was not associated with a worse long-term outcome. This could suggest that there is a greater tendency to myocardial stunning in women. Further studies are needed to confirm this finding.

Key words:

ST-elevation myocardial infarction; prognosis; sex factors; myocardial stunning

Background

Ischemic heart disease (IHD) and acute coronary syndromes (ACS)

Ischemic heart disease (IHD) includes all damage to the heart caused by ischemia, without considering the cause of ischemia (e.g. primary coronary artery occlusion or mismatch in myocardial oxygen supply and demand). Coronary artery disease (CAD) on the other hand is a term used to describe the pathological process of atherosclerotic plaque accumulation in the coronary arteries (1, 2). The term acute coronary syndrome (ACS) is used for a set of clinical symptoms suggesting acute myocardial ischemia. Both ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina are considered acute coronary syndromes (3).

Epidemiology

IHD is the most common cause of death worldwide, accounting for over 9 million (17%) of all deaths in 2016 (4). Ischemic heart disease develops approximately 7 to 10 years later in women than in men (1). Women with ACS are older, have more comorbidities and are more likely to present with NSTEMI or instable angina compared to men (5). Of all patients presenting with STEMI, approximately one third are women (6). In addition, ACS without CAD is more frequently observed in women than in similarly aged men (7). In the predominantly female group of patients with myocardial infarction (MI) and no obstructive CAD; plaque rupture or ulceration, as well as coronary vasospasm, have been proposed to be the underlying mechanisms (8).

In Sweden, approximately 5500 patients had STEMI in 2019 and in general 30 percent of all

patients with MI present with ST-elevation on admission electrocardiography (ECG). During the late 1990s, the proportion of STEMI and NSTEMI in Sweden decreased and increased respectively. However, over the last ten years the proportion of STEMI and NSTEMI have been stable (9).

Myocardial infarction

MI can be defined as myocardial cell death due to a prolonged period of ischemia (10). In a clinical setting, patients with MI are identified through the presence of ischemic symptoms together with changes in electrocardiogram (ECG) and dynamic troponin elevation with at least one value above the 99th percentile upper reference limit (10, 11).

Cardiac troponins

Troponins are found in cardiac and skeletal muscle, where they take part in mediating the muscle contraction. There are three types of troponins, troponin C, troponin I and troponin T, which together form the troponin complex, a component of thin filament (12). When the myocardium is injured, cardiac troponins (cTn) are released from myocardial cells, which can be detected as an increase in cTn-values in blood samples. Cardiac troponin I (cTnI) and T (cTnT) are the preferred biomarkers for myocardial injury. Myocardial injury is present when there is evidence of elevated cTn with at least one value above the 99th percentile upper reference limit. Elevated cTn values are not specific for acute myocardial ischemia and can also be observed in patients with e.g. heart failure, myocarditis, pulmonary embolism, takotsubo syndrome, sepsis, chronic kidney disease or stroke. If the elevation is dynamic, i.e. if there is a rise and/or fall of cardiac troponin values, the myocardial injury is considered

acute (10).

Symptoms

Patients with MI can present with ischemic symptoms such as chest pain; epigastric pain or discomfort; radiation of pain to an upper extremity, neck or jaw; or with dyspnea, fatigue or syncope. Sometimes the symptoms are more atypical or diffuse, e.g. palpitations or no symptoms at all. Compared to men, women are more likely to present with symptoms other than chest pain, as well as more likely to present with atypical pain or referred pain (13, 14).

Causes and classification of myocardial infarction

There are different possible causes of MI. Myocardial ischemia and myocardial cell necrosis can be caused by coronary artery disease and acute coronary artery occlusion, which is classified as a type 1 myocardial infarction. In contrast, MI can also be the result of a relatively low oxygen supply in relation to oxygen demand, due to e.g. other acute severe medical conditions such as sepsis or severe anemia; or as a result of tachyarrhythmias. This is defined as a type 2 myocardial infarction. Even though a type 2 myocardial infarction is not caused by a primary atherothrombotic plaque rupture, coronary artery disease is a common finding in this patient group as well. Type 3 myocardial infarction is a diagnosis used when a patient with strong clinical implications of an MI dies before collection of blood samples for troponin analysis can be collected. Additionally, MI associated with PCI is classified as a type 4a myocardial infarction; stent thrombosis as a type 4b; restenosis as a type 4c and MI associated with CABG as a type 5 myocardial infarction (10).

ST-elevation- versus non-ST-elevation myocardial infarction

If presenting ECG shows ST-segment elevations in two or more contiguous leads, or new bundle branch blocks with ischemic repolarization patterns, the patient is said to have a STEMI. Patients fulfilling criteria for MI without presenting ECG-changes listed above, are diagnosed with NSTEMI (10). There are different treatment guidelines for STEMI and NSTEMI, respectively (11).

ST-elevation myocardial infarction (STEMI)

Emergency care and treatment

Timely initiation of reperfusion therapy is essential in patients with a clinical suspicion of STEMI in order to improve survival rate (15). A 12-lead ECG recording should be obtained and interpreted within 10 minutes from first medical contact, and should be repeated if the first ECG does not show changes suggesting MI. As soon as a clinical suspicion of STEMI arises it is recommended to start ECG monitoring to enable detection of life-threatening arrhythmias. (11).

The first line reperfusion treatment recommended today for patients with STEMI is primary percutaneous coronary intervention (PCI) within 12 hours of symptoms onset if it can be achieved within 120 minutes from STEMI diagnosis and by an experienced team. If the expected time to PCI is over 120 minutes from STEMI diagnosis, the recommended therapy is instead fibrinolysis achieved through a bolus of fibrinolytics (11).

The use of primary PCI has increased dramatically in Sweden since 1995 (9). During the

procedure, coronary stenting with a bare-metal stent or with a drug-eluting stent is often used, instead of balloon angioplasty alone. The use of new generation drug-eluting stents is preferred over the use of bare-metal stents. Arterial access is given through the radial or femoral artery, where radial access is considered first choice (16).

It is recommended that all STEMI patients receive dual antiplatelet therapy (DAPT) before PCI, with the combination of aspirin together with a P2Y12 receptor inhibitor (preferably prasugrel or ticagrelor) (17). An intravenous anticoagulant is given during the procedure (11).

Management post-reperfusion

After the primary PCI procedure, all STEMI patients should be admitted to a coronary care unit or intensive cardiac care where ECG monitoring for at least 24 hours after symptom onset is recommended. The total length of hospital stay is determined through an individual risk assessment but discharge after an additional 24 to 48 hours is often safe in low-risk patients. Evaluation of left ventricular function and left ventricular ejection fraction (LVEF), in most cases rendered through echocardiography, is recommended before hospital discharge.

In addition to lifestyle interventions such as quitting smoking, information on healthy dietary habits and exercise rehabilitation, guidelines recommend life-long treatment with aspirin in combination with a P2Y12 inhibitor for up to 12 months in STEMI patients treated with PCI. Other routine drug treatments recommended in the absence of any contraindication are treatment with oral beta-blockers and statins; in patients with left ventricular dysfunction and heart failure, additional treatment with an ACE inhibitor, in some cases in combination with a

mineralocorticoid receptor antagonist (MRA), is recommended (11).

