ORIGINAL RESEARCH

Sex Differences in Cardiovascular Outcomes of Older Adults After Myocardial Infarction

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BACKGROUND: Evidence on the impact of sex on prognoses after myocardial infarction (MI) among older adults is limited. We evaluated sex differences in long-term cardiovascular outcomes after MI in older adults.

METHODS AND RESULTS: All patients with MI ≥70 years admitted to 20 Finnish hospitals during a 10-year period and discharged alive were studied retrospectively using a combination of national registries (n=31 578, 51% men, mean age 79). The primary outcome was combined major adverse cardiovascular event within 10-year follow-up. Sex differences in baseline features were equalized using inverse probability weighting adjustment. Women were older, with different comorbidity profiles and rarer ST-segment–elevation MI and revascularization, compared with men. Adenosine diphosphate inhibitors, anticoagulation, statins, and high-dose statins were more frequently used by men, and renin-angiotensin-aldosterone inhibitors and beta blockers by women. After balancing these differences by inverse probability weighting, the cumulative 10-year incidence of major adverse cardiovascular events was 67.7% in men, 62.0% in women (hazard ratio [HR], 1.17; CI, 1.13–1.21; P<0.0001). New MI (37.0% in men, 33.1% in women; HR, 1.16; P<0.0001), ischemic stroke (21.1% versus 19.5%; HR, 1.10; P=0.004), and cardiovascular death (56.0% versus 51.1%; HR, 1.18; P<0.0001) were more frequent in men during long-term follow-up after MI. Sex differences in major adverse cardiovascular events were similar in subgroups of revascularized and non-revascularized patients, and in patients 70 to 79 and ≥80 years.

CONCLUSIONS: Older men had higher long-term risk of major adverse cardiovascular events after MI, compared with older women with similar baseline features and evidence-based medications. Our results highlight the importance of accounting for confounding factors when studying sex differences in cardiovascular outcomes.

Key Words: cohort study ■ coronary artery disease ■ gender differences ■ myocardial infarction ■ outcomes

Despite decreasing rates of myocardial infarction (MI) during the past 50 years, MI is a major contributor to morbidity in both sexes, and ischemic heart disease remains the leading cause of death globally.[1] Emerging evidence highlights sex differences in the pathophysiology, clinical presentation, and outcomes of MI.[2,3] In general, women experience their first MI at an older age and have higher comorbidity burdens than men. Women are traditionally thought to present more often with atypical MI symptoms, although the factuality of this statement has recently been questioned.[4]

In addition, women may experience longer delays to reperfusion, lower revascularization rates, and less active pharmacological secondary prevention.[5,6] Partly because of these differences, many studies have reported higher mortality after MI among women, compared with men, in unadjusted analyses.[7–9] After adjusting for relevant confounding factors such as age, comorbidities, and treatment of MI, results have been more mixed.[8–11] Furthermore, worse prognoses after MI in women may be limited to hospitalization periods, not out-of-hospital deaths and long-term outcomes.[9,12]

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CLINICAL PERSPECTIVE

What Is New?

- After adjusting for age, comorbidities, myocardial infarction (MI) type, revascularization, and evidence-based medications, older men (≥70 years) with MI had a 17% higher 10-year risk of a major adverse cardiovascular event than women.
- These findings persisted in subgroup analyses among patients with MI aged 70 to 79 or ≥80 and among revascularized and nonrevascularized patients.

What Are the Clinical Implications?

- Our results highlight the importance of accounting for a wide range of confounding factors, including MI type and treatment, when studying sex differences in cardiovascular outcomes after MI.
- Among older adults, female sex is not an independent negative prognostic factor after MI, but long-term cardiovascular prognosis is worse among men.

Nonstandard Abbreviations and Acronyms

IPW   inverse probability weighting
MACE   major adverse cardiovascular event

Older patients have long been underrepresented in acute coronary syndrome trials, and a paucity of data exists about outcomes and their determinants after MI in older adults.[13] Older patients with acute coronary syndrome are more likely to present atypically, have more comorbidities, and worse outcomes than younger patients.[14] Many studies have demonstrated that, although short-term mortality after MI may be higher among younger women compared with younger men, this sex difference is attenuated with increasing age.[15,16] Analyses of sex differences in MI outcomes focusing on older adults (≥70 years) are few and mostly do not support poorer prognoses among older women.[9,16] Although many previous studies exploring sex differences among older adults have focused on short- and intermediate-term mortality after MI,[15,17] evidence on long-term cardiovascular outcomes is limited.

Acknowledging the aforementioned gaps in the current knowledge, we explored sex differences in long-term cardiovascular outcomes after MI in older adults. We used nationwide longitudinal register-linkage data and addressed important confounders, including age, comorbidities, and type and treatment of MI by using inverse probability weighting (IPW) adjustments.

METHODS

Study Design

From the Care Register for Health Care in Finland, we retrospectively collected data on all consecutive patients with MI aged ≥70 years admitted to participating hospitals in Finland between January 1, 2005 and December 31, 2014 and discharged alive. Participating hospitals comprised all MI-treating hospitals in Finland equipped with a coronary catherization laboratory (n=20, including 5 hospitals with emergency cardiac surgery). The index MI was defined as the first-time admission for an out-of-hospital MI during the study period, with *International Classification of Diseases, Tenth Revision (ICD-10)* code I21 as the primary discharge diagnosis. Exclusion criteria were death within 90 days after MI admission, admission duration >180 days, valvular or aortic surgery, and missing follow-up data (0.3% of patients) (Figure S1). The IPW method was used to create sex groups with balanced baseline features. Ward and hospital transfers were combined as a single admission.

The primary outcome of interest was composite major adverse cardiovascular event (MACE; new MI, ischemic stroke, or cardiovascular death). Secondary outcomes were cardiovascular death, new MI, and ischemic stroke. Outcomes were followed for 10 years, beginning 90 days after the index MI. In addition, we explored the use of evidence-based secondary preventive cardiovascular medications within 90 days of discharge from the index MI, including both newly prescribed medications as well as medications that were continued during the 90-day period after MI. Outcomes, comorbidities, and medications are defined in Data S1, Tables S1 and S2.

