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# **Gender Difference in Prevalence and Prognostic Impact of Renal Insufficiency in Patients with ST-elevation Myocardial Infarction treated with Primary PCI**

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## INTRODUCTION

End stage renal failure is a well known independent risk factor both for the development and for poor outcome of coronary artery disease [CAD]. (1, 2) More recently mild to moderate renal insufficiency [RI] has also been shown associated with adverse outcome among patients with acute coronary syndrome [ACS]. (3-6) According to previous studies RI prevalence seems to be higher in women compared to men among patients with myocardial infarction [MI]. (3, 7) Although, it is not clear whether this is explained by higher age and co-morbidity in female compared to male MI patient, or if female sex itself is an independent predictor of RI in this setting.

Several studies have shown worse outcome in women than in men with ST-elevation MI [STEMI] also after multivariable adjustments, but few studies have investigated the role of RI. (8-10) We wanted to know if there exists sex differences in occurrence and importance of RI in a population with STEMI, why we choose to study all consecutive STEMI patients in one year that arrived to our PCI unit for primary angioplasty because of STEMI.

We hypothesized that:

- 1) Female sex is an independent predictor of RI in STEMI.
- 2) The association between RI and outcome after STEMI is stronger in women than in men.

## METHODS

### Population

Since January 1<sup>st</sup> 2005 all patients in the county of Östergötland (425 000 inhabitants) with signs of STEMI (symptoms suspicious for ACS combined with ST-elevation or new Bundle Branch Block on the ECG) are directly transferred to the cath lab at the Heart Centre at Linköping University Hospital for primary PCI. The patients are consecutively logged on a log sheet at the coronary care unit [CCU] regarding information about onset of symptoms and ECG findings. They are also registered in the prospective observational Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) (11) and in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). (12)

For this study, we consecutively included all patients between the January 1<sup>st</sup> to December 31<sup>st</sup> 2005 who fulfilled the criteria of ST elevation or Bundle Branch Block on the admission ECG, who underwent an acute coronary angiography with the intention of primary PCI because of STEMI and who got a MI diagnosis at discharge. In case the patient had more than one STEMI during the study period only the first STEMI was included.

### Methods

Data about ECG on admission, cardiovascular risk factors, Killip class on arrival, medications, results of investigations, complications during hospital care, diagnoses at discharge and the occurrence of a new MI during the first year after the index STEMI were retrieved from RIKS-HIA. Key times were retrieved from the log sheet at the CCU. Angiographic data including data about complications after PCI which was also used for information about any new angiography or PCI within the first year after the index MI was retrieved from SCAAR.

Serum creatinine [ $S_{cr}$ ] on arrival was retrieved from patient files. As  $S_{cr}$  at arrival may be affected by the acute condition with possible acute heart failure, acute bleeding/dehydration, admitted drugs etc. we performed a sensitivity analysis using  $S_{cr}$  values from within one year

before or within one year after the acute event (two weeks after event excluded). At least one more  $S_{cr}$  was found in 249 of the 274 patients (91%). The correlation between the eGFR on admission and the eGFR based on earlier or later taken s-creatinine levels was high,  $r = 0.76$ ,  $p < 0.001$  (in women  $r = 0.66$ ,  $p < 0.001$ , in men  $r = 0.69$ ,  $p < 0.001$ ) and the difference between these two eGFR means was not statistically significant,  $p = 0.68$  (in women  $p = 0.92$ , in men  $p = 0.19$ ). Estimated glomerular filtration rate [eGFR] was calculated for each patient using The Modification of Diet in Renal Disease [MDRD] Study equation;  $GFR \text{ (mL/min/1.73 m}^2\text{)} = 186 \times (S_{cr}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$  (SI units). According to guidelines from the National Kidney Foundation we analyzed MDRD eGFR at  $\geq 90$  (CKD stages 1), 60.0 to 89.9 (CKD stage 2), 45.0 to 59.9 (CKD stage 3a), 30.0 to 44.9 (CKD stage 3b), 15.0 to 29.9 (CKD stages 4) and  $< 15.0 \text{ mL/min/1.73 m}^2$  (CKD stage 5). Reduced kidney function was defined as below  $60 \text{ mL/min/1.73 m}^2$  ( $\geq$  CKD stages 3).