Infarct localization and culprit coronary artery

The location of ST-segment elevation on ECG may help in determining the culprit coronary artery. Anterior ST-segment elevation (leads V2-V4 but commonly involving any of the leads V1-V6) is typically seen when the culprit artery is the left anterior descending artery (LAD). Inferior ST-segment elevation (leads II, aVF, III) generally indicates an occlusion of the right coronary artery (RCA) or the left circumflex coronary artery (LCx). Posterior ST-segment elevation cannot be observed with the standard 12-lead ECG, instead the diagnostic suspicion is raised in the presence of reciprocal ST-segment depressions in anterior leads (V1-V3). The diagnosis can be confirmed by ST-segment elevation in posterior leads (V7-V9). Lateral ST-segment elevation (leads aVL, I, V5, V6) often indicates a larger area of infarction as part of an anterolateral or inferolateral myocardial infarction (18). Isolated lateral ST-segment elevation is uncommon indicating an occlusion in the obtuse marginal branch (OM) of LCx or the first diagonal branch of LAD (D1) (19).

Patients with myocardial infarctions involving LAD as culprit vessel have been considered to a worse prognosis compared to patients with non-LAD related myocardial infarction (20). Proximal LAD occlusion in particular has been shown to have the worst prognosis (21).

Myocardial stunning

With repeated, short periods of ischemia that is not sufficient to cause myocardial cell necrosis, the myocardium is protected from a subsequent, longer period of ischemia; giving

rise to a smaller infarct size than would be predicted, a phenomenon designated as ischemic preconditioning. After a short period of ischemia, a reversible loss of contractile function is also seen, designated as myocardial stunning (22). In the ischemic setting, myocardial stunning is a phenomenon where after reperfusion, there are post-ischemic mechanical dysfunction without irreversible myocardial damage (23). The mechanical dysfunction and loss of contractile function seen after an MI is thought to be partly caused by irreversible myocardial necrosis, and partly by reversible myocardial stunning, both contributing to the reduction of myocardial function (11). Several studies have shown that myocardial stunning is a phenomenon seen in MI patients receiving reperfusion treatment with percutaneous coronary intervention (PCI) (24, 25).

Myocardial stunning and the Takotsubo syndrome

Takotsubo syndrome (TS) is characterized by an acute left ventricular dysfunction not caused by any coronary occlusive lesion. TS, which is often preceded by an emotional or a physical stressor, usually presents with so called “apical ballooning”, referring to the typical echocardiographic finding of akinesia in the apical segments (and hyperkinesia in the basal segments) of the left ventricle (26). Recovery of the left ventricular function is seen after hours to days, with full recovery of left ventricular function generally seen after a few weeks (27). Mortality in TS is similar to that of acute MI, but interestingly, patients with TS often have more widespread akinesia at presentation than what would be compatible with life in a corresponding patient with MI (26). Patients with TS often present with ECG changes suggesting ischemia, e.g. ST-segment elevations, and with transient elevations in cTn values. Coronary angiography, excluding coronary artery obstruction, is mandatory to differentiate

TS from e.g. STEMI. The transient nature of the left ventricular dysfunction in TS, with recovery of left ventricular function over two to four weeks, often confirm the TS-diagnosis (10). It has been proposed that TS is caused by myocardial stunning (26, 28). TS is epidemiologically characterized by its female predominance, with approximately 90 percent being postmenopausal women (26, 29), which could indicate that the female sex is associated with a stronger tendency to develop myocardial stunning.

Complications following STEMI

The most common complication after STEMI is acute ischemic heart failure (AIHF) caused by left ventricular systolic dysfunction. Left ventricular systolic dysfunction can be diagnosed through various imaging techniques, routinely through transthoracic echocardiography. Other complications seen after STEMI includes left ventricular aneurysm, left ventricular thrombus and secondary mitral valve regurgitation. Right ventricular involvement is most frequently observed in patients with inferior STEMI (11).

Acute ischemic heart failure

In the new reperfusion era, mortality after myocardial infarction have decreased, but at the same time an increase in the incidence of heart failure have been observed (30). In addition, patients presenting with acute heart failure complicating myocardial infarction are more likely to suffer adverse in-hospital outcomes, including death (31, 32). Diagnosis of AIHF is based on the presence of typical symptoms and findings in the clinical examination and on chest X-ray (11).

The Killip classification can be used to assess the severity of acute heart failure, where the patients are classified into one of four groups based on the presence of clinical signs of cardiac decompensation. The Killip classification defines AIHF as: Killip class I) no clinical signs of heart failure; Killip class II) signs of acute heart failure such as basal rales on lung auscultation or lung X-ray finding suggesting pulmonary congestion; Killip class III) pulmonary edema; and Killip class IV) cardiogenic shock (32). Cardiogenic shock is defined as persistent systolic blood pressure (SBP) < 90 mmHg and signs of insufficient peripheral perfusion such as oliguria, altered mental status and cyanosis. If intravenous inotropes and/or mechanical support are needed to sustain an SBP > 90 mmHg in the patient, it is also considered cardiogenic shock (11).

To evaluate the extent of myocardial damage and assess the left ventricular function, transthoracic echocardiography is used. Echocardiography is also of value for ruling out other causes of heart failure in STEMI patients, such as free valve- or ventricular septal rupture (11). An alternative to LVEF for evaluation of left ventricular function is wall motion score index (WMSI), which has been shown to have a higher prognostic value than LVEF after acute MI (33). WMSI tends to be greater, i.e. more widespread myocardial dysfunction, in patients with Killip class ≥ 2 (34, 35). Calculating percentage left ventricular akinesia is yet another technique that has been used previously in experimental animal models to describe extent of akinetic left ventricular endocardium (36, 37), although not being an established method in the clinical setting.

Sex differences in STEMI patients

Several studies have shown sex differences in morbidity and mortality after STEMI, such as female sex being associated with a higher risk of presenting with AIHF and with a worse short-term survival (38, 39). However, other studies have shown results implicating that female sex is not associated with a worse long-term risk of death after myocardial infarction (6, 40).

The worse short-term outcome seen in women after myocardial infarction have previously been suggested to be a result of greater prevalence of other known negative prognostic factors, such as diabetes or more advanced age (41). Sex differences in acute care and treatment after myocardial infarction has also been discussed as a factor contributing to the higher short-term mortality seen in women (42). However, it is not known if the worse short-term outcome observed in women in part can be explained by a higher tendency of myocardial stunning in women.

Aim

The primary aim of this study was to explore sex differences in long-term prognosis in patients with first-time STEMI treated with primary PCI. As secondary objectives we sought to investigate how AIHF in first-time STEMI patients treated with primary PCI contributes to short- and long-term prognosis in women versus men, as well as to explore how the extent of myocardial dysfunction (akinesia and hypokinesia), serving as a proxy for myocardial stunning, contributes to the development of AIHF in women and men, respectively. The formulated hypothesis was that among patients with STEMI, women have more acute AIHF

and more left ventricular dysfunction within 72 hours when compared to men, but that this does not translate to a worse long-term prognosis for women.

