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Long-term survival of Icelandic women following acute myocardial infarction

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ABSTRACT

Objective. To evaluate the impact of sex on treatment and survival after acute myocardial infarction (AMI) in Iceland. *Methods*. A retrospective, nationwide cohort study of patients with STEMI (2008–2018) and NSTEMI (2013–2018) and obstructive coronary artery disease. Patient and procedural information were obtained from a registry and electronic health records. Survival was estimated with Kaplan–Meier method and Cox regression analysis used to identify risk factors for long-term mortality. Excess mortality from the AMI episode was estimated by comparing the survival with age- and sex-matched population in Iceland at 30-day interval. *Results*. A total of 1345 STEMI-patients (24% women) and 1249 NSTEMI-patients (24% women) were evaluated. Women with STEMI (mean age: 71 ± 11 *vs.* 67 ± 12) and NSTEMI (mean age: 69 ± 13 *vs.* 62 ± 12) were older and less likely to have previous cardiovascular disease. There was neither sex difference in the extent of coronary artery disease nor treatment. Although crude one-year post-STEMI survival was lower for women (88.7% *vs.* 93.4%, $p = .006$), female sex was not an independent risk factor after adjusting for age and co-morbidities after STEMI and was protective for NSTEMI (HR 0.67, 95% CI: 0.46–0.97). There was excess 30-day mortality in both STEMI and NSTEMI for women compared with sex-, age- and inclusion year-matched Icelandic population, but thereafter the mortality rate was similar. *Conclusion*. Women and men with AMI in Iceland receive comparable treatment including revascularization and long-term survival appears similar. Prognosis after NSTEMI is better in women, whereas higher early mortality after STEMI may be caused by delays in presentation and diagnosis.

Introduction

Mortality from coronary artery disease has decreased considerably in recent decades in Western Societies [1,2], but less in women compared with men [3]. Possible explanations for this difference include delayed medical attention, atypical presenting symptoms, less awareness, and also a higher incidence of myocardial infarction with nonobstructive coronary arteries (MINOCA) in women [4,5]. Women are more likely to have chest pain and rise in cardiac enzymes without coronary artery obstruction, and although this is sometimes due to plaque rupture, women are also more likely to have other conditions such as spontaneous coronary artery dissection, coronary artery spasm or Takotsubo cardiomyopathy that have a different pathophysiology, treatment and prognosis [6].

Coronary angiography is the gold standard to diagnose and treat obstructive coronary artery disease. International guidelines recommend the same treatment of women and men presenting with acute myocardial infarction (AMI) [7], but some previous studies suggest that women with AMI are less likely to receive treatment according to guidelines

[8–11]. When men and women with non-ST-elevation acute myocardial infarction (NSTEMI) receive comparable treatment, especially early invasive therapy, there is little difference in their mortality [12,13]. At the time of myocardial infarction, women tend to be older than men and with more comorbidities [14], which may contribute to female sex being an independent factor for survival in various research studies. Although some have showed persistent sex difference in outcomes after adjusting for multivariate factors [15], other have not [16,17].

The aim of this study was to compare treatment and survival of men and women with NSTEMI or STEMI and obstructive coronary artery disease, to identify independent prognostic factors for long-term mortality and estimate the impact of sex on relative survival.

Methods

Patients and material

This was a retrospective observational cohort study of all patients in Iceland aged 18 years and older who underwent

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coronary angiography for acute myocardial infarction (AMI) during the study period. All procedures were performed at Landspitali, the University Hospital of Iceland, which is a tertiary referral center and the only institution performing coronary angiographies and revascularization in Iceland. The study period was from 01 January 2008 to 31 December 2018 for ST elevation myocardial infarction (STEMI) and from 01 January 2013 to 31 December 2018 for non-ST elevation myocardial infarction (NSTEMI). For multiple admissions, the first was retained (Figure 1).

Information about patient demographics, cardiovascular risk factors, comorbidities, angiographic results and treatment were obtained from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), a Swedish Web-based database also used in Iceland that prospectively records both patient- and procedure-related factors [18]. All data were registered by the treating physician and nurses at the time of the procedure.