Information about other co-morbidities was obtained from the National Patient Register which was also used to find hospitalisations for stroke within one year from index STEMI. The Cardiac Surgery database at the Heart Centre of Östergötland and the Swedish Heart Surgery Register were examined to find patients who had undergone Coronary Artery Bypass Grafting [CABG] after the index STEMI. From the National Cause of Death Register information was available about the vital status of all Swedish citizens.

Patients were followed for one year regarding death, new MI, new revascularisation and rehospitalisation for stroke. A major adverse cardiac event [MACE] was defined as death, non-fatal MI, stroke or new revascularisation not planned at the index event within the first year after the index STEMI. No patient was lost for follow up.

### **Ethics approval**

This study complies with the Declaration of Helsinki and was approved by the local ethics committee at Uppsala University.

### **Statistics**

Categorical variables were presented as numbers and percents and compared by the Chi Square test. Continuous variables were presented as means with standard deviations or medians with interquartile ranges and the t test or the Mann-Whitney U test was used.

Multivariable logistic regression analyses were used to define independent predictors of RI (defined as  $eGFR < 60 \text{ mL/min/1.73 m}^2$ ). Covariates included were: age (in 10 years increment) as a continuous variable and the dichotomous variables sex, active smoker, symptom to needle time more than 3 hours, primary PCI performed, diabetes, hypertension, previous MI, previous PCI, previous heart failure, previous stroke, COPD, cancer within the last 3 years and therapy on arrival (ACE-inhibitors/Angiotensin Receptor Blockers [ARB], statins, aspirin, other platelet inhibitors and/or beta-blockers). Backward elimination was used and variables with  $p$ -values  $< 0.05$  were kept in the final model.

Multivariable logistic regression analyses were also used to define if there was an interaction between sex and eGFR regarding one year mortality and one year MACE, respectively. The covariates were the same as above but instead of therapy on arrival therapy at discharge was used. In addition the continuous variable eGFR (in  $10 \text{ mL/min/1.73 m}^2$  increment) was added and the product of sex and eGFR as an interaction term. Backward elimination was used and variables with  $p$ -values  $< 0.05$  were kept in the final model.

Separate analyses on men and women were also performed regarding one year mortality and one year MACE with the same variables included as above. Backward elimination was then done for each sex separately in the same way as previously described.

Kaplan–Meier estimates for women and for men stratified according to CKD stage for one year mortality and one year MACE were determined and presented as event curves and the log rank test was used to compare the strata. All p-values were two-sided, and a p-value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed on SPSS version 15.0 (SPSS, Chicago, Illinois).

## RESULTS

Two hundred and seventy four patients were included in the study, 98 women and 176 men. The women were older, had higher prevalence of hypertension and COPD and wore more often treated with platelet inhibitors, digitalis or diuretics before admission. There was no sex difference in delay times or in admission ECG-findings. (Table I)