Method

Study population and data collection

Patients with first-time STEMI admitted to Sahlgrenska University Hospital for primary PCI from August 31, 2016 to January 28, 2019 were collected through Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Patients with previous acute myocardial infarction, severe valvular stenosis or insufficiency or pre-existing EF <50% were excluded in order to avoid confounding pre-existing cardiac conditions. After exclusion 960 patients remained in the final study population (Figure 1).

Data was collected from patient medical charts, including information on baseline characteristics; comorbidities; clinical admission parameters; in-hospital complications, arrhythmias, medical treatment, laboratory results and outcome within 72 hours; and discharge medication.

Patient medical records were also used to gather the information needed to assess Killip class. Full data from the first echocardiographic examination was available in a subgroup of 166 of the study patients. This data was used to evaluate cardiac dysfunction through measurement of percent akinesia and hypokinesia. The percent akinesia and hypokinesia was defined as the length of akinetic and hypokinetic left ventricular endocardium in the two chamber (2C) and four chamber (4C) view divided by the total length of the left ventricular endocardium

measured in end-diastole both in four- and two chamber view. Consequently, the percent akinesia and hypokinesia and percent akinesia was calculated as follows:

$$\%akinesia\ and\ hypokinesia = \frac{\frac{(length\ akinesia\ 2C)+(length\ hypokinesia\ 2C)}{total\ length\ 2C}+\frac{(length\ akinesia\ 4C)+(length\ hypokinesia\ 4C)}{total\ length\ 4C}}{2}$$

$$\%akinesia = \frac{\frac{(length\ akinesia\ 2C)}{total\ length\ 2C}+\frac{(length\ akinesia\ 4C)}{total\ length\ 4C}}{2}$$

Prognosis was defined as short- (72 hours) and long-term (1 year) survival. SCAAR was used to obtain the one-year survival rate which could not be collected through examination of patient medical records due to patient confidentiality.

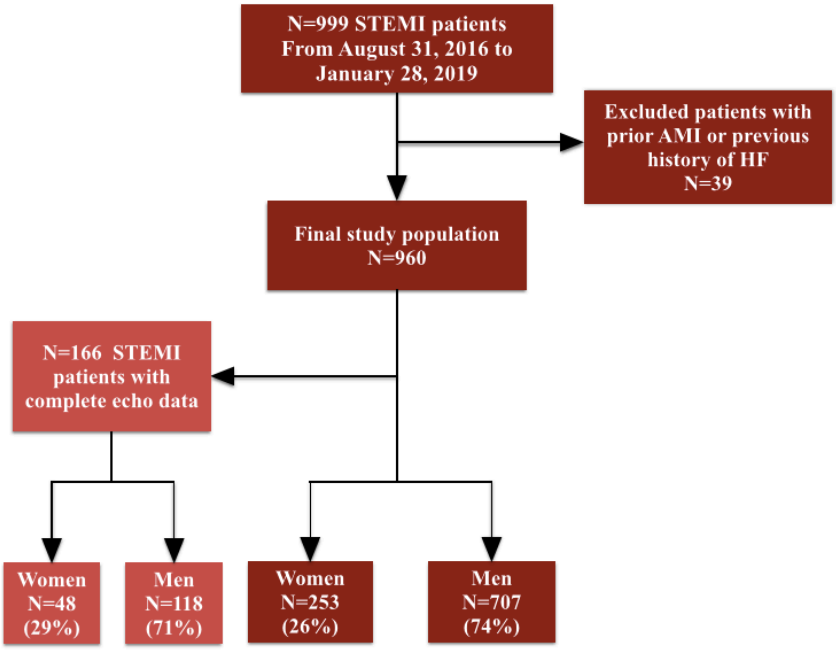

Figure 1. Flow diagram. The study population consisted of 999 patients with first-time STEMI admitted to Sahlgrenska University Hospital for primary PCI from August 31, 2016 to January 28, 2019. After exclusion of patients with prior acute myocardial infarction or previous history of heart failure with EF <50%, 960 patients remained in the final study population. The subgroup with complete data from the first echocardiogram (echo) consisted of 166 patients.

Statistical analysis

Baseline characteristics, treatment, in-hospital complications and outcomes were compared between groups in univariate analysis. Comparison between the groups were made using Chi-square test for categorical variables, independent t-test for normally distributed continuous variables and Mann-Whitney U-test for non-normally distributed continuous variables. Categorical variables are reported as quotients and percentages, whereas continuous variables are reported as either mean ±SD or median with interquartile range (IQR) for normally- and non-normally distributed variables, respectively.

Multiple logistic regression was used to analyze the association between AIHF and death stratified by sex in the main study population. The analysis for death within 72 hours was adjusted for age, and the analysis for death within 1 year for age, diabetes and minutes from symptom onset to PCI-start. The association between sex and the outcome death within 1 year was investigated with multiple logistic regression adjusted for age, AIHF, diabetes, minutes from symptom onset to PCI-start and chronic kidney disease (CKD). For the subgroup analysis of patients with available echocardiographic data, multiple logistic regression (adjusted for age) was used to examine the association between percentage akinesia; percentage akinesia and hypokinesia; ejection fraction (EF) and AIHF. SPSS version 26.0 was used for all statistical analyses. A two-sided p-value <0.05 was considered statistically significant.

Ethics

Ethical approval was obtained from the Swedish Ethical Review Authority for the main project in which this study was a part of (diary number 2019-02459). The data was pseudonymized; all patients were assigned a code and the code key was stored in an environment where the only people with access were the responsible researchers. Permission to enter patient medical charts was granted by Head of Cardiology Department at Sahlgrenska University Hospital.

Results

Baseline characteristics of the final study population (n=960) are shown in Table 1. Women were older and were more likely to have a history of hypertension, prior stroke, peripheral artery disease (lower extremity) and diabetes. Women were also more likely to present with dyspnea and back pain and presented with lower diastolic blood pressure and lower oxygen saturation levels compared to men. Regarding medical therapies on admission, women were more likely to be treated with beta blockers, acetylsalicylic acid (ASA), ACE-inhibitors or angiotensin II receptor blockers (ARB), and diuretics. Women demonstrated lower baseline levels of hemoglobin and higher levels of HDL, cholesterol and LDL, whereas men exhibited higher baseline creatinine levels. Concerning Killip class on admission, 87% of women and 92% of men presented with no signs of acute heart failure, i.e. Killip class I. In the female group 6.3% presented with Killip class II, 2.4% with Killip class III and 4.0% with Killip class IV. Among males, 5.1% presented with Killip class II, 1.1% with Killip class III and 2.3% with Killip class IV. No statistically significant sex differences in Killip class on admission were detected in univariate analysis. Any sign of AIHF (Killip class ≥2) on

admission was present in 13% of women and 8.5% in men (p=0.054).