Study Data

Data of all hospital and emergency room admissions and major interventional procedures in Finland (Care Register for Health Care in Finland registry) and data on malignancies (Finnish Cancer Registry) were obtained from the National Institute for Health and Welfare of Finland (permission no: THL/2245/5.05.00/2019). Data on mortality were obtained from Statistics Finland (permission no: TK-53-484-20). Data on prescription medication purchases and drug reimbursement permissions were obtained from the Social Insurance Institution of Finland (permission no: 91/522/2015). The aforementioned registries are mandatory by law and have full coverage of

the Finnish population.[18] As our study used routinely recorded administrative health records, informed consent was not required, nor were the participants contacted. Like all studies utilizing only registry data, the study was exempt by law from institutional review board review. Legal grounds for the data handling are public interest and scientific research (European Union General Data Protection Regulation 2016/679, Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6).

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

Statistical Analysis

Differences between study groups were analyzed with *t* test, Jonckheere-Terpstra test, and chi-square test. Effect sizes in baseline characteristics between groups were evaluated with standardized mean difference. Propensity scores based on age, alcohol abuse, anemia, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, coagulopathy, dementia, depression, heart failure, hypertension, hypothyroidism, insulin-dependent diabetes, liver disease, malignancy, noninsulin dependent diabetes, paralysis, peripheral vascular disease, prior coronary artery bypass grafting, psychotic disorder, rheumatic disease, renal failure, valvular disease, revascularization by percutaneous coronary intervention or coronary artery bypass grafting, type of MI, use of cardiovascular medications after MI (adenosine diphosphate (ADP) receptor inhibitors, anticoagulants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, aldosterone antagonists, antiarrhythmics, beta blockers, ezetimibe, and statins), treating hospital, and study year for female sex were created with logistic regressions. The inverse probability weight was calculated using a propensity score, and IPW was stabilized (mean 1.00; SD 0.48). Weighting resulted in balanced study groups with 0.003 standardized mean difference of propensity score (Table 1). Separate IPW balancing without post-MI medications in the propensity score was performed to study medication use. Subgroup analyses with separate propensity scoring and IPW balancing were performed for revascularized and nonrevascularized patients and for patients aged 70 to 79 and ≥80 years. Patient features and used medications were balanced in all subgroups (standardized mean difference ≤0.011 for all variables). The extent of unmeasured confounding was estimated by the E-value.[19] The Kaplan–Meier method and Cox regression were used to analyze time-dependent outcomes. Median follow-up was 4.8 (interquartile range 2.3–7.5) years. Mean follow-up was 5.1 years in men and 4.9 years in women. Cause-specific hazard models were applied in outcome analyses.[20] Proportional hazard assumptions were confirmed by Schoenfeld residuals. Logistic regression was used for the analysis of medication use. All analyses of balanced cohorts were weighted with stabilized IPW. In addition, multivariable Cox models adjusted with the same variables that were used for propensity scoring were analyzed. Results are given as the mean, percentage, hazard ratio (HR), or odds ratio with 95% CI or ±SD. Statistical significance was inferred at *P* value <0.05. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Unadjusted Cohort

In the unadjusted cohort, men were younger and had chronic pulmonary disease, malignancies, peripheral vascular disease, history of coronary artery bypass grafting or MI, and ST-segment–elevation at presentation more often, and were more frequently revascularized, than women (Table S3). Atrial fibrillation, heart failure, hypertension, hypothyroidism, dementia, psychiatric, and rheumatic diseases were more common among women in the unadjusted cohort. Nonadjusted cumulative incidence of MACE, MI, and cardiovascular death was higher among women (Table S4).

IPW-Adjusted Cohort
Risk of MACE

Differences in baseline features and the use of post-MI medications were equalized with IPW adjustments, resulting in a balanced study population of 16 083 men and 15 495 men with a median age of 79 years (Table 1). MACE occurred in 8508 men and 7620 women in the IPW cohort during the follow-up period (Figure 1). The cumulative incidence of MACE was 18.6% in men versus 15.8% in women after 1-year follow-up (*P*<0.0001), 47.0% versus 41.9% after 5-year follow-up (*P*<0.0001), and 67.7% versus 62.0% at the end of 10-year follow-up (HR, 1.17; CI, 1.13–1.21; *P*<0.0001). The E-value was 1.62 (CI, 1.51–1.71). Multivariable adjusted HRs in the unadjusted cohort were comparable to IPW-adjusted results (Table S4).

Secondary Outcomes

A new MI occurred in 4059 men and 3617 women (Figure 2). The cumulative incidence of new MI was

Table 1. Baseline Features of Inverse Probability Weighted Older Men and Women With Myocardial Infarction

Variable	Men n=16 083	Women n=15 495	P value	|SMD|
Age, y (SD)	79.3 (6.1)	79.3 (6.1)	0.858	0.002
Comorbidities				
Alcohol abuse	1.2%	1.1%	0.898	0.001
Anemia	5.0%	4.9%	0.849	0.002
Atrial fibrillation	22.1%	22.4%	0.619	0.006
Cerebrovascular disease	14.9%	14.8%	0.875	0.002
Chronic pulmonary disease	15.5%	15.7%	0.655	0.005
Coagulopathy	0.4%	0.4%	0.642	0.005
Dementia	8.5%	8.3%	0.648	0.005
Depression	10.7%	10.7%	0.942	0.001
Diabetes	27.5%	27.5%	0.883	0.002
Insulin dependent	9.0%	9.2%	0.707	0.004
Noninsulin dependent	18.4%	18.4%	0.913	0.001
Heart failure	30.6%	30.7%	0.919	0.001
Hypertension	57.6%	57.8%	0.715	0.004
Hypothyroidism	5.9%	5.9%	0.977	0.0003
Liver disease	0.7%	0.8%	0.667	0.005
Malignancy	15.9%	16.2%	0.429	0.009
Metastatic tumor	0.3%	0.3%	0.887	0.002
Paralysis	0.4%	0.4%	0.975	0.0003
Peripheral vascular disease	9.3%	9.3%	0.928	0.001
Prior CABG	4.4%	4.4%	0.841	0.002
Prior MI	22.9%	23.0%	0.893	0.002
Psychotic disorder	2.9%	2.9%	0.815	0.003
Rheumatic disease	7.3%	7.3%	0.865	0.002
Renal failure	4.2%	4.1%	0.624	0.006
Valvular disease	7.4%	7.4%	0.906	0.001
Revascularization	42.7%	42.3%	0.534	0.001
Percutaneous coronary intervention	36.4%	36.1%	0.627	0.005
CABG	6.8%	6.8%	0.754	0.004
ST-segment–elevation MI	29.1%	29.2%	0.948	0.001
Anterior*	53.2%	52.9%	0.819	0.005
Post-MI medication				
ADP inhibitor	53.8%	53.9%	0.935	0.001
Prasugrel or ticagrelor†	6.8%	6.5%	0.530	0.002
Anticoagulant	17.3%	17.4%	0.906	0.001
Direct oral anticoagulant ‡	0.9%	0.6%	0.136	0.039
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker	63.2%	63.3%	0.953	0.001
Aldosterone antagonist	4.5%	4.4%	0.770	0.003
Antiarrhythmic	1.3%	1.4%	0.640	0.005
Beta blocker	81.9%	81.9%	0.874	0.002
Ezetimibe	1.5%	1.5%	0.943	0.001
Statin	73.2%	73.3%	0.930	0.001
High-dose statin§	10.6%	10.6%	0.976	0.0004
Treating hospital (n=20)			0.234	0.003
Admission year			0.816	0.003

