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FULL RESEARCH PAPER

Less revascularization in young women but impaired long-term outcomes in young men after myocardial infarction

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Aims Female sex has previously been associated with poorer outcomes after myocardial infarction (MI), although evidence is scarce among young patients. We studied sex differences in cardiovascular outcomes after MI in young patients <55 years old.

Methods and results Consecutive young (18–54 years) all-comer patients with out-of-hospital MI admitted to 20 Finnish hospitals ($n = 8934$, 17.3% women) in 2004–2014 were studied by synergizing national registries. Differences between the sexes were balanced by inverse probability weighting. The median follow-up period was 9.1 years (max 14.8 years). Young women with MI had more comorbidities at baseline, were revascularized less frequently, and received fewer evidence-based secondary prevention medications (P2Y12 inhibitors, renin–angiotensin signalling pathway inhibitors, statins, and lower statin dosages) after MI than young men. Long-term mortality or the occurrence of major adverse cardiovascular events (MACE; recurrent MI, stroke, or cardiovascular death) did not differ between the sexes in the unadjusted analysis. However, after baseline feature and treatment-difference adjustment, men had poorer outcomes after MI. Adjusted long-term mortality was 21.3% in men vs. 17.2% in women [hazard ratio (HR) 1.29; 95% confidence interval (CI) 1.10–1.53; $P = 0.002$]. Cumulative MACE rate was 33.9% in men vs. 27.9% in women during follow-up (HR 1.23; 95% CI 1.09–1.39; $P = 0.001$). Recurrent MI and cardiovascular death occurrences were more frequent among men. Stroke occurrence did not differ between the sexes.

Conclusions Young women were found to receive less active treatment after MI than young men. Nevertheless, male sex was associated with poorer long-term cardiovascular outcomes after MI in young patients after baseline feature adjustment.

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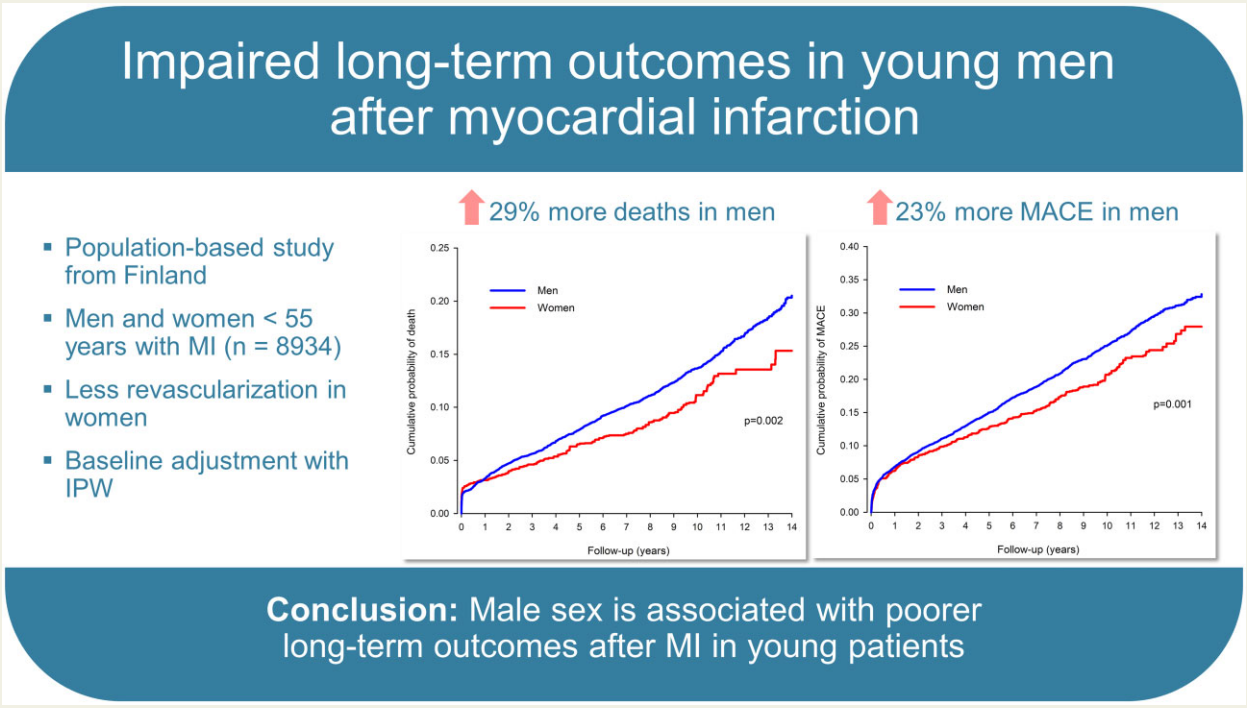

Keywords Myocardial infarction • Sex • Mortality • Outcomes • Pharmacology • Cohort study