Clinical definitions

Cases of acute myocardial were defined as STEMI and NSTEMI, according to the current European Society of Cardiology guidelines, as determined by the attending cardiologist [19]. The NSTEMI diagnosis was introduced into the database 2013 and at the same time the troponin assay was changed, explaining the shorter study period for NSTEMI patients. All patients without significant coronary artery stenoses were excluded. Cardiovascular risk factors, including hypertension, diabetes mellitus, smoking status, statin use, body mass index (BMI) and renal function were recorded prospectively. Chronic kidney disease (CKD) was staged according to the Kidney Disease Outcome Quality Initiative (KDOQI) classification. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and CKD was defined as eGFR < 60 mL/min/1.73 m^2 (stage 3–5).

Prior MI, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) were recorded as defined in the database. Since these were AMI patients, they were all done urgently but it was also recorded whether they were done acutely as primary PCIs. The results of the coronary angiography were expressed as the number of vessels with significant stenoses or left main stem disease based on angiographic results with further physiological studies (IVUS or flow measurements) as deemed necessary by the operator. If PCI was performed, it was recorded whether patients received aspirin (acetylsalicylic acid) or an adenosine diphosphate receptor (ADP) inhibitor before or during the procedure. The choice of treatment, medical therapy alone, PCI or CABG, was at the discretion of the attending interventional cardiologist and/or the heart team.

Observed and expected survival

Data for all-cause mortality were extracted through linkage with Statistics Iceland. Patients were followed up for their vital status after hospitalization, with censoring at the end of follow-up on 23 October 2019. For STEMI, median follow-up was 5.4 years (range 0–11.8) but the median follow-up for NSTEMI was 3.0 years (range 0–6.4). Expected survival was derived from the general population of Iceland matched to observed survival for the study population by sex, age and year of hospitalization and compared at 30-day interval.

Patient involvement

This research was registry-based, and therefore, it was conducted without patient consent and the patients or the public were not involved in the design of the study.

Statistical analysis

All calculations were performed using R software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). All continuous variables were normally distributed and were compared with Student's t-test and presented as mean ± standard deviation (SD). Categorical variables were compared using Chi-square test if the observed data were over five, otherwise Fisher's exact test was performed. Statistical significance was prespecified at 5% ($p < .05$)

Kaplan–Meier curve was plotted to assess the estimated long-term survival and the two groups were compared using a log-rank test. To identify independent prognostic factors for survival, a Cox multivariate analysis was used and individual prognostic factors presented as hazard ratios with 95% confidence intervals. All variables met the proportionality assumption. Excess mortality rate was calculated by comparing the survival of patients to an expected survival of an age-, sex- and year of admission matched reference population using Relsurv package [20]. The difference between the observed number of deaths in the patient populations and estimated number of deaths in the reference population was tested at every 30-day interval using a Chi-squared goodness-of-fit test to compare long-term prognosis between the groups.

The study was approved by the Icelandic National Bioethics Committee (ref: VSN-19-183) and the Icelandic Data Protection Commission.