Complications and outcomes in the main study population are presented in Table 2. Women had a longer time to reperfusion from symptom onset compared to men. After arrival at ward, the complications bleeding TIMI minor, erythrocyte transfusion and asystole >10 seconds were more likely to occur in females. Women were more likely to die both within 72 hours and within one year compared to men in univariate analysis (4.0% versus 1.3%, p=0.009 and 9.6% versus 5.3%, p=0.045).

Table 1. Baseline characteristics of the main study population

Variable	Total (n=960)	Women (n=253)	Men (n=707)	p-value
Age (years)	67±12	71±12	65±12	<0.001
BMI (kg/m²)	27±4.2	27±5.1	27±3.8	0.188
Current smoking	280/958 (29%)	74/252* (29%)	206/706* (29%)	0.960
Hypertension	417/960 (43%)	129/253 (51%)	288/707 (41%)	0.005
Hyperlipidemia	110/960 (12%)	31/253 (12%)	79/707 (11%)	0.644
Prior stroke	49/960 (5.1%)	19/253 (7.5%)	30/707 (4.2%)	0.043
History of AF	36/960 (3.8%)	13/253 (5.1%)	23/707 (3.3%)	0.176
History of stable angina	17/960 (1.8%)	7/253 (2.8%)	10/707 (1.4%)	0.162
History of claudication	16/960 (1.7%)	9/253 (3.6%)	7/707 (1.0%)	0.006
Diabetes mellitus	141/960 (15%)	50/253 (20%)	91/707 (13%)	0.007
Insulin treatment	58/959 (6.0%)	26/252* (10%)	32/707 (4.5%)	<0.001
Presenting symptom				
Angina	913/960 (95%)	238/253 (94%)	675/707 (96%)	0.375
Dyspnea	173/960 (18%)	57/253 (23%)	116/707 (16%)	0.030
Syncope	41/960 (4.3%)	10/253 (4.0%)	31/707 (4.4%)	0.770
Palpitation	5/960 (0.5%)	3/253 (1.2%)	2/707 (0.3%)	0.087
Back pain	137/960 (14%)	62/253 (25%)	75/707 (11%)	<0.001
Fatigue	48/960 (5.0%)	17/253 (6.7%)	31/707 (4.4%)	0.144
Abdominal pain	44/960 (4.6%)	13/253 (5.1%)	31/707 (4.4%)	0.623
Clinical presentation				
Heart rate	77±18	78±18	76±18	0.159
Systolic blood pressure	140±26	140±28	140±25	0.194
Diastolic blood pressure	85±16	81±15	86±16	<0.001
Oxygen saturation	96 (94-98)	96 (94-98)	96 (95-98)	0.045
Anterior ST-elevation	444/958 (46%)	105/253 (42%)	339/705* (48%)	0.072
AIHF (Killip class ≥2)	92/960 (9.6%)	32/253 (13%)	60/707 (8.5%)	0.054
Killip class I	868/960 (90%)	221/253 (87%)	647/707 (92%)	0.054
Killip class II	52/960 (5.4%)	16/253 (6.3%)	36/707 (5.1%)	0.457
Killip class III	14/960 (1.5%)	6/253 (2.4%)	8/707 (1.1%)	0.158
Killip class IV	26/960 (2.7%)	10/253 (4.0%)	16/707 (2.3%)	0.155
Medication on admission				
Beta blockers	121/953 (13%)	47/251* (19%)	74/702* (11%)	<0.001
ASA	52/953 (5.5%)	21/251* (8.4%)	31/702* (4.4%)	0.018
Warfarin	11/953 (1.2%)	3/251* (1.2%)	8/702* (1.1%)	0.944
NOAC	20/953 (2.1%)	5/251* (2.0%)	15/702* (2.1%)	0.891
ACEi or ARB	235/953 (25%)	79/251* (32%)	156/702* (22%)	0.004
Calcium antagonists	171/953 (18%)	48/251* (19%)	123/702* (18%)	0.570
Statins	99/953 (10%)	26/251* (10%)	73/702* (10%)	0.986
P2Y12 inhibitor	9/953 (0.9%)	3/251* (1.2%)	6/702* (0.9%)	0.632
MCRA	9/953 (0.9%)	3/251* (1.2%)	6/702* (0.9%)	0.632
Diuretics	100/953 (11%)	47/251* (19%)	53/702* (7.5%)	<0.001
Oral antidiabetics	91/953 (9.5%)	28/251* (11%)	63/702* (9.0%)	0.313
Laboratory data on admission				
Hb (g/L)	140±16	130±16	140±15	<0.001
TnT (ng/L)	190 (54-690)	210 (50-640)	170 (55-720)	0.959
HDL (mmol/L)	1.2 (0.98-1.5)	1.4 (1.1-1.6)	1.2 (0.96-1.4)	<0.001
Cholesterol (mmol/L)	5.0 (4.3-5.7)	5.2 (4.5-6.1)	4.9 (4.2-5.6)	<0.001
LDL (mmol/L)	3.5 (2.9-4.3)	3.6 (3.0-4.5)	3.5 (2.8-4.2)	0.017
HbA1c (mmol/mol)	38 (35-43)	39 (36-44)	38 (35-42)	0.102
Creatinine (µmol/L)	81 (69-94)	69 (60-84)	84 (73-97)	<0.001

AIHF, acute ischemic heart failure (Killip class ≥ 2); ASA, acetylsalicylic acid; NOAC, novel oral anticoagulants; ACEi, ACE inhibitors; ARB, angiotensin II receptor blocker; MCRA, mineralocorticoid receptor antagonists; Hb, hemoglobin; TnT, troponin T; HDL, high-density lipoprotein; LDL, low-density lipoprotein
*missing data

Table 2. In-hospital complications and outcomes in the main study population

	Total (n=960)	Women (n=253)	Men (n=707)	p-value
Minutes symptom to PCI-start	185 (120-358)	220 (137-453)	175 (116-330)	<0.001
In-hospital complications				
Ischemic stroke	3/960 (0.3%)	2/253 (0.8%)	1/707 (0.1%)	0.112
Cerebral hemorrhage	0/960 (0%)	0/253 (0%)	0/707 (0%)	–
AKIN 1	55/960 (5.7%)	13/253 (5.1%)	42/707 (5.9%)	0.637
AKIN 2	4/960 (0.4%)	1/253 (0.4%)	3/707 (0.4%)	0.951
AKIN 3	0/960 (0%)	0/253 (0%)	0/707 (0%)	–
Bleeding TIMI major	6/960 (0.6%)	2/253 (0.8%)	4/707 (0.6%)	0.697
Bleeding TIMI minor	111/960 (12%)	43/253 (17%)	68/707 (9.6%)	0.002
Erythrocyte transfusion	12/960 (1.3%)	7/253 (2.8%)	5/707 (0.7%)	0.011
Plasma transfusion	1/960 (0.1%)	0/253 (0.0%)	1/707 (0.1%)	0.549
VF	55/960 (5.7%)	11/253 (4.3%)	44/707 (6.2%)	0.271
Sustained VT	24/960 (2.5%)	5/253 (2.0%)	19/707 (2.7%)	0.534
VF/sustained VT	74/960 (7.7%)	14/253 (5.5%)	60/707 (8.5%)	0.131
Asystole >10 seconds	28/960 (2.9%)	14/253 (5.5%)	14/707 (2.0%)	0.004
Cardiac arrest	66/960 (6.9%)	19/253 (7.5%)	47/707 (6.6%)	0.642
Outcomes				
72-h mortality	19/960 (2.0%)	10/253 (4.0%)	9/707 (1.3%)	0.009
30-day mortality	38/943 (4.0%)	14/250* (5.6%)	24/693* (3.5%)	0.240
1-year mortality	61/943 (6.5%)	24/250* (9.6%)	37/693* (5.3%)	0.045