Introduction

Although the incidence of myocardial infarction (MI) has decreased in older populations, MI remains a major cause of morbidity and mortality among young individuals, who did not have a similar decline in incidence.[1] The risk-factor profile among younger MI patients is different from older adults: some traditional cardiovascular risk factors, such as smoking and a family history of premature coronary artery disease (CAD), are more common; women are likelier to be premenopausal; and many comorbidities and frailties are less frequent.[2,3] The mechanisms of MI may also differ between younger and older individuals, although plaque rupture is the most common aetiology among both groups.[2]

Along with the unique features of young MI patients, a plethora of evidence underscores differences in MI mechanisms, clinical presentation, and outcomes by sex. Women represent approximately 10–25% of young MI patients and have more comorbidities than men.[1,3] Myocardial infarction with non-obstructive coronary arteries is especially common among premenopausal women.[1,4] Treatment of MI may be less active among women regarding less frequent and more delayed revascularizations and less frequent use of guideline-based pharmacological therapies.[5–8] According to previous studies, the prevailing perception is that women experience worse outcomes after MI than men.[9] Evidence implies that sex differences in adverse outcomes after MI may attenuate, disappear, or even reverse after adjustments for age, comorbidities, type of MI, and treatment differences,[10–13] warranting sufficiently broad adjustments in future studies to control confounding by these factors. However, some studies imply that, even after adjustments for baseline characteristics, early mortality after MI is increased in young women compared with men.[14,15] Importantly, most studies indicating worse MI prognoses in women have focused only on short-term outcomes after MI.[1,10,14–16] Evidence on sex differences in long-term outcomes after MI is more conflicting and limited among young individuals, with some studies reporting either higher, similar, or lower mortality rates among women compared with men,[11,17–19] and only a few exploring the risk of non-fatal cardiovascular events.[18,19]

We aimed to study sex differences in short- and long-term outcomes after MI among young adults below 55 years old, including both mortality and major adverse cardiovascular events (MACE) during a follow-up period of up to 14 years. We used longitudinal nationwide register data and balanced baseline differences in age, comorbidities, and type and treatment of MI between sexes using an inverse probability weighting (IPW) adjustment.

Methods

Study design and patients

We studied the impact of sex on received treatment and short- and long-term outcomes in young MI patients under 55 years old. The IPW method was used to create study groups with comparable features. Consecutive MI patients aged 18–54 years admitted to participating hospitals between 1 April 2004 and 31 December 2014, were retrospectively identified from the Care Register for Health Care in Finland (CRHC). This nationwide registry includes data on all hospital admissions and

major interventional procedures in Finland.[20] All hospitals in Finland that treat MI patients ($n = 20$; 5 with emergency coronary surgery) were included. Index MI was identified with ICD-10 code I21 as the primary discharge diagnosis. Only out-of-hospital (admitted from the emergency department or paramedic services) MI patients were included. Patients lost to mortality follow-up ($n = 98$) and those treated with aortic or valvular surgery during MI admission ($n = 23$) were excluded (Supplementary material online, *Figure S1*).

Comorbidities, revascularization procedures, and prescription drugs are defined in the Supplementary material online. Usage of cardiovascular prescription medication after MI was defined as a drug purchase within 90 days after discharge. Sequential admissions and hospital transfers after MI admission were considered single admissions.

Outcomes and follow-up

The patients were followed up until 31 December 2018. Short-term mortality was evaluated as in-hospital mortality and 30-day mortality among all MI patients. Long-term outcomes of interest were all-cause mortality among all MI patients and MACE (recurrent MI, stroke, or cardiovascular death) among hospital survivors. Long-term outcomes were assessed at 5 years, 10 years, and at the end of the follow-up. The definitions of outcomes are explained in detail in the Supplementary material online.

Data sources

The CRHC registry data were obtained from the National Institute for Health and Welfare of Finland (permission no: THL/2245/5.05.00/2019). Mortality data were obtained from the nationwide cause-of-death registry held by Statistics Finland (permission no: TK-53-484-20). Prescription drug purchase data and drug reimbursement permission data were obtained from the Social Insurance Institution of Finland (permission no: 91/522/2015). The included registries have full coverage of the Finnish population and are mandatory by law. As this study used only routinely recorded administrative health records, informed consent from patients was not required, nor were the participants contacted. Like all studies utilizing only registry data, the study was exempt by law from institutional board review. The legal basis for processing personal data is public interest and scientific research [EU General Data Protection Regulation 2016/679 (GDPR), Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6].

Statistical analysis

Balance in baseline characteristics between groups was evaluated by standardized mean difference (SMD). Propensity scores based on age, comorbidities [alcohol abuse, anaemia, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, coagulopathy, dementia, depression, diabetes, drug abuse, heart failure, hypertension, hypothyroidism, liver disease, malignancy, paralysis, peripheral vascular disease, psychotic disorder, prior MI, prior coronary artery bypass grafting (CABG), rheumatic disease, renal failure, and valvular disease], revascularization by percutaneous coronary intervention (PCI) or CABG, type of MI [ST-elevation MI (STEMI) vs. non-STEMI], treating hospital, and study year were created with logistic regression. Inverse probability weights were calculated using propensity scores. Patients with non-overlapping propensity scores ($n = 41$ men) were excluded, and IPWs were stabilized to improve balancing. Probability weighting resulted in balanced sex groups (*Table 1*). The mean of stabilized weights was 1.00 (min 0.20, max 5.75). Separate balancing was performed only for age (SMD < 0.001 for age), for the cohort without revascularization as a propensity variable (for studying revascularization; SMD < 0.030 for all covariables), for the cohort of hospital survivors using both baseline features and post-discharge medications (*Table 2*) as propensity variables (for studying potential influence of differences in pharmacotherapy on outcomes; SMD < 0.036 for all covariables), and subgroup cohorts of revascularized and non-revascularized patients (SMD < 0.049 for all covariables). Unmeasured confounding was estimated by the *E*-value (Supplementary material online).[21]