ADP indicates adenosine diphosphate; CABG, coronary artery bypass grafting surgery; MI, myocardial infarction; and SMD, standardized mean difference.
* Of patients with ST-segment–elevation MI.
†Of ADP inhibitor users.
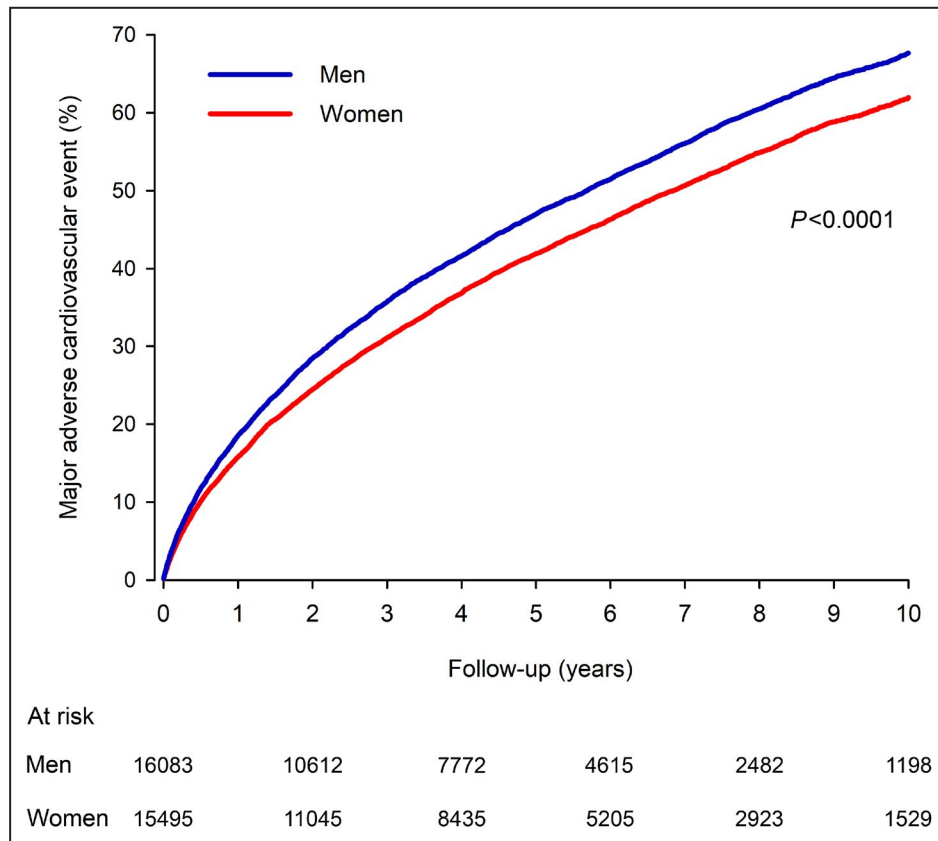‡Of anticoagulant users.
§Of statin users.

Figure 1. Adjusted cumulative incidence of major adverse cardiovascular events in older men and women after myocardial infarction.

10.5% in men versus 9.1% in women within the 1-year follow-up period (*P*=0.0003). At 10 years, the cumulative incidence of new MI was 37.0% in men and 33.1% in women (HR, 1.16; CI, 1.11–1.21; *P*<0.0001). During the follow-up period, 1874 men and 1783 women had an ischemic stroke, with cumulative incidence of 3.7% in men versus 3.2% in women (*P*=0.045) at 1 year and 21.1% versus 19.5% at 10 years (HR, 1.10; CI, 1.03–1.18; *P*=0.004) (Figure 2). Deaths due to cardiovascular causes occurred in 6596 men and 5876 women. The cardiovascular mortality rate was 10.6% in men versus 8.5% in women at 1 year (*P*<0.0001) and 56.0% versus 51.1% at 10-year follow-up (HR, 1.18; CI, 1.13–1.22; *P*<0.0001) (Figure 3). Also for secondary outcomes, multivariable adjusted HRs in the unadjusted cohort were comparable to IPW-adjusted results (Table S4).

Subgroup Analyses

Men had a higher hazard of MACE after MI in the subgroups of revascularized and non-revascularized patients, and in patients aged 70 to 79 and ≥80 years (Table 2). Differences in adjusted hazards of MACE, ischemic stroke, and cardiovascular death were similar in

the revascularized and nonrevascularized patients and in both age groups. A new MI was more frequent in nonrevascularized men compared with nonrevascularized women, but no sex difference was detected in revascularized patients (Table 2).

