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Women Undergoing Coronary Angiography for Myocardial Infarction or Who Present With Multivessel Disease Have a Poorer Prognosis Than Men

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Abstract

Background: Coronary artery disease affects both men and women. In this study, we examine sex-specific differences in occurrence of major adverse cardiovascular events (MACEs) after coronary angiography. **Methods:** We analyzed data from the coronary angiography cohort Utrecht Coronary Biobank (n = 1283 men, 480 women). Using Kaplan-Meier and multivariable Cox-regression, we tested for sex differences in MACE occurrence. Additionally, we compared mortality with an age- and sex-matched control group from the general Dutch population. **Results:** During a median follow-up of 2.1 years (interquartile range 1.6-2.8), MACEs occurred in 265 men and 103 women (20.7% vs 21.3%, $P = .744$). Women with myocardial infarction (MI) had significantly more MACE during follow-up than men (hazard ratio [HR] 1.66 for female sex, 95% confidence interval [CI] 1.10-2.50, $P = .015$), which was also the case for women who had multivessel disease (HR 1.41, 95% CI 1.03-1.94, $P = .031$). During follow-up, mortality in women presenting with MI was higher than mortality of women in the general population; men with MI did not show this disadvantage. **Conclusion:** MACEs occurred more often in women than in men who presented with MI or who had angiographic multivessel disease upon coronary angiography. **Clinical trial registration:** Clinicaltrials.gov identifier: NCT02304744. URL: https://clinicaltrials.gov/ct2/show/NCT02304744.

Keywords

epidemiology, sex differences, coronary angiography, major adverse cardiovascular events

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide with a total of 17.5 million deaths in 2012, of which 7.4 million were due to coronary artery disease (CAD).[1] While ischemic heart disease has been labeled a men's disease for decades,[2] in the United States, more women than men die of CVD each year.[3,4] In the last decades, CAD incidence showed a tremendous decrease mainly as a result of better detection and control of major risk factors and more effective treatment options such as widely accessible percutaneous coronary intervention (PCI).[2,5]

Specifically for women, the American Heart Association launched campaigns in order to increase awareness of the risk of CAD and published women-specific guidelines, resulting in a substantial increase in awareness among women (from 30% in 1997 to 54% in 2009).[6] Also, sex-specific research designated preeclampsia, gestational diabetes mellitus, early menopause,

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and possibly estrogen replacement therapy[7] as female-specific risk factors for CAD.[2,4,8-10]

In spite of the advances in knowledge about CAD in women, unfortunately recently in the United States, a concerning increase in mortality rate is seen among women of relatively young age.[6,11] Among these women, increasing rates of diabetes and obesity possibly nullify the effects of the reduced smoking prevalence and improved hypertension treatment.[12] Contrary to the United States, however, in the European Union (EU), no increase in mortality rates has been observed among women, only plateauing of these rates occurred in a minority of the EU countries among younger individuals of both sexes.[12]

Given changes in risk factors (higher prevalence of obesity and diabetes) and declining incidence rates of myocardial infarction (MI) in the EU, we investigated whether the previously reported sex differences in outcome still exist in a contemporary European cohort of coronary angiography patients and if so, whether sex differences are observed in certain patient groups with CAD specifically (ie, stable CAD or MI). In addition, we examined whether survival of men and women differed from age- and sex-matched samples of the general Dutch population. For this purpose, we evaluated the occurrence of all-cause mortality and major adverse cardiovascular events (MACEs) among men and women from the Utrecht Coronary Biobank (UCORBIO) cohort, consisting of patients undergoing coronary angiography in the Netherlands.

Based on the current, mainly United States, literature, we hypothesized that women from the UCORBIO cohort have a higher incidence of MACE and higher mortality than men, despite a lower burden of epicardial CAD.[13] This difference may be partly explained by differences in risk factor burden between men and women.

Methods

Study Population

We analyzed data from the UCORBIO cohort (clinicaltrials.gov identifier: NCT02304744), an observational cohort study of patients undergoing coronary angiography for any indication in the University Medical Center in Utrecht, the Netherlands. From October 2011 to December 2014, a total of 2589 patients, >18 years of age, were enrolled from the catheterization laboratories. For the current study, patients presenting with MI (either ST-segment elevation MI [STEMI] and non-ST-segment elevation MI [NSTEMI]), chest pain without release of cardiac enzymes (stable and unstable angina), dyspnea on exertion, silent ischemia, or the need for preoperative screening (for non-cardiac surgery) were selected (n = 2390). All-cause mortality of these UCORBIO patients was compared to the general Dutch population as explained subsequently.

Within the UCORBIO cohort, only patients who had been enrolled for more than 1 year and thus reached their first follow-up contact moment were analyzed (n = 1763). Figure 1 depicts the selection of study patients.

This study was approved by the Medical Ethics Committee of the UMC Utrecht (reference number 11-183). All patients provided written informed consent, and this study conforms to the Declaration of Helsinki.

Control Group From General Population

In order to compare mortality risks of both men and women undergoing coronary angiography with the general population, an age- and sex-matched control group from the Dutch population registry[14] was obtained. For every UCORBIO patient, 4 age- and sex-matched controls were randomly selected as registered on January 1, 2011, from the Dutch population registry. We compared data on these individuals' survival until January 1, 2015, with survival in the UCORBIO cohort.