AKIN, Acute Kidney Injury Network classification; Bleeding TIMI major, bleeding with haemoglobin drop >50 g/L or any intracranial bleeding or fatal bleeding; Bleeding TIMI minor, bleeding with haemoglobin drop 30 to <50 g/L or requiring medical attention or any overt sign of haemorrhage requiring intervention, investigation, change in medication or prolonged hospitalization; VF, ventricular fibrillation; VT, ventricular tachycardia
*lost to follow-up

After multivariable analysis stratified by sex, admission Killip class II and -IV, and Killip class II, -III and -IV were found to be predictive variables of death within 72 hours and 1 year, respectively, in women (Table 3 and 4). For males, admission Killip class III and -IV were found to be statistically significant predictors of death within 72 hours and 1 year, after multivariable analysis (Table 3 and 4). Female sex was found to be a predictor of death within 1 year in univariate analysis (OR 1.88, 95% CI 1.10-3.22, p=0.021), but in multivariable analysis female sex was not an independent predictor of death within 1 year (Table 5).

Table 3. Association between AIHF and death within 72 hours, multivariable analysis

	Women		Men	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Killip II*	12.9 (1.89-88.8)	0.009	14.8 (0.852-256)	0.064
Killip III*	N/A**	N/A**	367 (19.8-6790)	<0.001
Killip IV*	70.3 (8.92-554)	<0.001	242 (21.7-2700)	<0.001
AIHF (Killip ≥2)	25.6 (4.95-132)	<0.001	84.4 (9.89-720)	<0.001

Adjusted for age. AIHF, acute ischemic heart failure; *Killip class on admission; **zero events in one of the categories

Table 4. Association between AIHF and death within 1 year, multivariable analysis

	Women		Men	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Killip II*	4.42 (1.05-18.6)	0.043	1.60 (0.337-7.62)	0.553
Killip III*	22.5 (1.61-315)	0.021	39.6 (7.00-224)	<0.001
Killip IV*	34.7 (6.65-181)	<0.001	29.5 (8.85-98.3)	<0.001
AIHF (Killip ≥2)	10.8 (3.59-32.2)	<0.001	8.72 (3.82-19.9)	<0.001

Adjusted for age, diabetes and minutes from symptom onset to PCI-start. AIHF, acute ischemic heart failure; *Killip class on admission

Table 5. Association between sex and death within 1 year

	Univariate		Multivariable*	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Female sex	1.88 (1.10-3.22)	0.021	1.12 (0.602-2.07)	0.725

*Adjusted for age, acute ischemic heart failure (AIHF), diabetes, minutes from symptom onset to PCI-start and chronic kidney disease.

Baseline characteristics of the subgroup of study patients with reviewed echocardiograms are shown in supplementary Table 1. Females in the subgroup were older and more likely to have a prior history of hypertension compared to men. Women were also more prone to present with dyspnea and back pain compared to men and were more likely to be treated with beta blockers and ACE inhibitors or ARB prior to index event. Men presented with higher baseline levels of hemoglobin and creatinine. There was no significant difference in ejection fraction

(EF) or composite percentage akinesia and hypokinesia between sexes, but women were found to have greater percentage left ventricular akinesia compared to men (Table 6 and Figure 2).

Table 6. Subgroup echocardiographic variables

	Total (n=166)	Women (n=48)	Men (n=118)	p-value
Ejection fraction (%)	50 (40-55)	50 (40-55)	50 (40-55)	0.372
Akinesia (%)	0 (0-30.4)	14 (0-38)	0 (0-26)	0.041
Akinesia and hypokinesia (%)	21 (7.2-35)	27 (13-43)	18 (6.2-33)	0.052

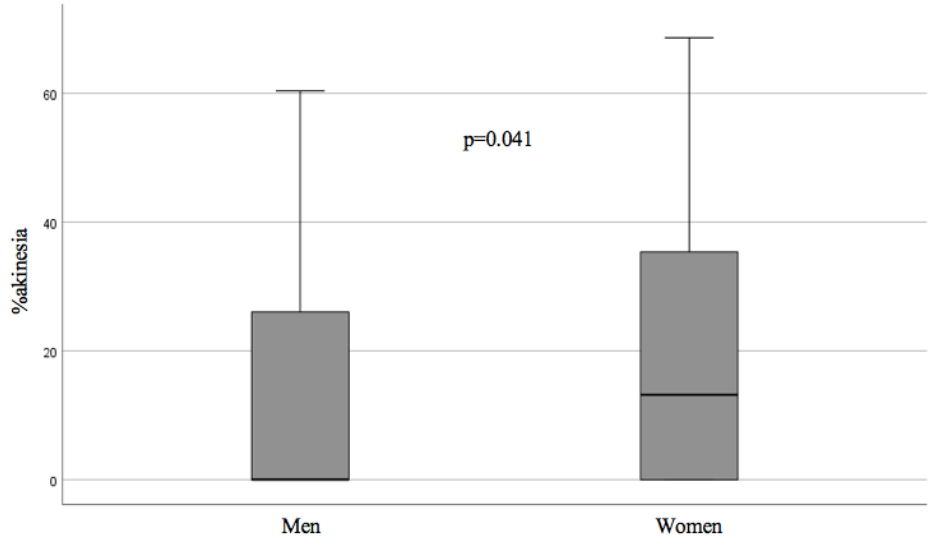

Figure 2. Box plot showing percentage left ventricular akinesia in men and women.

In-hospital complications and outcomes in the echo-subgroup are presented in supplementary table 2. There was no statistically significant difference between sexes in bleeding complications, but women were more likely to receive erythrocyte transfusion than men. Ventricular fibrillation (VF) was less common among females, but no significant sex difference was found when comparing the incidence of the composite variable of any VF or sustained ventricular tachycardia (VT). Regarding the outcome death, there were no

significant sex-differences in neither short- (72 h) nor long-term (1 year) mortality in the subgroup.

Ejection fraction (EF) was found to have a statistically significant negative association with AIHF on admission in men (OR 0.901, 95% CI 0.838-0-968, p=0.004). However, for women EF had no significant association with AIHF on admission (OR 0.956, 95% CI 0.884-1.04, p=0.268). Furthermore, the composite variable percentage of akinesia and hypokinesia was also found to be a significantly associated with AIHF on admission in men but not in women (Table 7).