Results

Patient characteristics

Baseline characteristics of NSTEMI and STEMI patients are shown in Table 1. Of the patients presenting with STEMI, 1347 out of 1416 were diagnosed with obstructive CAD and for NSTEMI patients, 1249 out of 1605 had obstructive CAD. Women were older in both groups, for STEMI, the mean age was 68.5 years versus 61.9 years for men ($p < .001$) and for NSTEMI 71.0 years versus 67.1 years for men ($p < .001$). Cardiovascular risk factors were similar but women had lower BMI. In the NSTEMI group, women were more likely to have chronic kidney disease, whereas in the
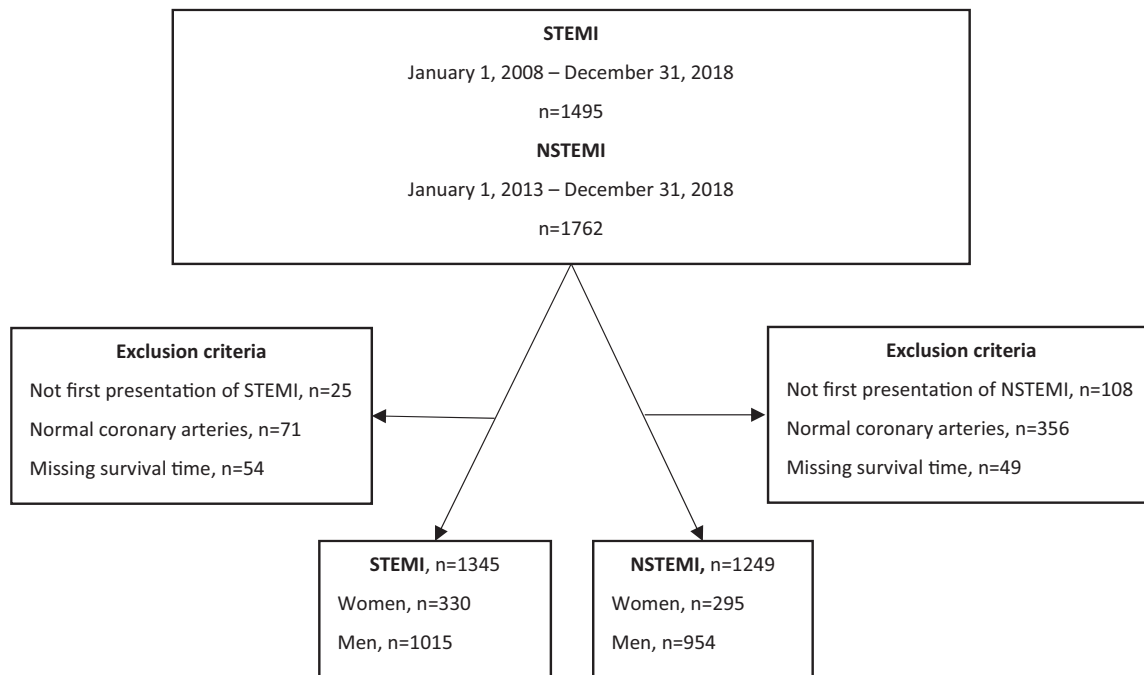
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┌─────────────────────────────────────────────────────────────┐
│                            STEMI                             │
│              January 1, 2008 – December 31, 2018             │
│                          n=1495                              │
│                           NSTEMI                             │
│              January 1, 2013 – December 31, 2018             │
│                          n=1762                              │
└─────────────────────────────────────────────────────────────┘
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┌──────────────────────────────────┐   ┌──────────────────────────────────┐
│   Exclusion criteria   │   │   Exclusion criteria   │
│ Not first presentation of STEMI, │   │ Not first presentation of NSTEMI, │
│ n=25   │   │ n=108   │
│ Normal coronary arteries, n=71   │   │ Normal coronary arteries, n=356   │
│ Missing survival time, n=54   │   │ Missing survival time, n=49   │
└──────────────────────────────────┘   └──────────────────────────────────┘

┌──────────────────────────┐   ┌──────────────────────────┐
│   STEMI, n=1345   │   │   NSTEMI, n=1249   │
│   Women, n=330   │   │   Women, n=295   │
│   Men, n=1015   │   │   Men, n=954   │
└──────────────────────────┘   └──────────────────────────┘

Figure 1. Flowchart of exclusion of the analytical cohort. AMI: acute myocardial infarction; NSTEMI: non-ST-elevation acute myocardial infarction; STEMI: ST-elevation acute myocardial infarction.

Table 1. Baseline characteristics of patients hospitalized with acute myocardial infarction, stratified by gender.