Clinical Data

The investigators completed standardized electronic case report forms at baseline containing age, sex, cardiovascular risk factors, indication for angiography, medication use before admission, angiographic findings, and eventual treatment. Angiographic findings were categorized by the interventional cardiologists into 4 groups: no CAD, minor CAD (wall irregularities, <50% stenosis), single-vessel disease (>50% stenosis[15]), and multivessel disease (containing both double and triple vessel disease). SYNTAX scores[16] were calculated by 2 independent observers using SYNTAX score calculator version 2.11 as[17] described earlier.[13]

Biomarkers

Blood samples collected from the arterial sheath used for coronary angiography were immediately centrifuged, and plasma was frozen at −80°C. In 2013, N-terminal probrain natriuretic peptide (NT pro-BNP) levels were measured in the first 982 patients from thawed EDTA plasma using a validated in-house sandwich enzyme-linked immunosorbent assay. High-sensitivity troponin I (hsTnI) was measured in the first 936 patients using the clinically validated ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Laboratories, Lisnamuck, Longford, Ireland).

Follow-Up

On a yearly basis, patients received a questionnaire to check for hospital admissions and occurrence of MACEs. When the patient did not complete or did not return the questionnaire, or reported a hospital admission suspect for MACE, the general practitioner or reported hospital was contacted for confirmation. In the case of a possible adverse event or death, medical records were obtained and details about the adverse event or death were determined. The occurrence of events was scored by Crystel M. Gijsberts and Bernadet T. Santema. When uncertain about the relevance or classification of an event (n = 46), the case was discussed by an expert panel of cardiologists (consisting of at least 2 of the following cardiologists: MJM, FWA, MV, or PA). Additionally, all cases of possible

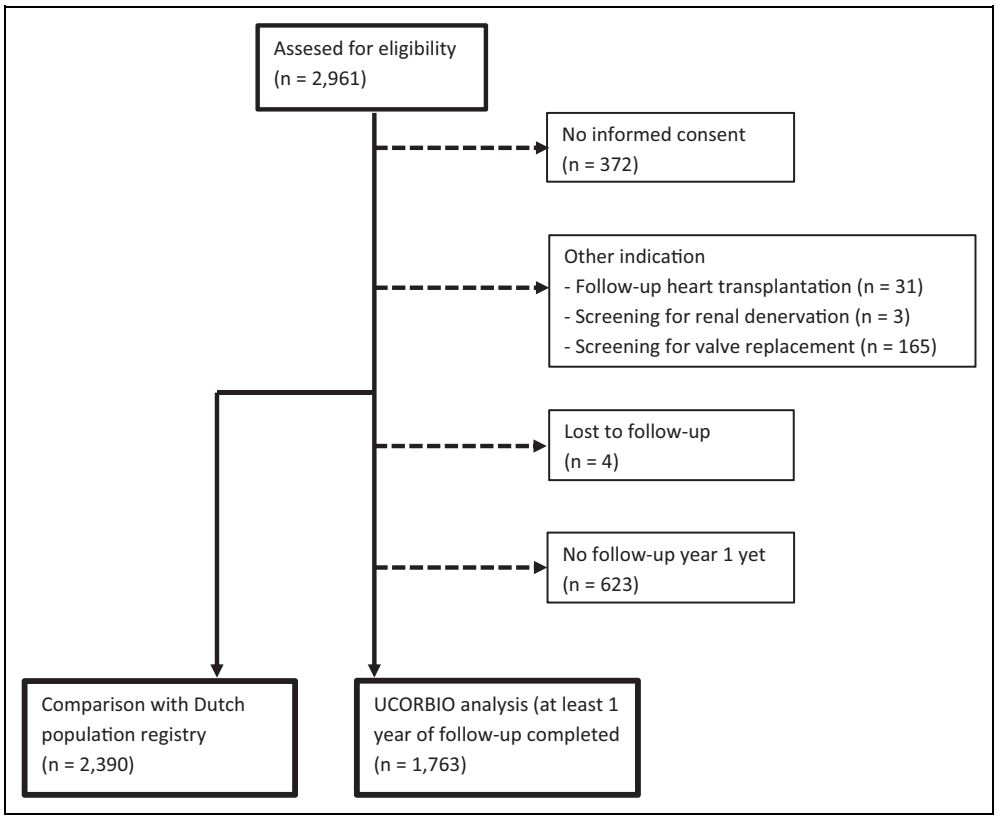

Figure 1. Flowchart of study population selection process. All-cause mortality was available for all study patients regardless of duration of follow-up or loss to follow-up. Therefore, all 2390 patients could be compared to the general Dutch population. For detailed study follow-up (occurring on a yearly basis, hence excluding patients who had not reached 1 year yet) 1763 patients were available.

in-stent restenosis (n = 80) were scrutinized by an interventional cardiologist (PA or MV). The composite end point MACE was defined as any and the first of the following clinical events: all-cause death, nonfatal MI, unplanned revascularization, both cardiac (PCI and coronary artery bypass graft [CABG]) and noncardiac intervention, stroke, and admission for heart failure.