Table 7. Echocardiographic variables and association with AIHF on admission

	Women		**Men**	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Visual EF*	0.956 (0.884-1.04)	0.268	0.901 (0.838-0.968)	0.004
%akinesia	1.01 (0.970-1.05)	0.659	1.02 (0.984-1.05)	0.315
%akinesia and hypokinesia	1.04 (0.994-1.08)	0.097	1.05 (1.01-1.09)	0.007

Adjusted for age. *Visually estimated EF, ejection fraction.

Discussion

Main findings

Short- and long-term prognosis

The main finding in the present study was that crude mortality rates were higher in women than in men both within 72 hours and within 1 year, however; after adjusting for age, AIHF, diabetes, minutes from symptom onset to PCI-start, and chronic kidney disease; female sex was not associated with a higher risk of death within 1 year, a finding that goes in line with what previous studies have reported. In a study by Kosmidou et al, women with STEMI had a significantly higher adjusted one-year risk of heart failure hospitalization compared to men, but not of death, after adjustment for age and other confounders (40). Redfors et al reported that women with STEMI, although having a worse short-term prognosis, had a similar long-term prognosis compared to men (43). In our cohort, women were older and had more comorbidities at baseline compared to men, findings that corresponds with results of previous studies (38, 39) and which probably explains the unadjusted sex-difference in mortality. In accordance with these findings, women were also more likely to have ongoing treatment with beta blockers, ASA, diuretics and ACE-inhibitors or ARB on admission compared to men.

Killip class and risk of death

We found a clear trend towards women presenting with more severe AIHF compared to men in the main study population (12.6% versus 8.5%, p=0.054) and Killip class II-IV was numerically higher in women both in the main study population and in the subgroup analysis. However, these results did not reach statistical significance. In a considerably larger cohort (n=48,118) Redfors et al found that women with STEMI were more at risk to develop

cardiogenic shock, i.e. to be classified as Killip class IV (43). The absence of significant differences in AIHF between women and men in our cohort might be explained by the smaller sample size.

In our study, presenting with Killip class III and -IV were significant predictors of death in men both within 72 hours and 1 year. In women, Killip class II and -IV and Killip class II, -III and -IV on admission were found to be predictors of death within 72 hours and 1 year, respectively. None of the women presenting with Killip class III (n=6) died within 72 hours. In summary, AIHF predicted death within 72 hours and 1 year similarly in both men and women.

Cardiac dysfunction and risk of AIHF

Another important finding in our study was that women exhibited a statistically significant greater percentage left ventricular akinesia compared to men. There was also a trend towards higher composite percentage left ventricular akinesia and hypokinesia in women compared to men (27% versus 18%, p=0.052).

In a study by Mehilli et al, female sex was identified as an independent predictor of higher salvage index after myocardial infarction (44), a finding that was also reported in a study by Canali and colleagues (45). Kosmidou et al reported that infarct size did not differ significantly between women and men, and LVEF was significantly higher in women vs. men, measured after a median of 4 days after PCI. Furthermore, infarct size predicted the composite risk of death and heart failure hospitalization similarly in both sexes (40). De Luca

et al found that women with STEMI had a smaller infarct size, evaluated 30 days post PCI, than men, seen in all age categories investigated (41). Thus, several previous studies have shown results that do not support the idea that a larger infarct size might contribute to worse outcome in women after STEMI. As cardiac magnetic resonance imaging (cMR) is not part of clinical routine after STEMI, infarct size could not be evaluated in this study. Our echocardiographic assessment of percentage left ventricular akinesia, and the composite of percentage left ventricular akinesia and hypokinesia, captures cardiac dysfunction, constituted by both necrosis and contractile dysfunction caused by myocardial stunning.

It is a known fact that women with ACS more often than men present with more atypical symptoms (13, 14), and in this study female sex was also associated with a higher tendency to present with dyspnea and back pain. Presenting with more atypical symptoms may result in both patient- and doctors delay which may prolong the time to reperfusion (46). In our study, the observed longer time from symptom onset to PCI in women may have resulted in prolonged ischemia compared to men, possibly explaining the greater percentage akinesia seen in the female group. However, a smaller infarct size in women have been reported despite of similar time from symptom onset to reperfusion between the two sexes (45). Additionally, a similar infarct size in women and men have been recorded when time to reperfusion where greater in the female population (median time in minutes 216, IQR 148-302, versus 182, IQR 130-265) (40). Considering this, it is possible that the larger contractile dysfunction we observed in women is due to a greater propensity in females to develop myocardial stunning after STEMI.

While no significant association between percentage left ventricular akinesia and AIHF on admission were found in neither males nor females, the composite percentage of akinesia and hypokinesia was found to have a significant association with AIHF on admission in men but not in women. Additionally, visually estimated ejection fraction (EF) was found to have a statistically significant negative association with AIHF on admission in men while no such association was found in women. Thus, the greater contractile dysfunction in females does not seem to entirely translate to more clinical signs of heart failure. This finding might seem contradictory to the trend towards women presenting with more acute AIHF on admission that we observed in the present study and what have been reported by other studies in the past (38, 39). However, women had longer time to reperfusion which may indicate prolonged ischemia in the female group and the numerically higher degree of AIHF observed in women does not indicate how cardiac dysfunction per se relates to AIHF in women and men respectively. Heart failure with preserved ejection fraction (HFpEF) is more common in women than in men (47, 48). It is possible that a greater prevalence of subclinical HFpEF in our female study patients would explain why left ventricular dysfunction and LVEF were not found to have a significant association with AIHF in females while women simultaneously tended to present with more acute AIHF on admission.

As previously described, the extensive akinesia often seen in TS-patients would be expected to lead to death in a corresponding MI-patient, suggesting that myocardial stunning could serve as a protective mechanism in TS (26). Our observed greater contractile dysfunction in women compared to men could hypothetically be attributed to a greater propensity for myocardial stunning among female STEMI-patients. Under those circumstances, female

STEMI-patients may share some pathophysiological elements with the predominantly female TS-patients. Possibly, female STEMI-patients could be protected due to a proportionally larger degree of myocardial stunning in relation to necrosis and therefore present with less AIHF than a corresponding male STEMI-patient with proportionally less myocardial stunning. In addition, female sex was not associated with a higher risk of death within 1 year in multivariable analysis, which could suggest that female patients with STEMI, although having more contractile dysfunction on presentation, exhibit more recovery of the left ventricular function compared to men after suffering a MI.

In future studies, with larger sample sizes including echocardiographic data, the association between contractile dysfunction and death should be elucidated, in order to determine the role of the more widespread wall motion disturbances observed in women in relation to their worse short-term prognosis. In addition, future prospective studies, including serial echocardiographic examinations to observe recovery of left ventricular function, could help to differentiate between infarcted and stunned myocardium. If subsequent research would support myocardial stunning as the explanation of the more widespread contractile dysfunction observed in our female study population, this would not only help to explain the discrepancy between contractile dysfunction and mortality between the sexes but could also raise questions regarding sex-specific guideline-therapy after STEMI. For instance, calcium channel blockers nifedipine and verapamil have been shown to improve contractile function in stunned myocardium (49, 50). In addition, it has been proposed that treatment with inotropes may be unfavorable in TS-patients (51), which possibly could also be true for a subset of patients with MI sharing some of the characteristics of TS-patients.