	NSTEMI 2013–2018			STEMI 2008–2018		
	Women $n = 295$ (24)	Men $n = 954$ (76)	p Value	Women $n = 330$ (24)	Men $n = 1015$ (76)	p Value
Age, year	71.0 ± 11.4	67.1 ± 11.6	**<.001**	68.5 ± 13.3	61.9 ± 12.1	**<.001**
Cardiovascular risk factors						
- Hypertension	194 (66)	607 (64)	.6	177 (55)	459 (47)	**.01**
- Diabetes	68 (23)	192 (20)	.4	44 (13)	118 (12)	.5
- Current smoker	85 (29)	235 (25)	.2	199 (36)	383 (40)	.3
- Statin use as a risk marker	157 (51)	509 (54)	.8	81 (25)	298 (31)	.08
- Body mass index (kg/m^2)	29.1 ± 6.5	28.3 ± 5.4	**.05**	27.7 ± 5.1	28.5 ± 4.8	**.02**
- Chronic kidney disease*	103 (35)	204 (22)	**<.001**	21 (12)	68 (15)	.5
History of AMI	45 (16)	258 (25)	**.01**	33 (11)	153(17)	**.02**
History of PCI	33 (12)	167 (18)	**.02**	19 (6)	115 (11)	**.007**
History of CABG	20 (7)	122 (13)	**.006**	10 (3)	36 (4)	.8

Mean ± SD or number (%).
AMI: acute myocardial infarction; CABG: coronary artery bypass graft; NSTEMI: non-ST-elevation acute myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation acute myocardial infarction..
*eGFR < 60 mL/min/1.73 m^2.

STEMI group, women more often had history of hypertension.

Procedural characteristics

There was no sex difference in the prevalence of acute coronary angiographies between either for STEMI or NSTEMI (Table 2). Radial artery access for STEMI patients increased during the study period. During the period 2008–2012, the ratio was 18% and from 2013 to 2018 it had risen to 93% without sex difference. In the NSTEMI group, female sex was associated with a slightly lower ratio of radial artery access (88% vs. 92%, $p = .03$).

There was little sex difference in the extent of the CAD. Furthermore, there was no difference in treatment, women were as likely as men to receive revascularization, and if PCI was performed, there was no difference in medical therapy before the procedure, with either aspirin or ADP-inhibitor.

Overall survival

Long-term survival following NSTEMI and STEMI is shown in Figure 2. There was no sex difference in long-term survival in the NSTEMI group (Figure 2(a)), with one-year all-cause mortality 5.1% for women compared with 5.6% for men ($p = .8$). After adjusting for confounders, the risk for long-term mortality was lower in women with HR 0.67 (95% CI: 0.46–0.97) (Table 3). For the STEMI patients, women had higher mortality, with one-year all-cause mortality 11.8% compared with 6.8% for men ($p = .004$) (Figure 2(b)). The unadjusted HR for all-cause mortality was higher

Table 2. Procedural characteristics of NSTEMI and STEMI patients, stratified by gender. Number (%).

	NSTEMI 2013–2018			STEMI 2008–2018		
	Women	Men	p Value	Women	Men	p Value
Radialaccess						
• 2008–2012				28 (18)	91 (17)	.9
• 2013–2018	260 (88)	882 (92)	**.03**	161 (92)	461 (93)	.7
Acute coronary angiography	25 (8)	111 (12)	.2	313 (95)	967 (95)	1.0
Aspirin before PCI	219 (97)	719 (96)	.4	291 (95)	933 (96)	.2
ADP-inhibitor before PCI	194 (86)	671 (86)	1.0	222 (72)	709 (73)	.8
Coronary angiography results			.1			.1
- One vessel	148 (50)	408 (43)		200 (59)	534 (50)	
- Two vessels	73 (25)	264 (28)		76 (22)	311 (29)	
- Three vessels	45 (15)	185 (19)		40 (12)	152 (14)	
- Left main stenosis	29 (10)	97 (10)		19 (6)	55 (5)	
Treatment			.6			.2
- Medical therapy alone	31 (11)	101 (11)		16 (5)	26 (3)	
- PCI	225 (76)	748 (78)		308 (93)	969 (95)	
- CABG	37 (13)	98 (10)		5 (2)	17 (2)	

ADP-inhibitor: adenosine diphosphate receptor; CABG: coronary artery bypass graft; NSTEMI: non-ST-elevation acute myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-elevation acute myocardial infarction.

for women, HR 1.55 (95% CI: 1.21–1.98) but after adjusting for confounders, female sex was not a significant risk factor for long-term mortality (HR 0.98 95% CI: 0.75–1.29).