Statistical Analysis

Baseline characteristics were reported as means and standard deviations for continuous variables and percentages for categorical variables. Sex-specific survival curves were plotted using Kaplan-Meier analysis; sex differences in survival were tested by means of a log-rank test. As to identify patient groups in which sex differences could be more pronounced, we further stratified the analysis by indication for angiography and angiographic CAD severity. A similar approach was used for the differences between our patient cohort and the general Dutch population. Hereafter, in order to correct for baseline differences between men and women, we performed Cox regression analysis for the patient groups in which sex differences were observed (patients with angiographic multivessel disease and patients presenting with MI). Significant baseline differences between men and women and factors that were associated with outcome in a univariable analysis (P value <0.1) were selected as covariates in the multivariable Cox regression analysis. Consequently, Cox regression was performed with the following covariates: age, hypertension, hypercholesterolemia, diabetes mellitus, smoking, history of acute coronary syndrome (ACS), history of PCI, history of CABG, history of peripheral arterial disease, history of cerebrovascular accident (CVA), use of P2Y12 receptor antagonists, renin–angiotensin–aldosterone system inhibitors, statins or diuretics, angiographic CAD severity, and treatment of CAD (conservative, PCI, or CABG).

The NT pro-BNP levels (available in n = 982), hsTnI levels (n = 936), left ventricular ejection fraction (LVEF, n = 1318), and SYNTAX scores (n = 627) were not available in all patients and therefore not included in the Cox model. However, they were added to the model one by one in order to assess their effects on the difference between men and women.

All statistical analyses were performed using the R software package (version 3.1.2, Vienna, Austria).[18] A 2 sided P value of <.05 was considered statistically significant.

Results

Patient Characteristics

We examined a total of 1763 patients who underwent coronary angiography. The majority of patients were male (n = 1283,

Table 1. Baseline Characteristics of UCORBIO Patients Stratified by Sex.[a]

	Male	Female	*P* Value
N	1283	480	
Age (mean ± SD)	63.3 ± 10.7	66.5 ± 11.0	<.001
BMI (mean ± SD)	27.2 ± 4.1	26.9 ± 5.3	.294
Diabetes, %	22.2	22.1	1
Hypertension, %	55.3	63.1	.004
Hypercholesterolemia, %	48.9	42.7	.022
Smoking, %			<.001
Current smoker	25.5	23.3	
Exsmoker	31.0	21.4	
Nonsmoker	43.5	55.3	
History of ACS, %	33.7	23.5	<.001
History of PCI, %	32.3	22.5	<.001
History of CABG, %	14.3	5.8	<.001
History of CVA, %	9.7	9.8	1
History of PAD, %	12.3	9.0	.059
Kidney failure, %	3.0	1.9	.274
COPD, %	8.3	9.0	.750
LVEF, %			<.001
Normal	54.6	67.2	
Mildly reduced	23.6	16.5	
Moderately reduced	13.5	9.2	
Severely reduced	8.3	7.0	
Aspirin, %	59.6	60.2	.862
P2Y12, %	25.8	19.4	.006
RAAS, %	51.3	51.0	.970
Beta-blocker, %	55.7	57.1	.641
Statin, %	64.2	56.9	.006
Diuretics, %	26.1	38.5	<.001
Indication, %			.267
Stable complaints	54.2	55.8	
Unstable angina	10.2	9.6	
Myocardial infarction	29.4	26.2	
Other	6.2	8.3	
CAD severity, %			<.001
No CAD	4.3	13.0	
Minor CAD	15.4	20.7	
Single vessel disease	35.0	31.0	
Multi vessel disease	45.4	35.4	
Procedure, %			<.001
Conservative	30.4	41.6	
PCI	64.1	53.8	
CABG	5.6	4.6	
SYNTAX score, median (IQR)	11.0 (6.0-17.5)	9.0 (5.0-15.5)	.022
NT pro-BNP, median (IQR)	38.0 (8.3-113.3)	47.3 (16.1-138.7)	.027
Troponin-I, median (IQR)	8.2 (4.1-30.0)	5.90 (3.1-18.6)	.002

Abbreviations: BMI, body mass index; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular function; P2Y12, $P2Y_{12}$ receptor antagonist; RAAS, renin–angiotensin–aldosterone system; CAD, coronary artery disease; PCI, percutaneous coronary intervention; NT pro-BNP, N-terminal probrain natriuretic peptide; IQR, interquartile range; SD, standard deviation; UCORBIO, Utrecht Coronary Biobank.

[a]Continuous variables are presented in means ± SD when normally distributed and as medians with interquartile ranges when nonnormally distributed. Categorical variables are presented in percentages. *P* values are from *t*-test for normally distributed continuous data, from Kruskal-Wallis tests for nonnormally distributed data, and from chi-square testing for categorical data.

72.8%) and 480 patients were female. The baseline characteristics are displayed in Table 1, stratified by sex. The most important baseline differences were age, with women being significantly older (66.5 ± 11.0 years vs 63.3 ± 10.7 years, $P < .001$) and having a higher prevalence of hypertension (63.1% vs 55.3% in men, $P = .004$). Also, women used diuretics significantly more often (38.5% vs 26.1%, $P < .001$). Men on the other hand had higher rates of hypercholesterolemia (48.9% vs 42.7%, $P = .022$) and a history of ACS (33.7% vs 23.5%), PCI (32.3% vs 22.5%), and CABG (14.3% vs 5.8%).

There were no major differences in indication to perform angiography between men and women, with stable complaints being the most frequent; 54.2% in men and 55.8% in women. Myocardial infarction (either STEMI or NSTEMI) was the indication in 29.4% of all men compared to 26.2% in women. Women were more likely to have a normal LVEF 67.2% versus 54.6% in men, $P < .001$.