Use of Secondary Preventive Medications

The use of evidence-based medication after MI differed between sexes after IPW adjustment for baseline features including age, multiple comorbidities, revascularization, and MI type (Table 3). ADP receptor inhibitors, anticoagulants, and statins were used more frequently by men. Furthermore, when used, statins were more often at high dosages in men (Table 3). Beta blockers, renin-angiotensin-aldosterone system inhibiting medications, and ezetimibe were used more frequently by women (Table 3). Sex differences in ADP receptor inhibitor use were present in nonrevascularized patients with MI (35.1% in men versus 31.6% in women) but not in revascularized patients (81.7% versus 81.6%, respectively) (Table S5). Women were more likely to use angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, and ezetimibe, regardless of revascularization status. There was no sex difference in statin use (88.6%
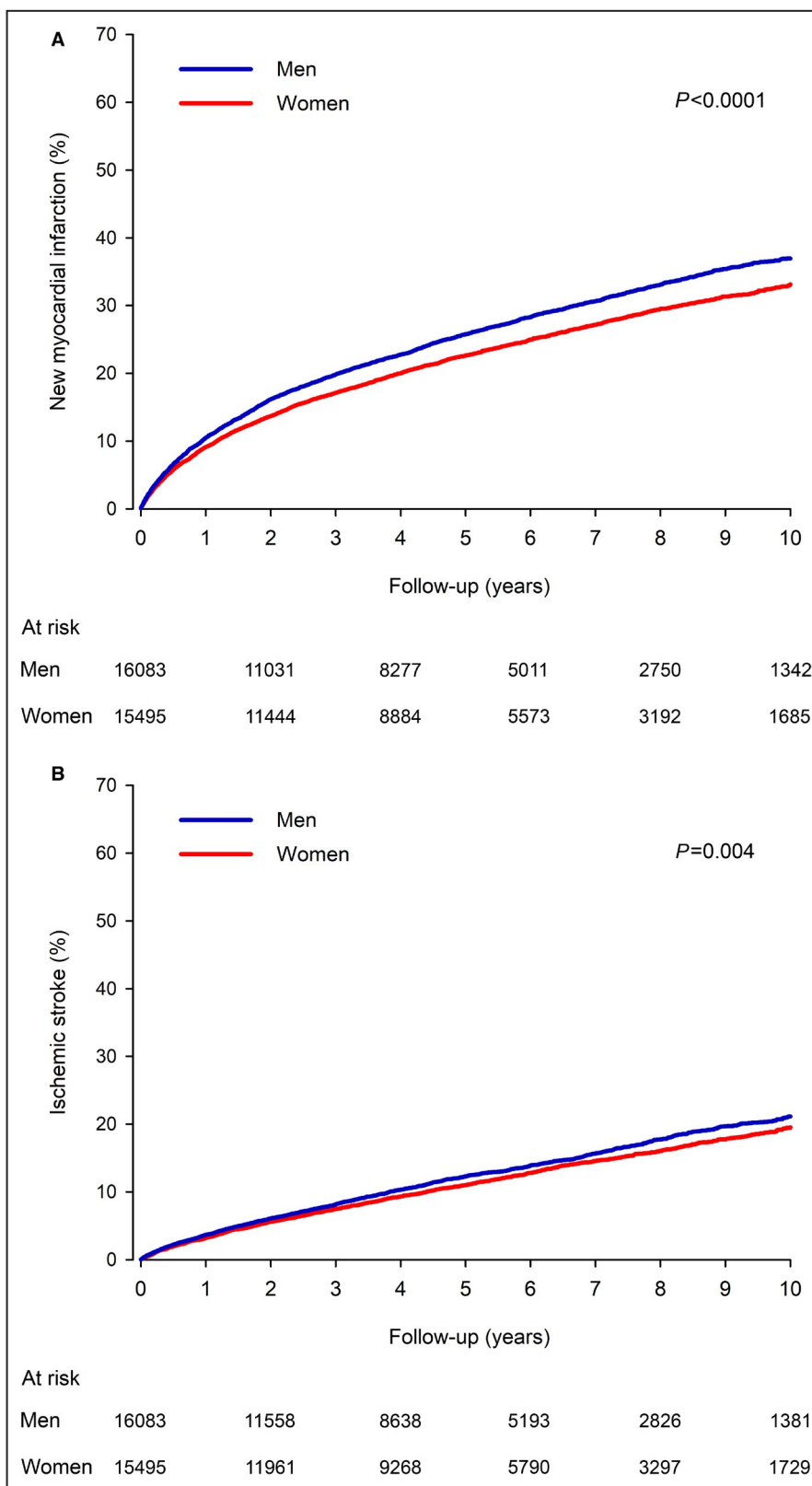
Figure 2. Adjusted cumulative incidence of new myocardial infarction (A) and ischemic stroke (B) in older men and women after myocardial infarction.
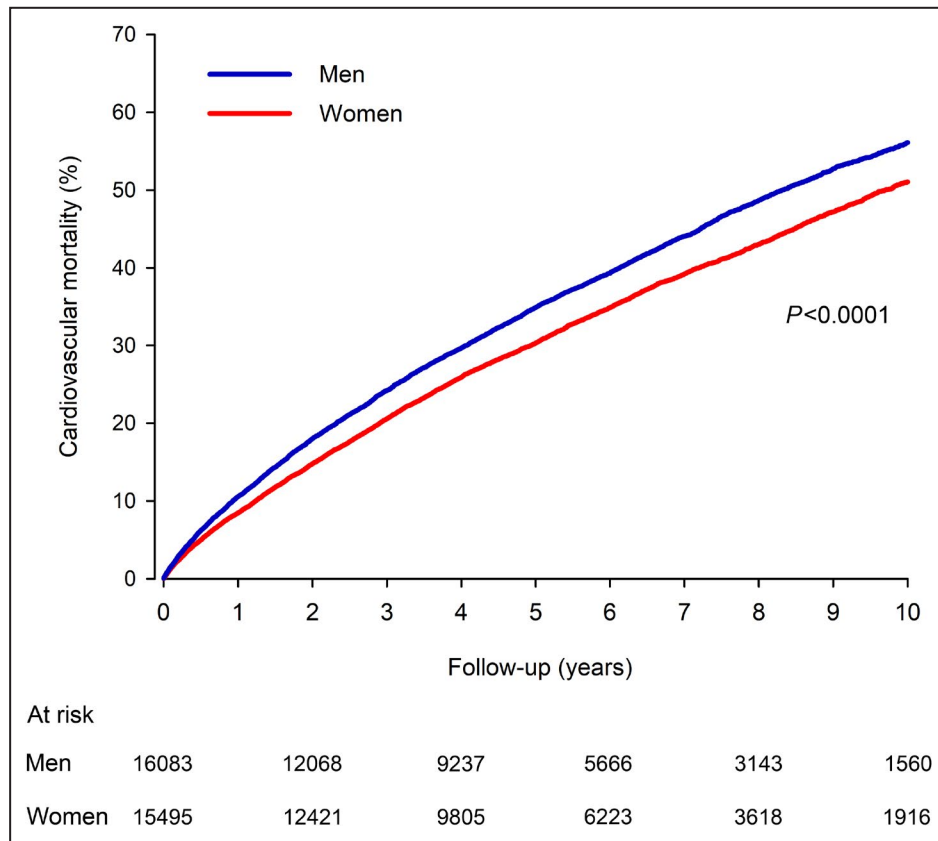
Figure 3. **Adjusted cardiovascular mortality in older men and women after myocardial infarction.**

in both sexes) and the proportion of high-dose statin users in the subgroup of revascularized patients.