Comparison with the general Icelandic population

There was excess mortality for the NSTEMI patients during the first 30 days after coronary angiography compared with age- and sex-matched Icelandic population (Figure 3(a)). However, after the first 30 days, there was no difference in survival between the AMI and the reference population. For the STEMI patients, women had excess mortality during the first 30 days after the event but for men, the excess mortality lasted for 60 days (Figure 3(b)).

Discussion

In this nationwide study, we found that the extent of coronary artery disease and treatment appeared to be equal for both women and men. There was no sex difference in survival for NSTEMI patients and after adjusting for comorbidities, long-term mortality was lower in women. However, for STEMI patients, survival for women was lower than that of men. That might partially stem from their higher age because female sex was not found to be a significant risk factor for long-term mortality after adjustment. For women with STEMI or NSTEMI, there was higher excess mortality during the first 30 days compared with the Icelandic population, but the difference was not evident after that.

Our study showed that women are a few years older than men at the time of AMI. This is in line with previous studies [8,10,14], where AMI usually presents six to eight years later in women than in men. The reason is thought to be the protective effects of circulating estrogen on the vascular endothelium in premenopausal women [21]. After menopause, cardiovascular risk increases considerably and the sex difference decreases. Women tended to have higher prevalence of cardiovascular comorbidities but the difference was not significant like studies have shown [8–10]. The reason

for this is probably the lack of statistical power in our study due to the small size of the study population.

Women had a higher incidence of nonobstructive coronary artery disease. In 199 (40%) women with NSTEMI diagnosis, there were no significant stenoses, this may indicate a fairly low threshold for doing a coronary angiography in women, but one limitation of our study is that we cannot exclude sex-based reference bias for angiography resulting in underdiagnosis of coronary disease in Icelandic women since we do not have accurate data on those that did not have angiography. It has been previously reported that women more often present with MINOCA than men. Possible mechanisms have been addressed, for example plaque erosion, coronary artery spasm, Takotsubo syndrome and myocarditis which is based on a different pathology and needs another work-up and treatment [6].

The use of radial artery access increased considerably during the study period for STEMI patients, and there was no sex difference. It has been shown to reduce bleeding and vascular complications, especially for women [22]. The overall number of patients treated with PCI was high. Women with NSTEMI and STEMI were as likely to undergo PCI or CABG as men. These results are according to current practice guidelines for STEMI [23], but the benefit for women with NSTEMI has been less clear. However, a recent study from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) register showed that early invasive therapy for NSTEMI resulted in equal reduction in mortality in women (RR 0.46, 95% CI 0.38–0.55) and men (RR 0.45, 95% CI 0.40–0.52) [12].