The prevalence of multivessel disease was higher in men (45.4% vs 35.4%), whereas women more frequently had no CAD (13.0% vs 4.3%, *P* for overall difference <.001). Men, as a consequence, were more likely to undergo PCI than women (64.1% vs 53.8%, $P < .001$).

SYNTAX score in patients with multivessel disease did not differ significantly, with 15 (interquartile range [IQR] 10-21) for men and 13 (IQR 8-19.5) for women, $P = .220$. Among patients presenting with MI, levels of hsTnI were not different between women (median 171.8, IQR 11.1-612.4) and men (median 94.5, IQR 12.6-813.3). The NT pro-BNP levels were significantly higher in women (55.0 [IQR 9.8-161.8] vs 91.3 [IQR 27.1-292.0]) than in men, $P = .030$.

Sex Differences in Follow-Up Events

The median duration of follow-up was 2.1 years for men (IQR 1.6-2.8) and 2.2 years for women (IQR 1.6-2.8). An overview of the number of events and 2-year Kaplan-Meier event rate estimates is displayed in Table 2. During follow-up of this study, a total of 74 (6.4%) men and 25 (6.5%) women died. Nonfatal MI occurred in 5.9% of all men and 6.6% of women (66 men vs 28 women). The only significant difference in adverse event rate was the incidence of transient ischemic attack (TIA), which occurred in 9 (2.1%) women but only in 5 (0.4%, $P = .002$) men. The composite end point MACE, consisting of all-cause death, nonfatal MI, unplanned revascularization, stroke, and admission for heart failure occurred in 265 men and 103 women. Its overall incidence did not differ between men and women (20.7% in men vs 21.3% in women, $P = .744$).

Stratification by Indication for Angiography

We found a significantly higher occurrence of MACE in women who presented with MI and HR for female sex 1.66 (95% confidence interval [CI] 1.10-2.50, $P = .015$), Figure 2 (left panel). Among stable patients with CAD, however, women appeared to have a similar prognosis as men (HR for female sex 0.80 [95% CI 0.58-1.10], $P = .163$). A significant

Table 2. Number of Events and 2-Year Kaplan-Meier Estimates by Sex.[a]

Event	N male	% Male	N Female	% Female	*P* Value
MACE	265	20.7	103	21.3	.744
Death	74	6.4	25	6.5	.687
Cardiovascular death	35	2.8	9	2.4	.346
Noncardiovascular death	38	3.5	14	3.6	.980
Nonfatal myocardial infarction	66	5.9	28	6.6	.549
STEMI	11	1.1	5	0.8	.712
NSTEMI	31	2.8	15	4.1	.389
Unstable angina	26	2.1	10	2.4	.934
Re-PCI	108	9.4	36	7.6	.563
New lesion	53	4.6	22	4.5	.645
Instent restenosis	60	5.1	20	4.5	.650
CABG	11	0.8	3	0.6	.622
Heart failure	38	3.0	15	3.7	.859
CVA/TIA	20	2.0	16	3.6	**.019**
CVA	15	1.6	8	1.8	.408
TIA	5	0.4	9	2.1	**.002**
Heart or vascular intervention	59	5.0	18	4.6	.439
Noncardiac stent	25	2.3	6	1.8	.328
Noncardiac vascular surgery	17	1.5	6	1.4	.902
Amputation due to PAD	6	0.4	1	0.2	.438
Hospital admission for PAD	1	0.1	0	0.0	.541
Valve surgery	7	0.4	1	0.2	.344
Percutaneous valve implantation	6	0.6	3	1.0	.668
Device implantation	69	5.4	20	4.7	.303
Heart rhythm disorder	47	3.9	11	2.4	.154
Hemorrhagic event (extra cerebral)	18	1.5	13	2.3	.064

Abbreviations: MACE, major adverse cardiovascular event; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; TIA, transient ischemic attack; PAD, peripheral arterial disease.

[a]Percentages: 2-year Kaplan Meier estimates. In 3 patients, cause of death was unknown. The sum of the number of subtypes of events (eg, STEMI, NSTEMI, and unstable angina) can exceed the number of "main" events (eg, nonfatal myocardial infarction), which can only be counted once in each patient. Only the first event of each patient is counted.

P-values printed in bold were considered significant ($p < 0.05$).

interaction was found between sex and indication for angiography for the occurrence of MACE ($P = .005$), indicating that the impact of female sex on MACE occurrence significantly differed between the angiography indications stable CAD and MI. The sex difference in MACE occurrence was mainly driven by the higher occurrence of TIAs (3.8% vs 0.5%, $P = .017$) and re-PCIs (8.7% vs 5.6%, $P = .029$) in women than men (supplemental Table 1).

Stratification by Severity of CAD

When stratified for baseline angiographic severity of CAD, we found a significantly lower MACE-free survival probability in women than men with multivessel disease, HR for female sex 1.41 (95% CI 1.03-1.94, $P = .031$), Figure 2 (right panel). This contrasted with women presenting with no, minor, or single-vessel CAD, where no difference was observed in MACE between the sexes, HR for female sex 0.85 (95% CI 0.61-1.19, $P = .347$). The difference in MACE-free survival between men and women thus differed by angiographic CAD severity (P for interaction .031). The sex difference in MACE occurrence was mainly driven by the higher occurrence of heart failure admissions (9.1% vs 2.7%, $P = .003$) and CVA/TIAs (8.7% vs 2.0%, $P < .001$) in women than in men (supplemental Table 2).