Differences between study groups were analysed using a *t*-test, Jonckheere–Terpstra test, and χ^2 test. Dichotomous outcomes (in-hospital and 30-day mortality, usage of revascularization at index admission, and usage of cardiovascular medication after MI) were studied using logistic regression.

Time-related and long-term outcomes were studied using the Kaplan–Meier method and Cox regression. Cause-specific hazard models were applied. Schoenfeld residuals were used to confirm the proportional hazard assumptions. Regression models were weighted with stabilized IPW using women as the reference in all analyses. In addition, multivariable Cox models were used to study the association of baseline features with all-cause mortality separately in women and men. Results are given as the mean, median, percentage, SMD, odds ratio (OR), or hazard ratio (HR) with 95% confidence interval (CI), interquartile range (IQR), or ±standard deviation. Statistical significance was inferred at $P < 0.05$. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the analyses.

Results

Before IPW adjustment, women had a higher frequency of many comorbidities than men (diabetes, cerebrovascular and peripheral vascular disease, hypertension, hypothyroidism, heart failure, malignancies, pulmonary disease, rheumatic disease, valvular disease, anaemia, depression and psychotic disorders, and renal failure) (*Table 1*). However, alcohol abuse, atrial fibrillation, and prior MI were more frequent among men, and MI was presented with ST elevation more frequently in men.

Differences in age, comorbidities, type of MI, revascularization, study year, and treating hospital between the sexes were balanced by IPW adjustment, resulting in an adjusted study population of 8888 patients (1538 women) (*Table 1*). For analyses of post-MI medications and long-term outcomes, a balance was maintained in the cohort of hospital survivors ($n = 8714$, SMD < 0.035 for all variables).

Short-term outcomes

Revascularization during MI admission was more frequent in men in both absolute terms (*Table 1*) and after IPW adjustment (72.1% vs. 60.5%; OR 1.69; CI 1.49–1.92; $P < 0.0001$). Percutaneous coronary intervention was performed on 66.4% of men and 56.8% of women ($P < 0.0001$) and CABG on 6.5% of men and 4.1% of women ($P = 0.0003$) in the adjusted cohort. Median duration of MI admission was 5 (IQR 4–7) days in both sexes ($P = 0.261$).

Unadjusted in-hospital (1.8% in men, 2.8% in women) and 30-day mortality (1.9% in men, 2.9% in women) were higher in women than in men ($P = 0.0009$ for both). Age-only adjustment did not change the results ($P = 0.007$ for both). After full IPW adjustment, short-term mortality after MI was similar between the sexes when measured by in-hospital mortality (1.9% in men, 2.4% in women; OR 0.80; CI 0.55–1.15; $P = 0.242$) or 30-day mortality (2.0% in men, 2.4% in women; OR 0.81; CI 0.56–1.16; $P = 0.252$).

Among the IPW-balanced cohort of hospital survivors, the usage of evidence-based secondary preventive cardiovascular medications

Table 1 Baseline features of women and men aged 18–54 years with out-of-hospital myocardial infarction