DISCUSSION

Focusing on adults aged ≥70 years, this IPW study investigated sex differences in long-term outcomes following admission for MI in a nationwide Finnish setting. Older men were found to have 1.2-fold hazard of 10-year MACE, compared with older women, after equalizing differences in baseline features, including secondary preventive medications, comorbidities, MI type, and revascularization. Worse long-term prognoses in men were apparent in subgroups aged 70 to 79 and ≥80 years, as well as in revascularized and nonrevascularized patients. Our findings were consistent across our secondary outcomes, which comprised cardiovascular death, new MI, and ischemic stroke.

Despite the high burden of coronary heart disease in older adults, evidence to guide decision-making in older patients with MI is sparse.[13] Means for risk stratification applicable to older adults are needed to identify those patients most likely to benefit from interventions and more aggressive secondary prevention.[21] Previous

studies have suggested that, while younger women may have impaired short-term prognoses after MI compared with younger men, this sex difference disappears or even reverses in older adults.[9,16] Our finding of male sex as a predictor of adverse long-term cardiovascular outcomes is well aligned with a few previous studies focusing on adults aged ≥70 years.[6,17] A Spanish multicenter study evaluating long-term outcomes among 680 acute coronary syndrome patients aged ≥90 years showed that, despite more frailty, disability, and lower percutaneous coronary intervention frequency, women had better survival after percutaneous coronary intervention.[17] A Swedish registry study reported lower 1-year mortality after MI among female 28-day survivors aged 75 to 84 years, compared with their male counterparts.[9] In our previous study within the same register-linkage setting, 30-day and 1-year case fatality rates after MI were lower in women ≥70, compared with men, after extensive adjustments for comorbidity burdens and guideline-recommended treatments.[22] Now, we have discovered that this survival disadvantage in older men extends 10 years after an index MI.

In line with our results, previous studies have revealed a pattern of improving prognoses in women, along with

Table 2. Sex-Based Outcomes in IPW-adjusted Subgroups of Revascularized and Nonrevascularized Patients and of Patients Aged 70 to 79 and ≥80 Years After Myocardial Infarction

	Ten-year incidence		HR (95% CI)	*P* value
	Men	Women		
All patients				
Major adverse cardiovascular event	67.7%	62.0%	1.17 (1.13–1.21)	<0.0001
New myocardial infarction	37.0%	33.1%	1.16 (1.11–1.21)	<0.0001
Ischemic stroke	21.1%	19.5%	1.10 (1.03–1.18)	0.004
Cardiovascular death	56.0%	51.1%	1.18 (1.13–1.22)	<0.0001
Revascularized patients				
Major adverse cardiovascular event	52.7%	47.3%	1.15 (1.08–1.21)	<0.0001
New myocardial infarction	25.9%	23.9%	1.06 (0.97–1.15)	0.181
Ischemic stroke	16.8%	15.0%	1.13 (1.01–1.26)	0.027
Cardiovascular death	37.7%	33.8%	1.17 (1.09–1.25)	<0.0001
Nonrevascularized patients				
Major adverse cardiovascular event	79.5%	73.4%	1.21 (1.16–1.25)	<0.0001
New myocardial infarction	47.0%	41.5%	1.23 (1.16–1.29)	<0.0001
Ischemic stroke	25.9%	24.1%	1.10 (1.01–1.19)	0.024
Cardiovascular death	70.8%	64.5%	1.21 (1.16–1.26)	<0.0001
Age 70 to 79 y				
Major adverse cardiovascular event	55.9%	49.8%	1.20 (1.14–1.26)	<0.0001
New myocardial infarction	29.4%	26.2%	1.16 (1.08–1.24)	<0.0001
Ischemic stroke	18.6%	17.3%	1.10 (1.00–1.20)	0.0499
Cardiovascular death	40.4%	35.6%	1.23 (1.16–1.30)	<0.0001
Age ≥80 y				
Major adverse cardiovascular event	85.1%	80.5%	1.18 (1.13–1.23)	<0.0001
New myocardial infarction	49.6%	45.0%	1.19 (1.12–1.27)	<0.0001
Ischemic stroke	26.1%	24.1%	1.11 (1.00–1.23)	0.046
Cardiovascular death	80.4%	74.7%	1.17 (1.12–1.23)	<0.0001

HR indicates hazard ratio, IPW indicates inverse probability weight

increasing adjustments for sex differences in age, risk factors, comorbidities, and treatments.[9,12] A meta-analysis of 35 observational studies exploring sex differences in 1-year mortality after primary percutaneous coronary intervention-treated ST-segment–elevation MI concluded that the seemingly higher mortality rate in women is likely to be confounded by differences in cardiovascular risk factors and clinical profile.[2] A report from the SWEDEHEART register showed that, although women with ST-segment–elevation MI had a lower probability of reperfusion therapy and higher short-term mortality than men, long-term mortality was higher in men in multivariable-adjusted analyses.[12] The nonadjusted incidence of cardiovascular outcomes was also higher among women in our data. Adequate adjustments are thus crucial in studies aiming to explore the independent effects of sex on cardiovascular outcomes.

Biological, social, environmental, and community factors may contribute to sex/gender differences in health. Why female sex has, in many previous studies, been a predictor of case fatality after MI, especially among younger adults, is a matter of debate.

Although adjustments for age and comorbidities have attenuated sex differences, additional explanations include dissimilarities in pathophysiology and inequities in evidence-based treatment. The mechanisms of MI may differ between sexes, too, with more plaque erosions, coronary spasms, and spontaneous coronary artery dissections, especially in younger women.[3,23,24] These differences, however, may not characterize older women. A study of 6022 ST-segment–elevation MI patients showed that worse prognoses among women were apparent only in patients with prehospital delays lasting more than 1 hour, suggesting that women may be more vulnerable to prolonged, untreated ischemia.[25]

Both younger and older women may receive less active pharmacological and invasive treatments after MI than their male counterparts.[6,26–28] An Austrian study of MI patients ≥80 years revealed a lower intention to coronary intervention among women, compared with men, which was not explained by differences in risk factors for adverse events.[6] Despite this, the benefit of coronary procedures was higher among older women.[6] In line with these findings, we observed a

Table 3. Adjusted Use of Cardiovascular Prescription Medication After Myocardial Infarction, by Sex, in Older Patients