Multivariable Analysis

The differences found with univariable analyses were adjusted for possible confounders. Hazard ratios for women presenting with MI remained 1.61 (95% CI 1.00-2.61, $P = .051$), for women with multivessel disease HR was 1.43 (95% CI 1.01-2.04, $P = .046$).

In order to further evaluate confounding factors, we added NT pro-BNP levels, hsTnI levels, SYNTAX scores, and LVEF measurements to the multivariable model one by one. With the addition of these parameters, statistical power decreased due to missing values, resulting in wider CIs and thus nonsignificant HR estimates. However, the point estimates of the HRs barely changed upon correction for any of these 4 parameters (HRs for female sex ranging from 1.53 to 1.83 among patients with MI and from 1.33 to 1.56 among patients with multivessel disease) as can be observed from Figure 3.

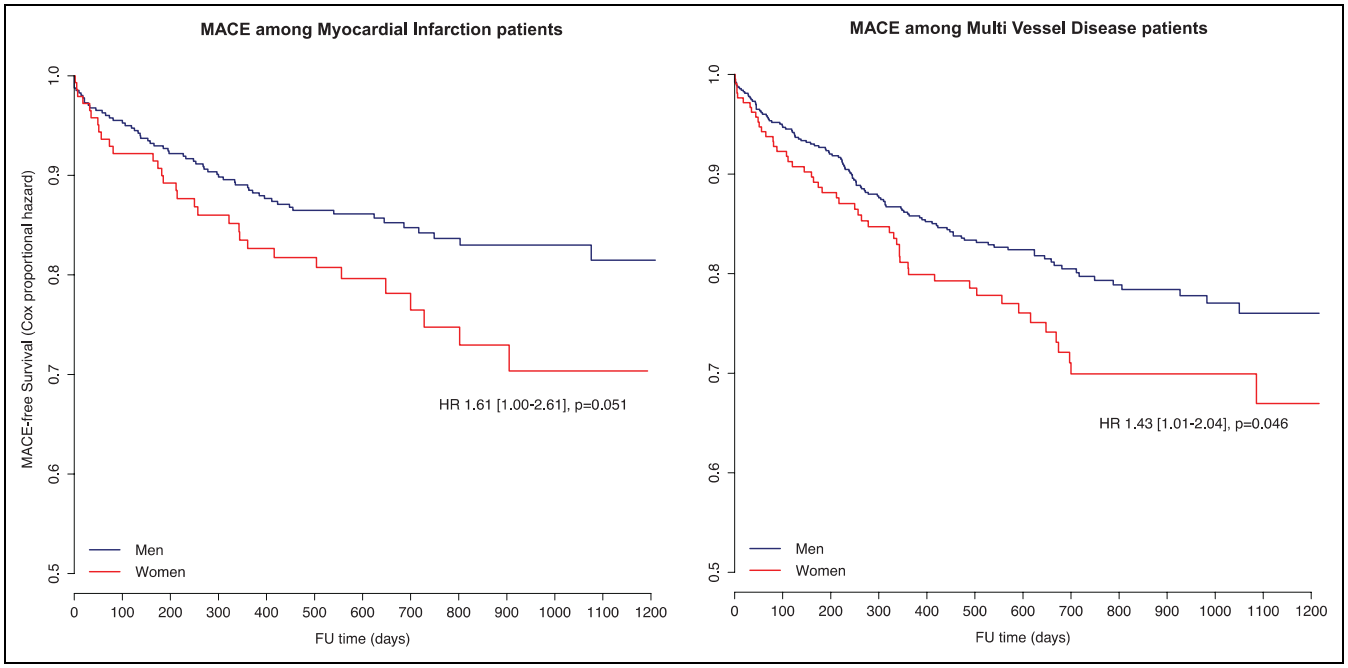

Figure 2. The left panel shows the multivariable adjusted sex differences in the occurrence of major adverse cardiovascular event (MACE) among patients with myocardial infarction (MI) derived from Cox regression analysis. The right panel shows those differences among patients with multi-vessel disease. The MACE consists of all-cause mortality, MI, stroke, unplanned revascularization, and admission for heart failure. The presented results were adjusted for age, indication for angiography (not in MI analysis), angiographic coronary artery disease (CAD) severity (not in multivessel disease analysis), hypertension, hypercholesterolemia, history of percutaneous coronary intervention (PCI), history of coronary artery bypass graft (CABG), history of acute coronary syndrome (ACS), history of cerebrovascular accident (CVA), use of renin–angiotensin–aldosterone system (RAAS) medication, history of PCI, history of CABG, history of ACS, history of CVA, use of RAAS medication, use of diuretics, use of $P2Y_{12}$ receptor antagonist (P2Y12) inhibiting medication, use of statins, history of PAD, diabetes, kidney failure, treatment of CAD (conservative, PCI or CABG), and smoking status (nonsmoker, exsmoker, or current smoker).

Comparison With the General Population

All-cause mortality in men presenting with complaints of stable CAD was higher than in the general population. The Kaplan Meier (KM) 2-year estimated all-cause mortality rate was 6.2% versus 4.1% in the general population, $P = .014$, Figure 4. For women with stable CAD, no difference in all-cause mortality was found ($P = .559$). Women presenting with MI, on the other hand, showed a trend toward higher all-cause mortality than the general population group (KM 2-year estimated all-cause mortality rate 7.3% vs 3.2%, $P = .071$), whereas men with MI had similar survival rates as their counterparts from the general population (KM 2-year estimated all-cause mortality rate 4.6% vs 4.1%, $P = .315$).