**Table I. Baseline characteristics**

	<b>Women (n=98)</b>	<b>Men (n=176)</b>	<b>p-value</b>
Age, mean (SD)	70.2 (10.7)	63.9 (12.0)	<0.001
<b>ECG on admission</b>			
ST-elevation on admission ECG (%)	89 (90.8)	160 (90.9)	0.98
Bundle Branch Block on admission ECG (%)	6 (6.1)	11 (6.3)	0.97
Other admission ECG (%)	3 (3.1)	5 (2.8)	0.92
<b>Co-morbidity</b>			
Active smoker (%)	31 (32.0)	49 (28.3)	0.53
Diabetes (%)	20 (20.4)	31 (17.6)	0.57
Hypertension (%)	56 (57.7)	60 (34.5)	<0.001
Chronic Obstructive Pulmonary Disease (%)	17 (17.9)	14 (8.0)	0.02
Previous myocardial infarction (%)	14 (14.3)	34 (19.3)	0.29
Previous percutaneous coronary intervention (%)	10 (10.2)	29 (16.5)	0.15
Previous coronary artery bypass grafting (%)	2 (2.0)	7 (4.0)	0.39
Previous stroke (%)	10 (10.2)	14 (8.0)	0.53
Previous heart failure (%)	8 (8.4)	8 (4.6)	0.21
Previous hospital diagnosis of cancer within the last 3 years (%)	3 (3.2)	7 (4.0)	0.72
<b>Kidney function</b>			
Creatinine, mean (SD)	99 (24)	105 (18)	0.03
eGFR in ml/min on arrival, mean (SD)	54 (13)	68 (13)	<0.001
Chronic Kidney Disease Stage 1, eGFR ≥ 90 ml/min (%)	0 (0)	10 (5.7)	<0.001
Chronic Kidney Disease Stage 2, eGFR 60-89 ml/min (%)	32 (33.3)	118 (67.8)	
Chronic Kidney Disease Stage 3a, eGFR 45-59 ml/min (%)	47 (49.0)	39 (22.4)	
Chronic Kidney Disease Stage 3b, eGFR 30-44 ml/min (%)	12 (12.5)	6 (3.4)	
Chronic Kidney Disease Stage 4, eGFR 15-29 ml/min (%)	5 (5.2)	1 (0.6)	
Chronic Kidney Disease Stage 5, eGFR<15 ml/min (%)	0 (0)	0 (0)	
<b>Delay times</b>			
Symptom to ECG time, median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	125 (69, 240)	117 (56, 249)	0.64
Symptom to needle time, median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)	221 (155, 379)	211 (143, 378)	0.59
<b>Killip class on admission</b>			
Killip class I on admission (%)	83 (84.7)	163 (92.6)	0.15
Killip class II on admission (%)	7 (7.1)	6 (3.4)	
Killip class III on admission (%)	1 (1.0)	0 (0)	
Killip class IV on admission (%)	7 (7.1)	7 (4.0)	
<b>Therapy on admission</b>			
Angiotensin receptor inhibitor/Angiotensin II receptor blocker (%)	19 (19.4)	39 (22.2)	0.59
Aspirin (%)	35 (35.7)	42 (23.9)	0.04
Clopidogrel/ other non-acetylic acid platelet inhibitor (%)	7 (7.1)	7 (4.0)	0.25
Warfarin/other anticoagulant drug (%)	8 (8.2)	8 (4.5)	0.22
Beta-blocker (%)	39 (39.8)	55 (31.3)	0.15
Calcium channel inhibitor (%)	15 (15.3)	16 (9.1)	0.12
Statin (%)	19 (19.4)	39 (22.2)	0.59
Diuretics (%)	36 (36.7)	22 (12.5)	<0.001
Digitalis (%)	6 (6.1)	3 (3.3)	0.05

Long acting nitroglycerine (%)	13 (13.3)	12 (6.8)	0.08
Data presented as numbers (percentages) if not otherwise indicated. SD, Standard Deviation; ECG, Electrocardiography; eGFR, estimated Glomerular Filtration Rate;			

PCI as well as stenting were performed more seldom in women who had higher incidence of non-obstructive angiography and more often TIMI 2-3 flow before PCI. (Table II)