	Men	Women		
	n=16 085	n=15 489	OR (95% CI)	*P* value
ADP inhibitor	55.0%	52.7%	1.10 (1.05–1.15)	<0.0001
Prasugrel or ticagrelor*	6.7%	6.7%	1.00 (0.87–1.13)	0.998
Anticoagulant	17.7%	16.9%	1.10 (1.05–1.15)	<0.0001
Direct oral anticoagulant†	0.5%	0.9%	0.61 (0.32–1.17)	0.139
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker	61.9%	64.7%	0.89 (0.85–0.93)	<0.0001
Aldosterone antagonist	4.1%	4.8%	0.86 (0.77–0.95)	0.005
Antiarrhythmic	1.4%	1.3%	1.05 (0.86–1.27)	0.642
Beta-blocker	80.7%	83.1%	0.85 (0.81–0.90)	<0.0001
Ezetimibe	1.2%	1.9%	0.60 (0.50–0.72)	<0.0001
Statin	73.8%	72.7%	1.06 (1.01–1.11)	0.029
High-dose statin‡	11.0%	10.0%	1.10 (1.02–1.20)	0.021

ADP indicates adenosine diphosphate; and OR, odds ratio.

*Of ADP inhibitor users.

†Of anticoagulant users.

‡Of statin users.

lower revascularization rate in older women, compared with men (35% versus 49% in unadjusted cohorts), but among revascularized and nonrevascularized patients, men had worse long-term outcomes. The low revascularization rate among women with MI may be related to an increased prevalence of nonobstructive coronary artery disease in coronary angiography, a finding that is linked to better prognoses.[29]

Factors possibly contributing to poorer long-term outcomes among older men are multifold. Men with acute coronary syndrome often present with more severe atherosclerosis, obstructive lesions, necrotic plaques, and plaque ruptures in their coronary arteries than women.[3,30] We did not have data on smoking, which may contribute to worse long-term outcomes among men. These factors may have contributed to the 16% higher risk of reinfarction among men in our cohort, which was apparent in subgroups aged 70 to 79 and ≥80, and in nonrevascularized patients. In general, women have a higher life expectancy and lower risk of sudden cardiac death than men, which is likely to be reflected in the observed sex differences in cardiovascular mortality rates.[31] Hypothetical biological explanations for this survival gap include an asymmetric inheritance of sex chromosomes that exposes males to deleterious recessive mutations in the X chromosome and differing hormonal profiles and responses to oxidative stress and inflammatory stimuli.[32]

In older adults, frailty is a strong predictor of mortality and associated with impaired outcomes after MI.[33,34] An interesting phenomenon linked to sex, frailty, and survival is the "male–female health-survival paradox," which refers to the inverse association of older women experiencing more multimorbidity and frailty but living longer than men.[35] Even though we accounted for a wide range of comorbidities associated with frailty, it may be considered a potential confounder in our analyses.

The sex differences in the secondary preventive medications noted in our study deserve some attention. Although differences were small, older women were dispensed angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, aldosterone antagonists, and ezetimibe slightly more often than older men were. Conversely, men were more often dispensed ADP receptor inhibitors, anticoagulants, and statins. This difference was also apparent in high-intensity statin treatment. Among older populations, the benefits of statin use are well established in secondary prevention[36] and may be associated with lower mortality rates also in primary prevention.[37] Interestingly, following high-intensity statin treatment, coronary atheroma regression measured by intravascular ultrasound may be more pronounced among women than men.[38] Overall, although statins are the cornerstone of MI secondary prevention, the proportion of patients with a dispensed statin prescription was rather low in both sexes (72%–74%), warranting special attention to post-MI pharmacotherapy in older adults. Usage of new ADP receptor inhibitors and direct oral anticoagulants was low during our study period and there were no sex-dependent differences in their appliance. Potential sex differences in prasugrel or ticagrelor and direct oral anticoagulants usage later in the transition phase to these new more potent therapies remains to be studied. Poor adherence to secondary preventive medications has been associated with female sex in both younger and older patients and especially after non-ST-segment–elevation MI.[39] Because we described the frequency of drugs dispensed from pharmacies within the maximum length of 1 reimbursement period (90 days) after discharge, our

findings reflect the early usage of secondary preventive medications after MI rather than long-term adherence. Of note, unlike all other cardiovascular medications, aspirin is available over the counter without prescription in Finland and was therefore not included in our analyses.

The strengths of the study deserve brief discussion. We used a combination of previously validated, nationwide registries to avoid selection bias and adjusted the results with a broad coverage of confounders.[40] Propensity scoring and IPW are valuable tools for controlling confounding factors in observational studies.[41] Residual confounding by factors not recognized in the national health registries is nevertheless possible and may influence the results of the study. We lacked more detailed information on laboratory measures, imaging, socioeconomic status, lifestyle, and functional impairment. Based on the E-value, the observed HR of 1.17 could be explained by an unmeasured confounder that was associated with sex and MACE by a risk ratio of 1.6-fold each, above and beyond the measured confounders, but weaker confounding could not do so.[19] We did not have data on the race or ethnic backgrounds of study subjects, but because the Finnish population is predominantly White, the generalizability of our results to more diverse populations may be limited. An inherent limitation to administrative registries is that of coding errors. However, it is likely that these errors happen at a similar rate in both sexes, and thus it is unlikely that they would significantly affect our main findings.

CONCLUSIONS

In conclusion, after adjustments for a broad spectrum of confounding factors including age, baseline comorbidities, and treatment of MI, older men had worse long-term cardiovascular prognoses after MI compared with older women. Our results highlight the importance of comprehensive adjustments for confounding factors when studying sex differences in cardiovascular outcomes. Although we recognize that women of all ages may receive fewer evidence-based treatments after an MI than men, our findings indicate that, when no dissimilarities in risk factors, comorbidities, clinical presentation, and treatment of MI exist, male sex is an independent negative prognostic factor after MI in older adults. Based on our findings, we believe that, in addition to emphasizing intention to coronary procedures and intensive pharmacological secondary prevention on the same grounds in both sexes, older men may deserve special attention after MI because of their worse long-term cardiovascular prognoses.

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Supplementary Material

Data S1
Tables S1–S5
Figure S1
Reference 42

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Data S1.

Supplemental Methods

Data sources:

Following nationwide, mandated-by law registry data were collected and combined from all study

patients:

- All hospital and emergency room admissions (International Classification of Diagnosis / ICD-
  10) and operational codes (Nordic Classification of Surgical Procedures) collected from the
  CRHC registry obtained from the National Institute for Health and Welfare of Finland.