All-cause mortality rates for both men and women with no or minor CAD were comparable with the general population (KM 2-year estimated all-cause mortality rate 5.2% vs 4.1%, $P = .196$ in men and 5.0% vs 3.2%, $P = .111$ in women). Both men and women with multivessel disease had a significantly worse survival than their general population counterparts (KM 2-year estimated all-cause mortality rate 9.2% vs 4.1%, $P = .002$ in men and 11.5% vs 3.2%, $P = .004$ in women). For the other indications and severities of CAD, there was no difference in survival when compared to the general population.

Discussion

Women presenting with MI or with multivessel disease at angiography had a higher occurrence of MACE as compared to men. Among women presenting with MI, mortality was higher than in the general population. Surprisingly, this was not the case for men. On the contrary, men with stable complaints had higher mortality compared to the general population, whereas women with stable CAD showed similar mortality.

Myocardial Infarction

As long as sex-specific differences after MI have been studied, reports of women having a worse prognosis were published.[19-21] Although the risk factor burden changed the last years, our study still reveals a more disadvantageous prognosis for women than for men. A persisting sex difference in delay among patients presenting with MI might be part of the cause. Both patient delay (time from symptom onset to first medical contact) and doctors delay (door-to-balloon time) have been reported to contribute to a poorer prognosis in women.[8,22,23] Several studies reported that the sex difference in delay can be as long as 1 hour.[20] Longer delays might result in greater loss of myocardium and consequently lower LVEF, higher