	All patients				Adjusted patients			
	Women	Men			Women	Men		
Variable	N = 1546	N = 7388	P-value	|SMD|	N = 1538	N = 7350	P-value	|SMD|
Age, years (SD)	48.2 (5.5)	48.0 (5.4)	0.331	0.027	48.1 (5.4)	48.1 (5.4)	0.591	0.015
Comorbidities								
Alcohol abuse	3.1%	4.4%	0.020	0.069	4.1%	3.9%	0.746	0.009
Anaemia	1.6%	0.5%	<0.0001	0.104	0.7%	0.7%	0.931	0.002
Atrial fibrillation	1.7%	3.0%	0.005	0.084	2.7%	2.5%	0.603	0.014
Cerebrovascular disease	4.4%	2.9%	0.003	0.078	3.6%	3.2%	0.418	0.022
Chronic pulmonary disease	11.3%	5.4%	<0.0001	0.215	6.5%	6.3%	0.778	0.008
Coagulopathy	0.5%	0.2%	0.072	0.044	0.3%	0.2%	0.534	0.016
Dementia	0.2%	0.2%	0.943	0.002	0.2%	0.2%	0.757	0.009
Depression	17.1%	8.6%	<0.0001	0.258	10.0%	10.1%	0.934	0.002
Diabetes	22.2%	13.5%	<0.0001	0.266	16.2%	15.3%	0.390	0.023
Insulin dependent	10.4%	4.5%	<0.0001	0.226	6.0%	5.7%	0.631	0.013
Non-insulin dependent	11.8%	9.0%	0.001	0.093	10.2%	9.6%	0.467	0.020
Drug abuse	0.5%	0.6%	0.498	0.020	0.5%	0.5%	0.769	0.008
Heart failure	9.2%	7.1%	0.004	0.077	7.4%	7.4%	0.973	0.001
Hypertension	37.5%	29.6%	<0.0001	0.169	31.4%	31.0%	0.780	0.008
Hypothyroidism	6.5%	1.2%	<0.0001	0.277	2.2%	2.1%	0.860	0.005
Liver disease	1.4%	1.0%	0.176	0.036	1.4%	1.1%	0.334	0.026
Malignancy	4.7%	1.9%	<0.0001	0.159	2.5%	2.4%	0.738	0.009
Metastatic tumour	0.2%	0.2%	0.683	0.008	0.2%	0.2%	0.800	0.016
Paralysis	0.3%	0.3%	0.934	0.002	0.4%	0.3%	0.514	0.019
Peripheral vascular disease	3.6%	2.1%	0.001	0.089	2.6%	2.5%	0.706	0.010
Prior CABG	1.3%	1.2%	0.842	0.006	1.2%	1.3%	0.979	0.001
Prior myocardial infarction	21.6%	24.5%	0.015	0.069	24.5%	24.0%	0.680	0.012
Psychotic disorder	3.9%	2.2%	0.009	0.069	2.7%	2.9%	0.804	0.007
Rheumatic disease	5.1%	2.3%	<0.0001	0.147	2.9%	2.8%	0.816	0.006
Renal failure	3.6%	1.6%	<0.0001	0.126	2.3%	2.1%	0.526	0.017
Valvular disease	1.8%	0.9%	0.003	0.073	1.0%	1.0%	0.822	0.006
Revascularization	59.6%	72.6%	<0.0001	0.277	69.6%	70.2%	0.638	0.013
PCI	55.5%	66.9%	<0.0001	0.236	64.6%	64.9%	0.793	0.007
CABG	4.6%	6.4%	0.008	0.078	6.0%	6.0%	0.970	0.001
STEMI	47.1%	54.8%	<0.0001	0.154	53.0%	53.3%	0.794	0.007
Anterior[a]	52.1%	48.3%	0.0613	0.075	48.8%	49.0%	0.944	0.003
Treating hospital (n = 20)			0.040	0.060			0.578	0.016
Study year			0.451	0.026			0.401	0.008

Features of all patients and inverse probability weight balanced cohort.
SMD, standardized mean difference.
[a]Of STEMI patients.

after MI differed by sex (*Table 2*). Women used P2Y12 inhibitors, angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and statins less frequently than men. Furthermore, if statins were used, the dosage was high more often among men with corresponding baseline features (*Table 2*). The results in a subgroup of non-revascularized patients were similar to the total cohort (Supplementary material online, *Table S4*), but there were no sex differences except for statin intensity in the subgroup analysis of revascularized patients (Supplementary material online, *Table S5*).

Long-term outcomes

There was no difference between the sexes in long-term mortality in the original cohort (20.8% in men vs. 18.9% in women; $P = 0.886$) or in the age-only adjusted cohort ($P = 0.304$; Supplementary material online, *Figure S2*). During follow-up, there were 1150 deaths (163 women) in the full IPW-adjusted cohort. Median follow-up was 9.1 (min 4.0, max 14.8) years, with no difference between the sexes ($P = 0.586$). Long-term mortality was higher in men after balancing sex differences in patient features (including revascularization) with IPW adjustment (*Figure 1*). Cumulative mortality was 7.9% in men

Table 2 Usage of cardiovascular prescription medication after myocardial infarction by sex in hospital survivors of original unadjusted cohort and inversive probability-adjusted cohort

	Unadjusted				IPW-adjusted			
	Women	Men			Women	Men		
	N = 1503	*N* = 7258	OR (95% CI)[a]	*P*-value	*N* = 1502	*N* = 7212	OR (95% CI)[a]	*P*-value
P2Y12-inhibitor	75.3%	81.9%	1.49 (1.30–1.70)	<0.0001	78.4%	81.5%	1.21 (1.06–1.39)	0.006
Anticoagulant	6.4%	6.5%	1.01 (0.81–1.27)	0.931	6.8%	6.4%	0.93 (0.74–1.16)	0.501
ACEi or ARB	65.7%	70.4%	1.24 (1.10–1.39)	0.0004	66.2%	70.4%	1.22 (1.08–1.37)	0.001
Aldosterone antagonist	1.9%	2.0%	1.07 (0.71–1.61)	0.758	2.1%	2.0%	0.95 (0.64–1.40)	0.779
Beta-blocker	86.8%	89.0%	1.23 (1.04–1.45)	0.016	88.3%	88.9%	1.05 (0.88–1.25)	0.566
Ezetimibe	3.5%	4.4%	1.30 (0.96–1.75)	0.089	3.7%	4.4%	1.21 (0.90–1.61)	0.210
Statin	85.6%	91.0%	1.70 (1.44–2.00)	<0.0001	88.1%	90.7%	1.30 (1.09–1.55)	0.003
Statin intensity[b]				<0.0001				<0.0001
High	17.9%	22.9%	1.36 (1.17–1.60)	<0.0001	17.2%	23.0%	1.42 (1.22–1.75)	<0.0001
Moderate	79.3%	75.8%			80.2%	75.7%		
Low	2.8%	1.3%			2.6%	1.3%		

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; OR, odds ratio.
[a]Female sex as reference group.
[b]Of statin users.