In the present study, female sex was not significantly associated with higher odds for death within 1 year in multivariable analysis. However, Otten et al reported that women under the age of 65 years had an increased risk of death after STEMI treated with primary PCI both at 30 days and at 1 year compared with their male counterparts, while there was no difference in 1-year-mortality in the age group >65 years (52). In this study we did not stratify our analyses by age. Considering that TS commonly affects postmenopausal women, another question to be raised is if women of all ages are equally prone to develop myocardial stunning after STEMI, or if postmenopausal women have the highest propensity.

Strengths and limitations

This study has several limitations, one being the retrospective design, making causative relationships more uncertain. Killip class was appointed in retrospect based on information gained from patient medical charts, such as documented rales on lung auscultation or findings on chest X-ray, which may have led to misclassification in some individual cases. Additionally, the sample size including echocardiographic data was too small to investigate the relationship between contractile dysfunction and mortality. The wide and rather imprecise confidence intervals gained in some analyses can be attributed to the small sample size, which may not have provided enough power to detect an effect of myocardial dysfunction and LVEF on AIHF in women.

Multivariable logistic regression analysis was used to determine the association between AIHF and short- and long-term prognosis in men versus women, as well as the association

between extent of akinesia and development of AIHF in both sexes. Because of few events, i.e. deaths, in our study population, we overstepped the "one in ten rule" in our multivariable analyses of risk of death, by testing a minimum of two independent variables. Hence, the risk of overfitting must be considered. Moreover, regarding risk of death, we cannot be sure that pre-hospital deaths not captured by our study design would not have affected the results, and in addition we did not asses the cause of death but merely death of all causes. Furthermore, we did not correct for multiple testing.

In this study, we excluded patients with previous acute MI and/or history of heart failure to be able to discriminate between new onset AIHF and decompensated chronic heart failure. This means that our results are only applicable on patients with first-time STEMI and no previous history of heart failure.

Conclusions and implications

In conclusion, women presented with more contractile dysfunction compared to men, but this did not translate to a worse 1-year mortality for women. There was also a trend towards women presenting with more AIHF. However, contractile dysfunction was more closely associated with AIHF in men compared to women in sex-stratified analysis, hypothetically explained by a higher propensity for developing myocardial stunning in females. Future, larger studies are needed to establish the relationship between contractile dysfunction, AIHF and mortality in women versus men; and to elucidate the role of myocardial stunning in STEMI.

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Populärvetenskaplig sammanfattning

Könsskillnader i långtidsprognos, väggrörlighetsstörning och akut hjärtsvikt efter ST-höjningsinfarkt

Bland de som insjuknar med hjärtinfarkt har en tredjedel det man kallar för ST-höjningsinfarkt. ST-höjningsinfarkt beror på ett akut stopp i ett av hjärtats kranskärl som resulterar i att hjärtmuskeln inte får tillräckligt med syre och att hjärtmuskelceller dör. Idag är förstahandsbehandlingen vid ST-höjningsinfarkt så kallad PCI, ballongvidgning av kranskärl, för att undanröja stoppet i kranskärlet. Den vanligaste komplikationen efter ST-höjningsinfarkt är plötsligt nedsatt pumpförmåga, så kallad akut hjärtsvikt, på grund av nedsatt rörlighet i hjärtmuskeln. För att utvärdera hjärtats pumpförmåga efter en hjärtinfarkt görs ultraljudsundersökning av hjärtat där man bland annat tittar på utbredningen av eventuell nedsatt rörlighet i hjärtmuskelväggen (väggrörlighetsstörning).

Efter en hjärtinfarkt kan en del av hjärtmuskelcellerna som inte har dött av syrebristen ligga vilande och sedan återhämta sig efter några dagar till veckor, ett fenomen som på engelska kallas för ”*myocardial stunning*” och som i denna text benämns som *stunning*. Ett område som tidigare var orörligt på hjärtultraljudet kan således återfå en del av sin rörlighet och därmed kan även hjärtats pumpförmåga till viss del återhämta sig efter en tid. Tidigare studier har visat att kvinnor löper ökad risk för hjärtsvikt och död de första dagarna efter en ST-höjningsinfarkt jämfört med män, men att kvinnor inte har sämre långtidsprognos jämfört med män. Om det faktum att kvinnor har sämre korttidsprognos, men inte sämre långtidsprognos efter hjärtinfarkt jämfört med män kan bero på att kvinnor i högre grad utvecklar stunning, är dock inte klarlagt.

I denna retrospektiva studie ville vi studera könsskillnader i långtidsprognos efter ST-höjningsinfarkt. Vi ville också titta på hur graden av akut hjärtsvikt påverkar prognosen, och hur utbredningen av väggrörlighetsstörning påverkar risken för akut hjärtsvikt hos kvinnor respektive män med ST-höjningsinfarkt. I studien ingick 960 patienter med förstagångsinsjuknande i ST-höjningsinfarkt som erhöll behandling med PCI på Sahlgrenska Universitetssjukhuset mellan 31 augusti 2016 och 28 januari 2019, varav 253 (26%) var kvinnor och 707 (74%) män. Relevant information från vårdtillfället samlades in genom journalgranskning, och det första hjärtultraljudet efter PCI eftergranskades hos 166 studiepatienter för att mäta utbredningen av väggrörlighetsstörning.

I vår studie dog kvinnorna i högre utsträckning än männen både inom 72 timmar och inom ett år, men när vi tog hänsyn till bland annat ålder i vår analys såg vi att kvinnligt kön i sig inte var associerat med en ökad risk för död inom ett år. Fler kvinnor (13%) än män (8,5%) hade akut hjärtsvikt vid ankomsten till sjukhus, men denna skillnad var inte statistiskt säkerställd. Vi såg också att kvinnor hade mer utbredd väggrörlighetsstörning jämfört med män, men att väggrörlighetsstörning gav akut hjärtsvikt i större utsträckning hos männen än hos kvinnorna, vilket teoretiskt kan indikera att kvinnor har en större andel av det mer godartade fenomenet stunning jämfört med män. Om man i framtida studier kan slå fast att kvinnor i högre utsträckning än män utvecklar stunning efter hjärtinfarkt kan detta bidra till att förklara varför kvinnor har sämre överlevnad på kort sikt, men likvärdig överlevnad på lång sikt.