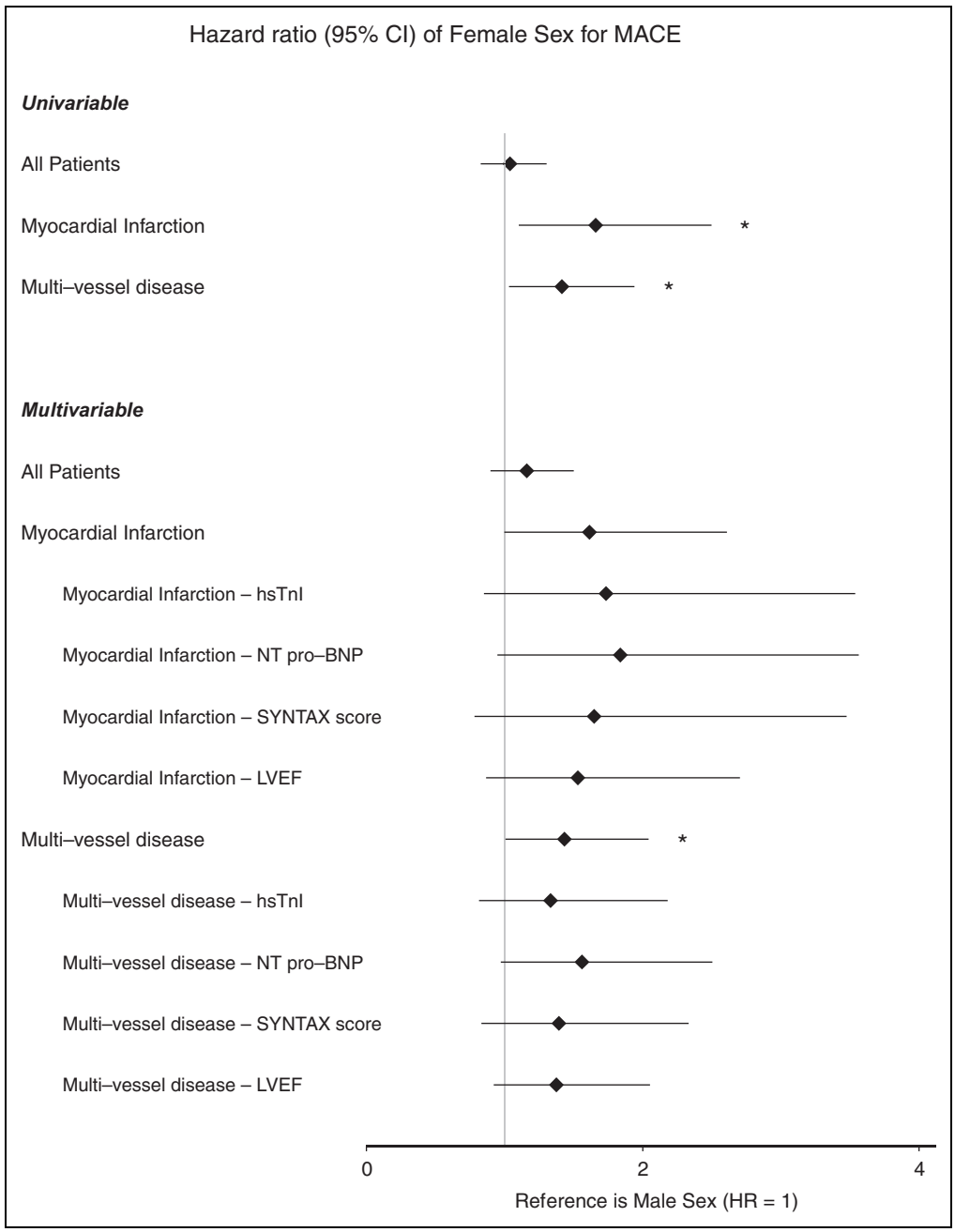

Figure 3. Hazard ratios with 95% confidence intervals are shown. The upper 3 estimates are from univariable Cox regression analysis. The remaining estimates are derived from multivariable Cox regression analysis adjusting for age, indication for angiography (not in MI analysis), angiographic coronary artery disease (CAD) severity (not in multivessel disease analysis), hypertension, hypercholesterolemia, history of percutaneous coronary intervention (PCI), history of coronary artery bypass graft (CABG), history of acute coronary syndrome (ACS), history of cerebrovascular accident (CVA), use of renin–angiotensin–aldosterone system (RAAS) medication, history of PCI, history of CABG, history of ACS, history of CVA, use of RAAS medication, use of diuretics, use of P2Y12 inhibiting medication, use of statins, history of PAD, diabetes, kidney failure, treatment of CAD (conservative, PCI, or CABG) and smoking status (nonsmoker, exsmoker, or current smoker). Additionally, among patients with myocardial infarction (MI) and multi-vessel disease, we added high-sensitivity troponin I (hsTnI), N-terminal probrain natriuretic peptide (NT pro-BNP), SYNTAX score, and left ventricular ejection fraction (LVEF), respectively, to the model in order to observe changes in the hazard ratio (HR) estimate. *Indicates significant association of female sex with major adverse cardiovascular event (MACE; $P < .05$).

hsTnI levels, and higher NT pro-BNP levels. Therefore, we additionally adjusted the multivariable correction for these factors in a multivariable Cox regression model (Figure 4) did not change our findings, suggesting that loss of myocardium did not account for the observed differences between men and women.

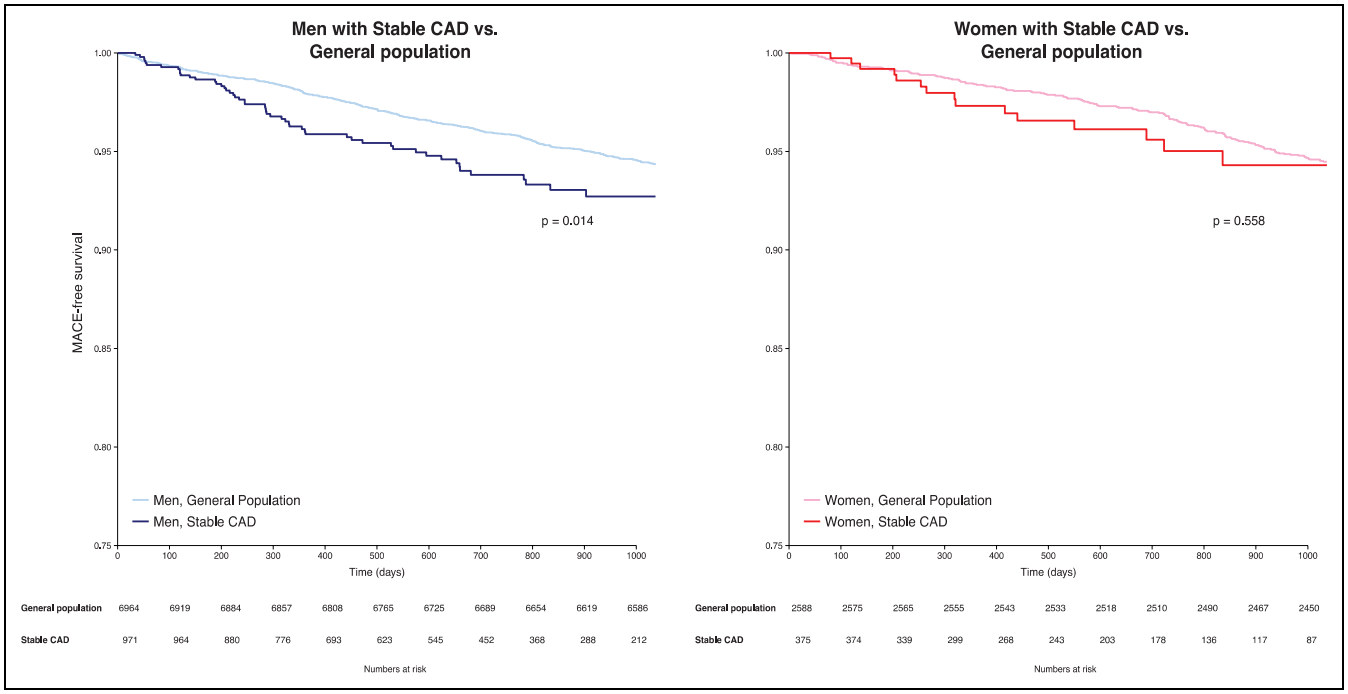

Figure 4. Kaplan-Meier plots of all-cause mortality among patients with stable coronary artery disease (CAD) and the general age and sex-matched Dutch population. On the left panel, men with stable CAD are depicted in dark blue, general population men in light blue (significant difference between the 2 groups, $P = .014$). On the right panel, women with stable CAD are depicted in dark red, women from the general population are in pink (no significant difference between the 2 groups, $P = .558$).

Both laboratory tests have several drawbacks. Higher NT pro-BNP levels in women and elderly individuals are common,[24,25] and hsTnI release depends on left ventricular mass.[26] Therefore, the role of tissue loss and consequent diminished LVEF cannot entirely be excluded in explaining the worse prognosis in women.