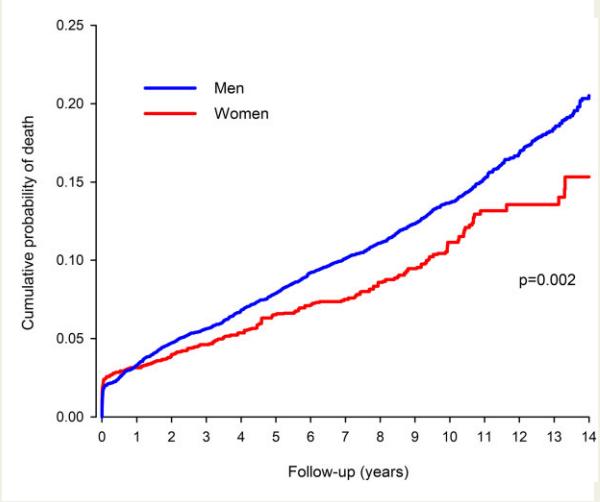

Figure 1 The cumulative probability of all-cause mortality after myocardial infarction by sex in the inverse probability weight-adjusted cohort.

and 6.5% in women at the 5-year follow-up and 13.7% and 11.2%, respectively, at the 10-year follow-up after MI. At the end of the 14.8-year follow-up, mortality was 21.3% in men and 17.2% in women (HR 1.29; CI 1.10–1.53; $P = 0.002$). The *E*-value was 1.90 (CI 1.43–2.43). Adjusted HR for death was 1.43 in men vs. women ($P = 0.0002$) among hospital survivors (*Table 3*). Diabetes, heart failure, peripheral vascular disease, renal failure, atrial fibrillation, alcohol abuse, and malignancy were associated with increased risk, and revascularization with decreased risk, of long-term mortality in multivariable analyses in both women and men (Supplementary material online, *Table S6*). Advancing age and peripheral vascular disease were associated with mortality in men but not in women (Supplementary material online, *Table S6*).

In the unadjusted cohort, the cumulative MACE occurrence was 33.3% in men and 28.8% in women ($P = 0.160$). Adjustment with age only had no influence on MACE ($P = 0.159$; Supplementary material online, *Figure S3*). Major adverse cardiovascular events occurred in 2143 full-weighted hospital survivors (329 women) during follow-up (*Figure 2*). Cumulative occurrence of MACE in women following index MI was 12.8% at 5 years, 20.7% at 10 years, and 27.9% at the end of follow-up after full IPW adjustment. The corresponding MACE rates in men were 15.0% at 5-year, 25.1% at 10-year, and 33.9% at 14.8-year follow-ups (HR 1.23 vs. women; CI 1.09–1.39; $P = 0.001$). The *E*-value for MACE was 1.76 (CI 1.40–2.13). Recurrent MI occurred in 24.8% of men and 19.6% of women during follow-up (HR 1.19; CI 1.03–1.38; $P = 0.018$) (*Figure 3*). Cumulative stroke rate after index MI was 9.4% in men and 8.3% in women (HR 1.01; CI 0.79–1.30; $P = 0.913$) during the follow-up (*Figure 3*). Cardiovascular mortality rate during follow-up of hospital survivors was 12.0% in men and 7.8% in women (HR 1.61; CI 1.24–2.10; $P = 0.0004$) (*Figure 3*). Long-term sex differences in mortality and MACE were parallel in adjusted subgroups of revascularized and non-revascularized patients, but there was no sex difference for recurrent MI in revascularized patients (Supplementary material online, *Table S7*). Additional adjustments for cardiovascular medication usage and statin dosage did not significantly alter the results obtained from long-term outcome analyses with adjustments for baseline features and revascularization (*Table 3*).