- Cancer data from the Finnish Cancer Registry obtained from the National Institute for Health
  and Welfare of Finland.

- Drug purchases including Anatomical Therapeutic Chemical (ATC)-codes and purchase dates
  obtained from the Social Insurance Institution of Finland.

- Drug purchase reimbursement permissions including permission codes and underlying ICD
  diagnoses obtained from the Social Insurance Institution of Finland.

- Mortality data including date and causes of death obtained from the Statistics Finland.

Outcomes

The primary outcome of interest was composite major adverse cardiovascular event. Secondary

outcomes were new myocardial infarction, ischemic stroke, and cardiovascular death. Follow-up

started from 90 days after MI and ended at 10-years later. Follow-up data was available to Dec 31st

2018.

Definitions:

- Major adverse cardiovascular event: New myocardial infarction, ischemic stroke, and
  cardiovascular death.

- New myocardial infarction: ICD-10 code I21* or I22* as primary diagnosis in new hospital
  admission or as any cause of death.

- Ischemic stroke: ICD-10 code I63* as diagnosis in new hospital admission or as any cause of death.

- Cardiovascular death: Death with ICD-10 code I* as the underlying cause of death.

- Usage of prescription drug after myocardial infarction: Drug purchase within 90 days after discharge from combined index MI admission. Drug ATC-codes are listed in Table S2.

	ICD-10 codes	Prescription drug reimbursement codes	Operational codes
Alcohol abuse	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51, Z50.2, Z71.4, Z72.1	309	
Anemia (history of)	D50.0, D50.8, D50.9, D51-D53	107, 122,175, 376	
Atrial fibrillation	I48	342, 351	
Cerebrovascular disease	G45, G46, H34.0, I60–I69		
Chronic pulmonary disease	I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3	203, 210, 284, 304, 348, 356	
Coagulopathy	D65–D68, D69.1, D69.3– D69.6	126, 161, 172, 194, 332, 357, 375	
Dementia	A81.0, F00–F03, F05.1, G30, G31	307	
Depression*	F20.4, F31.3–F31.5, F32, F33, F34.1, F41.2, F43.2		
Diabetes	E10-E14	103, 215, 160, 162, 358, 171, 177, 285, 346, 371, 382	
Heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, P29.0	201, 283, 354, 381	
Hypertension	I10-I13, I15	205	
Hypothyroidism	E00-E03, E89.0	104	
Liver disease	B18, I85, I86.4, I98.2, K70, K71.1, K71.3– K71.5, K71.7, K72– K74, K76.0, K76.2– K76.9, Z94.4		

Malignancy (history of)	C	115, 116, 128, 130, 155, 156, 158, 159, 163, 167, 168, 169, 173, 176, 180, 184, 185, 189, 191, 192, 197, 198, 302, 311, 312, 322, 323, 324, 325, 328, 329, 337, 340, 341, 343, 352, 360, 361, 362, 363, 369, 372, 373, 378	
Paralysis	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0–G83.4, G83.9		
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9		
Prior CABG	Z951		FNA, FNB, FNC, FND, FNE**
Prior myocardial infarction	I21**, I22, I25.2		
Psychotic disorder	F20, F21–F25, F28, F29, F30.2, F31.2, F31.5	112, 188	
Rheumatic disease	L94.0, L94.1, L94.3, M05, M06, M08, M12.0, M12.3, M30, M31.0– M31.3, M32–M35, M45, M46.0, M46.1, M46.4, M46.8, M46.9	202, 281	
Renal failure	I120, I13.0, N18, N19, N25.0, Z49.0– Z49.2, Z94.0, Z99.2	137, 138, 320	

Valvular disease	A52.0, I05–I08, I09.1, I09.8, I34– I39, Q23.0–Q23.3, Z95.2– Z95.4	
Revascularization		
PCI		FN2AA, FN2AB, FN2BA, FN2CA, FN2CB, FN2CC, FN2CD, FN2CE, FN2CT, FN2DA, FN2DB, FN2EA, FN1AT, FN1BT, FN1YT, FNG00, FNG10, FN2DA, TFN40, TFN50, TFN10, FN2EF, FN2EB, FN2EC, FN1ST
CABG		FNA, FNB, FNC, FND, FNE
ST-elevation MI	I21.0-21.3	
Anterior	I21.0	

* Or purchase of antidepressant medication within 90 days prior to MI. ** Before index MI admission.

Table S1. Definitions for co-morbidities and patient baseline features. International Classification of Diseases (ICD) coding algorithms adopted with minor modifications from the publication by Quan and coworkers.[42]

	ATC-codes
ADP-inhibitor	B01AC04, B01AC05, B01AC22, B01AC24
Anticoagulant	B01AA, B01AE, B01AF, B01AX06
Antidepressant	N06A, N06CA
Antidiabetic	A10
Insulin	A10A
Non-insulin	A10B
ACEi or ARB	C09, C10BX04, C10BX06, C10BX07, C10BX10, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15
Aldosterone antagonist	C03DA01, C03DA04
Antiarrhythmic	C01B
Beta-blocker	C07, C09BB, C09DA, C09BX02, C09DX05
Ezetimibe	C10AX09, C10BA02, C10BA05, C10BA06
Statin	C10AA, C10BA, C10BX

Table S2. Anatomical Therapeutic Chemical Classification (ATC) codes for studied prescription drugs. ADP = adenosine diphosphate, ACEi = Angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker. High intensity statin therapy was defined as in ≥40 mg of atorvastatin, ≥20 mg of rosuvastatin, or 80 mg of simvastatin per day.