**Table II. Hospital stay**

	<b>Women (n=98)</b>	<b>Men (n=176)</b>	<b>p-value</b>
<b>Coronary angiography</b>			
Coronary angiography performed (%)	95 (96.9)	176 (100)	0.02
Coronary angiogram without significant stenoses (%)	8 (8.4)	2 (1.1)	<0.01
One vessel disease (%)	35 (36.8)	78 (44.3)	0.23
Two vessel disease (%)	34 (35.8)	66 (37.5)	0.78
Three vessel disease (%)	18 (18.9)	30 (17.0)	0.70
TIMI 2-3 before percutaneous coronary intervention (%)	42 (44.2)	55(31.3)	0.03
TIMI 2-3 after percutaneous coronary intervention (%)	87 (91.6)	164 (93.2)	0.63
Percutaneous coronary intervention performed (%)	82 (83.7)	169 (96.0)	<0.001
<b>Echocardiography</b>			
Echocardiography performed during hospital care (%)	69 (70.4)	146 (83.0)	0.02
Normal left ventricular function	25 (32.9)	48 (30.8)	0.74
<b>Complications during hospital stay</b>			
New myocardial infarction during hospital care (%)	3 (3.6)	5 (3.1)	0.85
Stroke during hospital care (%)	2 (2.0)	2 (1.1)	0.55
Significant bleeding or pseudoaneurysm (%)	7 (7.1)	7 (4.0)	0.25
Atrioventricular blockage II-III (%)	3 (3.1)	2 (1.2)	0.26
Resuscitation during hospital care (%)	7 (7.1)	9 (5.1)	0.49
Continuous Positive Airway Pressure Therapy (%)	6 (6.1)	6 (3.4)	0.29
In-hospital death (%)	9 (9.2)	8 (4.5)	0.13
<b>Therapy prescribed at discharge</b>			
Angiotensin receptor inhibitor/Angiotensin II receptor blocker (%)	75 (76.5)	142 (81.1)	0.37
Aspirin (%)	82 (83.7)	163 (93.1)	0.01
Clopidogrel/other non-acetylic acid platelet inhibitor (%)	76 (77.6)	157 (89.2)	0.01
Warfarin/other anticoagulant drug (%)	9 (9.2)	6 (3.2)	<0.05
Betablocker (%)	86 (87.8)	160 (91.4)	0.33
Calcium channel inhibitor (%)	9 (9.2)	11 (6.3)	0.38
Statin (%)	83 (84.7)	161 (92.0)	0.06
Diuretics (%)	33 (33.7)	37 (21.1)	0.02
Digitalis (%)	3 (3.1)	5 (2.9)	0.92
Long acting nitroglycerin (%)	14 (14.3)	16 (9.1)	0.19
Data presented as numbers (percentages) if not otherwise indicated. TIMI, Thrombolysis in Myocardial Infarction			

There was no sex difference in Killip class on admission (Table I) or in complications during hospital care. LV-assessment was done more seldom in women. At discharge, statins and antiplatelet therapy was prescribed more often to men whereas diuretics and anticoagulants were prescribed more often to women. (Table II)

The in-hospital (Table II) as well as the one year mortality was all almost twice as high in women as in men, but the differences were not statistically significant. There was no sex difference in MACE within the first year after the index infarction. (Table III)

**Table III. Long term outcome**

	<b>Women (n=98)</b>	<b>Men (n=176)</b>	<b>p-value</b>
New myocardial infarction the first year after index myocardial infarction (%)	11 (11.2)	13 (7.4)	0.28
Stroke the first year after index myocardial infarction (%)	3 (3.1)	8 (4.5)	0.55

New revascularization the first year after index myocardial infarction (%)	20 (20.4)	47 (26.7)	0.25
One year mortality (%)	15 (15.3)	16 (9.1)	0.12
One year MACE* (%)	31 (31.6)	50 (28.4)	0.58

Data presented as numbers (percentages) if not otherwise indicated.

\*Major Adverse Cardiac Event = death, non-fatal myocardial infarction, stroke or new revascularisation not planned at index MI within 1 year

The mean creatinine level was higher in men than in women, (Table I) but after estimating the GFR for each patient, RI was more common in women (67 %) than in men (26 %), 5.06 (95 % CI 2.66 – 9.59)  $p < 0.001$  after multivariable adjustments. (Table IV).

**Table IV. Sex difference in Estimated Glomerular Filtration Rate < 60 mL/min/1.73 m<sup>2</sup>**

	Crude OR Women compared to men (95% CI)	Age-adjusted OR Women compared to men (95% CI)	Multivariable adjusted OR Women compared to men (95% CI)
Female sex	5.57 (3.24 - 9.57) $p < 0.001$	4.39 (2.45 – 7.87) $p < 0.001$	5.06 (2.66 – 9.59) $p < 0.001$
Age in 10 years decrement	-	2.26 (1.69 -3.01) $p < 0.001$	2.09 (1.53 -2.85) $p < 0.001$
Previous PCI	-	-	3.10 (1.07 - 8.97) $p = 0.04$
Previous heart failure	-	-	8.77 (1.47 – 52.19) $p = 0.02$
Aspirin on admission	-	-	2.78 (1.19 -6.50) $p = 0.02$
Statin on admission	-	-	2.58 (1.12 -5.93) $p = 0.03$

Data presented as Odds Ratio (95% Confidence Interval) and p-values if not otherwise indicated.