Table 3 Sex differences in outcomes of hospital survivors after myocardial infarction during 14.8-year follow-up

	Unadjusted		Model 1		Model 2	
	HR (95% CI)[a]	*P*-value	HR (95% CI)[a]	*P*-value	HR (95% CI)[a]	*P*-value
All-cause mortality	1.08 (0.91–1.28)	0.390	1.43 (1.19–1.73)	0.0002	1.41 (1.17–1.69)	0.0003
MACE	1.09 (0.96–1.23)	0.160	1.23 (1.09–1.39)	0.001	1.20 (1.06–1.36)	0.004
Recurrent myocardial infarction	1.06 (0.92–1.22)	0.428	1.19 (1.03–1.38)	0.018	1.16 (1.01–1.34)	0.042
Stroke	0.89 (0.70–1.13)	0.345	1.01 (0.79–1.30)	0.913	1.01 (0.79–1.29)	0.932
Cardiovascular death	1.22 (0.96–1.55)	0.111	1.61 (1.24–2.10)	0.0004	1.53 (1.18–1.98)	0.001

Unadjusted analyses were performed on original cohort. Model 1 was inverse probability weight (IPW) adjusted for baseline features (age, comorbidities, type of MI, treating hospital, and study year) and revascularization listed in *Table 1*. Model 2 was IPW adjusted for baseline features, revascularization, and post-MI usage of cardiovascular medications (*Table 2*, including statin intensity).
CI, confidence interval; HR, hazard ratio.
[a]Female sex as reference group.

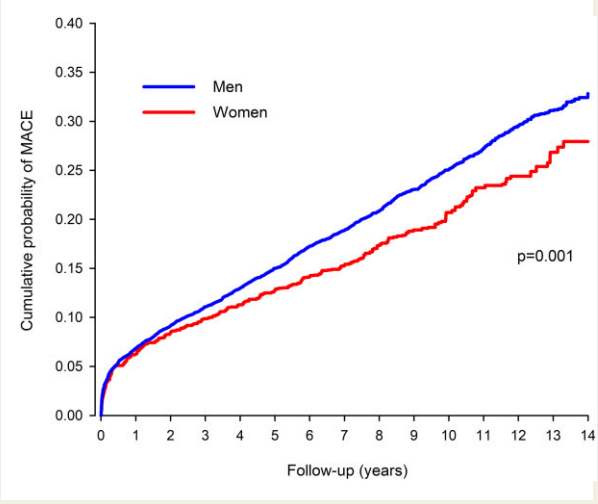

Figure 2 The cumulative probability of major adverse cardiovascular events after myocardial infarction by sex in the hospital surviving inverse probability weight-adjusted cohort.

Discussion

This nationwide register-linkage study investigated sex differences in early mortality and long-term outcomes after MI in Finnish MI patients under 55 years old, followed up for a maximum of 14.8 years. After adjusting for baseline differences in comorbidities, type, and treatment of MI, we demonstrated a higher risk of long-term mortality, MACE, recurrent MI, and cardiovascular death among young men compared with young women with MI. We found no sex differences in the adjusted early mortality rates. Our results challenge the perception of female sex as a risk factor for adverse outcomes after MI among young individuals when men and women have comparable underlying baseline characteristics.[9] Of note, we did not evaluate the impact of female-specific risk factors, such as pregnancy complications and early menopause, on MI outcomes, and their prognostic value after MI has to be clarified by future studies.

Current evidence on sex differences among young MI patients generally points towards impaired in-hospital and 30-day mortality among women compared with men, although this difference may be attenuated or no longer significant after adjustments for age and comorbidities.[9,10] According to a large clinical registry study with data on over 8000 patients with acute coronary syndrome (ACS) from 41 centres in 12 countries, the relative risk of 30-day mortality after MI is especially high among young women, even after adjustments for baseline characteristics.[14] Potential explanations for this survival gap among women with MI include atypical presentation, under-recognition of MI by health professionals, and underuse of evidence-based medications and invasive treatment strategies.[9] Following previous evidence, young women in this study had a higher 30-day mortality rate after MI than men in unadjusted analyses. Differences in baseline features between the sexes included women having a higher prevalence of most comorbidities and less frequent STEMI, and being less frequently revascularized than their male counterparts. After adjusting for these differences, we found no sex differences in early mortality. Our results imply that female sex is not an independent risk factor for early mortality after MI, but worse 30-day survival is linked to comorbidity burden, differences in MI type, and the frequency of invasive treatment.

Evidence on sex differences for long-term outcomes after MI is conflicting, partly outdated, and remains poorly understood.[13] A meta-analysis on sex differences in 1-year mortality among STEMI patients of all ages treated with primary PCI showed that the seemingly poorer survival rate among women was likely to be a result of confounding by baseline cardiovascular risk factors and differences in clinical profile.[22] Comparably, a systematic review of sex differences after MI during follow-up of 5 years or more showed that while many studies have demonstrated higher unadjusted mortality rates among women compared with men at both 5 and 10 years, these differences diminished or even disappeared after multivariable adjustments.[13] However, some studies have reported even better long-term survival after MI among women compared with men after adjustments for age and other baseline characteristics.[18,23] An analysis of over 54 000 STEMI patients from the SWEDEHEART register revealed that despite higher in-hospital mortality among women, men with STEMI had