Multivessel Disease

Women with multivessel disease show higher mortality rates than men even after correcting for baseline differences. This does not seem to be a result of women in this group having more severe CAD, since SYNTAX scores (quantification scores of angiographic CAD severity) were not significantly different between the sexes among patients with multivessel disease: median SYNTAX score 15.0 (IQR 10.0-21.0) in men, 13.0 (IQR 8.0-19.5) in women, $P = .220$. Women have been reported to have a smaller and stiffer vasculature in general, resulting in a reduced reserve capacity to supply the endangered myocardium when necessary.[4] Theories of women more often having microvascular dysfunction on top of epicardial CAD than men might explain the greater occurrence of events.[8,27,28] Hypothetically, it might even be so that with progression of epicardial disease, microvascular disease progresses as well in women and thereby even further increasing the myocardium at risk. While in men, the disease might be more restricted to the larger coronary arteries, which are accessible for intervention. This hypothesis fits well with our data, as we show an increase in MACE occurrence with increasing severity of epicardial CAD in women but not in men. This theory warrants further investigation on the etiology, diagnostic tools, and treatment of microvascular dysfunction.

Another explanation might lie in a higher prevalence of diastolic heart failure among women.[29] In our cohort, women with multivessel disease have a higher incidence of heart failure admissions after coronary angiography than men. At baseline, EF is more likely to be normal, and NT pro-BNP levels are higher in women than in men, suggesting that heart failure with preserved EF[30] might be the problem.

Both for women with MI and women with multivessel disease, an index event bias[31] is not unlikely. Female sex is protective for the occurrence of a first cardiovascular event. However, when women do develop severe CAD, for example, MI or multivessel disease, in our cohort, their prognosis appears to be worse than men's.

Comparison With General Population

Interestingly, men with stable complaints have a lower survival probability than men from the general population, however, no such difference is observed among women. This may be due to the fact that men with stable complaints have angiographically more severe CAD than women, demonstrated by higher SYNTAX scores.[13] Women present with stable complaints more often than men, but these complaints are not necessarily of a cardiac origin. For women presenting with stable complaints, 16% have no CAD, whereas this is only 4.5% in men. Patients with stable complaints as indication for coronary

angiography not only comprised patients with stable angina but also patients with diagnostic results suspicious for CAD. Noninvasive testing for CAD is of limited predictive accuracy in women, especially due to many false positive tests,[3,4,32] resulting in more invasive testing and consequently finding more women without significant epicardial CAD upon angiography than men. This phenomenon could also be applicable to our study population and might be explain why women with no or minor CAD have a similar prognosis compared to the general population, which is in contrast to results observed in the United States where both men and women without obstructive CAD show a poorer prognosis.[8,33] To avoid unnecessary procedural risk of coronary angiography, a noninvasive diagnostic test with a high negative predictive value is needed. Possibly, coronary computed tomography[34] can assist in this need.

Strengths and Limitations

Our longitudinal observational cohort has a large sample size and a sufficient number of events during follow-up, enabling stratified analysis. Lost to follow-up was limited, comprising of only 4 (0.2%) patients. Since patients with diverse indications were studied, our cohort presents a valuable reflection of daily clinical practice in a tertiary center.

Since we only included patients who provided written informed consent, there is a possibility of selection bias in this study toward inclusion of less severe cases, who are more willing to participate in research.

All-cause mortality in our cohort was compared with the Dutch general population, this end point cannot be misclassified. However, the composite end point MACE also comprised other cardiovascular events, which could have been more subjected to the clinical judgment of the treating cardiologist, for example, for the diagnosis of unstable angina. Nonetheless, the greater part of MACE involved all-cause death, MI, and re-PCI, which are very relevant and less arguable cardiovascular events.

Clinical Implications

Clinicians should be aware of a worse long-term prognosis for women presenting with MI or women who have multivessel disease at angiography. An accurate prediction of long-term prognosis for both patient and clinician is of great importance, since this could have implications for the eventual treatment.

When it comes to medication therapy, men tend to be treated more aggressively than women, experience less side effects and tend to be more compliant to therapy.[28,35-38] A recent meta-analysis about statin compliance, notorious for its side-effects, showed that women were 10% less likely to be adherent to statin therapy than men.[39] Lower compliance could be a factor leading to higher adverse event rates. Since guidelines advise a conservative treatment in women more often than in men, for example, low-risk women presenting with NSTEMI,[40] noncompliance to medication might have greater consequences for women. Medication therapy should be optimized in women, and clinicians should stress the importance of medication compliance.

Future Perspectives

In order to understand these sex-specific differences, further research enrolling large numbers of women is of utmost importance. Primary and secondary prevention should be optimized specifically in high-risk women in order to reduce their risk of recurrent adverse events.

On the other hand, in order to protect the low-risk women from possible procedure-related complications of unnecessary diagnostic coronary angiography, biomarkers or other noninvasive tools indicative of the severity of CAD in women would be extremely helpful.

Conclusion

During a median follow-up duration of 2.1 years after coronary angiography, women presenting with MI or who had multivessel disease at angiography had a higher occurrence of MACE than men, also when adjusted for potential confounders. For women presenting with MI, all-cause mortality was higher as compared to the general population, whereas men with MI did not differ from the general population. This was reversed for patients with stable CAD, where men had higher mortality rates than the general population, but women did not.

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Supplemental Material

The online [appendices/data supplements/etc] are available at http://ang.sagepub.com/supplemental.

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