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Appendices

Supplementary table 1. Baseline characteristics of the subgroup with reviewed echocardiograms

Variable	Total (n=166)	Women (n=48)	Men (n=118)	p-value
Age (years)	66±12	72±12	64±12	<0.001
BMI (kg/m²)	27±3.8	27±4.1	27±3.8	0.676
Current smoking	48/165 (29%)	15/47* (32%)	33/118 (28%)	0.610
Hypertension	89/166 (54%)	34/48 (71%)	55/118 (47%)	0.005
Hyperlipidemia	24/166 (15%)	9/48 (19%)	15/118 (13%)	0.316
Prior stroke	6/166 (3.6%)	2/48 (4.2%)	4/118 (3.4%)	0.808
History of claudication	3/166 (1.8%)	2/48 (4.2%)	1/118 (0.8%)	0.146
Diabetes mellitus	26/166 (16%)	10/48 (21%)	16/118 (14%)	0.242
Insulin treatment	10/166 (6.0%)	4/48 (8.3%)	6/118 (5.1%)	0.425
Presenting symptom				
Angina	161/166 (97%)	47/48 (98%)	114/118 (97%)	0.655
Dyspnea	28/166 (17%)	15/48 (31%)	13/118 (11%)	0.002
Syncope	11/166 (6.6%)	4/48 (8.3%)	7/118 (5.9%)	0.573
Palpitation	2/166 (1.2%)	1/48 (2.1%)	1/118 (0.8%)	0.508
Back pain	29/166 (18%)	15/48 (31%)	14/118 (12%)	0.003
Fatigue	9/166 (5.4%)	4/48 (8.3%)	5/118 (4.2%)	0.291
Abdominal pain	16/166 (9.6%)	5/48 (10%)	11/118 (9.3%)	0.828
Clinical presentation				
Heart rate	77±18	80±16	76±18	0.206
Systolic blood pressure	140±27	140±30	140±26	0.572
Diastolic blood pressure	86±16	83±14	87±16	0.087
Oxygen saturation	96 (94-98)	96 (92-98)	96 (95-98)	0.132
Anterior ST-elevation	77/166 (46%)	23/48 (48%)	54/118 (46%)	0.801
AIHF (Killip class ≥ 2)	17/166 (10%)	6/48 (13%)	11/118 (9.3%)	0.540
Killip class I	149/166 (90%)	42/48 (88%)	107/118 (91%)	0.540
Killip class II	10/166 (6.0%)	3/48 (6.3%)	7/118 (5.9%)	0.938
Killip class III	2/166 (1.2%)	1/48 (2.1%)	1/118 (0.8%)	0.508
Killip class IV	5/166 (3.0%)	2/48 (4.2%)	3/118 (2.5%)	0.579
Medication on admission				
Beta blockers	26/166 (16%)	13/48 (27%)	13/118 (11%)	0.010
ASA	15/166 (9.0%)	6/48 (13%)	9/118 (7.6%)	0.321
Warfarin	2/166 (1.2%)	1/48 (2.1%)	1/118 (0.8%)	0.508
NOAC	2/166 (1.2%)	1/48 (2.1%)	1/118 (0.8%)	0.508
ACEi or ARB	47/166 (28%)	19/48 (40%)	28/118 (24%)	0.040
Calcium antagonists	36/166 (22%)	13/48 (27%)	23/118 (20%)	0.282
Statins	19/166 (11%)	7/48 (15%)	12/118 (10%)	0.418
P2Y12 inhibitor	1/166 (0.6%)	1/48 (2.1%)	0/118 (0.0%)	0.116
MCRA	3/166 (1.8%)	0/48 (0.0%)	3/118 (2.5%)	0.265
Diuretics	19/166 (11%)	9/48 (19%)	10/118 (8.5%)	0.059
Oral antidiabetics	21/166 (13%)	8/48 (17%)	13/118 (11%)	0.321
Laboratory data on admission				
Hb (g/L)	140±15	130±16	140±14	0.003
TnT (ng/L)	270 (56-940)	310 (44-1100)	240 (61-740)	0.877
HDL (mmol/L)	1.2 (0.96-1.4)	1.3 (1.1-1.6)	1.1 (0.94-1.3)	0.001
Cholesterol (mmol/L)	4.8 (4.2-5.7)	5.0 (4.4-5.9)	4.6 (4.2-5.6)	0.199
LDL (mmol/L)	3.5 (2.8-4.2)	3.8 (2.8-4.6)	3.4 (2.8-4.1)	0.344
HbA1c (mmol/mol)	39 (36-45)	40 (36-43)	39 (35-46)	0.644
Creatinine (μmol/L)	77 (66-91)	63 (55-80)	82 (73-94)	<0.001

AIHF, acute ischemic heart failure (Killip class ≥ 2); ASA, acetylsalicylic acid; NOAC, novel oral anticoagulants; ACEi, ACE inhibitors; ARB, angiotensin II receptor blocker; MCRA, mineralocorticoid receptor antagonists; Hb, hemoglobin; TnT, troponin T; HDL, high-density lipoprotein; LDL, low-density lipoprotein
*missing data

Supplementary table 2. In-hospital complications and outcomes in the subgroup with reviewed UCG

	Total (n=166)	**Women (n=48)**	**Men (n=118)**	**p-value**
In-hospital complications				
Ischemic stroke	0/166 (0.0%)	0/48 (0.0%)	0/118 (0.0%)	–
Cerebral hemorrhage	0/166 (0.0%)	0/48 (0.0%)	0/118 (0.0%)	–
AKIN 1	10/166 (6.0%)	1/48 (2.1%)	9/118 (7.6%)	0.174
AKIN 2	2/166 (1.2%)	1/48 (2.1%)	1/118 (0.8%)	0.508
AKIN 3	0/166 (0.0%)	0/48 (0.0%)	0/118 (0.0%)	–
Bleeding TIMI major	0/166 (0.0%)	0/48 (0.0%)	0/118 (0.0%)	–
Bleeding TIMI minor	22/166 (13%)	7/48 (15%)	15/118 (13%)	0.747
Erythrocyte transfusion	2/166 (1.2%)	2/48 (4.2%)	0/118 (0.0%)	0.026
Plasma transfusion	0/166 (0.0%)	0/48 (0.0%)	0/118 (0.0%)	–
Any cardiac arrest	9/166 (5.4%)	1/48 (2.1%)	8/118 (6.8%)	0.226
VF	11/166 (6.6%)	0/48 (0.0%)	11/118 (9.3%)	0.029
Sustained VT	2/166 (1.2%)	1/48 (2.1%)	1/118 (0.8%)	0.508
VF/sustained VT	13/166 (7.8%)	1/48 (2.1%)	12/118 (10%)	0.079
Asystole >10 seconds	4/166 (2.4%)	1/48 (2.1%)	3/118 (2.5%)	0.861
Cardiac arrest	9/166 (5.4%)	1/48 (2.1%)	8/118 (6.8%)	0.226
Outcomes				
72-h mortality	1/166 (0.6%)	0/48 (0%)	1/118 (0.8%)	0.520
30-day mortality	2/160 (1.3%)	0/46* (0%)	2/114* (1.8%)	0.370
1-year mortality	5/160 (3.1%)	2/46* (4.3%)	3/114* (2.6%)	0.570

AKIN, Acute Kidney Injury Network classification; VF, ventricular fibrillation; VT, ventricular tachycardia
*lost to follow-up