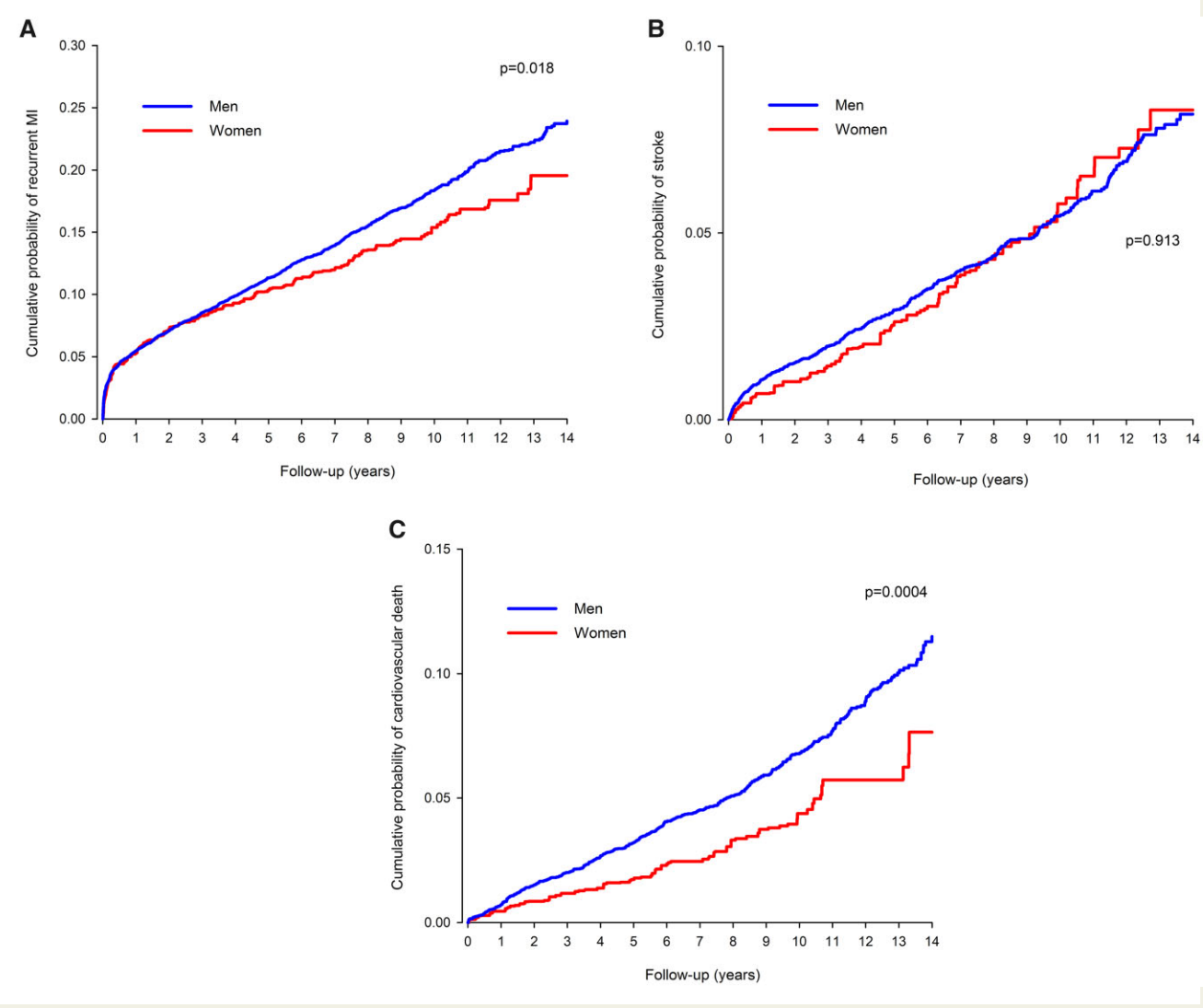

Figure 3 The cumulative probability of recurrent myocardial infarction (*A*), stroke (*B*), and cardiovascular death (*C*) after myocardial infarction by sex in the hospital surviving inverse probability weight-adjusted cohort.

worse multivariable-adjusted long-term survival.[18] A prospective Norwegian registry study demonstrated that multivariable-adjusted 5-year mortality was similar among women and men with STEMI, but lower among women compared with men with non-STEMI.[23] In a recent study among older adults ≥70 years old from our group, men had higher long-term risk of MACE after MI than women with similar baseline features and evidence-based medications.[24]

Studies on long-term survival and non-fatal cardiovascular outcomes after MI among young adults are surprisingly limited. Our results indicate that male sex may be an independent predictor of adverse long-term outcomes after MI among young people. After a follow-up of 14.8 years, the risk of death, MACE, cardiovascular death, and recurrent MI were increased by 30%, 20%, 60%, and 20%, respectively, among young men compared with young women with similar baseline features. The IPW-adjusted results were comparable among the subgroups of revascularized and non-revascularized patients, with the exception of no sex difference in recurrent MIs after revascularization. In the unadjusted analyses, however, there were no sex differences in long-term outcomes despite less active pharmacological and invasive treatment strategies among women. In contrast to our results, in a 2000–2009 Danish nationwide cohort study including MI patients under 50 years old, the 10-year multivariable-adjusted mortality rate ratio was higher for women than men (3-fold and 1.7-fold, respectively).[17] However, their analyses were conducted with less extensive adjustments than ours (type of MI and revascularization were not included).