There was rather high early mortality event rate in women compared with men following STEMI, with the survival curves separating almost immediately. There are several possible explanations, including higher age of women, possibly delayed presentation and therefore less benefit from PCI. However, there was no apparent difference in access to revascularization following coronary angiography and after adjusting for comorbidities, female sex was not a significant
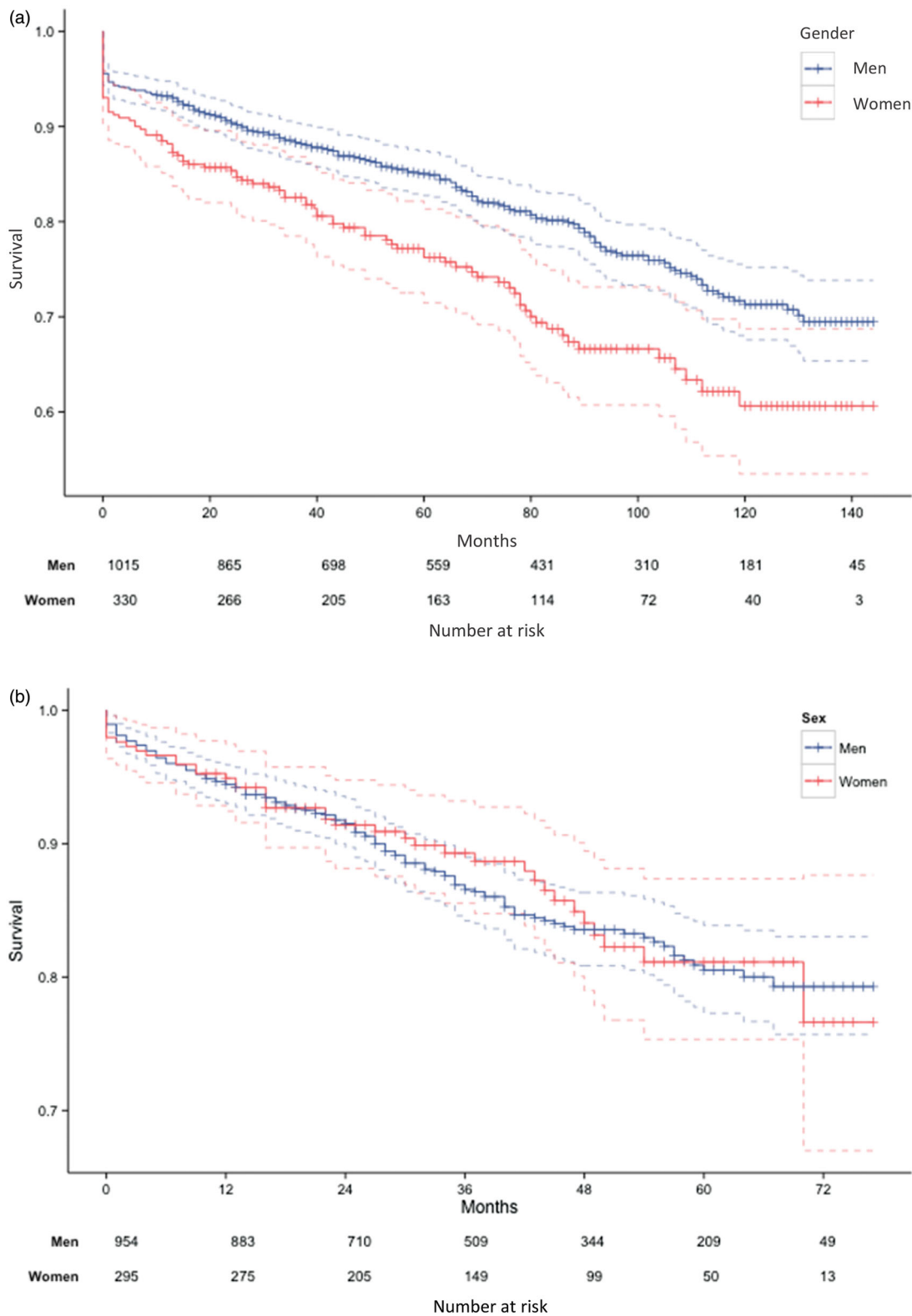
Figure 2. (a) Overall survival after ST-elevation myocardial infarction following coronary angiography in Iceland 2008–2018 with 95% cofidence interval (broken lines). (b) Overall survival after non-ST-elevation myocardial infarction following coronary angiography in Iceland 2013–2018 with 95% cofidence interval (broken lines).

risk factor for long-term mortality. This is in line with a recent meta-analysis of 68.536 STEMI patients which showed higher crude mortality in women both in hospital and at one year, but this was not significant after adjusting for baseline characteristics [15].

There was no sex difference in survival after NSTEMI and after adjusting for comorbidities, women had 33% lower risk of long-term mortality compared with men, which is in line with recent studies from Sweden and Norway [10,24]. However, we only included AMI patients who had

Table 3. Independent risk factors for long-term mortality following NSTEMI and STEMI.