The primary model included 18 covariates. Backward elimination was used and covariates with  $p < 0.05$  were kept in the final model. OR, Odds Ratio; CI, Confidence Interval; PCI, Percutaneous Coronary Intervention

Kaplan Meier curves with log rank tests showed that higher CKD stage was significantly associated with higher one year mortality and one year MACE in women borderline significance in men regarding MACE (Figure 1 and 2). In order to adjust for possible confounding factors, logistic regression analyses were done. After backward elimination analysing each sex separately, the final models showed that each 10 mL increment of eGFR was associated with a 63% risk reduction of one year death and 39% reduction of one year MACE in women. In men, no such associations were found. (Table V)

**Table V. Prognostic impact of reduced eGFR in women and men**

	Crude OR for eGFR per 10 ml incline (95% CI)		Age-adjusted OR for eGFR per 10 ml incline (95% CI)		Multivariable adjusted OR for eGFR per 10 ml incline (95% CI)	
	Women	Men	Women	Men	Women	Men
One year mortality	0.46 (0.28 – 0.76) $p < 0.01$	0.87 (0.59 – 1.30) $p = 0.50$	0.54 (0.31 – 0.93) $p = 0.03$	1.02 (0.65 – 1.60) $p = 0.92$	0.37 (0.15 – 0.89) $p = 0.03$	1.05 (0.63 – 1.76) $p = 0.85$
Major Cardiac Adverse Events	0.59 (0.40 - 0.85) $p < 0.01$	0.92 (0.71 - 1.18) $p = 0.49$	0.64 (0.42 – 0.98) $p = 0.04$	1.00 (0.76 – 1.32) $p = 0.99$	0.61 (0.40 - 0.92) $P = 0.02$	1.05 (0.79 – 1.40) $p = 0.73$

Data presented as Odds Ratio (95% Confidence Interval) and p-values if not otherwise indicated.

The primary model included 18 covariates. Backward elimination was used and covariates with  $p < 0.05$  were kept in the final model. OR, Odds Ratio; CI, Confidence Interval.

The interaction tests showed a borderline significant interaction between sex and eGFR regarding one year mortality; OR 2.05 (95% CI 0.93 – 4.50,  $p = 0.08$ ) and but no significant interaction at one year MACE; OR 1.42 (95% CI 0.93 – 2.17,  $p = 0.11$ ) for the interaction term.

## DISCUSSION

As far as the investigators are aware, ours is the first study to investigate gender differences regarding the influence of renal impairment on outcome after STEMI. Women have been shown to have 10-20% higher odds for early mortality in STEMI even after adjustment for all kinds of possible confounders, (8-10, 13) and the existence of a special, yet unknown, sex factor has been discussed. Anyhow, GFR has seldom been included in these multivariable analyses. (8-10, 13) Our findings of female sex being an independent strong predictor of RI in

STEMI patients and its possibly higher prognostic impact in women could be important explanations to this observed sex difference.

### **Prevalence of RI**

By calculating the eGFR based on the MDRD formula, a more accurate method of evaluating renal function than creatinine values, we found that women had RI far more often than men. Several studies have suggested that a cut off value for an eGFR of less than 60 ml/min/1.73 m<sup>2</sup> is predictive of adverse cardiovascular outcomes, i.e.  $\geq$ CKD stage 3. (14, 15) In our study 67% of women, had RI compared to only 26% of the men. Of those with eGFR > 60mL/min, only 20% were women, compared to 83% in the population with eGFR < 30 mL/min. In concordance to our findings, Sadeghi et al showed in the CADILLAC trial that the proportion of women was 51% in the group with RI compared to 21% in the group without. (16) Similar results were shown in The ExTRACT-TIMI 25 Trial, where 12% were women in the group with eGFR > 90 mL/min compared to 59% in the group with eGFR < 30 mL/min. (4) These findings have been attributed to their higher age and higher incidence of hypertension and diabetes whereas our study showed that female sex is a strong independent factor for impaired renal function in MI patients, even after adjustment for these variables. In fact, female sex was associated with 5 times higher risk for RI than in men.