The factors behind the higher risk of adverse long-term outcomes after MI among young men are not clarified in this study. Hypothetical explanations include biological factors such as sex hormones,[25] differences in the spectrum of the pathophysiological mechanisms of MI, and the extent of coronary atherosclerosis. Although plaque rupture is the predominant cause of MI across sex and age groups, young women with MI may more frequently have non-obstructive CAD, which may be associated with more favourable

outcomes.[26] In addition, young women may have spontaneous coronary artery dissection, microvascular disease, plaque erosions, coronary vasospasm, and Takotsubo cardiomyopathy more often than men.[27] These differences in MI pathophysiology may be attenuated among patients over 65 years old.[27] Women with obstructive CAD of all ages have fewer focal coronary artery stenoses, a lower plaque burden, and fewer vascular calcifications than men.[28] In contrast, men with ACS generally have a higher coronary plaque burden,[27] a finding that may predict the risk for future cardiovascular disease events and death.[29]

In this study, young women had a lower likelihood of undergoing revascularization (both PCI and CABG) and being managed with guideline-based MI medications (P2Y12 inhibitors, ACEi or ARB, statins, and high-intensity statin treatment). Similar findings of less active MI treatment among women have been made across the world,[5,6,30] and regarding younger MI patients, specifically.[31,32] Although these findings are in line with previous studies showing that after adjusting for age, comorbidity, and the extent of CAD, women are less likely to undergo PCI than men,[7,33] we cannot exclude the possibility that the observed sex differences in revascularization rates are at least partly driven by sex differences in clinical presentation and angiography findings and not by gender bias. Furthermore, the gender gap in the use of guidelines recommended medications was only apparent among non-revascularized patients, with the exception of lower statin intensity among young women regardless of revascularization status. Although the present data do not allow for the analysis of MI aetiology, the causes of MI among non-revascularized patients may be heterogeneous, less likely to be obstructive CAD, and—most importantly—differ between the sexes. This may explain some of the observed sex differences in the use of evidence-based medications. On another note, we did not analyse long-term adherence to these medications, which may also affect survival.[34] Women with an indication for statin therapy may not only be offered statins less often than men but may also decline and discontinue statins more frequently.[35] Sex-specific risk assessment, including the evaluation of female-specific risk factors, such as pregnancy-related disorders, breast cancer, and timing of menarche and menopause, is needed to improve preventive care in women.[36]

The strengths of this study include the nationwide dataset in which MI diagnoses have been previously validated.[37] To adjust for a plethora of confounders, including a vast range of comorbidities and the type and treatment of MI, we used propensity scoring and IPW, which are simple yet powerful tools for controlling confounding in observational studies.[38] We did not have access to laboratory results, angiographical data, more detailed clinical data (e.g. Killip class, heart rate, blood pressure), socioeconomic status, delays in care, sex-specific risk factors, such as early menarche or menopause or adverse pregnancy outcomes, or lifestyle-related factors, which may cause residual confounding. For example, smoking is more prevalent among Finnish men than women,[39] and is associated with worse long-term cardiac outcomes after MI.[40] Based on the *E*-value, the observed sex difference in long-term mortality could be explained by an unmeasured confounding associated with sex and outcome by a risk ratio of 1.9 each, above and beyond the measured confounders, but weaker confounding could not do so.[21] The study population represents the young, predominantly White Finnish MI population, but the results may not be directly generalizable to more racially and ethnically diverse populations.

In conclusion, the results of this population-based study among almost 9000 individuals under 55 years old with MI indicate that after adjustment for several confounding factors, young men had worse long-term outcomes than young women, with no sex differences in short-term survival. These findings were apparent, although young women with MI received guideline-recommended pharmacological therapies less often and were more infrequently revascularized. Our results indicate that on a long-term scale, male sex is an independent negative prognostic factor after MI among young adults. Our results call for equal attention to coronary procedures in both sexes and highlight the importance of effective secondary prevention strategies among young adults, regardless of sex. A special focus on preventive measures is needed for women due to the observed gap in current post-MI pharmacological care. For men, worse long-term cardiovascular outcomes warrant attention to intensive cardiovascular risk modifications.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Conflict of interest: A.M.K. has received speaker fees from Boehringer-Ingelheim and Sanofi and has attended advisory boards of Pfizer, Gilead, and Boehringer-Ingelheim, and received congress sponsorship from Pfizer, Celgene, UCB Pharma, Mylan, and Roche. A.P. has received grants from the Finnish Medical Foundation, the Finnish Foundation for Cardiovascular Research, and the Turku University Hospital Research Foundation, a consulting fee from Pfizer, a lecture fee from MSD, Pfizer, and Sanofi and travel expenses from Bristol-Myers-Squib and Novartis. P.R.: none. V.K. has received scientific consultancy fees (AstraZeneca), speaker fees (Bayer, Boehringer-Ingelheim, Roche), travel grants, and congress sponsorship (AstraZeneca, Boehringer-Ingelheim, Bayer, and Pfizer).

Data availability

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Findata at http://findata.fi/en.

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