	NSTEMI 2013–2018			STEMI 2008–2018		
	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Age	1.09	1.07–1.11	**<.001**	1.11	1.09–1.12	**<.001**
Female gender	0.67	0.46–0.97	**.03**	0.98	0.75–1.29	.9
Diabetes	2.26	1.62–3.16	**<.001**	2.17	1.55–3.04	**<.001**
Hypertension	1.60	1.08–2.39	**.02**	1.29	0.99–1.67	.06
Current smoker	1.63	1.09–2.44	**.01**	1.84	1.37–47	**<.001**
BMI	0.96	0.92–0.99	**.02**	1.00	0.97–1.04	.8

BMI: body mass index; CI: confidence interval; NSTEMI: non-ST-elevation acute myocardial infarction; STEMI: ST-elevation acute myocardial infarction.
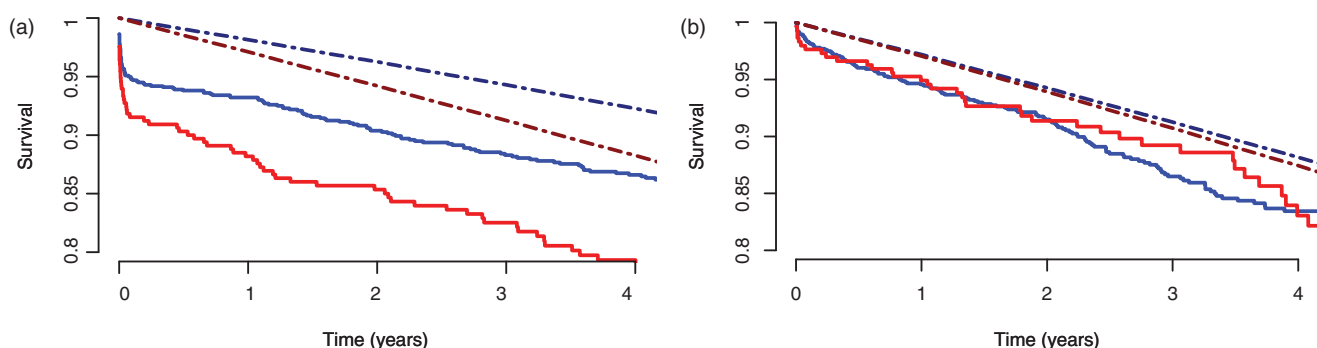

Figure 3. (a) Survival of patients following ST-elevation myocardial infarction compared to the expected survival of Icelandic population (broken lines). Red colour indicates women and blue colour indicates men. (b) Survival of patients following non-ST-elevation myocardial infarction compared to the expected survival of Icelandic population (broken lines). Red colour indicates women and blue colour indicates men.

obstructive coronary arteries which makes comparison with these studies more difficult. In their survival analysis, they included those who had nonobstructive coronary artery disease, which might result in better survival for women.

In Iceland, the survival is better for women than for men. In 2018, the life expectancy in Iceland was 84.1 years for women and 81.0 years for men [25]. There was a higher excess mortality for the NSTEMI patients during the first 30 days after the coronary angiography compared with age- and sex-matched Icelandic population. For STEMI patients, there was also higher excess mortality during the first 30 days after coronary angiography for women and the first 60 days for men but after that the mortality was similar.

It is a strength that this is a whole nation study over an extensive time period with prospective variable recording and a reliable follow-up for survival, but we accept that the overall low mortality and a small population results in a risk of type two error due to lack of power. We chose to study patients with confirmed obstructive coronary arteries since our aim was to study atherosclerotic coronary artery disease. We only enrolled patients who had coronary angiography so we cannot draw conclusions regarding those patients who were treated conservatively. The high number of women with non-obstructive disease does not suggest that coronary angiography was withheld from women.

Conclusion

In this nationwide study of AMI patients that underwent coronary angiography and had obstructive coronary artery disease, we present an overview of treatment and survival for women following AMI in Iceland. The extent of

coronary artery disease was similar between women and men and there was no difference in treatment either. Long-term crude survival was comparable between men and women following NSTEMI and after adjusting for comorbidities in the NSTEMI group, the risk for all-cause mortality in women was lower. Initial mortality after STEMI was higher for women which may stem from delays in presentation and diagnosis and possibly higher age rather than treatment. Our findings indicate that women and men are equally likely to receive invasive diagnosis and treatment after AMI and have similar outcomes. An interesting follow-up would be to investigate treatment of patients who have conservative treatment and outcomes such as treatment compliance and follow-up of female and male patients in Iceland.

Disclosure statement

Funding

Supplementary material

The data underlying this article will be shared on reasonable request to the corresponding author.

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