### **Prognostic importance of RI**

The association between mild to moderate RI and poor outcome after ACS and/or PCI has become evident from different studies during the recent years. E.g. the CADILLAC study showed that in patients undergoing primary PCI a reduced eGFR was found to be a powerful independent predictor of 30-day and 1 year mortality. (16) Data from four well known ACS trials demonstrated that mild to moderate RI was an independent predictor of adverse outcome with around 20% risk reduction for death in 180 days for each 10 mL/min increment in eGFR.(5) Data from the HERS I and II studies, including postmenopausal women, showed that baseline renal function was among the strongest predictors of cardiovascular events, especially long term. (17) The ExTRACT TIMI 25 including STEMI patients found 30% higher relative risk for 30 day mortality per 10mL/min decline in eGFR.(4)

Thus, an association between mRI and ACS outcome both in men and women seems evident, but there is a lack of studies comparing the genders. One Swedish single centre study of mixed ACS patients showed that creatinine value on admission above the normal upper limit was an independent risk factor for long term mortality in women, but not in men. (18) Chen et al studied an unselected cohort of patients undergoing coronary angiography and found that in all levels of CKD, the multivariate adjusted hazard ratios of 7-year mortality were much higher in women than in men but statistically significant in both sexes. In concordance with Chen et al, we found a stronger association between RI and poor outcome in women than in men, both regarding one year mortality and MACE. We also showed in the Kaplan Meier curves with log rank test that higher CKD stage was significantly associated with higher one year mortality and MACE in women but not in men. The reason why RI does not appear to affect outcome in men in our study we interpret as a result of too few men with different stages of RI in combination with few events. Anyhow, in order to confirm these findings we performed an interaction test between sex and the effect of reduced eGFR per 10 mL/min decline for mortality as well as for MACE which did not show significance (borderline regarding mortality).

## **Possible mechanisms**

The pathophysiological mechanisms behind the association between RI and poor outcome after ACS and PCI are not clearly understood. Many possible explanations could be found (19) such as the high prevalence of diabetes mellitus and hypertension in these patients (20) as well as their higher risk of contrast induced nephropathy [CIN] after PCI. (21) The undertreatment with less revascularisation and less medical therapy (6, 22, 23) may also contribute to reduced survival. Besides this, renal failure is associated with metabolic abnormalities (19) such as oxidative stress, hypoalbuminemia, hyperhomocysteinemia, hyperfibrinogenemia, insulin resistance, lipid abnormalities, inflammation, and derangements in the calcium–phosphate homeostasis that all may contribute to an independent excess cardiovascular risk. (24-29) The reason why women have RI more often than men among STEMI patients even after multivariable adjustment is unknown. IHD risk factors are the same in women as in men (30, 31) but diabetes as well as smoking have previously been shown to be more powerful risk factors in women (32) and according to our data this could also be true for RI.

## **Limitations**

This is a small single centre study with few mortality events, but because of this, we also studied a cardiovascular composite outcome with the same findings. The calculations of eGFR were based on creatinine on presentation, which may not have been at a steady state, and thus, may not represent a true estimation of patients' baseline kidney function. A sensitivity analysis was done using s-creatinine values taken either before or after the STEMI event with no significant difference in either sex.

## **Strengths**

Our study is unique as it reflects current management of STEMI in patients with different stages of CKD based on an unselected cohort, and reveals, to the best of our knowledge for the first time, gender as an independent predictor for RI and a possible gender difference in prognostic impact of RI in STEMI patients.

## **CONCLUSION**

Female gender was found to be a strong independent predictor for RI in STEMI. This is important as RI affects dosage of many drugs and increases the risks of CIN and bleeding after PCI. We also found a stronger association between adverse outcome and decline in eGFR in women. Anyhow, testing interaction between gender and eGFR regarding adverse outcome only showed borderline significance, which could be explained by few events. A possible gender difference regarding prognostic importance of RI has to be confirmed in studies with more patients and events.

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**Conflict of interest:** non declared.

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**Figure legends:**

*Figure 1. Kaplan Meier curves of 1 year mortality for women vs. men. Log rank test p-value 0.02 for women, 0.14 for men*

*Figure 2. Kaplan Meier curves of 1 year MACE for women vs. men. Log rank test p-value <0.01 for women, 0.08 for men*

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