Variable	Men n=16152	Women n=15408	P-value	|SMD|
Age, years (SD)	78.0 (5.7)	80.8 (6.2)	<0.0001	0.470
Co-morbidities				
Alcohol abuse	1.8%	0.5%	<0.0001	0.119
Anemia	4.3%	5.6%	<0.0001	0.060
Atrial fibrillation	21.5%	23.4%	<0.0001	0.046
Cerebrovascular disease	15.0%	14.8%	0.607	0.006
Chronic pulmonary disease	16.2%	14.3%	<0.0001	0.053
Coagulopathy	0.3%	0.4%	0.364	0.010
Dementia	6.8%	9.9%	<0.0001	0.112
Depression	7.9%	13.6%	<0.0001	0.184
Diabetes	27.1%	27.8%	0.211	0.014
Insulin dependent	8.9%	9.1%	0.468	0.008
Non-insulin dependent	18.3%	18.7%	0.365	0.010
Heart failure	26.7%	35.4%	<0.0001	0.189
Hypertension	52.4%	63.9%	<0.0001	0.234
Hypothyroidism	2.5%	9.6%	<0.0001	0.300
Liver disease	0.7%	0.7%	0.828	0.002
Malignancy	19.2%	11.8%	<0.0001	0.203
Metastatic tumor	0.3%	0.2%	0.043	0.023
Paralysis	0.3%	0.4%	0.362	0.010
Peripheral vascular disease	10.4%	7.9%	<0.0001	0.087
Prior CABG	5.9%	2.8%	<0.0001	0.153
Prior MI	24.3%	21.1%	<0.0001	0.077
Psychotic disorder	2.2%	3.7%	<0.0001	0.093
Rheumatic disease	5.6%	9.3%	<0.0001	0.141
Renal failure	4.9%	3.3%	<0.0001	0.081
Valvular disease	6.6%	8.3%	<0.0001	0.066
Revascularization	49.3%	34.8%	<0.0001	0.298
PCI	41.0%	30.8%	<0.0001	0.214
CABG	8.9%	4.3%	<0.0001	0.187
ST-elevation MI	30.9%	27.6%	<0.0001	0.074
Anterior*	52.1%	55.0%	0.007	0.056
Post-MI medication				
ADP-inhibitor	58.5%	48.1%	<0.0001	0.209

Prasugrel or ticagrelor **	7.2%	5.6%	<0.0001	0.065
Anticoagulant	18.0%	16.8%	0.003	0.034
DOAC***	0.6%	0.7%	0.596	0.014
ACEi or ARB	63.1%	63.9%	0.174	0.015
Aldosterone antagonist	3.9%	5.0%	<0.0001	0.053
Antiarrhythmic	1.5%	1.1%	0.001	0.037
Beta-blocker	81.9%	81.8%	0.862	0.002
Ezetimibe	1.3%	1.5%	0.242	0.013
Statin	77.4%	68.6%	<0.0001	0.198
High-dose statin****	12.0%	8.7%	<0.0001	0.108
Treating hospital (n=20)			0.0004	0.058
Admission year			<0.0001	0.087

Table S3. Baseline features of older men and women with myocardial infarction in non-adjusted cohort. ACEi = Angiotensin-converting-enzyme inhibitor, ADP = adenosine diphosphate, ARB = angiotensin receptor blocker, CABG = Coronary artery bypass grafting surgery, MI = Myocardial infarction, PCI = Percutaneuos coronary intervention, SMD = Standardized mean difference. *Of ST-elevation MI patients. ** Of ADP-users. *** Of anticoagulant users. ****Of statin users.

	Non-adjusted incidence		Univariable		Multivariable	
	Men	Women	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Major adverse cardiovascular event						
1-year	16.5%	17.9%		0.001		<0.0001
10-year	63.4%	67.4%	0.89 (0.86-0.92)	<0.0001	1.22 (1.18-1.26)	<0.0001
New myocardial infarction						
1-year	9.1%	10.2%		0.001		<0.0001
10-year	33.9%	36.6%	0.90 (0.86-0.94)	<0.0001	1.20 (1.14-1.26)	<0.0001
Ischemic stroke						
1-year	3.5%	3.5%		0.999		0.028
10-year	20.1%	20.9%	0.95 (0.89-1.01)	0.112	1.13 (1.06-1.22)	0.0004
Cardiovascular death						
1-year	9.1%	10.2%		0.001		<0.0001
10-year	50.8%	57.4%	0.83 (0.80-0.86)	<0.0001	1.25 (1.20-1.29)	<0.0001

Table S4. Non-adjusted sex-based cumulative incidence of outcomes at 1-year and 10-years. Results of unadjusted and multivariable adjusted Cox-models (see methods for details). HR = hazard ratio within 10-year follow-up.

	Revascularized patients				Non-revascularized patients			
	Men	**Women**			**Men**	**Women**		
	N=7976	**N=5380**	**OR (95%CI)**	***P*-value**	**N=8129**	**N=10103**	**OR (95%CI)**	***P*-value**
ADP-inhibitor	81.7%	81.6%	1.00 (0.92-1.10)	0.925	35.1%	31.6%	1.17 (1.10-1.25)	<0.0001
Prasugrel or ticagrelor *	8.7%	8.7%	0.99 (0.87-1.14)	0.895	3.1%	2.7%	1.19 (0.88-1.61)	0.270
Anticoagulant	17.2%	15.8%	1.11 (1.01-1.22)	0.029	18.1%	17.8%	1.02 (0.94-1.10)	0.648
DOAC**	0.3%	0.9%	0.36 (0.11-1.12)	0.078	0.7%	0.8%	0.82 (0.36-1.88)	0.646
ACEi or ARB	69.7%	72.6%	0.87 (0.80-0.94)	0.0003	56.1%	59.0%	0.89 (0.84-0.94)	<0.0001
Aldosterone antagonist	3.9%	4.8%	0.81 (0.68-0.96)	0.014	4.3%	4.8%	0.89 (0.77-1.03)	0.106
Antiarrhythmic	1.5%	1.8%	0.93 (0.63-1.09)	0.174	1.3%	0.9%	1.37 (1.03-1.81)	0.029
Beta-blocker	85.7%	88.5%	0.78 (0.70-0.86)	<0.0001	76.9%	79.0%	0.88 (0.82-0.95)	0.001
Ezetimibe	1.5%	2.8%	0.54 (0.42-0.68)	<0.0001	0.9%	1.3%	0.71 (0.54-0.95)	0.019
Statin	88.6%	88.6%	0.99 (0.89-1.11)	0.907	62.6%	61.0%	1.07 (1.01-1.14)	0.020
High-dose statin**	13.8%	12.8%	1.09 (0.98-1.21)	0.131	8.1%	7.2%	1.14 (0.99-1.32)	0.061

Table S5. Usage of cardiovascular prescription medication after myocardial infarction by sex in inverse probability weighted subgroups of revascularized and non-revascularized patients. ACEi = Angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, DOAC = direct oral anticoagulant, OR = Odds ratio, CI = Confidence *interval. * Of ADP-users. ** Of anticoagulant users. ***Of statin users.*

Figure S1. Study flow-chart. IPW = inverse probability weight.